A Case Study in Reproducibility: The Threshold of Toxicological Concern for Non-Cancer Endpoints

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Washington, DC

Society for Risk Analysis

2-6 December 2018

New Orleans, LA

Reproducibility Background

- Reproducibility
- Repeatability
- Reliability
- Replicability
- Robustness
- Credibility
- Validity
- Generalizability

- NAS (Forthcoming) "Reproducibility and Replicability in Science"
  - Define terms
  - What does it mean to successfully reproduce/replicate?

Threshold of Toxicological Concern (TTC) Background

- Evolved from the FDA 1993 Threshold of Regulation for food contact materials.

- Munro et al (1996) proposed TTC values for non-cancer effects based on analyses of NOEL distributions for chemicals separated into 3 classes using the Cramer et al (1978) scheme.

- Kroes et al (2004) proposed a TTC value for chemicals with genotoxic structural alerts.

- Current discussions in Codex Alimentarius about a screening approach for chemicals with insufficient toxicity data to conduct a risk assessment.

# Revisiting Munro et al (1996)

- Took as given the Munro et al classifications of 613 organic substances using Cramer scheme:
  - Class I: 137; Class II: 28; Class III: 448
  - Classification uncertainty ignored
- Initially was unable to reproduce the TTC values (5th percentiles) reported by Munro et al (1996) based on the reported table of lowest reported NOELs for each of 613 substances.

Revisiting Munro et al (1996)

- Leeman et al. 2014. Reevaluation of the Munro dataset to derive more specific TTC thresholds. Regulatory Toxicology and Chemistry. 69(2):273-8.
  - Tip of the hat to Grace Patlewicz (EPA/ORD)
- Description of methods by Munro et al is ambiguous. There are notes to the table of NOEL values that an additional safety factor of 3 was applied to values from subchronic and reproductive studies. But the reported table of NOEL values does not reflect that additional safety factor.
- After adjusting the reported NOELs, obtain TTC values much closer to the reported results.
- Yang et al 2017 - identified some errors in the table of NOEL values reported by Munro et al. (1996) from primary sources

Revisiting Munro TTC for Non-Cancer Effects
Variability Distributions of Non-Cancer NOEL's

Munro et al 1996	NOEL~Lognormal			
	NOEL (mg/kg-bw-d)			
Structural Class	5%ile (reported)	50%ile (reported)		
I (n = 137)	3	116		
II (n = 28)	0.91	26		
III (n = 448)	0.15	9		
Re-analysis	NOEL~Lognormal		NOEL~Weibull	
	NOEL (mg/kg-bw-d)		NOEL (mg/kg-bw-d)	
Structural Class	5%ile MLE (95% CI)	50%ile MLE (95% CI)	5%ile MLE (95% CI)	50%ile MLE (95% CI)
I (n = 137)	**2.94 (1.66 – 5.20)**	113.30 (78.12 – 164.32)	**1.36 (0.58 – 3.21)**	161.11 (112.30 – 231.11)
II (n = 28)	**0.95 (0.31 - 2.92)**	24.36 (11.74 – 50.54)		
III (n = 448)	0.15 (0.11 - 0.22)	9.42 (7.47 - 11.88)		

Revisiting Munro et al (1996)
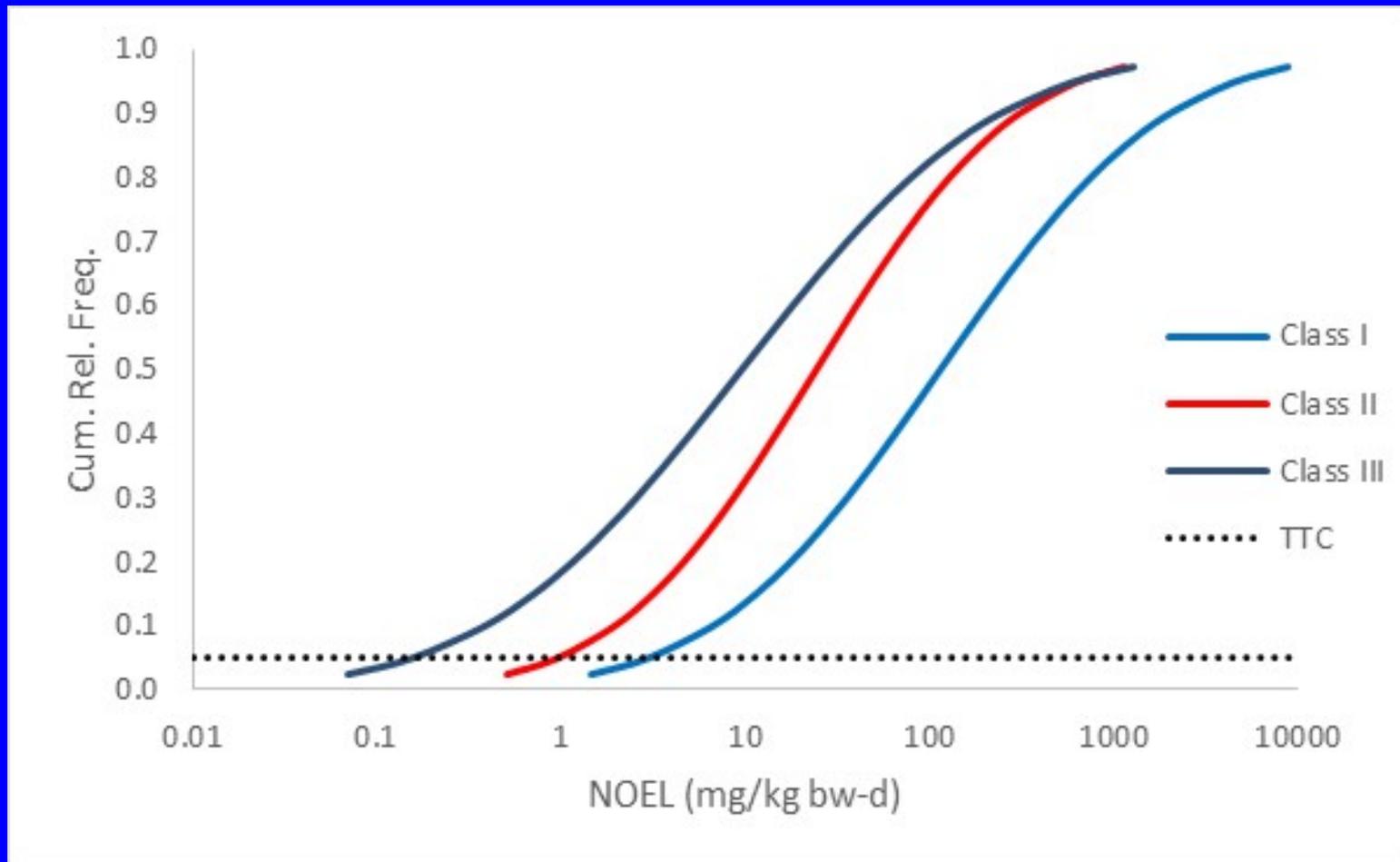
# Revisiting Munro et al (1996)
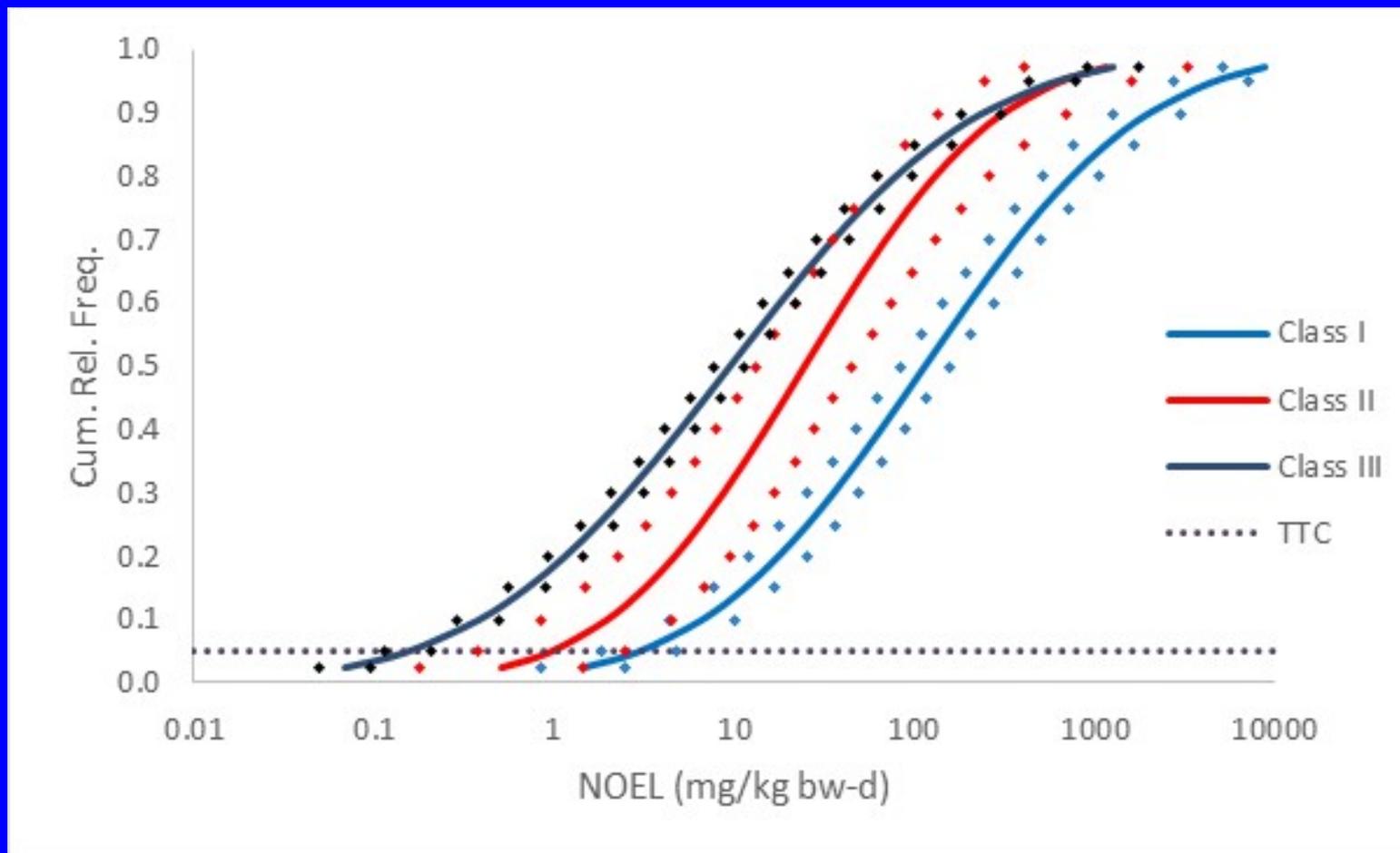
Class I - Lognormal
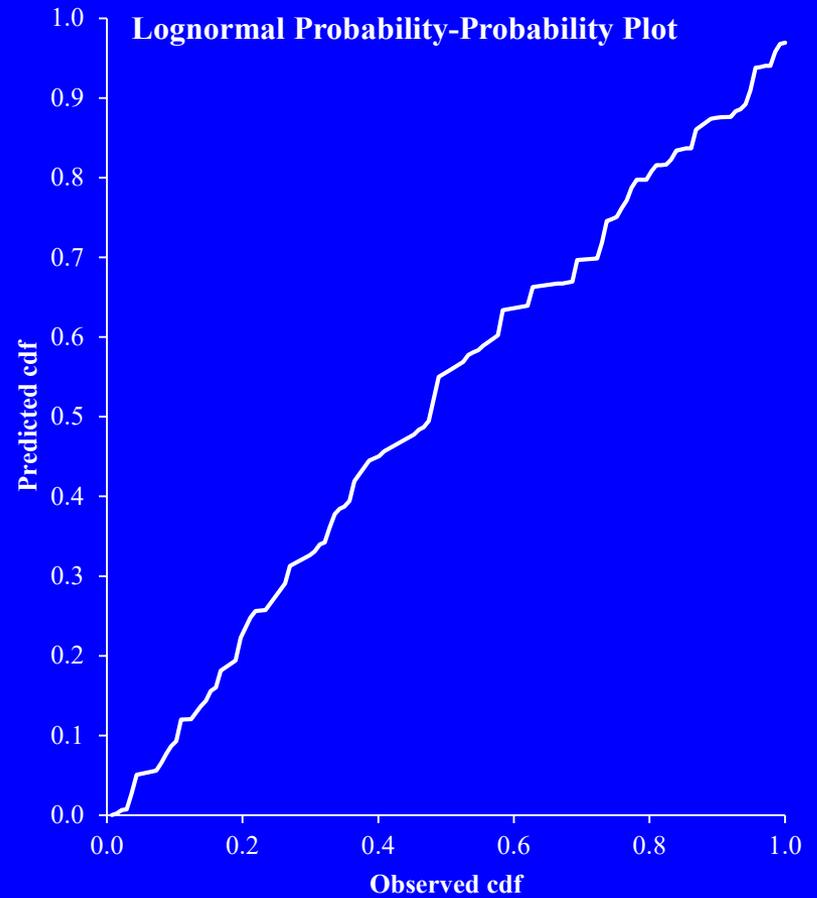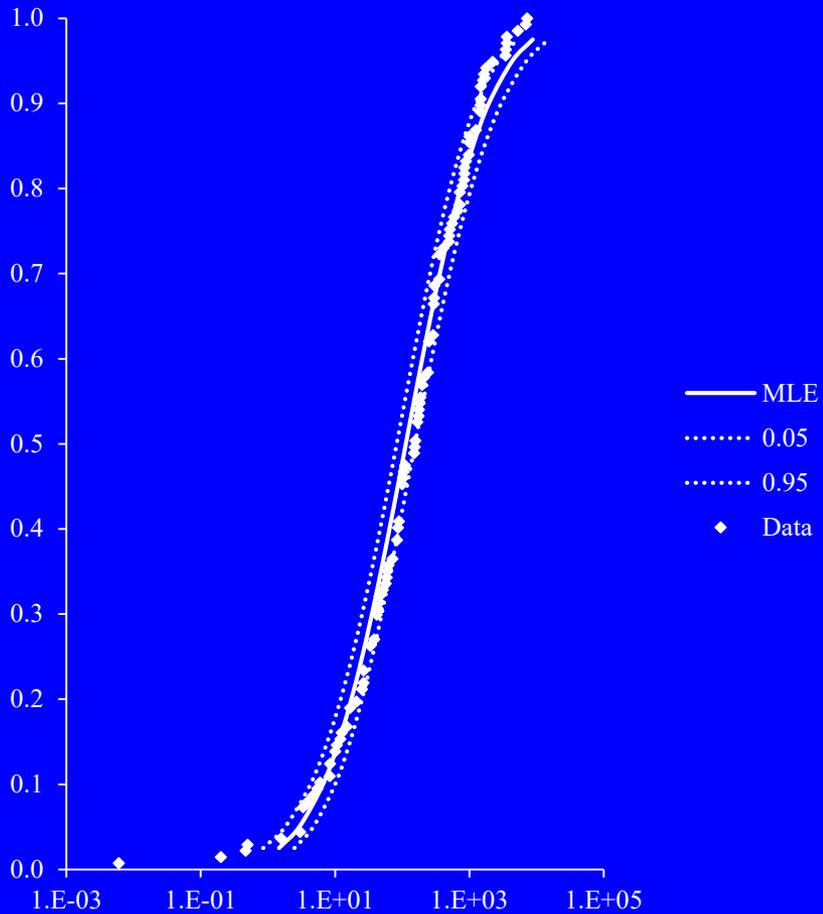
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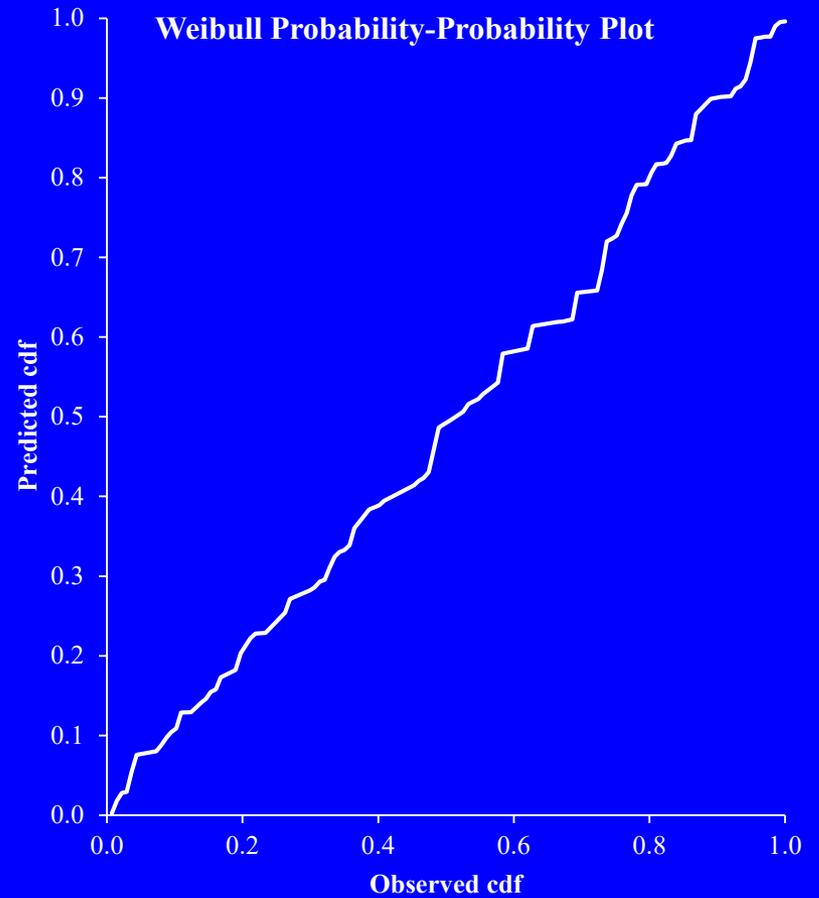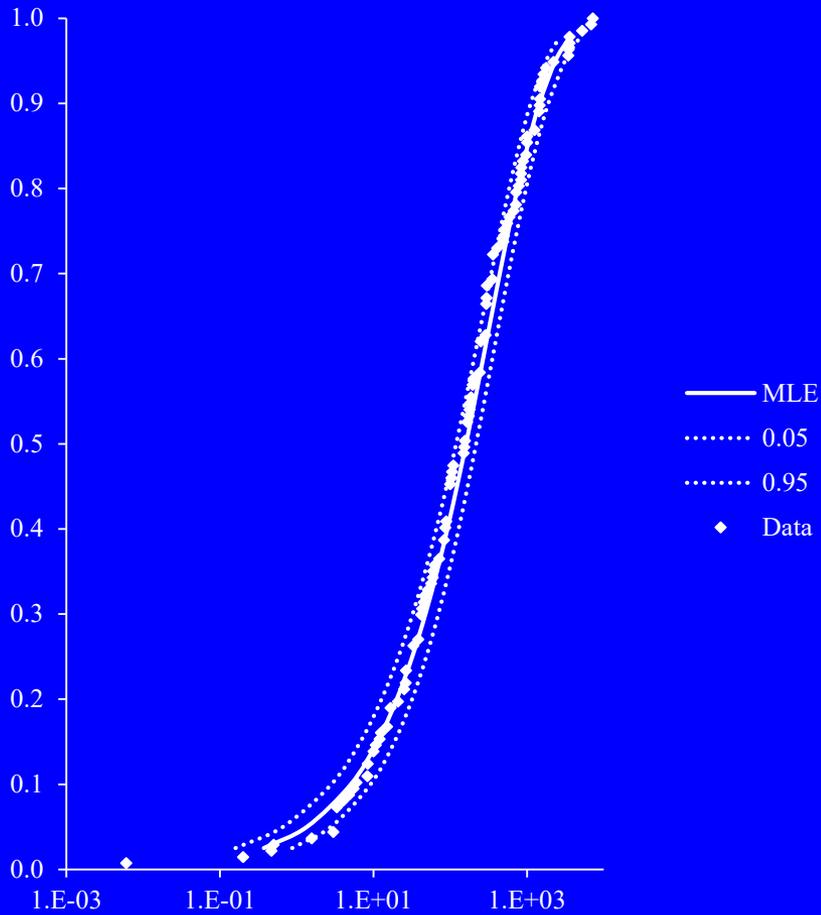
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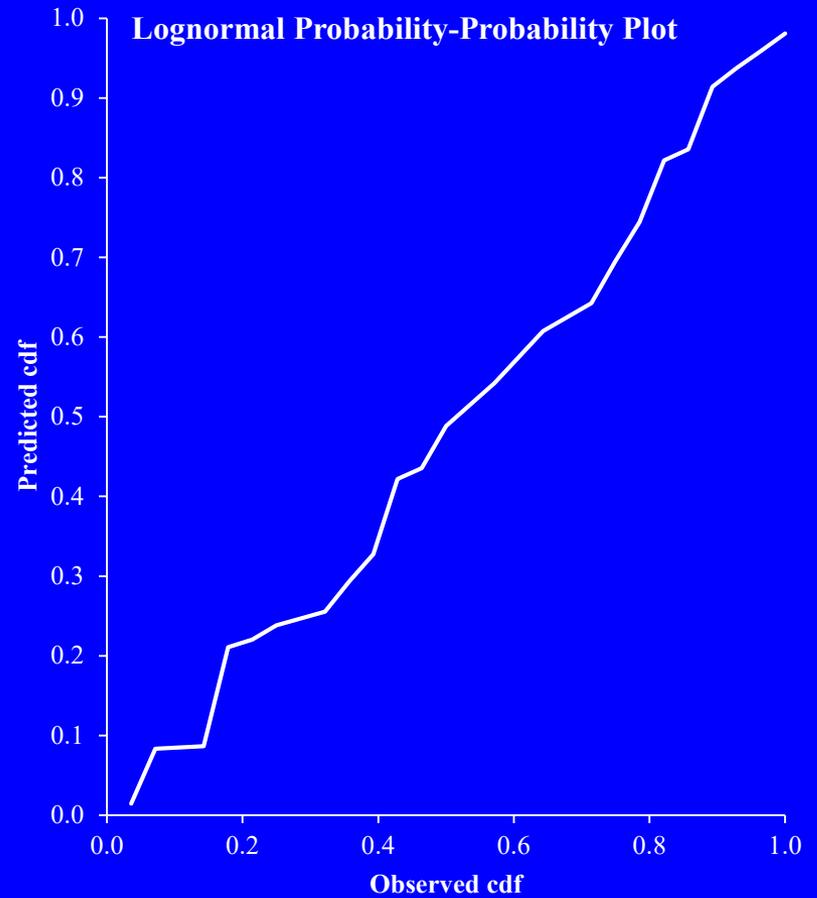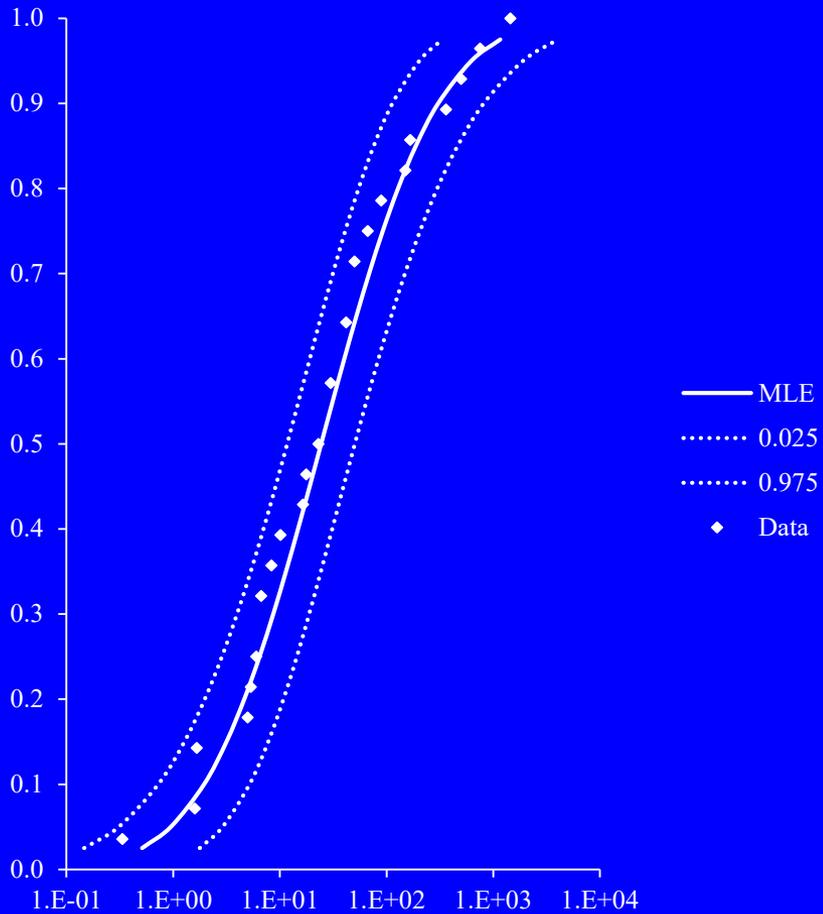
Class III - Lognormal
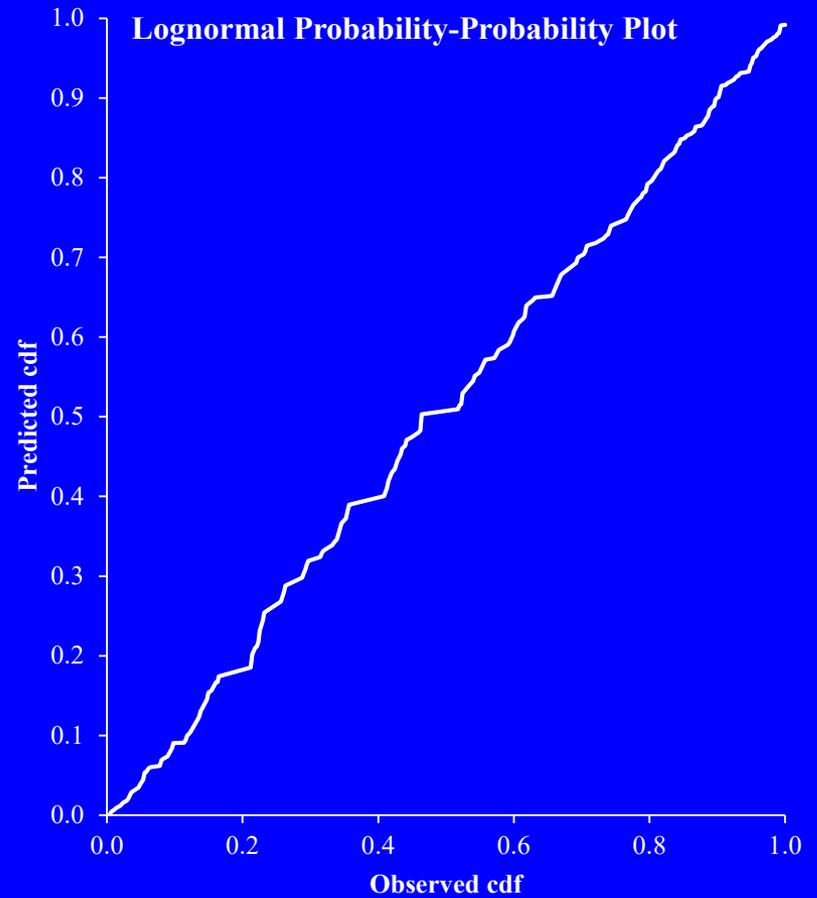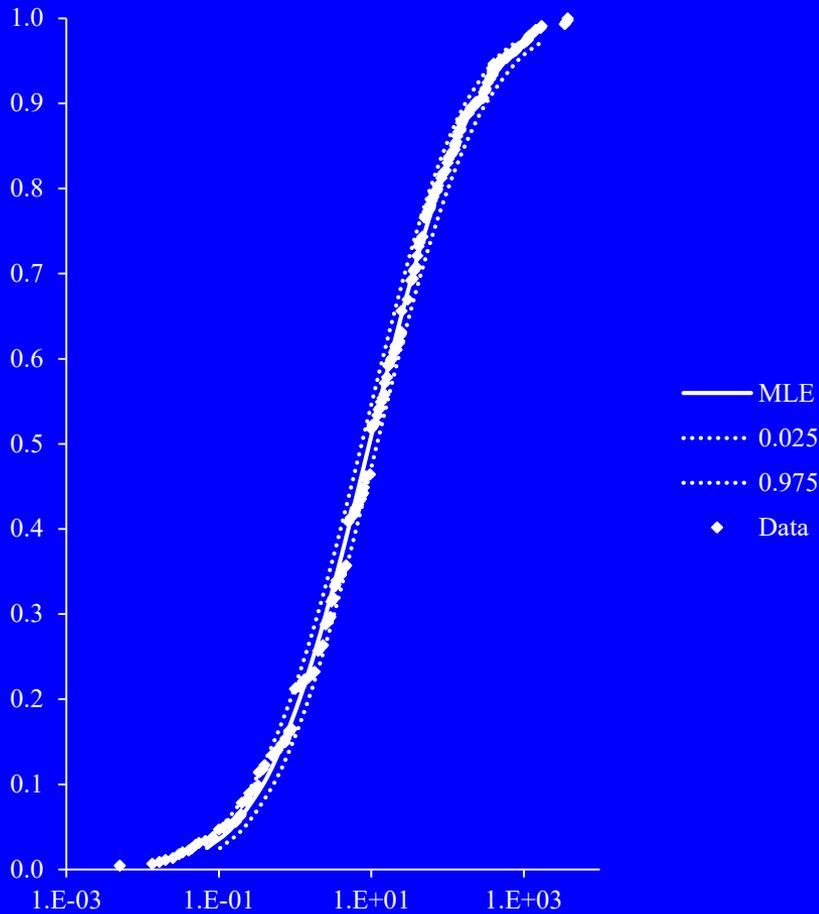
Discussion

- What is your definition of reproducibility?

- Does the requisite extent of "reproducibility" depend on the decision context?

- Have I successfully reproduced the results reported by Munro et al (1996)?

Disclaimers

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