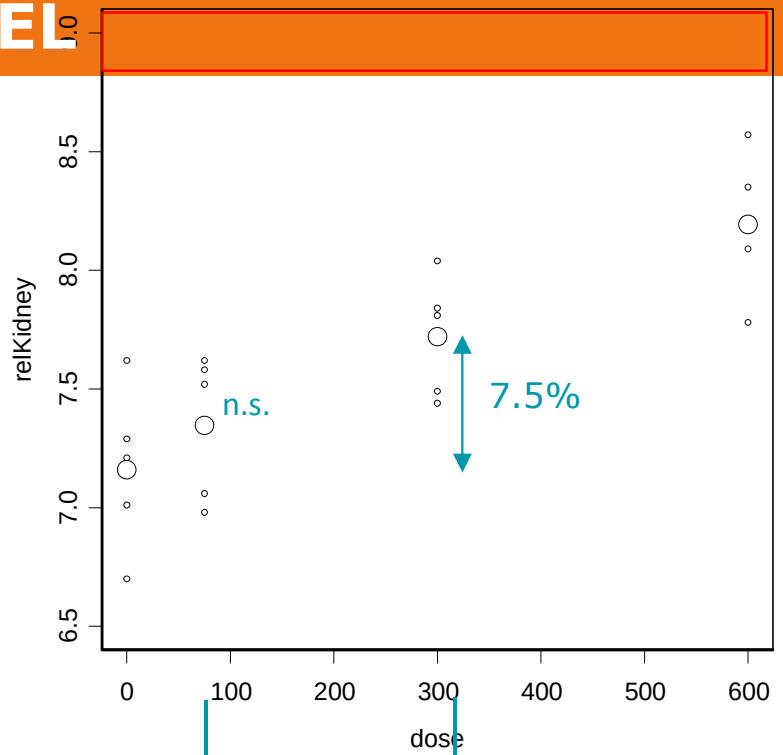
General considerations

March 1, 2017

efsa
European Food Safety Authority

IDENTIFYING A NOAEL



Range of assessed NOAELs:
25 up to 300 mg/kg

NOAEL, based on the mean remaining within the scatter of the controls

NOAEL, based on effect size < 10%

NOAEL, based on statistical (non)significance

LOAEL, based on overall trend in dose-response

DO WE SEE AN EFFECT?

The NOAEL approach:		Reality:
we see an effect	→	there is an effect
we don't see an effect	✗	there is no effect

wrong

SAMPLING ERROR

Consider a container with a huge number of balls, 90% is white, 10% is red

take a sample of 10 balls

they are all white (probability of 10 white balls is 35%)

CONCLUSION: there are no red balls in the container

This similarly holds for any tox study where we take samples of animals

SAMPLING ERROR

10% red balls

10% red balls

take a sample of 10 balls

none are red

two are red

difference in non-significant

SAMPLING ERROR

1% red balls

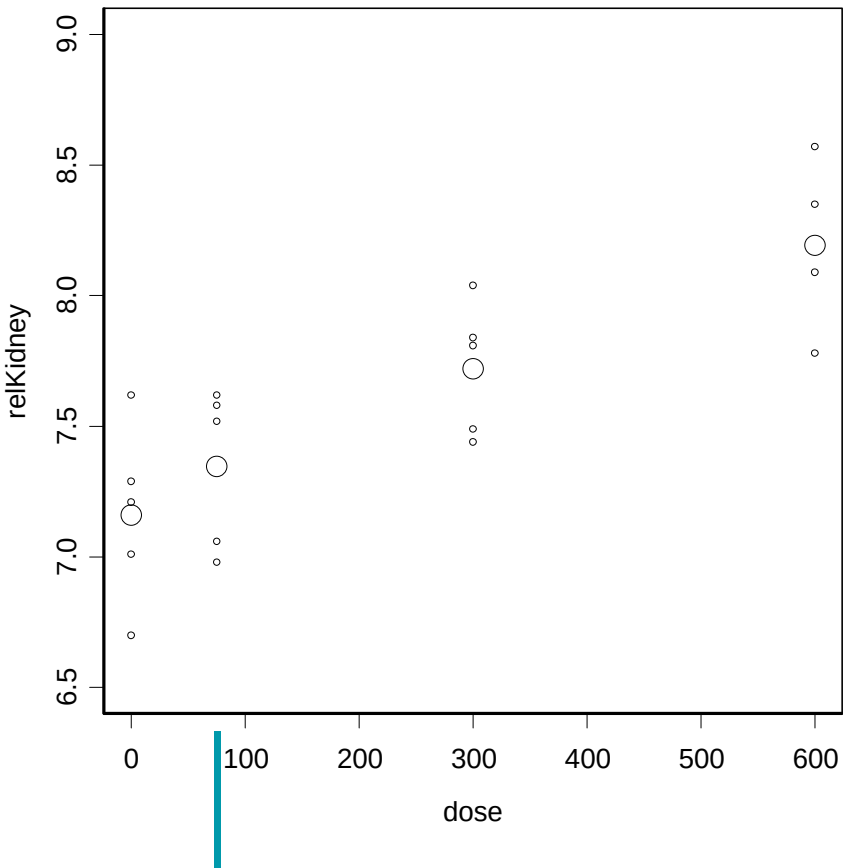
15% red balls

take a sample of 10 balls

none are red

none are red

difference in non-significant



The NOAEL does not guarantee there is no effect

we cannot say if the difference in observed response is caused by sampling error or by a real effect

this dose is non-significant

DO WE SEE AN EFFECT?

The NOAEL approach is based on:
do we see an effect or not?

Reality:

we see an effect → there is an effect

?

we don't see an effect → X there is no effect

wrong

WHAT DO WE MEAN BY "THERE IS NO EFFECT"?

The effect is *in reality*

50 %

5 %

0.1 %

0.001 %

10^{-10} %

0 % = 10^{-INF} %

what is the borderline between effect and no effect ?

ESTABLISHING NO EFFECT

No effect is: an effect of size zero, or infinitely small

can be established with infinite group sizes only

AVERAGE EFFECT SIZE AT NOAEL

Various review papers show that the size of the effect at the NOAEL is, on average over studies:

~ 5% for continuous data

~ 10% for quantal data

So, in individual datasets the effect size may even be larger

The level of protection of the associated ADI is unknown

THE BMR

The effect is *in reality*

effect size at the NOAEL — 50 %

20 %

"visible" — 10 %

5 % — Benchmark response (nominal value)

1 %

"invisible" — 0.1 %

.
.
.

0 %

effect size at the BMD:

WHAT IS A NOAEL?

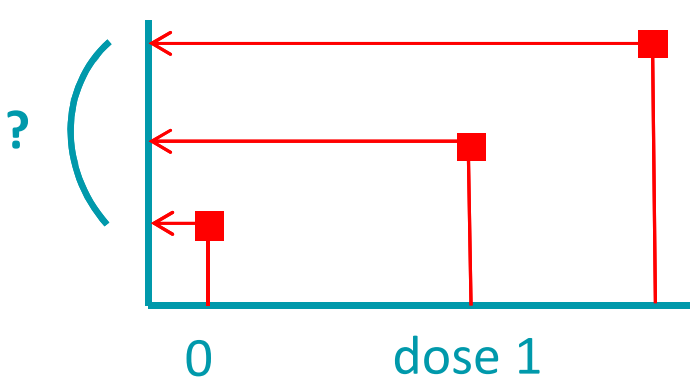
A NOAEL is a dose where the effect is assumed to be small, but we cannot guarantee that

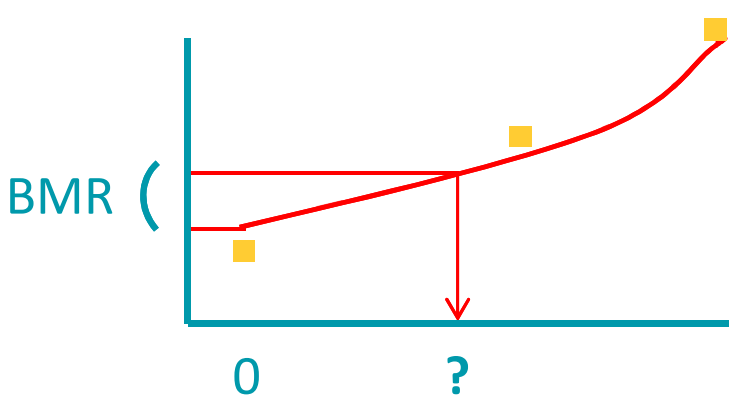
FROM NOAEL TO BMD APPROACH

Step 1: "do we see an effect?" → "how large is the effect"

statistically: significance test → confidence interval

Step 2: focus on effect → focus on dose

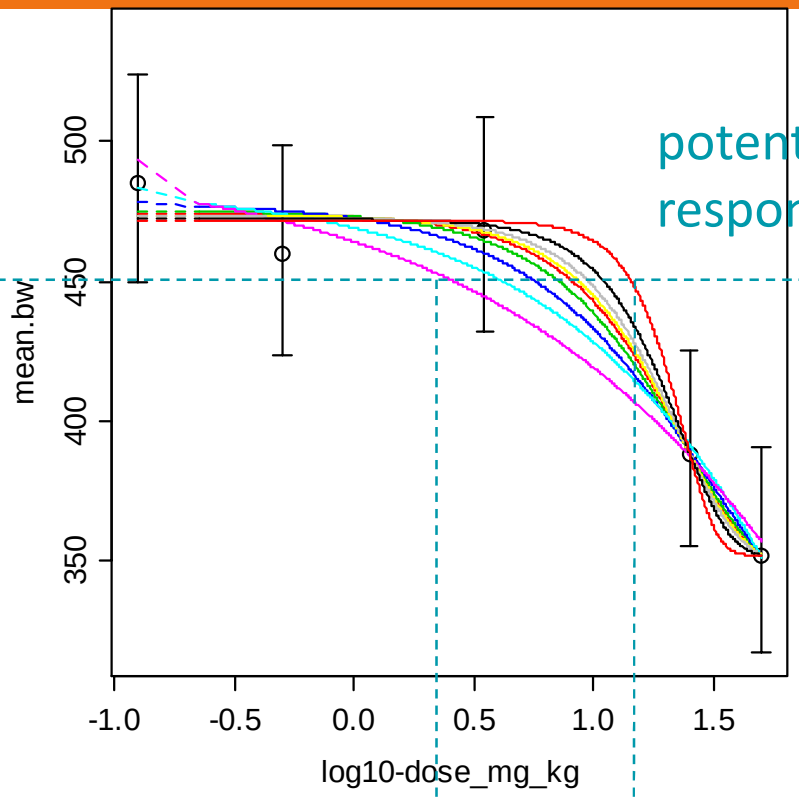




SOME DISADVANTAGES OF THE NOAEL

- The NOAEL is subject to the assessor's view of how to assess it
- The NOAEL is subject to dose selection
- The uncertainty in the NOAEL is not made visible / ignored in practice
- As a result, NOAELs cannot be compared among studies
- Very rich datasets and very poor datasets both result in one single number, without acknowledging for the quality of the data
- The true effect size at a NOAEL remains unknown (is it protective?)
- It does not use all dose-response information available

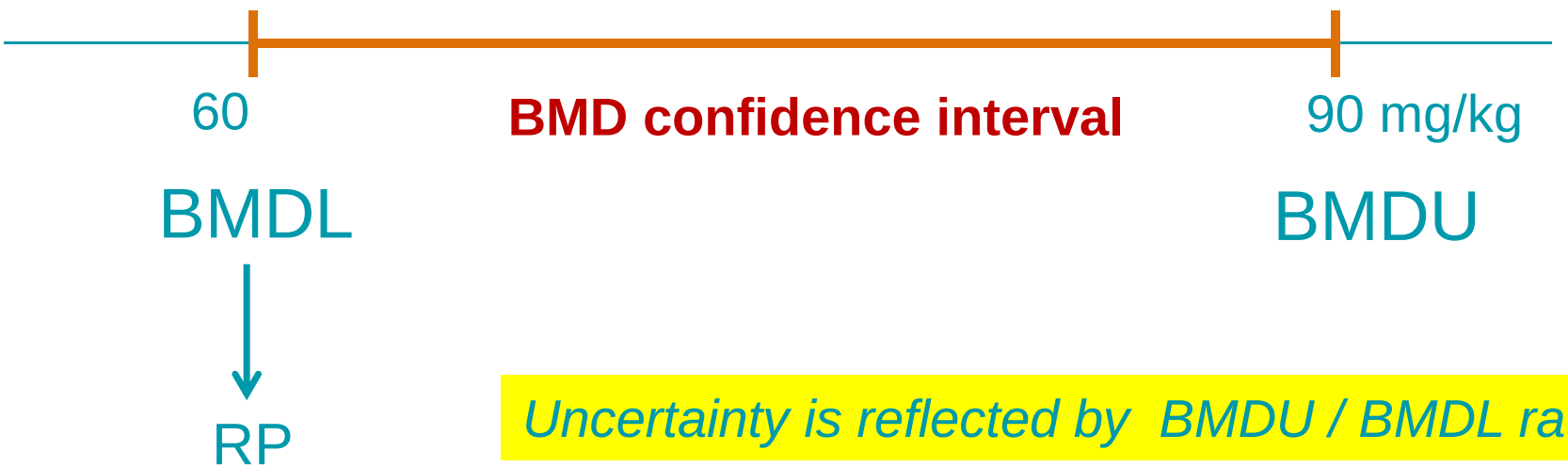
THE BMD APPROACH



THE OUTCOME OF A BMD ANALYSIS

We are interested in the *true* value of the BMD, not in its best estimate

The BMD confidence interval is the essential output from a BMD analysis



Uncertainty is reflected by BMDU / BMDL ratio

(not BMD / BMDL !)

USE OF BMDL AND BMDU

When the data are relatively informative:

When they are relatively un-informative:

BMDL remains equally “protective”

BMDU tells you how much higher the BMDL might have been with better data

THE DIFFERENCE BETWEEN BMDL AND NOAEL

A BMDL is a dose at which the effect is smaller than the BMR (with defined confidence)

A NOAEL is a dose where the effect is assumed to be small

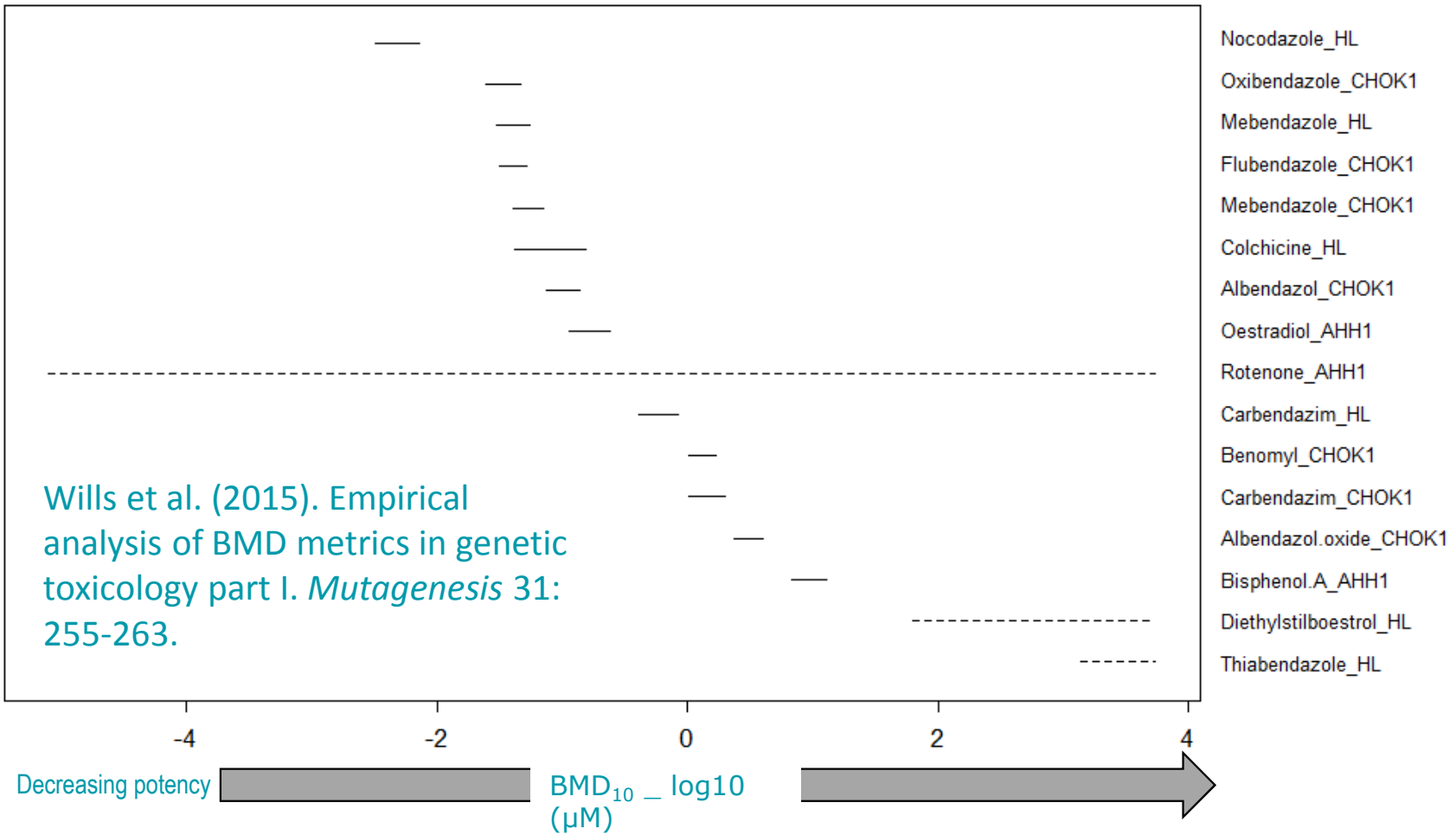
So, the NOAEL is a poor version of the BMDL

CONSEQUENCES FOR ESTABLISHING HBGV

NOAEL and BMDL have, *on average,* similar values

Therefore, the same assessment factors apply

BMD AND POTENCY COMPARISON

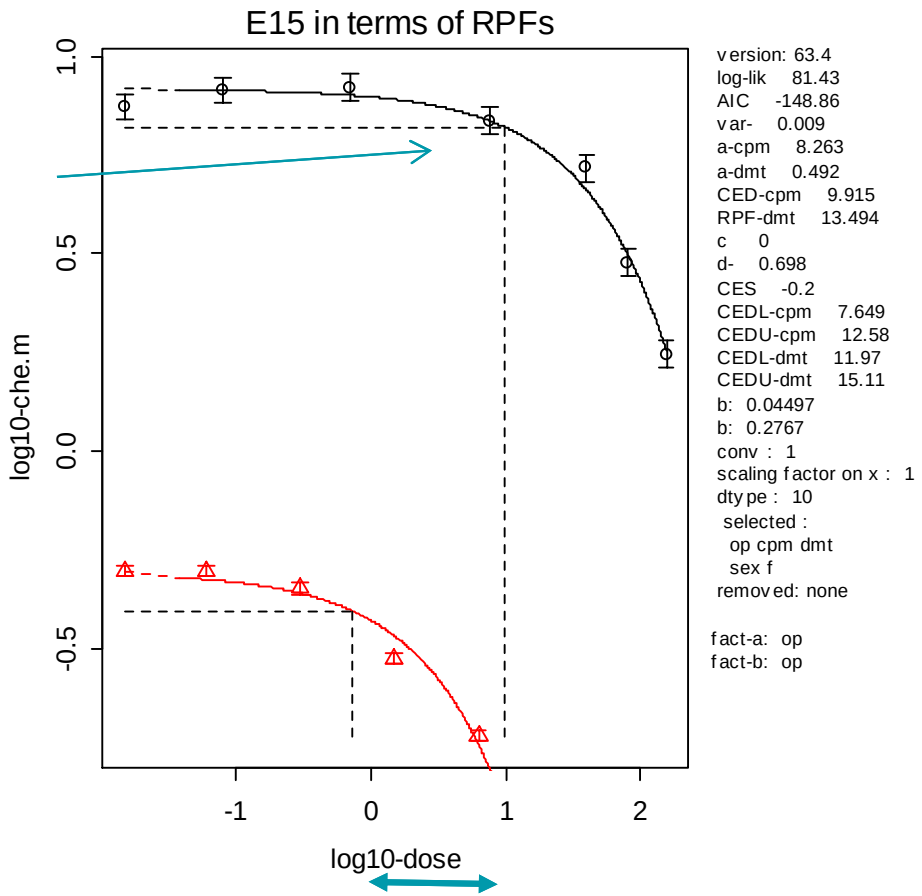


Wills et al. (2015). Empirical analysis of BMD metrics in genetic toxicology part I. *Mutagenesis* 31: 255-263.

16 aneugens tested in vitro

ESTIMATING RELATIVE POTENCY FACTOR (RPF)

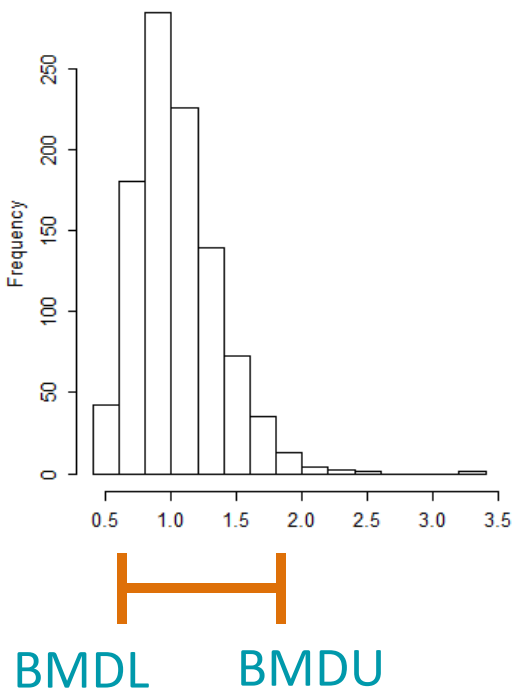
reference compound



RPF : (12.0, 15.1)

BMD AND PROBABILISTIC RISK ASSESSMENT

A BMD analysis can also produce an uncertainty distribution for the BMD



which can be combined with uncertainty distributions for the assessment factors

↓

probabilistic ADI (IPCS, 2014)

BMD AND PROGRESS

The BMD approach opens the way to progress in risk assessment methodology, in optimal animal use, and in validating alternative methods

End of General Considerations