Impact of handling BLQ PK data on PD estimation

Explicit modeling of BLQ data in WinBUGS® reduced bias in the PD predictions - a preclinical example

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Agenda

- Objective
- Method
  - Data
  - Exploratory analysis
  - Modeling approach
- Results
  - PK modeling
  - Impact on PD modeling
- Conclusion

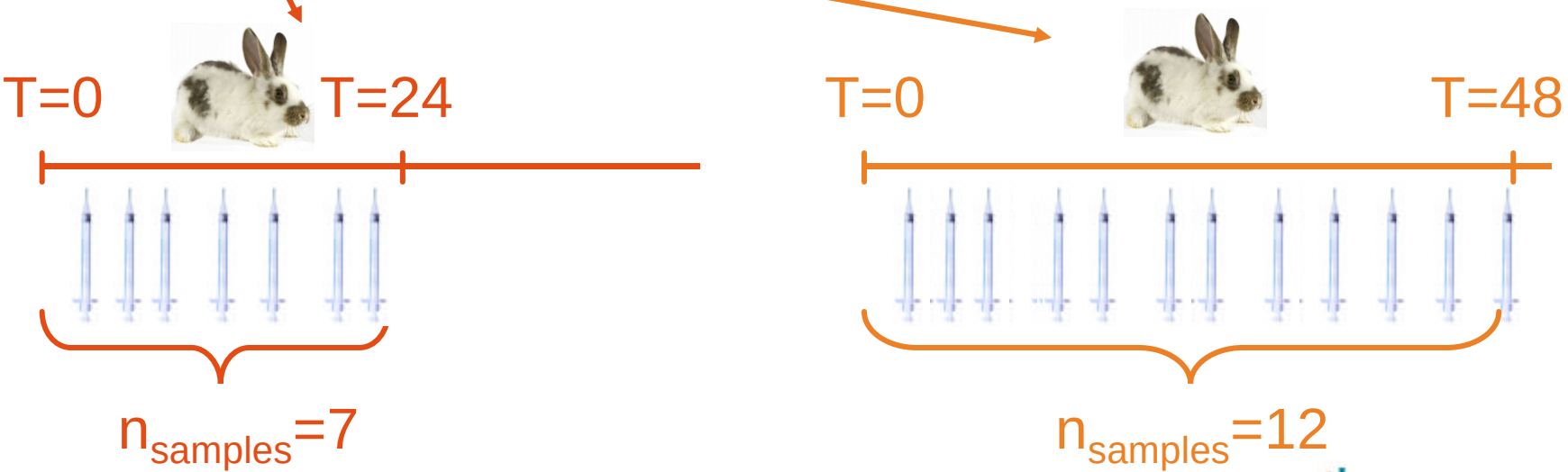
Objective

- To compare 2 drugs, a lead compound and its backup on a pharmacodynamic endpoint based on their relative potency in animals
  - These 2 drugs are from the same therapeutic class
  - The pharmacodynamic endpoint studied is a biomarker activity
  - The effect of the drugs is to produce its inhibition

Method
Data

- Study designs:

	LEAD					BACKUP			
	DOSAGE in mg/kg								
	0.1	0.3	1	2	10	2	10	30	100
STUDY 1				$N_{animals}$=6					
STUDY 2	$N_{animals}$=4				$N_{animals}$=4		$N_{animals}$=4		



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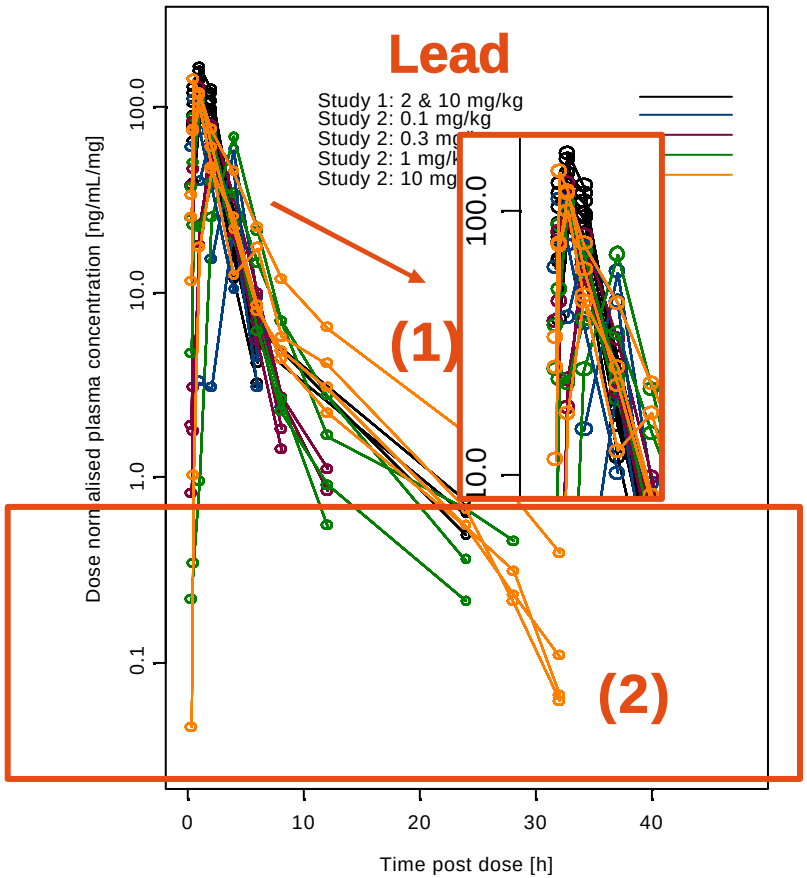
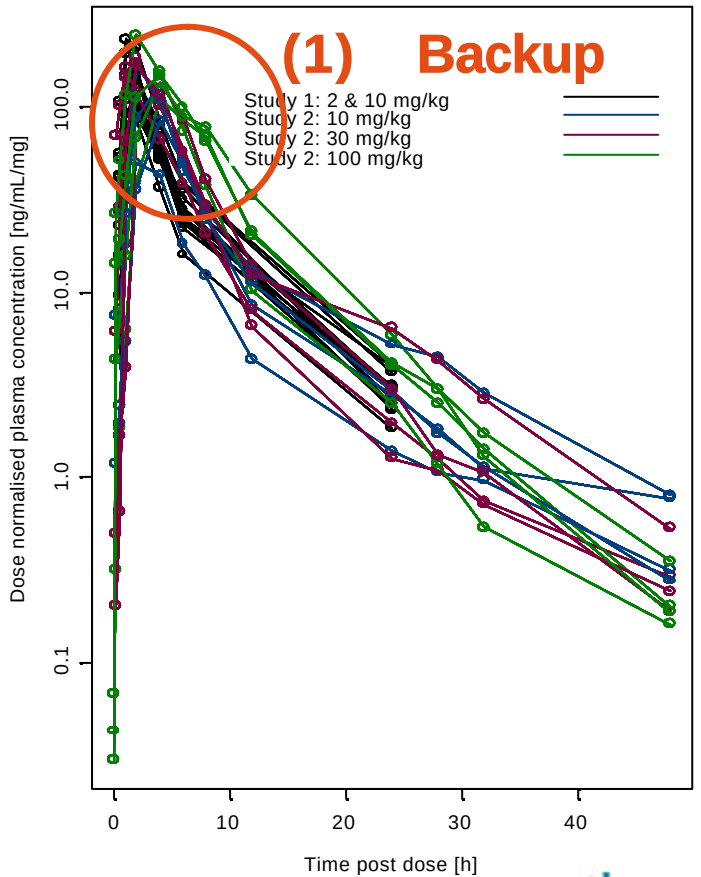
Method

Exploratory analysis (PK)

- Absorption variable (Cmax and Tmax) (1)
- Paucity of data in IC50 area for the lead (2)





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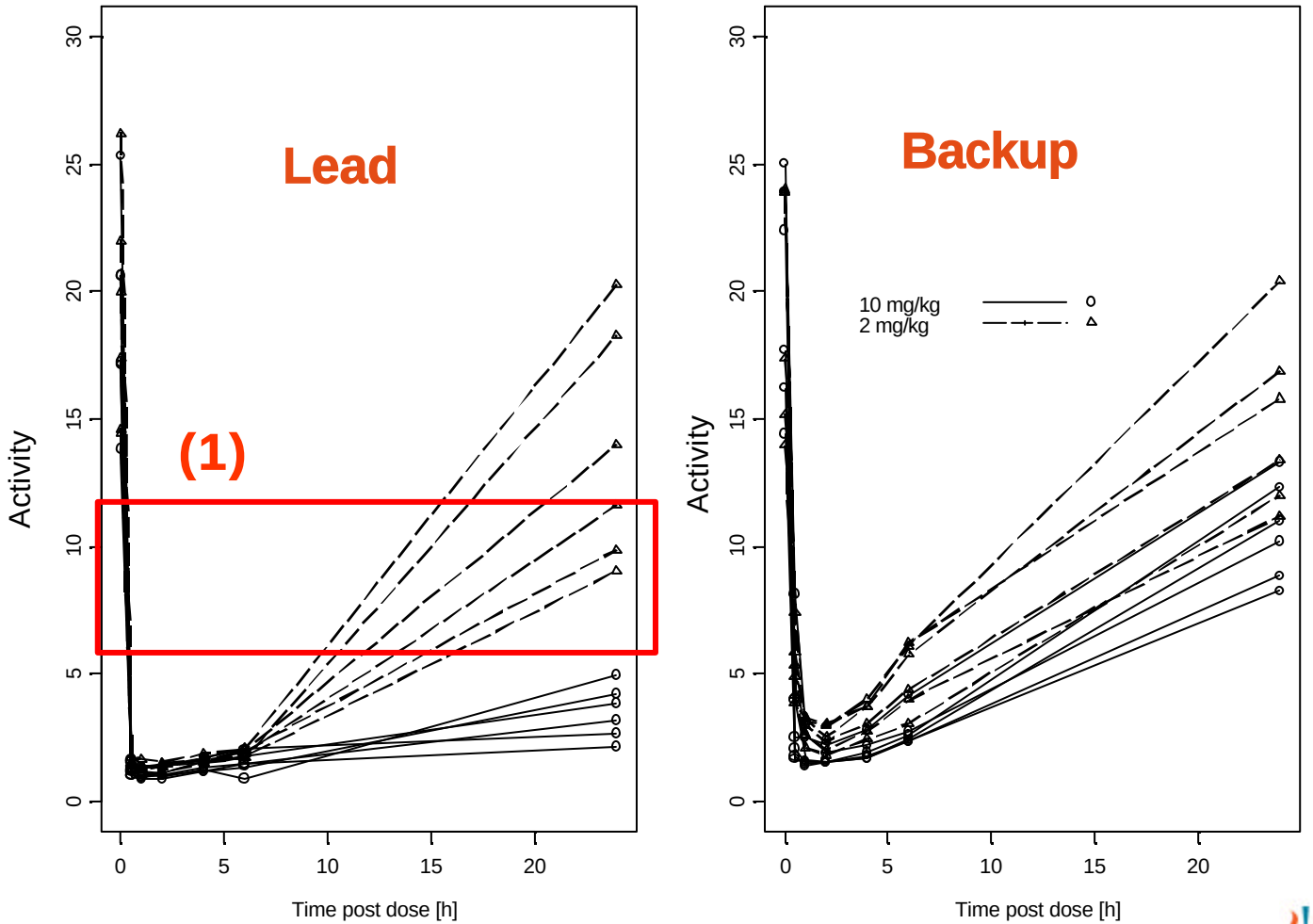
Method

Exploratory analysis (PD)

- STUDY 1 : Paucity of data in IC50 area for the lead (1)



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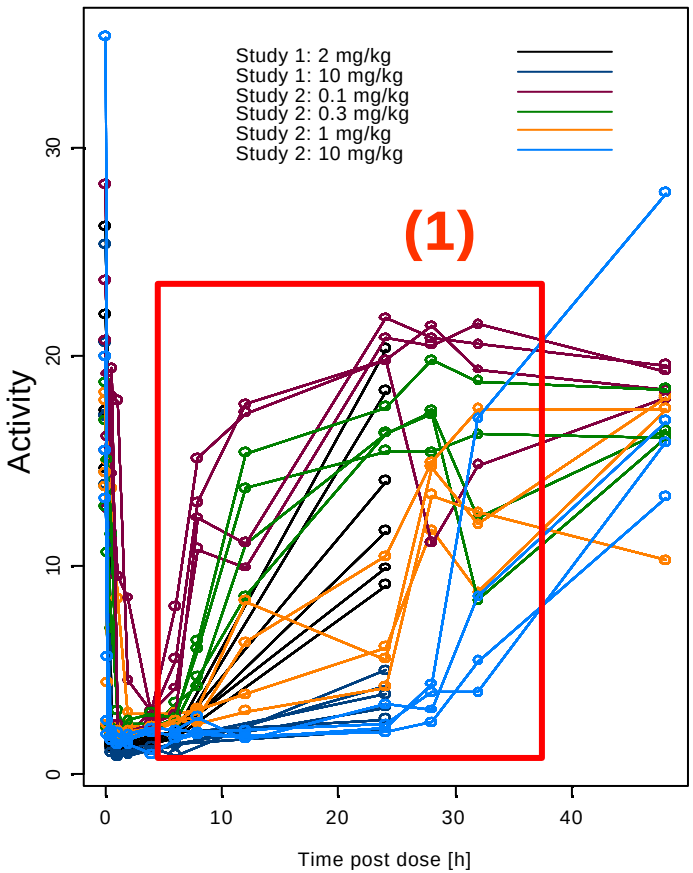
Method

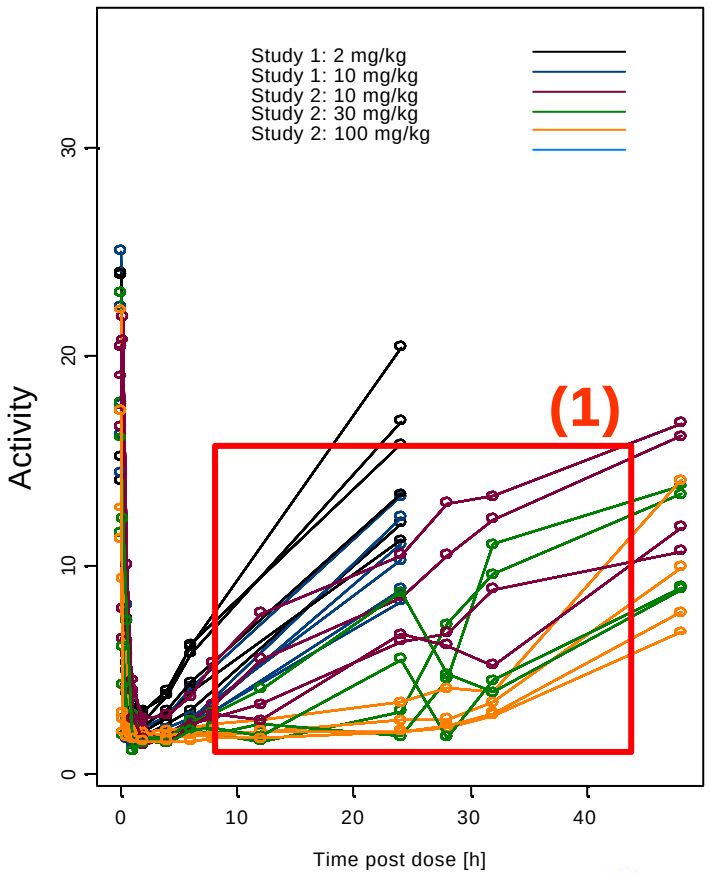
Exploratory analysis (PD)

- STUDY 2: a lot of noise specially in the recovery phase (1)

Lead



Backup



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Method

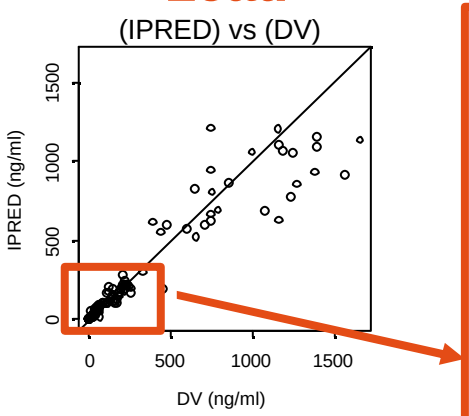
Exploratory analysis → Modeling approach

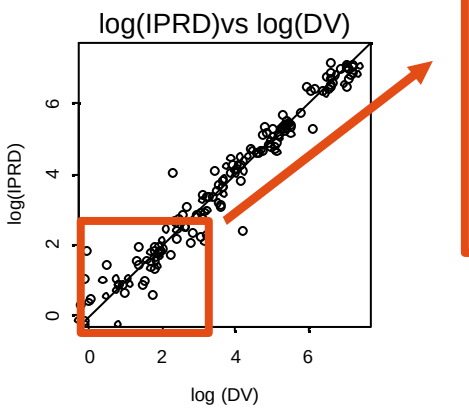
- Sequential PKPD with non linear mixed effect modeling
  - A lot of BLQ data in the PK (n=75/292 / n=2/292, Lead / Backup), paucity of data in IC50 area (Lead), a lot of noise in the PD (Lead / Backup), impossibility to use PD to better estimate PK.
  - Use individual PK prediction as an input for the PD.
- Diverse PK approach tested
  - Challenge for low concentrations and BLQ data
    - NONMEM V (IOV on F and Ka, log transformation of data), all BLQ data discarded
    - WinBUGS ® (LOQ taken into account identifying BLQ data, log transformation of data, each occasion = different animals)
- PD modeling in NONMEM
  - same Emax for the 2 drugs, different IC50s, different error models for the 2 studies

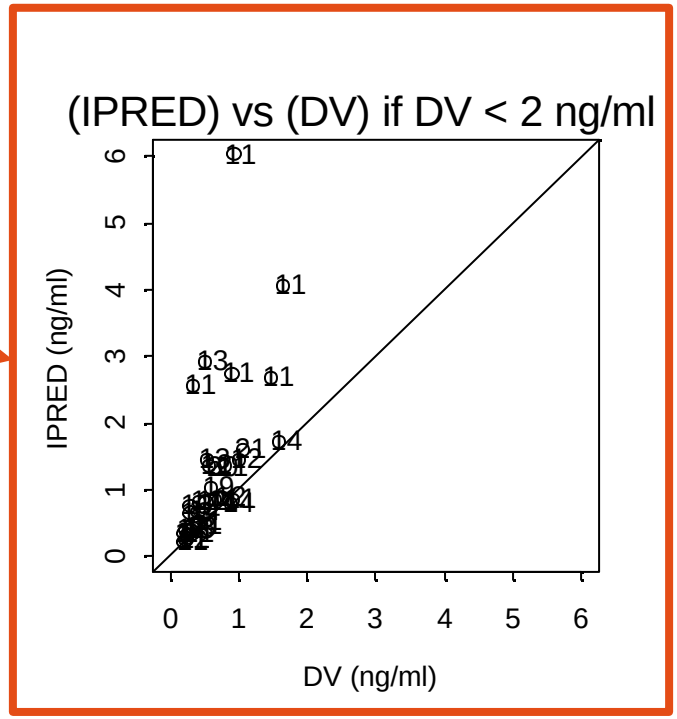
Results
PK modeling

- Goodness of fit, NONMEM
  - For the lead, biased estimation of individual predictions in IC50 area

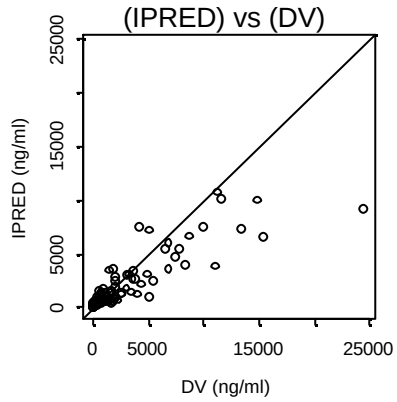
Lead

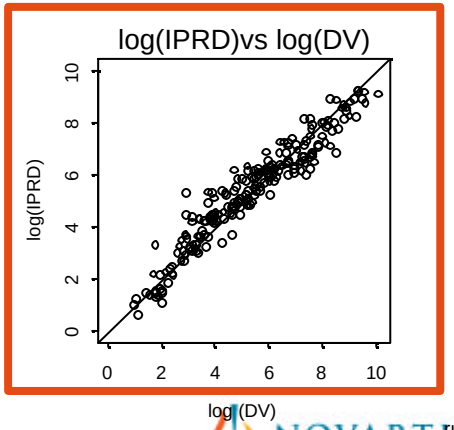






Backup





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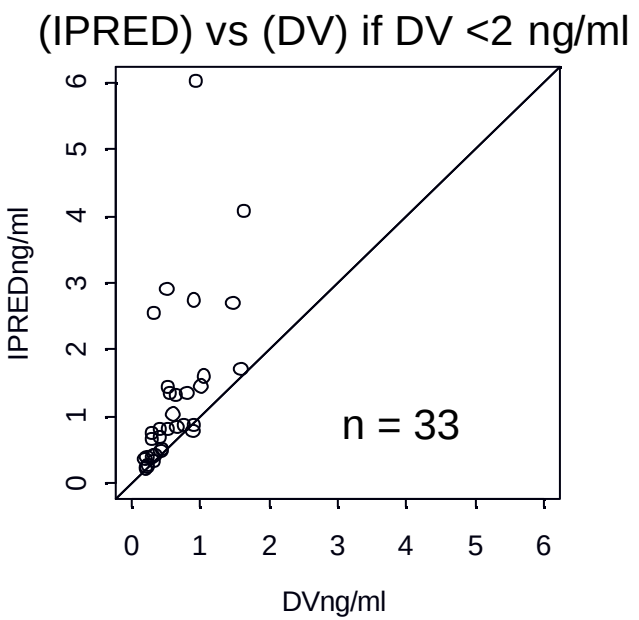
Results

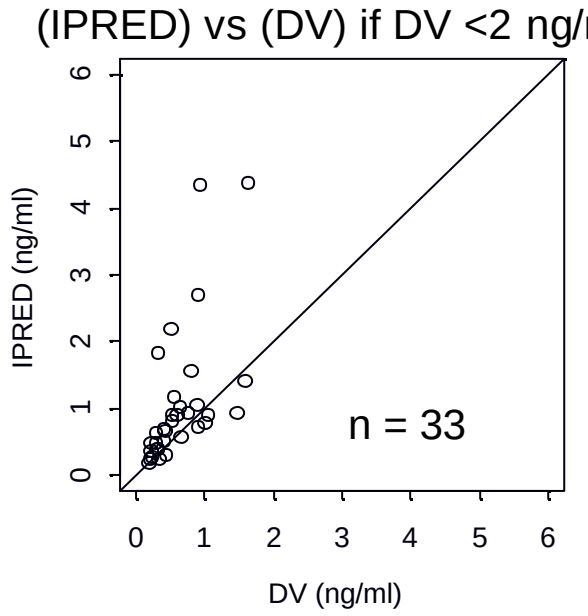
PK modeling, for the LEAD

- Goodness of fit in IC50 area, comparison with WinBUGS ®
  - Biased estimation of individual predictions in IC50 area
  - No real distinction between NONMEM and WinBUGS ®

NONMEM



WinBUGS ®



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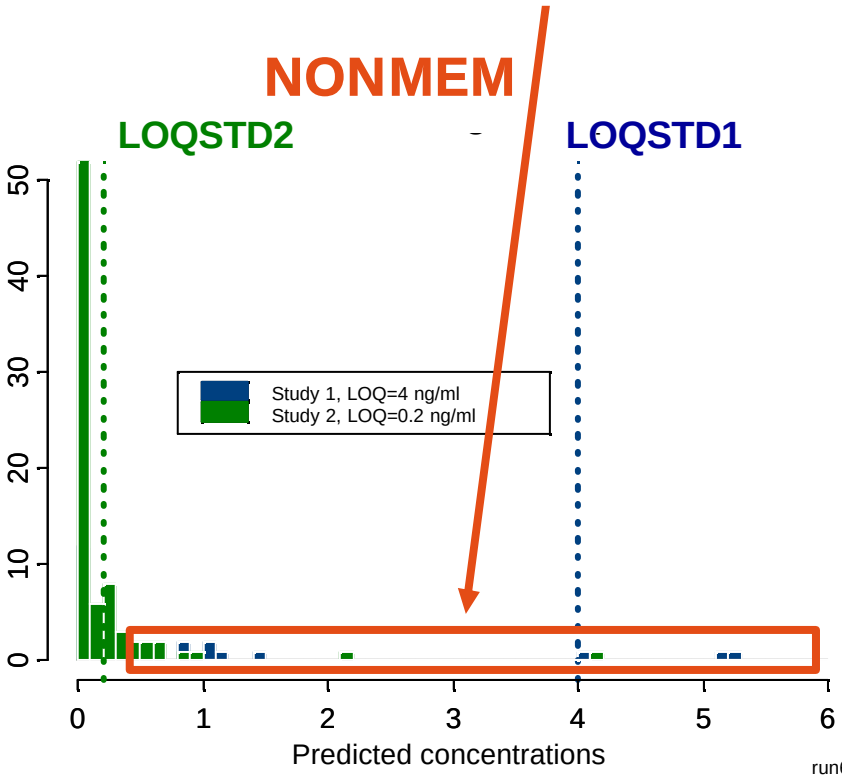
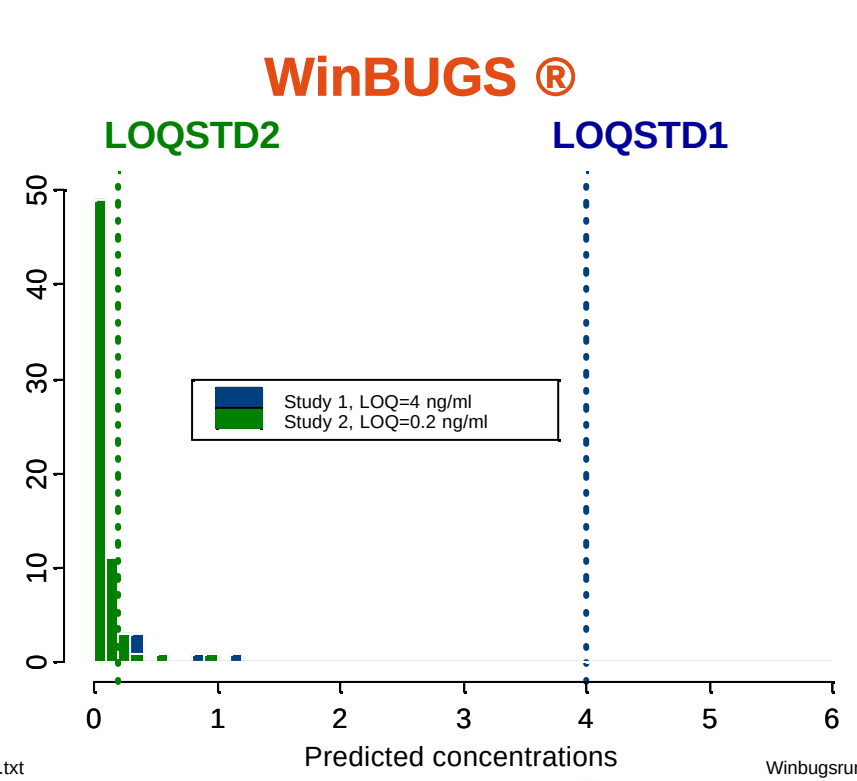
Results

PK modeling, for the LEAD

- Distribution of BLQ predictions, comparison with WinBUGS ® Estimation of BLQ data above LOQ for the 2 studies (in error)
  - Frequent in NONMEM, unusual for WinBUGS ®





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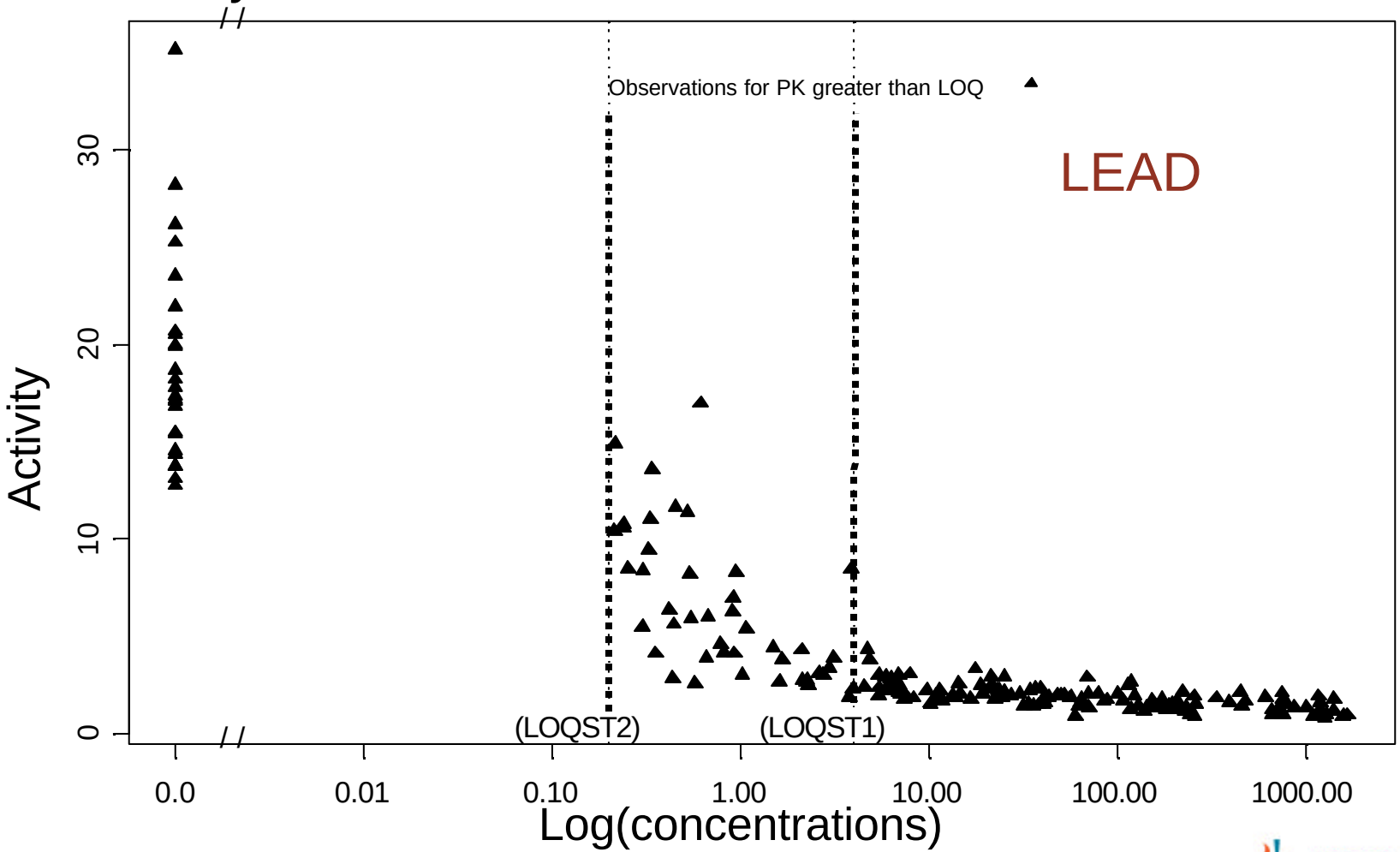
Results

PK influence on PD estimation

- If only observed PK data



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Results

PK influence on PD estimation

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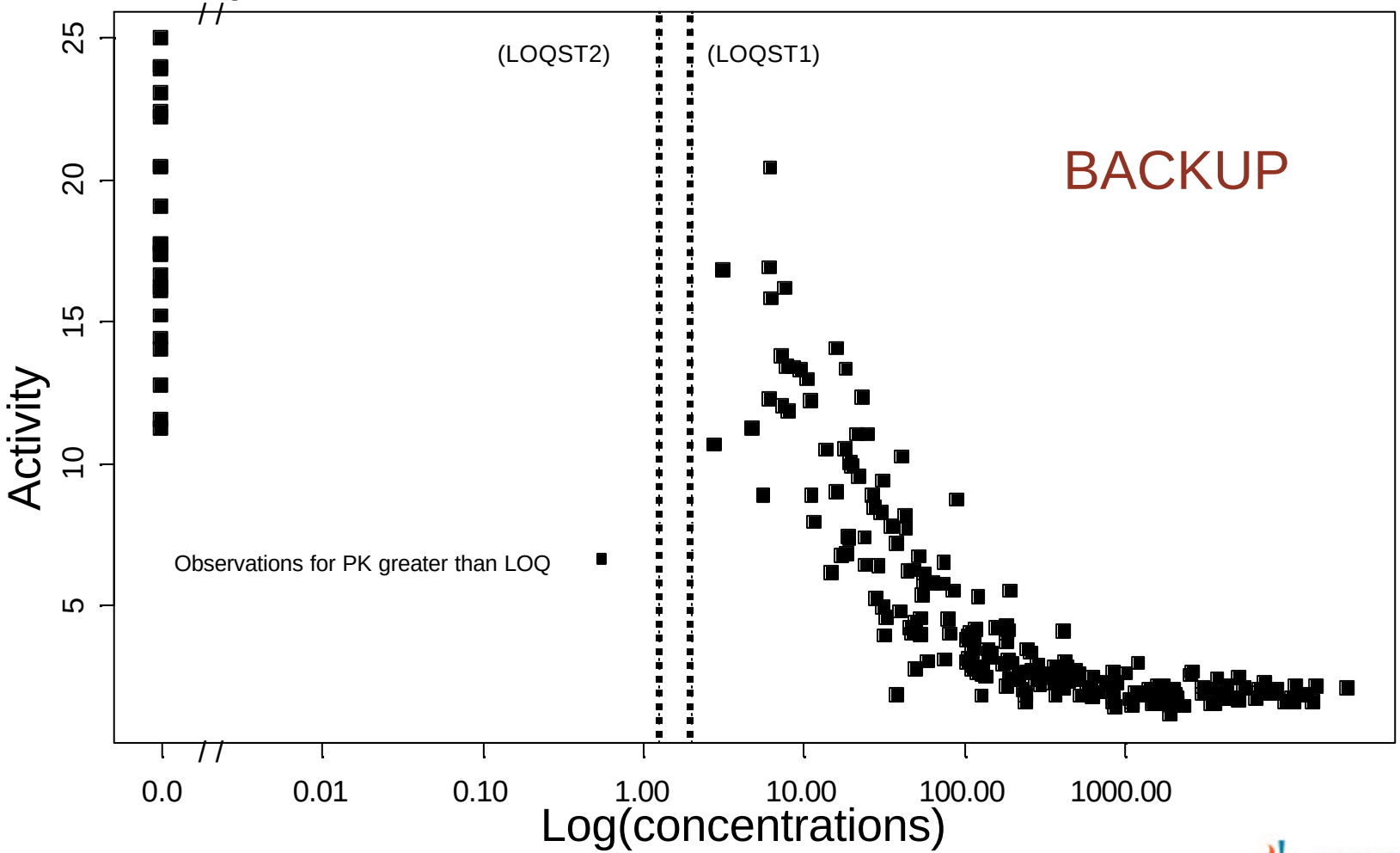

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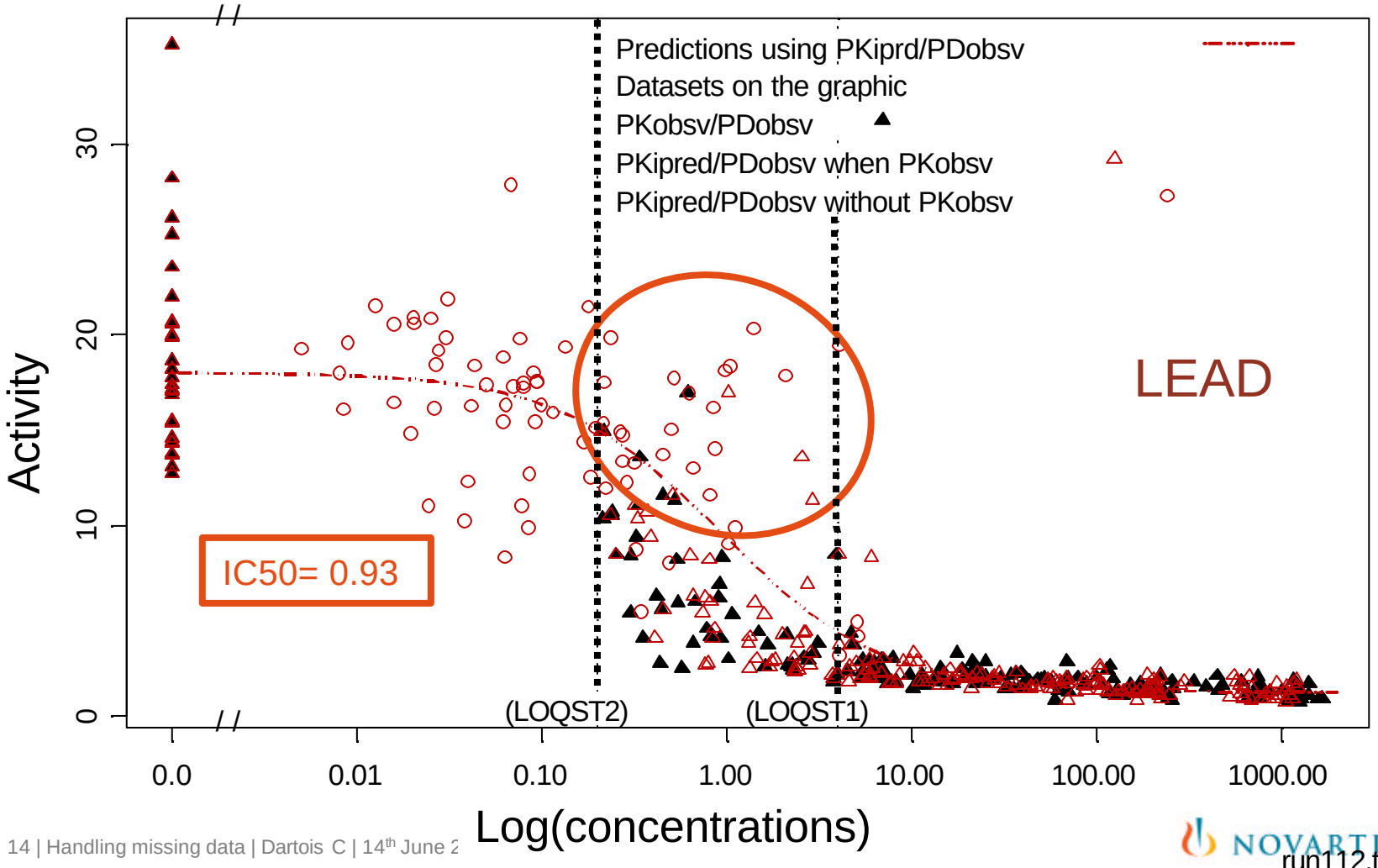
Results

PK influence on PD estimation

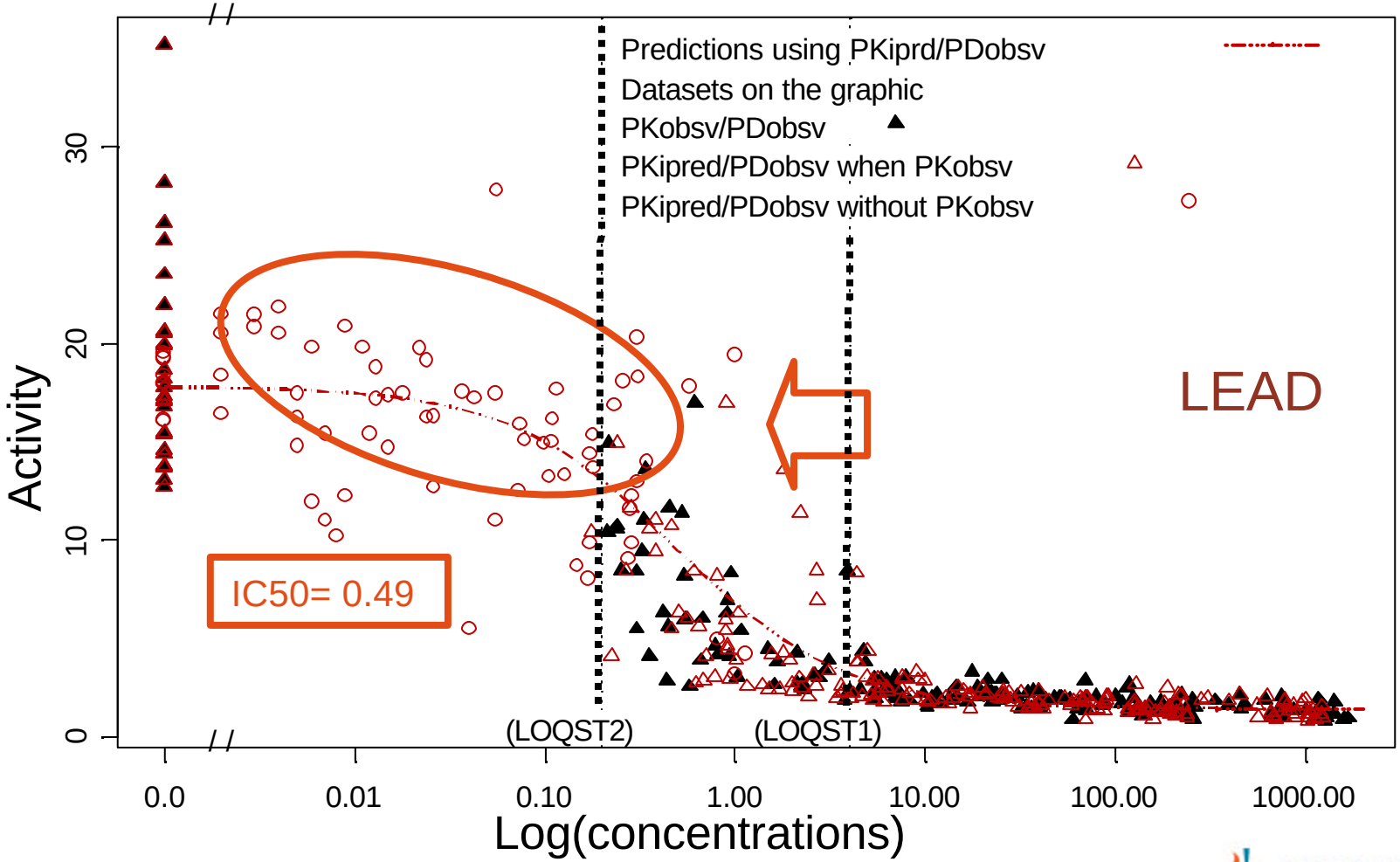
- If PK data predicted by NONMEM



Results

PK influence on PD estimation

- If PK data predicted by WinBUGS ®, IC50 estimations different



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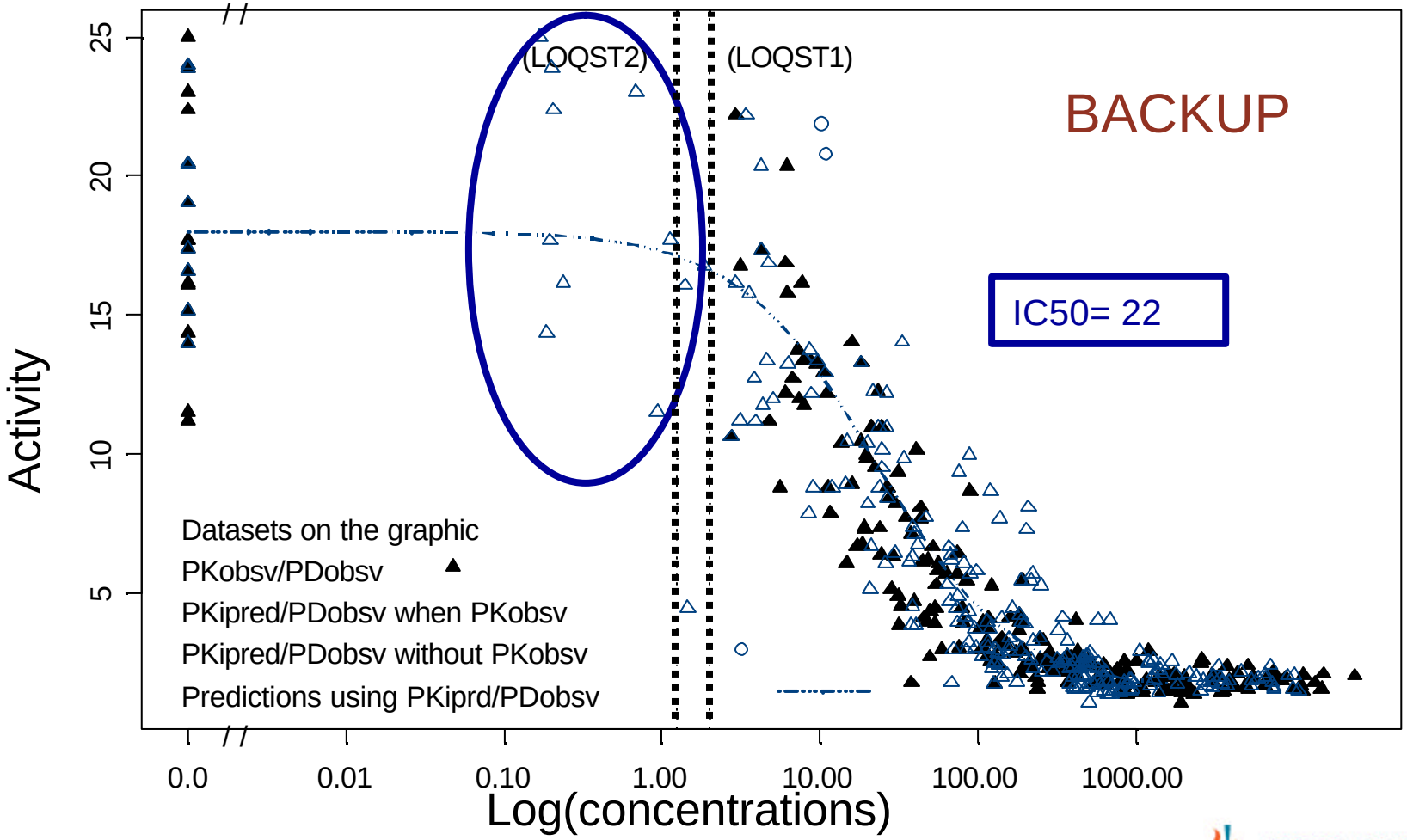
Results

PK influence on PD estimation

- If PK data predicted by NONMEM



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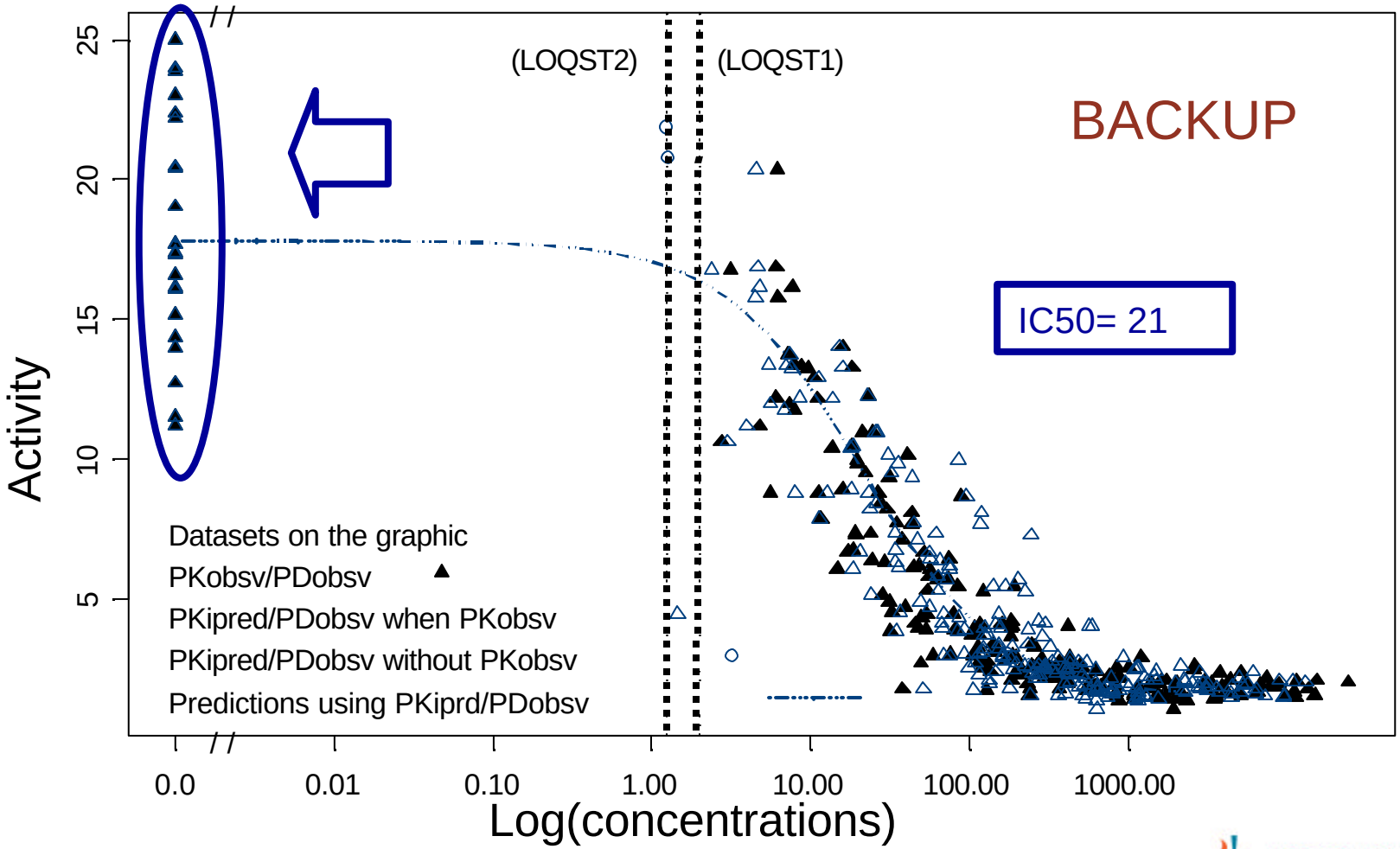
Results

PK influence on PD estimation

- If PK data predicted by WinBUGS ®, IC50 estimations identical



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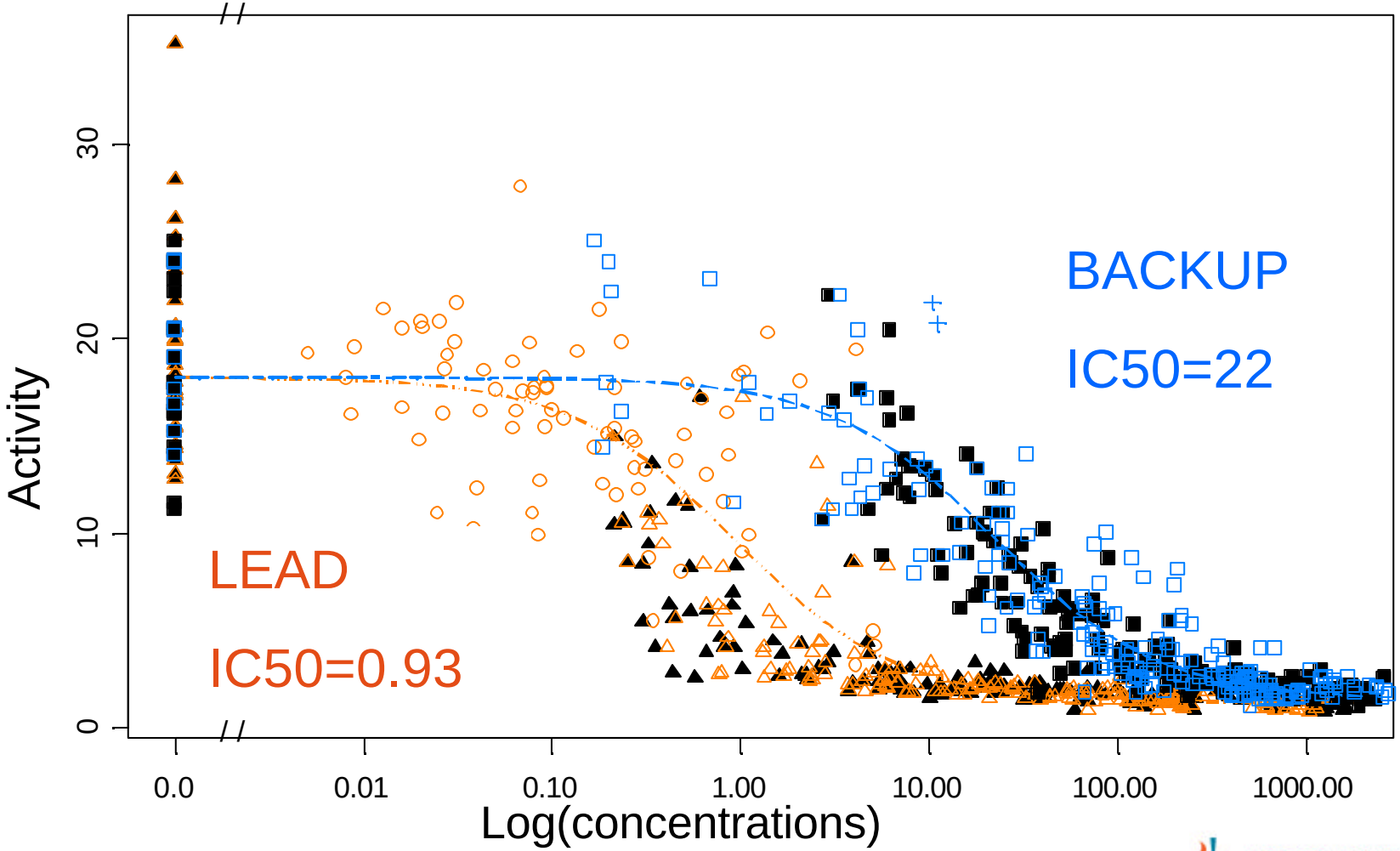
Results

PK influence on PD estimation, relative potency

- IC50 ratio estimated at 24, if PK data predicted by NONMEM



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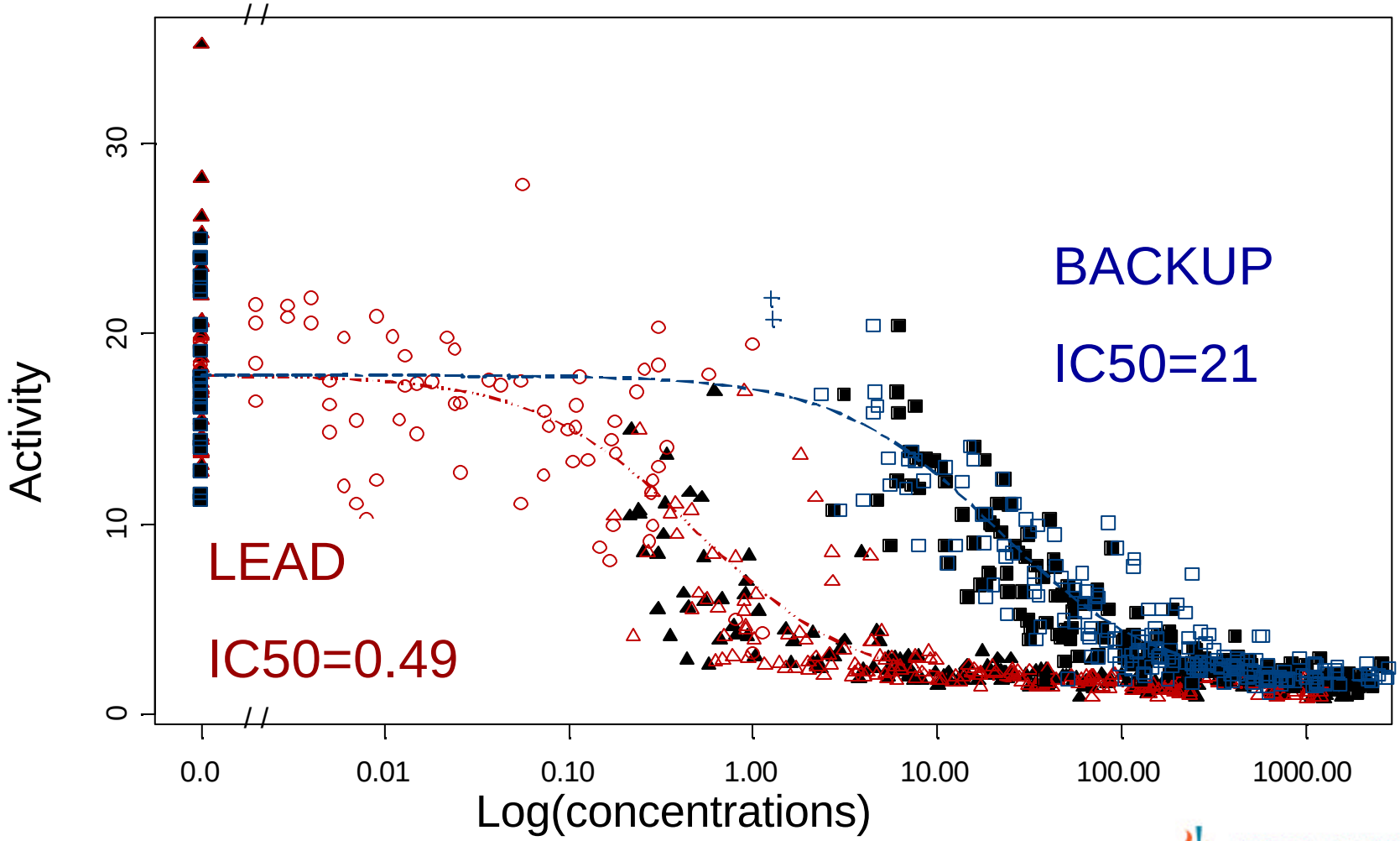
Results

PK influence on PD estimation, relative potency

- IC50 ratio estimated at 43, if PK data predicted by WinBUGS ®



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Conclusion

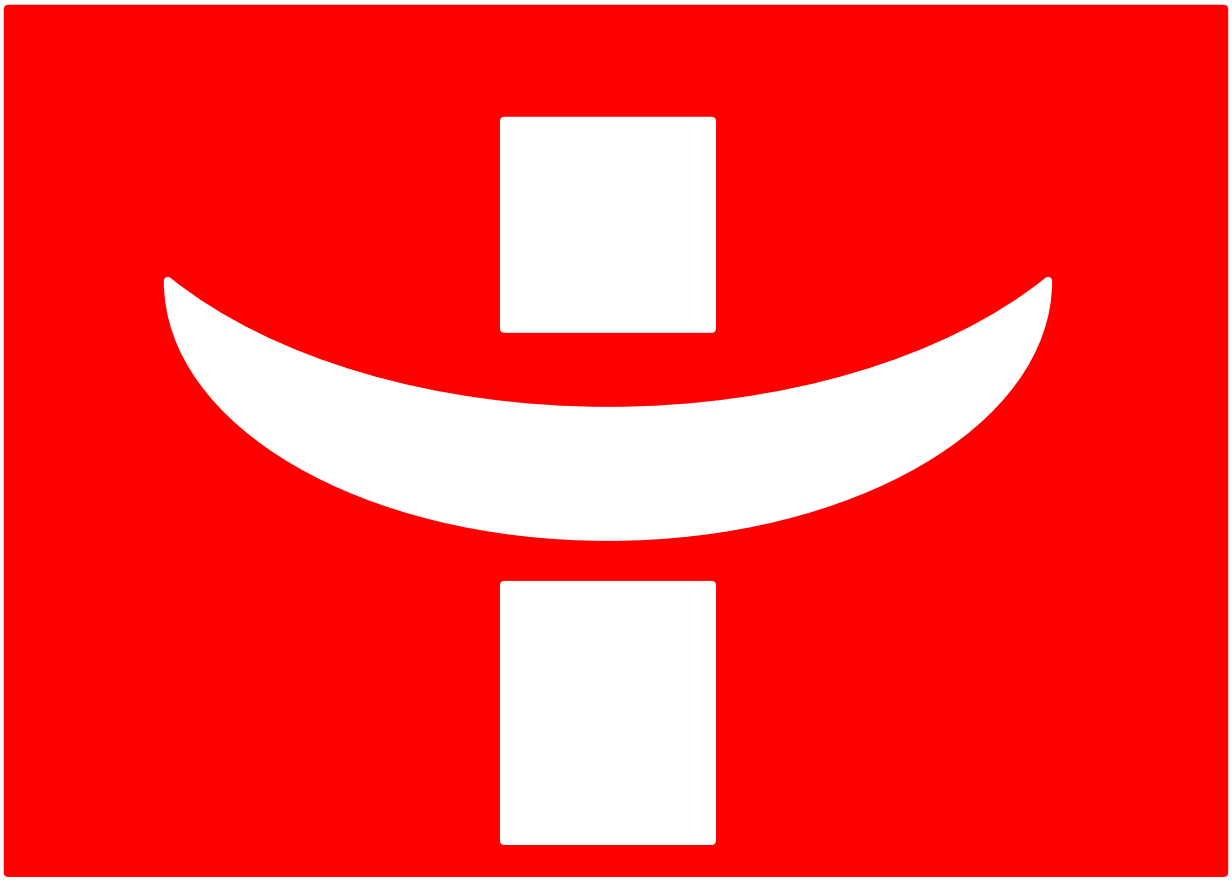
- Handling BLQ data, already important for PK, can be crucial for PD estimation when IC50 around LOQ
- A large diversity of methodologies exists [1-2]
- Until now, due to implementation complexity and no big difference in efficiency, the simplest method (discarding all BLQ data) in NONMEM V was encouraging [1]
- In this study, we tested this method against Winbugs (for which LOQ is taken into account to explain BLQ data)

[1] Beal. JPP, 2001,28(5):481-504 [2] Beal. JPP, 2005, 32(2):213-243.

Conclusion - Perspectives

- The only graphic allowing to distinguish the methods was the BLQ distribution against the LOQ : Winbugs showed better results on PK, predicting only few concentrations above LOQ.
- This PK result had a great impact on PD estimation and reduce bias on relative potency (ratio of 43 instead of 24)
- As drugs are more and more potent and efficiency of analytical methods cannot always quantify with accuracy the concentrations of interest, a real need of handling BLQ data exists in PKPD modeling.
- New methods implemented in NONMEM VI represent an improvement. They need to be tested on this example.

Any questions?



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