IDENTIFYING A NOAEL

- 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

Range of assessed NOAELs: 25 up to 300 mg/kg
DO WE SEE AN EFFECT?

The NOAEL approach:

- we see an effect
- we don’t see an effect

Reality:

- there is an effect
- there is no effect

wrong
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

none are red

take a sample of 10 balls

two are red

10% red balls

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?

Theoretical answers:
- we see an effect
- we don’t see an effect

Reality:
- there is an effect
- there is no effect

X wrong
WHAT DO WE MEAN BY “THERE IS NO EFFECT”? 

The effect is in reality

50 %
5 %
0.1 %
0.001 %

what is the borderline between effect and no effect?

$10^{-10} \%$

0 % = $10^{-\infty} \%$
ESTABLISHING NO EFFECT

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

can be established with infinite group sizes only
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

<table>
<thead>
<tr>
<th>Effect Size at the NOAEL</th>
<th>Effect Size at the BMD:</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;visible&quot;</td>
<td>50%</td>
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<tr>
<td></td>
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<td>10%</td>
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<tr>
<td>&quot;invisible&quot;</td>
<td>0.1%</td>
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<tr>
<td></td>
<td>0%</td>
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</tbody>
</table>

Benchmark response (nominal value)
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

Plausible values for the BMD

Confidence interval

potential dose-response relationships

BMR

log10-dose_mg_kg

mean.bw
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:

60 90 mg/kg

When they are relatively un-informative:

0.12 120 mg/kg

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

Therefore, the same assessment factors apply
BMD AND POTENCY COMPARISON


16 aneugens tested in vitro
ESTIMATING RELATIVE POTENCY FACTOR (RPF)

RPF: (12.0, 15.1)
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)
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