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Species Sensitivity Distributions for Engineered Nanomaterials

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Ⓢ *Supporting Information*

ABSTRACT: Engineered nanomaterials (ENMs) are a relatively new strain of materials for which little is understood about their impacts. A species sensitivity distribution (SSDs) is a cumulative probability distribution of a chemical's toxicity measurements obtained from single-species bioassays of various species that can be used to estimate the ecotoxicological impacts of a chemical. The recent increase in the availability of acute toxicity data for ENMs enabled the construction of 10 ENM-specific SSDs, with which we analyzed (1) the range of toxic concentrations, (2) whether ENMs cause greater hazard to an ecosystem than the ionic or bulk form, and (3) the key parameters that affect variability in toxicity. The resulting estimates for hazardous concentrations at which 5% of species will be harmed ranged from <1 ug/L for PVP-coated n-Ag to >3.5 mg/L for CNTs. The results indicated that size, formulation, and the presence of a coating can alter toxicity, and thereby corresponding SSDs. Few statistical differences were observed between SSDs of an ENM and its ionic counterpart. However, we did find a significant correlation between the solubility of ENMs and corresponding SSD. Uncertainty in SSD values can be reduced through greater consideration of ENM characteristics and physiochemical transformations in the environment.
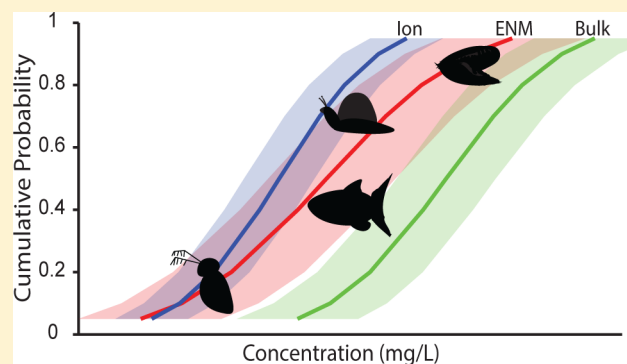
■ INTRODUCTION

Engineered nanomaterials (ENMs) represent a new and emerging class of pollutants but we understand relatively little about their effects in the environment. ENMs are used in a variety of consumer products including electronics, textiles, cosmetics, medicine, and food.[1] They are also used in energy, aeronautics, and military applications. The International Organization for Standardization (ISO) classifies ENMs into three main groups: (i) nanoparticles, for which all three dimensions are between 1 and 100 nm; (ii) nanoplates, for which only one dimension is between 1 and 100 nm; and (iii) nanofibers, for which two dimensions are between 1 and 100 nm.[2] Seven major classes of ENMs are carbonaceous nanomaterials (e.g., CNTs), semiconductors (ex. Quantum dots), metals (ex. n-Ag), metal oxides (ex. TiO_2), nanopolymers (ex. dendrimers), emulsions (ex. acrylic latex), and nanoclays. Various ENMs exist as single, aggregated, or agglomerated particles and can be manufactured with different shapes, coatings, and surface functionalities. Additionally, some ENMs dissolve in the environment, which can result in toxic effects similar to those of the dissolved ion, while other ENMs may not dissolve. In the latter case, toxic effects are usually related to ENM size, reactivity, and coating,[3] resulting in toxicity from the ENM that can exceed that of the ionic or bulk form signifying a nanotoxic effect.[4]

ENMs are released into the environment either during their use, through spillages, by intentional release for environmental remediation applications, or as end-of-life waste.[5] Increasing production and use of ENMs enhances the potential for release into the environment, thus increasing environmental exposures and incentives to better understand and quantify the ecosystem impacts of ENMs.[6] Substantial effort is now being made to quantify releases, exposures, and toxicity of ENMs throughout their industrial lifecycle.[7−9]

A few studies have developed preliminary estimates of the range of ENM exposure concentrations[3,9] and the few environmental concentrations that have been measured empirically fall within the same order of magnitude as those predicted by models.[7,10−12] What we do not yet adequately understand is the impacts of exposure to biological receptors under natural environmental conditions. To provide predictions of the potential biological impacts in nature the relatively large volume of information from laboratory toxicity tests with ENMs can be used to generate species sensitivity distributions (SSDs), which model the range in sensitivities of different species to a wide range of ENMs.[13,53] SSDs provide an estimate of the potentially affected fraction (PAF) of species that will be harmed from exposure to ENMs, and are used to establish threshold concentrations, which, when exceeded, indicate that management actions should be taken. For example, the lower fifth percentile of the SSD indicates that 95% of species are not impacted by a pollutant and thus, hypothetically, provides

environmental concentrations that are expected to safeguard most species, and thus an ecosystem's structure and function.[13] While our understanding of ENM toxic effects is still relatively limited, progress is being made in determining toxic concentrations for a wide-variety of both terrestrial and aquatic species.[54]

Single species toxicity data from multiple species can be combined to predict the exposure concentrations at which a percent of species in an ecosystem will be affected.[13] Specifically, SSDs are models of the variation in sensitivity of species to a particular stressor,[13] and are generated by fitting a statistical or empirical distribution function to the proportion of species affected as a function of stressor concentration or dose. Traditionally, SSDs were created using data from single-stressor laboratory toxicity tests, such as median lethal concentrations (LC_{50}). The key assumption in applying SSDs is that the species toxicity data represent a random sample from a statistical distribution that is representative of a community or ecosystem, with the idea that limited toxicity testing of only a handful of species can allow us to extrapolate to a community level of risk associated with a specific toxicant. As more data become available for various species, the accuracy of SSDs in predicting ecosystem toxicity effects will increase.

Many SSDs have been developed for a variety of organic and inorganic pollutants[15,16] with many focused on pesticides[17−20] and herbicides.[21,22] There are a few examples of SSDs constructed specifically for metals. SSD and the corresponding predicted hazardous concentration at which no species are harmed (HC_0) and at which 5% of species are harmed (HC_5) were created for zinc for aquatic species with the goal of finding the best cumulative distribution function.[23] SSDs have also been developed for specific taxonomic groups for copper to estimate acute-chronic ratios for different taxa.[24] An acute toxicity SSD was developed for mercury to estimate HC_5 and the predicted no effect concentration (PNEC) for freshwater species.[25] SSDs can also be used in life cycle assessments (LCAs) to determine characterization factors (CFs) for ecotoxicity.[26,27] CFs for toxic pollutants are substance-specific, quantitative factors that convert life-cycle emissions of toxic substances to the common unit of the toxic impact indicator.[28] As LCAs are being developed for nanoparticles, SSDs can provide the information on PAF needed to calculate the CF.[28−30]

SSDs are used in ecological risk assessment to derive maximum acceptable concentrations of pollutants in the environment from a limited set of laboratory based ecotoxicity data.[19,25,26] The utility of an SSD depends on the quality and relevance of the data used, which usually are secondary data taken from literature or a database. The objective of this study is to develop SSDs for as many nanoparticles as possible and to determine if, according to the SSDs, the ENMs cause greater toxicity than the ionic or bulk form. The results of this work can be used to begin to make judgments regarding the risk of using and releasing different ENMs into the environment.

■ DATA AND METHODS

Data were collected from >300 published articles that explicitly provided single species toxicity data including median lethal concentration (LC_{50}), half maximal effect concentration (EC_{50}), median lethal dose (LD_{50}), lowest observed effect concentration (LOEC), no observed effect concentration (NOEC), and the half maximal inhibitory concentration (IC_{50}). If a published article did not specifically state one of these values, even if they provided dose−response curves, the information was not used in our analysis. Our initial search did not limit the types of nanoparticles that could be included, as we needed to determine the extent of available data across both environmental media and ENMs. Not all ENMs or environments had enough data points to create an SSD. However, as research progresses and more data become available, they can be combined with the data provided in Supporting Information (SI) Table S-1 to create improved SSDs.

While there was sufficient data to build SSDs from EC_{50} values, there were more data available across all types of ENMs to build SSDs using LC_{50} values. These studies varied in length from 15 min to 28 day exposures depending on the species and end-points. We elected not to account for the time range by using dose as our SSD metric because concentration is the standard metric used in SSDs. In addition, because the data cover a range of species with very different life histories and life spans, dose is not always a comparable metric.

SSDs are frequently based on chronic, sublethal toxic effects because exposure to toxins in the environment is typically at low concentrations over the long-term. However, we only had sufficient data to develop SSDs for acute freshwater toxicity. This was because of the limited data available on both marine and terrestrial toxicity and the limited number of studies conducted to date on chronic ENM toxicity across the board.[29−32] In some cases, short-term toxicity data can make use of an extrapolation factor to accurately describe the chronic SSD.[33,34] One approach for converting data from acute to chronic is to simply use a factor of 10 (i.e., a left shift of SSD based on LC_{50} to obtain an SSD for the no observed effect concentration (NOEC)).[34] Another study found that using an acute to chronic ratio ranging from 1.6 to 4.4 was more accurate.[33] We determined that there is not yet sufficient evidence to implement a conversion factor based on data available for ENMs.

We also collected toxicity data on freshwater species for both the ions of the associated metals and nominal data on bulk particles to compare to the ENM data. We did this by reviewing data collected for the ENMs where comparative tests were often done on ionic or bulk equivalents, through a general literature review, and querying the EPA's ECOTOX database by compound. We limited the search to studies completed in a lab as opposed to field research so as to match the ENM data set, in freshwater systems that reported LC_{50} values.

To build SSDs, we implemented the Species Sensitivity Distribution Generator, provided by the Environmental Protection Agency (EPA), which has been used for many other chemicals.[35,36,21,37,38] The process requires a list of exposure intensities at which different species exhibit a standard response to a stressor. The reported LC_{50} values are then ranked and plotted along the x-axis. The cumulative probability, calculated as the fraction of species affected at a certain concentration, is plotted along the y-axis, along with the 95% confidence interval, using a probability density function (PDF). We then calculated the hazardous concentration at which 5% of species will likely be harmed (HC_5),[28] indicating that 95% of species in an ecosystem will be protected provided that the environmental concentration remains below that associated with the HC_5. A minimum of four data points are needed to generate an SSD, though the predictive power of SSD models greatly increased with 10 or more data points from published studies.[10,26,28] Our ENM SSD data varied from 8−64 data points from published studies covering a range of species, though they did not always include a wide range of taxa, which is also preferred when creating a SSD.[13]
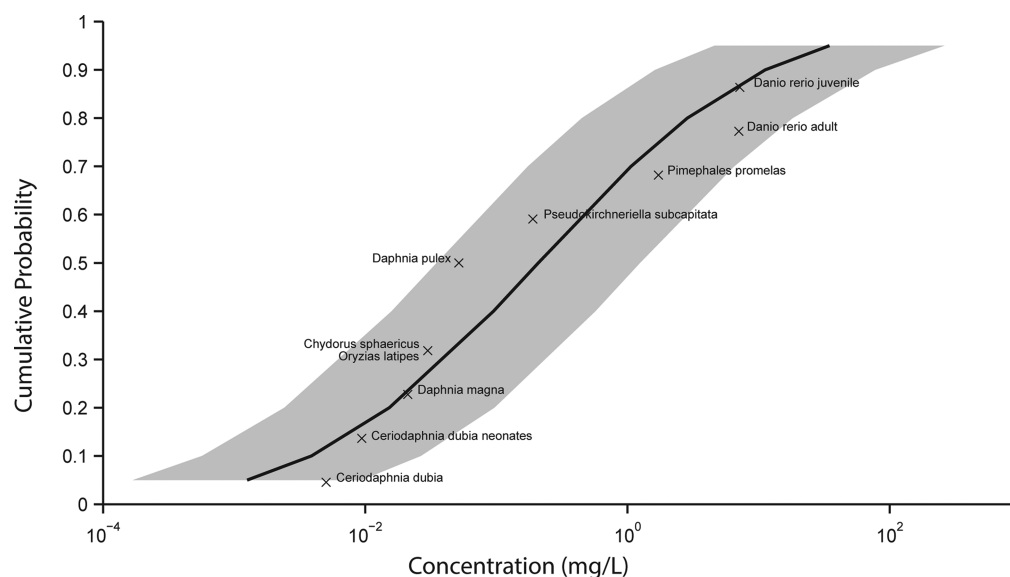
Figure 1. Species sensitivity distribution for uncoated n-Ag, based on 10 species. The 95% confidence interval is shown by the gray shaded area around the curve, which indicates a range in values of about 1 order of magnitude.
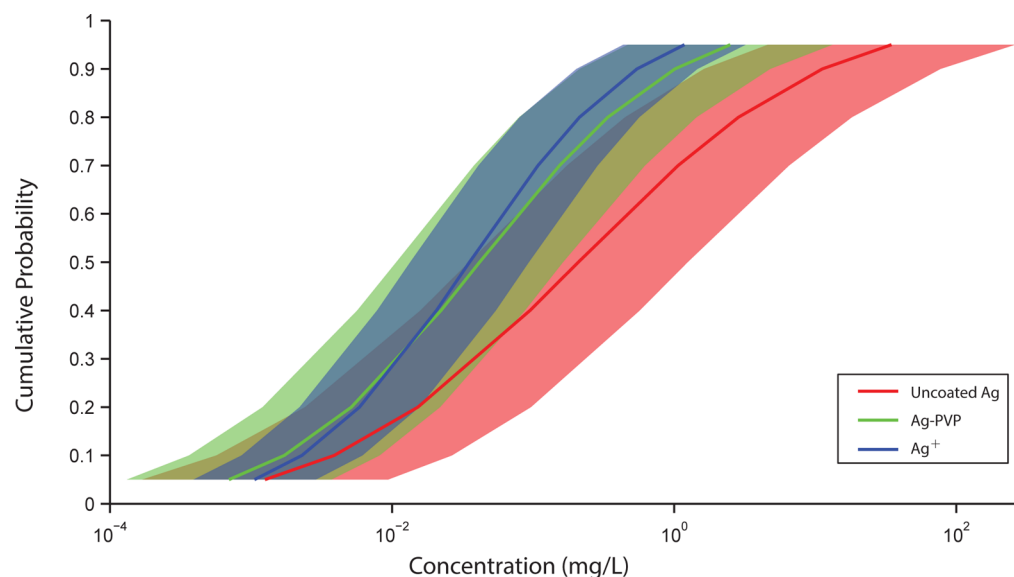

Figure 2. Comparison of silver SSDs, including uncoated n-Ag, PVP-coated n-Ag, and Ag$^+$ derived from dissolving AgCl and AgNO$_3$. The 95% CI for each curve is depicted by the corresponding shaded area.

■ RESULTS

A comprehensive review of the literature on Web of Knowledge and Google Scholar using a range of search terms to cover all types of ENMs, environments, toxicity tests, and species resulted in over 300 studies, although only 101 studies reported data adequate in quality for our analysis (SI Table S1). Sufficient data were collected to build SSDs for uncoated n-Ag, PVP-coated n-Ag, n-Al$_2$O$_3$, n-C$_{60}$, CNTs, n-Cu, n-CuO, n-TiO$_2$, and n-ZnO using acute LC$_{50}$ values. For n-CeO$_2$, we collected sufficient data to build an SSD using only acute EC$_{50}$ values.

The SSD for uncoated n-Ag (Figure 1) indicates that the ENM was toxic to some species at ug L^{-1} concentrations, while other species tolerate concentrations three or more orders of magnitude higher, at g L^{-1} concentrations with a range of 1 order of magnitude for the 95% confidence interval.

We constructed separate SSDs for PVP-coated n-Ag (SI Figure S1) and ionic silver from either AgCl or AgNO$_3$ (SI Figure S2).

Ag$^+$ derived from dissolving AgNO$_3$ was considerably more toxic than when AgCl was used, but given that the toxicity is probably due to metal ion exposure rather than the salt, we chose to combine the data sets to develop a more robust SSD. The ENM SSDs were then compared to the Ag$^+$ ion SSD to determine whether the toxicities varied (Figure 2). While Ag$^+$ is generally more toxic than coated or uncoated n-Ag, at low exposure concentrations, there are only minor differences between Ag-PVP and Ag$^+$. For most species, uncoated n-Ag was considerably less toxic than PVP-coated Ag, most likely due to increased aggregation and reduced bioavailability.[27] Uncoated n-Ag has a higher toxicity threshold than Ag$^+$, particularly at higher exposure concentrations.

We then constructed SSDs for two copper nanoparticles, n-Cu (SI Figure S3) and n-CuO (SI Figure S4), and Cu^{2+} derived from combining toxicity end points for CuCl$_2$, Cu(NO$_3$)$_2$, and CuSO$_4$ (SI Figure S5). The difference in Cu^{2+} toxicity between the

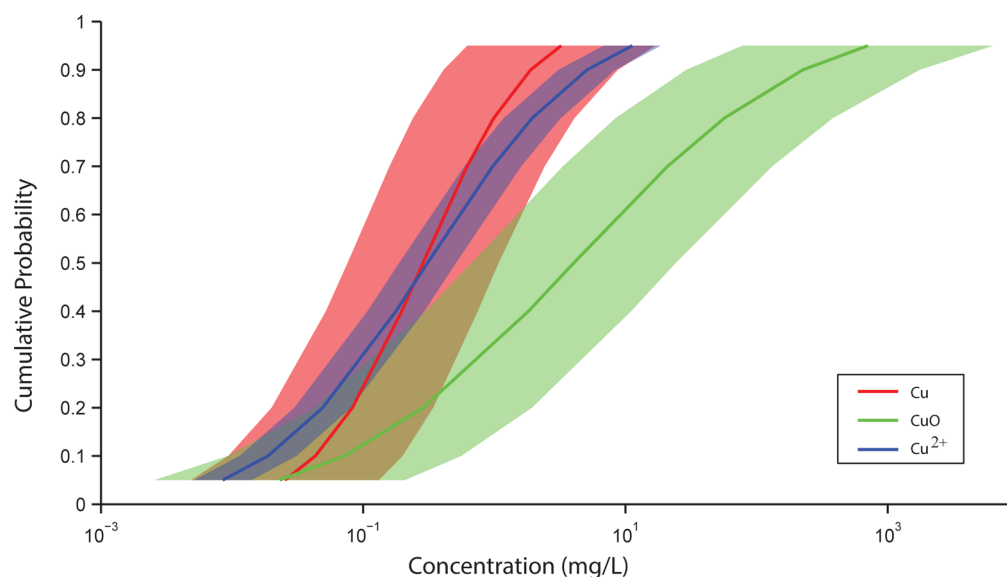**Figure 3.** Comparison of copper SSDs, including n-Cu, n-CuO, and Cu^{2+} derived from dissolving $CuCl_2$, $Cu(NO_3)_2$, or $CuSO_4$. The 95% CI is depicted as the shaded region in color corresponding to each curve.
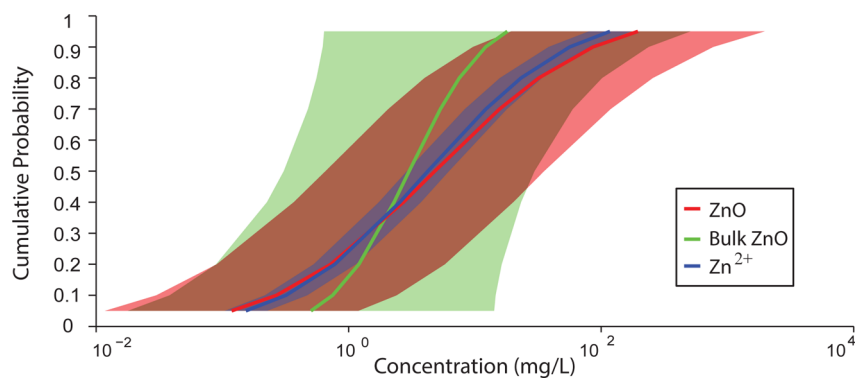

Figure 4. Comparison of zinc SSDs, including n-ZnO, bulk-ZnO, and Zn^{2+} derived from dissolving $ZnCl_2$ and $ZnSO_4$. The shaded region in the color corresponding to each curve shows the 95% CI.
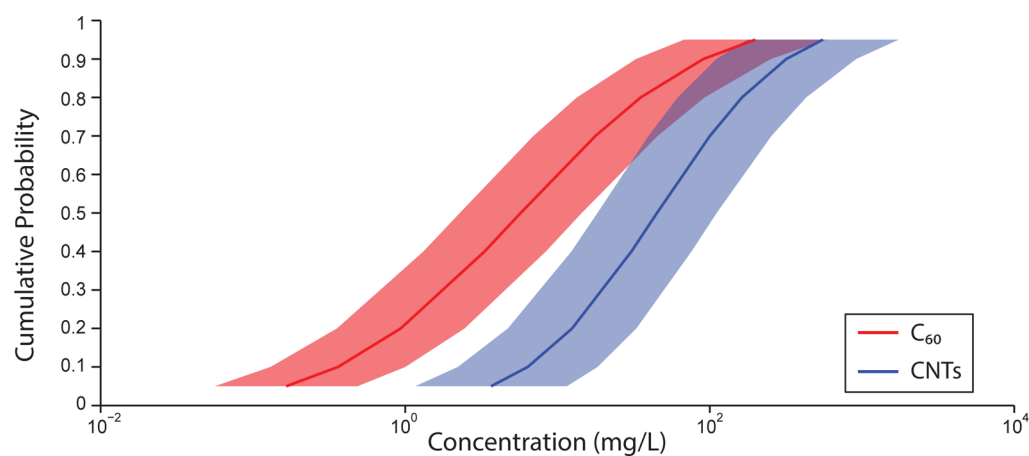

Figure 5. Comparison of carbonaceous nanoparticle SSDs, including n-C_{60} and CNTs. The shaded region around each curve depicts the 95% CI.

various copper salts was smaller than observed for the silver salts (SI Figure S5), possibly due to the larger number of data points for each Cu^{2+} SSD. However, the toxicity threshold was significantly lower for Cu^{2+} from $CuCl_2$ than from $Cu(NO_3)_2$ and $CuSO_4$. A comparison of the nano and ionic copper SSDs indicated that the toxicity thresholds for n-CuO were much

higher than for n-Cu or Cu^{2+} (Figure 3). Additionally, the difference between the SSDs for n-Cu and Cu^{2+} was smaller than between n-CuO and Cu^{2+}, with n-CuO consistently less toxic than either n-Cu or Cu^{2+}. As expected, given the much smaller number of data points for the two nanoparticles, the confidence intervals were much wider than for Cu^{2+}. The lower toxicity of n-

CuO in freshwater may reflect its slower dissolution at low ionic strength and in the presence of organic matter (present in any aquatic system with biota).[39]

For zinc, we compared n-ZnO (SI Figure S6), bulk ZnO (SI Figure S7), and Zn^{2+} derived from $ZnCl_2$ and $ZnSO_4$ (SI Figure S8). There were minimal differences in the SSDs for Zn^{2+} derived from $ZnCl_2$ and $ZnSO_4$. A comparison shows that the SSDs for n-ZnO and Zn^{2+} are nearly identical, and that of bulk ZnO is also similar (Figure 4), indicating that for this ENM most of the toxicity is due to dissolved Zn^{2+}. There was little statistical difference between the three lines because the small sample size results in low statistical power.

The SSDs of n-Al_2O_3 (SI Figure S9) and Al^{3+} (SI Figure S10) indicate that except at high concentrations, n-Al_2O_3 is less toxic that Al^{3+} (SI Figure S11). There are some difference in toxicity between Al^{3+} derived from $AlCl_3$ and $Al_2(SO_4)_3$ (SI Figure S10), with $AlCl_3$ slightly more toxic than $Al_2(SO_4)_3$, although there is overlap in their confidence intervals which are broad due to the lower number of data points. For n-CeO_2 (SI Figure S12) and n-TiO_2 (SI Figure S13) n-CeO_2 appears to be more toxic than n-TiO_2 (SI Figure S14), even though n-TiO_2 has shown phototoxicity while n-CeO_2 generally quenches photoactivity. A recent review of n-CeO_2 provides a more detailed analysis of the behavior and toxicity of this nanomaterial.[40]

We collected sufficient data to develop SSDs for two carbonaceous nanomaterials, n-C_{60} (SI Figure S15) and CNTs (SI Figure S16), though there were not enough data to create distinct SSDs for single-walled carbon nanotubes (SWCNTS) or multiwalled carbon nanotubes (MWCNTs). Overall n-C60 is more toxic than CNTs, with overlap in the confidence intervals only in the higher concentrations (Figure 5). C_{60} has a notably lower toxicity threshold than CNTs. It is important to note that CNTs have a very wide range of properties (e.g., tube diameter, tube length, surface functionalization, residual metals, chirality) that limit the strength of our SSD. As more toxicity information becomes available, separate SSD may be needed for different classifications of CNTs.

One approach for considering the relative toxicity of the ENMs is to compare their HC_5. For the ENMs considered in this study, HC_5 values range over 4 orders of magnitude (from <1 ug/L for silver nanoparticles to >3.5 mg/L for CNTs) (Figure 6). The results confirm the hypothesis that nanoparticle solubility, with the corresponding release of metal ions, is a strong predictor of toxicity, as seen for n-Ag, n-ZnO, n-Al_2O_3, and nanocopper compounds. For Ag and Zn there was little to no difference between the mean of the HC_5 for a nanoparticle and the HC_5 for the corresponding metal ion. For Cu and Al, the differences are more significant, reflecting the slower dissolution rates of these nanomaterials, particularly Al_2O_3. For the ENMs that are less likely to dissolve (C60, CNTs, CeO_2, and TiO_2) the HC_5 values range from 0.1–10 mg L^{-1}, which are concentrations that are less likely to be encountered, on average, in aquatic systems based on recent estimates.[4,5,26] The breadth of the range is largely a result of availability of data; compounds with more data generally had a much smaller range than those with fewer data available.

■ DISCUSSION

ENMs are released into the environment at various stages during their life-cycle, but our understanding of the environmental implications is still quite limited.[3] Our results serve to identify concentrations of concern for various ENMs with regard to freshwater ecological toxicity. While these SSDs are preliminary estimates, they represent the first attempt at predicting the PAF
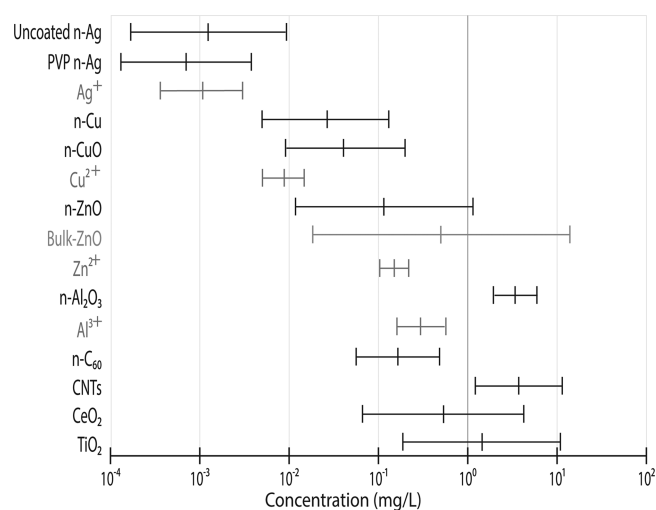

Figure 6. Mean and 5th and 95th percentile HC_5 for nanomaterials in black and corresponding ions in gray, listed immediately below each ENM. Zinc, silver, aluminum, and copper nanoparticles were found to dissolve over the course of days to weeks whereas ceria, titanium dioxide, and carbon-based nanomaterials experience negligible dissolution in freshwater over months or longer.[3]

of species at various exposure concentrations in the aquatic environment for multiple ENMs. Exposure models that estimate the exposure of individuals or populations can be compared with the HC_5 values estimated here to predict the ecotoxicological effects of ENMs and give an idea of how significant the risk associated with their use could be.

When working with ENMs, consideration must be made for the various possible configurations (e.g., size, shape, charge, and presence of a coating or functional group) that can all alter chemical behavior in the environment and impact toxicity.[3] For example, if two different Ag nanoparticles have different primary diameters and one is spherical while the other is cubic, the LC_{50} values for each could be as different as if they were entirely different chemicals (See SI Table S1 for examples). In addition, transformations of the ENM during toxicity tests,[44] or the presence of species that can alter how ENMs interact with biota, can influence the outcomes of single species laboratory assays.[45,46] Thus, it is important to take into consideration both ENM characteristics and possible environmental transformations that increase the uncertainty and reliability in toxic outcomes that underlie the SSDs. As such, it would be preferable to separate ENMs by type and structure as well as dispersion media before building SSDs from the data. Given data limitations, we were only able to do this for uncoated versus PVP-coated n-Ag (Figure 2). We did not have quite enough data to also build a separate SSD for citrate-coated n-Ag, which would have improved our understanding of how toxicity is affected by the presence of a coating. There was also insufficient data to separate particles by size group (e.g., 1–10 nm, 10–50 nm, and 50–100 nm). The accuracy of the SSDs will likely improve by incorporating some of these distinctions. For example, the SSD for uncoated n-Ag and PVP-coated n-Ag are statistically different at the higher exposure concentrations, but this distinction would not have been clear had we combined all the Ag ENMs into one SSD (Figure 2). Because we only have limited examples of each ENM variable, our conclusions are limited in their strength. However, as more data become available to separate ENMs into clearly defined physico-chemically distinct groups (e.g., those based on size, shape, or coating) when developing SSDs, we will

better be able to distinguish between the extent of toxic effects as physicochemical characteristics are altered.

The accuracy and utility of an SSD depends on the quality and relevance of the data used, which in this case are secondary data taken from literature and the ECOTOX database. Ideally, an SSD should be not generated from the synthesis of results from experiments that used a wide variety of protocols, for example, by combining impacts from chronic sublethal effects on reproduction with the impacts on survival or with acute lethal test results, all of which are commonly reported toxicity end points.[37] This limits the generation of SSDs for ENMs, especially for aquatic species where there is a bias toward acute mortality data, despite the likelihood that chronic sublethal effects may have enormous impacts on the individual survival and reproduction, of populations and thus population abundance and persistence.[14] This is in part due to the difficulty in maintaining a constant state and concentration of a nanoparticle in an aquatic experiment over the long-term. As such, we limited our study to short-term acute toxic effects due to the scarcity of chronic toxicity information. More useful SSDs would be generated for each ENM using a variety of species, for instance those that vary in their sensitivity across a range of taxa and trophic levels, for a specific ecosystem or region of concern. Distinguishing SSDs between early and late life stages of a species would also be useful as the values can differ in sensitivity with each life stage. While there are a reasonable number of species represented in these SSDs, the diversity in taxa and life stage is not comprehensive. It is important to recognize the uncertainty associated with our results as the range of sensitivities of the species we included is quite variable from ENM to ENM, and no SSD was constructed with enough species to represent a comprehensive ecosystem. Despite these limitations, our results are useful in gauging and comparing the ecotoxicological impact of different ENMs. Useful next steps would include generating SSDs for ENMs based on chronic toxicity data,[37,47−52] and developing a robust framework for predicting long-term effects on populations, communities, or ecosystems.

■ ASSOCIATED CONTENT

ⓈSupporting Information

All data collected and used to develop SSDs are provided in Table S1 including the ENM, the size, the species tested, and the toxicity end point. Detailed SSDs for each ENM and the bulk and ionic counterparts are also provided in the Supporting Information. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.5b00081.

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Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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