# Guidance to apply the BMD approach: part 1

March 1, 2017

efsa
European Food Safety Authority

# OUTLINE

- Data types
- BMR
- dose-response models and parameter constraints

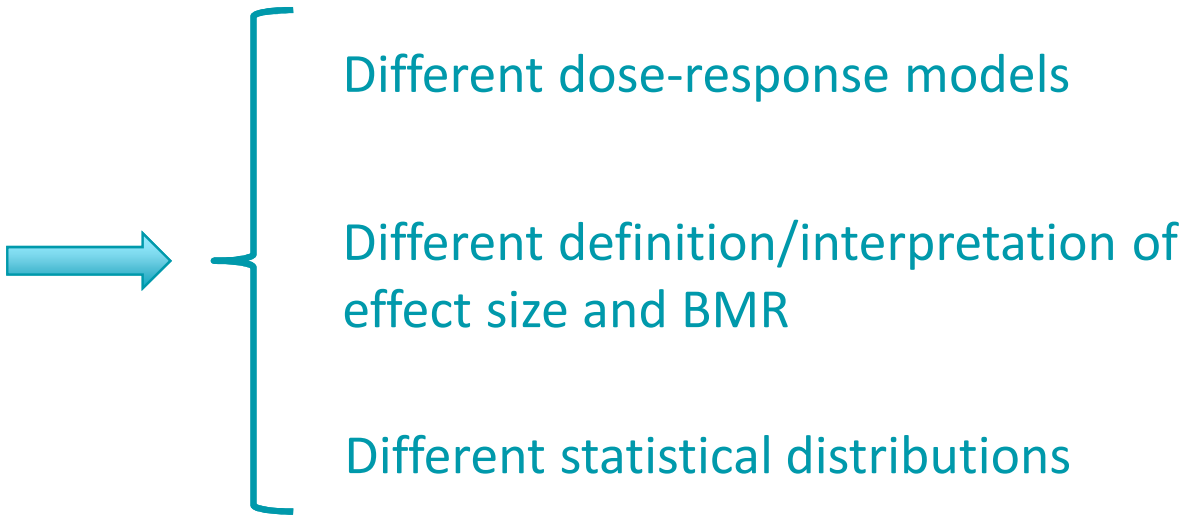
# DATA TYPES

## CONTINUOUS DATA

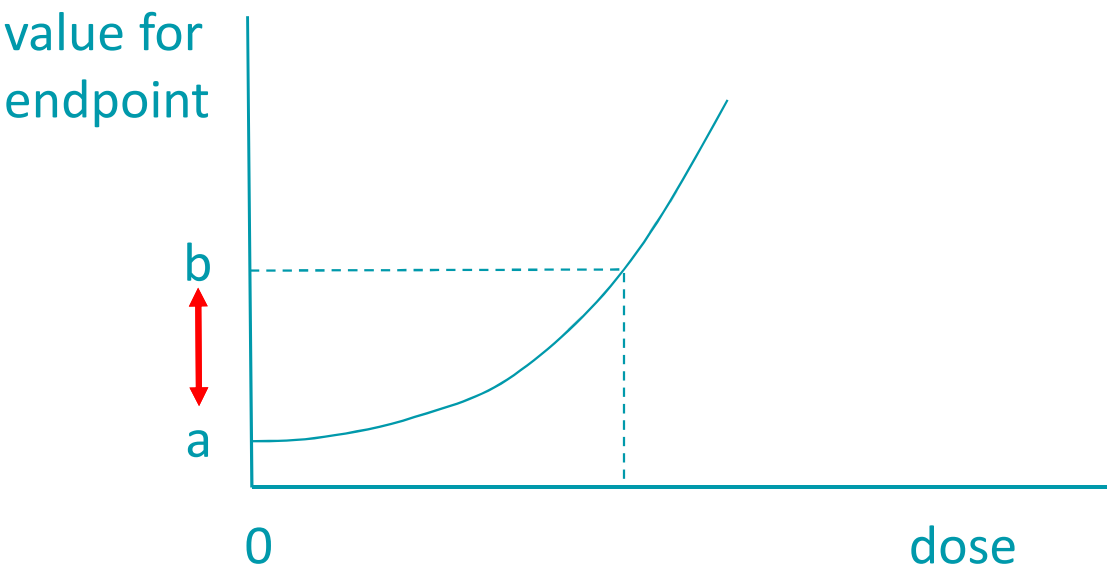
The values of a biological parameter in *individual* animals

## QUANTAL DATA

The fraction of animals with a specific effect *in a population*



# DOSE-RESPONSE AND EFFECT SIZE




an effect (response) is a *change* in the value of the endpoint relative to the control "response"

the size of the change is the *effect size*

or: the *distance* between b and a

**BMR** → definition ?
→ value ?

# EFSA'S DEFAULT BMR (CONT DATA)

EFSA recommends a **5% change** as the default BMR

*on average over datasets*

main argument: $BMDL_{05} \approx$ NOAEL

and use other values if deemed appropriate

e.g. a 5% change is ALT is "smaller" than a 5% change in RBCs

(liver enzyme in serum)

(red blood cells)

# DEFINITION OF BMR (QUANTAL DATA)

- additional risk

  incidence at d - incidence at 0

*on average*

$BMDL_{10} \approx$ NOAEL

- **extra risk**

**default value: 10%**

additional risk / non-affected fraction

=

$$\frac{\text{incidence at d - incidence at 0}}{\text{100\% - incidence at 0}}$$

# DOSE-RESPONSE MODELS (CONT DATA)

EFSA recommends two models:

- **Exponential model:**

$$y = f(x) = a\,[\,c - (c - 1)\exp(-b\,x^{d})]$$

- **Hill model:**

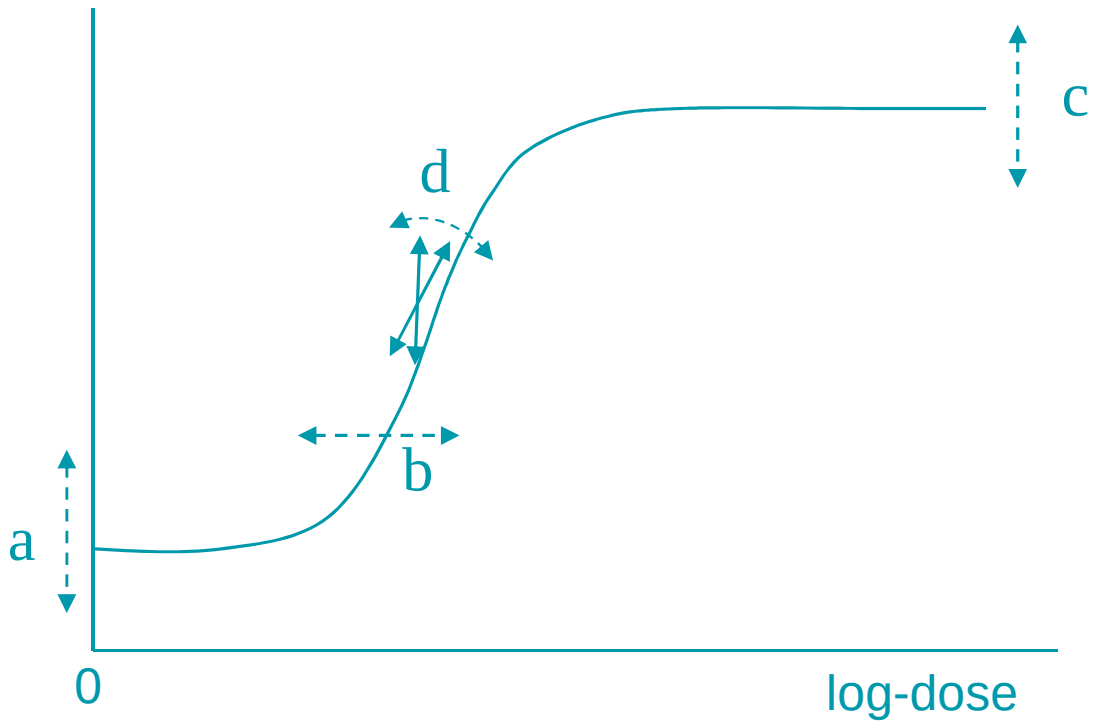
$$y = f(x) = a\,[\,1 + (c - 1)\,x^{d} / (b^{d} + x^{d})\,]$$

# PROPERTIES OF THE RECOMMENDED MODELS

- They always predict positive values
- They are monotonic (either decreasing or increasing)
- They are known to describe a wide variety of endpoints
- They contain four parameters with the same interpretation
- They allow for including covariates in a meaningful way

# MODEL PARAMETERS (CONT DATA)

continuous response




*scale parameters*

a: background response parameter

b: potency parameter ⟺ BMD

*shape parameters*

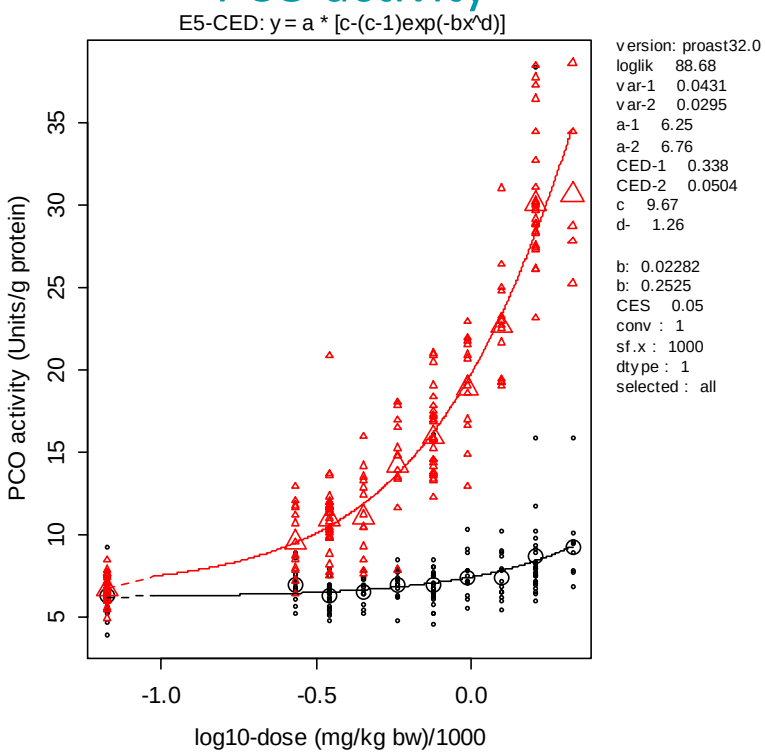
c: maximum response parameter

d: “steepness” parameter

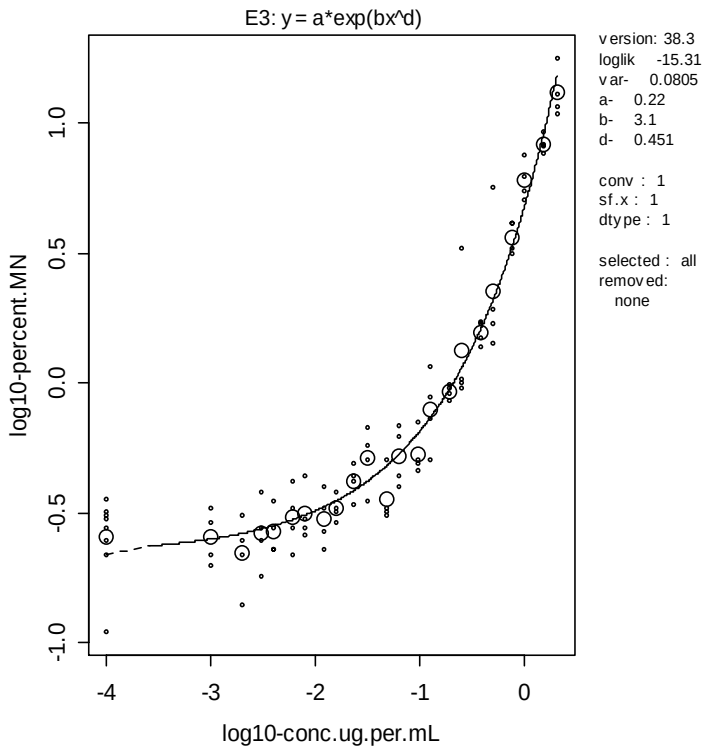
# THE MODELS ADEQUATELY DESCRIBE REAL DATA

Slob and Setzer (2014) reviewed a large number of (informative) toxicological datasets

## PCO activity

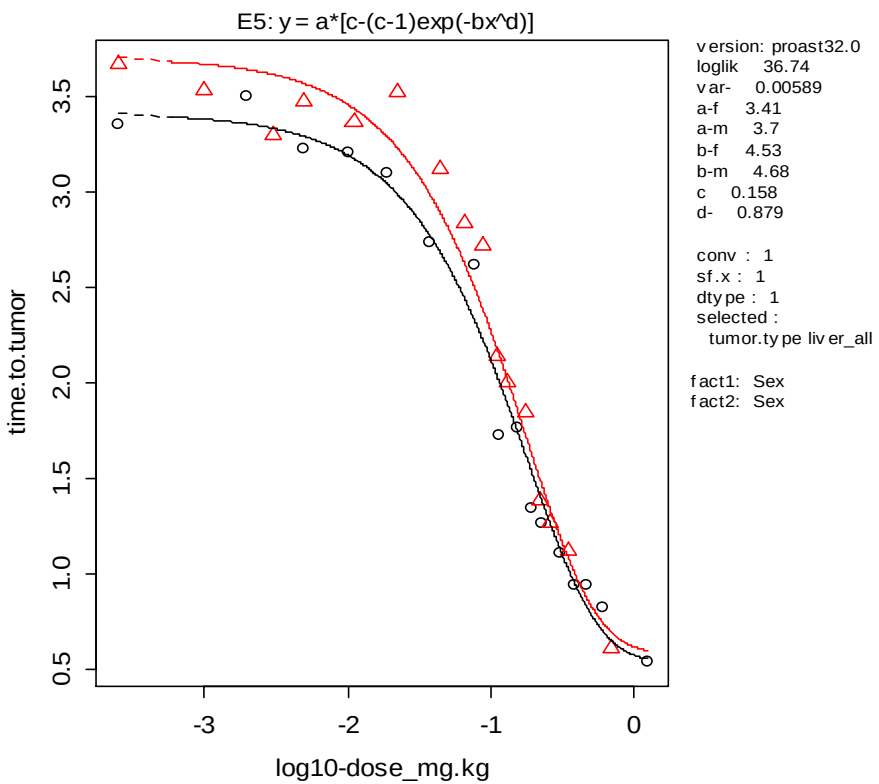



## MN counts



# THE MODELS ADEQAUTELY DESCRIBE REAL DATA

## time-to-tumor

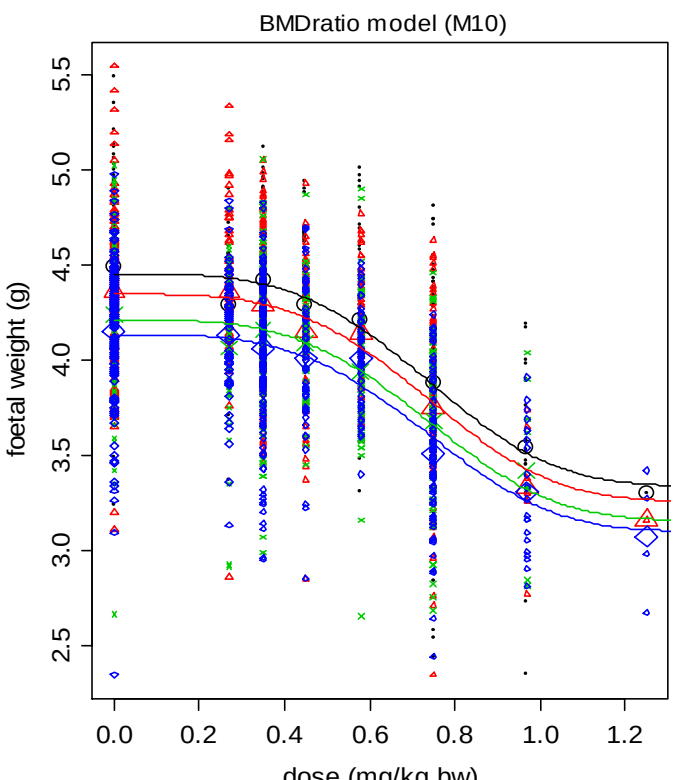



version: proast32.0
loglik 36.74
var- 0.00589
a-f 3.41
a-m 3.7
b-f 4.53
b-m 4.68
c 0.158
d- 0.879

conv : 1
sf.x : 1
dtype : 1
selected :
tumor.type liver_all

fact1: Sex
fact2: Sex

## foetal body weight




Proast22.8
var- 0.008566
a-1 4.455
a-2 4.347
a-3 4.213
a-4 4.135
b- 0.8151
c 0.7486
BMDratio 1.261
loglik 2098.93
conv : 1
sf.x : 1000
dtype : 1
selected : all

fact1: sex*treatment duratic
L05- 1.207
L95- 1.318

# ARE THESE TWO MODELS SUITABLE?

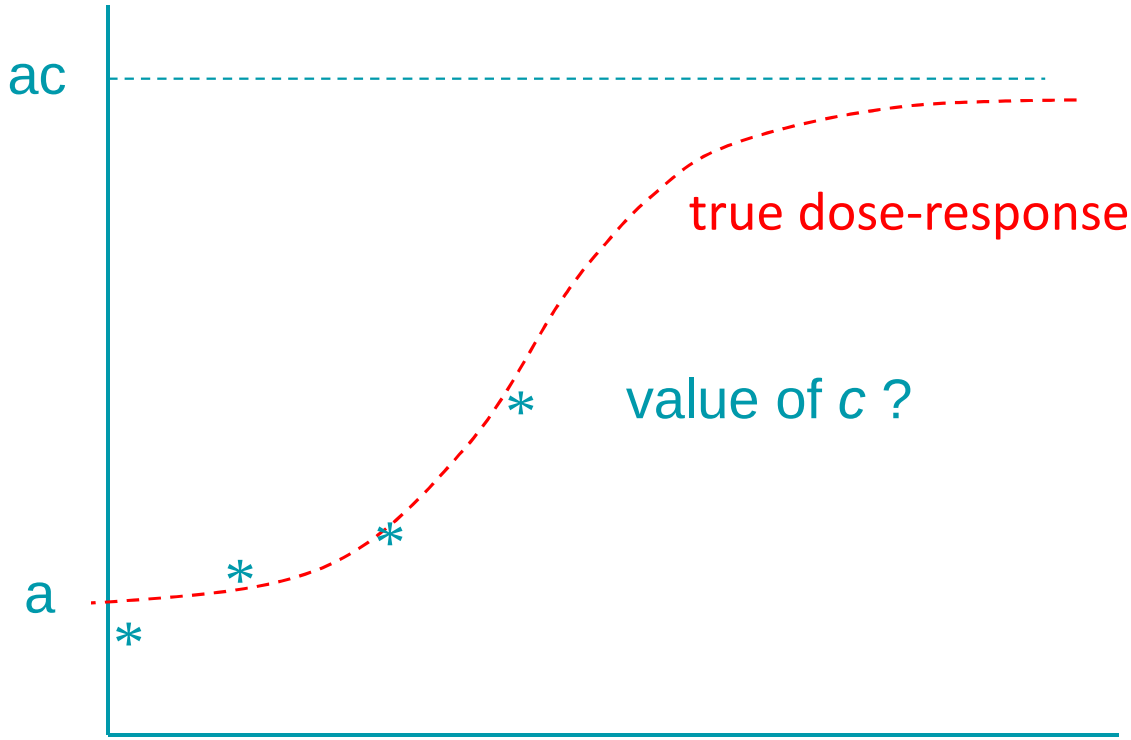
Conclusion: Yes, and either of these two models perform equally well

In addition:

- the maximum response (*c*) appears to be a characteristic of the endpoint
- the steepness (*d*) appears to be pretty conserved (varying around 1)

# OMITTING PARAMETERS FROM THE DR-MODEL

Practical problem: The dose-response data may not inform all four parameters



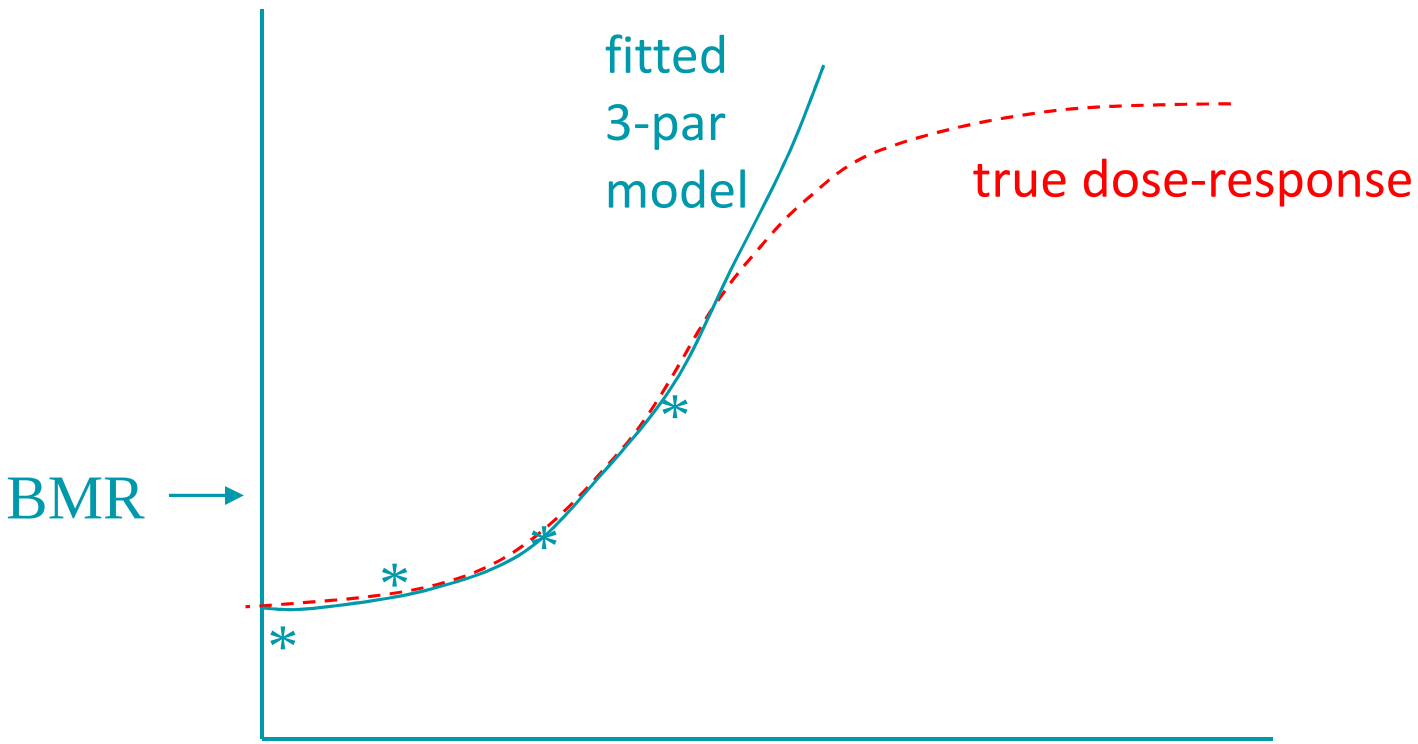
4-par model

$$y = a\,[\,c - (c-1)\exp(-b\,x^{d})\,]$$

$c = 0$

3-par model

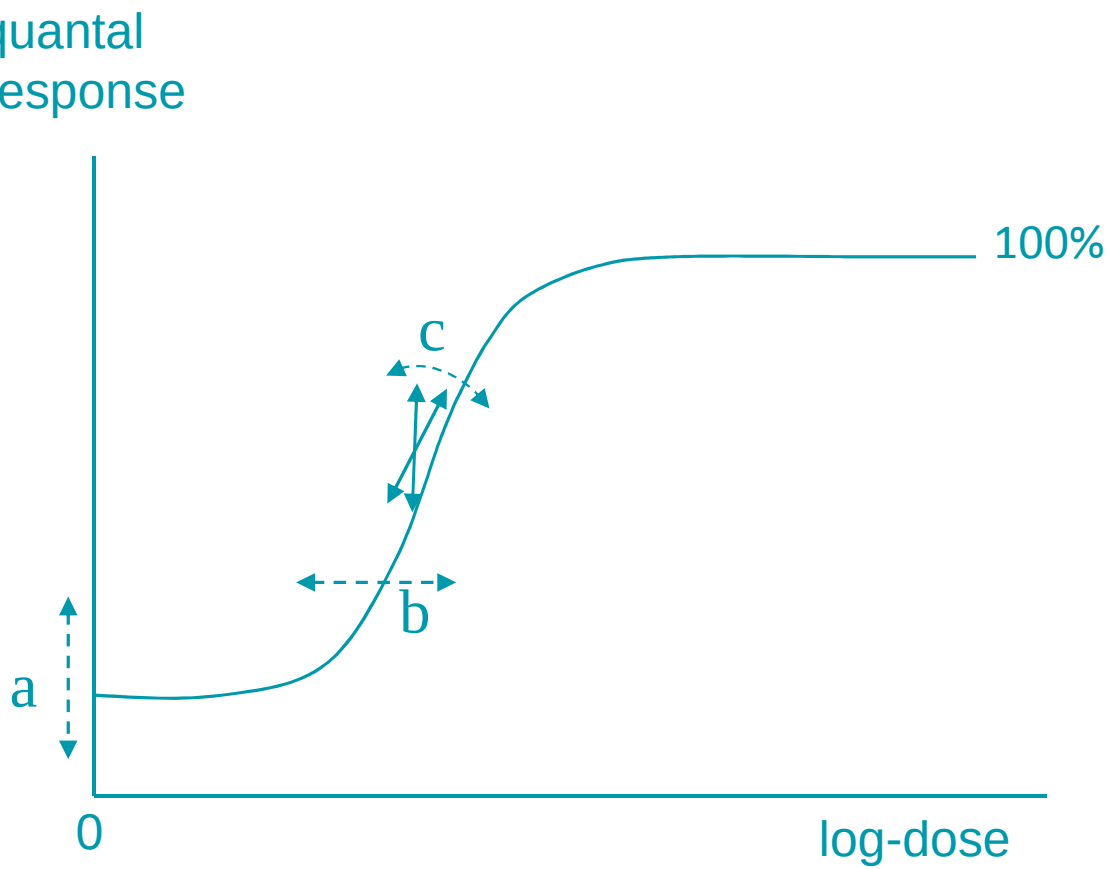
$$y = a\,\exp(-b\,x^{d})$$



# MODEL SELECTION FROM NESTED FAMILY

The decision to leave out parameter *c* (i.e. select the 3-par model or the 4-par model) is based on statistical grounds (AIC, to be discussed later)

# DOSE-RESPONSE MODELS (QUANTAL DATA)




*scale parameters*

a: background response parameter

b: potency parameter

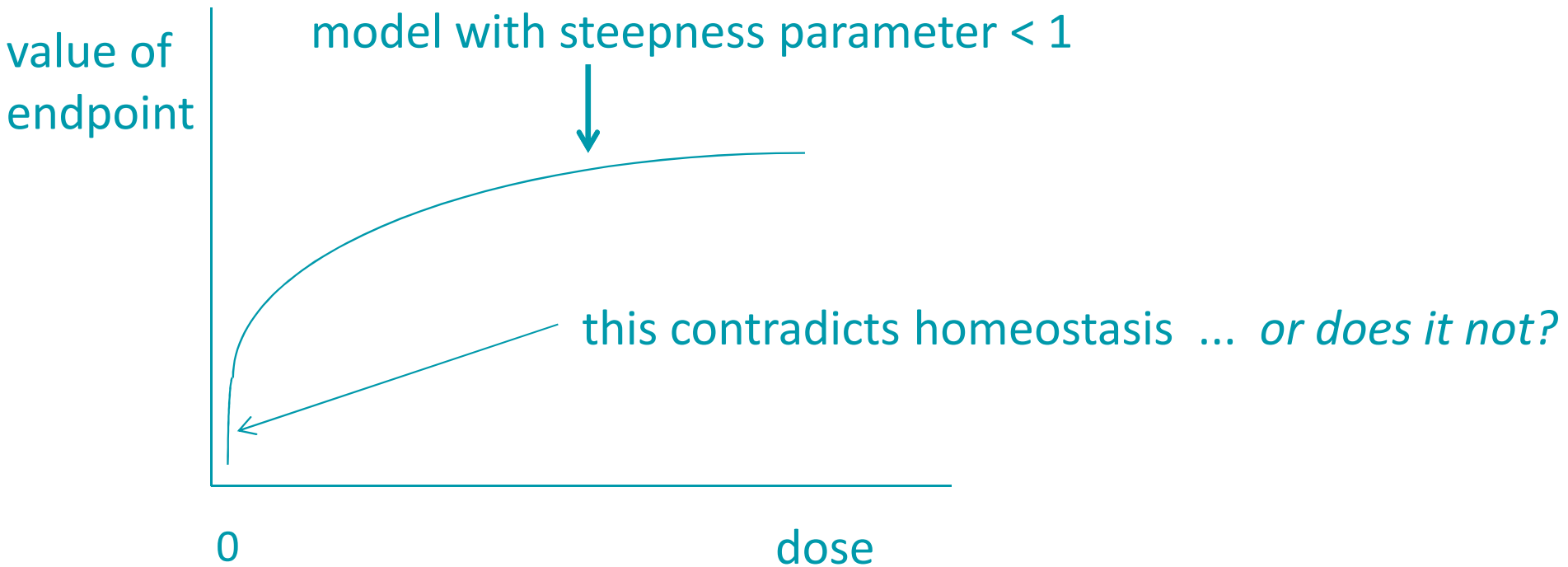
*shape parameters*

c: “steepness” parameter

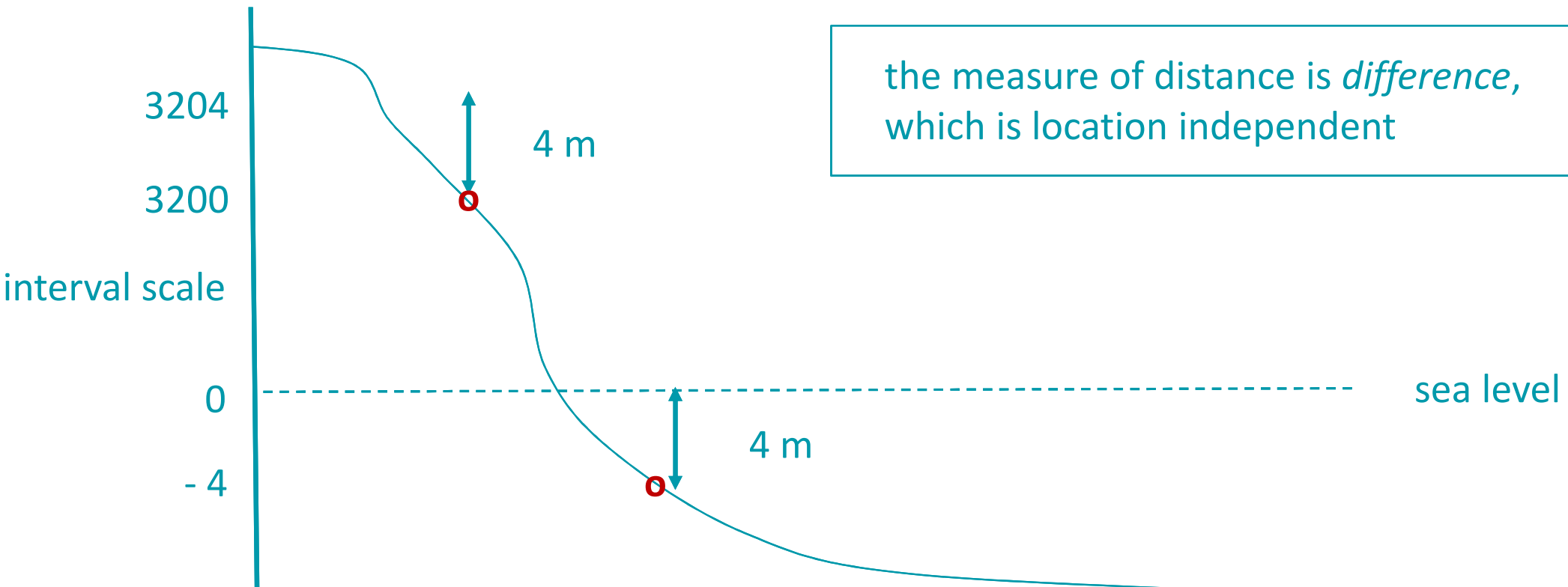
# RECOMMENDED QUANTAL MODELS

| Model | #parameters | Model expression mean response ($y$) as function of dose ($x$) | Constraints |
|---|---|---|---|
| Logistic | 2 | $y = 1/(1 + \exp(-a-bx))$ | $b > 0$ |
| Probit | 2 | $y = \text{CumNorm}(a + bx)$ | $b > 0$ |
| Log-logistic | 3 | $y = a + (1-a)/(1 + \exp(-\log(x/b)/c))$ | $0<a<1$, $b > 0$, $c > 0$ |
| Log-probit | 3 | $y = a + (1-a)\ \text{CumNorm}(\log(x/b)/c)$ | $0<a<1$, $b > 0$, $c > 0$ |
| Weibull | 3 | $y = a + (1-a)\ \exp((x/b)^c)$ | $0<a<1$, $b > 0$, $c > 0$ |
| Gamma | 3 | $y = a + (1-a)\ \text{CumGam}(bx^c)$ | $0<a<1$, $b > 0$, $c > 0$ |
| LMS (two-stage) model | 3 | $y = a + (1-a)(1-\exp(-bx-cx^2))$ | $0<a<1$, $b > 0$, $c > 0$ |
| Latent variable model (LVM) | 3 | Exponential (see continuous data) | See cont. models |
| Latent variable model (LVM) | 3 | Hill (see continuous data) | See cont. models |

# CONSTRAINT ON THE STEEPNESS PARAMETER

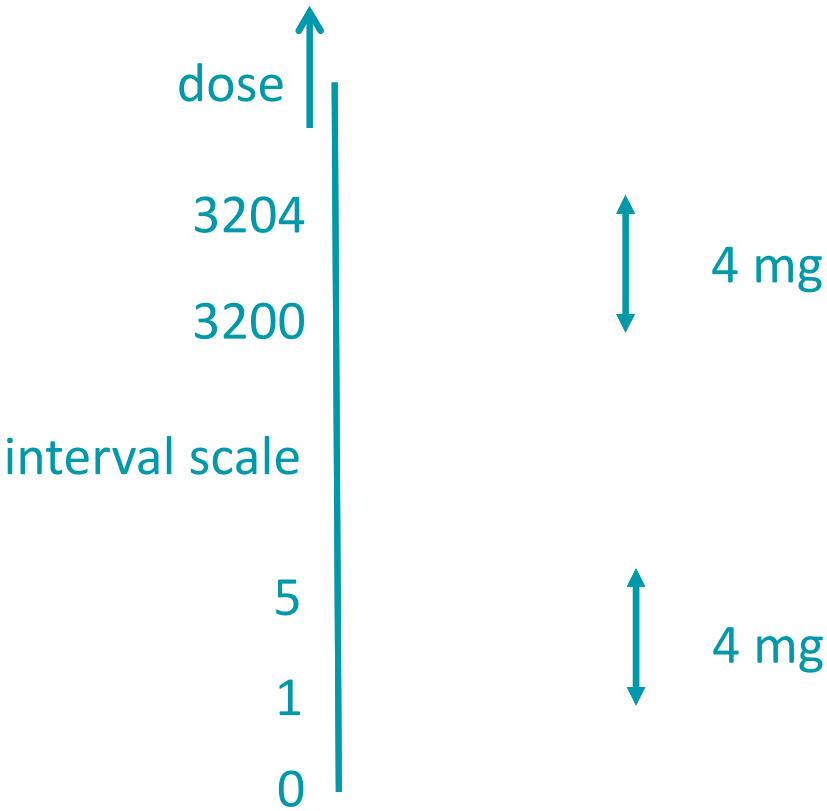


# MEASURING DISTANCE



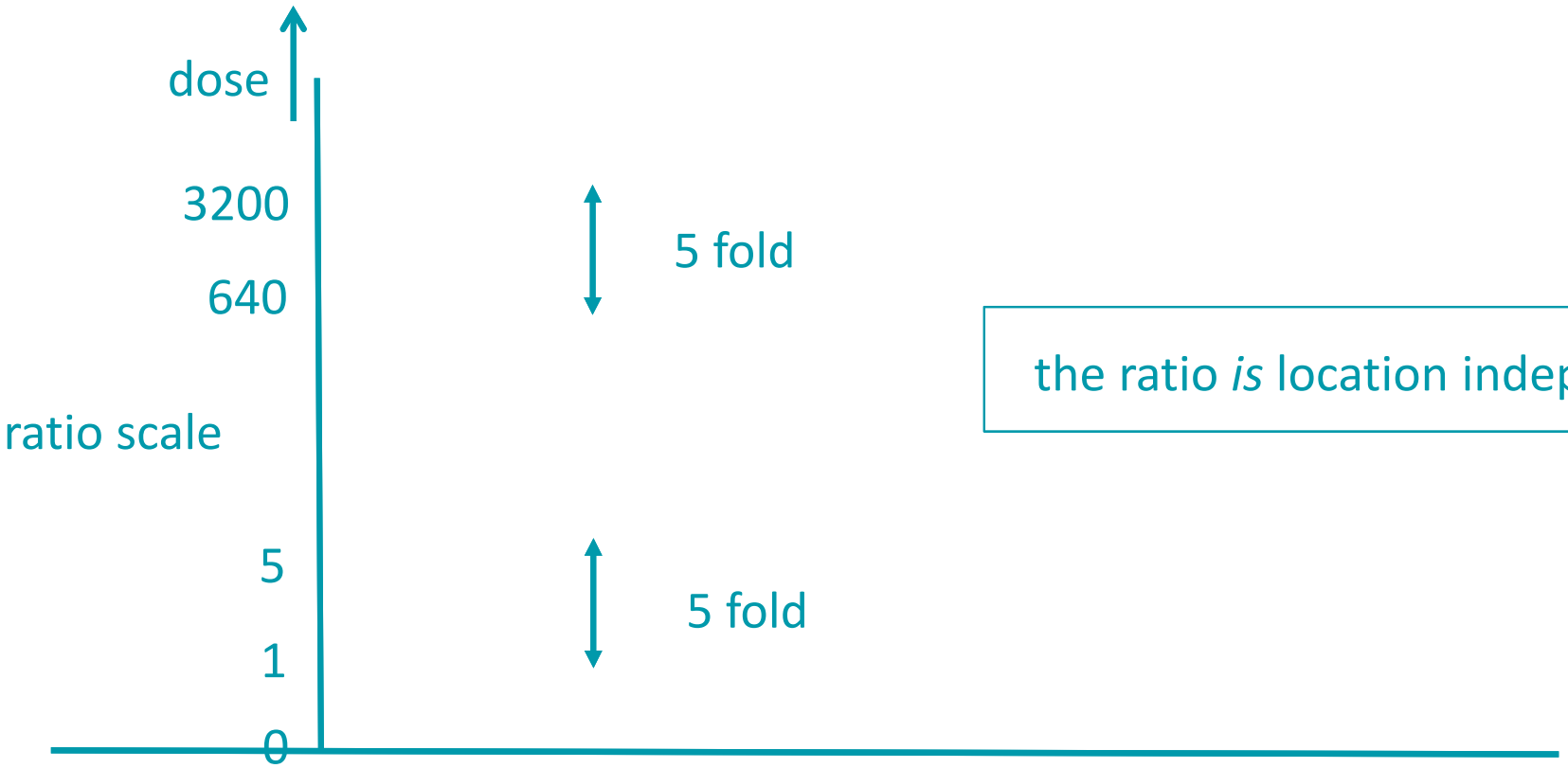

the measure of distance is *difference*, which is location independent

# MEASURING DISTANCE BETWEEN DOSES




the difference is *not* location independent

# MEASURING DISTANCE BETWEEN DOSES



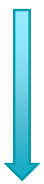

the ratio *is* location independent

dose 0 is an infinitely low dose

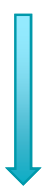
# LOG-DOSE SCALE

The (original) dose scale regards equal differences as similar,

which is not correct

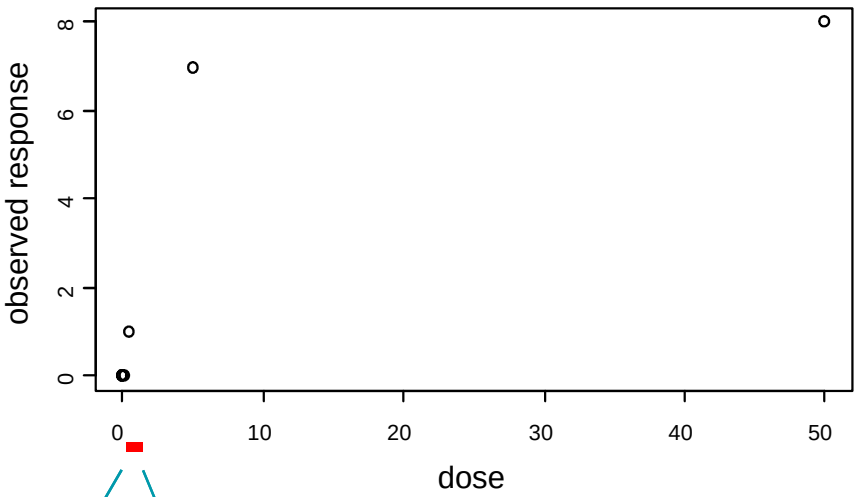


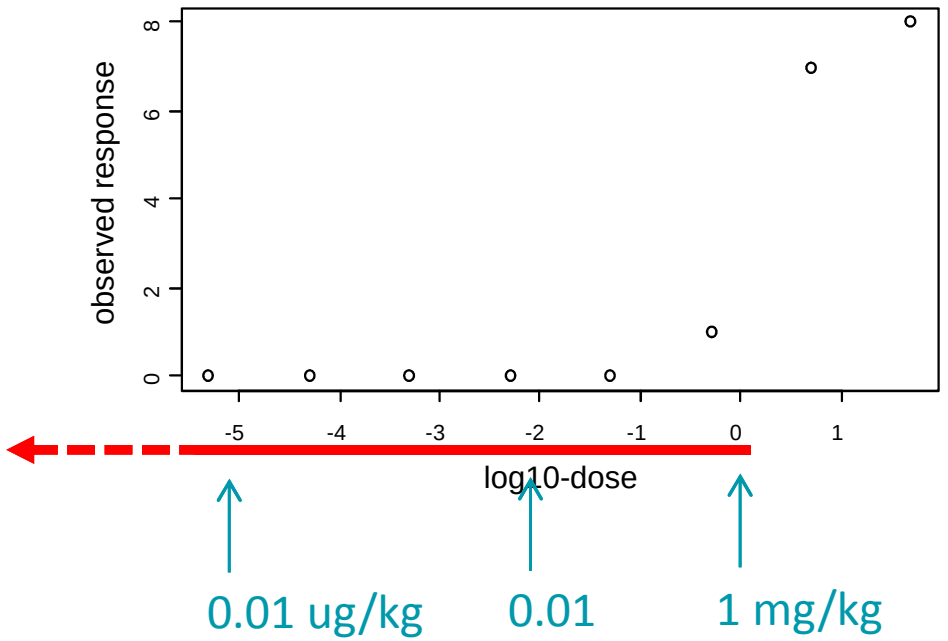
The shape of a dose-response, plotted against dose, has no meaning



Infinite slope against (original) dose is meaningless

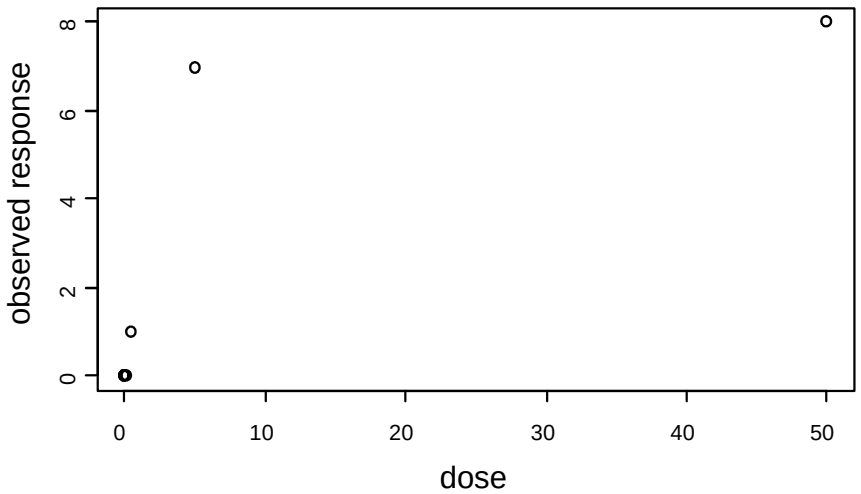
# RESPONSE AGAINST DOSE VS. LOG-DOSE

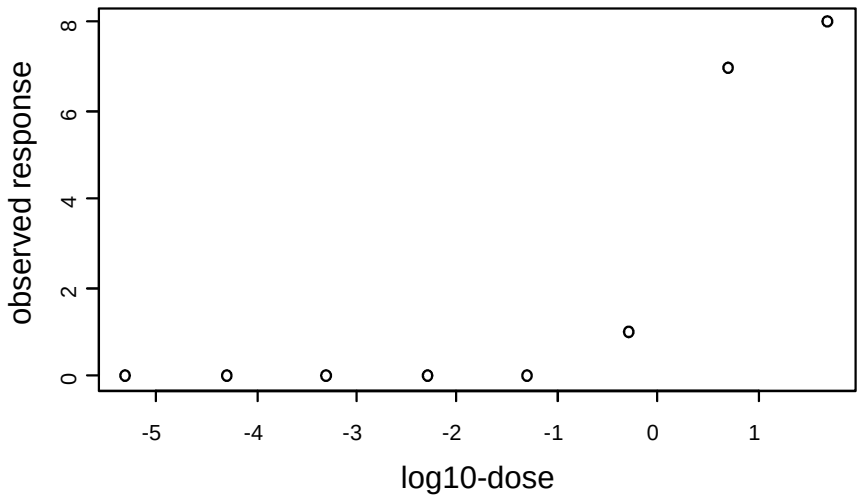



0 to 1 mg/kg is a huge range of doses

# SUPRA/SUBLINEAR




What appears to be supralinear ....

is, in reality, sublinear

# CONCLUSION ON STEEPNESS CONSTRAINT

The constraint on the steepness parameter cannot be justified and should not be applied

In specific datasets this may result in very wide BMD confidence intervals with very low BMDLs

Future development:
Use prior distributions on the shape parameters, based on historical data; this will prevent the problem in most cases

# end of part 1