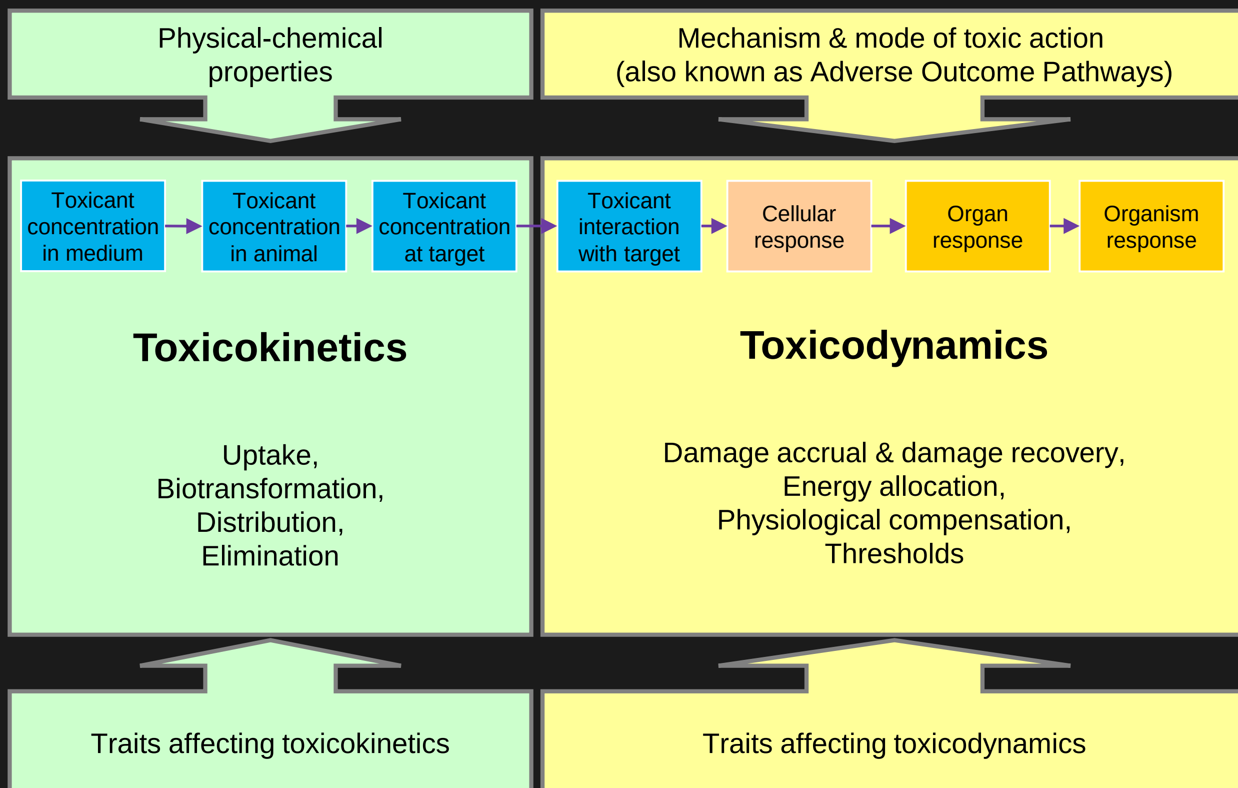
ECO39: Recent progress on toxicokinetic-toxicodynamic models

–

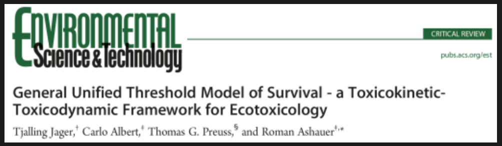
Roman Ashauer (University of York, UK) & Tjalling Jager (DEBtox research, NL)

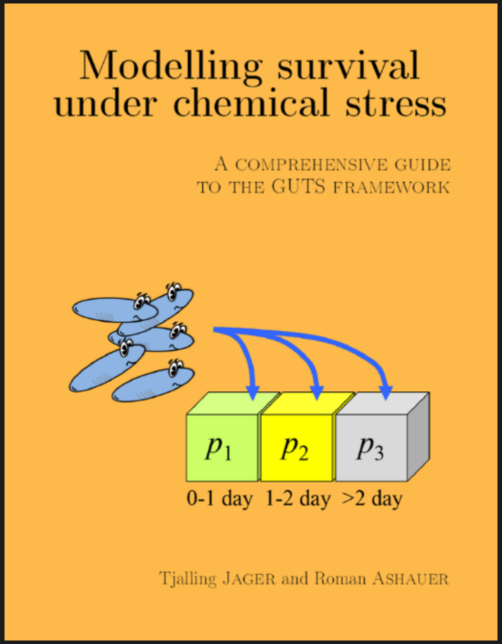
Toxicokinetic-Toxicodynamic (TKTD) models



Ashauer & Escher (2010) *JEM.*
Rubach *et al.* (2011) *IEAM*

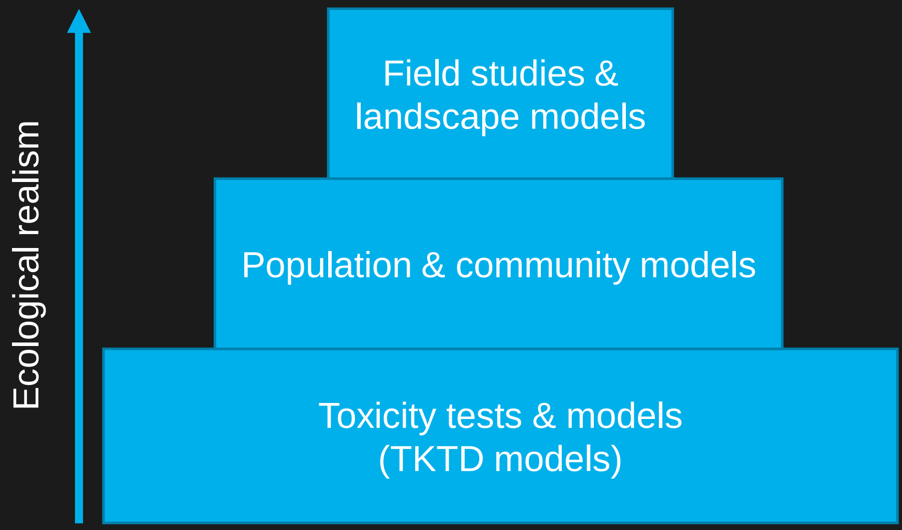
TKTD models for environmental risk assessment


Environmental Science & Technology
CRITICAL REVIEW
pubs.acs.org/est
General Unified Threshold Model of Survival - a Toxicokinetic-Toxicodynamic Framework for Ecotoxicology
Tjalling Jager,[†] Carlo Albert,[‡] Thomas G. Preuss,[§] and Roman Ashauer[‡,*]



https://leanpub.com/guts_book

Environmental risk assessment of pesticides



Modified from: European Food Safety Authority (EFSA) Journal, 2013. **11**(7)

EFSA opinion on TKTD models

SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 27 June 2018

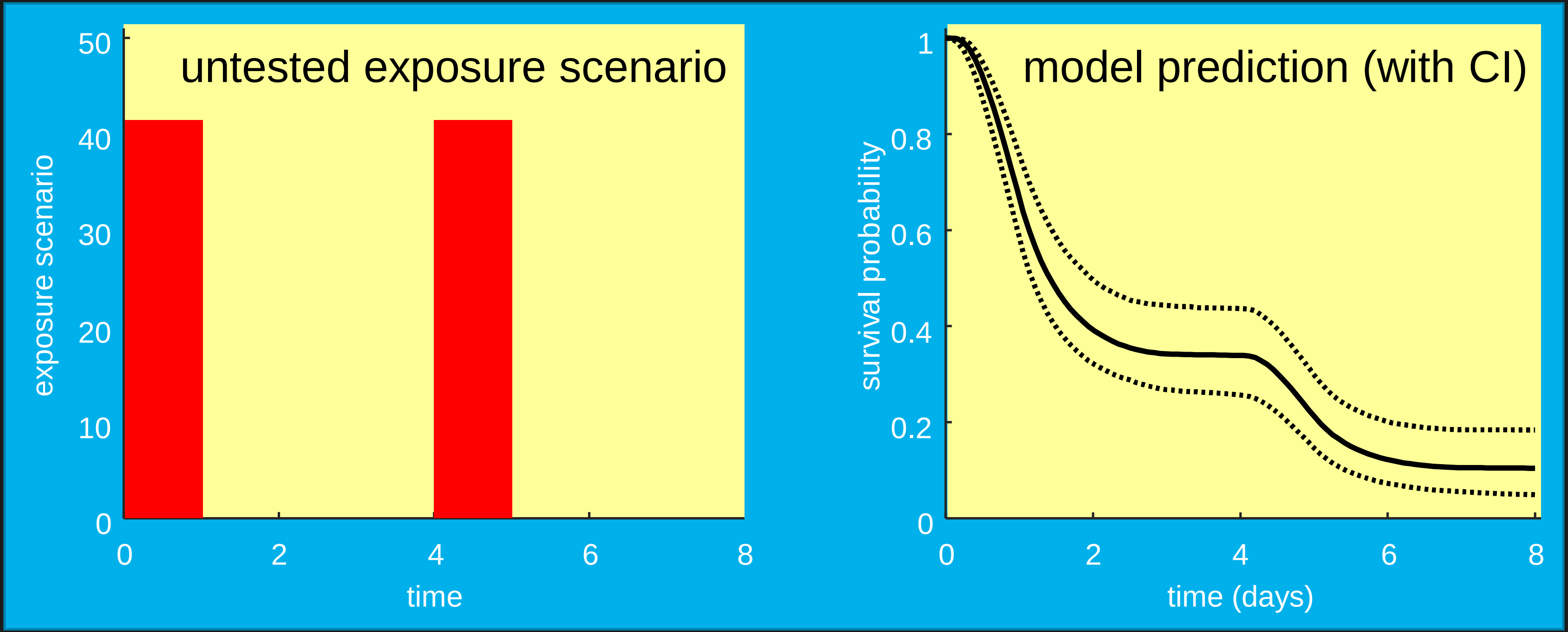
doi: 10.2903/j.efsa.2018.5377

Scientific Opinion on the state of the art of Toxicokinetic/Toxicodynamic (TKTD) effect models for regulatory risk assessment of pesticides for aquatic organisms

"The GUTS model and the *Lemna* model are considered **ready to be used** in risk assessment."

Predict effects from time-variable exposure

- For example as proposed in the recent EFSA scientific opinion on TKTD modelling for aquatic risk assessment of pesticides.



From GUTS to the EFSA opinion on TKTD models

ecotoxmodels

2010 TKTD workshop

Jager, Albert, Preuss & Ashauer (2011): General Unified Threshold Model of Survival - a Toxicokinetic-Toxicodynamic Framework for Ecotoxicology. *ES&T*

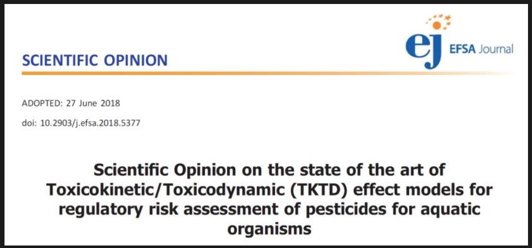
"GUTS"

Ashauer, Thorbek, Warinton, Wheeler & Maund (2013): A method to predict and understand fish survival under dynamic chemical stress using standard ecotoxicity data. *ET&C*

2015 TKTD workshop

Ashauer, R. *et al.* (2016): Modelling survival: exposure pattern, species sensitivity and uncertainty. *Scientific Reports*

Ring-test



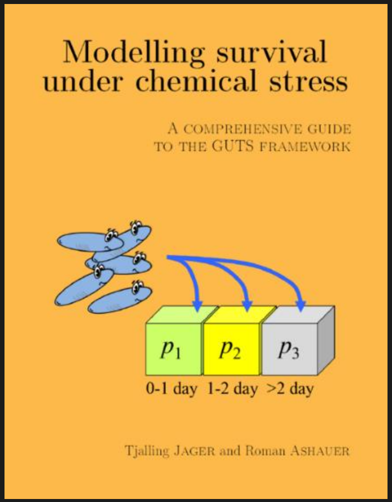
SCIENTIFIC OPINION

ej EFSA Journal

ADOPTED: 27 June 2018

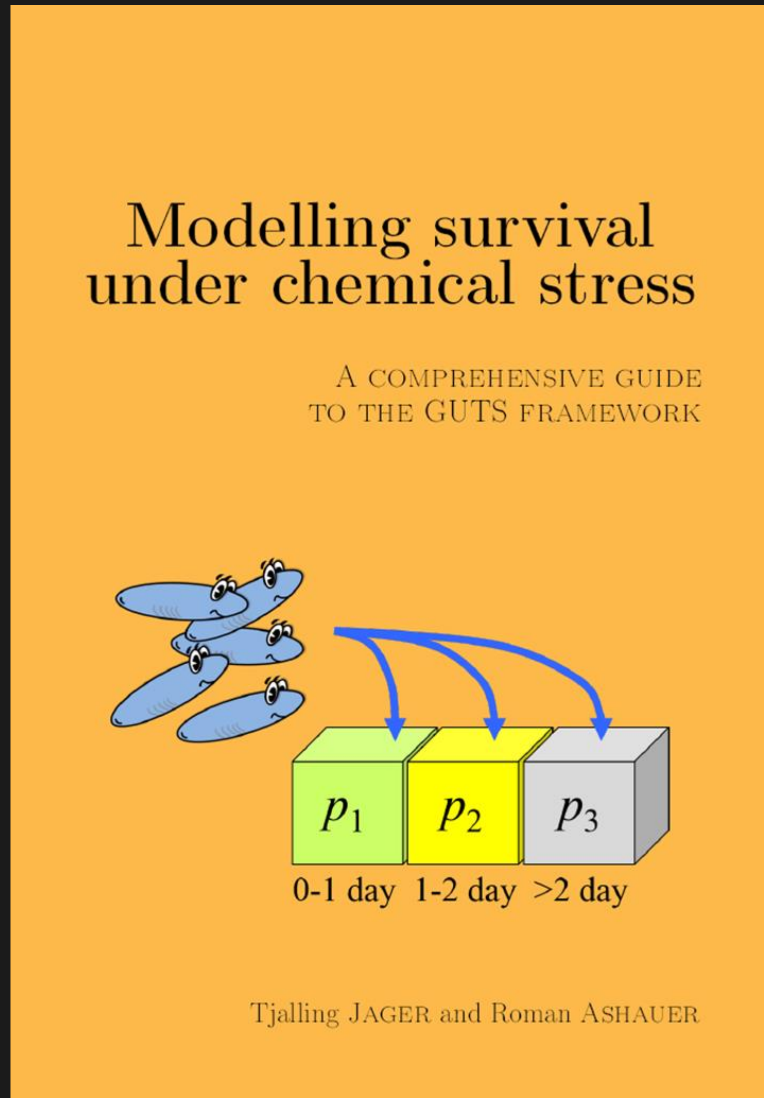
doi: 10.2903/j.efsa.2018.5377

Scientific Opinion on the state of the art of Toxicokinetic/Toxicodynamic (TKTD) effect models for regulatory risk assessment of pesticides for aquatic organisms



ECO39.2: Nov 2018 End-user workshop

ECO39.1 – The GUTS e-book



https://leanpub.com/guts_book

The GUTS e-book

Contents

ECO39.1 – Papers

Environmental Science Processes & Impacts

PERSPECTIVE

View Article Online
View Journal

Check for updates

Cite this: DOI: 10.1039/c7em00328e

Physiological modes of action across species and toxicants: the key to predictive ecotoxicology†

Roman Ashauer *[a,b] and Tjalling Jager [c]

As ecotoxicologists we strive for a better understanding of how chemicals affect our environment. Humanity needs tools to identify those combinations of man-made chemicals and organisms most likely to cause problems. In other words: which of the millions of species are at risk from pollution? And which of the tens of thousands of chemicals contribute most to the risk? We identified our poor knowledge on physiological modes of action (how a chemical affects the energy allocation in an organism), and how they vary across species and toxicants, as a major knowledge gap. We also find that the key to predictive

Integrated Environmental Assessment and Management — Volume 9999, Number 9999—pp. 1–11

Received: 17 October 2017 | Returned for Revision: 8 December 2017 | Accepted: 20 December 2017 1

Special Series

How to Evaluate the Quality of Toxicokinetic—Toxicodynamic Models in the Context of Environmental Risk Assessment

Tjalling Jager† and Roman Ashauer‡*

†DEBtox Research, De Bilt, the Netherlands

‡Environment Department, University of York, York, United Kingdom

ECO39.2 OBJECTIVES

Development of user-friendly, robust GUTS software

- → User-friendly & robust software (end-user input via stakeholder workshop)
- → Freely-available, incl. source code: GNU GPLv3 (open-source software)
- → Thoroughly tested & benchmarked against ring-test data
- → With user manual

TKTD models for sub-lethal effects

EFSA opinion on TKTD models

SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 27 June 2018

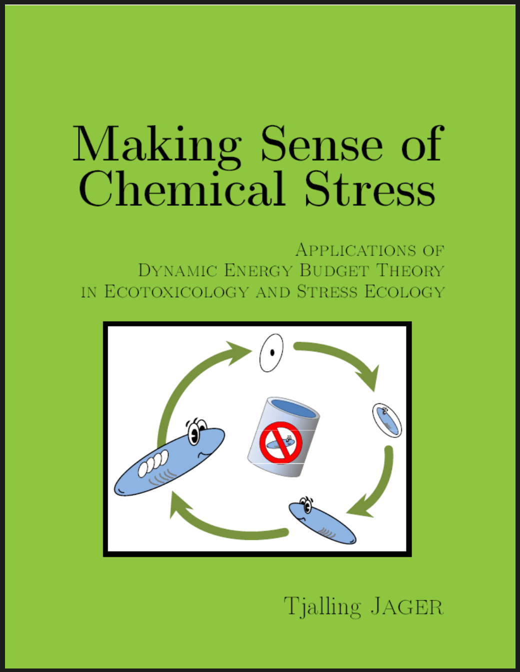
doi: 10.2903/j.efsa.2018.5377

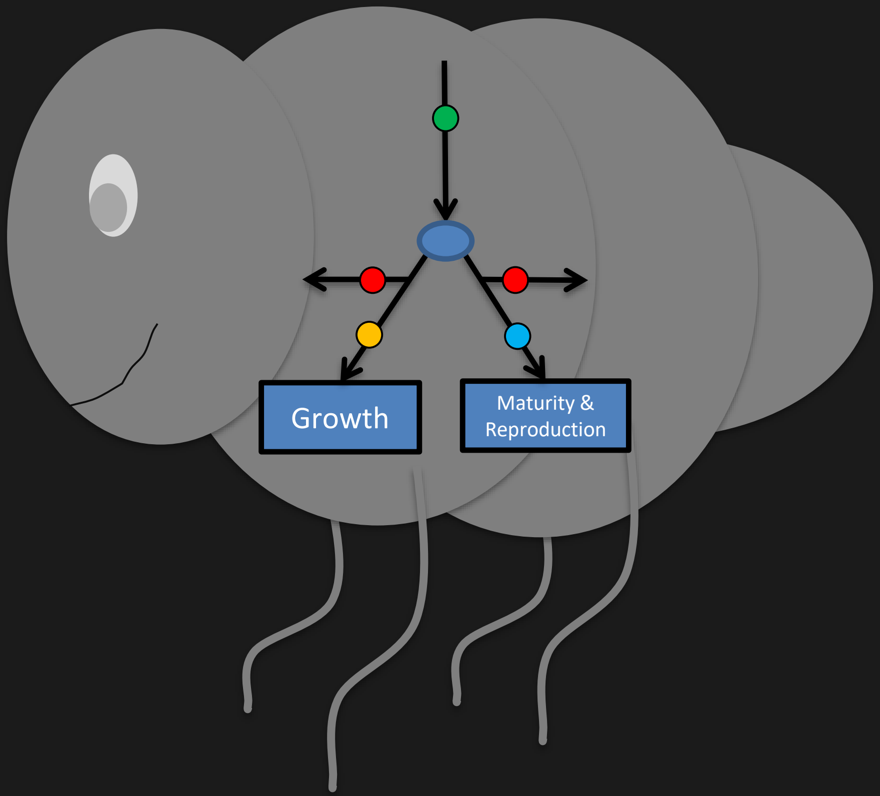
Scientific Opinion on the state of the art of Toxicokinetic/Toxicodynamic (TKTD) effect models for regulatory risk assessment of pesticides for aquatic organisms

"The GUTS model and the *Lemna* model are considered **ready to be used** in risk assessment."

"…the DEBtox modelling approach is currently limited to research applications. However, its great **potential for future use** in prospective ERA for pesticides is recognised."

DEBtox for growth & reproduction

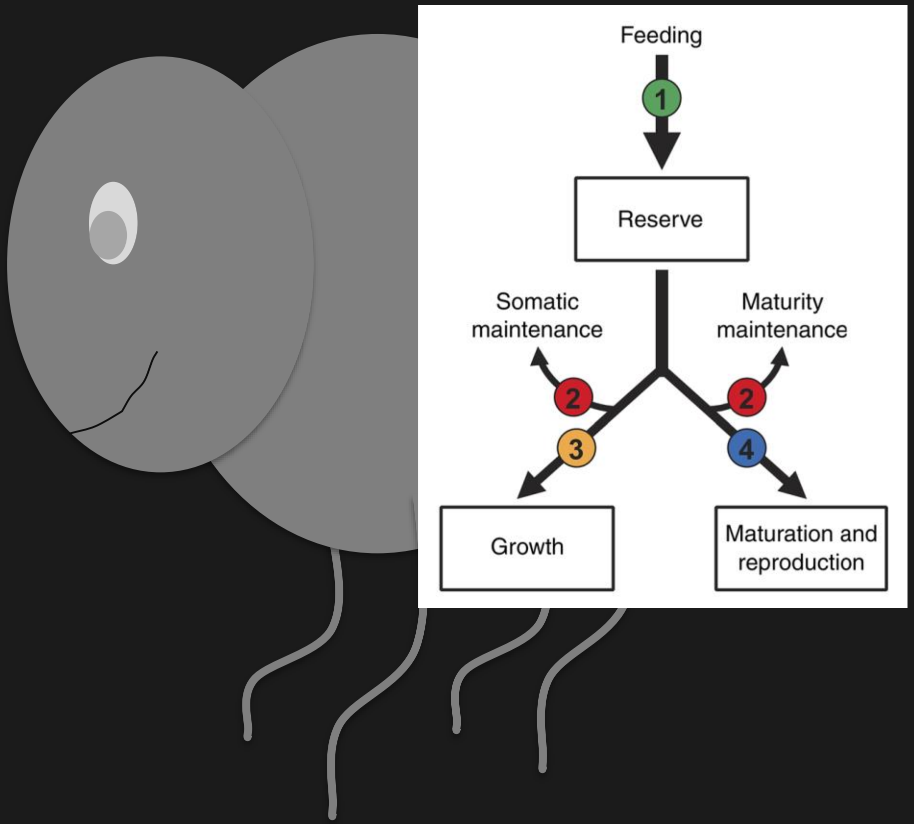




DEBtox: physiological mode of action (pMoA) is key

Stress type (pMoA)

1. **Feeding & assimilation**
2. **Maintenance**
3. **Growth**
4. **Reproduction**



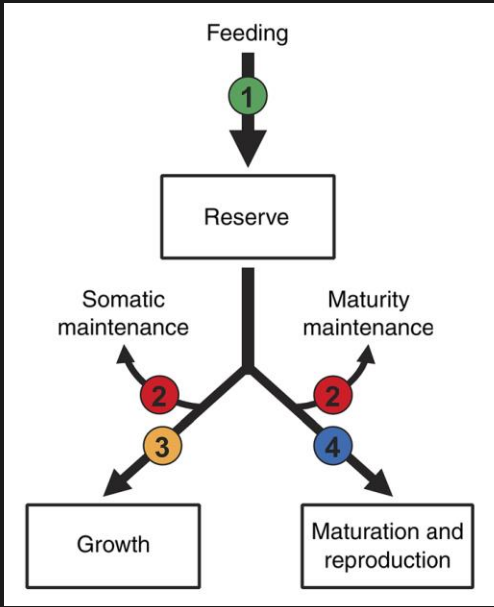
Martin, B., et al. 2014. Ecological Applications, 24(8), 1972-1983.

Ashauer, R. and T. Jager, *Physiological modes of action across species and toxicants: the key to predictive ecotoxicology.* Environ Sci Process Impacts, 2018. **20**(1): p. 48-57.

Jager, T., Making sense of chemical stress. Application of Dynamic Energy Budget theory in ecotoxicology and stress ecology. 2015, Amsterdam: Leanpub. https://leanpub.com/debtox_book

DEBtox: physiological mode of action (pMoA) is key

			Acrobeloides nanus	Caenorhabditis elegans	Dendrobaena octaedra	Lumbricus rubellus	Capitella teleta	Folsomia candida	Daphnia magna	Moina micrura	Mytilus californianus	Mytilus galloprovincialis	Mytilus edulis	Crassostrea gigas	Lymnaea stagnalis	Danio rerio	Strongylocentrotus droebachiensis
Baseline toxicants	Neutral organics	PAH mixture														A	
	Neutral organics	Benzo(k)-fluoranthene														A	
	Neutral organics	Fluoranthene		G+R, G+R					R								
	Neutral organics	Pyrene							R								
	Neutral organics	Pyridine							M								
	Neutral organics	Acetone													A		
	Neutral organics	Diquat													A/M		
	Neutral organics	Pentachlorobenzene	A	G+R													
	Anilines	3,4-dichloroaniline							R/H								
	Aromatic triazine	Atrazine		M													
	Phenols	Pentachlorophenol											A+M				
Specific toxicity	Imidazoles, carbamate esters	Carbendazim	A	A													
	Oxime carbamate ester	Aldicarb		M													
	Monothiophosphate ester, halopyrdines	Chlorpyrifos						R									
	Esters, Benzyl Nitriles, Pyrethroids	Fenvalerate							A								
	Neutral organics[1]	Tetradifon							A								
	Phenols	Nonylphenol					G+R										
	n.a.	Tributyltin													A		
	n.a.	Triphenyltin						M									
Metals	Metals[2]	Cadmium	G	A, A, A, A/M				A, A	A								
	Metals[2]	Copper		A	A	M+R, A			G								
	Metals[2]	Uranium		A, A/M					A							M+G	
	Metals[2]	Zinc				M			A/M								
	Metals[2]	Mercury										A		A/M			
	n.a.	Zinc-oxide nanoparticles										A+M					
Others	n.a.	Toxic cyanobacteria								A/M							
	n.a.	pH (ocean acidification)															M
	n.a.	Produced water									A+M	A+M					

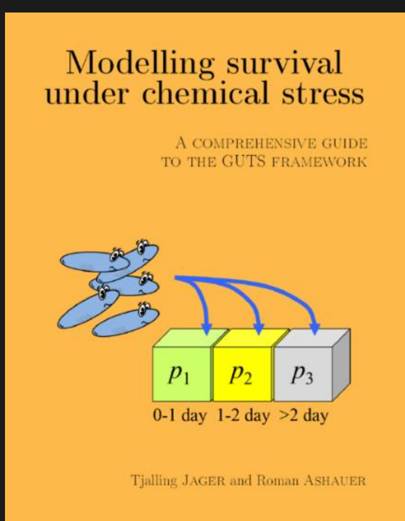


1. Feeding & assimilation [A]
2. Maintenance [M]
3. Growth [G]
4. Reproduction [R]

Ashauer, R. and T. Jager, *Physiological modes of action across species and toxicants: the key to predictive ecotoxicology.* Environ Sci Process Impacts, 2018. **20**(1): p. 48-57.

ECO39: What have we achieved so far?

- Ring-test helped to gain acceptance & broaden user base
- GUTS book informed writing of EFSA opinion
- Influential review paper on sub-lethal TKTD modelling & ecotoxicology



Ring test conclusions

1) Reduce user induced error and variability
   - By standardising user choices
     - Treatment of time-variable exposure
     - Initial values / priors
2) Standardise computational approaches
   - By developing a user-friendly, robust software
     - Parameter search algorithm
     - Numerical solvers
     - Bayesian vs Frequentist framework

Additional lessons

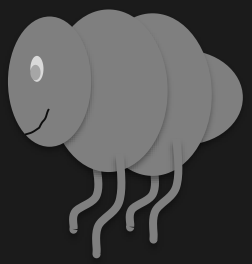
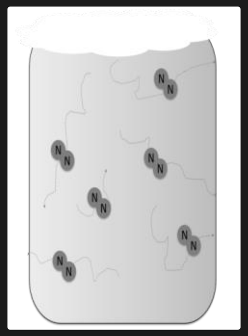
1) Freely available GUTS implementations (e.g. Matlab, R, Mathematica, Python) require programming skills to use → not user-friendly

2) The implementations that have a user-friendly GUI (e.g. DELPHI, EasyGUTS) are owned by a company → this stops uptake by regulators

Potential uses within REACH

Application	Benefit
Oil pollution assessment	Can assess time-variable exposure
REACH regulation, Section 1.5 of Annex XI: Grouping of substances and read-across	Predict toxicity of untested substances because model parameters can be read-across
REACH chapter R.6: qsars and grouping of chemicals, R.6.2: Guidance on the Grouping of Chemicals, R.6.2.1: Explanation of the chemical category approach	Read-across of toxicity data with GUTS can be based on the category or the analogue approach
REACH Endpoint specific guidance R.7b	Calculate LC50 (and LD50) values for any exposure duration
REACH, R.10.3.3 Calculation of PNEC for water in the case of intermittent releases	GUTS explicitly accounts for organism recovery and the temporal aspects of toxicity. Its application improves the assessment of intermittent release scenarios.
REACH: Characterisation of dose [concentration]-response for environment (Chapter R.10)	Calculate dose response for any exposure duration. Calculate dose response from tests with changing exposure.
REACH: Endpoint specific guidance R.7b, R.7.8.5 Conclusions for aquatic pelagic toxicity and integrated testing strategy (ITS).	GUTS can help with the extrapolation of toxicity across species. Within reach that could support the integrated testing strategy.

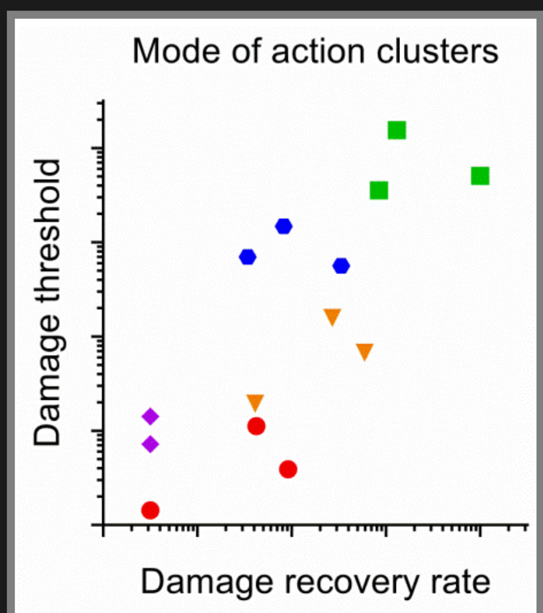
Ecotoxicology: missing theory

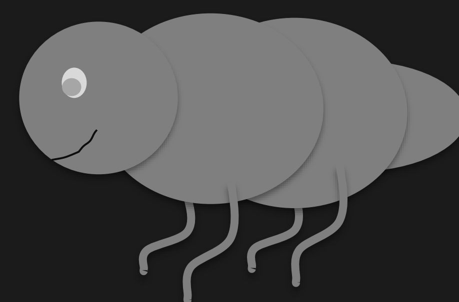
	Physical chemistry	(Eco)toxicology
Macroscopic scale	 Perfect gas $p \times V = \text{constant}$ (Boyle’s law)	 Generic organism stress = $1/C_T \times \max(0,C_V - C_0)$ (DEBtox)
	↑ Emerges	↑ Missing theory
Molecular scale	 Kinetic model of gases • Random motion • Size negligible • Elastic collisions only	 Cellular pathways • Reaction networks • -omics • Pathway models

Ashauer & Jager 2018

Toxicodynamic parameters & mode of action

C_{water} $\xrightarrow{TK}$ $C_{internal}$ $\xrightarrow{GUTS}$ Survival



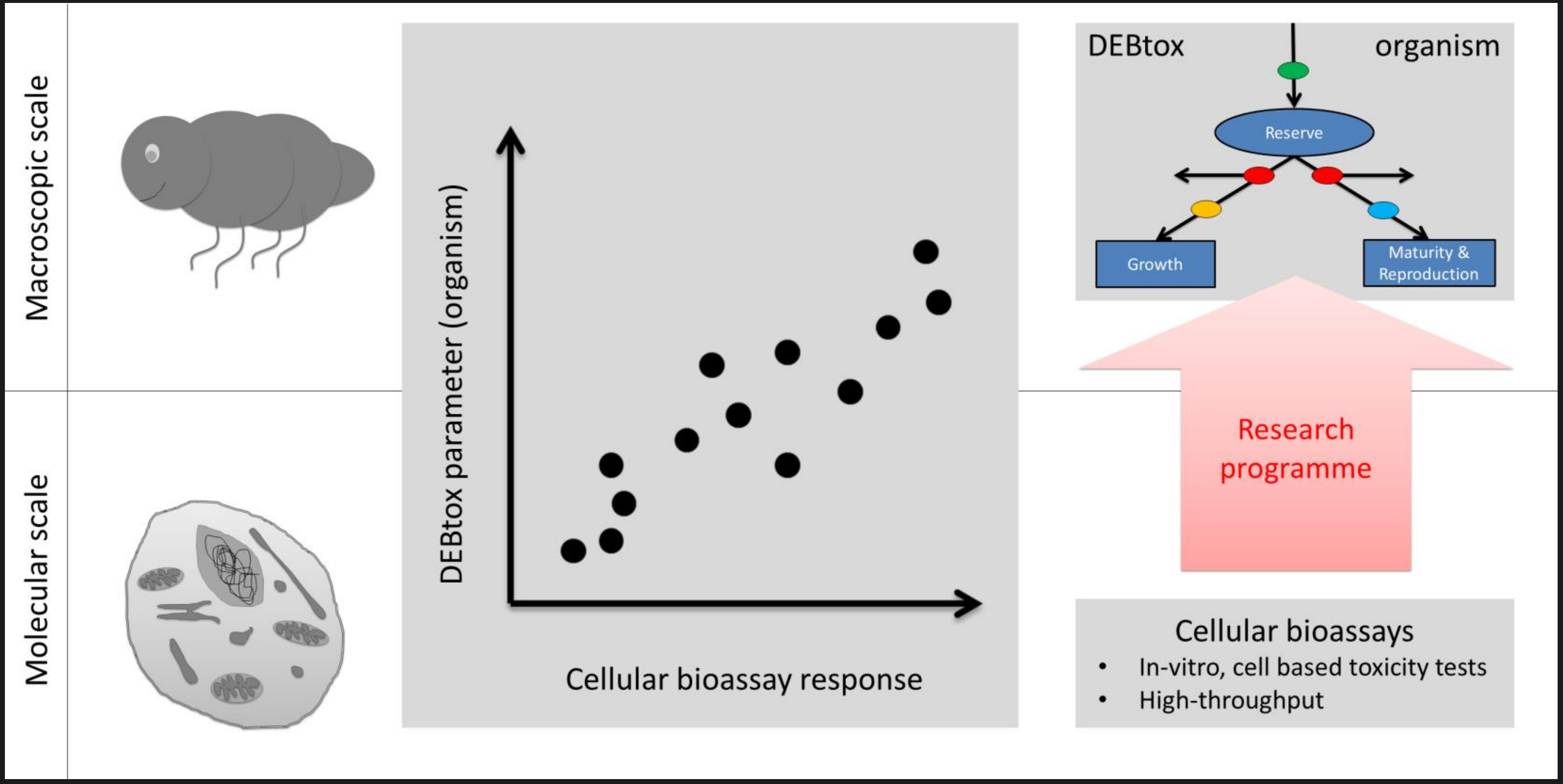


Toxicodynamic parameters cluster according to mode of action!

→ Biochemistry (MoA) is reflected at organism level (TD parameters)!

Ashauer, O'Connor, Hintermeister, Escher (2015): Death Dilemma and Organism Recovery in Ecotoxicology. *Environ. Sci. Technol. 49*, (16),

The challenge



Ashauer & Jager 2018

THANK YOU!