A user-friendly program of a TK-TD model to link variable exposure to effects on survival of aquatic organisms

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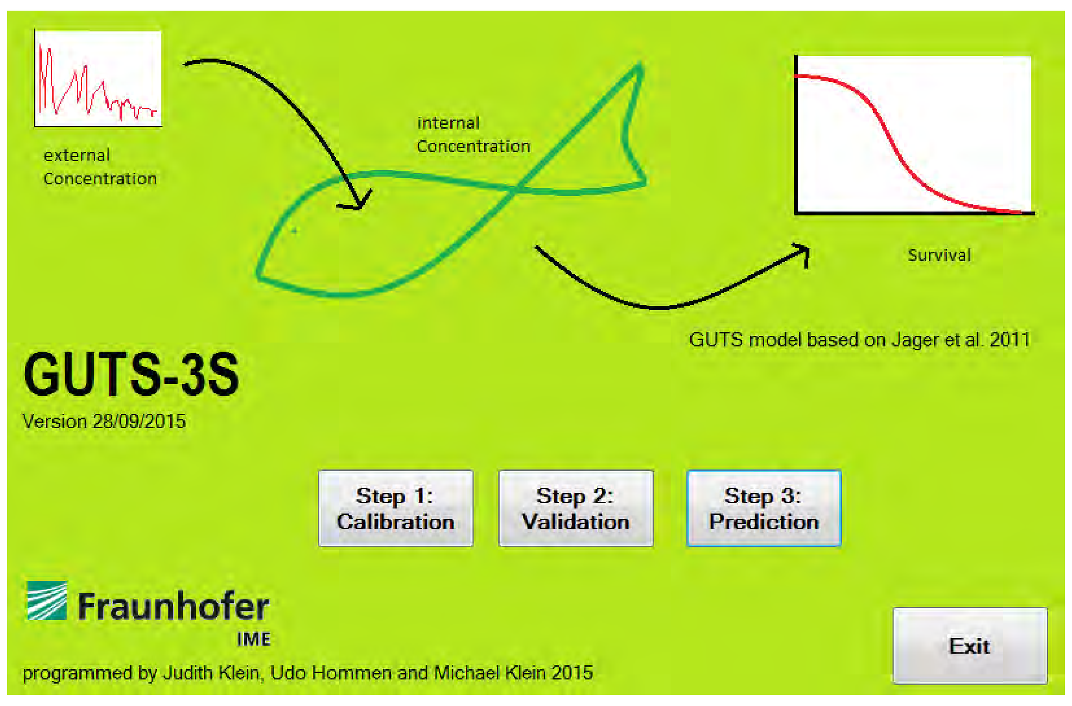
Motivation

Exposure of aquatic organisms to plant protection products in edge-of-field waters can be highly dynamic over time. Toxikokinetic-toxicodynamic models, e.g. the General Unified Threshold Model of Survival (GUTS) [Jager et al., 2011], offer a mechanistic way to predict effects of such dynamic exposures patterns. We aim to provide a user-friendly program of GUTS covering all necessary steps for its use in risk assessment, i.e. as a tier 2 tool according to the aquatic guidance document [EFSA PPR Panel, 2013]:

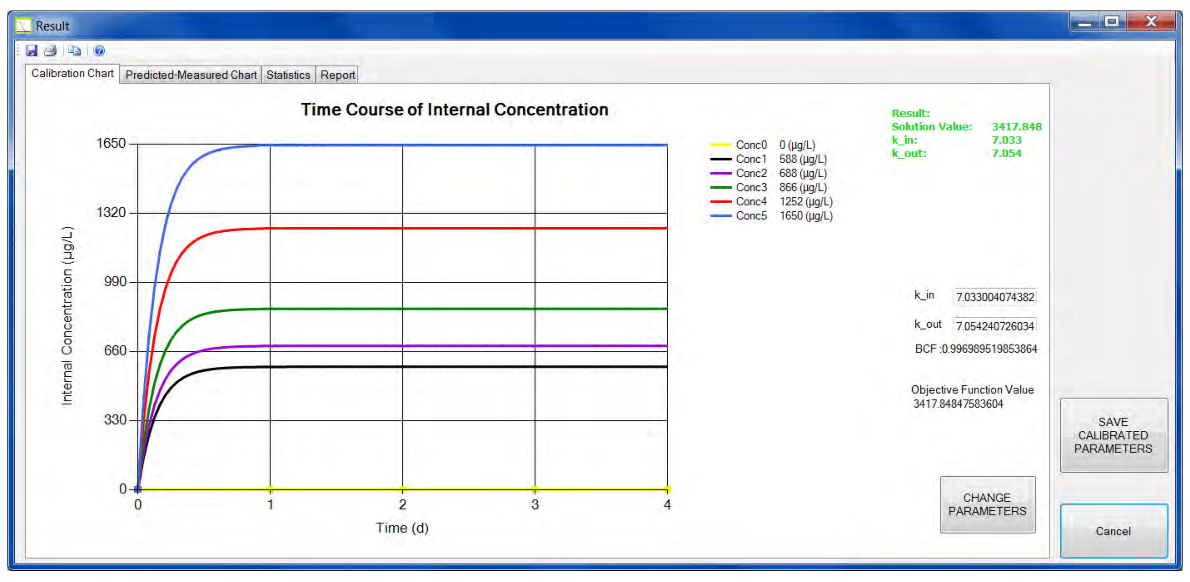
1. Calibration of the substances and species specific parameters using results of ecotoxicological tests
2. Validation of the calibrated model based on results of additional tests
3. Prediction for exposure scenarios not tested



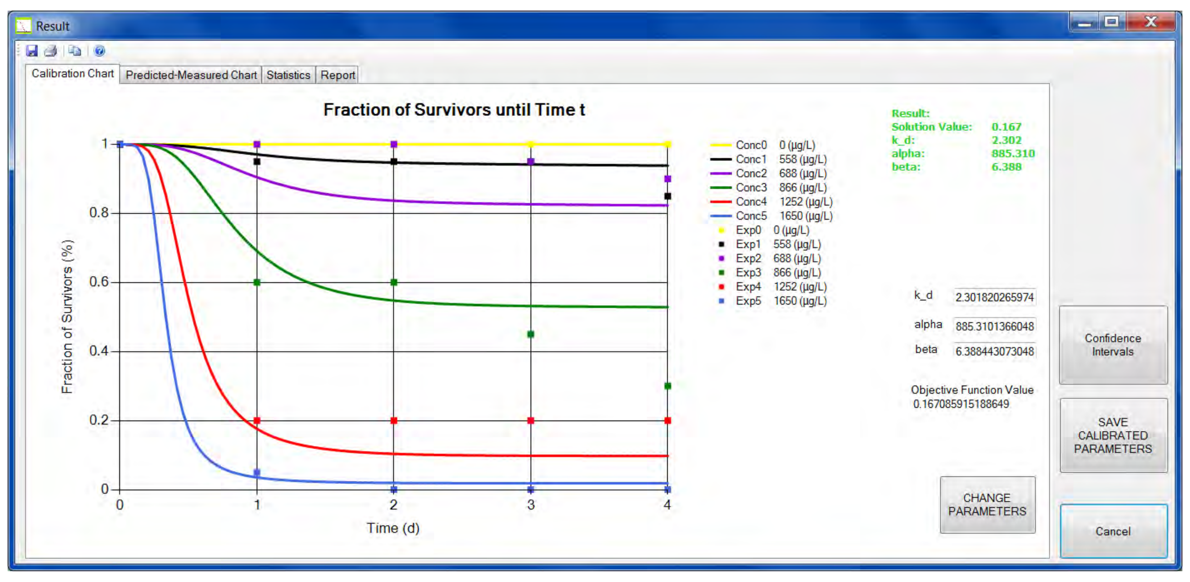
Step 1: Calibration

Depends on available experimental data sets:

If e.g. a Bioconcentration Study OECD 305 is available, uptake and elimination rates can be used to describe the TK part while the TD parameters are calibrated using ecotoxicological test data.



Else TK and TD parameters are calibrated based e.g. on a standard Acute Toxicity Fish Test OECD 203.



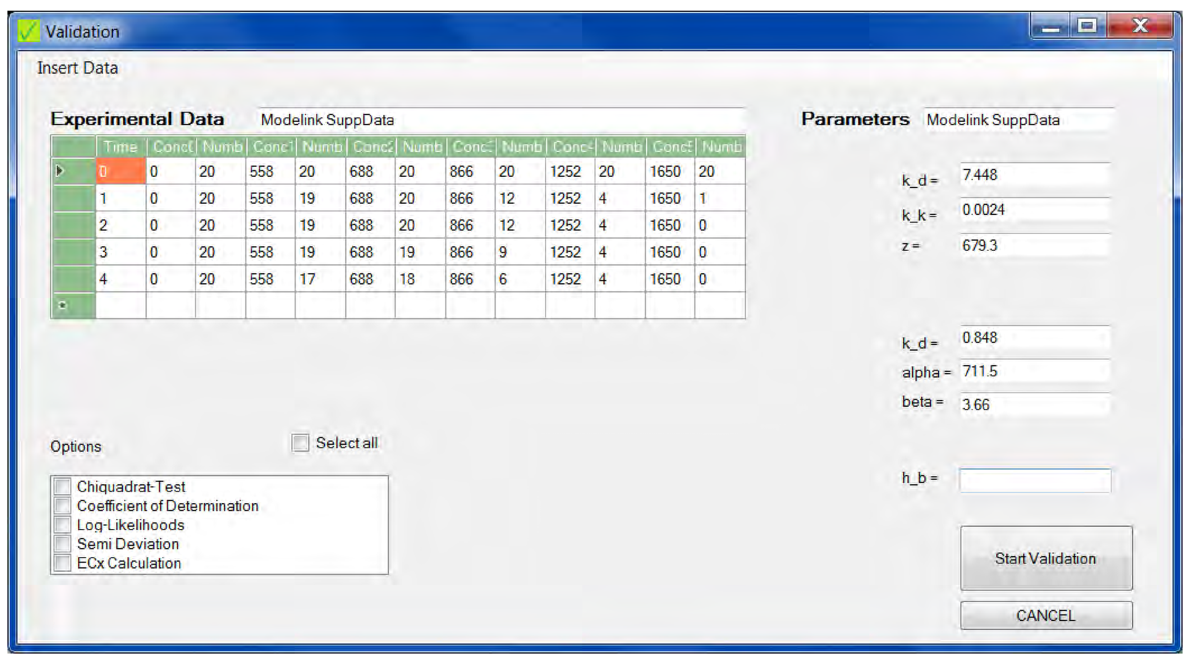
Mathematically: nonlinear nonconvex optimization problem, no guarantee of global optimum

Calibration procedure can be influenced by

- The selection of start values: initials, lowers, uppers, fix values
- Objective function: Maximum Log-Likelihood versus Least Square
- Solver, tolerance of solver, stopping criteria, algorithm etc.
- Method of solving the differential equations

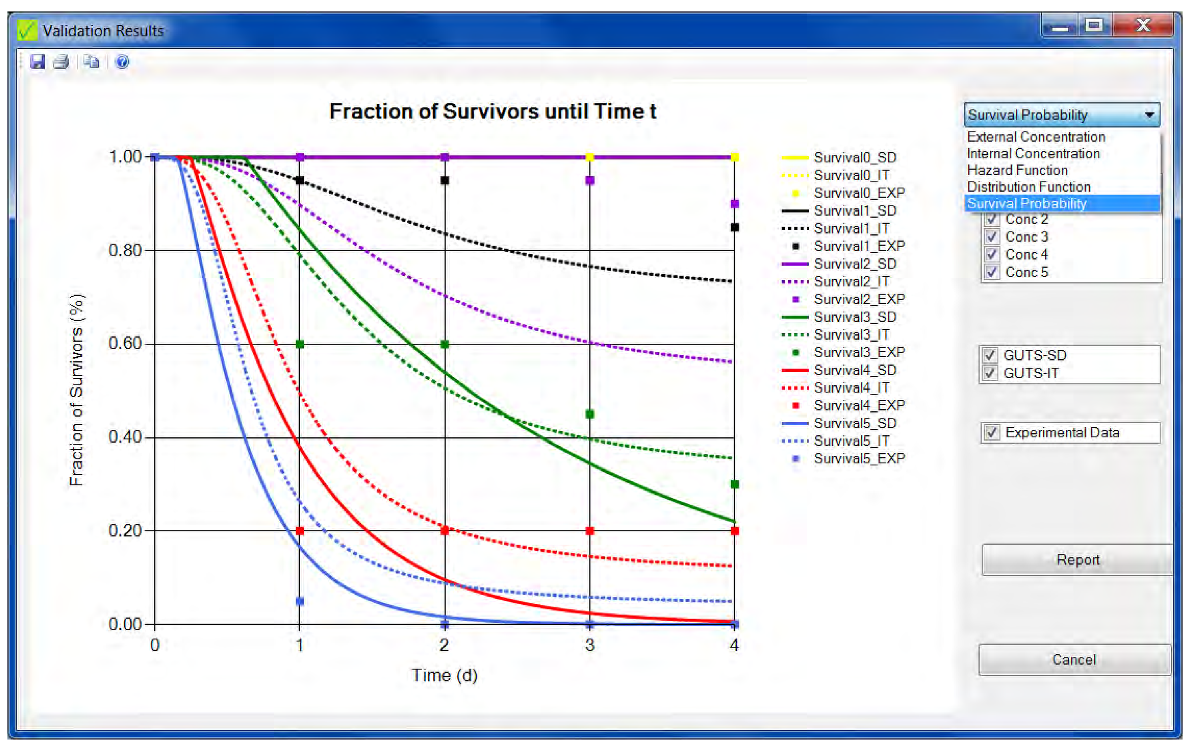
Step 2: Validation

The fitted model should be tested on a data set not used for calibration, e.g. a toxicity test with different exposure profile (e.g. pulsed instead constant exposure).



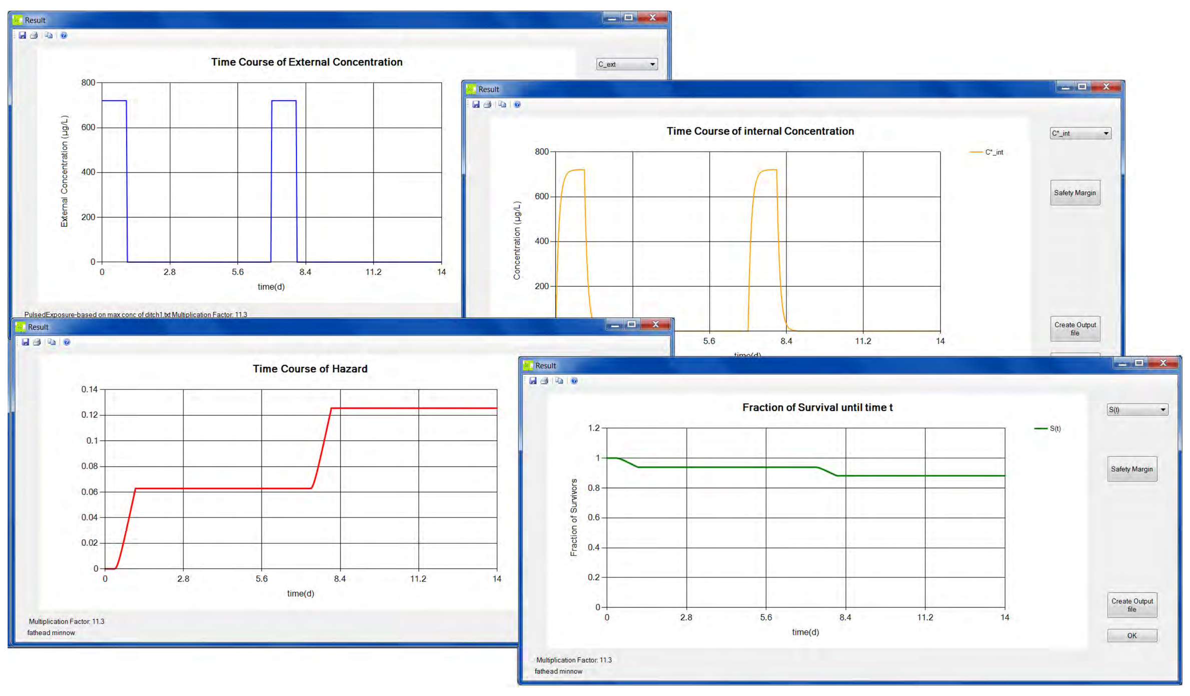
Quality of the correspondence of data and predictions are provided by

- χ^2-Test $\chi^2 = \sum_{i=1}^{n} \frac{(C_i - O_i)^2}{(\frac{\epsilon}{100}\cdot \bar{O})}$
- Model Error
  $\epsilon = 100 \cdot \frac{1}{\bar{O}} \cdot \sqrt{\frac{1}{\chi^2_{tab}} \cdot \sum_{i=1}^{n} (C_i - O_i)}$
- Coefficient of Determination
  $$r^2 = \left(\frac{\sum_{i=1}^{n} (O_i - \bar{O})(C_i - \bar{C})}{\sqrt{\sum_{i=1}^{n} (O_i - \bar{O})^2 \cdot \sum_{i=1}^{n} (C_i - \bar{C})^2}} \right)^2$$
- Model Efficiency
  $$EF = 1 - \frac{\sum_{i=1}^{n} (C_i - O_i)^2}{\sum_{i=1}^{n} (O_i - \bar{O})^2}$$
- Scaled Root Mean Squared Error
  $$SRMSE = \frac{1}{\bar{O}} \sqrt{\frac{1}{n} \sum_{i=1}^{n} (C_i - O_i)^2}$$
- Scaled Total Error $STE = \frac{\sum_{i=1}^{n} |C_i - O_i|}{\sum_{i=1}^{n} O_i}$

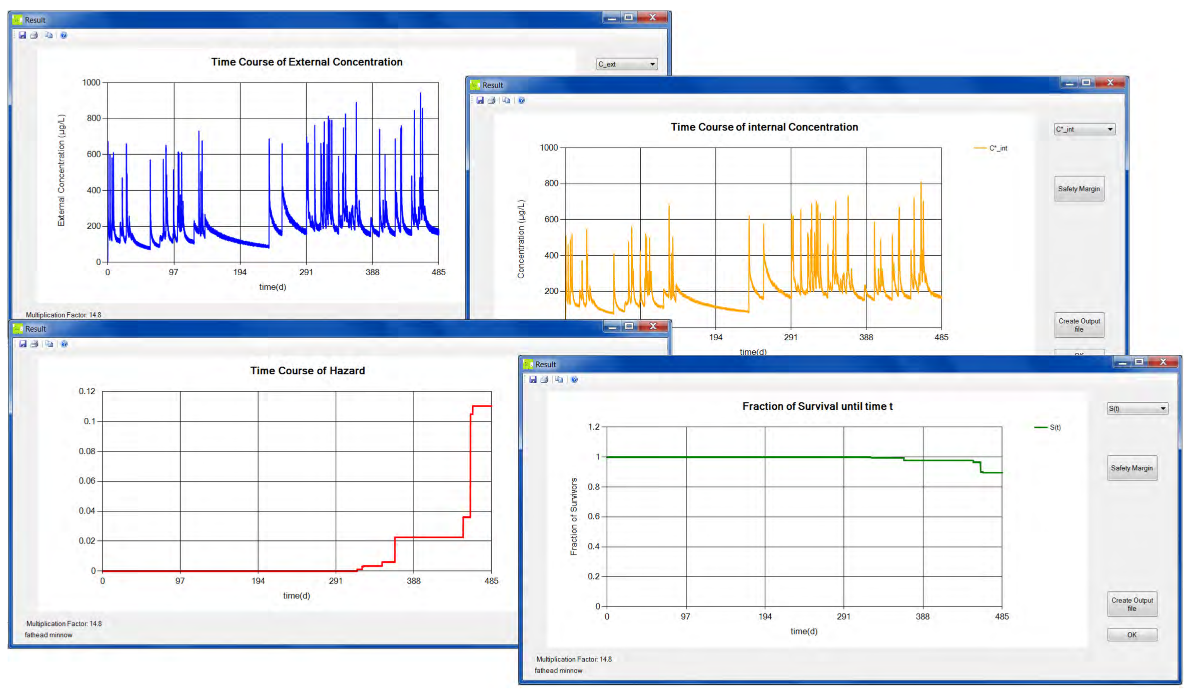


Step 3: Prediction

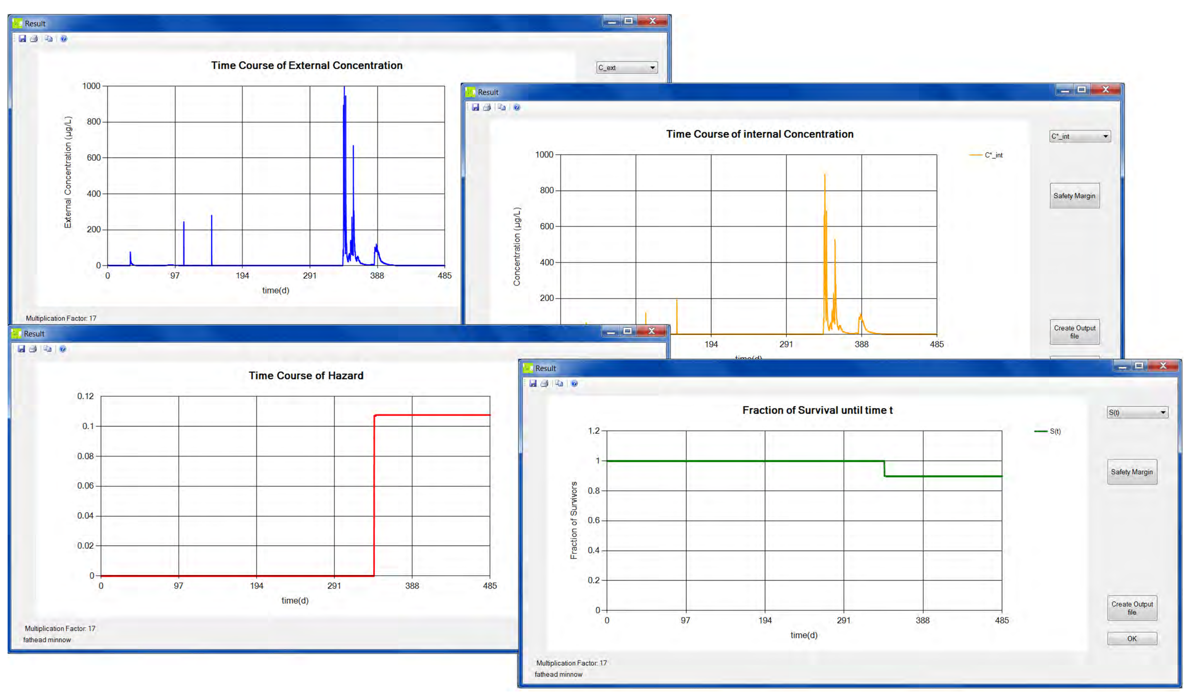
Simple or complex exposure pattern e.g. FOCUS scenarios can serve as input to predict internal concentration, hazard and survival over time. Example 1: Pulsed Exposure (14 d) $C_{max} = 64$, Safety Margin 11.3 :



Example 2: FOCUS model prediction for exposure in a ditch (485 d) $C_{max} = 64$, Safety Margin 14.8:



Example 3: FOCUS model prediction for exposure in a stream (485 d) $C_{max} = 59$, Safety Margin 17:



Summary

GUTS was implemented in a program including different calibration and validation options as well as options to use the outputs of commonly used exposure models (e.g., FOCUS step 3 and 4) to predict the effects of time variable exposure on survival of organisms (tier 3: [EFSA PPR Panel, 2013]). The GUTS model implementation was verified by means of example data for fish published by [Ashauer et al., 2010] and [Ducrot et al., 2015].

Outlook

It is planned to expand the model to be able to consider variation within and between ecotoxicological tests. It is also intended to integrate the option to use the model to support designing of experiments (identifying a realistic worst case exposure pattern for testing or a pattern which is best to reduce model uncertainty). The program will be made freely available after testing and finalization of the documentation according to the Good Modelling Practice Opinion [EFSA PPR Panel, 2014].