Article title

hb or not hb - when and why accounting for background mortality in toxicological survival models matters?

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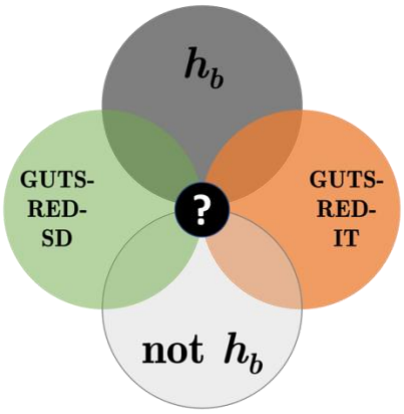
Abstract

Decisions in Environmental Risk Assessment (ERA) about impacts of chemical compounds on different species are based on critical effect indices such as the 50% lethal concentration (LC_{50}). Regulatory documents recommend dose-response model fitting on standard toxicity test data to get LC_{50} values. However, toxicokinetic-toxicodynamic (TKTD) models proved their efficiency to better exploit toxicity test data, at Tier-2 but also at Tier-1, delivering time-independent indices. In particular, LC_{50} values can be obtained from the reduced General Unified Threshold model of Survival (GUTS-RED) with both variants, Stochastic Death and Individual Tolerance, that include parameter h_b, the background mortality. Estimating h_b during the fitting process or not depends on studies and fitting habits, while it may strongly influence the other GUTS-RED parameters, and consequently the LC_{50} estimate. We hypothesized that estimating h_b from all data in all replicates over time should provide more precise LC_{50} estimates. We then explored how estimating h_b impacted: (i) GUTS-RED model parameters; (ii) goodness-of-fit criteria (fitting plot, posterior predictive check, parameter correlation); (iii) LC_{50} accuracy and precision. We finally show that estimating h_b does not impact the LC_{50} precision while providing more accurate and precise GUTS parameter estimates. Hence, estimating h_b would lead to a more protective ERA.

Graphical abstract



Specifications table

Subject area	Environmental Science
More specific subject area	*Toxic effects of chemical substances on survival over time: control data matter in estimating GUTS model parameters simultaneously*
Name of your method	*Fixed or not fixed h_b for GUTS*
Name and reference of original method	Jager et al. (2011), Jager & Ashauer (2018), Baudrot & Charles (2021)
Resource availability	*https://zenodo.org/deposit/7565504*

Method details

Motivation

Environmental Risk Assessment (ERA) aims at investigating the impact of chemical substances that can be potentially toxic, such as pharmaceuticals, plant protection products, metals, etc. This assessment is performed on different species, and it serves to advise regulatory bodies and professionals, for instance those of the food-processing industry. ERA is organized according to 4 tiers which extend from standard laboratory tests, on the one species / one compound principle, to ground tests at the ecosystem scale, including both the time and the space dimensions. Once Tier-1 is completed for the compound of interest on few classical species, several methods can be employed at Tier-2 to refine the effect potency evaluation [1]. Hence, in the perspective of better mimicking the environmental reality, additional toxicity tests can be performed under time-variable exposure profiles, either for the same species than those used at Tier-1, or for additional ones. Benefiting of both toxicity test data at Tier-1 and Tier-2, the environmental risk can be assessed by employing toxicokinetic-toxicodynamic (TKTD) models that allow to account for both the concentration and the time dependencies.

Recently, TKTD models have been recognized advantageous for the risk assessment, especially for aquatic organisms exposed to pesticides [2]. Among available TKTD models, the General Unified Threshold model of Survival (GUTS) was particularly highlighted being considered as ready-to-use with survival test data within a regulatory context. Indeed, the GUTS theoretical framework is well established [3, 4], and turnkey tools are available to implement it. On a general point of view, GUTS allows (i) to translate the exposure concentration over time into an internal dose that may cause damages, and (ii) to translate these damages in terms of visible effects on the individual survival over time. Once calibrated on standard survival test data, and validated on additional survival data collected under time-variable

exposure profiles, GUTS serves to predict lethal concentrations *LC(x,t)* at any target time t and for any chosen x% [5] thus providing refined toxicity indicators in support of decision makers.

In this paper, we focus on the context of regulatory ERA. As stated by EFSA [2], GUTS may be used in its reduced (RED) version, itself comprising two variants: the Stochastic Death (GUTS-RED-SD) variant and the Individual Tolerance (GUTS-RED-IT) variant. Both variants include four parameters, among them the toxicokinetic parameter k_d, called the dominant rate constant; and the background mortality rate h_b, corresponding to the natural mortality that may occur even if the organisms are not exposed to a xenobiotic. Because of a presumed independence from parameters directly related to the potential toxicity of the chemical of interest (i.e., k_d and the two others), the h_b parameter is often fixed from the control data, while the other three GUTS parameters are estimated by fitting the model to all of the collected data. This way of doing has pros and cons which this paper aims at investigating with regards to a simultaneous fitting of GUTS providing estimates of the four parameters.

Independently setting the h_b parameter before the fitting process means that only three of the four GUTS parameters will be estimated. Fixing the h_b parameter may be a biological choice (e.g., any individual died until the end of the experiment under control conditions), or a computing-based choice (e.g., either to facilitate the convergence of the fitting process, or to increase the estimation precision, when data are sparse or when the experiment was not ideally designed). However, setting the h_b parameter implies several implicit assumptions: (i) the h_b parameter is not correlated to the three other GUTS parameters, and (ii) there is no information on the background mortality within the toxicity data. Consequently, setting the h_b parameter amounts to neglect the fact that the experimental design may contain very low tested concentrations for which no effect can be observed, as under control conditions. Also, neglecting the potential correlation of h_b with the three other parameters may impact their respective estimates, and subsequently the *LC(x,t)* estimate.

So, the aim of this paper is to evaluate the impact of estimating or not the h_b parameter, on both the estimates of the three other GUTS parameters, and the subsequent estimation of the LC_{50} at final time. We performed our study with both variants of the reduced GUTS, namely GUTS-RED-SD and GUTS-RED-IT, on a collection of 38 data sets comprising different species-compound combinations. Our results are first discussed from a modelling perspective, to statistically assess the impact of estimating or not estimating h_b; then discussed in the perspective of regulatory ERA, to propose the best compromise between the rapid and daily completion of risk assessments and having sufficient scientific and statistical rigor so that the results on which decisions are based are reliable.

Modelling

Both variants of the reduced GUTS, namely GUTS-RED-SD and GUTS-RED-IT, were systematically used, both under option 1 (h_b simultaneously estimated with the other three parameters) and option 2 (h_b estimated on control data only), as detailed below. The GUTS-RED-SD variant assumes that all individuals are identically sensitive to the chemical substance by sharing a common threshold internal dose, and that mortality is a stochastic process whose intensity is linearly increasing once this threshold is reached. In contrast, the GUTS-RED-IT variant is based on the critical body residue approach, which assumes that individuals differ in their thresholds following a given probability distribution and that they die as soon as the internal dose reaches the individual-specific threshold [5].

Option 1 (denoted O1) stands for the fitting of the two GUTS-RED variants in their complete form, both involving four parameters, among which k_d and h_b as described earlier. In addition, variant GUTS-RED-SD has parameters z_w (the internal threshold from which effects may appear) and b_w (the "killing rate", that is a parameter related to the intensity of the effect) to describe the instantaneous mortality rate as a function of the internal dose via a linear stepwise function:

$$h(t) = b_w max_{0 \leq \tau \leq t}(D_w(\tau) - z, 0) + h_b \qquad (1)$$

where $D_w(\tau)$ stands for the internal dose at time τ. Variant GUTS-RED-IT also has two additional parameters, related to the fact that the individual threshold is usually assumed to follow a log-logistic probability distribution, of median m_w and spread β. This leads to the following cumulative distribution function:

$$F(x) = \frac{1}{1+(x/m_w)^{-\beta}} \qquad (2)$$

with $max_{0<\tau<t}(D_w(\tau)) = x$, the maximal internal dose reached during the exposure period.

Option 2 (denoted O2) stands for the fitting of the two GUTS-RED variants, the h_b parameter being fixed from control data only, according to the following calculation:

$$S(t_{final}) = \frac{Nsurv(t_{final})}{Nsurv(t_{init})} = e^{-h_b \times t_{final}}$$

$$\Leftrightarrow h_b = \frac{1}{t_{final}} ln\left(\frac{Nsurv(t_{init})}{Nsurv(t_{final})}\right) \qquad (3)$$

In equation (3), $Nsurv$ stands for the observed number of survivors either at initial time, $Nsurv(t_{init})$, or at final time, $Nsurv(t_{final})$, of the experiment. In the end, four situations were investigated crossing the two GUTS-RED variants (SD and IT) with the two options (O1 and O2). Hereafter, each situation is always associated with the same color code: dark green for SD-O1; light green for SD-O2; dark orange for IT-O1; light orange for IT-O2. Both GUTS-RED variants were fitted with the R-package “morse” [6] under R version 4.2.1 ("Funny-Looking Kid", 2022-06-23). In particular, function “survFit()” was used, with option “model_type” equal to “SD” (for variant GUTS-RED-SD) or “IT” (for variant GUTS-RED-IT) and option “hb_value” equal TRUE (for option 1) or FALSE (option 2). Under option 2, parameter h_b was always calculated before the fitting process. Finally, function “doseResponse_survFitCstExp” of package “morse” was adapted to get the posterior probability distribution of the LC_{50} estimate for each of the four situations SD-O1, SD-O2, IT-O1 and IT-O2.

Data sets

To ensure reliable results, the above-mentioned procedure was used with a total of 38 data sets (Table 1). Each data set was fitted under each of the four situations SD-O1, SD-O2, IT-O1 and IT-O2, leading to a total of 152 fitting outputs. For each data set, fitting outputs of SD and IT variants were stored in two separated PDF files, each including for both options 1 and 2: (i) fitting plots ; (ii) parameter estimates, expressed with the median, the 95% credible interval and the precision ; (iii) the fixed h_b value (option 2 only) ; (iv) the posterior predictive check (PPC) ; (v) the comparison of prior and posterior marginal probability distributions for each estimated parameter ; (vi) the correlation matrix between estimated parameters ; (vii) the deviance information criteria (DIC) and the calculation of the difference between option 1 and option 2. Note that a negative value of the “Diff_DIC” indicates that the model with parameter h_b simultaneously estimated with the three other parameters will be preferred. Finally, LC_{50} estimates are given for both options 1 and 2, expressed with the median and the 95% credible interval. All these output files were analyzed regarding the different goodness-of-fit criteria: (i) the visual fit, (ii) the PPC, (iii) the prior-posterior comparison, and (iv) the correlations between parameters.

Table 1: *Details on the 38 data sets that were analyzed in this study, namely information about the species and the chemical compound used for toxicity tests for the 38 data sets.*

Code name	**Species**	**Chemical**	**Comments**	Reference
TOX03-SPE19	*Daphnia magna*	Copper		[7]
TOX04-SPE19	*Daphnia magna*	Zinc		[7]
TOX10-SPE19	*Daphnia magna*	Cadmium		[7]
TOX10-SPE15	*Lymnaea stagnalis*	Cadmium		[8, 9]
TOX05-SPE19	*Daphnia magna*	Dichromate potassium		[10]
TOX06-SPE19	*Daphnia magna*	Oxolinic acid		[10]
TOX07-SPE19	*Daphnia magna*	Streptomycine		[10]
TOX08-SPE19	*Daphnia magna*	Sulfadiazine		[10]
TOX12-SPE16	*Pimephales promelas*	*NA*		[11]
TOX01-SPE02_b	*Asellus aquaticus*	Chlorpyrifos		[12]
TOX01-SPE03_b	*Chaoborus crystallinus*	Chlorpyrifos		[12]
TOX01-SPE04_b	*Cloeon dipterum*	Chlorpyrifos		[12]
TOX01-SPE17	*Epeorus assimilis*	Chlorpyrifos		[12]
TOX01-SPE18	*Rhithrogena semicolorata*	Chlorpyrifos		[12]
TOX01-SPE19-11	*Daphnia magna*	Chlorpyrifos	T = 11°C	[12]
TOX01-SPE19-14	*Daphnia magna*	Chlorpyrifos	T = 14°C	[12]
TOX01-SPE19-17	*Daphnia magna*	Chlorpyrifos	T = 17°C	[12]
TOX01-SPE19-20-1	*Daphnia magna*	Chlorpyrifos	T = 20°C, n°1	[12]
TOX01-SPE19-20-2	*Daphnia magna*	Chlorpyrifos	T = 20°C, n°2	[12]
TOX09-SPE19	*Daphnia magna*	Ivermectine		[13]
TOX02-SPE19	*Daphnia magna*	Chlordan		[14]
TOX11-SPE05	*Gammarus pulex*	Propiconazole		[15]
TOX01-SPE01	*Anax imperator*	Chlorpyrifos		[16]
TOX01-SPE02_a	*Asellus aquaticus*	Chlorpyrifos		[16]
TOX01-SPE03_a	*Chaoborus obscuripes*	Chlorpyrifos		[16]
TOX01-SPE04_a	*Cloeon dipterum*	Chlorpyrifos		[16]
TOX01-SPE05	*Gammarus pulex*	Chlorpyrifos		[16]
TOX01-SPE06	*Neocaridinia denticulata*	Chlorpyrifos		[16]
TOX01-SPE07	*Notonecta maculata*	Chlorpyrifos		[16]
TOX01-SPE08	*Parapoynx stratiotata*	Chlorpyrifos		[16]
TOX01-SPE09	*Plea minutissima*	Chlorpyrifos		[16]
TOX01-SPE10	*Procambarus spec. (adults)*	Chlorpyrifos		[16]
TOX01-SPE11	*Procambarus spec. (neonates)*	Chlorpyrifos		[16]
TOX01-SPE12	*Ranatra linearis*	Chlorpyrifos		[16]
TOX01-SPE13	*Sialis lutaria*	Chlorpyrifos		[16]
TOX01-SPE19	*Daphnia magna*	Chlorpyrifos		[16]
A1	Simulated with GUTS-RED-SD, true h_b value = 0.01			[4]
A2	Simulated with GUTS-RED-IT, true h_b value = 0.02			[4]

Outcomes

In general, our results show that option 1 (that is estimating the h_b parameter) provides more precise and accurate estimates of the three other parameters for both SD and IT GUTS-RED variants. Surprisingly, our results show that simultaneously estimating the four parameters of GUTS-RED variants does not provide better LC_{50} estimates. Consequently, in terms of ERA, if only the LC_{50} is of interest, fitting GUTS-RED variants by fixing h_b (option 2) could be sufficient.

Influence of estimating h_b on parameter estimates

As illustrated in Figure 1, for both data sets A1 and A2 (Table 1), the estimated h_b values under option 1 ($h_{b,1}$) are closer to the true h_b value than the calculated h_b value under option 2 ($h_{b,2}$). This results in favor of option 1 is also observed with the other data sets we analyzed (see supplementary information). For all data sets except one, whatever the GUTS-RED variant, values of $h_{b,1}$ and $h_{b,2}$ were different; the exception was obtained with data set TOX01-SPE12 (Table 1, Figure S1), a particular data set with only four time points and a very wide range of tested concentrations that could explain some fitting difficulties whether the h_b parameter is estimated or not. As also illustrated in Figure S1, option 2 tends to underestimate the background mortality, with 56/72 $h_{b,1}$ estimates greater than $h_{b,2}$ values. In addition, for all datasets, $h_{b,1}$ estimates are quite precise, both with SD and IT. Even though it may seem obvious, estimating parameter h_b with the others allow the quantification of its uncertainty in the same way.

Regarding the other parameters, Figure 1 shows that, under option 1, z_w and b_w (data set A1), as well as m_w (data set A2) are closer to the true value than under option 2. Firstly, option 2 overestimates z_w with GUTS-RED-SD (data set A1) and m_w in GUTS-RED-IT (data set A2). This result for z_w is confirmed with the remaining data sets, among which 14/36 data sets show a difference in z_w estimation between option 1 ($z_{w,1}$) and 2 ($z_{w,2}$, Figure S3). Twelve out of these 14 data sets lead to a $z_{w,1}$ value greater than the $z_{w,2}$ value. The two exceptions concern data sets TOX01-SPE17 and TOX01-SPE18 with a long exposure period of 96 days during which 13 time points were distributed in triplets of closely spaced time points. Also, in these two data sets, the range of the tested concentrations is very large with quite widely spaced concentrations which could prevent a precise estimate of z_w whatever the option. Similar results were obtained for m_w with GUTS-RED-IT. Indeed, seven data sets show different m_w estimates between option 1 ($m_{w,1}$) and 2 ($m_{w,2}$, Figure S5). Six out of these seven data sets show a $m_{w,1}$ greater than the $m_{w,2}$ value, the only exception being obtained with data set TOX01-SPE17 for which difficulties have already been identified (see above) for the estimation of z_w. Because parameters z_w and m_w correspond to a No-Effect Concentration (NEC) within the model, this means that option 2 tends to overestimate the internal dose above which the chemical compound will have an effect on individuals.

Secondly, whatever the data sets, our results reveal that option 2 underestimates b_w in GUTS-RED-SD (see Figure 1, for an illustration with data sets A1 and A2). Ten data sets led to b_w estimates different between options 1 ($b_{w,1}$) and 2 ($b_{w,2}$, Figure S4). Out of these 10 data sets, eight data sets led to $b_{w,2}$ less than $b_{w,1}$. The two other data sets are TOX01-SPE03_a, and TOX05-SPE19 for which the dose-response curve at final time is very steep, making difficult the estimation of b_w whatever the option. So, reminding that parameter b_w stands for the intensity of the chemical effect on individuals, it appears that option 2 tends to underestimate this effect.

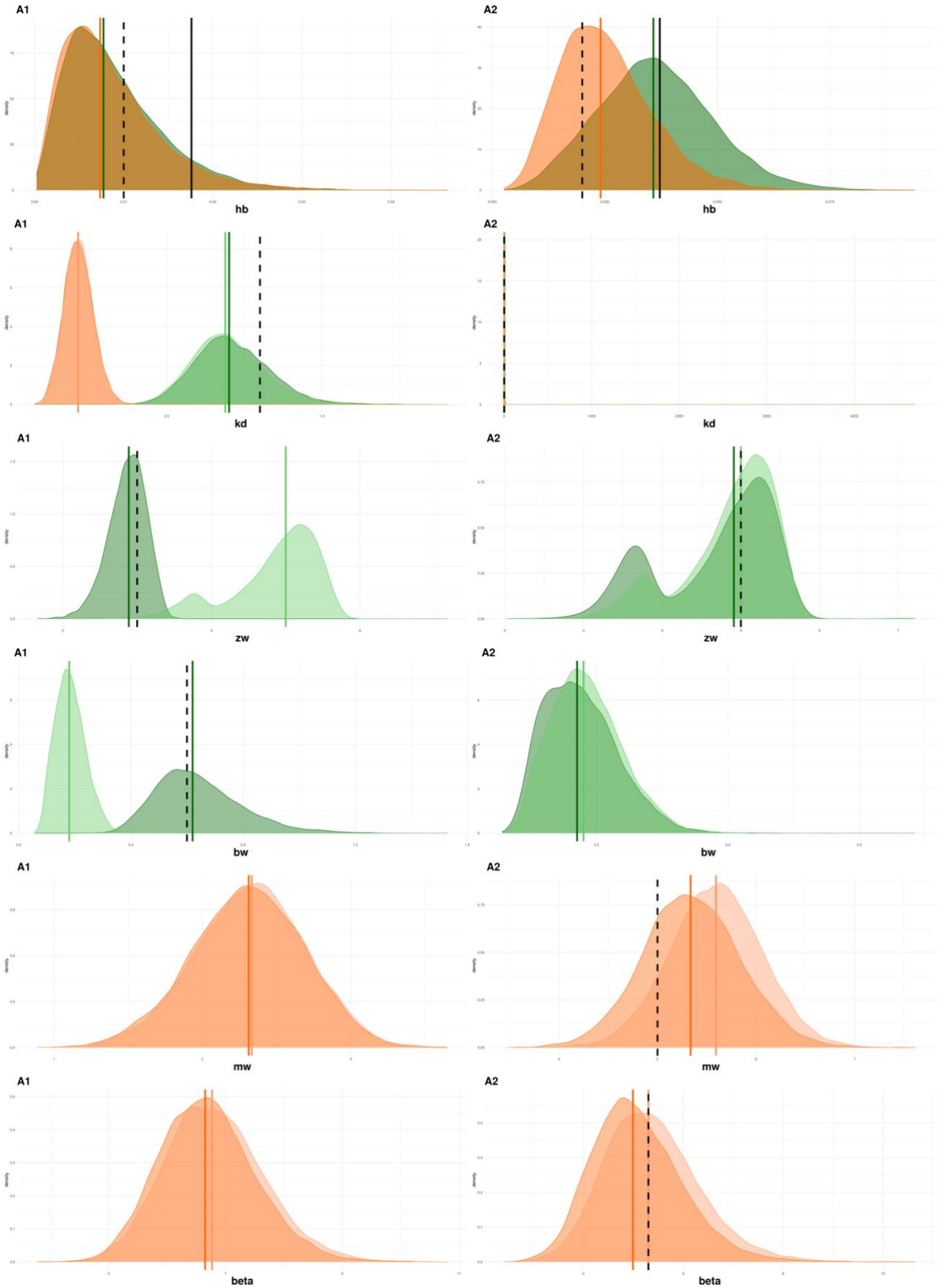


Figure 1: *Marginal posterior probability distributions of both GUTS-RED variants, SD (in green), IT (in orange), for both options 1 (dark colors) and 2 (light colors), and for data sets A1 and A2. Colored solid vertical lines stand for the median of the posterior probability distribution; the black dashed vertical line stands for the true parameter values as used to simulate data points of data sets A1 and A2; and the black solid vertical line stands fo the calculated fixed h_b value.*

While the β parameter does not inspire any specific comment, the k_d parameter that corresponds to the toxicokinetic part of the model, also appears close to the true value but only with GUTS-RED-SD, indeed GUTS-RED-IT clearly underestimates k_d (Figure 1, data set A1). Similar results were obtained with the other data sets. A total of 18/36 data sets fitted with both GUTS-RED-SD and GUTS-RED-IT gave different k_d estimates whatever the option (Figure S2). For these 18 data sets, the k_d estimate with GUTS-RED-IT was systematically lower than the one obtained with GUTS-RED-SD. This means that for half of the data sets we analyzed, the speed of the kinetic is underestimated, either by GUTS-RED-SD or GUTS-RED-IT. This corroborates the current well-known inability to anticipate the use of one or the other GUTS-RED variants for a particular species-compounds combination [2].

Our results on parameter estimates lead us to the conclusion that estimating the background mortality (option 1) provides h_b values closer to the reality. Because option 2 tends to overestimate z_w and m_w, and to underestimate b_w, using option 1 will provide more protective predictions in terms of ERA.

Influence of estimating h_b on goodness-of-fit criteria

Looking at fitting plots of posterior predictive checks for all data sets shows no difference whether parameter h_b is estimated or not. Looking at parameter correlations seems to be the most convenient way to highlight the impact on estimating h_b or not on the estimation of the three other parameters. Indeed, fixing h_b before the inference process leading the other three estimates (option 2) means completely ignoring any correlation of h_b with the other three parameters. However, as illustrated in Figure 2, not estimating h_b hardly changes correlations between the other three parameters. In addition, we can see that when estimated, h_b is only weakly correlated with the other three parameters. This result holds true for all other datasets we analyzed. Finally, whatever the GUTS-RED variants we used, whatever the datasets we analyzed, whatever the goodness-of-fit criteria we looked at, there was virtually no difference between the options 1 and 2. Nevertheless, because the parameters are better estimated under option 1 (see above-mentioned arguments and Figure 1), we discuss only based on option 1 hereafter.

Figure 3 confirms that h_b is poorly correlated to the other three parameters for all data sets. Correlation coefficients rarely exceed 0.25, and when exceeding 0.25, it happens more often with GUTS-RED-IT than with GUTS-RED-SD. With two or three exceptions, parameters of the GUTS-RED-IT variant are always positively correlated, while correlation coefficients are distributed around 0 with GUTS-RED-SD. The h_b parameter is most often highly correlated with the β parameter, and the correlations of h_b with both k_d and m_w is very similar most of the time; this is due to a strong correlation between k_d and m_w that inherently exists in GUTS-RED-IT [18]; see Figure S8 to visualize this for all the data sets we analyzed in this study. With variant GUTS-RED-SD, the correlation coefficients are more often negative between the parameters h_b and k_d than with the two other parameters; also, when positive, this correlation is very small. Biologically speaking, this means that the background mortality rate is more correlated to the toxicokinetic than to the toxicodynamic of the compound. Such a result is particularly interesting because it highlights a possible trade-off between the survival of organisms and their bioaccumulation of chemical substances.

Influence of estimating h_b on the LC_{50} estimate

As illustrated on Figure 4, whatever the data set, with one or two exceptions, there is almost no difference between the LC_{50} with both GUTS-RED-SD and GUTS-RED-IT whether parameter h_b is estimated or not. However, LC_{50} estimates may sometimes strongly differ whether GUTS-RED-SD or GUTS-RED-IT is used (see for example Figure 4, on the right). Two LC_{50} estimates were considered significantly different when their 95% credible intervals did not or very few overlap. Hence, in total, only 6 out of the 38 data sets exhibited significantly different LC_{50} values. This result is consistent with other works also illustrating the impossible choice between both GUTS-RED variants [2].

Looking at Figure S8, in addition to the fact that the LC_{50} estimates are not very different, their precision also is similar both between option 1 and option 2, and between the use of GUTS-RED-SD and GUTS-RED-IT. This result is quite counterintuitive with the fact that option 1 provides more precise parameter estimates. An explanation may be that the h_b parameter is poorly correlated to the other three parameters. Consequently, in terms of ERA, if only LC_{50} estimates are needed to decide, estimating h_b or not does not matter a lot.

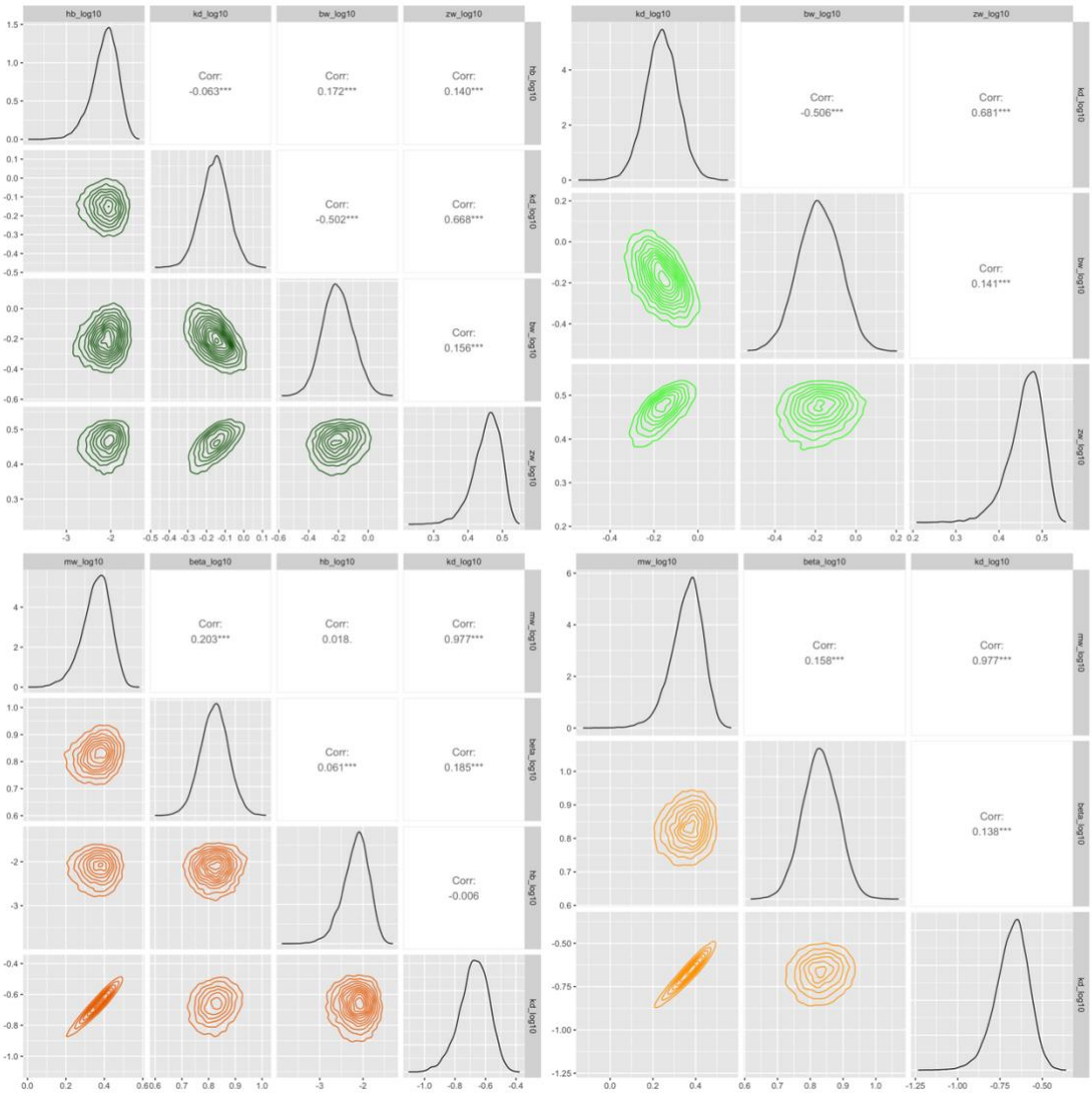


Figure 2: *parameter correlations for data set A1: upper left with SD-O1; upper right with SD-O2; lower left with IT-O1; lower right with IT-O2.*

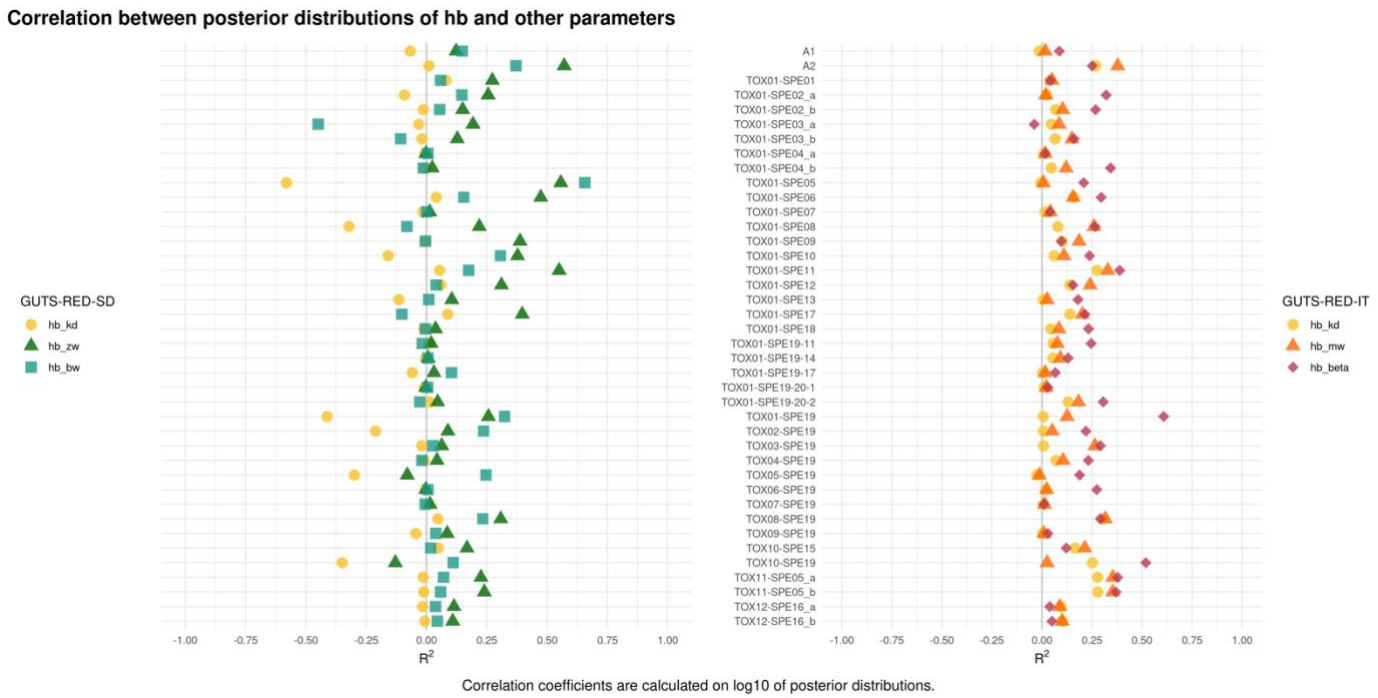


Figure 3: *parameter correlations between parameter h_b and the three other ones for all data sets and both GUTS-RED-SD (left panel) and GUTS-RED-IT (right panel).*

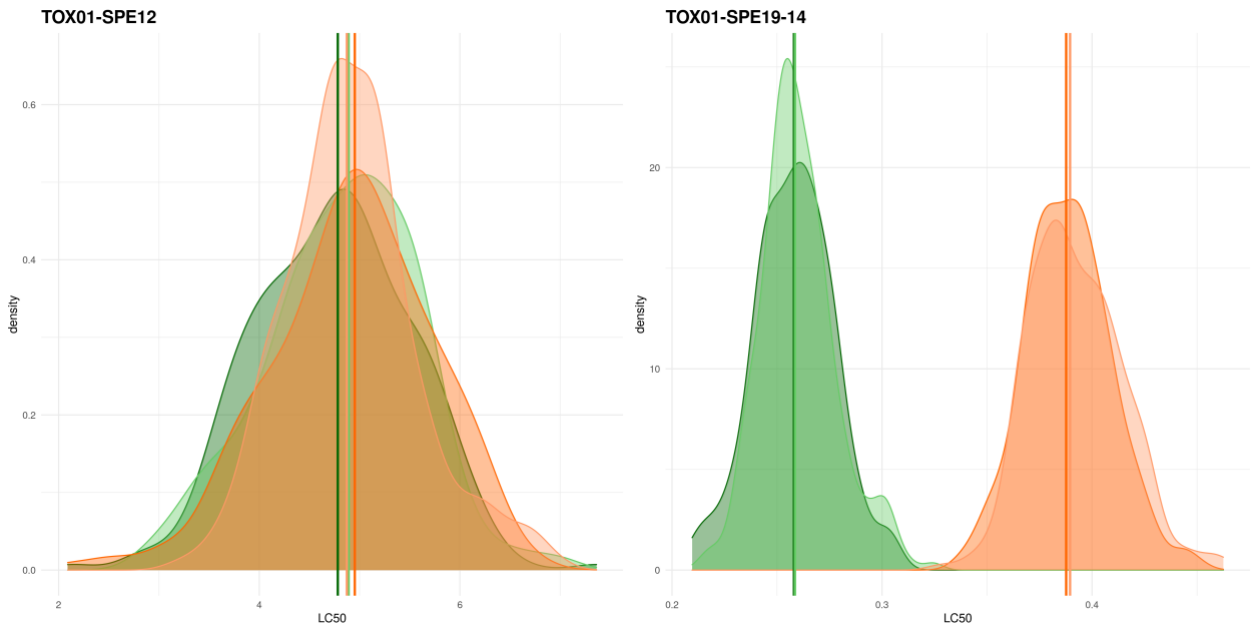


Figure 4 *Distributions of LC_{50} at final time with SD O1 (dark green), SD O2 (light green), IT O1 (dark orange) and IT O2 (light orange): on the left for data set TOX01-SPE12; on the right for data set TOX01-SPE19-14. See table 1 and 2 for details on data sets.*

Conclusion

Our study clearly illustrated that background mortality (h_b) values were almost always different between options 1 and 2. When estimated (option 1), parameter h_b was always closer to the expected background mortality, and its estimate was quite precise. On the other hand, when h_b was calculated from control data (option 2), it was always underestimated. We also noticed that option 2 tended to provide underestimated no-effect concentrations: parameter z_w in GUTS-RED-SD or parameter m_w in GUTS-RED-IT. Parameter b_w displayed a similar pattern for GUTS-RED-SD, meaning that option 2 underestimated the intensity of the chemical effect on individuals. Regarding k_d estimates (i.e., the kinetic quickness), there was no difference between options 1 and 2. Nevertheless, k_d estimates differed according to the GUTS-RED variant, sometimes underestimated, either with GUTS-RED-SD or GUTS-RED-IT. This confirms our inability to anticipate which of the GUTS-RED variants would be more appropriate for a particular species-compound combination. Furthermore, we showed that neither the GUTS-RED variant nor the option had an impact on any of the goodness-of-fit criteria. Estimating h_b or not only had tiny effects either on LC50 medians or its precision, while the choice of the GUTS-RED variant could sometimes provide different LC50 estimates. Altogether, for ERA mainly needing LC_{50} precise estimates, estimating the background mortality or not is of little importance. In contrast, benefiting of the most precise parameter estimates for GUTS-RED models may be of strong interest if the objective is to safely predict a survival probability under an environmentally realistic scenarios along which the exposure concentration is varying over time.

CRediT author statement

Julie Plantade: Conceptualization, Data curation, Investigation, Methodology, Validity tests, Visualization, Writing - Original draft preparation. **Virgile Baudrot**: Methodology, R code writing - Reviewing and Editing. **Sandrine Charles:** Investigation, Supervision, Validation, Writing - Reviewing and Editing.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

Supplementary material and additional information

- ***Supplementary material***

All supplementary material is available at https://zenodo.org/deposit/7565504.

- ***Additional information:***

All data analyses performed to get the results of this work can identically be reproduced either with the MOSAIC web platform and its GUTS-fit module [18], or directly within the R software and the use of the 'morse' package [19].

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