Ready-to-use modelling and statistical tools for advanced environmental risk assessment

Sandrine CHARLES, Virgile BAUDROT, Benoît GOUSSEN,

Aurélie SIBERCHICOT, Guillaume GENCE and Philippe VEBER

Toxicity tests carried out within laboratories, according to standardized protocols

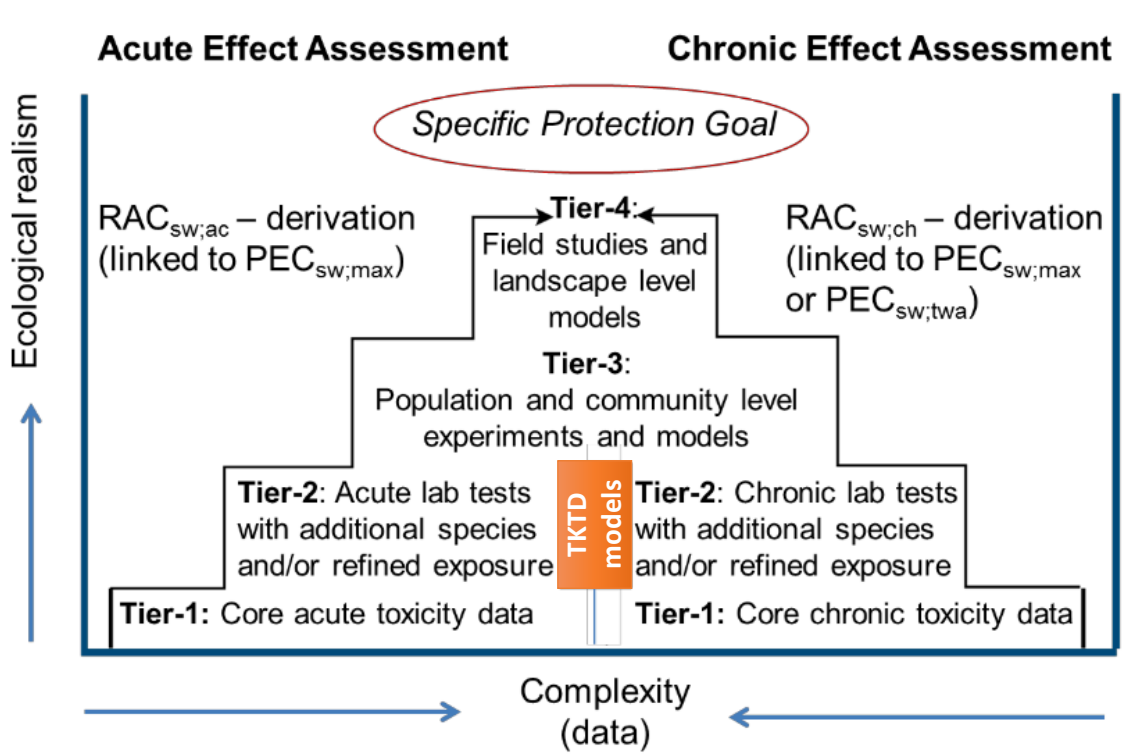
Appropriate and reliable mathematical models and statistical inference methods

Exposure-response/effect models → Classical outputs such as LCx/ECx estimates

Toxicokinetic-toxicodynamic (TKTD) models → advanced analyses accounting for the **time-dependency** of the data.

Environmental Risk Assessment (ERA)

2013 – Aquatic Guidance Document



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European Food Safety Authority

2018

SCIENTIFIC OPINION

EFSA Journal

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Scientific Opinion on the state of the art of Toxicokinetic/Toxicodynamic (TKTD) effect models for regulatory risk assessment of pesticides for aquatic organisms

EFSA Panel on Plant Protection Products and their Residues (PPR), Colin Ockleford, Paulien Adriaanse, Philippe Berny, Theodorus Brock, Sabine Duquesne, Sandro Grilli, Antonio F Hernandez-Jerez, Susanne Hougaard Bennekou, Michael Klein, Thomas Kuhl, Ryszard Laskowski, Kyriaki Machera, Olavi Pelkonen, Silvia Pieper, Robert H Smith, Michael Stemmer, Ingvar Sundh, Aaldrik Tiktak, Christopher J. Topping, Gerrit Wolterink, Nina Cedergreen, Sandrine Charles, Andreas Focks, Melissa Reed, Maria Arena, Alessio Ippolito, Harry Byers and Ivana Teodorovic

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Main conclusions

- **GUTS models** (General Unified Threshold models of Survival) for lethal effects of pesticides on animals are well established and can be used in the ERA scheme when exposure varies over time.
- **DEBtox models** (Dynamic Energy Budget for ecotoxicity) for sublethal effects of pesticides on growth and reproduction are considered to be in an advanced state but not yet ready-to-use for ERA.
- Among species–specific models accounting for the effects of pesticides on **primary producers**, the *Lemna* model is suitable for use in ERA while some shortcomings prevent to recommend the *Myriophyllum* and algae models as fit-for-purpose.

1 Calibration

Fit a TKTD model on toxicity test data and get parameter estimates associated with their uncertainty

2 Validation

Simulate an effect over time under a time-variable exposure profile and compare with observed data from a refined toxicity test

→ Three validation criteria are recommended by EFSA

3 Prediction

Make simulations under realistic scenarios to assess risk on how far is the exposure profile from causing a pre-defined effect.

Using GUTS models → Concept of the x% Lethal Profile (LPx) = Multiplication Factor leading to an additional x% reduction in the final survival rate.

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workflow for ERA

moRse

an R-package dedicated to ecotoxicology

https://CRAN.R-project.org/package=morse

Ready-to-use tools: GUTS as a case-study

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ONLINE

MOSAIC
modeling and statistical tools for ecotoxicology

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GUTS Shiny App
A web-platform to simulate survival rate under timevariable exposure concentration profiles

http://lbbe-shiny.univ-lyon1.fr/guts-shinyapp/

Ready-to-use tools: GUTS as a case-study

The R-package moRse

Calibration of classical exposure-response/effect models to get LCx/ECx estimates associated with the quantification of their uncertainty through 95% credible intervals within a **Bayesian framework**;

1. **Calibration** of the General Unified Threshold model of Survival (GUTS) to get parameter estimates for both SD or IT reduced versions, as for example the No Effect Concentration (NEC) or the dominant rate constant (k_d);
2. **Validation** of GUTS model outputs by comparison with observed data, based on results on parameter estimates from a GUTS model calibration;
3. **Prediction** of lethal effects under realistic time-variable exposure concentration scenarios to get x% Lethal Profiles (LPx) estimates, that is the multiplication factor applied to the profile that leads to x% of reduction in the final survival rate.

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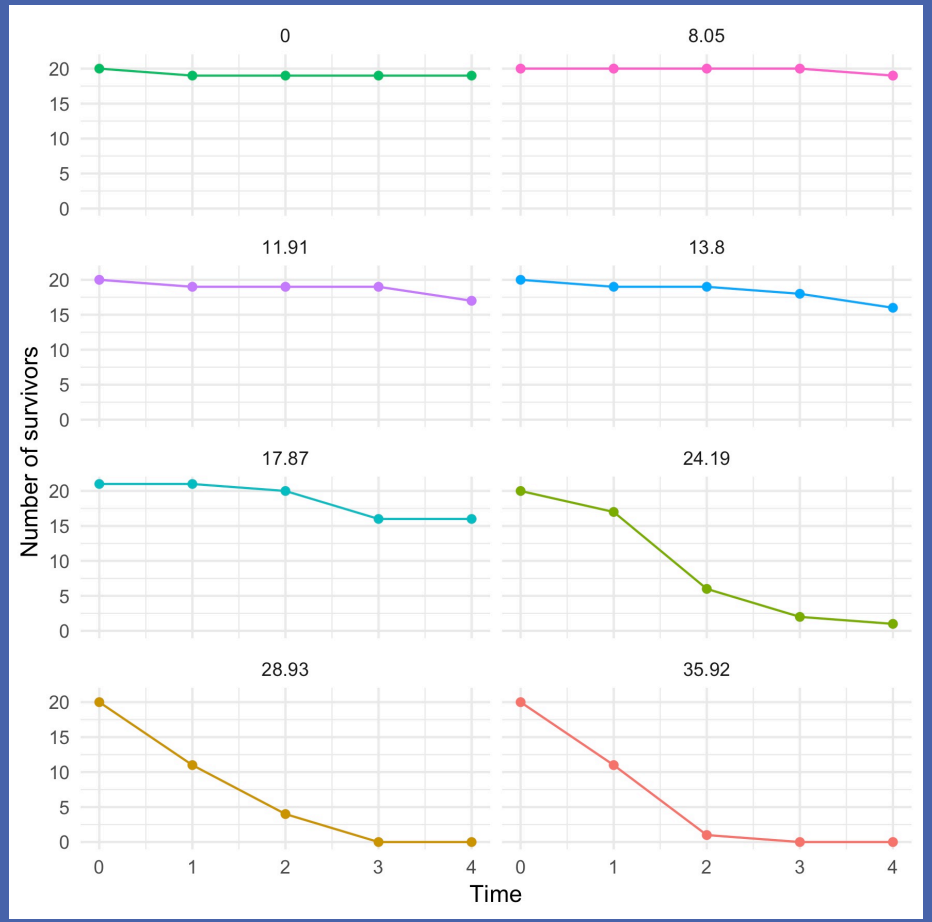
```
# (1) Load the 'morse' package in your R session
library('morse')
```

GUTS analyses – 1 Calibration

```
# (2) Load an example (survival data set)
data("propiconazole")
# (3) Create a surv morse object
sdat <- survData(cadmium2)
# (4) Plot raw data (survival)
plot(sdat)
```



Nyman, A.-M., Schirmer, K., Ashauer, R., (2012) Toxicokinetic-toxicodynamic modelling of survival of *Gammarus pulex* in multiple pulse exposures to propiconazole: model assumptions, calibration data requirements and predictive power. *Ecotoxicology*, (21), 1828-1840.

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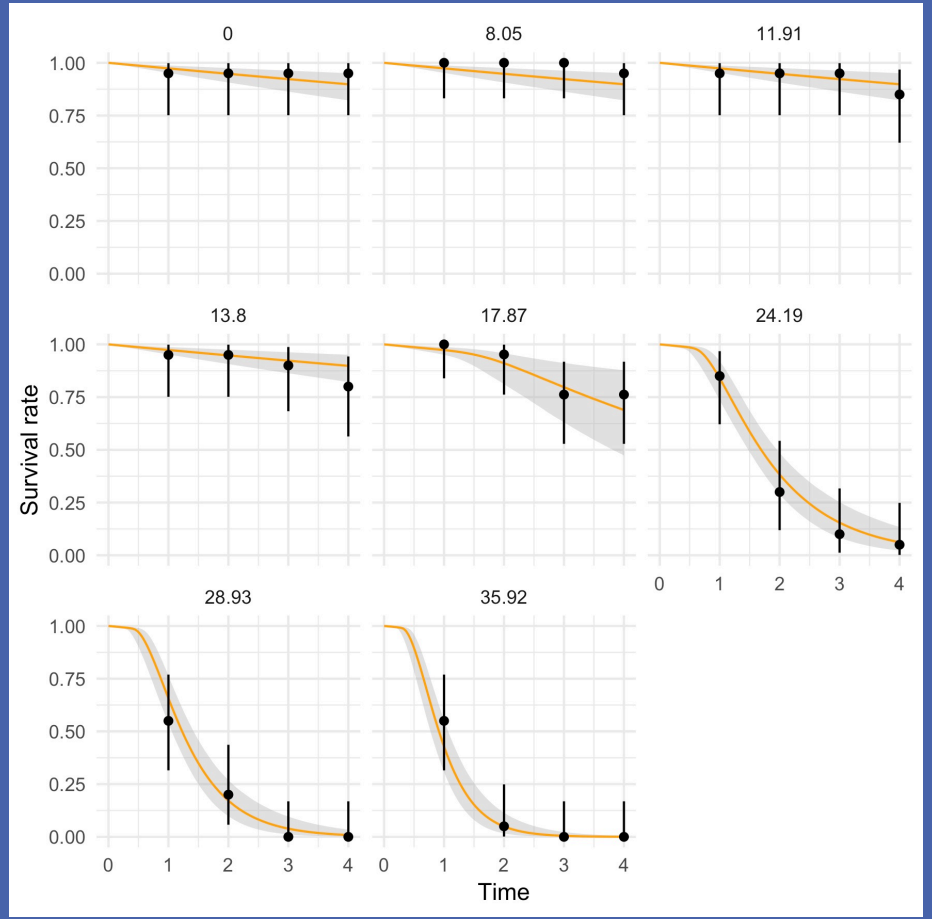
# (4) Plot raw data (survival)
plot(sdat)
# (5) Fit a GUTS-RED-SD model
sfit <- survFit(sdat, model_type = 'SD')
# (6) Get model parameter estimates
summary(sfit)
# (7) Plot fit
plot(sfit, xlab = "Time", adddata = TRUE)
```



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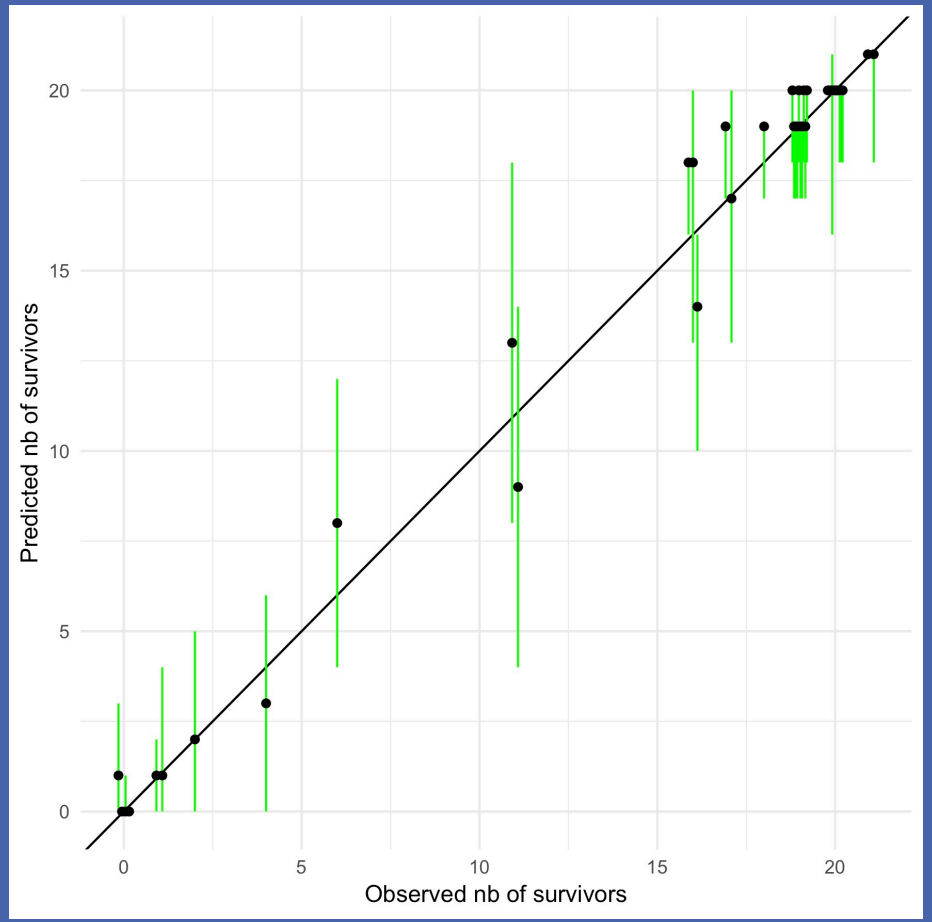
# (7) Plot fit
plot(sfit, xlab = "Time", adddata = TRUE)
# (8) Check goodness-of-fit
ppc(sfit)
```



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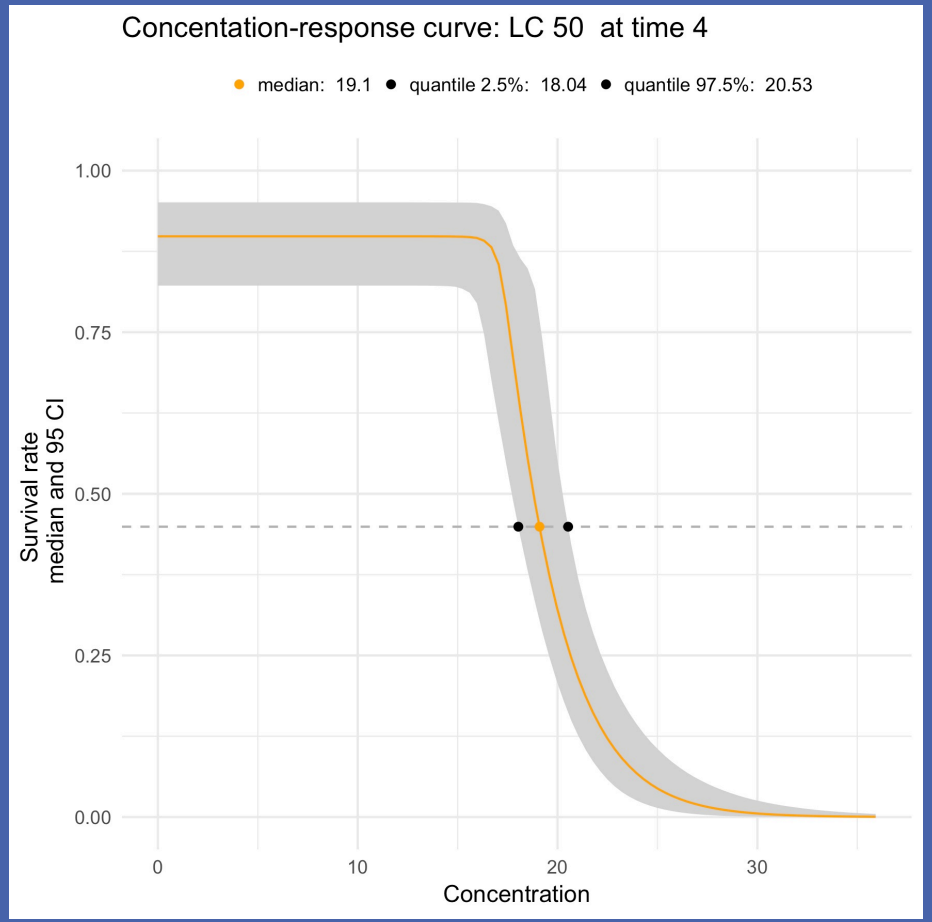
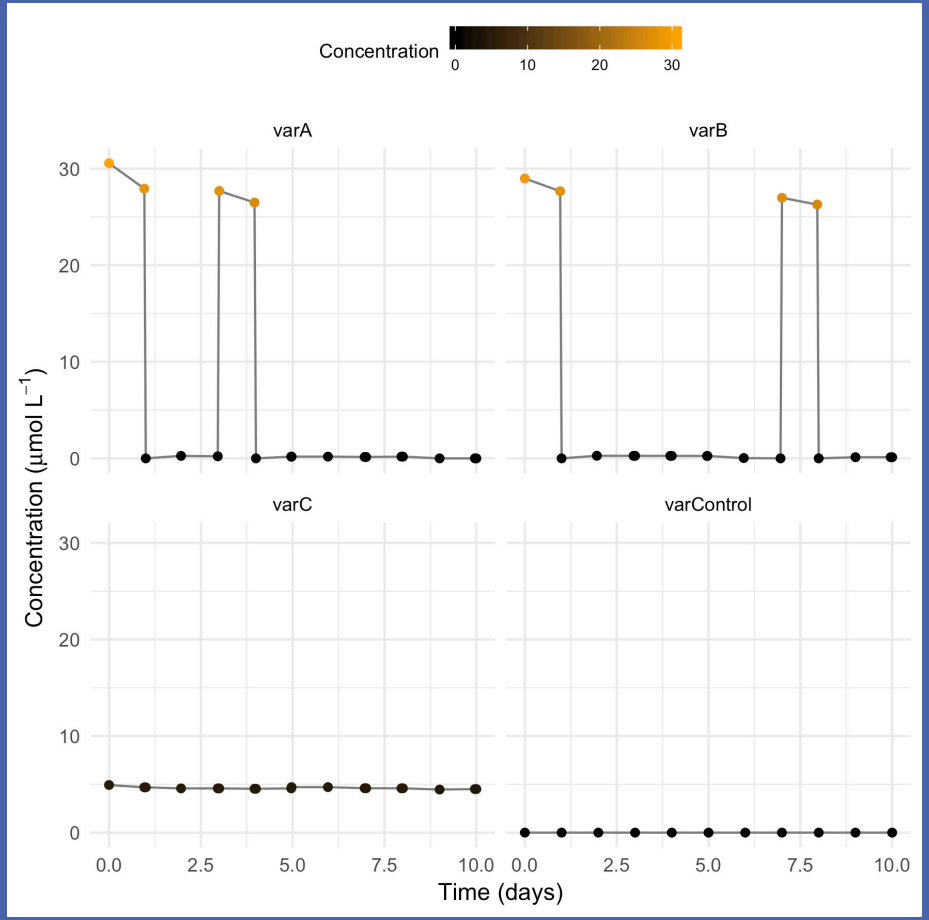
sfit <- survFit(sdat, model_type = 'SD')
# (6) Get model parameter estimates
summary(sfit)
# (7) Plot fit
plot(sfit, xlab = "Time", adddata = TRUE)
# (8) Check goodness-of-fit
ppc(sfit)
# (9) Predict the LC50 at final time
LCx(sfit, X = 50)$df_LCx
plot(LCx(sfit, X = 50))
```



GUTS analyses – 2 Validation

```
# (10) Exposure profile
data("propiconazole_pulse_exposure")
```



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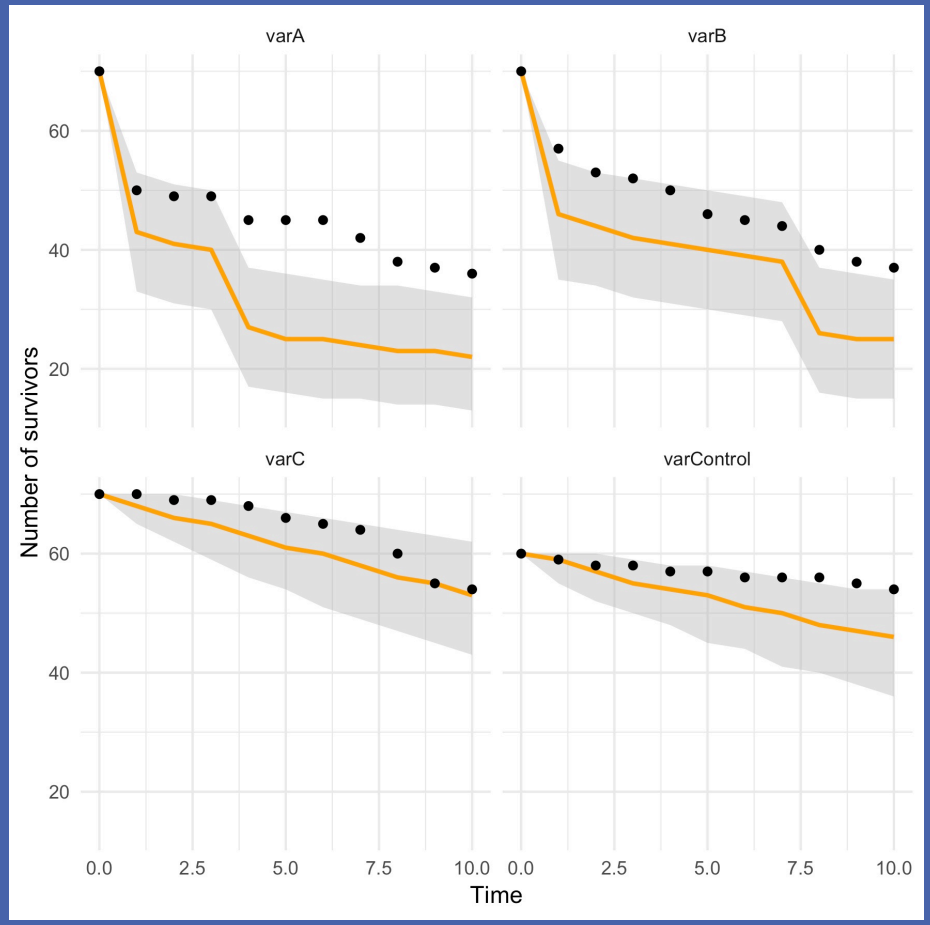
GUTS analyses – 2 Validation

```
# (10) Exposure profile
data("propiconazole_pulse_exposure")
# (11) Predict the number of survivors
predict_Nsurv_cstTOvar <- predict_Nsurv(sfit,
propiconazole_pulse_exposure)
### Note that computing can be quite long
### (until several minutes)
# (12) Plot validation
plot(predict_Nsurv_cstTOvar)
```



GUTS analyses – 2 EFSA validation criteria

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predict_Nsurv_cstTOvar <- predict_Nsurv(sfit,
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### Note that computing can be quite long
### (until several minutes)
# (12) Plot validation
plot(predict_Nsurv_cstTOvar)
# (13) EFSA validation criteria
predict_Nsurv_check(predict_Nsurv_cstTOvar)
```

```
$Percent_PPC
     replicate        PPC
1         varA   36.36364
2         varB   63.63636
3         varC  100.00000
4   varControl   81.81818

$Percent_PPC_global
[1] 70.45455
```

Percentage of observations within the predicted uncertainty limits.

Based on experience, results less than 50% of the observations within the uncertainty limits indicate poor model performance.

GUTS analyses – 2 EFSA validation criteria

```
# (10) Exposure profile
data("propiconazole_pulse_exposure")
# (11) Predict the number of survivors
predict_Nsurv_cstTOvar <- predict_Nsurv(sfit,
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### Note that computing can be quite long
### (until several minutes)
# (12) Plot validation
plot(predict_Nsurv_cstTOvar)
# (13) EFSA validation criteria
predict_Nsurv_check(predict_Nsurv_cstTOvar)
```

```
$Percent_NRMSE
     replicate      NRMSE
1         varA  31.153292
2         varB  19.959361
3         varC   5.853125
4   varControl   9.130619

$Percent_NRMSE_global
[1] 17.08304
```

Normalized Root Mean Square Error expressed in %.

Based on experience, it is expected that the NRMSE should not exceed the upper limit of 50%.

GUTS analyses – 2 EFSA validation criteria

```
# (10) Exposure profile
data("propiconazole_pulse_exposure")
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predict_Nsurv_cstTOvar <- predict_Nsurv(sfit,
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### (until several minutes)
# (12) Plot validation
plot(predict_Nsurv_cstTOvar)
# (13) EFSA validation criteria
predict_Nsurv_check(predict_Nsurv_cstTOvar)
```

```
$Percent_SPPE
     replicate      NRMSE
1         varA  20.000000
2         varB  17.142857
3         varC   1.428571
4   varControl  13.333333
```

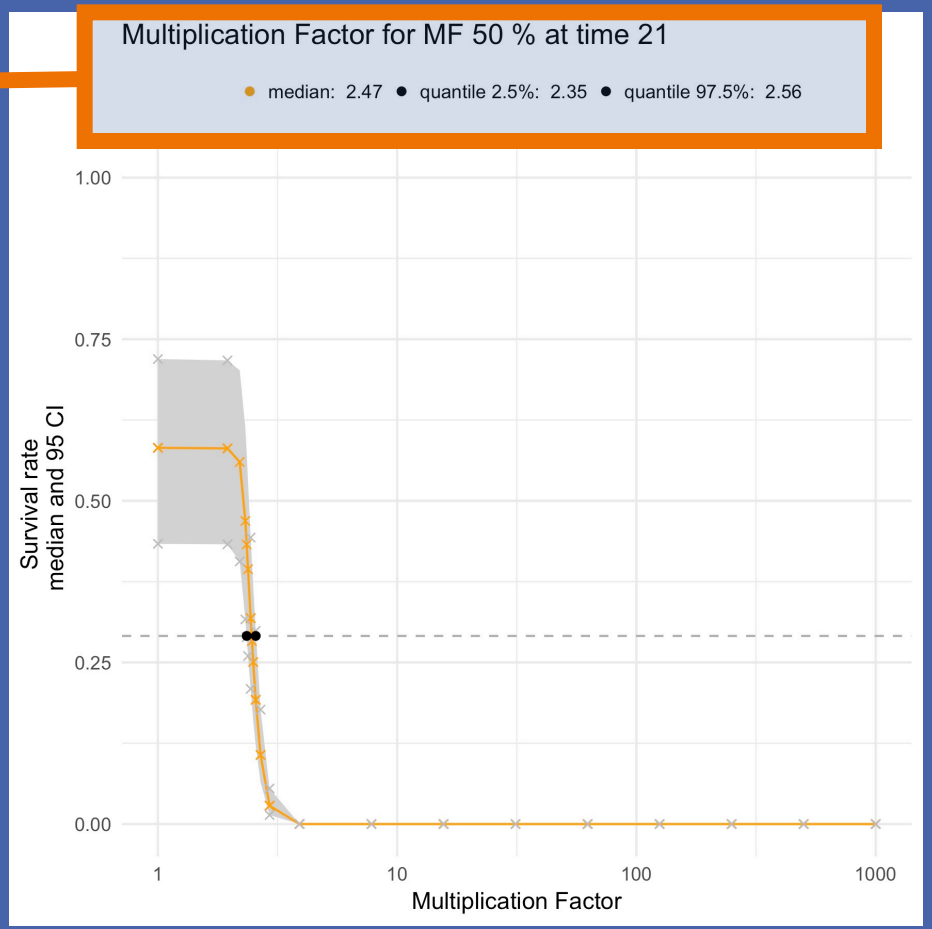
Survival Probability Prediction Error standing for model accuracy considering survival probabilities **at the end** of the exposure profile.

The SPPE value is negative for an underestimation of effects, else it is positive.

GUTS analyses – 3 Predictions

```
# (14) Import the exposure scenario
# (15) Estimate the MF50 at final time
MF50 <- MFx(object = sfit, data_predict
= scenario, quiet = TRUE)
MF50$df_MFx
plot(MF50, log_scale = TRUE)
```

LP_{50} = 2.47 [2.35 ; 2.56]



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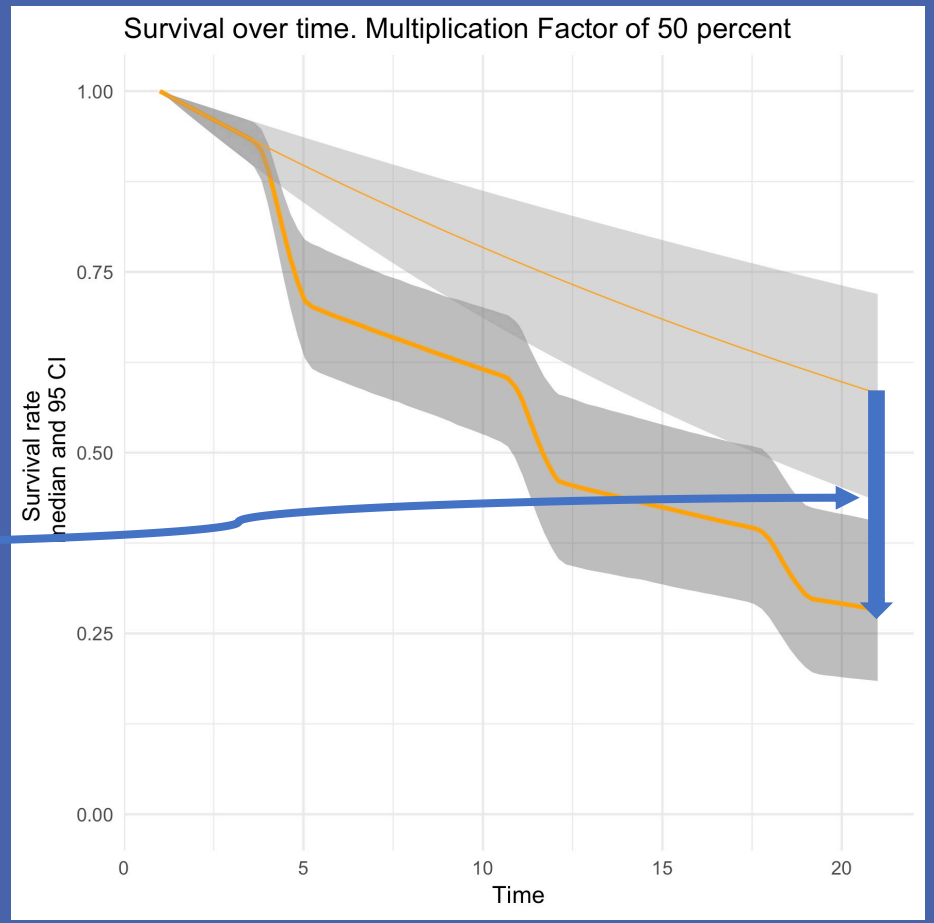
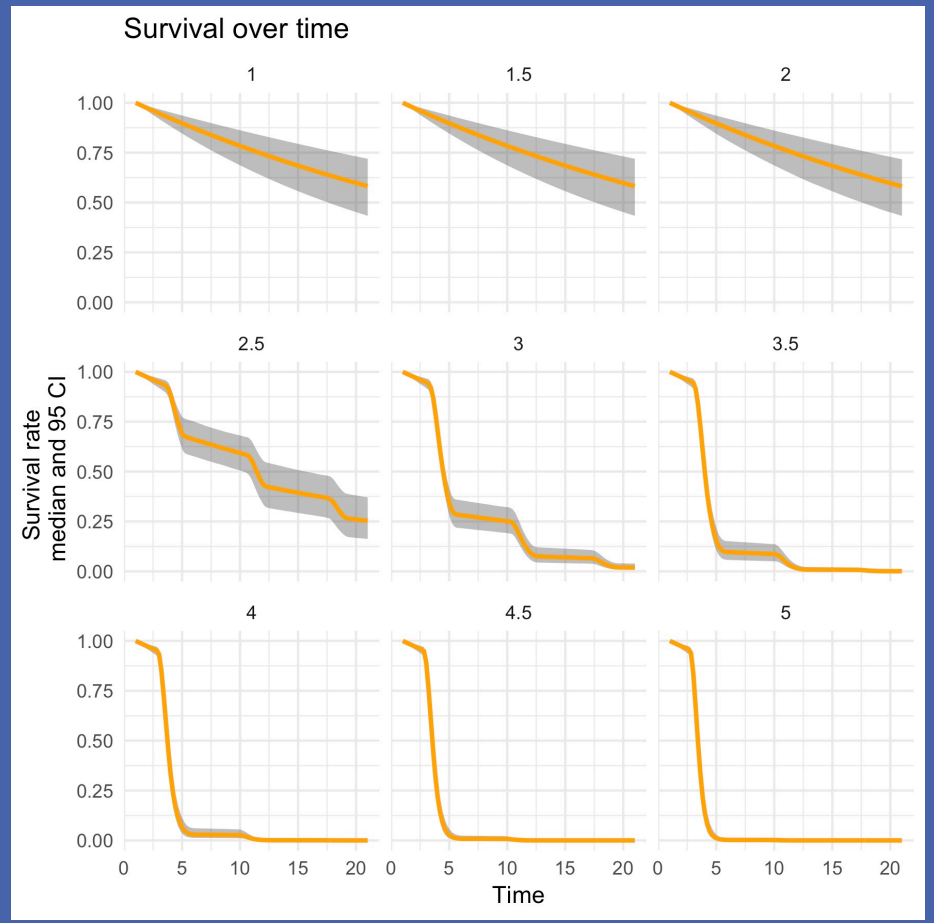
plot(MF50, log_scale = TRUE)
plot(MF50, x_variable = "Time")
```

LP_{50} = 2.47 [2.35 ; 2.56]



GUTS analyses – 3 Predictions

```
# (14) Import the exposure scenario
# (15) Estimate the MF50 at final time
MF50 <- MFx(object = sfit, data_predict
= scenario, quiet = TRUE)
MF50$df_MFx
plot(MF50, log_scale = TRUE)
plot(MF50, x_variable = "Time")
# (16) Plot the MF-response curve
MF <- MFx(object = sfit, data_predict =
scenario, X = NULL, MFx_range =
seq(1,5,0.5))
plot(MF)
# (17) Plot the survival rate over time
for various MF
MF <- MFx(object = sfit, data_predict =
scenario, X = NULL, MFx_range =
seq(1,3.5,0.5))
plot(MF, x_variable = "Time")
```



All the previous analyses can be done directly on-line

http://pbil.univ-lyon1.fr/software/mosaic/

Video-01

Few seconds/minutes later…

EFSA workflow: calibration (step 1)

Video-02

EFSA workflow steps 2 and 3

http://lbbe-shiny.univ-lyon1.fr/guts-shinyapp/

Video-03

MOSAIC

modelling and statistical tools for ecot

Contact: mosaic@univ-lyon1.fr

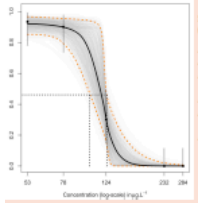
OSAIC is a turnkey decision-making tool for otoxicologists, regulators and industrials. Without wasting e on extensive mathematical and statistical technicalities, rs are given advanced and innovative methods for a luable quantitative environmental risk assessment (ERA).

Complete analysis of bioassay **survival** data, including descriptive summaries of the data and estimates of x% **lethal concentrations** (LCx) under a **Bayesian framework**.

Input: data from standard bioassays where survival has been recorded through time at different concentrations. Data from different replicates of a same experimental condition are pooled.

Model: a three parameters log-logistic model (concentration-exposure part) associated with a binomial stochastic part (binary data).

Output: LC_x values (x = 5, 10, 20, ..., 80%) expressed as median estimates associated with their 95% credible intervals.



Survival rate as a function of concentration (log-scale)

- **Black curve**: predicted survival rate with median parameter values;
- **Dotted orange curves**: 95% credible band;
- **Dots and segments**: observed data with their corresponding binomial confidence intervals;
- **Dotted segments**: 95% credible interval on LC_{50}.

LC_{50} = 117.7 mg.L^{-1} [103.8 ; 124.9]

Complete analysis of bioassay **reproduction** data, including descriptive summaries of the data and estimates of x% **effective concentrations** (ECx) under a **Bayesian framework**.

Input: data from standard bioassays with survival and repr simultaneously recorded through time at different conce Survival leads to the effective life where individuals have rep and reproduction rate writes **per individual-days**.

Model: a three parameters log-logistic model (concentration- part) associated with a negative binomial stochastic part (co between-replicate variability).

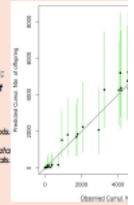
Output: EC_x values (x = 5, 10, 20, ..., 80%) expressed as estimates associated with their 95% credible intervals.

Posterior Predictive Check (PPC): observations vs estimated predictions

- **Black dots**: observed reproduction at a given concentration (x-scale) and the corresponding predicted values (y-scale);
- **Green segments**: 95% credible intervals of each predicted value;
- **Bisecting line**: y = x.

Replicates are slightly shifted on the x-axis.

We expect having 95% of the data within the intervals.



EC_{50} = 112.9 mg.L^{-1} [9

MOSAIC is free and user-friendly

MOSAIC ensures the privacy of the data, the reproducibility of the results and the use of open methods

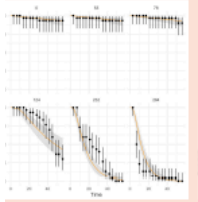
CALIBRATION

Time-dependent analysis of bioassay **survival** data based on the **General Unified Threshold model of Survival** (GUTS) under a **Bayesian framework**.

Input: data from standard bioassays where survival has been recorded through time at different concentrations. Data from different replicates of a same experimental condition are pooled.

Models: either the GUTS Stochastic Death model (GUTS-RED-SD) or the GUTS Individual Tolerance model (GUTS-RED-IT) can be chosen, associated with a binomial stochastic part (binary data).

Output: LC_x values (x = 5, 10, 20, ..., 80%) given by default at final time, expressed as median estimates associated with their 95% credible intervals.



Survival rate as a function of time for the different tested concentrations

- **Orange curves**: predicted survival rate over time with median parameter values for the different tested concentrations;
- **Grey zones**: 95% credible bands;
- **Black dots and segments**: observed data with their corresponding binomial confidence intervals.

LC_x curve at final time

Species Sensitivity Distribution fitted to **hazardous concentration for p% (HC_p)** of t Parameters of the probability distribution are from toxicity thresholds under a **frequentist fr**

Key issue: HC_p values are estimated **even when toxicity thres censored.**

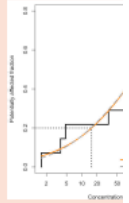
Input: toxicity threshold values of a given toxic compound LC_x or EC_x) estimated for a battery of species.

Models: log-logistic or log-normal probability distributions (use

Output: HC_p values (p = 5, 10, 20, 50%) expressed as median associated with their 95% bootstrap intervals.

Potentially affected fraction as a function of the concentration in log-scale

- **Black stepped curve**: data (48h-EC50 values for macroinvertebrates and zooplancton exposed to fluazinam);
- **Grey and orange lines**: fitted distribution laws;
- **Dotted black segments**: HC_{20} point estimate.



HC_{20} = 15.5 mg.L^{-1} [3.80 ; 83.0]

LIDATION & PREDICTION of GUTS models → Go to the Shiny App: http://lbbe-shiny.univ-lyon1.fr/guts-shinyapp/

ancial support

Institutions

Try MOSAIC **Use our toy examples**

Contact — http://pbil.univ-lyon1.fr/software/mosaic/

— mosaic@univ-lyon1.fr

GUTS Shiny App

A web-platform to simulate survival rate under timevariable exposure concentration profiles

http://lbbe-shiny.univ-lyon1.fr/guts-shinyapp/

Aurélie SIBERCHICOT*, Virgile BAUDROT** and Sandrine CHARLES*

* Université Lyon 1, UMR CNRS 5558, Laboratoire de Biométrie et Biologie Évolutive, 69100 Villeurbanne, France, ** BioSP, INRA, 84914 Avignon, France

The GUTS Shiny App allows interactive simulations of the General Unified Threshold model of Survival (GUTS) based on the scaled internal concentration either with a constant or a time-variable exposure concentration profile. The two reduced (RED) versions are implemented: the stochastic death version (GUTS-RED-SD) and the individual tolerance ve sion (GUTSRED-IT) [1, 2]. All calculations can be run directly within the R software by using the package morse: https://CRAN.R-project.org/package=morse.

ut your concentration profile

upload a two-column file in text format. Default is comma-separated but other separators can be chosen. Columns with headers must be the ings:

me points at which you measured concentrations (header = "time");

measured concentrations (header = "conc").

e of constant exposure, the second column must be filled-in with the alue whatever the time point.

a txt or csv file

erator

Comma

Semicolon

Tab

Here are six example files to test the GUTS-Shiny App:

conc-cst.csv

conc-sin1.csv

conc-sin2.csv

FOCUS-SW.csv

conc-highbeta-sin1.txt

conc-highbeta-sin2.txt

Model and parameters

Choose one model

- GUTS-RED-SD
- GUTS-RED-IT

OR

Choose both models

- GUTS-RED-SD
- GUTS-RED-IT

Distributed parameters:

- yes — Be careful, with distributed parameters, calculation may be long. Be patient!
- no

OR **No distributed parameters** — Short fixed parameters can not be used when both models are selected.

Choose a txt or csv file

Browse... No file chosen

The file that contains the distributed parameters must be with 4 columns named "bb", "hz", "bw" and "bw", with a tab as separator and a dot for decimals.

Such a file may come from a fit with the R package morse or have been saved after running MOSAIC-GUTS.xls [5].

Example file: SD_morse.txt

Parameter values

- k_a value (time[-1]) is the background mortality of the species — 0
- k_e value (time[-1]) is a value for the dominant rate constant — 0.3
- z_w value (conc) is the threshold concentration (NEC) — 12.5
- b_w value (conc[-1].time[-1]) is the killing rate — 0.5
- m_w value (conc) is the median of the threshold distribution — 13.2
- β value (dimensionless) is the shape of this distribution — 2

Choose a phase

alidation

Validate a GUTS model for a given contaminant.

Prediction of the number of survivors over time and comparison with observed data. [4]

a txt or csv file

erator

Comma

Semicolon

Tab

Two example files:

Nsurv-highbeta-SD-sim1.txt

Nsurv-highbeta-SD-sim2.txt

Calculate and Display

Calculations can take a long time, be patient!

validation criteria [3]

range of PPC is: 36.36%

range of NRMSE is: 29.03%

range of SPPE is: 78.57%

% PPC is the percentage of 95% prediction intervals that intersect the 1:1 line in the Posterior Predictive Check (PPC) plot. Based on experience, PPC resulting in less than 50% of the observations within the uncertainty limits indicate poor model performance. See [3] for details.

% NRMSE is the Normalized Root Mean Square Error (NRMSE), expressed as a percentage. Based on experience, it is expected that the NRMSE should not exceed the upper limit of 50%. See formula in [3].

% SPPE is the Survival Probability Prediction Error (SPPE) gives as indication of model accuracy considering survival probabilities only at the end of the exposure profile. The SPPE indicator is negative (between -100% and 0%) for an underestimation of effects, and positive (between 0% and 100%) for an overestimation of effects. An SPPE value of 0% means an exact prediction of the observed survival probability at the end of the experiment. See formula in [3].

Prediction

Predict the survival rate over time, whatever the exposu concentration profile.

Margin of Safety

The concept of "margin-of-safety" corresponds to the concept of "x% Lethal Profile" or LPx as emphasized the recent Scientific Opinion from EFSA [3].

Define:

- a multiplication factor to apply
- a percentage of reduction in the final survival rate

Multiplication factor: 1

Calculate and Displa

Calculations can take a long time, be patient!

Survival at day 10 is 32.91% [31.81 ; 44.97] % with GUTS-RED-SD.

The gray zone corresponds to the propagation of the uncertainties on parameters.

OR

Define:

- a multiplication factor to apply
- a percentage of reduction in the final survival rate

Percentage of reduction: 50

Calculate the quantiles (in addition to the median)

- yes
- no

First quantile: 0.025

Second quantile: 0.975

Calculate and Displa

Calculations can take a long time, be patient!

The multiplication factor for 20% is 1.0829 [1.0613 ; 1.1397] with GUTS-RED-SD (2.5% and 97.5% quantiles are provided). The gray zone corresponds to the propagation of the uncertainties on parameters. Plots are displayed for the median multiplication factor.

Downloads

e a plot

al concentration

Choose a dataset

Survival rate over time

- txt (tab separator)
- csv (comma separator)

Build a report

PDF

[1] Jager T, Albert C, Preuss T, Ashauer R, 2011, General Unified Threshold Model of Survival – a Toxicokinetic-Toxicodynamic Framework for Ecotoxicology, Environ. Sci. Technol., 45:2529–2540.

[2] Ashauer R, Albert C, Augustine S, Cedergreen N, Charles S, Ducrot V, Focks A, Gabsi F, Gergs A, Goussen B, Jager T, Kramer N, Nyman A, Poulsen V, Reichenberger S, Schäfer RB, Van den Brink PJ, Veltman K, Vogel S, Zimmer EI, Preuss TG, 2016, Modelling survival: exposure pattern, species sensitivity and uncertainty, Nat. Sci. Rep., 6:29700.

[3] EFSA PPR Panels, 2018, Scientific Opinion on the state of the art of Toxicokinetics/Toxicodynamic (TKTD) effect models for regulatory assessment of pesticides for aquatic organisms, EFSA Journal, 16: 5377.

[4] Nyman AMK, Schirmer K, Ashauer R, 2012, Toxicokinetic-toxicodynamic modeling of survival of Gammarus pulex in multiple exposures to pro-toxicant: model assumptions, validation and predictive power, Ecotoxicology, 21:1963–1973.

[5] Baudrot V, Veber P, Gence G, Charles S, 2018, Fit GUTS reduced models online: from theory to practice, Integrated Environmental Assessment and Management, 14:623–633.

moRse

an R-package dedicated to ecotoxicology

Virgile BAUDROT*, Benoît GOUSSEN** and Sandrine CHARLES***

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the official Comprehensive R Archive Network, the R-package morse offers functions dedicated to the mathematical modelling and the statistical analysis of ata,

rity of the R-package morse lies in the use of Bayesian inference to estimate associated with a robust quantification of their uncertainty.

ckage morse, it is thus possible to:

te classical dose–response models, and get LCx/ECx estimates associated with ion of their uncertainty through 95% credible intervals;

te advanced TKTD models from survival data available as function of both time tion, namely the General Unified Threshold model of Survival (GUTS), and get r estimates for both reduced SD or IT versions, as for example the No Effect n (NEC) or the dominant rate constant (kd);

GUTS model calibration, follow recent EFSA recommendations [1] to validate outputs by comparison with observed data;

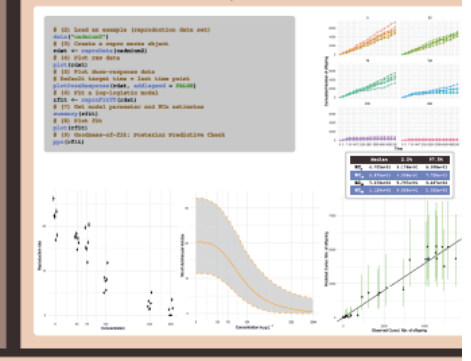
recent EFSA recommendations [1] to predict lethal effects under realistic exposure concentration scenarios and get x% Lethal Profiles (LPx) estimates, multiplication factor applied to the profile that leads to x% of reduction in the at final exposure time.

https://CRAN.R-project.org/package=morse

'morse' package in your R session

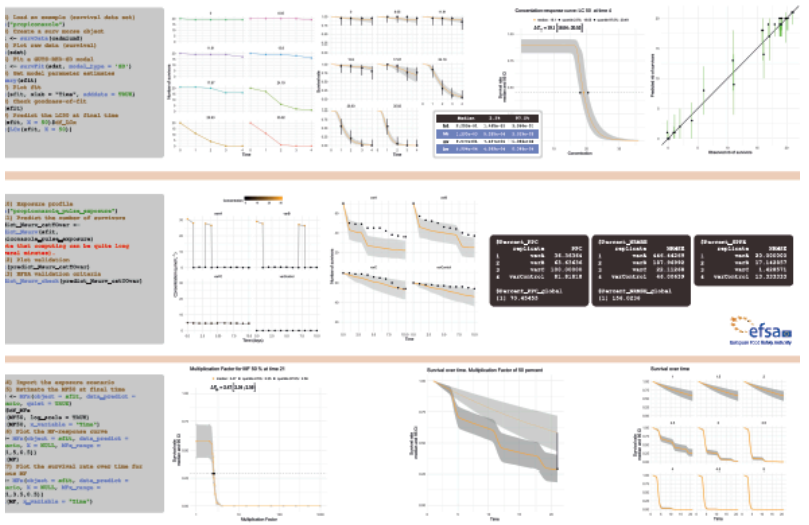
Classical dose-response analyses

Based on standard toxicity test data



vanced TKTD (GUTS) analyses

Based on survival data through time and concentration



Do analyses directly on-line

MOSAIC http://pbil.univ-lyon1.fr/software/mosaic/

GUTS Shiny App http://lbbe-shiny.univ-lyon1.fr/guts-shinyapp/

https://sites.google.com/view/preditox2020

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General information

Reference : UMR5558-SANCHA-002
Workplace : VILLEURBANNE
Date of publication : Friday, March 22, 2019
Type of Contract : FTC Technical / Administrative
Contract Period : 12 months
Expected date of employment : 3 June 2019
Proportion of work : Full time
Remuneration : Between 2423€ and 2612€ of monthly gross pay according to experience
Desired level of education : Higher than 5-year university degree
Experience required : 1 to 4 years

Missions

The main mission lies in revisiting species sensitivity distribution (SSD) methods in the context of environmental risk assessment of pesticides on non-target terrestrial plants (NTTP). In particular, the applicant will have to:
- Select appropriate non-linear models to obtain statistically robust estimates of concentrations for which there is a 50% effect on the species tested (ER50);
- Define an SSD procedure to include censored ER50 estimates (ie defined as intervals and / or unbounded values) allowing to statistically estimate hazardous concentrations for 5% of species (HC5), covering the full range of sensitivities displayed in studied sets of NTTP;
- Apply this SSD procedure to construct an applicable decision tree for risk assessment based on case studies;
- Design a user-friendly user interface, compatible with good laboratory practices (GLP) applicable to computer systems, making it easy to implement the decision tree and the SSD procedure.


Thank you!