Bayesian Benchmark Dose Analysis for Probabilistic Risk Assessment
– Another Revolution in Dose-Response Assessment

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Outline of the Presentation

• Introduction on benchmark dose method
  – In a Bayesian framework

• Introduction on the features of BBMD
  – Cross platform
  – Probabilistic
  – Reliability
  – Advanced BMD estimation (model averaging available)
  – Analyzing epidemiological data
  – Probabilistic low-dose extrapolation

• Plan for future development
Dose-Response Analysis

- Step 1: Deriving Point of Departure (POD)
- Step 2: Inference (or “Extrapolation”)

![Dose-Response Modeling Graph](image-url)
POD Derivation – Traditional Method

• NOAEL/LOAEL

(Data from NTP 2006)  (Data from NTP 2006)
Limitations of NOAEL/LOAEL

- Highly depends on study design
- Partially uses the information in toxicity study
- Improperly characterizes the uncertainty in responses

(Data from NTP, 2000)
NOAEL’s Inappropriateness in Quantifying Uncertainty

Study Conducted with 50 Animals per Dose

Study Conducted with 10 Animals per Dose

LOAEL
P-value=0.0163

NOAEL
P-value=0.2368

LOAEL
P-value=0.0006

NOAEL
P-value=1.000
Benchmark Dose Methodology

- BMD Steps:
  - Fit a DR model
  - Define Benchmark Response (BMR)
  - Calculate BMD/BMDL

- BMD recognized
  - EFSA (2009)
  - US EPA (2012)
### 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., $\downarrow N = \downarrow \text{BMDL}$)</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>
Bayesian Benchmark Dose Method

• Most important features of Bayesian BMD
  – Probabilistic estimation
  – Ability to incorporate existing information

• First Revolution in DR assessment
  – NOAEL → BMD

• Second Revolution
  – Point BMD → Probabilistic BMD

• Bayesian BMD (BBMD) estimation system
Frequentist vs. Bayesian

• Frequentist: Parameter ($\theta$) is a fixed but unknown quantity.
  – Using samples to estimate the quantity
  – Different sample may result in different estimates – resulting sampling distribution

• Bayesian: Parameter ($\theta$) is considered as a random variable
  – Using distribution to describe the random variable
  – A state of belief, using data to update the belief
Outline of the Presentation

• Introduction on benchmark dose method
  – In a Bayesian framework
• Introduction on the features of BBMD
  – Cross platform
  – Probabilistic
  – Reliability
  – Advanced BMD estimation (model averaging available)
  – Analyzing epidemiological data
  – Probabilistic low-dose extrapolation
• Plan for future development
Feature I: Web-based Application

• Available at:
  – https://benchmarkdose.com (or https://benchmarkdose.org)

• Cross-platform accessibility (i.e., not limited by Operation System, Windows, Mac or Linux), anytime and anywhere (with internet access)

• Full Bayesian Analysis featuring the use of Markov Chain Monte Carlo (MCMC)
Feature II: Probabilistic Estimates

- Graphical and Textual output of parameter estimation
Feature II: Probabilistic Estimates

- Interactive dose-response plot - Visual inspection
Feature II: Probabilistic Estimates

- Probabilistic BMD estimation for individual models and model averaged BMD
  - BMDs estimated from individual continuous model
  - Model averaged BMD estimates
Feature III: Reliability of BBMD

### Comparison of BBMD and BMDS for Dichotomous Data

<table>
<thead>
<tr>
<th></th>
<th>Quantal-linear</th>
<th>Logistic</th>
<th>Probit</th>
<th>Weibull</th>
<th>Multistage 2</th>
<th>LogLogistic</th>
<th>LogProbit</th>
<th>Dich Hill</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMDS</strong></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of Failed BMD</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>773(^a)</td>
</tr>
<tr>
<td>No. of Failed BMDL</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>12</td>
<td>1</td>
<td>0</td>
<td>8</td>
<td>833(^a)</td>
</tr>
<tr>
<td>BMD/BMDL Ratio (at BMR=0.1)</td>
<td>1.51 (1.21 ~ 2.69)</td>
<td>1.30 (1.13 ~ 3.19)</td>
<td>1.31 (1.15 ~ 3.03)</td>
<td>1.70 (1.20 ~ 8.41)</td>
<td>1.62 (1.18 ~ 5.73)</td>
<td>1.89 (1.21 ~ 10.5)</td>
<td>1.49 (1.20 ~ 4.75)</td>
<td>1.69 (1.11 ~ 10.3)</td>
</tr>
<tr>
<td>BMD/BMDL Ratio (at BMR=0.01)</td>
<td>1.51 (1.21 ~ 2.67)</td>
<td>1.50 (1.22 ~ 15.5)</td>
<td>1.51 (1.20 ~ 13.9)</td>
<td>2.51 (1.24 ~ 56.2)</td>
<td>2.14 (1.42 ~ 68.0)</td>
<td>3.22 (1.24 ~ 16.8)</td>
<td>1.65 (1.24 ~ 10.2)</td>
<td>4.91 (1.23 ~ 93.6)</td>
</tr>
<tr>
<td>No. of Reduced Model</td>
<td>NA</td>
<td>NA</td>
<td>183 to QuantalLinear</td>
<td>184 to QuantalLinear</td>
<td>31 to Logistic</td>
<td>63 to Probit</td>
<td>124 to LogLotistic</td>
<td></td>
</tr>
<tr>
<td><strong>BBMD</strong></td>
<td></td>
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</tr>
<tr>
<td>No. of Failed BMD</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>No. of Failed BMDL</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BMD/BMDL Ratio (at BMR=0.1)</td>
<td>1.53 (1.21 ~ 2.51)</td>
<td>1.29 (1.09 ~ 2.20)</td>
<td>1.29 (1.10 ~ 2.06)</td>
<td>1.69 (1.12 ~ 4.39)</td>
<td>1.60 (1.24 ~ 2.59)</td>
<td>1.77 (1.13 ~ 5.40)</td>
<td>1.47 (1.08 ~ 3.81)</td>
<td>2.31 (1.19 ~ 190.7(^b))</td>
</tr>
<tr>
<td>BMD/BMDL Ratio (at BMR=0.01)</td>
<td>1.53 (1.21 ~ 2.50)</td>
<td>1.51 (1.22 ~ 4.30)</td>
<td>1.50 (1.20 ~ 3.92)</td>
<td>3.38 (1.42 ~ 17.5)</td>
<td>2.23 (1.31 ~ 3.49)</td>
<td>3.56 (1.51 ~ 19.36)</td>
<td>2.00 (1.28 ~ 7.01)</td>
<td>4.23 (1.35 ~ 593(^b))</td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Correlation Coef. For BMD</td>
<td>0.991</td>
<td>0.998</td>
<td>0.997</td>
<td>0.842</td>
<td>0.969</td>
<td>0.830</td>
<td>0.857</td>
<td>0.837</td>
</tr>
<tr>
<td>Correlation Coef. For BMDL</td>
<td>1.000</td>
<td>0.985</td>
<td>0.978</td>
<td>0.945</td>
<td>0.988</td>
<td>0.898</td>
<td>0.955</td>
<td>0.855</td>
</tr>
<tr>
<td>Ratio of BMDs</td>
<td>1.00 (0.829 ~ 1.18)</td>
<td>1.02 (0.714 ~ 1.25)</td>
<td>1.02 (0.494 ~ 1.32)</td>
<td>1.57 (0.481 ~ 24.7)</td>
<td>0.929 (0.205 ~ 1.67)</td>
<td>1.54 (0.737 ~ 29.8)</td>
<td>1.58 (0.865 ~ 8.98)</td>
<td>1.26 (0.530 ~ 29.8)</td>
</tr>
<tr>
<td>Ratio of BMDLs</td>
<td>1.00 (0.888 ~ 1.89)</td>
<td>1.03 (0.973 ~ 2.44)</td>
<td>1.02 (0.942 ~ 2.71)</td>
<td>1.18 (1.02 ~ 9.63)</td>
<td>1.06 (0.530 ~ 1.29)</td>
<td>1.93 (1.05 ~ 18.0)</td>
<td>1.66 (1.06 ~ 6.10)</td>
<td>1.59 (0.079 ~ 21.5)</td>
</tr>
</tbody>
</table>

\(^a\) The BMDS directly reports “error” for BMD and BMDL when the number of dose groups is fewer than the number of model parameters in the Dichotomous Hill model. 186 out of the 518 datasets have only 3 dose groups, therefore, 744 (=186 \times 4) in these failed BMDs or BMDLs are due to insufficient dose groups.

\(^b\) For the BMD/BMDL ratios calculated using the Dichotomous Hill model in the BBMD system, all results from the 518 datasets (including those having only three dose groups) are included. (From Shao and Shapiro, 2017, in press)
### Feature III: Reliability of BBMD

#### Comparison of BBMD and BMDS for Continuous Data

<table>
<thead>
<tr>
<th>BMDS</th>
<th>Linear</th>
<th>Power</th>
<th>Hill</th>
<th>Exponential 2</th>
<th>Exponential 3</th>
<th>Exponential 4</th>
<th>Exponential 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Failed BMD</td>
<td>2</td>
<td>0</td>
<td>34&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>36&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>No. of Failed BMDL</td>
<td>2</td>
<td>2</td>
<td>38&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>37&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMD/BMDL Ratio (at rel change=0.1)</td>
<td>1.28 (1.07 ~ 2.85)</td>
<td>1.39 (1.05 ~ 12.9)</td>
<td>2.16 (1.08 ~ 1.72e7)</td>
<td>1.28 (1.07 ~ 2.14)</td>
<td>1.34 (1.07 ~ 6.97)</td>
<td>1.54 (1.09 ~ 207)</td>
<td>2.16 (1.13 ~ 441)</td>
</tr>
<tr>
<td>BMD/BMDL Ratio (at rel change=0.01)</td>
<td>1.28 (1.07 ~ 2.85)</td>
<td>1.85 (1.07 ~ 33.4)</td>
<td>4.49 (1.20 ~ 1.32e6)</td>
<td>1.27 (1.07 ~ 2.14)</td>
<td>1.63 (1.07 ~ 46.96)</td>
<td>1.65 (1.11 ~ 211)</td>
<td>4.64 (1.32 ~ 985)</td>
</tr>
<tr>
<td>No. of Reduced Model</td>
<td>NA</td>
<td>52 to Linear</td>
<td>NA</td>
<td>NA</td>
<td>57 to Exponential 2</td>
<td>24 to Exponential 2</td>
<td>22 to Exponential 3/4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BBMD</th>
<th>Linear</th>
<th>Power</th>
<th>Hill</th>
<th>Exponential 2</th>
<th>Exponential 3</th>
<th>Exponential 4</th>
<th>Exponential 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Failed BMD</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No. of Failed BMDL</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BMD/BMDL Ratio (at rel change=0.1)</td>
<td>1.27 (1.07 ~ 2.28)</td>
<td>1.33 (1.06 ~ 4.50)</td>
<td>2.05 (1.12 ~ 11.3)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.25 (1.07 ~ 2.16)</td>
<td>1.30 (1.06 ~ 5.66)</td>
<td>1.59 (1.17 ~ 22.5)</td>
<td>1.98 (1.06 ~ 32.5)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>BMD/BMDL Ratio (at rel change=0.01)</td>
<td>1.27 (1.07 ~ 2.28)</td>
<td>3.07 (1.13 ~ 23.0)</td>
<td>3.91 (1.44 ~ 36.1)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.25 (1.07 ~ 2.16)</td>
<td>3.29 (1.12 ~ 25.1)</td>
<td>1.69 (1.22 ~ 19.6)</td>
<td>3.95 (1.44 ~ 25.8)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Comparison</td>
<td>Correlation Coef. For BMD</td>
<td>0.999</td>
<td>0.946</td>
<td>0.822</td>
<td>0.989</td>
<td>0.919</td>
<td>0.960</td>
</tr>
<tr>
<td>Correlation Coef. For BMDL</td>
<td>0.994</td>
<td>0.960</td>
<td>0.927</td>
<td>0.992</td>
<td>0.950</td>
<td>0.861</td>
<td>0.847</td>
</tr>
<tr>
<td>Ratio of BMDs</td>
<td>0.988 (0.685 ~ 1.29)</td>
<td>1.22 (0.797 ~ 34.0)</td>
<td>1.13 (0.036 ~ 1537)</td>
<td>0.988 (0.823 ~ 1.27)</td>
<td>1.34 (0.848 ~ 32.8)</td>
<td>0.874 (0.113 ~ 1.32)</td>
<td>1.05 (0.093 ~ 7.57)</td>
</tr>
<tr>
<td>Ratio of BMDLs</td>
<td>0.994 (0.719 ~ 2.09)</td>
<td>1.43 (0.916 ~ 10.0)</td>
<td>1.68 (0.639 ~ 4.5e6)</td>
<td>0.986 (0.802 ~ 1.37)</td>
<td>1.41 (0.954 ~ 11.7)</td>
<td>0.871 (0.039 ~ 94.3)</td>
<td>1.30 (0.080 ~ 181)</td>
</tr>
</tbody>
</table>

<sup>a</sup> The BMDS directly reports “error” for BMD and BMDL when the number of dose groups is fewer than the number of model parameters in the Hill model and Exponential 5 model. 16 out of the 108 datasets have only 3 dose groups, therefore, 32 (=16 × 2) in these failed BMDs or BMDLs are due to insufficient dose groups.

<sup>b</sup> For the BMD/BMDL ratios calculated using the Hill model and Exponential 5 model in the BBMD system, all results from the 108 datasets (including those having only three dose groups) are included. (Cited from Shao and Shapiro, 2017 in press)
Feature IV: Advanced BMD Calculation

• BBMD: posterior predictive p-value (PPP):
  – Use likelihood as the key statistic
  – Likelihood value of predicted responses and original data are calculated and compared
  – 0.05 <= PPP <= 0.95

• BBMD: model weight
  – Compute model weight was introduced in Wasserman (2000) using two equations below:

\[
\log(m_j) = \ell_j - \frac{q_j}{2} \log(n)
\]

\[
\Pr(M_j|Data) = \frac{\hat{m}_j}{\sum_{k=1}^{K} \hat{m}_k}
\]
Feature IV: Advanced BMD Calculation

- Model averaged BMD for **dichotomous and continuous** data (Shao et al 2018)
  - The model averaged BMD can be expressed as:
    
    \[
    \Pr(BMD_{ma}|Data) = \sum_{k=1}^{K} \Pr(BMD_{k}|\mathcal{M}_{k}, Data) \Pr(\mathcal{M}_{k}|Data)
    \]
    
    \[
    \Pr(\mathcal{M}_{j}|Data) = \frac{\hat{m}_{j} \Pr(\mathcal{M}_{j})}{\sum_{k=1}^{K} \hat{m}_{k} \Pr(\mathcal{M}_{k})}
    \]

- Define BMD based on central tendency or tails for continuous data
  - Traditional approach and hybrid approach
Feature IV: Advanced BMD Calculation

- Based on tails (i.e., hybrid approach Crump 1995)

Hill Model (Example 1)

- 9.24% above cutoff
- 10.9% above cutoff; 10% extra risk

Hill Model (Example 2)

- 1% below cutoff
- 6.52% below cutoff
- 10.9% below cutoff; 10% extra risk
Feature V: Analyzing Epidemiological Data

- Subjects have a unique exposure and response level
Feature VI: Probabilistic Low-dose Extrapolation

• For cancer risk assessment
  – Distributional estimates of cancer slope factor (CSF)
    • Currently: $CSF = \frac{BMR}{BMDL}$
    • New: $CSF = \frac{BMR}{BMD(\text{distribution})}$
Feature VI: Probabilistic Low-dose Extrapolation

- Available in the BBMD system
- UFs are expressed as lognormal distributions [traditional UF separated to difference ($\mu$) and uncertainty ($\sigma$)]
- Monte Carlo simulations are implemented to derive the final human dose distribution
Available at:  
https://benchmarkdose.com (or https://benchmarkdose.org)
Additional Discussion: Prior of Model Parameters

- Significant impact on model shape
- Significant impact on model weight
- Goal: Flexible and Objective!

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

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>0.01</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>0.05</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>0.5</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Logistic: $\beta_1 = -1.7; \beta_2 = 88.5$
Log-logistic: $\beta_1 = 0; \beta_2 = 6.7; \beta_3 = 1.47$
Prior of Model Parameters

### Logistic Model

- BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>0.48</td>
<td>50</td>
<td>5</td>
</tr>
<tr>
<td>0.5</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>0.52</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

**Logistic:** $\beta_1 = -54.9; \beta_2 = 109.8$

### Log-logistic Model

- BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL

**Log-logistic:** $\beta_1 = 0; \beta_2=12.49; \beta_3=18$
## Prior of Model Parameters

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>0.25</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>0.96</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>0.99</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Logistic: $\beta_1 = -47.6; \beta_2 = 50.9$

Log-logistic: $\beta_1 = 0; \beta_2 = 2.54; \beta_3 = 18$
Impact of Parameter Priors

Logistic model: 
\[ f(d) = \frac{1}{1 + \exp(-a - b \times d)} \]

Prior in BBMD | A Very Specific Prior
---|---
a ~ Unif (-50, 50) | a ~ N (0, 1)
b ~ Unif (0, 100) | Log(b) ~ N(0, 1)

Uniform Prior | Specific Prior
---|---
BMD = 941.77 | BMD = 870.85 | BMD = 570.62

Dataset_26 Plot | Dataset_26 Plot | Dataset_26 Plot
Impact of Parameter Priors

LogLogistic model: 

\[ f(d) = a + \frac{1-a}{1+\exp[-b-g\times\log(d)]} \]

<table>
<thead>
<tr>
<th>Prior in BBMD</th>
<th>A Very Specific Prior</th>
</tr>
</thead>
<tbody>
<tr>
<td>a ~ U(0,1)</td>
<td>a = ( \frac{1}{\pi} \arctan(\Psi) + \frac{1}{2} )</td>
</tr>
<tr>
<td>b ~ U(-5,15)</td>
<td>\Psi \sim N(0,100)</td>
</tr>
<tr>
<td>g ~ U(r,15)</td>
<td></td>
</tr>
</tbody>
</table>

Show the BBMD system
Impact of Parameter Priors

LogLogistic model: \( f(d) = a + \frac{1-a}{1+\exp[-b-g\times \log(d)]} \)

- **Uniform Prior**: BMD = 1400.37
- **Specific Prior**: BMD = 911.79
- BMDL = 1340.37

Log-Logistic Model, with BMR of 10% Extra Risk for the BMD and 0.95 Lower Confidence Limit for the BMDL
Impact on Model Weight

**Logistic model**

Without impact of parameter prior
\[ \log \hat{\mu}_j = \hat{\beta}_j - \frac{d_j}{2} \log n \]

**Probit model**

Without impact of parameter prior

**BIC Weighting**
\[ \Pr(M_j | D) = \frac{\exp(-0.5BIC_j)}{\sum_{j=1}^{BIC} \exp(-0.5BIC_j)} \]

With impact of parameter prior
\[ m_j = \frac{L_j(\theta_j) p_j(\theta_j)}{p_j(\theta_j | y^n)} \]
Plan for Future BBMD Development

• Key features of BBMD: probabilistic estimation and ability to incorporate information

• Ongoing developments
  – Batch processing for dichotomous and continuous data
  – Bayesian categorical data analysis for BMD estimation

• Short-term: incorporating informative prior probability distributions for dose-response models (supported by NIH/NCATS)
  – Empirical prior distributions for different endpoints
  – User can specify the prior distributions

• Long-term: a smart quantitative chemical risk assessment system

• Monthly webinar on BBMD system introduction and software updates
  – Please subscribe to BBMD list by sending an email to: BBMD-L-SUBSCRIBE@INDIANA.EDU
Thank You!
Questions?

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