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Modeling Nanomaterial Fate and Uptake in the Environment: Current Knowledge and Future Trends

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Nano impact

In this paper, we critically review recent progress in modeling the environmental fate and uptake of nanomaterials within the context of assessment of their environmental health and safety. Trade-offs between model complexity and data availability are discussed for aquatic, terrestrial and organismal uptake models. Recommendations for future directions and research priorities include focusing on parameterizing existing models and generating lab and field data to validate them, to advance the field rapidly.

Abstract

Modeling the environmental fate of nanomaterials (NMs) and their uptake by cells and organisms in the environment is essential to underpin experimental research, develop overarching theories, improve our fundamental understanding of NM exposure and hazard, and thus to enable risk assessment of NMs. Here, we critically review the state-of-the-art of the available models that can be applied/adapted to quantify/predict NM fate and uptake in aquatic and terrestrial systems, and make recommendations regarding future directions for model development.

Fate models evolved from substance flow analysis models, that lack nano-specific processes, to more advanced mechanistic models that (at least partially) take nano-specific (typically non-equilibrium, dynamic) processes into account, with a focus on key fate processes such as agglomeration, sedimentation and dissolution. Similarly, NM uptake by organisms is driven by dynamic processes rather than by equilibrium partitioning. Hence, biokinetic models are more suited to model NM uptake, compared with the simple bioaccumulation factors used for organic compounds. Additionally, biokinetic models take speciation processes (*e.g.* particulate versus ionic uptake) into account, although identifying essential environment-specific processes to include in models remains a challenge.

The models developed so far require parameterization, calibration and validation with available data, e.g. field data (if available), or experimental data (*e.g.* aquatic and terrestrial mesocosms), rather than extension to more complex and sophisticated models that include all possible transformation process. Collaborative efforts between experimentalists and modelers to generate appropriate ground-truth data would advance the field most rapidly.

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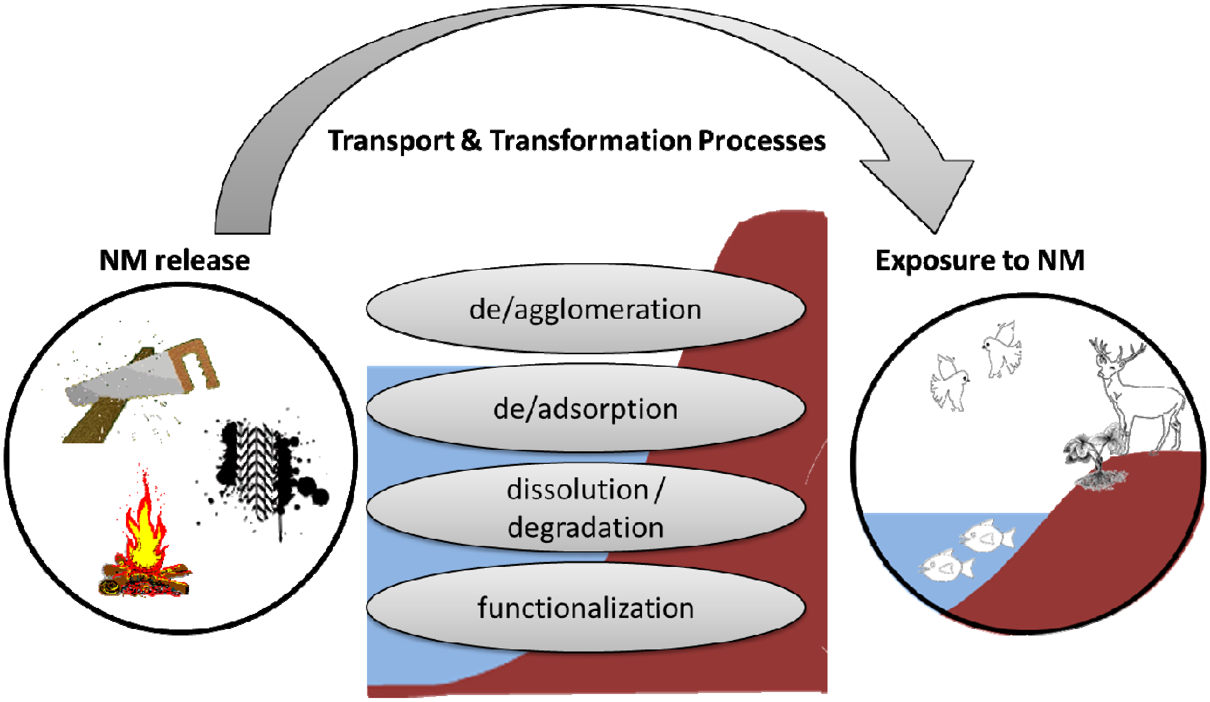

Air, Water, Soil

Schematic summary of the most important transformation processes a NM may undergo during environmental transport, and thus the parameters of highest importance for inclusion in models of NM environmental fate and uptake.

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1. Introduction

Engineered nanomaterials (NMs) are a form of chemical substance, defined by their size being in the range of 1 to 100 nm [1,2], often with unique and novel properties. For example, silver and gold NMs change color at sizes *ca.* < 40 nm.[3] Gold, inert at micron scale, becomes catalytically active as sizes becomes *ca.* < 5 nm.[4] Cerium oxide NMs have a higher proportion of Ce^{3+} atoms at sizes *ca.* < 15 nm leading to higher redox activity,[5,6]. These novel properties of NMs have given rise to myriad applications to improve product performance, enhance process efficiency and reduce waste[7]. Consequently, the nanotechnology market is growing exponentially with global research and development investments of billions of dollars each year, global markets worth trillions of dollars[8,9], increased NMs production volumes[10] (hundreds to thousands of metric tons) and development of thousands of novel applications for NMs[7].

The release of NMs from NM-containing consumer products during usage has been widely demonstrated. Exposure to NMs (*e.g.,* those released from consumer products) in environmental systems is already occurring[11-17], and is set to increase with rapidly expanding production and consumer applications for NMs[18]. NMs are already listed as emerging contaminants of environmental concern (CEC) in several national and international reports[19], requiring in depth risk assessment. Risk assessment consists of two key elements: (1) hazard (toxicity) characterization, and (2) exposure (environmental concentration) characterization. So far, the risk-related research on NMs has had a strong focus on the NM toxic effects with thousands of published studies[20], whereas exposure assessment research, including emission, transport and fate, is lagging behind. This growing gap in assessing NM exposure in environmental compartments is due to difficulties in measuring NM concentration and properties in complex environmental samples[21,22] and the complex and dynamic transformation processes that NM experience in different environmental compartments[23-26]. While analytical methods to measure NMs in environmental media are being developed and validated, the environmental health and safety scientific community has attempted to fill this knowledge gap by developing mathematical models to assess NM distribution in the environment, and to place bounds on the predicted environmental concentrations of NM.

The environmental compartment for which modeling is most advanced is air, given that this exposure route is of high relevance for human health in addition to environmental fate and thus extensive earlier research on ambient ultrafine particles. Several models for airborne particles are available, which can be classified into pure transport and chemical transport models. The latter also include chemical reactions of particles with gaseous and liquid compounds allowing further reactions to be implemented. Available models cover different spatial scales ranging from microscale, street canyon, to local, regional, hemispheric and global scale. The basic principle, the stepwise modelling of transport and physical as well as chemical reactions is the same for all available models. The more sophisticated chemical transport models for air are e.g. EURAD, LOTUS EUROS, CHIMERE [27]. They also discriminate particle sizes such as ultrafine particles, hence applying also in the nanoscale size range. Modeled processes of the particles in air comprise e.g. homogeneous and heterogeneous agglomeration, condensation, catalytic reaction, wet and dry depositions. NMs and their agglomerates do not behave totally differently in air (compared to ultrafine particles) so that they can be modelled in these models, especially since a size differentiation of these particles from others can be made. A review of NM fate models in air compartment can be found elsewhere [27]. Further discussion of these models is excluded from the rest of this review as its focus is on NM fate and

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uptake within each environmental compartment (water, soil and organisms), rather than transport between environmental compartments.

The aim of this paper is to review the state-of-the-art of **(1)** fate and transport models for NMs in environmental systems (aquatic and terrestrial), and **(2)** NM uptake and accumulation models in biota. We evaluate the existing models for NM fate, behavior and uptake and identify additional modeling needs to fully address the fate, behavior, uptake and risk of NMs in the context of environmental exposure assessment. The reader is referred to comprehensive reviews for a detailed understanding of the processes and factors determining the fate and behavior of NMs in aquatic [24,26,28] and terrestrial [25] compartments, and the processes and factors determining NM uptake [29].

2. Fate models in aquatic systems

a. General overview

Fate models for NMs are still being developed. However, especially for the aquatic compartment, different basic approaches have been used to model NM environmental behavior and fate[30]. Some of the models resulting from these basic approaches apply to laboratory or mesocosm scale experimental studies[31], whereas other models are developed to mimic NM fate and behavior at larger scales, e.g. at a sub-continental scale (e.g. rivers[32]) or global scale[33].

In parallel, experimental data regarding NM fate and behavior are being generated, both in simple electrolyte solutions and in more complex matrices, with the aim to improve the general understanding of NM fate and behavior in the environment and to discover novel NM-specific environmental fate processes. This knowledge is instrumental to NM fate modeling, informing modelers of the key processes to be taken into account in NM fate modeling, and in some instances, provides data sets that can be used for model calibration. The discussion below summarises the current state-of-the-art of NM fate modeling in aquatic systems, their validation status and the availability of data to parameterize and calibrate them.

b. Common approaches to fate modelling and recent progress

To date, few approaches to NM aquatic fate modelling have been developed. Most developed models are based on the general concept of mass flow analysis, supplemented with nano-specific process descriptions when possible. As an illustrative example, Mueller and Nowack[18] predicted environmental concentrations in air, water and soil compartments in Switzerland on the basis of a substance flow analysis of NMs in different products and the resulting emissions. A probabilistic approach to materials flow analysis was subsequently applied to account for the large uncertainty and variability of model input parameters that are typical for the current state of knowledge regarding estimated production volumes and NM behavior in the environment[34,35]. Simplifying assumptions are often invoked in these models, e.g. absence of transformation or rapid sedimentation relative to advective transport, in order to obtain a range of predicted environmental concentrations[36,37]. The assessment was further refined using probabilistic material-flow modelling, showing that the production volume and the compounds' inertness are crucial factors determining the final concentrations of a NM[38].

A more mechanistic approach to NM environmental fate modeling was developed by Praetorius et al., who adapted a well-established multimedia box model for organic pollutants to NM fate modeling[32] by adjusting fate process descriptions to account for NM-specific properties and behavior within the environment The mechanistic approach of Praetorius et al. was extended by Meesters et al.[39]. These authors identified the lack of field data available to test the validity of NM fate models as

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a key bottleneck in adapting fate models for conventional chemicals for NMs. Meesters et al. presented a fate model that uses first-order kinetics to estimate environmental background concentrations for NMs, in an approach that deviates from that of Liu and Cohen[40] as Liu and Cohen used time-independent partitioning ratios for agglomeration and attachment of NMs. Compared to the Simple-box model that is the basis for the European Union System for Evaluation of Substances (EUSES), the fate model of Meesters et al. contains three major adaptations to make it fit for use with NMs:

1 – Transformation processes are considered as altered species of the same NM;
2 – Dissolution is implemented as a removal mechanism;
3 – Thermodynamic equilibrium is not expected to be representative of reality.

The modified Simple-box model of Meesters et al. requires experimentally derived values for the parameterizations that are not fully covered by existing colloid theory (e.g., agglomeration and attachment efficiencies). Experimental data are available for all environmental parameters included in the model (e.g. surface water and sediment composition, and typical dimensions of the individual compartments at various geographic scales), but not yet for specific properties for all types of NMs as relevant under different environmental media compositions (e.g. medium-dependent kinetics of dissolution, or particle-specific attachment frequencies). This indicates that the required experiments can be performed successfully but also stresses the need for more experimental investigation. In cases where experimental data are unavailable to calibrate and validate fate models, theoretically derived parameter values are used and the resulting uncertainty is provided[39].

The currently available NM fate models show different levels of complexity. Praetorius et al. 2012 suggested categorization of existing approaches into more detailed bottom-up mechanistic modeling and more simplified top-down modeling [32]. The bottom-up modeling includes information about important mechanisms affecting NM behavior and fate in the environment such as agglomeration, sedimentation and/or dissociation or other relevant processes[32]. Therefore, if possible, knowledge from other natural sciences such as colloid chemistry or (organic) chemical kinetics and theories dealing with colloids or organic chemicals are included. Problems can occur when modeling processes where no experimental data or relevant rate constant values are available, e.g. the attachment efficiency for different NMs to natural sediments and other porous materials.

Models based on the top-down or engineering approach have a simplified structure. In these models, the environmental compartment is treated as a black box and no specific information about the fate processes is included in the model. The drawback with this approach is the limited predictive potential for new or not tested materials or processes. Hence, this type of model is currently used e.g. to describe the emissions of NMs to the environment and subsequent mobility using partitioning factors. Top-down models differentiate between the different fractions e.g. transported into other compartments, remaining in the water phase, etc. A summary of fate and transport process models and analytical studies analyzing the environmental concentration of NMs in different compartments can be found elsewhere[41].

A general overview of the main features of a selection of the currently available NM fate models is given in Table 1. Further details on the cited models in Table 1 can be found in the original publications. Clearly, NM fate modeling has progressed from simple mass flow/balance models[18,35,42] that use transfer factors to describe the distribution of NMs among and within compartments to probabilistic models that adopts a range of these transfer factors to examine different scenarios of NM transport[43], to NP-processes based models[32,44-47]. The later models differentiate NM from

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molecular contaminants by taking into account the dynamic nature of NM environmental behavior such as heteroaggregation, dissolution, and sulfidation. This approach explicitly recognizes the fundamental difference between equilibrium driven partitioning of so-called conventional (molecular) chemicals (i.e., chemical substances in atomic/ionic or molecular forms, dissolved in water or in the gas phase), and substances present in a particulate form. Making such an adjustment is challenging because of the fundamental differences in transport and transformation mechanisms between NMs and solutions. A major difficulty in making models for conventional chemicals fit for NNs is that hardly any field data are available to test the validity of nano-adjusted models. The initial attempts using mass flow models to model NM environmental fate were intended to provide a first step in environmental exposure estimation of NM and to provide average background exposure concentrations for NM on a regional and national scales[34,35], using scientifically justified simplifications combined with a pragmatic approach which has brought fate modelling of NMs a significant step forward.

Furthermore, the majority of these models (*i.e.* those published prior 2015) have been solved at steady state (*i.e.* ignored temporal variability) [32,37,39] and/or been spatially unresolved, averaging concentrations over large regions (e.g. countries) [18,35,38-40]. All these models have ignored stream loads from surface runoff (e.g. from NM-containing biosolids used as fertilizer, or NM in stormwater) [39,40], and none have considered spatiotemporal variability in sediment transport rates, described NP chemistry as a function of environmental conditions, tracked NP reaction by products (metal ions, metal sulfides, *etc.*), or considered overbank flow and NM deposition in the floodplain. These simplifying assumptions could misrepresent NM mobility and risk in potential NM hot spots, which have been scrutinized recently[47-50]. Several models suggested that using spatiotemporally explicit models allow prediction of NM speciation and NM hot spots as a function of time and space[47-50]. Below we highlight an example of these spatiotemporal explicit models.

Using a spatially resolved model (30 km average stream segment length) for the James River Basin, Virginia, Dale *et al.* (2015), assessed the impact of the typical simplifying assumptions (discussed above and summarized in Table 1) of NM fate models on the utility of NP fate models to predict NM environmental fate and to capture potential NM risks [48]. They demonstrated that **1)** spatial and temporal variability in sediment transport rates can lead to high NP transport such that <6% of NM-derived metals were retained in the river and sediments, **2)** chemical transformations entirely eliminated ZnO NP and doubled Zn mobility in the stream relative to Ag, **3)** agricultural runoff accounted for 23% of the total metal stream loads from NPs, and **4)** the average NP-derived metal concentrations in the sediment varied spatially up to 9 orders of magnitude, with highest concentrations in segments that had low stream velocities and high sediment deposition.

Although, this model is more realistic compared to mass flow models and spatiotemporally averaged models, the key assumptions of this model (Table 1) need further testing and evaluation. In particular, the assumption of complete heteroaggregation of NP as several studies demonstrated the occurrence of induvial nano-sized particles in surface waters (e.g. natural and incidental nanoparticles[51-53]). This model ignored NM sources other than wastewater effluent and agricultural runoff from sludge treated soils. Additionally, this model did not consider overbank flow and the possible deposition of NPs in the floodplain, which could significantly impact NP transport rates depending on the river system[54].

1 **Table 1.** Summary of the key features of NM-environmental fate models

Reference	Media	NM specific fate and transport processes considered	Approach adopted	Assumptions	Advantages	Disadvantages	Comments
				Spatiotemporally averaged: Mass flow models			
Mueller and Nowack (2008)[18]	Water, air, soil	Removal in waste water treatment plant Release from products	Modelling based on established methods for assessing exposure to non-particulate chemicals	Instant homogeneous mixing in all compartments System in steady state Substance flow rates similar for all NMs Secondary compartments (sediment and groundwater) not considered	Simplicity of model input	Worst case assumptions only NM-specific fate and transport processes not considered No model validation for NMs performed	Size and functionality of NMs not considered
Gottschalk et al., (2009)[35]	Water, air, soil, sludge treated soil	Dissolution Sedimentation Removal in waste water treatment plant	Probabilistic material flow analysis from a life-cycle perspective as the basis for calculation of environmental concentrations	Environmental compartments homogeneous and well-mixed Constant annual flows Nano-Ag dissolved by less than 1 % in natural waters	Probabilistic methods allow inconsistency and variability of model input parameters to be taken into account Possibility to incorporate extreme events	Mainly qualitative data available on NM-specific processes and NM-specific mass flows Uncertainties in input and output parameters high Model validation needed	Further fine-tuning of the model needed in order to include local conditions, specific scenarios and quantitative data on NM-specific processes Insufficient consideration of impact of media and AgNM properties on dissolution
Blaser et al., (2008)[37]	Water, sediment	Dissolution of Ag NMs embedded in a polymer matrix	Modelling of silver flows that result from the application of Ag NMs as biocides, using a commonly applied fate model	Nanoparticles are embedded in a (stagnant) polymer matrix Only silver ions are released and not entire silver NMs	Basic fate model available Limited: Ag NM-specific adaptation of model needed	Not all applications of Ag NMs considered	Flows of Ag-ions modelled instead of Ag NMs Under-estimation of actual flows as not all application of Ag NMs Age considered NM-specific assumptions need in-depth evaluation

							No consideration of impact of NM specific properties like surface coating and size on dissolution
Liu and Cohen, (2014)[40]	Air, water, sediment, soil	Heteroaggregation Transformation (including phototransformation and dissolution) Sedimentation Deposition Bioconcentration	Multimedia fate modelling on the basis of advective transport, taking NM-specific processes into account and including particle size distributions	Environment considered as a collection of compartments, including the biotic compartment, linked via intermedia transport processes Assumption of first order kinetics suffices for first tier analysis	Particle size distribution included in modelling Most relevant fate determining processes of NMs considered within first-tier approach	No validation performed	Further verification of the basic assumptions needed
Spatiotemporally averaged: Process based models							
Dale et al., (2013)[44]	Sediment	Dissolution Sulfidation Solid phase partitioning Particle diffusion	One-dimensional diagenetic modelling of silver distribution / speciation in freshwater sediments	Kinetics of AgNM sediment chemistry respond to redox conditions Speciation of Ag in sediments contingent on displacement of iron from iron sulfide to form metal sulfides of very low solubility Linearity of reaction rates with concentration, but AgNM oxidative dissolution assumed to decrease exponentially in response to Ag NM sulfidation	Key processes included in modelling, including physical processes like particle mixing due to bioturbation	Temporal evolution of NM size and aggregation not possible Data collected at high spatial and temporal density needed to further validate the model	Calibration to (single pulse) experimental data on AgNM dosing of artificial wetland mesocosms Homoaggregation not considered, which is justified as heteroaggregation dominates homoaggregation
Lazareva and Keller,	Effluent, water, soil	Transformation Agglomeration in wastewater treatment	Life cycle modeling approach to predict environmental releases of	Similarity of fate determining processes of NMs in surface waters and in wastewater	Limited number of processes considered	Needs high quality input data regarding: - Local variations in water	Model applied to estimate NM releases in three major cities across the globe

(2014)[45]		facility Sedimentation	NMs	treatment plants		chemistry - Size and flow conditions of receiving environment, as these determine NM concentrations in receiving waters.	Despite significant uncertainty in model parameters, ENM concentration estimates within same order of magnitude as experimental data
Van Koetsem et al., (2014)[46]	Natural surface waters	Stability (aggregation) and settling (sedimentation) of CeO_2 NMs Co-precipitation of NMs with aluminium- and iron-containing natural colloidal materials	A semi-empirical first-order settling rate model (first proposed by Quik et al., 2012)	Limited number of input parameters Model validated by means of measurements using natural waters	Key assumption: settling of particles depends on particle properties and on the physicochemical characteristics of the receiving medium	NM concentrations in natural waters will be a lot lower compared to those tested. Increased shear stress due to turbulent flow conditions, or interactions with organisms are not considered	Excluded data sets
Money et al., (2014)[55]	Water	Ag NM aggregation, dissolution, and deposition NM parameters: fractal dimension, collision rate, and attachment efficiency,	Bayesian network	Utilizes a combination of expert and empirical knowledge bases related to the aquatic behavior and exposure of nano-Ag as a function of environmental conditions and particle characteristics. Influence of changes in environmental conditions, and particle characteristics, on particle fate.	Ability to integrate multiple knowledge bases, refine probabilities as new data become available, and accurately predict concentrations of nano-Ag despite numerous uncertainties and data gaps	The model complexity reduces its ability to propagate information throughout the network. The large amount of missing data in the literature case file used to revise the baseline parameters (26.2% complete)	Model improved via inclusion of mesocosm data Further validation via additional mesocosm and field experiments is necessary.
Praetorius et al., (2012)[32]	River water, sediment	Homo- and hetero-agglomeration (modelled on basis of attachment efficiency) Dissolution	Established multimedia environmental fate model for organic pollutants used as the basis for environmental fate modelling of NMs, yielding	Transport potential of NMs dependent on NM properties and system properties (advective transport rates and properties of suspended particulate matter in terms of	Highly flexible modelling framework	Model applied to TiO_2 NMs only Spatial and temporal variation not included in modelling	No model validation although it is claimed that modelling results are representative for a large range of realistic cases

		Sedimentation	NM concentrations in water and sediment as function of distance from source	concentration, size and density)		Single value for hetero-aggregation rate for all NMs	
Meesters et al., (2014)[39]	Air, water, sediment, soil	Advective ENM transport Homo- and heteroaggregation Dissolution Degradation: biodegradation and photolysis	Multimedia fate modelling of NMs on the basis of (pseudo) first-order rate constants for: (1) advective transport, (2) removal by transport to outside the system, (3) uptake of NMs in aggregates or attachment to surfaces of larger particles, and (4) removal processes such as degradation and dissolution	Environmental fate of NMs is kinetically driven, as opposed to thermodynamically based equilibration of non-particulate chemicals	Mechanistic formulations of key processes Model output in terms of mass concentrations of NMs as free dispersive species, heteroaggregates with natural colloids, and larger natural particles in each compartment in time and at steady state	Need to acquire parameter values (rate constants) for more diverse sets of NMs	Limited evaluation of model performance: only reworking of a previously published dataset
Markus et al., (2015)[56]	Water	Sedimentation and resuspension Dissolution and transformation Homo- and heteroaggregation Mineralization Potential for extension to NM uptake in organisms	Process-based model with each process described as a functional expression on the basis of mass concentration NMs are viewed as a particulate constituent, not as a collection of individual particles	Several fractions of NMs are distinguished to describe the phenomena. Individual experiments are unified in a single set of equations and parameters with terms that have a physical–chemical meaning. This allows one to make predictions about the behavior in other circumstances	Can quantify the relative importance of the various processes using the mass balance Can be applied in combination with models for other constituents, for instance, an algal growth model, so that attachment to living or dead organic material can be modelled	Parameters are determined via an automatic optimization method (Powell, 2009). Results for several initial concentrations are used together, rather than the results of individual time series	Expected to be generally applicable to metal and metal oxide NMs. Validated against data laboratory data for CeO$_2$ and TiO$_2$ NMs [57,58]
Spatially/temporally resoled models							
Sani-Kast et al., (2015)[50]	River water and sediment	Homo- and hetero-agglomeration Dissolution	Spatial variability in environmental conditions incorporated in existing NM fate model	Combined effect of water chemistry parameters like pH, ionic strength, and complexation by natural organic matter determines NM fate in	Spatially resolved effects of water chemistry on NM fate properly incorporated in model	Variability in emission sources and emission magnitudes not considered Single value for hetero-	Model validation not performed, General trends observed in line with experimental data

		Surface transformation Sedimentation		surface waters Cluster analysis applied to identify key features affecting overall NM fate		aggregation rate for all NMs	
Dumont et al., (2015)[47]	Freshwater, sediment	Heteroagglomeration Sedimentation	Spatially resolved modeling of nano-Ag and nano-ZnO monthly concentrations based on detailed emission inventories and temporally varying water and weather conditions.	First order loss coefficients are suitable to characterize NM sedimentation and dissolution	Model represents non-equilibrium concentrations in surface water	Only exposure due to household use of NMs considered Uncertainties in model output proportional to highly uncertain data on NM release from consumption and use Transformation processes not considered	Weather data simulated on basis of 31 years of data collection
Dale et al., (2015)[48]	Water	Hetero-aggregation, dissolution, sedimentation, resuspension and burial to deeper sediments	Coupling watershed model to water quality modeling suits WASP7, and configure both to model ZnO and Ag NP fate	ZnO and Ag NPs and their transformation byproducts entered the model via wastewater treatment facility effluent and biosolids assplication to row crops, hay, and pasture land. Land applied biosolids and soil were eroded and carried to stream during rain events. NP heteroaggregates completely with silt/fines in all media Absence of bedload shift	Taking into account spatiotemporal variability enables better assessment of potential hotspots of NMs and their environmental risks	Did not consider overbank flow and the possible deposition of NPs in the floodplain	Other sources of NP such as urban runoff (other than agricultural runoff), atmospheric deposition, *etc.* n were ignored, which might impact NP fate

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c. Validation of NM fate models

The key question in model validation is whether or not a given model can reproduce the experimental data (*e.g.* NM concentrations) that represents the conditions assumed in the model. Model validation can be achieved by 1) fitting to experimental data, 2) fitting field observations.

The first approach, fitting to experimental data, raises an issue of the applicability of a model to the complex field scenario, unless the developed model is validated against a wide range of conditions covering a wide complexity and interplay between variable conditions. There are no such models available at this stage due to the lack of experimental data that cover the breadth of the environmental conditions and scenarios and the variability in the experimental setups and conditions used by different research groups. The second approach, fitting field data, raises the issue of specificity of the site and applicability to other sites. In this case the model might need re-calibration to take into account the specificity of the sites, which directly affect NM behavior including attachment efficiency, mobility, or bioavailability. Fitting models with field data is also limited by lack of field data on NM concentration and characteristics. Therefore, an intermediate solution is to validate NM fate models using data at the mesocosm scale, followed by adoption to field scenarios and ultimately validating such models with field data when they become available.

d. Data availability

Measured concentration profiles of NMs in the field would provide the optimal data sets to calibrate and validate NM fate models. However, such data is absent in the literature because of the significant challenges in detecting and quantifying NM concentrations in complex environmental matrices. Significant progress has nevertheless been made in recent years, notably in developing single particle-inductively coupled plasma-mass spectroscopy (sp-ICP-MS)[59-62] and quantitative microscopy approaches[63,64]. However, no single analytical technique is sufficient to fully assess the occurrence and concentrations of NMs in complex environmental matrices, and a multi-method approach is needed to overcome these challenges. A more detailed review of the challenges and possible approaches that can be adopted to detect and quantify NMs in aquatic environments is provided elsewhere[21].

On the other hand, the majority of experimental “lab-based” data is collected without modeling considerations in mind and thus, most literature data are not suitable for calibration and validation of NM fate models. Laboratory studies have commonly focused mainly on investigating the behavior of NMs under simplified environmental conditions in order to understand and quantify the influence of different individual parameters (particle and media properties) on the behavior of NMs, which is not possible under environmental conditions due to the lack of sensitive instruments, making this kind of data unsuitable for NM fate model validation.

There are only a few studies available analyzing the fate of NMs at a mesocosm scale[65-67]. These studies were conducted with natural compartments but at a smaller scale than field studies. With this experimental set-up, inter-related parameters which occur under natural conditions can be generated. The results of these studies are easier to transfer to realistic (field) conditions. However, with increasing complexity also the requirements for sensitive detection methods increase.

3. Fate models in terrestrial systems

a. General overview

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Soils and sediments are often regarded as sinks in NM risk assessment, but further transport, e.g. to neighboring soils, groundwater tables or rivers may still be possible. NM modelling in soil has mainly focused on transport modelling, which is reviewed in some detail below. Transport modelling allows discovery of the underlying mechanisms and/or prediction of how NMs spread in the soil profile, from the point of entry, e.g. sludge addition in the plow layer or dry/wet deposition from air [39,40], to deeper soil layers. Models for NM bioavailability or transformation reactions, i.e. changes in NM speciation over time, have not yet been developed for terrestrial systems. Models for NM fate and transport in porous media such as soils have been built, to a large extent, on established concepts for particle dynamics in porous media[68], because most of the processes controlling relatively larger natural colloids in porous media are also relevant for NM[25].

b. Common approaches to fate modeling

Excellent reviews are available on models developed for colloid transport modelling[69-72] or on the applicability of such modeling for NMs[73,74]. These reviews show that nearly all transport models for both colloids and NMs are based on mass balances expressed as a partial differential equation (see supporting info). The differences between models only revolves around the modelling of the deposition mechanisms, i.e. the processes that leads to NM interaction with pore walls and in some cases, release of previously deposited NMs from the pore wall. The most used mechanisms considered for modelling this term are given in Table 2, with the corresponding equations given in the supporting info. Table 2 shows that different mechanisms have been postulated for deposition of colloids, going from simple partitioning coefficients, that assume equilibrium develops between deposited and suspended NMs, to ever more complex mechanisms including reversible attachment, dual deposition and preferential flow. Some mechanisms are only relevant for high concentrations of NMs in soils.[75] For example, blocking occurs when a significant proportion of sites is occupied by previously deposited NMs thus lowering the deposition rate. Ripening implies the opposite effect, i.e. where previously deposited NMs increase deposition rates because there is a high NM-NM affinity.[75] To date, not all of these mechanisms have been considered for modelling NM fate in soils (Table 2). Straining, i.e. the physical filtration of particles and/or arrival of particles in dead-ends, is a common mechanism restricting transport of natural particles, but its relevance is debated for NMs because of their relatively smaller sizes. Figure 1 shows simulated breakthrough curves (BTCs) and depth profiles determined according to some of the mechanisms listed in Table 2. Ripening is not shown because this mechanism is only relevant when using relatively high NM concentrations, and thus is only relevant for intentional NM additions (e.g. zerovalent iron for soil remediation[76]). Table 2 shows that equilibrium partitioning is seldom considered when modelling NM fate. A recent discussion in this journal revolved around the appropriateness of partition coefficients to describe environmental fate of NMs[77-79]. It may be advocated that partitioning coefficients have their use when modelling NM fate at large regional scales, where mechanistic modelling would prove elusive[78]. At smaller temporal and spatial scales, heterogeneity becomes somewhat more manageable and more accurate, and thus mechanistic modelling is possible and should be utilized. However, NM processes are essentially non-equilibrium and the equilibrium assumption makes partitioning coefficients unfit for purpose when mechanistic modeling is attempted.

Colloid filtration theory (CFT) is the simplest, but also most used approach to model NM fate in terrestrial systems (Table 2), where α_{att}, the attachment or collision efficiency, is the crucial parameter that quantifies the extent by which deposition is altered from the ideal case, i.e. in the absence of all repulsive NM – pore wall interactions[69]. α_{att} for a particular NM – surface combination could in theory be calculated based on DLVO theory, but α_{att} is in practice mostly fitted to breakthrough curves from column experiments (see SI) and thus becomes in effect an empirical parameter that lumps together many different mechanisms.[73,78]

When NMs are added at higher concentration, NM homoagglomeration may be important, and mechanisms such as blocking or ripening may play a role[75]. In addition, evidence is accumulating that NMs heteroagglomerate with natural colloids in terrestrial systems, as they probably do in aquatic systems also[58,80,81]. Straining is not expected to be quantitatively important for non-agglomerated NMs as they are too small.[82] However, any kind of agglomeration increases the size of NMs and thus enhances the effects of straining.[25,80] Moreover, early elution is often observed for NM, which may be explained by exclusion of larger heteroagglomerates from small pores[80,83,84]. Agglomeration of NM during transport can therefore be taken into account by assuming size exclusion and/or straining[58,78,80,81].

Table 2. Different processes associated with deposition of colloids that have also been considered during modelling of NM transport in sand columns and/or soils.

Mechanism	Description	Sand columns	Natural soils
Equilibrium Partitioning	Equilibrium is established between NMs releasing from pore walls and NMs continuously being deposited onto the pore walls	Fe[85]	
Irreversible attachment	NMs are deposited in the primary energy minimum of pore walls and are therefore only released in special circumstances (e.g. sudden drop in ionic strength and/or shear forces).	C_{60} [86,87]	Ag[88,89]; C_{60} [87,90] CNT[91]
Colloid filtration theory	Same as irreversible attachment, but the deposition rate constant is characterized based on DLVO theory using the attachment efficiency (α) and single-collector contact efficiency (η_0)	B [92]; C_{60} [93,94]; CeO_2 [95]; CNT [96]; Fe [97,98]; nHAP[99]; TiO_2[100]; QD [101,102]	Ag[88]; TiO_2 [103]
Reversible attachment	Deposition occurs in secondary energy minima from which NMs can relatively easily detach (i.e. without a sudden change in chemistry or shear forces)	Ag [103]; CNT [104-106]	Ag [88]; CNT[106]
Blocking	Deposition sites have a maximum capacity, $S_{\max}$	C_{60} [86,87]; CNT [105,107]	C_{60} [90]
Straining	NMs can be filtered mechanically or by reaching dead ends in a soil. The extent of straining decreases with depth with a coefficient β	C_{60} [87]; nHAP [108]; SiO_2 [109]	CNT [106]
Ripening	Previously deposited NMs increase the attachment efficiency	Fe[74], nHAP[110]	-
Pore clogging	Previously deposited NMs reduce access to some part of the pore network	Fe[74]	-
Dual deposition	Two different deposition sites exist, for of which one of the mechanisms above is assumed valid	CNT [106,107]; Fe [85]; nHAP [108] SiO_2 [109,111]	Ag [88]

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Preferential flow	NMs are constricted to a subset of relatively large pores in which water flows faster (on average) compared to the bulk water flow	-	-
Air-NM deposition	Deposition in unsaturated soils not only occurs on pore walls, but also at air-water interfaces	-	-

C_{60}	Fullerene
CNT	Carbon nanotubes
nHAP	nanohydroxyapatite
QD	Quantum dots

c. Model validation

As with all environmental systems, a distinction needs to be made between small-scale transport models for terrestrial systems, validated based on column tests, and larger-scale (field) models validated using lysimeters. Validating the latter models is currently impossible because such data cannot be obtained. The NM concentration reaching a lysimeter cup would be extremely low given the observed poor mobility of NMs in most terrestrial mobility experiments so far and selectively analysing NM at any concentration is extremely challenging given the high background of natural particles, or a dissolved background of the same element(s) of which the NMs are composed.[112]

It must also be emphasized that the models in Table 2 are *backward* models, i.e. the parameters are calibrated to the experimental data that was obtained. Such an approach cannot, by definition, be validated, as its aim is to discover which mechanisms control NM transport in the specific soil column under study. There is thus a lack of *forward* models for NMs in soils, i.e. where transport of NMs can be predicted based on the NM properties as well as the terrestrial media composition. While any forward modelling will not be highly accurate, given the heterogeneity of terrestrial systems, it would at least allow a better estimate of NM bioavailability to terrestrial organisms than the current approach based on total NM concentrations.

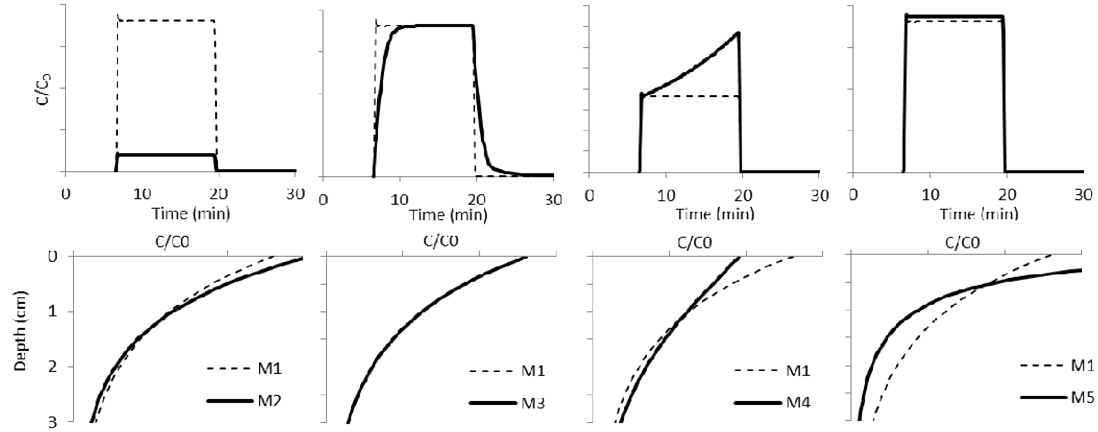

Figure 1. Hypothetical breakthrough curves (column outflow concentrations as a function of time) or depth profiles (solid concentrations as a function of depth after 20 minutes) following a 2 pore volume pulse of a 1.5 mg L^{-1} NM suspension in saturated 15 cm columns (K_s = 0.00825 cm s^{-1}, u = 1 cm s^{-1}, ρ = 2.7 g cm^{-3}). Four models were calculated using Hydrus 1D. M1: only irreversible attachment (k_a = 0.5 s^{-1}); M2: only irreversible attachment (k_a = 0.6 s^{-1}); M3: irreversible attachment (k_a = 0.5 s^{-1}) and reversible attachment (k_d = 0.2 s^{-1}; k_d = 0.05 s^{-1}); M4: irreversible attachment (k_a =

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0.5 s^{-1}) and Langmuirian blocking (S_{max} = 0.3 mg kg^{-1}); M5: depth dependent straining (k_{str} = 4.1; β = 0.43). Please refer to supporting info for equations and explanation of symbols.

Figure 1 illustrates how the backward models in Table 2 are not always robust, even when applied to relatively simple systems such as stacked sand columns, and their mechanistic accuracy is uncertain. The depth profiles presented in Figure 1 show that straining results in exponentially or hyperexponentially decreasing depth profiles with a higher particle removal at the column entrance where the NM feed enters the channel. Figure 1 also illustrates that both BTCs and depth profiles are necessary to apply a particular model from Table 2. Models M1 – 4 all show very similar depth profiles and differences are only clear when also fitting the BTC. Models M1 and M5 in Figure 1 show an example where the BTC may look very similar even when two entirely different sets of parameters have been selected. However, current models often fail to describe the depth profile.[73] Figure 1 shows that modelled depth profiles are always exponentional or hyperexponentional curves, whereas experimental data often shows entirely different trends that cannot be explained with these models.[73] Possibly, inclusion of some of the mechanisms that have thus far not been considered during NM modelling (heteroagglommeration, size exclusion, air-water deposition) could improve fits with experimental results, but would introduce even more parameters that have to be fitted to a limited number of data points. In addition, obtaining BTCs for NMs saturated stacked columns of clayey soils is not possible currently;, not only is the required pressure too high, NMs often interact strongly with clays[25].

Finally, extrapolating validated small-scale models to field situations can lead to large inaccuracies, because the experimental set-up of most column experiments introduces mechanisms that are not relevant for field situations and any conclusions drawn from column experiments are limited to the system under study. Detection limits of analytical equipment and possibly also the desire to observe breakthrough, leads to use of a pulse input of a very high NM concentration or most often a step input. This leads to unrealistically high NM concentrations in soils (on the order of mg or even g kg^{-1}) compared to the situation in the field where ng kg^{-1} concentrations are expected[80]. High NM concentrations leads to homoagglomeration and site blocking or even ripening becoming more important, whereas heteroagglomeration with more abundant natural particles, possibly associated with size exclusion, are probably the dominant processes at realistic (low) NM concentrations. Nearly all the studies in Table 2 have administered NMs to soil columns using a well-dispersed aqueous NM suspension pumped into one end of the column. Unintentional NM exposure in soils likely occurs through application of sludge to the top layer of soils[108]. NMs are heteroagglomerated with e.g. bacteria or natural particles within sludge and first need to deagglomerate from these particles before transport[96]. Adding NM together with sludge to a soil results in a much lower mobility compared to addition of pure NM suspensions to soils [113]. In addition, the parameters in Table 2 have been applied to experimental data obtained from different systems going from stacked column of well-defined spheres (e.g. glass beads), to saturated columns of soils to, in one case[89], intact soil cores. Realistic systems are harder to characterize, e.g. in terms of pore structure, and the experiments are almost impossible to replicate making it hard to obtain robust, universal fate descriptors for NMs that can be applied to a given, poorly characterized field situation. More realistic systems, such as intact cores also increase the required complexity of the models in terms of the number of interactions from Table 2 that need to be taken into account and also the number of parameters that needs to be calibrated.

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4. Uptake and accumulation in organisms

a. General overview

Uptake of NMs by organisms is governed by their physicochemical properties, the physicochemical properties of the environment and of the organism. Several studies reported uptake of a range of different NMs, which is also evidenced by the fact that BioConcentration Factors (BCFs) greater than 1 have been reported[114]. Additionally, several articles provide a review of the current state-of-the-art in terms of NM uptake and accumulation in organisms, describing routes of NM uptake, and discussing the specific factors that drive NM uptake by organisms[29,114]. However, very little information is available on modelling the uptake and accumulation of NMs in organisms. For conventional chemicals, different modelling approaches have been developed to predict the uptake by organisms. Among the most used are i) the application of Accumulation Factors, generally used for organic compounds (e.g. Bioaccumulation Factor (BAF), Bioconcentrations Factor (BCF), Biomagnification Factor (BMF)), ii) biotic ligand models (BLMs) to model uptake of metals by organisms and iii) biokinetic models, which use uptake and elimination kinetic parameters to model the accumulation of contaminants in organisms. Below, we critically discuss the applicability of these models to the case of NM uptake from the environment (see Table 3 for an overview of selected studies).

b. Common approaches to uptake modeling

Accumulation factors have been widely used to predict the accumulation of organic compounds by organisms. Predicting accumulation of NMs by organisms using accumulation factors can only be performed by assuming that the levels of the NM in the organisms have reached a steady state in relation to the ambient concentrations, which is governed by equilibrium partitioning between the environmental compartment and the organism[115]. The application of accumulation factors is rather straightforward and provides insight into the potential for NM uptake by organisms (see e.g. Hou et al. 2013[114] for an overview). However, the assumption of steady-state is not always validated in NM-studies; longer term studies may be needed to verify this approach. The application of partitioning coefficients may also not apply to NM[79]. Furthermore, reaching steady state may be different for different form of the same NM (e.g. ionic form, functionalized forms), which may affect accumulation factors based on bulk concentrations. Hence, although the application of accumulation factors may seem to be relatively simple, the results should be considered with some care.

BLMs have been developed for metal ions, both for aquatic and soil organisms[116]. BLMs model uptake of metal ions by organisms by taking into account the metal concentrations, competition for metal binding to biotic ligand sites, and complexation processes in solution driving the speciation and bioavailability of the metal. In BLMs, the metal ions compete for binding to the biotic ligand sites with all other ions in solution. Similarly, NMs may also compete for cellular uptake, e.g. by limited availability of binding sites (receptors). This may allow for the development of a similar modelling approach[117]. NM binding affinity and capacity is generally quantified in short term binding tests. BLMs relate the short term binding affinity of NMs for the biotic ligands to NM acute toxicity, in a quantitative way[118]. Most studies using BLMs to model NM affinity and binding in organisms, applied exposure durations of generally 24-96 hours[119,120]. These studies showed that BLMs can be used to quantify the number of transport or binding sites and the affinity of NMs for these sites[119-121], which can be used to model influx rates. Application of BLMs appears to be feasible to model uptake of both NMs as well as their ionic form(s) without the need to modify the BLM construct. However, this is limited to short term exposure and acute effects, and specific NM-parameters need to be derived.

Table 3. Summary of selected studies that have applied the three main uptake modelling approaches to address the uptake NMs by different organisms

Modelling approach	Compartment	NM-type	Key findings	Remarks	Ref.
Accumulation factors	Aquatic, several invertebrate species	Different types, reference is a review	Variety of Accumulation factors	Aquatic focus on Daphnids with Accumulation Factor > 1. Accumulation in Annelids from sediment generally < 1	114
Accumulation factors	Terrestrial, several invertebrate species	Different types, reference is a review	Most Accumulation factors < 1	Earthworm uptake relatively low, accumulation in isopod also reported	114
Accumulation factors	Aquatic vertebrates, several species	Different types, reference is a review	A range of Accumulation Factors	Aquatic exposure with Accumulation Factors > 1, dietary exposure generally results in low factors.	114
BLM	Aquatic, daphnid and oligochaete	Ag (± 10nm), different coatings	BLM approach confounded when ingestion of NMs occurs, applies well when toxicity is related to "dissolved" concentrations	BLM approach is predictive of acute toxicity after short term (waterborne) exposure	120
BLM	Aquatic, daphnid	Ag (80 nm), no coating	Toxicity related to ionic form of Ag	BLM only used to calculate acute EC_{50} for ionic exposure, no application to NM	122
BLM	Aquatic, L. stagnalis	Ag, citrate capped (17 nm), HA capped (13 nm)	Binding site capacity and binding affinity varied greatly between NM	BLM parameters used to interpret differences in waterborne uptake between different species of Ag	121
Biokinetic	Aquatic, L. stagnalis	Ag, citrate capped (17 nm), HA capped (13 nm)	Dietary uptake more important than waterborne uptake for all Ag-species	Kinetic models used to predict steady state concentrations in snails, for both waterborne and dietary exposure	121
Biokinetic	Aquatic, L. stagnalis	CuO (7 nm)	Dietary uptake more important than waterborne. Accumulation occurs due to low elimination rates	Kinetic modelling was applied to delineate the contribution of ionic and NM CuO species to the total accumulation of Cu	119

Abbreviations: EC_{50}: Half maximal effective concentration, i.e. concentration at which 50% lethality is observed.

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Biokinetic models use toxicokinetics parameters (quantifying rates of uptake and elimination of contaminants by organisms, potentially also including their internal distribution and metabolism) to model accumulation patterns in organisms. Biokinetic models have also been developed to describe NM uptake by organisms[119,121]. The biokinetic modeling approach describes NM uptake in organisms by taking into account NM transfer from one compartment (e.g. water or soil) to another (the organism). Excretion is also considered in biokinetic models in a similar way *vice versa*. Biokinetic models can be extended beyond direct uptake and elimination [123], and may also incorporate other environmental elimination mechanisms such as sedimentation [124]. Unlike BML models, biokinetic models can be used to assess processes over a longer time-frame, which allows the development of more realistic, long term, accumulation models.

The following section discusses some general issues in modelling NM uptake by organisms, elimination and food webs transfer illustrated with a modelling exercise. The issues are applicable to all modelling approaches, but the example will be illustrated using biokinetic models, which can be used on the appropriate time-scale.

Absorbed/adsorbed NM: When considering the accumulation of NMs in organisms, it is essential to differentiate between NMs that may be adsorbed onto the surface of organisms, or that are accumulated in the gut lumen, and NMs that are actually transferred into the cells and tissues. NMs that are not transferred across the membranes may have limited toxicological impact, although adsorption to algae may have toxic impact [125]. Nevertheless, NM in the gut of a prey or adsorbed to algae may be transferred to higher trophic level consumer/predators[124], similar to trace metals[126]. In neonate daphnids, it was shown that most of the gold NMs were located in the gut[127], and that feeding algae to the animals decreased NM uptake rate and increased NM depuration rate. Uptake and depuration were modelled using a first order rate model (Eq. 13 Supplementary information).[127] Experimentally derived uptake and depuration rates varied between NM sizes and capping agent. It was shown that 10 nm particles accumulated to higher extent in the gut of daphnids. In the case of the citrate capped 10 nm particles, no steady state was even reached within the duration of the experiment (24h).

Speciation of NM-uptake: Modelling NM uptake and elimination across biological membranes can also be approached using models[121]. Insoluble NMs can be accumulated as the particulate form, whereas uptake of soluble NM may be in particulate and/or ionic form. Intracellular dissolution of NMs may also be significant, as it was shown in that dissolution of Ag-NM was approximately 50 times higher in RAW 264.7 cells than in distilled water[128]. NM uptake (and excretion) from the environment by organisms, including extra- and intra-cellular dissolution, can be conceptualized as shown in Figure 2. The derived model equation (Eq.12) is presented in the supplementary information,

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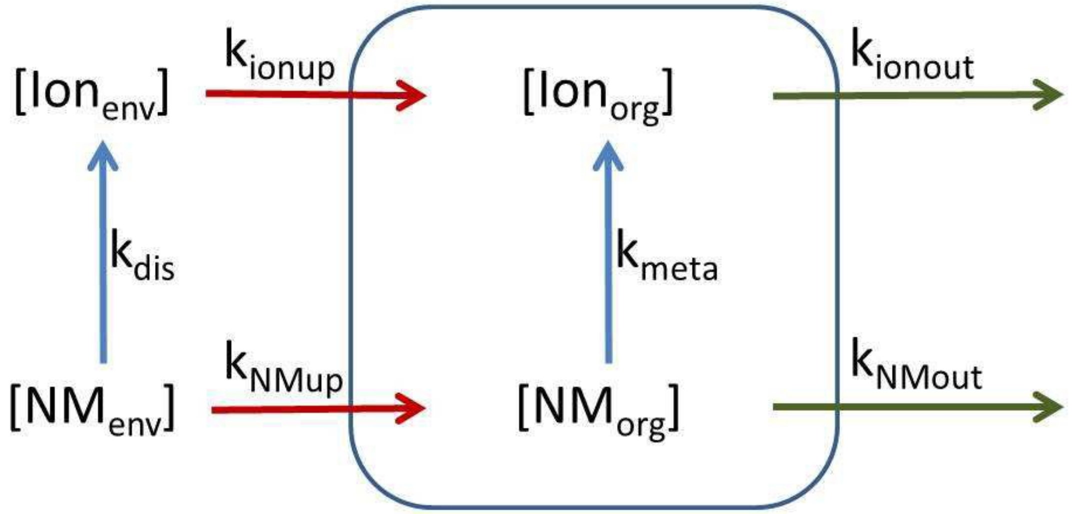

Figure 2. Conceptual display of routes of uptake and excretion of NMs from the environment by organisms. [NM$_{env}$] concentration of NM in environmental compartment (mg/kg or mg/L), [Ion$_{env}$] concentration of ionic form in environmental compartment (mg/k, or mg/L), [NM$_{org}$] concentration of NM in organism (mg/kg dw), [Ion$_{org}$] ionic concentration in organism (mg/kg dw), k_{NMup}: uptake rate constant for NMs from soil (as an example) to organism (g_{soil}*$g_{worm}$$^{-1}$*day^{-1}), K_{Ionup}: uptake rate constant for ions from soil to organism (g_{soil}*$g_{worm}$$^{-1}$*day^{-1}), K_{NMout}: excretion rate of NMs from organism (day^{-1}), K_{Ionout}: excretion rate of ions from organism (day^{-1}), k_{dis}: dissolution rate of NMs to ions in soil (day^{-1}), k_{meta}: dissolution rate NMs to ions in organism (day^{-1}).

Using the concepts presented in Figure 2, accumulation of NMs in organisms can be modelled (equations 14 and 15, Supplementary information). As an example, parameters were selected or deduced indirectly from literature for silver NMs (Table 4). For k_{meta} no direct values were available, this is based on an *in vitro* study[128]. Parameter values are derived from different studies e.g. uptake and elimination rates in worms[129], and dissolution from an aquatic[130] or an *in vitro* study[128]. This is not optimal for a detailed modelling exercise, and thus may have limited actual value, but it allows a first insight into the relative impacts of the different processes and parameters.

Figure 3 illustrates that inclusion of dissolution in the soil increased the uptake of ionic species (Figure 3b) resulting in higher total metal uptake than when dissolution is not modeled (Figure 3a). This is because the uptake rate of ions is assumed to be higher than the uptake rate of NMs (Table 4). Including internal dissolution in the uptake model results in lower total metal concentrations, and after 48 days a larger part of the NM has dissolved (Figure 3a *vs.* 3c). The lower total internal metal concentrations in the organisms are because NM and ionic species are excreted independently; hence there is an extra excretion route (i.e. ion excretion of 0.001 day^{-1} in addition to NM excretion of 0.001 day^{-1}; Table 4). When considering intra- and extra- organism dissolution of NMs, the relative concentrations of particulate NM become even smaller (Figure 3b *vs.* 3d). The concentrations presented here, and the associated conclusions, should be regarded with caution due to the fact that kinetic parameters were not derived specifically for the application to soil organisms. However, the modelled concentrations are in the same range as quantified in an earlier study[131].

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Table 4. Parameters used as inputs in equations 14 and 15 (supplementary information), resulting in modelled concentrations as shown in Figure 4.

Parameter	Value	unit	Reference	Remarks
K_{dis}	0-0.00632	day^{-1}	130	Based on Figure 4 in reference 119, geometric mean of Ag-NM 23nm (0.352 mg/l): k≈0.02 and Ag-NM 20 (10 mg/l): k≈0.002
k_{NPup}	0.00125	$kg_{soil}*kg_{worm}^{-1}*day^{-1}$	129	Approximated from Figure 3 in reference 118
k_{NPout}	0.001	day^{-1}	129	Approximated from Figure 3 in reference 118
k_{ionup}	0.0025	$kg_{soil}*kg_{wornm}^{-1}*day^{-1}$	129	Approximated from Figure 3 in reference 118
k_{ionout}	0.001	day^{-1}	129	Approximated from Figure 3 in reference 118
k_{meta}	0-0.3	day^{-1}	128	0-50 times k_{dis}, according to reference 117

The results in Figure 3 indicate that biokinetic models can be used to model accumulation of NMs in organisms, also including speciation. More detailed models may be feasible, including for instance settling of NM[127] in aquatic systems or functionalization of NM under environmental conditions. However derivation of parameters for the different processes may be difficult. In this context, the use of isotopically labelled NMs can be very helpful to e.g. differentiate ionic from particulate uptake[132]. Additionally, there is need for detailed methods and tools to characterize and quantify NM speciation (particulate and ionic) in tissues[133].

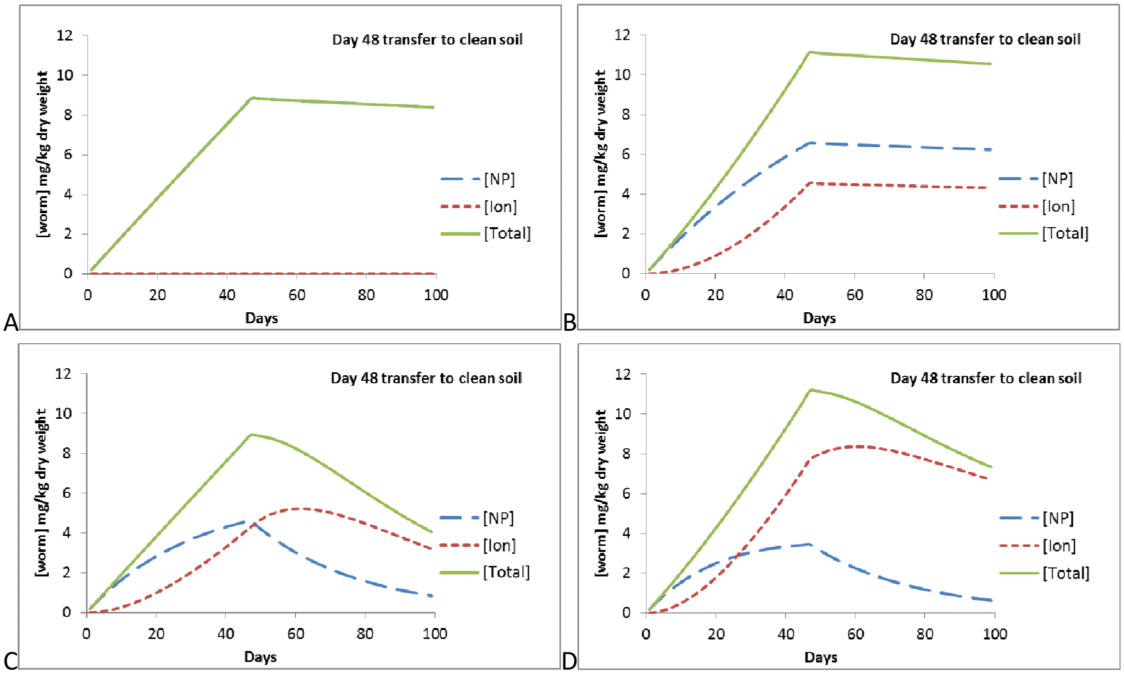

Figure 3. Modelled concentrations of AgNMs and ionic Ag in earthworms (equations 14 and 15 in Supplementary information). Worms are exposed to 150 mg/kg AgNMs in soil (initial ionic Ag concentration = 0), with different dissolution kinetic parameters (Table 4). A. k_{dis}=0, k_{meta}=0; B. k_{dis} = 0.00632, k_{meta} = 0; C. k_{dis}=0,

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k_{meta} = 0.0316; D. k_{dis} = 0.00632, k_{meta} 0.0316. [NP]: concentrations of AgNM; [Ion]: concentration of ionic Ag; [Total]: total Ag concentrations.

c. Model validation and calibration

There is great potential for adopting existing accumulation models for use with NM, and several studies have been carried out to quantify modelling parameters (see for a selection Table 3). Similar to the models used to address environmental fate of conventional chemicals, the developed accumulation models are *backward* models, i.e. parameters are calibrated to the experimental data. No *forward* modelling studies are known to the authors, which validate modelling approaches with independent observations of NM uptake by organisms. Limited information is available on the effects of NM properties and environmental conditions on the uptake/excretion kinetics[114], which hampers the read-across between different NMs to derive kinetic parameters (using a QSAR approach). Hence, systematic studies are needed under standardized test conditions, including quantification of the different forms of the NM in both exposure medium as well as organisms. For such quantification, optimized detection and quantification methods are needed e.g. sp-ICP-MS or AF4-ICP-MS, combined with procedures for sample preparation and NM-extraction that minimize impact on NM-properties[133]. An additional challenge will be to include variability in environmental conditions, taking into account the spatio-temporal scales of the organisms and the environmental fate and behavior of the NM. The available modelling frameworks seem applicable, although with some limitations. Hence, most emphasis in the near future should be placed on the derivation of model parameters, and especially calibration and validation of the models.

5. Future Needs and Perspectives

Significant progress in developing NM fate and uptake models has been made over the past decade; nonetheless, as discussed above, further progress is required to produce models appropriate for NM risk assessment as well as to advance our fundamental understanding of, and ability to predict, NM fate and uptake. Below, we summarize the imminent needs to advance the field of NM fate and uptake modeling.

a. Fate modeling in aquatic systems

The key challenge in modeling NM fate in aquatic systems is to account for spatial and temporal variability of NM transport and fate. This is to be performed by integrating the dynamics of the behavior of the relevant NM forms released from NM products and composite bound NMs, with a focus on the impact of NM transformation on environmental fate. Examples of such models have recently been published[47-50] and are being developed. As demonstrated by these spatiotemporally resolved models, future modelling approaches regarding the aquatic compartment need to focus on identifying the most important NM fate processes, and improving the spatial resolution of NM fate models. Despite not being a fundamental modeling problem, generating data on NM fate processes rates as a function of water chemistry under realistic environmental conditions will enable more realistic prediction of NM environmental fate and concentrations. Irrespective of applying mechanistic-based or engineering type modelling, model validation against experimental and field data over appropriate timescales needs to be addressed in the near future.

b. Fate modeling in terrestrial systems

The relevance of highly accurate mechanistic models based on unrepresentative column studies to the field situation is questionable. It can thus be argued that more basic fate descriptors, such as K_d or K_r values do not necessarily invoke more uncertainties, e.g. in a large-scale risk assessment [77,78].

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At the same time, the basic assumption of equilibrium used in the case of K_d-values can give rise to false conclusions [77,78]. Future work should therefore focus on developing less rather than more sophisticated models for terrestrial systems and associated measurement protocols for the required fate descriptors. Such an approach more likely strikes a balance between operational simplicity and mechanistic accuracy. Moreover, a simpler protocol is easier to standardize and more likely to produce larger datasets of fate parameters that can e.g. be related to NM descriptors and/or soil characteristics. Such relations allow extrapolation of fate parameters towards new soils and/or NMs that have not been studied *per se* and thus truly predictive models, i.e. models that do not need calibration, can be developed. However, accuracy of these models can only be validated, similarly to aquatic compartments, if analytical methods for NM in complex environmental media are developed further.

c. Uptake modeling

The different modelling approaches currently available appear to be suitable to address NM uptake in organisms, although each with specific limitations. Accumulation factors and BLM may be applied in a similarly manner as for molecular contaminants, although with some limitations. In the case of biokinetic models, different processes and NM-species can be included in the model descriptions. However, currently there is a lack of proper parameters describing the rates of NM uptake, elimination, transformation and dissolution. Hence, future research activities should not necessarily be focused in describing more complex and sophisticated models that include all possible transformation process. Simple models should be parameterized, see for instance Croteau et al.[110] In particular, the quantification of rate constants and parameters is paramount, and should be pursued. Establishment of uptake rates of different NM-species (starting with NM and ionic form), excretion rates and rates of dissolution in the environment and in tissues could be a starting point. For this however, detailed measurements are needed, that characterize and quantify the different forms of the NM in environmental matrices and tissues. Currently, new methods based on enzymatic digestion of organismal tissues, in combination with sp-ICP-MS are being proposed, which may provide the necessary data[133]. When conducted in a time resolved manner, such experiments will allow the derivation of rate constants, needed to populate the models.

d. Simplified empirical models based on fate and behavior descriptors

There is a difference between “scientific” and “empirical or engineering” type of models [78]. Scientific models are mathematical descriptions of the environmental fate of chemicals that are to a large extent based on relatively detailed and specific descriptions of individual processes, and are intended to reflect a mechanistic understanding of the system that is modeled. These models often require an extended set of parameters and this has precluded the use of such comprehensive models in routine and/or large scale risk assessments in which very basic engineering-type of models have been more common. One reason is that detailed model parameters that accurately describe fate processes in well-controlled laboratory-scale systems are often inaccessible in the field or even in mesocosms where highly heterogeneous conditions predominate so that no effective gain is reached when applying highly accurate models based on inaccurate model parameters[77,78].

Therefore, it is highly unlikely that complex mechanistic models will be used routinely in NM risk assessments. The many parameters required for these models are absent in most cases and obtaining these for all produced NM would require an irrational investment effort. Routine models will more likely be a compromise between technical accuracy and operational simplicity, similarly to conventional contaminants where K_d values have seen widespread use despite the obvious limitations[134]. Similar fate descriptors therefore need to be designed for NMs as well as a modeling

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framework and standardized protocols to obtain the data to parameterize the models. Such an approach could e.g. lead to establishing relationships between NM characteristics (coating length, hydrophobicity, size,…), characteristics of the receiving medium (pH, ionic strength,…) and NM fate. These fate descriptors and accompanying models need not necessarily be the most accurate approach possible, but the simplified methodology may be more conducive to generation of large databases and the subsequent deduction of empirical equations to extrapolate the fate descriptor's values to new NMs in new environments. Such fate descriptors cannot emerge from the same equilibrium assumption that has conceived e.g. the K_d values, because the equilibrium assumption does not hold for NMs at any given point, leading to grave errors in terms of fate prediction[77,79]. Alternatively, kinetic parameters such as collision and attachment efficiencies may be used[32,77] or empirical rate constants[31,58,135].

e. Integrated theoretical models taking into account all environmental fate processes

In order to develop new or extend/improve existing models for environmental fate & behavior of NMs, it is important to fully understand the processes involved in controlling fate of NMs in the natural environment and to be able to derive quantitative descriptions (*e.g.* rate constants) of the relevant fate process as well as to develop models to predict NM fate and behavior descriptors. There are currently some mathematical models (either theoretical or empirical) that describe these processes individually; nonetheless, there is a need for integrated models that consider the interplay between these processes, and their dependence on NM properties and environmental conditions. Integrated models require that common model variables be used as either model input or output, e.g. surface area or particle number, or that a way to convert between model outputs is developed, i.e. the output of one model must be able to serve as an input to the others. This requirement also implies the need for unification of model variables. Finally, there is the common need to validate the developed mathematical models and test their domains of applicability, etc.

f. Novel experimental setups to extract descriptors of NM behavior in the environment

There is currently very limited field data available on the occurrence and concentrations of engineered NMs in the natural environment due to the difficulties in detecting and quantifying their concentrations against a background of naturally occurring colloids, many of similar compositions.[112] Such a gap in data can be filled by developing novel experimental approaches that simulate NM fate in environmental systems or provide a measurable parameter that can be used to predict NM fate in the environment. For instance, data from restricted, well-controlled, environments like aquatic micro- or mesocosms or columns and flumes may be reasonable data sources to learn more about the kinetics of the most important processes determining the environmental fate of NMs. Development of simple measures specific to NMs (equivalent of the biological oxygen demand in waste water systems) could also be a useful tool.

g. Future generation of NMs

To date, the majority of NMs in use in products are simply nanoscale version of particles that have been in use for decades, such as silica, titania and ceria, or new nanoscale materials such as quantum dots and carbon nanotubes, engineered to have specific properties. However these are relatively simple materials in comparison to many of the advanced materials that will be available in the future, which will be multi-component (e.g. core-shell, segmented, layered materials with complex geometries and the potential for evolution or self-healing)[136-138]. These new NMs are being developed to achieve novel properties and functionalities, which may impact NM transformation processes and rates compared with those of the currently available NMs. The majority of the models

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described in this manuscript have been developed using the assumption of roughly spherical particles, and thus there will be a considerable effort needed to account for the effect of non-sphericity of particles, where for example, the presence of sharp edges or points might be sources of enhanced dissolution, aggregation or uptake and processes for synthesis of such advanced materials may result in introduction of additional defects in the underlying crystal structure or voids at the surface, all of which are linked to enhanced reactivity and thus may lead to altered fate and behavior. Careful consideration of whether NMs geometry and/or multiple constituent compositions may lead to alterations to the fundamental processes being modelled is needed, prior to generating data that may not be fit for purpose.

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