Issues with plant tests in the open literature

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Extrapolation

Problems:

• No Dose-response design
• Extrapolation (dose-resp, but ERx outside of range)
• Selection of Effect level (ER_{10}, ER_{20}, ER_{25}, ER_{50})
• SSDs and „Greater than-values“
Extrapolation

Problem:
No Dose-response design, ERx wanted, but only control + one dose tested
No Dose-response design

Problem:
ERx wanted, but only control + one dose (20 g/ha) tested

Response of 18 weeds to tribenuron
(0.02 kg/ha ai post-em)

25% inhib.

50% inhib.

**ER**

ER$_{50}$: >20 >20 >20 >20 >20 <20 <20 20 20 <20 <20 <20 <20 20 >20

ER$_{25}$: >20 >20 20 >20 <20 <20 <20 <20 <20 <20 <20 <20 <20 >20
Extrapolation

Problem:

Dose-response design,
but the ERx is outside the range tested
Extrapolation of endpoints

Problem:
Tested treatment levels do not cover desired endpoint

Wanted: $ER_{25}$

Tested levels 0.02, 0.05, 0.1 * FAR

$ER_{25}$ of different species range between 0.02 and 4.0 FAR
Extrapolation

Reproductive endpoint 0.08 FAR

Inhibition vs. dose (FAR)
Extrapolation

Vegetative endpoint: 4 FAR.
Extrapolation

Vegetative endpoint – random change of replicates

![Graph showing inhibition vs. dose (FAR)](image)
Extrapolation

Vegetative endpoint – random change of replicates
Extrapolation

Vegetative endpoint – random change of replicates
Extrapolation

Vegetative endpoint – random change of replicates
Extrapolation

Vegetative endpoints with sufficient test rates...
Extrapolation

Vegetative endpoints with sufficient test rates...
...but these vegetative **extrapolations** were reported.
Extrapolation

After spotting this, we checked with one of the Authors, who confirmed that these were indeed mathematical extrapolations, not just a typo.

What would you do with these values?

We decided to include them, but only as greater-than values...

*extrapolations \leq 2 considered to be acceptable*
Selection of Effect level (ER_{10}, ER_{20}, ER_{25}...)

Problem:
Reliability of endpoints varies with effect level
Central estimates always more reliable than estimates at the tails of a distribution
Selection of Effect level ($\text{ER}_{10}$, $\text{ER}_{20}$, $\text{ER}_{25}$...)

Confidence intervals (95%)

- $\text{ER}_{50}$: 10.4 – 31.8 = 2.9-fold
- $\text{ER}_{25}$: 2.2 – 12.1 = 5.4-fold
- $\text{ER}_{20}$: 1.4 – 10.2 = 7.3-fold
- $\text{ER}_{10}$: 0.34 – 6.6 = 19.4-fold
- $\text{ER}_{05}$: <? – 3.5 = ???-fold
Selection of Effect level (ER$_{10}$, ER$_{20}$, ER$_{25}$...)

Problem:
Reliability of endpoints varies with effect level

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Confidence interval (95%)</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER$_{50}$</td>
<td>10.4 – 31.8</td>
<td>2.9 - fold</td>
</tr>
<tr>
<td>ER$_{25}$</td>
<td>2.2 – 12.1</td>
<td>5.4 - fold</td>
</tr>
<tr>
<td>ER$_{20}$</td>
<td>1.4 – 10.2</td>
<td>7.3 - fold</td>
</tr>
<tr>
<td>ER$_{10}$</td>
<td>0.34 – 6.6</td>
<td>19.4 - fold</td>
</tr>
<tr>
<td>ER$_{05}$</td>
<td>&lt; ? – 3.5</td>
<td>&gt; ?? - fold</td>
</tr>
</tbody>
</table>

Use ER$_{50}$ (with assessment factor), or ER$_{25}$ & AF (also this would make US-EPA data available), but any lower ERx would be unreasonably uncertain.
SSDs and „Greater than-values“

Problem:
Endpoints with “>“ or “<“

5 options to handle data:

a) Exclude the species with censored endpoints
b) Include censored data, ignoring the “>“
c) Include censored data with a correction factor
   e.g. $f = 2$ (UBA 2014???)
d) Consider censored data for $n$, but discard numeric values (HC 2008)
e) Consider censored data with a MLE-method
   (bootstrapping, e.g. MOSAIC script 2014)
SSDs and „Greater than values“

Data: (AMRAP Case C)

<table>
<thead>
<tr>
<th>Data no.</th>
<th>Toxicity data</th>
<th>Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>Lemna gibba</td>
</tr>
<tr>
<td>2</td>
<td>1.7</td>
<td>Lagarosiphon major</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>Myriophyllum heterophylli</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Ceratophyllum demersum</td>
</tr>
<tr>
<td>5</td>
<td>3.2</td>
<td>Potamogeton pectinatus</td>
</tr>
<tr>
<td>6</td>
<td>3.4</td>
<td>Mentha aquatica</td>
</tr>
<tr>
<td>7</td>
<td>3.8</td>
<td>Valisneria americana</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>Elodea canadensis</td>
</tr>
<tr>
<td>9</td>
<td>5.1</td>
<td>Ranunculus lingula</td>
</tr>
<tr>
<td>10</td>
<td>5.3</td>
<td>Glyceria maxima</td>
</tr>
</tbody>
</table>

1.5 Lemna gibba
1.7 Lagarosiphon major
2 Myriophyllum heterophylli
3 Ceratophyllum demersum
3.2 Potamogeton pectinatus
>3.4 Mentha aquatica
>3.8 Valisneria americana
>5.0 Elodea canadensis
>5.1 Ranunculus lingula
>5.3 Glyceria maxima
SSDs and „Greater than-values“

a) Exclude the species

(no good idea)
SSDs and „Greater than-values“

b) Include censored data, ignoring the “>“
SSDs and „Greater than-values“

c) include data with a correction factor, e.g. $f = 2$
SSDs and „Greater than-values“

d) Consider data for n, but discard numeric value

Fundamentally not possible with ETX 2.0
SSDs and „Greater than-values“

e) Consider censored data with maximum likelihood

e.g. MOSAIC script in R
again not possible with ETX 2.0

MOSAIC-Online version and R-script (University Lyon)
using two custom libraries (fitdistrplus), (actuar)

SSDs and „Greater than-values“

## Results:

<table>
<thead>
<tr>
<th>Option</th>
<th>$\text{HC}_{0.05}$ (50% prob)</th>
<th>$\text{HC}_{0.50}$ (50% prob)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) (5 species)</td>
<td>1.18</td>
<td>2.14</td>
</tr>
<tr>
<td>b) (10 species $&lt;&gt;$ as values)</td>
<td>1.43</td>
<td>3.08</td>
</tr>
<tr>
<td>c) (10 species, $&lt;&gt;$ with correction factor, e.g. $f = 2$)</td>
<td>1.15 (ETX) 1.44 (LSQ)</td>
<td>4.40 (ETX) 4.35 (LSQ)</td>
</tr>
<tr>
<td>d) (10 species, 5 used for fitting)</td>
<td>1.25</td>
<td>3.49</td>
</tr>
<tr>
<td>e) (MLE bootstrap; 10 spec, 5 censored) (MOSAIC)</td>
<td>1.24</td>
<td>4.15</td>
</tr>
</tbody>
</table>
SSDs and „Greater than-values“

Recommendation?

a) and b): Ignore censored data, or include, ignoring < >: most commonly used, (simplest, but least satisfying)

c): Consider censored data with a correction factor (f = 2) also simplistic, but not generally accepted (UBA?)

d): Consider censored data for n, but discard numeric values (relatively straightforward, no tool available yet)

e): Consider via MLE-method, censored data affect distribution (MOSAIC, bootstrap), (complex, still not perfect: Treatment of less-than values problematic; HC₅ may get unreasonably low)
Thank you!