How to reduce computation effort for GUTS modelling while retaining output reliability for risk assessment use?

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Background

The practicability of approaches can influence their usability in environmental risk assessment (ERA). The anticipated 20-year data [1] in aquatic RA would considerably amplify computational effort and therefore pose a challenge for General Unified Threshold Model of Survival (GUTS) applications in ERA. We investigated the dependence of GUTS projections on the completeness of data aiming to suggest refinements which could reduce computation effort without compromising the reliability of GUTS projections. This case study is based on using a Bayesian approach [2] for parameter estimation.

(A) Evaluating a set of exposure profiles to deduce worst cases

A selection of worst-case exposure profiles is suggested, to ensure no underestimation of effects.

Suggested criteria for selection

- Maximum peak exposure concentrations (PEC_{max}),
- Number of events exceeding defined thresholds (derived from LC_{50}) and their maximum area under the curve (AUC_{max}), computed using EPAT [3],
- Safety factors from GUTS model simulations [4] using one best fit parameter set.

Table 1: Fraction of the decision table for standard Step 3 TOXSWA 5.5.3 exposure profiles of toxicant diazinon applied on winter cereals. Color coding helps with the identification of worst cases (dark red).

Scenario	Waterbody	Events for Thresholds 0.0009 (µg/L)	0.009 (µg/L)	PEC_{max} (µg/L)	AUC_{max} (µg/L)	safety factor	Worst case
D1	Ditch	3		5.77	2266	1592	X
D1	Stream	8		5.04	680	2930	
D2	Ditch	31		8.76	637	1350	
D2	Stream	36		5.67	89	1872	(*)
D3	Ditch	1		5.69	105	7100	
D4	Pond			0.20	0	35683	
D4	Stream	1		4.93	35	16464	
D5	Pond			0.20	0	34895	
D5	Stream	1		5.32	48	14104	
D6	Ditch	5		6.61	809	2695	
R1	Pond			0.56	0	11760	
R1	Stream	6	1	9.52	95	1881	
R3	Stream	6	2	12.32	267	819	X
R4	Stream	3		4.61	57	3070	

(*) Scenario D2 is only relevant on national level in France and was therefore not suggested as worst case.

(B) Identifying relevant exposure time windows for projections

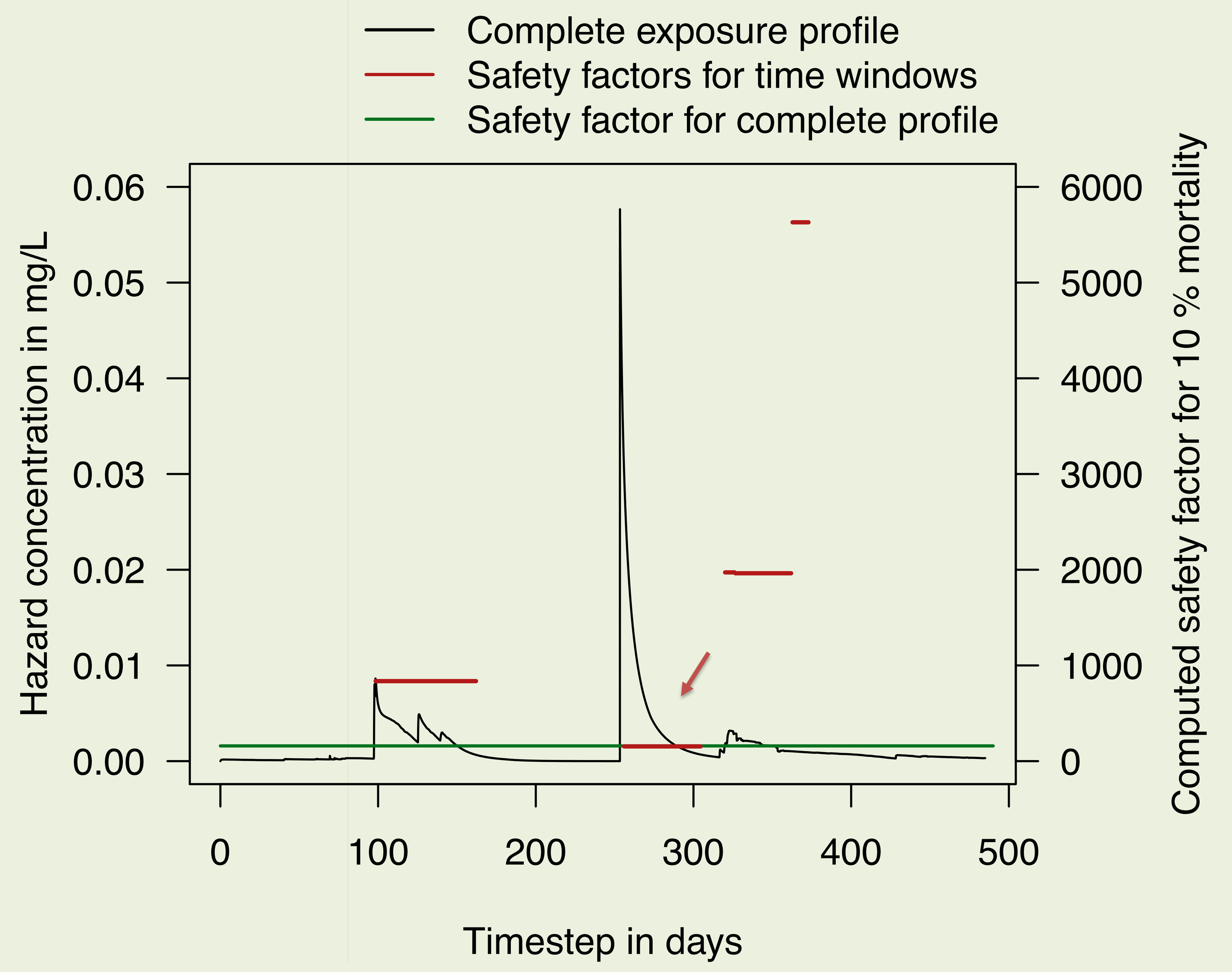

Figure 1: Exposure profiles often show short time windows of critically high exposure levels (e.g. immediately after product application), while longer periods show negligible exposure. Further, species biology determines periods of high vulnerability (e.g. at early life stages).

The plot presents computed safety factors for relevant fragments of an example exposure profile. The fragments alone were used as exposure for simulations. Exposure beneath a threshold of significance was ignored. It is suggested to consider a recovery time after each relevant event and append it to the time window. The obtained safety factors were compared to those obtained with the complete profile. The example shows a typical case that projections with highest and longest peak exposure represent the results of projections of the full profile.

(C) Reducing the amount of replicates used for projections

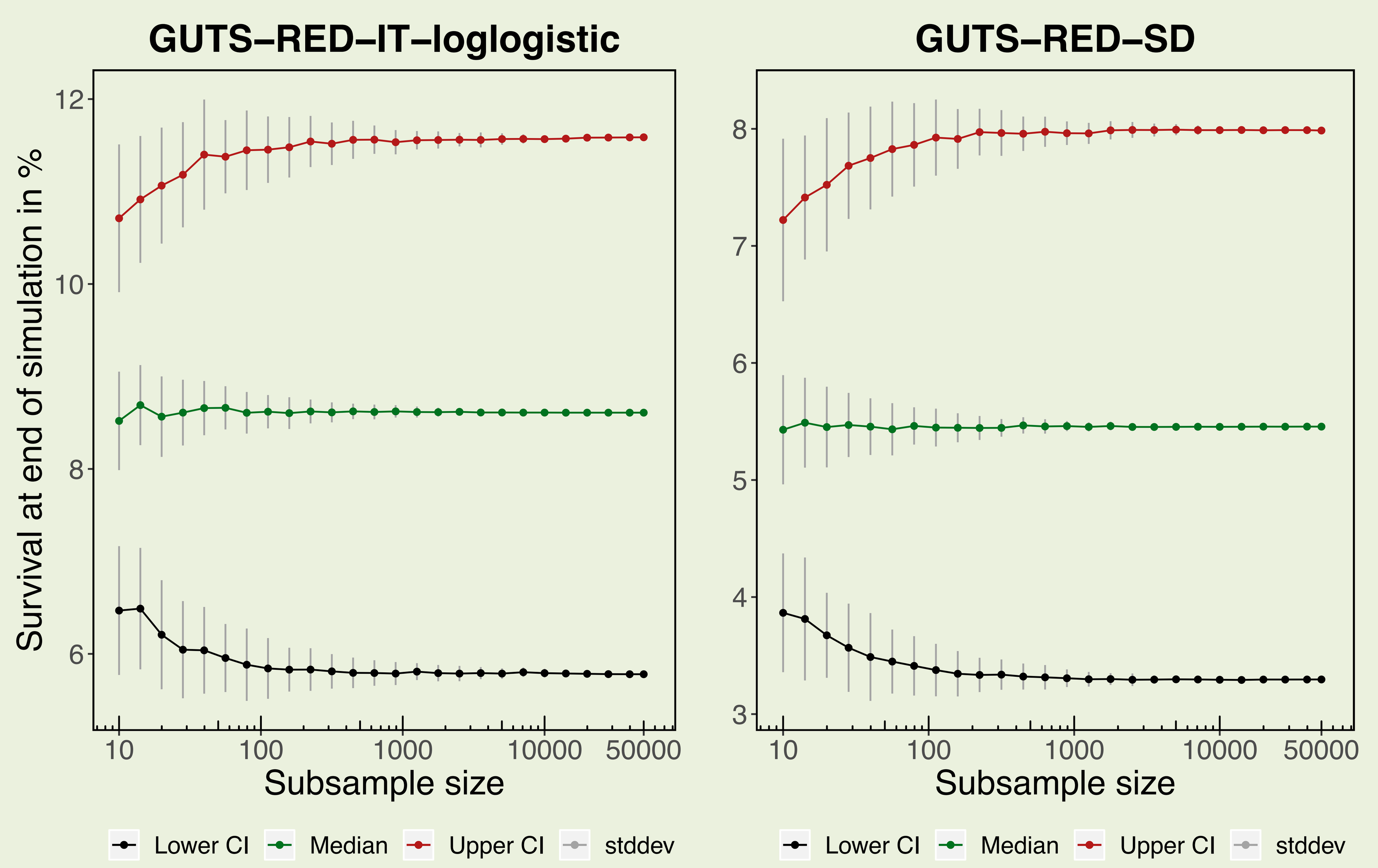

Figure 2: GUTS calibrations must be replicated many times and result in large parameter sets (~ 50,000 samples). The number of replicates needed for reliable projections was investigated.

The plots show the median and the confidence intervals of the predicted survival at the end of simulations, dependent on the number of replicates. Error bars indicate the standard deviations from 100 iterations for each subsample size. For calibration, acute toxicity data of diazinon in fathead minnow was used [5]. It was performed using the two suggested GUTS reduced (RED) death mechanism models individual tolerance (IT) and stochastic death (SD) [6].

A small share of the sample appeared to be sufficient to obtain reliable results, as standard deviations decreased quickly.

A requirement for reliable results refers to the evaluation of parameter uncertainties and assessment of their distributions as proposed in the EFSA opinion on good modelling practice in ERA [7].

Conclusions

- Computational effort can significantly be reduced by focusing on worst case exposure profiles (A).
- Conducting GUTS projections only on time sections with significant effect reduces computational effort and the results are comparable to those achieved by simulating the full profiles (B).
- Thinning of the parameter set to a certain extent results in nearly the same projection of the confidence intervals of survival and should therefore be reliable for the calculation of safety factors (C).

Practical advice for GUTS modelling

Computational effort could successfully be reduced without critically impairing projection reliability. We demonstrated three options, which can be used solely or in combination to ensure practicability of GUTS model projections.

References: **(1)** EFSA 9th EU Modelling Workshop, Copenhagen (2018): FOCUS surface water scenarios: updates on the repair action **(2)** Albert C, Vogel S, Ashauer R (2016) Computationally Efficient Implementation of a Novel Algorithm for the General Unified Threshold Model of Survival (GUTS). PLoS Comput Biol 12(6): e1004978. **(3)** Rifcon GmbH (2018). EPAT: Exposure Pattern Analysis Tool version 1.2. **(4)** Carlo Albert. Sören Vogel. Oliver Jakoby. Alexander Singer and Dirk Nickisch (2019). GUTS: Fast Calculation of the Likelihood of a Stochastic Survival Model. R package version 1.1.1. https://CRAN.R-project.org/package=GUTS. **(5)** Geiger. D. L.; Call. D. J.; Brooke. L. T. Acute toxicities of organic chemicals to fathead minnow (*Pimephales promelas*). Volume IV.; University of Wisconsin-Superior: Superior. Wisconsin. USA. 1988. **(6)** EFSA PPR Panel (2018). Scientific Opinion on the state of the art of Toxicokinetic/Toxicodynamic (TKTD) effect models for regulatory risk assessment of pesticides for aquatic organisms. EFSA Journal 2018; 16(8):5377. **(7)** EFSA PPR Panel (2014) Scientific Opinion on good modelling practice. EFSA Journal 12(3):3589.