ECO39: Recent progress on toxicokinetic-toxicodynamic models

Roman Ashauer (University of York, UK) & Tjalling Jager (DEBtox research, NL)
Toxicokinetic-Toxicodynamic (TKTD) models

Physical-chemical properties
- Toxicant concentration in medium
- Toxicant concentration in animal
- Toxicant concentration at target

Toxicokinetics
- Uptake, Biotransformation, Distribution, Elimination

Toxicodynamics
- Damage accrual & damage recovery, Energy allocation, Physiological compensation, Thresholds

Mechanism & mode of toxic action (also known as Adverse Outcome Pathways)
- Toxicant interaction with target
- Cellular response
- Organ response
- Organism response

Traits affecting toxicokinetics

Traits affecting toxicodynamics

Ashauer & Escher (2010) JEM, Rubach et al. (2011) IEAM
TKTD models for environmental risk assessment

Environmental risk assessment of pesticides

- Toxicity tests & models (TKTD models)
- Population & community models
- Field studies & landscape models

Ecological realism

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

https://leanpub.com/guts_book
EFSA opinion on TKTD models

“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

2010 TKTD workshop


Ring-test

2015 TKTD workshop


“GUTS”

2010 TKTD workshop


Ring-test

2015 TKTD workshop


“GUTS”

2010 TKTD workshop


Ring-test

2015 TKTD workshop


“GUTS”

2010 TKTD workshop


Ring-test

2015 TKTD workshop


“GUTS”
ECO39.1 – The GUTS e-book

Modelling survival under chemical stress

A COMPREHENSIVE GUIDE TO THE GUTS FRAMEWORK

Tjalling JAGER and Roman ASHAUER

https://leanpub.com/guts_book
The GUTS e-book

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

Roman Ashauer*ab and Tjalling Jagerc

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 ecotoxicology and ecotoxicological risk characterization of chemicals and complex mixtures is the physiological mode of action.
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

“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

Making Sense of Chemical Stress
Applications of Dynamic Energy Budget Theory in Ecotoxicology and Stress Ecology

Tjalling Jager
Stress type (pMoA)

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


DEBtox: physiological mode of action (pMoA) is key

<table>
<thead>
<tr>
<th>Baseline toxicants</th>
<th>Specific toxicity</th>
<th>Metals</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral organics</td>
<td>Fluoranthene</td>
<td>Potassium</td>
<td>Toxic cyanobacteria</td>
</tr>
<tr>
<td>Benz(a)-fluoranthene</td>
<td>Pyrene</td>
<td>Calcium</td>
<td>pH (ocean acidification)</td>
</tr>
<tr>
<td>Neutral organics</td>
<td>Acetone</td>
<td>Sodium</td>
<td>Produced water</td>
</tr>
<tr>
<td>Neutral organics</td>
<td>Diquat</td>
<td>Nickel</td>
<td></td>
</tr>
<tr>
<td>Neutral organics</td>
<td>Pentachlorobenzene</td>
<td>Mercury</td>
<td></td>
</tr>
<tr>
<td>Phenols</td>
<td>2,4-dichlorophenol</td>
<td>Aromatic triazine</td>
<td></td>
</tr>
<tr>
<td>Imidazoles, carbamate esters</td>
<td>Carbendazim</td>
<td>Aldicarb</td>
<td></td>
</tr>
</tbody>
</table>
| Quinone carbamate ester | Turbutyl | Men 

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

<table>
<thead>
<tr>
<th>Application</th>
<th>Benefit</th>
</tr>
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<tbody>
<tr>
<td>Oil pollution assessment</td>
<td>Can assess time-variable exposure</td>
</tr>
<tr>
<td>REACH regulation, Section 1.5 of Annex XI: Grouping of substances and read-across</td>
<td>Predict toxicity of untested substances because model parameters can be read-across</td>
</tr>
<tr>
<td>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</td>
<td>Read-across of toxicity data with GUTS can be based on the category or the analogue approach</td>
</tr>
<tr>
<td>REACH Endpoint specific guidance R.7b</td>
<td>Calculate LC50 (and LD50) values for any exposure duration.</td>
</tr>
<tr>
<td>REACH, R.10.3.3 Calculation of PNEC for water in the case of intermittent releases</td>
<td>GUTS explicitly accounts for organism recovery and the temporal aspects of toxicity. Its application improves the assessment of intermittent release scenarios.</td>
</tr>
<tr>
<td>REACH: Endpoint specific guidance R.7b, R.7.8.5 Conclusions for aquatic pelagic toxicity and integrated testing strategy (ITS).</td>
<td>GUTS can help with the extrapolation of toxicity across species. Within reach that could support the integrated testing strategy.</td>
</tr>
</tbody>
</table>
Ecotoxicology: missing theory

<table>
<thead>
<tr>
<th>Macroscopic scale</th>
<th>Physical chemistry</th>
<th>(Eco)toxicology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfect gas</td>
<td>$p \times V = \text{constant}$ (Boyle’s law)</td>
<td>Generic organism stress $= \frac{1}{C_T} \times \max(0, C_V - C_0)$ (DEBtox)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Molecular scale</th>
<th>Kinetic model of gases</th>
<th>Cellular pathways</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random motion</td>
<td>Size negligible</td>
<td>Reaction networks</td>
</tr>
<tr>
<td>Elastic collisions only</td>
<td></td>
<td>-omics</td>
</tr>
</tbody>
</table>

Emerges

Missing theory

Ashauer & Jager 2018
Toxicodynamic parameters & mode of action

$C_{\text{water}} \rightarrow C_{\text{internal}} \rightarrow \text{Survival}$

Toxicodynamic parameters cluster according to mode of action!

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

The challenge

Macroscopic scale

Molecular scale

DEBtox parameter (organism)

Cellular bioassay response

DEBtox organism

Reserve

Growth

Maturity & Reproduction

Research programme

Cellular bioassays
- In-vitro, cell based toxicity tests
- High-throughput
THANK YOU!