

General Unified Threshold model for Survival (GUTS)

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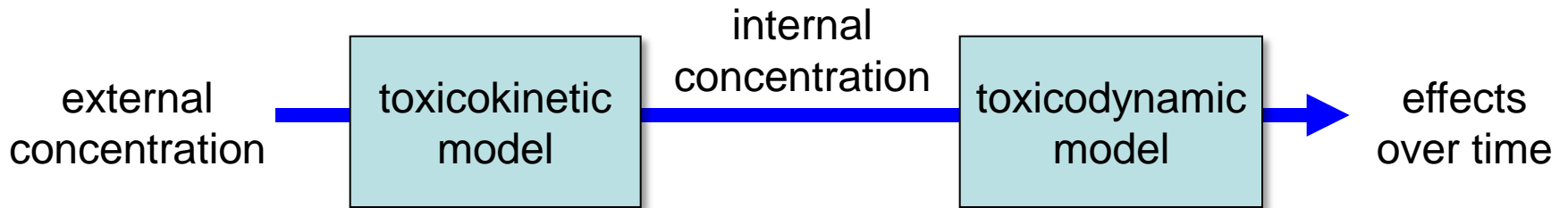


Kastanienbaum workshop 2010



eawag⁷⁵
aquatic research 1936-2011 ooo

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?

$\theta D = k_r \frac{D}{k_r} \bar{r}$

$\frac{d}{dt} C_i = k_{in} C_w - k_{out} C_i$
 $k_{out} (B(C) C_w - C_i)$

$\frac{d}{dt} D = k_k C_i - k_r D$
 $= k_r (DAF C_i - D) \quad DAF = \frac{k_k}{k_r}$

$\frac{dH}{dt} = \theta \max(D - D_0, 0)$
 $\frac{d}{dt} (d - C_i) = k_r (d - C_i) - k_{in} C_w + k_{out} C_i$

$D = \frac{D}{DAF} \quad d = \frac{D}{DAF}$

$\frac{d}{dt} d = k_r (C_i - d)$

$\frac{d}{dt} H = k_k \max(d - d_0, 0)$

$C_i = \dots \quad k_r = \frac{k_r}{k_r} \cdot \theta$
 $\frac{d}{dt} d = \frac{k_k}{k_r} \cdot \theta$
 $d_0 = \frac{D_0}{k_r}$

$S = e^{-H(t)}$

$\int_0^{\infty} e^{-d_0 s} ds = -e^{-d_0 s} \Big|_0^{\infty} = L - 0 \checkmark$
 $-k_k \max(d - d_0, 0)$

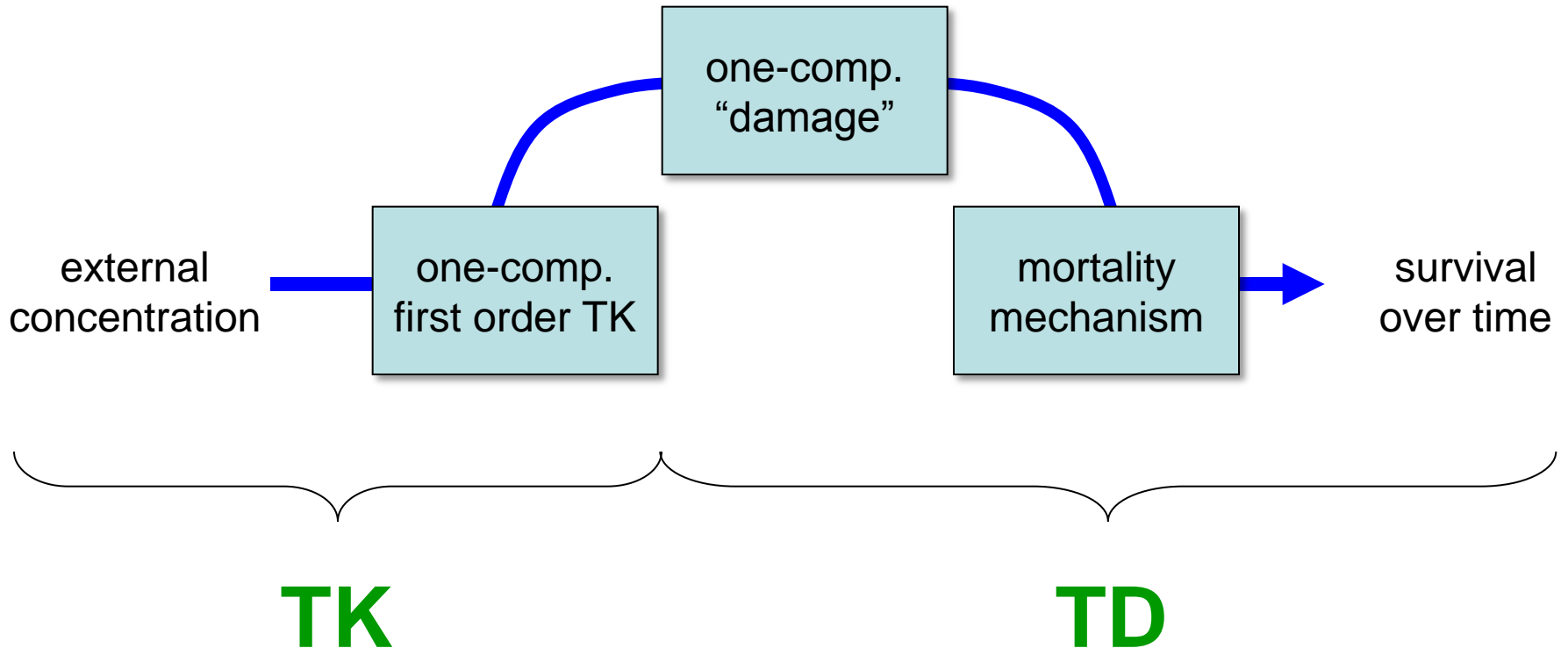
$S = e$

$f(d_0) = \int_0^{\infty} e^{-d_0 s} ds$

$M(t) = \int_0^{\infty} f(d_0) dd_0 = 1 - e^{-\dots}$

$S^* = \frac{S(t+\Delta t) - S(t)}{S(t)}$

Main similarities



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”
 - ...

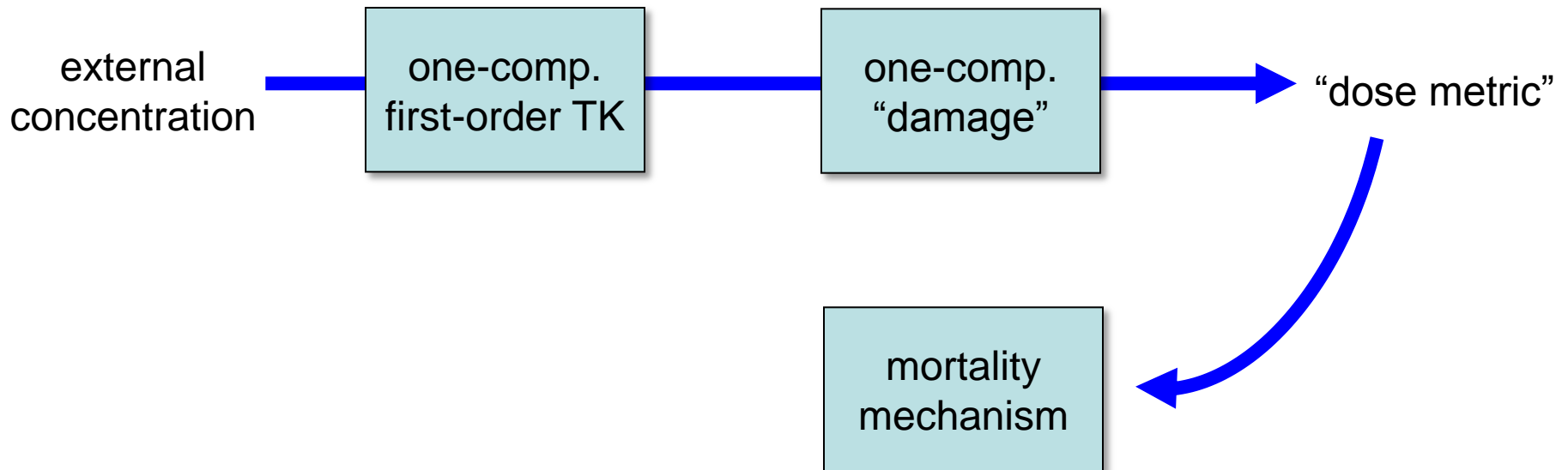
Complete damage model ...

body residue TK

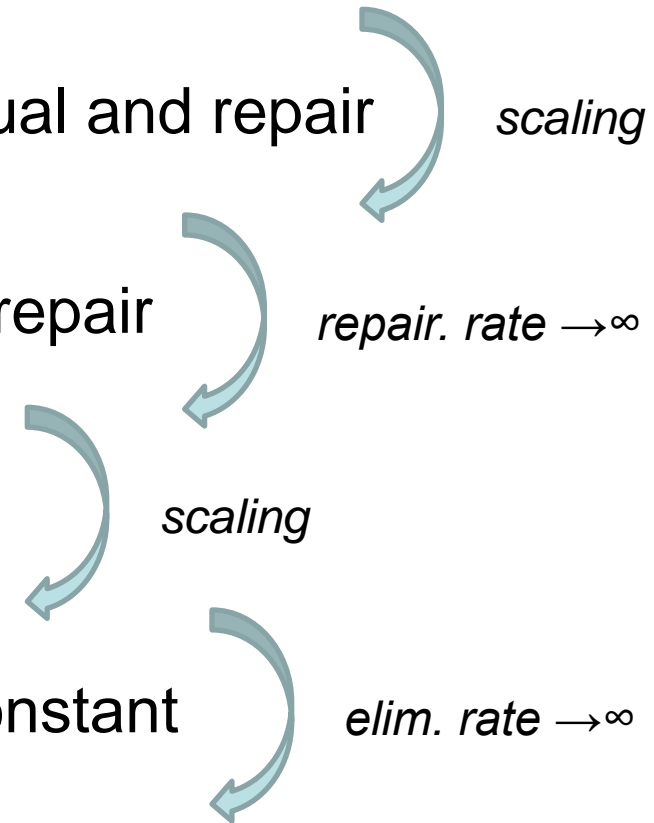
- uptake rate
- elimination rate

damage TD

- damage accrual rate
- damage repair rate

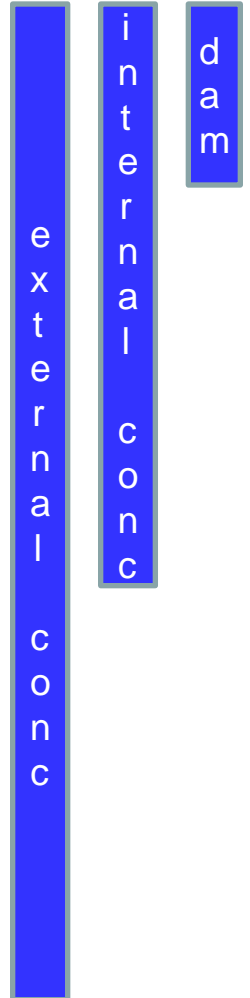


Dose metric unification

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
- 
- scaling
- repair. rate $\rightarrow \infty$
- scaling
- elim. rate $\rightarrow \infty$

Data requirements

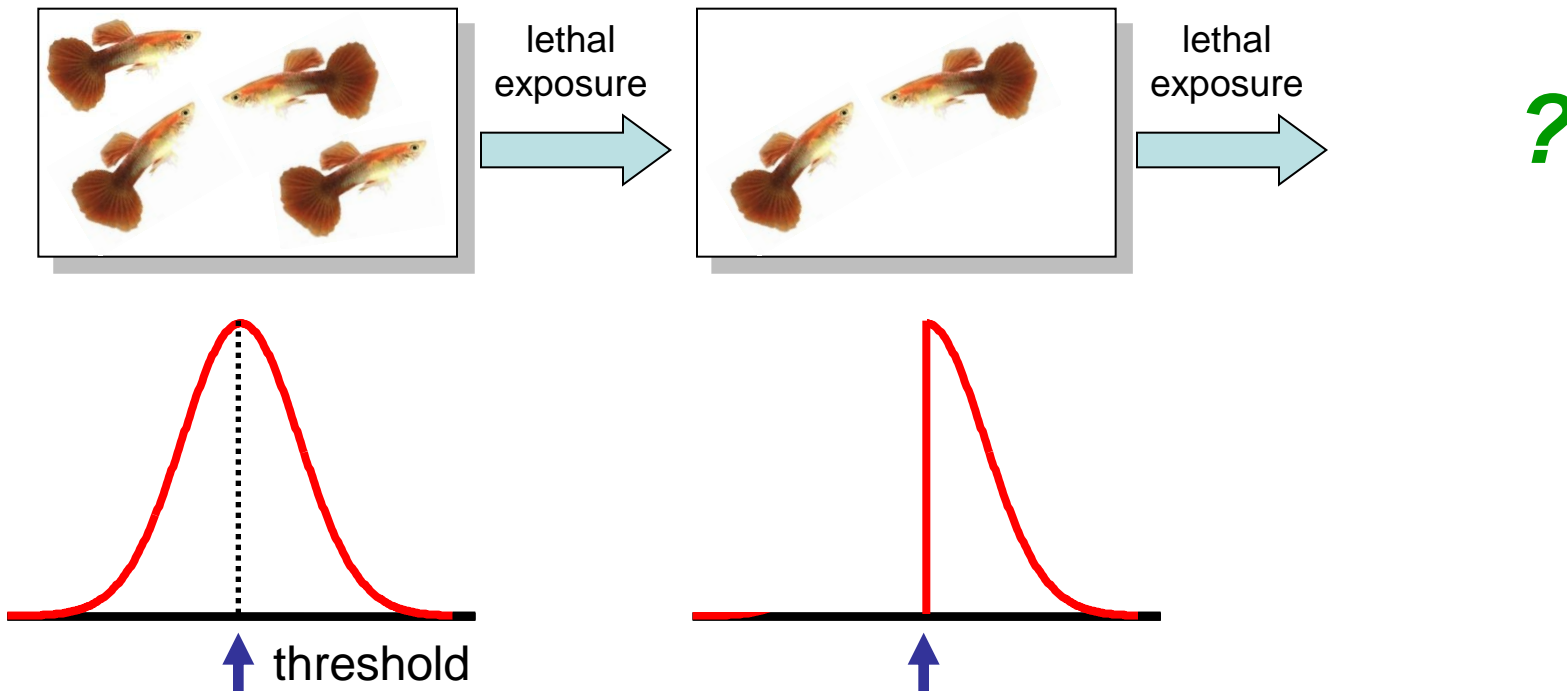
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Death mechanism 1

Individual Tolerance (IT)

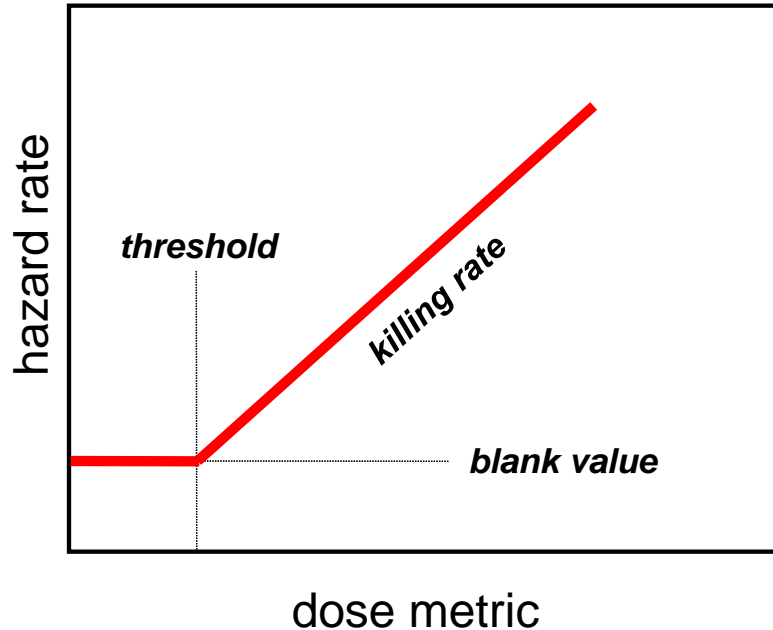
- death is immediate if dose metric $>$ threshold
- Individuals differ in value of threshold



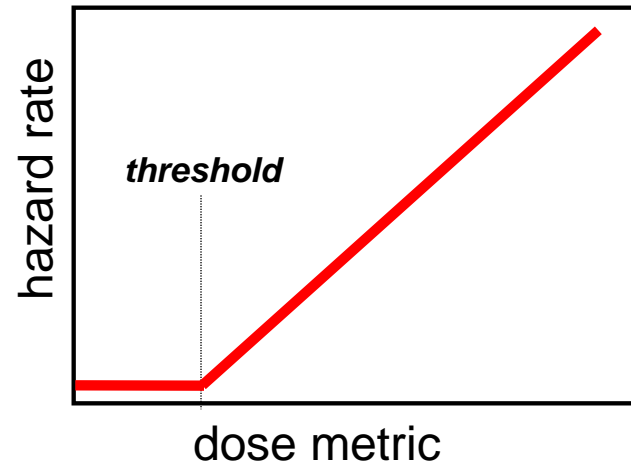
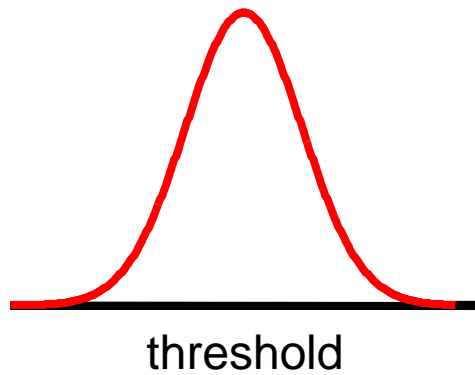
Death mechanism 2

Stochastic Death (SD)

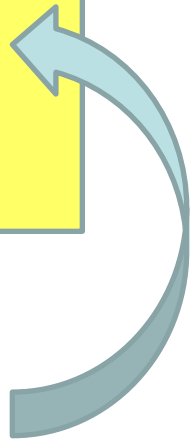
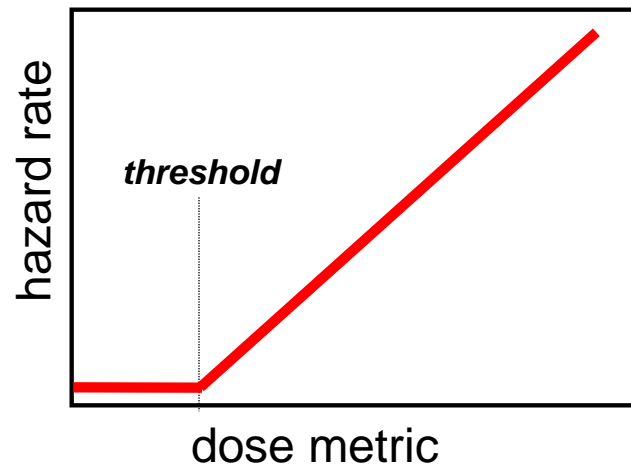
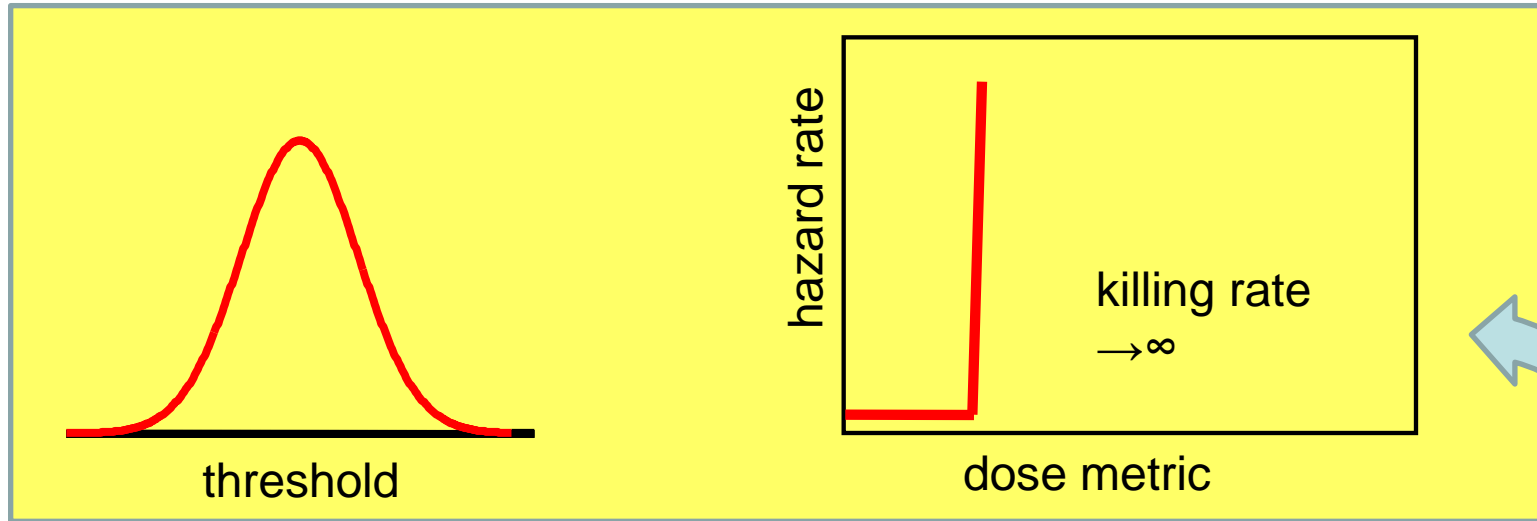
- all individuals are identical
- dose metric increases probability to die



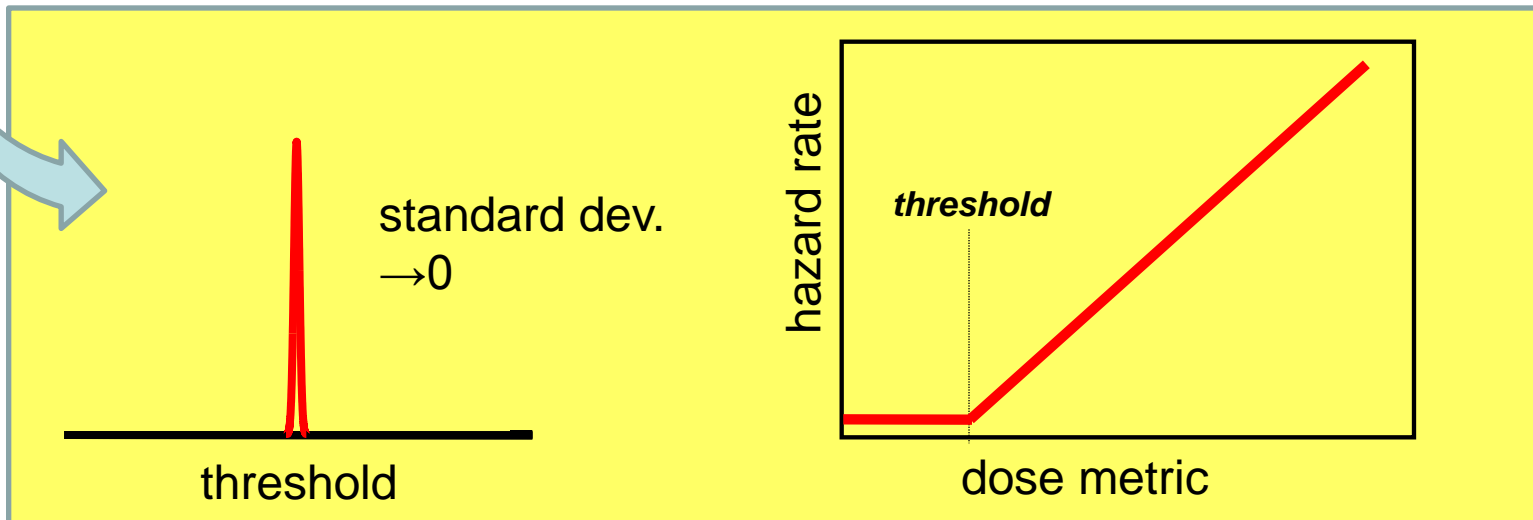
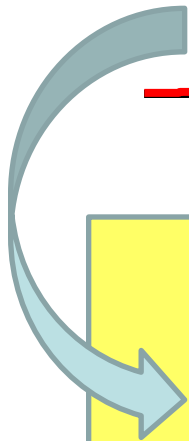
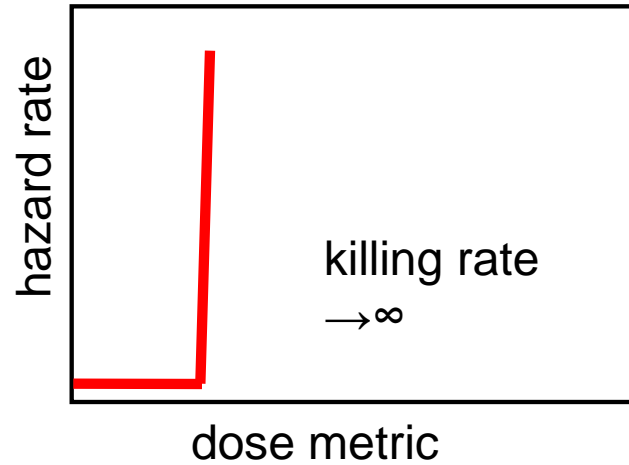
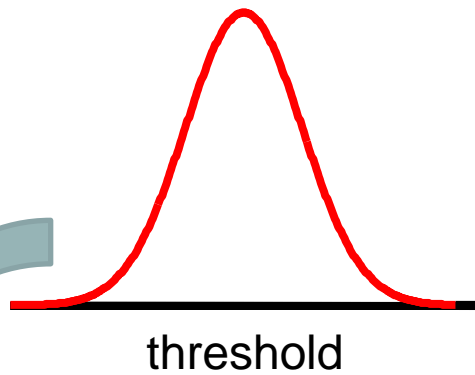
SD / IT unification



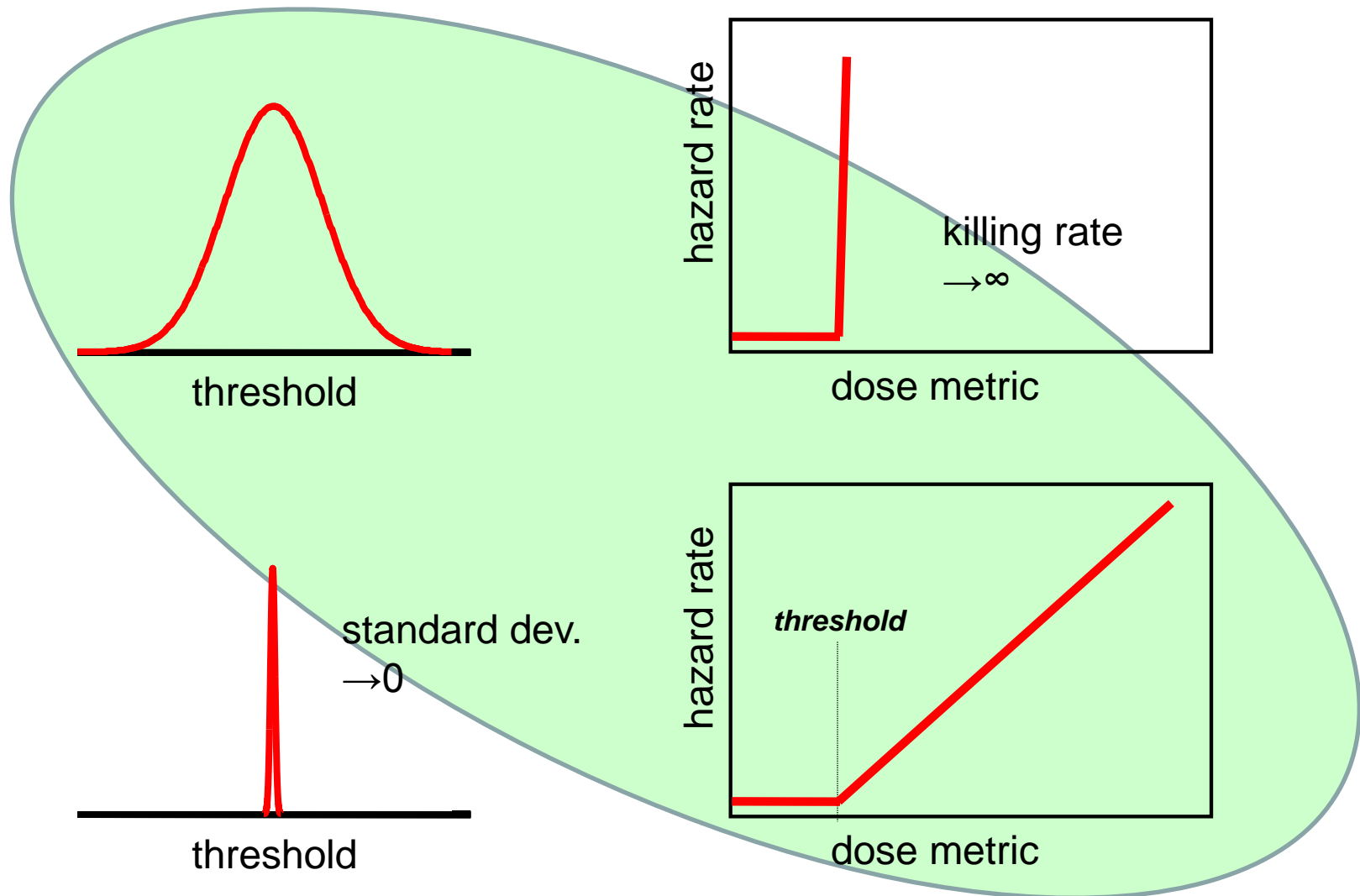
SD / IT unification



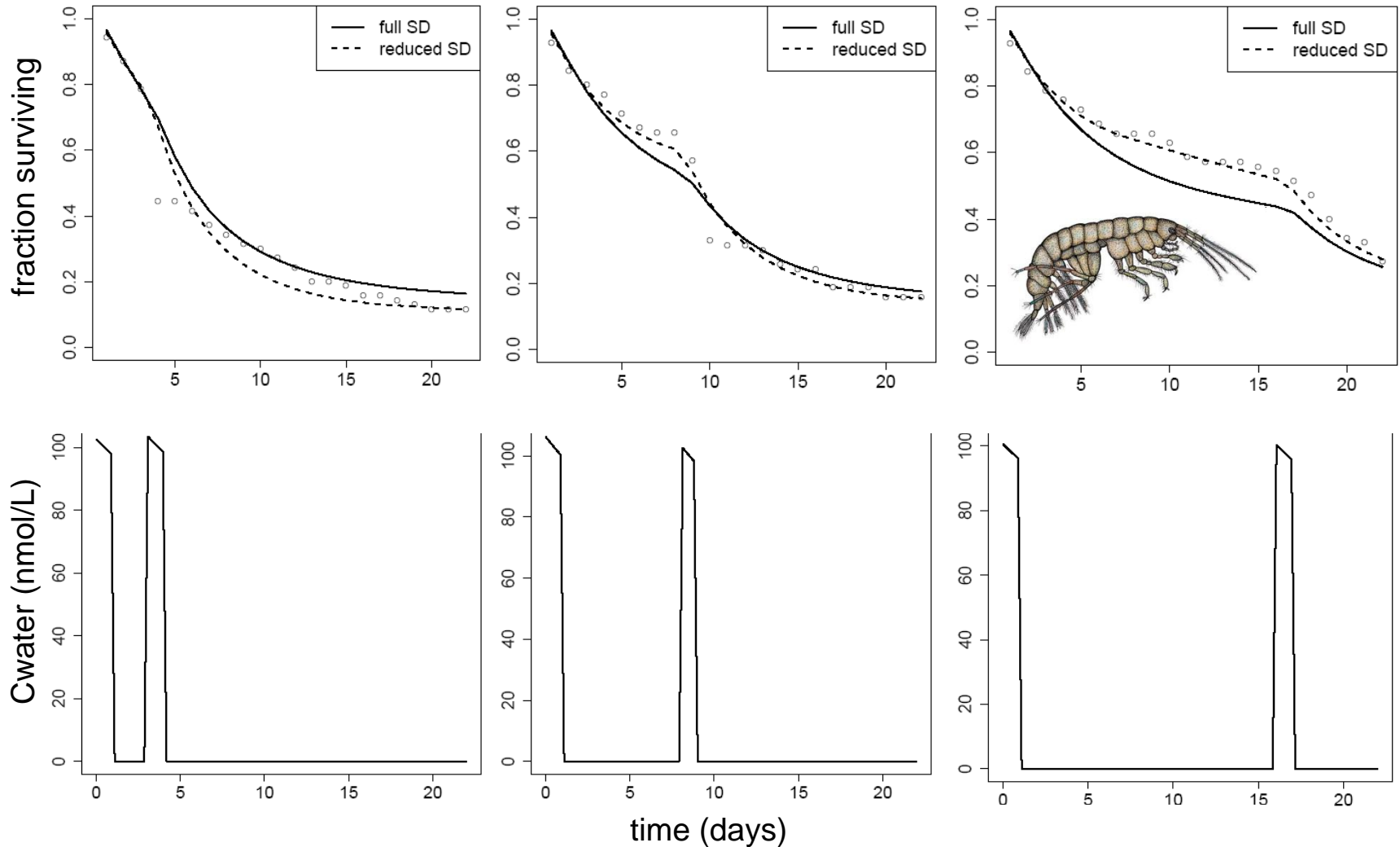
SD / IT unification



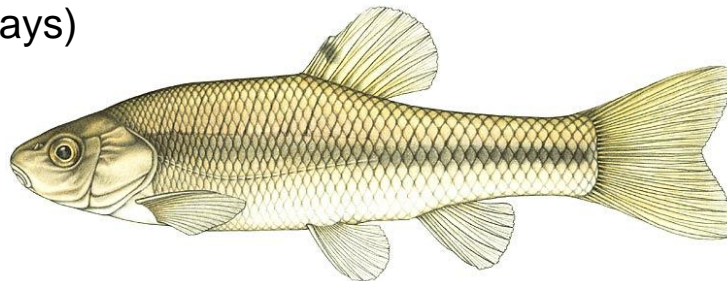
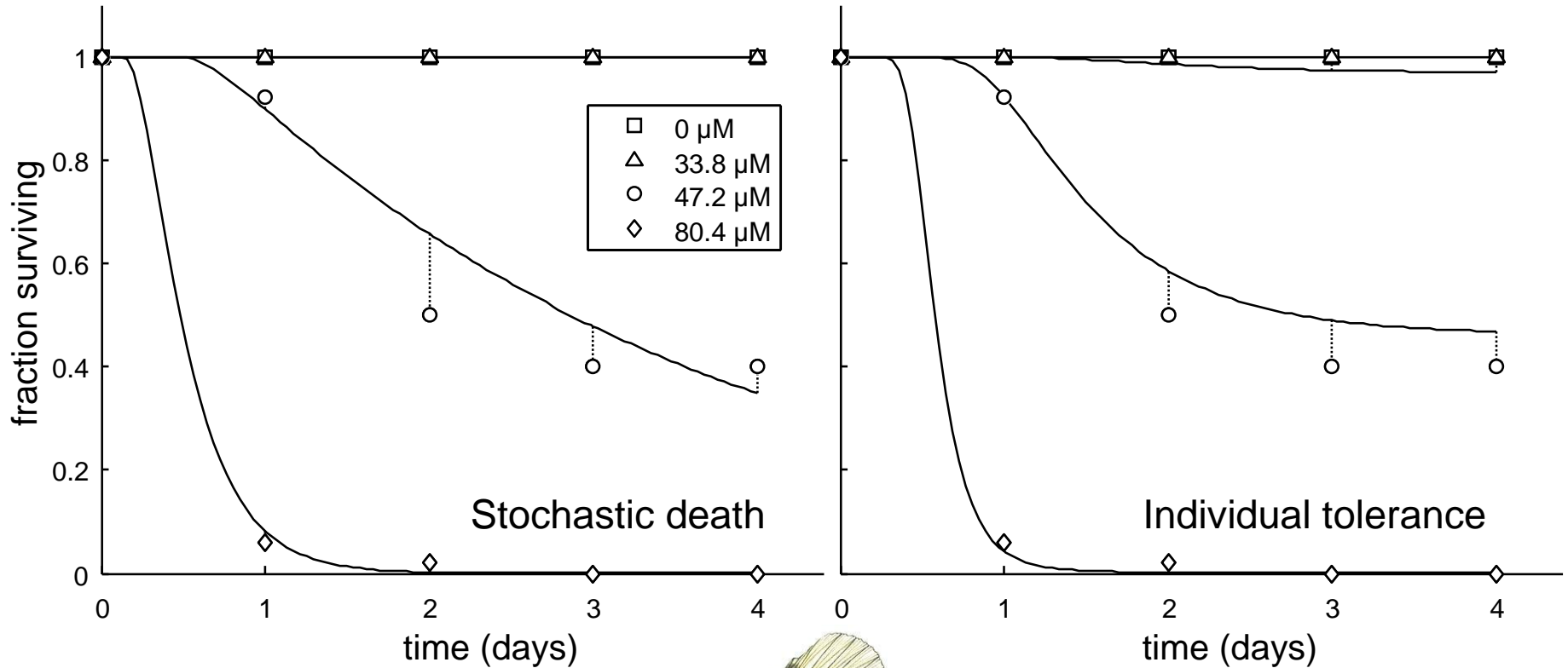
SD / IT unification



Gammarus+diazinon



Pimephales+naphthalene



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

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CRITICAL REVIEW

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

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 Supporting Information

[dx.doi.org/10.1021/es103092a](https://doi.org/10.1021/es103092a) | *Environ. Sci. Technol.* 2011, 45, 2529–2540

Matlab implementation on: <http://www.bio.vu.nl/thb/users/tjalling/debtox/>