General Unified Threshold model for Survival (GUTS)

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TKTD models

Advantages

– understand rather than describe effects
– derive time-independent toxicity parameters
– interpret time-varying exposure
– make predictions for untested situations
TKTD model confusion

- For survival …
  - many models have been published …
  - CBR, DAM, DEBtox, TDM, CTO, etc., etc.
  - how do they relate to each other?

- The Kastanienbaum mission (or part thereof):
  - clarify the differences
  - agree on common terminology
  - look for unification
Unification possible?
Main similarities

- one-comp. first order TK
- one-comp. "damage"
- external concentration
- mortality mechanism
- survival over time

TK

TD
Main differences

Death mechanism
- Why don’t all animals die at the same time?
  - differences in sensitivity (IT)
  - death is a stochastic process (SD)

Dose metric
- What is the relevant dose for toxicity?
  - internal concentration (which one, where?)
  - scaled internal concentration
  - some form of “damage”
  - …
Complete damage model …

- body residue TK
  - uptake rate
  - elimination rate

- damage TD
  - damage accrual rate
  - damage repair rate

- one-comp. first-order TK

- one-comp. “damage”

- mortality mechanism

- external concentration

“dose metric”
Dose metric unification

1. Actual damage level
   - uptake, elimination, damage accrual and repair

2. Scaled damage level
   - uptake, elimination rate, damage repair

3. Actual internal concentration
   - uptake and elimination rate

4. Scaled internal concentration
   - “elimination” or “dominant” rate constant

5. External concentration
   - no parameters
Data requirements

1. Actual damage level
   – uptake, elimination, damage accrual and repair

2. Scaled damage level
   – uptake, elimination rate, damage repair

3. Actual internal concentration
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5. External concentration
   – no parameters
Death mechanism 1

Individual Tolerance (IT)

- death is immediate if dose metric > threshold
- Individuals differ in value of threshold
Death mechanism 2

Stochastic Death (SD)

- all individuals are identical
- dose metric increases probability to die

![Graph showing hazard rate vs. dose metric]

- threshold
- killing rate
- blank value

hazard rate
dose metric
SD / IT unification
SD / IT unification

threshold

standard dev. → 0

threshold

hazard rate

→ ∞

killing rate

dose metric

dose metric

threshold

hazard rate
SD / IT unification

threshold

standard dev. → 0

killing rate → ∞

don dose metric

threshold

dose metric

threshold

dose metric

hazard rate

hazard rate
Gammarus + diazinon

![Graphs showing the fraction surviving over time for Gammarus with full SD and reduced SD in water containing diazinon at different concentrations.](image-url)
Pimephales + naphthalene

Stochastic death

Individual tolerance

0 µM
33.8 µM
47.2 µM
80.4 µM

fraction surviving

0
0.2
0.4
0.6
0.8
1

time (days)
0
1
2
3
4

fish image
Conclusions

- GUTS unifies (almost) all TKTD models for survival
- Provides a common reference model
- Main open questions:
  - which dose metric / death mechanism is realistic?
  - can we extend to other endpoints?
What about sub-lethal?

- Mechanisms of SD and IT deal with quantal data
  - an event happens, yes or no
  - count affected individuals in the test population

- Graded responses like growth and reproduction require different mechanisms
  - e.g., Dynamic Energy Budget (DEB) theory
  - note that growth and repro will affect TK too ...
Recently appeared

General Unified Threshold Model of Survival - a Toxicokinetic-Toxicodynamic Framework for Ecotoxicology

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Supporting Information


Matlab implementation on: http://www.bio.vu.nl/thb/users/tjalling/debtoxm/