Non-Clinical Statistics Conference
24-26 September 2012, Potsdam, Germany

9/24/2012

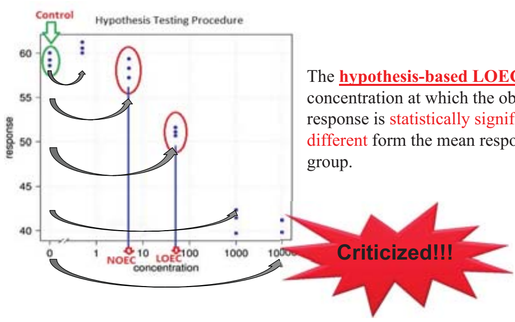
Evaluation of statistical methods to construct confidence intervals for the lowest observed effect concentration

Xiaoqi Jiang
Division of Biostatistics

GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

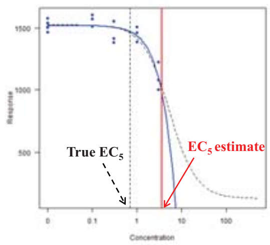
Motivation of the study

- **LOEC**: The **L**owest **O**bserved **E**ffect **C**oncentration



The **hypothesis-based LOEC** is the lowest concentration at which the observed mean response is statistically significantly different form the mean response of control group.

Model-based approaches: EC_5, EC_{10}, etc.



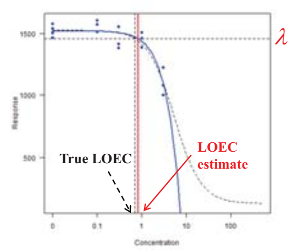
The problem of ECx approach

One possible solution: fix the parameter of the lower or upper asymptote (or both) to a constant value

Difficulties:

- true value of asymptote is not available
- limit a lot the flexibility of the model

The model-based LOEC



For a fixed and pre-specified effect level λ:

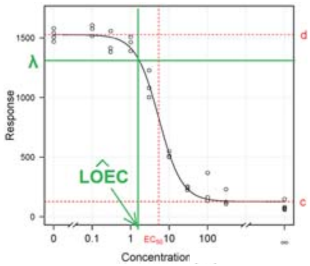
$$y = f(x,\theta) = \lambda \quad \Rightarrow \quad LOEC: x = f^{-1}(\lambda,\theta)$$

The LOEC based on four-parameter log-logistic model

Four-parameter log-logistic model:

$$y = f(x;\ b,c,d,e) = c + \frac{d-c}{1+\left(\frac{x}{EC_{50}}\right)^{b}}$$

c: the lower asymptote of the curve
d: the upper asymptote of the curve
b: the slope of the curve (Hill slope)
EC_{50}: produce the half-maximal effect



$$L\hat{O}EC = \hat{e}\,(\frac{\hat{d}-\lambda}{\lambda-\hat{c}})^{1/\hat{b}} \qquad (\hat{c} < \lambda < \hat{d})$$

Methods to construct confidence intervals for the LOEC

❖ **Wald confidence interval (CI):**

$$\widehat{\text{LOEC}} \pm percentile \times se(\widehat{\text{LOEC}}) \qquad (se:\ \text{standard error})$$

- based on asymptotic or large sample results

➢ **Delta Method:** approximate → $se(\widehat{\text{LOEC}})$ / $se(\log(\widehat{\text{LOEC}}))$ → Log back-transformation

➢ **Reparameterize** the log-logistic model:

$$f(x;\ b,c,d,LOEC) = c + \frac{d-c}{1+(\frac{d-\lambda}{\lambda-c})(\frac{x}{LOEC})^{b}} \Rightarrow se(\widehat{\text{LOEC}})$$

Methods to construct confidence intervals for the LOEC

❖ **Profile likelihood based CI:**

Profile t function of the parameter LOEC:

$$\tau(LOEC) = sign(LOEC - L\hat{O}EC)\frac{\sqrt{\min_{b,c,d}\sum_{i=1}^{n}[y_i - f(x_i, LOEC)]^2 - \sum_{i=1}^{n}[y_i - f(x_i,\hat{b},\hat{c},L\hat{O}EC)]^2}}{\sqrt{\sum_{i=1}^{n}[y_i - f(x_i,\hat{b},\hat{c},L\hat{O}EC)]^2/(n-p)}}$$

The (1-α) CI for the LOEC is defined as the set of all LOEC values for which the rule

$$|\tau(LOEC)| \le t_{(1-\alpha/2),(n-p)}$$

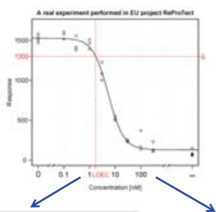
❖ **Bootstrap Method:**

➢ Generate bootstrap samples from the original data:
  - nonparametric bootstrapping
  - parametric bootstrapping

➢ Construct confidence interval:
  - percentile interval
  - Bias-corrected (BC) interval

Simulation Study

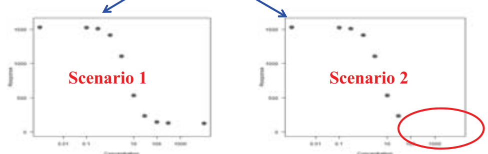
Real data set:



true parameters:
b=1.45
c=127.51
d=1526.95
e=exp(1.68)

chose λ=1300

true LOEC value =1.7289



1000 data sets generated by $y_{ij}^{sim} = f(x_i, b, c, d, e) + \varepsilon_{ij}$, where $\varepsilon_{ij} \sim N(0, SD)$

SD: 112.41(good) , 224.82 (extremely poor)

Simulation Study

- Compare the seven approaches to construct the 95% CI for the LOEC:
  1. delta method based CI (**delta**)
  2. back-transformed from log scale based CI (**fls**)
  3. profile likelihood based CI (**profile**)
  4. nonparametric bootstrap percentile based CI (**nbp**)
  5. nonparametric bootstrap BC-based CI (**nbb**)
  6. parametric bootstrap percentile-based CI (**pbp**)
  7. parametric bootstrap BC-based CI (**pbb**)

- ❖ coverage probability
- ❖ mean/median CI length
- ❖ distribution of lower/upper limits

R-Function "LOEC" (only for four-parameter log-logistic model)

LOEC (object, lambda, interval = c("none", "delta", "fls", "profile", "nbp", "nbb", "pbp", "pbb"), alpha=0.05, profile.delta.t=3, relTol=1e-8, nboot=NULL, display=TRUE)

Results: bootstrap methods

The coverage probabilities

Mehtod \ Scenario	1 (a)	1 (b)	2 (a)	2 (b)
nonparametric bootstrap (percentile)	0.823	0.852	0.826	0.855
nonparametric bootstrap (bias-corrected)	0.825	0.841	0.825	0.829
parametric bootstrap (percentile)	0.889	0.898	0.892	0.899
parametric bootstrap (bias-corrected)	0.893	0.906	0.894	0.861

Scenario 1: concentration-response curve completely supported by data points
Scenario 2: concentration range not adequate to observe the complete relationship
(a): $\varepsilon_{ij} \sim N(0, 112.41)$
(b): $\varepsilon_{ij} \sim N(0, 224.82)$

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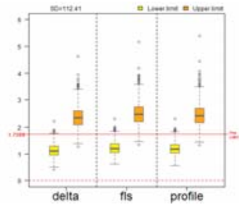
Results: scenario 1 (concentration-response curve completely supported by data points)

Distributions of lower and upper limits

1(a): slightly variable data

Methods	Mean length	Coverage Probability
delta	1.25	0.956
fls	1.28	0.948
profile	1.26	0.950



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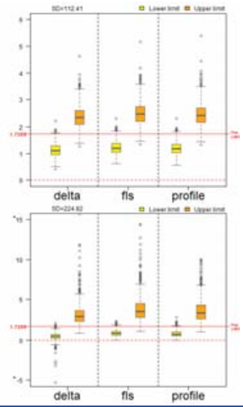
1(b): highly variable data

Methods	Mean length	Coverage Probability
delta	4.26	0.947
fls	**1.25e+26**	0.951
profile	2.85	0.951



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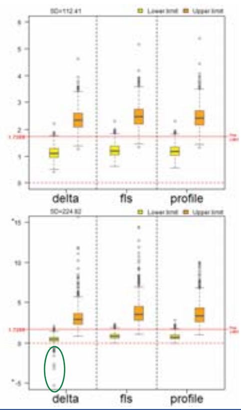

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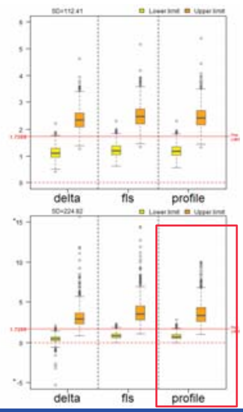
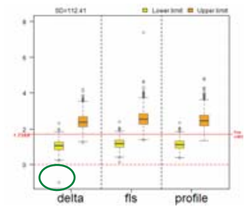


Results: scenario 2 (concentration range not adequate to observe the complete relationship)

Distributions of lower and upper limits

1(a): slightly variable data

Methods	Mean length	Coverage Probability
delta	1.36	0.944
fls	1.41	0.947
profile	1.37	0.957



Recommendations for computation CIs for the LOEC

relevant **DATA QUALITY** ➡ how to design experiments efficiently

Methods	Data quality			
	good	highly variable	lack some high concentration levels	very poor
standard delta methods	✓.	X.	X.	X.
back-transformed approach of the delta method	✓.	✓.	✓.	X.
profile likelihood method	✓.	✓.	✓.	X.
various bootstrap methods	X.	X.	X.	X.

✓. highly recommended ✓. recommended X. not recommended

Results: scenario 2 (concentration range not adequate to observe the complete relationship)

Distributions of lower and upper limits

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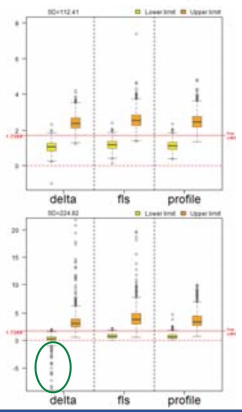
delta	1.36	0.944
fls	1.41	0.947
profile	1.37	0.957

1(b): highly variable data

Methods	Mean length	Coverage Probability
delta	12.95	**0.914**
fls	1.19e+97	**0.936**
profile	2.95	**0.928**



Thank you for your attention !