Benchmark Dose Modeling – Introduction

Allen Davis, MSPH
Jeff Gift, Ph.D.
Jay Zhao, Ph.D.

National Center for Environmental Assessment, U.S. EPA
The views expressed in this presentation are those of the author(s) and do not necessarily reflect the views or policies of the US EPA.
Contributors – Software and Training Development

- **U.S. EPA National Center for Environmental Assessment (NCEA)**
  - Jeffrey Gift, Ph.D.
  - Jay Zhao, Ph.D.
  - J. Allen Davis, MSPH
  - Kan Shao, Ph.D. (ORISE Research Fellow)

- **Lockheed Martin**
  - Geoffrey Nonato
  - Louis Olszyk
  - Michael Brown

- **Bruce Allen Consulting**
  - Bruce Allen, M.S.
Learning Objectives of the CLU-IN Courses

• Provide participants with training on:
  • General BMD methods and their application to dose-response assessment
  • U.S. EPA risk assessment and BMD guidance
  • The use of U.S EPA’s Benchmark Dose Software (BMDS)

• This course is not intended to be a primer on basic concepts of toxicology, nor a detailed examination of the statistical underpinnings of dose-response models
Final draft of the EPA’s Benchmark Dose Technical Guidance document was published in 2012:
http://www.epa.gov/raf/publications/benchmarkdose.htm

This training workshop is based upon the 2012 BMD TG and will cover methodologies contained therein

Other guidance documents relevant to BMD modeling available at:
http://epa.gov/iris/backgrd.html
Other sources of BMD Guidance

Risk Assessment/Management

RESEARCH
- Epidemiological studies
- Controlled human exposure studies
- Animal studies
- In vitro, in silico, and genomics studies
- Modeling

RISK ASSESSMENT
- Hazard Identification
- Dose-Response Assessment
- Exposure Assessment
- Risk Characterization

RISK MANAGEMENT
- Legal & economic factors
- Social factors
- Decision: Ban, More research, Standards: air, water, food, Priorities: research, regulation

Information

Research Needs

Assessment Needs
• **Adverse effect** – biochemical change, functional impairment, or pathologic lesion that affects health of whole organism

• **Dose-response relationship** – relationship between a quantified exposure and some measure of a biologically significant effect, such as changes in incidence for dichotomous endpoints, or changes in mean levels of response for continuous endpoints

• **Point of departure** – point on dose-response curve that marks the beginning of low-dose extrapolation

• **Reference value** – estimate of exposure for a given duration to the human population that is likely to be without appreciable risk of adverse health effects over a lifetime.  
  • **Reference concentration** – inhalation exposures
  • **Reference dose** – oral exposures
  • Derived from a point of departure, with uncertainty/variability factors applied to reflect limitations of the data used.

Sources: Adapted from Online IRIS Glossary, http://www.epa.gov/iris/help_gloss.htm
Characterizing Non-cancer Hazards in Risk Assessments

- NOEL
- NOAEL
- LOAEL
- FEL

- RfD/RfC
- UF

- Slight Body Weight Decrease
- Enzyme Change
- Convulsions
- (Critical Effect)
Identify Point of Departure (POD) for the critical effect based on external dose, either as:
- No-observed-adverse-effect-level (NOAEL)
- Lowest-observed-adverse-effect-level (LOAEL)

Convert animal external doses or concentrations to human equivalent dose (HED) or concentration (HEC) using:
- Default dosimetric methods
- Physiologically-based pharmacokinetic (PBPK) models

Apply uncertainty factors (UFs) to derive reference dose (RfD) or reference concentration (RfC).
Calculation of the RfC/RfD

- **RfC or RfD = POD (NOAEL or LOAEL) ÷ UF**

- **Uncertainty Factors used in the IRIS Program**
  - Interspecies extrapolation – characterizes toxicokinetic and toxicodynamic differences between species
  - Intraspecies variability – accounts for potentially susceptible subpopulations
  - LOAEL to NOAEL extrapolation
  - Duration extrapolation – for extrapolating from subchronic to chronic durations
  - Database uncertainty – accounts for deficiencies in the database, i.e., missing types of data
  - Can be factors of 10, 3 ($\sqrt{10} = 3.16$, rounded to 3), or 1
Limitations of Using a NOAEL

<table>
<thead>
<tr>
<th>Subject</th>
<th>NOAEL/LOAEL Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose selection</td>
<td>NOAEL/LOAEL limited to doses in study only</td>
</tr>
<tr>
<td>Sample size</td>
<td>The ability of a bioassay to detect a treatment response decreases as sample size decreases (i.e., $\downarrow N = \uparrow$ NOAEL)</td>
</tr>
<tr>
<td>Cross-study comparison</td>
<td>Observed response levels at the NOAEL or LOAEL are not consistent across studies and can not be compared</td>
</tr>
<tr>
<td>Variability and uncertainty in experimental results</td>
<td>Characteristics that influence variability or uncertainty in results (dose selection, dose spacing, sample size) not taken into consideration</td>
</tr>
<tr>
<td>Dose-response information</td>
<td>Information, such as shape of the dose-response curve (i.e., how steep or shallow the response is), not taken into consideration</td>
</tr>
<tr>
<td>May be missing from study</td>
<td>A LOAEL cannot be used to derive a NOAEL, in this case an uncertainty factor (usually 10) is applied</td>
</tr>
</tbody>
</table>
Study Conducted with 100 Animals/Dose

Gamma Multi-Hit Model

- NOAEL: p-value = 1.000
- LOAEL: p-value < 0.0001

Fraction Affected vs. Dose

- NOAEL: p-value = 1.000
- LOAEL: p-value < 0.0001

Gamma Multi-Hit

12:07 10/18 2012
Study Conducted with 10 Animals/Dose

Gamma Multi-Hit Model

NOAEL
p-value = 0.4737

LOAEL
p-value = 0.0325
## A Brief History of the BMD Method

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>EPA workshop on epigenetic carcinogenesis</td>
</tr>
<tr>
<td>1985–1994</td>
<td>Several EPA BMD-related publications and workshops</td>
</tr>
<tr>
<td>1995</td>
<td>EPA Risk Assessment Forum discusses use of BMD in risk assessment</td>
</tr>
<tr>
<td>1995</td>
<td>First IRIS BMD-based RfD (Methylmercury)</td>
</tr>
<tr>
<td>2000</td>
<td>EPA benchmark dose draft technical guidance released</td>
</tr>
<tr>
<td>2000</td>
<td>EPA benchmark dose software (BMDS) released</td>
</tr>
<tr>
<td>2000–2011</td>
<td>Multiple versions of BMDS released</td>
</tr>
<tr>
<td>2012</td>
<td>EPA benchmark dose final technical guidance released</td>
</tr>
</tbody>
</table>
**Benchmark Response (BMR)** - a change in response for an effect relative to background response rate of this effect

- Basis for deriving BMDs
- User defined

**Examples include:**

- 1 standard deviation increase in body weight (continuous response)
- 10% increase in hepatocellular hyperplasia (dichotomous response)
Benchmark dose or concentration (BMD or BMC) - the maximum likelihood estimate of the dose associated with a specified benchmark response level

- BMD – oral exposure
- BMC – inhalation exposure

However, the term benchmark dose modeling is frequently used to the modeling process for both oral and inhalation exposures.
**Benchmark Dose – Key Terminology**

- **Benchmark dose or concentration lower-confidence limit (BMDL or BMCL)** – the lower limit of a one-sided confidence interval on the BMD (typically 95%)
  - BMDL – oral exposure
  - BMCL – inhalation exposure

- **Accounts for elements of experimental uncertainty, including:**
  - Sample size
  - High background response
  - Response variability

- **Preferred POD**
Calculation of the RfC/RfD Using a BMDL

• Equation for an RfD or RfC becomes: BMDL ÷ UF

• Uncertainty Factors used in IRIS
  • Interspecies extrapolation – characterizes toxicokinetic and toxicodynamic differences between species
  • Intraspecies variability – accounts for potentially susceptible subpopulations
  • LOAEL-to-NOAEL extrapolation
  • Duration extrapolation – for extrapolating from subchronic to chronic durations
  • Database uncertainty – accounts for deficiencies in the database, i.e., missing types of data
  • Can be factors of 10, 3 (√10 = 3.16, rounded to 3), or 1
# Advantages of BMD Approach

<table>
<thead>
<tr>
<th>Subject</th>
<th>BMD Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose selection</td>
<td>BMD and BMDL not constrained to be a dose used in study</td>
</tr>
<tr>
<td>Sample size</td>
<td>Appropriately considers sample size: as sample size decreases, uncertainty in true response rate increases (i.e., $\downarrow N = \downarrow BMDL$)</td>
</tr>
<tr>
<td>Cross-study comparison</td>
<td>Observed response levels at a selected BMR are comparable across studies (recommended to use BMD as point of comparison)</td>
</tr>
<tr>
<td>Variability and uncertainty in experimental results</td>
<td>Characteristics that influence variability or uncertainty in results (dose selection, dose spacing, sample size) are taken into consideration</td>
</tr>
<tr>
<td>Dose-response information</td>
<td>Full shape of the dose-response curve is considered</td>
</tr>
<tr>
<td>NOAEL not identified in study</td>
<td>A BMD and BMDL can be calculated even when a NOAEL is missing from the study</td>
</tr>
</tbody>
</table>
Gamma Multi-Hit Model with 0.95 Confidence Level

- **NOAEL**: $p$-value = 1.000
- **LOAEL**: $p$-value < 0.0001
- **BMDL** = 77.1
- **BMD** = 86.5

Study Conducted with 100 Animals/Dose
Study Conducted with 10 Animals/Dose

Gamma Multi-Hit Model with 0.95 Confidence Level

- NOAEL p-value = 0.4737
- LOAEL p-value = 0.0325
- BMD = 86.5
- BMDL = 52.9

Gamma Multi-Hit

Fraction Affected

Dose

0 50 100 150 200

BMDL = 52.9
BMD = 86.5

LOAEL p-value = 0.0325
NOAEL p-value = 0.4737

12:04 10/18 2012
Challenges in the Use of the BMD Method

• Requires knowledge on how to use software and interpret results

• In some cases, more data are required to model benchmark dose than to derive a LOAEL/NOAEL
  • Continuous data require a measure of variability (SD or SE) for each dose group’s mean response
  • Individual animal-level data are required for some models
  • Results highly dependent on the quality of the data

• Sometimes the data cannot be adequately fit by the available models in BMDS
• Evaluate database as for NOAEL/LOAEL approach
  • Select high quality studies
  • Select studies using appropriate durations and routes of exposure
  • Select endpoints of concern that are relevant to human health
  • Do PBPK models for the chemical of concern exist?

• Model all potentially adverse endpoints, especially if different UF$s$ may be used.
Are the Data Worth Modeling? (Data Criteria)

- At least a statistically or biologically significant dose-response trend
- Distinct response information between extremes of control level and maximal response
- Response near low-end of dose-response region (ideally near BMR)
- Reasonable (<50%) background response rate
- General rule of thumb for large databases: consider excluding endpoints with LOAELs >10-fold above lowest LOAEL in the database
Are the Data Worth Modeling? (Data Criteria)
## Comparison of NOAELs and BMDLs

<table>
<thead>
<tr>
<th>NOAELs and LOAELs With Corresponding BMRs and BMDLs (mg/kg-day)</th>
<th>Liver Lesions</th>
<th>NOAEL</th>
<th>LOAEL</th>
<th>BMR</th>
<th>BMDL</th>
<th>POD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gaines and Kimbrough, 1970</strong></td>
<td></td>
<td>0.065 (M)</td>
<td>0.35 (M)</td>
<td>10%</td>
<td>0.026 (M)</td>
<td>0.026 (M)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.4 (F)</td>
<td>2.3 (F)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NTP, 1990</strong></td>
<td></td>
<td>0.07 (M)</td>
<td>0.7 (M)</td>
<td>10%</td>
<td>0.2 (M)</td>
<td>0.08 (F)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.08 (F)</td>
<td>0.7 (F)</td>
<td></td>
<td>0.08 (F)</td>
<td></td>
</tr>
<tr>
<td><strong>Cataract Development</strong></td>
<td></td>
<td>None</td>
<td>0.5</td>
<td>5%</td>
<td>0.028</td>
<td>0.028</td>
</tr>
<tr>
<td><strong>Chu et al., 1981b</strong></td>
<td></td>
<td>0.4</td>
<td>2.3</td>
<td>N/A</td>
<td>N/A</td>
<td>0.4 (NOAEL)</td>
</tr>
<tr>
<td><strong>Gaines and Kimbrough, 1970</strong></td>
<td></td>
<td>7.0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>7.0 (NOAEL)</td>
</tr>
<tr>
<td><strong>Testicular Histopathology</strong></td>
<td></td>
<td>7.0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>7.0 (NOAEL)</td>
</tr>
<tr>
<td><strong>Yarbrough et al., 1981</strong></td>
<td></td>
<td>0.4</td>
<td>2.3</td>
<td>N/A</td>
<td>N/A</td>
<td>0.4 (NOAEL)</td>
</tr>
<tr>
<td><strong>Chu et al., 1981a</strong></td>
<td></td>
<td>0.4</td>
<td>2.3</td>
<td>N/A</td>
<td>N/A</td>
<td>0.4 (NOAEL)</td>
</tr>
<tr>
<td><strong>Decreased Litter Size</strong></td>
<td></td>
<td>None</td>
<td>0.5</td>
<td>1 SD</td>
<td>0.48</td>
<td>0.48</td>
</tr>
</tbody>
</table>
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
1. Choose BMR(s) and dose metrics to evaluate.

2. Select the set of appropriate models, set parameter options, and run models.

3. Do any models adequately fit the data?

4. Estimate BMDs and BMDLs for the adequate models. Are they sufficiently close?

5. Is one model better than the others considering best fit and least complexity (i.e., lowest AIC)?

6. Document the BMD analysis, including uncertainties, as outlined in reporting requirements.
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 1)

10:50 04/25 2014
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.
Measurement of Increased Risk

• For dichotomous data, BMRs are expressed as:
  • **Added risk** – \( AR(d) = P(d) – P(0) \)
  • **Extra risk** – \( ER(d) = \frac{P(d) – P(0)}{1 – P(0)} \)

• **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) = .50
P(d) = 0.10 + P(0) = 0.10 + 0.50 = \textbf{0.60}

10% Extra Risk
0.10 = \frac{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 = \textbf{0.55}

\textbf{The dose will be lower for a 10\% Extra risk than for a 10\% Added risk if P(0) > 0}
BMD Analysis – Six Steps

1. Choose BMR(s) and dose metrics to evaluate.
2. Select the set of appropriate models, set parameter options, and run models.
3. Do any models adequately fit the data?
4. Estimate BMDs and BMDLs for the adequate models. Are they sufficiently close?
5. Is one model better than the others considering best fit and least complexity (i.e., lowest AIC)?
6. Document the BMD analysis, including uncertainties, as outlined in reporting requirements.
### 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
### Traditional Dichotomous Models

<table>
<thead>
<tr>
<th>Model name</th>
<th>Functional form</th>
<th># of Parameters&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Low Dose Linearity</th>
<th>Model fits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multistage</td>
<td>( y + (1 - y) \left[ 1 - \exp\left{ - \sum_{j=1}^{k} \beta_j X^j \right} \right] )</td>
<td>1+k</td>
<td>Yes, if ( \beta_1 &gt; 0 ) No, if ( \beta_1 = 0 )</td>
<td>All purpose</td>
</tr>
<tr>
<td>Logistic</td>
<td>( \frac{1}{1 + \exp{- (\alpha + \beta X)}} )</td>
<td>2</td>
<td>Yes</td>
<td>Simple; no background</td>
</tr>
<tr>
<td>Probit</td>
<td>( \Phi(\alpha + \beta X) )</td>
<td>2</td>
<td>Yes</td>
<td>Simple; no background</td>
</tr>
<tr>
<td>Log-logistic</td>
<td>( \frac{y + (1 - y)}{1 + \exp{-[\alpha + \beta \ln(X)]}} )</td>
<td>3</td>
<td>No</td>
<td>All purpose; S-shape with plateau at 100%</td>
</tr>
<tr>
<td>Log-probit</td>
<td>( y + (1 - y) \Phi{\alpha + \beta \ln(X)} )</td>
<td>3</td>
<td>No</td>
<td>All purpose; plateau S-shape with plateau at 100%</td>
</tr>
<tr>
<td>Gamma</td>
<td>( y + (1 - y) \int_0^x t^{\alpha-1} e^t dt / \Gamma(\alpha) )</td>
<td>3</td>
<td>No</td>
<td>All purpose</td>
</tr>
<tr>
<td>Weibull</td>
<td>( y + (1 - y)[1 - \exp{-\beta X^\alpha}] )</td>
<td>3</td>
<td>No</td>
<td>&quot;Hockey stick&quot; shape</td>
</tr>
<tr>
<td>Dichotomous Hill</td>
<td>( \frac{v \times g + \frac{(v - v \times g)}{1 + \exp { -a - b \times \ln(X) }}}{1 + \exp { -a - b \times \ln(X) }} )</td>
<td>4</td>
<td>Yes</td>
<td>Symmetrical, S-shape with plateau</td>
</tr>
</tbody>
</table>

<sup>a</sup> Background parameter = \( y \). Background for hill model = \( v \times g \)
Curve Shapes with Increasing Background Response

log-probit model with \(\alpha = 2\), \(\beta = 2\), and \(\gamma = 0, .1, .2, .3, \text{ and } .4\)
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

Multistage Model with 0.95 Confidence Level

Fraction Affected vs. Dose

22:08 06/25 2009
Multistage Model – Betas Restricted

Multistage Model with 0.95 Confidence Level

Fraction Affected

Dose

BMDL  BMD

22:05 06/25 2009
Models with Unrestricted Power or Slope Parameters

Weibull Model with 0.95 Confidence Level

Gamma, Weibull, Hill, Log-Logistic, or Log-Probit models
Models with Restricted Power or Slope Parameters

Gamma, Weibull, Hill, Log-Logistic, or Log-Probit models

Weibull Model with 0.95 Confidence Level

Fraction Affected

Weibull

Gamma, Weibull, Hill, Log-Logistic, or Log-Probit models

BMDL BMD

10:25 03/04 2010
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
BMD Analysis – Six Steps

1. Choose BMR(s) and dose metrics to evaluate.

2. Select the set of appropriate models, set parameter options, and run models.

3. Do any models adequately fit the data?

4. Estimate BMDs and BMDLs for the adequate models. Are they sufficiently close?

5. Is one model better than the others considering best fit and least complexity (i.e., lowest AIC)?

6. Document the BMD analysis, including uncertainties, as outlined in reporting requirements.
Does the Model Fit the Data?

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

Chi^2 = 1.24  d.f. = 3  P-value = 0.7446

AIC: 361.607
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 1: When **Not** to Drop the High Dose

<table>
<thead>
<tr>
<th>Dose (mg/m³)</th>
<th>N</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>180</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>300</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>750</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>1200</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

Multistage Model with 0.95 Confidence Level

P = 0.94
Example 2: When to Drop the High Dose

<table>
<thead>
<tr>
<th>Dose (mg/m³)</th>
<th>N</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>180</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>300</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>750</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>1200</td>
<td>12</td>
<td>5</td>
</tr>
</tbody>
</table>

Multistage Model with 0.95 Confidence Level

\[ P = 0.0526 \]
Example 2: When to Drop the High Dose

<table>
<thead>
<tr>
<th>Dose (mg/m³)</th>
<th>N</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>180</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>300</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>750</td>
<td>12</td>
<td>6</td>
</tr>
</tbody>
</table>

Multistage Model with 0.95 Confidence Level

\[ P = 0.3676 \]
### Example 3: Use of a Model with Asymptote Term

<table>
<thead>
<tr>
<th>Dose (mg/m³)</th>
<th>N</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>180</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>300</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>750</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>1200</td>
<td>12</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fraction Affected</th>
<th>BMDL</th>
<th>BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Dichotomous-Hill Model with 0.95 Confidence Level**

- **P = 0.9094**

14:11 11/03 2010
Further Recommendations – Poor Global Goodness-of-Fit

- **Log-transformation of doses**
  - Consult a statistician to determine if log-transformation is appropriate, special care often needs to be taken with the control dose (i.e., $\log_{10}(0)$ is undefined)
  - Both $\log_{10}$ 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., $C_{\text{max}}$ 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
For dichotomous data:

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

- **Global goodness-of-fit p-values are not enough to assess local fit**
  - Models with large p-values may consistently “miss the data” (e.g., always on one side of the dose-group means)
  - Models may “fit” the wrong (e.g. high-dose) region of the dose-response curve.

- **Scaled Residuals** – measure of how closely the model fits the data at each point; 0 = exact fit
  
  \[
  \frac{\text{Obs} - \text{Exp}}{\sqrt{(n*p(1-p))}}
  \]
  
  - Absolute values near the BMR should be lowest
  - Question scaled residuals with absolute value > 2
Scaled Residuals

The image shows a graph of scaled residuals from a BMDS 2.4 analysis. The graph plots the residuals against the dose, with error bars indicating the confidence intervals. Below the graph, there is a table listing goodness of fit information, including dose, estimated probability, expected, observed, size, and scaled residual values. The table also includes a chi-squared test result with a p-value of 0.7446, indicating a good fit of the model to the data.
Does the Model Fit the Data?

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

Multistage Model with 0.95 Confidence Level

- BMD
- BMDL

22:08 06/25 2009
22:05 06/25 2009
START

1. Choose BMR(s) and dose metrics to evaluate.

2. Select the set of appropriate models, set parameter options, and run models

3. Do any models adequately fit the data?

4. Estimate BMDs and BMDLs for the adequate models. Are they sufficiently close?

5. Is one model better than the others considering best fit and least complexity (i.e., lowest AIC)?

6. Document the BMD analysis, including uncertainties, as outlined in reporting requirements.

Have all models & model parameters been considered?

Yes

Data not amenable for BMD modeling

No

Use lowest reasonable BMDL

No

Consider combining BMDs (or BMDLs)

No

Use BMD (or BMDL) from the model with the lowest AIC

Yes
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.
BMD Analysis – Six Steps

1. Choose BMR(s) and dose metrics to evaluate.

2. Select the set of appropriate models, set parameter options, and run models.

3. Do any models adequately fit the data?

4. Estimate BMDs and BMDLs for the adequate models. Are they sufficiently close?

5. Is one model better than the others considering best fit and least complexity (i.e., lowest AIC)?

6. Document the BMD analysis, including uncertainties, as outlined in reporting requirements.

Have all models & model parameters been considered?

Data not amenable for BMD modeling

Use lowest reasonable BMDL

Consider combining BMDs (or BMDLs)

Use BMD (or BMDL) from the model with the lowest AIC
BMD Analysis – Six Steps

1. Choose BMR(s) and dose metrics to evaluate.
2. Select the set of appropriate models, set parameter options, and run models.
3. Do any models adequately fit the data?
4. Estimate BMDs and BMDLs for the adequate models. Are they sufficiently close?
5. Is one model better than the others considering best fit and least complexity (i.e., lowest AIC)?
6. Document the BMD analysis, including uncertainties, as outlined in reporting requirements.
Comparing Model Fit Across Models

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

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

- **AIC = -2 x LL + 2 x p**
  - LL = log-likelihood at the maximum likelihood estimates for parameters
  - p = number of model degrees of freedom (dependent on total number of model parameters, number of model parameters that hit a bound, and the number of dose groups in your dataset)

- Only the DIFFERENCE in AIC is important, not actual value

- As a matter of policy, any difference in AIC is considered important. This prevents “model shopping”
BMD Analysis – Six Steps

START

1. Choose BMR(s) and dose metrics to evaluate.

2. Select the set of appropriate models, set parameter options, and run models.

3. Do any models adequately fit the data?

4. Estimate BMDs and BMDLs for the adequate models. Are they sufficiently close?

5. Is one model better than the others considering best fit and least complexity (i.e., lowest AIC)?

6. Document the BMD analysis, including uncertainties, as outlined in reporting requirements.
1. Choose BMR(s) and dose metrics to evaluate.

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5. Is one model better than the others considering best fit and least complexity (i.e., lowest AIC)?

6. Document the BMD analysis, including uncertainties, as outlined in reporting requirements.
### 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)*

<table>
<thead>
<tr>
<th>Model</th>
<th>Goodness-of-fit</th>
<th>BMD$_{10%}$</th>
<th>BMDL$_{10%}$</th>
<th>Basis for Model Selection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$p$-value</td>
<td>AIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logistic</td>
<td>0.6024</td>
<td>35.5306</td>
<td>528.905</td>
<td>341.987</td>
</tr>
<tr>
<td>Log-logistic</td>
<td>0.9743</td>
<td>32.1664</td>
<td>193.575</td>
<td>93.947</td>
</tr>
<tr>
<td>Log-probit</td>
<td>0.5825</td>
<td>35.4276</td>
<td>426.494</td>
<td>232.739</td>
</tr>
<tr>
<td>Probit</td>
<td>0.6248</td>
<td>35.4027</td>
<td>489.595</td>
<td>317.868</td>
</tr>
<tr>
<td>Dichotomous Hill</td>
<td>0.9352</td>
<td>34.1023</td>
<td>160.508</td>
<td>--</td>
</tr>
<tr>
<td>Gamma</td>
<td>0.9338</td>
<td>32.3299</td>
<td>228.574</td>
<td>129.306</td>
</tr>
<tr>
<td>Weibull</td>
<td>0.9338</td>
<td>32.3299</td>
<td>228.574</td>
<td>129.306</td>
</tr>
<tr>
<td>Linear</td>
<td>0.9338</td>
<td>32.3299</td>
<td>228.574</td>
<td>129.306</td>
</tr>
<tr>
<td>Multistage 2°</td>
<td>0.9338</td>
<td>32.3299</td>
<td>228.574</td>
<td>129.306</td>
</tr>
<tr>
<td>Multistage 3°</td>
<td>0.9338</td>
<td>32.3299</td>
<td>228.574</td>
<td>129.306</td>
</tr>
</tbody>
</table>

---

$^a$ 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/m$^3$ were 0.000, 0.434, -0.154, -0.089, respectively.
Additional Models for Dichotomous Data

- For most of the quantal models in BMDS, there are two alternative versions available:
  
  - Background response parameter, \( \gamma \):
    \[
    P(\beta, x, \gamma) = \gamma + (1-\gamma) F\{\beta, x\}
    \]
  
  - Background parameter additive to dose, \( \eta \):
    \[
    P(\beta, x, \eta) = F\{\beta, (x+\eta)\}
    \]
  
- Background response models are the “traditional” models that are typically used in EPA assessments.
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

Log-probit with background dose, alpha = -0.1, beta = +1
bg_dose = 3, 2.5, 2, 1.5, 1, 0.5, 0, left to right
Dichotomous Data – Creating a Dataset in BMDS
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
Creating a Dataset – Open New Generic Dataset

Enter data manually
Creating a Dataset – Import an Existing Dataset

In BMDS 2.4, under the File menu, choose ‘Import Data From’ to select the desired file format. Options include:
- Tab Delimited Text File (*.txt)
- Space Delimited Text File (*.txt)
- Comma Separated Values (*.csv)
- Excel File (*.xls)
- BMDS 1.xx Dataset (*.set)
Creating a Dataset – Renaming Column Headers
Creating a Dataset – Renaming Column Headers
Creating a Dataset – Data Transformations

Variable Transformation:
- Transformation: SE to Standard Deviation (SD)
- Standard Error: Col1
- Subj. in Dose Grp: Col1
- Enter "X" Value: 

100 row(s) added.
Creating a Dataset – Open new Formatted Dataset
Creating a Dataset – Open New Formatted Dataset
Creating a Dataset – Open Existing Dataset
Creating a Dataset – Open Existing Dataset
Running an Individual Model – Select a Model Type

- Continuous
- Dichotomous
- Dichotomous_Alt
- Nested_Dichotomous
- Rptd_Resp_Measures
- Conc_x_Time

Effect | Effect2 | Effect3 | Percent | Col7
--- | --- | --- | --- | ---
100 | 0 | 5 | 1 | 2.34
100 | 5 | 10 | 68 | 4.58
100 | 30 | 33 | 78 | 42.5
150 | 100 | 65 | 67 | 88 | 60
200 | 100 | 90 | 93 | 98 | 90.23

95 row(s) added.
Running an Individual Model – Select a Model

EPA
Running an Individual Model – Proceed to Option Screen
Selecting Column Assignments

- **Column Assignments**
  - Dose
  - # Subjects in Dose Group
  - Incidence
  - % Positive

- **Other Assignments**
  - Risk Type
  - BMR
  - Confidence Level
  - BMD Calculation
  - BMDL Curve Calc.
  - Dose Groups
  - Restrict Power > 1

- **Optimizer Assignments**
  - Iteration: 500
  - Relative Function: 1.00E-08
  - Parameter: 1.00E-08

- **Parameter Assignments**
  - Background
  - Slope
  - Power

- **User Notes**: BMDS Model Run
- **Data File**: C:\Users\adavis10\BMDS24\Data\Dichotomous.dat
- **Out File Name**: C:\Users\adavis10\BMDS24\Dichotomous_BMDL.dat

- Buttons:
  - Save
  - Save As
  - Set Values To Default
  - Optimize Initial Param. Values
  - Run
  - Close
Selecting Model Options

- **Column Assignments**
  - Dose
  - Subjects in Dose Group
  - Incidence
  - % Positive

- **Other Assignments**
  - Risk Type: Extra
  - BMR
  - Confidence Level: 0.95
  - BMD Calculation
  - BMDl Curve Calc
  - Dose Groups: 5
  - Restrict Power > 1

- **Optimizer Assignments**
  - Iteration: 500
  - Relative Function: 1.00E-08
  - Parameter: 1.00E-08

- **Parameter Assignments**
  - Background: Default
  - Slope: Default
  - Power: Default

- **User Notes**: BMDS Model Run
- **Data File**: C:\Users\adavis10\BMDS240\Data\Dichotomous.dat
- **Output File Name**: C:\Users\adavis10\BMDS240\Dehalogen_Dichotomous_Opt.out

- Buttons: Save, Save As, Set Values To Default, Optimize Initial, Param Values, Run, Close

Image file successfully drawn!
Specifying Model Parameters

[Image of model parameter assignments and user notes]
Dichotomous Model Plot and Output Files

**Graph:**
A graph showing a line plot with error bars indicating a gamma multi-hit model with BMDR of 10% and a 95% lower confidence limit for the BMDL.

**Output File:**
```
---
Gamma Model. (Version: 2.16; Date: 2/28/2013)
Input Data File: C:/Users/adavis10/BMDS240/Data/gam_Dichotomous_Opt.(d)
---

BMDS_Model_Run

The form of the probability function is:

\[ P[\text{response}] = \text{background} + (1-\text{background}) \cdot \text{CumGamma}[\text{slope} \cdot \text{dose}, \text{power}] \]

where \( \text{CumGamma}(.) \) is the cumulative Gamma distribution function.

Dependent variable = Effect
Independent variable = Dose
Power parameter is restricted as power > 1
---
```
Dichotomous Model Parameter Estimates

Parameter Estimates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Std. Err.</th>
<th>Lower Conf. Limit</th>
<th>Upper Conf. Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Slope</td>
<td>0.0402678</td>
<td>0.00696178</td>
<td>0.0265732</td>
<td>0.0539413</td>
</tr>
<tr>
<td>Power</td>
<td>5.16216</td>
<td>0.57623</td>
<td>3.69428</td>
<td>7.04219</td>
</tr>
</tbody>
</table>

NA - Indicates that this parameter has hit a bound implied by some inequality constraint and thus has no standard error.

Analysis of Deviance Table

<table>
<thead>
<tr>
<th>Model</th>
<th>Log(likelihood)</th>
<th># Param's Deviance Test d.f.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td>-178.191</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>
Dichotomous Model Fit Statistics

**Scaled Residual of Interest (local fit)**

**Goodness-of-fit p-value (global fit)**
BMD and BMDL Estimates

**Graphical Representation:**
- Gamma multi-hit model with BMD of 10% extra risk for BMD and 0.05 lower confidence limit for BMDL.

**Data Table:**
- Benchmark dose computation with:
  - Chit2 = 1.24
  - d.f. = 3
  - P-value = 0.7446

**Benchmark Dose Computation:**
- Specified effect = 0.1
- Risk Type = Extra risk
- Confidence level = 0.95

**Estimated Values:**
- BMD = 66.0374
- BMDL = 57.6299
Opening Output and Plot Files after Analysis

[Image of BMDS software interface showing options to view plot, output file, and options.

UNITED STATES
ENVIRONMENTAL PROTECTION AGENCY

100 row(s) added.

Num Lock]
New Flexibility in Datafile Structure

![Datafile Structure](image)

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>Effect</th>
<th>Effect2</th>
<th>Effect3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>100</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>100</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>100</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>150</td>
<td>100</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>200</td>
<td>100</td>
<td>90</td>
<td></td>
</tr>
</tbody>
</table>

This data is from Rogers et al. 1975
Liver hyperplasia in Wistar Rats
Effect 1 = males, Effect 2 = females
New Flexibility in Datafile Structure
New Flexibility in Datafile Structure
New Flexibility in Datafile Structure
New Flexibility in Datafile Structure

Please close the "Options Screen" and fix the following issue(s) before continuing:

One or more dataset rows are missing values. Enter valid data for any blank cells in the mapped columns. Refer to the Options Screen to view the mapped columns for the dataset.
Dichotomous Data – Exercise #1
Manually enter these data and save as Exercise_1.dax
Dichotomous Exercise #1

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

[Image of BMDS software interface with Column Assignments, Other Assignments, Optimizer Assignments, and Parameter Assignments sections.]

- **Column Assignments**
  - Dose
  - # Subjects in Dose Group
  - Incidence
  - % Positive

- **Other Assignments**
  - Risk Type: Extra
  - BMR: 0.1000
  - Confidence Level: 0.95
  - BMD Calculation: √
  - BMDl Curve Calc: √
  - Dose Groups: 4
  - Restrict Betas > 0: √
  - Degree of Polynomial: 1

- **Optimizer Assignments**

- **Parameter Assignments**
  - Background: Default
  - Beta1: Default
  - Beta2: Default
  - Beta3: Default

- **User Notes**

- **Data File**
  - C:\Users\davis10\BMDS24\Data\clu_in\exercise_1.dax
  - Show/Run

- **Output File Name**
  - C:\Users\davis10\BMDS24\Data\clu_in\exercise_1_Opt1
  - Set To...

- **Buttons**
  - Save
  - Save As...
  - Set Values To Default
  - Optimize Initial Param Values
  - Close

96 row(s) added.
**BMDS Summary Table**

<table>
<thead>
<tr>
<th></th>
<th>Multistage 1^st degree</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD$_{10}$</td>
<td>55.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMDL$_{10}$</td>
<td>44.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIC</td>
<td>160.271</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.2788</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scaled residual</td>
<td>-1.750</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Dichotomous Exercise #1

- Run the Multistage (2\textsuperscript{nd} degree) model against the Exercise #1 data using the Individual Model Run option
  - Make sure to change the Degree Polynomial = 2
Dichotomous Exercise #1
<table>
<thead>
<tr>
<th></th>
<th>Multistage 1(^{st}) degree</th>
<th>Multistage 2(^{nd}) degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD(_{10})</td>
<td>55.2</td>
<td>94.7</td>
</tr>
<tr>
<td>BMDL(_{10})</td>
<td>44.81</td>
<td>55.6</td>
</tr>
<tr>
<td>AIC</td>
<td>160.271</td>
<td>158.884</td>
</tr>
<tr>
<td>p value</td>
<td>0.2788</td>
<td>0.5802</td>
</tr>
<tr>
<td>Scaled residual</td>
<td>-1.750</td>
<td>-0.606</td>
</tr>
</tbody>
</table>
Run the Log-Probit model (restricted slope, must manually select in option file) against the Exercise #1 data using the Individual Model Run option
Dichotomous Exercise #1

Logistic Model with BMR of 10% Extra Risk for the BMD and 0.05 Lower Confidence Limit for the BMDL

AIC: 157.776

Goodness of Fit

<table>
<thead>
<tr>
<th>Dose</th>
<th>Est. Prob.</th>
<th>Expected</th>
<th>Observed</th>
<th>Size</th>
<th>Residual</th>
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<td>37.000</td>
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</tbody>
</table>

Chi² = 0.00  d.f. = 2  P-value = 1.0000

Benchmark Dose Computation

Specified effect = 0.1
Risk Type = Extra risk
Confidence level = 95%

BMD = 111.502
BMDL = 51.9515
BMDS Summary Table

<table>
<thead>
<tr>
<th></th>
<th>Multistage 1&lt;sup&gt;st&lt;/sup&gt; degree</th>
<th>Multistage 2&lt;sup&gt;nd&lt;/sup&gt; degree</th>
<th>Log-probit</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD&lt;sub&gt;10&lt;/sub&gt;</td>
<td>55.2</td>
<td>94.74</td>
<td>111.50</td>
</tr>
<tr>
<td>BMDL&lt;sub&gt;10&lt;/sub&gt;</td>
<td>44.81</td>
<td>55.56</td>
<td>81.95</td>
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<tr>
<td>AIC</td>
<td>160.271</td>
<td>158.884</td>
<td>157.776</td>
</tr>
<tr>
<td>p value</td>
<td>0.2788</td>
<td>0.5802</td>
<td>1.000</td>
</tr>
<tr>
<td>Scaled residual</td>
<td>-1.750</td>
<td>-0.606</td>
<td>0.004</td>
</tr>
</tbody>
</table>
Dichotomous Exercise #1

- **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
### BMDS Summary Table

<table>
<thead>
<tr>
<th></th>
<th>Multistage 1(^{st}) degree</th>
<th>Multistage 2(^{nd}) degree</th>
<th>Log-probit</th>
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</thead>
<tbody>
<tr>
<td>(\text{BMD}_{10})</td>
<td>55.2</td>
<td>94.74</td>
<td>111.50</td>
</tr>
<tr>
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<td>44.81</td>
<td>55.56</td>
<td>81.95</td>
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<td>(\text{AIC})</td>
<td>160.271</td>
<td>158.884</td>
<td>157.776</td>
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<tr>
<td>(p\text{ value})</td>
<td>0.2788</td>
<td>0.5802</td>
<td>1.000</td>
</tr>
<tr>
<td>(\text{Scaled residual})</td>
<td>-1.750</td>
<td>-0.606</td>
<td>0.004</td>
</tr>
</tbody>
</table>
Dichotomous Data – Batch Processing using the BMDS Wizard
The BMDS Wizard

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

Control Panel:

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

AUTORUN

Study and Modeling Inputs:

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<th>BMDS Model Version:</th>
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<td>Study &amp; Year:</td>
<td>Smith_2000</td>
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<td>Endpoint Description:</td>
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<td>Dose Units:</td>
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<td>BMD or BMC Calculated?:</td>
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</tr>
<tr>
<td>Select Dataset Type:</td>
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<td>Enter Study Data:</td>
<td>Click here to enter data</td>
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</table>
BMDS Wizard – Entering Data

**BMDS Input Data**

---

### Notes and Calculations from Dose Response Data

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

### Dose-Response Data Inputs

<table>
<thead>
<tr>
<th>Column Name in BMDS</th>
<th>Dose</th>
<th>Incidence</th>
<th>NumAnimals</th>
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<td>Column Type Assignment</td>
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**Clear Data**
### BMDS Wizard – Entering Data

#### BMDS Input Data

**Notes and Calculations from Dose Response Data**

<table>
<thead>
<tr>
<th>Number of Dose Groups</th>
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</thead>
</table>

**Data Trend**
(continuous only)

**Notes (included in BMDS output)**
[study notes]

#### Dose-Response Data Inputs

<table>
<thead>
<tr>
<th>Column Name in BMDS</th>
<th>Dose</th>
<th>Incidence</th>
<th>NumAnimals</th>
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<table>
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</tbody>
</table>

**Cell Color Coding**

- **Input Cells**
- **Calculated Cells**

**Clear Data**

**Excel**

- **File**
- **Home**
- **Insert**
- **Page Layout**
- **Formulas**
- **Data**
- **Review**
- **View**
- **Add-Ins**

**Summary**

- The BMDS Wizard interface is used for entering dose-response data.
- The data includes the number of dose groups, data trend, and dose-response data inputs with columns for dose, incidence, and number of animals.
### BMDS Wizard – Model Parameters

**Main**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Type and/or Format</th>
<th>Gamma</th>
<th>Logistic</th>
<th>LogLogistic</th>
<th>Probit</th>
<th>LogProbit</th>
<th>Weibull</th>
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<tr>
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BMDS Wizard – Model Parameters

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<th>Parameter</th>
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<td>Restriction</td>
<td>Dropdown</td>
<td></td>
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<td>Adverse Direction</td>
<td>Dropdown</td>
<td></td>
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<td>Dropdown</td>
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<td>Constant Variance?</td>
<td>Boolean</td>
<td></td>
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</tr>
</tbody>
</table>

Click here to enter data

Excel file: dichotomus_example.xlsx
Last modified: 4/4/2014
BMDS Wizard – Adding Models to Session

Add new models to BMDS Session:
- Gamma
- Dichotomous-Hill
- Logistic
- Probit
- LogProbit
- Weibull
- Multistage
- Quantal
- Alternative: Gamma-BigDose
- Alternative: Logistic-BigResponse
- Alternative: LogProbit-BigDose
- Alternative: Probit-BigResponse
- Alternative: Weibull-BigDose
- Alternative: Multistage-BigDose

Add Model & Load Model Defaults

Clear All Models

BMDS Model Option Setups:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Type and/or Format</th>
<th>Gamma</th>
<th>Logistic</th>
<th>LogLogistic</th>
<th>Probit</th>
<th>LogProbit</th>
<th>Weibull</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model Type [or filename]</td>
<td>String</td>
<td>Gamma</td>
<td>Logistic</td>
<td>LogLogistic</td>
<td>Probit</td>
<td>LogProbit</td>
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</tr>
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<td>Animal ID</td>
<td>String</td>
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<td>Dose</td>
<td>Dose</td>
<td>Dose</td>
<td>Dose</td>
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</tr>
<tr>
<td># Subjects in Dose Group</td>
<td>String</td>
<td>NumAnimals</td>
<td>NumAnimals</td>
<td>NumAnimals</td>
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<td>String</td>
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<td>Response</td>
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<td>Incidence</td>
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<td>String</td>
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<td></td>
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</table>
BMDS Wizard – AutoRunning BMDS

Control Panel:
1) Setup Instructions
2) Build Session
3) Run Session in BMDS
4) Import Results
AUTORUN

Study and Modeling Inputs:

BMDS Model Version: BMDS 2.4
BMDS Installation Directory: C:\USEPA\BMDS240\ 
Output File Directory: C:\Users\adavis10BMD240\Data\clu_m
BMD ID Number: 1
Study & Year: Smith_2000
Endpoint Description:
Dose Units:
BMD or BMC Calculated?
Select Dataset Type: Dichotomous
Enter Study Data: Click here to enter data
### BMDS Wizard – Results

#### Results Table

<table>
<thead>
<tr>
<th>OUT File Name</th>
<th>View Output File</th>
<th>Model Type (comment includes graph)</th>
<th>Risk Type</th>
<th>BMRF</th>
<th>Restricted Model</th>
<th>BMD</th>
<th>BMDL</th>
<th>BMD / BMDL</th>
<th>p-value Test 4</th>
<th>AIC</th>
<th>Scaled Residual for Dose Group near BMD</th>
<th>Parametric Hit Bound?</th>
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</thead>
<tbody>
<tr>
<td>1-Smith_2000-Gamma-10Pct-4d.out</td>
<td>View Output</td>
<td>Gamma</td>
<td>Extra</td>
<td>0.1</td>
<td>TRUE</td>
<td>131</td>
<td>73.2</td>
<td>1.80</td>
<td>0.496</td>
<td>181.64</td>
<td>FALSE</td>
<td>FALSE</td>
</tr>
<tr>
<td>1-Smith_2000-Logistic-10Pct-4d.out</td>
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<td>Logistic</td>
<td>Extra</td>
<td>0.1</td>
<td>TRUE</td>
<td>130</td>
<td>107</td>
<td>1.22</td>
<td>0.885</td>
<td>179.44</td>
<td>FALSE</td>
<td>FALSE</td>
</tr>
<tr>
<td>1-Smith_2000-LogLogistic-10Pct-4d.out</td>
<td>View Output</td>
<td>LogLogistic</td>
<td>Extra</td>
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<td>153</td>
<td>86.1</td>
<td>1.78</td>
<td>0.335</td>
<td>182.11</td>
<td>0.635</td>
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<td>1-Smith_2000-Probit-10Pct-4d.out</td>
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<td>Probit</td>
<td>Extra</td>
<td>0.1</td>
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<td>121</td>
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<td>1.20</td>
<td>0.963</td>
<td>179.29</td>
<td>0.012</td>
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<tr>
<td>1-Smith_2000-LogProbit-10Pct-4d.out</td>
<td>View Output</td>
<td>LogProbit</td>
<td>Extra</td>
<td>0.1</td>
<td>FALSE</td>
<td>157</td>
<td>86.1</td>
<td>1.82</td>
<td>0.242</td>
<td>182.54</td>
<td>0.819</td>
<td>FALSE</td>
</tr>
<tr>
<td>1-Smith_2000-Weibull-10Pct-4d.out</td>
<td>View Output</td>
<td>Weibull</td>
<td>Extra</td>
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<td>FALSE</td>
<td>126</td>
<td>71.9</td>
<td>1.74</td>
<td>0.720</td>
<td>181.32</td>
<td>0.249</td>
<td>FALSE</td>
</tr>
<tr>
<td>1-Smith_2000-Multi2-10Pct-4d.out</td>
<td>View Output</td>
<td>Multistage 2°</td>
<td>Extra</td>
<td>0.1</td>
<td>TRUE</td>
<td>118</td>
<td>63.4</td>
<td>1.86</td>
<td>0.857</td>
<td>181.22</td>
<td>0.104</td>
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<td>1-Smith_2000-Quantal-10Pct-4d.out</td>
<td>View Output</td>
<td>Quantal-Linear</td>
<td>Extra</td>
<td>0.1</td>
<td>TRUE</td>
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<td>39.6</td>
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</table>
## BMDS Wizard – Results

### Table: BMDL and BMD Analysis Results

<table>
<thead>
<tr>
<th>BMDL</th>
<th>BMD / BMDL</th>
<th>p-value Test 4</th>
<th>AIC</th>
<th>Scaled Residual for Dose Group near BMD</th>
<th>Parameter Hit Bound?</th>
<th>Parameter Summary</th>
<th>Model Warnings</th>
<th>BMDS Wizard Bin Placement</th>
<th>BMDS Wizard Recommendation</th>
<th>BMDS Wizard Recommendation Not</th>
<th>Include in Summary Table?</th>
<th>User Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>73.2</td>
<td>1.80</td>
<td>0.458</td>
<td>181.64</td>
<td>FALSE</td>
<td>FALSE</td>
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<td>None</td>
<td>Viable</td>
<td>Alternate</td>
<td>Include</td>
<td>Include</td>
<td></td>
</tr>
<tr>
<td>107</td>
<td>1.22</td>
<td>0.885</td>
<td>179.44</td>
<td>FALSE</td>
<td>FALSE</td>
<td>[response]</td>
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<td>Viable</td>
<td>Alternate</td>
<td>Include</td>
<td>Include</td>
<td></td>
</tr>
<tr>
<td>86.1</td>
<td>1.78</td>
<td>0.335</td>
<td>182.11</td>
<td>FALSE</td>
<td>FALSE</td>
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<td>Viable</td>
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<td>Include</td>
<td>Include</td>
<td></td>
</tr>
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<td>1.20</td>
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<td>FALSE</td>
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<td>Viable</td>
<td>Alternate</td>
<td>Include</td>
<td>Include</td>
<td></td>
</tr>
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<td>86.1</td>
<td>1.82</td>
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<td>Viable</td>
<td>Alternate</td>
<td>Include</td>
<td>Include</td>
<td></td>
</tr>
<tr>
<td>71.8</td>
<td>1.74</td>
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<td>181.32</td>
<td>FALSE</td>
<td>FALSE</td>
<td>[response]</td>
<td>None</td>
<td>Viable</td>
<td>Alternate</td>
<td>Include</td>
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<tr>
<td>63.4</td>
<td>1.86</td>
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<td>181.22</td>
<td>FALSE</td>
<td>FALSE</td>
<td>[response]</td>
<td>None</td>
<td>Viable</td>
<td>Alternate</td>
<td>Include</td>
<td>Include</td>
<td></td>
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<tr>
<td>35.6</td>
<td>1.24</td>
<td>0.0383</td>
<td>186.25</td>
<td>-1.49</td>
<td>FALSE</td>
<td>[response]</td>
<td>None</td>
<td>Questionable</td>
<td>Goodness of fit</td>
<td>Include</td>
<td>Include</td>
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</tbody>
</table>
### BMDS Wizard

**Model Recommendation Decision Logic**

BMDL range deemed “sufficiently close” to use lowest AIC instead of lowest BMDL in viable models:

<table>
<thead>
<tr>
<th>Model Recommendation/Bin Placement Logic</th>
<th>3</th>
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<table>
<thead>
<tr>
<th>Test Description</th>
<th>Dichotomous</th>
<th>Dichotomous</th>
<th>Continuous</th>
<th>Test Threshold (where appropriate)</th>
<th>Bin Placement if Test is True</th>
<th>Notes to Show</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMD is not calculated</td>
<td>on</td>
<td>on</td>
<td>on</td>
<td>N/A</td>
<td>BMD not calculated</td>
<td>Goodness of fit p-value &lt; 0.1</td>
</tr>
<tr>
<td>BMDL is not calculated</td>
<td>on</td>
<td>on</td>
<td>on</td>
<td>N/A</td>
<td>BMDL not calculated</td>
<td>Goodness of fit p-value &lt; 0.1</td>
</tr>
<tr>
<td>BMDU is not calculated</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>0.1</td>
<td>Questionable Bin</td>
<td>Variance not well modeled (Test 3 p-value &lt; 0.1)</td>
</tr>
<tr>
<td>AIC is not calculated</td>
<td>off</td>
<td>off</td>
<td>off</td>
<td>0.1</td>
<td>Questionable Bin</td>
<td>Variance not well modeled (Test 3 p-value &lt; 0.1)</td>
</tr>
<tr>
<td>Wrong variance model</td>
<td>off</td>
<td>off</td>
<td>on</td>
<td>0.1</td>
<td>Questionable Bin</td>
<td>Variance not well modeled (Test 3 p-value &lt; 0.1)</td>
</tr>
<tr>
<td>Variance modeled poorly</td>
<td>off</td>
<td>off</td>
<td>on</td>
<td>0.1</td>
<td>Questionable Bin</td>
<td>Variance not well modeled (Test 3 p-value &lt; 0.1)</td>
</tr>
<tr>
<td>Goodness of fit p-test</td>
<td>on</td>
<td>on</td>
<td>on</td>
<td>0.1</td>
<td>Questionable Bin</td>
<td>Variance not well modeled (Test 3 p-value &lt; 0.1)</td>
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<tr>
<td>Goodness of fit p-test (cancer)</td>
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<td>off</td>
<td>off</td>
<td>0.05</td>
<td>Questionable Bin</td>
<td>Variance not well modeled (Test 3 p-value &lt; 0.1)</td>
</tr>
<tr>
<td>Ratio of BMD/BMDL (serious)</td>
<td>on</td>
<td>on</td>
<td>on</td>
<td>20</td>
<td>Questionable Bin</td>
<td>Variance not well modeled (Test 3 p-value &lt; 0.1)</td>
</tr>
<tr>
<td>Ratio of BMD/BMDL (cancer)</td>
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<td>on</td>
<td>on</td>
<td>5</td>
<td>No Bin Change (Warning)</td>
<td>Variance not well modeled (Test 3 p-value &lt; 0.1)</td>
</tr>
<tr>
<td>Abs(Residual of interest) too large</td>
<td>on</td>
<td>on</td>
<td>on</td>
<td>2</td>
<td>Questionable Bin</td>
<td>Variance not well modeled (Test 3 p-value &lt; 0.1)</td>
</tr>
<tr>
<td>BMD higher than highest dose</td>
<td>on</td>
<td>on</td>
<td>on</td>
<td>1</td>
<td>No Bin Change (Warning)</td>
<td>Variance not well modeled (Test 3 p-value &lt; 0.1)</td>
</tr>
<tr>
<td>BMDL lower than lowest dose (warning)</td>
<td>on</td>
<td>on</td>
<td>on</td>
<td>3</td>
<td>No Bin Change (Warning)</td>
<td>Variance not well modeled (Test 3 p-value &lt; 0.1)</td>
</tr>
<tr>
<td>BMDL lower than lowest dose (warning)</td>
<td>on</td>
<td>on</td>
<td>on</td>
<td>10</td>
<td>Questionable Bin</td>
<td>Variance not well modeled (Test 3 p-value &lt; 0.1)</td>
</tr>
<tr>
<td>BMDL lower than lowest dose (serious)</td>
<td>on</td>
<td>on</td>
<td>on</td>
<td>10</td>
<td>Questionable Bin</td>
<td>Variance not well modeled (Test 3 p-value &lt; 0.1)</td>
</tr>
<tr>
<td>Abs(Residual at control) too large</td>
<td>on</td>
<td>on</td>
<td>on</td>
<td>2</td>
<td>No Bin Change (Warning)</td>
<td>Variance not well modeled (Test 3 p-value &lt; 0.1)</td>
</tr>
<tr>
<td>Poor control dose std dev</td>
<td>off</td>
<td>off</td>
<td>on</td>
<td>1.5</td>
<td>Questionable Bin</td>
<td>Variance not well modeled (Test 3 p-value &lt; 0.1)</td>
</tr>
<tr>
<td>d.f. equals 0</td>
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<td>on</td>
<td>NA</td>
<td></td>
<td>Questionable Bin</td>
<td>Variance not well modeled (Test 3 p-value &lt; 0.1)</td>
</tr>
<tr>
<td>BMDS Model Warnings</td>
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<td>on</td>
<td>N/A</td>
<td>BMD not calculated</td>
<td>Goodness of fit p-value &lt; 0.1</td>
</tr>
</tbody>
</table>

**Notes to Show**

- BMD not calculated
- BMDL not calculated
- BMU not calculated
- AIC not calculated
- Questionable Bin
### BMDS Wizard – Results

#### BMDS Wizard Bin Placement

<table>
<thead>
<tr>
<th>Case</th>
<th>BMDL (μg/kg)</th>
<th>BMD / BMDL</th>
<th>p-value Test 4</th>
<th>AIC</th>
<th>Parameter Hit Bound?</th>
<th>Parameter Summary</th>
<th>BMDS Wizard Bin Placement</th>
<th>BMDS Wizard Recommendation</th>
<th>BMDS Wizard Recommendation Note</th>
<th>Include in Summary Table?</th>
<th>User Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73.2</td>
<td>1.80</td>
<td>0.458</td>
<td>181.64</td>
<td>FALSE</td>
<td>[Response] None</td>
<td>Viable</td>
<td>Alternate</td>
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<td>1.22</td>
<td>0.885</td>
<td>179.44</td>
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<td>Viable</td>
<td>Alternate</td>
<td></td>
<td>Include</td>
<td>Include</td>
</tr>
<tr>
<td>3</td>
<td>86.1</td>
<td>1.78</td>
<td>0.335</td>
<td>182.11</td>
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<td>4</td>
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<td>0.953</td>
<td>179.29</td>
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<td>Recommend</td>
<td>Lowest AIC</td>
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<td>Include</td>
</tr>
<tr>
<td>5</td>
<td>86.1</td>
<td>1.82</td>
<td>0.242</td>
<td>182.54</td>
<td>FALSE</td>
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<td>Viable</td>
<td>Alternate</td>
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<td>Include</td>
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<tr>
<td>6</td>
<td>71.8</td>
<td>1.74</td>
<td>0.720</td>
<td>181.32</td>
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<td>Viable</td>
<td>Alternate</td>
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<td>Include</td>
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<td>7</td>
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<td>0.857</td>
<td>181.22</td>
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<td>Viable</td>
<td>Alternate</td>
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<td>35.6</td>
<td>1.24</td>
<td>0.0383</td>
<td>180.25</td>
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<td>Questionable</td>
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</table>
BMDS Wizard – Automatic Report Generation

**BMDS Wizard**

**Summary Report**

**Output Options**

<table>
<thead>
<tr>
<th>Print BMDS Summary Table</th>
<th>TRUE</th>
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</thead>
<tbody>
<tr>
<td>Show Report Being Created</td>
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</tbody>
</table>

**BMDS Reporting**

<table>
<thead>
<tr>
<th>Print BMDS Figure</th>
<th>Print BMDS Output File</th>
</tr>
</thead>
<tbody>
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<table>
<thead>
<tr>
<th>Print Selected Model</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Print Included Model</td>
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</tbody>
</table>

**Template Location**

<table>
<thead>
<tr>
<th>Template Directory</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Template Filename</td>
<td></td>
</tr>
</tbody>
</table>

**Output Word Report Location**

<table>
<thead>
<tr>
<th>Report Output Directory</th>
<th>C:\Users\davis10\BMDS240\Data\clu_in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report Filename (no extension)</td>
<td>1-Smith 2000-</td>
</tr>
<tr>
<td>Report Extension</td>
<td>docx</td>
</tr>
</tbody>
</table>

**BMDS Figure Settings**

<table>
<thead>
<tr>
<th>Figure Width in Report (in)</th>
<th>5.69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure Height in Report (in)</td>
<td>3</td>
</tr>
</tbody>
</table>
1.1. BMDS Summary of Liver Hyper (Smith_2000)

Table 1. Model predictions for Liver Hyper (Smith_2000)

<table>
<thead>
<tr>
<th>Model</th>
<th>Goodness of fit</th>
<th>BMD_50 (ppm)</th>
<th>BMDL_95 (ppm)</th>
<th>Basis for model selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma</td>
<td>0.468</td>
<td>181.94</td>
<td>181</td>
<td>79.2</td>
</tr>
<tr>
<td>Dichotomous HI</td>
<td>0.235</td>
<td>182.11</td>
<td>182</td>
<td>86.1</td>
</tr>
<tr>
<td>Logistic</td>
<td>0.035</td>
<td>179.44</td>
<td>179</td>
<td>107</td>
</tr>
<tr>
<td>Probit</td>
<td>0.053</td>
<td>178.29</td>
<td>178</td>
<td>100</td>
</tr>
<tr>
<td>Weibull</td>
<td>0.242</td>
<td>182.54</td>
<td>182</td>
<td>89.1</td>
</tr>
<tr>
<td>Quasi-2-Liner</td>
<td>0.033</td>
<td>184.23</td>
<td>184</td>
<td>39.6</td>
</tr>
<tr>
<td>Tukey8</td>
<td>N/A*</td>
<td>183.10</td>
<td>183</td>
<td>57.4</td>
</tr>
</tbody>
</table>

* Selected model in bold; criteria exclude for selected models: for dose 0, 100, 300, and 800 ppm were 0.178, 0.213, 0.619, and 0.655, respectively.

No available degree of freedom to calculate a goodness of fit value.

Data from Smith_2000

Probit Model (Version 3.1, Date 2/28/2013)
The form of the probability function is: \( P(\text{response}) = \text{CumNorm}(\text{Intercept} + \text{Slope} \times \text{Dose}) \), where CumNorm is the cumulative normal distribution function.

Slope parameter is not restricted.

Benchmark Dose Computation:

BMD = 10% Extant Risk

BMDL at the 95% confidence level = 100.297

Parameter Estimates:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>Default/Initial Parameter Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td></td>
<td></td>
</tr>
<tr>
<td>slope</td>
<td>-0.384</td>
<td>0.0041608</td>
</tr>
</tbody>
</table>

Analysis of Deviance Table

<table>
<thead>
<tr>
<th>Model</th>
<th>Deviation</th>
<th>Deviance</th>
<th>Test df</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full model</td>
<td>37.5944</td>
<td>5</td>
<td>0.0524</td>
<td></td>
</tr>
<tr>
<td>Fitted model</td>
<td>37.6432</td>
<td>2</td>
<td>0.0524</td>
<td></td>
</tr>
<tr>
<td>Restricted</td>
<td>37.8701</td>
<td>1</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

AIC = 179.287

Goodness of Fit Table

<table>
<thead>
<tr>
<th>Dose</th>
<th>Expected</th>
<th>Observed</th>
<th>Size</th>
<th>Scaled Resid</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.34</td>
<td>1</td>
<td>50</td>
<td>-0.179</td>
</tr>
<tr>
<td>100</td>
<td>1.13</td>
<td>1</td>
<td>50</td>
<td>0.012</td>
</tr>
<tr>
<td>300</td>
<td>0.40</td>
<td>1</td>
<td>50</td>
<td>0.118</td>
</tr>
<tr>
<td>800</td>
<td>0.14</td>
<td>1</td>
<td>50</td>
<td>-0.133</td>
</tr>
</tbody>
</table>

Chisq = 0.1 df = 2 p-value = 0.9526
Dichotomous Data – Exercise #2
Dichotomous Exercise #2

- Open the default Wizard Template named “BMDS Wizard-dichotomous.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 it’s not necessary for this exercise
Dichotomous Exercise #2

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

<table>
<thead>
<tr>
<th>Dose-Response Data Inputs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column Name in BMDS</td>
</tr>
<tr>
<td>Dose</td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Column Type Assignment</td>
</tr>
<tr>
<td>Dose Group 1</td>
</tr>
<tr>
<td>Dose Group 2</td>
</tr>
<tr>
<td>Dose Group 3</td>
</tr>
<tr>
<td>Dose Group 4</td>
</tr>
<tr>
<td>Dose Group 5</td>
</tr>
</tbody>
</table>

- On Main worksheet tab, click “AUTORUN”

- Results will automatically import to Results worksheet tab

- Which model would you pick, and why?
Dichotomous Exercise #2

BMDS Wizard

Results Table

<table>
<thead>
<tr>
<th>OUT File Name</th>
<th>View Output File</th>
<th>Model Type (comment includes graph)</th>
<th>Risk Type</th>
<th>BMRF</th>
<th>Restricted Model</th>
<th>BMD</th>
<th>BMDL</th>
<th>BMD / BMDL</th>
<th>p-value Test 4</th>
<th>AIC</th>
<th>Scaled Residual for Dose Group near BMD</th>
<th>Parametric Hit Bound?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise_2-Gamma-10Pct-5d.out</td>
<td>View Output</td>
<td>Gamma</td>
<td>Extra</td>
<td>0.1</td>
<td>TRUE</td>
<td>66.0</td>
<td>57.6</td>
<td>1.15</td>
<td>0.745</td>
<td>361.61</td>
<td>0.632</td>
<td>FALSE</td>
</tr>
<tr>
<td>Exercise_2-Logistic-10Pct-5d</td>
<td>View Output</td>
<td>Logistic</td>
<td>Extra</td>
<td>0.1</td>
<td>TRUE</td>
<td>69.6</td>
<td>61.2</td>
<td>1.14</td>
<td>0.484</td>
<td>363.96</td>
<td>-0.416</td>
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<tr>
<td>Exercise_2-LogLogistic-10Pct-5d</td>
<td>View Output</td>
<td>LogLogistic</td>
<td>Extra</td>
<td>0.1</td>
<td>TRUE</td>
<td>68.2</td>
<td>59.3</td>
<td>1.14</td>
<td>0.454</td>
<td>362.98</td>
<td>0.320</td>
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<tr>
<td>Exercise_2-Probit-10Pct-5d</td>
<td>View Output</td>
<td>Probit</td>
<td>Extra</td>
<td>0.1</td>
<td>TRUE</td>
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<td>58.3</td>
<td>1.15</td>
<td>0.769</td>
<td>362.05</td>
<td>-0.272</td>
<td>FALSE</td>
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<tr>
<td>Exercise_2-LogProbit-10Pct-5d</td>
<td>View Output</td>
<td>LogProbit</td>
<td>Extra</td>
<td>0.1</td>
<td>FALSE</td>
<td>66.1</td>
<td>58.7</td>
<td>1.13</td>
<td>0.265</td>
<td>364.27</td>
<td>1.16</td>
<td>FALSE</td>
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<tr>
<td>Exercise_2-Weibull-10Pct-5d</td>
<td>View Output</td>
<td>Weibull</td>
<td>Extra</td>
<td>0.1</td>
<td>TRUE</td>
<td>64.2</td>
<td>55.2</td>
<td>1.16</td>
<td>0.999</td>
<td>360.40</td>
<td>-0.087</td>
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<tr>
<td>Exercise_2-Multi2-10Pct-5d</td>
<td>View Output</td>
<td>Multistage 2^</td>
<td>Extra</td>
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<td>49.0</td>
<td>44.1</td>
<td>1.09</td>
<td>0.0865</td>
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<td>-1.87</td>
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<tr>
<td>Exercise_2-Quasil-10Pct-5d</td>
<td>View Output</td>
<td>Quasil-Linear</td>
<td>Extra</td>
<td>0.1</td>
<td>TRUE</td>
<td>17.7</td>
<td>15.6</td>
<td>1.13</td>
<td>0.0</td>
<td>423.53</td>
<td>-4.75</td>
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