Hierarchical Models for Quantifying Uncertainty in Human Health Risk/Safety Assessment

Ralph L. Kodell, Ph.D.
Department of Biostatistics
University of Arkansas for Medical Sciences
Little Rock, AR
Risk/Safety Assessment: A Multi-step Process

Hazard Identification → Dose-Response Assessment ← Exposure Assessment
Outline

• Background on Human Risk/Safety Assessment
• Exposure-to-Dose Response
  – PK/PD relationship via hierarchical model
  – Benchmark dose estimation (distributions)
  – How uncertainty can be reduced by PK information
• Dose Response-to-Risk/Safety Characterization
  – Inter-species and intra-species uncertainties
  – BMD conversion via hierarchical model
• Summary and Conclusions
• Challenges and Needs
  – Model uncertainty
Uncertainty Analysis

• **Issue**: There are many uncertainties in getting from Hazard and Dose-Response Assessment in experimental (animal) settings to Exposure and Risk/Safety Characterization for human settings.

• **Challenge**: How to properly reflect these uncertainties.

• **Today’s Talk**: How Hierarchical Probabilistic Models can help to characterize and manage these uncertainties.
Usual Approach to Exposure Setting: Two-Step Process

- Human Exposure (Risk) =

**Animal-Derived Benchmark Dose (Risk)**
Animal → Average Human → Sensitive Human

(Exposure → Dose-Response)
(Dose-Response → Risk/Safety Characterization)
Dose-Response Modeling for BMD Estimation: Illustration

<table>
<thead>
<tr>
<th>D</th>
<th>n</th>
<th>#tumors</th>
<th>Observed</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
<td>5</td>
<td>0.10</td>
<td>0.096</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>7</td>
<td>0.14</td>
<td>0.157</td>
</tr>
<tr>
<td>20</td>
<td>50</td>
<td>13</td>
<td>0.26</td>
<td>0.239</td>
</tr>
<tr>
<td>40</td>
<td>50</td>
<td>20</td>
<td>0.40</td>
<td>0.407</td>
</tr>
</tbody>
</table>

- Weibull model: \( P(D) = \alpha + (1-\alpha)[1-\exp(-\beta D^\gamma)] \)
- \( P(D)=0.096 + 0.904 \ [1-\exp(-0.0035D^{1.30})] \)
- Goodness-of-fit p-value = 0.61
Weibull Model with 0.95 Confidence Level

Fraction Affected

BMD Lower Bound

BMDL BMD

0 5 10 15 20 25 30 35 40
dose

0.71 2.25
Exposure → Dose-Response

• Context: Dose-response analysis for cancer
  – Fit a mathematical model to D-R data: \( \text{Prob}(\text{tumor}|D) = F(D) \)
  – \( D \) is administered (external) dose

• Generally acknowledged that PK information on \textit{internal dose} \( (d) \) should be incorporated whenever possible
  – e.g., \( d = \text{mean AUC in tissue or blood} \)
PK/PD Hidden Structure

• However, most often there is no formal attempt to separate the hidden Pharmacokinetic (PK) and Pharmacodynamic (PD) components of F that might explain the transformation of an external exposure into the development of a tumor
  – e.g., F(D), F(d): multistage, probit, Weibull
Hierarchical Model

- The most natural way to link the PK and PD components of a dose-response model is via a hierarchical model

\[
P(tumor \mid D) = P_0 + \left(1 - P_0\right) \int_0^\infty g(tumor \mid x) f(x \mid D) \, dx
\]

Background Risk

PD Model

PK Model
How to implement the model

- **PK:** Experiment, e.g., rats, n animals/D
  - Calculate mean and s.d. of $d \equiv \text{AUC}$
  - Assume normal distribution for $f(d|D)$
    - Simple PK: variability in internal dose
    - Complex PK: variability + parameter uncertainty

- **PD:** Mechanism/Mode of Action?
  - e.g., two-stage clonal growth model for cancer
  - OR, multistage, probit, Weibull

- Numerical integration to fit hierarchical model
Example

• PK analysis
  – \( f(d|D) \sim \text{Normal} \left[ \mu = \frac{2D}{10+D}, \sigma = 0.2\mu \right] \)
  – \( f(d|D) = \frac{1}{\sigma \sqrt{2\pi}} \exp\left\{-\frac{1}{2}\left[\frac{(d-\mu)}{\sigma}\right]^2\right\} \)

• PD model
  – \( g(\text{tumor}|d) \): Weibull model
  – \( g(\text{tumor}|d) = 1 - \exp(-\beta d^k) \)

• Fit hierarchical model using nonlinear least squares with numerical integration (e.g., SAS NLIN)
## Results

<table>
<thead>
<tr>
<th>D</th>
<th>n</th>
<th>#tumors</th>
<th>proportion</th>
<th>PK/PD fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>50</td>
<td>5</td>
<td>0.10</td>
<td>0.098</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>7</td>
<td>0.14</td>
<td>0.145</td>
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<tr>
<td>20</td>
<td>50</td>
<td>13</td>
<td>0.26</td>
<td>0.256</td>
</tr>
<tr>
<td>40</td>
<td>50</td>
<td>20</td>
<td>0.40</td>
<td>0.402</td>
</tr>
</tbody>
</table>

- $\mu = \frac{2D}{(10 + D)}$, $\sigma = 0.2\mu$ (from PK analysis)
- $\beta = 0.0406$, $k = 4.65$ (from fit to tumor data)
Benchmark Doses

• Can get BMD on scale of external (administered) dose
  – Fix the parameters at estimated values
  – Let the desired BMD, e.g., BMD$_{10}$, be the “parameter” of interest
  – Set BMR (0.10) = $[P(\text{tumor}|D)-P_0]/[1-P_0]$

• Estimated BMD$_{10}$ is 13.91 (SAS NLIN)
Uncertainty Analysis

• Can simulate a complete distribution of $\text{BMD}_{100BMR}$ for any BMR using Monte Carlo bootstrap re-sampling of the tumor data.

• Similarly, can simulate a distribution of excess risks for any D
Use 5\textsuperscript{th} percentile as 95\% BMDL\textsubscript{100}BMR

Useful for managing risk:
BMDL\textsubscript{10} = 6.86
BMDL\textsubscript{01} = 0.95
Reduced Uncertainty in BMDs

<table>
<thead>
<tr>
<th>PK (f)</th>
<th>PD (g)</th>
<th>BMR</th>
<th>BMDL(05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mic-Men (mean only)</td>
<td>Weibull</td>
<td>0.01</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.10</td>
<td>6.29</td>
</tr>
<tr>
<td>Mic-Men (distribution)</td>
<td>Weibull</td>
<td>0.01</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.10</td>
<td>6.86</td>
</tr>
<tr>
<td>None</td>
<td>Weibull</td>
<td>0.01</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.10</td>
<td>4.80</td>
</tr>
</tbody>
</table>

• Nonlinear PK info can reduce the spread of distributions of BMDs *(reduce the data uncertainty)*. But, *mean* internal dose seems sufficient.
Why the Mean Seems Sufficient

\[ P(\text{tumor} \mid D) = P_0 + (1 - P_0) \int_{0}^{\infty} g(\text{tumor} \mid x) f(x \mid D) \, dx \]

\[ [P(\text{tumor} \mid D) - P_0] / (1 - P_0) = \int_{0}^{\infty} g(\text{tumor} \mid x) f(x \mid D) \, dx \]

\[ E_f [g(\text{tumor} \mid d) \mid D] \cong g[\text{tumor} \mid E_f (d \mid D)] \]
## Comparison of Variation from Hierarchical Model with Ordinary Binomial Variation

<table>
<thead>
<tr>
<th>D</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Bin. SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>100</td>
<td>0.1432</td>
<td>0.0466</td>
<td>0.0495</td>
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<tr>
<td>20</td>
<td>100</td>
<td>0.2450</td>
<td>0.0620</td>
<td>0.0620</td>
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<tr>
<td>40</td>
<td>100</td>
<td>0.4066</td>
<td>0.0659</td>
<td>0.0695</td>
</tr>
</tbody>
</table>

- **Model**: Hierarchical model with $P_0=0.098$, $g$: Weibull $(0.0406, 4.65)$, $f$: $N(2D/(10+D), 0.4D/(10+D))$
- **Mean**: average of $N$ generated tumor proportions
- **SD**: observed std dev of $N$ generated tumor proportions
- **Bin. SD**: std dev calculated by $[p(1-p)/50]^{1/2}$, where $p=$observed mean and 50 is number of animals/group
Combining PK and PD Results
OSHA: Methylene Chloride 1997

- Internal dose from PK analysis
- Risk estimate from PD model
  - Mean d
  - MLE excess risk
  - UCL on excess risk
- UCL on d
  - MLE excess risk
  - UCL on excess risk
Usual Approach to Exposure Setting: Two-Step Process

• Human Exposure =

Animal-Derived NOAEL or Benchmark Dose

Animal → Average Human → Sensitive Human

(Exposure → Dose-Response)

(Dose-Response → Risk/Safety Characterization)
Dose-Response →
Risk Characterization

• **Inter-species extrapolation:**
  – Animal → Human

  – *Location* extrapolation, from susceptibility of test animal to center (mean), $\mu_H$, of human susceptibility distribution

  – Uncertainty is due to a lack of knowledge about $\mu_H$, because of the variability among chemicals in their differential effects on test animals and humans
Dose-Response → Risk Characterization (cont.)

• **Intra-species extrapolation:**
  – Human → Human
  – **Scale** extrapolation, from the center, $\mu_H$, of the human susceptibility distribution to an extreme tail area
  – Uncertainty is due to the inherent inter-individual *variability* in human sensitivity
BMD Conversion

• Suppose we have BMD or BMDL for animals, say, $D_a$
• Let $T_a$ be a random variable representing the ratio of human-to-animal sensitivity over all chemicals
• Let $T_h$ be a random variable representing the ratio of human-to-human sensitivity to the tested chemical
• Need to “convert” $D_a$ to $D_h$ to $D_s$
Conditional Distribution of Human Susceptibility

• Assume that $T_a$ has a shifted lognormal distribution with pdf
  $- f_a(t_a | \mu_a, \sigma_a, \tau_a)$

• Assume that $T_h$ has a prior shifted lognormal distribution with pdf
  $- f_h(t_h | \mu_h = c, \sigma_h, \tau_h)$

• Then, conditional on $T_a = t_a$, $T_h$ has a shifted lognormal distribution
  $- f_h(t_h | \mu_h = \log(t_a) + c, \sigma_h, \tau_h)$
Unconditional Distribution of Human Susceptibility

• Hierarchical model for pdf of $T_s$:

$$f_s (t_s \mid \sigma_h, \tau_h, \mu_a, \sigma_a, \tau_a) =$$

$$\int_0^\infty f_h (t_h \mid \mu_h = \log(t_a) + c, \sigma_h, \tau_h) f_a (t_a \mid \mu_a, \sigma_a, \tau_a) dt_a$$

Human to Human

Animal to Human
Human Extrapolated Dose

• Lower 100p% statistical confidence limit on human extrapolated dose:

• Instead of $\frac{D_a}{(T_{a,100p} T_{h,100p})}$

$[\frac{D_a}{(10^{10})}]$

• Calculate by $\frac{D_a}{T_{s,100p}}$
  – where $T_{s,100p}$ is the 100p$^{th}$ percentile of the unconditional human susceptibility distribution

• In general, $T_{s,100p}$ can be expected to be smaller than $T_{a,100p} \times T_{h,100p}$
Illustrations

- $T_a(0, 0.58, 1)$: $T_{50} = 2$, $T_{95} = 10$
  - $T_{a,95} = 100$
  - $T_{s,95} = 34$

- $T_h(0, 0.61, 0)$
  - $T_{a,95} * T_{h,95} = 100$
  - $T_{s,95} = 34$
  - $T_{s,99} = 100$

- $T_a(0, 0.697, 1)$: $T_{50} = 2$, $T_{95} = 15$
  - $T_{a,95} = 225$
  - $T_{s,95} = 60$
  - $T_{s,97} = 100$

- $T_h(0, 0.715, 0)$
  - $T_{a,95} * T_{h,95} = 225$
  - $T_{s,95} = 60$
  - $T_{s,97} = 100$
Exposure → Dose-Response

Conclusions

• Information on internal dose though PK analysis can reduce uncertainty in BMD estimation (both data and model uncertainty) by improving the estimate of the mean risk

• But, the complete distribution of internal dose does not appear to affect the characterization of uncertainty…the mean internal dose seems sufficient

• The only measure of uncertainty in risk arises from the ultimate endpoint, presence or absence of an adverse effect
Hierarchical probabilistic models can be useful for managing the uncertainties in the extrapolation process of converting animal-derived exposures into human-equivalent exposures for risk characterization by providing vehicles for proper quantification and propagation of the uncertainties.
Overall Summary
Hierarchical models are useful for understanding and quantifying uncertainties in doing:

\[ \text{Exposure} \rightarrow \text{Dose-Response} \rightarrow \text{Risk Characterization} \]

\[ D^{-1}\{ \text{BMR} = \int_0^\infty g(tumor \mid x, \beta, k) f(x \mid D, \mu, \sigma) dx \} \]

\[ T^{-1}\{ 100 \rho = \int_{\tau_a}^{\tau_h} \int_{\tau_h}^\infty f_h(t_h \mid \mu_h = \log(t_a) + c, \sigma_h \tau_h) f_a(t_a \mid \mu_a, \sigma_a, \tau_a) dt_a dt_h \} \]
Challenges and Needs

• Correct propagation of uncertainty
  – Don’t overstate or misstate
  – Hierarchical models
    • PK→PD, $A_{\text{average}} \rightarrow H_{\text{average}}$, $H_{\text{average}} \rightarrow H_{\text{sensitive}}$

• Model uncertainty
  – Don’t ignore
  – Model averaging
    • Which and how many?
    • Confidence limits on model-averaged BMDs
    • Should you average BMDLs?
References


