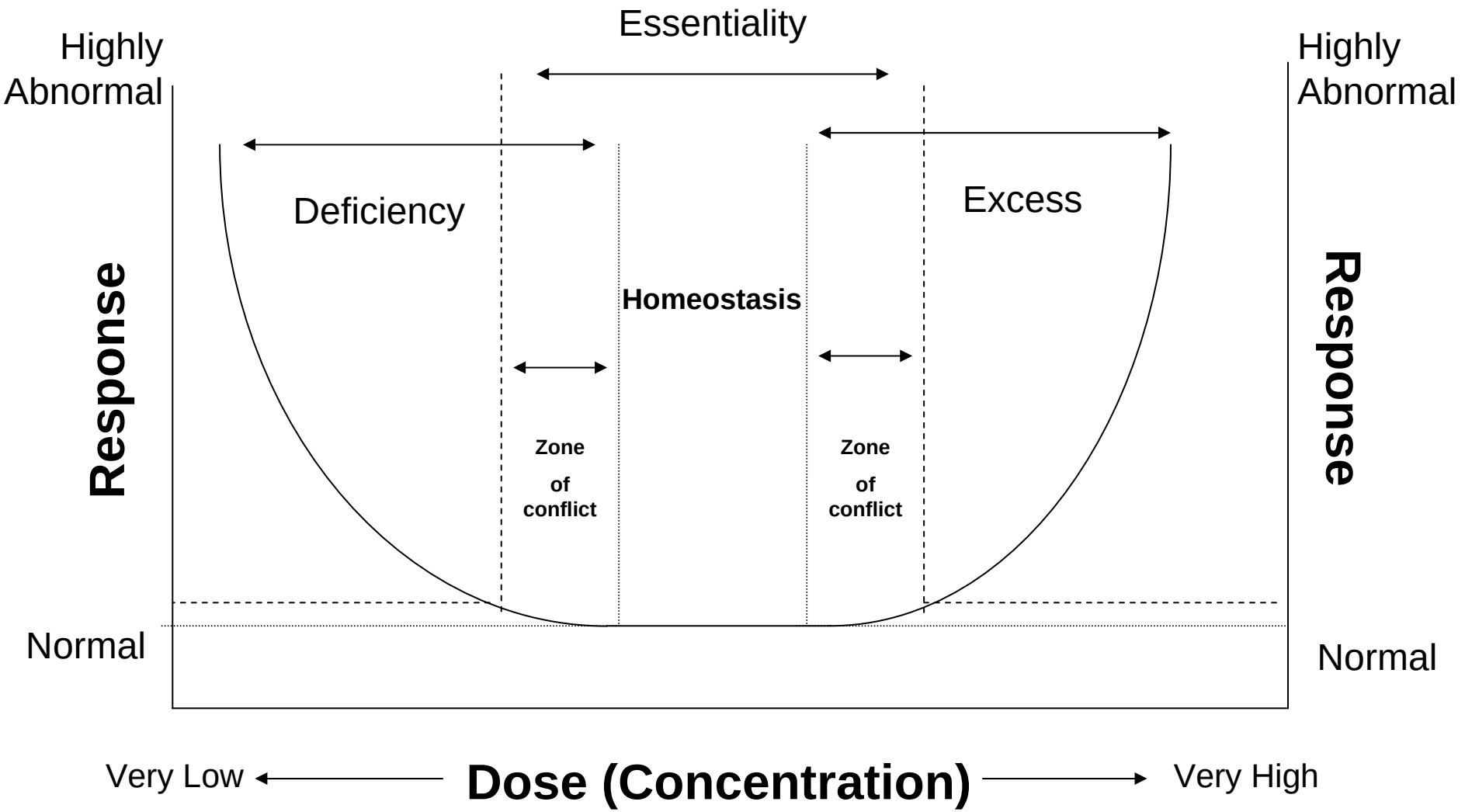
Dose-Response Relationship of Essential Metallic Elements

The Application of Categorical Regression

Example: Copper

Problem: Dose-response relationship for essential trace elements is complex



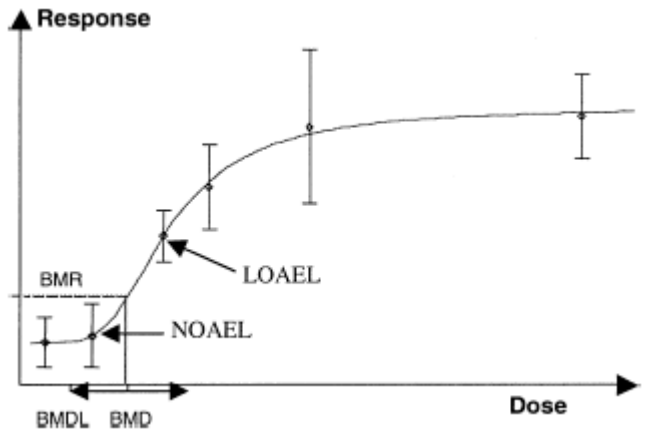
Outline

- Modeling Methods
  - NOAEL/LOAEL
  - Benchmark Modeling
- Overview of Categorical Regression
  - Background
  - Applications
  - CatReg Software
- Copper Risk Assessment
  - JTEH Review
  - Copper Database
  - Preliminary Results
  - Future Directions

Modeling Methods

- NOAEL/LOAEL
  - Simple and traditional method
  - Limited use of the available dose-response information
  - Single dose-time data point
  - Little uncertainty characterization

- Benchmark Dose
  - Entire dose-response curve is utilized instead of a single dose
  - Quantitative uncertainty characterization
  - Responses within experimental range are used
  - Empirical curve-fitting



Categorical Regression

- Can be used when mechanistic models are lacking & insufficient evidence is available to support a complex dose-response relationship
- Can be used to model multiple studies and endpoints simultaneously using a common toxicity metric
- A dose-response model may be fitted to data where only severity ratings are available

Categorical Regression & Copper

- Heterogeneity amongst available experimental studies on copper (specie, dose, endpoints, route of exposure), limits the application of traditional methods
- Traditional dose-response approaches where RfD: NOAEL/UF may bring the resulting value into the deficiency range

Advantages of Categorical Regression

- Define the relationship by increasing severity of response
- Ensures that the best available evidence is utilized and integrated into a single quantitative analysis
- Can combine data from multiple studies & utilize information on multiple species
- Curve no longer based on the most sensitive strain, specie, sex – may be more predictive of actual human risk
- Scatter demonstrated in regression provides useful information on the uncertainty in the dose-response model

CatReg Capabilities

- A computer program developed to support toxicologists & health scientists conduct exposure-response analyses
- Developed by U.S. EPA
- Executes a regression analysis of the severity scores and exposure parameters
- Three statistical models available:
  - Logistic (logit)
  - Normal (probit)
  - Gumbel (log-log)

CatReg Capabilites

- Determine whether the coefficients for concentration and time differ by severity level
- Methods for estimation and hypothesis testing of model parameters
- Range of options for sensitivity analysis
- Can produce graphical displays of data and fitted models
- Combine data sets from different experiments
  - Statistical testing for differences between combined experiments

Monograph II: Copper Risk Assessment

Journal of Toxicology and Environmental Health, Part B, 10:157–222, 2007

ISSN: 1093-7404 print / 1521-6950 online
DOI: 10.1080/10937400600755911

Taylor & Francis

COPPER AND HUMAN HEALTH: BIOCHEMISTRY, GENETICS, AND STRATEGIES FOR MODELING DOSE-RESPONSE RELATIONSHIPS

Bonnie Ransom Stern[1], Marc Solioz[2], Daniel Krewski[3], Peter Aggett[4], Tar-Ching Aw[5], Scott Baker[6], Kenny Crump[7], Michael Dourson[8], Lynne Haber[8], Rick Hertzberg[9], Carl Keen[10], Bette Meek[11], Larisa Rudenko[12], Rita Schoeny[9], Wout Slob[13], Tom Starr[14]

[1]Consulting in Health Sciences and Risk Assessment, BR Stern Associates, Annandale, Virginia, USA, [2]Department of Clinical Pharmacology, University of Berne, Berne, Switzerland, [3]McLaughlin Centre for Population Health, Institute of Population Health, University of Ottawa, Ottawa, Ontario, Canada, [4]Lancashire School of Health and Postgraduate Medicine, University of Central Lancashire, Preston, United Kingdom, [5]Kent Institute of Medicine and Health Sciences, University of Kent, Canterbury, Kent, United Kingdom, [6]International Copper Association, New York, New York, USA, [7]KS Crump Group/Environ Corporation, Ruston, Louisiana, USA, [8]Toxicology Excellence for Risk Assessment (TERA), Cincinnati, Ohio, USA, [9]U.S. Environmental Protection Agency, Atlanta, Georgia, USA, [10]Department of Nutrition, University of California at Davis, Davis, California, USA, [11]Environmental Contaminants Bureau, Health Canada, Ottawa, Ontario, Canada, [12]Integrative Biostrategies, LLC, Washington, DC, USA, [13]National Institute for Public Health and the Environment, Bilthoven, The Netherlands, and [14]Raleigh, North Carolina, United States

Data Collection Process

- Review scientific literature
- Identifying papers on copper toxicity due to excess and deficiency
- Review papers for quality
- Select key studies using a consensus approach

Hazard Identification Criteria

- Consensus approach reviewed over 600 papers for hazard identification and dose response assessment
- Excluded studies included:
  - Exposures in utero
  - No reliable level of exposure
  - Depletion / repletion phases
  - Only pharmacokinetic data
  - Case reports with no known exposure duration

Criteria Used for Exclusion

Most Useful ⟷ Least Useful				
1	2	3	4	5
Multiple dose or multiple outcomes from intact animals or humans Adequate Reporting Physiological Measures	Multiple or single dose from intact animals or humans Fairly Good Reporting Likely to yield useful information Change in time Points Cellular effects	Single dose or clinical study / case report with indeterminate dose Tracer or PK Study Info re. body burden or kinetics Mechanistic or cellular effects	No dose information Physiological information Review	No Utility

Results of the Hazard Identification

~600 Papers

Selected through criteria:
92 papers

Animal Species (6)

Doses

•Single dose

•Repeat dose

Systems Affected (24)

Routes of administration

•Water

•Capsule

•Feed

Copper species (~10)

Results of the Hazard Identification

- 92 papers example closely and
  - NOAELs and Benchmark Doses were determined
  - Each endpoint assigned a severity score of either 0, 1, 2, or 3 for the categorical regression, where:
    - 0=homeostasis
    - 1=enzyme changes
    - 2=metabolic perturbations
    - 3=gross toxicity or deficiency
- Both excess and deficiency studies were based on the same scoring system

Severity Scoring Summary

Deficiency Endpoints	**Severity Score**	**Toxicity Endpoints**
Copper Burden; metallothionein; urine copper	0	Cu burden; metallothionein; urine Cu
Loss of Cu-dependent enzyme function (SOD); Changed blood cell # or function	1	Changes in cholesterol and triglyceride levels in blood/liver; large Cu burden; body weight; nausea; diarrhea; enzyme changes without histopathology
Organ weight changes; plasma glucose/insulin; heart rate; EKG changes; minor histopatholgy; white blood cell activity/counts	2	Body weight; anemia; hemolysis; vitamin levels; liver enzymes; inflammation; organ weight changes
Mortality; gross histopathology reproductive function changes	3	Death; gross histopathology

Copper Database

- Total of 3,844 severity scores assigned
- Maximum severity scores (312) selected from each dose group in each study

Marker	Ref.id	Exp	Group	Species	Sex	mg/kg bw	Weeks	GpSize	BestNum
1	1	1	1	MU	F	0.06	5.6	1	1
2	1	1	2	MU	F	0.6	5.6	1	2
3	4	1	1	RA	M	0.02	6	1	1
4	4	1	2	RA	M	0.25	6	1	2
5	4	1	3	RA	M	0.8	6	1	3
6	8	1	1	MU	F	0	4	1	1
7	8	1	2	MU	F	1.5	4	1	3

Interspecies Scaling

- Interspecies scaling based on four dose metrics:

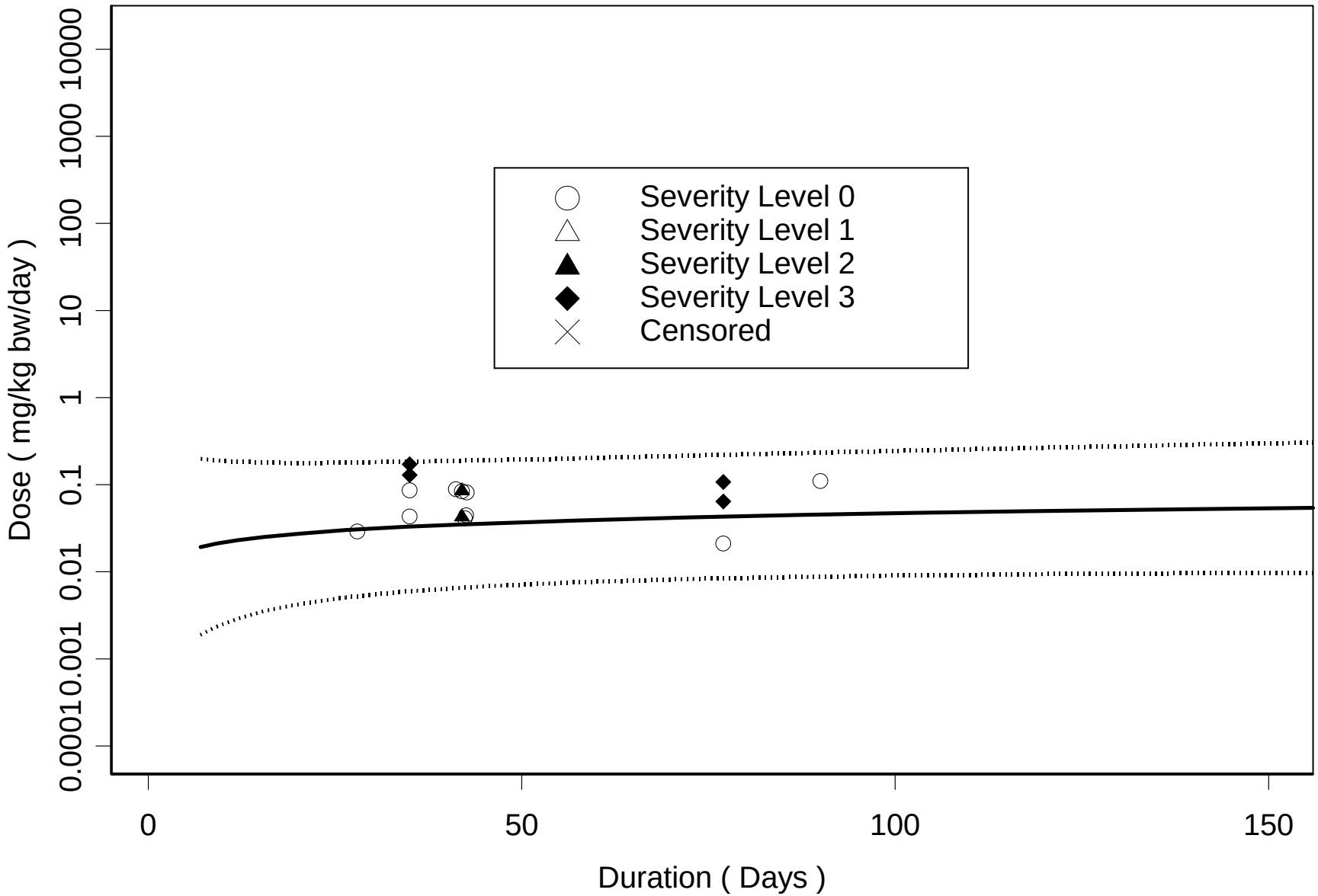
  body weight: mg/kg bw/day

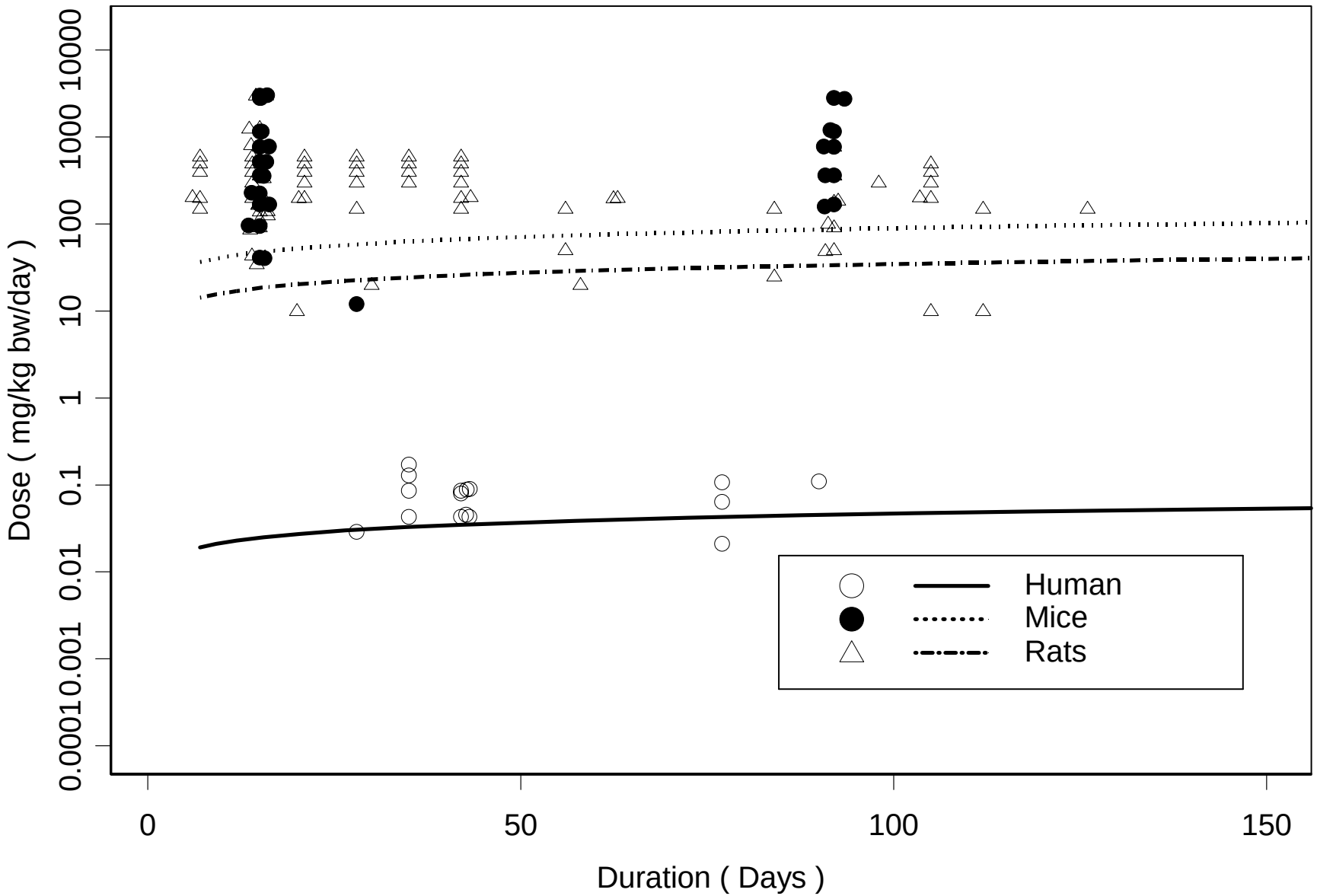
  surface area: $bw^{2/3}$

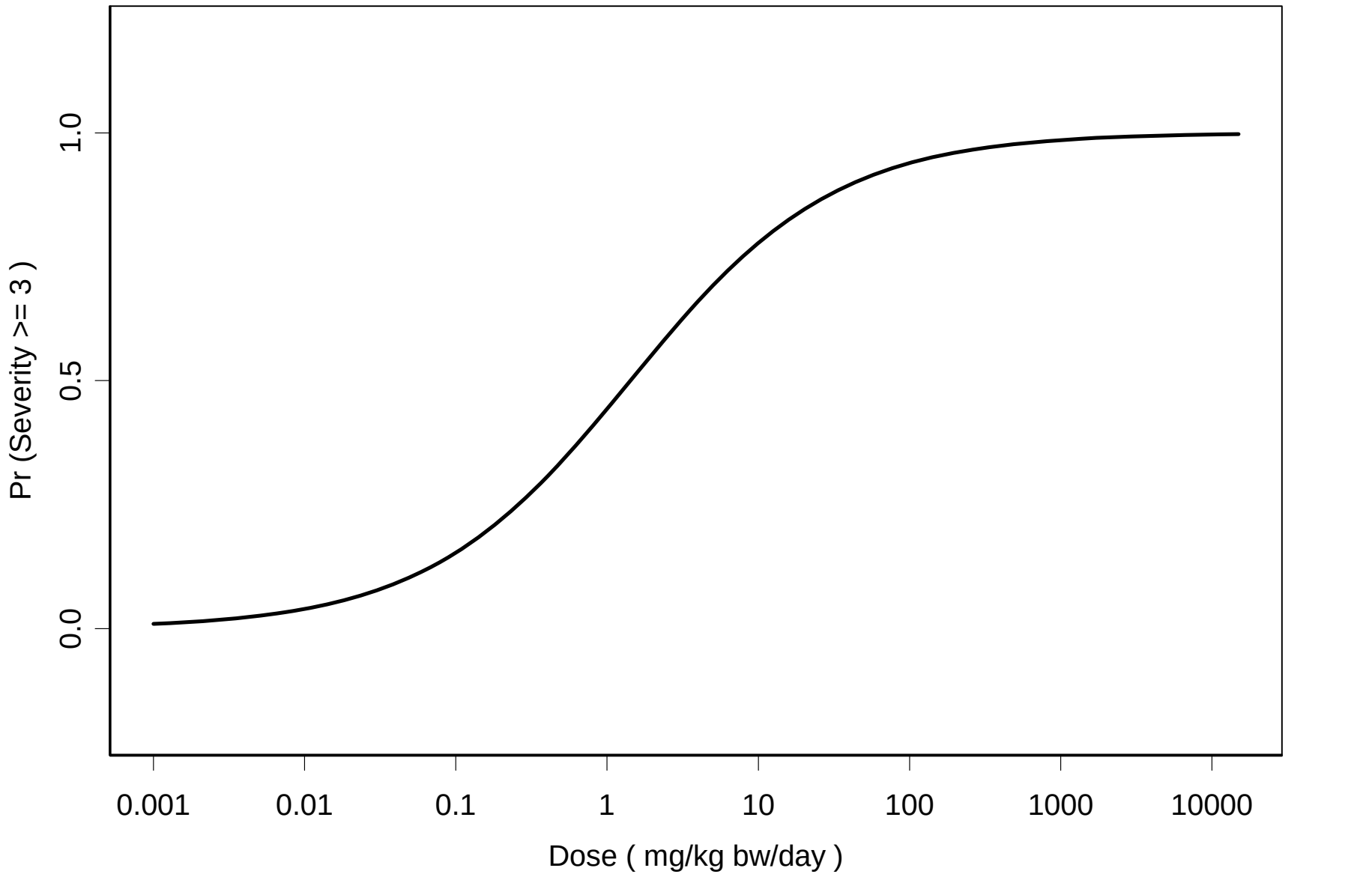
  intermediate: $bw^{3/4}$ *(Travis & White , 1988)*

  total intake: mg/day

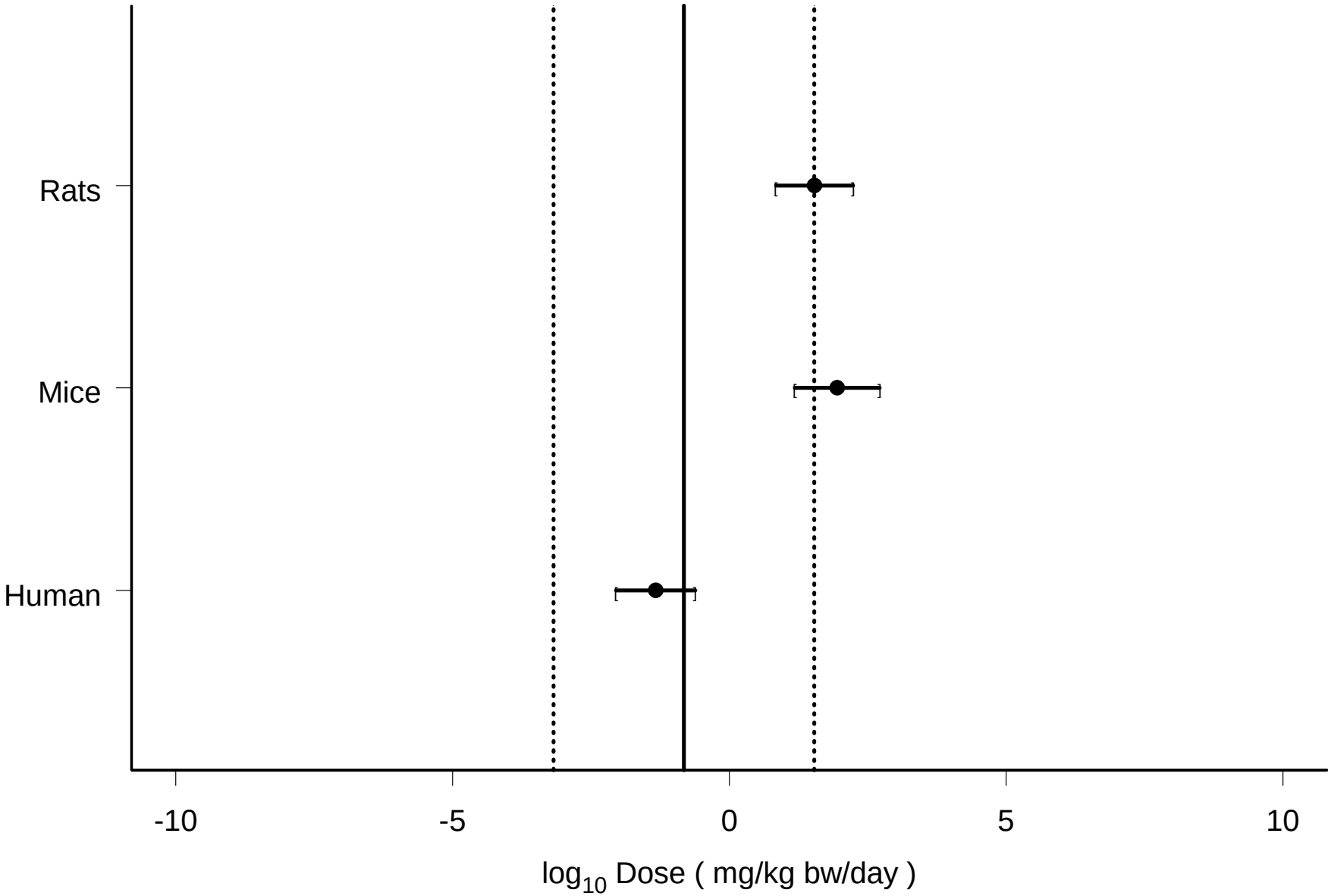
Dose - Duration Curves for Toxicity due to Copper Excess

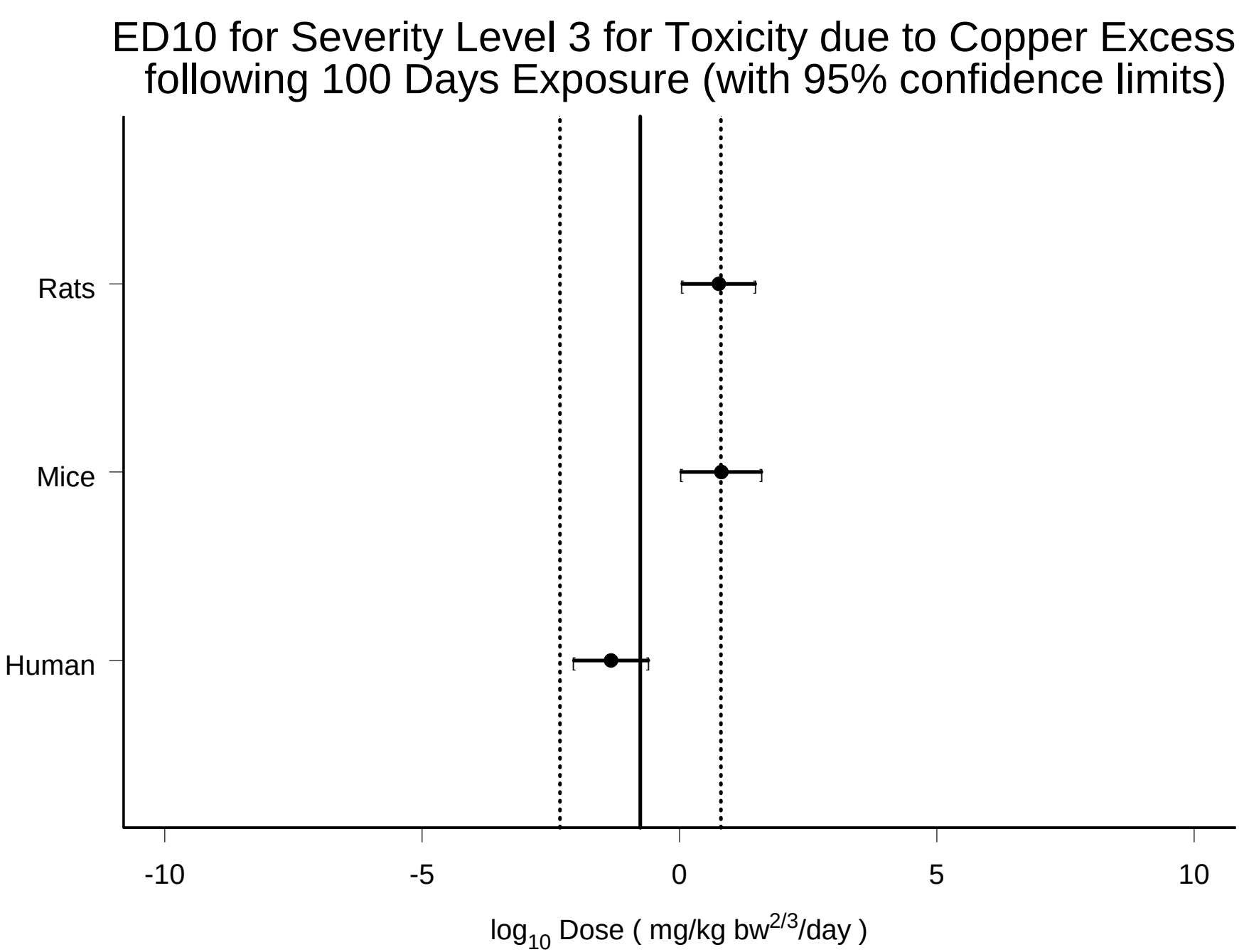

ED10 Dose - Duration Curves for Severity Level 3 for Toxicity due to Copper Excess (with 95% confidence limits) for Human (n=20)
Dose (mg/kg bw/day)
0.0001
0.001
0.01
0.1
1
10
100
1000
10000
Duration (Days)
0
50
100
150
Severity Level 0
Severity Level 1
Severity Level 2
Severity Level 3
Censored

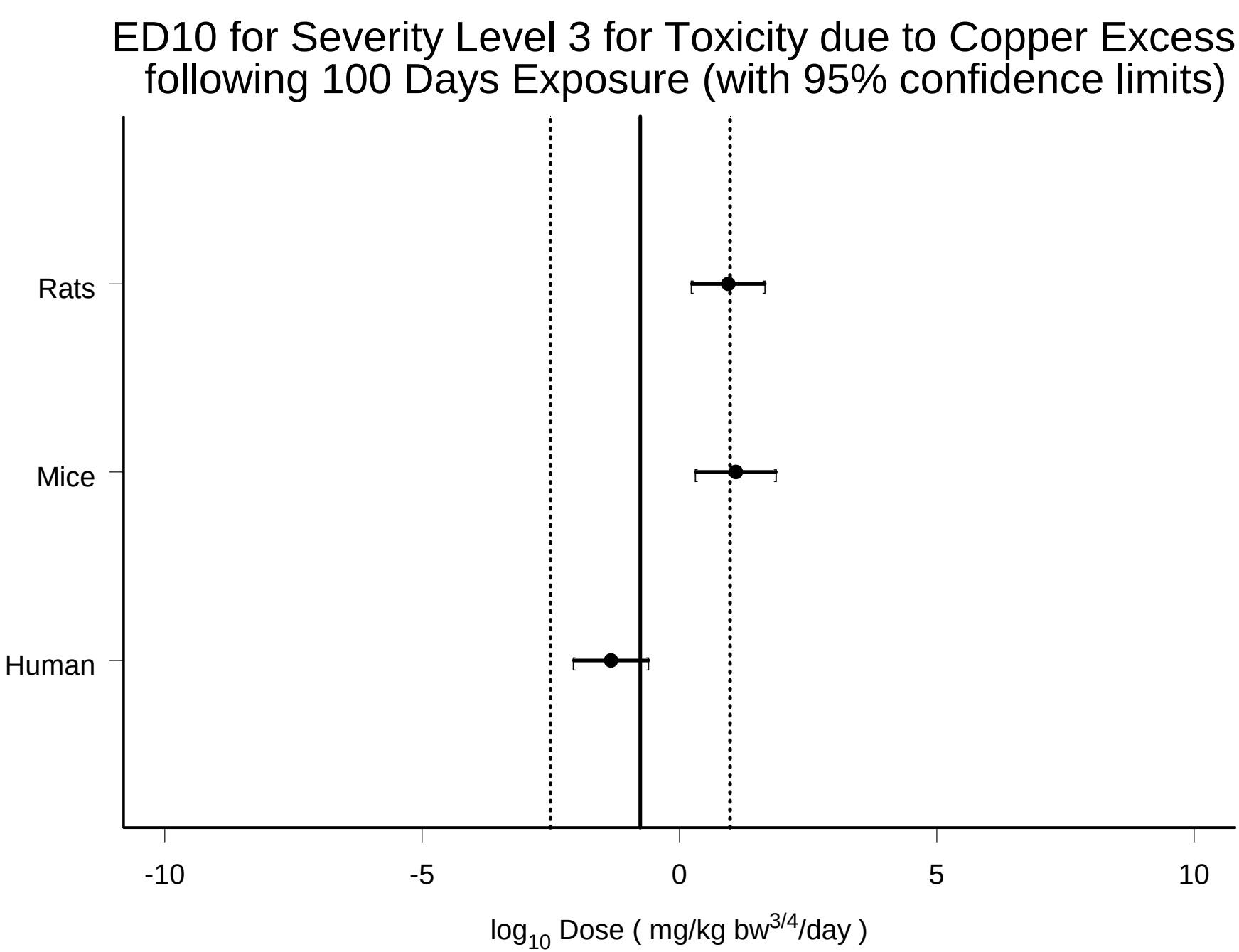

ED10 Dose - Duration Curves for Severity Level 3
for Toxicity due to Copper Excess
Dose (mg/kg bw/day)
0.0001
0.001
0.01
0.1
1
10
100
1000
10000
0
50
100
150
Duration (Days)
Human
Mice
Rats

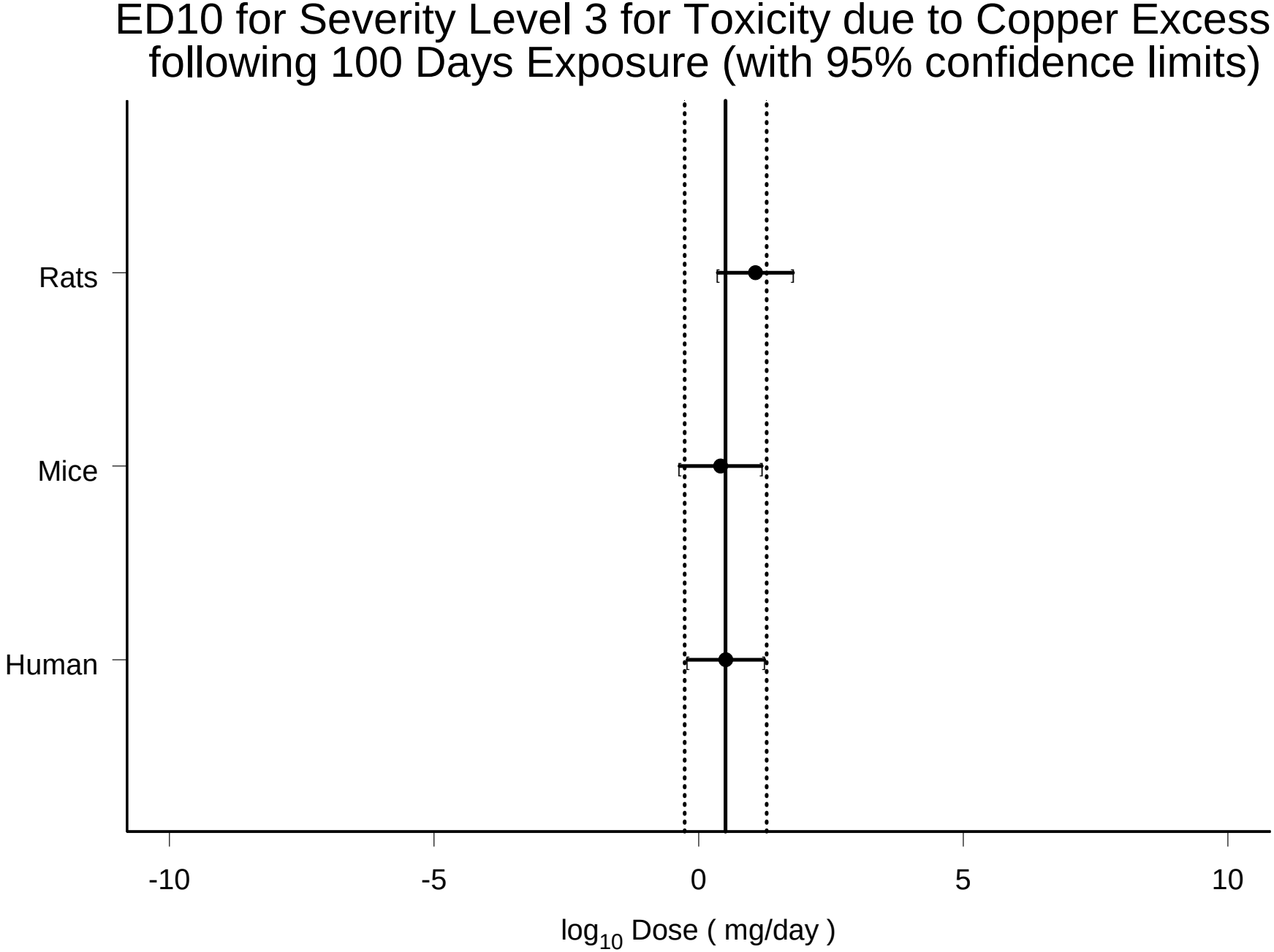

ED10 Dose Response Curves for Severity Level 3 for Toxicity
due to Copper Excess following 100 Days Exposeure for Human (n=20)
Pr (Severity >= 3)
0.0
0.5
1.0
0.001
0.01
0.1
1
10
100
1000
10000
Dose (mg/kg bw/day)

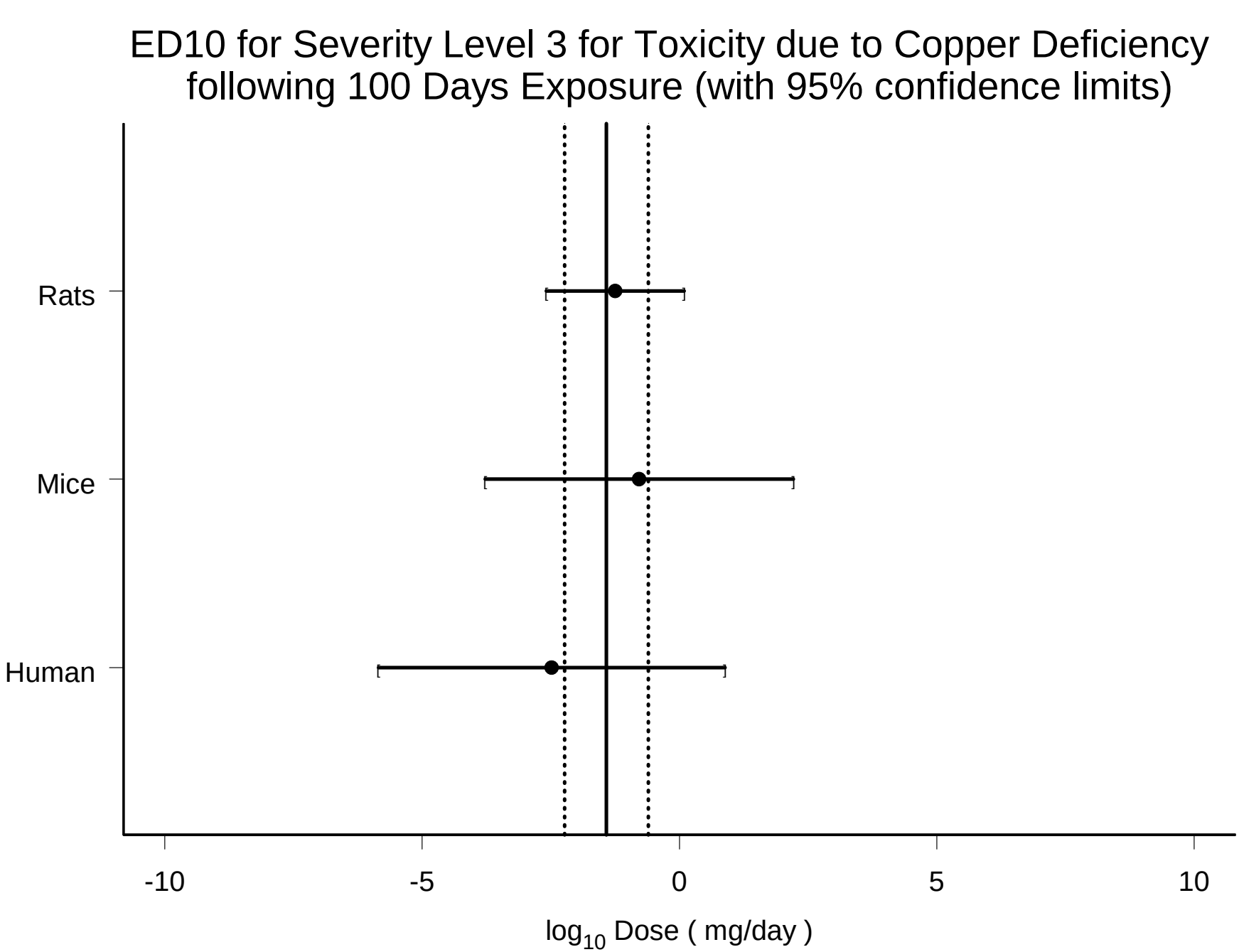
Comparison of Scaling Methods


ED10 for Severity Level 3 for Toxicity due to Copper Excess following 100 Days Exposure (with 95% confidence limits)
Rats
Mice
Human
-10
-5
0
5
10
log10 Dose (mg/kg bw/day)

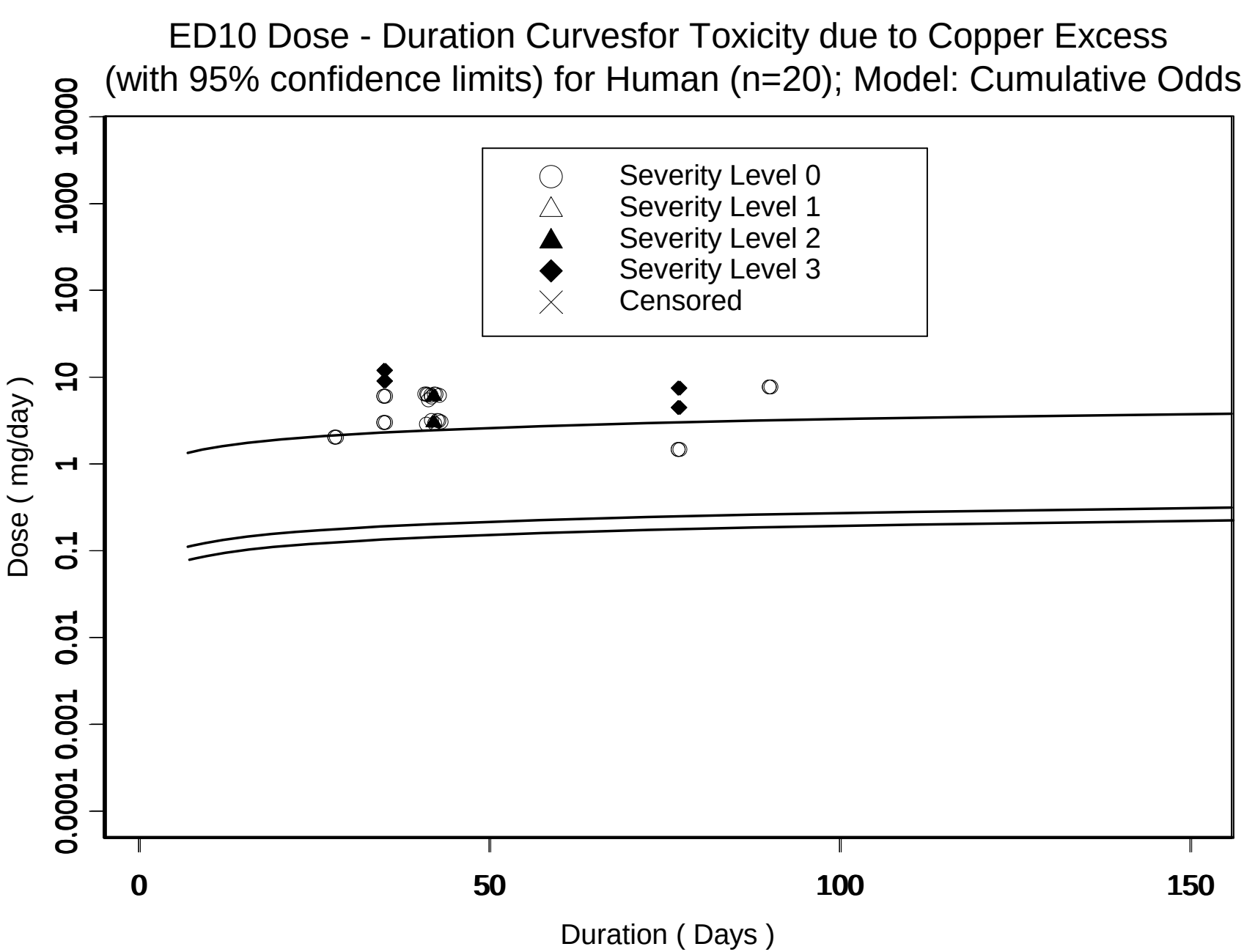

ED10 for Severity Level 3 for Toxicity due to Copper Excess following 100 Days Exposure (with 95% confidence limits)
Rats
Mice
Human
-10
-5
0
5
10
log10 Dose (mg/kg bw2/3/day)


ED10 for Severity Level 3 for Toxicity due to Copper Excess following 100 Days Exposure (with 95% confidence limits)
Rats
Mice
Human
-10
-5
0
5
10
log10 Dose (mg/kg bw3/4/day)

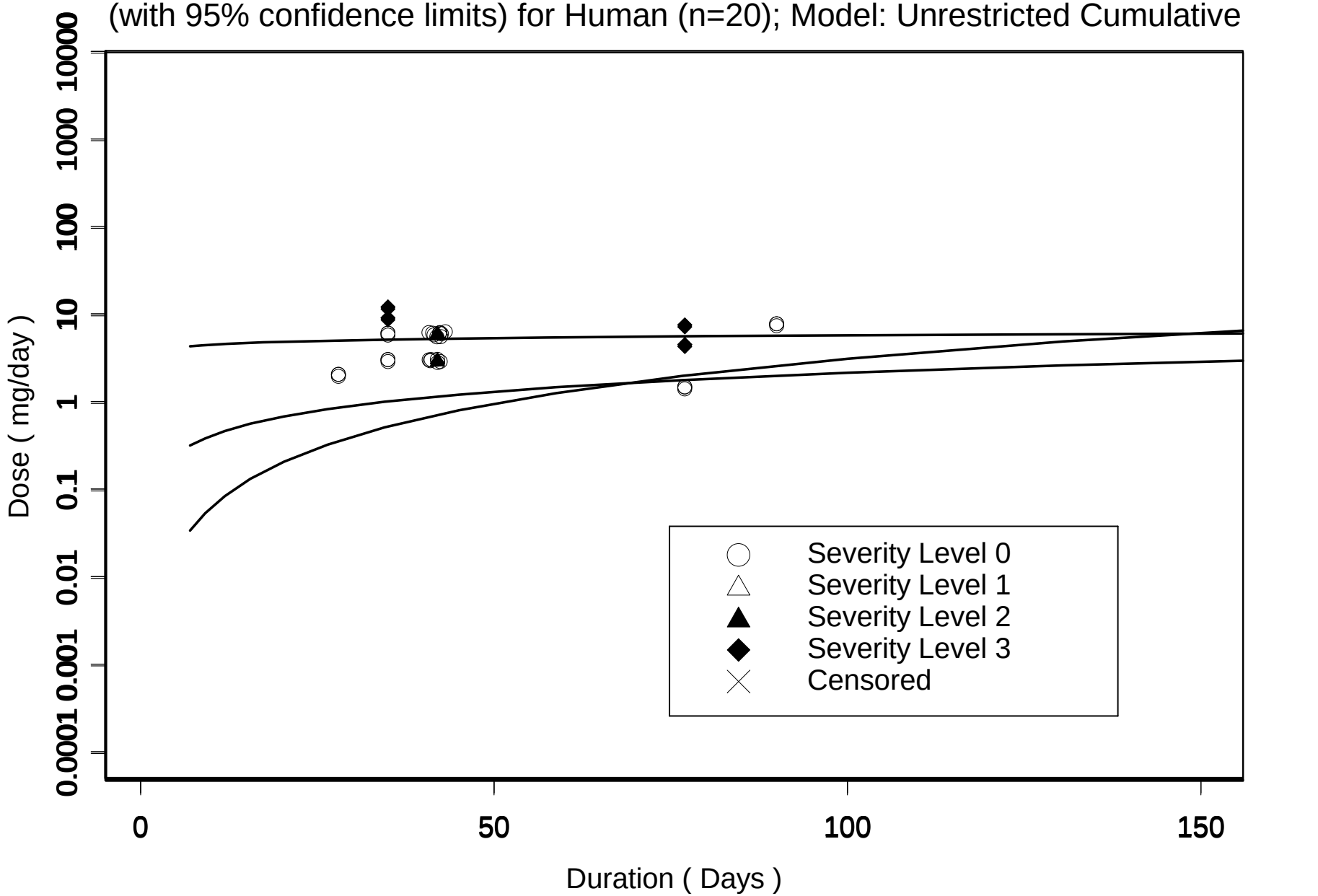

ED10 for Severity Level 3 for Toxicity due to Copper Excess following 100 Days Exposure (with 95% confidence limits)
Rats
Mice
Human
-10
-5
0
5
10
log10 Dose (mg/day)


ED10 for Severity Level 3 for Toxicity due to Copper Deficiency following 100 Days Exposure (with 95% confidence limits)
Rats
Mice
Human
-10
-5
0
5
10
log10 Dose (mg/day)

Model 1: Cumulative Odds (parallel dose response curves)


ED10 Dose - Duration Curvesfor Toxicity due to Copper Excess
(with 95% confidence limits) for Human (n=20); Model: Cumulative Odds
Severity Level 0
Severity Level 1
Severity Level 2
Severity Level 3
Censored
Dose (mg/day)
0.0001
0.001
0.01
0.1
1
10
100
1000
10000
0
50
100
150
Duration (Days)

Model 2:
Unrestricted Cumulative
(non-parallel dose-response curves)


ED10 Dose - Duration Curves for Toxicity due to Copper Excess
(with 95% confidence limits) for Human (n=20); Model: Unrestricted Cumulative
Dose (mg/day)
0.0001
0.001
0.01
0.1
1
10
100
1000
10000
0
50
100
150
Duration (Days)
Severity Level 0
Severity Level 1
Severity Level 2
Severity Level 3
Censored

Future Analysis

- Update the current copper database
- Include additional species
- Select Model:
  - Restricted vs unrestricted
  - Cumulative vs conditional odds
  - Exposure duration (10 – 100 days)
  - Select final dosimetry (mg/day?)
- Examine multiple levels of severity
- Conduct a qualitative analysis of all data to determine the endpoints of the homeostatic range for copper
- Consider uncertainty factors for sensitive individuals