Variation in Regional Risk of Engineered Nanoparticles: nanoTiO2 as a Case Study

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Environmental Significance:

Nanoparticles are used in a wide variety of commercially available product categories (e.g. food, automotive, paints, and skin care), and their widespread use and greater reactivity relative to larger particles elevates the need to understand their risk. Currently, nanoparticles are difficult to detect in environmental media, thereby evaluating their risk requires the use of fate and transport models of which model nanoparticle behavior in the environment. Previous work has investigated risk imposed by nanoparticles to either specific environmental compartments (e.g. freshwater) or has evaluated risk at a large scale (e.g. country level). Here, we evaluate risk at the watershed level for environmental compartments of 6 watersheds with unique land use fractions and environmental characteristics to elucidate regional variability of nanoparticle risk.

Variation in Regional Risk of Engineered Nanoparticles: nanoTiO_2 as a Case Study

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ABSTRACT

Predicting environmental concentrations of engineered nanomaterials (ENMs) is key for assessing their risk. We hypothesize the environmental concentrations are a strong function of the environmental characteristics and waste management practices of the locations where the ENMs are used and released. We conducted a case study for nanoTiO_2 in six watersheds (Los Angeles, New York, Des Moines, Rome, London, and Zurich). For a near-field analysis, we investigated the 500 m freshwater reach downstream of a point source in Zurich. The analysis was conducted with nanoFate, a dynamic multimedia fate and transport model which considers daily variability in release, climatic, and hydrological conditions. ENM release fractions to environmental compartments differ regionally by up to 28%, compartment concentrations vary regionally by up to three orders of magnitude, high daily variability of nanoTiO_2 observed within air and freshwater, and adverse effects to aquatic organisms such as respiratory inflammation may be present in the freshwater compartment of Los Angeles and downstream of the Zurich point source (peak concentrations of 1,490 and 619 µg/L respectively). Concerns to aquatic organisms in Los Angeles are episodic, depend on meteorological variations, and would not have been predicted by steady-state or material flow analysis models. This highlights the significance of refining spatio-temporal resolution for a more comprehensive ENM risk assessment.

INTRODUCTION

The rise of nanomaterial applications, due to their unique properties relative to bulk materials, has brought considerable attention to the potential risks of engineered nanomaterials (ENMs) to human and environmental health. ENMs have increased chemical reactivity as a result of differences in surface free energy, increased surface area, variations in structure such as bond angles, bond lengths, vacancies near and on the particle surface, and the modification of the electronic structure, which merits an independent assessment of their risk relative to bulk materials of the same composition.[1] Currently available toxicological studies for metal oxide ENMs have demonstrated effects such as lethality to fish embryos, inhibition of growth/proliferation, neurotoxicity, cytotoxicity, respiratory system inflammation, deleterious effects to proteins, increased oxidative stress, and genotoxicity. [2–9] The toxicological effects are generally specific to ENM composition, size, coating, aspect ratio, bioavailability, and other characteristics of the ENM and the test media.[10,11] It is unclear at this time if the risk, based on current ENM production volumes and application, is unacceptable to human and environmental health. To better understand the risk imposed by nanomaterials in the absence of technologies capable of efficiently distinguishing between nano and larger scale particles in environmental media, fate and transport models serve as useful tools. This study builds on previous advancements in the prediction of PECs of nanoparticles by evaluating the effects of localized environmental characteristics and daily variability in release and transport with nanoFate, an ENM-specific fate and transport model.[12]

Previously, environmental concentrations of ENMs within a specific environmental compartment or to technical compartments have been predicted at the global, country, or state scale.[13–15] Other work has expanded the analysis to predict concentrations at the continental and country scale to all bulk environmental media (e.g. soil, air, and water)[16–22], or have estimated concentrations at a more localized level that are attributable to a specific product or product category, point of emission (e.g. wastewater), single water body, or watershed[12,23–30]. This study is unique with respect to previous work in that concentrations are predicted for all use categories and bulk environmental media for six watersheds which encompass a broad range of climates, environmental characteristics, and land use fractions within Europe and the United States to enable an evaluation of variation in regional risk. Within the United States, Los Angeles, New York, and Des Moines were evaluated. Regions investigated within Europe include Rome, London, and Zurich; in addition, to better understand the issue related to near- and far-field concentrations, the 500 m reach downstream of the Werdholzi wastewater treatment plant (WWTP) in Zurich was modeled in detail. Distinct environmental characteristics as well as regional social factors such as land use, population density, local meteorology and hydrology, municipal waste management, wastewater treatment, and biosolids disposal practices are considered.

To evaluate nanoparticle risks with higher spatial and temporal resolution, one of the most widely used ENMs, nanoTiO_2, was selected as a case study particle. The global production of nanoTiO_2 is estimated to have increased annually by an average (throughout this study, the arithmetic mean) of 3% from 2002-2016, to more than 100,000 metric tons globally.[31] This number is subject to high uncertainty, as establishing accurate ENM production estimates is based on production data that has been highly restricted, with the exception of manufacturers in France, Belgium, Denmark, and Norway, of whom are required to report production volumes.[32–36] Even for countries with required reporting, production volumes are highly variable. For instance, the 2015 French Report provides nanoTiO_2 production and import volumes of 10,000-100,000 tonnes, while the 2016 reported volume is > 1,000 tonnes.[36] For this investigation, The Global Market for Nanomaterials 2002-2016 report will be utilized to calculate release. To evaluate the source for reliability, the global production data and methods described here within for calculating country level consumption were used to calculate the French production volume of nanoTiO_2 in 2016. The calculated volume for France was 1,600 tonnes, which is within the range of the most recently reported production volumes for France (2016).

METHODS

NanoFate was utilized to predict environmental concentrations (PECs) of TiO_2 ENMs. In brief, nanoFate accounts for processes relevant to nanocolloids, such as erosion, deposition, sedimentation, resuspension, and advection. A key difference relative to most other ENM fate and transport models is the accounting of dissolved ions and the influence of the specific water chemistry of the various aqueous compartments (e.g. freshwater, marine, groundwater); while dissolution is less relevant for nanoTiO_2, it is important to account for water chemistry when considering hetero- and homo-aggregation. NanoFate differs from multi-media fate and transport models such as USEtox[37] and nanoparticle specific models SimpleBox4Nano[38] in its ability to account for daily variability in contaminant release and transport processes (runoff, flow rate, etc.) and considers 26 sub-compartments (e.g. aerosols; suspended sediments in each type of water body; soil air, water and solid phases in four different types of land uses) for improved spatial resolution.[12] Model output is a commas separated file with the concentrations in each of the 26 compartments predicted at a daily time step, as well as concentrations within the 'bulk' compartments, e.g. the net concentration in air, water, sediment, urban soil, undeveloped soil, agricultural soil, and agricultural soil to which biosolids are applied.

Watersheds studied were selected to encompass a range of land uses and climates surrounding dense urban areas and/or agricultural land within the United States and Europe. The delineation of boundaries and the compilation of environmental data for regions in the United States were conducted according to methodologies published in the nanoFate User Guide[12]. For European regions, the boundaries were delineated utilizing European Commission Joint Research watershed boundaries.[39] The watersheds were derived from post processing shuttle radar topography mission elevation data. The watersheds were selected to act as regional boundaries and were chosen based on those which best fit the political boundaries of each watershed of interest, but still drain towards a common outlet (*Supplementary Information (SI) Section 1: Regional Summaries*).[40] Each region was subdivided into land uses using the Coordination of Information on the Environment (CORINE) land use dataset.[41] The dataset was generated from ground truth survey, aerial photographs, and satellite observation data. For coastal regions, the marine compartment included inland estuaries as well as the open ocean up to 1 km from the coast. All environmental compartment data was collected, as available, using geospatially interpolated datasets for the land uses of each region. For data not available as geospatially interpolated, the mean of available physical and chemical data from specific sites within the regions were utilized. More detailed information regarding regional compartment sizes and characteristics is available in the *SI Section 1: Regional Summaries* and *SI Section 2: Environmental Data*.

NanoTiO_2 release estimates were predicted according to methods published by Keller and Lazereva (2013)[13] of which scale global nanomaterial production[31] by the population[42] residing in the environmental compartments of the respective watershed and the index of human development of the watershed's country[43]. Release to environmental compartments were predicted from the market sector demand[31], product use types within the sector, as well as the probability of release to the environment during use and disposal as calculated by Keller and Lazereva (2013)[13]. Release from most life-cycle phases was considered: use, wastewater treatment, and waste disposal; release from production of nanoTiO_2 was not considered given that there is no specific information on nanoTiO_2 production facilities for these six urban areas and is likely a small contribution, since it is estimated to be less than 2% of the overall release.[44] Product categories utilized to estimate the release of nanoTiO_2 include: aerospace and automotive; coatings, paints, and pigments; food additives; personal care products; energy; environment; agriculture; plastics; and textiles. Release by product category considered likelihood of ENM release to an environmental compartment, but did not include a lag in release from a given product type (e.g. variability in product wear leading to ENM release) due to limited data for many product categories.

The quantity of nanoTiO_2 within each product category is based on product demand estimates.[31] The release for the near-field analysis of the Werdholzi WWTP differed from the far-field analyses in that only release from WWTP effluent was considered, with a serviced population of ~400,000 people, and only the freshwater and freshwater sediment compartments were considered. A benefit to modeling WWTP effects in Zurich is that the analysis allowed for an evaluation of risk to the rivers within the watershed. The impacts of ENMs to rivers within the watershed were poorly represented in the Zurich watershed due to Lake Zurich representing a significant fraction of the modeled freshwater compartment, which serves to attenuate the simulated impact of ENMs to the freshwater compartment. The Werdholzi WWTP analysis boundary was the freshwater area from the point of effluent to 500m downstream. Regional nanoTiO_2 release variability accounted for in wastewater from each region includes the proportion of wastewater treated, treatment methods, and the sludge disposal pathways. [43,45–47] Variability in sewage sludge and municipal solid waste disposal considers biosolids applied to agricultural land and sludge or waste disposal via landfill and incineration.[13,45–49] For more details regarding release estimates, see *SI Section 3: Release Data*.

Scenarios explored for the release of nanoTiO_2 include a low release scenario which maximized release to landfills (low environmental release), a high release scenario which minimized release to landfills (high environmental release), and a default release scenario for which the mean values of the low and high release parameters were utilized. PECs of nanoTiO_2 in different regions were estimated using nanoFate considering 10 years of release for the period of 2005-2014. Simulations were conducted using local information on daily precipitation, wind speed, temperature, and flow data for the major waterbody intersecting the region. Initial (background) ENM concentrations were calculated from a 10-year simulation for 1995-2004, the 10 years prior to the period of study, and assuming that nanoTiO_2 concentrations were negligible prior to 1995. Release for the 1995-2004 scenario were based on ENM production estimates from available marketing data for 2002-2004[31] and for 1995-2001, the extrapolation of annual production data available for 2002-2016 with a linear model. The modeled rate of increase of production, based on Future Markets nanomaterial production data[31], was 2.7% per year.

Due to the need to account for the indirect release of nanoTiO_2 from treated WWTP waste to the biosolids compartment (agricultural land to which treated WWTP waste is applied), the biosolids compartment necessitated additional consideration to the aforementioned release methods. Data pertaining to the rate of regional biosolids application to land was limited and varies by facility. To estimate the application rate of biosolids, the regional sewage sludge content, regional biosolids legislation, and suggested rates of application were evaluated.[50–53] For Europe, recommended biosolids application rates to meet crop fertilization needs nearly exceeded regulatory limits.[50,54] Thus, it was assumed co-fertilization (use of an additional fertilizer) would be required and that only 50% of the maximum allowable biosolids application rate was utilized to allow for a margin of safety and prevent exceeding regulatory thresholds. The application rate and land area necessary to dispose of the biosolids was calculated from the quantity of biosolids produced annually, legal criteria for allowable heavy metals and the average sewage sludge content of the contaminants.[46,52,55,56] Zurich is the exception, since Switzerland has banned land application and landfilling of sewage sludge waste, thereby all WWTP waste was routed to incineration.[57] In the United States, the rate of biosolids application and area were based on the amount of biosolids produced and recommended application rates to meet crop fertilization needs (22.4 dry metric tons per hectare[54]). This approach was used rather than 50% of the allowable biosolids application limit used for Europe due to less stringent biosolids application regulations within the United States; it is unlikely that regulations will be exceeded even after 20 years of biosolids application.[51–54,58]

As a condition of the default biosolids application scenario, the biosolids were exported if more than 5% of available agricultural land was required to dispose of biosolids to meet soil contaminant loading criteria of the watersheds respective country. This value was also used to account for regional limitations in soils and crops suited for biosolids application, as well as farmer preference for other fertilizers. Highly urbanized regions such as London, Los Angeles, and New York have to transport a substantial amount of their biosolids to agricultural regions outside their boundaries since the local use is limited by available agricultural area. To evaluate the sensitivity to the assumptions utilized for biosolids application rates, two alternative scenarios were evaluated. The first assumed maximum allowable biosolids application rate (Europe) and the high application rate for agricultural fertilization (United States, 44.8 dry metric tons per hectare [54]). The second maintained constant application rates for the simulation period, but no biosolids were exported (i.e. >5% of agricultural land was utilized to dispose of the biosolids within the region).

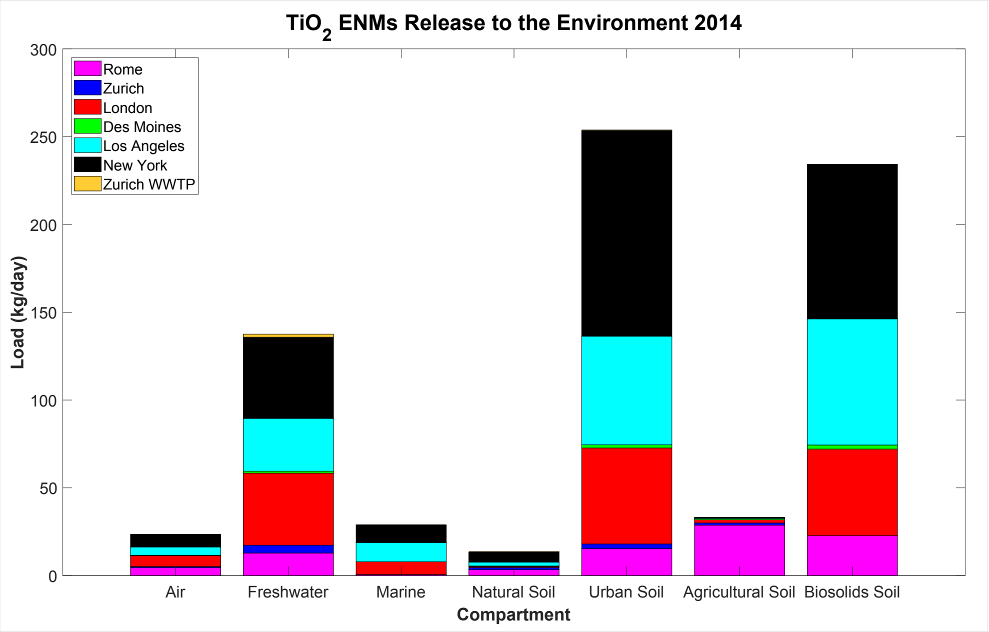
Sensitivity was also evaluated in the aquatic compartment, which may exhibit high volume variability during precipitation events. To explore the sensitivity of PECs to changes in freshwater compartment volume, the Los Angeles freshwater compartment was evaluated. The fluctuations in compartment size in Los Angeles were estimated based on the regional flow rates observed during precipitation events. In Los Angeles, the flow frequently increases by 4-fold during rain events[59], thus to evaluate compartment size effects, the default compartment depth (0.17 m) was increased to 0.68 m (4xDepth scenario). Since nanoFate cannot currently account for variability in compartment size during a simulation, the 4-fold compartment size was held constant for each day of the scenario.

RESULTS AND DISCUSSION

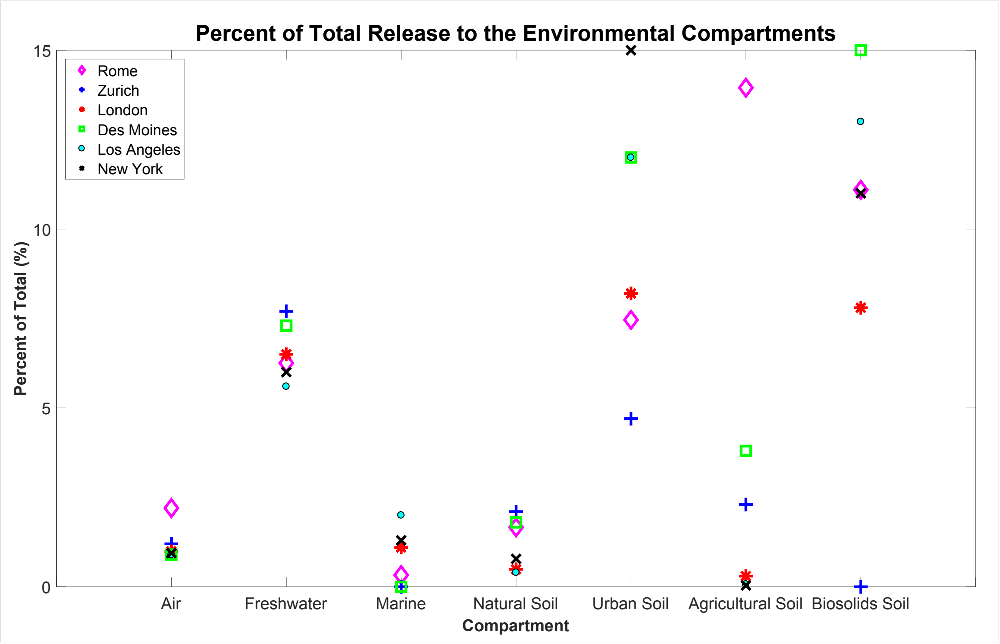
Predicted release to the environmental compartments within each region is strongly dependent on land use, population density and other local characteristics (see **Table S13** *SI Section 3: Release Data*). Within each region, landfills were predicted to receive the highest loads of nanoTiO_2. The compartment with the second highest load varied by region, but the cumulative release from all regions was greatest in urban soil **(Figure 1)**. For all U.S. regions except New York City, the biosolids compartments were predicted to receive the second highest load of nanoTiO_2, however, this was not observed for European regions due to more stringent regulations for biosolids application. In Zurich, the freshwater compartment received the second highest load, while in London, Rome, and New York, the second highest load was released to urban soil due to the high urban population density. Of note for the urban soil compartments of European regions, lower fractions of release were predicted relative to U.S. regions. This is attributable to the high fraction of septic systems in urban environments within the U.S. regions (10-23%). Although Rome also has a high fraction of septic systems (39% of wastewater treatment), a higher proportion of residents in the U.S. study regions lived in urban areas relative to Rome, where many residents still live in the agricultural areas of the region.[42,45,46,48,60] Due to the higher agricultural population in Rome, a larger fraction of the total release was predicted in its agricultural compartment (14%) relative to other regions (< 4%).[42]

Figure 1. (a) Summary of the total nanoTiO_2 estimated to be released to the environment in the regions investigated for the average release scenario and **(b)** the release fractions by compartment. The Zurich WWTP load is released 100% to freshwater and is not depicted.

(a)



(b)



Predicted Environmental Concentrations

NanoFate generates estimated daily PECs for 26 compartments, which are aggregated into 9 bulk compartments: air, freshwater, freshwater sediment, seawater, marine sediment, natural soil, urban soil, agricultural soil, and biosolids treated soils. The PECs for each region's bulk environmental compartment as of 2014 are included in *SI Section 4: Predicted Environmental Concentrations*. The highlights are discussed below, with comparisons where feasible to previous studies. All values reported in this study are the arithmetic mean for the concentration of nanoTiO_2 observed in 2014.

Table 1. PECs for the bulk compartments of the average release scenario in 2014. Bolded values indicate the far-field regions with the highest mean, bolded and italicized values indicate maximum concentrations

Region	Statistic	Air (ng/m3)	Freshwater (μg/L)	Freshwater Sediment (mg/kg)	Marine (μg/L)	Marine Sediment (mg/kg)	Undeveloped Soil (μg/kg)	Urban Soil (μg/kg)	Agricultural Soil (μg/kg)	Biosolids Treated Soil (mg/kg)
Rome	mean	22.8	35.0	38.2	0.328	0.63	49.9	61.1	**46.2**	2.63
	max	37.1	92.1	42.5	0.340	0.68	51.6	62.2	***47.0***	2.68
	min	2.58	15.8	35.9	0.313	0.56	48.2	59.8	45.0	2.56
Zurich	mean	9.38	0.926	1.79	NA	NA	16.6	21.4	18.8	NA
	max	14.6	0.96	1.86	NA	NA	17.2	21.9	19.5	NA
	min	3.43	0.899	1.71	NA	NA	15.9	20.6	18.1	NA
London	mean	**30.3**	58.7	93.0	**5.20**	**5.60**	**59.2**	124	24.2	6.26
	max	***46.2***	87.2	97.4	***5.25***	***5.95***	***61.4***	127	25.1	6.49
	min	14.6	43.7	89.6	5.03	4.98	57	121	23.4	6.03
Des Moines	mean	0.146	0.479	0.759	NA	NA	2.16	7.03	0.264	6.66
	max	0.234	5.71	0.809	NA	NA	2.21	7.21	0.269	6.78
	min	0.026	0.243	0.720	NA	NA	2.09	6.80	0.257	6.48
Los Angeles	mean	17.2	**61.9**	**111**	1.02	0.662	9.00	95.1	10.1	23.7
	max	19.9	***1,490***	***116***	1.03	0.688	9.33	98.8	10.5	24.7
	min	3.89	33.4	106	0.998	0.637	8.69	91.8	9.66	22.7
New York	mean	6.24	33.5	66.7	0.0449	0.0284	47.6	**198**	23.6	**77.8**
	max	10.3	62.4	69.3	0.0460	0.0295	49.4	***206***	24.5	***80.7***
	min	1.09	27.5	63.9	0.0440	0.0273	45.9	191	22.8	75.1
Zurich WWTP	mean	NA	613	32.4	NA	NA	NA	NA	NA	NA
	max	NA	619	39.8	NA	NA	NA	NA	NA	NA
	min	NA	603	23.4	NA	NA	NA	NA	NA	NA

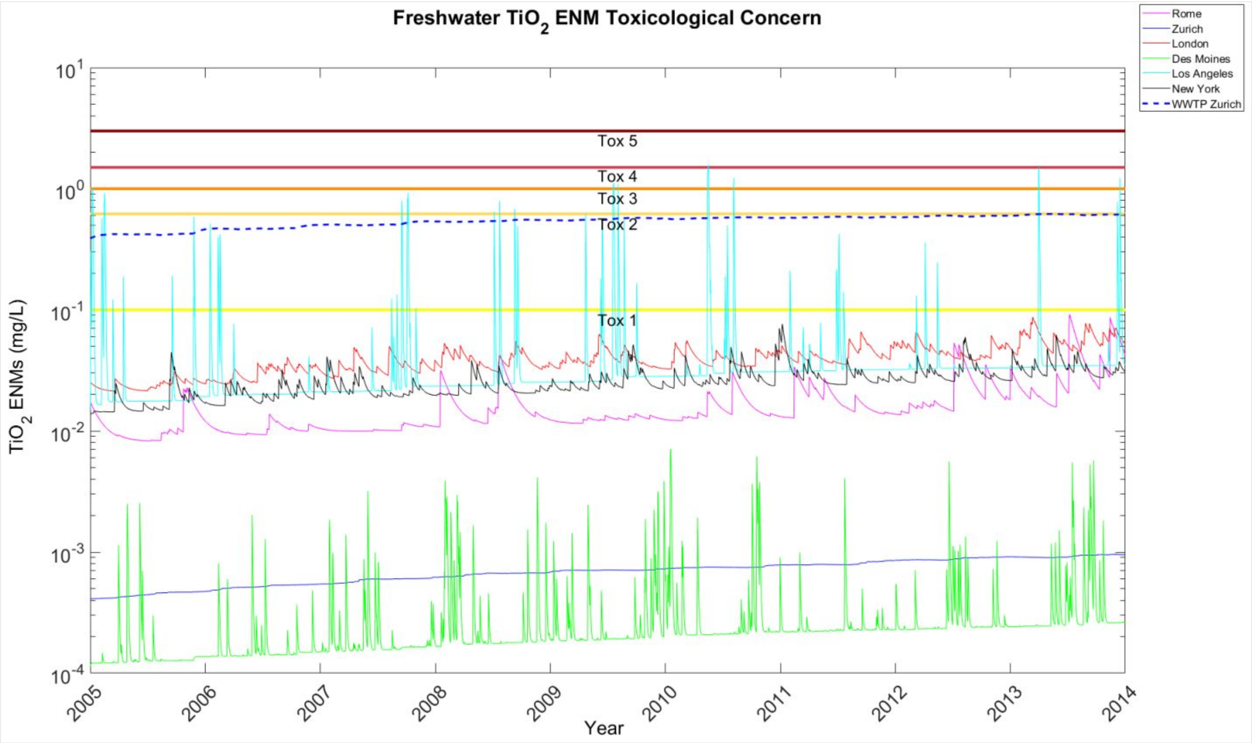
observed for each compartment. Note that the units are ug/kg for most soils except biosolids-treated soil which is reported in mg/kg.

Freshwater and Freshwater Sediment

NanoTiO$_2$ PECs in the freshwater column of the more densely populated regions (Rome, London, New York, and Los Angeles) were similar (34-62 μg/L), while the PECs in Zurich and Des Moines were 1-2 orders of magnitude smaller, 0.9 and 0.5 μg/L respectively (see **Table 1**). PECs for the less densely populated regions and/or large compartment sizes with respect to population, Zurich and Des Moines, were generally within an order of magnitude of PECs presented in other studies for freshwater compartments (central tendency (metric varied by study) 0.021-2.17 μg/L).[16–18,20–22] In the more populated regions (London, Rome, Los Angeles, and New York), PECs in this study exceeded previous estimates by 0.5-3 orders of magnitude since previous analyses considered larger environmental compartments (national or continental) and thus much lower population densities and estimated release rates per unit area. [16–18,20,22] This finding highlights the importance of estimating PECs at a more local scale, as large scale estimation methods fail to account for variability in release in sub-watersheds of the study area, which may be subject to significantly higher or lower nanoparticle release rates.

Substantial daily variability was predicted within the freshwater column in most regions, driven by the transport of ENMs in storm runoff (**Figure 2**), since we assumed no variability in WWTP discharge. Substantial loads of nanoTiO$_2$ are predicted in storm water runoff as a result of (1) the large urban and agricultural areas relative to the freshwater compartment; and (2) the accumulation of ENMs from paints and coatings in urban soils, and from agricultural lands subject to biosolids application. There is empirical evidence that ENMs are retained near the surface of soils, releasing particles (possible attached to soil particles) during high runoff events.[61] In light of these factors, nanoTiO$_2$ concentrations were predicted to briefly increase following precipitation, by up to two orders of magnitude in some regions. The highest variability was observed in Los Angeles (62-1490 μg/L) and the lowest in Zurich (0.90-0.96 μg/L). The high variability observed in Los Angeles is attributable to infrequent precipitation, very small freshwater compartment volume relative to overall area, and low flow. Low variability in Zurich is due to the large size of the freshwater compartment relative to land area (Lake Zurich was included). When the low and high release were considered for the far-field scenarios (*SI Section 3: Release Data*), PECs for freshwater are 0.38-37 μg/L and remain similar to the concentration range of the default release scenario (0.5-62 μg/L). This finding demonstrates low model sensitivity for the ranges of releases considered here.

Figure 2. PECs of nanoTiO_2 in freshwater for 2005-2014 relative to the concentrations at which negative effects have been observed in freshwater organisms (Tox 1 – Tox 5). Tox1 (0.1 mg/L): Gill inflammation in rainbow trout (*Oncorhynchus mykiss*).[4] Tox 2 (0.62 mg/L): NOEC modeled from multiple species ecotoxicological studies.[62] Tox 3 (1 mg/L): Inhibition concentration of 25% of green algae (*Pseudokirchneriella subcapitata*).[19] Tox 4 (2.5 mg/L) and Tox 5 (3 mg/L): IC25 and LC50 respectively for the invertebrate *Ceriodaphnia dubia*.[20]



In the Werdholzi WWTP near-field analysis, we estimate a freshwater PEC of 613 µg/L, which is at least an order of magnitude higher than all far-field regions and two and a half orders of magnitude higher than in the broader Zurich region (note the only load considered in the near-field scenario was from the Werdholzi WWTP effluent, since no runoff was considered; daily variability was smaller). While the ecotoxicological threshold exceedances of the PECs for Los Angeles serve to illustrate the importance of considering unique regional release of nanoparticles and compartment characteristics, the PECs of the Werdholzi WWTP demonstrate how spatial resolution can have significant implications in PECs of nanoparticles and should be considered in the evaluation and mitigation of risk.

PECs predicted here for nanoTiO_2 in population dense regions (average annual concentration of 34-62 µg/L for Rome, London, Los Angeles, and New York) were similar to WWTP effluent PECs in previous studies (central tendency 3.5-44 µg/L), and measured Ti concentrations in WWTP effluent.[16,18,20–22] In highly urbanized regions, freshwater flows may be wastewater effluent-dominated (e.g. Los Angeles and some freshwater reaches of large cities such as New York, London, and Rome), and may explain the similarity to predicted surface water concentrations within the urbanized regions and WWTP effluent concentration predictions and observations of the aforementioned studies.[42,63–66] These findings suggest surface water PECs for nanoTiO_2 may be similar to wastewater effluent for highly urbanized regions.

The fraction of nanoTiO_2 estimated to be removed by WWTPs in this study was based on removal rates for Ti measured by Westerhoff et al. [67] and Kiser [68]. The annual mean PECs for freshwater in the more populated regions investigated here (Rome, London, Los Angeles, and New York) were higher than the modal Ti (<9 µm in diameter) concentrations measured in WWTP effluent by Kiser et al. [67] (< 10 µg/L), and the mean concentration of 20 µg/L measured for Ti particles(< 7 µm in diameter) by Westerhoff et al. [68]. This was noteworthy in that TiO_2 ENMs would be expected to have significantly lower concentrations with respect to Ti particles, as Ti is produced and used at substantially higher levels than nanoTiO_2. Titanium pigments alone are produced in quantities two orders of magnitude greater than the high end of current production estimates for all nanoTiO_2.[31,69] PECs reported here and in previous studies[16,18,20–22] are similar to measured Ti concentrations in WWTP effluent, which suggests release rates currently used in ENM risk assessments may be too high.

Freshwater sediment PECs were 3-4 orders of magnitude higher than the freshwater column PECs, and were typically the highest of all environmental compartments due to the high release fraction to water, small compartment size with respect to the load received, and sedimentation of nanocolloids from the water column (**Table 1**). Sediment PECs are estimated to be higher than the water column, 0.7-76 mg/kg (modeled density for sediment and freshwater 2400 kg/m^3 and 1000 kg/m^3 respectively) due to continuous deposition of nanocolloids that accumulate over time and due to the negligible dissolution of nanoTiO_2. Low daily variability was predicted for nanoTiO_2 in sediment with respect to the water column due to reduced compartment transport rates. Sediment PECs were similar to previous estimates for Europe and Switzerland presented by Sun[22] (21.3-43.1mg/kg) and Sani-Kast[27] (0-2.7 mg/kg). The near-field freshwater sediment PEC for the Zurich WWTP, 32 mg/kg, was an order of magnitude higher than the far-field PEC for Zurich. However, unlike the freshwater compartment, the near-field sediment PEC was not substantially higher than the far-field analyses due to the short time for the particles to settle prior to being transported from the compartment via stream flow. Again, concentrations in the Zurich WWTP freshwater and freshwater sediment compartments reflect only the effects of the Werdholzi WWTP effluent to the local freshwater environment. The total concentrations for freshwater near-field analyses within urban environments need to consider other variables such as upstream effects, industrial effluent, and storm water infrastructure, which were not evaluated here due to lack of information.

Seawater and Marine Sediment

For the seawater column and marine sediment compartments, lower variability and PEC values (0.9-5 µg/L and 0.7-5 mg/kg respectively) were predicted with respect to the corresponding freshwater column and sediment due to the larger sizes of the marine compartments (*SI Section 1: Regional Summaries* and *Section 4: PECs, Figure S2*). Variability was also reduced due to the assumption in nanoFate that runoff first enters the freshwater compartment and is then transferred by advection to coastal waters, which dampens the signal. The highest nanoTiO_2 PECs in seawater and marine sediment were for the Thames River estuary downstream from London, which had the highest per capita to compartment size ratio.

Soil

The agricultural compartment subjected to the application of biosolids had the highest PECs (**Table 1**), and PECs continued to increase throughout the analysis period (*SI Section 4: PECs, Figure S2*). The agricultural land to which biosolids were applied received 8-15% of the total regional nanoTiO_2 released (**Figure 1b**), and this compartment was predicted to have 1 to 4 orders of magnitude higher nanoTiO_2 PECs relative to soils in other land uses (note difference in units between biosolids soils (mg/kg) and the other soils (µg/kg) in **Table 1**). This reflects the large mass fraction of ENMs predicted to pass through WWTPs and end up in biosolids, and highlights the significance in accounting for the different land uses and corresponding soil compartments in ENM risk assessment.[16,17,24,67,68,70] For the biosolids treated soil, the range of PECs for the regions investigated was 2-81 mg/kg, with the U.S. regions predicted to have higher PECs due to less stringent legislative standards. In previous work by Sun et al.[22] , the concentration of nanoTiO_2 in sludge treated soils in Europe was predicted to have similar concentrations (reported mean 61 mg/kg). PECs for nanoTiO_2 in biosolids (distinct from biosolids treated soils) in previous studies ranged from 107-7,007 mg/kg[13,16,17,22,70,71] and are similar to concentrations of total Ti measured in biosolids in other work, 19-7,020 mg/kg[24,53,68,72], again suggesting current release estimates from WWTPs for nanoTiO_2 presented here and in other work are likely too high. [16,18,20–22]

To better understand the effects of nanoTiO_2 release estimates and their sensitivity on PECs in different regions, we evaluated two scenarios. The first scenario assumed maximum application rates of biosolids that abide regulations and the second assumed default biosolids application rates with no biosolids export in population dense regions. In the maximum allowable application analysis, PECs increased by factors of 2-7.4 in biosolids treated soils (see *SI Section 4: PECs*). The increase in applied biosolids affected PECs in other compartments by a factor of 1-1.6, with the freshwater sediment predicted to have the highest increase, as a result of runoff from agriculture. In the “no biosolids export” scenario, the application rate was the same as the default, but biosolids were not exported from the region. Biosolids were disposed of into the biosolids soil compartment, and the biosolids land area was increased (and agricultural land with no biosolids decreased) to maintain the estimated biosolids application rate. For this scenario, PECs were expected to increase by a factor of 1-1.1 in all compartments, demonstrating low sensitivity to biosolids export assumptions (see *SI Section 3: PECs)*. The small increase in PECs for other compartments is attributable to the small size of the biosolids compartment relative to the size of the other compartments, even when expanded to accommodate all regional biosolids. The highest increase in PECs for the “no exports” scenario was observed for the freshwater and freshwater sediment compartments within Los Angeles due to the smaller size ratio of the compartments with respect to the biosolids compartment.

Air

The air compartment had the lowest PECs of all compartments reviewed, 0.1-30 ng/m^3. The low concentrations are attributable to the small loading rates, about 2% or less of the total, the low predicted contribution from resuspension of ENMs from soils to the atmosphere, and the large compartment size. High intra-annual variability was predicted in the compartment due to wet deposition during precipitation events.

Uncertainty and Limitations

Uncertainty is a measure of the disparity between data with respect to the true value. The uncertainty of concentrations predicted here is not quantifiable due to the high innate variability of environmental characteristics for which insufficient spatiotemporal monitoring data is available (e.g. suspended particulates, aerosols concentration, and soil moisture), and the absence of data for some input parameters which required expert judgment (e.g. sediment advection). Previous work has sought to address uncertainty in nano PECs with probabilistic modeling.[19,20,22] Although these methods are useful in quantifying uncertainty and likely outcomes given sufficient data, they fail to prove effective for quantifying PEC uncertainty when data is limited. In our efforts, the input to which models are most sensitive is ENM release. As previously mentioned, there is significant variability (and likely uncertainty) in ENM production reports, even in countries that mandate reporting of ENMs, such as France[36]. Previous work by Sun et. al (2016), amidst uncertainty in release data, modeled the uncertainty of PECs based on probabilistic distributions of model inputs, including ENM release. However, only 7 release estimates were available during their study, 3 of which were assigned a degree of belief of 20%.[73] Given highest model sensitivity to release, and limited spatiotemporal availability for environmental characteristic data, the evidence for the calculated uncertainty representing true uncertainty in the PECs is limited. Although we were unable to quantify data uncertainty, we are utilizing representations of relevant environmental processes and best available data to provide an estimate of *how* nanoTiO_2 ENM risk varies with characteristics of the environment, e.g. high urban land use, high land surface area to water ratio, and biosolids application. We believe the discussion of predicted concentration flux, differences between regions, and loading in respective compartments elucidates important considerations for future monitoring efforts and mitigating risk.

Limitations to the current assumptions for PECs include:

1) The high uncertainty associated with current TiO_2 ENM production estimates. For instance, the production estimates for TiO_2 used in this study for 2011 in the United States, was 7,654 tonnes/year. This value was in agreement with the lower limit to the production range calculated for the United States by Hendren et al. 2011, 7800 tonnes/year.[74] Other work by Piccinno[75] and published in 2012 has suggested notably lower production quantities globally, 3,000 tonnes/year.
2) Data for the release of TiO_2 ENMs from products and waste management is limited and uncertain, and estimates from production and manufacturing processes, accidental spills, transport, and stocks were not included.
3) The population distribution was calculated utilizing geospatial population datasets that were constructed based on census block data.[42] The integrity of the dataset has not been evaluated utilizing ground-truth surveys and may not accurately reflect population densities per given land use.
4) Watersheds were used as a proxy for regional boundaries, although advective transport (inflows and outflows) are considered in nanoFate. However, different watershed scales can be considered arbitrarily, and there are no clear boundaries for airsheds. Thus there is importance in considering both near- and far-field scales.
5) In predicting the concentration of nanoTiO_2 in the freshwater compartment, we currently assume wastewater effluent enters all freshwater in the region, although in reality not all freshwater segments may be subjected to wastewater effluent. The appropriate scale may be needed for different regions and subregions to account for WWTP discharge correctly, as shown in the Zurich WWTP nearfield analysis.
6) Many environmental characteristics are variable and have limited spatiotemporal data, such as suspended particles, pH, and the organic fraction of material in the water column, and simulated daily variability in the environment only accounted for release, climate, and hydrology.

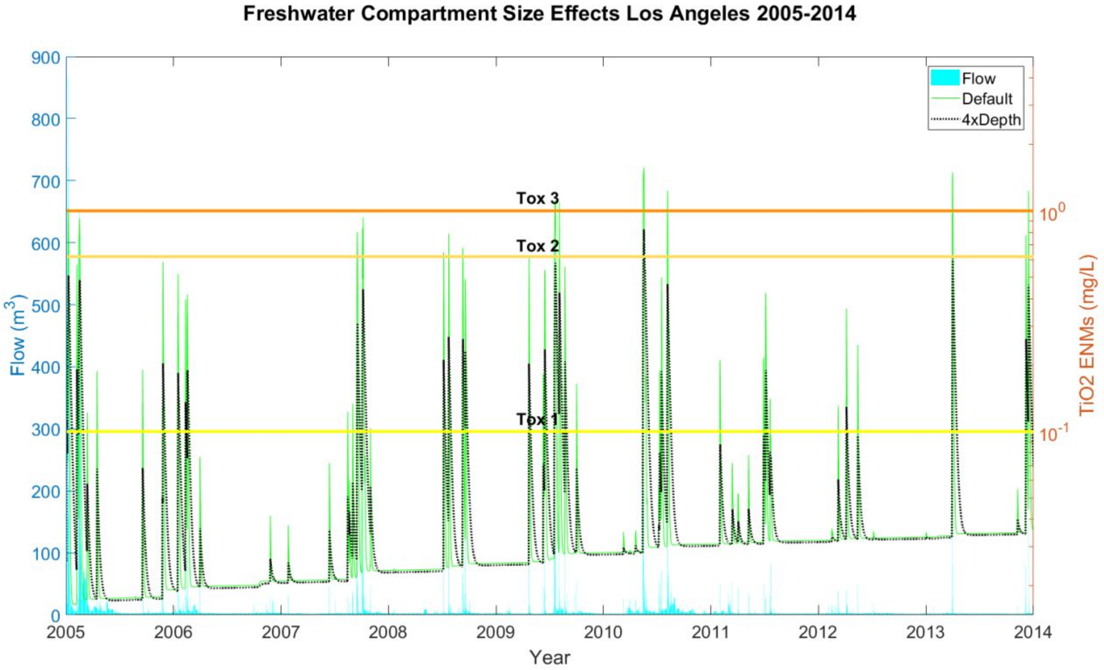
Risk Assessment

PECs of nanoTiO_2 were evaluated for ecotoxicological concerns within the freshwater compartment. Ecotoxicological data available for other compartments were limited, and available effect concentrations were generally greater than PECs in this study by an order of magnitude, indicating generally low risk. Notably however, sediment, soil, and atmospheric toxicological data were more limited than for aquatic data. Coll et al.[73] conducted a probabilistic risk assessment and predicted the soil NOEC for nanoTiO_2 to be between 2-4 mg/kg, which is generally exceeded by biosolids soil PECs in this study (2-81 mg/kg). However, other soil toxicity studies reviewed and compared to the soil PECs in this study suggest low risk for soil dwelling organisms, as observed effect concentrations were 1,000-10,000 mg/kg.[73,76–83] Further toxicological research in soils is needed to better assess risk within the compartment.

Of the regions evaluated, the freshwater compartment in Los Angeles and downstream of the Zurich WWTP had PECs at which adverse effects have been observed in laboratory studies (**Figure 2**). The following acute and chronic endpoints were exceeded between 2005-2014: NOEC, LOEC, respiratory inflammation, EC50, and the inhibition concentration of 25% (IC25) of organisms for one or more of the following taxa: unicellular organisms, algae, invertebrates, and vertebrates.[3,5,24,25,62,84–93] Of the exceeded endpoints, only three are discussed here as they were exceeded by PECs. Within the Los Angeles freshwater compartment, the mean days of continuous exceedance in 2014 of the endpoints gill inflammation in rainbow trout (*Oncorhynchus mykiss*)[5], NOEC modeled from multiple species ecotoxicological studies[62], and IC25 of green algae (*Pseudokirchneriella subcapitata*) were 4, 3, and 2 days respectively, while the maximum days of continuous exceedance was 13, 5, and 4 days respectively (see **Figure 2**). Notably, had we assumed no daily meteorological variability, Los Angeles would not have exceeded any of these toxicological endpoints. In the Zurich WWTP nearfield analysis, the concentrations for the 10-year simulation period exceeded the rainbow trout gill inflammation toxicological endpoint each day and nearly exceeded the green algae IC25 toxicological end point in 2014.

In most models, including nanoFate, the freshwater compartment size is held constant, although it may change significantly during major precipitation events. Although this assumption will have a small effect at a large scale (e.g. country or continental), for smaller regions/compartments, assuming a constant volume may yield unrealistic PECs during precipitation events when the compartment size expands substantially. In some regions, such as Los Angeles, the freshwater compartment is known to change significantly. To evaluate the sensitivity of PECs to changes in the freshwater compartment size, events where concentrations of nanoTiO_2 exceeded ecotoxicological thresholds were counted for the 4xDepth scenario (compartment size increased by four times relative to the default) and default scenario (see **Figure 3**). Events are defined here as an increase in nanoTiO_2 concentration relative to the previous day, as attributable to changes in meteorological or hydrological factors. The maxima PECs decrease for the 4xDepth scenarios, due to the larger compartment size, and there were fewer exceedances of the ecotoxicological endpoints at higher nanoTiO_2 concentrations. The trout gill inflammation ecotoxicological endpoint for the 4xDepth scenario was exceeded during 28 events, while the default compartment depth scenario exceeded the endpoint in 46 events. The NOEC endpoint was exceeded during 1 event in the 4xDepth scenario and 15 events in the default, while the IC25 of green algae was not exceeded in the 4xDepth scenario, but 7 events exceeded the threshold in the default scenario. The reduction in exceedance events in the 4xDepth scenario illustrates the significance in accounting for compartment size variability which is not accounted for in previous surface water nanomaterial risk assessments. [12–27,94–96]

Figure 3. Effects observed to freshwater compartment variability in consideration of compartment size expansion during precipitation events. See **Figure 2** for Tox 1-Tox 3 endpoint descriptions.



Environmental Significance

Based on current use and waste handling of nanoTiO_2, the highest predicted environmental release is to freshwater, urban soil, and soil to which biosolids are applied, but this is highly dependent on local conditions that may not be valid for all urban regions in a state/province, country, or larger scales. Due to the transport of nanoTiO_2 via runoff from urban and agricultural soils to surface water, we estimate higher

PECs in surface waters of regions with greater fractions of urban areas or soils receiving biosolids application, relative to surface water compartment size. We predict based on available toxicological data and PECs, that nanoTiO_2 may pose some ecotoxicological concerns to freshwater compartments downstream of WWTPs and near urbanized regions, especially in areas of infrequent precipitation events and small land to freshwater compartment ratios such as Los Angeles. Furthermore, we have demonstrated that more accurate risk assessment of contaminants requires specific consideration of the:

- near field region downstream of large WWTPs and waters isolated from WWTPs;
- differences in land use that can result in differential accumulation of ENMs in various soils;
- potential change in the volume of the freshwater compartment during large storms, particularly in drier regions (e.g. Los Angeles);
- ratio between urban land area and receiving freshwater volume, which varies significantly between regions.

Within the atmospheric and terrestrial compartments, we have predicted orders of magnitude differences in PECs of the regions evaluated that are attributable to differences in population density, land uses, and waste management practices. As we seek to understand and mitigate the potential effects of ENMs in the absence of reliable environmental monitoring methods, regional propensities for the release and accumulation of nanoTiO_2 need to be evaluated via modeling. Awareness of regional and compartmental vulnerability to ENMs would provide opportunities to risk managers to prepare effective mitigation strategies and evaluate whether adverse effects observed in an environment may be influenced by high concentrations of ENMs.

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