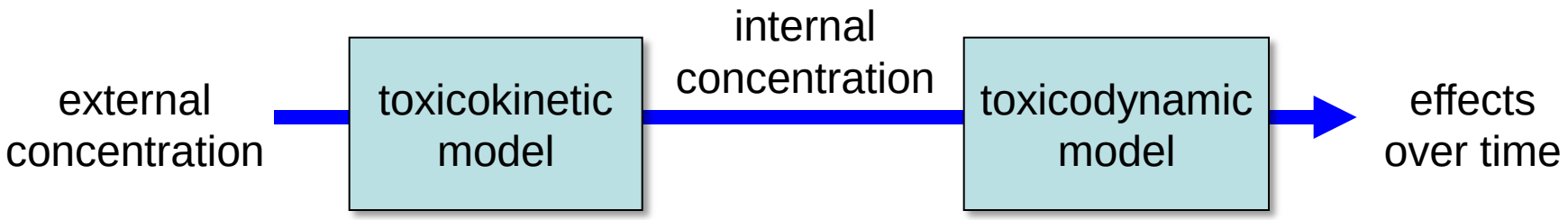
General Unified Threshold model for Survival (GUTS)

Tjalling Jager, Carlo Albert, Thomas G. Preuss, Roman Ashauer

Kastanienbaum workshop 2010

TKTD models



Advantages

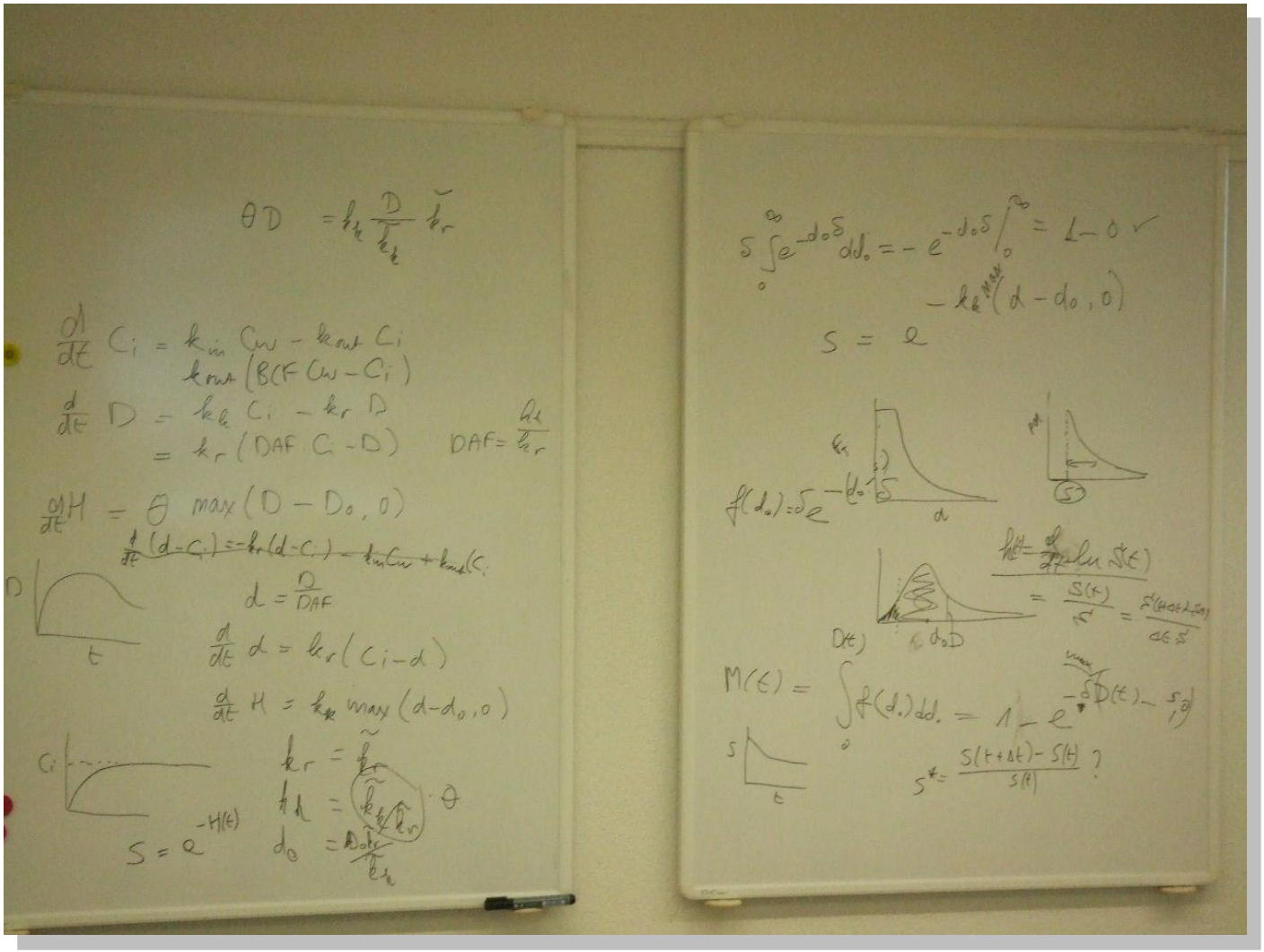
- understand rather than describe effects
- derive time-independent toxicity parameters
- interpret time-varying exposure
- make predictions for untested situations

TKTD model confusion

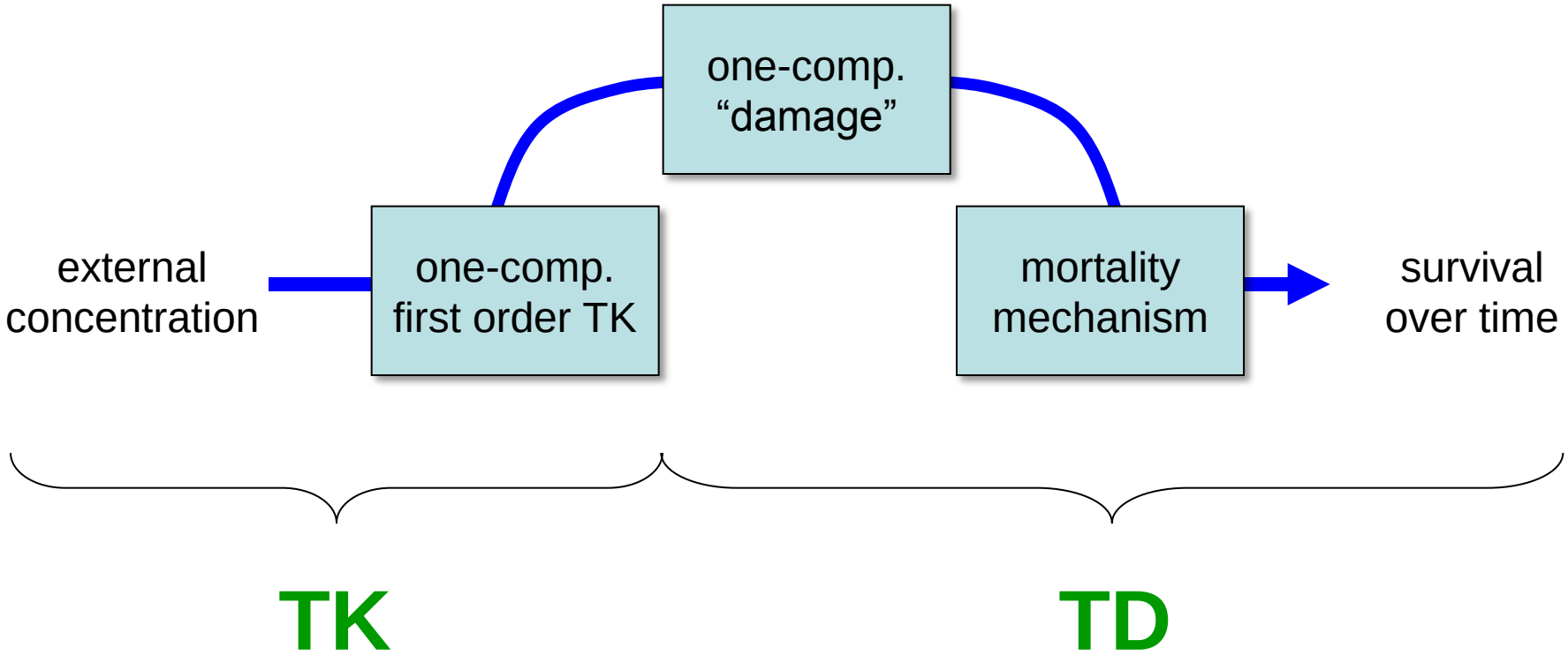
- For survival …
  - many models have been published …
  - CBR, DAM, DEBtox, TDM, CTO, etc., etc.
  - how do they relate to each other?

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

Unification possible?



Main similarities



Main differences

Death mechanism

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

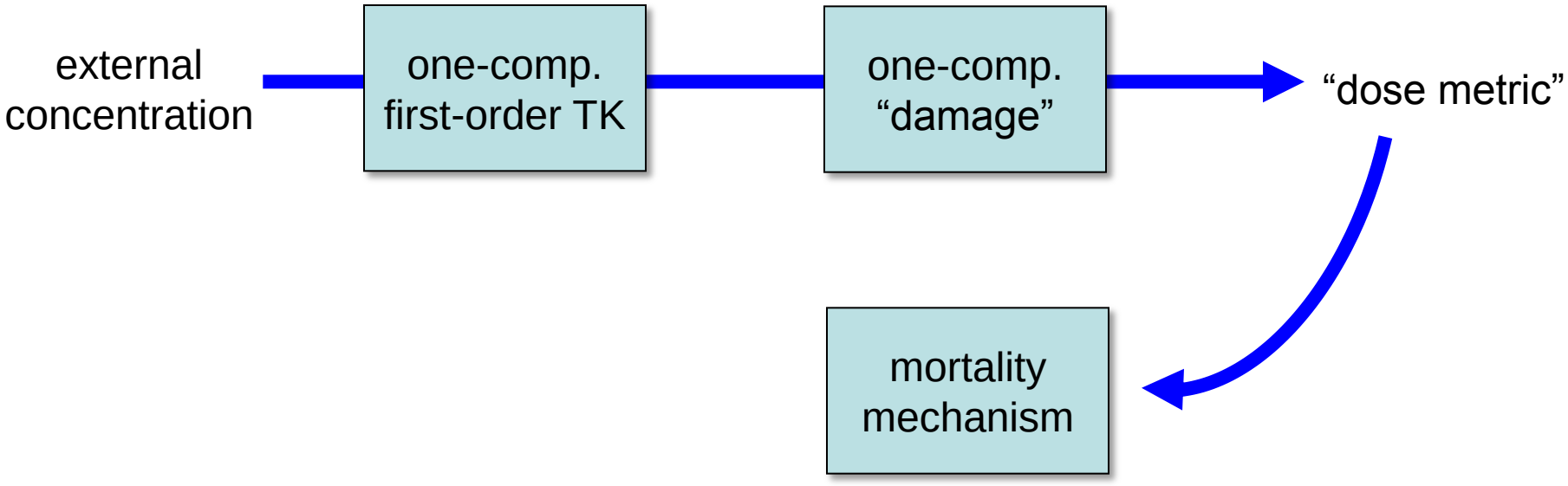
Dose metric

- 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

scaling

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

repair. rate $\rightarrow\infty$

3. Actual internal concentration
   - uptake and elimination rate

scaling

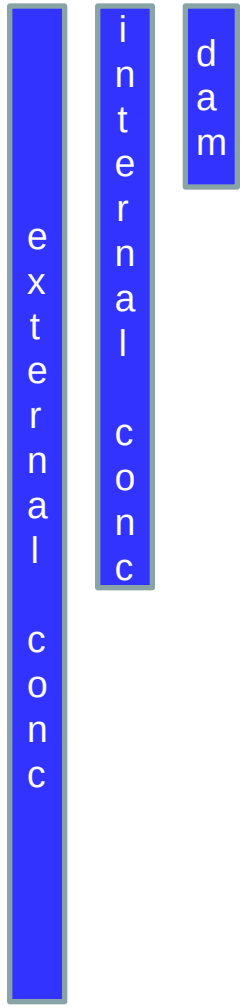
4. Scaled internal concentration
   - “elimination” or “dominant” rate constant

elim. rate $\rightarrow\infty$

5. External concentration
   - no parameters

Data requirements

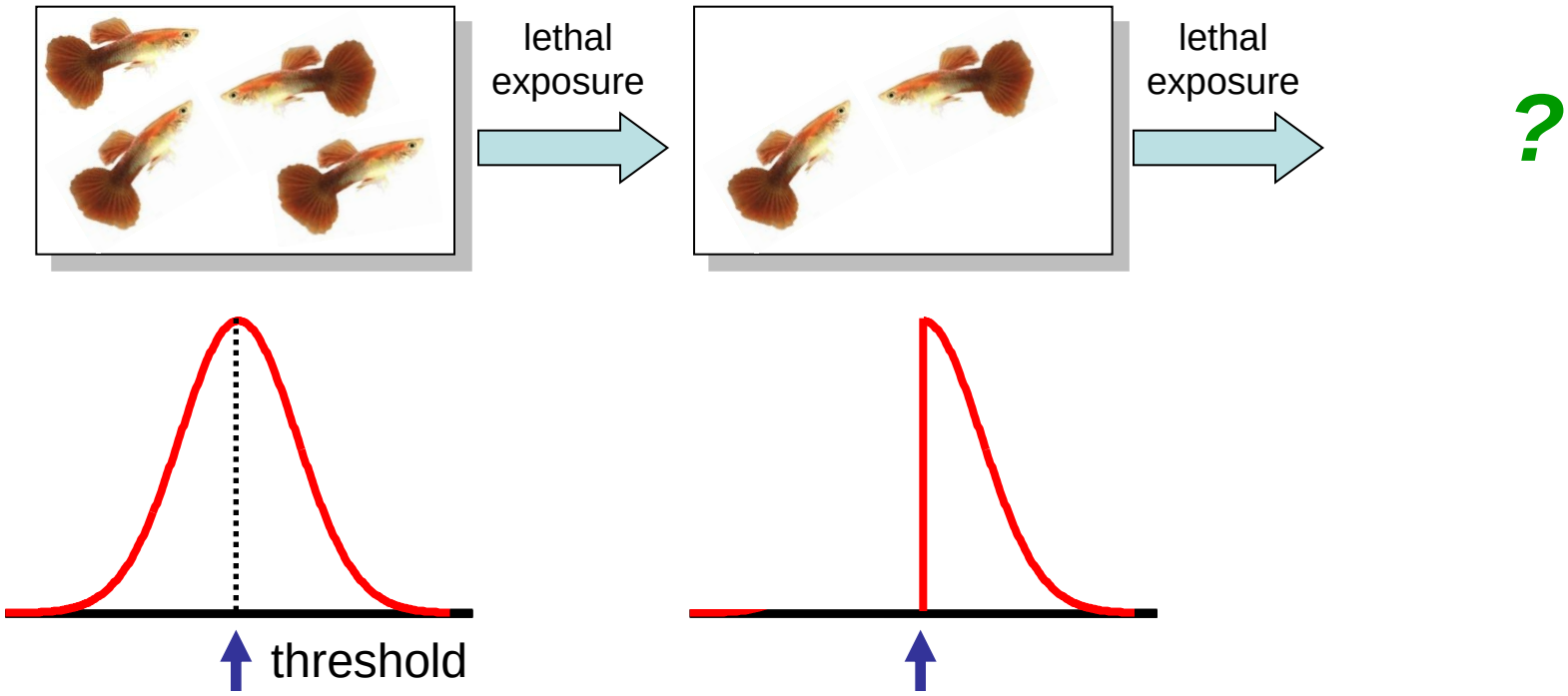
1. Actual damage level
   - uptake, elimination, damage accrual and repair
2. Scaled damage level
   - uptake, elimination rate, damage repair
3. Actual internal concentration
   - uptake and elimination rate
4. Scaled internal concentration
   - “elimination” or “dominant” rate constant
5. External concentration
   - no parameters



Death mechanism 1

Individual Tolerance (IT)

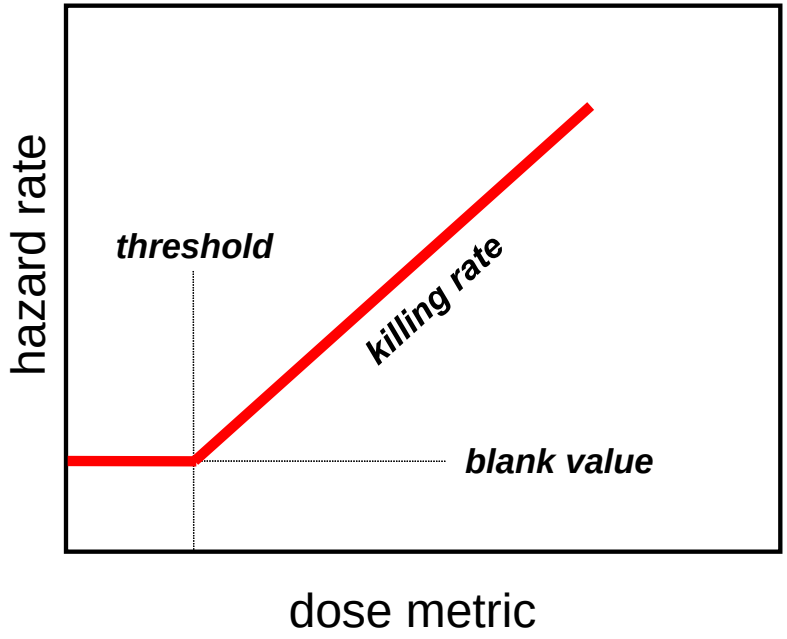
- death is immediate if dose metric > threshold
- Individuals differ in value of threshold



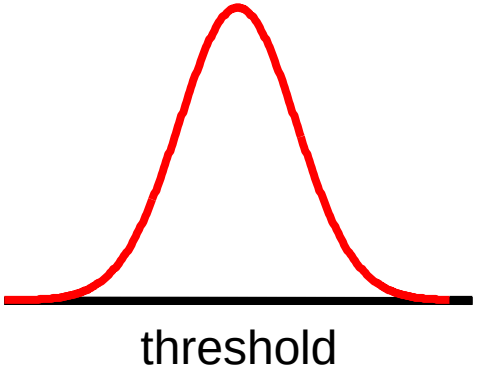
Death mechanism 2

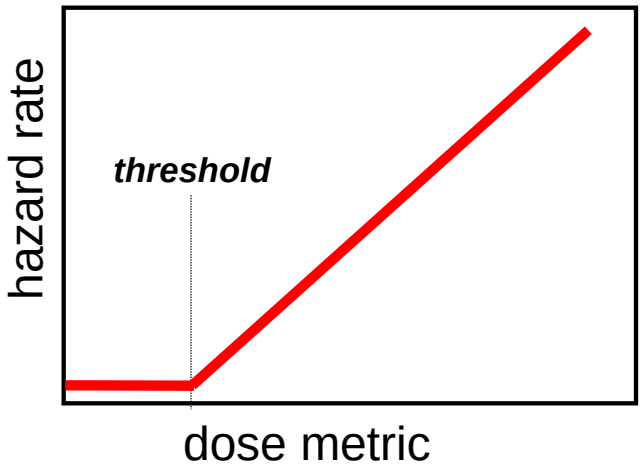
Stochastic Death (SD)

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

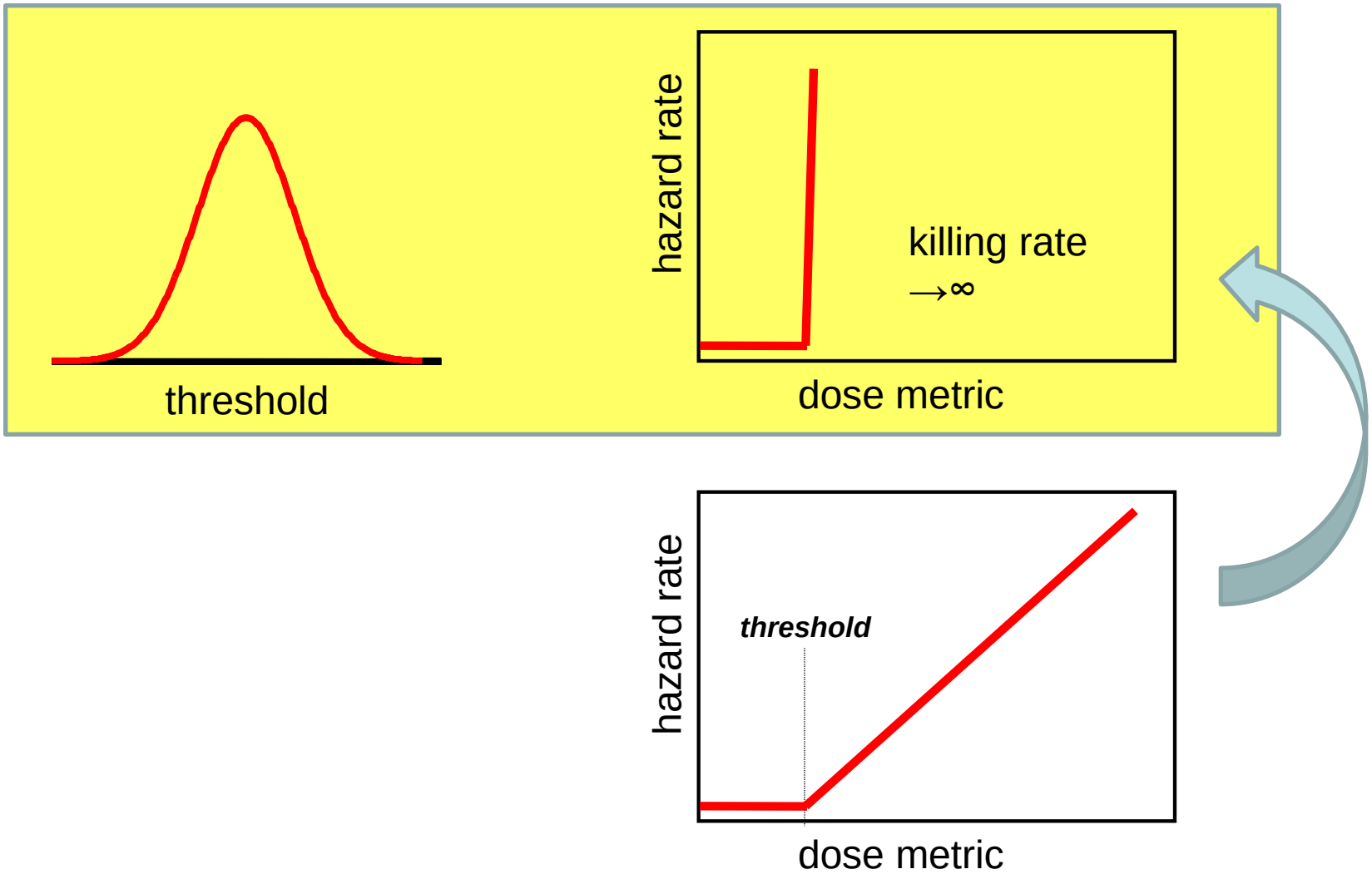


SD / IT unification

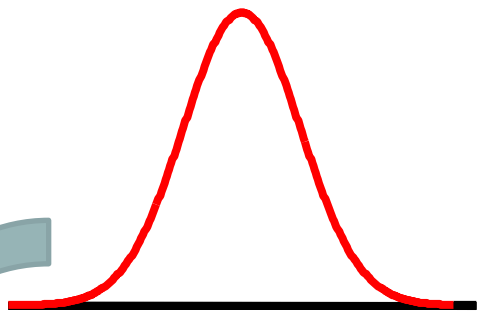




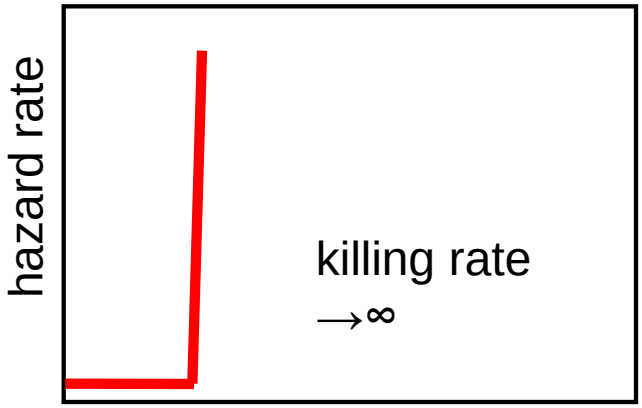
SD / IT unification

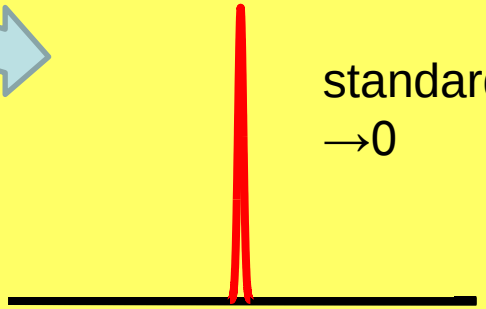


SD / IT unification



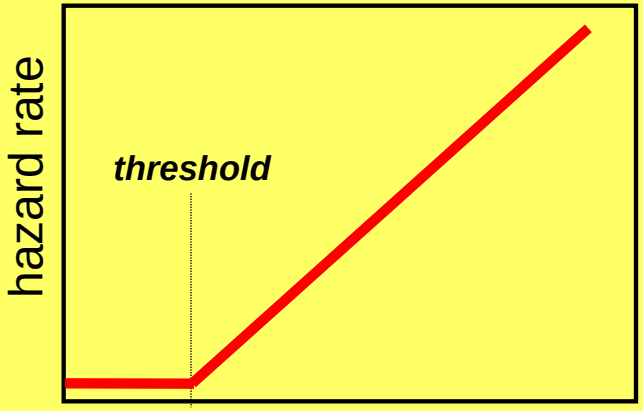
threshold



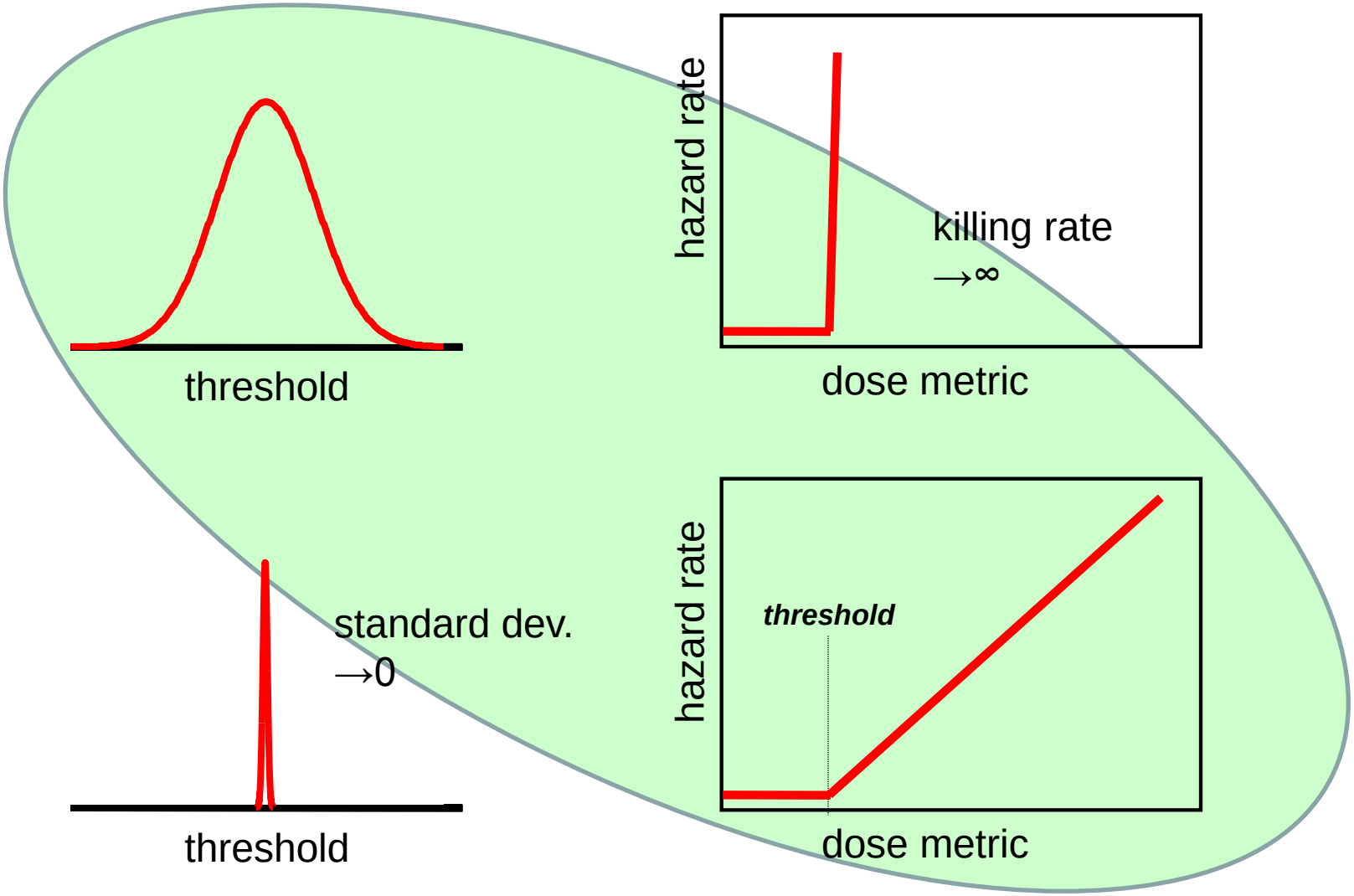


standard dev.
→0

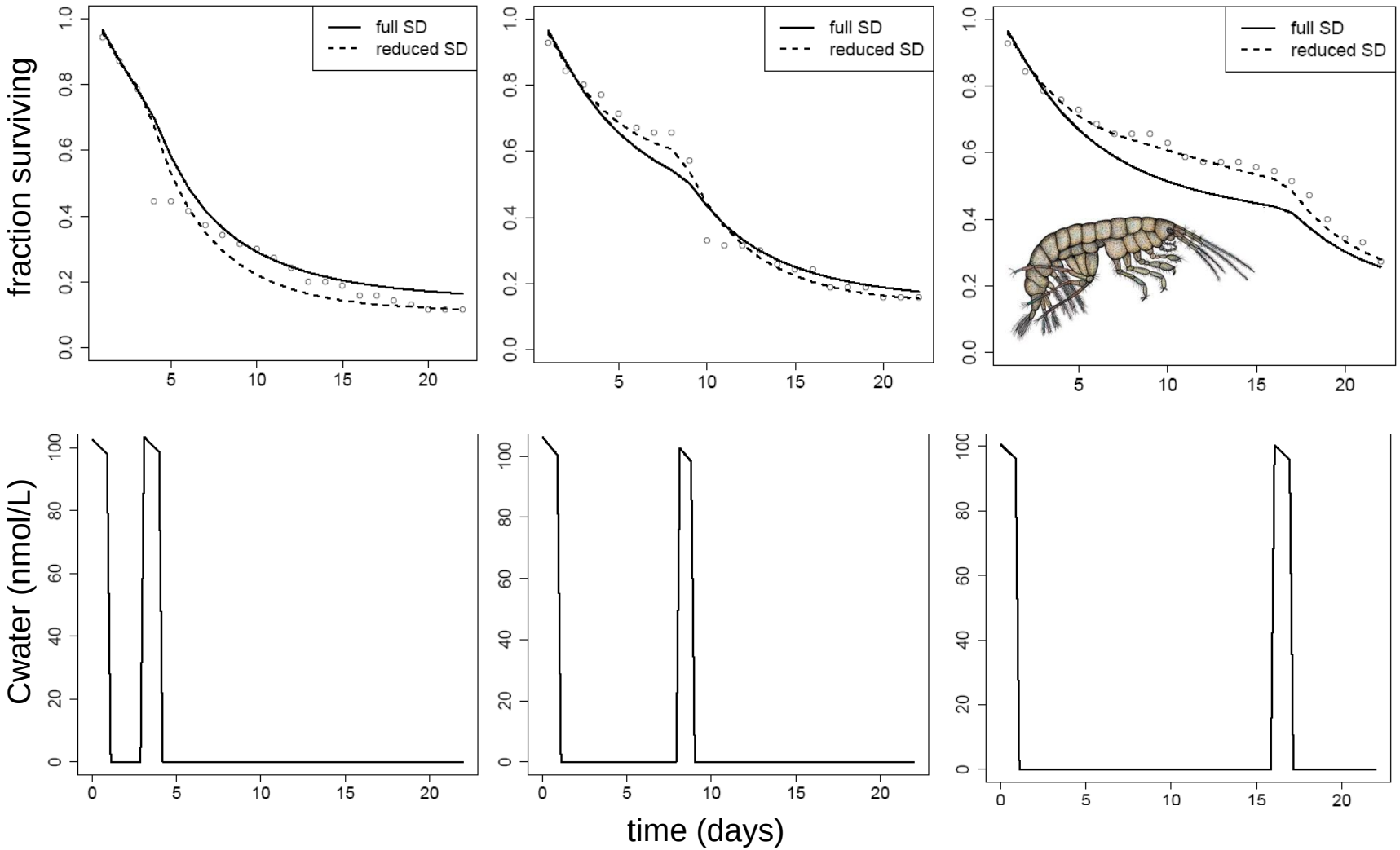
threshold



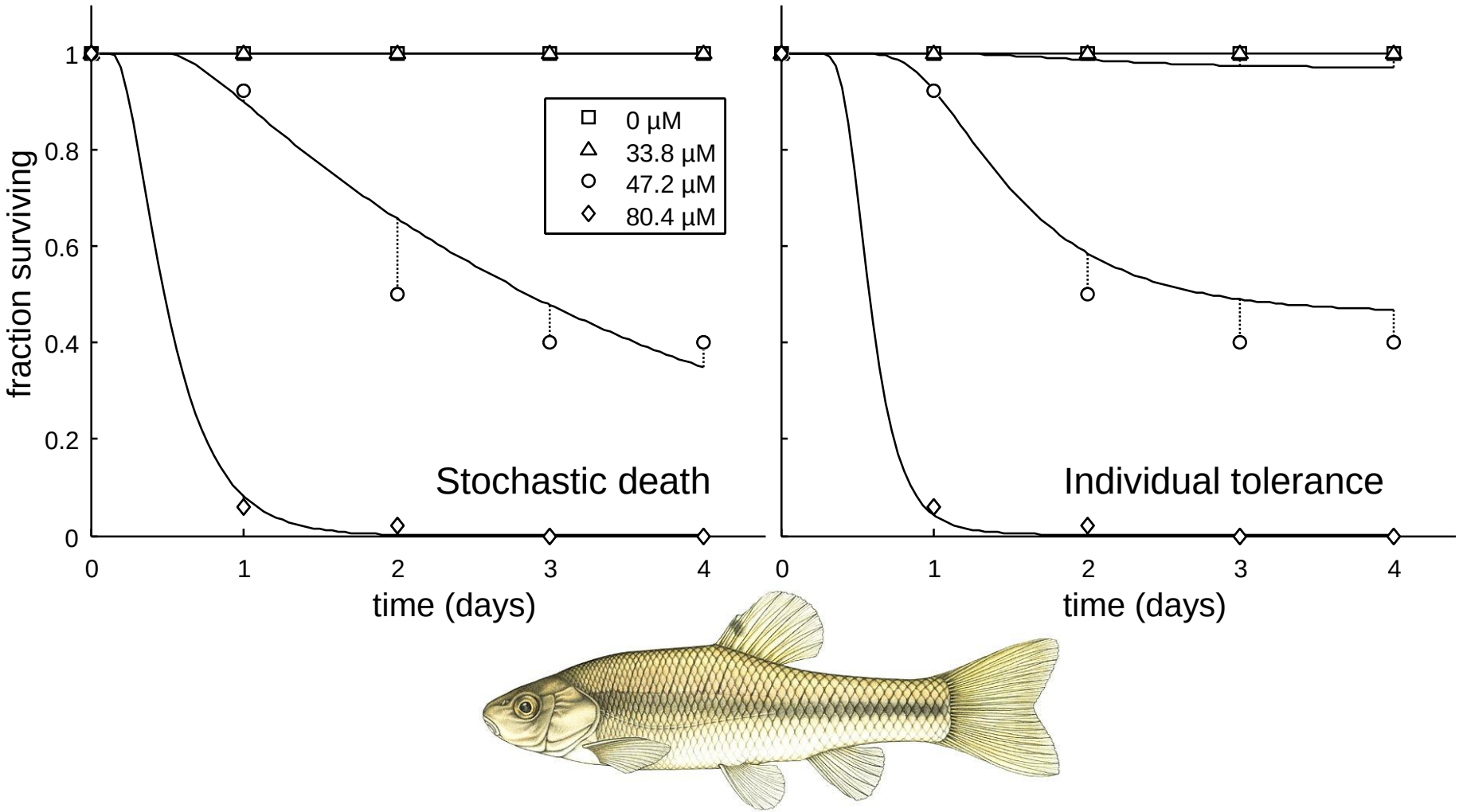
SD / IT unification



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 | *Environ. Sci. Technol.* 2011, 45, 2529–2540

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