DEB(tox) development project

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Context

EFSA‘ s opinion on DEBtox model (2018)

Objectives

Develop a consistent and relevant modelling approach for the regulatory environmental risk assessment of sub-lethal effects of chemical compounds with the DEB(tox) model

- Transparent and ready-to-use for risk assessment software (R-package)
- Calibration, validation and prediction steps as recommended by EFSA
- Providing uncertainty propagation to model predictions

Methods

DEB(tox) models

- **DEB model**
  - Full standard DEB will be used as a starting point, in order to relate to parameter values on the add-my-pet database and to allow higher flexibility in the model predictions
  - Simplified DEB models might also be considered
- **TKTD**
  - Same approach than in GUTS, damage dynamics are driving the effects on the organism.
  - In absence of body residue measurements, (scaled) damage densities are directly linked to external concentrations.
  - Dilution by growth, scaling of the rate constants with surface:volume ratio, losses with reproduction. To be included or not?
- **Modes of Actions**
  - The 5 most used MoAs will be separately considered: (1) Decrease in assimilation, (2) Increase in the costs for growth, (3) Increase in the costs for maintenance, (4) Increase in the cost for producing an egg, (5) Hazard during oogenesis
  - Direct effects on DEB primary parameters

Methods

Bayesian inference

- Marginal and joint posterior distributions give direct access to parameter uncertainty and their correlations

- Straightforward uncertainty propagation from physiological and toxicological parameters to model predictions

- Prior information, like AmP parameter values, could be used to guide and facilitate the estimation of the physiological DEB parameters

DEB calibration possibilities

	Bayesian inference				Predictions	
	Data	*Estimated Parameters*	*Priors* *Phy.*	*Priors* *Tox.*	*Phy.*	*Tox.*
Calibration 1	Tox. test data	Tox. only, Phy. fixed	/	Weakly informative, Exp. design	AmP parameters	Est.
Calibration 2	Tox. test data	Both Tox. and Phy.	AmP parameters	Weakly informative, Exp. Design	AmP parameters	Est.
Calibration 3	Tox. test data	Both Tox. and Phy.	AmP parameters	Weakly informative, Exp. Design	Est.	Est.

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- Calibration 2 is a good compromise between EFSA‘ s recommendations for regulatory acceptance, scientific rigour and ease of use.
- Comparisons with calibrations 1 and 3 could help to understand in what extent the use of AmP parameters has a impact on the outcome and the uncertainty propagation in the model predictions.

Case studies

Experimental data

- Calibration: Growth and reproduction data for different constant exposures to chemicals showing a large range of effect intensity (low to high)
- Validation: Growth and reproduction data for time-varying exposures
- Calibration and validation of the model on *D. magna* and *O. mykiss* growth and reproduction data for chronic exposure to chemicals

Challenges

- Unified DEBtox model
- Guide users in the choice of DEB model and MoAs
- Definition of a systematic procedure to choose prior distributions for toxicological parameters
- Inference methods which handles constant and variable concentrations – statistical challenge for ODE integration
- Handling of starvation due to lack of food or decrease in assimilation/increase in maintenance

Thank you for your attention!