CAN YOU REDUCE VALIDATION EFFORT WHEN JOINTLY CALIBRATING GUTS MODELS FOR MULTIPLE SPECIES?

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Background information

- In the EU, effect modelling has been included as an option for endpoint refinement in aquatic risk assessment for nearly 10 years (Tier IIC, EFSA Aquatic Guidance 2013[1]).
- The EFSA opinion on TKTD modelling[2] (2018) gives a detailed description of the models that are fit for purpose, their application and underlying data requirements.
- For lethal effects, there is a clear recommendation for the parameterization of the (reduced) **General Unified Threshold models of Survival (GUTS)**.
- PPP (Plant Protection Product) Notifiers are very interested in the modelling approaches to solve higher tier risk assessment questions.
- However, effect modelling is often ultimately discarded as an approach due to the combination of uncertainties in regulatory acceptance and the high cost associated with calibration and validation experiments.
- The high costs are driven by the inability to use existing data sets for key species, as these do not include the necessary information for parameterization, and the number of species to be tested.

We want to propose (and open a discussion on) different options that can increase the certainty of the approach and reduce the experimental effort for multi-species assessment involving effect modelling.

The model needs reliable underlying data to be used as a tool in risk assessment

What is needed to still have a reliable model?

Can the data generation effort be reduced?

Problem definition

Discussion points

Calibration and validation of multiple species requires a large effort

Do all species need a full calibration and validation data set for a multispecies assessment?

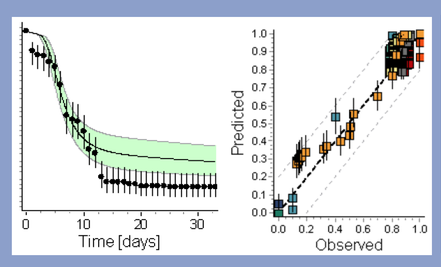
BOX 1: Main parameter of a GUTS-SD model[2]

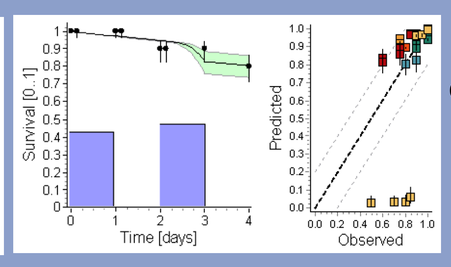
- Dominant rate k_D
  - The dominant rate constant links the external concentration of a chemical to the internal concentration of an organism.
  - k_D can be dominated by elimination or **damage** recovery.
- Threshold z
  - z is a fixed parameter that describes when a hazard (chemical) results in mortality, i.e. once the internal damage threshold is exceeded
- Killing rate k_k
  - k_k relates the probability of a mortality event to the scaled damage as it rises above the threshold z.
  - Increased scaled damage increases mortality.

Potential solutions

- To enable a GUTS model to predict toxicological outcomes and endpoints, it needs to be parameterized using compound and species-specific data → **Calibration**
- To confirm if a model is running correctly and reliably, a second compound and species-specific data set must be used → **Validation**

Calibration of a model
cannot be circumvented without **compromising** the outcome of the risk assessment.





Validation of a model
could potentially be reduced, if assessing the same compound for multiple species, which is the usual process in regulatory risk assessment of PPPs.

➢ **Reduction of validation effort is only possible, if it is proven that the compound acts similar in the species.**
➢ **The proof can be conducted by three different methods based on the calibration dataset.**

Chemical/species characteristics

- A toxicokinetically driven dominant rate k_D can be predicted by:
  - QSARs
  - Measured internal concentration
  - Surface to Volume Ratio of species or developmental stages[3]

➢ Requirements for this approach:
  - The other main parameters (BOX 1: threshold z and killing rate k_k) considerably overlap.
  - Species difference is solely by toxicokinetics (dominant rate k_D)

➢ **Validation effort could be reduced to 1 species**

Parameter correlations

- The main GUTS-SD parameters were shown to correlate with each other across species[4]:
  - Killing rate k_k correlates negatively with the threshold z
  - Dominant rate k_D correlates negatively with the killing rate k_k

➢ Requirements for this approach:
  - Correlations need to be confirmed in the calibration
  - Validation efforts could be made dependent on correlating parameters; e.g. for each parameter that is independent, additional species could be validated

➢ **Validation effort could be reduced to 1 species, if all GUTS-SD parameters correlate**
➢ **Validation effort could be reduced (e.g. to 2 species), if z and k_k correlate (GUTS-SD)**

Effect concentration (EC_x) aggregation

- Using confidence intervals (CI) to account for uncertainty of EC_{50} values in an SSD approach[5]:
  - Highlights the uncertainty propagation from EC_{50} to HC_5
  - Highlights for which species uncertainty occurs

➢ Requirements for this approach:
  - Ability to group species by their overlapping CIs on EC_x values
  - For SSDs, EC_x – CI values may overlap for one or more groups of species.

➢ **Validation effort could be reduced to representative species per CI group.**

Conclusion/discussion points/summary

- We presented three approaches which would make efficient use of available data
- With all these approaches we move from statistical data interpretation into the testing of mechanistic hypothesis.
- Following these approaches would reduce efforts to generate and evaluate data for using TKTD models for a SSD and increase the certainty of the approach

References:
1 EFSA PPR Panel (EFSA Panel on Plant Protection Products and their Residues) (2013). Scientific Opinion - Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Journal 2013; 11(7): 3290.. 2 EFSA TKTD Opinion. 3 Gergs, A., Kulkarni, D., & Preuss, T. G. (2015). Body size-dependent toxicokinetics and toxicodynamics could explain intra-and interspecies variability in sensitivity. Environmental Pollution, 206, 449-455.. 4 Gergs, A., Rakel, K. J., Liesy, D., Zenker, A., & Classen, S. (2019). Mechanistic effect modeling approach for the extrapolation of species sensitivity. Environmental science & technology, 53(16), 9818-9825., 5 Charles, S., Wu, D., & Ducrot, V. (2021). How to account for the uncertainty from standard toxicity tests in species sensitivity distributions: An example in non-target plants. PloS one, 16(1), e0245071.