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Linking Exposure and Kinetic Bioaccumulation Models for Metallic Engineered Nanomaterials in Freshwater Ecosystems

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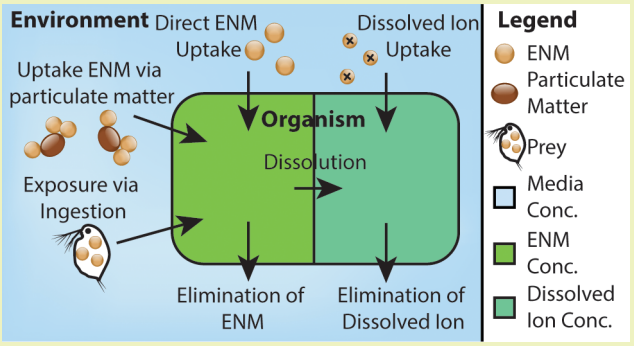
Supporting Information

ABSTRACT: We developed a model (nanoBio) to simulate long-term kinetic bioaccumulation of metallic engineered nanomaterials (ENMs) across trophic levels within a freshwater aquatic ecosystem based on current understanding of environmental and biological fate. Seven species were chosen to understand exposure pathways, accumulation through trophic levels, and the potential for biomagnification. Uptake, elimination, and dissolution of the ENM are the only processes modeled, though different routes and rates are accounted for with each species. We explored the bioaccumulation of nCuO, $nTiO_2$, and nZnO. nanoBio estimates the potential range in average body concentration across populations. Estimated bioconcentrations ranged from 1.7×10^{-8} pg nCuO g^{-1} for *Selenastrum capricornutum* to 27 μg $nTiO_2$ g^{-1} for *Oncorhynchus mykiss*. The highest overall biomagnification was predicted for $nTiO_2$ within the highest trophic level species. ENM dissolution decreases total biomagnification; however, the released metal ions may still cause toxicity. nanoBio results serve to (1) highlight trophic levels at potentially higher risk of bioaccumulation; (2) temporal patterns that influence peaks in concentration; (3) processes which require more experimental data to reduce uncertainty. Based on a sensitivity analysis, the most significant parameters to the variability in estimates include uptake rates from multiple exposure routes and assimilation efficiency, which has a substantial impact on biomagnification. Better understanding of the mechanisms and processes that impact bioaccumulation through targeted laboratory testing will greatly improve the predictive accuracy of nanoBio. We should stress the conditional nature of the rate constants used in this study, because the environment, the biology, and the toxicity itself can alter these parameter values over time. The model also can be used to guide testing protocols to determine key parameter values that influence bioaccumulation.



KEYWORDS: *Nanoparticle, Trophic transfer, Biomagnification, Modeling*

INTRODUCTION

Engineered nanomaterials (ENMs) represent an emerging class of materials for which little is understood regarding their impacts on ecosystems. ENMs are being used with increasing frequency in industrial applications and in consumer and medical products.[1] Their increasing use means increasing environmental exposure, which in turn creates a compelling need to understand and predict their accumulation in organisms.[2] Because limited technologies exist for *in situ* measurements, model driven estimates are particularly important.[3,4] The first step to estimating bioaccumulation is estimating exposure concentrations in the water column and sediments. We previously developed the nanoFate model to predict the environmental fate of metallic ENMs at watershed scale environments.[5] nanoFate can thus be used to predict exposure concentrations for freshwater ecosystems, among other environmental compartments. Because carbonaceous ENMs may partition quite differently from metallic ENMs and would require different considerations, this study focused only on metallic ENMs.

Following exposure, only a fraction of the ENMs present in the environment enter an organism, and a smaller fraction is retained within the organism.[6] Exposure to the ENM and its transformation products is determined by the processes that ENMs undergo in the environment such as aggregation, dissolution, oxidation, sulfidation, binding to larger particulate matter, and surface alterations which are often determined by the size, shape, and charge of the ENM as well as the characteristics of the environmental media.[7−15] ENM biotransformations are also likely but much more difficult to currently account for in a model, given the limited information, thus they are not considered.[16−18] These various transformations make it difficult to predict what happens to ENMs after they enter an organism and the significance of each process. Although the number of ENM aquatic food chain studies is limited, they indicate that bioaccumulation of ENMs

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and their transformed forms (i.e., metal ions) is likely.[19,20,29,30,21−28]

Studies have shown that individual and homoaggregated nanoparticles and nanoparticles heteroaggregated with larger particulate matter can accumulate and subsequently distribute throughout the body of an organism[25,31−35] While the literature is limited regarding the bioavailability of metallic nanoparticles and their subsequent accumulation in organisms, exposure is expected to occur via individual free nanoparticles, homoaggregates, and heteroaggregates formed with sediments or particulate organic, and for soluble ENMs as dissolved metal ions.[11] The form of exposure can have an impact on the rate of accumulation and on the resulting toxic effects. For example, soluble metallic nanoparticles release metal ions from the surface of the particle; these metal ions are known to cause latent free-ion toxicity,[36−38] which may result in different toxic impacts than exposure to the original nanoparticle.

Understanding bioaccumulation is key to both ecotoxicity and risk assessment, because it determines the internal dose of a potential toxicant.[39,40] Typical measures for assessing bioaccumulation of organic compounds include the octanol−water partition coefficient (K_{ow}), which is a surrogate for the tendency of an organic chemical to partition into the lipid compartment of an organism.[40−42] However, this is not applicable to metal ions or metallic ENMs.[43] As such, an alternate model for predicting the bioaccumulation of metallic ENMs in organisms is needed. Given the focus on ENM accumulation, the Biotic-Ligand Model (BLM)[44−46] was not used for this study because there is no evidence to suggest that it can be applied to particulate metals and numerous studies indicate that uptake of nanoparticles does occur. While BLM has been successfully applied to dissolved Cu and Zn,[44−49] given that we explore dynamic ENM and metal ion bioaccumulation, a different model is needed.

A few models of ENM bioaccumulation in single organisms and two species models have been developed based on intensive laboratory studies.[21,22,50−54]Accumulation can be simplified to a series of first-order processes that represent uptake, elimination, and transformations within an organism.[55−62] These rates depend on the biological traits and conditions of the organism (e.g., age, size, maturity), the environment (e.g., food density, temperature), and the size, type, chemical composition, functionalization, and stability of the ENM.[27,63−65] Single species models exist for specific ENMs including the accumulation and effects of nZnO on *Mytillus galloprovincialis*,[62] CdSe quantum dot on *Pseudomonas aeruginosa*,[59] $nTiO_2$ and nAl_2O_3 on *Ceriodaphnia dubia*,[60] indicating that this mathematical approach is a viable methodology for modeling ecosystem ENM accumulation. A biodynamic accumulation model was developed for accumulation and effects of nAg on *Peringia ulvae* and *Lymnaea stagnalis*[53] and a biokinetic model predicted the accumulation of nAg and Ag^+ in earthworms using parameters selected or deduced indirectly from the literature as a way of identifying key processes and parameters.[35]

Trophic transfer of ENMs up the food chain has also been investigated in a few studies.[23−27,29,66,67] Current evidence suggests that ENM accumulation does occur and that uptake from primary producers up through the trophic levels is also probable.[68] This indicates a potential concern for biomagnification with body concentrations increasing up the food chain. Preliminary studies do not conclusively indicate there is the likelihood of biomagnification because most are limited to low trophic levels. For example, nZnO was found to assimilate into *L. stagnalis* through dietary exposure. nAu and nAg were found both to transfer up the food chain and, in some cases, indicating the possibility of biomagnification.[23,53,66,67] $nTiO_2$, however, was found to transfer but not to biomagnify.[27] In a terrestrial food chain, nAu was found to transfer, but tissue concentration decreased with each trophic step.[25] $nCeO_2$ accumulated in the terrestrial food chain though it was not clear whether it was the nanoparticles that accumulated with increasing trophic steps or a transformed form of the ENM.[26] In another study, $nCeO_2$ was not found to accumulate or magnify significantly in a simple aquatic food chain involving filter feeders.[29] Carboxylated and biotinylated quantum dots were found to transfer to higher trophic levels though no significant bioconcentration or biomagnification was observed.[30] CdSe quantum dots on the other hand were found to biomagnify in a simple aquatic system.[24] Few studies have considered bioaccumulation resulting from an extended food chain.

To better understand the ENM processes affecting ENM bioaccumulation and the possible extent, we developed the nanoBio model, which we use to explore the bioaccumulation of ENMs in a freshwater food chain. In this study, we focus specifically on the potential bioaccumulation of three metal oxide nanoparticles: nCuO, $nTiO_2$, and nZnO. This simplified system accounts for (i) the external ENM and metal ion concentrations; (ii) exposure via water, particulate matter, and sediment; (iii) dietary ingestion; (iv) metabolic transformation of the nanoparticle to the dissolved metal; and (v) elimination. The actual accumulation is the net result of these processes over time[7,11,68] and is dependent on ENM characteristics,[69−71] species-specific traits,[72,73] and species−species interactions.[74] Our objective is to build a simple model for estimating the possible range of accumulation through a food chain that can help improve our understanding of ENM environmental and biological fate and impact. Identifying key biological processes that affect bioaccumulation can also target future research. Because of substantial data limitations and the necessary simplification associated with these limitations, a global Monte Carlo uncertainty and sensitivity analysis was used to identify the range of bioaccumulation, the significance of different processes, and priority areas for further research.

METHODS

The nanoBio model was constructed to simulate a simplified freshwater ecosystem with seven species and their corresponding populations. Because the model is designed to investigate long-term accumulation, each population and its total biomass is assumed to remain static. While life expectancy of the individual organism is accounted for, growth, reproduction, and life stages are not. The system is bounded and assumes no immigration or emigration. Seven species were chosen to understand exposure pathways, accumulation through trophic levels, and the potential for biomagnification (Figure 1). Two phytoplankton species were included at the primary producer (autotroph) level: a zooplankton and a benthic invertebrate represent the herbivore level, while a bivalve and a planktivorous fish represent the primary predatory species; and an upper trophic level fish represents the secondary predatory species in the simulated freshwater ecosystem. This is similar to the combined, branched food web used in Mackay et al. 2016.[75] Diet is assumed to consist exclusively of the species that represents the same trophic guild as typical prey.[41] Thus, the representative zooplankton species consumes only the representative phytoplankton species.

In addition to the seven species, the freshwater ecosystem contains water, suspended particulate matter, and sediment. Predicted ENM

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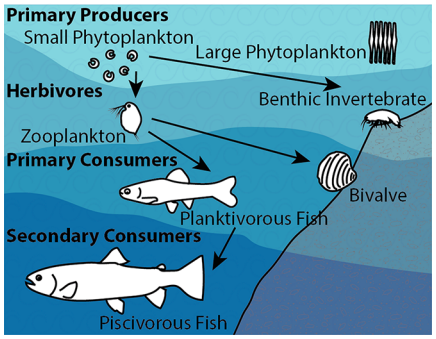

Figure 1. Conceptual food web in freshwater system.

and dissolved metal ion environmental concentrations were estimated using the nanoFate model based on conditions in the San Francisco Bay area (Figure S1).[1,5,76] These were directly used in nanoBio, and reflect the temporal variability in concentrations due to meteorological and hydrological conditions over a 10 year period. Since we model a freshwater ecosystem, nanoBio uses the freshwater concentrations predicted by nanoFate, considering the water chemistry of the freshwater inflows to the Bay. An implicit assumption in nanoBio and nanoFate is that ENMs and dissolved metal ions are homogeneously distributed within the environment (i.e., perfect mixing), and thus within organisms. In selecting ENMs, we chose both soluble and insoluble types for comparison because, while both the particulate and the dissolved form can accumulate, dissolution within the organism has the potential to cause accumulation at cumulatively higher concentrations.[11,77] nanoBio can also be used with measured ENM environmental concentrations or predicted concentrations from other models.

nanoBio assumes that the exchange of ENMs and ions between an organism and the environment can be described using a series of first-order differential equations where rate and exposure are species-specific. Uptake, elimination, and dissolution of the ENM are the only processes modeled, though different routes and rates are accounted for with each species.[62] Each species is connected within the food chain, where the n^{th} level (n = 2, 3, 4, etc.) represents that species (eq 1). The model assumes that all biological parameters and rate constants do not change over time; thus the average body burden across the population for the n^{th} trophic level ($C_{b,n}$) is

$$\frac{dC_{b,n}}{dt} = k_{u,n}C_w + \alpha_n\alpha_{ENM}k_{d,n}C_{b,n-1} - k_{e,n}C_{b,n} - k_{dis}C_{b,n} - D_nC_{b,n} \quad (1)$$

where $k_{u,n}$ is uptake rate from the surrounding medium (e.g., water), C_w is water concentration, α_n is assimilation efficiency from prey, α_{ENM} is assimilation efficiency of the ENM from the prey, $k_{d,n}$ is the feeding rate for the n^{th} level species in the food chain, $C_{b,n-1}$ is internal body concentration in prey (lower trophic level, $n - 1$), $k_{e,n}$ is elimination rate of ENMs, $C_{b,n}$ is body concentration, and k_{dis} = dissolution rate of the ENM. Internal dissolution rate is assumed to occur at the same rate as dissolution in water because internal species-specific dissolution rates for metallic ENMs are not available (detailed dissolution rates are provided in Table S2 and are taken from Garner et al. 2017).[5] While assuming the dissolution rate is the same internally as externally is an important simplification, the internal dissolution rate is likely to be of the same order of magnitude as the external rate, and can be adjusted in the future as additional experimental information on internal dissolution rates becomes available. Maximum dissolution within an organism is not allowed to exceed the dissolution equilibrium of its surrounding media at a pH similar to that of the organism. *Visual MINTeq* (version 3.1)[78] was used to predict metal speciation across a range of pH values for standard freshwater as reported in Keller et al., 2010, to estimate the equilibrium dissolution concentration across a range of metal ion concentrations (Figure S2).[79] If the dissolution rate predicts a dissolved concentration that exceeds equilibrium, then the dissolved concentration is set to the equilibrium value. Details of the *Visual MINTeq* simulation inputs and outputs are presented in Tables S11–13.

Concentration of the dissolved metal ion in the n^{th} trophic level, $C_{dis,n}$, resulting from uptake of the dissolved metal ion, internal dissolution of the ENM to the dissolved ion, and subsequent elimination of the dissolved ion was modeled as

$$\frac{dC_{dis,n}}{dt} = k_{udis,n}\alpha_{bio}C_{w,dis} + k_{dis}C_{b,n} - k_{e_{dis},n}C_{dis,n} - D_nC_{dis,n} \quad (2)$$

where $k_{udis,n}$ is uptake of dissolved metal ion from water, α_{bio} is the bioavailable fraction, $C_{w,dis}$ is dissolved ion concentration in water, and $k_{edis,n}$ is elimination rate of dissolved ion. The bioavailable fraction of the dissolved metal (α_{bio}) was also determined using *Visual MINTeq*.

Lifespan (L_n) of an individual organism is accounted for by assuming a daily mortality rate that allows us to model turnover in the population:

$$D_n = \frac{1}{L_n} \quad (3)$$

This is included because the model is run for a longer time period than the average lifespan of any individual organism and we assume that the populations remain constant over time, thus the effect of birth and death limits modulates the average body concentration across the population. At this stage in model development, we could not account for changes in mortality due to bioaccumulation.

For species with multiple routes of nondietary exposure, such as filter feeders, uptake and exposure can occur from water, suspended particulates and dietary ingestion of phytoplankton (Figure 2).[39] In this case, the first pair of variables in eq 1 are expanded to include multiple $k_{u,m}$ and C_m pairs that vary depending on the uptake exposure route and ENM concentration in the medium, m.[31] The Supporting Information (SI) provides all species-specific equations.

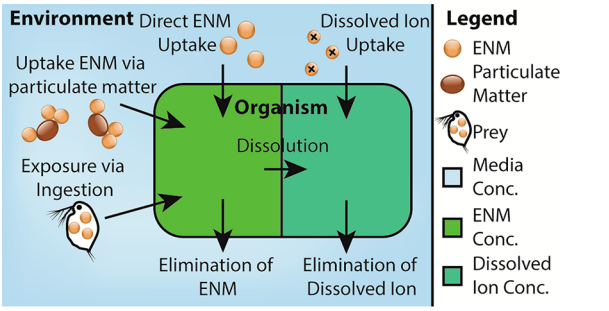

Figure 2. Conceptual model of organism and uptake, elimination, and transformation processes.

Species-specific rates of uptake and elimination were identified from the literature in a tiered approach, presented in detail in the SI. First, if ENM-specific rates were available for the specific ENM and species, these were preferred as they were considered more accurate.[53,59,62] When such data were not available, then ENM-specific rates, either from similar ENMs or from similar organisms using the same ENM, were selected. If these were also unavailable, then species-specific metal (not ENM or particle) rates were implemented. The same selection process applied to uptake and elimination rates for the dissolved metal. Table S1 presents the environmental parameter values used in nanoBio for San Francisco Bay. Table S3 shows data for all species in a food chain for nCuO, $nTiO_2$, and nZnO. Table S4 presents ENM parameters that are specific to each species. For example, dietary assimilation rates for ENMs and metals are quite rare, so we combined the assimilation efficiency of food with an assumed 10% assimilation of the ENM.[80] The implicit assumptions in this data selection process were that (i) rates are similar across metallic ENMs and metals and (ii) species

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with similar life history traits also have similar uptake and elimination rates. These assumptions can be modified as more ENM-specific data becomes available.

For some species, such as phytoplankton, adsorption to the surface of the phytoplankton may be a more significant process than actual internal accumulation.[11,81] Thus, in the model, even though uptake in phytoplankton is treated the same as uptake via respiration and ingestion in fish, it is really an adsorption process where uptake is the association of the nanoparticles relative to the volume of the phytoplankton,[59] which sorbs at a rate determined by the characteristics of the surrounding environment and the ENM. In this case, the rate is represented as the heteroaggregation rate constant for the ENM in freshwater based on lab studies of heteroaggregation with natural organic matter in freshwater, accounting for the relative concentration of ENMs and the phytoplankton in the sample freshwater system.[5,82−85]

Biomagnification was estimated for heterotrophic species as the long-term average wet-weight body concentration of the organism over the long-term average wet-weight body concentration in the prey organism.[41]

Model performance was evaluated through comparison to laboratory experimental results where available; the model was run with a constant ENM concentration, at the same level as the comparable experimental study, rather than the variable ENM concentrations predicted for San Francisco Bay. A Monte Carlo-based uncertainty and global sensitivity analysis was also conducted. Uncertainty analysis was conducted by varying all biological parameters by ±50% with a uniform distribution over 10 000 simulations, due to the assumption of relatively high uncertainty implicit in these parameters. The uncertainty analysis provides a range in the distribution of probable accumulation concentrations for both the ENM and the dissolved metal ion for each species. The same Monte Carlo sample of the inputs and outputs of nanoBio was used to run the global sensitivity analysis.[86] The analysis was based on the Kolmogorov−Smirnov distances between cumulative distribution functions and was applied to evaluate the importance of the input parameters that significantly impact accumulation results and the variance of the output.[87,88] This method was selected because it provides transformation invariant global sensitivity measures.[87,88] The resulting global sensitivity analysis generates a ranking of parameter significance on results.

RESULTS

Because direct comparisons with field data are not currently feasible (no such data sets exist and reliable methods for detecting nanoparticles in tissues are still under development), we compared nanoBio model results to laboratory studies (Table S5). We considered a constant exposure at a fixed ENM concentration, replicating laboratory conditions. Note that nanoBio considers both direct uptake from the aqueous medium or sediments (depending on the species) and dietary exposure, while in many laboratory studies the exposure is only via the medium or the prey. For *O. Mykiss* (trout) exposed to 0.1 mg/L $nTiO_2$ for 14 d, nanoBio predicts a concentration of 0.17 mg/g wet weight (WW), compared to a measured 0.54−0.8 mg/g WW,[89] assuming a conversion of 4.5 to 5 from dry weight (DW) to WW.[90] When the exposure of *O. Mykiss* is increased to 5 mg/L for 14 d, nanoBio predicts 3.5 mg/g WW, which falls within the laboratory exposure finding of 2.0−4.4 mg/g DW.[89] For nZnO, *O. Mykiss* exposed to 0.5 mg/L are predicted to accumulate 7.2 mg/g WW in 14 d, while the corresponding laboratory exposure resulted in an accumulation of 1.7−2.55 mg/g WW.[89] Comparing bivalves, nanoBio predicts that *V. constricta* exposed to nCuO at 150 mg/kg in sediment for 35 d will accumulate 0.23 mg/g WW, while a comparable laboratory exposure for *M. balthica* resulted in an accumulation of 0.04−0.25 mg/g WW, using a conversion of 9.3 to 25 from DW to WW.[91] Exposure of *V. constricta* to 0.1 mg/L of nZnO is predicted to result in 0.65 mg Zn/g WW, while in the laboratory exposure of the marine bivalve *M. galloprovincialis* under the same conditions resulted in 0.8−0.9 mg Zn/g WW. Thus, for fish and bivalves the model predictions are within a factor of 2−5. As more experimental data becomes available, the parameters that result in the highest sensitivity in the predictions can be improved.

There was a more significant discrepancy between model results and laboratory experiments for bioaccumulation of ENMs and dissolved metal ions in *D. magna*. While laboratory experiments exposing *D. magna* to 0.07 mg/L nCuO for 9 d resulted in an uptake of 0.09−0.18 mg/g WW,[92] using a conversion of 11 to 20 from DW to WW,[93] the model predicted only 0.0036 mg/g WW, both in terms of total Cu. For $nTiO_2$ at 0.1 mg/L, the model predicts 0.0098 mg/g WW, while experimental results indicate concentrations of 0.23−0.45 mg/g WW.[94] Therefore, *D. magna* appear to have a much higher ability to accumulate ENMs than can be predicted using with the current model parameter values (Table S4). Additional experimental data, with an emphasis on obtaining the experimental ENM uptake and elimination rates for *D. magna*, would serve to improve our understanding and predictive capabilities.

To translate these laboratory results to a more realistic setting, we then simulated the bioconcentrations of ENMs and dissolved ions that may occur in the San Francisco Bay. A comparison of estimated bioaccumulation over time in the freshwater ecosystem for the three ENMs and their dissolved component shows that the bioaccumulation patterns depend substantially on environmental concentrations and vary across ENMs and organisms (Figure 3). Pseudo-steady-state concentrations are reached at different points for different organisms (see SI Tables S6−S8 for time to pseudo-steady-state and the corresponding concentrations). For phytoplankton and daphnia, pseudo-steady-state is reached within the first year for all ENMs (Figure 3A,C,E). For all species, reaching

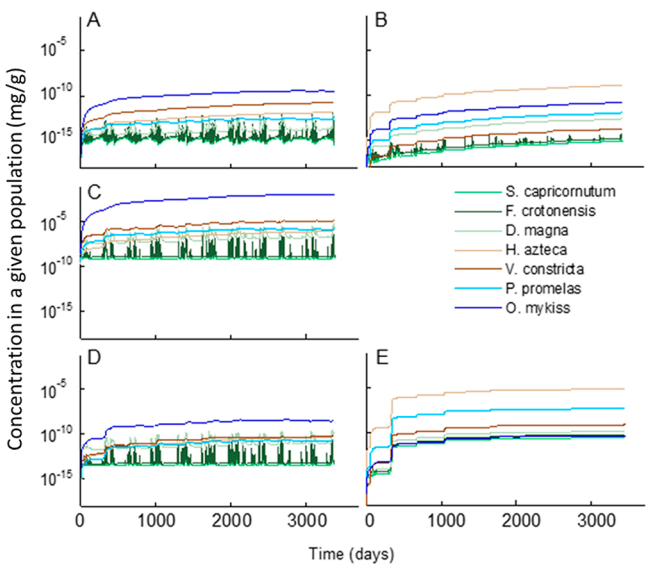

Figure 3. Estimated accumulation of (A) nCuO, (B) dissolved Cu^{2+}, (C) $nTiO_2$, (D) nZnO, and (E) dissolved Zn^{2+} in a simple freshwater food web. The phytoplankton and daphnia are depicted in various green tones, the benthic copepod and bivalve are depicted in brown tones, and the fish are depicted in blue tones.

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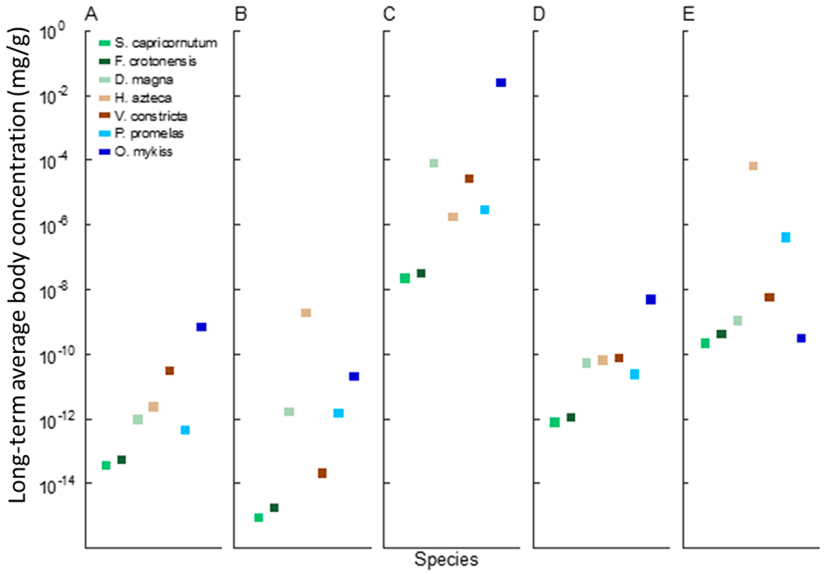

Figure 4. Comparison of predicted long-term ENM and dissolved ion bioconcentrations across food chain species. (A) nCuO; (B) Cu^{2+}; (C) $nTiO_2$; (D) nZnO; and (E) Zn^{2+}.

pseudo-steady-state for the dissolved ions requires between 3 and 9 years (Figure 3B,F). $nTiO_2$ (Figure 3C) appears to follow a similar pattern to nCuO regarding accumulation rates, although we assume there is no dissolution of $nTiO_2$, resulting in a shorter average time to pseudo-steady-state. These simulations consider starting from a clean background, i.e., zero ENM concentrations. In most cases, after 100 days ENM and dissolved ion concentrations in the water column reach a pseudo-steady-state, except for dissolved Cu^{2+}. ENM and dissolved ion concentrations in suspended sediment and sediment bed also continue to increase over the 10 years. For $nTiO_2$, which has been used for decades, this may not be as representative of the background concentrations.

Total bioaccumulation across all species is highest for $nTiO_2$, then nZnO, and lowest for nCuO, reflecting the predicted concentrations of these ENMs in San Francisco Bay. Comparing the long-term accumulation concentrations shows ENM bioaccumulation may be slightly more significant than dissolved ion bioaccumulation for CuO (Figure 4A,B), whereas the opposite trend is seen for ZnO (Figure 4E,F). Daphnia, benthic copepods (*H. azteca*) and planktivorous fish (*P. promelas*) are the only species to show consistently higher accumulation of the dissolved ion over the ENM. Benthic species and fish exhibit the highest accumulation of both ENM and dissolved ions.[5]

Biomagnification factors were calculated for heterotrophs and results indicate that biomagnification does increase up the trophic chain (Figure 5). Biomagnification is highest for $nTiO_2$ and nCuO (Figure 5A,B). *D. magna* and *H. azteca* exhibit an opposite pattern where biomagnification is highest in nZnO and lowest in nCuO (Figure 5A,C). The fish at the top of the food chain, *O. mykiss* has the highest predicted biomagnification overall for all ENMs and all species.

The distribution of results from the uncertainty analysis provides a range in bioaccumulation concentrations when all input parameters are varied by ±50% for each species and each ENM (Figure S3). The range in predicted bioconcentrations typically is one to 2 orders of magnitude, with the most variable results for *O. mykiss* and *S. capricornutum* across all ENMs and dissolved ions, followed closely by *P. promelas* for

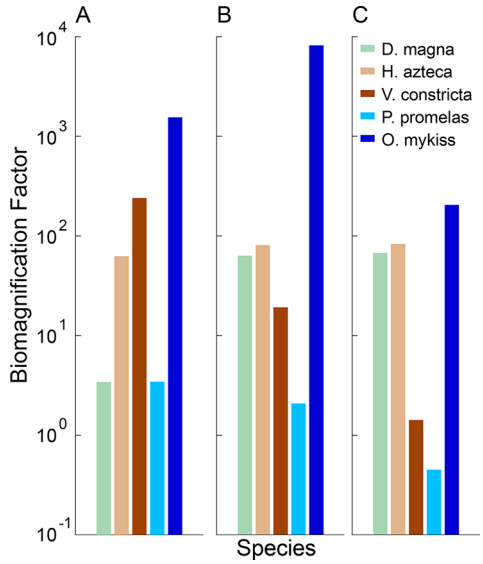

Figure 5. Predicted biomagnification of ENMs relative to the concentration of the ENM in the prey species for (A) nCuO, (B) $nTiO_2$, and (C) nZnO.

all ENMs but not dissolved Cu^{2+} or Zn^{2+}. The benthic species and *D. magna*, on the other hand, tended to have a fairly narrow range in predicted concentrations. In general, the range resulting from varying parameters by 50% was narrowest for nCuO and notably wider for $nTiO_2$ and nZnO (see Table S9 for geometric standard deviations for each distribution).

Sensitivity rankings were calculated from the Monte Carlo simulation using the Kolmogorov−Smirnov test and used to identify key parameters. The nanoBio parameters that most impact bioaccumulation vary across ENMs and species, although there are some clear trends (Figure 6; all values provided in Table S10). Key parameters for ENM accumulation in ranked order include lifespan (L), uptake from water ($k_{u2,w}$), assimilation efficiency (α), uptake from suspended sediment/sediment ($k_{u2,s}$), dissolution rate (k_{dis}), and elimination rate (k_e). Assimilation efficiency increases in signifi-

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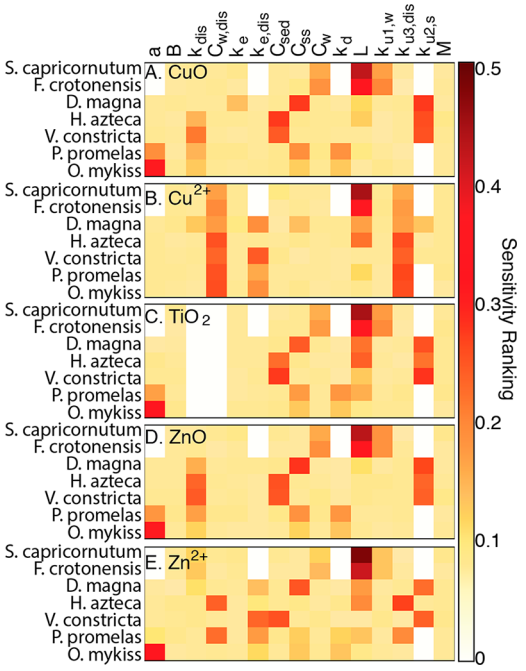

Figure 6. Sensitivity ranking of parameters for bioaccumulation of (A) nCuO, (B) Cu^{2+}, (C) $nTiO_2$, (D) nZnO, and (E) Zn^{2+}. Species are on the *y*-axis from phytoplankton to fish, and the biological and environmental parameters are on the *x*-axis. A higher sensitivity ranking indicates ENM bioaccumulation in a given organism is more sensitive to a particular parameter. A value of zero means that the parameter does not apply to that ENM or organism.

cance as trophic level increases. Conversely, lifespan decreases with importance as trophic level increases. ENM dissolution rate, dissolved ion elimination rate, and uptake from suspended sediment and sediment are most significant for benthic species and filter feeders. Uptake of dissolved ion was a significant parameter for all species exposed to Cu^{2+} (Figure 6B), but surprisingly only significant to the benthic and filter feeders exposed to Zn^{2+} (Figure 6E).

DISCUSSION

nanoBio predicts that biomagnification up trophic levels occurs for ENMs, to varying degree, although it does not necessarily increase consistently up the food chain. Biomagnification factors are highest for $nTiO_2$, due to its negligible rate of dissolution, and lowest for nZnO across all organisms, which reflects the extent of dissolution of each ENM combined with the predicted exposure concentrations.

nanoBio predicts that benthic species and higher trophic level fish will accumulate ENMs in the greatest quantities, due to the higher exposure rates and accumulation via dietary uptake relative to transformation and elimination rates. Interestingly, the benthic copepod accumulates the most dissolved Cu^{2+} and Zn^{2+}, which reflects the high observed uptake rates in *H. azteca* for both ions[95] compared to that observed for other species.[96−102] It is hard to predict what the potential impacts of these estimated accumulations may be because transformations, such as intracellular interactions, may be quite significant,[103] and nanoBio does not predict where in the organism the ENMs and dissolved metal ions are accumulating, which can determine toxic impact.[104] In addition, individual organism accumulation can be altered by growth, feeding, and survival resulting from accumulation of the ENMs and metal ions, which is not accounted for within nanoBio. A study with daphnids did indicate that feeding may not be significantly affected, even at high exposure concentrations.[105]

Establishing the relationship between exposure and toxic effect(s) requires an understanding of the internal, and sometimes organ specific, concentration in the organism. Environmental concentration is often used as a surrogate for the organ specific concentration. nanoBio provides a range of possible internal bioconcentrations that can be connected with specific observed toxic effects beyond simply exposure and mortality.

Some organisms, particularly phytoplankton are very sensitive to variations in environmental concentrations and average population accumulation varies significantly over the ten-year period. This has implications for short-term toxicity due to seasonal and other temporal variations. Other species, such as fish, reach pseudo-steady-state concentrations within the ten-year period. Generally, the larger and longer lived the species, the more stable the body burden. For smaller organisms, pseudo-steady-state concentrations were predicted within the first year, but concentrations vary substantially with time and ENMs. nanoBio results indicate that, at the ecosystem level, short-term lab experiments may not effectively reflect the maximum bioaccumulation possible for most organisms.[31,51,106,107]

Few studies have measured the internal, mostly short-term, accumulation of various ENMs for species included in this study. We are limited in our comparison because most studies are short-term at high exposure concentrations that are well above expected environmental exposures. The difficulty with comparing nanoBio results to those from studies on nCuO and nZnO is that most studies measure the total accumulated metal, regardless of how much is dissolved or particulate, so we must compare our results for ENM and dissolved metal accumulation to total metal accumulation. There are also many studies that could not be used for comparison because they studied terrestrial organisms or other types of ENMs.[19,20,50,51,53,54,59,60,108,21,23,26,29,32−35]

Modeling bioaccumulation is significantly limited by the availability of parameter values. Although ENM specific rates were available for some species, they were mostly for marine species, such as *M. galloprovincialis* uptake of nZnO.[62,104] In some instances, we were able to identify uptake rates that are specific to the metals (such as ionic copper uptake from freshwater for *H. azteca*[95]), which were used in preference to generic uptake rates. In the situations where specific uptake rates were substituted with either similar chemical uptake rates or when we had to assume 100% assimilation efficiency given known ingestion rates, the accuracy of the model is clearly limited. The rates used in the model may also vary substantially depending on ENM aggregation state, which also relates to variations in the environment. For example, if the pH of the freshwater system were to increase, agglomeration of many ENM would also likely increase[109−112] and this might decrease the uptake rates from water or the assimilation of the ENM into the organism during respiration, which would decrease the accumulation in water column species. It is also possible that there is a maximum accumulation beyond which the ENM simply passes through the organism, as with *M. galloprovincialis*.[16,104]

We should stress the conditional nature of the rate constants, because the environment, the biology, and the

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toxicity itself can alter these parameter values over time. One key variable is the transformation of the ENM, both in the environment and inside the organism through biotransformation. These transformations can alter the uptake and elimination rates, and our level of understanding of these processes is still quite limited for ENMs. In addition, because nanoBio treats the organism as a single compartment it does not account for variable impacts or transfer rates within an organism.

Quantification of rate constants for uptake of ENMs, excretion rates, and transfer through simple food chains should be a primary research focus. Toxicity studies should also measure ENM body burden and speciation after entering the organism in addition to measuring external exposure and toxic effect. This would greatly improve the ability to model bioaccumulation dynamics. Additionally, there is a need to differentiate between uptake and accumulation of ionic and particulate ENMs as the toxic impacts may vary. One option, proposed by Baalousha et al. (2016) and used by Ramskov et al. (2015), is the use of isotopically labeled ENMs to track uptake, accumulation and speciation.[11,113]

Modeling feedback of changes to biological rates as a result of exposure to ENMs (e.g., ingestion and respiration may decrease as a result of increasing exposure and accumulation) is currently also a major gap in our understanding of bioaccumulation and potential biomagnification of ENMs. This limitation could be addressed by incorporating feedback into accumulation and toxicity assessments (e.g., for *M. galloprovincialis* and *O. mykiss*).[16,29,89,104] In addition to this feedback, it would be useful to incorporate mortality as a result of accumulation.

We found uptake, assimilation, dissolution, and elimination are very important parameters for predicting bioaccumulation. Assimilation efficiency will prove to be important specifically for predicting biomagnification, whereas uptake from the various environmental media depends largely on the primary routes of exposure for each species.[89,114] The results of the sensitivity analysis can be used to guide future research, specifically on primary modes of uptake and how rates vary with time. In addition, the assimilation efficiency and elimination will have a substantial impact on the actual accumulation of nanoparticles within organisms.[88,115] While we identified which parameters are most sensitive, vis-à-vis their impact on accumulation, this does not tell us which may be more sensitive to accumulation feedbacks or environmental changes. For example, uptake can vary greatly by temperature and prey density.[116] Collectively, this research serves as a means to screen the potential for bioaccumulation characteristics of ENMs relative to biological parameters and identifies which parameters are most important for further research and refinement vis-à-vis accumulation mechanisms and rates. Though uncertainty in the predictions is significant, nanoBio can improve cost-effectiveness in research by targeting specific sensitive biological and environmental parameters.

CONCLUSIONS

We have developed a useful tool (nanoBio) for understanding the bioaccumulation of metallic ENMs in different freshwater species within a simplified food chain. While there is a significant need for parameter values for many processes, nanoBio can serve to guide experimental studies in terms of the most relevant data for determining bioaccumulation and trophic transfer of metallic ENMs and the associated dissolved ions. The highest overall bioconcentration was predicted for $nTiO_2$ within the highest trophic level species. Benthic species and fish exhibit the highest accumulation of ENM and dissolved ions. ENM dissolution from nCuO and nZnO decreases total ENM biomagnification, but nanoBio does predict significant increases in dissolved Cu^{2+} and Zn^{2+} in all trophic levels.

While true steady-state may not be reached in a dynamic system with increasing ENM releases, meteorological variations and the variability of biological processes, nanoBio can serve to determine the likely pseudo-steady-state concentrations. For phytoplankton and daphnia, this is reached within the first year for all ENMs. Pseudo-steady-state for other species could take several years. Thus, maximum bioaccumulation of ENMs and the dissolved ions would require long-term experimental studies.

The results from nanoBio serve to (1) highlight trophic levels at potentially higher risk of bioaccumulation; (2) temporal patterns that influence peaks in concentration; (3) processes which require more experimental data to reduce uncertainty. The parameters that are most significant for modeling and understanding ENM accumulation are lifespan (L), uptake from water ($k_{u2,w}$), assimilation efficiency (α), uptake from suspended sediment/sediment ($k_{u2,s}$), dissolution rate (k_{dis}), and elimination rate (k_e), in that order. While these results cannot yet be validated with field observations or the available short-term laboratory studies, they serve to better understand the likely bioaccumulation and ecological exposure to metallic ENMs and their transformation products.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.8b01691.

Data selection process (tiers) equations for all biological species; environmental parameter values used in nanoBio model for San Francisco Bay; ENM dissolution rates considered in nanoFate and nanoBio; species-specific parameter values considered in nanoBio; ENM-specific parameter values for the various species used in nanoBio; summary of exposure conditions and concentrations in biological tissue for laboratory experiments; pseudo-steady-state mean and time to mean for nCuO; pseudo-steady-state mean and time to mean for $nTiO_2$; pseudo-steady-state mean and time to mean for nZnO; geometric standard deviations for each chemical and biological species; sensitivity ranking of all model parameters for each ENM; freshwater composition considered in MINTEQ; Cu and Zn speciation considered in MINTEQ; fraction of dissolved Cu^{2+} or Zn^{2+} in freshwater as calculated using MINTEQ and the freshwater composition from Table S10; environmental exposure concentrations from nanoFate model; dissolution curves from *MINTeq*; probability distribution of predicted organism ENM and dissolved metal ions (PDF)

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