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Demographic Toxicokinetic−Toxicodynamic Modeling of Lethal Effects

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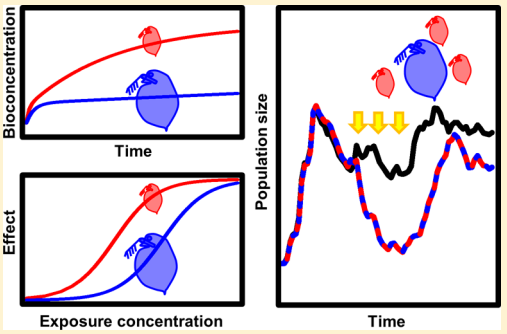
Supporting Information

ABSTRACT: The aquatic effect assessment of chemicals is largely based on standardized measures of toxicity determined in short-term laboratory tests which are designed to reduce variability. For this purpose, uniform individuals of a species are kept under environmental and chemical exposure conditions which are as constant as possible. In nature, exposure often appears to be pulsed, effects might last longer than a few days, sensitivity might vary among different sized organisms and populations are usually size or age structured and are subject to demographic processes. To overcome this discrepancy, we tested toxicokinetic−toxicodynamic models of different complexities, including body size scaling approaches, for their ability to represent lethal effects observed for *Daphnia magna* exposed to triphenyltin. The consequences of the different toxicokinetic and toxicodynamic assumptions for population level responses to pulsed exposure are tested by means of an individual based model and are evaluated by confronting model predictions with population data for various pulsed exposure scenarios. We provide an example where increased model complexity reduces the uncertainty in model outputs. Furthermore, our results emphasize the importance of considering population demography in toxicokinetics and toxicodynamics for understanding and predicting potential chemical impacts at higher levels of biological organization.



INTRODUCTION

Aquatic effect assessment uses data from short-term laboratory experiments in which it is deliberately attempted to keep exposure conditions constant and to minimize interindividual variability.[1] As regards exposure, chemical entry pathways into the aquatic environment are influenced by a wide range of environmental, topographic, and climatic conditions,[2] which means that exposure profiles are rarely constant, but rather pulsed and highly fluctuating. As for ecotoxicity, effects should be referred to populations, not to individuals,[3] since the overall population response to chemical exposure results from the sensitivity of each individual within that population.[4] Populations are, in most species, size- or age-structured.[5,6] Body size is an important demographic attribute, not only because it determines population properties such as abundance[6] but also because it controls the main ecological processes regulating population dynamics such as density-dependence and intraspecific competition dependence[6−8] or size-selective predation.[9,10] Under toxicant exposure conditions, differences in the initially exposed size/life stage were shown to generate different intrinsic sensitivities to chemicals,[12,13] leading to different demographic outcomes at population level.[11] Size- or stage-dependent sensitivity has been observed in aquatic[14,15] as well as terrestrial species.[11]

Another limitation in interpreting toxicity relates to the use of simple toxicity estimates from short-term experiments such as LC_{50},[16,17] whereas exposed organisms usually exhibit an increased apparent sensitivity over time,[18,19] which implies that the dynamics of toxicity have to be taken into account, especially when simulating time-variable exposure effects. No less important, delayed effects have been reported for different freshwater insects and crustacean species[20,21] which could not be observed in standard acute laboratory test periods unless a postexposure or chronic test is conducted.

This complex and realistic picture of toxicity exposure and effects confounds simple extrapolation to the population level from effects measured on basic endpoints and on 'identical' individuals. Models taking toxicokinetics and toxicodynamics

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into account[22] are needed to bridge the gap between standard experiment results and effects in reality.

In this work, we tested toxicokinetic−toxicodynamic models of different complexities, including body size scaling approaches, for their ability to represent lethal effects observed for *Daphnia magna* exposed to triphenyltin. To assess the consequences of these approaches on the population, we simulated different scenarios using an individual-based model and compared predictions with population data for pulsed exposure scenarios. Our aim was to evaluate the importance of considering population demography in toxicokinetics and toxicodynamics for understanding and predicting potential chemical impacts at higher levels of biological organization.

MATERIAL AND METHODS

Toxicokinetic−Toxicodynamic Model. Toxicokinetic−toxicodynamic modeling is based on the general unified threshold model of survival (GUTS).[23] Within this process-based modeling framework, survival can be linked to various dose metrics such as scaled internal concentration and scaled damage. The change in scaled internal concentration C_i* is modeled as a one-compartment model (eq 1), where C_w denotes the exposure concentration, and k_d the dominant rate constant. The use of the dominant rate constant indicates that either a toxicokinetic or a toxicodynamic process is triggering the temporal change of the dose metric.

$$\frac{dC_i^*}{dt} = k_d(C_w - C_i^*) \tag{1}$$

To account for differences in body size we extended the GUTS model by scaling the dominant rate constant with the surface to volume ratio $1/L$, relative to the maximum surface to volume ratio $1/Lm$; L is the volumetric length, L_m the maximum volumetric length of an animal (eq 2). For further details see refs 13 and 15.

$$\frac{dC_i^*}{dt} = k_d\frac{L_m}{L}(C_w - C_i^*) \tag{2}$$

As a second option for the dose metric and analogous to the scaled internal concentration, we used the scaled damage D*, which links internal concentration to survival. The change in internal concentration is represented by a two compartment toxicokinetic model. Here, the organism is divided into two compartments, with the internal concentration being the sum of the fractionated concentrations C_{i1} and C_{i2}. In this toxicokinetic model, we assume that the internalization of the exposure concentration C_w depends on the surface to volume ratio of an animal and thus introduce the L_m/L ratio in the first term of eq 3. Furthermore, we assumed that changes in C_{i1} (second term in eq 3) and in C_{i2} (eq 4) depend on the animal volume once the external concentration is internalized into the first compartment. For a biological interpretation see the Results and Discussion section.

$$\frac{dC_{i1}}{dt} = k_{u1}\frac{L_m}{L}C_w - k_{e1}\frac{L_m}{L}C_{i1} + k_{e2}\frac{L_m^3}{L^3}C_{i2} - k_{u2}\frac{L_m^3}{L^3}C_{i1} \tag{3}$$

$$\frac{dC_{i2}}{dt} = k_{u2}\frac{L_m^3}{L^3}C_{i1} - k_{e2}\frac{L_m^3}{L^3}C_{i2} \tag{4}$$

The change in scaled damage D* is calculated based on the internal concentration in the first compartment (C_{i1}), assuming that this is the damage-causing fraction within the body, and the damage repair rate k_r which describes the toxicodynamic recovery (eq 5).

$$\frac{dD^*}{dt} = k_r(C_{i1} - D^*) \tag{5}$$

We use the toxicodynamic concepts of stochastic death (SD) and individual tolerance (IT), two special cases of the GUTS framework, to link the dose metric ($M = D^*$ or $M = C_i^*$) to survival probability. In SD models, the survival probability decreases once the dose metric exceeds a threshold value for survival. Beyond the threshold z, the hazard H for an individual increases in a linear fashion with the background hazard rate constant h_b and the dose metric; the killing rate k_k determines the slope of the hazard rate distribution (eq 6). The resulting survival probability S is given in eq 7.

$$\frac{dH}{dt} = k_k\max(M - z, 0) + h_b \tag{6}$$

$$S(t) = \exp(-H(t)) \tag{7}$$

In IT models, the threshold for an effect follows a cumulative log−logistic frequency distribution within a population (eq 8), and death is instantaneous for an individual organism once the dose metric exceeds the individual's survival threshold. As a consequence, half of a given population dies when the dose metric reaches the distribution median α. The shape parameter β determines the slope of the frequency distribution. Using the maximum dose metric over time ensures that dead individuals cannot revive if the dose metric decreases over time. The corresponding survival probability is calculated by using eq 9.

$$F(t) = \frac{1}{1 + \left(\frac{\max_{0<\tau<t} M(\tau)}{\alpha}\right)^{-\beta}} \tag{8}$$

$$S(t) = (1 - \mathrm{F(t)})\exp(-h_b t)) \tag{9}$$

In the following sections, the different dose metrics and body size extensions of the GUTS model are referred to as GUTS-SIC (scaled internal concentration, eq 1), GUTS-SICS (size-dependent scaled internal concentration, eq 2), and GUTS-SIDS (scaled damage and size-dependent bioaccumulation, eqs 3, 4, 5).

Individual Based Population Model. For testing different effect model assumptions and predicting long-term population level effects of TPT pulsed exposure, we used an individual based model (IBM) that was previously described, parametrized and tested.[8] Briefly, life histories of individual daphnids are represented based on dynamic energy budget theory.[24] For each individual, the model quantifies the rates at which food is assimilated into reserves and energy is allocated to structure, the reproductive system and maintenance costs. If supplied with sufficient food, then the individual grows (i.e., increases in structure), matures, and reproduces when reaching puberty. If food is scarce, then the individual may suffer from starvation and survival probability is decreased in a size dependent manner.[25] A second death mechanism considered in the model is aging. In the IBM, individuals may adapt to conditions of low food availability by increasing their food intake rate and changing the energy allocation within the body depending on their reserve density. Furthermore, individuals sense population density and suffer from crowding conditions

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via decreased food intake and respond by producing fewer but bigger offspring. In the IBM, as in nature, population dynamics emerge from individual-level properties and the interaction between individuals, i.e., the competition for food and space. As a third death mechanism, we considered the lethal effects caused by TPT exposure. We therefore implemented the different GUTS assumptions as described above in the IBM. Moreover, we used a log−logistic concentration response curve (immediate response model) as a reference effect model. The IBM simulations were carried out to mimic population experiments as described below.

Model Parametrization and Evaluation. Effect model parameter estimation was done by maximizing the likelihood function[23] for survival and minimizing least-squares[26] for bioaccumulation, using the Simplex-Algorithm.[27] We employed the concept of profiling the likelihood functions[28] to compute 95% confidence intervals for parameter estimates. For the evaluation of IBM predictions the Nash-Sutcliffe model efficiency (NSE)[29] was used. The NSE can have negative values and can reach a maximum value of 1, which indicates a perfect prediction. NSE = 0 means that the model and the mean of the data perform equally well.

Bioconcentration and Toxicity Tests. Triphenyltin hydroxide (TPT, Sigma-Aldrich) was used as a test substance; for details see.[14] Here, a stock solution of 1 mg/L TPT was prepared daily. All experiments were conducted in open borosilicate glass vessels at a constant water temperature (20 ± 1 °C) and a light-dark rhythm of 16:8 h. *Daphnia magna* were used as the test organisms. Daphnid culture conditions prior to experimentation have previously been described.[30] In both culture and experiments, M4 was used as a medium.[31]

Uptake and elimination of TPT were studied for three different *D. magna* size classes (small, medium, large, see caption Figure 1). Body size measurements were made by scanning and subsequent digital image analysis, details described in.[32] For uptake experiments, daphnids were exposed to radiolabeled TPT in 20 mL medium (small size class) or 80 mL medium (others). For excretion experiments, daphnids were transferred after a 48 h incubation period to untreated medium, which was renewed daily. Radioactivity was measured in 1 mL water samples with liquid scintillation counting (LS 5000 TD, Beckmann Instruments, Germany) using 4 mL scintillation cocktail (Lumasafe, Lumac-LSC, Germany). The glass was rinsed with methanol prior to measurement of adsorbed TPT. Adult and juvenile daphnids were individually homogenized in 1 mL methanol, whereas for small *D. magna*, 5 individuals were pooled. This experimental design lead to 4 measured replicates for small daphnids and 8 for medium and large daphnids per time point and per experiment (uptake and elimination) respectively. The total recovery of the radioactivity within the experiments was 102 ± 2% after 72 h. The absorption to glass was negligible, and the concentrations in the media remained constant over the whole study period.

For toxicity testing, large daphnids were exposed in groups of 4 in 80 mL vessels to pulsed concentrations of TPT, including single pulses at different concentrations and double pulse scenarios differing in the timing of the second pulse. Pulsed exposure was terminated by transferring daphnids to toxicant free medium. During the bioconcentration and toxicity experiments, daphnids were fed with *Desmodesmus subspicatus* at a concentration of 0.1 mg C daphnid^{-1}.day^{-1}.

Effects from time variable exposure to TPT on populations of *D. magna* were assessed for various exposure scenarios with

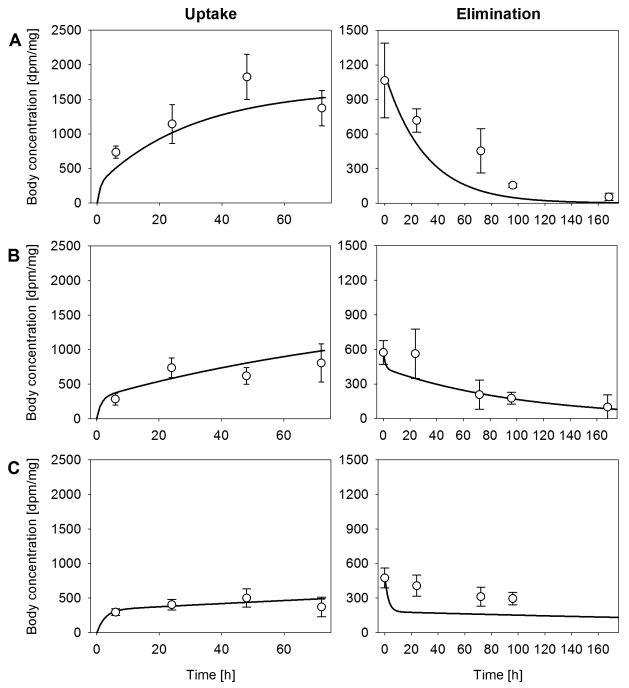

Figure 1. Bioconcentration of TPT in *Daphnia magna*. Uptake and elimination as a function of time in three daphnid size classes: (A) small: 1.38 ± 0.15 mm, (B) intermediate: 2.12 ± 0.21 mm, and (C) large: 3.75 ± 0.16 mm (mean ± standard deviation). Dots represent mean and standard deviation of measured internal concentrations, lines represent simultaneous model fit (eqs 3 and 4) to the three data sets (R^2 = 0.86).

different levels of complexity. These included two single peak exposure scenarios at different concentrations and six three-peak exposure scenarios (with different timings and magnitudes). In the multiple exposure scenarios, the same mean concentration of 6.3 μg l^{-1} d^{-1} was applied but the daphnids were exposed to different profiles with respect to magnitude and duration of peaks. For the sixth scenario, the mean concentration was lower (4.9 μg L^{-1} d^{-1}) and time between the peaks was reduced. In addition, population level effects from more complex and realistic exposure scenarios were studied; the derivation of these scenarios is described in the Supporting Information. For an overview of the exposure scenarios see Table S19. Population experiments were carried out using 900 mL medium and three replicates per treatment. The initial populations consisted of 2−3 adult daphnids (28−35 days old) and 5 neonates (<24 h) per test vessel. Daphnids were fed daily with 0.5 mg C vessel^{-1} during the whole test period. Animals were counted three times a week and abundance within three size classes was determined by sieving (for details, see ref 32). Corresponding size classes were as follows: < 1.25 mm (small), ≥ 1.25 − < 2.1 mm (medium) and ≥2.1 mm (large) (see ref 8).

RESULTS AND DISCUSSION

Bioconcentration. Bioconcentration of TPT by *Daphnia magna* differed considerably among the size classes tested (Figure 1). Uptake and elimination were rapid in small sized daphnids whereas hardly any elimination was observed for large conspecifics. The two-compartment toxicokinetic model generally fits the observed dynamics for the three size classes well (Figure 1). Corresponding parameter values are given in

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Table S1. The internal concentrations observed for medium sized specimens are comparable to those measured by Looser et al.[33] for juvenile daphnids. Also, when applying a one-compartment toxicokinetic model[23] to describe the uptake of TPT we obtained rate constants similar to the ones determined by Looser et al.[33] However, the estimated elimination rate constant was too high to make a reasonable prediction for the slow elimination of TPT (Figure S1). A first order toxicokinetic model is thus not applicable to adequately describe the current data set.

It has previously been demonstrated that bioconcentration can scale with organism volume or weight.[34] Moreover, animal lipid content can influence bioconcentration of organic chemicals[35] and lipid content may vary among different body sizes interspecifically.[36] When assuming that the mechanism for chemical exchange between medium and body is passive diffusion, both the uptake and the elimination rates can be interpreted as diffusion coefficients times the area for exchange over the animal volume, which is the rationale for the surface-to-volume scaling used to describe the kinetics for the first compartment in eqs 3 and 4. The second assumption is that the active surface for the uptake and elimination of chemicals, such as the integument, gut wall, or gills, is proportional to the squared volumetric size. Once the chemical has entered the body, it might be distributed in the organism and eventually be stored in lipids. We therefore scaled the uptake and elimination for the second compartment with animal volume. This assumption is supported by the general finding that the reserve makes up a fixed portion of animal mass or volume.[37] Scaling uptake and elimination kinetics with volumetric size, however, requires that the shape of an organism does not change during ontogeny,[13] which is a reasonable assumption for *D. magna*.

Effects on Survival. The GUTS-SIDS was applied to link size dependent bioaccumulation and survival. The resulting model fits for large daphnids under pulsed exposure are shown in Figure 2, while parameter values are listed in Table S1. Both the SD and the IT models generally described the data well, although the IT model tended to overestimate survival under single pulse exposure (Figure 2).

On the basis of the large daphnid parametrization, the GUTS-SIDS is also able to make reasonable predictions for the higher acute toxicity in neonates when correcting bioaccumulation for body size (Figure S5), although the IT model slightly overpredicts and the SD model underpredicts TPT toxicity. This test provides evidence for differential toxicokinetics being a main trigger in life-stage dependent differences in sensitivity to TPT and different sized conspecifics being equally responsive to the same internal concentration. Similarly, Gerritsen et al.[38] found that young and adult *D. magna* were equally sensitive to alkylphenols in terms of the threshold for an effect. The killing rate and the differential sensitivity were a result of different elimination rates.

In contrast to the above procedure, we parametrized the GUTS-SIC based on the results obtained from a TPT 48h acute toxicity test using neonate daphnids; for the SD parametrization see,[15] for the IT model fit see Figure S3 and Table S1. As previously demonstrated,[15] the recalculation of the dominant rate constant k_d (as estimated for neonate *D. magna*) by means of eq 2 allows adequate predictions for acute toxicity in conspecifics that differ in size. However, in the current study, the prediction of the GUTS-SIC for the adult response to TPT pulse exposure based on neonate parametrization is poor (Figure 2). This might be due to the latency of effects observed

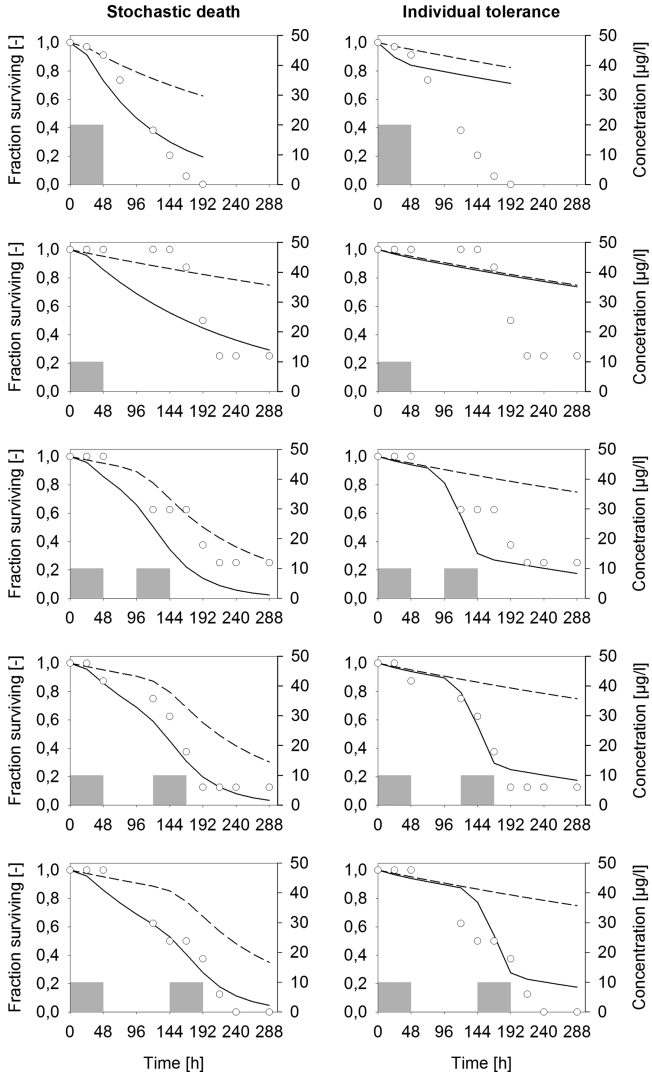

Figure 2. Survival as a function of time in large bodied *Daphnia magna* exposed to pulses of TPT. Dots represent measured effects, lines represent simulated survivorship based on the toxicodynamic assumptions of stochastic death and individual tolerance within the GUTS framework, respectively. Solid lines indicate GUTS-SIDS (scaled damage and size-dependent bioaccumulation) fit to the data set. Coefficients of determination for the GUTS-SIDS fits are 0.85 and 0.42 for stochastic death and individual tolerance, respectively. Dashed lines are independent predictions by the GUTS-SIC (scaled internal concentration) fitted to data as derived from a 48-h acute toxicity using neonate daphnids (Figure S2 and ref 15) with the dominant rate constant k_d being corrected for body size. For body size measurements see caption of Figure 1. For the control see Figure S4.

in the pulse exposure experiment with adult daphnids (Figure 2), which cannot be observed in shorter acute toxicity tests with neonates. However, effect latency was less pronounced in neonate daphnids compared to adult response, as revealed by a prolongation of the acute test without any exposure, which is in turn in close alignment with the predictions of the GUTS-SIDS (Figure S6). Effect latency is observable as a response to toxicant after the termination of exposure and has previously been reported for daphnids[39,40] and other species.[31,42] It has been hypothesized that damage caused by toxicants can only manifest at later developmental stages, e.g., at moulting events or metamorphosis.[41] Our results support another hypothesis: that latency is a consequence of toxicokinetics.[40,43,44] Having

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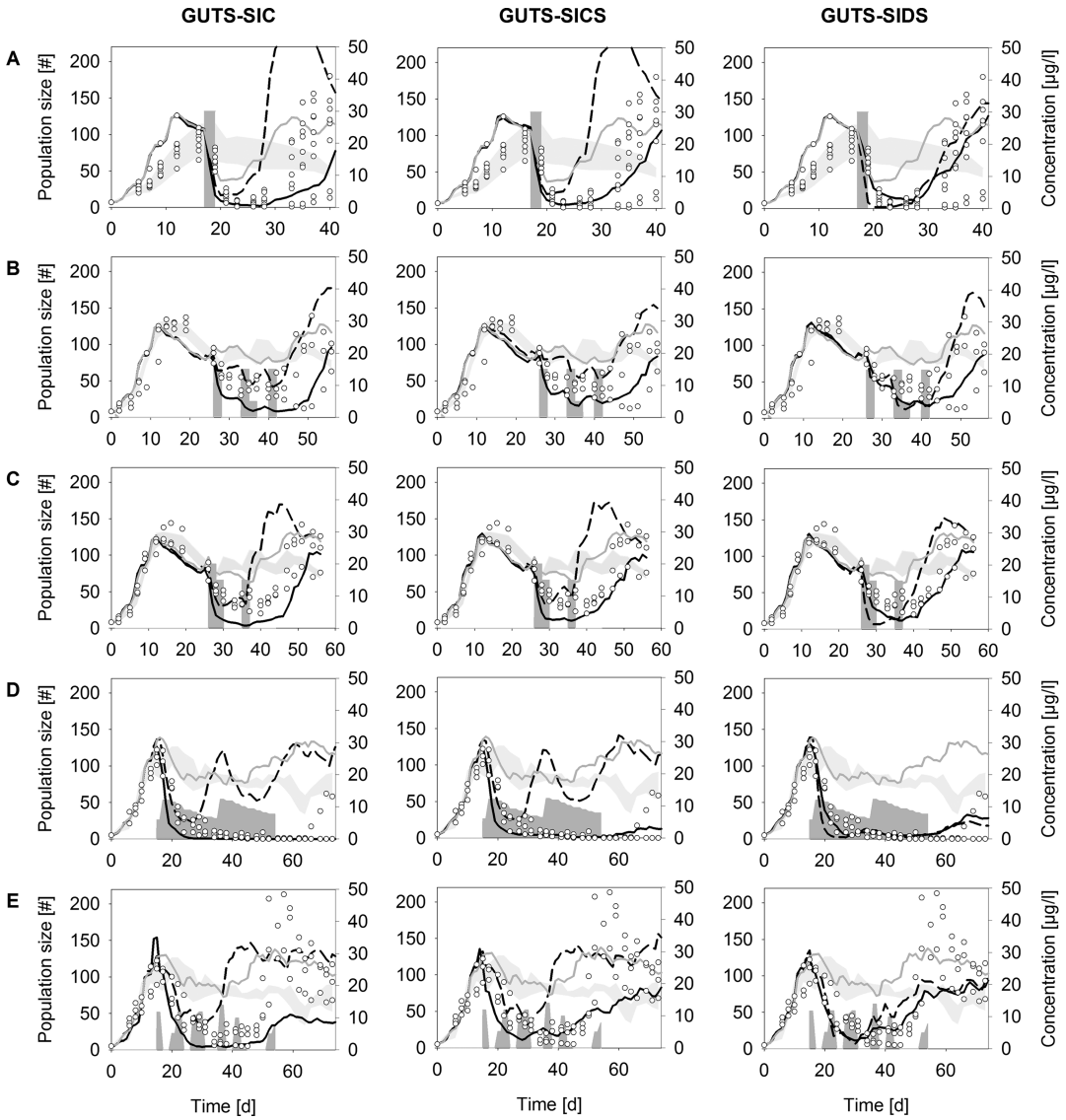

Figure 3. Population level effects of pulsed exposure to TPT. (A) Single pulse scenario, (B, C) multiple pulse scenarios, and (D, E) realistic exposure scenarios. The three panels correspond to different GUTS model assumptions; SIC: scaled internal concentration; SICS: size-dependent scaled internal concentration; and SIDS: scaled damage and size-dependent bioaccumulation. Dots represent measured population size in pulse exposure experiments, gray bars represent exposure concentrations, the light gray shade is the range of empirical control population size. Lines represent IBM predictions using different effect model assumptions: GUTS stochastic death (black solid line), GUTS individual tolerance (black dashed line), and concentration response curve as reference model (gray solid line). For a full overview of IBM simulations see Figures S7−S15.

entered the body, TPT is hardly eliminated at all by large bodied daphnids (Figure 1). As a consequence, retained internal toxicant concentration can lead to an increase in damage and effects occur or continue if a damage threshold is exceeded even though the organism is no longer externally exposed. In turn, the relatively fast elimination in small size daphnids compared to large ones (Figure 1) can explain why effect latency was found to be less pronounced in neonates (Figure S6).

Population Level Effects. The IBM was generally able to predict the dynamics in control populations in terms of size and population structure well (Figure S7). The relatively low model efficiency (NSE = 0.33) for the controls, however, was mainly due to higher total abundance predicted by the IBM for the Control 1 experiment (Figure S7) compared to empirical results (for Controls 2 and 3 NSE = 0.82). In the experiments, all of the chosen TPT exposure scenarios resulted in negative effects on population size (Figures 3 and, e.g., S8). In contrast, the immediate response model (based on survival observed after 24 h exposure, see Figure S2), which here served as a reference model, hardly predicted any negative effects (NSE = −0.98) with the exception of the two single pulse experiments (Figure 3). In this model, toxicokinetics and damage accrual were not considered. As a consequence, effects only occur when organisms are externally exposed, and the LC_{50}, i.e., the concentration at which half of a population dies, is assumed to be constant, which ignores the fact that LC_{50} declines gradually with time, until reaching an incipient LC_{50}.[43,45,46] In contrast, processes leading to lethal effects are accounted for in the GUTS framework. However, the IBM integrations of the different toxicokinetic and toxicodynamic assumptions perform differently, as indicated by the NSE calculated for total population size (Table 1).

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Table 1. Model Efficiency for IBM Predictions of Total Population Size under TPT Exposure Based on Different GUTS Model Assumptions: SIC: Scaled Internal Concentration; SICS: Size-Dependent Scaled Internal Concentration; and SIDS: Scaled Damage and Size-Dependent Bioaccumulation

	stochastic death	individual tolerance
GUTS-SIC	0.37	−1.52
GUTS-SICS	0.56	−1.46
GUTS-SIDS	0.66	0.48

The populations in our laboratory experiments were size structured, as revealed by grading daphnids into three size classes (Figure S7), with intermediate sized individuals being most dominant. The size class dynamics in exposure experiments were captured reasonably well by the IBM as shown for the SD models (Figure S15). In particular, overprediction of effects in larger size classes might be due to relatively smaller modeled sizes compared to empirical adult daphnid size later in the experiments. Considering that small-bodied daphnids are more sensitive to TPT exposure than larger conspecifics[15] can help to explain why effects predicted by the GUTS-SIC (which was parametrized based on neonate data) were stronger than those predicted by the size scaling approaches (Figure 3, S15). In one extreme case, the GUTS-SIC predicted population extinction where actually a few larger population members could survive. In contrast, this was adequately predicted by the SD size scaling approaches and the GUTS-SIDS IT (Figure 3D and Figure S14).

In addition to mortality, chemical exposure might induce sublethal effects, e.g., on reproduction, which can influence population dynamics. In our experiments, we chemically exposed daphnid populations during a capacity phase where reproduction was generally low (Figure S7) due to crowding effects and competition for food,[8] and thus purely sublethal effects at low exposure concentrations are unlikely to be observed. In contrast, a release from crowding and competition as a consequence of increased mortality led to higher reproductive output in chemically exposed populations (Figure S14) compared to the controls. Sublethal effects that might occur to some extent during this phase of the experiments have, however, been ignored in our modeling approach.

In nature, population structures can differ considerably from those we observed in the laboratory. For instance, oscillating resource-consumer interactions can lead to shifts in population structure: small daphnids were reported to be numerically dominant in growing populations,[12] whereas large ones are better able to resist starvation in phases of population decline.[47] Moreover, predators can alter population structure both in a trait-mediated manner[50] and directly via size selectivity,[48,49] which in extreme cases can lead to population extinction, although toxicant exposure alone may only result in minor effects.[10] These various environmental conditions can be accounted for by the demographic toxicokinetic−toxicodynamic approach presented in this study if altered sensitivity has purely allometric reasons and no additional stressor increases sensitivity to a toxicant. This remains to be tested in future trials.

The two toxicodynamic assumptions SD and IT can be seen as two extremes within the GUTS framework. In SD models, death is stochastic at the individual level, and the threshold for survival is identical for all population members. In contrast, in IT models, individuals differ in their sensitivity, thus mortality is stochastic at the population level.[23] As a consequence, in IT models a first toxicant pulse resulting in the exceedance of the threshold dose metric kills the most sensitive individuals and subsequent exposures will have less or no impact. If sufficient time remains between pulses, then it will allow organism recovery (note that in Figure 2, continuous mortality in the IT model after the second pulse is due to the background hazard rate). This assumption of the IT models leads to overall lower population level effects predicted by the GUTS-SIC, both with and without consideration of body size, in the single exposure compared to multiple exposure scenarios, and modeled recovery was usually fast (Figures 3, S12, and S13). In SD models, population members will continuously die as long the dose metric is beyond their threshold for survival, and each toxicant pulse will have the same impact at the population level given full organism recovery. The GUTS-SIC and GUTS-SICS SD models thus generally predicted higher population level effects and slower recovery than their IT counterparts (Figure 3). Differences in population level predictions of IT and SD are less pronounced for GUTS-SIDS (Figure 3, Table 1), due to the shared toxicokinetic model. As in SD, in the IT model damage can increase, leading to further death events in the sensitive fraction of the population. Moreover, unlike the individual level toxicity test, new population members are born which can be more sensitive than the average remainder (assuming that sensitivity is not passed on by the mother). This is an example where increased model complexity can decrease uncertainty in the model output. Given that the uncertainty arising from the differences between SD and IT assumptions is accounted for, the short-to-long-term, constant-to-pulsed exposure and thus individual-to-population extrapolation from acute toxicity testing with *D. magna* is deemed possible when using the size scaling approach for the GUTS-SIC. In what is probably good news for the risk assessment community, demographic toxicokinetic−toxicodynamic modeling can provide meaningful predictions for population level responses to toxicants.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.6b01113.

One-compartment toxicokinetic model fit, GUTS fits and predictions, IBM predictions for controls and TPT exposure experiments, GUTS parameter values, raw data for bioconcentration, survival and population experiments, and derivation of realistic exposure scenarios (PDF)

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Notes

The authors declare no competing financial interest.

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