Bayesian Hierarchical Models for Fitting Dose-Response Relationships

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Dose Response Estimates using Hierarchical Models

- Hierarchical Bayesian methods enable simultaneous evaluation of
  - multiple studies, evaluating
    - different species
    - sex
    - biomarkers
  - single studies
    - Structuring hierarchies based on species, sex or measured health endpoints (biomarkers)
  - Hierarchies allow information to be shared between parameter estimates
  - Can be biologically informed

Advantages of Bayesian Hierarchical Models

- Prior parameter distributions can chosen to be "informationless" (yielding results similar to classical methods) or "informed" to reflect some mechanistic knowledge relative to the species, sexes, or endpoints
  - Results using alternative informed priors can and should be compared with each other and with informationless priors
  - Able to more easily constrain parameters known to be non-negative (or non-positive)
- Computational methods well established and readily available (e.g., WINBUGS)

Options for Data Pooling

- Allow us to treat data sets in complementary ways
- These also allow for comparison with bounding assumptions in other approaches
  - Pooling data
- Can compare results of models fit:

1. to each individual study;
2. hierarchically with parameters for each study (e.g., species, gender, or endpoint) *sampled* from a parent distribution (including hyperparameters that are also fit); or
3. with all data combined as if a single study

→ *The results in approaches 1-3 form a continuum*

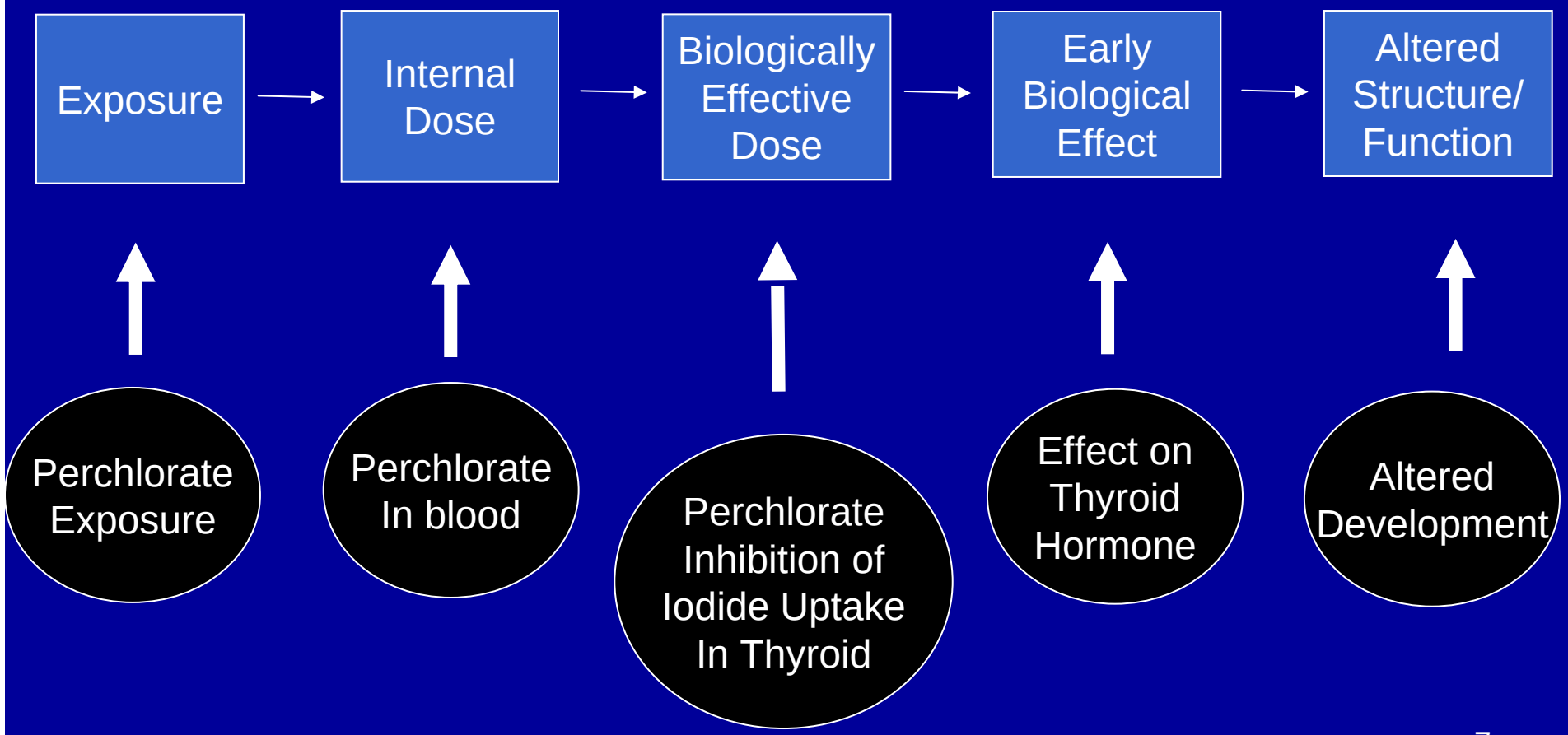
Previous HB work

- Preview of possible approach
- HB can also provide a format for toxicologists and statisticians to develop models together

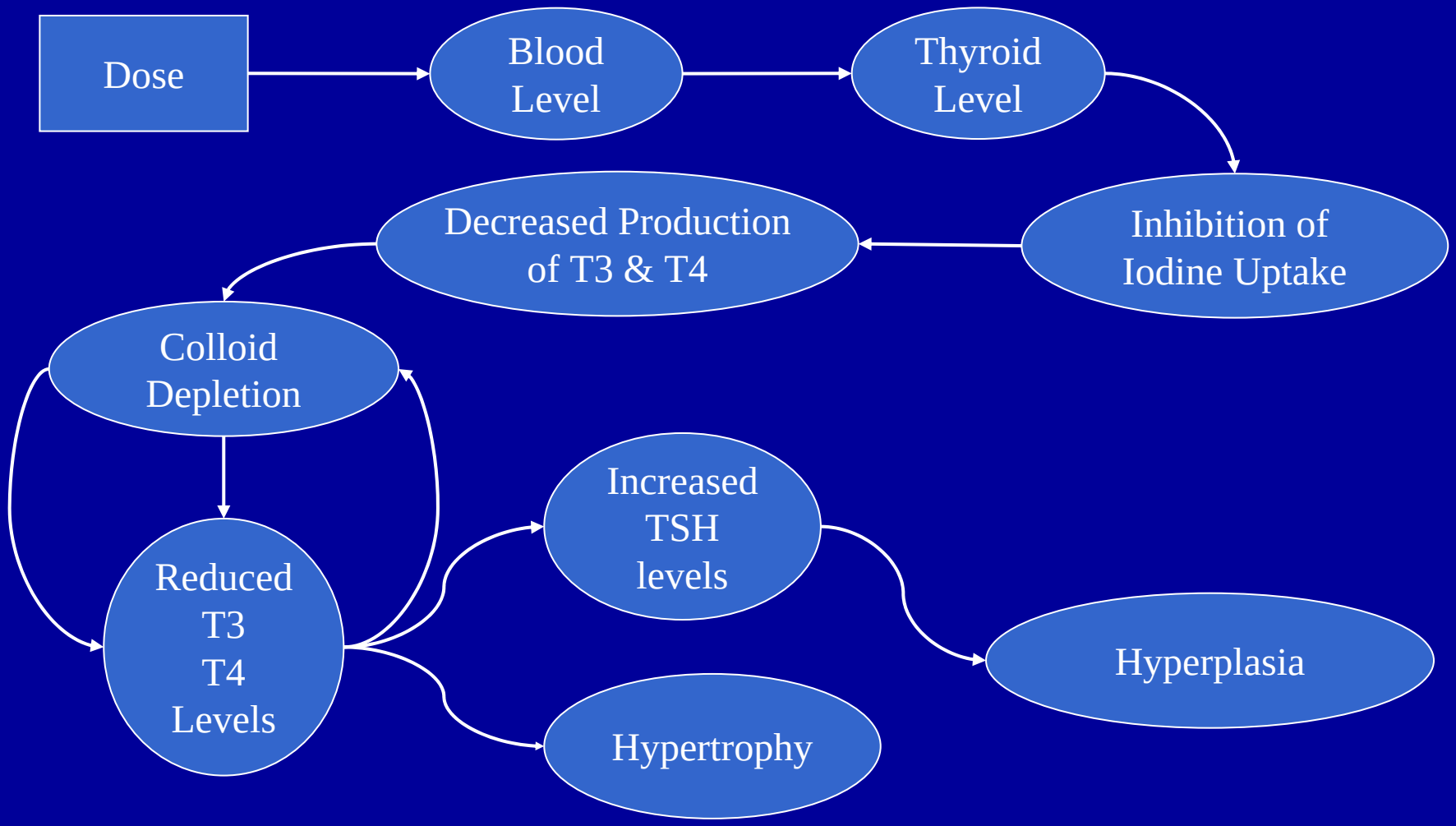
Method

- Mechanistic Diagram
- Bayesian Hierarchical dose-response model
  - Implemented in Bayesian Inference Using Gibbs (BUGS) software
  - Markov Chain Monte Carlo (MCMC)
  - Samples from posterior distribution
- Benchmark Dose (BMD)
  - Multi-endpoint BMD
  - BMDL

Mode of action framework for (Perchlorate)

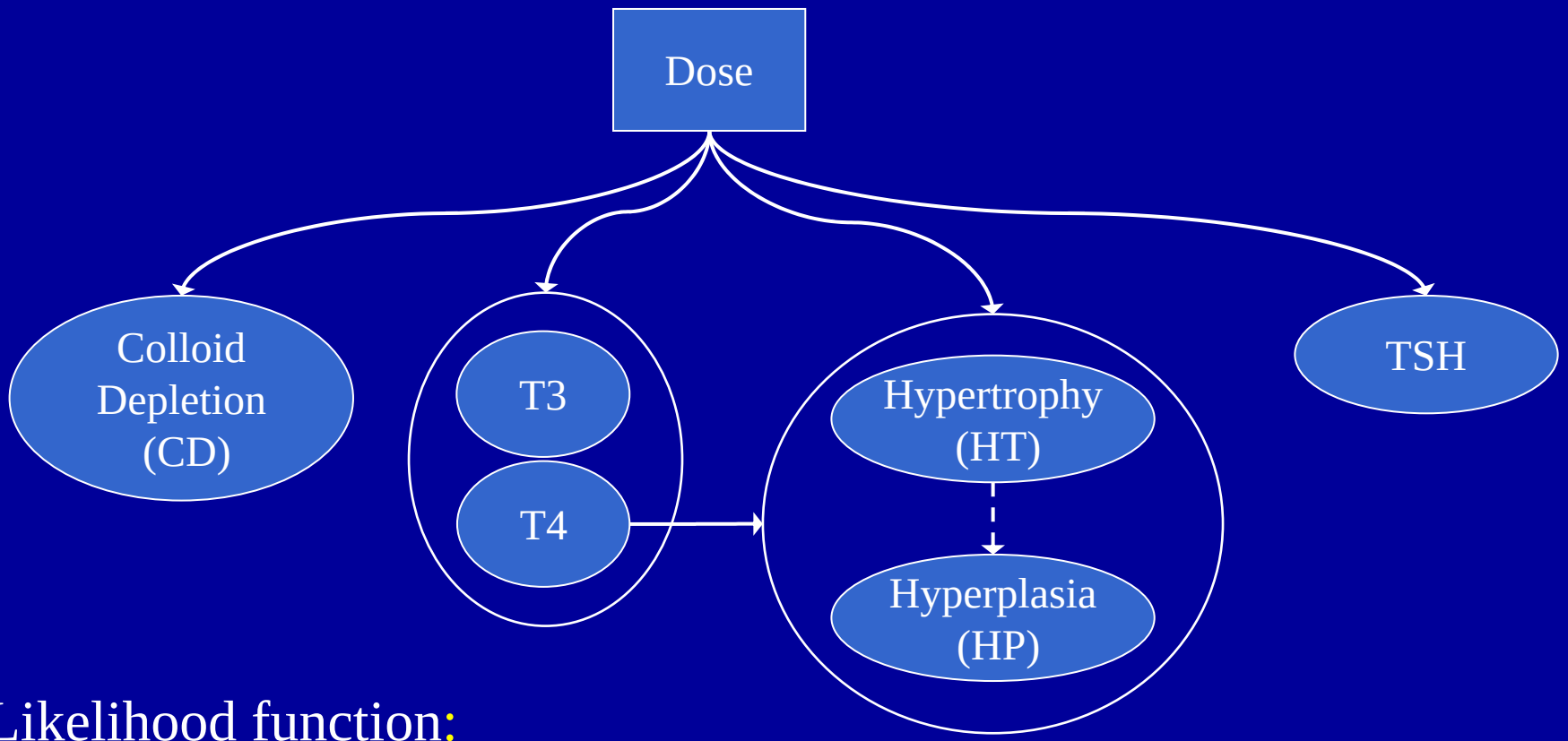


Mechanistic Diagram



Linked Model for Multiple Endpoints

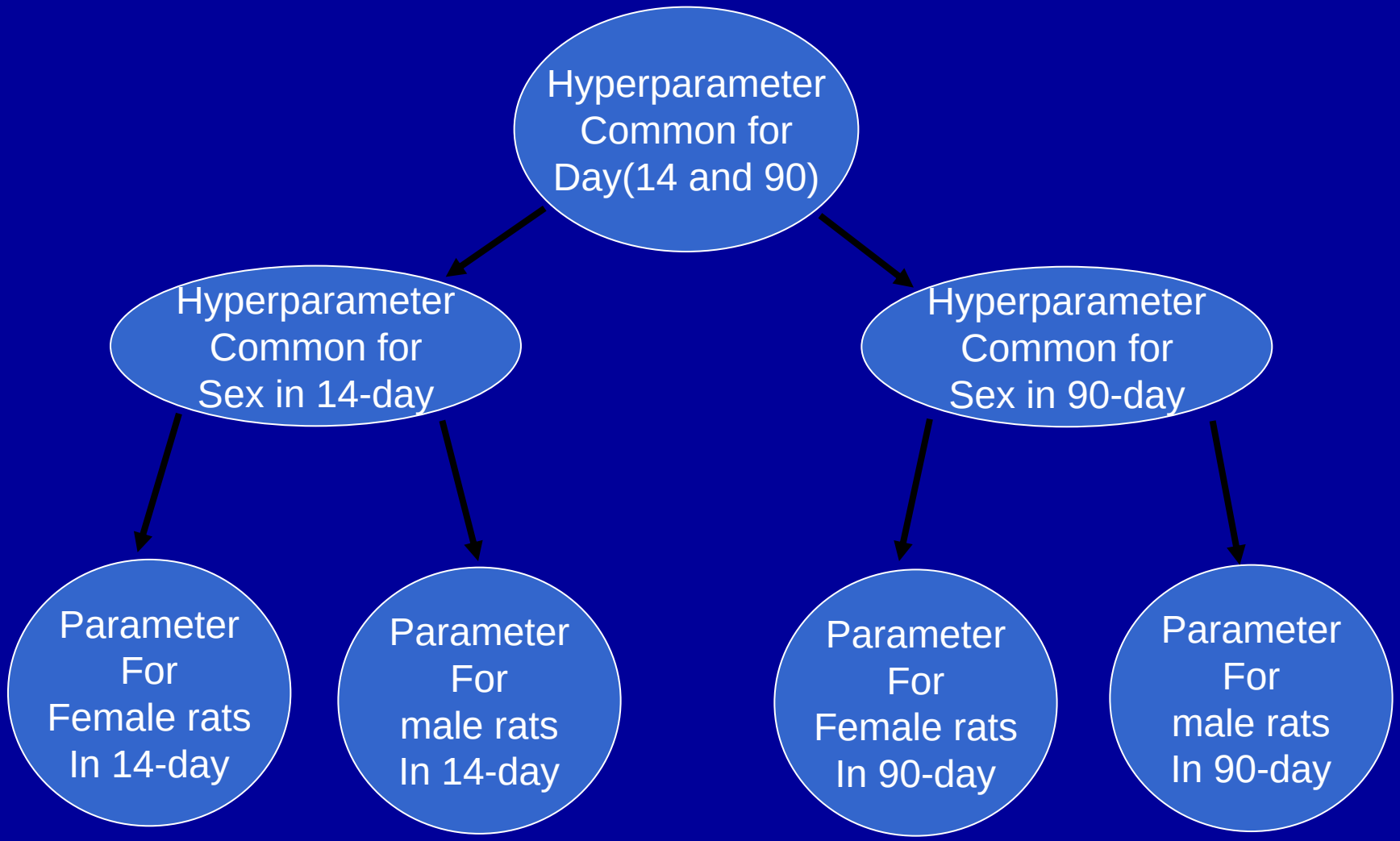
(preliminary)



Likelihood function:

$$f(\mathrm{CD} \mid \mathrm{dose})\, f\left(\begin{pmatrix}\mathrm{T3}\\ \mathrm{T4}\end{pmatrix} \mid \mathrm{dose}\right) f(\mathrm{TSH} \mid \mathrm{dose})\, f(\mathrm{HT} \mid \mathrm{T4}, \mathrm{dose})\, f(\mathrm{HP} \mid \mathrm{HT\ occurred}, \mathrm{T4}, \mathrm{dose})$$

Hierarchy for sex and time point (day)



Potential Hierarchical Structures

- Data set 2 Frambozadrine: *Different sex*
  - male and female rats
- Data set 3 Nectorine: *Different endpoints*
  - respiratory epithelial adenoma and olfactory epithelial neuroblastoma in rats
- Data set 4 Persimonate: *Different studies*
  - same species, gender, and endpoint

Example of Possible Hierarchical Model for Data Set 2: Frambozadrine with Male and Female Rats

1. Assume quantal-linear (simple exponential with background) model with:

Prob[Response] = B + (1-B) * [1-EXP(-S*D)] ;

where B is fitted background parameter and S is fitted slope parameter

2. Specify model:

For rat gender j; $j = 1, 2$

$B_i \sim Beta\ (\alpha_B, \beta_B)$

where α_B, β_B are the hyperparameters for the global distribution of background B across genders

Note: A beta distribution is chosen since B is constrained to (0, 1)

$S_i \sim Normal\ (\mu_S, \sigma_S)$

where μ_S, σ_S are the hyperparameters for the global distribution of slope S across genders

3. Specify prior:

Vague α_B, β_B : flat on the range (1, infinity) (If parameters = 1, represents U(0,1) prior for the B_j

Vague μ_S, N(0, large); and vague σ_S , Gamma(1, 1)

Multiple Endpoints: Prob[one *or* other]

Data set 3 Nectorine:

E1 = respiratory epithelial adenoma

E2 = olfactory epithelial neuroblastoma

Pr[E1 <u>or</u> E2] = Pr[E1] + Pr[E2] – Pr[E1 <u>and</u> E2]

If E1 and E2 truly independent, Pr[E1 <u>and</u> E2] = Pr[E1]*Pr[E2]

Can then compare this result to alternative assumptions regarding dependency, e.g., Pr[E2|E1] = γ * Pr[E2|not E1], where γ ranges from 1 to 10.

(Of course would help to have the different endpoints measured on the same test animals!)

Data Set 1 Parameter Estimates

(Exponential Model: Pr[R] = B + (1-B) * [1-EXP(-S*D)])

	Parameter Estimate (Std. Err.)			BMD5		BMD10	
	B	S	Parameter Correlation Coefficient	MLE	LCL95	MLE	LCL95
Classical (EPA BMDS):	0.025 (0.0243)	0.011 (0.0022)	-0.33	4.6	3.4	9.5	7.0
Bayesian (WINBUGS):	0.037 (0.03)	0.010 (0.0023)	-0.41	4.7	3.4	9.6	7.0

Data Set 2 Parameter Estimates

(Exponential Model: Pr[R] = B + (1-B) * [1-EXP(-S*D)])

	Parameter Estimate (Std. Err.)			BMD5		BMD10	
	B	S	Par. Corr.	MLE	LCL95	MLE	LCL95
Dataset 2 (Male Only) Classical (EPA BMDS):	0.068 (0.0249)	0.007 ((0.0017)	-0.3	7.8	5.8	16.1	11.0
Dataset 2 (Male Only) Bayesian (WINBUGS):	0.072 (0.025)	0.0073 (0.0017)	-0.26	7.1	4.8	15	9.9
Dataset 2 (Female Only) Classical (EPA BMDS):	0.0569 (0.022)	0.0082 (0.0016)	-0.23	6.7	4.9	13.7	10.1
Dataset 2 (Female Only) Bayesian (WINBUGS):	0.027 (0.031)	0.0088 (0.0014)	-0.39	5.8	4.6	11.9	9.5
Dataset 2 (Both) Bayesian (WINBUGS):	0.047 (0.019)	0.0080 (0.0014)	-0.56	6.4	4.4	13.1	9

Distribution of BMDs

Dose