Benchmark Dose Modeling – Introduction

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Disclaimer

The views expressed in this presentation are those of the author(s) and do not necessarily reflect the views or policies of the US EPA.

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Learning Objectives of the CLU-IN Courses

- **Provide participants with training on:**
  - General BMD methods and their application to ***dose-response assessment***
  - U.S. EPA risk assessment and BMD guidance
  - The use of U.S EPA's Benchmark Dose Software (BMDS)

- **This course is not intended to be a primer on basic concepts of toxicology, nor a detailed examination of the statistical underpinnings of dose-response models**

U.S. EPA Benchmark Dose Technical Guidance

- ***Final*** **draft of the EPA's Benchmark Dose Technical Guidance document was published in 2012: http://www.epa.gov/raf/publications/benchmarkdose.htm**

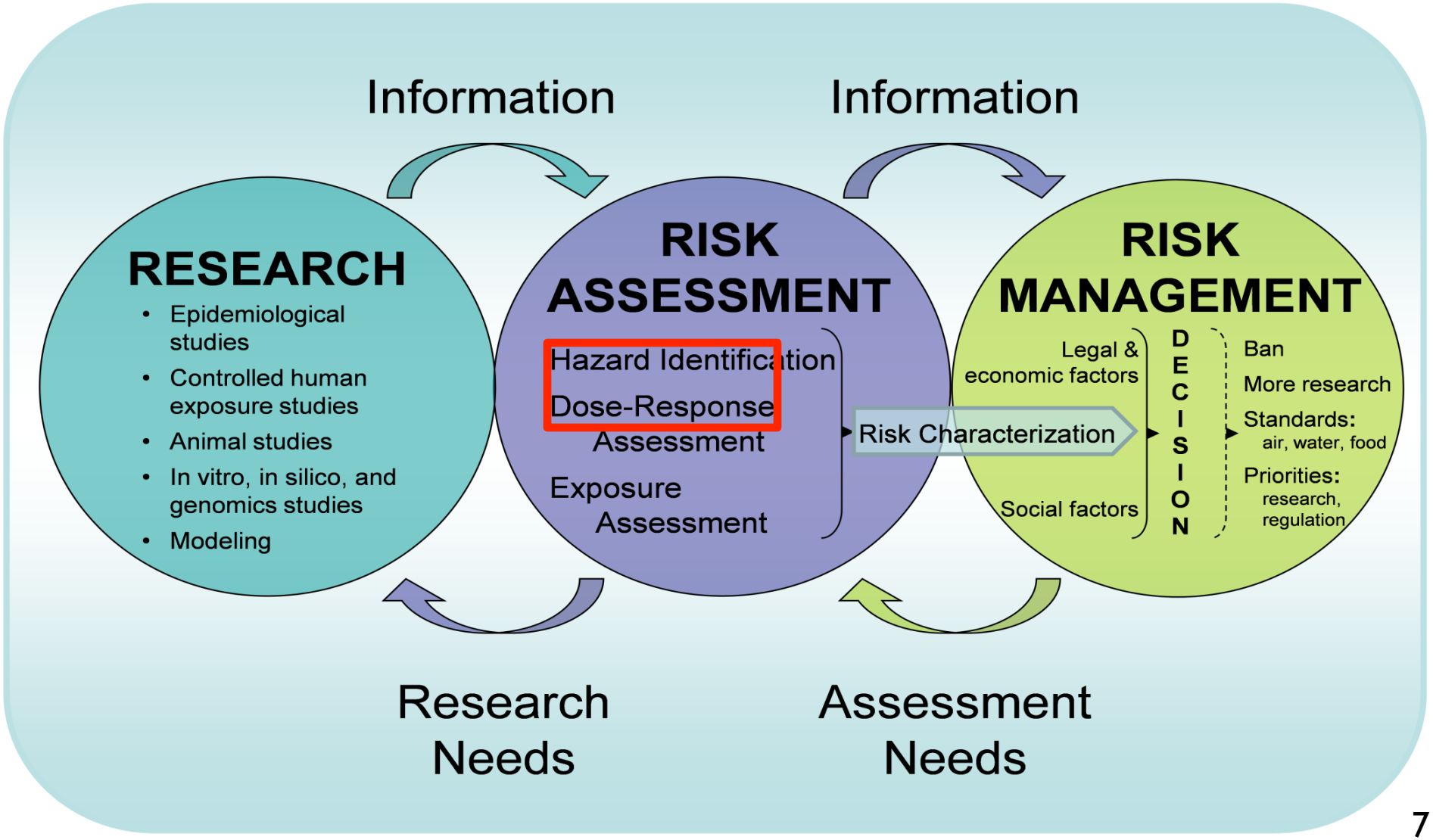
- **This training workshop is based upon the 2012 BMD TG and will cover methodologies contained therein**

- **Other guidance documents relevant to BMD modeling available at: http://epa.gov/iris/backgrd.html**

Other sources of BMD Guidance

- Filipsson et al. (2003). The benchmark dose method – a review of available models, and recommendations for application in health risk assessments. Crit Rev Toxicol 33:505-542
- Filipsson and Victorin (2003). Comparison of available benchmark dose softwares and models using trichloroethylene as a model substance. Regul Toxicol Pharmacol 37:343-355
- Gaylor et al. (1998). Procedures for calculating benchmark doses for health risk assessment. Regul Toxicol Pharmacol 28:150-164
- Parham and Portier (2005). Chapter 14: Benchmark dose approach. In: Edler, L; Kitsos, CP; eds. Recent advances in quantitative methods in cancer and human health risk assessment. Chichester, UK: John Wiley & Sons, Ltd; pp. 239-254
- Sand et al. (2002). Evaluation of the benchmark dose method for dichotomous data: model dependence and model selection. Regul Toxicol Pharmacol 36:184-197
- Sand (2005) Dose-response modeling: Evaluation, application, and development of procedures for benchmark dose analysis in health risk assessment of chemical substances [Thesis]. Karolinska Institute, Stockholm, Sweden. Available online at: http://publications.ki.se/jspui/bitstream/10616/39163/1/thesis.pdf
- Sand et al. (2008). The current state of knowledge in the use of the benchmark dose concept in risk assessment. J Appl Toxicol 28:405-421
- Davis et al. (2010). Introduction to benchmark dose methods and U.S. EPA's benchmark dose software (BMDS) version 2.1.1. Toxicol Appl Pharmacol. 254(2): 181-91
- Slob (2002). Dose-response modeling of continuous endpoints. Toxicol Sci. 66(2): 298-312.

Risk Assessment/ Management

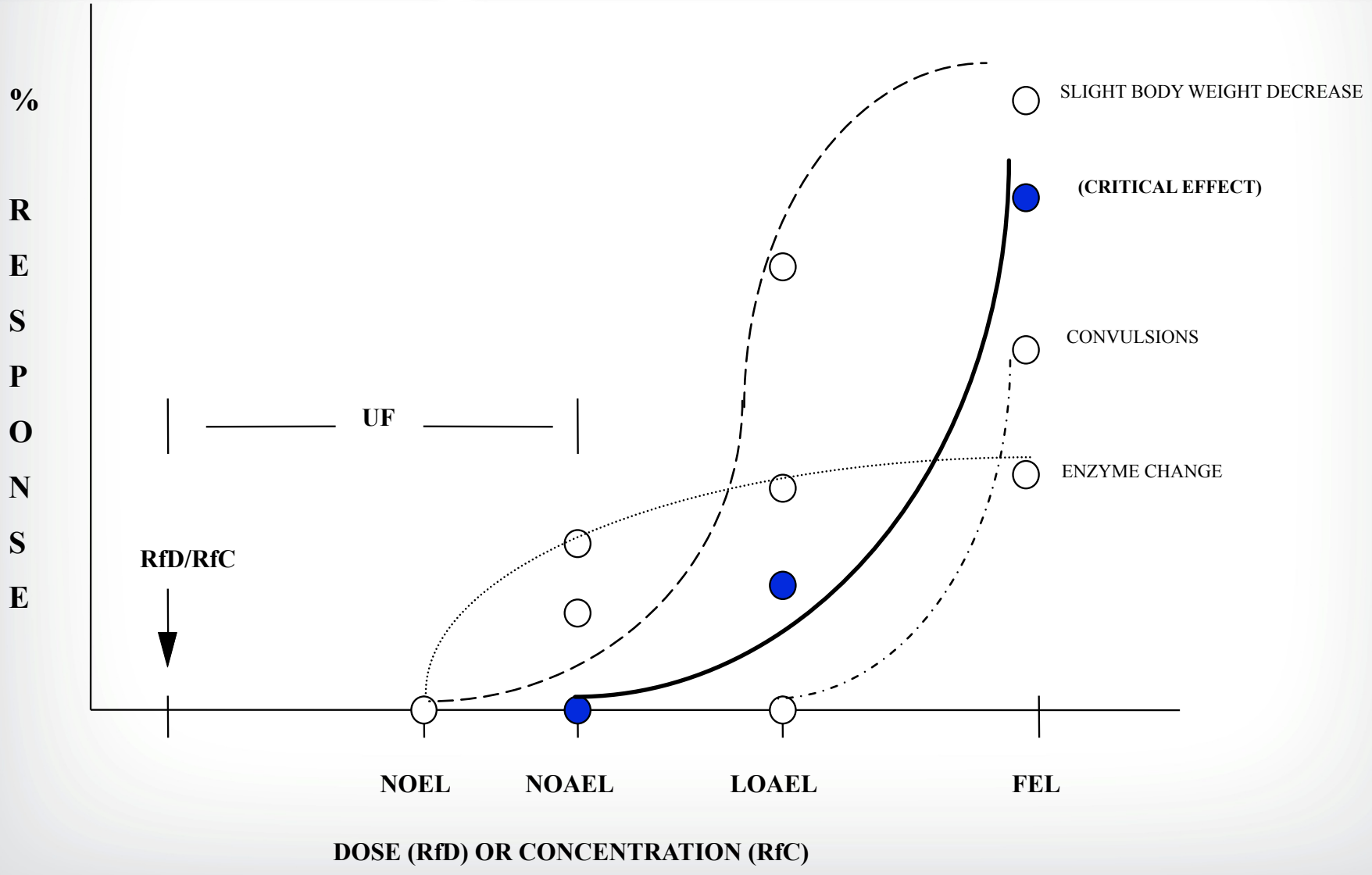


Review of Key Terminology

- **Adverse effect – biochemical change, functional impairment, or pathologic lesion that affects health of whole organism**
- **Dose-response relationship – relationship between a quantified exposure and some measure of a biologically significant effect, such as changes in incidence for dichotomous endpoints, or changes in mean levels of response for continuous endpoints**
- **Point of departure – point on dose-response curve that marks the beginning of low-dose extrapolation**
- **Reference value – estimate of exposure for a given duration to the human population that is likely to be without appreciable risk of adverse health effects over a lifetime.**
  - **Reference concentration** – inhalation exposures
  - **Reference dose** – oral exposures
  - Derived from a point of departure, with uncertainty/variability factors applied to reflect limitations of the data used.

Sources: Adapted from Online IRIS Glossary, http://www.epa.gov/iris/help_gloss.htm

Characterizing Non-cancer Hazards in Risk Assessments



Traditional Non-cancer Risk Assessment – NOAEL Approach

- **Identify Point of Departure (POD) for the critical effect based on external dose, either a:**
  - No-observed-adverse-effect-level (NOAEL)
  - Lowest-observed-adverse-effect-level (LOAEL)
- **Convert animal external doses or concentrations to human equivalent dose (HED) or concentration (HEC) using:**
  - Default dosimetric methods
  - Physiologically-based pharmacokinetic (PBPK) models
- **Apply uncertainty factors (UFs) to derive reference dose (RfD) or reference concentration (RfC).**

Calculation of the RfC/RfD

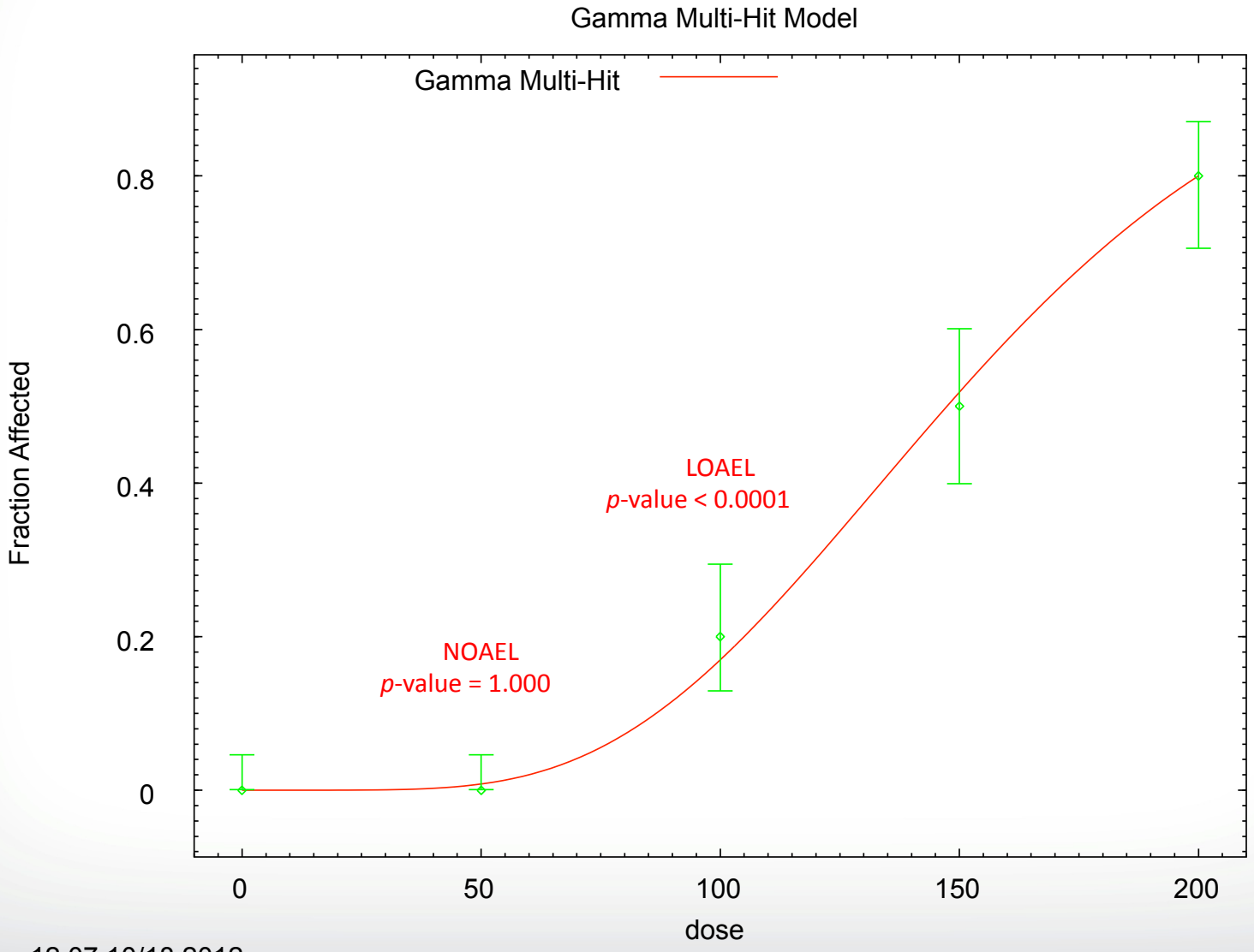
- **RfC or RfD = POD (NOAEL or LOAEL) ÷ UF**

- **Uncertainty Factors used in the IRIS Program**
  - Interspecies extrapolation – characterizes toxicokinetic and toxicodynamic differences between species
  - Intraspecies variability – accounts for potentially susceptible subpopulations
  - LOAEL to NOAEL extrapolation
  - Duration extrapolation – for extrapolating from subchronic to chronic durations
  - Database uncertainty – accounts for deficiencies in the database, i.e., missing types of data
  - Can be factors of 10, 3 ($\sqrt{10}$ = 3.16, rounded to 3), or 1

Limitations of Using a NOAEL

Subject	NOAEL/LOAEL Approach
Dose selection	NOAEL/LOAEL limited to doses in study only
Sample size	The ability of a bioassay to detect a treatment response decreases as sample size decreases (i.e., ↓ N = ↑ NOAEL)
Cross-study comparison	Observed response levels at the NOAEL or LOAEL are not consistent across studies and can not be compared
Variability and uncertainty in experimental results	Characteristics that influence variability or uncertainty in results (dose selection, dose spacing, sample size) not taken into consideration
Dose-response information	Information, such as shape of the dose-response curve (i.e., how steep or shallow the response is), not taken into consideration
May be missing from study	A LOAEL cannot be used to derive a NOAEL, in this case an uncertainty factor (usually 10) is applied

Study Conducted with 100 Animals/Dose



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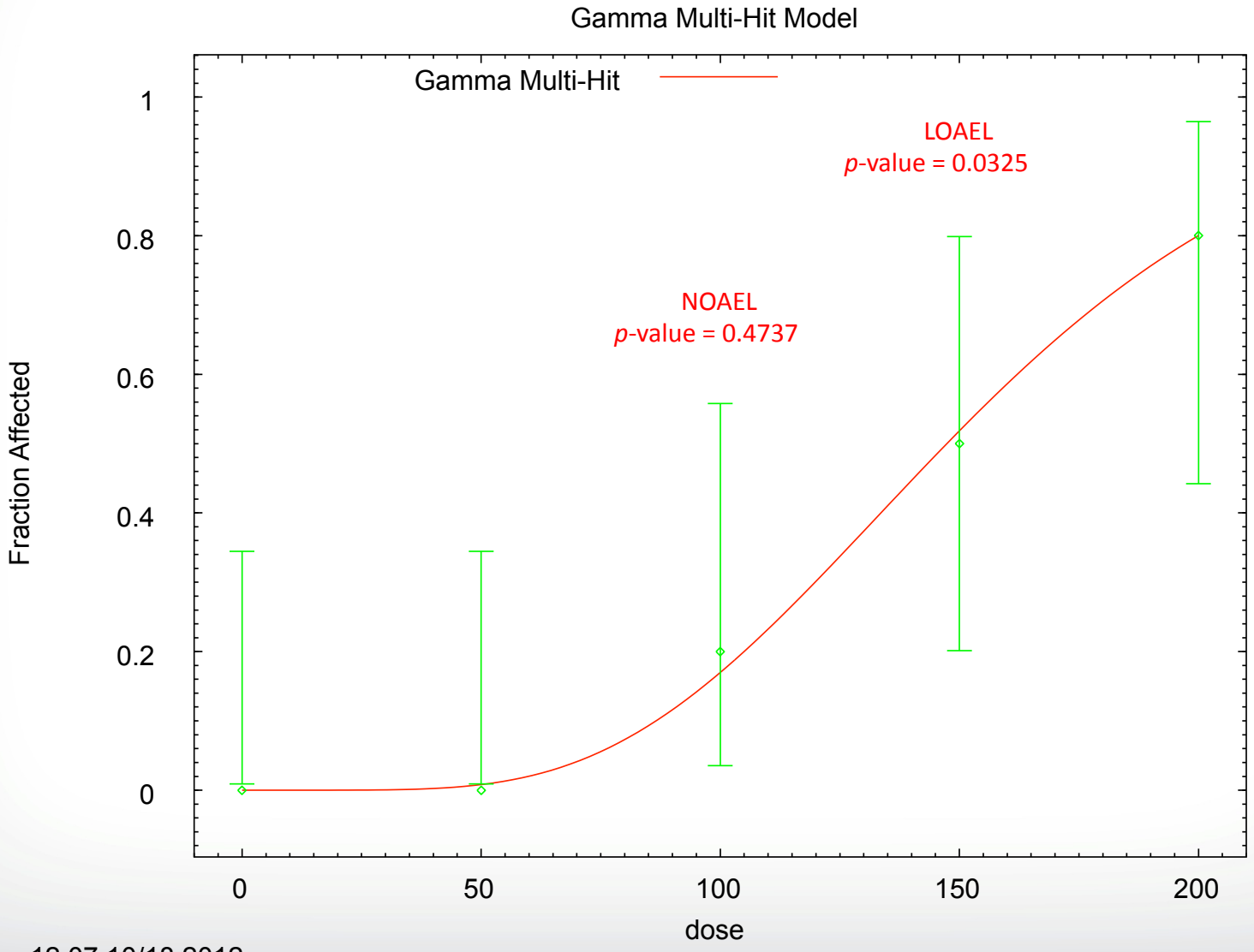
Study Conducted with 10 Animals/Dose



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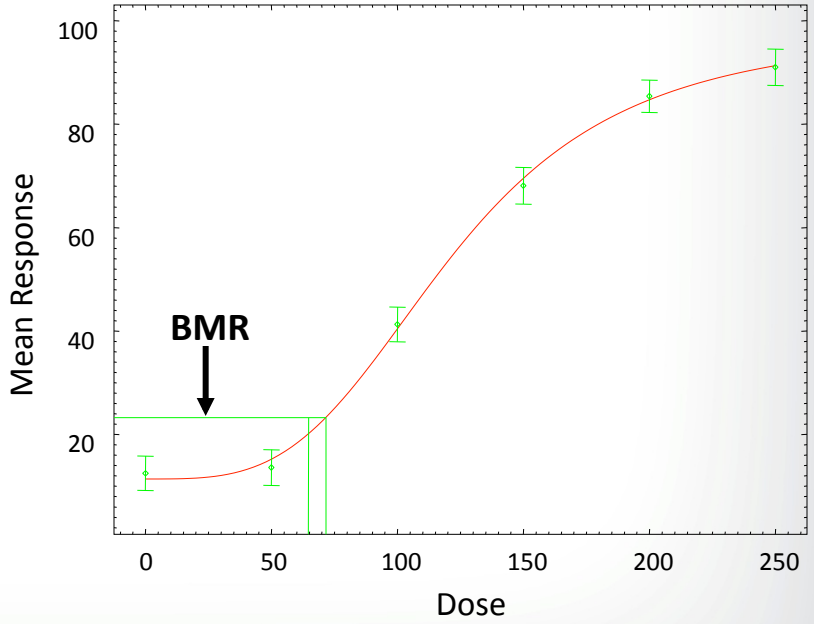
A Brief History of the BMD Method

1983	EPA workshop on epigenetic carcinogenesis
1984	"Benchmark dose" coined by Kenneth Crump: Crump, K.S. (1984) A new method for determining allowable daily intakes. Fundamental and Applied Toxicology 4:854-871.
1985–1994	Several EPA BMD-related publications and workshops
1995	EPA Risk Assessment Forum discusses use of BMD in risk assessment
1995	First IRIS BMD-based RfD (Methylmercury)
2000	EPA benchmark dose draft technical guidance released
2000	EPA benchmark dose software (BMDS) released
2000–2011	Multiple versions of BMDS released
2012	EPA benchmark dose final technical guidance released

Benchmark Dose – Key Terminology

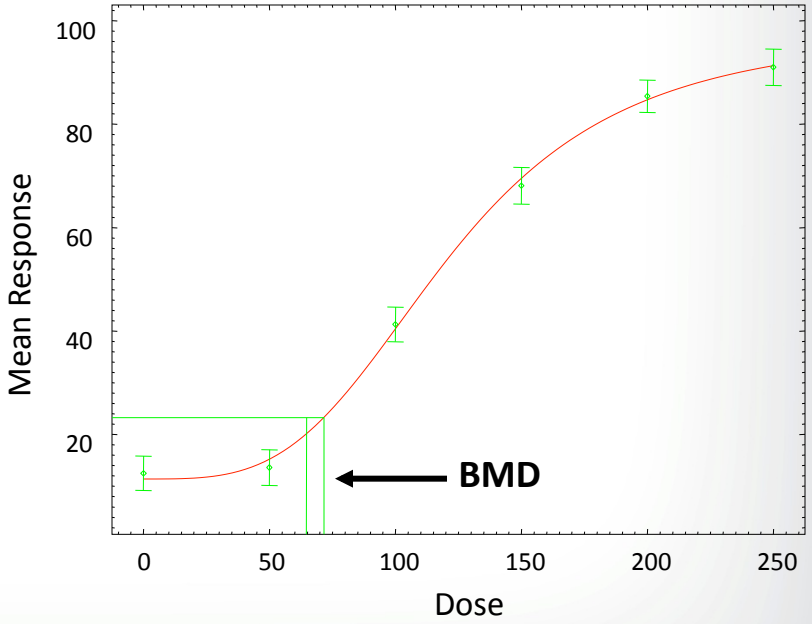
- **Benchmark Response (BMR) - a change in response for an effect relative to background response rate of this effect**
  - Basis for deriving BMDs
  - User defined

- **Examples include:**
  - 1 standard deviation increase in body weight (continuous response)
  - 10% increase in hepatocellular hyperplasia (dichotomous response)



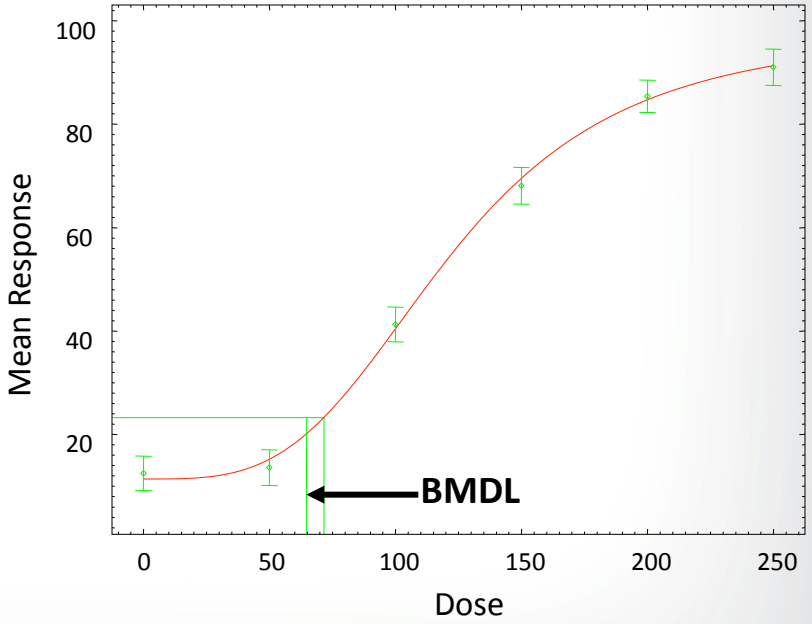
Benchmark Dose – Key Terminology

- **Benchmark dose or concentration (BMD or BMC) - the maximum likelihood estimate of the dose associated with a specified benchmark response level**
  - BMD – oral exposure
  - BMC – inhalation exposure
- **However, the term benchmark dose modeling is frequently used to the modeling process for both oral and inhalation exposures.**



Benchmark Dose – Key Terminology

- **Benchmark dose or concentration lower-confidence limit (BMDL or BMCL) – the lower limit of a one-sided confidence interval on the BMD (typically 95%)**
  - BMDL – oral exposure
  - BMCL – inhalation exposure
- **Accounts for elements of experimental uncertainty, including:**
  - Sample size
  - High background response
  - Response variability
- **Preferred POD**



Calculation of the RfC/RfD Using a BMDL

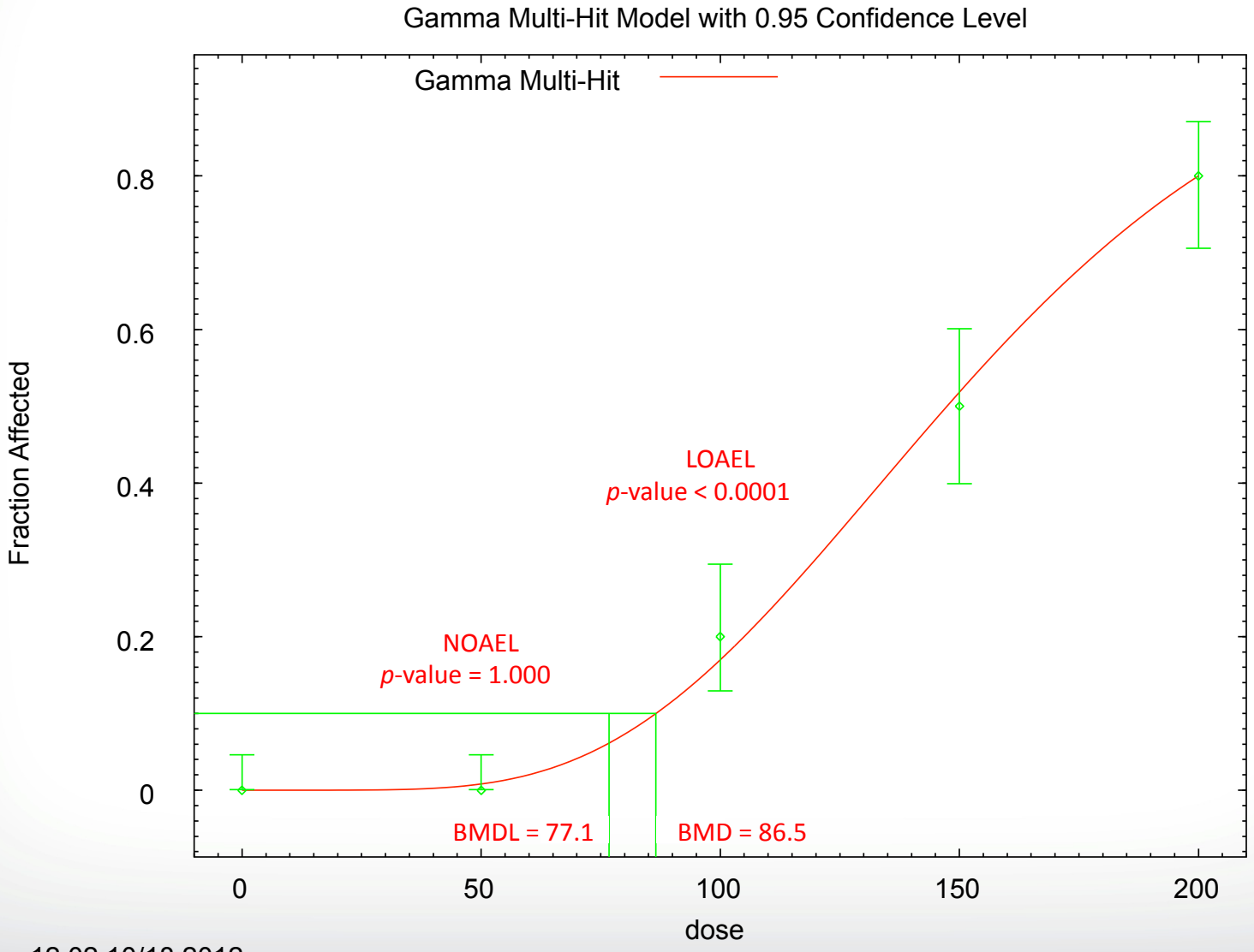
- **Equation for an RfD or RfC becomes: BMDL ÷ UF**

- **Uncertainty Factors used in IRIS**
  - Interspecies extrapolation – characterizes toxicokinetic and toxicodynamic differences between species
  - Intraspecies variability – accounts for potentially susceptible subpopulations
  - ~~LOAEL to NOAEL extrapolation~~
  - Duration extrapolation – for extrapolating from subchronic to chronic durations
  - Database uncertainty – accounts for deficiencies in the database, i.e., missing types of data
  - Can be factors of 10, 3 ($\sqrt{10}$ = 3.16, rounded to 3), or 1

Advantages of BMD Approach

Subject	BMD Approach
Dose selection	BMD and BMDL not constrained to be a dose used in study
Sample size	Appropriately considers sample size: as sample size decreases, uncertainty in true response rate increases (i.e., ↓ N = ↓ BMDL)
Cross-study comparison	Observed response levels at a selected BMR are comparable across studies (recommended to use BMD as point of comparison)
Variability and uncertainty in experimental results	Characteristics that influence variability or uncertainty in results (dose selection, dose spacing, sample size) are taken into consideration
Dose-response information	Full shape of the dose-response curve is considered
NOAEL not identified in study	A BMD and BMDL can be calculated even when a NOAEL is missing from the study

Study Conducted with 100 Animals/Dose



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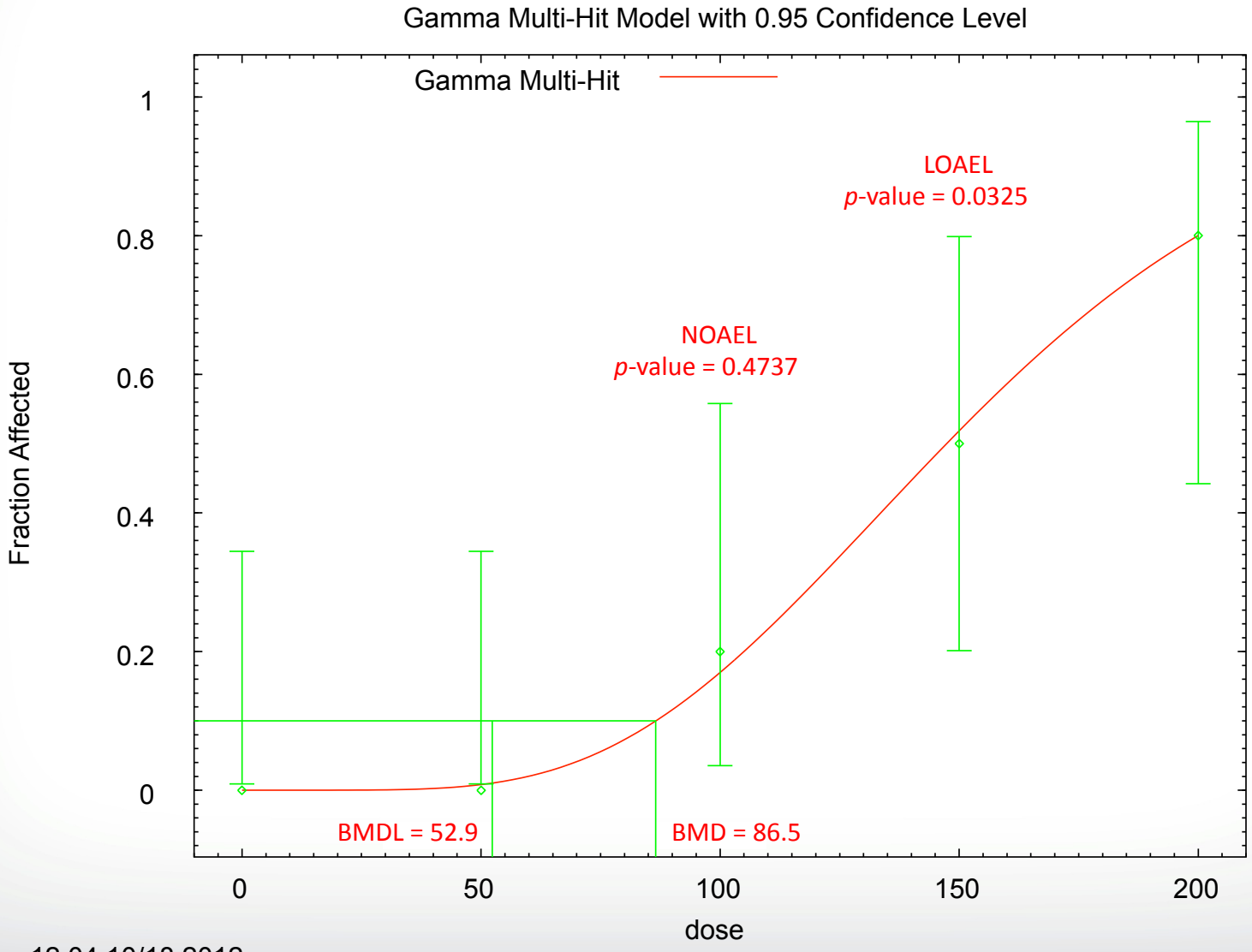
Study Conducted with 10 Animals/Dose



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Challenges in the Use of the BMD Method

- **Requires knowledge on how to use software and interpret results**
- **In some cases, more data are required to model benchmark dose than to derive a LOAEL/NOAEL**
  - Continuous data require a measure of variability (SD or SE) for each dose group's mean response
  - Individual animal-level data are required for some models
  - Results highly dependent on the quality of the data
- **Sometimes the data cannot be adequately fit by the available models in BMDS**

Are the Data Worth Modeling? (Study/Endpoint Criteria)

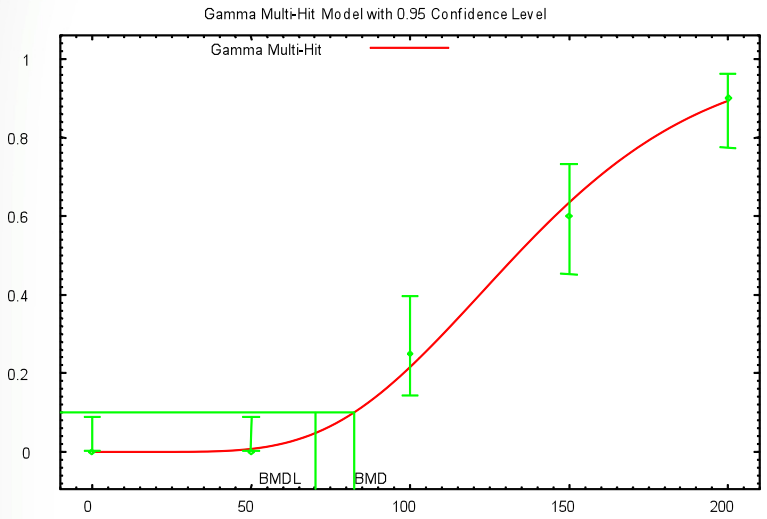
- **Evaluate database as for NOAEL/LOAEL approach**
  - Select high quality studies
  - Select studies using appropriate durations and routes of exposure
  - Select endpoints of concern that are relevant to human health
  - Do PBPK models for the chemical of concern exist?

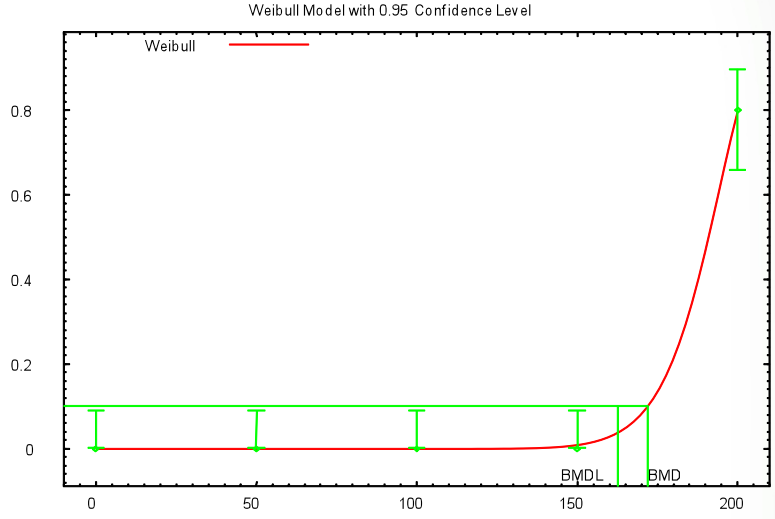
- **Model all potentially adverse endpoints, especially if different UFs may be used.**

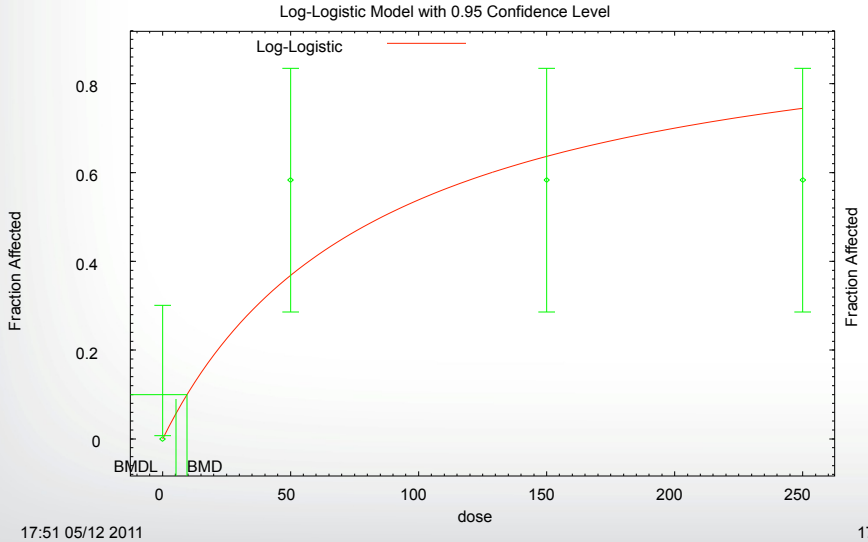
Are the Data Worth Modeling? (Data Criteria)

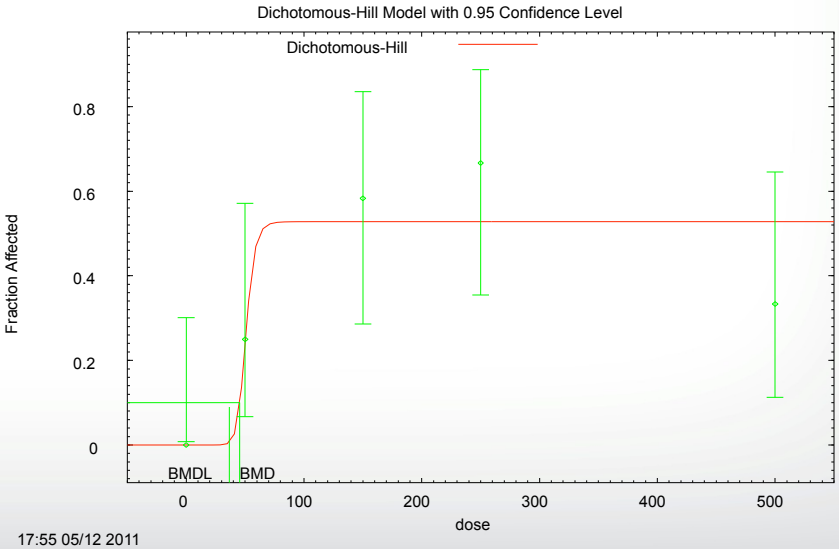
- **At least a statistically or biologically significant dose-response trend**
- **Distinct response information between extremes of control level and maximal response**
- **Response near low-end of dose-response region (ideally near BMR)**
- **Reasonable (<50%) background response rate**
- **General rule of thumb for large databases: consider excluding endpoints with LOAELs >10-fold above lowest LOAEL in the database**

Are the Data Worth Modeling? (Data Criteria)









Comparison of NOAELs and BMDLs

NOAELs and LOAELs With Corresponding BMRs and BMDLs (mg/kg-day)					
Liver Lesions	**NOAEL**	**LOAEL**	**BMR**	**BMDL**	**POD**
Gaines and Kimbrough, 1970	0.065 (M) 0.4 (F)	0.35 (M) 2.3 (F)	10%	0.026 (M)	0.026 (M)
NTP, 1990	0.07 (M) 0.08 (F)	0.7 (M) 0.7 (F)	10%	0.2 (M) 0.08 (F)	0.08 (F)
Cataract Development					
Chu et al., 1981b	None	0.5	5%	0.028	0.028
Gaines and Kimbrough, 1970	0.4	2.3	N/A	N/A	0.4 (NOAEL)
Testicular Histopathology					
Yarbrough et al., 1981	7.0	11.0	10%	2.0	2.0
Chu et al., 1981a	7.0	N/A	N/A	N/A	7.0 (NOAEL)
Decreased Litter Size					
Gaines and Kimbrough, 1970	0.4	2.3	N/A	N/A	0.4 (NOAEL)
Chu et al., 1981b	None	0.5	1 SD	0.48	0.48