Multiple Data Sources Multiple Endpoints

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Introduction

- Risk assessment is typically concerned with a single critical effect using a single study.
- What happens when there are multiple studies and multiple effects?
- This talk is to try to spur discussion rather than promote any one method.

- Potential Benefits
  - More Data → Better estimate of dose-response curve?
  - Correlated Endpoints → More realistic estimate of knowledge on the entire hazard?
  - Multiple Species → Some idea of interspecies variability?

- **Difficulties:**
  - More complicated models/modeling choices:
    1. Over Dispersion.
    2. Define Correct model/ more assumptions
    3. No off the shelf software.
  - What data should be included?
  - Differing study lengths, how does this get included in the model.
  - Is it research or regulatory?

Case Studies

- Let's look at a few case studies and look at the issues that arise.
- What are ways we can push science forward with existing data?
- What are data needs to do what we really want?

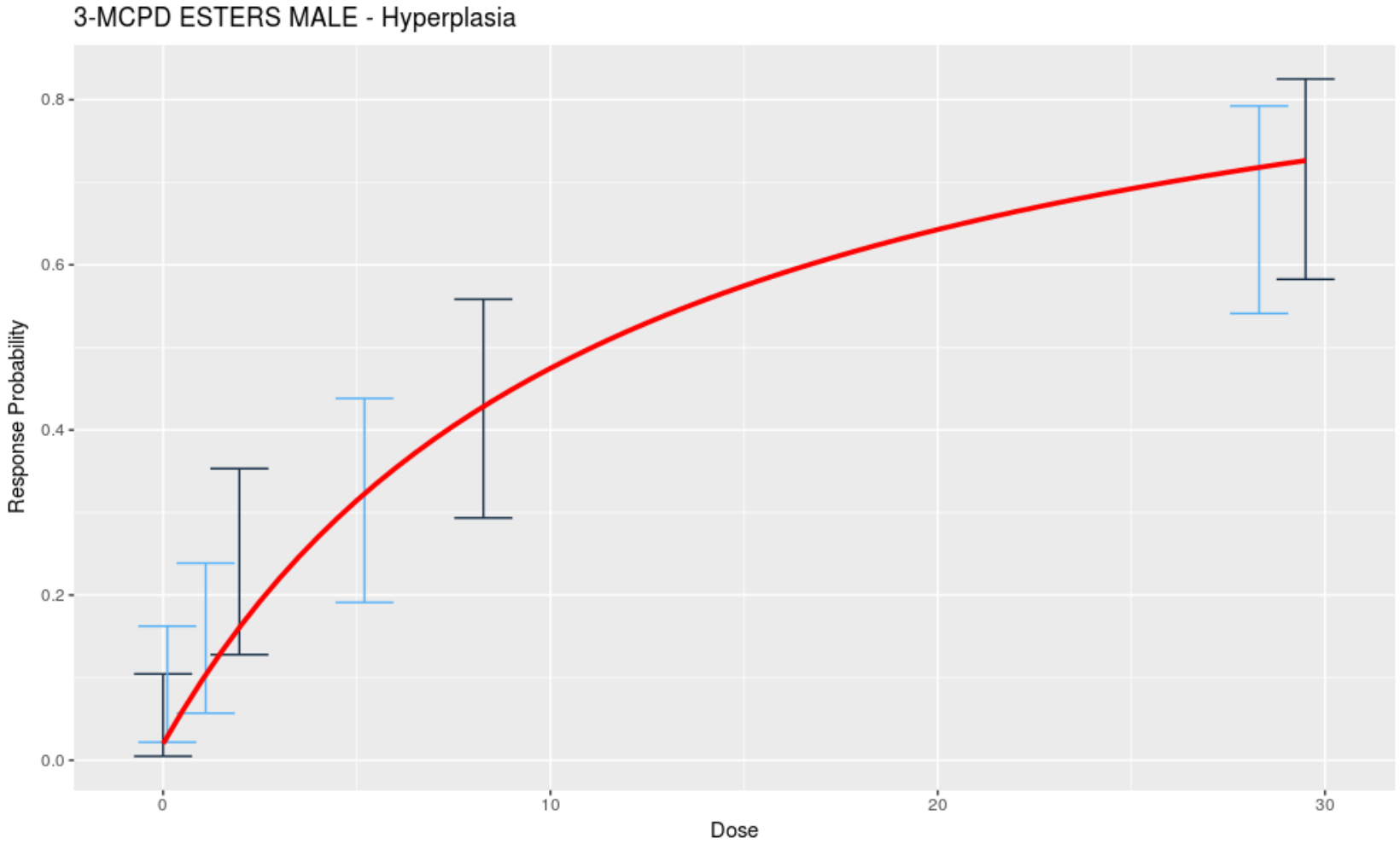
GOAL: How do we make risk assessment science better?

Case 1: 3-MCPD Esters

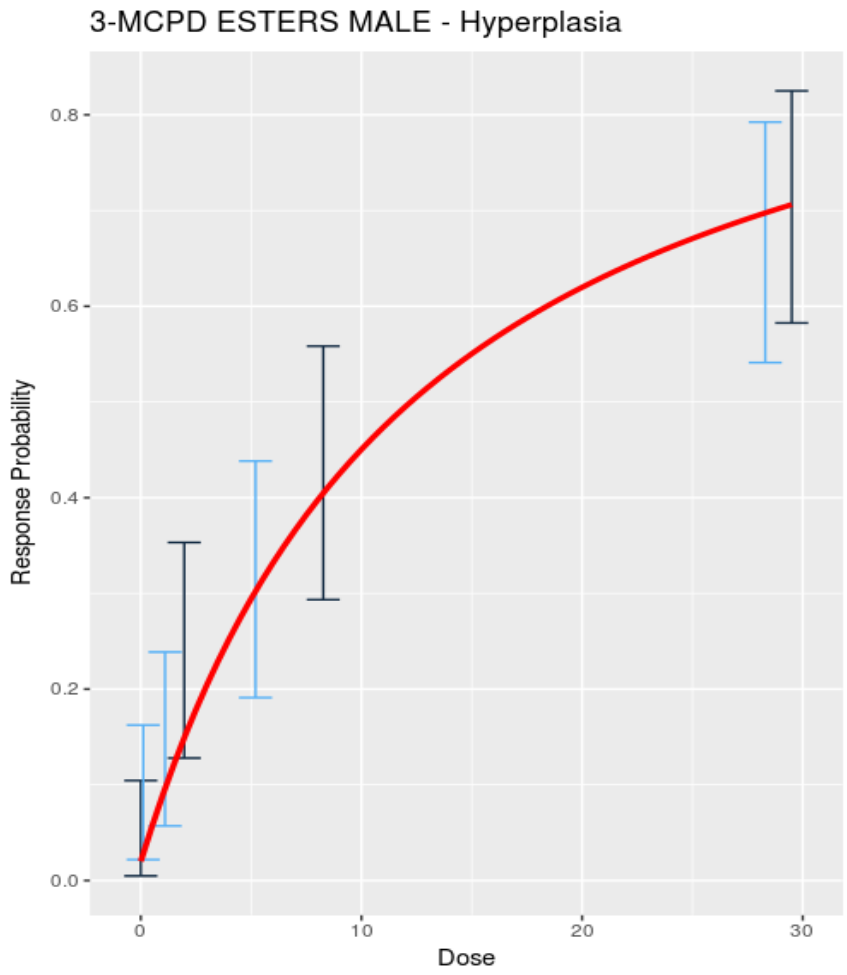
			Hyperplasia Cho et al (2008)		Nephropathy	
			Male	Female	Male	Female
	Dose (ppm)	N	Obs	Obs		
Cho et al. (2008)	0	50	1	1	15	6
	1.97	50	11	0	27	8
	8.27	50	21	1	39	23
	29.5	50	36	10	41	42
Sunahara et al (1993)	0.11	50	3	2	36	24
	1.1	50	6	4	40	23
	5.2	50	15	20	45	42
	28.3	50	34	31	49	48

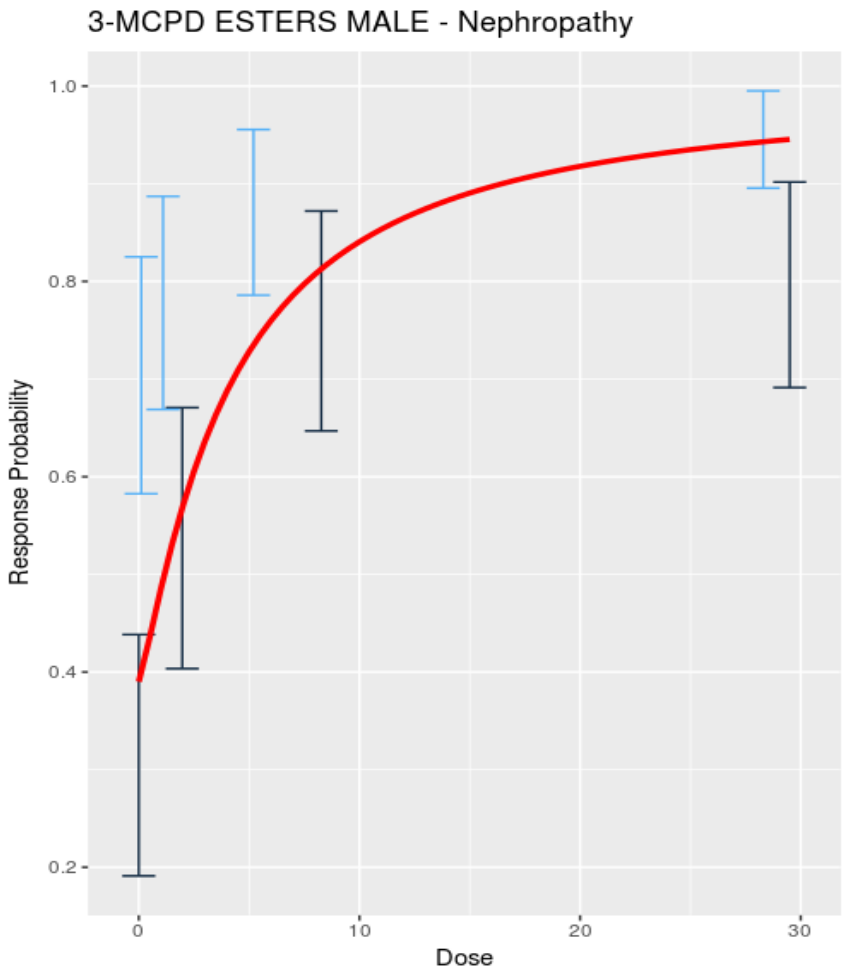
- These data are subject to considerable debate:
  - In 2016 EFSA used the Cho et al data establishing a POD of 4 ppm.
  - The committee at the 83rd JEFA recommended a POD of 83 ppm using the same data.
- Though the difference is based upon constraining/ unconstraining models: can we use “all of the data” and avoid the problem.
- Look at the unconstrained Log-Logistic model.
  - There will be some modifications to this model for the purposes of fitting the data.

Model 1: Just the Hyperplasia



Model 2: All endpoints





Resulting Population BMD

Method	BMD	(BMDL,BMDU)
BMDS	0.83	(**0.22**,1.88)
Model 1*	1.48	(**0.96**,2.83)
Model 2*	1.40	(**0.93**,4.74)

*These were Bayesian models using random effects to illustrate what *could* be done.

**All BMDs were calculated using the excess risk definition.

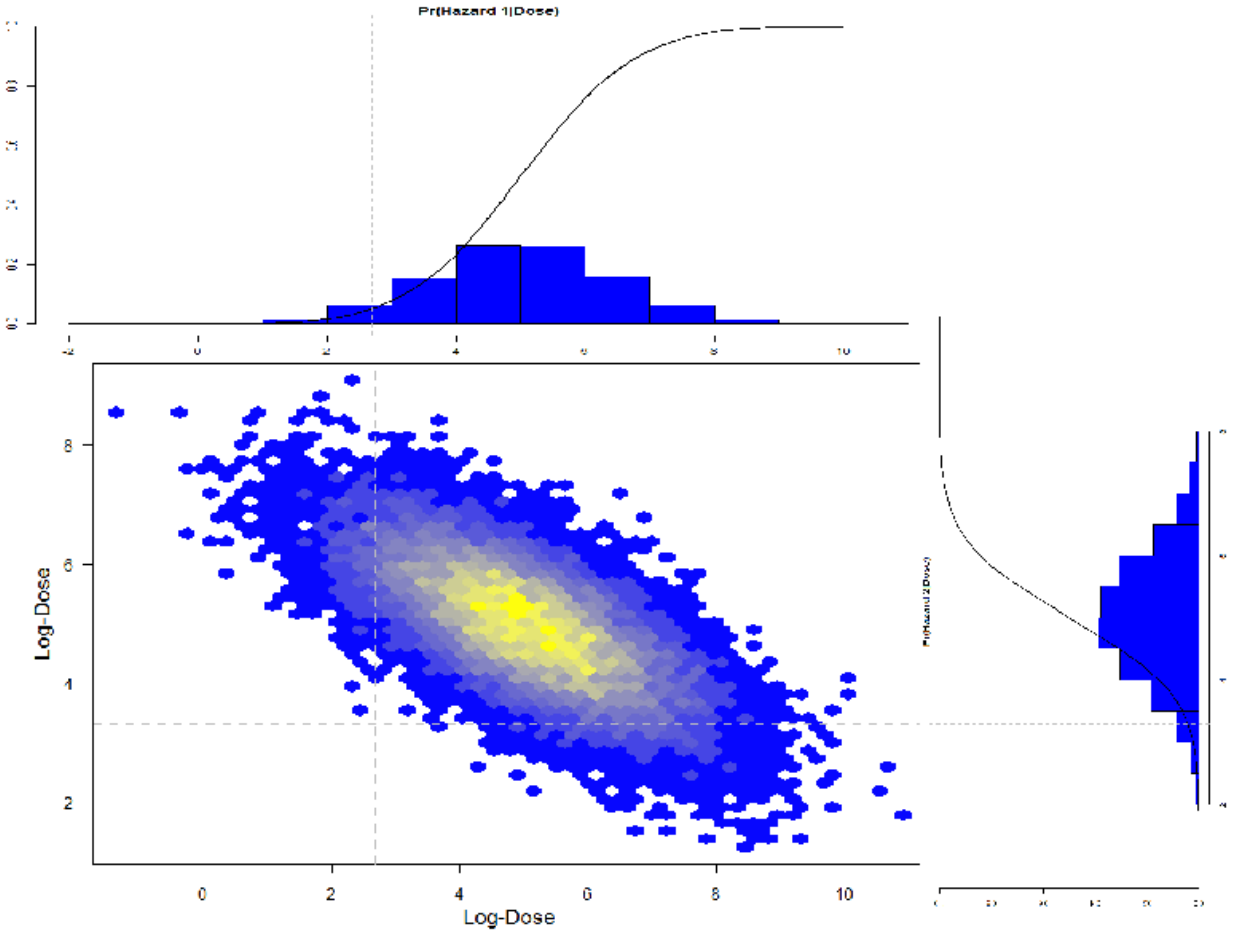
Issues

1. Limited number of studies require more assumptions on the random effects. What are good assumptions?
2. Can't learn the correlation coefficient → not enough info, are the results robust?
3. Could we sidestep some of these issues if we had the individual animal data?

Case2 : Multiple Studies Different Lengths

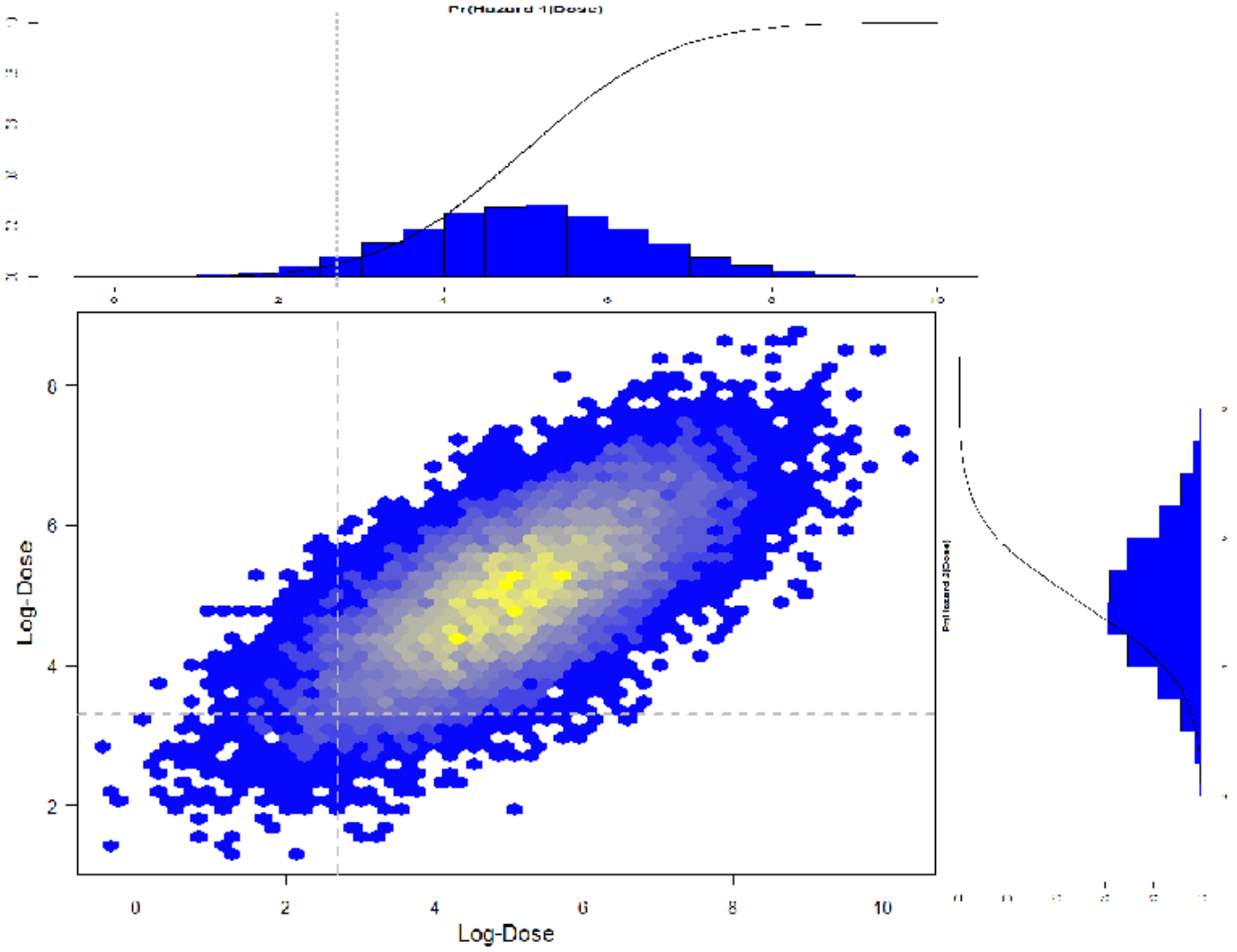
- NTP studies may have studies on the same chemical with different lengths and multiple endpoints.
- How do we integrate this information?
- What does a BMD mean in this context.
- The endpoints are correlated.
- Risk assessment should be based upon all information.

Rosy View of the World



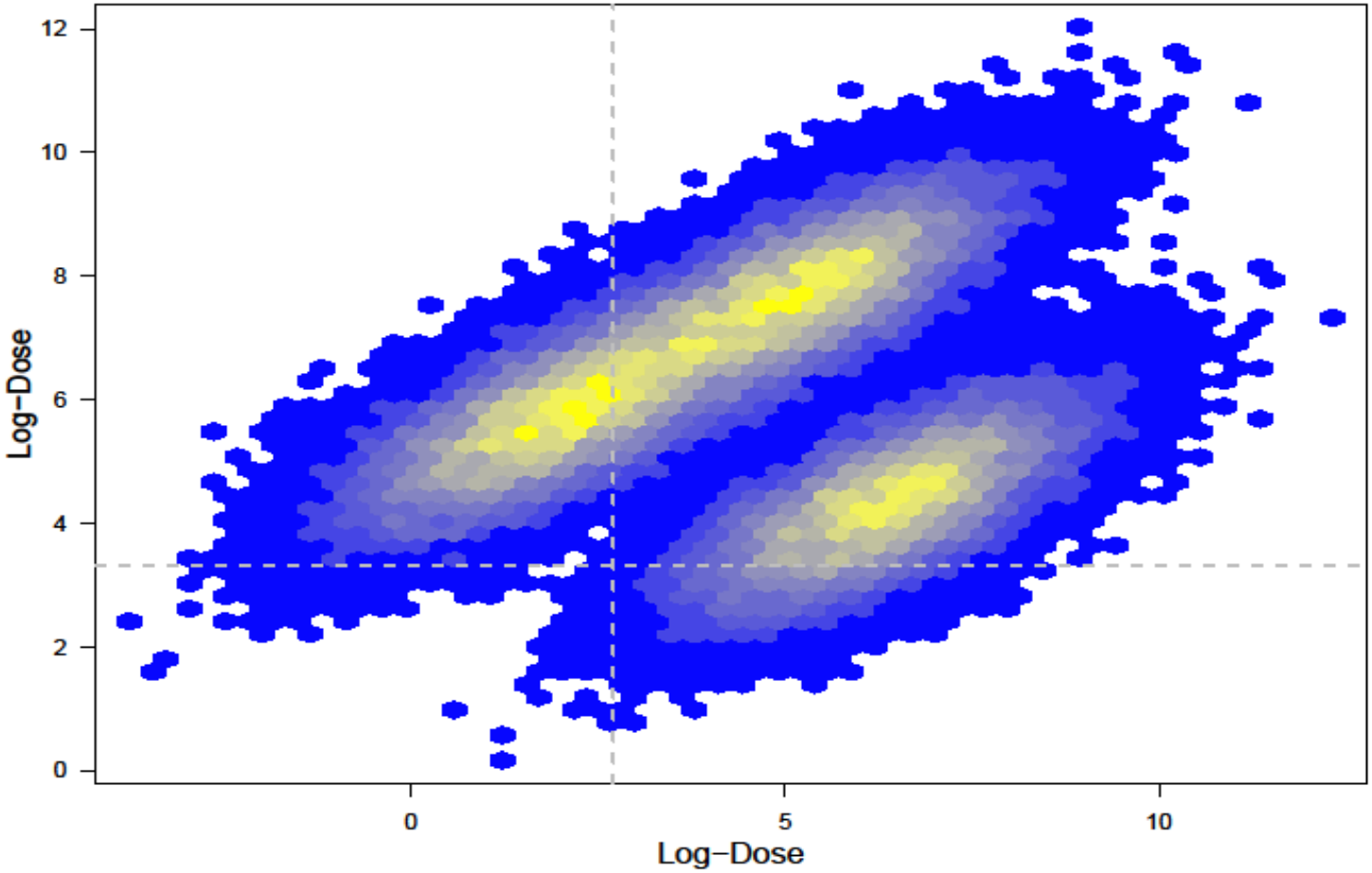
- In the previous slide, each person has a different tolerance distribution to the probability of response.
- The bivariate nature of this response is negatively correlated.
- Take two real endpoints like lung and liver cancer. Is it reasonable to assume they are negatively correlated?

More realistic view of the world



- Now the bivariate nature of this response is positively correlated, which is probably more reasonable.
- Is it reasonable to assume they come from a single heterogeneous population?

Reality: Multiple sub populations, multiple endpoints.



- Now we have a much more reasonable situation:
  - Multiple subpopulations.
  - Multiple positively correlated endpoints.
- Now the real problem is “Where do we find the data?”
- Then how do we put it together to make something out of it?
- Dosing from different studies may not be comparable.

NTP Datasets

Chemical	Doses	Lengths
Chloroprene	12 ppm	14-day
	32 ppm	22-day
	80 ppm	90-day
	200 ppm	
	500 ppm	
Carbon Tetrachloride	50 mg/kg	3 Hours
	100 mg/kg	6 Hours
	500 mg/kg	24 Hours
	750 mg/kg	48 Hours
	1000 mg/kg	72 Hours
		15 Days
Acetaminophen	50 mg/kg	3 Hours
	100 mg/kg	6 Hours
	500 mg/kg	18 Hours
	750 mg/kg	24 Hours
	1000 mg/kg	48 Hours

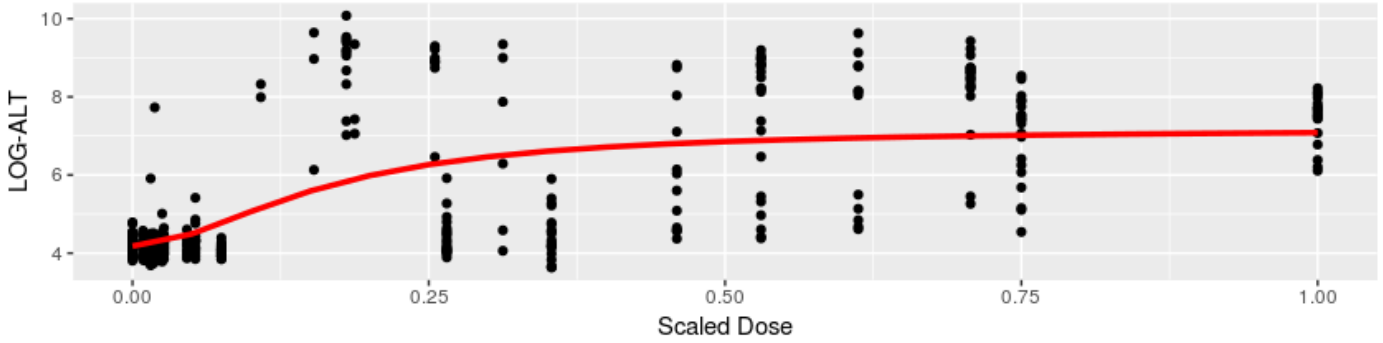
- Here we have to conceptualize a model for internal concentration:
  - PBPK ?
  - Simple scaling:

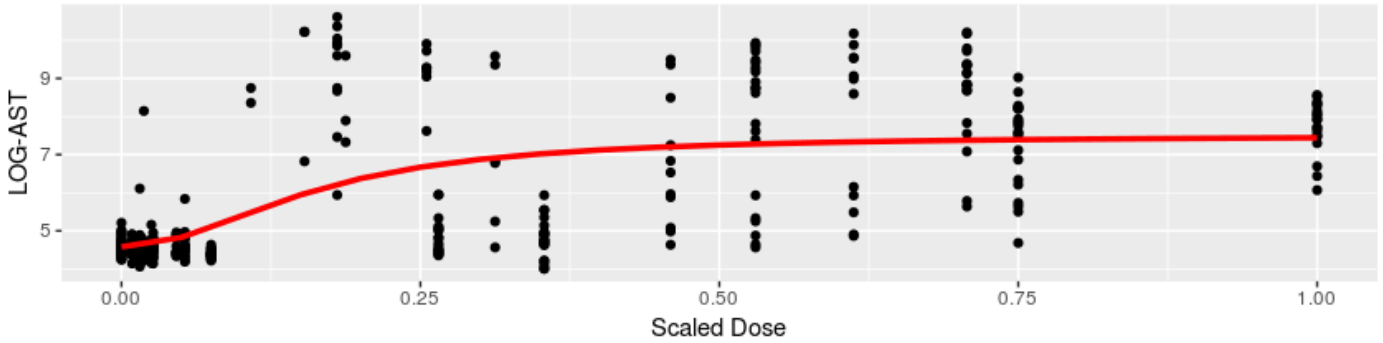
    Scaled-Dose = Dose * Time ?

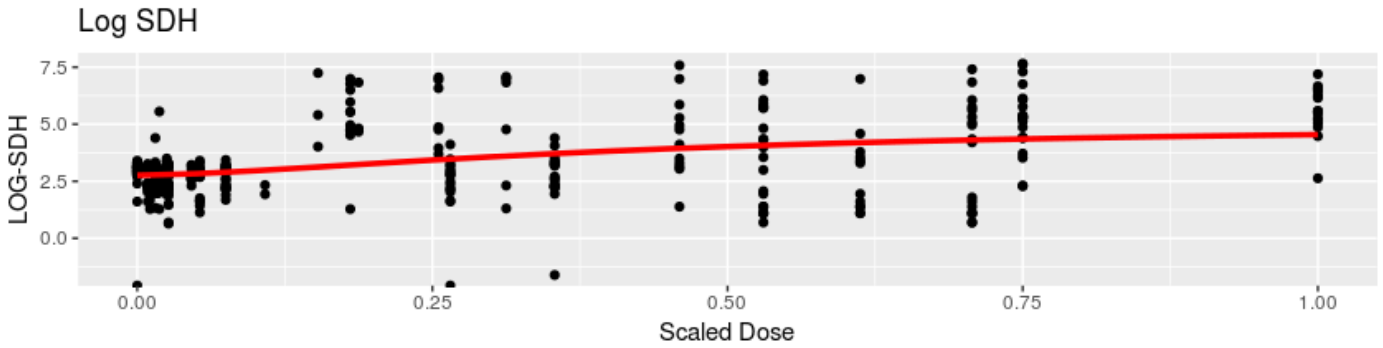
    Scaled-Dose = Dose * Time^(2/3) ?

    Scaled-Dose = Dose * Time^(1/2)?
- Does this vary from dose to dose and study to study?
- Look at a hypothetical model for Acetaminophen for three continuous endpoints

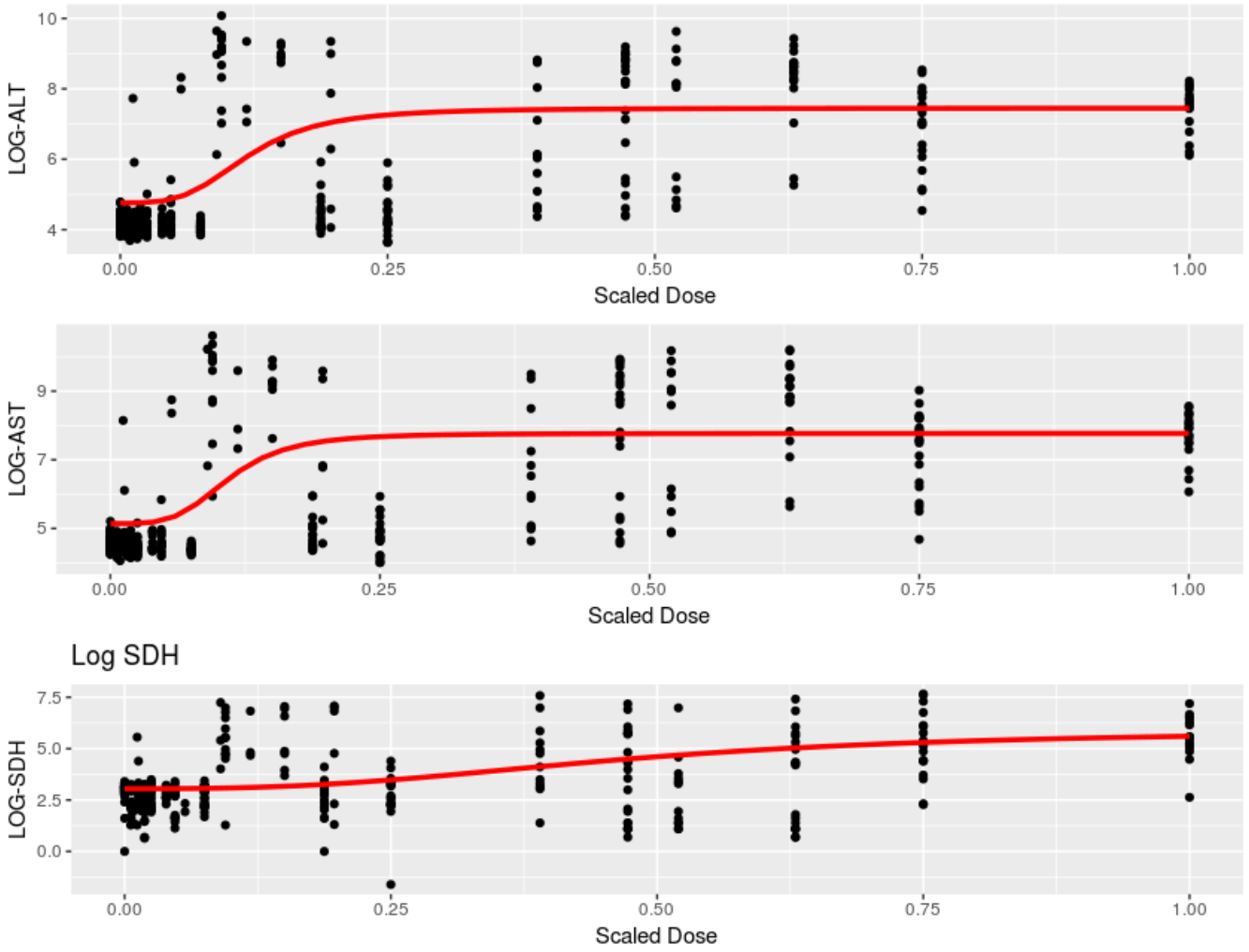
Correlated Endpoint Model with Time ½ * Dose







Correlated Endpoint Model with Time $^{2/3}$ * Dose



How do we deal with dose?

- Transform the dose like epi study?
- PBPK estimate for internal concentration is more correct for short term studies…
  - This adds more model/study variability
- Dose is now a function of time thus any BMD is essentially a function of time as well.

Example 3: Integrating Evidence

- Currently we have little understanding about setting BMRs for continuous endpoints.
- Dichotomous endpoints are simple (e.g. cancer), but this does not translate well over to continuous endpoints.
- Challenge: What does a 10% increase in ALT mean vs. 10% decrease in liver weight.

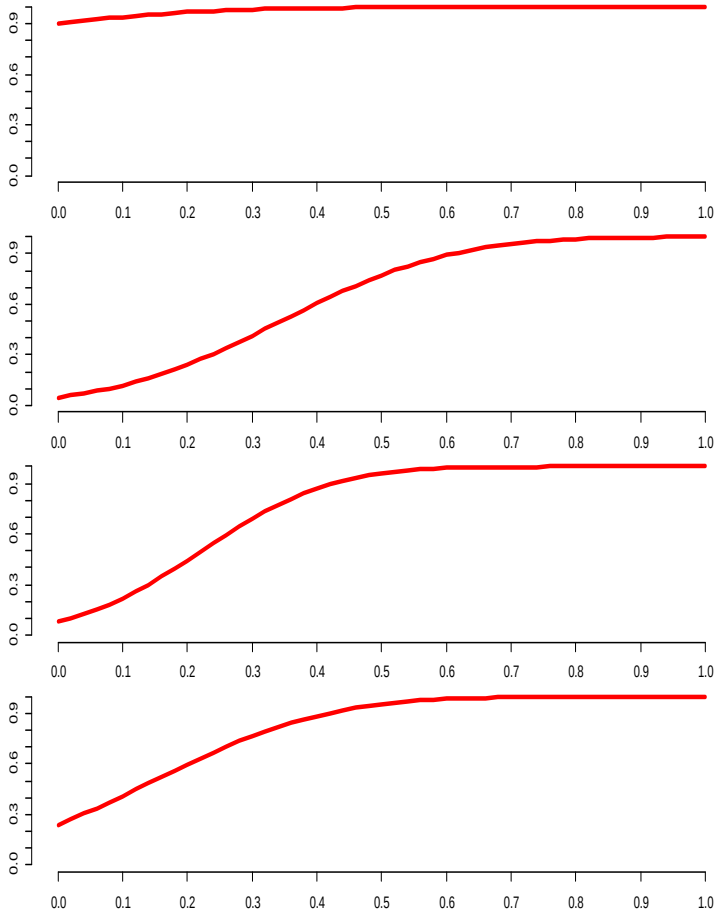
Idea: Develop model that looks at correlation between a dichotomous endpoint with a known pathology (e.g., hypertrophy) to a continuous measurement.

Data: All NTP short term studies for all chemicals.

Challenges: Standard Study to study variability, complicated model -> model form?

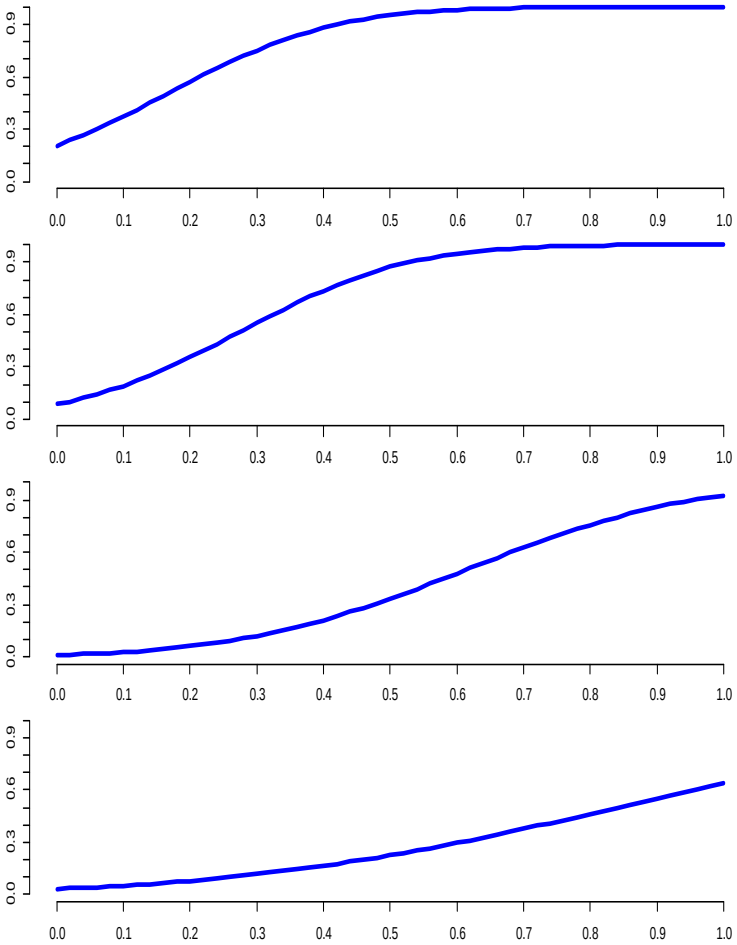
Conceptual Model

Endpoint we don't know what to do with.



Correlation?

Endpoint from which QRA is routine.



- The endpoints we are less comfortable with:
  - Continuous endpoints.
    - The severity of the endpoint is not clear.
  - In-vitro assays.
    - Even more difficult to tie these to actual response.
  - Genetic dose response.
    - No clue what to do.

Such an analysis may tie these two groups of studies together.

Conclusions/Thoughts

- There are many ways to look at the multiple/study multiple endpoint problem.

- I gave three possibilities, there are more.

Conclusions/Thoughts

Regardless of the Problem we need data!

Keys:

- Raw Data
- Available Data
- Well designed studies