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Individual sensitivity distribution evaluation from survival data using a mechanistic model: Implications for ecotoxicological risk assessment

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ABSTRACT

Two main alternatives are typically used to model mechanistically dose-survival relationship in ecotoxicity tests. Effects are related to a concentration of concern, for instance body concentration, and, to account for their differences relative to time-to-death, individuals have either different concentration thresholds for death (“individual tolerance approach”), or equal probability to die, with death occurring randomly (“stochastic death approach”). A general framework to unify both approaches has recently been proposed. We derived a model from this framework to analyse five datasets (daphnids exposed to selenium, guppies exposed to dieldrin and second, third and fourth instars chironomids exposed to copper), by extending the standard stochastic death approach. We showed the possibility to estimate properly the toxicity parameters together with inter-organisms differences of sensitivity for at least one of these parameters (here the threshold for effect). For the daphnids, there was no improvement of using the extended model, which confirms the expected low variability among genetically identical individuals. For all the other datasets, our model outperformed the standard approach without accounting for differences of sensitivity. We estimated coefficients of variations in the distribution of the logarithm of the threshold from 44% to 4% and showed, for chironomids, a decrease of inter-individual differences of sensitivity with the age of the larvae. All standard threshold estimates were close but above the medium value of the distribution in the new approach, which means that a concentration equal to the standard threshold would ultimately result in the death of more than half of the exposed organisms. A more relevant parameter, such as the concentration protecting 95% of the population, would be 2–4 times inferior to the standard threshold.

1. Introduction

Ecotoxicological risk assessment is largely based on extrapolations from available ecotoxicity data. Extrapolation has to be performed from a limited number of species to ecosystems, from given test durations to large range of times, and from a limited number of constant concentrations to any kind of exposure profile. The relevance of the extrapolation depends both on the quality of the data and on their statistical analyses. Mechanistic models can greatly help in such extrapolations (Ashauer and Escher, 2010; Jager et al., 2011). First, most of these models distinguish between kinetics and effects. Kinetics is accounted for through a toxicokinetic model, which describes chemicals accumulation and elimination in the tissues. Effects are then related to the concentration of the chemicals in the tissues. With such TK–TD (Toxicokinetics–toxicodynamics) approaches, it becomes straightforward and relevant to simulate temporal aspects of toxicity and assess risk of fluctuating or pulsed exposures to pollutants (Péry et al., 2001, 2002; Ashauer and Escher, 2010). Second, the relevance of the extrapolation between exposure concentrations is supported by the mechanistic relationship between internal concentration and effects. For sublethal effects, such a mechanistic relationship is strengthened when relying on a dynamics energy budget model, able to describe the rates of energy acquisition and expenditure by individual organisms and how toxicants affect these rates (Muller et al., 2010; Ashauer et al., 2011). For effects on survival, data on post-exposure observation of mortality have proved that relating internal concentration to an instantaneous probability of dying, as TK–TD models do, is toxicologically pertinent (Péry et al., 2002). However, in some cases, it is much more relevant to use a toxicodynamic model describing the dynamics of damages as a function of internal concentration, instead of assuming a direct relationship between death rate and internal concentration (Ashauer et al., 2010).

In the literature, two alternatives have been proposed to model this dose–response relationship. Either individuals have different

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sensitivities with effects occurring as soon as their threshold for effects is exceeded by chemical concentration in target tissues, or individuals have equal probability to suffer an adverse effect with variability resulting from stochasticity. For survival data, Jager et al. (2011) distinguish between "stochastic death", (some individuals die because they are unlucky compared to the rest of the population) and "individual tolerance" (individuals die because they are more sensitive than others). The truth is certainly somewhere between both models for it is both unrealistic that all individuals in a population have exactly the same sensitivity and that the probability of dying changes suddenly from 0% to 100% for a given tissue concentration. Jager et al. (2011) have proposed a general framework (the general unified threshold survival model, or GUTS model) to unify both approaches, but up to now, no specific model from the GUTS model has combined "stochastic death" and inter-individual variability to analyse some data.

DEBtox model for the analysis of survival data (Bedaux and Kooijman, 1994) belongs to the "stochastic death" category. In this model, the instantaneous probability of death is proportional to the difference between the internal concentration and a threshold concentration, called the *NEC* (No Effect Concentration). This probability is assumed to be the same for all exposed individuals. A previous study focusing on the analysis of lethal rodent toxicity data showed that a mathematical model accounting for differences in sensitivity among a population and incorporating factors such as time dependence outperformed all other approaches, including DEBtox model (Péry et al., 2010).

In this work, we aim at extending the DEBtox model in the context of the GUTS model to combine differences in sensitivity and stochasticity. Individuals have different threshold for effects resulting in different probabilities to die, but, contrary to the "individual tolerance approach", this probability is not infinite as soon as the threshold is exceeded. Moreover, in our model, there is no such thing as an absolute "no effect concentration". Any concentration is expected to have an effect, but only on a fraction of the exposed population. We used five sets of survival data to estimate the parameters of our model and to compare the goodness of fit with the one obtained with DEBtox model. We finally discuss how the adoption of this modelling approach could contribute to ecological risk assessment, with adapted experimental designs and methods of parameters' estimation.

2. Materials and methods

2.1. Experimental data

We analysed data from two papers. The first one is related to guppies exposed in natural sea water to the pesticide dieldrin. It was one of the two first datasets analysed with DEBtox model for survival (Bedaux and Kooijman, 1994). Survival was monitored each day during 7 d, 8 water concentrations were tested (0, 3.2, 5.6, 10, 18, 32, 56 and 100 $\mu g\,L^{-1}$), and 20 organisms per concentration were exposed. The other three datasets correspond to organisms from the species *Chironomus riparius* exposed to copper-spiked sediments during 3 d, then clean sediments during 2 d at three different larval stages (Péry et al., 2003), the second, the third and the fourth ones. Survival was monitored each day, six concentrations were tested (0, 25, 45, 92, 165, and 345 $mg\,kg^{-1}$), and 60 organisms per concentration were exposed.

In addition, we used data we produced with daphnids exposed to selenium. Exposed organisms originated from *Daphnia magna* cultures (clone obtained from INERIS Verneuil en Halatte, France) maintained in continuous parthenogenic reproduction in artificial freshwater M4 medium (Elendt, 1990) and renewed twice a week (Zeman et al., 2008). Selenium was obtained from Sigma–Aldrich (Saint–Quentin Fallavier, France) as selenite Na_2SeO_3 and dissolved at 1 $g\,L^{-1}$ Se. Tested selenium concentrations were 6200, 3500, 2000, 1100 and 660 $\mu g\,L^{-1}$, with 40 organisms exposed per concentration. Selenium and major ionic concentrations were quantified prior to and post 48 h-exposure in acute condition tests. Quantification was carried out after post filtration (2 μm), by ICP-AES (Optima 4300DV, Perkin Elmer – detection limit = 10 $\mu g\,L^{-1}$ for Se; 0.5 $mg\,L^{-1}$ for major cations) and ionic chromatography (Dionex DX-120, Sunyvale, CA, USA – Quantification limit = 100 - $\mu g\,L^{-1}$ for major anions). All water samples were stored at 4 °C in the dark before analysis. All concentrations remained within 10% of nominal concentrations. pH was similarly monitored and remained within 0.1 unit of nominal pH 8.0. The number of survivors was counted at 24 h and 48 h. Growth was largely reduced in all the replicates with occurrence of mortality.

2.2. Description of the model

Basically, the model to describe effects on survival is the one presented in Bedaux and Kooijman (1994) for non-growing organisms. The authors used this model to analyse the guppies data. This model can also be used to analyse the chironomids data, as counting the number of survival each day prevented the larvae from building their tubes and growing at high rate.

In this model, kinetics is accounted for through a simple one-compartment model, with internal concentration normalised by the bioconcentration factor, i.e. the ratio between maximum internal concentration and exposure concentration, yielding the following equation for kinetics:

$$\frac{dc_i}{dt} = k_e(c_i(t) - c_e(t)) \tag{1}$$

With k_e the elimination rate, c_e the exposure concentration and c_i the internal concentration.

Toxic effects occur only when $c_i(t)$ exceeds a threshold, the *NEC* (No Effect Concentration), which corresponds to the maximal toxicant concentration at target organ level that can be handled without generating detectable effects on mortality. Death being assumed to be a stochastic process, the probability $q(t)$ to survive until time t is defined as:

$$q(t) = e\left(-\int_0^t h(\tau)d\tau\right) \tag{2}$$

where $h(\tau)$ is the hazard rate at time τ, which linearly increases with the difference between $c_i(t)$ and the *NEC* value when this *NEC* is exceeded:

$$\begin{cases} \text{if } c_i(t) > NEC \quad h(\tau) = b(c_i(t) - NEC) + d \\ \text{if } c_i(t) < NEC \quad h(\tau) = d \end{cases} \tag{3}$$

where b is the so-called killing rate, a descriptor of the intensity of effects, and d the background mortality.

In this paper we assumed that the *NEC* was not the same for all organisms but had a statistical distribution ($P(NEC)$), with a median value and a standard deviation. We selected a log-normal one (with μ and σ the mean and standard deviation, respectively, of the variable natural logarithm), as it is the common choice of distribution to account for differences in sensitivities, especially, for species (Maltby et al., 2005).

2.3. Estimation of the parameters

The parameters of the models and their confidence intervals were estimated through maximum likelihood methods. More precisely, we maximised the logarithm of the likelihood of the data (Bedaux and Kooijman, 1994):