Time-dependent SSDs

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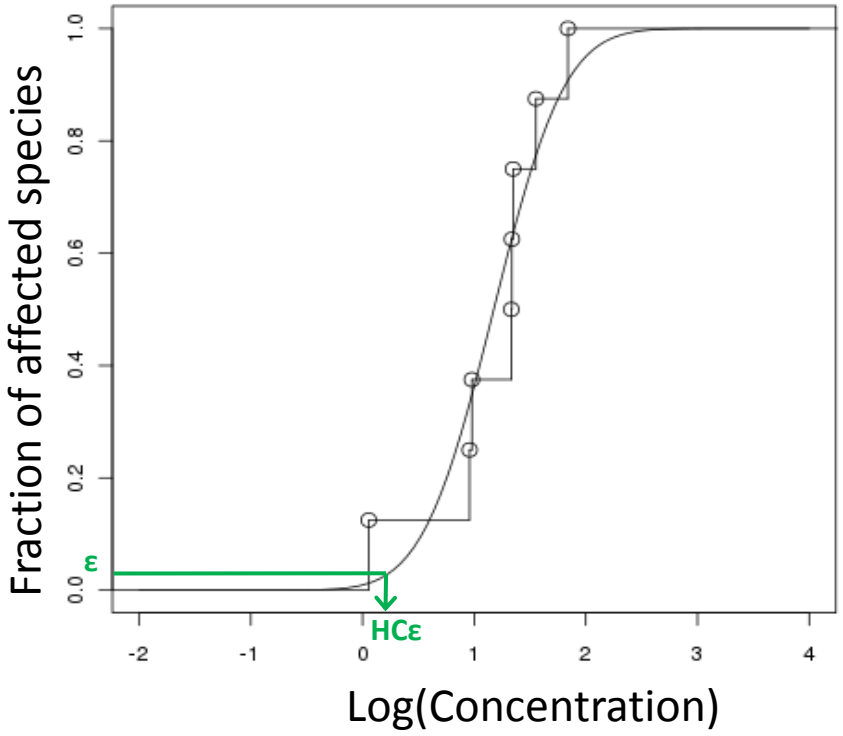
Derivation of trigger values

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

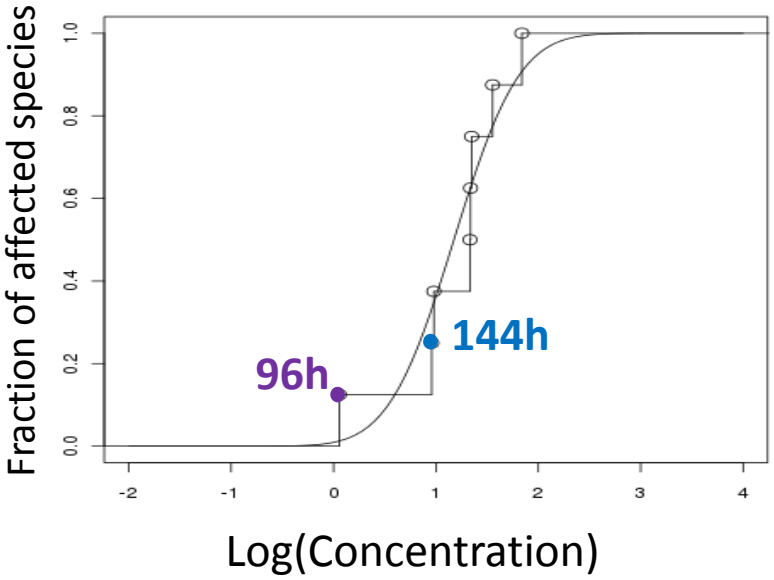
- A Species Sensitivity Distribution is fitted to TVs (e.g. log-normal, log-logistic, Burrlioz)

- A trigger value is derived as a concentration hazardous for a small fraction of species (e.g. 0.01, HC1)



Question

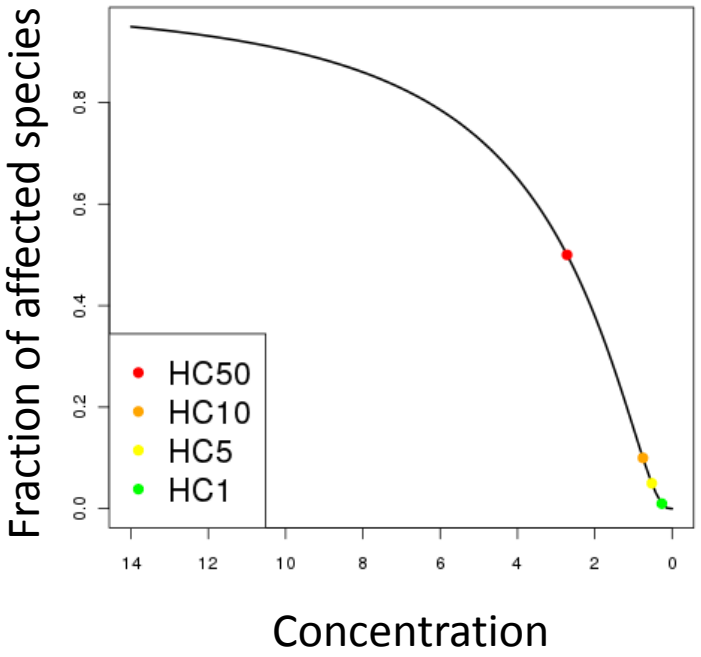
- Toxicity values are expected to vary with time
- The choice of test duration, even if following standard experimental protocols, seems somewhat arbitrary
- Toxicity values corresponding to different exposure durations are pooled



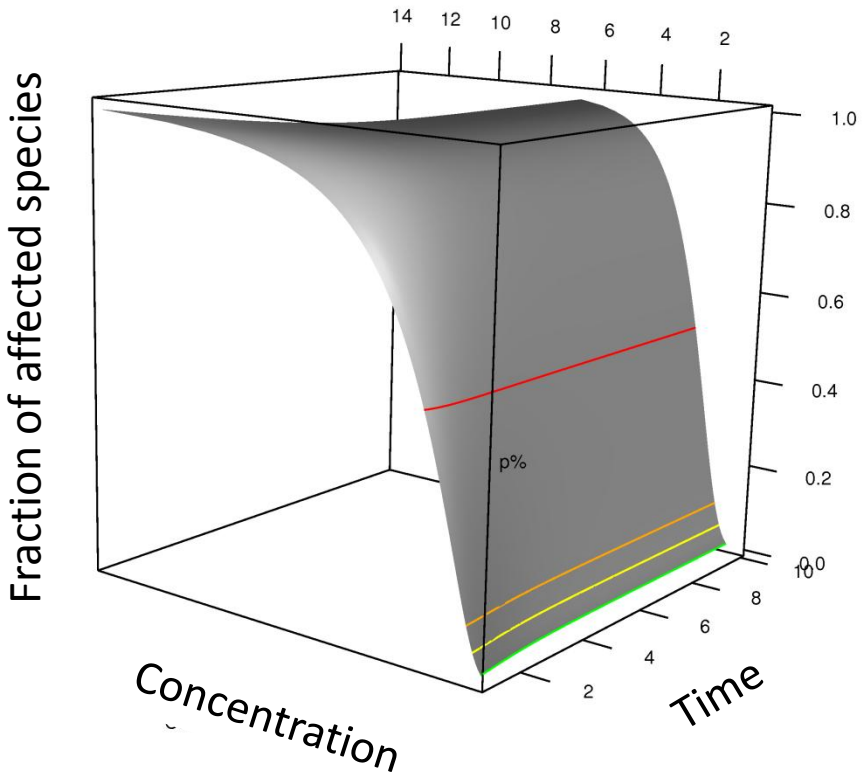
- What impact on the derived SSD and HCs?

Investigating the time dimension

2D SSD



3D SSD



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

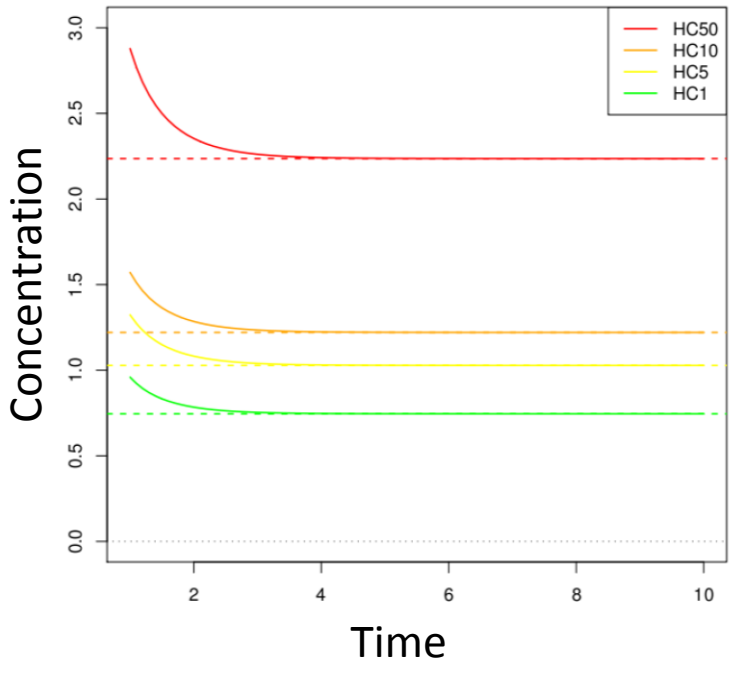
- $E[X_t]$ is expected to decrease with time (chronic toxicity values are usually smaller than acute ones)

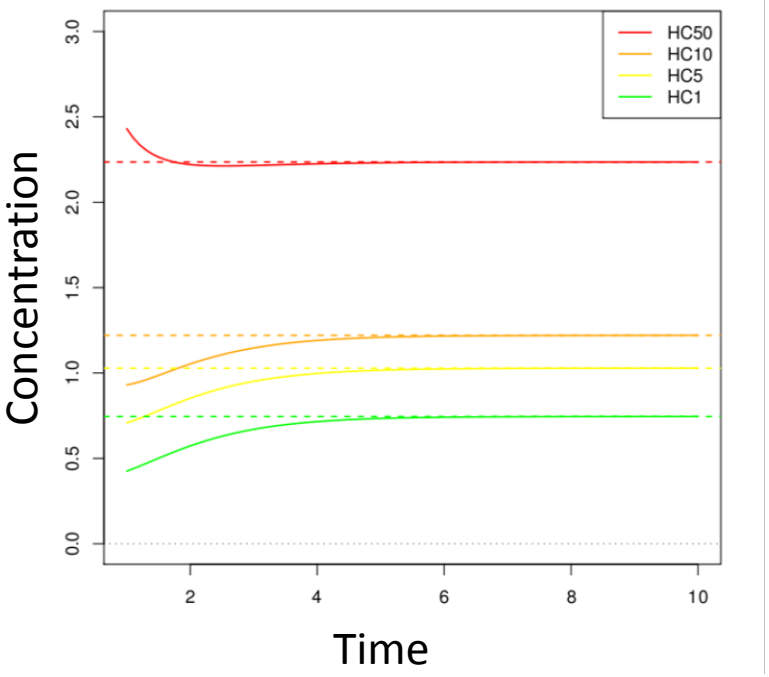
→ Test of different decreasing time-models

- $CV[X_t]$ 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





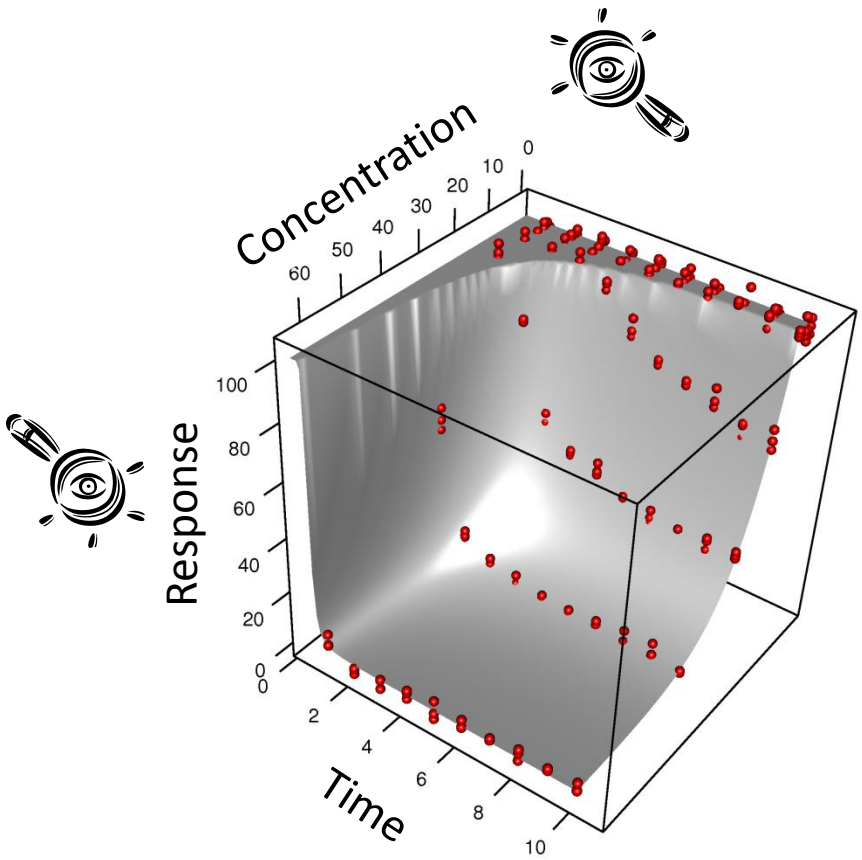
- The shape of HCs time-pattern is a trade-off between the time-models for $E[X_t]$ and $CV[X_t]$ and the affected fraction of species

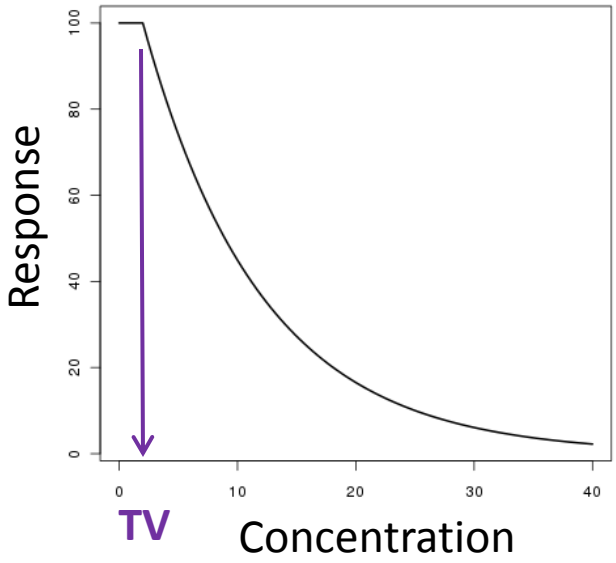
- HCs decrease with decreasing mean and increase with decreasing scatter

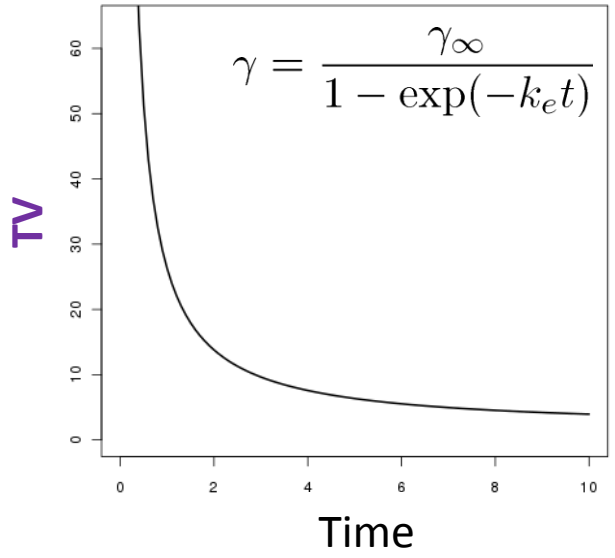
In practice

- 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

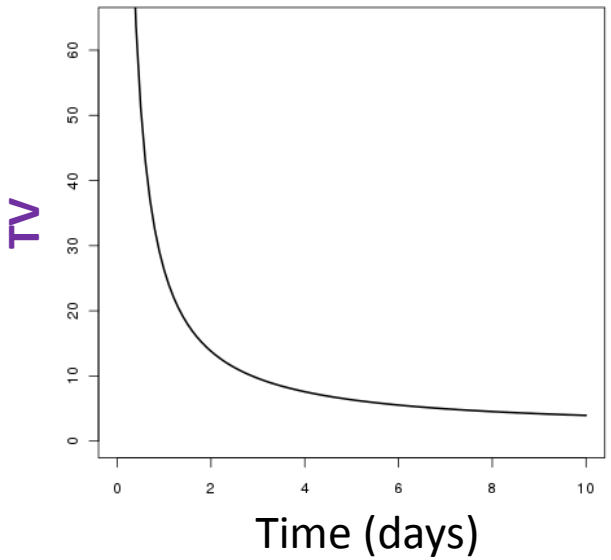
Example for one species







Simulation of data sets



Baseline toxicity model (Escher and Hermens, 2002)

Asymptotic/incipient TV

$$\gamma = \frac{\gamma_\infty}{1 - \exp(-k_e t)}$$

Elimination rate

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

$$\gamma_\infty \sim logNorm(meanlog = 1, sdlog = 1)$$

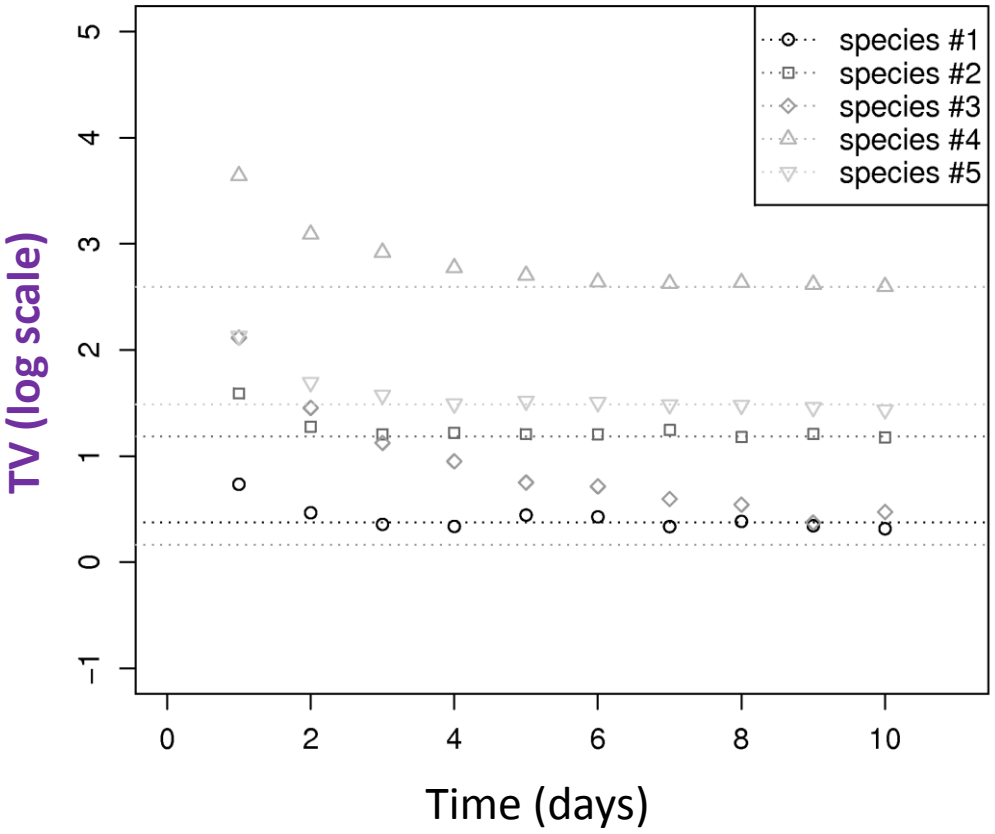
$$k_e \sim logNorm(meanlog = -1, sdlog = 1)$$

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

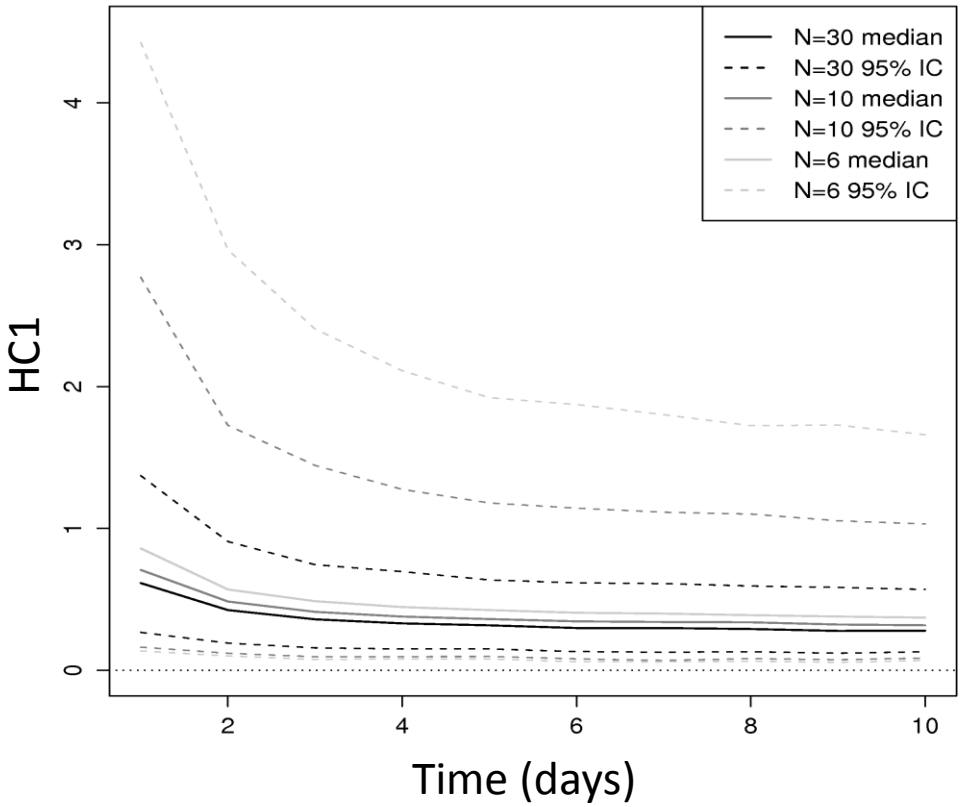
Estimation of toxicity values



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

N=6 $HC1_{1\text{-day}} = 232\%\ HC1_{10\text{-day}}$

N=10 $HC1_{1\text{-day}} = 223\%\ HC1_{10\text{-day}}$

N=30 $HC1_{1\text{-day}} = 220\%\ HC1_{10\text{-day}}$

- 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?