RIFCON

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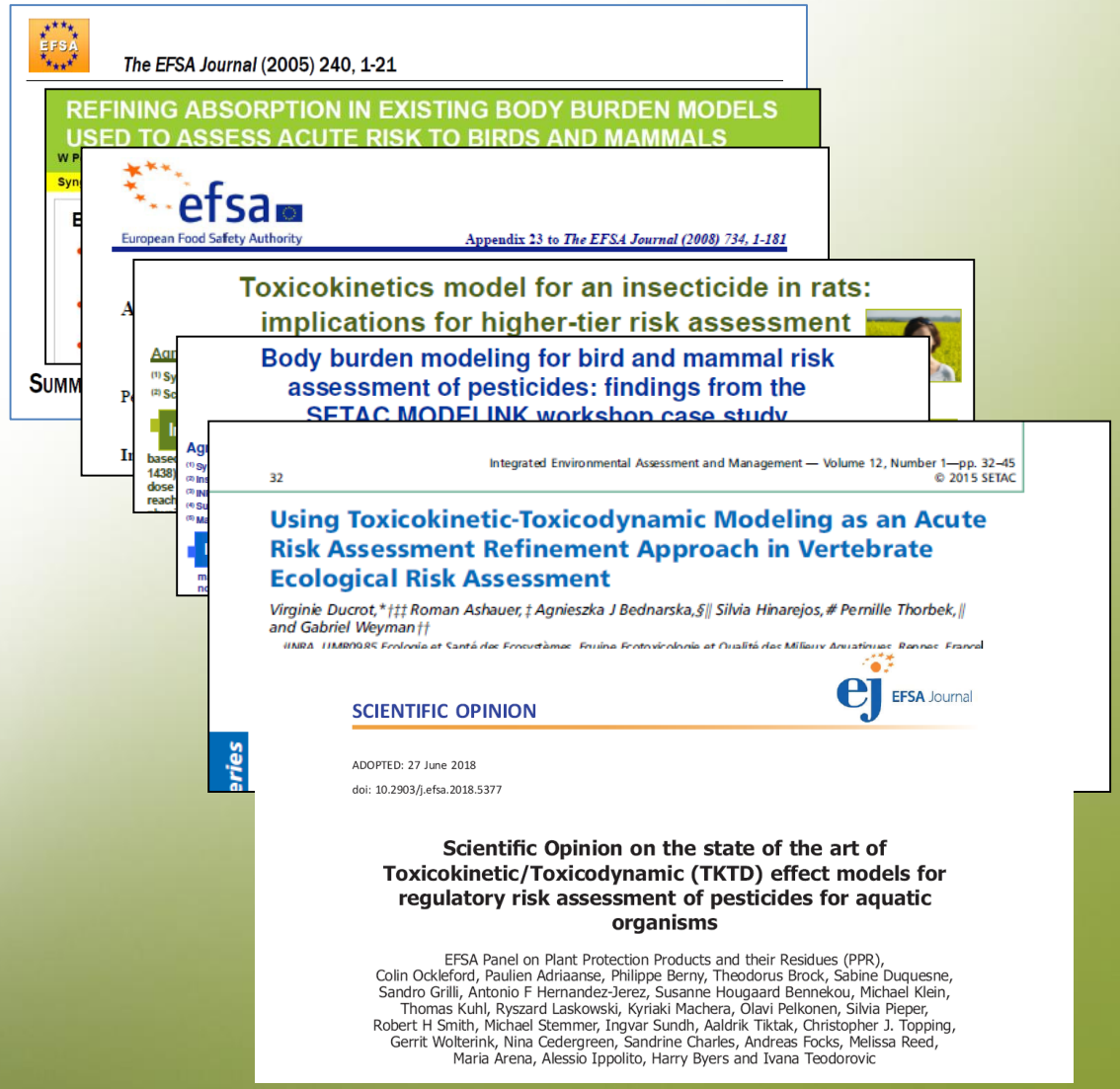
A standardised approach to identify worst-case FOCUS surface water exposure profiles using a TK/TD model

Outline

- History of TK modelling in the registration process
- Definition of problem
- Approach in the past (EPAT)
- GUTS approach
- Step-wise approach
    1. Calculation of PECsw
    2. Calibration of GUTS based on standard laboratory data
    3. Forecast calculation with PECsw considering the EU assessment factor
    4. Selection of worst case exposure profiles
    5. Derivation of laboratory exposure profile
- Outcome

History of TK modelling



Pirimicarb (Carbamate) 2005

SETAC 2007

GD 2009

SETAC 2012

SETAC 2013

IEAM 2015

Recommendations on how to use TK/TD model in acute risk assessment for vertebrates.

EFSA August 2018

SO TK/TD modeling

TKTD guidance ??
Official tool ??

TK (Body burden): Acceptance

Northern Zone (GD)

(Higher Tier Risk Assessment for Birds and Mammals in Northern Zone)

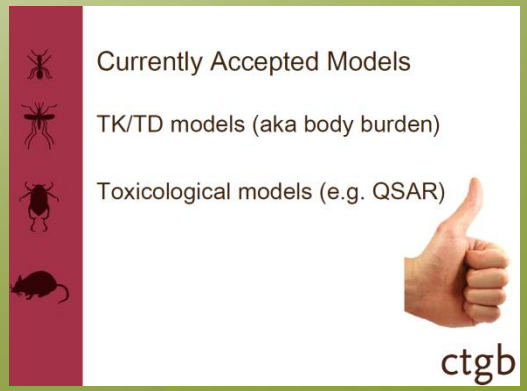
- […] body burden approach are not considered appropriate for the Northern Zone until validated models and guidance for use are available.

Mediterranean Countries

- Body burden modelling accepted at national level (e.g. PORTUGAL, Expert judgment needed for SPAIN)
- GREECE (national requirement, *6. Ecotoxicology*)
  - Use of Body Burden Model for higher Tier assessment is acceptable

Central Zone

- CTGB (NL)



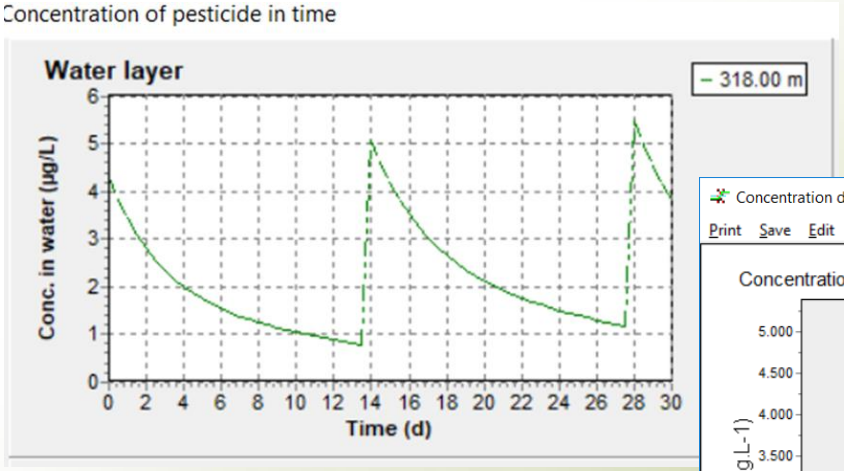
Problem definition

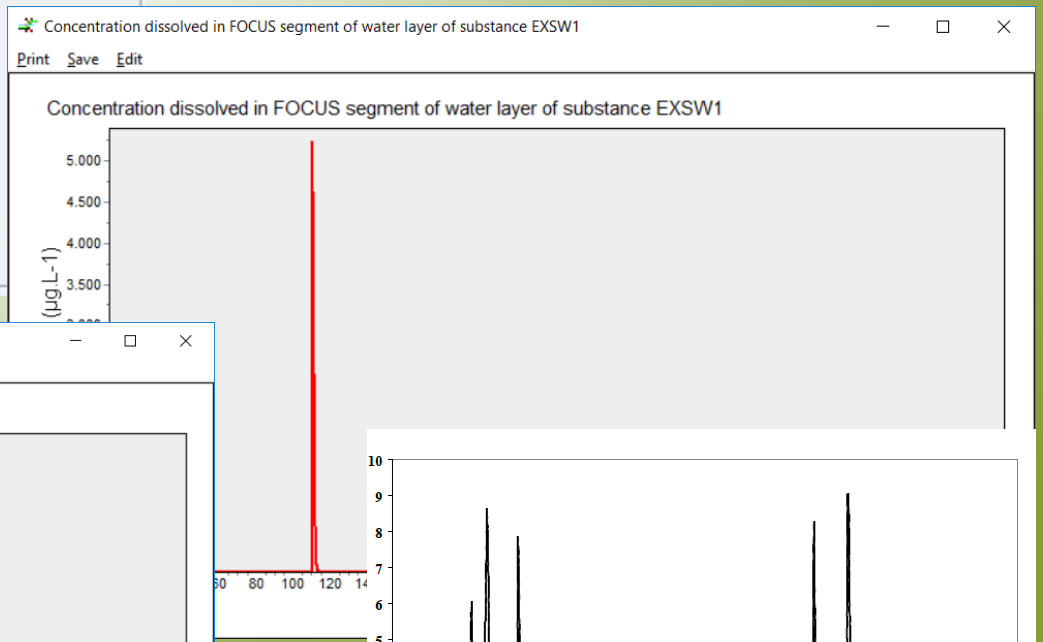
Why do we need TK/TD models in aquatic risk assessments?

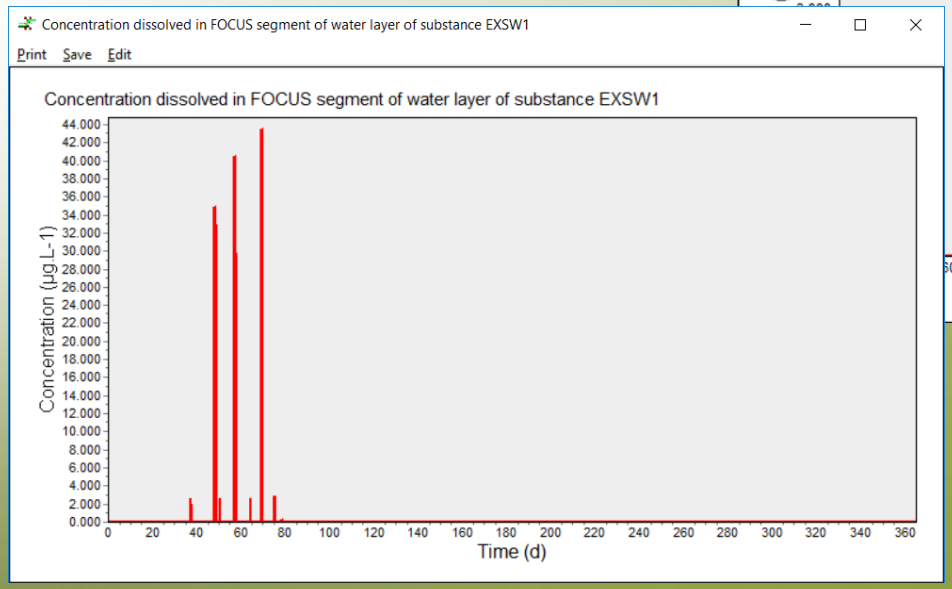
PEC > RAC

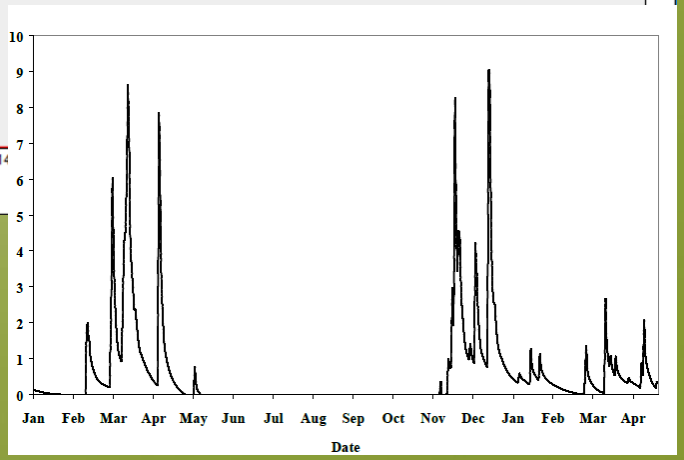
- Tier 1 aquatic risk assessment for PPPs frequently calls for the use of higher tier approaches to evidence an acceptable risk to aquatic organisms.
- Laboratory pulsed exposure experiments (Tier 2c) can be used to test the effects of varying exposure concentrations on the mortality and/or immobilization of organisms
- How to determine the relevant exposure profiles?

Exposure peaks

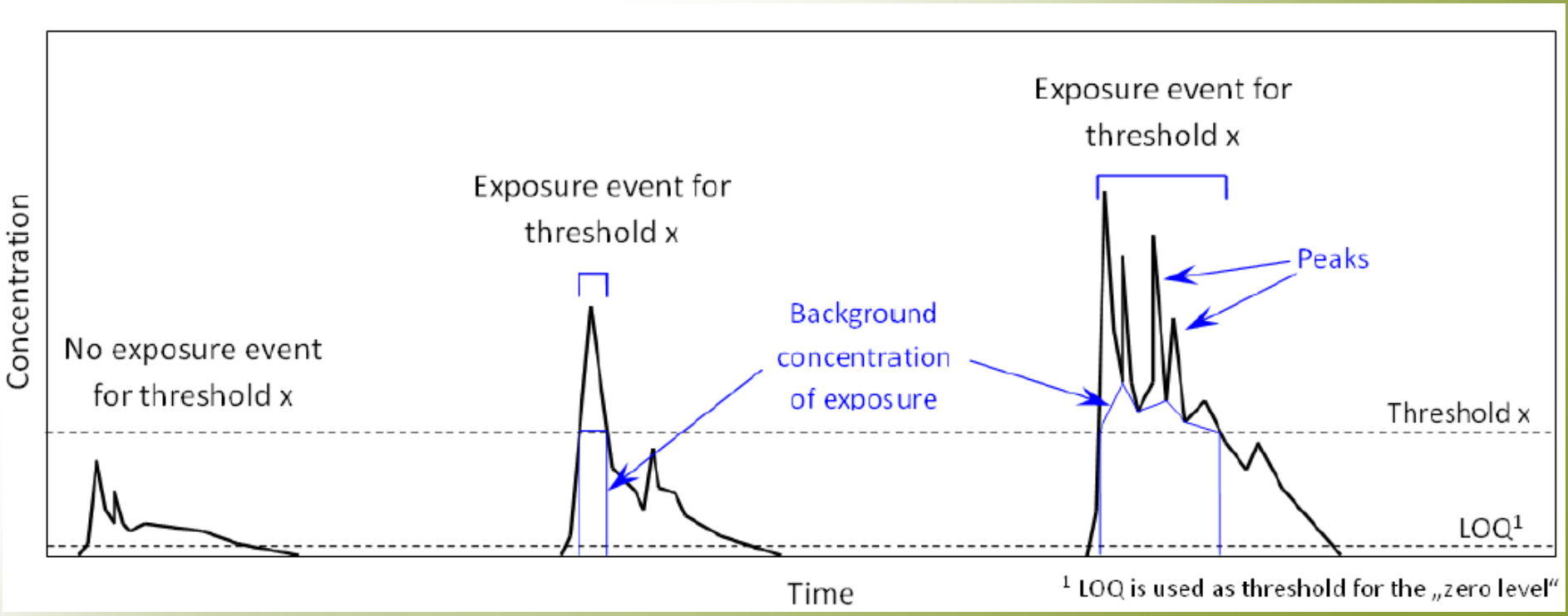








EPAT approach

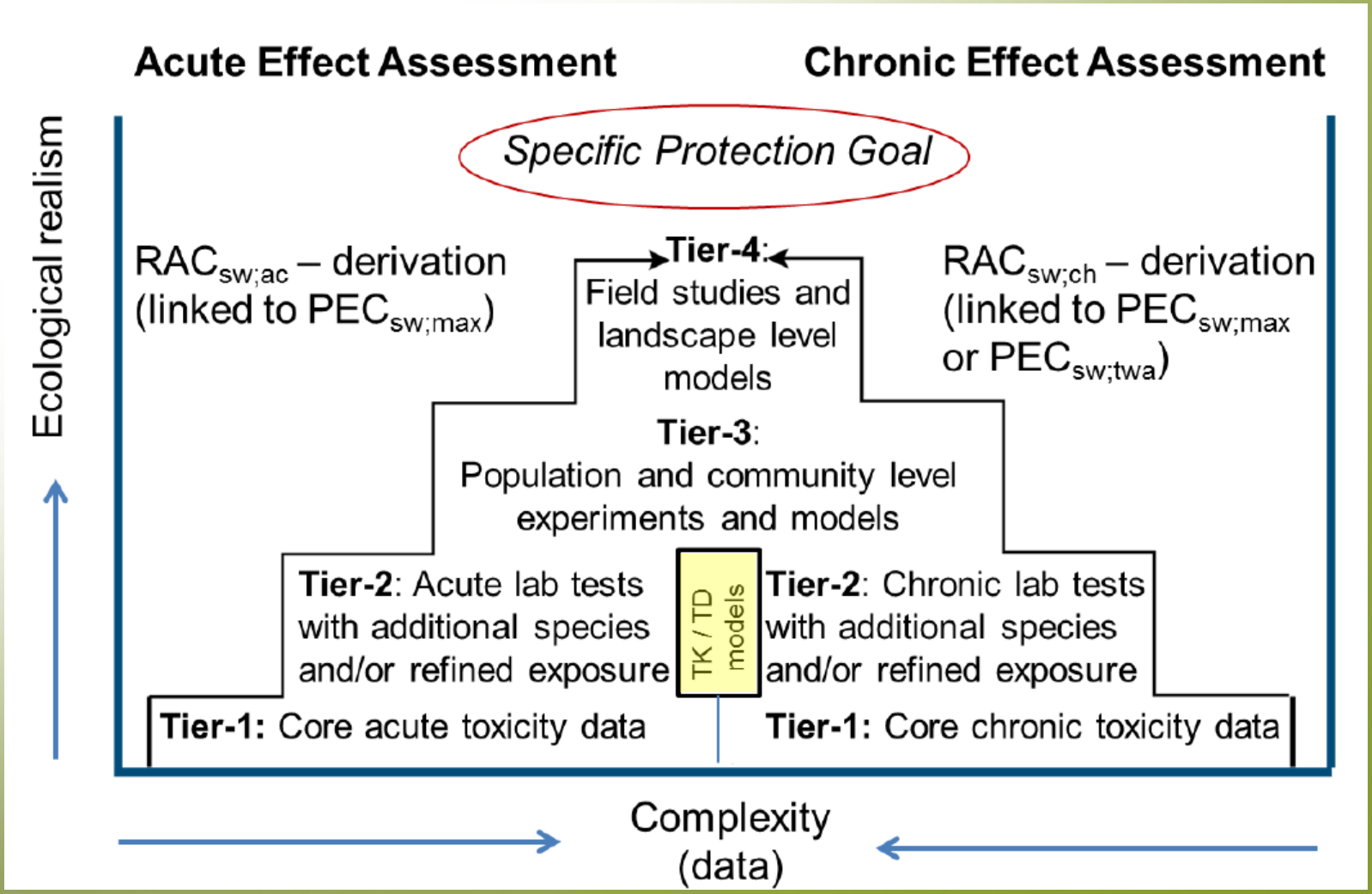


Definition of exposure events and peaks calculated in EPAT.

Threshold conc.	Event no.	Start date & time	t[day]	Max.conc.	Duration [days]	Interval [days]	No.extrema	AUC [µg/L*h]	TWAC-event [µg/L]	TWAC-background [µg/L]
1.000e-10	1	01.01.1986 01:00:00	0.042	1.635e-03	364.958	-	114	2.644e+00	3.019e-04	1.178e-05
1.000e-05	1	01.01.1986 01:00:00	0.042	1.635e-03	364.958	-	114	2.644e+00	3.019e-04	1.178e-05
1.000e-03	1	13.09.1986 07:00:00	255.292	1.426e-03	0.250	-	1	7.985e-03	1.331e-03	4.075e-05
1.000e-03	2	19.10.1986 06:00:00	291.250	1.507e-03	0.375	35.708	1	1.243e-02	1.382e-03	4.087e-05

Example EPAT event file

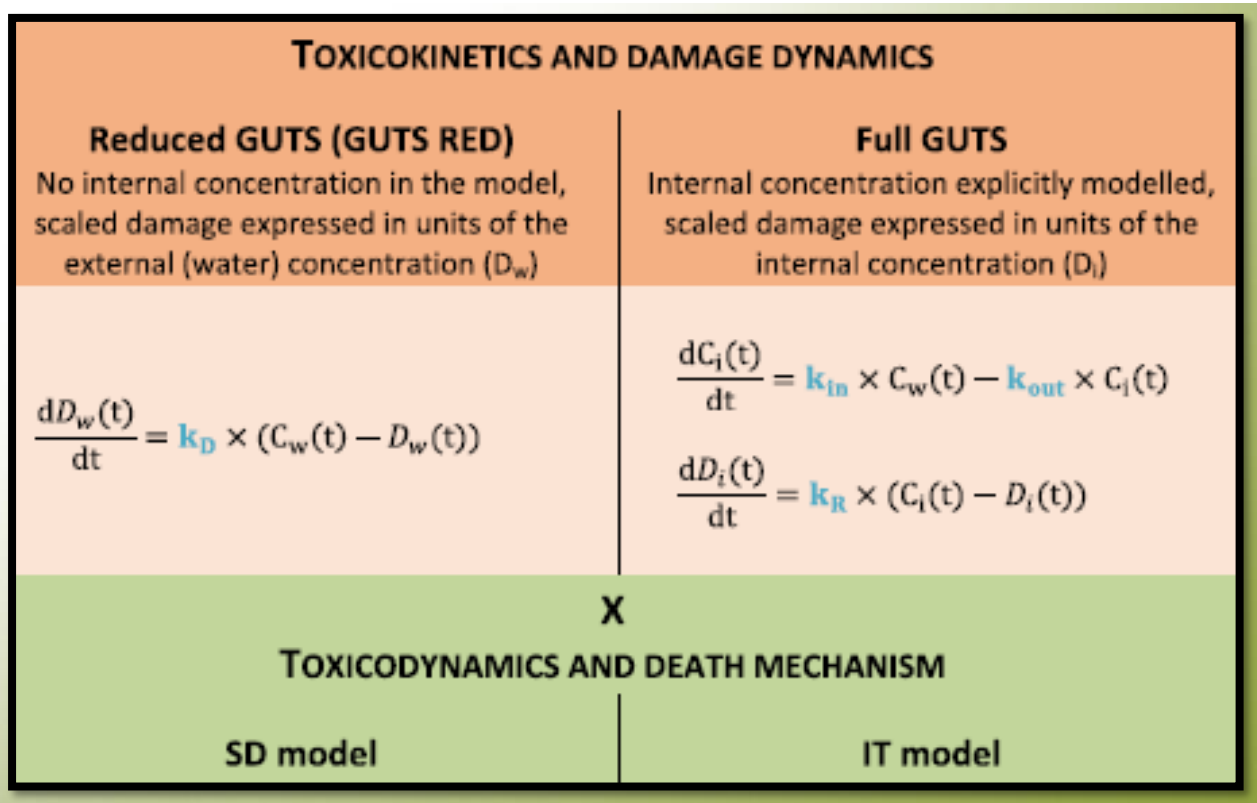
GUTS approach



EFSA PPR Panel. Guidance on tiered risk assessment for plant protection products for aquatic organisms in edge-of-field surface waters. EFSA Journal 11, 2009.

GUTS approach

Exposure

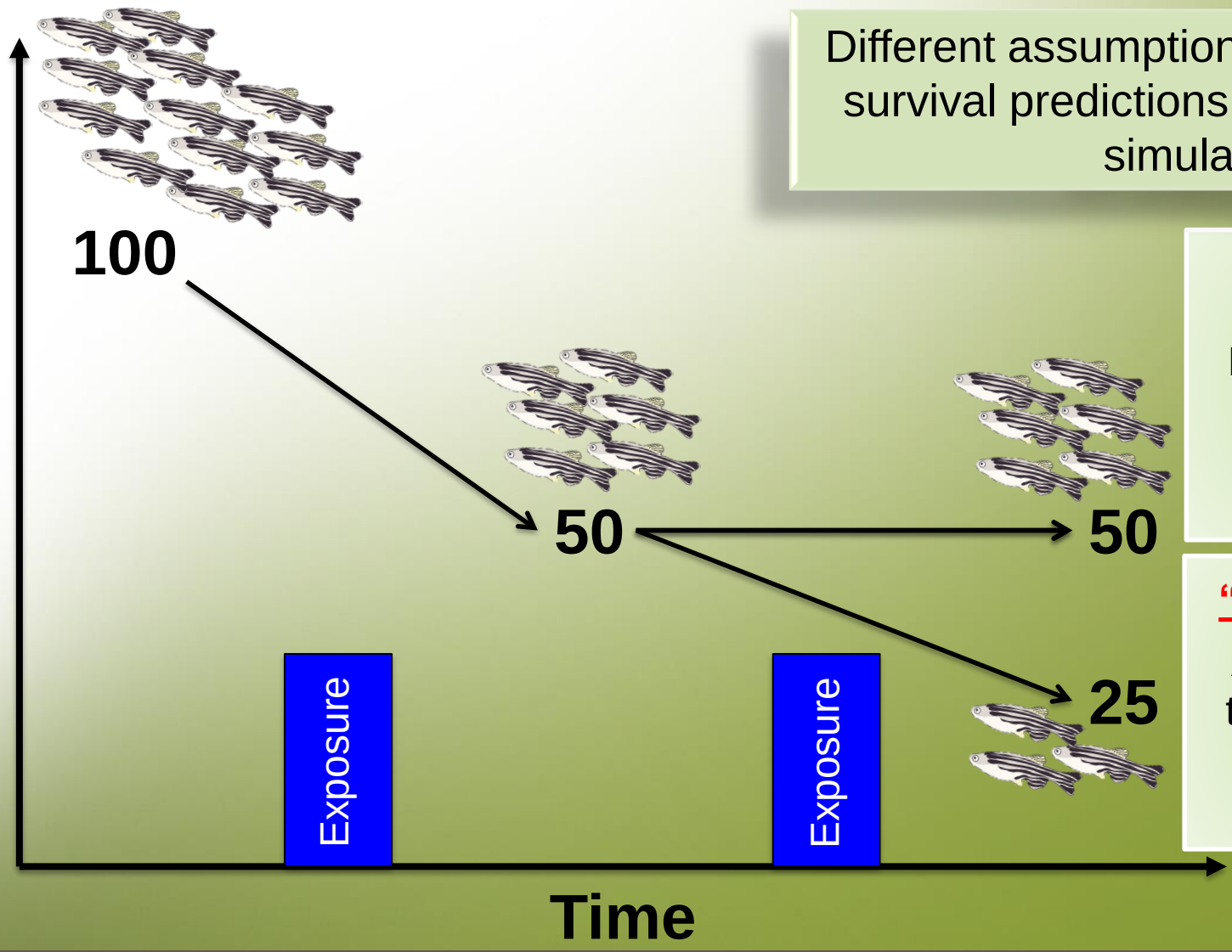


Mortality

EFSA, SO TKTD (2018)

- **Toxicokinetics:** What the organism does with the toxicant
- **Toxicodynamics**: What the toxicant does to the body

GUTS-Toxicodynamics (TD)



Death assumptions

Different assumptions lead to different survival predictions at the end of the simulation

"Individual Tolerance"

Each individual has different "tolerance", when exceeded ➔ death

"Stochastic Death"

All individuals have the same tolerance. Death is a chance process

Model selection

- Higher tier procedures regarding modelling differ between exposure and effect risk assessment:

Exposure modelling:

- Check model
- Check scenarios
- Check mitigation measures

➢ Applicant knows the outcome of the RA

Effect modelling:

- Select a model of your choice
- Send calculations, program, manual, TRACE document and source code

➢ Applicant does not know the outcome of the RA

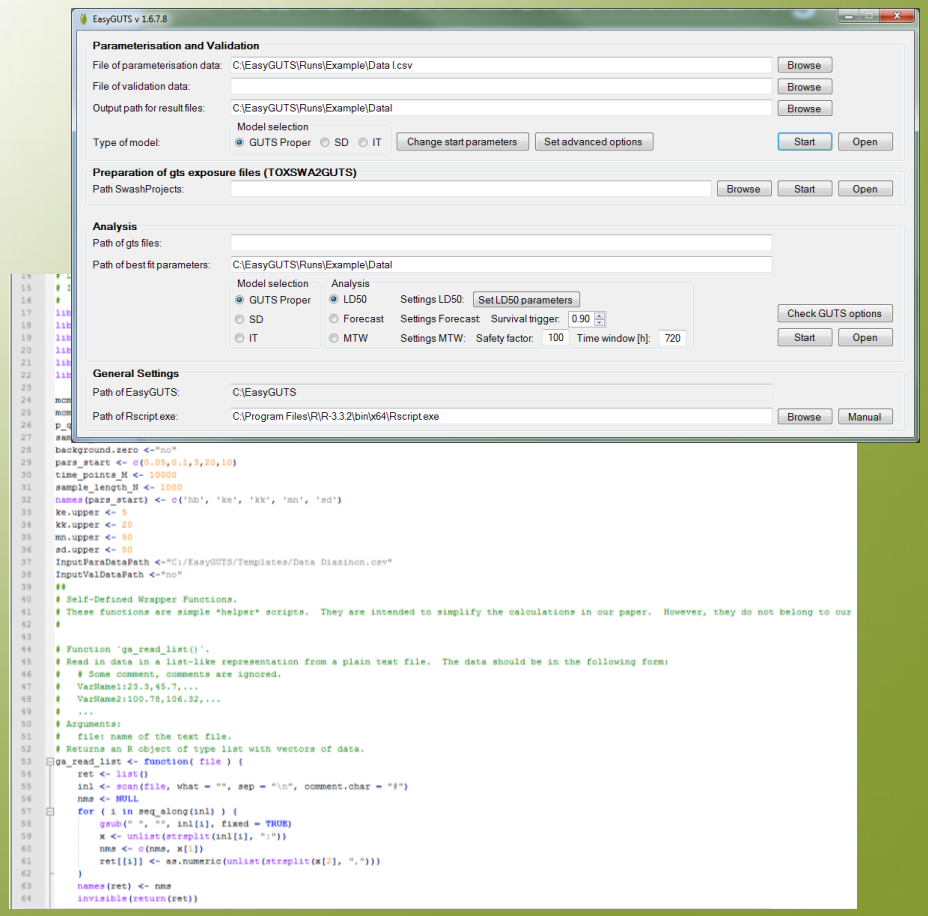
GUTS implementations

Software	Participant(s)	Affiliation
BYOM / Matlab	Tjalling Jager	DEBtox research
DEBtox	Tjalling Jager	DEBtox research
DELPHI	**Andre Gergs, Thomas Preuss**	**Bayer Crop Science**
EpyTox	Raymond Nepstad	Sintef
GUTS 3S	**Udo Hommen, Judith Klein**	**Fraunhofer IME**
Mathematica	Andreas Focks	Alterra
ModelMaker	Roman Ashauer	University of York
OpenModel	Nina Cedergreen, Kristoffer Dalhoff	University of Copenhagen
R/JAGS	Sandrine Charles, Virgile Baudrot	University of Lyon
EasyGUTS	**Dirk Nickisch**	**RIFCON**
GATEAUX	Sam Maynard	Syngenta

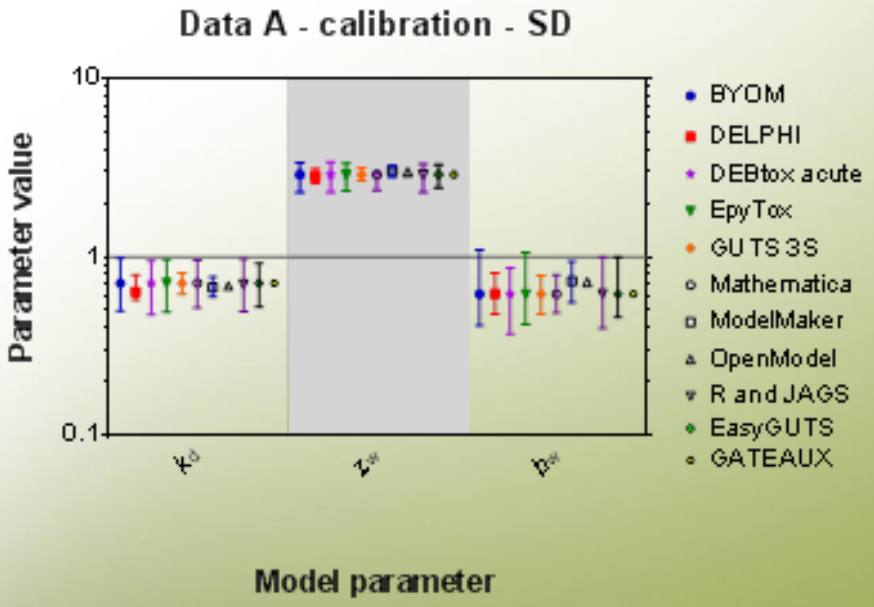
Jager T. & Ashauer R. Modelling survival under chemical stress - A comprehensive guide to the GUTS framework (2018)

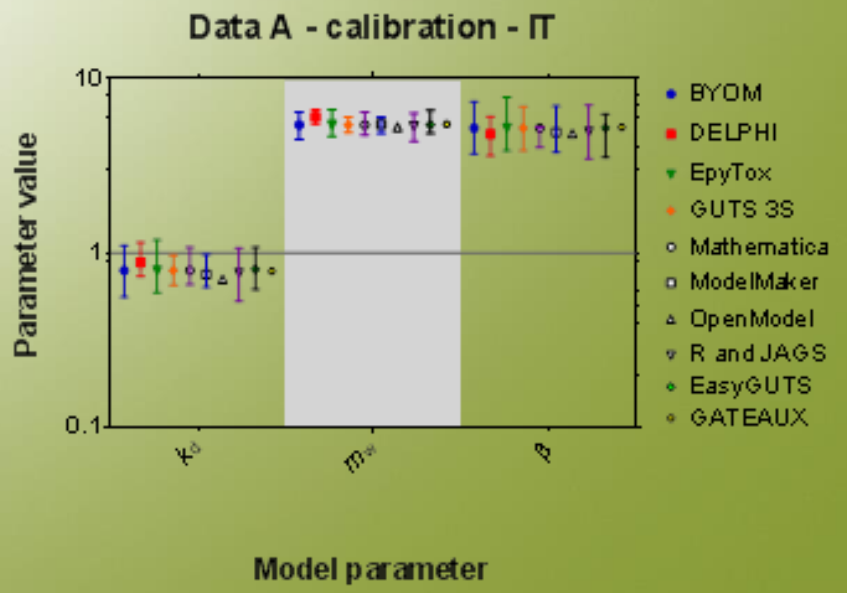
EasyGUTS

- EasyGUTS is an user interface to handle and run R scripts
- Approach comparable to the KinGUI package (Windows GUI + Rscript.exe)
- Based on R package “GUTS” and calibration approach published by Albert *et al.* 2016



Example results



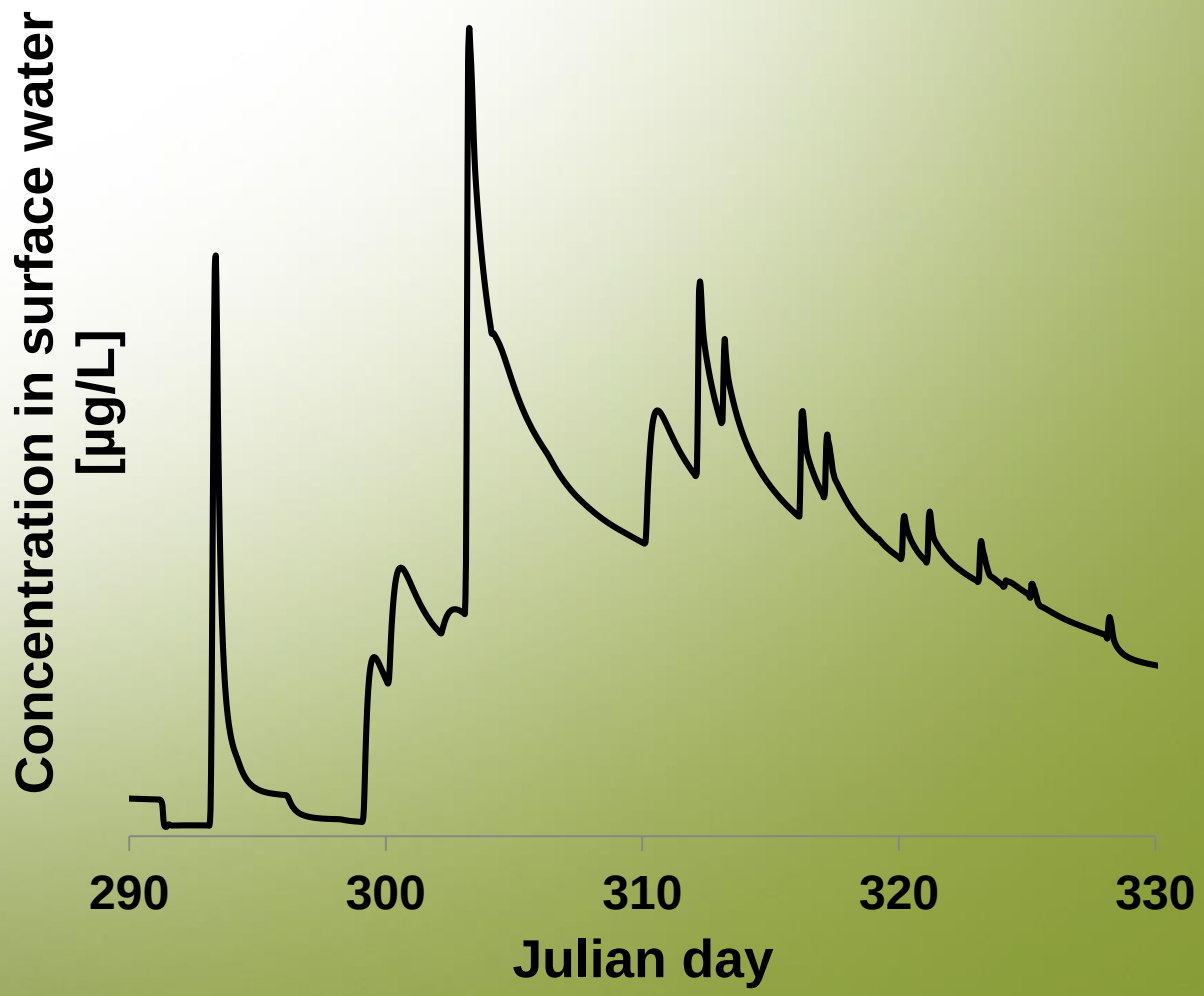


Jager T. & Ashauer R. Modelling survival under chemical stress - A comprehensive guide to the GUTS framework (2018)

Stepwise GUTS approach

1. Calculation of PECsw
2. Calibration and Validation of GUTS based on standard laboratory data
3. Forecast calculation with PECsw
4. Selection of worst case exposure profiles
5. Derivation of laboratory exposure profile

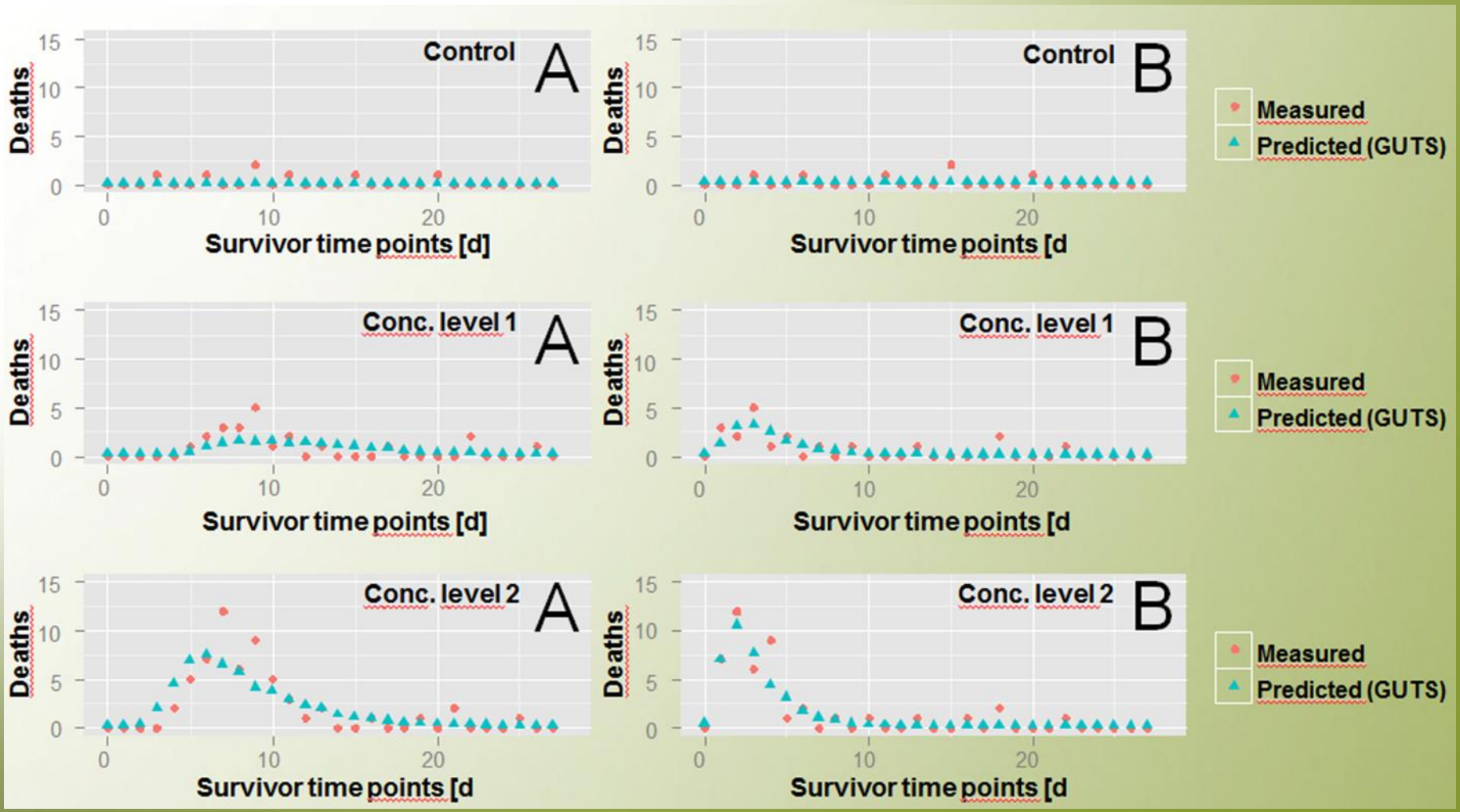
Stepwise approach: 1) PECsw



Calculation of predicted exposure patterns with FOCUS-SW models, e.g. drift and drainage inputs according to the FOCUS D2 (ditch) scenario.

Stepwise approach: 2) GUTS Calibration

A: Late onset of effect (TOE) **B: Early onset of effect (TOE)**



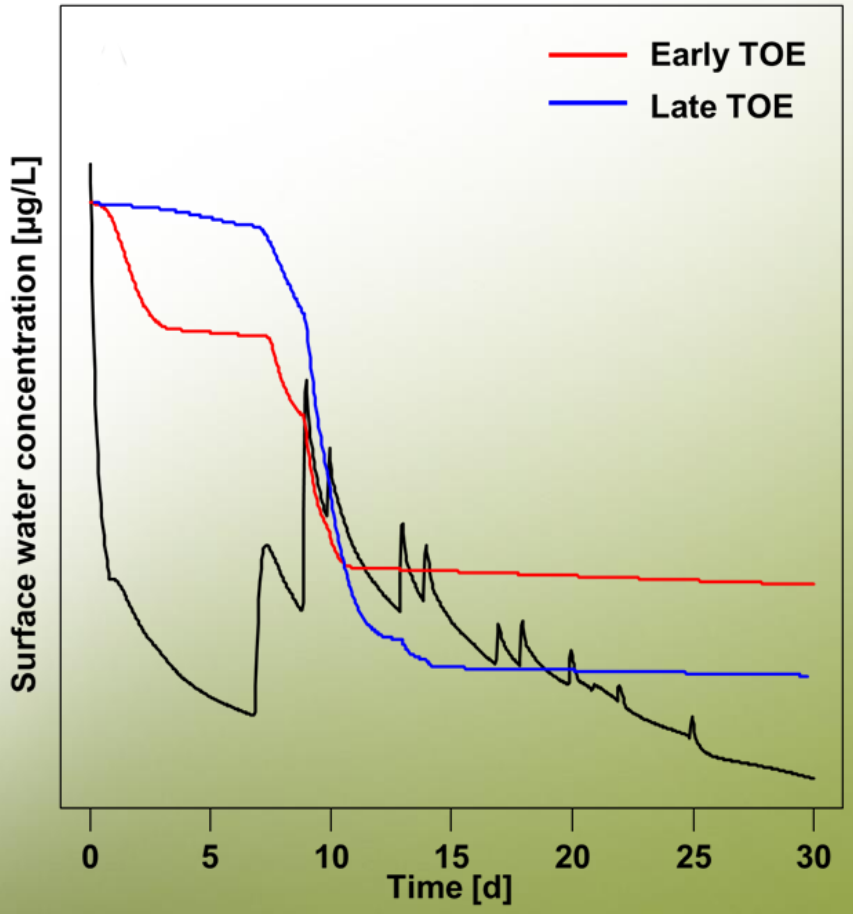
Stepwise approach: 3) Forecast

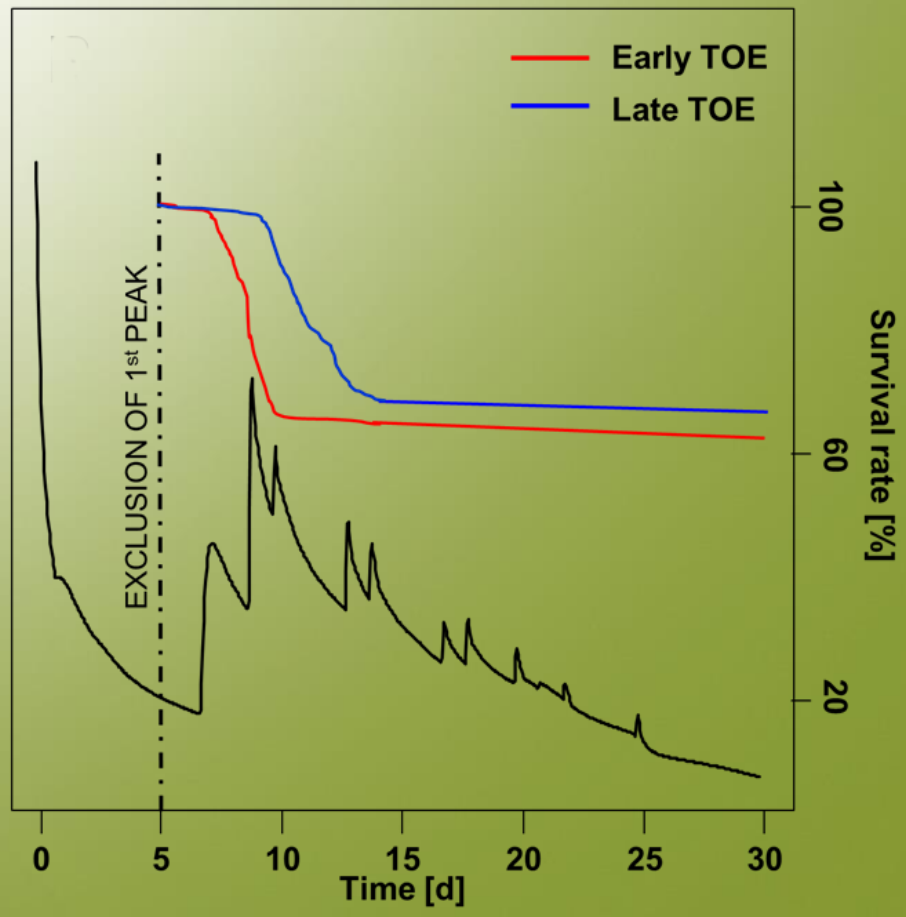
Estimated mortalities (%) compared to controls calculated with a calibrated GUTS model and exposure profiles based on FOCUS SW models.

Crop / Application rate	GUTS	D1 ditch	D1 stream	D2 ditch	D2 stream	D3 ditch	D4 pond	D4 stream	D5 stream	D6 ditch
Winter OSR / 150 g/ha	A	-	-	+ 5.9	+ <0.1	0	0	0	0	0
	B	-	-	+26.5	+ 3.2	0	0	0	0	0
Leafy vegetables / 150 g/ha	A	-	-	-	-	0	0	0	-	+ <0.1
	B	-	-	-	-	0	0	0	-	+ 14.8
Pome fruits / 1500 g/ha	A	-	-	-	-	+3.7	+ <0.1	0	0	-
	B	-	-	-	-	+38.4	+1.8	+ <0.1	+ <0.1	-
Winter cereals / 100 g/ha	A	+ 0.2	0	+ 64.9	+ 0.7	0	0	0	0	0
	B	+ 11.3	+ 10.5	+ 52.7	+ 9.8	0	0	0	0	0

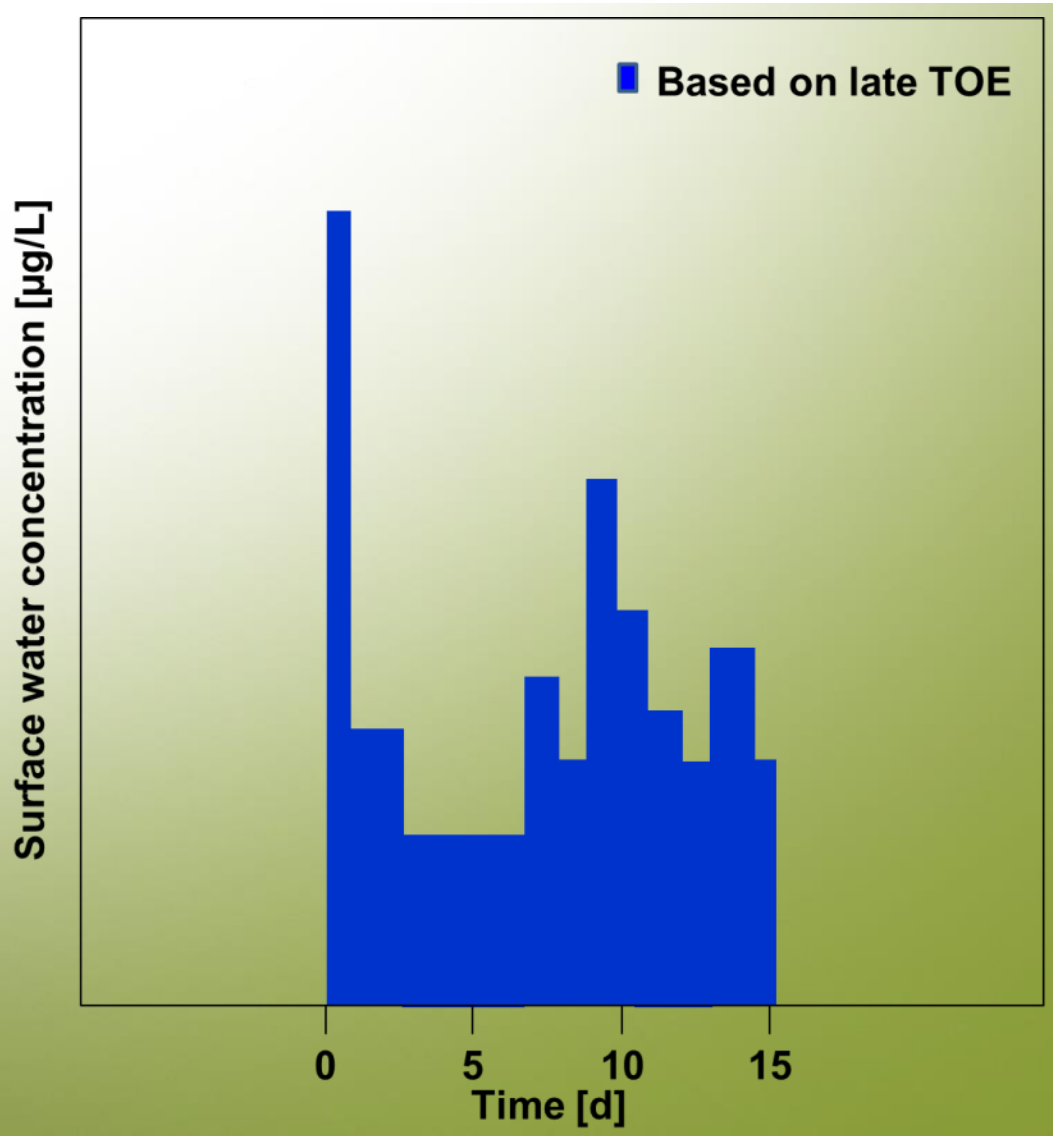
.....

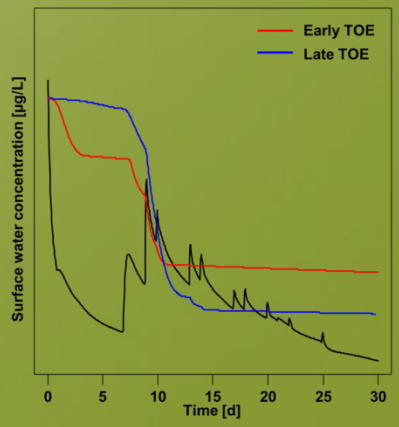
Stepwise approach: 4) Selection worst case





Stepwise approach: 5) Lab exposure





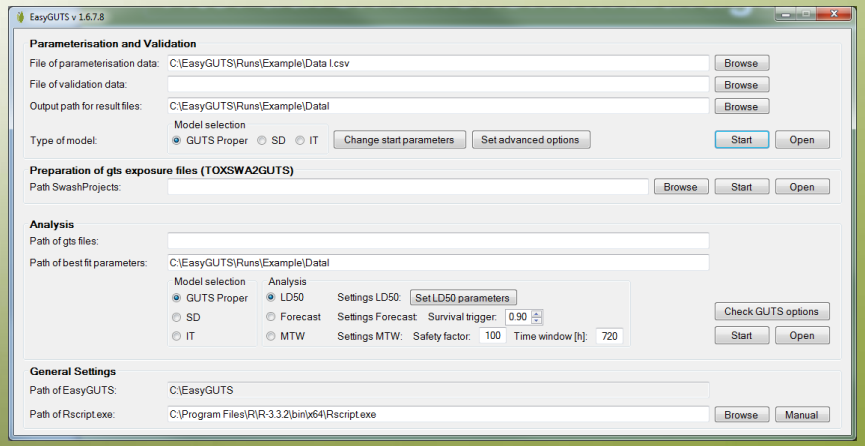
Conclusion I

- Time of onset of effects (TOE) and internal carry-over toxicity also strongly affects the response of test organism
- Step-wise approach is a valuable and reproducible tool to select ecotoxicologically relevant concentration profiles for pulsed-exposure studies
- Easy-to-use and provides a reproducible and scientifically sound way to demonstrate conservative exposure profiles in higher tier aquatic risk assessments

Conclusion II

- GUTS is a powerful tool to predict effects on surival from various exposure scenarios
- Simulation of effects allows an accurate prediction of lethal effects
- Windows Implementations of GUTS model available:

  - EasyGUTS, Delphi version, GUTS 3S



EPAT and EasyGUTS can be downloaded:

https://www.rifcon.de/en/downloads

Thank you for your attention