Time-dependent SSDs

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Derivation of trigger values

- Toxicity tests provide toxicity values (TVs) (e.g. NOEC, EC10, NEC) for a few species

- A Species Sensitivity Distribution is fitted to TVs (e.g. log-normal, log-logistic, Burrlioz)

- A trigger value is derived as a concentration hazardous for a small fraction of species (e.g. 0.01, HC1)
Toxicity values are expected to vary with time.

The choice of test duration, even if following standard experimental protocols, seems somewhat arbitrary.

Toxicity values corresponding to different exposure durations are pooled.

What impact on the derived SSD and HCs?

![Graph showing fraction of affected species vs log(Concentration) with data points at 96h and 144h.]
Investigating the time dimension

2D SSD

3D SSD

Fraction of affected species

Concentration

Fraction of affected species

Concentration

Time

HC50

HC10

HC5

HC1
In theory

• Consider $X_t$, a time-dependent random variable standing for the toxicity value of one species among an infinite number of species

• Assuming that $X_t$ follows a log-normal distribution (SSD), the latter can be characterized by its expected value $E[X_t]$ and coefficient of variation $CV[X_t]$

• HCs time-course can be mathematically related to $E[X_t]$ and $CV[X_t]$ time-models

• $E[X_t]$ is expected to decrease with time (chronic toxicity values are usually smaller than acute ones)
  → Test of different decreasing time-models

• $CV[X_t]$ is expected to decrease with time (Kooijman, 1987, Duboudin et al., 2004) or to be constant (De Zwart, 2002)
  → Test of both kinds of models
In theory

- The shape of HCs time-pattern is a trade-off between the time-models for $E[X_t]$ and $CV[X_t]$ and the affected fraction of species.

- HCs decrease with decreasing mean and increase with decreasing scatter.
In practice

- SSDs are fitted to a finite number of TVs

- TVs are estimated after a certain duration using hypothesis-testing or concentration-response models

- Adding consideration of time, simulation of
  - fictitious response of fictitious species
  - time-concentration-response data

- Fictitious experimental design
  - Control + 7 exposure concentrations (1, 2, 4, 8, 16, 32, 64 conc. units)
  - Measurements for 10 time units (say daily for 10 days)
  - 3 samples/replicates
Example for one species

\[
\gamma = \frac{\gamma_\infty}{1 - \exp(-k_c t)}
\]
Simulation of data sets

Baseline toxicity model (Escher and Hermens, 2002)

Asymptotic/incipient TV

\[ \gamma = \frac{\gamma_\infty}{1 - \exp\left(-k_e t\right)} \]

Elimination rate

- 1,000 fictitious species, each having their own parameter values

\[ \gamma_\infty \sim \log\text{Norm}(\text{meanlog} = 1, \text{sdlog} = 1) \]

\[ k_e \sim \log\text{Norm}(\text{meanlog} = -1, \text{sdlog} = 1) \]
Derivation of SSDs

- Random sampling of N species among the 1,000 fictitious species

- At each time point (for 10 days)
  - From the data set simulated for those species, (Max. Lik.) estimation of toxicity value (using the same concentration-response model as for the simulation step)
  - Fitting of a log-normal SSD to the N toxicity value estimates
  - Derivation of HC1s

Procedure performed 5,000 times for N=6, 10 and 30
Estimation of toxicity values

The time-pattern of estimates matches the underlying model (baseline toxicity model).

Toxicity values tend to an asymptote, sooner or later.
Derivation of SSDs and HCs

Time-decreasing pattern for both:

- the median values
  
  \[ \begin{align*}
  N=6 & \quad H_{C1}^{\text{1-day}} = 232\% \ H_{C1}^{\text{10-day}} \\
  N=10 & \quad H_{C1}^{\text{1-day}} = 223\% \ H_{C1}^{\text{10-day}} \\
  N=30 & \quad H_{C1}^{\text{1-day}} = 220\% \ H_{C1}^{\text{10-day}}
  \end{align*} \]

- the magnitude of HC1 95% CI

When the sample size is small, its impact is predominant.
Pooling of different exposure durations

- In actual toxicity assessment studies, chronic/subchronic toxicity values are pooled while test durations differ.

- Example of Australian practices (van Dam et al., ETC, 2010): toxicity of magnesium sulfate to 6 freshwater species exposed for 72h (algae, hydra), 96h (duckweed, snail, trout gudgeon) or 144h (cladoceran).

- Same simulation framework as before but random selection of TV estimates at those time points.

- HC1 median and 95% IC similar to those before-obtained at 96h which equals the arithmetic mean of 2 x 72h + 3 x 96h + 1 x 144h.

- Pooling seems equivalent to time-averaging exposure durations.
Discussion

• To our knowledge, lack of actual data suitable to address the question of the time-dependence of SSDs
  BTW: Call for data

• Study necessarily model-based and results dependent of modelling assumptions

• Difficult to discuss with literature because nothing likewise

• Only a few literature studies dealing with SSDs acute-to-chronic extrapolation
Conclusion

• Our results suggest that too short exposure durations may lead to under-protective trigger values (HC1). How close to asymptotic level are TVs derived from chronic/subchronic toxicity tests?

• Results also highlight the critical issue of sample size for SSDs

• Biological background and practical considerations are essential for setting test protocols. Models and statistics can also be helpful for guiding experimental design.

• All time points are informative: summarizing the response over the exposure duration (e.g. growth rate) is wasting data.
Questions? Suggestions?