# Statistical modelling issues arising from PK/PD bridging in paediatrics

The Trileptal Example

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Workshop on Modelling in Paediatric Drug Development and Use

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# Outline

- Background
- Pediatric Decision Tree
- The problem: “observational data”, potential confounding
- The solution: diagnostics for confounding
- Lessons learned

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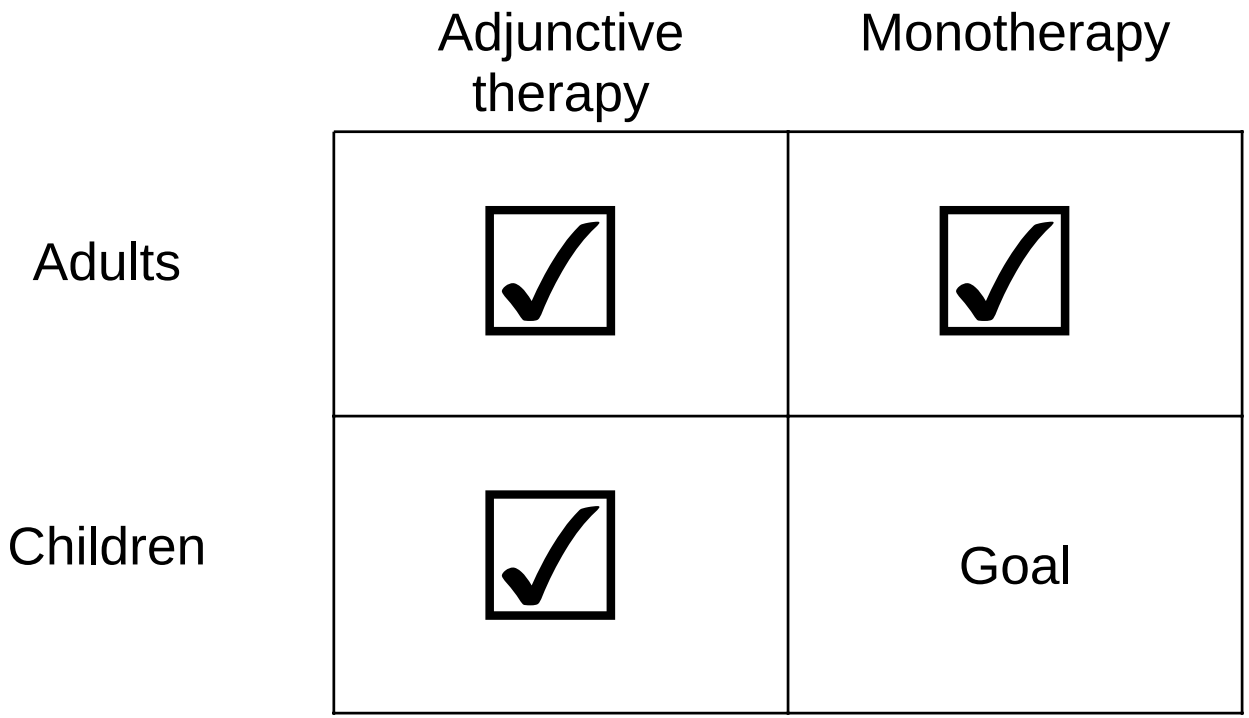
# Background: Trileptal

- Oxcarbazepine
- Anti-epileptic
- Activity primarily through active metabolite MHD
- “PK” refers to MHD concentrations
- “PD” refers to seizure rates

# Background: Initial approval status in the U.S.



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# Background: Available data

| | Adjunctive therapy | Monotherapy |
|---|---|---|
| Adults | **PK/PD** | **PK/PD** |
| Children | **PK/PD** | **PK** |

# Background: Bridging strategy

| | Adjunctive therapy | Monotherapy |
|---|---|---|
| Adults | **PK/PD** | **PK/PD** |
| Children | **PK/PD** | **PK** |

Goal



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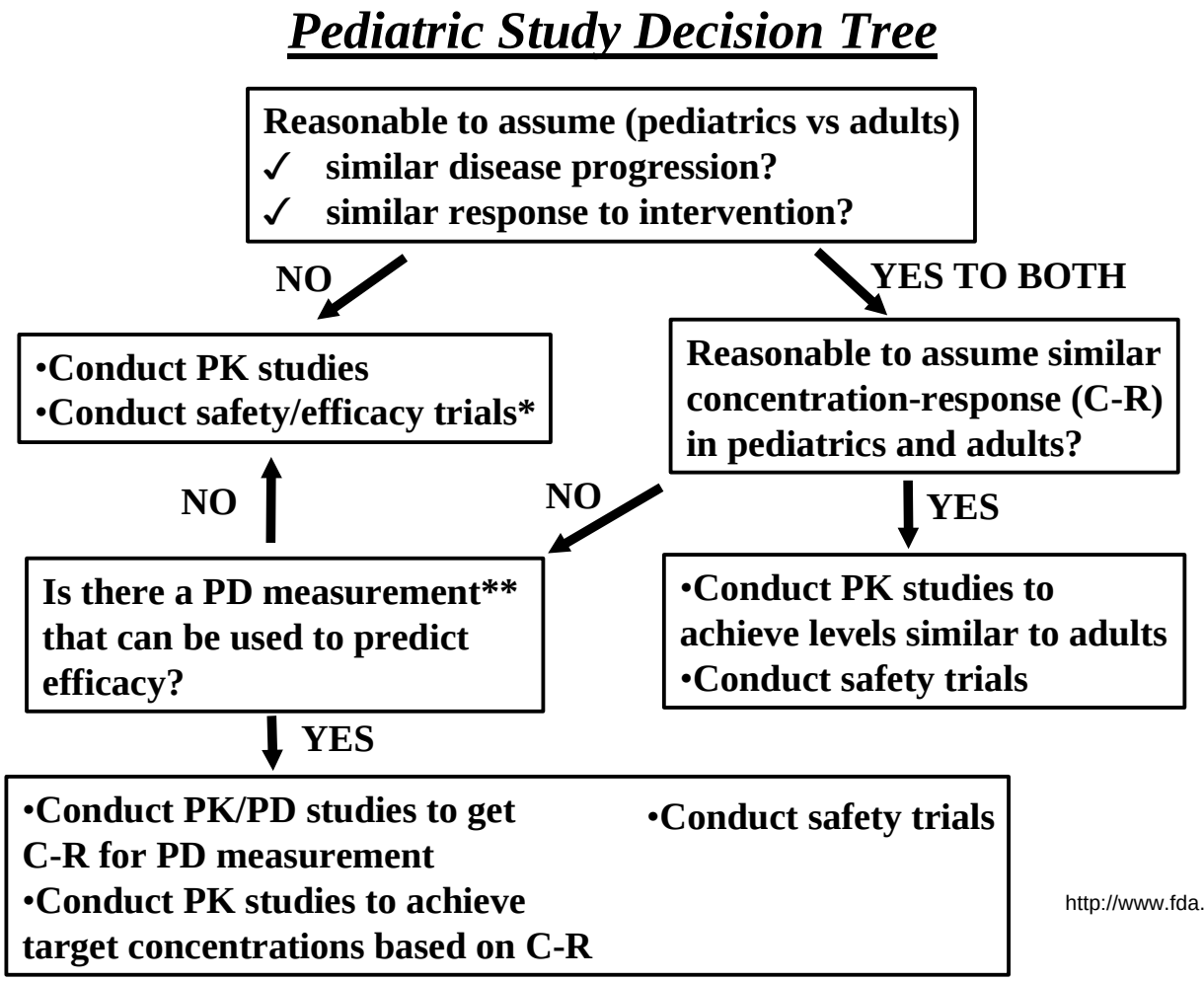
# Pediatric Decision Tree




http://www.fda.gov/cder/guidance/5341fnl.htm



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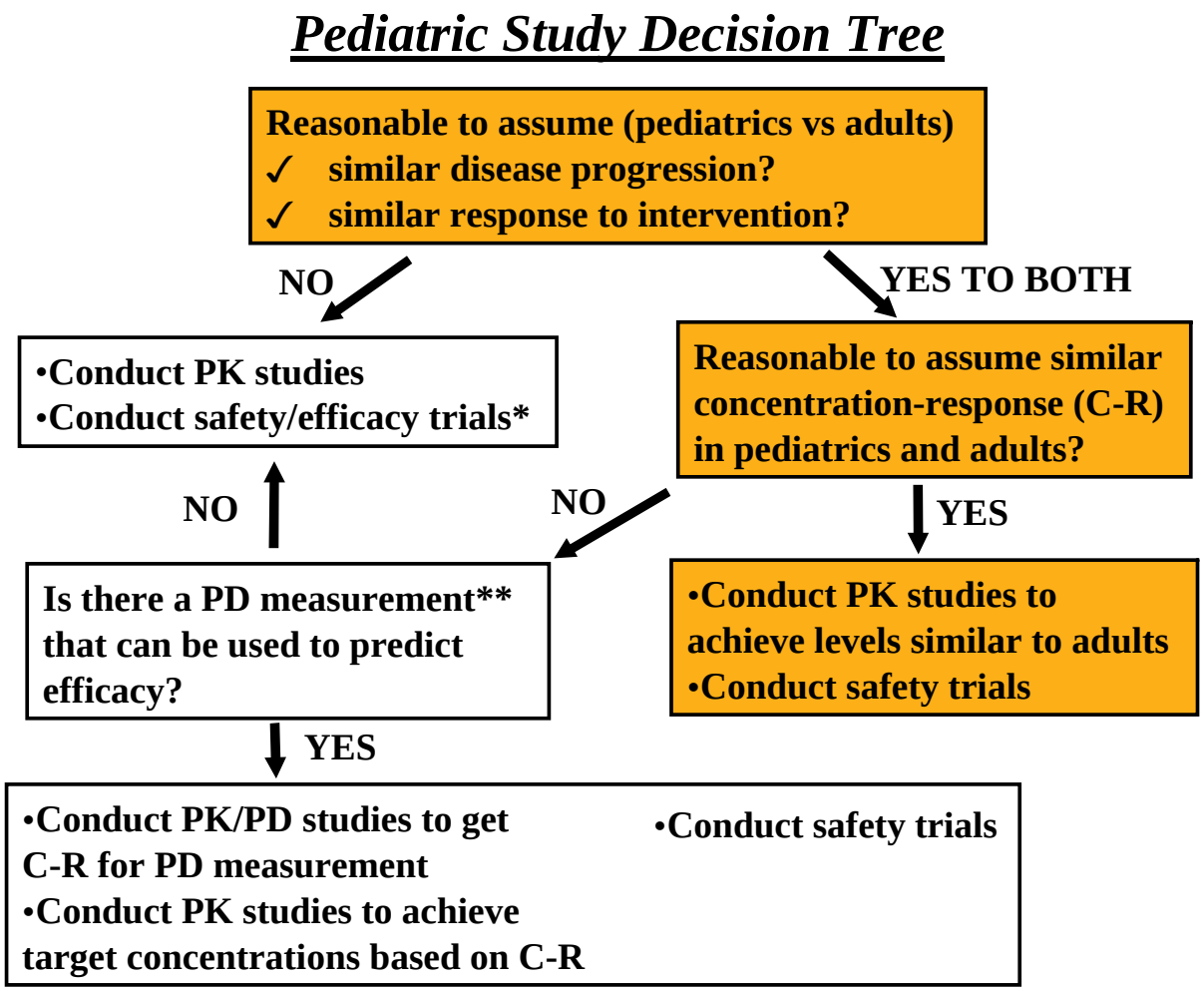
# Pediatric Decision Tree



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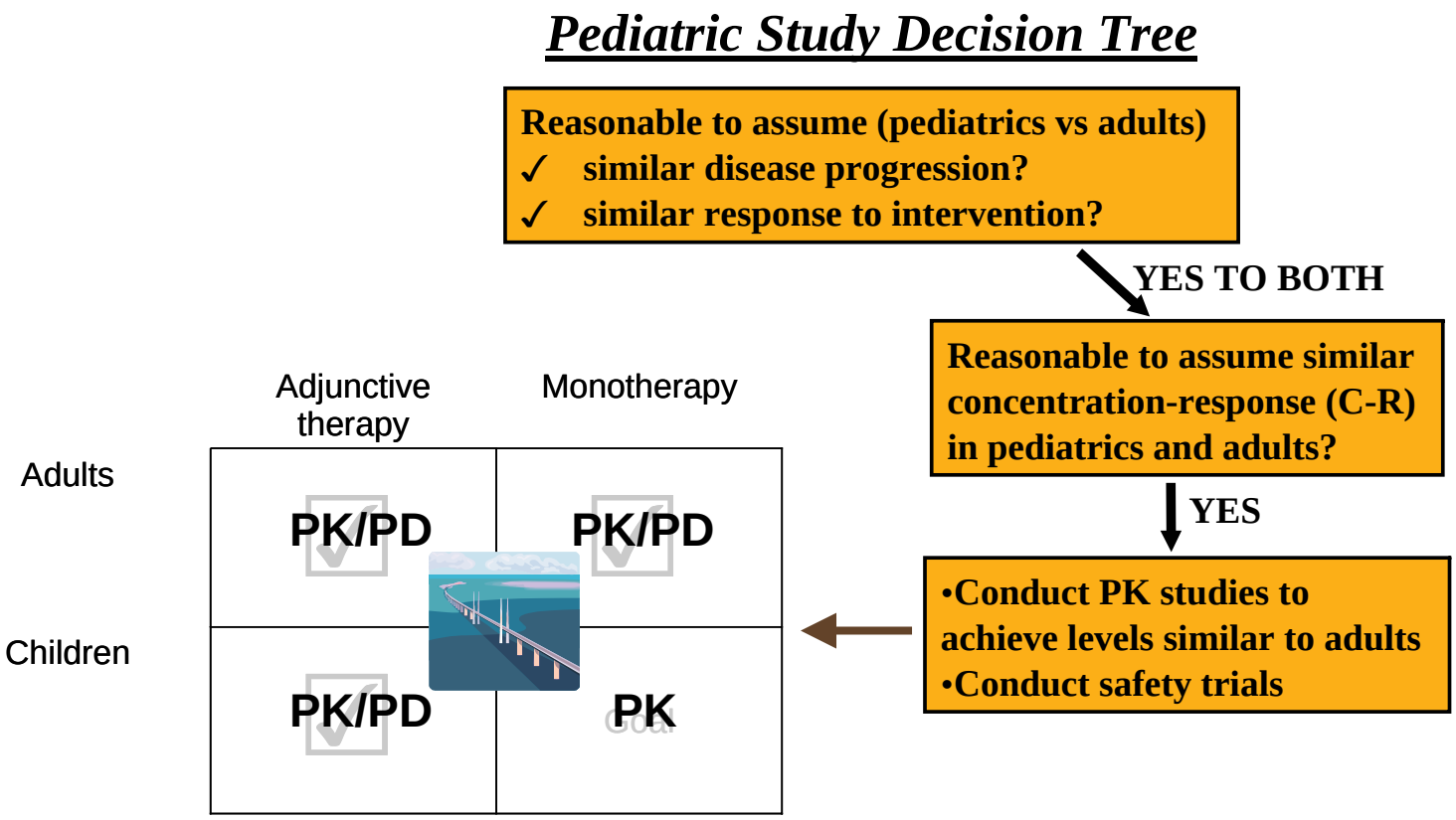
# Pediatric Decision Tree: Bridging (1)



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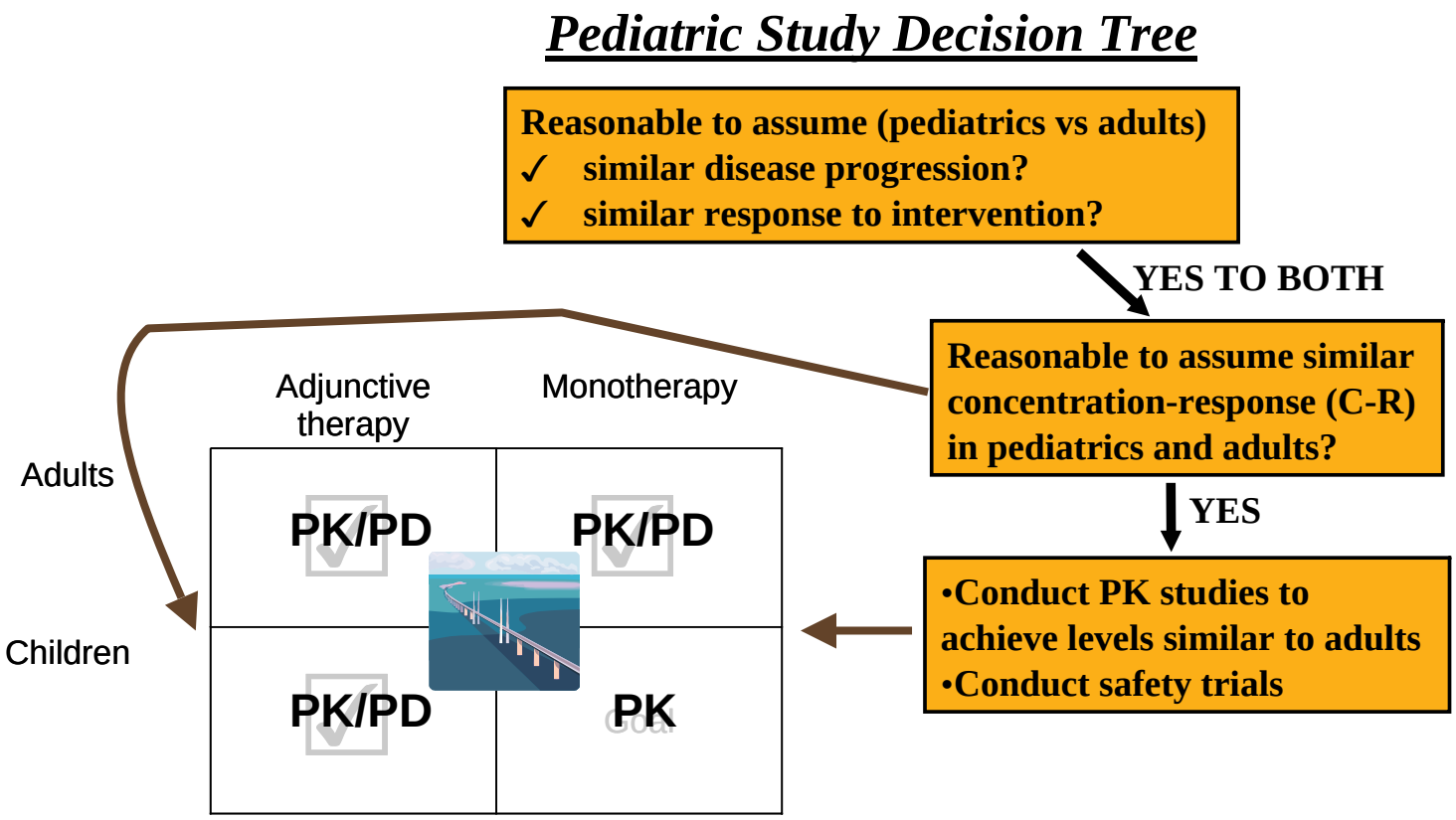
# Pediatric Decision Tree: Bridging (2)



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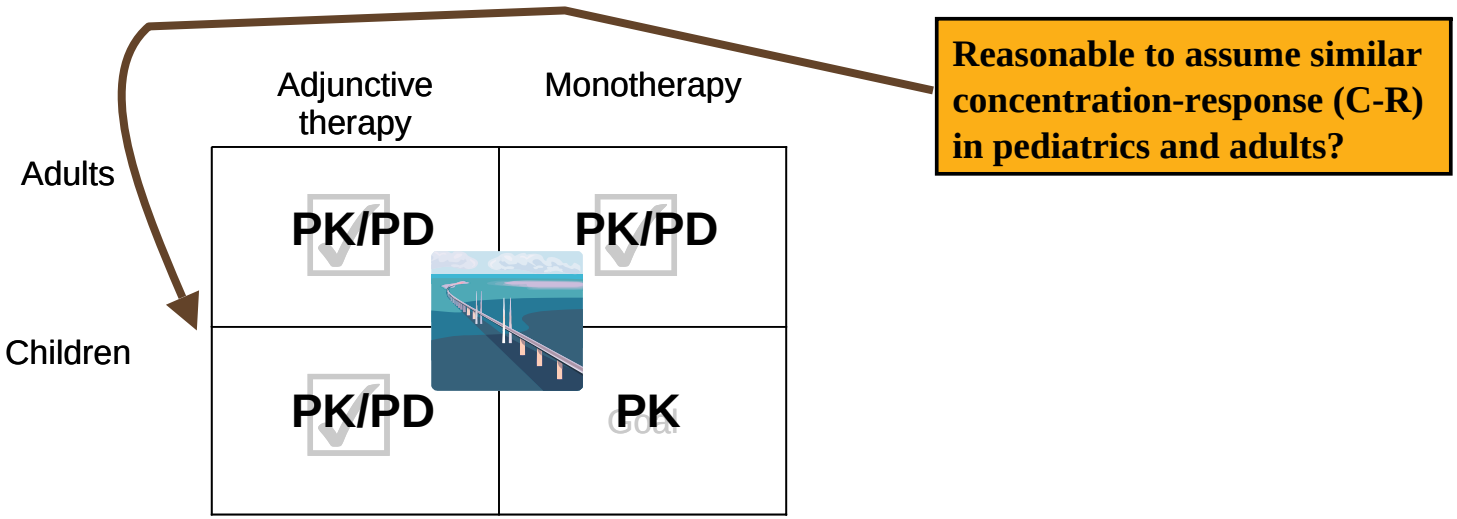
# Pediatric Decision Tree: Burden of proof



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# Pediatric Decision Tree: But first …

Are the estimated PK/PD (C-R) relationships acceptable in the first place?

**Reasonable to assume similar concentration-response (C-R) in pediatrics and adults?**

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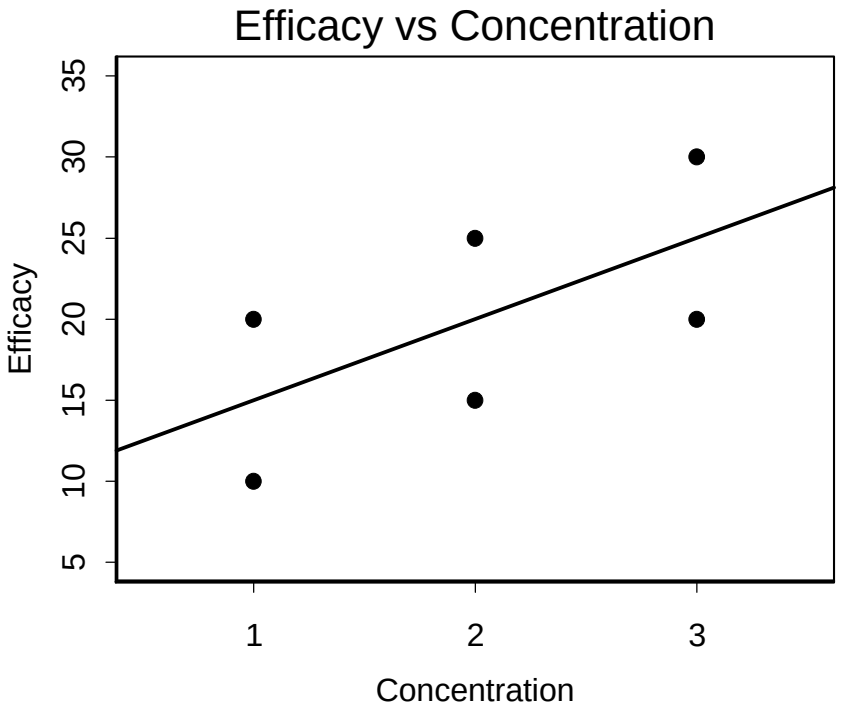
# Observational vs Experimental

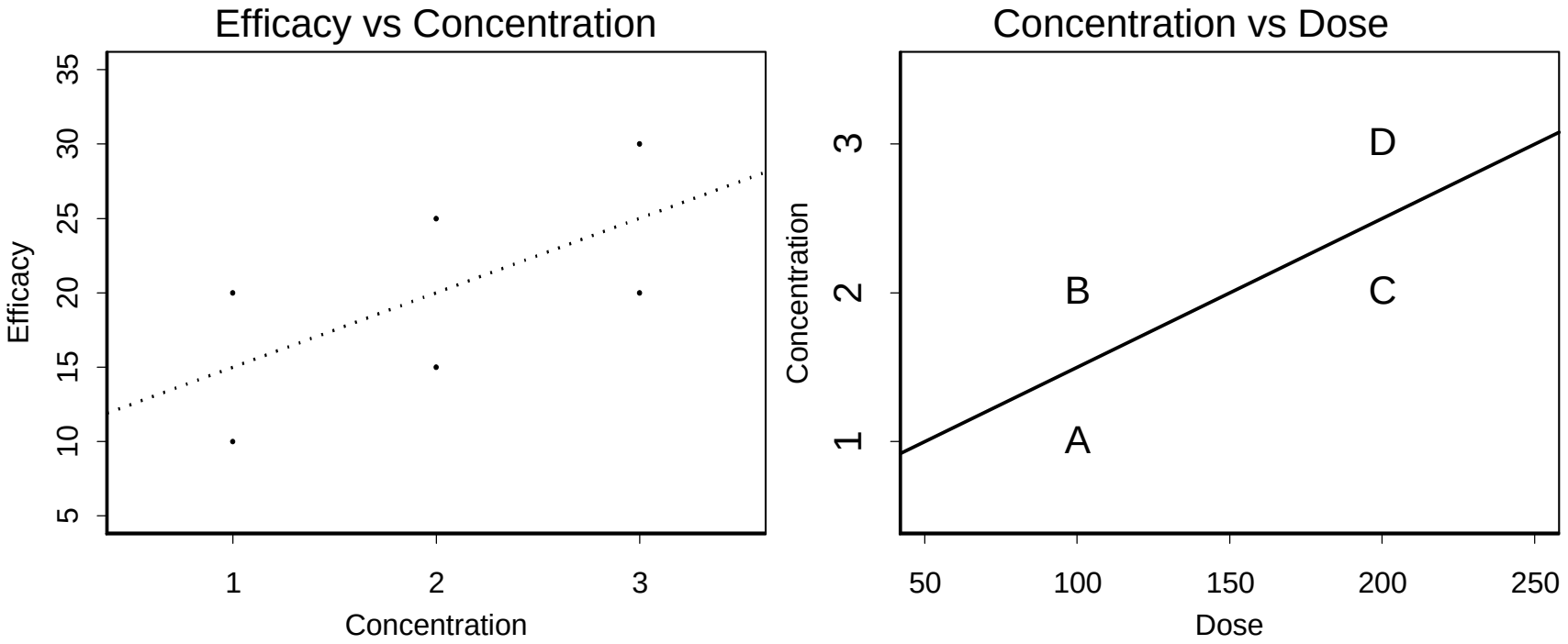
- "Relationship": Input → Output
- Experimental study: Input controlled by investigator
  - Usually assigned randomly to experimental units
  - E.g., dose-controlled trial, concentration-controlled trial
- Observational study: Input not controlled by investigator
  - E.g., PK → PD in a dose-controlled trial
  - PK is an output as well as an input
  - For PK/PD purposes, a dose-controlled trial is an observational study
- What can go wrong with observational PK/PD? ….

# Concentration-controlled PK/PD



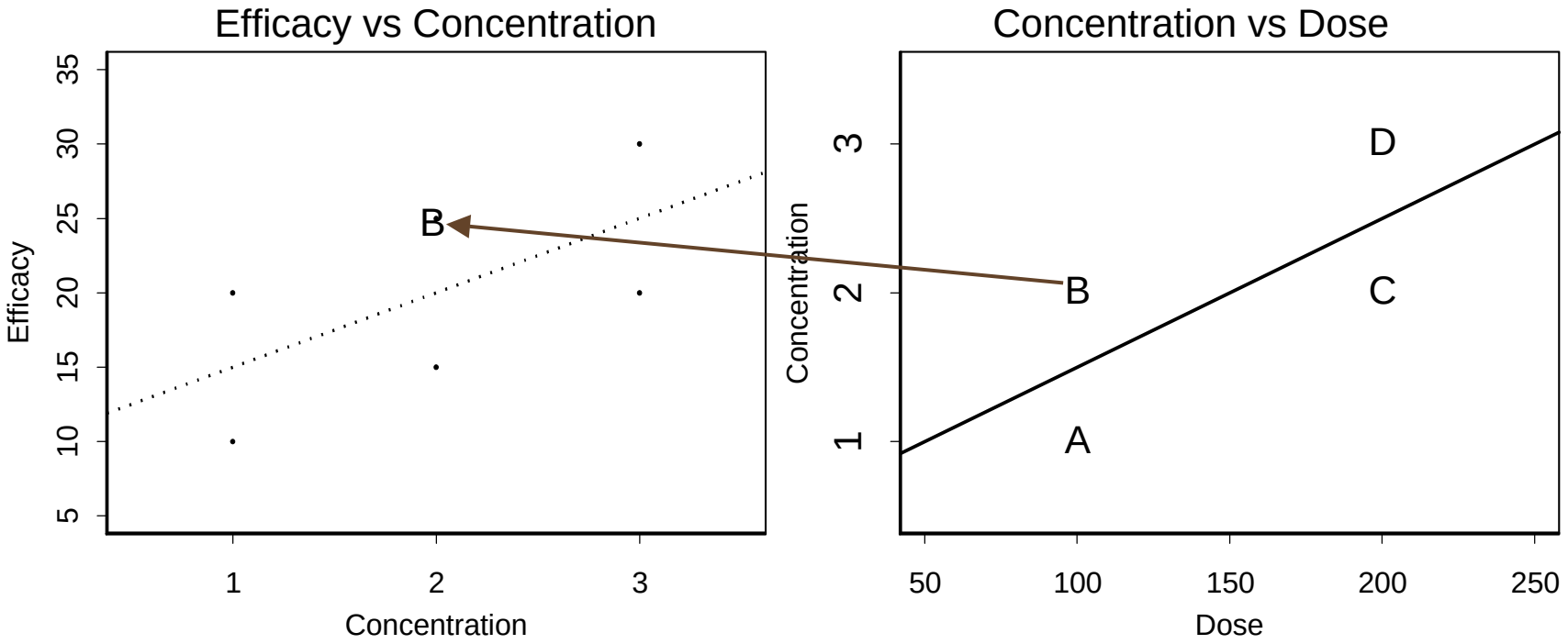

PK/PD data and least-squares model fit, assuming **concentration controlled trial**, with 3 concentrations, at each of which patients divide evenly into two groups of high and low responders

# Dose-controlled PK/PD, scenario 1




Suppose that in a dose-controlled trial, patients who have higher concentrations **at a given dose** also have higher efficacy **at a given concentration**, and lower goes with lower

# Dose-controlled PK/PD, scenario 1

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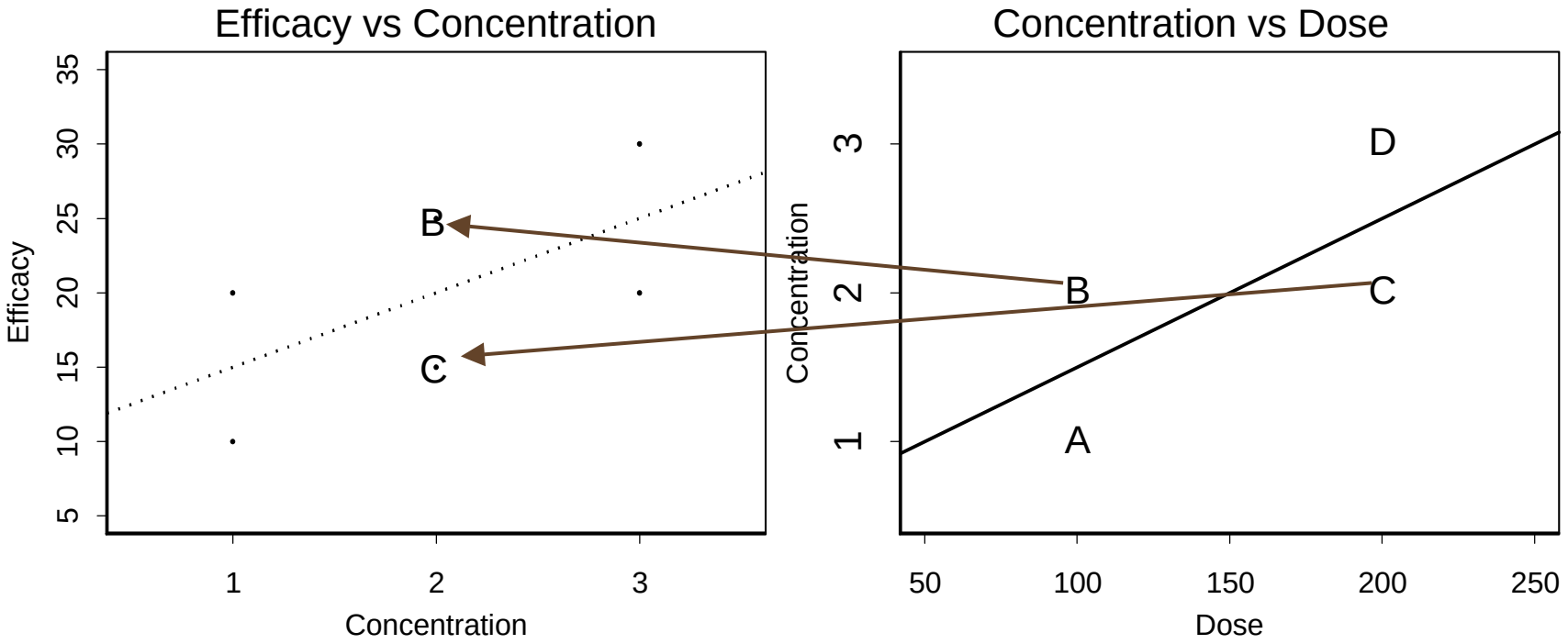


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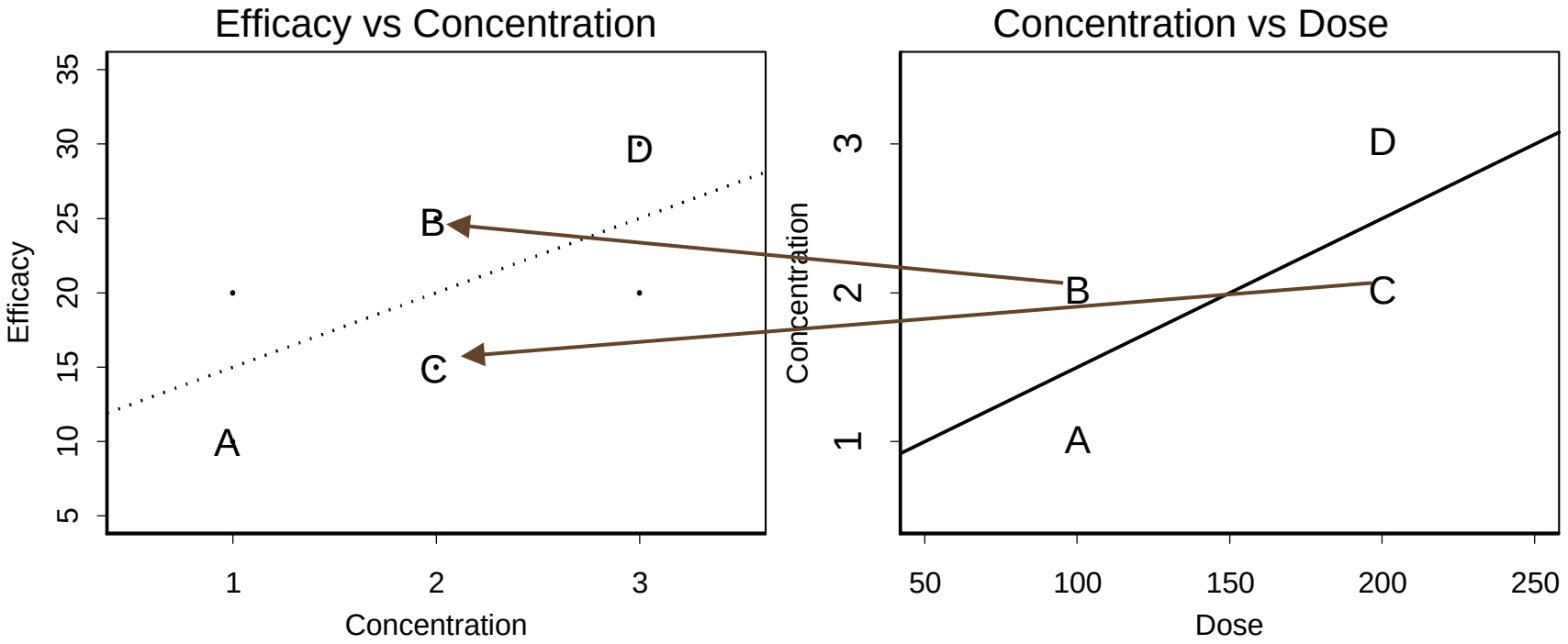


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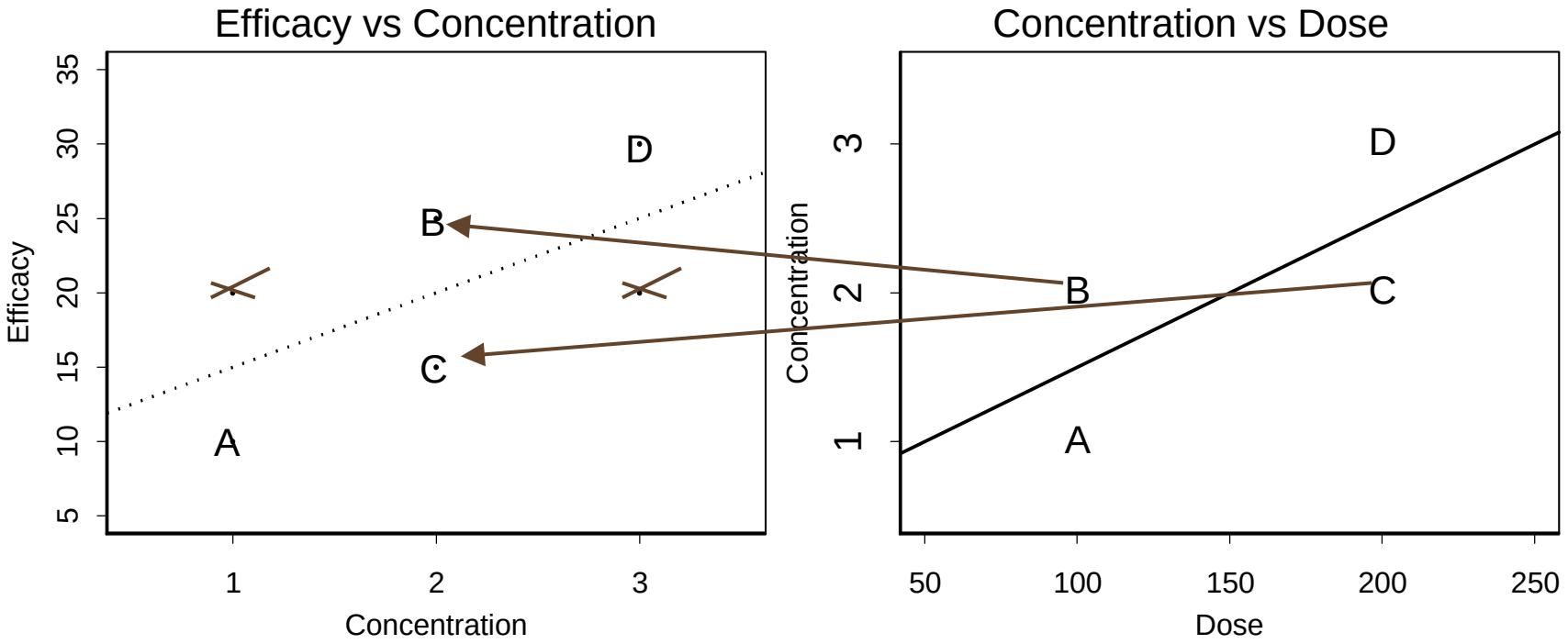


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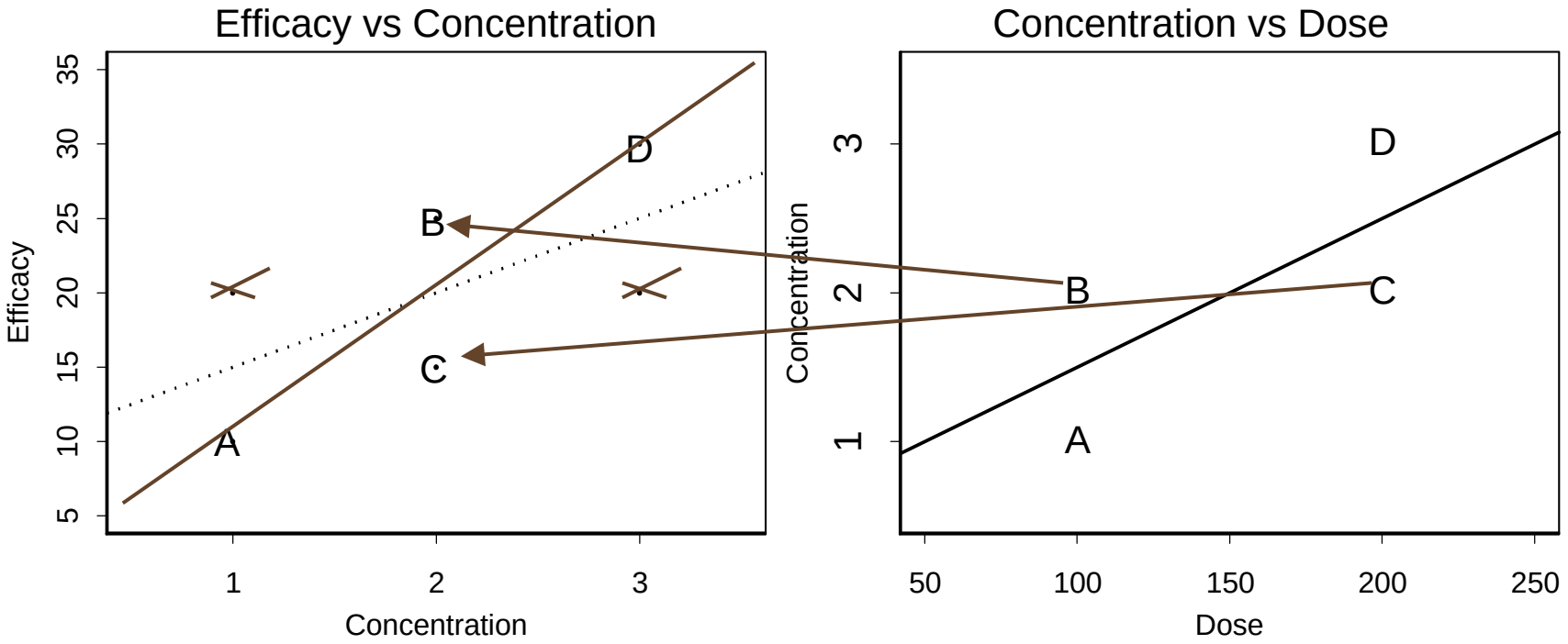


The least-squares fit to the resulting data is a biased (*confounded*) estimate of the true PK/PD relationship



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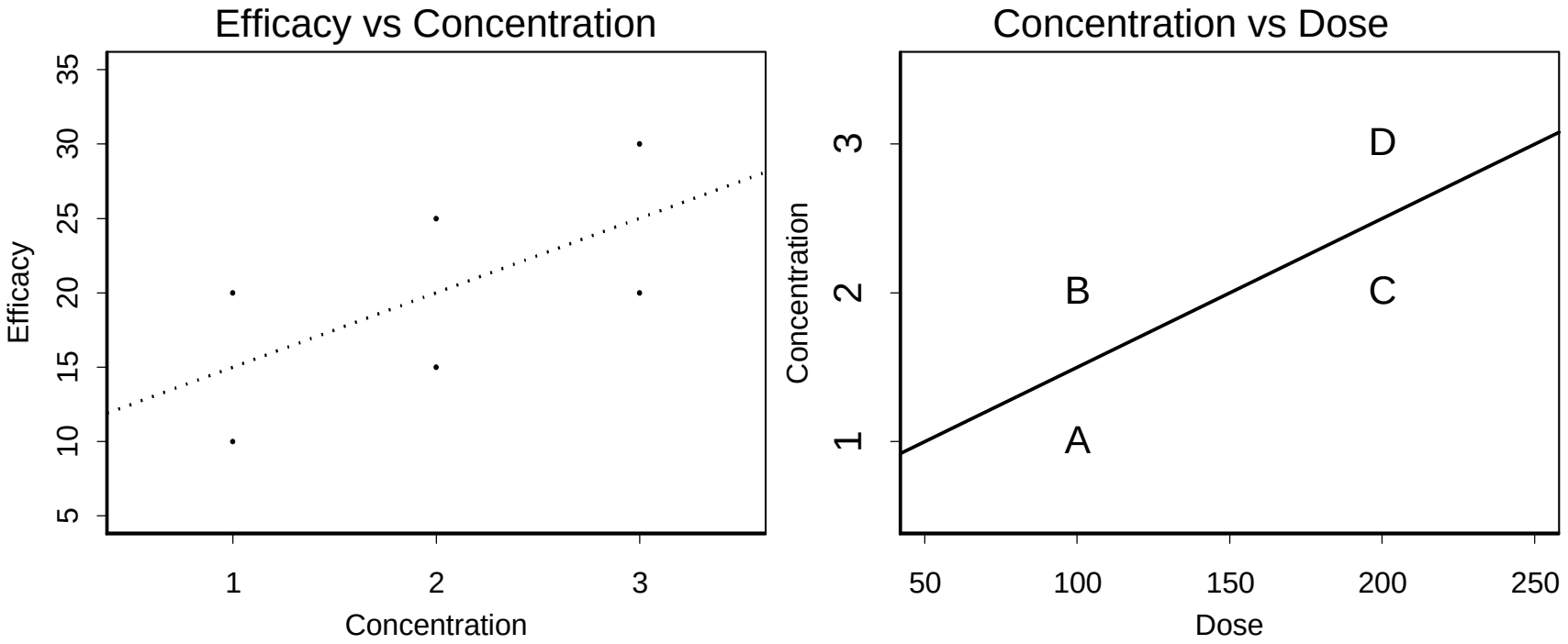
# Dose-controlled PK/PD, scenario 2




Suppose that in a dose-controlled trial, patients who have **higher concentrations at a given dose** are equally likely to have **high or low efficacy at a given concentration**, and the same for patients with lower concentrations



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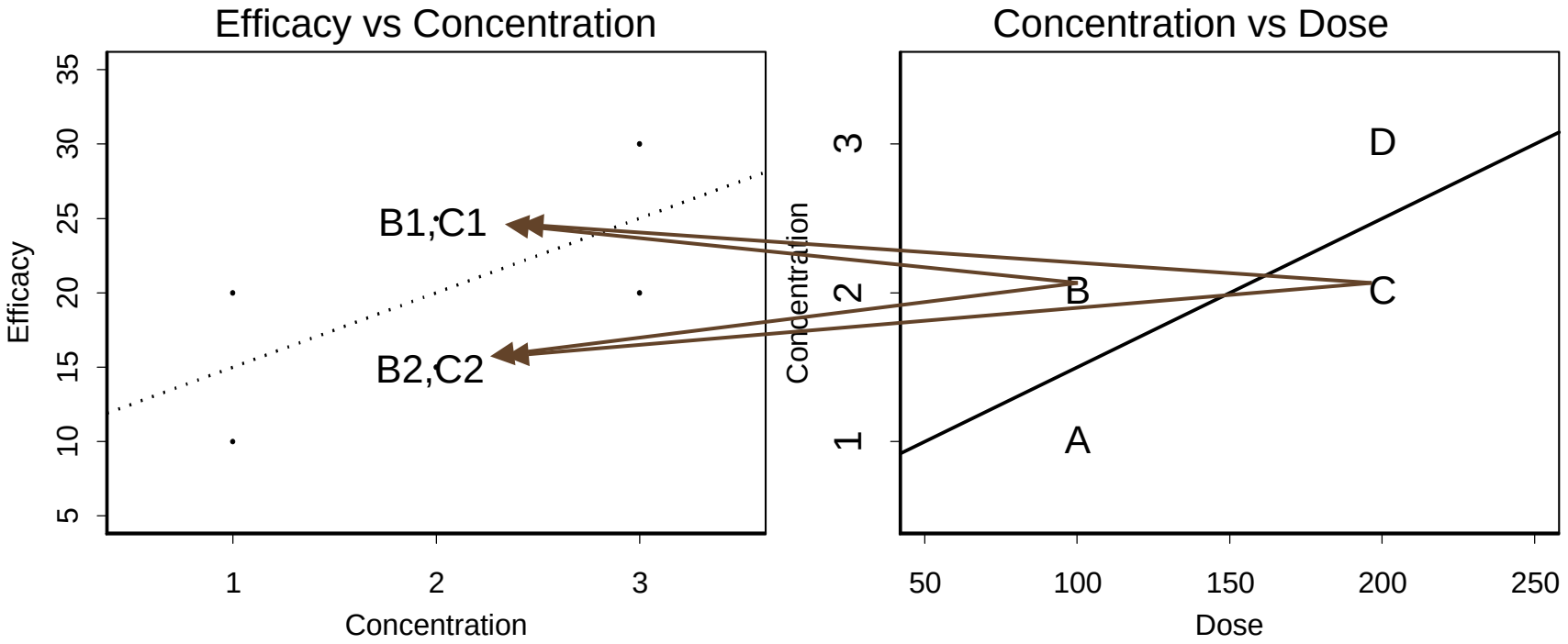


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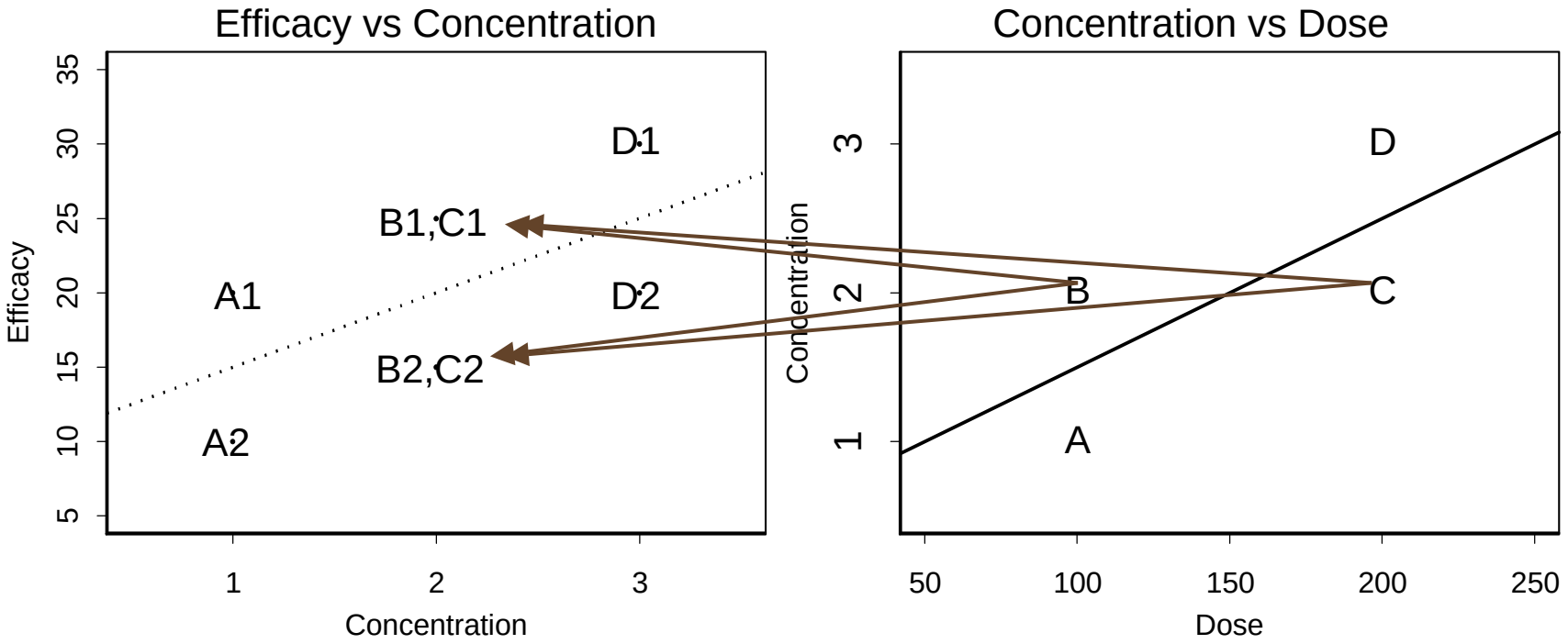


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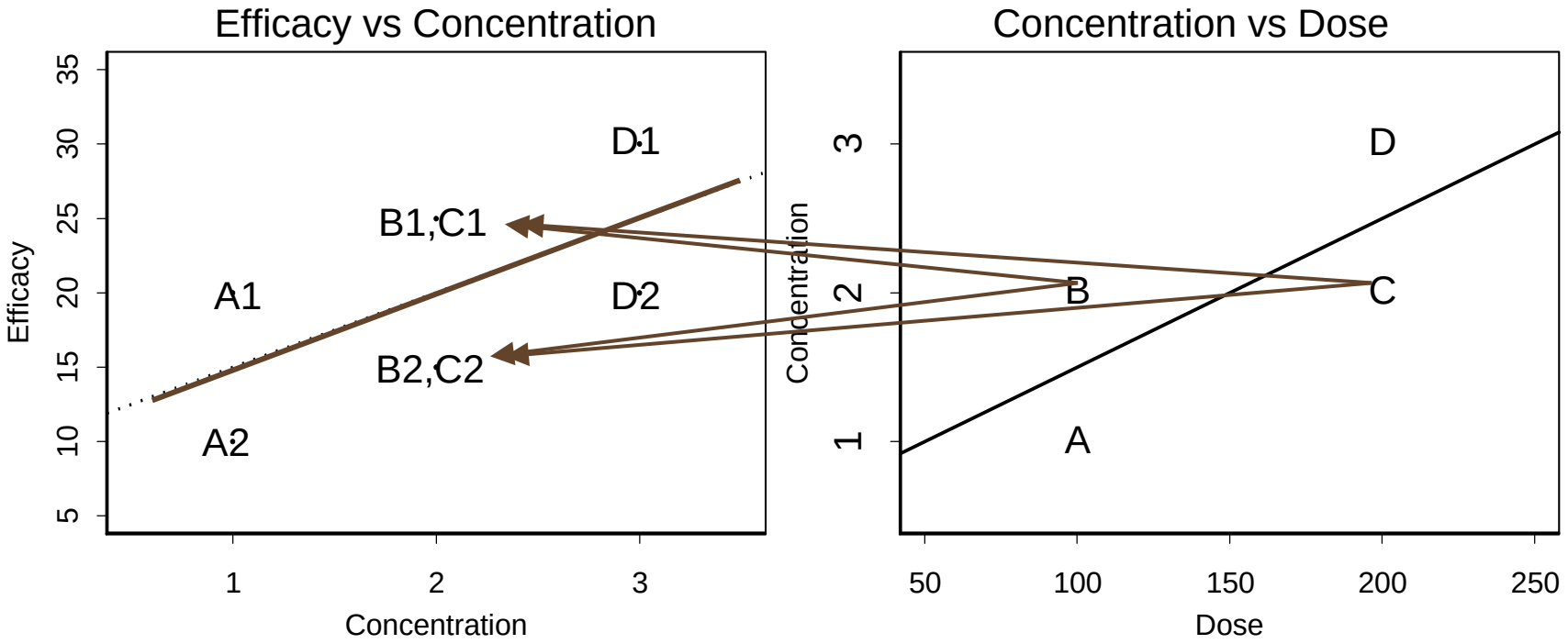


The least-squares fit to the resulting data is an unbiased (*unconfounded*) estimate of the true PK/PD relationship



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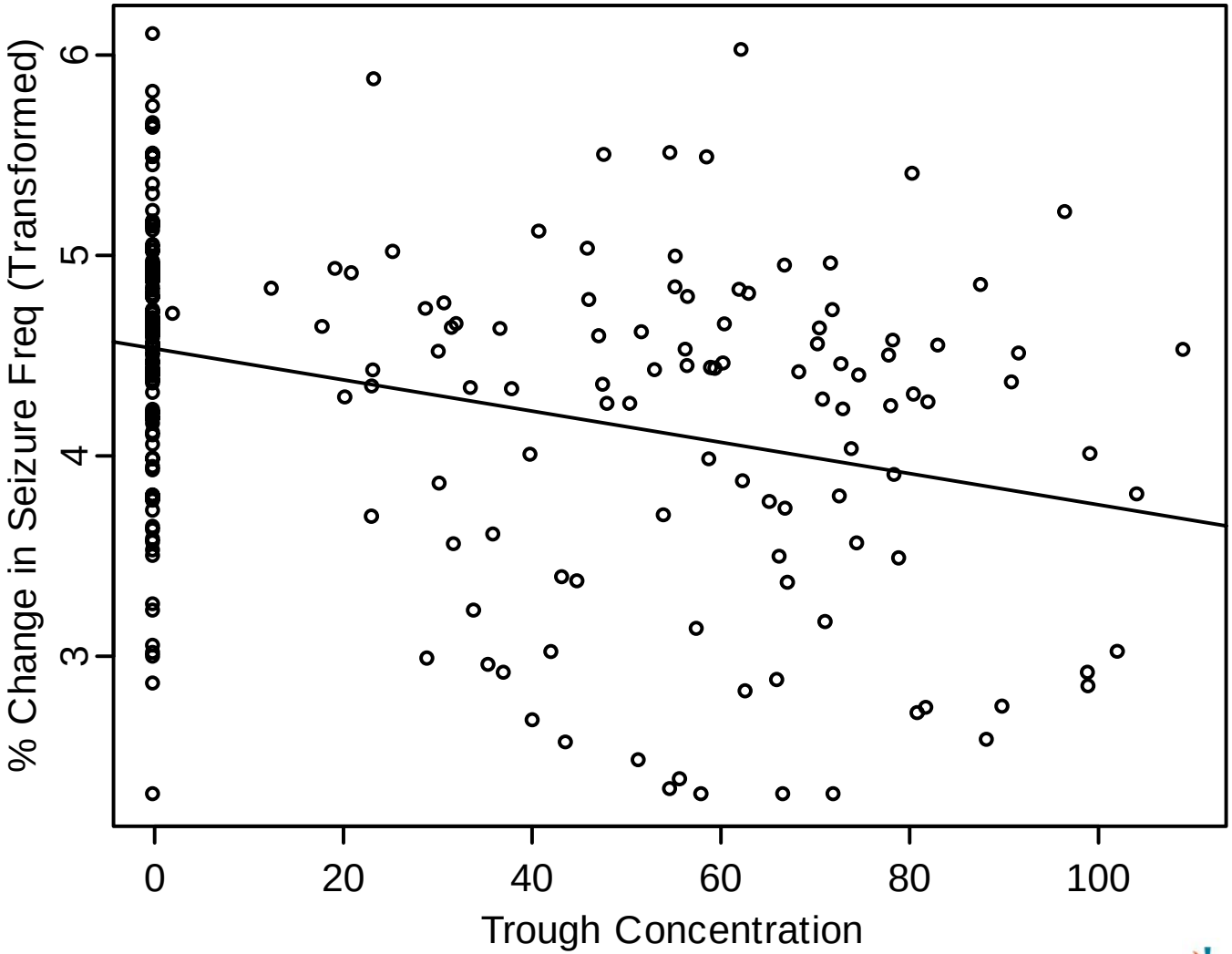
# Summary

- If the relationship of PK to PD is not independent of the relationship of dose to PK, then the estimated PK/PD relationship may be confounded.

# Trileptal adjunctive pediatric PK/PD



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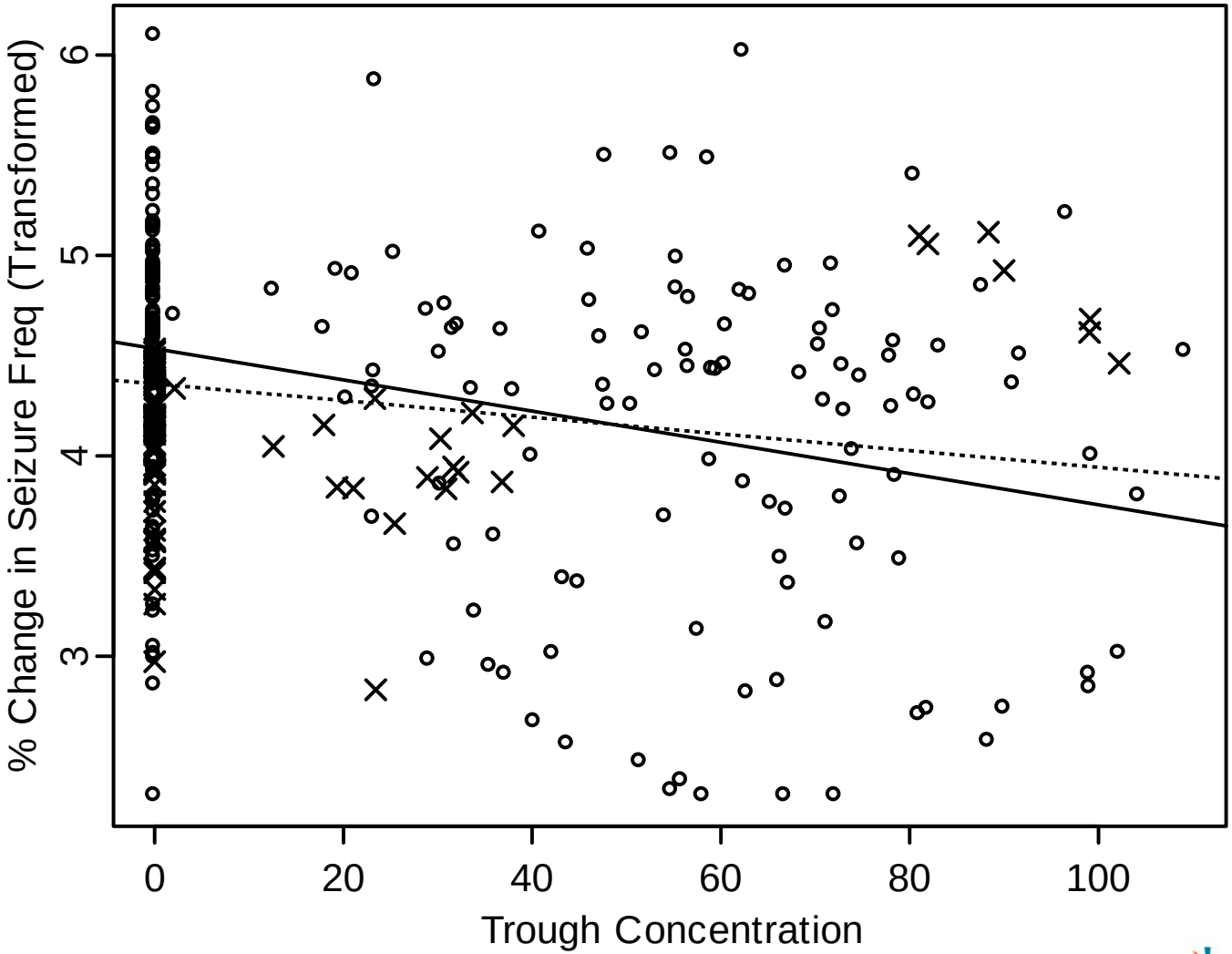
# … or Trileptal adjunctive pediatric PK/PD ???



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# Confounding or not – how do you know?

- You never do for certain
- Scientific reasoning may argue for implausibility of confounding
- Skeptic response: “There are more things in heaven and earth, Horatio, than are dreamt of in your philosophy”*
- Some diagnostics can be reassuring

*Hamlet, Act I, Scene V

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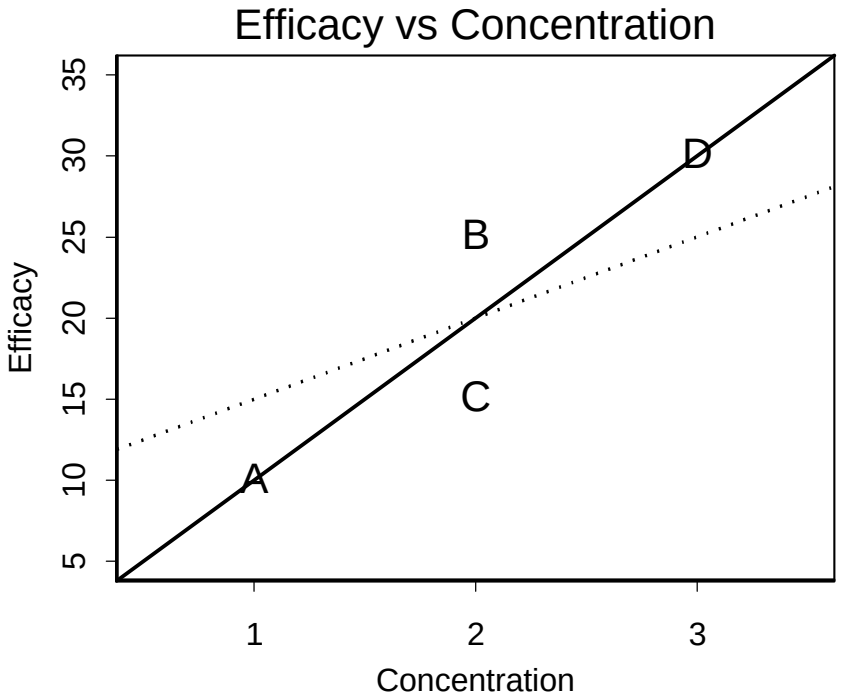
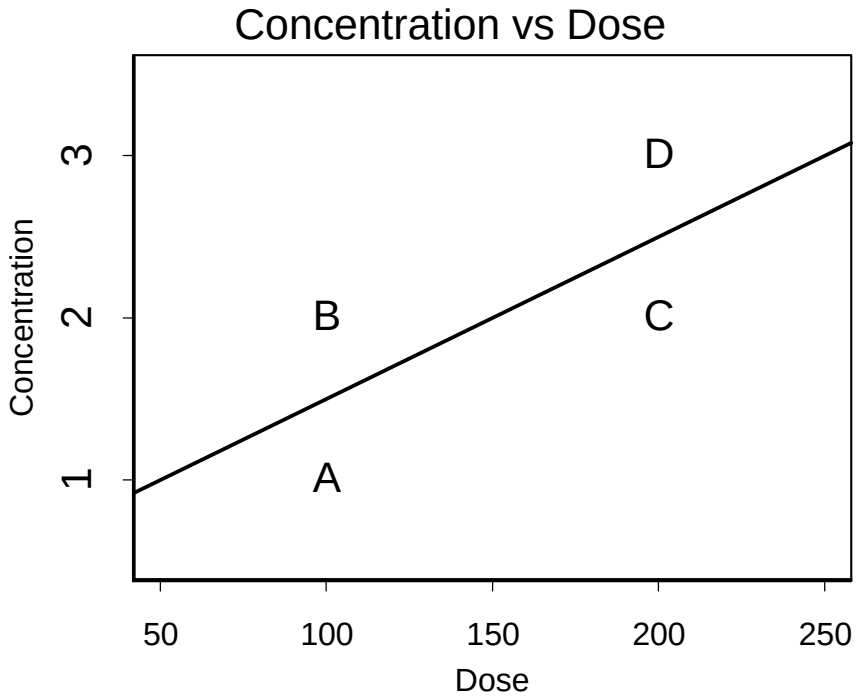
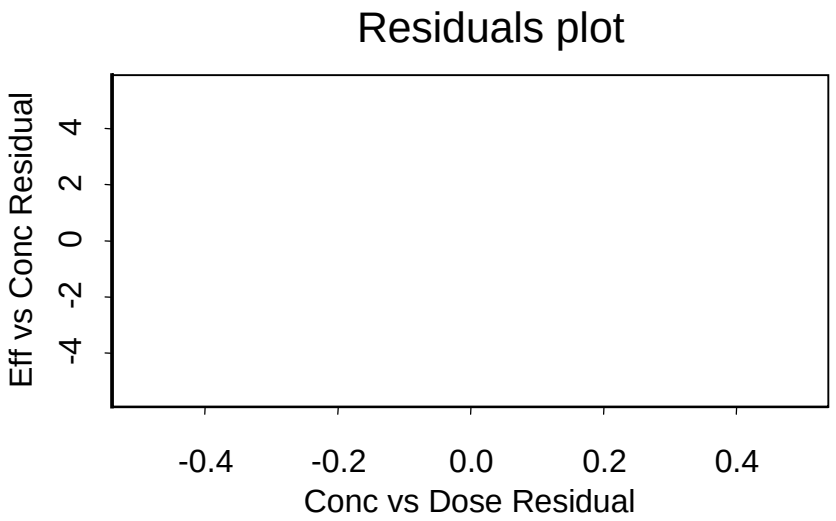
# Residuals for Scenario 1, bias in PK/PD



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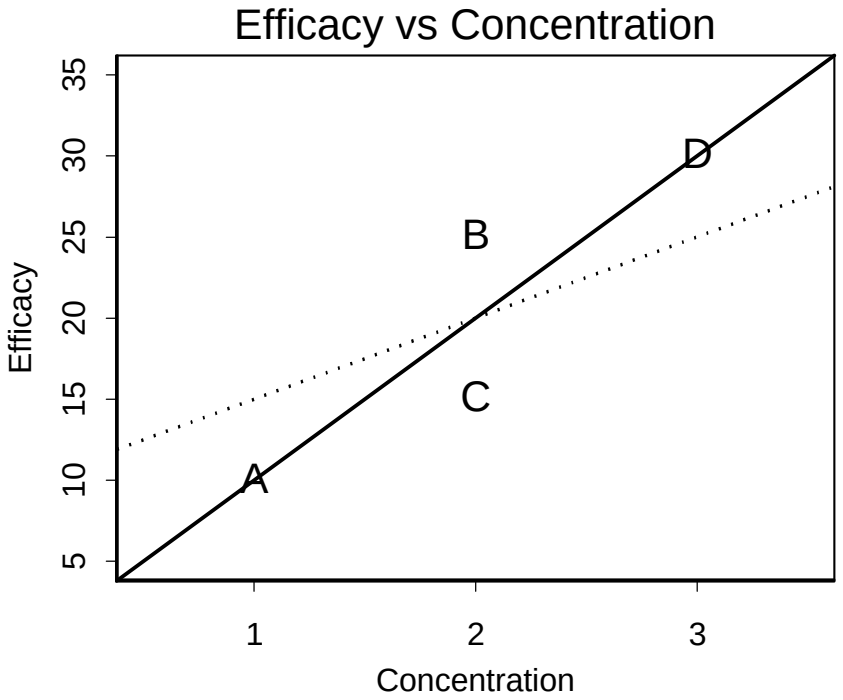


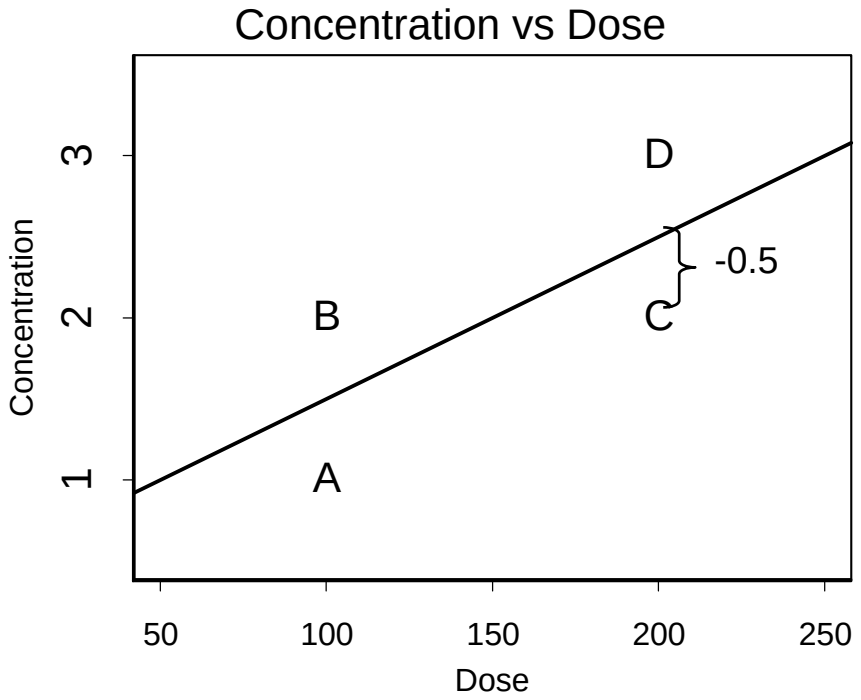


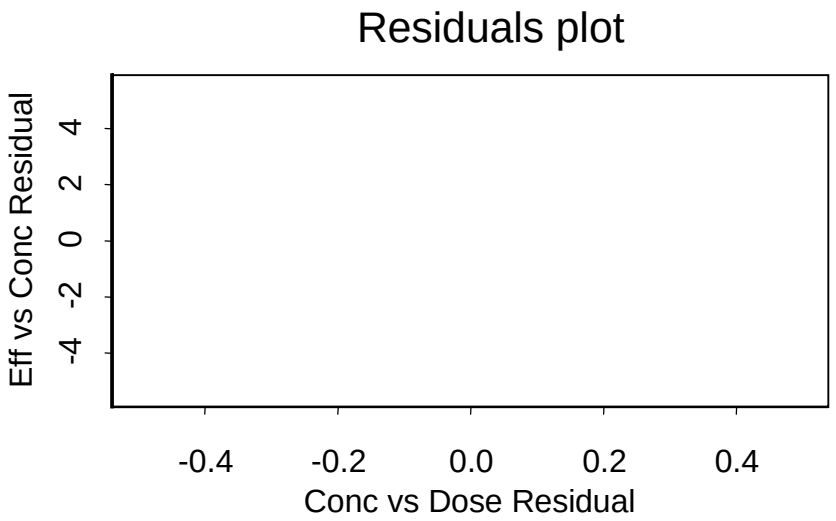




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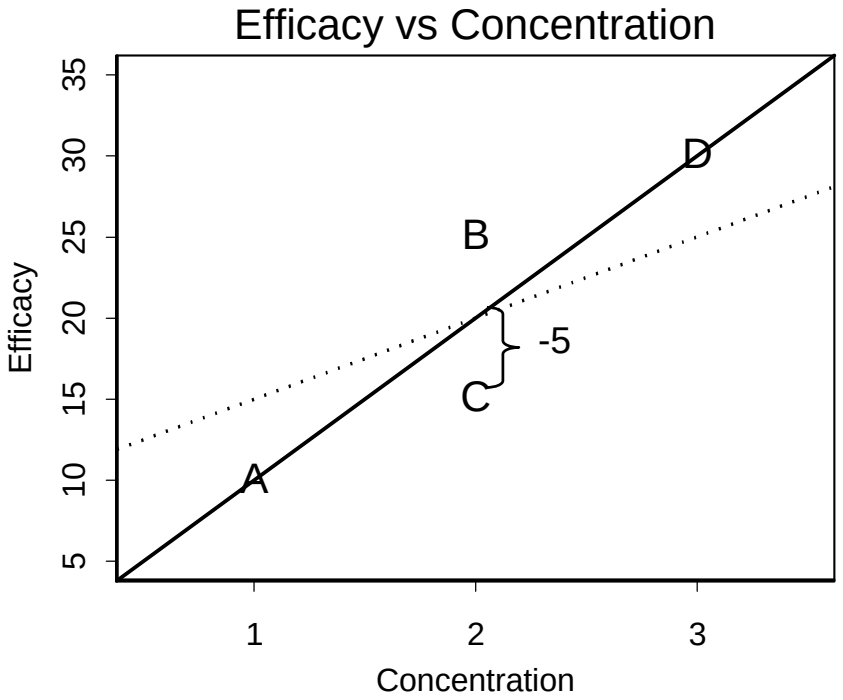


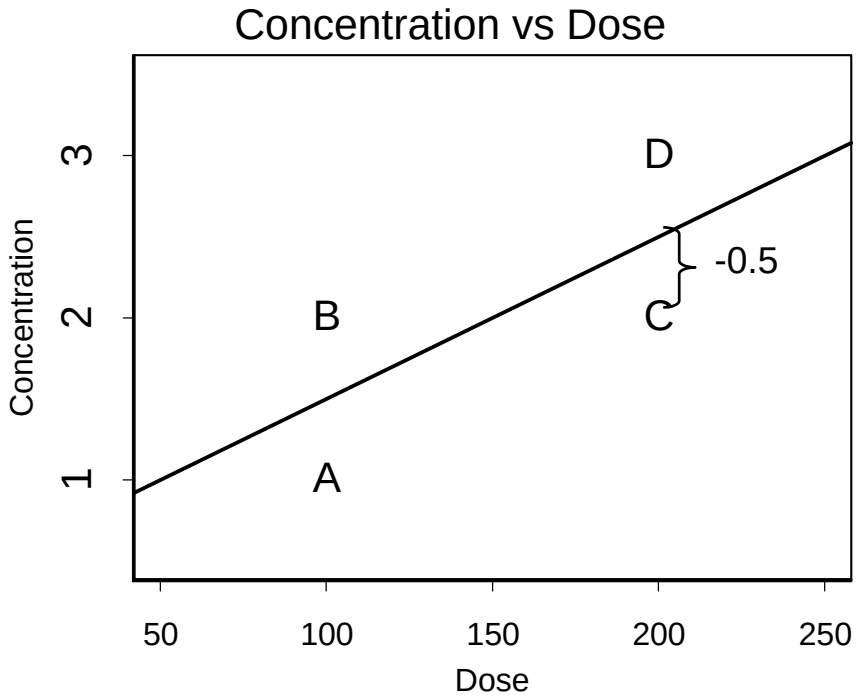


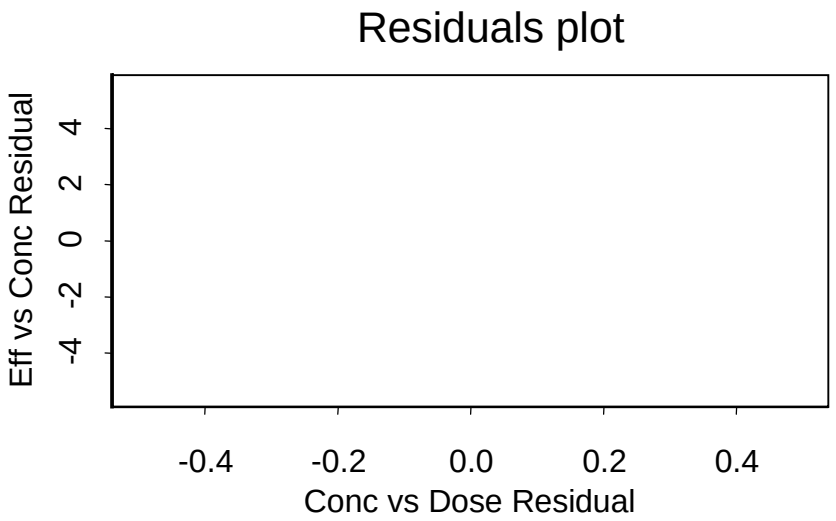




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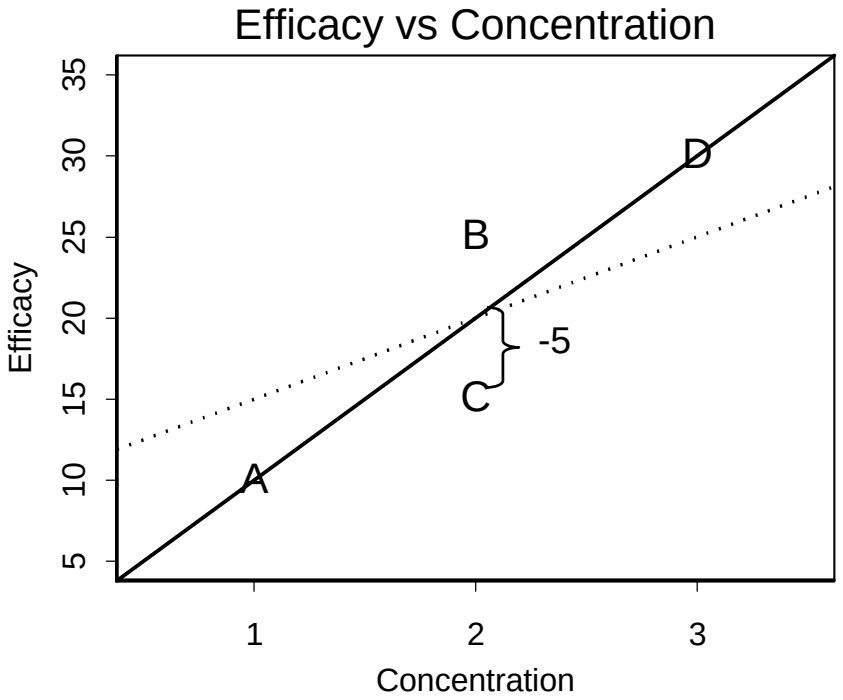


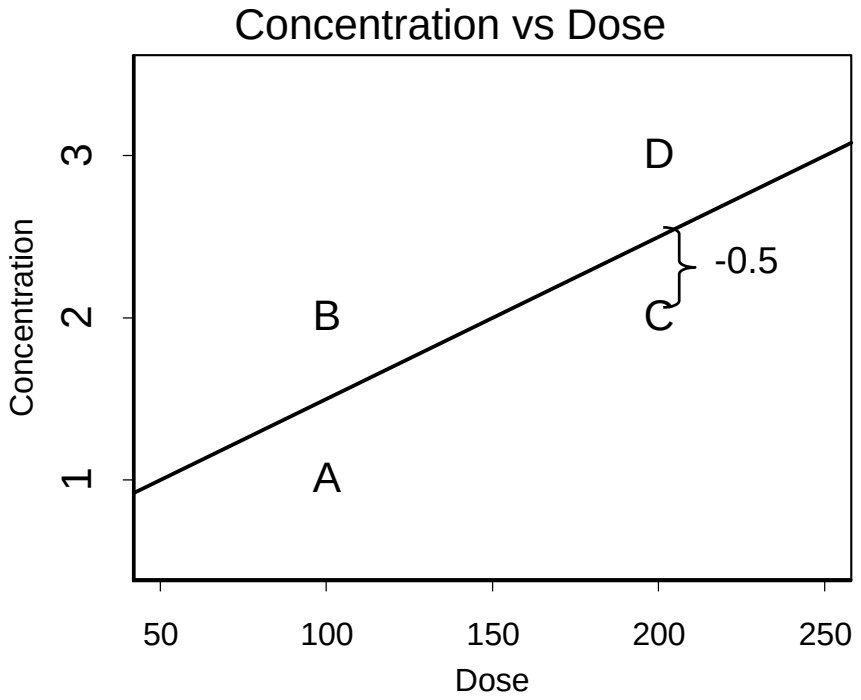


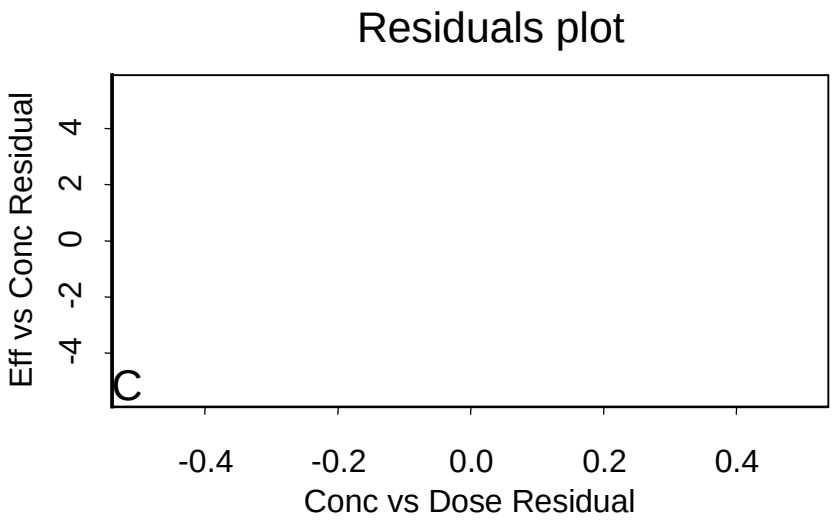




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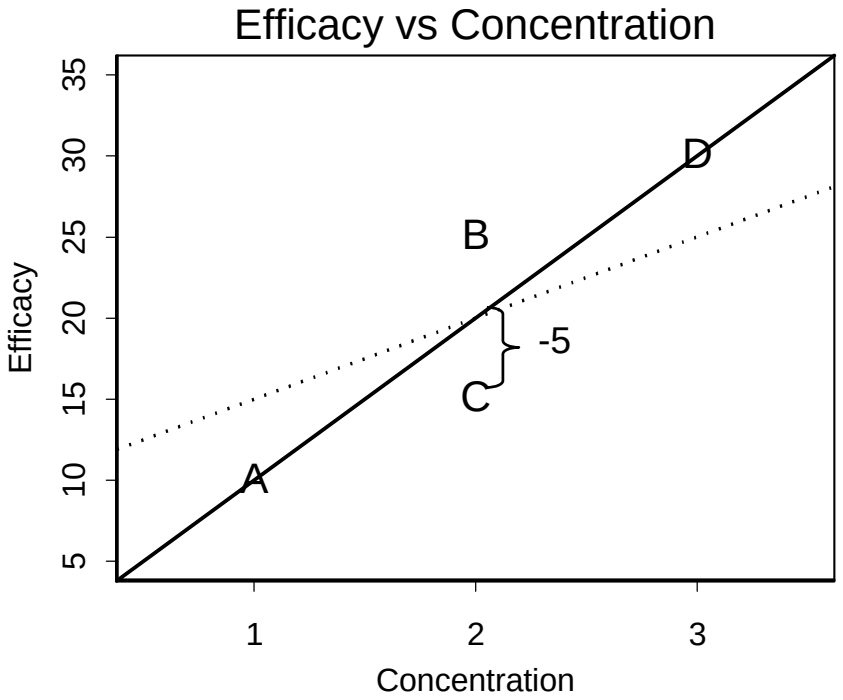


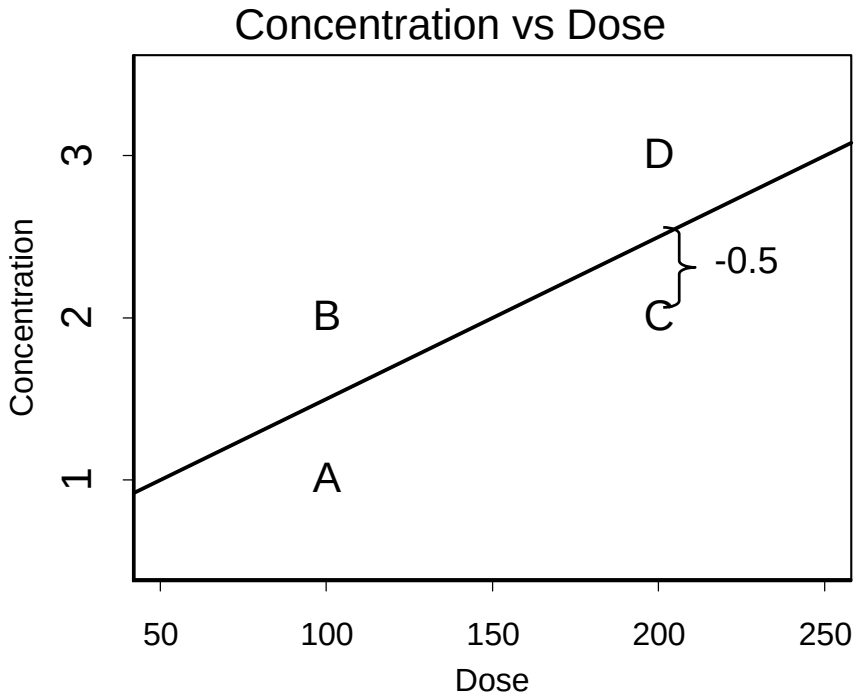


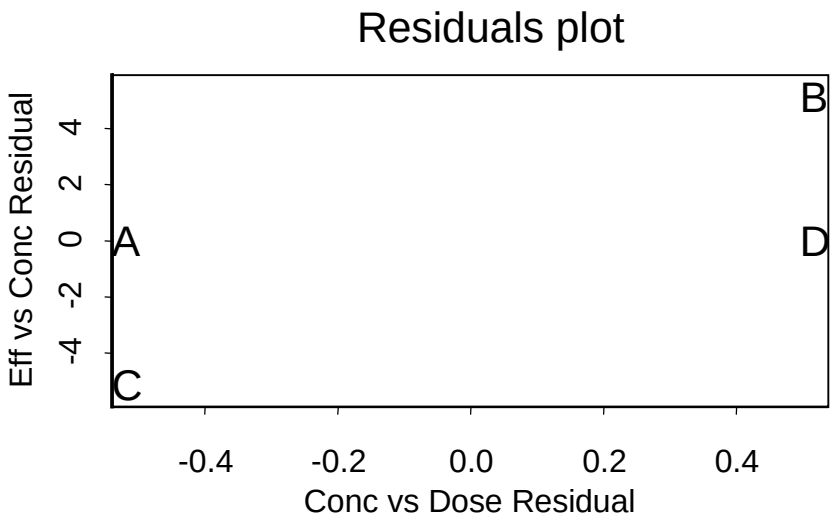




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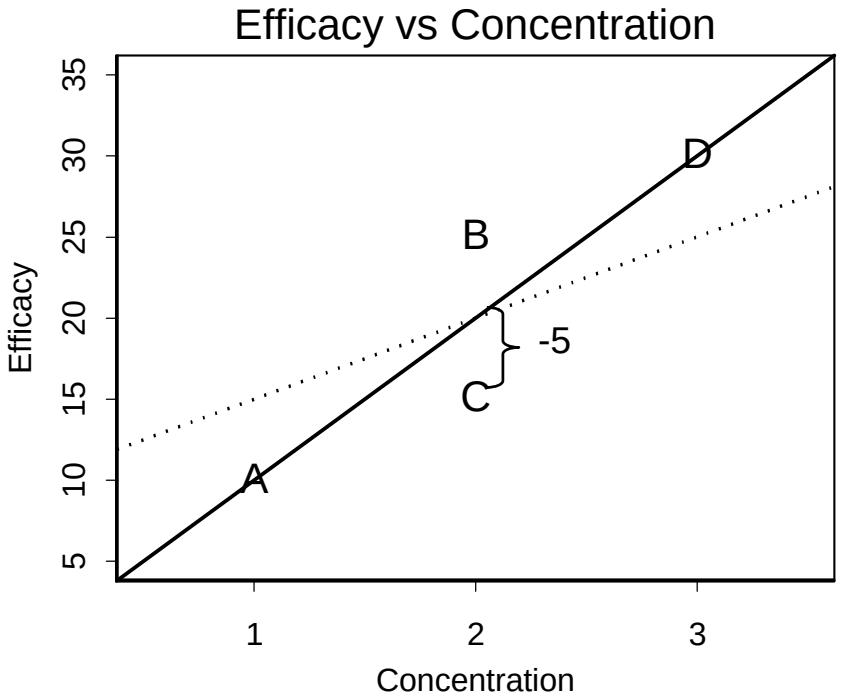


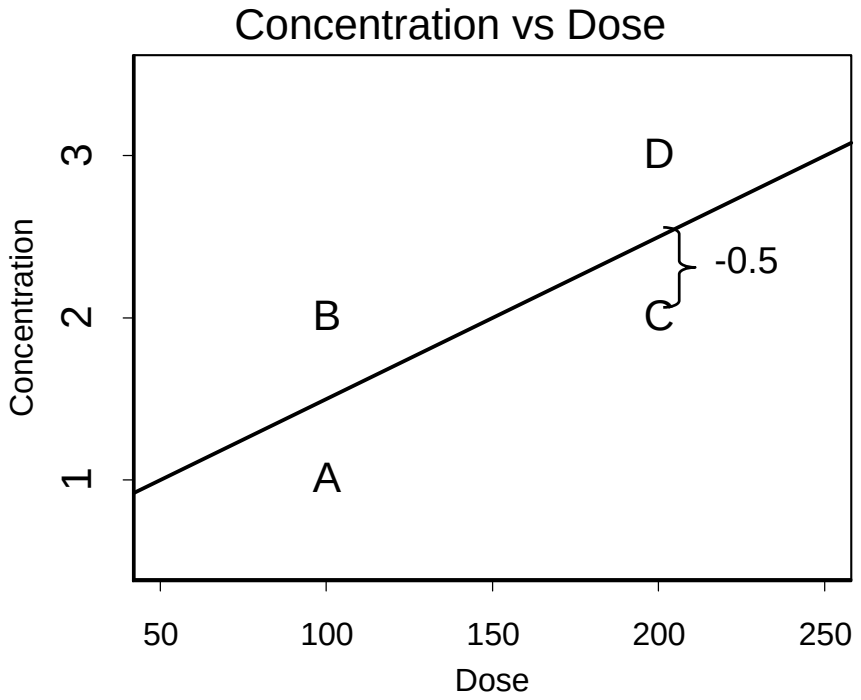


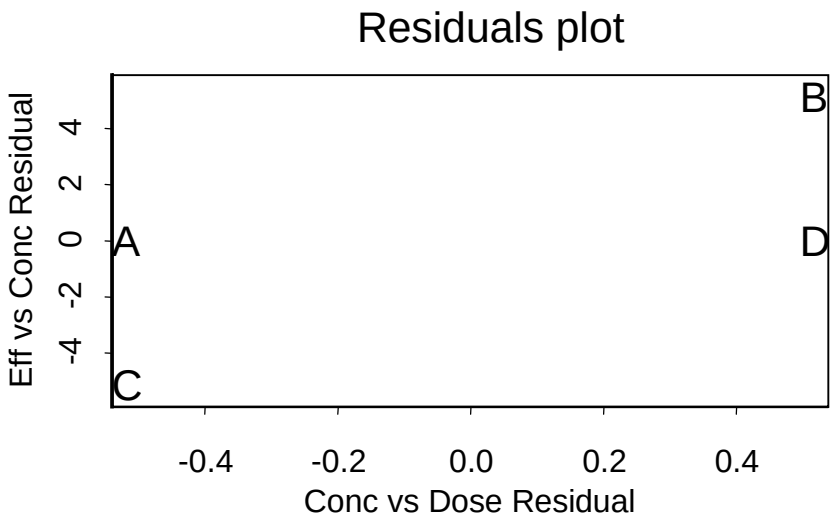


When the dose-controlled study causes confounding in the PK/PD relationship, the residuals exhibit correlation.



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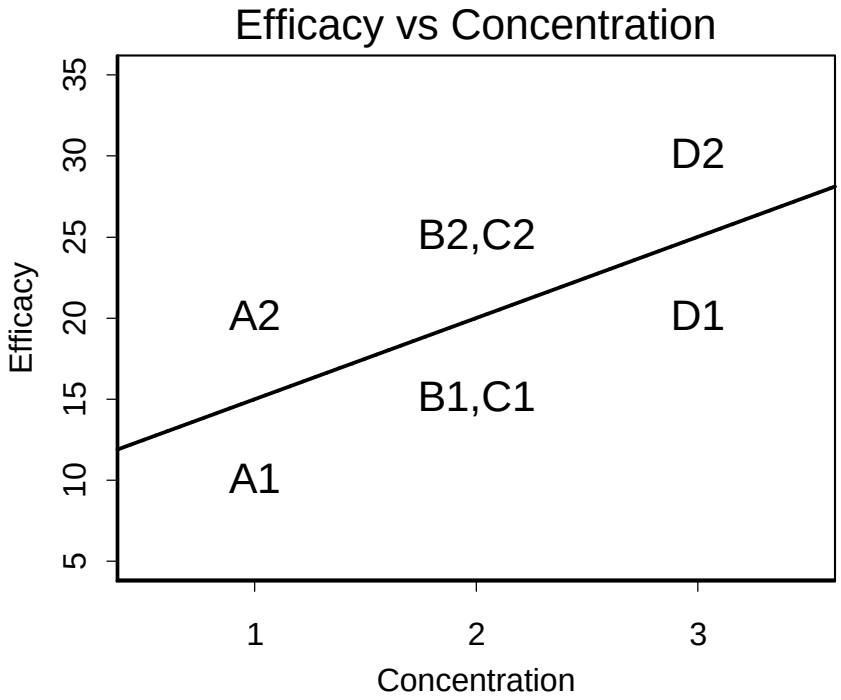
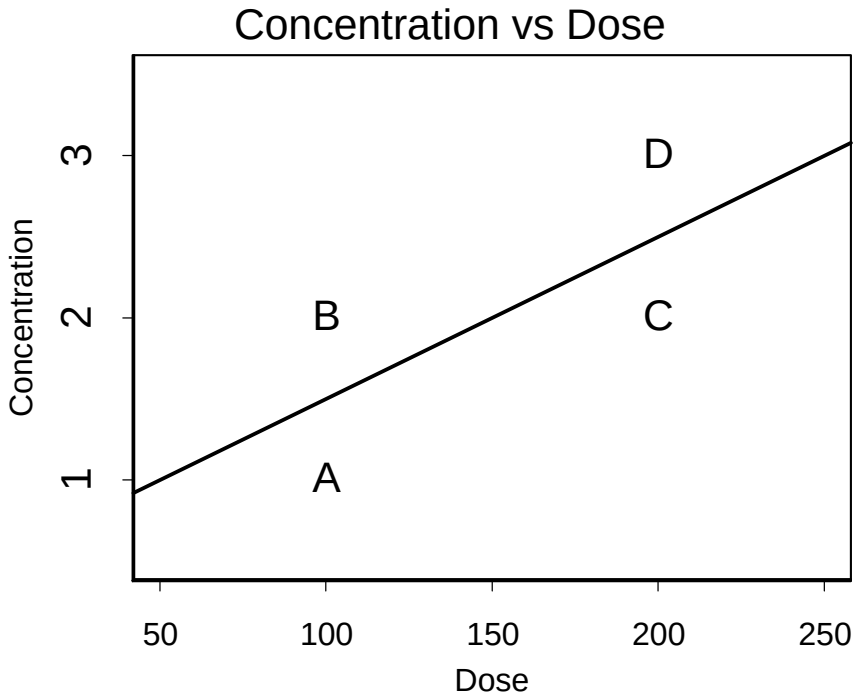
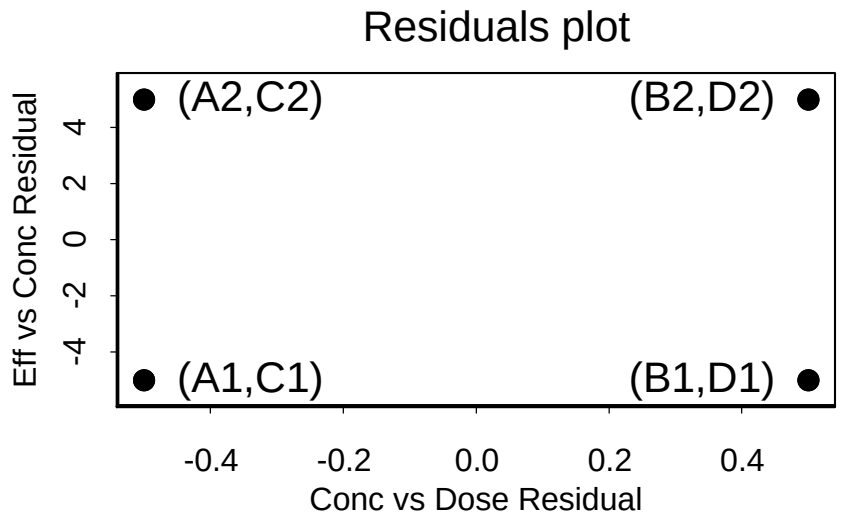
# Residuals for Scenario 2, ***no*** bias in PK/PD

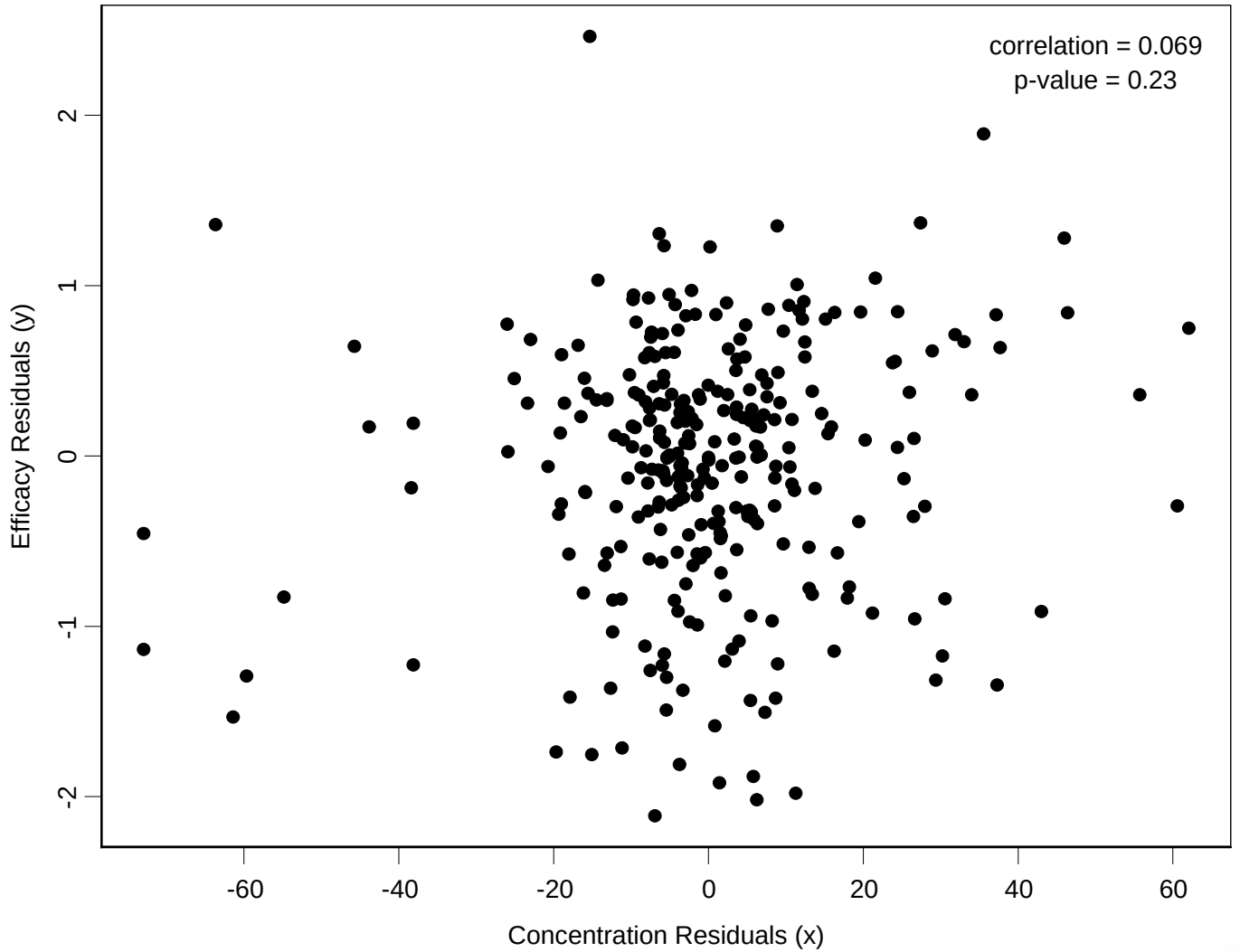



When the dose-controlled study **does not** cause confounding in the PK/PD relationship, the residuals **do not** exhibit correlation.

# No correlations were observed



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# Diagnostics for confounding

- Examine correlations of residuals
- Rubin-causal-model sensitivity analysis
- Instrumental-variables regression

- See *Statistics in Medicine* 2007; 26:290-308

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- The solution: diagnostics for confounding
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# Lesson learned

- When the stakes are high, modeling is held to a high standard
- Prospective validation of models is important

# Acknowledgements


- Donald B. Rubin, Lewis B. Sheiner
- David Aitken, Deborah Bennett, Joseph D'Souza, Hai Jing, Mary Ann Karolchyk, James Lee, Peter Mesenbrink, William Sallas, Werner Schmidt, Greg Sedek, Claire Souppart, Mara Stiles, Yvonne Sturm, Audrey Wong, Rocco Zaninelli
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