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TIME-DEPENDENT SPECIES SENSITIVITY DISTRIBUTIONS

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Abstract—Time is a central component of toxicity assessments. However, current ecotoxicological practice marginalizes time in concentration–response (C-R) modeling and species sensitivity distribution (SSD) analyses. For C-R models, time is invariably fixed, and toxicity measures are estimated from a function fitted to the data at that time. The estimated toxicity measures are used as inputs to the SSD modeling phase, which similarly avoids explicit recognition of the temporal component. The present study extends some commonly employed probability models for SSDs to derive theoretical results that characterize the time-dependent nature of hazardous concentration (HCx) values. The authors' results show that even from very simple assumptions, more complex patterns in the SSD time dependency can be revealed. Environ. Toxicol. Chem. 2013;32:xxx–xxx. © 2012 SETAC

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INTRODUCTION

The species sensitivity distribution (SSD) has been an important development in ecotoxicology. Its reliance on statistical principles rather than arbitrary assessment factors placed toxicity assessments on a more rational and, arguably, a defensible basis. However, several concerns have been raised with regard to various aspects of the SSD methodology, including but not limited to (1) underlying assumptions, such as the neglect of trophic structures and the representativeness of the sample data [1], and (2) computational aspects of the SSD process, such as the appropriateness of distributional form [2–6] and the incomplete and/or inappropriate treatment of uncertainty [7,8]. Here, we wish to draw attention to another facet of SSD modeling that hitherto has received relatively little attention—the temporal component.

Time is a key component of ecotoxicological studies [9,10], and its impact on the derivation of toxicity measures is attracting increasing attention [11,12]. For example, toxicokinetic and toxicodynamic (TKTD) models describe physical and chemical processes within organisms (see [13,14,15] for reviews), whereas less complex models are used to describe the relationship between concentration and response (concentration–response [C-R] curves), which are in turn used to generate the data for SSD modeling. Despite the trend toward the use of increasingly sophisticated statistical methods in SSDs [7,16–18], the temporal component of SSDs has not been incorporated in any unified manner. To our knowledge, only one study [19] examined the temporal pattern of SSDs from TKTD models applied to five species.

The inputs to an SSD are toxicity measures derived from experimental data, typically those generated from C-R experiments. Important considerations in the design of a C-R experiment center on the choice of endpoint (e.g., mortality, growth, reproduction), the dependent variable (e.g., survival rate, length, weight, number of offspring), and the set of concentrations to be used. Standard protocols often dictate most, if not all, design aspects including the duration of the experiment or the time at which the measurements of the endpoint are to be taken (e.g., recording survival numbers after 24, 48, or 96 h). For some C-R experiments, the duration of the experiment is predicated on biological considerations (such as model-species life cycle), whereas, in other cases, the duration is set somewhat arbitrarily and as a matter of convenience.

The nexus between time (as a duration) and toxicity is axiomatic in the definitions of acute and chronic, yet its importance is never accounted for in any meaningful way in subsequent SSD modeling. Indeed, all reference to time is lost in the SSD fitting process and, consequently, derived toxicity measures and hazardous concentrations (HCs) are treated as time invariant, something they clearly are not. When chronic data is insufficient to obtain reliable chronic toxicity measures, we reintroduce a temporal component by scaling acute toxicity measures using acute-to-chronic ratios [20]. This approach lacks scientific rigor and is a clumsy way of acknowledging the temporal dimension of toxicity measures and, by implication, SSDs and HCs.

Another approach developed by the U.S. Environmental Protection Agency (U.S. EPA) is to estimate chronic toxicity using the time course of mortality as determined from acute toxicity tests with several acute time points and hyperbolic time models [21–24]. We do not discount the utility of these studies, but the focus on acute-to-chronic conversions [25–27] might have distracted us from the more important task of developing a unified approach that explicitly recognizes time rather than marginalizing it.

We restrict our attention here to the single issue of time dependence in SSDs and its influence in the determination of HC values. Our motivation arises from two observations: (1) time is important, if for no other reason than that it differentiates between acute and chronic toxicity measures, and (2) the test duration of a C-R experiment is often arbitrary and sometimes has as much to do with logistics, cost, and convenience as it does with biology, thereby rendering the classification of the resulting toxicity measure as either acute or chronic rather imprecise.

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It is therefore of interest to gauge the potential impact on SSDs and HC values as a result of this incomplete and somewhat arbitrary treatment of time.

To assist with this assessment, we derive mathematical expressions for HCs derived from log-normal and log-logistic SSDs in which the parameters of the distribution are functions of time. We recognize that the results of these analyses are necessarily limited to the choice of SSD and the manner in which the temporal dimension has been incorporated and therefore may not be universally applicable. However, we believe that this is the first time an attempt has been made to characterize time dependency in HC values mathematically, and as such we believe the insights obtained are valuable and will lead to a better appreciation of the role of this parameter and of the potential consequences of ignoring it.

MATERIALS AND METHODS

One of the drawbacks of the SSD paradigm is the indeterminate nature of the functional form of the SSD, because there is no biological or statistical theory that guides the choice of an appropriate probability model. Although this indeterminacy provides the analyst with ample scope to fit any reasonable probability model to a collection of toxicity values, the downside is that different results can be obtained when different distributions are used to estimate quantities (e.g., HCs) from the SSD [2,4,5]. This fundamental limitation will also frustrate attempts to develop generic advice or recommendations regarding the treatment and/or impacts of time in SSD modeling. Nevertheless, we believe an initial first look into the time-varying nature of the HCs based on two commonly used probability models in SSD modeling, the log-normal and the log-logistic, may provide useful insights.

Species sensitivity distributions rely on the assumption that aquatic species of a community or assemblage differ in their sensitivity to a hazardous chemical. Toxicity values are used as indicators of the sensitivity and are assumed to follow a theoretical distribution accounting for the interspecies variability. The canonical form of an SSD is the cumulative distribution function (cdf) which represents the fraction of affected species (from 0 to 1) as a function of toxicant concentration. To introduce a temporal component, we define the random variable M_t as the toxicity value of a randomly selected species at time t.

Log-normal model

In this case, we assume $M_t \sim logNorm(\mu_t, \sigma_t^2)$. From standard statistical distribution theory, we have

$$E[M_t] = \exp\left(\mu_t + \frac{1}{2}\sigma_t^2\right) \tag{1}$$

and

$$Var[M_t] = \exp\left(2\mu_t + 2\sigma_t^2\right) - \exp\left(2\mu_t + \sigma_t^2\right) \tag{2}$$

for the (theoretical) mean and variance, respectively. After some algebra, we can show that

$$\begin{aligned}\mu_t &= \ln(E[M_t]) - \frac{1}{2}\ln\left(1 + \frac{Var[M_t]}{(E[M_t])^2}\right) \\ &= \ln(E[M_t]) - \frac{1}{2}\ln\left(1 + (CV[M_t])^2\right)\end{aligned} \tag{3}$$

and

$$\sigma_t^2 = \ln\left(1 + \frac{Var[M_t]}{(E[M_t])^2}\right) = \ln\left(1 + (CV[M_t])^2\right) \tag{4}$$

where

$$(CV[M_t])^2 = \frac{Var[M_t]}{(E[M_t])^2}$$

is the squared coefficient of variation of the toxicity measure M_t

Thus, by fixing two of the quantities $E[M_t]$, $Var[M_t]$, or $CV[M_t]$, we can examine the time-dependent behavior of the SSD and hence of its quantiles. Letting $(HCx)_t$ denote the concentration that is hazardous for fraction x of all species at time t, we have

$$(HCx)_t = \exp\left(\mu_t + \sigma_t \Phi^{-1}(x)\right) \tag{5}$$

where $\Phi^{-1}(\bullet)$ is the inverse standard normal cumulative distribution function.

Log-logistic model

In this case, we assume $M_t \sim logLogistic(\alpha_t, \beta_t)$. From standard statistical distribution theory, we have

$$E[M_t] = \alpha_t \frac{\pi/\beta_t}{\sin(\pi/\beta_t)} \tag{6}$$

and

$$Var[M_t] = \alpha_t^2\left(\frac{2\pi/\beta_t}{\sin(2\pi/\beta_t)} - \frac{(\pi/\beta_t)^2}{\sin^2(\pi/\beta_t)}\right) \quad \text{with} \quad \beta_t > 2 \tag{7}$$

for the (theoretical) mean and variance, respectively. After some algebra, we can show that

$$\alpha_t = E[M_t]\frac{\sin(\pi/\beta_t)}{\pi/\beta_t} \tag{8}$$

and

$$\frac{\tan(\pi/\beta_t)}{\pi/\beta_t} = \frac{E[M_t]^2 + Var[M_t]}{E[M_t]^2} = 1 + CV[M_t]^2 \tag{9}$$

$1 + CV[M_t]^2 > 1$ and $\beta_t > 2$; therefore, $\pi/\beta_t < \pi/2$. Let u_t be π/β_t

$$\lim_{u\to 0^+}\frac{\tan(u_t)}{u_t} = 1 \quad \text{and} \quad \lim_{u\to\left(\frac{\pi}{2}\right)^-}\frac{\tan(u_t)}{u_t} = +\infty$$

where $\frac{\tan(u_t)}{u_t}$ is a monotonously increasing function of u_t between 0 and $\frac{\pi}{2}$. Hence, there is a unique solution for $\frac{\tan(u_t)}{u_t} = 1 + CV[M_t]^2$. Equation 8 can be solved by iteratively running until convergence $u^* = \arctan((1 + CV[M_t]^2)u^*)$, with $u^* = \pi/\beta_t$.

Thus, by fixing two of the quantities $E[M_t]$, $Var[M_t]$, or $CV[M_t]$, we can examine the time-dependent behavior of the SSD and hence of its quantiles. As before, $(HCx)_t$ is the concentration that is hazardous for fraction x of all species at time $t>$, so we have the following

$$(HCx)_t = \alpha_t\left(\frac{x}{1-x}\right)^{1/\beta_t} \tag{10}$$

With these equations, we can examine the effect of different time models for $E[M_t]$ and $CV[M_t]$ on the derived $(HCx)_t$ value.

According to bioaccumulation kinetics models, toxicity values are expected to decrease with time until toxicity saturation occurs [13,28]. Acute-to-chronic ratios are a crude characterization of this time dependence, because they can be viewed as realizations of $\frac{M_{\text{short-term}}}{M_{\text{long-term}}}$ and are typically greater than one [29]. Empirical evidence for decreasing toxicity values with time is also available. For example, an analysis of toxicity data reported in Table 3 of Duboudin et al. [27] showed that, for vertebrates, the acute-to-chronic ratio (ACR) was greater than unity for all 22 substances tested. For invertebrates, the ACR exceeded unity for all 15 substances tested. To explore this dependence further, we have used three monotonically decreasing functions of M_t in time. Each of these simple functions is governed by two parameters, a and b. The parameter b controls the rate of decrease in mean toxicity to an asymptotic value, a. The three models are as follows: model EV1 is $E[M_t] = a + \exp(-bt)$; model EV2 is $E[M_t] = a + \frac{1}{bt}$; and model EV3 is $E[M_t] = \frac{a}{1-\exp(-bt)}$.

Model EV2 is also known as Green's model [30] and is used in the U.S. EPA acute-to-chronic estimation software [23,24]. Model EV3 arises from mechanistic assumptions of toxicity proportional to the concentration of the compound in an animal using one-compartment bioaccumulation kinetics [13,31]. It is sometimes referred to as a baseline toxicity model [13]. We note that these models were intended primarily to describe the time dependence of toxicity values at the level of a species, whereas we have used them to describe the expected value of toxicity for an infinite number of species.

The identification of a suitable model to describe the time-varying behavior of the coefficient of variation of toxicity is less straightforward. According to Kooijman [28], chronic toxicity values are expected to vary less among species than acute toxicity values, which implies a time-decreasing model for $CV[M_t]$. However, De Zwart [26] notes that the slopes of acute and chronic SSDs do not significantly differ from each other. An examination of the empirical evidence of Duboudin et al. [27] showed that, for vertebrates, the ratio $\frac{CV[M_{\text{acute}}]}{CV[M_{\text{chronic}}]}$ was greater than unity for 17 of the 22 substances examined, whereas for invertebrates, this was the case for 13 of 15 substances. In view of these equivocal findings, we have examined both a time-invariant model and a time-decreasing model for the coefficient of variation in toxicity values. Specifically, model CV1 is $CV[M_t] = c$, and model CV2 is $CV[M_t] = c + \exp(-dt)$, where c is strictly positive because a zero value for this parameter implies no interspecies variability in toxicity (and hence no basis for SSD modeling) either absolutely (if $c = 0$ in model CV1) or asymptotically (if $c = 0$ in model CV2).

The incorporation of time means that the SSD is now a surface rather than a curve. A typical example is shown in Figure 1. For fixed fraction x, the $(HCx)_t$ value would be derived in the usual manner from the curve, which results from taking a slice through Figure 1 at time t. Repeating this process at different times allows us to explore the time dependence in hazardous concentrations.

RESULTS

Figure 2 shows results obtained under the assumption of time invariance in the coefficient of variation (model CV1). In this case, the HCs are time decreasing irrespective of the chosen c. We obtained very similar results for log-normal and log-logistic SSDs. The shape of the curves differs slightly depending on which of the time models for mean toxicity is used (model EV1, EV2, or EV3). Nevertheless, all models reveal the same general features: (1) an asymptotic HCx as $E[M_t]$ tends to a, and (2) larger values of c result in smaller HCx values.

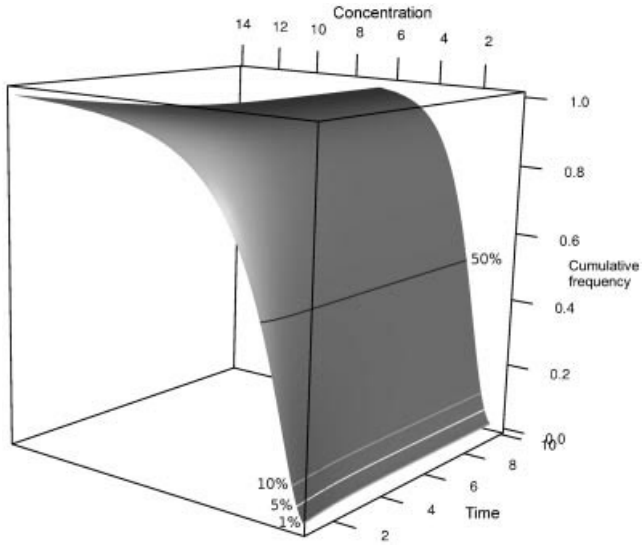

Fig. 1. 3D species sensitivity distribution (SSD). Fraction of affected species as a function of time and concentration. The fractions 50, 10, 5, and 1% are highlighted.

Under the assumption of a time-decreasing coefficient of variation (model CV2), again we obtained very similar results for log-normal and log-logistic SSDs. Various patterns were observed for the time dependence of HCx. As an example, results obtained with $c = 0.5$ and $d = 1$ are shown in Figure 3. For those parameter values, depending on the model used for the expected value, we observed a monotone increasing pattern for all highlighted HCx (EV1), a monotone decreasing HC50, and a pattern displaying a maximum for low-order HCx (EV2) or a monotone increasing pattern for low-order HCx and a pattern displaying a minimum for HC50 (EV3). Notice that all HCs tend to the same asymptotic values as $E[M_t]$ tends to a and $CV[M_t]$ tends to c.

As expected from Equation 5, the shape of the HCs time course is a trade-off between the affected fraction x, the time models for $CV[M_t]$ and $E[M_t]$, and their parameter values. Parameters b and d, which control the rate of decrease in $CV[M_t]$ and $E[M_t]$, respectively, have antagonistic impacts on HCs, because low-order HCs increase with decreasing variability and decrease with decreasing mean. This is highlighted in Figure 4, in which the impact of d on HC1 is examined under model EV3. When d is high ($d = 4$ in this example), the interspecies variability decreases faster than the mean, and the time course of HC1 is governed mostly by the time-decreasing model assumed for $E[M_t]$. In contrast, when d is low ($d < 2$ in this example), the time course of HC1 is dominated mostly by the time-decreasing model assumed for the variation among species.

DISCUSSION

The present study has examined the important issue of time dependence in species sensitivity distributions. We have not sought to compare different approaches to handling time; rather, our aim has been to highlight the arbitrariness of simple scalings such as the acute-to-chronic ratio and the subsequent lack of any comprehensive treatment of the temporal component in standard SSD methodologies. Interestingly, the ecotoxicology

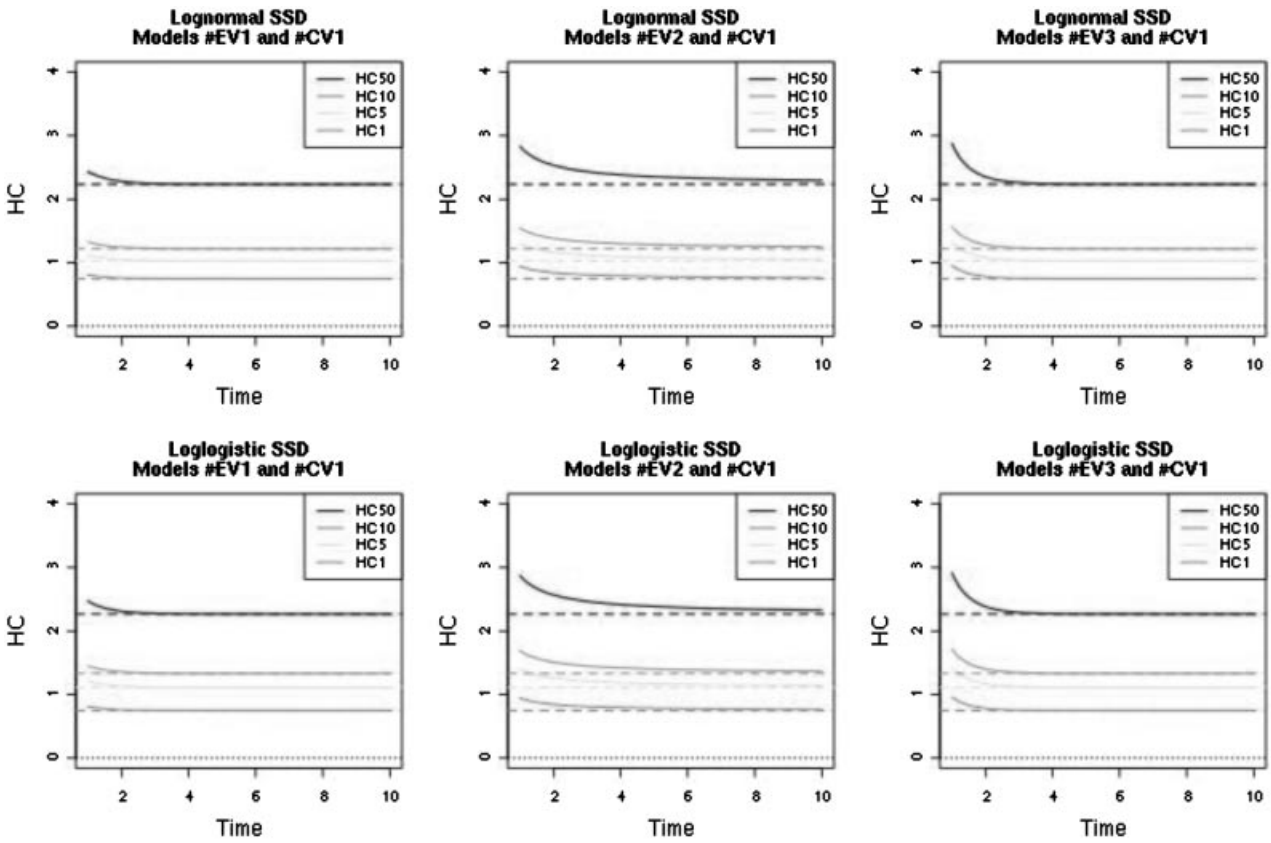

Fig. 2. Relationship between hazardous concentrations (HCs) and time derived from log-normal (top) and log-logistic (bottom) species sensitivity distributions (SSDs) when $CV[M_t]$ is time constant ($c = 0.5$): model EV1 (left), model EV2 (middle), and model EV3 (right) with $a = 2.5$ and $b = 1.5$.

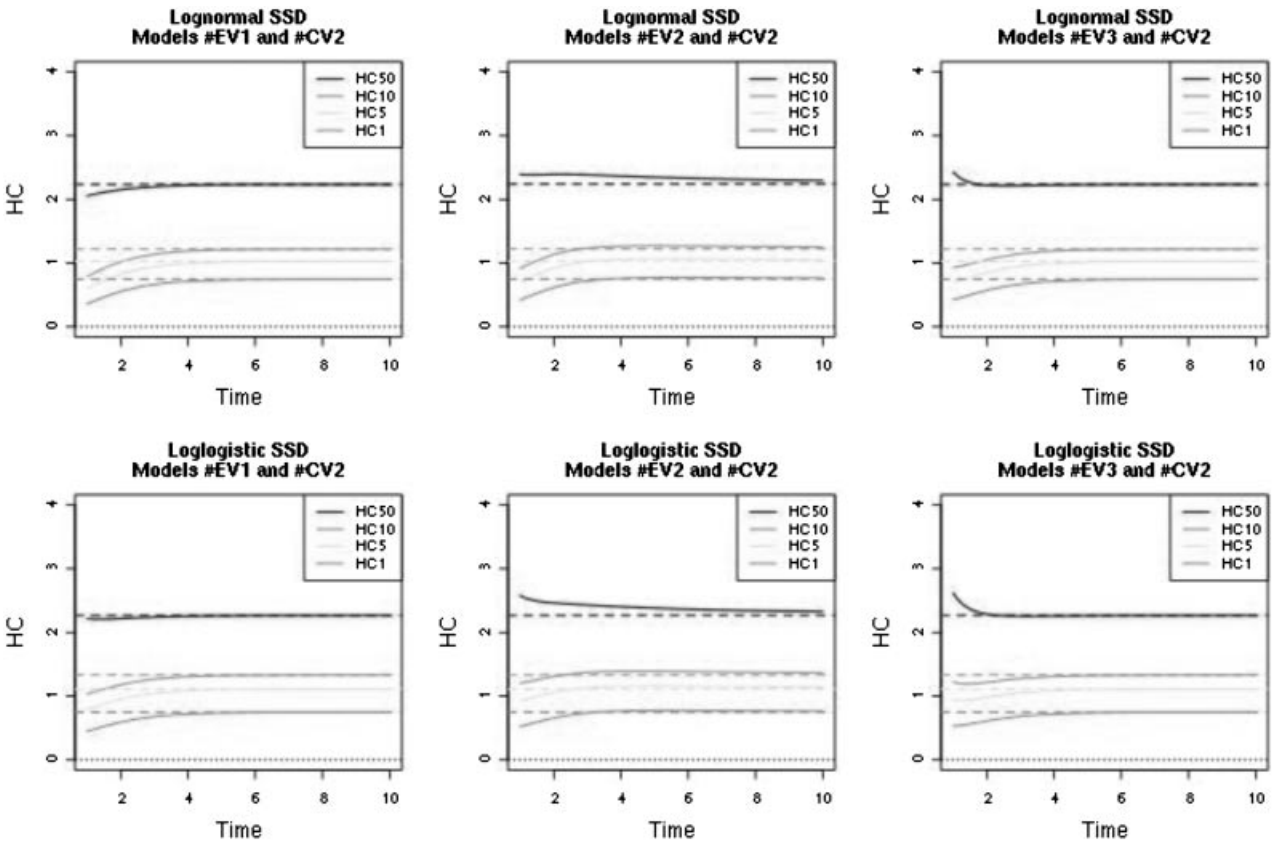

Fig. 3. Relationship between hazardous concentrations (HCs) and time derived from log-normal (top) and log-logistic (bottom) species sensitivity distributions (SSDs) when $CV[M_t]$ is time decreasing ($c = 0.5$ and $d = 1$): model EV1 (left), model EV2 (middle), and model EV3 (right) with $a = 2.5$ and $b = 1.5$.

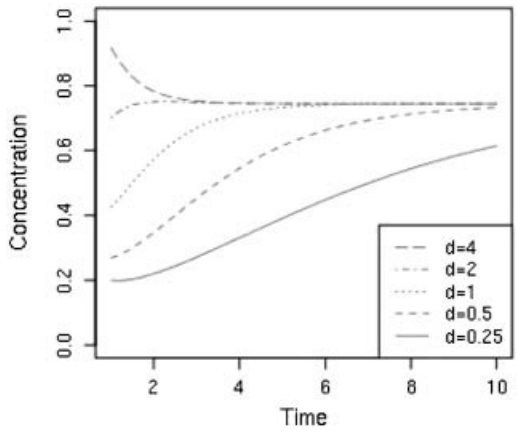

Fig. 4. Relationship between HC1 and time (log-normal species sensitivity distributions [SSD]) when comparing various decreasing rate d for models CV2 ($c = 0.5$) and EV3 ($a = 2.5$ and $b = 1.5$).

community now tends to use dynamic models (e.g., TKTD models [9–12]) in an attempt to represent and understand better the temporal dynamics at the single-species level, and this approach is also acknowledged as the way forward in regulatory guidelines [32,33].

We have derived some general results for commonly used distributions in species sensitivity distribution modeling, and these have provided useful insights that should motivate further research into and development of this important aspect of ecotoxicological practice.

Our results and insights are derived primarily from mathematical arguments rather than the analysis of a specific data set and are therefore potentially more generalizable provided that relatively weak assumptions are met in practice. For example, Kooijman [28] suggested that "chronic median lethal concentration (LC50) are expected to vary less among species than acute ones. This reduction in scatter is expected to greatly overcompensate for chronic LC50 being less than acute ones in the calculation of hazardous concentration for sensitive species" (i.e., low-order HCs would increase with time because they are dominated mostly by time-decreasing variation among species), but they did not substantiate this belief. In contrast, Smit et al. [19] presented results in which HCs decreased with time (which we conjecture to be a consequence of the HC's time course being dominated by the time-decreasing mean of the input toxicity measures). Not only has the present study shown both observations to be correct but, in addition, we have characterized the trade-off between time-decreasing CV and time-decreasing mean of input toxicity measures that underlies the resulting temporal behavior of HCx values.

We have shown that the temporal component of SSD modeling cannot be ignored, because critical quantities such as the HCx are not time invariant. Furthermore, the explicit incorporation of time as a functional parameter results in a more holistic description of the SSD and leads to a more informative characterization of the time–toxicity continuum. In addition, our analyses have provided key insights into the temporal behavior of HCx values as a function of time-varying patterns in the CV of the input toxicity data. We see this as an important development for which no analytic results have been previously derived.

For the cases considered, we have shown that, when the CV is constant over time, the HCx decreases monotonically to a stable, asymptotic value. This accords with general observations and the understanding that a chronic HCx is smaller than an acute HCx. Our results have also revealed some less obvious and more complex relationships among HCx as a function of time, CV, and x, and these held true for both the log-normal and the log-logistic SSDs. Though much work remains to be performed, we believe that the present study makes a small but valuable contribution to an improved understanding of the temporal dimension of SSDs.

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