

A model-based approach to support NOAEL determination illustrated by real data



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Introduction

In drug development, a “no-observed-adverse-effect level” (NOAEL) is derived from toxicity studies in animals and used to infer a maximal safe exposure for human in clinical studies, in particular first-in-human (FiH) [1,2]. The NOAEL determined by current descriptive practice relies on specific experimental conditions of the animal studies. We hypothesise that this practice may not represent the most efficient use of data, and may carry a risk of misrepresenting the true NOAEL [3-6].

Objectives

- To apply a longitudinal probabilistic dose-response model to toxicity data
- To compare the model-based and the descriptive approaches for NOAEL determination

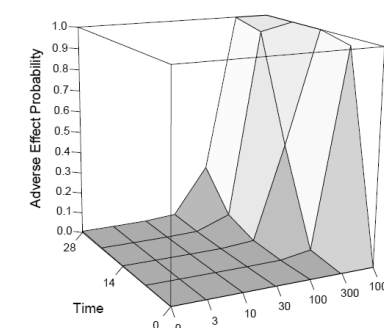
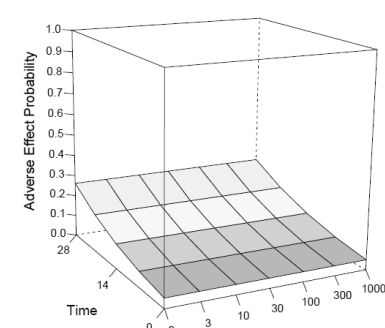
Methods

We first used simulations to explore the impact of experimental conditions on NOAEL. We then compared the two approaches for NOAEL determination. All modelling and simulation was done in R, version 3.0.2.

Simulation Case

Data and models to generate model-based probabilities of toxicities

Table 1: Simulation settings

• Typical study design supporting FiH package [1,2]	- 14 or 28 day study duration - Control group and 3 doses (log-equal increment) - 20 animals per dose group
• Models Linear logit model with background toxicity incidence a , TIME effect b & joint effect of TIME and DOSE effect c	$\text{logit} = a + b \cdot \text{TIME} \cdot (1 + c \cdot \text{DOSE})$ $\text{logit} = a + b \cdot \text{TIME}$
• Dose-time-toxicity relationships - Treatment-related toxicity, threshold type (left) - No treatment-related toxicity, flat type (right)	 

Process to compute predictive density of NOAEL values

Using each model and each design: 1) 1000 toxicology study datasets were simulated, 2) an NOAEL was estimated from each dataset using the operational definition of NOAEL (cf. table 2), and 3) predictive density of NOAEL was plotted.

Table 2: Operational definition of NOAEL

Control group → dose = 0

>0 meaning in this dose group the toxicity frequency is **higher** than in the control group

≤0 meaning in this dose group the toxicity frequency is **not higher** than in the control group

Real Case

Case	100 (mg/kg/day)	300 (mg/kg/day)	1000 (mg/kg/day)	NOAEL is
1	>0	>0	>0	<100
2	>0	≤0	>0	<100
3	>0	>0	≤0	<100
4	>0	≤0	≤0	<100
5	≤0	≤0	≤0	1000
6	≤0	>0	≤0	100
7	≤0	≤0	>0	300
8	≤0	>0	>0	100

Real Case

Data and model

- Toxicity described by 4 histopathology categorical descriptors, measured once (terminal sampling)
- Binary data (presence / absence) collected per animal and descriptor from 7 toxicity studies in rats (6 - 26 weeks in duration). Figure 2 gives a flavour of the amount of data available.
- Logit model using *glm* function in R. Model selection based on AIC criteria. Model evaluation based on simulation-based diagnostics using Poisson binomial distribution and accounting for sample size.

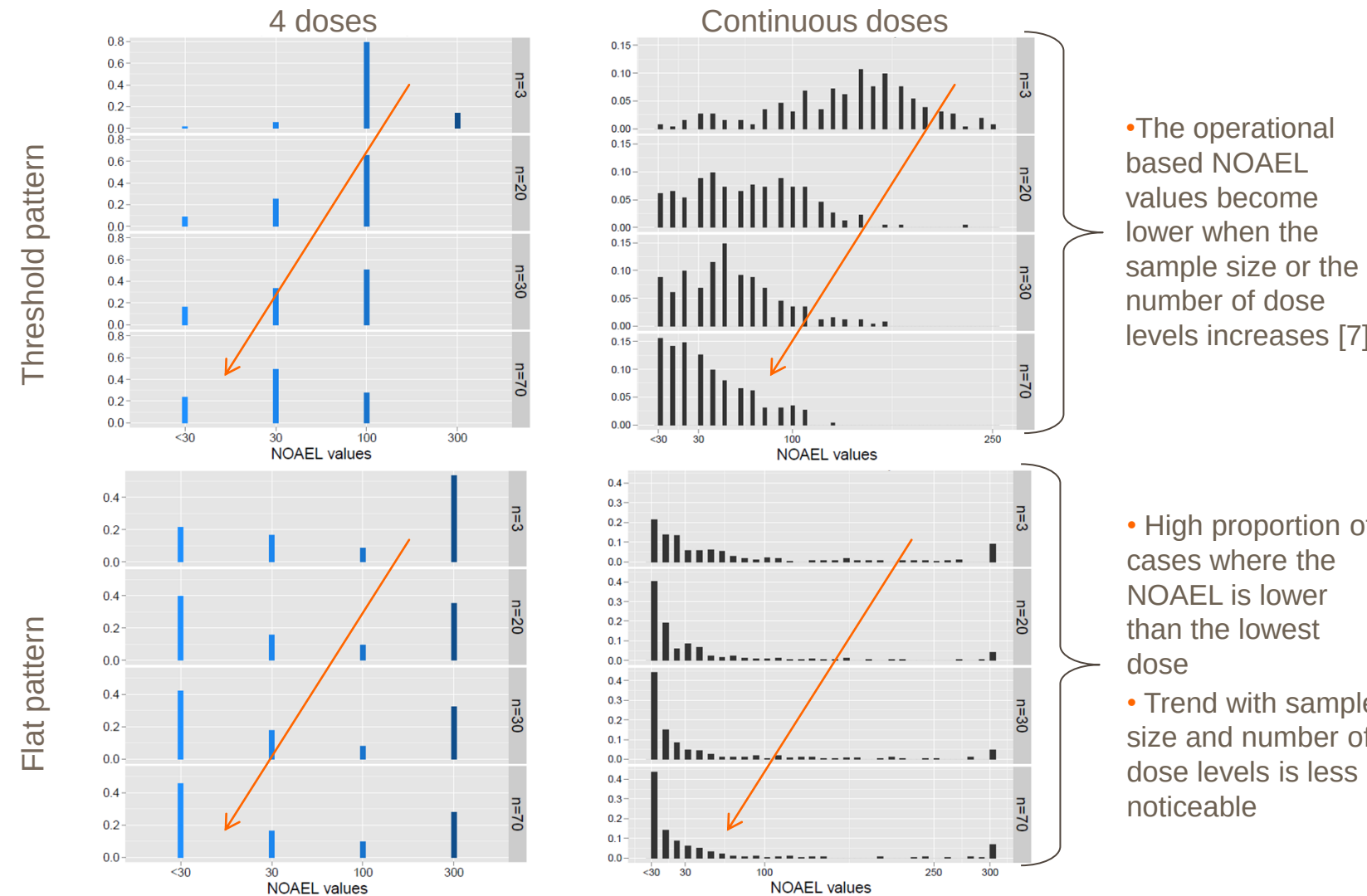
Model applications

- Compare a NOAEL value to its predictive density
 - Derivation of predictive NOAEL density for a 26 week study (same process as for simulations)
 - Graphical comparison with the NOAEL value derived from this observed toxicity study
- Link model-based approach with descriptive NOAEL approach
 - For any NOAEL value, graphical link of the model-based probability and its uncertainty
 - For any pre-defined threshold of probability, graphical link to the associated dose and its uncertainty [7]

Results

Simulation case

Figure 1: Impact of sample size and number of dose levels on predictive density of NOAEL
Example with a 14-day study duration



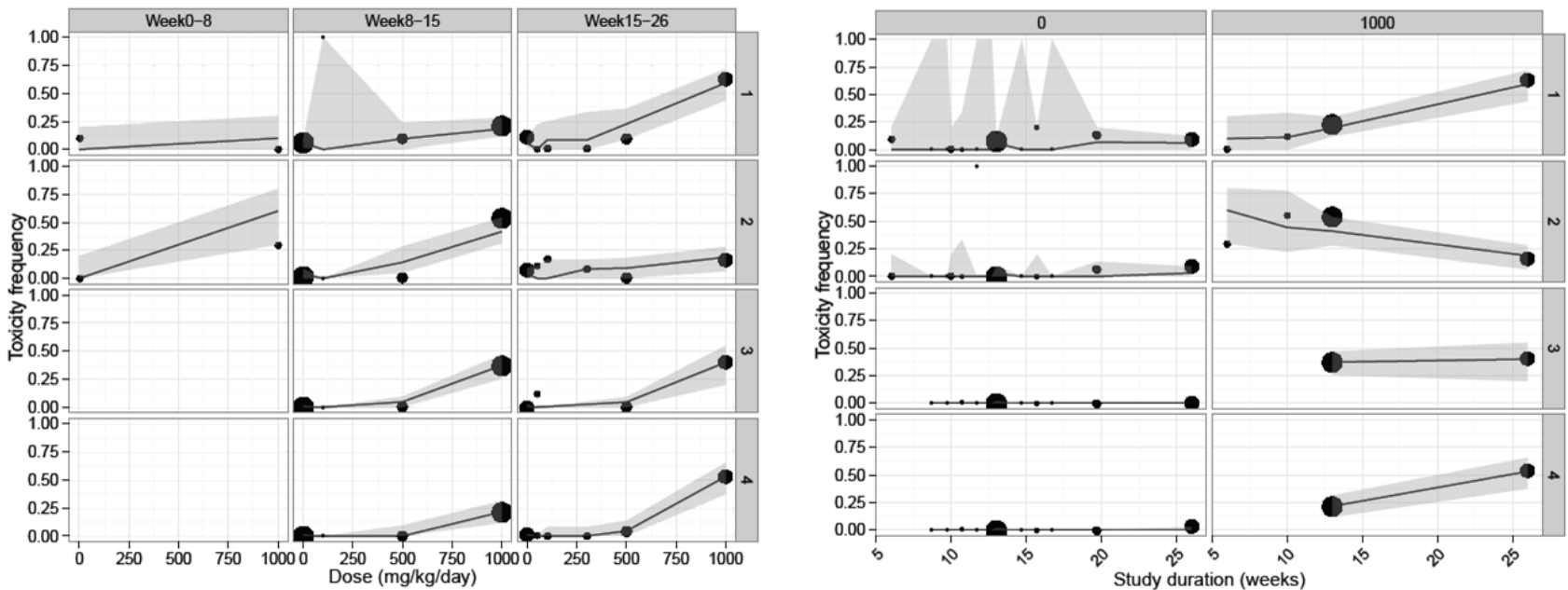
Real case model

- Final model : $\text{logit}(p) = x + y \cdot \text{DOSE} + z \cdot \text{DOSE} \cdot \text{TIME}$

Where: **x**, **y** and **z** depends on the pathology descriptor

- Satisfactory model based on simulation-based diagnostic plots (Fig. 2). High uncertainty due to low sample size (1 animal per dose group) is captured by the model.

Figure 2: GOF plots representing toxicity frequency as a function of dose (left) and study duration (right)



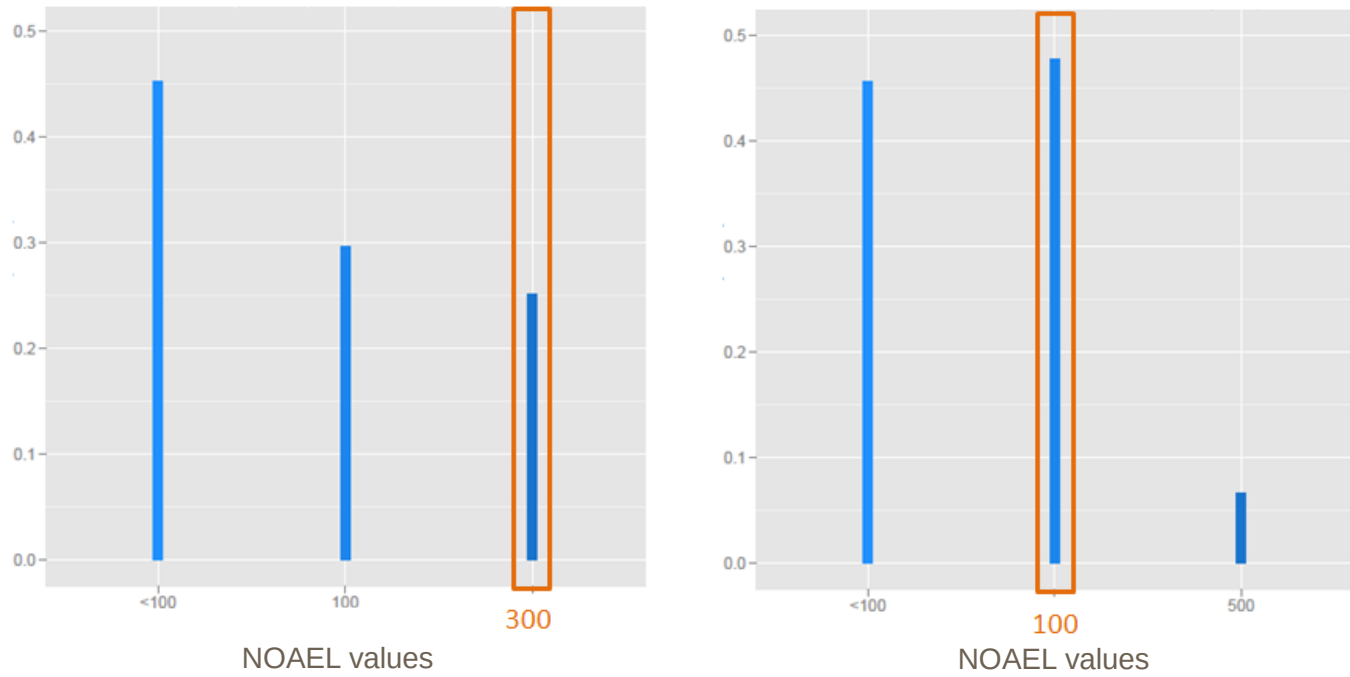
Dots: observed frequency (size proportional to the number of rats with histopathology assessment).
Line and shaded area: 50th and 5th to 95th percentiles of binomial Poisson distribution of the model prediction for each observation.

Real case model applications

Predictive NOAEL density

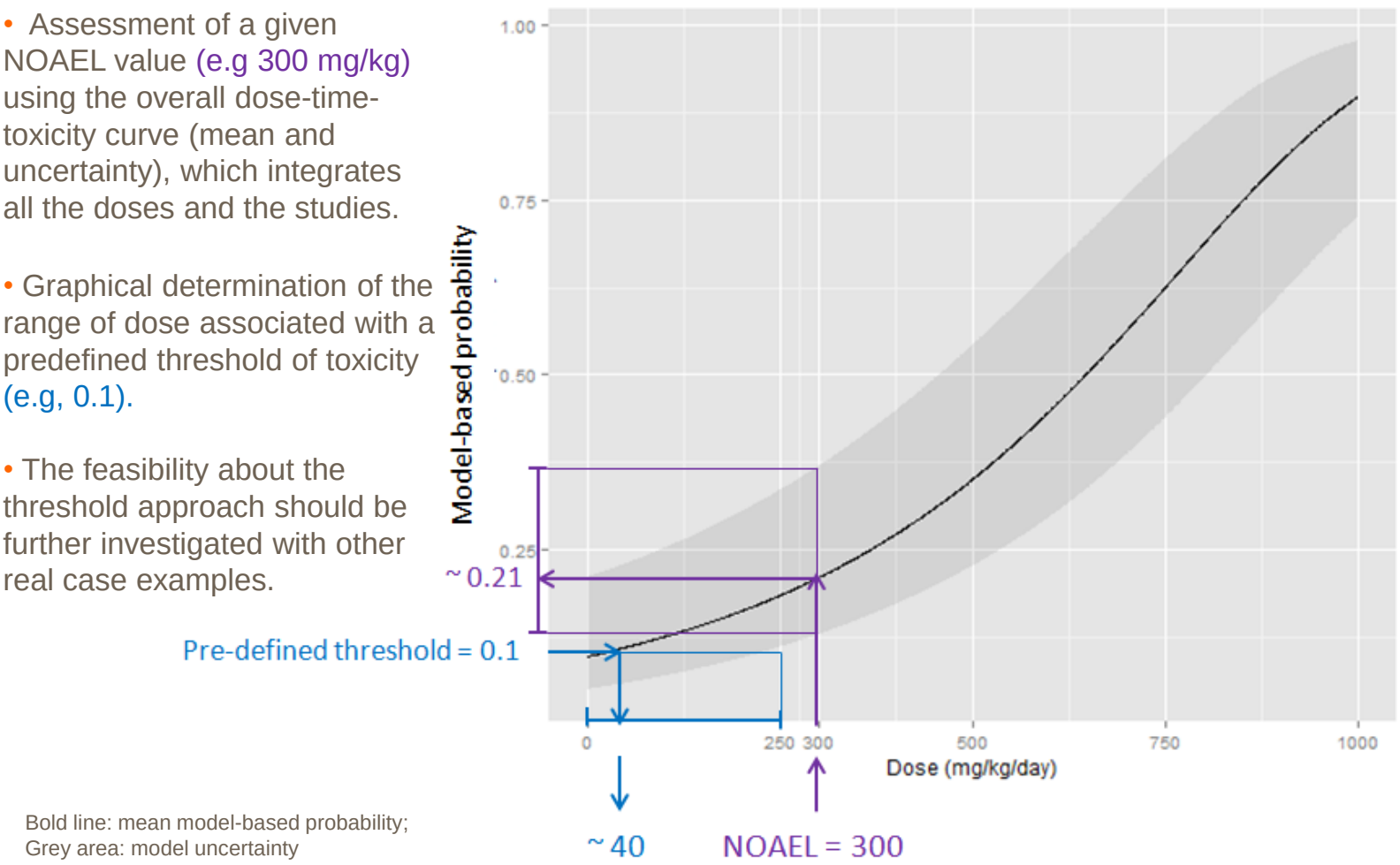
- In Figure 3, the NOAEL value determined by the descriptive approach (in orange) is superposed to the predicted NOAEL density.
- On the right plot, the descriptive NOAEL value corresponds to the most frequent value in the predicted density but on the left panel it does not.

Figure 3: Predictive NOAEL density from the operational definition of 2 different studies of 26 weeks



Link model-based approach to descriptive approach

Figure 4: Utility of model-based approach to complement NOAEL determination
Example with a 26-week study and a NOAEL dose of 300 mg/kg



Conclusion Simulations revealed the impact of choices of doses and sample size on the NOAEL that is descriptively estimated according to the current operational definition. The model-based approach enables an efficient use of data. It allows the choice of a toxicity tolerance level which can be determined according to benefit/risk ratio based on the indication and toxicity, an area for future work. The model can quantify the uncertainty of the NOAEL. A NOAEL determined in such a way does not decrease with higher sample size.

References

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