General Unified Threshold model for Survival (GUTS):
a toxicokinetic-toxicodynamic framework for ecotoxicology

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TKTD models for survival

Toxicokinetic-toxicodynamic (TKTD) models simulate the processes linking exposure concentrations to toxic effects over time. Even for a simple endpoint like survival, a large number of different approaches exist. These differ in their underlying hypotheses and assumptions, which are usually not explicitly stated. To clarify these assumptions, and to show how approaches relate to each other, we developed an integrated framework: the "General Unified Threshold model for Survival" (GUTS).

Special cases of GUTS

A range of models can be viewed as special cases of GUTS, including the dynamic Critical Body Residue (CBR) models, Damage Assessment Models (DAM), Threshold Damage Model (TDM), DEBtox survival model, Critical Target Occupation (CTO) model, etc. A full list is presented in the GUTS paper (Jager *et al.*, 2011).

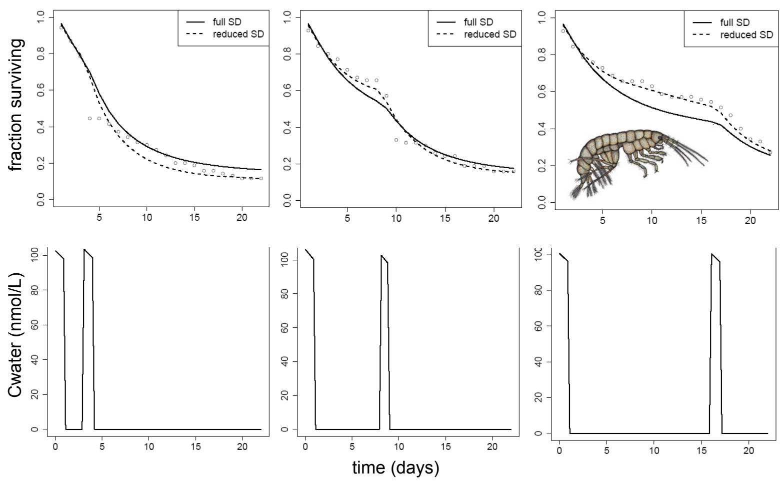

Fig. 2. Comparing two GUTS approaches for pulse exposure of Gammarus pulex to diazinon: full SD is stochastic death using a TK model incl. biotransformation and damage stage, whereas reduced SD uses a simple scaled TK model only.

Individual tolerance vs. stochastic death

An important distinction between TKTD approaches lies in the assumed cause of mortality. In GUTS, we integrate two common theories, allowing for either extreme, but also a combination of the two:

Individual tolerance assumes that death is immediate and deterministic when an internal threshold is exceeded; the value of the threshold is distributed in the test population.

Stochastic death assumes that death is a chance process at the level of the individual; the probability to die increases with exceedance of an internal threshold.

Conclusions

GUTS helps to increase application of TKTD models in research as well as environmental risk assessment. It unifies a wide range of apparently unrelated approaches, clarifies underlying assumptions, and facilitates interpretation and prediction of survival under stress.

Further research is needed to determine which "special case" is most appropriate for which chemical-species combinations.

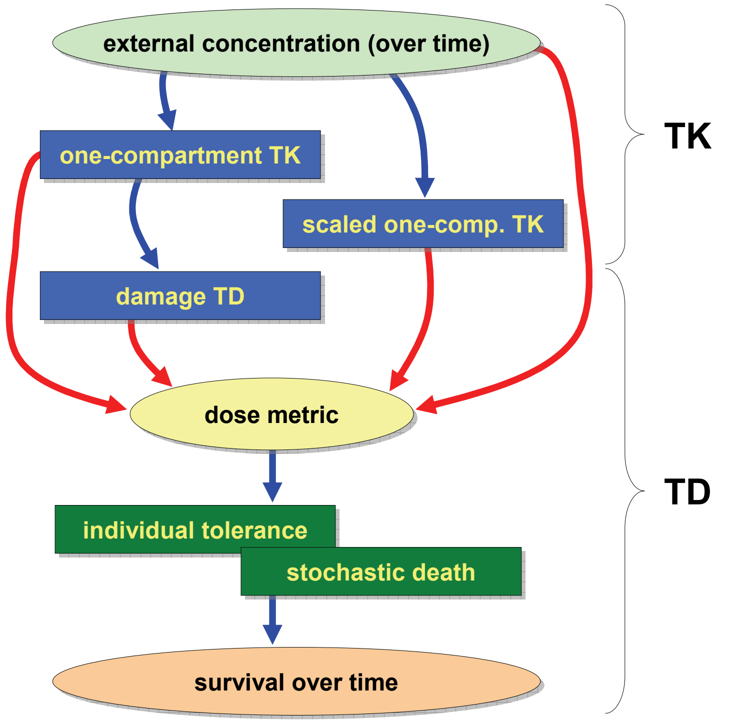

Fig. 1. Schematic representation of the GUTS structure.

Different dose metrics

TKTD models differ in the dose metric that they link to toxicity. The most appropriate dose metric depends on the chemical, species and on the available data (see Fig. 1). In GUTS you select between:

External concentration when chemical does not need to be taken up.
Actual internal concentration from a one-compartment TK model.
Damage level from a first-order model for damage accrual and repair.
Scaled internal concentration when internal concentrations are not measured; a TK rate constant is estimated from the effects data.

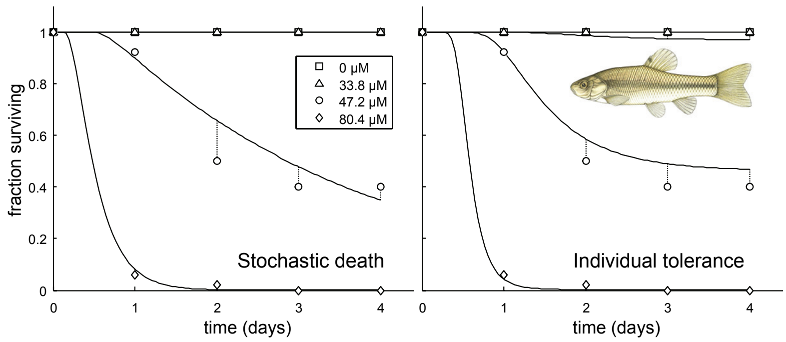

Fig. 3. Comparing two GUTS approaches for standard acute toxicity; fathead minnows exposed to naphthalene. In both cases, the scaled TK model is used, left with pure SD, right with pure IT.

Further materials

Further reading: Jager T, C Albert, TG Preuss, R Ashauer (2011). Environ. Sci. Technol. 45: 2529–2540.
Software: http://www.bio.vu.nl/thb/users/tjalling/debtoxm/
(freely downloadable Matlab implementation)