Extrapolating Contaminant Effects from Individuals to Populations: A Case Study on Nanoparticle Toxicity to Daphnia Fed Environmentally Relevant Food Levels

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Abstract

Ecological risk assessment (ERA) is charged with assessing the likelihood a chemical will have adverse environmental or ecological effects. When assessing the risk of a potential contaminant to biological organisms, ecologists are most concerned with the sustainability of populations of organisms, rather than protecting every individual. However, ERA most commonly relies on data on the effect of a potential contaminant on individuals because these experiments are more feasible than costly population-level exposures. In this work, we address the challenge of extrapolating these individual-level results to predict population-level effects. Previous per-capita population growth rate estimates calculated from individual-level exposures of Daphnia pulicaria to silver nanoparticles (AgNPs) at different food rations predict a critical daily food requirement for daphnid populations exposed to 200 μg/L AgNPs to avoid extinction. To test this, we exposed daphnid populations to the same AgNP concentration at three different food inputs, with the lowest ration close to the extinction threshold predicted from data on individuals. The two populations with the higher food inputs persisted, and the population with the lowest food input went extinct after 50 days but did persist through two generations. We demonstrate that we can extrapolate between these levels of biological organization by parameterizing an individual-level biomass model with data on individuals’ response to AgNPs and using these parameters to predict the outcome for control and AgNP-exposed populations. Key to successful extrapolation is careful modeling of temporal changes in resource density, driven by both the experimental protocols and feedback from the consumer. The implication for ecotoxicology is that estimates of extinction thresholds based on studies of individuals may be reliable predictors of population outcomes, but only with careful treatment of resource dynamics.

One important goal of ecological risk assessment (ERA) of chemicals is to estimate the effects of a potential contaminant on populations; however, population experiments are costly in terms of labor, materials, and organisms. In practice, ERAs often end up relying on data from experiments on individuals, and, in the case of ERAs for freshwater systems, they commonly use data from chronic toxicity tests (OECD 2012) in which Daphnia are exposed to increasing concentrations of a potential toxicant and their survival and reproduction are measured. From these individual-level data, it is possible to estimate metrics related to population-level responses, such as the long-run population growth rate in a constant environment (per-capita population growth rate, r), an approach that has been employed to predict the effect of toxicants on populations from individual-level data for many years (Kooijman and Metz 1984). However, such metrics do not directly permit prediction of population-level impacts, unless they take account of potentially important feedbacks (such as resource-consumer or predator–prey
interactions) between the individuals that comprise the population and their environment. Recognition of this limitation has inspired calls for the use of ecological modeling to incorporate ecological complexity into ERA (Forbes et al. 2009, 2011). The feasibility and challenges, of the use of models to extrapolate ecotoxicological impacts across levels of biological organization was demonstrated for Daphnia by (Martin et al. 2013a, b).

Our past work (Stevenson et al. 2017) studied the effect of silver nanoparticles (AgNPs) on individual Daphnia fed a range of algal food rations (mgC algal food per daphnid per day). We found that low food increased AgNP toxicity and that two AgNP exposures (75 and 200 μg/L) had direct effects on daphnid survival (Stevenson et al. 2017). Specifically, 200 μg/L AgNPs was overwhelmingly toxic at all but the highest food ration with no individuals exposed to 200 μg/L surviving to reproduce except two at the highest food ration. Other studies have similarly found that AgNPs are toxic at low, parts per billion concentrations to Daphnia (Garner et al. 2015; Griffitt et al. 2008; Hoheisel et al. 2012; Qin et al. 2015; Ribeiro et al. 2013; Stensberg et al. 2014; Ulm et al. 2015), including sublethal effects on growth and/or reproduction (Mackevica et al. 2015; Ribeiro et al. 2013; Sakamoto et al. 2015; Zhao and Wang 2011). Indeed, a recent review found that in a Species Sensitivity Distribution including 40 species and 7 mammalian cell lines, Daphnia were the most susceptible to AgNP toxicity (Liu et al. 2022). For population predictions, the most important outcome from Stevenson et al. (2017, see their Fig. 5) was identifying a critical combination of food ration per daphnid and stressor concentration for a contaminated population to be viable (r close to zero).

To empirically test our interpretation of our data on individuals, we exposed small populations of Daphnia pulicaria to 200 μg/L AgNPs at three food inputs and developed an Individual-Based Model (IBM) that, apart from one calibration, utilized only parameters estimated from our individual-level data or supporting literature. We then simulated the population-level impact of AgNPs on these daphnid populations.

IBMs, also known as Agent-Based Models, track individuals through time and population dynamics emerge as these individuals interact with each other and their shared environment. Multiple studies have used IBMs to extrapolate individual-level effects to the population-level for ecological (Martin et al. 2013a; Railsback and Grimm 2019) and ecotoxicological applications (Gergs et al. 2016; Martin et al. 2013b; Pereira et al. 2019; Preuss et al. 2010; Vlaeminck et al. 2021). Some studies have integrated IBMs into larger ecosystem models to extrapolate effects to higher levels of biological organization (Bartell et al. 2019; Forbes et al. 2019; Schmolke et al. 2019). Here, we incorporate a generalizable net production model (a variant of the model in Nisbet et al. 2004) into an IBM framework with modules to describe algal food and damage dynamics to connect individual to the population-level effects of AgNPs we observed empirically.

### Methods: Experimental

#### Silver Nanoparticles Characterization

We purchased 40-nm BioPure citrate-coated silver nanoparticles (AgNPs) from NanoComposix (San Diego, CA). We measured the size, dissolution, and reactive oxygen species (ROS) production of AgNPs in the light and in the dark (as these daphnid experiments were performed in the dark to control algal growth which would change the food concentration) and these data are reported in Stevenson et al. (2017). In summary, AgNPs at these exposures concentrations do not produce ROS, do no aggregate, and have very slow dissolution in the “low P” COMBO media (Kilham et al. 1998) used for the experiments reported here. Our data indicate that less than 1 μg/L of the 200 μg/L AgNP exposure is present after three days (the longest transfer interval) as ionic silver (Stevenson et al. 2017).

#### Daphnia Individual Experiments

The data used in this paper on individual exposures of Daphnia to AgNPs are reported in Stevenson et al. (2017). As described in that paper, these exposures were comprised of multiple experiments: an experiment at the highest food ration (0.01 mgC/daphnid/day, which ran for 26 days) and two experiments at the other food rations (which ran for the entire lifespan of the organisms). We conducted two experiments at the food rations 0.0005, 0.001, and 0.0025 mgC/ daphnid/day: the first experiment consisted of control and AgNP exposures (n = 8 for each treatment) and the second experiment consisted of six additional control individuals. We started additional control individuals because survival at the lower food rations was initially lower than we expected, and we wanted to ensure we had enough data to parameterize the control response of D. pulicaria to these lower food conditions (Stevenson et al. 2017).

#### Daphnia Population Experiment

To test the effect of AgNPs at different food inputs to populations of Daphnia, we set up 12 small populations, half of which were kept as controls and half of which were dosed with 200 μg/L AgNPs. The populations were fed one of three food inputs (0.07, 0.14, and 0.27 mgC/day), and there were two replicate populations per treatment. Populations were kept in 400 mL of autoclaved “low P” COMBO media.
We started the populations at the approximate neonate/adult ratio of *Daphnia pulex* populations at equilibrium, based on data from past experiments in our lab (unpublished data). This ratio is approximately 3 neonates or juveniles/1 adult, and we started the populations with small neonates (0.69–0.71 mm), large neonates (0.71–0.81 mm), and adults (2.0 ± 0.5 mm). We distinguished between “small” and “large” neonates because we can be confident that the small neonates are less than 24 h old; however, the larger neonates are of an unknown age. We removed *Daphnia* from our stock tanks 5 days prior to the experiment and placed them in tanks of fresh COMBO media for two days and then transferred them to another tank of fresh COMBO media for another 3 days to clean the individuals and minimize any carryover of algal cells or other detritus into the experimental containers. We started the populations at total population sizes proportional to the food input; the populations fed the highest food input (0.27 mgC/day) started with the most individuals (25 small neonates, 9 large neonates, and 11 adults), the middle food input started with approximately half that number of individuals (5 small neonates, 13 large neonates, and 5 adults), and the lowest food input started with approximately a quarter of the population size as the highest food input (2 small neonates, 7 large neonates, and 3 adults).

We sampled each population on a Monday–Wednesday–Friday schedule, resetting algal food densities, media, and AgNP exposure every 2, 2, and 3 days. For sampling, we poured the daphnid populations onto a 60-μm nylon net filter (Millipore NY60) and counted and identified the stage of all individuals using a dissecting scope (Leica M80). We identified developmental stages of the individuals under the microscopes using circles printed on a transparency film of known diameters to correspond to the stages of interest. There were two circles: neonates fit into the circle with diameter 1.0 mm, juveniles fit into the circle with diameter 1.8 mm, and any individuals larger than both circles were adults. We also identified pregnant adults and counted the number of eggs and embryos in the brood pouch. We then placed the individuals into fresh COMBO media dosed with 0 or 200 μg/L AgNPs and fed the populations.

We fed the *Daphnia Chlamydomonas reinhardtii* cells at three food inputs (0.07, 0.14, and 0.27 mgC/day). We chose these food inputs based on previous work with small populations of *D. pulex* in our lab (unpublished data) and calculated food inputs that we estimated would result in equilibrium population sizes not so large that it would be intractable to count every individual but large enough to not suffer from random extinction due to demographic stochasticity. The *C. reinhardtii* cells were from cultures 10–12 days old. We centrifuged a 500 mL algal batch culture on 7000 rpm for 4 min, re-suspended the cells in nanopure water, and then measured the concentration of chlorophyll fluorometrically (see methods in Stevenson et al. 2013). We then converted the chlorophyll a concentration to a carbon concentration using a fixed mg C: μg chlorophyll ratio that was measured empirically in our laboratory (0.22 mgC/μg chlorophyll a). We saved samples from throughout the population experiment and measured the concentration of algal carbon fed through time after the experiment ended. We did this by removing 5 mL of sample and drying the samples down in a drying oven and analyzing them for total carbon and nitrogen on a CN analyzer (Thermo Scientific Flash 200 CN Analyzer). We also measured the amount of algal food left behind by the populations fluorometrically, using chlorophyll a as a proxy for algal biomass (see methods in Stevenson et al. 2013).

We placed the experimental populations in the dark for the duration of the experiment to maintain the fed algal food input. The cultures were at a temperature of 21.8 ± 0.6 degrees Celsius (average ± standard deviation of hourly measurements taken by Maxim Integrated iButton DS1921G throughout experiment placed in 400 mL of water next to the experimental cultures). The experiment was run for 89 days for all treatments except the highest food input, AgNP treatments—in view of the high cost of AgNPs, those were concluded on Day 68 because these populations had never differed substantially from control treatments at this food input.

**Bacterial Cell Counts**

Throughout the experiment, we noticed that AgNP-exposed populations had more buildup of detritus, especially shed carapaces, compared to controls, potentially indicating AgNPs may be toxic to the bacterial populations in our experiment and hindering breakdown of organic material. We measured the bacterial population through DAPI staining (4’,6-diamidino-2-phenylindole), a commonly used method for counting cells as the stain binds to DNA and fluoresces. We removed 50 mL samples from media post-transfer (we removed the daphnid individuals and then took samples of the media left behind), fixed them with formalin, and then stained the samples with 0.8-μm backing filter (Fisherbrand General Filtration Membrane Filter) behind the 0.2-μm filter. We mounted the filters onto glass microscope slides and counted bacterial cells using epifluorescence microscopy (Olympus B202).
Methods: Theory

Individual Model Description

We fit a variant of the net production biomass-based model of individual daphnid growth and reproduction from Nisbet et al. (2004) to the data in Stevenson et al. (2017) on the effect of AgNPs on *D. pulicaria* fed different food rations (Table 1). The only difference from Nisbet et al. (2004) was that we assumed ingestion rate of food for individuals is proportional to carbon mass of the *Daphnia* rather than use a spline-based function as in the published paper. As our target population data came from transfer cultures where all food is eaten or sinks to the bottom of the culture flask (see below), this modification is expected to have small impact on model predictions of biomass and greatly eases fitting. It is, however, important to note that the omission of any allometry in net production removes any characterization of juvenile–adult competition for food which is likely critical for determining changes in population demography, notably any tendency to population cycling (de Roos and Persson 2013). It thus also likely eliminates the likelihood that the IBM will correctly characterize the dynamics early in the experiment, even in biomass. For this reason, our model analysis focused on the biomass dynamics near the end of the population experiments.

The model has three state variables—algal food density (mg C/L), carbon weight of an individual (mg C), and the cumulative number of eggs produced (eggs). The model distinguishes between juveniles and adults—any individual less than the weight at reproductive maturity (estimated from the individual data) is a juvenile, and any individual above that weight is an adult. The transition to the “adult” stage occurs at the size where the *D. pulicaria* started releasing free-swimming neonates; we made this decision because our individual and population-level models do not include explicit molts or any delay between energy committed to reproduction and the production of neonates.

Since our experiments were transfer cultures (where the media and food were replaced on a Monday–Wednesday–Friday schedule), the algal food densities reset to the food ration every 2, 2, and 3 days. In between the transfer intervals, daphnid individuals feed at a rate proportional to their weight and with a Type 2 functional response to instantaneous food density. Maintenance rate per unit of body weight is the same for all stages. Adults allocate assimilated carbon to either growth and maintenance or to reproduction, and the proportion of carbon allocated to reproduction is defined by the function $\gamma$. Juveniles do not allocate any carbon to reproduction. Adults produce eggs at a rate proportional to the amount of carbon assimilated that is allocated to reproduction, and this amount of carbon is converted to eggs based on the amount of carbon that is required to produce one egg ($\gamma$). Individuals in this model were allowed to shrink in terms of weight but could not re-utilize energy already previously allocated toward reproduction.

We initialized the model with all individuals starting at the weight at birth ($W_b$). We converted the measured length data to carbon weight for all length data using the equation in Paloheimo et al. (1982) for *D. pulex* ($W = 0.00624L^{2.4}$ for $W$ = weight in mg dry weight and $L$ = body length in mm). We previously verified that this relationship is consistent with data on *D. pulicaria* (Fig. S1), a species with very similar physiological parameters. We converted dry weight to mgC assuming that the daphnid is 42% carbon (Lampert 1977)).

Population Model Description

We modeled the dynamics of the empirical populations using an Individual-Based Model (IBM) coded in NetLogo (Tisue and Wilensky 2004) (version 6.2). Growth and reproduction of individual *Daphnia* were modeled using the net production model (Table 1) with parameters fit to the individual-level data from Stevenson et al. (2017) (Table 2) with a few additional parameters defined by the experimental setup or fit to the individual-level data (Table 3). The simulated populations are transferred into fresh food on

Table 1 Individual net production model (variant on Nisbet et al. (2004))

| State variables | Functions |
|-----------------|-----------|
| $F(t)$          | Algal food density at time $t$ (mgC/L) |
| $W(t)$          | Carbon weight of an individual at time $t$ (mgC) |
| $C(t)$          | Cumulative eggs produced at time $t$ |

**Balance equations**

**Juveniles** ($W < W_p$):

\[
\frac{dF}{dt} = \phi(t)V^{-1}
\]

Algal food

\[
\frac{dW}{dt} = \varepsilon \phi(t) - bW
\]

Juvenile growth\(^a\)

\[
\frac{dC}{dt} = 0
\]

Juvenile egg production

**Adults** ($W \geq W_p$):

\[
\frac{dF}{dt} = \phi(t)V^{-1}
\]

Food

\[
\frac{dW}{dt} = \chi(\varepsilon \phi(t) - bW)
\]

Adult growth\(^b\)

\[
\frac{dC}{dt} = \frac{\varepsilon\phi(t) - bW}{w_e}
\]

Adult egg production\(^b\)

\(^a\)Note that individuals can shrink in terms of weight if maintenance costs are greater than assimilated energy

\(^b\)If maintenance costs were greater than assimilated energy, $\frac{dC}{dt} = 0$. Energy allocated toward reproduction cannot be re-utilized
Mondays, Wednesdays, and Fridays (any food leftover from the previous feeding is removed, and food is supplied at the food supply rate for that population). Individuals release a neonate after allocating the appropriate amount of carbon for reproduction. New offspring are initialized with 0.0011 mgC. Any energy dedicated to egg production leftover after offspring release is saved until the next molt. Two new modules were added: a one-parameter “damage” module describing age and toxicant impacts on individual hazard rate (risk of death per unit time) and a module describing algal “sinking” (also called settling) to the bottom of the culture flasks where they become much less accessible to daphnids. We assumed that the sole physiological mode of action of the AgNPs is on mortality.

The IBM is initialized using the number and carbon mass of individuals that started the experiments which varied between the food supply rates (see earlier methods section, including distinctions between “small” and “large” neonates). All individuals started without eggs. The populations were simulated for up to 89 days or until all individuals died. Each food input and treatment (AgNP and control) was simulated 100 times because of the stochastic mortality term (discussed below).

The damage module is a simplified implementation of an approach to mortality estimation now widely used in ecotoxicology, notably in applications using GUTS (e.g., Jager et al. 2011). In brief, we couple a maximally simple characterization of toxicokinetics, and assume that in response, an organism accumulates physiological “damage,” an abstract concept that potentially encompasses a vast range of biological mechanisms. Hazard rate is assumed to be proportional to damage. Here, we assume that Daphnia individuals absorb AgNPs at a rate proportional to their biomass and define \( Q = \text{body burden of AgNP}, W = \text{biomass}, q = Q/W = \text{damage density}. \) Uptake rate of AgNP is assumed proportional to biomass, and we assume no loss or transformation of absorbed AgNP.

Then \( \frac{dQ}{dt} = aW \) and \( \frac{dq}{dt} = a - q\left(\frac{1}{W}\frac{dW}{dt}\right) \)

\( \text{dilution by growth} \)

\( = a - g(t)q \) with \( g = \frac{1}{W} \frac{dW}{dt}. \)

The immediate implication is that damage density increases faster when growth is slower.

To simplify subsequent parameterization considerably, we assume no mother-to-neonate transfer of AgNP, so that for all individuals \( q \) is zero at birth. A mathematical consequence of this assumption is that the ODE for \( q \) has a solution of the form

\[ q(t) = a \times \text{function independent of } a \text{ involving growth history} \]

We have no data on bioaccumulation and therefore cannot estimate the parameter \( a \). However, we can rescale and work with a differential equation for the ratio \( q/a \), (which has units of time) and which can be interpreted as a damage index.

\[ \frac{d\tau}{dt} = 1 - g(t)\tau. \]

Hazard rate (mortality rate) \( \mu \) is now assumed to be the sum of a background and a term proportional to damage density and we can thus set

\[ \mu = \mu_0 + A\tau, \]

where \( A \) (units 1/day) is a single parameter which can be estimated from the data in Stevenson et al. (2017). At each time step, the death rate is calculated and then compared to a random number picked between 0 and 1. If the death rate is greater than that random number, the individual dies.

We incorporated an algal sinking module into the IBM because we found that the populations only consumed roughly half of the algal food they were provided. In the algal sinking

| Parameters | Units | Estimate | Confidence interval |
|------------|-------|----------|---------------------|
| \( I \) | Maximum specific ingestion rate | mgC-A/(mgC-D * day) | 0.57 | [0.55 0.60] |
| \( F_h \) | Half saturation constant in functional response | mgC-A/L | 0.10 | [0.094 0.10]* |
| \( \rho \) | Parameter in size-dependent allocation to growth function | 1/mgC-D | 1742 | [1364 2246] |
| \( \varepsilon \) | Assimilation efficiency | mgC-D/mgC-A | 0.7 |
| \( \rho \) | Cost of egg production | – | 0.5 |
| \( b \) | Maintenance rate | 1/day | 0.06 |
| \( W_b \) | Weight at birth | mgC-D | 0.0011 |
| \( W_p \) | Weight at puberty | mgC-D | 0.014 |

*aHighest value of confidence interval restricted by range across which parameter was allowed to vary
module, the *C. reinhardtii* cells sink with an exponential rate \( \alpha \) such that the cells are no longer available to the *Daphnia* when they have sunk to the bottom of the container. Adding ingestion, the rate of change of algal food becomes

\[
\frac{dX}{dt} = -\alpha X - \frac{IFW}{F + F_h}. 
\]  
(5)

### Methods: Statistical

We estimated parameters (Tables 1 and 3) in a series of steps, executed sequentially.

1. Estimate control parameters for the model of growth and reproduction.
2. Assume that the population experimental results are impacted by variable algal food inputs and sinking algae using a combination of data from our experiments and from published literature.
3. Estimate background mortality for controls using data from Stevenson et al. (2017) and modify with an estimate of the damage related parameter \( \Lambda \) by calibrating the estimated long-run growth rate and comparison with Fig. 5 of Stevenson et al. (2017)
4. For 200 µg/L treatments, estimate the new parameter \( \Lambda \) by calibrating to fit the 200 µg/L estimates of \( r \) from Stevenson et al. (2017).

We describe each below.

1. We fixed parameters \( \epsilon \) and \( \gamma \) to values based on well-established estimates in the literature (summarized in Nisbet et al. [2004]). We calculated the value of \( b \) using the data in Stevenson et al. (2017), specifically growth at the food input of 0.001 mgC/daphnid/day. At this food ration, *Daphnia* did not reproduce and growth saturated around 1.9 mm (0.0122 mgC). We assumed an assimilation efficiency of 0.7, such that the *Daphnia* were assimilating approximately 0.0007 mgC/daphnid/day. Assuming all of that energy went toward growth and respiration (since the individuals did not reproduce), we calculated a value of the maintenance rate (\( b \)) to be 0.06 1/day, a value consistent with past studies of *Daphnia*. We estimated the remaining parameters using a likelihood method coded in the package BYOM ("Bring Your Own Model") platform for parameter estimation, developed by Tjalling Jager (http://debtos.info) for Matlab (Mathworks). Details on the fitting routines in this software can be found in Jager (2021). We estimated the values of parameters \( I \), \( F_h \), and \( \rho \) by fitting all food levels simultaneously. The negative log-likelihood value of the model fit is provided in the figure legend (Fig. 1). Confidence intervals were calculated using likelihood profiles (95% probability from the \( \chi^2 \) distribution).

2. Algal carbon data analyzed after the completion of this experiment showed that the algal carbon input varied throughout the experiment. To take account of this, we fit a three-parameter function, to measurements of the algal carbon fed throughout the experiment, such that the nominal daily ration at time \( t \) (\( X_C(t) \)) equals:

\[
X_C(t) = \zeta(1 + \beta te^{-\delta t})
\]  
(6)

We fit the three parameters equation 6 to our empirical data using Mathematica (the function NonlinearModelFit).

3. Data from measurements of residual algae yielded an estimate of 2.0 day\(^{-1}\) for the sinking rate \( \alpha \). Given our large uncertainty this estimate is consistent with a published estimate of 1.57 day\(^{-1}\) (Kearns and Hunter 2001). We used this published value in the simulations reported here.

4. We estimated the background mortality rate using the individual-level data (Stevenson et al. 2017), assuming a constant, exponential decay function. We estimated the value of the damage accumulation rate for controls

| Parameter            | Units | Value      | Source                  |
|----------------------|-------|------------|-------------------------|
| \( \alpha \)         | 1/day | 1.57       | Kearns and Hunter (2001) |
| \( \mu_0 \)          | 1/day | 0.04       | Individual data         |
| \( \Lambda \)        | 1/day | 0 (Control) | Individual data         |
| \( \Lambda \)        |       | 0.004 (AgNP) | Individual data         |
| \( \nu \)            | L     | 0.4        | Population experiment   |
| \( \zeta \)          | mgC/day | 0.163 | Fit to algal carbon data |
| \( \beta \)          | mgC/day | 0.209 | Fit to algal carbon data |
| \( \phi \)           | 1/day | 0.0587     | Fit to algal carbon data |
by manually adjusting the value of \( A \) until the final biomass in population controls with the highest food input was close to the long-term biomass we found in the population experiments. We then tested this value of \( A \) by computing the long-term population growth rate \( (r) \) applying the Euler-Lotka equation to simulations of the individual experiments with food inputs 0.01 and 0.0025 mgC/daphnid/day and comparing with the values calculated by Stevenson et al. (2017, Fig. 5).

(5) We used this method to estimate the value of \( A \) for the AgNP treatment: we adjusted the value of \( A \) until the calculated value for \( r \) matched the values found in Stevenson et al. (2017). For the AgNP treatments, only individuals at the highest food ration produced neonates, so only one value of \( r \) could be used. The damage accumulation rate for the AgNP treatment was estimated by matching this estimate of \( r \).

To analyze for statistically significant differences between bacteria cell counts and to calculate mortality rates for the IBM, we performed linear regression using R (version 3.2.3). To calculate average background mortality rates, we assumed survival followed an exponential decay function and calculated the slope of this function by taking the natural log of survival and time and calculating the slope of the resulting line. Confidence intervals were calculated in R using 'confint'.

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**Fig. 1** Fit of individual model to control *Daphnia pulex* individuals fed four food rations (Stevenson et al. 2017). Food rations are 0.0005, 0.001, 0.0025 and 0.01 mgC/daphnid/day. Negative log-likelihood value of this fit = -2323.96. Data points are averages, and error bars represent their standard error. Data points are from Stevenson et al. (2017)
Results: Parameter Estimates

Individual-Level Model Parameter Values

We fed the *Daphnia* algal food at the nominal food rations (0.0005, 0.001, 0.0025, 0.01 mgC/daphnid/day) assuming a fixed chlorophyll to carbon ratio (Stevenson et al. 2017). We measured the carbon concentration of food fed throughout the experiment and the actual concentrations fed were 0.00064, 0.0013, 0.0032, and 0.0128 mgC/daphnid/day (unpublished data). We used the measured values converted to an algal carbon density at the start of each transfer interval as the model food inputs (Fig. 1).

The fit of the individual-level model to our individual-level data is shown in Fig. 1. The model broadly matched the dynamics of growth and reproduction in *D. pulicaria* fed a wide range of food rations. There are some significant mismatches, specifically the model underpredicts growth at the lower food rations but recognizing the importance of reproduction for predicting population dynamics, the goal of this work, we accepted this limitation of our individual model.

Population-Level Model Parameter Values

The IBM required a few parameters not estimated for the individual-level model, specifically the background hazard rate, damage accumulation rate, and algal sinking rate. We also explicitly measured concentration of algal carbon fed to the populations and used these values for the food input rate.

Hazard Model

We calculated background hazard rate for unexposed individuals across the food rations (Fig. S2) assuming that the individuals die exponentially. The parameter value and confidence interval are reported in Table 3. We estimated these values by comparing the predicted $r$ values for these estimates of $A$ compared to the calculated $r$ values in Stevenson et al. (2017). Values were only calculated for the two highest food rations, 0.01 and 0.0025 mgC/daphnid/day, because those are the only two food rations at which the *Daphnia* reproduced, and no individuals exposed to AgNPs reproduced at food rations less than the highest. In the controls, the $r$ values calculated using the estimate of $A$ reported here are 0.046 and 0.20 1/day (0.03 ± 0.02 and 0.24 ± 0.03 in Stevenson et al. 2017), mean ± standard deviation of 1000 bootstrapped values), for 0.0025 and 0.01 mgC/daphnid/day, respectively. For the AgNP-exposed individuals, the $r$ value calculated using the estimate of $A$ reported here is 0.18 per day for 0.01 mgC/daphnid/day (0.06 ± 0.10 in Stevenson et al. 2017).

Algal Sinking Rate

We found that the daphnid populations did not consume 18–63% of the algal food they were fed, and this difference varied across the number of transfer days that had elapsed and, to a lesser extent, between the control and AgNP treatments (Fig. S3). We hypothesize that this is due to algal sinking, which we explicitly added to the IBM as described in the Methods section.

Kearns and Hunter (2001) measured the sinking or settling rate of *C. reinhardtii* spectrophotometrically and found a value of 1.57 1/day. When plugged into the algal sinking module, this value roughly predicts the concentration of algal food left behind we observed in our experiment (Figure S3). With this value of $\alpha$, the algal sinking model predicts: at the highest food input, the daphnid populations would eat roughly 50 and 40% of the algal food after 2 and 3 transfer days, respectively; at the medium food input, the daphnid populations would eat roughly 40 and 30% of the algal food after 2 and 3 transfer days, respectively; and at the lowest food input, the daphnid populations would eat roughly 40 and 30% of the algal food after 2 and 3 transfer days, respectively.

An obvious deviation between our model and data (Fig. S1) is that the model predicts that the daphnid populations would eat less of the food after the 3-day than the 2-day transfer interval; however, our data show that the populations ate more of the food after the longer transfer interval. This is probably due to the daphnid populations starting to root around at the bottom of the beaker after an extended period without food, possibly eating some of the algal cells that the model assumes are unavailable because they have sunk. Although there is this mismatch, this simplified model using the single parameter value from Kearns and Hunter (2001) broadly captures the algal food dynamics observed in our population experiments.

Algal Food Input Concentrations

To incorporate this variability into the IBM, we fit a function to track the variability in the mgC algae fed per day throughout the experiment (Fig. 2). The algal food fed on transfer days was multiplied by this function in the IBM to scale the food inputs across the experiment to match the mgC content of the algae the daphnid populations were being fed.
Results: Bacterial Measurements

The tested concentration (200 μg/L) of AgNPs has only a small effect on bacterial communities. We measured the bacterial population in all experimental cultures after a 2- and 3-day transfer interval to analyze for differences between AgNP and control cultures. We found no difference between control and AgNP bacterial populations after the 3-day transfer interval. (Fig. S4A); however samples taken after the 2-day transfer interval were significantly different (Fig. S4B). The food input (p=0.011) and AgNP treatment (p=0.010) both had significant effects on bacterial abundance.

These samples were taken on days 57 and 59 of the population experiment, as AgNP-exposed populations were recovering from the initial decline around day 50. It is unclear whether the significant or the not-significant result from the 2- and 3-day transfer results, respectively, more accurately describes the average state of the cultures throughout the experiment.

However, 200 μg/L AgNPs is probably not a high enough concentration to kill most bacterial species—a meta-analysis of AgNP toxicity studies to a variety of taxa found that the average median lethal concentration (LC50) or half maximal effective concentration (EC50) of AgNPs to bacteria is 7.10 mg/L, about 35 times higher than our exposure concentration (Bondarenko et al. 2013). A more recent review of silver nanoparticle toxicity found that EC50 or minimum inhibitory concentration (MIC) values of AgNPs to bacteria ranged from 0.27 to 250 mg/L with an average of 23.24 mg/L (Liu et al. 2022).

Data are an average of two replicates and the error bars are their standard error. See the “Methods” description for more details on fitting. Residual sum of squares of this fit=0.093
Results: Population Impacts of Exposure to AgNPs

200 μg/L AgNPs Only Impact Populations Substantially After 50 Days To Lowest Food Input

The tested concentration (200 μg/L) of AgNPs had no significant effect on viability of populations fed the two highest food inputs, and only had an effect on populations fed the lowest food input after 50 days (Figs. 3, 4, 5, S5–9). Although there is some variability, there are no large differences between control and AgNP treatments in the two highest food inputs (Fig. 3).

After 50 days, all populations begin to decline, with AgNP-exposed treatments decreasing more across all food inputs. We hypothesize that all populations are declining after their initial growth due to overshooting the equilibrium biomass allowed by the algal food input. This effect is stronger at lower food inputs—at 0.27 mgC/day, the populations return to control levels within 10 days and do not decline as sharply, while populations fed 0.14 mgC/day take about 15 days to return to control levels, and populations fed the lowest food input decline to extinction (Fig. 3). Populations exposed to AgNPs at the high and middle food inputs were able to recover to control levels, driven by boosts in fecundity between days 50 and 70 (Fig. S9) due to higher food inputs and reduced competition; however, populations fed the lowest food input never recovered. One AgNP-exposed replicate at the lowest food input went extinct immediately on day 54, while the other declined to one adult that continued to produce offspring every transfer interval; however, none of her offspring reached adulthood and the adult eventually died. While there are declines in the AgNP treatments across all stages (Figs. S6–8), adults seem to be the stage most affected by this decline in even the control treatments (Fig. S8). We can conjecture that the delay in responding is because the population starts with the “luxury” of undamaged adults who can produce many

Fig. 3 Total number of individuals in each of the daphnid populations fed different food inputs. Points are data from the daphnid population experiment: data points represent the average and the error bars their standard error. Each treatment (nanoparticle and food concentration) had 2 replicates. Note that the AgNP treatments at the highest food inputs were stopped on Day 68.
neonates before accumulating large levels of damage. The next generation starts accumulating damage from birth and hence has a much lower chance of surviving to reproduce. Indeed, 200 µg/L AgNPs had no effect on the survival, growth, or reproduction of adults fed 0.01 mgC/daphnid/day but decreased the survival of neonates at this food ration and AgNP concentration (Stevenson et al. 2017). These observations fit with our hypothesis: if the adults that started the experiment die around 40–50 days (which broadly fits individual survival for all but the lowest food ration; Fig. S2), then all remaining individuals producing new offspring were exposed to AgNPs as neonates and had been accumulating damage nearly their entire lives. If AgNPs decreased the reproductive output of these adults compared to the previous cohort, then control populations would be able to recover from the loss of the first adult cohort, while AgNP-exposed populations will have more difficulty recovering.

As noted earlier, we regard the most reliable test of the model to be biomass levels late in the experiment. Figure 4 displays the carbon biomass of the empirical daphnid populations through time compared to the IBM’s prediction of the carbon biomass of the daphnid population (the mean of the values of the carbon biomass of the simulated populations after Day 68 from 100 IBM runs and the error bars represent their standard deviation).

A Population Model Parameterized with Individual Data Predicts Pattern in Population Persistence and Long-term Biomass

We were able to predict the biomass toward the end of the population experiment using our IBM parameterized mostly using individual-level data for all treatments except the AgNP-exposed populations fed the highest food input (Fig. 4). We assumed AgNP bioaccumulation resulted in the accumulation of damage which increased the hazard rate. We get general agreement between the predicted long-term biomasses of the model compared to the data collected from our experiment (Fig. 4). Overall, the IBM slightly underpredicted the biomass at the lowest
food input in the control treatment but agreed with the middle and highest food inputs for the controls. Interestingly, the opposite was true for the AgNP treatments—the IBM underpredicted the highest food ration but matched the empirical populations better at the two lower food inputs. Importantly, the IBM successfully predicted that daphnid populations exposed to this concentration of AgNPs could go extinct at the lowest food input rate but could persist with more food: out of 100 IBM simulations, 0, 0, and 34 populations went extinct at the high, middle, and low food inputs, respectively.

Interestingly, explicit incorporation of the variability in the algal food input throughout the experiment (Fig. 2) greatly improved the IBM’s ability to describe the empirical data. The empirical daphnid populations and biomasses appear to have closely tracked the fluctuating food input.

**The IBM Does Not Accurately Predict the Size Structure of the Empirical Populations**

As anticipated in the model description, a simplifying assumption in the individual model removes the model’s capacity to correctly describe detailed demography and the transient biomass dynamics (Fig. S10). The IBM overpredicts the number of neonates and juveniles present (Figs. S11 and S12) and underpredicts the number of adults (Fig. S13) at the end of the experiments.

**Discussion**

Perhaps our most important conclusion for ecotoxicology is that estimation of extinction thresholds utilizing calculations of long-run growth rates based on studies on *individuals* turn out to be reliable predictors of population outcomes. Our
population outcome was broadly in line with what would be anticipated from the data on individuals. Stevenson et al. (2017) suggested a threshold with 200 μg/L exposure at around 0.01 mgC per day per animal. Our lowest food population experiments were given a little over 10 times that, with around half of the food sinking. This points to a population in single digits, obviously vulnerable to extinction due to stochasticity. Reliable estimates of $r$ do require individual data over longer time periods that is required in current standardized toxicity tests (OECD 2012), but this is still much less time consuming and expensive than population experiments.

A second take home message is that other population metrics are harder to predict. Our predictions of final biomasses in the exposed population fed the highest food input did not match the data well. This is a consequence of our assumption that we could describe the combined effects of toxicokinetics and toxicodynamics with a single parameter. We also assumed a single physiological mode of action—mortality.

Our decision to focus on mortality was reached after considerable preliminary work on the individual growth/reproduction data where we assumed AgNPs impacted sublethal processes such that it took more energy for an individual daphnid exposed to AgNPs to grow and reproduce than an unexposed individual. However, after attempting to estimate individual-level parameters to describe this effect, we realized that 200 μg/L AgNP did not appear to strongly impact sublethal processes, but rather impacted mortality such that AgNP-exposed individuals grew to smaller sizes and did not reproduce as much or at all because individuals died before reaching maturity (Stevenson et al. 2017). This differs from past studies that found that silver decreases reproduction in Daphnia (Sakamoto et al. 2015; Volker et al. 2013), even at concentrations at which mortality was not impacted (Bianchini and Wood 2003; Hook and Fisher 2001; Qin et al. 2015; Ribeiro et al. 2013).

Another finding that may have considerable generality is that low food enhances AgNP toxicity to populations of Daphnia. 200 μg/L AgNPs did not have a significant effect on the daphnid populations until around Day 50, when all AgNP-exposed populations declined sharply across all food inputs (Fig. 3). Populations at higher food inputs were able to survive the decline in AgNP-exposed populations around day 50, but the populations at the lowest food input went extinct, indicating the compounding effects of nano- and food stress. This conclusion follows our previous work (Stevenson et al. 2017) in addition to other studies that have found that decreased food availability increased the toxic effect of AgNPs (Mackevica et al. 2015; Sakka et al. 2016). Increased sensitivity at low food conditions could be due to the damage produced by AgNPs, either being diluted less due to the slower growth at lower food or damage requiring some amount of repair or mitigation that costs energy. Individuals at higher food rations may have a slightly greater energy reserve to deal with this stress than those at lower food rations. This reinforces the message by Stevenson et al. (2017) that in spite of the practical challenges, data on toxicity at ecologically relevant food concentrations (commonly low) are critical. This requires deviation from standardized test standards by feeding Daphnia low, environmentally relevant concentrations of food; in summer, average algal concentrations can vary between 0.009 (McCaulley and Murdoch 1987) and 0.07 (Murdoch et al. 1998) mgC/L compared to the required 1–4 mgC/L concentrations required in OECD tests (OECD 2012) (McCaulley and Murdoch 1987).

We end by commenting on the importance of the dynamics of the resource environment for determining population outcomes. One of the more interesting and striking results of this work are that 200 μg/L AgNPs is largely toxic to individuals exposed as neonates at all food rations (Stevenson et al. 2017), but this same concentration of AgNPs is not toxic to neonates when part of a larger population, except when the food input is very low (Fig. 3). We conjecture that this is because the transfer culture regime used in the population experiments resulted in some neonates being released into relatively high food environments. More broadly, the need to consider the dynamics of the resource environment, including feedbacks from an impacted population, needs further emphasis in all considerations of environmental stress. For example, Civitello et al. (2022) recently showed the importance of a snail’s resource in determining human risk of schistosomiasis from parasite release; under some circumstances, removing snails may increase risk. Schmolke et al. (2019) simulated the effect of reduced food availability on a fish population using a coupled IBM and aquatic food web model. Reducing different food items had differential effects on fish population and depended on the fish’s diet preferences (Schmolke et al. 2019). Models such as these and the work presented here emphasize the importance of the incorporation of ecological mechanisms when quantifying the impact of anthropogenic change on natural populations.

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Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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