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

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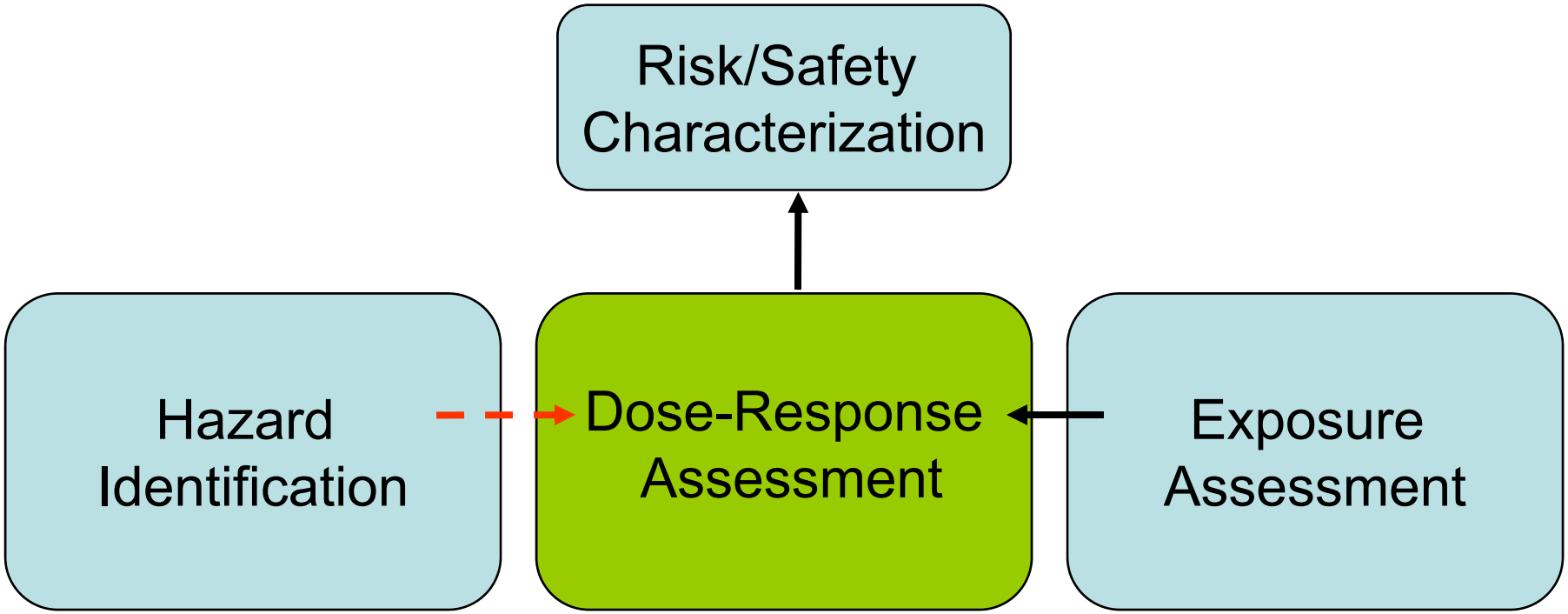
Risk/Safety Assessment: A Multi-step Process



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) =

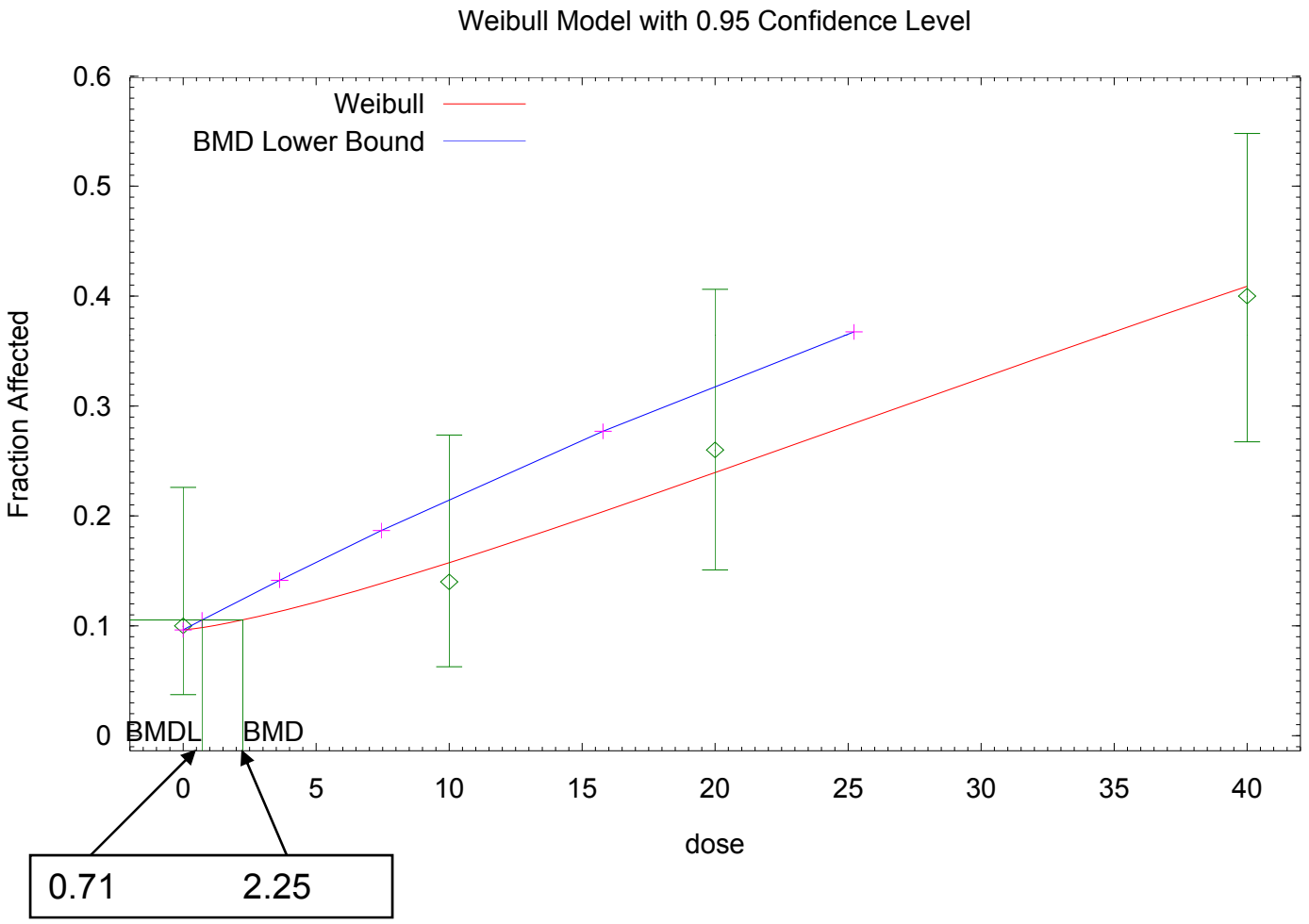
  Animal-Derived Benchmark Dose (Risk)
  Animal→Average Human→Sensitive Human

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

Dose-Response Modeling for BMD Estimation: Illustration

D	n	#tumors	Observed	Predicted
0	50	5	0.10	0.096
10	50	7	0.14	0.157
20	50	13	0.26	0.239
40	50	20	0.40	0.407

- 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
Weibull
BMD Lower Bound
Fraction Affected
0.6
0.5
0.4
0.3
0.2
0.1
0
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: $Prob(tumor|D) = F(D)$
  - D is administered (external) dose
- Generally acknowledged that PK information on *internal dose (d)* should be incorporated whenever possible
  - e.g., **d** = 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

$$P(tumor \mid D) = P_0 + (1 - P_0) \int_0^{\infty} g(tumor \mid x)\, f(x \mid D)\, dx$$

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** ≡ 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) ~ Normal [μ=(2D/(10+D), σ=0.2μ]
  - f(d|D)={1/[$\sigma\sqrt{(2\pi)}$]}exp{-½[(d- μ)/ σ]^2}
- PD model
  - g(tumor|d): Weibull model
  - g(tumor|d)=1-exp(-βd^k)
- Fit hierarchical model using nonlinear least squares with numerical integration (e.g., SAS NLIN)

Results

D	n	#tumors	proportion	PK/PD fit
0	50	5	0.10	0.098
10	50	7	0.14	0.145
20	50	13	0.26	0.256
40	50	20	0.40	0.402

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

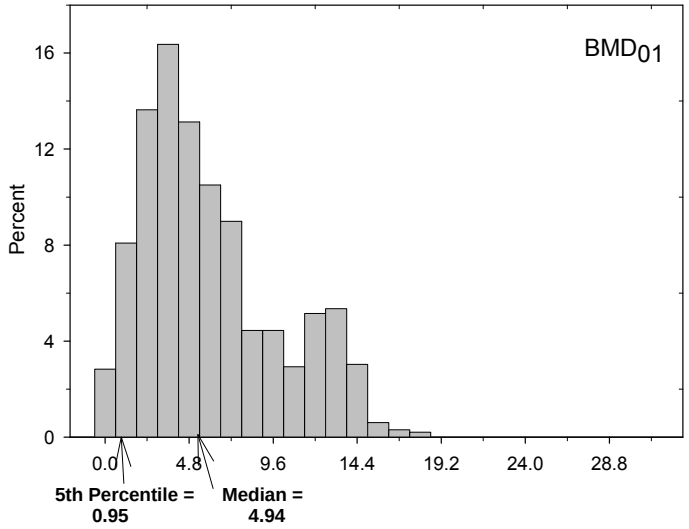
Benchmark Doses

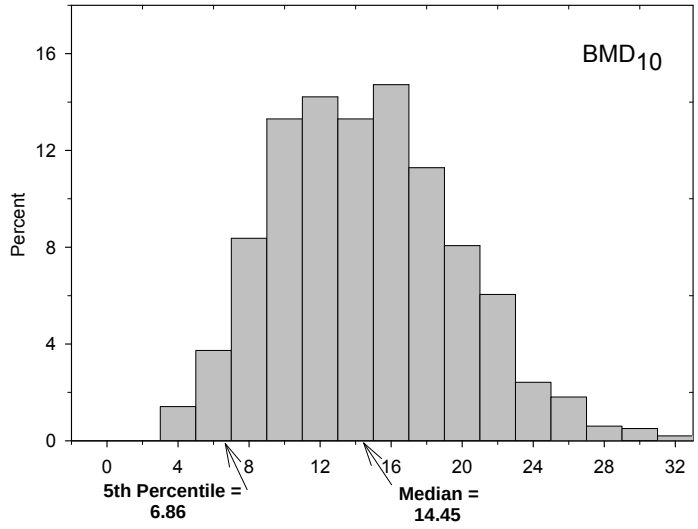
- Can get BMD on scale of external (administered) dose
  - Fix the parameters at estimated values
  - Let the desired BMD, e.g., BMD_{10}, be the "parameter" of interest
  - Set BMR (0.10) = $[P(tumor|D)-P_0]/[1-P_0]$
- Estimated BMD_{10} is 13.91 (SAS NLIN)

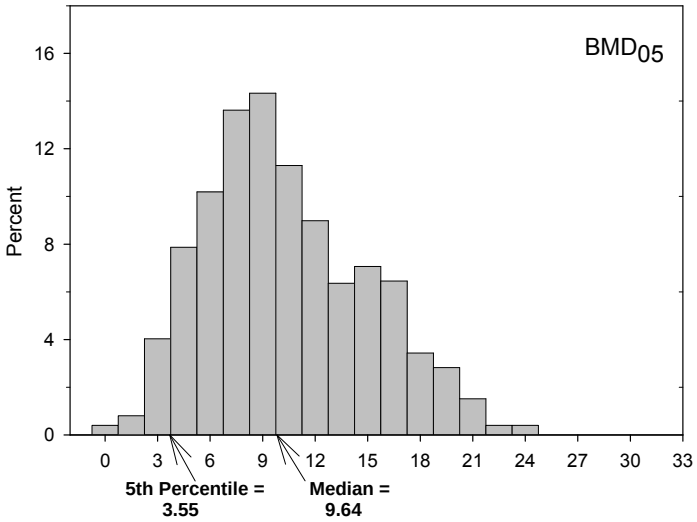
Uncertainty Analysis

- Can simulate a complete distribution of 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 5th percentile as 95% $BMDL_{100BMR}$

Useful for managing risk:
$BMDL_{10}$ = 6.86
$BMDL_{01}$ = 0.95

Reduced Uncertainty in BMDs

PK (f)	PD (g)	BMR	BMDL(05)
Mic-Men	Weibull	0.01	0.97
(mean only)		0.10	6.29
Mic-Men	Weibull	0.01	0.95
(distribution)		0.10	6.86
None	Weibull	0.01	0.09
		0.10	4.80

- 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

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

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

$$E_f [\, g(tumor \mid d) \mid D \,] \cong g[\, tumor \mid E_f (d \mid D)]$$

Comparison of Variation from Hierarchical Model with Ordinary Binomial Variation

D	N	Mean	SD	Bin. SD
10	100	0.1432	0.0466	0.0495
20	100	0.2450	0.0620	0.0620
40	100	0.4066	0.0659	0.0695

- Model: Hierarchical model with P0=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**
  - Mean d
  - UCL on d
- **Risk estimate from PD model**
  - MLE excess risk
  - UCL on excess risk
  - MLE excess risk
  - UCL on excess risk

Usual Approach to Exposure Setting: Two-Step Process

- Human Exposure =

$$\frac{\text{Animal-Derived NOAEL or Benchmark Dose}}{\text{Animal}\rightarrow\text{Average Human}\rightarrow\text{Sensitive Human}}$$

$$\left(\frac{\text{Exposure}\rightarrow\text{Dose-Response}}{\text{(Dose-Response}\rightarrow\text{Risk/Safety Characterization)}}\right)$$

Dose-Response → Risk Characterization

- Inter-species extrapolation:
  - Animal → Human
  - Location extrapolation, from susceptibility of test animal to center (mean), μ_H, of human susceptibility distribution
  - Uncertainty is due to a lack of knowledge about μ_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, μ_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:

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

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

Human to Human

Animal to Human

Human Extrapolated Dose

- Lower 100p% statistical confidence limit on human extrapolated dose:
- Instead of $D_a/(T_{a,100p}T_{h,100p})$ $[D_a/(10*10)]$
- Calculate by $D_a/T_{s,100p}$
  - 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 $T_{a,100p}*T_{h,100p}$

Illustrations

- $T_a(0, 0.58, 1)$: $T_{50}=2$, $T_{95}=10$
- $T_h(0, 0.61, 0)$ $T_{50}=1$, $T_{95}=10$
  - $T_{a,95} * T_{h,95} = 100$
  - $T_{s,95} = 34$ $T_{s,99} = 100$

- $T_a(0, 0.697, 1)$: $T_{50}=2$, $T_{95}=15$
- $T_h(0, 0.715, 0)$ $T_{50}=1$, $T_{95}=15$
  - $T_{a,95} * T_{h,95} = 225$
  - $T_{s,95} = 60$ $T_{s,97} = 100$

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

Dose-Response → Risk Characterization Conclusions

- 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:

$$\frac{\text{Exposure} \rightarrow \text{Dose-Response}}{\text{Dose-Response)} \rightarrow \text{Risk Characterization}}.$$

$$D^{-1}\left\{BMR = \int_0^{\infty} g(tumor \,|\, x, \beta, k)\, f(x \,|\, D, \mu, \sigma)\, dx\right\}$$

$$T^{-1}\left\{100\,p = \int_{\tau_h}^{T}\int_{\tau_a}^{\infty} f_h(t_h \,|\, \mu_h = \log(t_a) + c, \sigma_h \tau_h)\, f_a(t_a \,|\, \mu_a, \sigma_a, \tau_a)\, dt_a\, dt_h\right\}$$

Challenges and Needs

- Correct propagation of uncertainty
  - Don't overstate or misstate
  - Hierarchical models
    - PK→PD, $A_{average}$→$H_{average}$, $H_{average}$→$H_{sensitive}$
- Model uncertainty
  - Don't ignore
  - Model averaging
    - Which and how many?
    - Confidence limits on model-averaged BMDs
    - Should you average BMDLs?

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