OpenGUTS: user-friendly software for survival modelling

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About GUTS

The General Unified Threshold model for Survival (GUTS) is a framework for toxicokinetic-toxicodynamic (TKTD) modelling for the endpoint survival (Jager *et al.*, 2011, Jager & Ashauer, 2018). In 2018, the EFSA opinion on TKTD modelling concluded that GUTS is "ready to be used" in risk assessment of pesticides (EFSA, 2018), paving the way for routine application.

The software project

GUTS models are parameterised by fitting to toxicity data, which is not a trivial task. Routine application in risk assessment thus requires robust, automated, user-friendly software. In a project, funded by Cefic-LRI, we developed such a software in the form of a standalone Windows executable and a Matlab-based version. The software was launched in December 2019 on http://openguts.info/.

Models included

The software contains the reduced GUTS models for stochastic death (SD) and individual tolerance (IT), and is thus able to work with standard toxicity data (lacking information on body residues). The modelling concept is shown in Fig. 1.

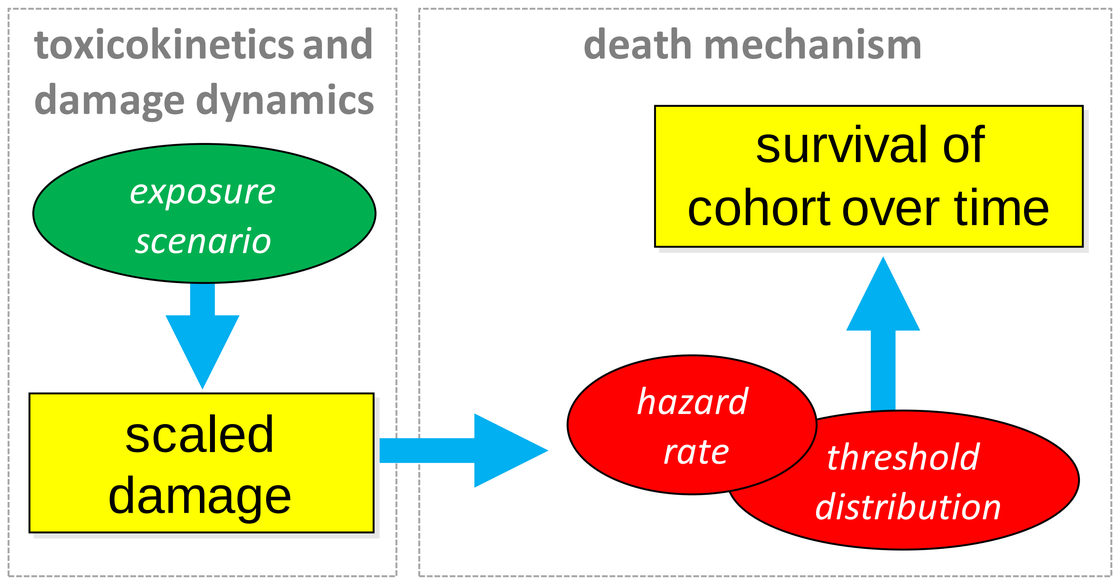

Fig. 1. Schematic representation of the reduced GUTS models. Toxicokinetics and damage kinetics are combined. The death mechanism either relies on a hazard rate (stochastic death) or on a distribution of thresholds (individual tolerance)

Workflow

The software is designed to follow the workflow as laid down in the EFSA opinion, shown in Fig. 2. In the prediction step, a safety margin or LP*x* can be calculated: the factor by which an exposure profile (e.g., output from FOCUS) needs to be multiplied to yield *x*% effect at the end of the profile.

Features

Open: the software is open source and freely downloadable, both as standalone executable and as more flexible Matlab version.
User-friendly: fit models and derive confidence intervals without requiring user interaction (fully automated).
Robust: find optima and intervals, even for awkward data sets.
Flexible: allow time-varying exposure, missing data, simultaneous fitting on multiple data sets, etc.
Efficient: rapid screening of exposure profiles (e.g., FOCUS output) by batch processing.

Statistical framework

The software applies likelihood-based (frequentist) inference, which can be automated in a robust manner. Optimisation and construction of confidence intervals relies on mapping of parameter space. A combination of grid search, a genetic algorithm, and likelihood profiling ensures a robust sample from parameter space (Fig. 2, top graph), without worrying about starting values or local optima. This sample forms the basis for confidence intervals on model parameters and model predictions.

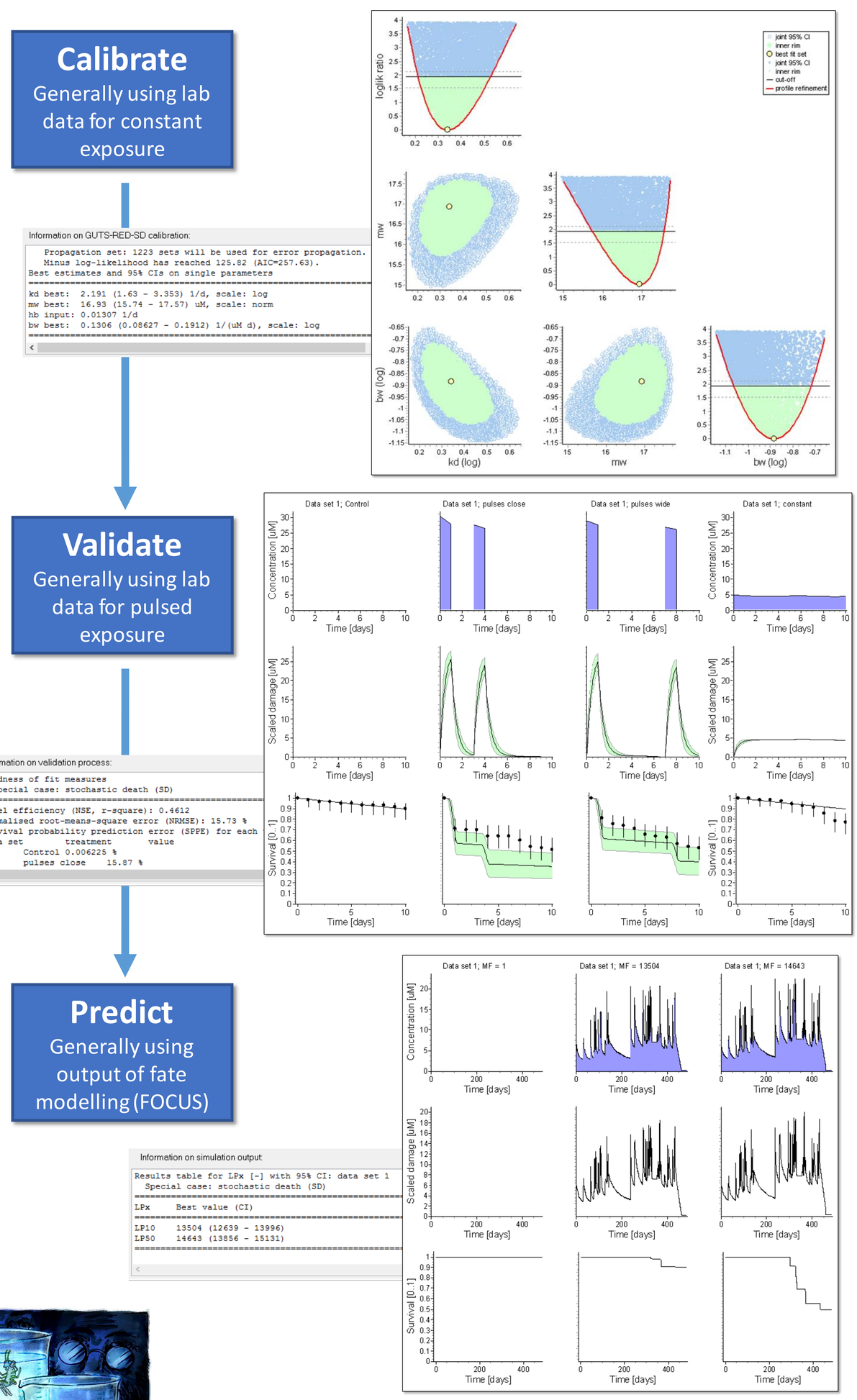

Fig. 2. Workflow for TKTD analysis following the EFSA opinion, shown with output from the openGUTS software. Data for propiconazole in Gammarus pulex.

References

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More info

http://openguts.info/

Acknowledgements

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