Current status of Benchmark Dose Modeling for 3-Monochloropropane-1,2-diol (3-MCPD)

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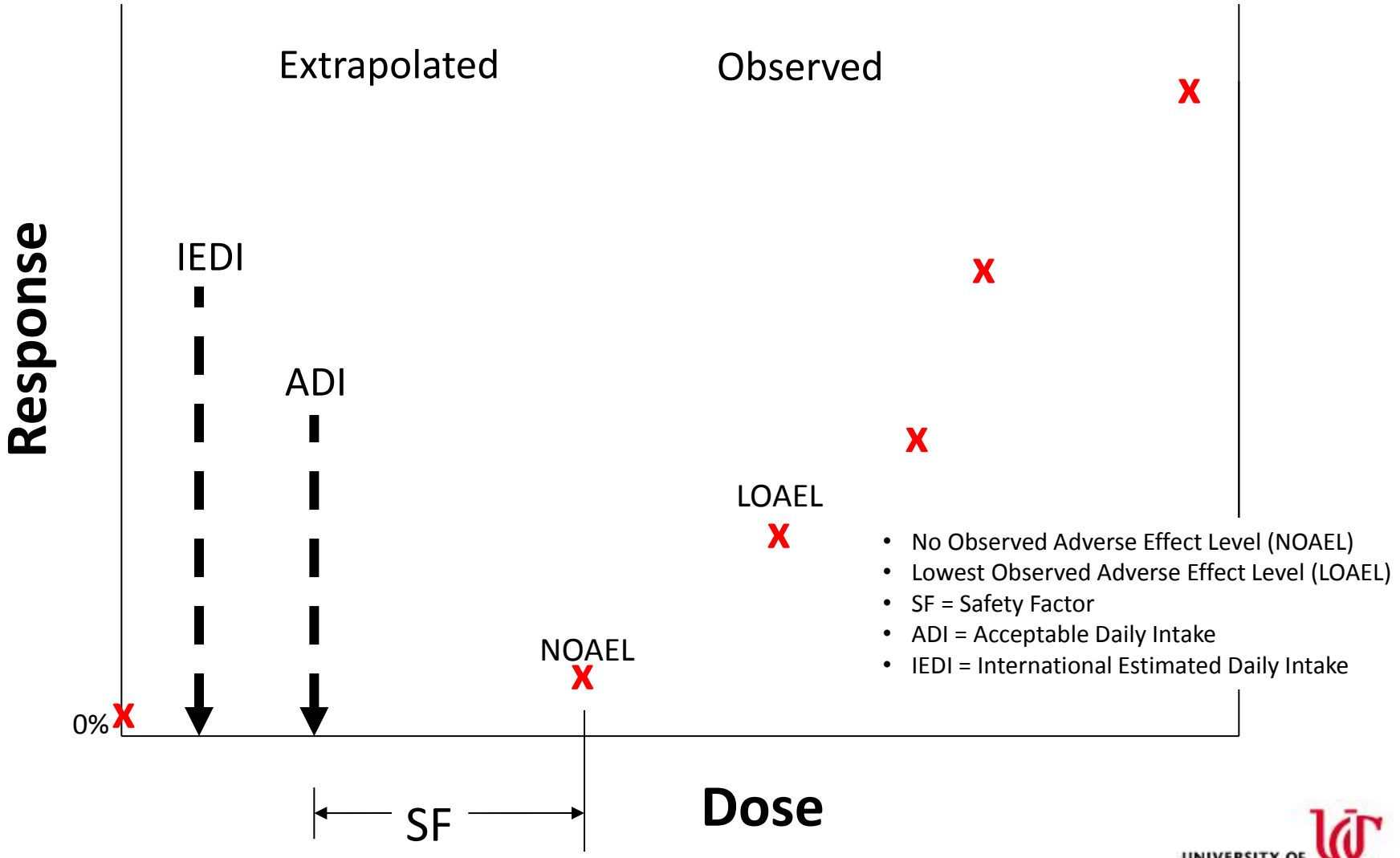
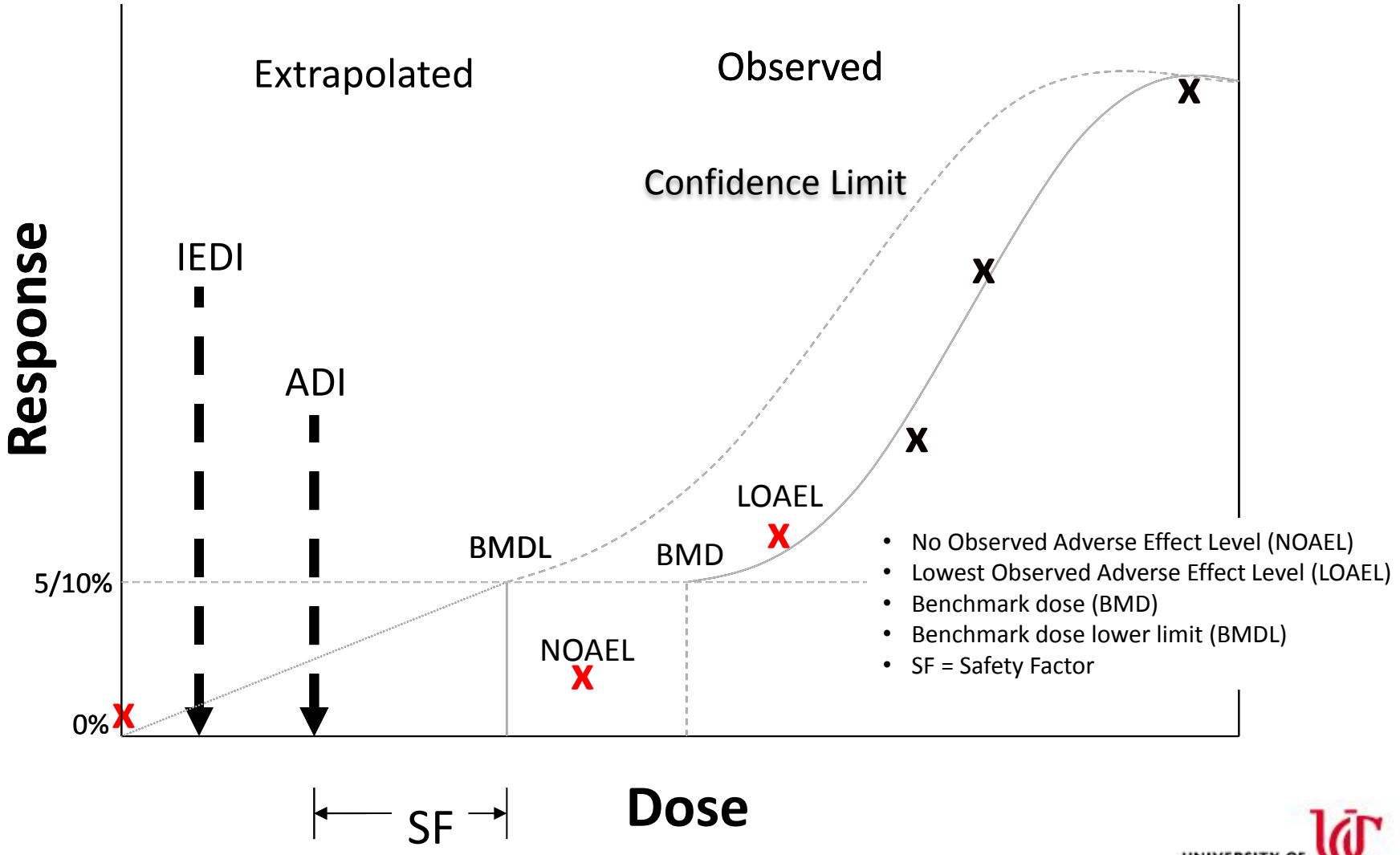
What we all do now…



- No Observed Adverse Effect Level (NOAEL)
- Lowest Observed Adverse Effect Level (LOAEL)
- SF = Safety Factor
- ADI = Acceptable Daily Intake
- IEDI = International Estimated Daily Intake

What we all could do now…



Benchmark Dose (BMD)

- Biologists need to determine a benchmark response (BMR) of the critical effect.
- A BMD is a mathematical fitting of toxicology data so that a NOAEL surrogate for the BMR can be selected.
- Clear advantages and disadvantages exist with BMD
  - Uses responses near the range of observation.
  - Includes a measure of variability in the response.
  - Determines a consistent measure of response.
  - Applies to fewer, more robust, toxicity data sets.
  - Accounts for more dose response of critical effect

Casarett and Doull (Sixth Edition) page 94

BMD Model Selection Criteria

- **Is the model statistically significantly different than data?**
  - **If the p-value is < 0.05, then the model fails to fit the data.**
  - **Models with p-values > 0.1 are desired.**
- Residual: How well does model fit the data at the BMR?
  - Absolute value of 2 or less is acceptable.
- **Visual fit: How well does the model fit the data overall?**
- Do BMDLs depend on model choice?
  - BMD to BMDL ratios of less than 2-fold are considered good.
- **Akaike Information Criterion (AIC): which model is statistically best?**
  - **Values of 2 or less from each other are considered similar.**
- **Overall professional judgment**

U.S. Environmental Protection Agency, 2012; EFSA, 2016 (bold-printed)

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3-Monochloropropane-1,2-diol (3-MCPD)

- Four groups have used BMD approach to derive a Tolerable Daily Intake (TDI) for 3-MCPD:
  - Abraham et al., 2012: TDI = 2.7 ug/kg
  - Hwang et al., 2009: TDI (equivalent) = 9 ug/kg-day
  - EFSA, 2016: TDI = 0.8 ug/kg
  - Reitjens et al., 2002: TDI = 7 ug/kg
- All groups included same study---Cho et al. (2008)--- and likewise used the incidence of kidney hyperplasia. Reitjens et al. (2002) also included the study of Sunahara et al. (2003)
- The resulting recommendations differ by 11-fold.

Table 2. BMDS results for renal hyperplasia in male rats from Cho et al. (2008).

Model Name	P-value	Visual Fit	Scaled residual nearest the BMD	Scaled residual control group	BMD/ BMDL Ratio	AIC	BMD	BMDL
LogLogistic (restricted)	0.61	Excellent	0.9	-0.2	1.4	195	1.2	0.87
Gamma (Unrestricted)	0.92	Excellent	0.0	0.0	7.1	196	0.53	0.07
Weibull (Unrestricted)	0.81	Excellent	0.0	0.0	4.7	196	0.63	0.13
LogLogistic (Unrestricted)	0.57	Excellent	0.0	0.0	3.7	196	0.83	0.22
LogProbit (Unrestricted)	0.54	Excellent	0.0	0.0	3.3	196	0.92	0.27
Multistage (Unrestricted)	0.25	Excellent	1.0	-0.2	1.4	197	1.3	0.90

Figure 1. BMDS LogLogistic (restricted) graph for renal hyperplasia in male rats from Cho et al. (2008).

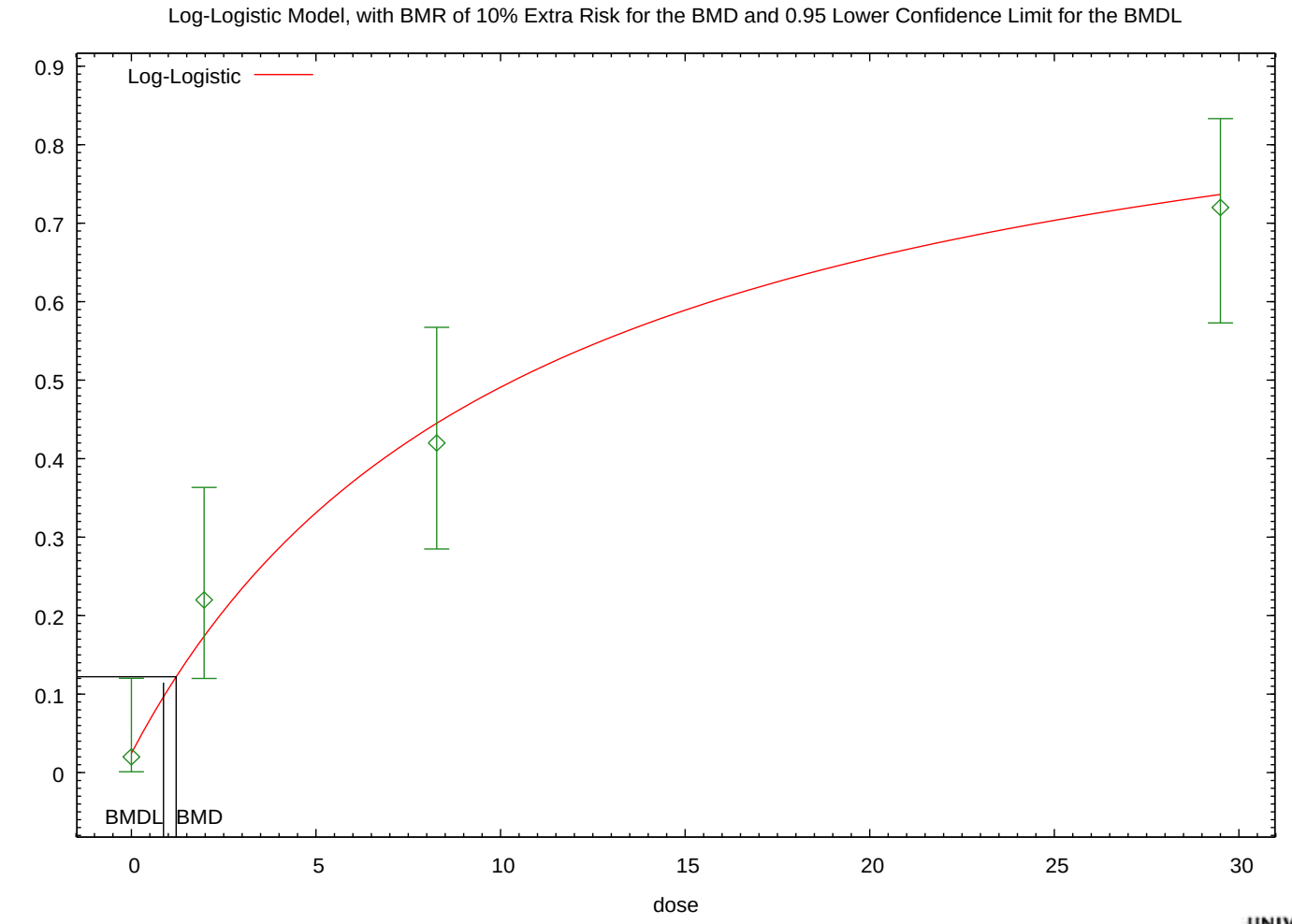

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Figure 2. BMDS Gamma (unrestricted) graph for renal hyperplasia in male rats from Cho et al. (2008).

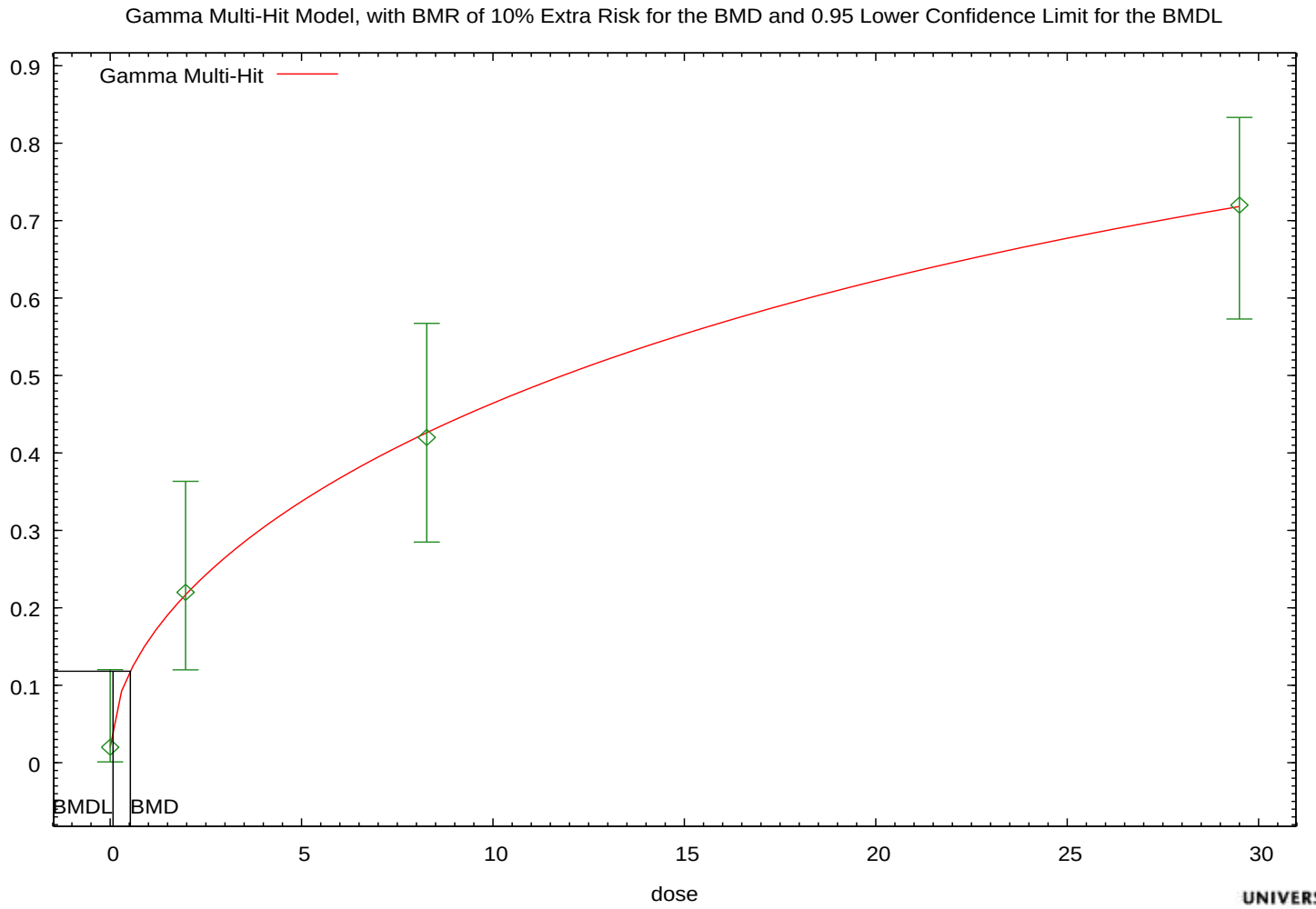

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Figure 3. BMDS Weibull (unrestricted) graph for renal hyperplasia in male rats from Cho et al. (2008).

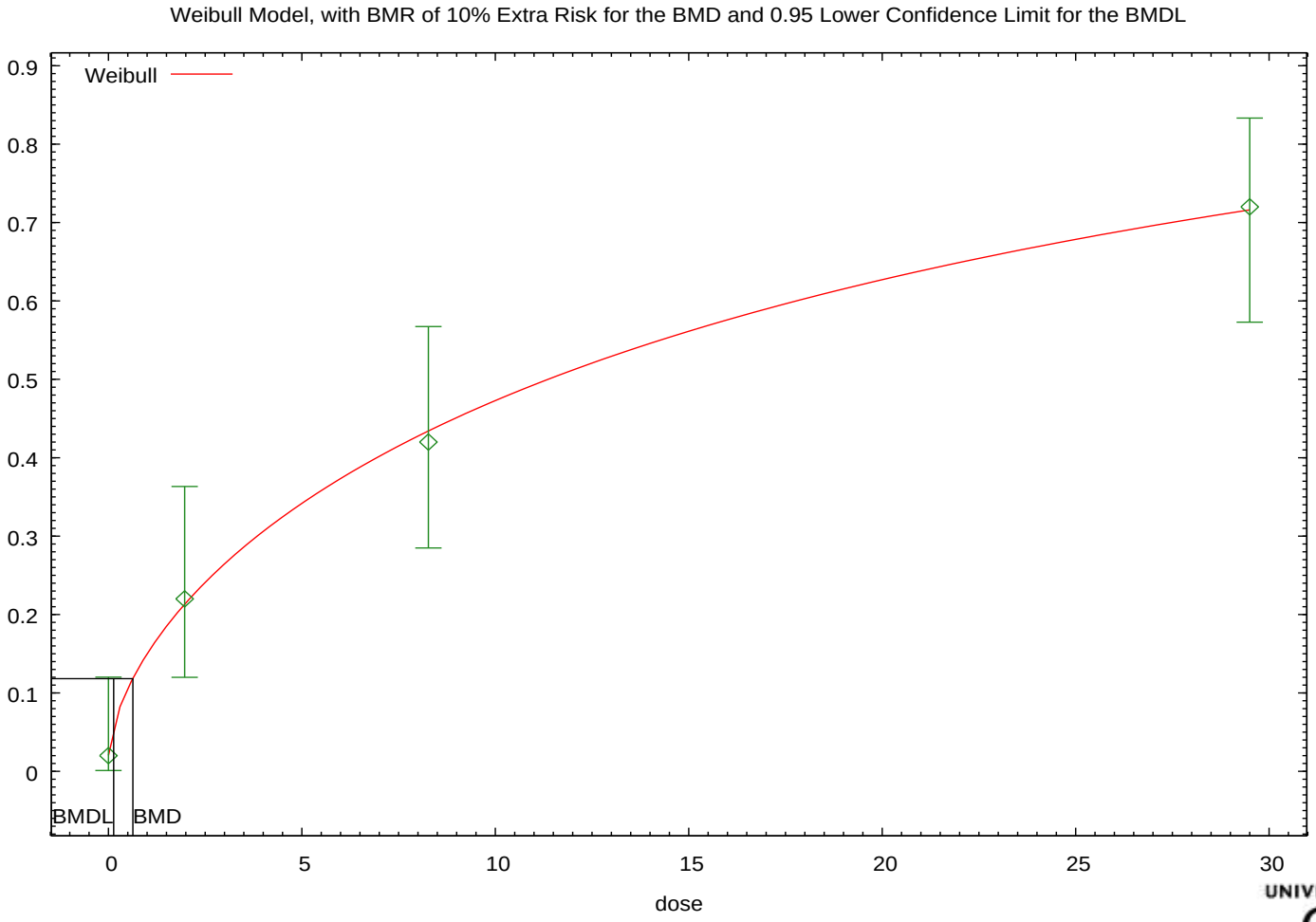

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Figure 4. BMDS LogLogistic (unrestricted) graph for renal hyperplasia in male rats from Cho et al. (2008).

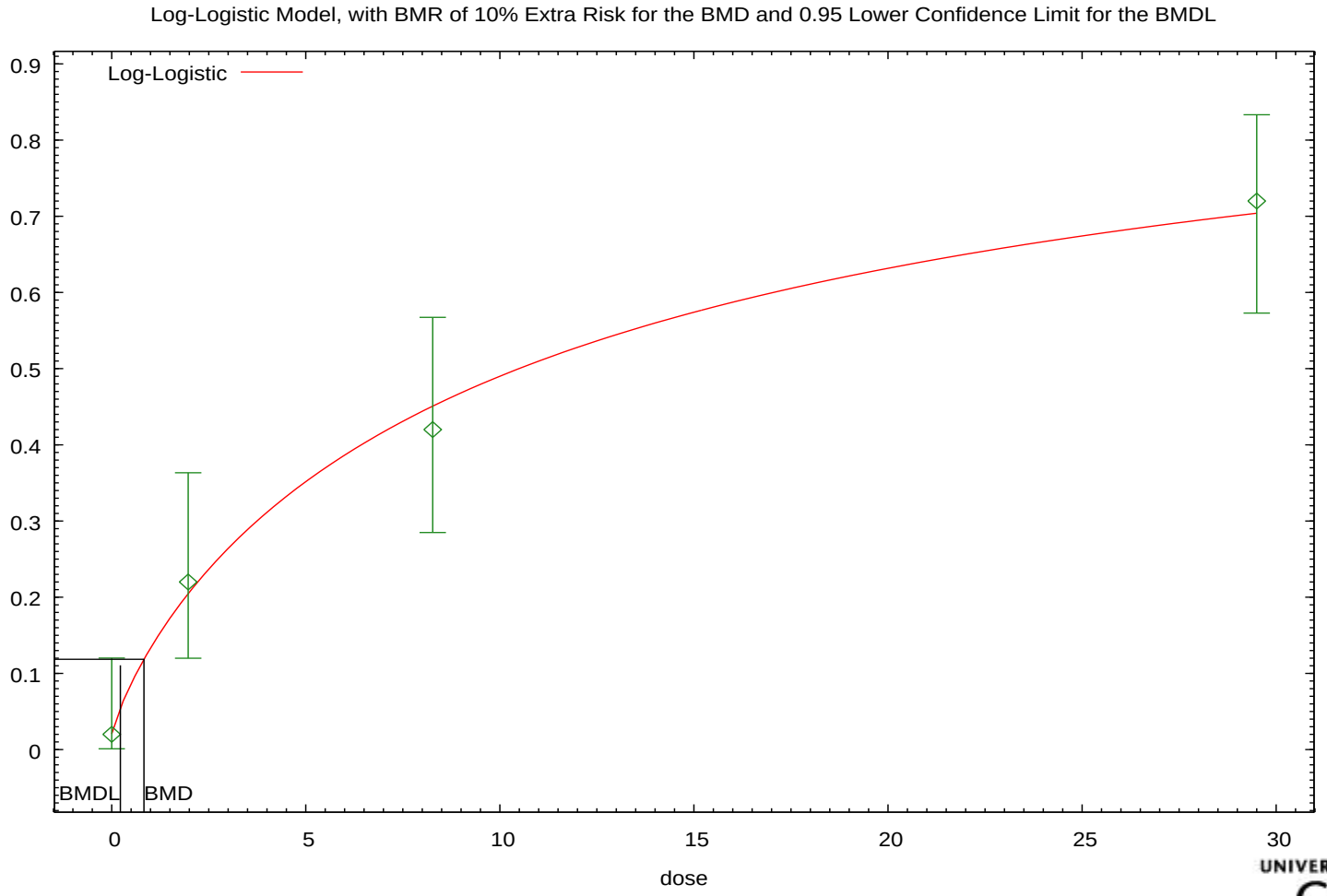

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Table 1. BMDS results for renal hyperplasia in male rats from Sunahara et al. (1993).

Model Name	P-value	Visual Fit	Scaled residual nearest the BMD	Scaled residual control group	BMD/ BMDL Ratio	AIC	BMD	BMDL
Gamma (Restricted)	0.63	Good	0.1	-0.4	1.3	188	2.6	1.9
Multistage-2 (Restricted)	0.63	Good	0.1	-0.4	1.3	188	2.6	1.9
Multistage-3 (Restricted)	0.63	Good	0.1	-0.4	1.3	188	2.6	1.9
Weibull (Restricted)	0.63	Good	0.1	-0.4	1.3	188	2.6	1.9
Quantal-Linear	0.63	Good	0.1	-0.4	1.3	188	2.6	1.9
Multistage-Cancer (Unrestricted)	0.63	Good	0.1	-0.4	1.3	188	2.6	1.9
Multistage-2 (Unrestricted)	1.00	Excellent	0.0	0.0	1.7	189	1.8	1.1
LogLogistic (Restricted)	0.99	Excellent	0.0	0.0	1.6	189	1.7	1.1

Table 3. Basis for TDIs of various investigators.

	TERA 2016	EFSA 2016	Abraham et al., 2012	Reitjens et al., 2012	Hwang et al., 2009
BMD (mg/kg-day)	1.2	0.54	0.92	1.27	1.2
BMDL (mg/kg-day)	0.87	0.077	0.27	0.72	0.87
TDI (ug/kg-day)*	9.0	0.8	2.7	7.0	9.0
Dataset POD	Cho 2008, male only	Cho 2008, male only	Cho 2008, male only	Cho 2008 + Sunhara 1993	Cho 2008, male only
BMD Model	LogLogistic (Restricted)	Gamma (Unrestricted)	LogProbit (Unrestricted)	Average of 7 models	LogLogistic (Restricted)
BMD/BMDL ratio	1.4	7.1	3.3	NA	1.4

NA = Not applicable; POD = point of departure

* note unit change; each BMDL has been divided by a 100-fold uncertainty factor to reflect experimental animal to human extrapolation and within human variability (10-fold each)

Summary

- The benchmark dose (BMD) is a simple extension of what is currently done, offering some advantages over NOAEL-LOAEL brackets. BMD cannot be used with all data.

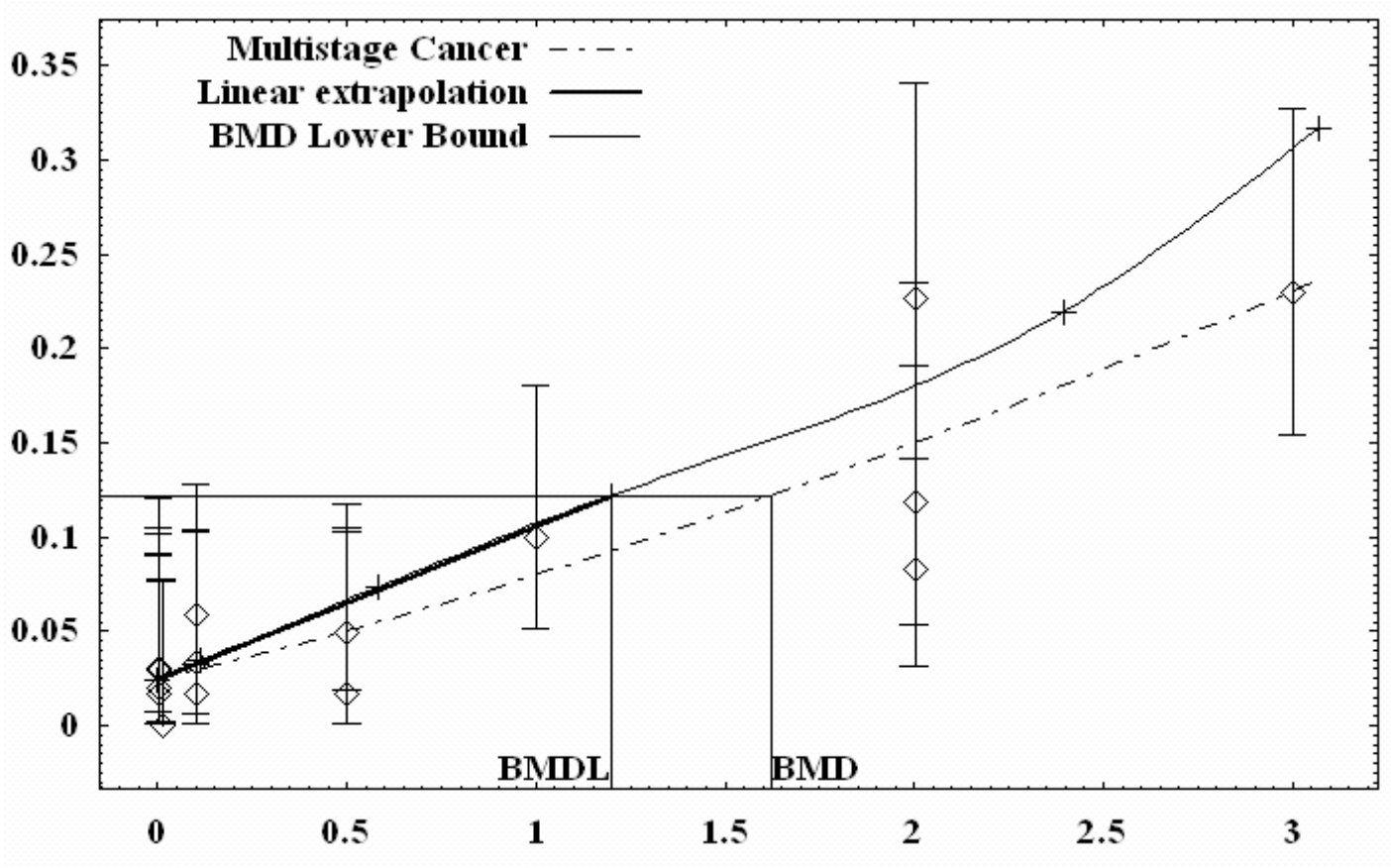
- BMD approach emphasizes biology first, mathematics second.

- Five investigating teams have analyzed the data for MCPD and agreed on the critical effect and BMR.

- An eleven-fold difference in the resulting TDIs is generally driven by choice of BMD model with unrestricted models generally yielding lower values.

Extra Slides

Multistage model fitted to pooled-all thyroid tumor data, showing little change in slope between the low and high dose regions.



Dourson et al., 2008

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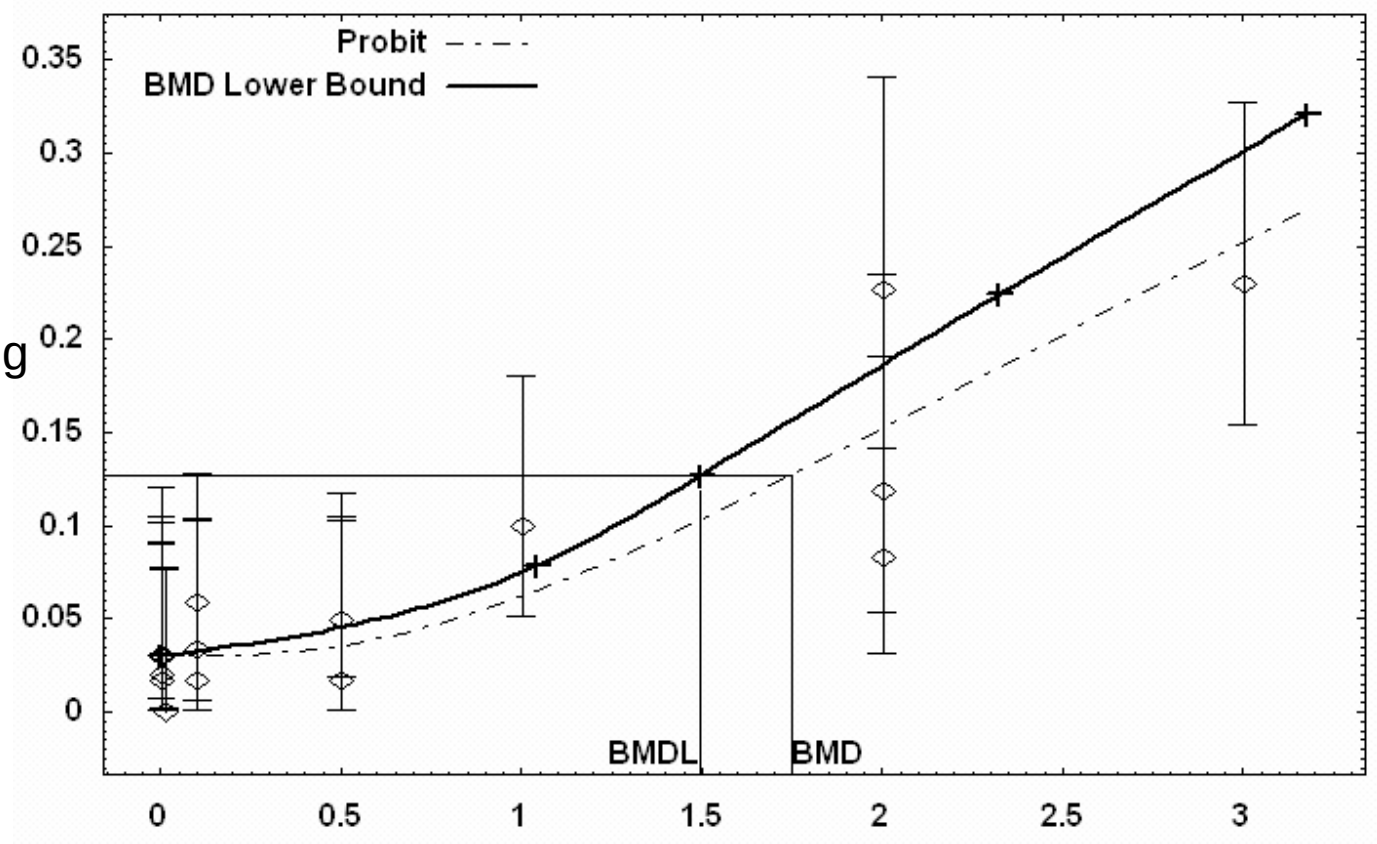
Probit model fitted to pooled-all thyroid tumor data, showing differing slopes between doses



Fraction responding

Dose (mg/kg-day)

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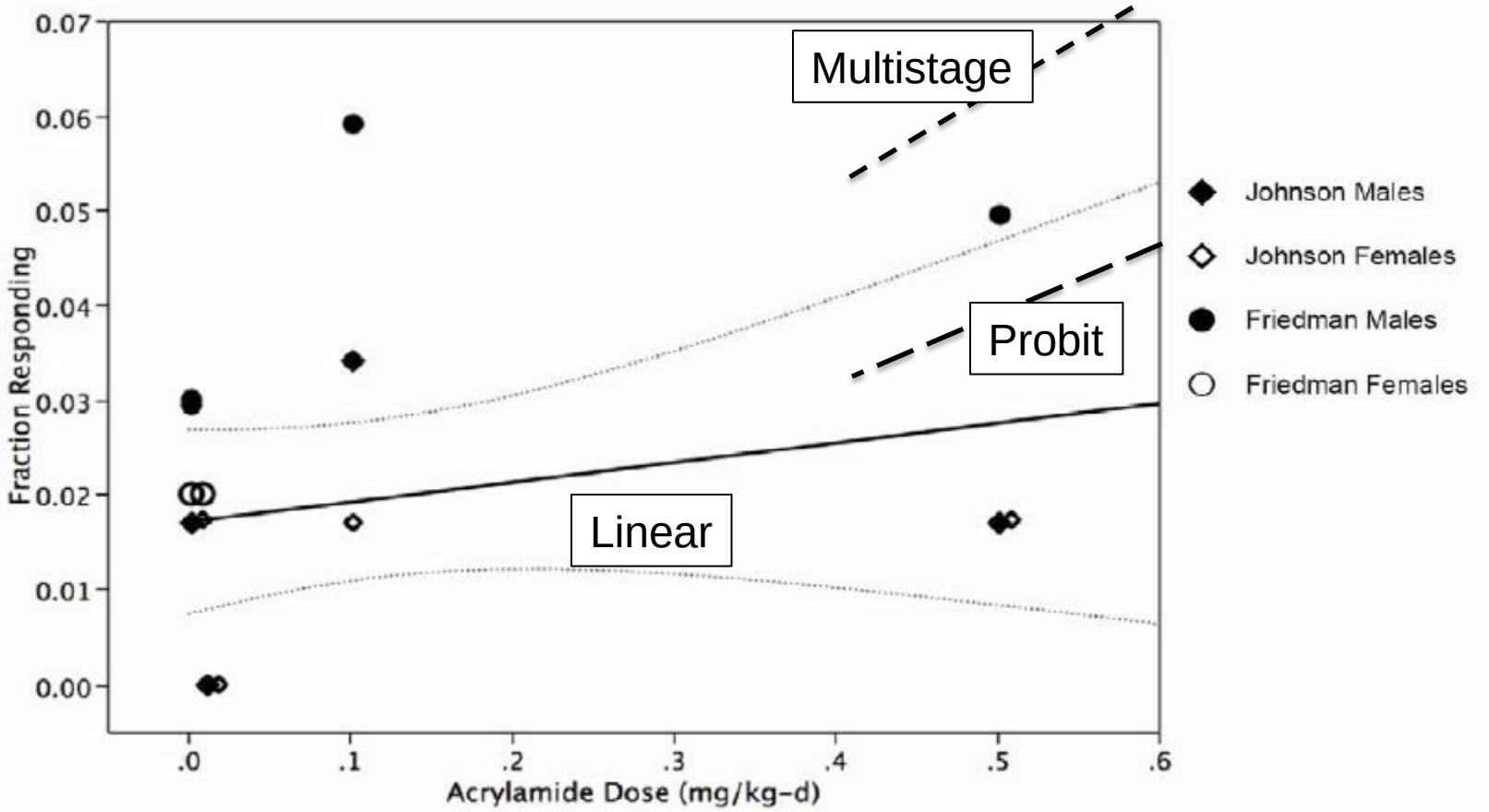
Weighted linear regression on low-dose, pooled data with 95% confidence



0 0.1 0.2 0.3 0.4 0.5

Dose (mg/kg-day)

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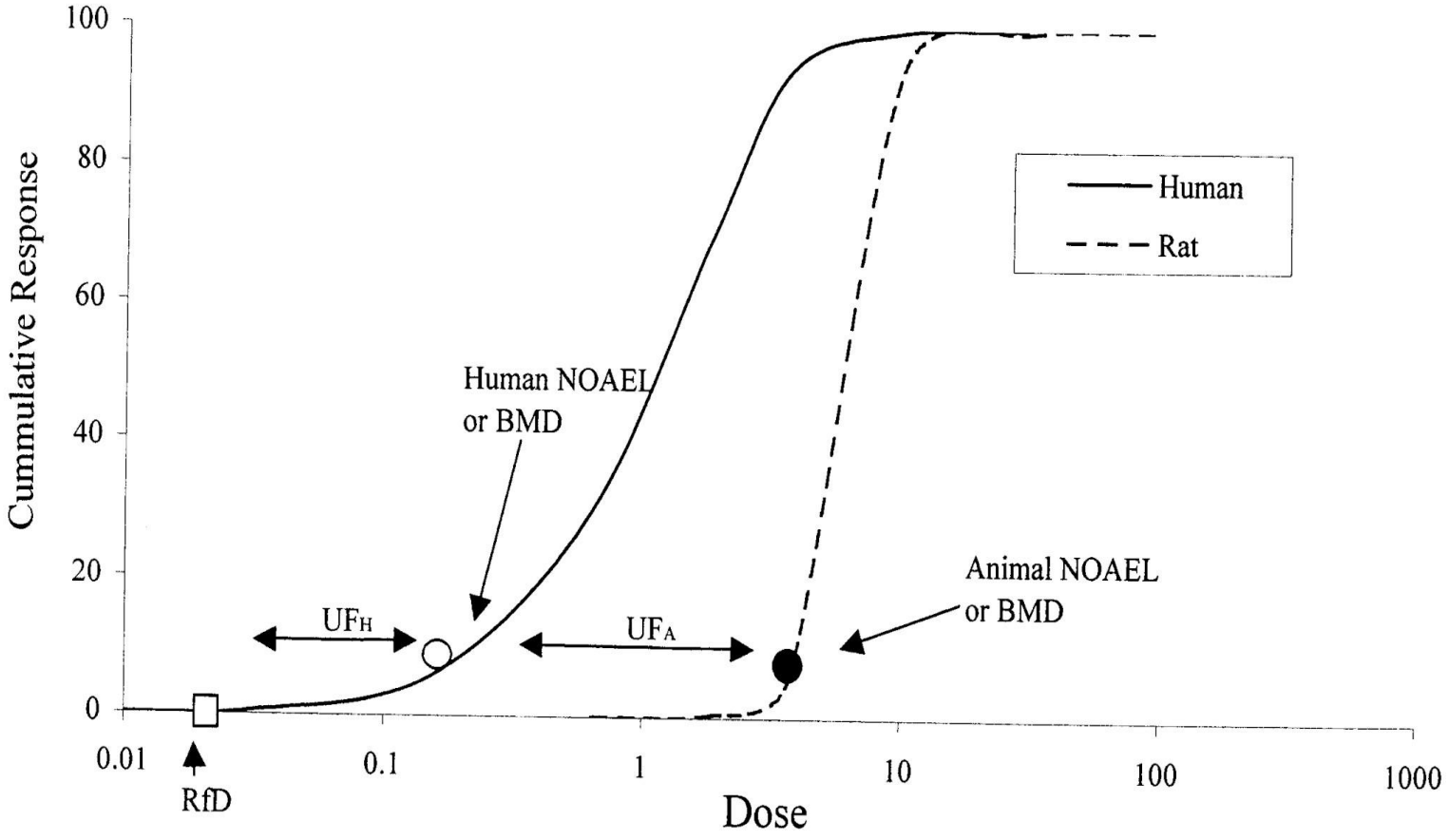
Traditional: Uncertainty Factors

- Uncertainty factors for within human variability, experimental animal to human extrapolation, LOAEL to NOAEL, subchronic to chronic, and lack of certain data.

- Misconceptions:
  - Studies with small "n" are not useful.
  - The variability of the human population is large; an uncertainty factor of 10-fold with human data is often not enough.

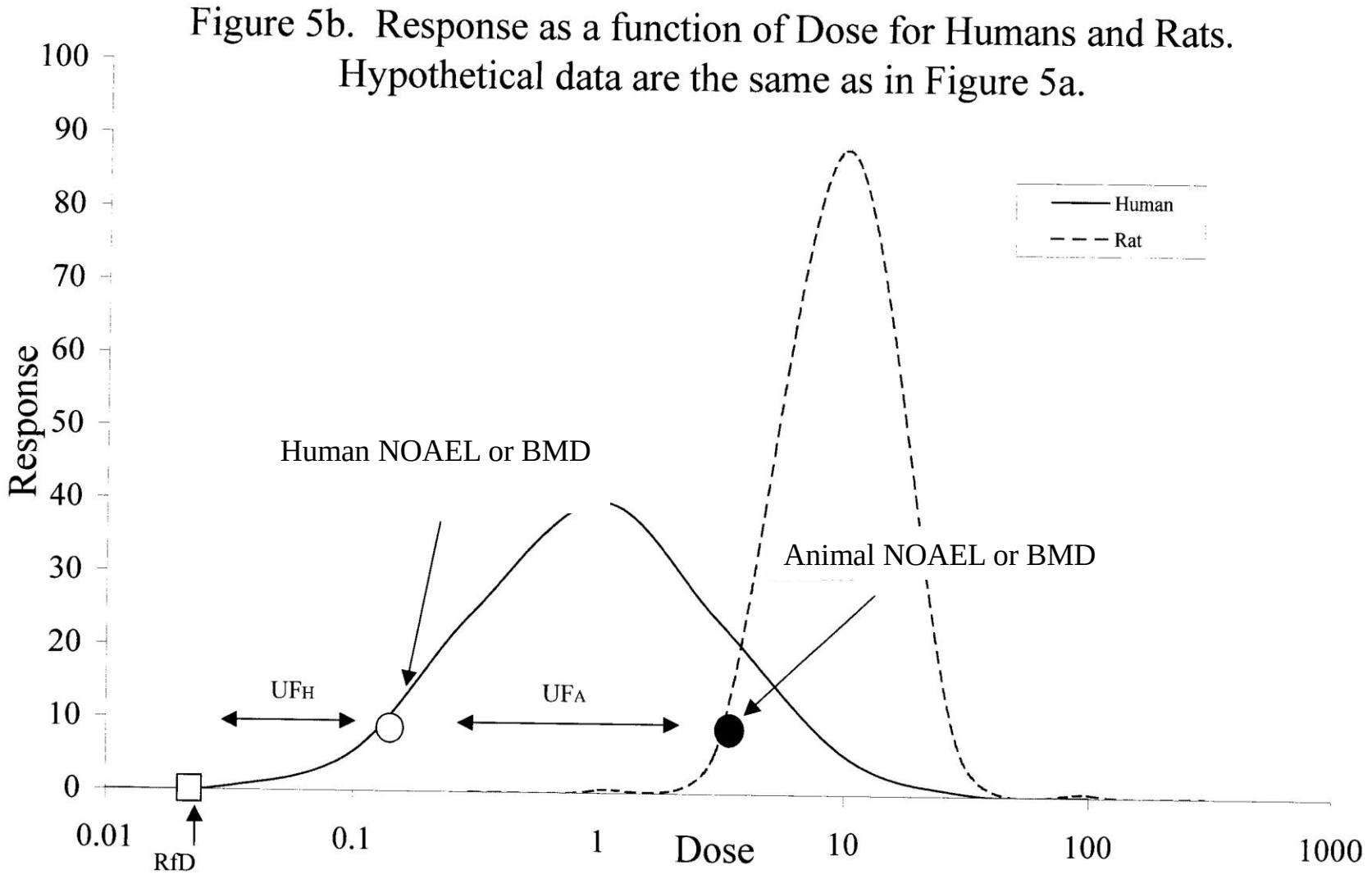
Factor of 10 Enough?

Figure 5a. Cumulative Response as a function of Dose for Humans and Rats. Data are hypothetical, but approximate real situations.



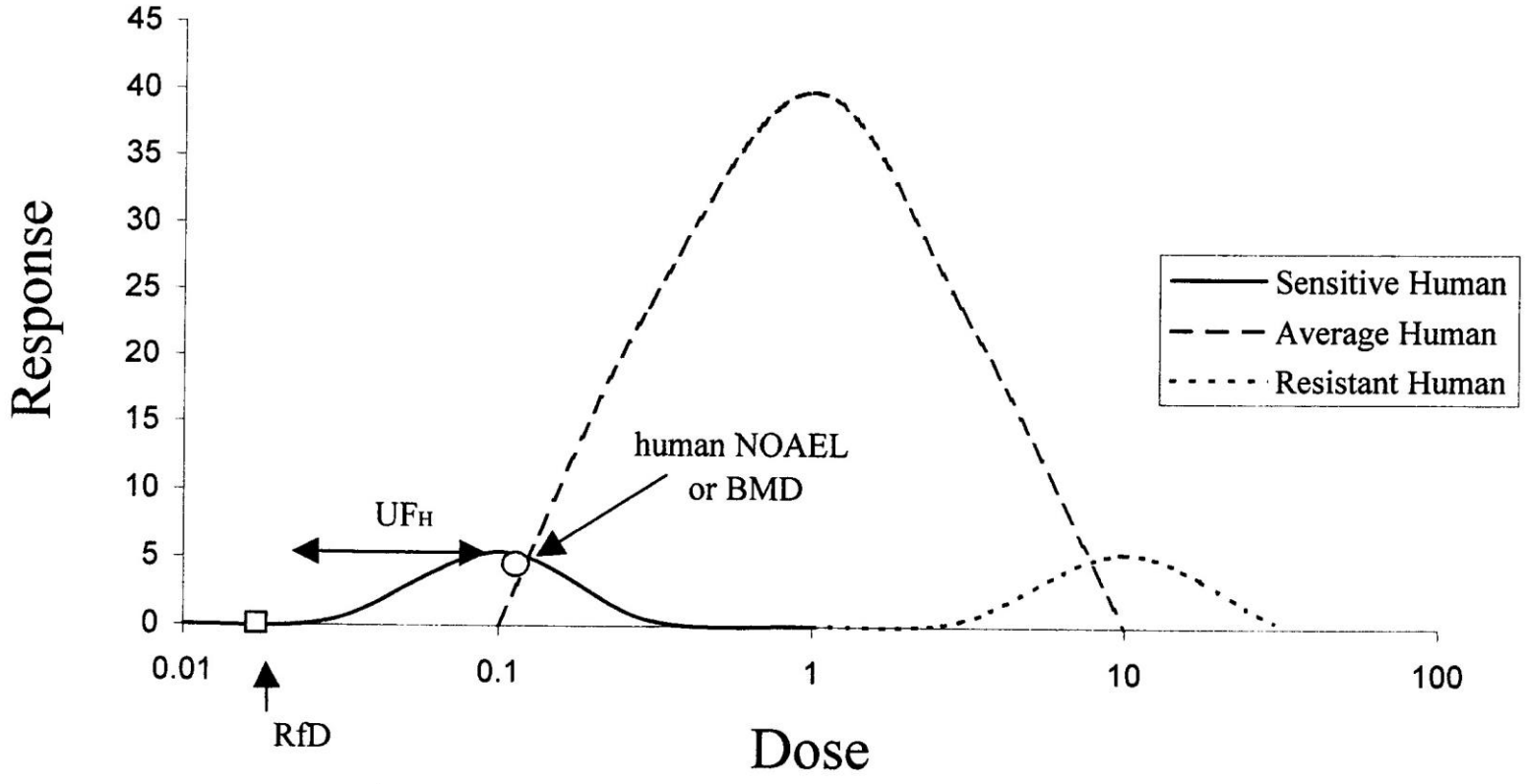
Dourson, M.L., G. Charnley and R. Scheuplein, 2002

Factor of 10 Enough?

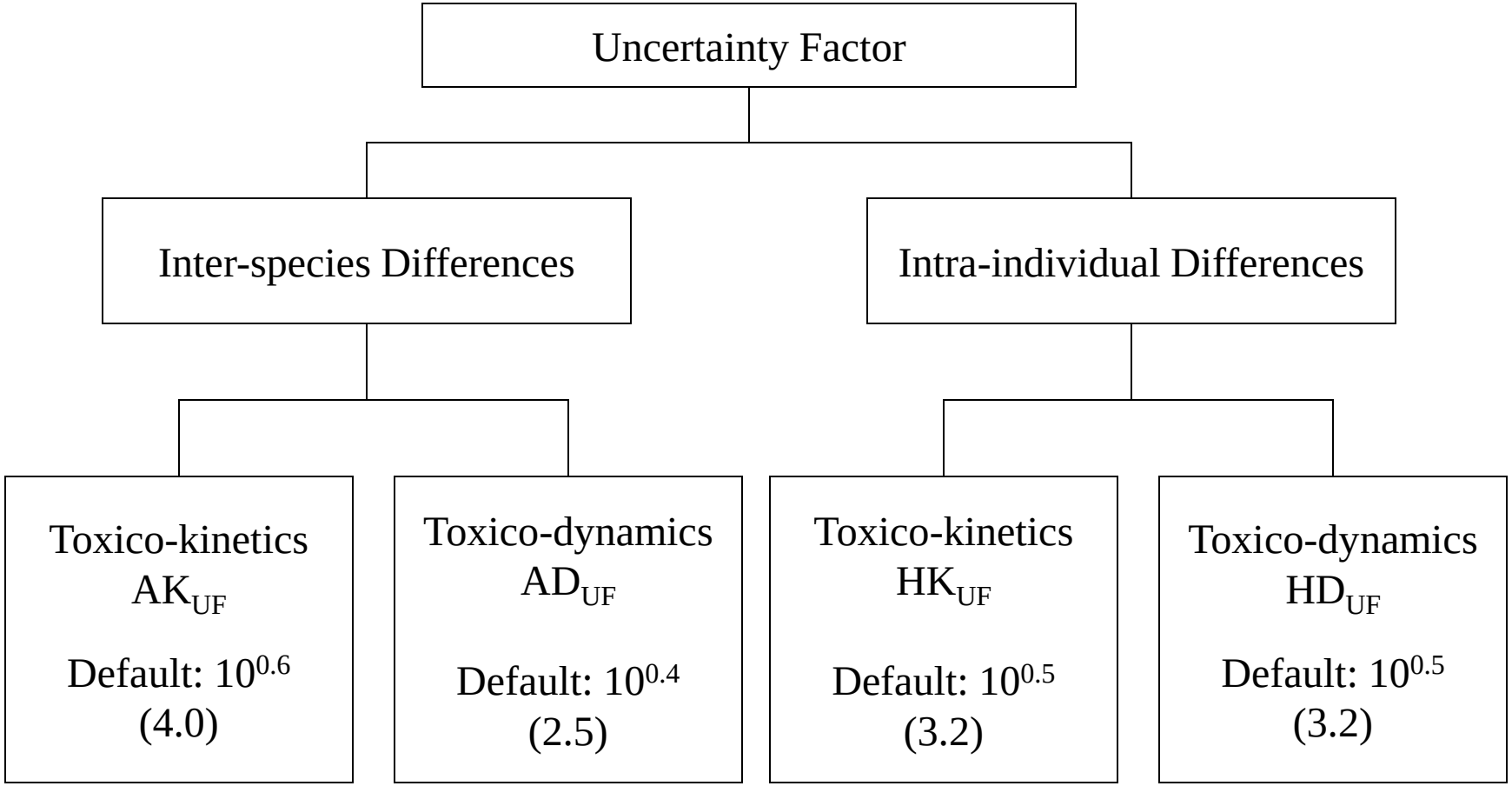


Factor of 10 Enough?

Figure 6a. Response as a function of dose for humans of different sensitivities. Hypothetical data for humans are the same as in Figure 5b.

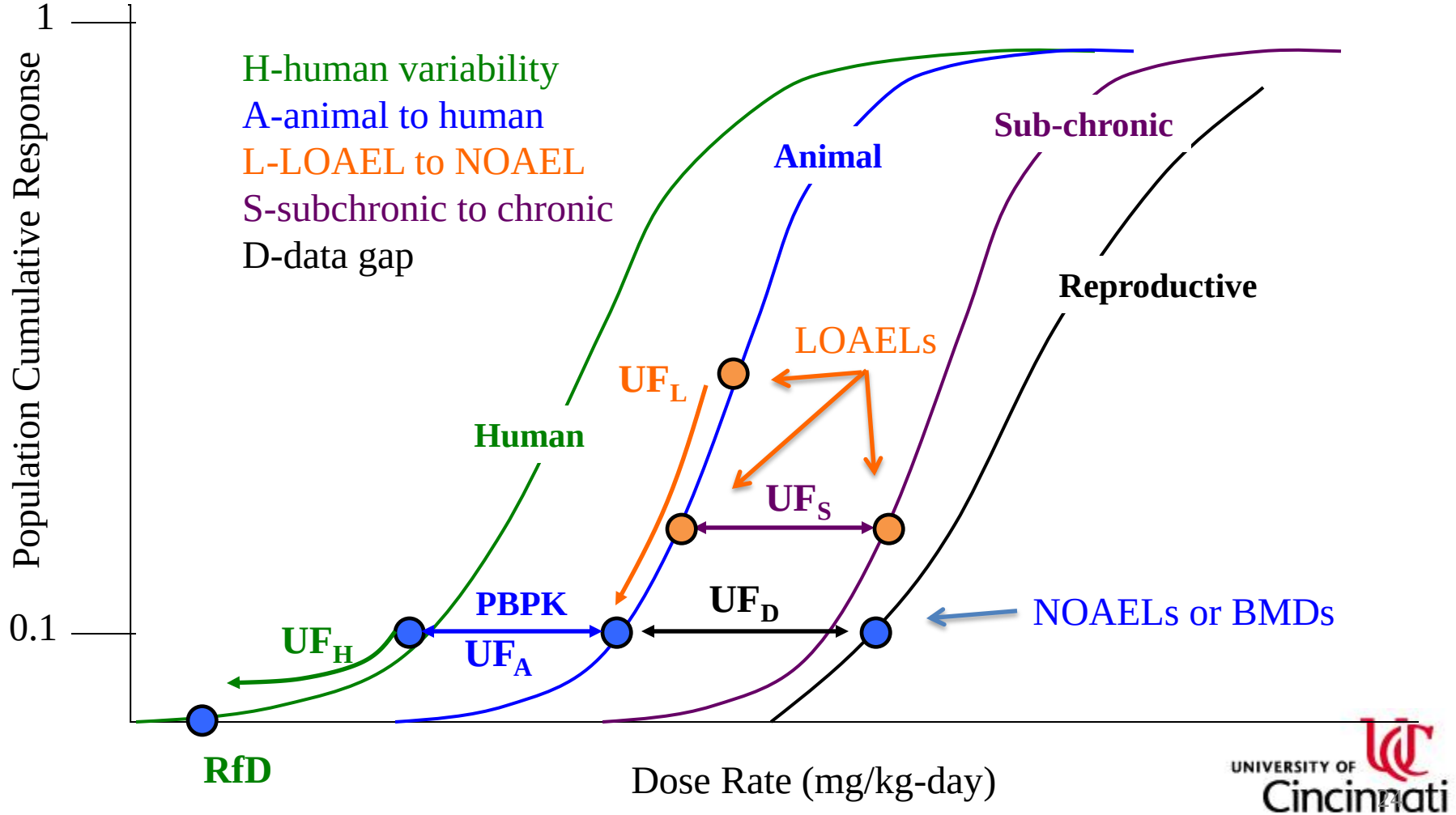


Contemporary: Chemical Specific Adjustment Factor (CSAF)



Renwick, 1991 & 1993; Health Canada, 1994; IPCS, 2005; USEPA, 2014

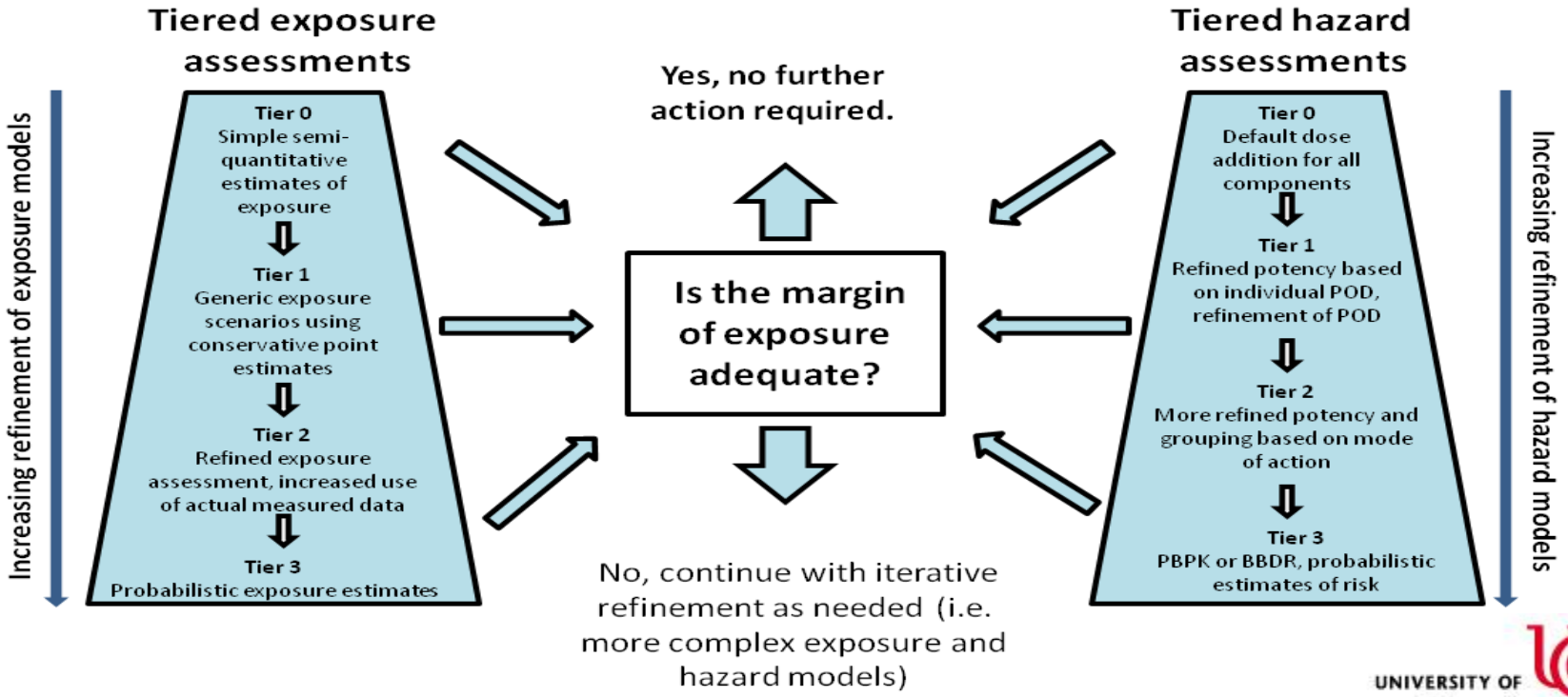
Uncertainties to Consider in Noncancer Dose Response Assessment



Problem Formulation for Combined Exposure Assessment

- *What is the nature of the exposure?*
- *Is exposure likely, taking into account the context?*
- *Is there a likelihood of co-exposure within a relevant timeframe?*
- *What is the rationale for considering compounds in an assessment group?*

Example Tiered Exposure and Hazard Considerations:
Mixture or Component Based



Meek et al., 2011

3-MCPD & GE

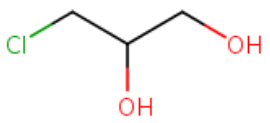
GMA Activities



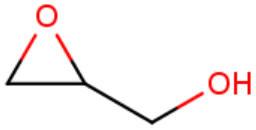
Introduction

Chemistry

- **3-MCPD** - chloride source (salt, chlorinated water, HCl, etc.) + glycerol or acylglycerides (lipid source) under acidic, high temperature conditions (> 200° C)
- **Glycidol** - intramolecular elimination of a fatty acid from diacylglycerides, and to a lesser extent from monoacylglycerides at high temperatures



3-MCPD



Glycidol

Recent milestones

- **2002**: JECFA and SCF determine a TDI for 3-MCPD of 2 mcg/kg
- **May 2016**: EFSA opinion revises TDI for 3-MCPD to 0.8 mcg/kg
- **June 2016**: EU Commission discusses draft limits for 3-MCPD and GE in oils and infant formula
- **November 2016**: JECFA risk assessment of 3-MCPD and GE
- **Q1, 2017**: Publication of JECFA risk assessment
- **Q3, 2017**: Estimated effective date of EU limits

Proposed EU limits

Food commodity	Sum of 3-MCPD and esters (mg/kg)	Sum of glycidol and esters (mg/kg)
Vegetable oils for human consumption or use as an ingredient in food	2.0	1.0
Infant formula and follow-on formula (powder)	0.125	0.075
Infant formula and follow-on formula (liquid)	0.015	0.010

- Oil suppliers would need to established more stringent specifications for oils used in infant formula
  - 3-MCPD: **0.3 mg/kg***
  - GE: **0.2 mg/kg***

*Based on assumption of formula (as-fed) with 5% oil

GMA Initiative: TERA TDI Assessment

- **Objective:** Conduct a scientific evaluation of the derivation of the Tolerable Daily Intake (TDI) for 3-MCPD using the benchmark dose (BMD) approach using best scientific practices

- **Expertise:** Scientists from Toxicology Excellence for Risk Assessment (TERA) at the University of Cincinnati

- **Output:** Information to be shared with relevant trade associations, and risk assessment agencies (e.g. JECFA, US FDA)

Engagement with International Trade Associations (TA)

- GMA has shared TERA report with Institute of Shortening and Edible Oils, FEDIOL, Food Drink Europe, Food & Consumer Products Canada, Infant Nutrition Council of America

Outcome of TA Outreach:

- TAs provided the TERA report to the EU Commission in advance of the Sept 2016 meeting
- The Commission informed the trades that they would send the TERA report to EFSA
- The Commission also informed the trades that they would delay finalizing limits for MCPD until after the JECFA risk assessment is complete

GMA Next step: Publication

- GMA recognizes the importance of publishing scientific studies to serve as reference for risk assessment
- TERA is wiling to has recommended publication of a paper describing the utility of the BMD approach in food risk assessment
  - The publication would also include examples of where the BMD could be applied to existing datasets, to provide examples of how this approach would be implemented
- GMA is currently working with other trade associations, including ISEO and INCA, to create a coalition to financially support the commissioning of this publication