Review, ring-test and guidance for TKTD modelling

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Rationale: The additional information and insight gained through the application of toxicokinetic-toxicodynamic (TKTD) modelling can strengthen the environmental risk assessment of chemicals, such as those applied in consumer products or plant protection products (PPPs). For the endpoint survival the most suitable and powerful tool is currently the General Unified Threshold model of Survival (GUTS), which consists of two complimentary models: GUTS-SD (stochastic death) and GUTS-IT (individual tolerance). GUTS has been submitted as part of the environmental risk assessment of PPPs, but it can also be used for purposes of REACH. In order to ease the use of GUTS and increase trust and acceptability we need to compare and test the range of software implementations available and generate guidance on how to use GUTS in Environmental Risk Assessment of chemicals. Beyond the endpoint survival, and beyond GUTS, TKTD models have broader applicability for sub-lethal endpoints, assessment of multiple stressors and reverse dosing for high-throughput toxicity testing. Reviewing the state of the science of TKTD modelling will enable development of a roadmap towards wider use of TKTD models in environmental risk assessment of chemicals in general and highlight synergies and differences with human safety evaluation methods.

Review the state of the science of TKTD modelling & roadmap towards broader applicability: **concept**

New project, Jan – Dec 2017:

- CEFICLRI ECO 39
- Review the state of the science of TKTD modelling in general and develop a roadmap towards broader applicability in chemical risk assessment.
- Ring test of different software implementations of the General Unified Threshold model of Survival (GUTS).
- Develop guidance on how to use GUTS for environmental risk assessment of chemicals.

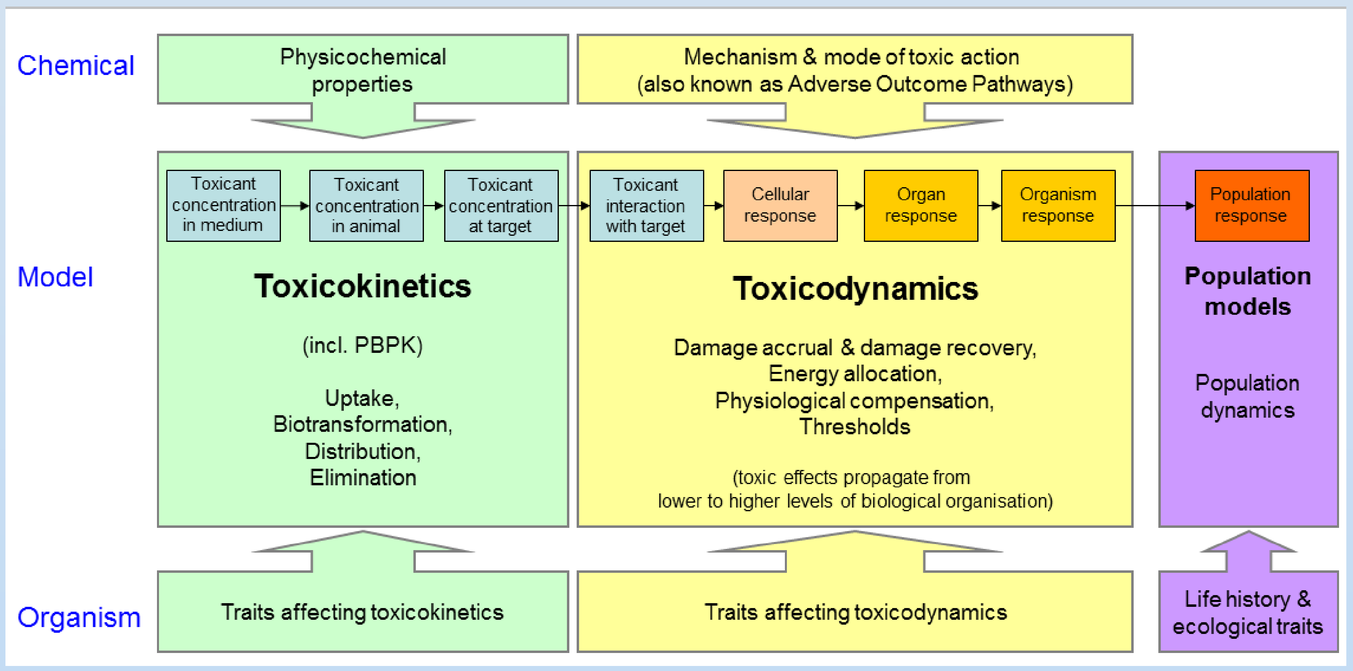
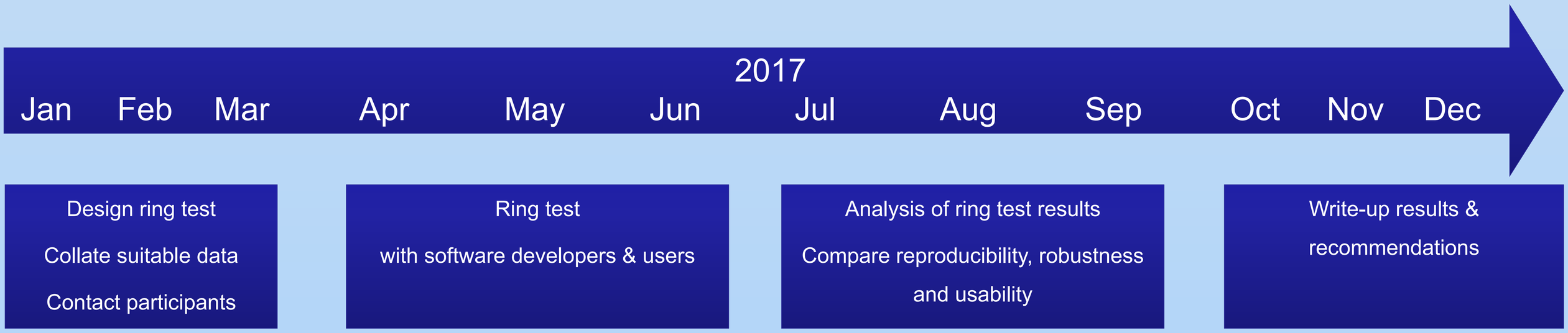


Figure 1: Toxicokinetics and toxicodynamics. Different chemical characteristics as well as different biological species traits are relevant for toxicokinetic and toxicodynamic processes.

(see: Ashauer, R. & Escher , B. I. (2010): Advantages of toxicokinetic and toxicodynamic modelling in aquatic ecotoxicology and risk assessment. *J. Environ. Monit.* **12**, 2056 - 2061)

Ring test of different software implementations of the General Unified Threshold model of Survival (GUTS): **timeline**



Develop guidance on how to use GUTS for environmental risk assessment of chemicals: **example topics**

Figure 2: Fit of GUTS-SD to survival in 4d-acute toxicity test.

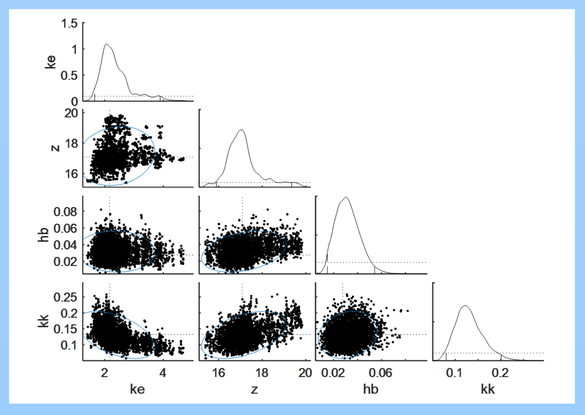


Figure 3: Bayesian MCMC sample of GUTS fit..

Figure 4: Percentage of surviving fish after 485 d as a function of the exposure factor (safety margin) for the various exposure scenarios under study.

Figure 5: A new paradigm for environmental risk assessment. Exposure assessment feeds into two stages of effects assessment to ultimately predict environmental impacts for a certain set of environmental conditions. The focus in this scheme lies on the effects assessment; the inputs for the parameters of the fate models are not specified.

Reference: Ducrot, V. *et al.* (2016) Using toxicokinetic-toxicodynamic modeling as an acute risk assessment refinement approach in vertebrate ecological risk assessment. *Integrated Environmental Assessment and Management* **12**, 32-45.

Reference: Jager, T. (2016): Predicting environmental risk: A road map for the future. *Journal of Toxicology and Environmental Health, Part A* **79**, 572-584,