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Predicting environmental concentrations of nanomaterials for exposure assessment - a review

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ABSTRACT

There have been major advances in the science to predict the likely environmental concentrations of nanomaterials, which is a key component of exposure and subsequent risk assessment. Considerable progress has been since the first Material Flow Analyses (MFAs) in 2008, which were based on very limited information, to more refined current tools that take into account engineered nanoparticle (ENP) size distribution, form, dynamic release, and better-informed release factors. These MFAs provide input for all environmental fate models (EFMs), that generate estimates of particle flows and concentrations in various environmental compartments. While MFA models provide valuable information on the magnitude of ENP release, they do not account for fate processes, such as homo- and heteroaggregation, transformations, dissolution, or corona formation. EFMs account for these processes in differing degrees. EFMs can be divided into multimedia compartment models (e.g., atmosphere, waterbodies and their sediments, soils in various landuses), of which there are currently a handful with varying degrees of complexity and process representation, and spatially-resolved watershed models which focus on the water and sediment compartments. Multimedia models have particular applications for considering predicted environmental concentrations (PECs) in particular regions, or for developing generic "fate factors" (i.e., overall persistence in a given compartment) for life-cycle assessment. Watershed models can track transport and eventual fate of emissions into a flowing river, from multiple sources along the waterway course, providing spatially and temporally resolved PECs. Both types of EFMs can be run with either continuous sources of emissions and environmental conditions, or with dynamic emissions (e.g., temporally varying for example as a new nanomaterial is introduced to the market, or with seasonal applications), to better understand the situations that may lead to peak PECs that are more likely to result in exceedance of a toxicological threshold. In addition, bioaccumulation models have been developed to predict the internal concentrations that may accumulate in exposed organisms, based on the PECs from EFMs. The main challenge for MFA and EFMs is a full validation against observed data. To date there have been no field studies that can provide the kind of dataset(s) needed for a true validation of the PECs. While EFMs have been evaluated against a few observations in a small number of locations, with results that indicate they are in the right order of magnitude, there is a great need for field data. Another major challenge is the input data for the MFAs, which depend on market data to estimate the production of ENPs. The current information has major gaps and large uncertainties. There is also a lack of robust analytical techniques for quantifying ENP properties in complex matrices; machine learning may be able to fill this gap. Nevertheless, there has been major progress in the tools for generating PECs. With the emergence of nano- and microplastics as a leading environmental concern, some EFMs have been adapted to these materials. However, caution is needed, since most nano- and microplastics are not engineered, therefore their characteristics are difficult to generalize, and there are new fate and transport processes to consider.

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1. Introduction

Nanotechnology has grown at a blazing pace, from the early work in the 1980s when the visualization of individual atoms and bonds was made possible by the invention of the scanning tunneling microscope, to today with the production of nearly 2 million metric tons of nanomaterials and projected to double in the next decade. The actual production and commercialization of nanomaterials began well before 1980 (Nowack et al., 2011; Wigger et al., 2018), as "ultrafine" materials (e.g., nano-silver, nano-silica, nano-titanium dioxide, carbon black), but the development of materials targeted at the nanoscale began in earnest once we began to understand their unique properties. By the early 21st century, nanomaterials were being used in a wide variety of consumer products, including pigments and coatings, as well as a number of automotive, electronics, medical, and personal care products (Keller et al., 2023). For example, titanium dioxide nanoparticles and zinc oxide nanoparticles have been widely used as sunscreens due to their ability to absorb UV light (Suzuki, 1987; Monteiro-Riviere et al., 2011; Tyner et al., 2011), while silver nanoparticles are increasingly used in textiles due to their antibacterial properties (Gokarneshan and Velumani, 2017). Apart from these consumer products, nanomaterials are used in a large number of applications in various industrial sectors. For example, in the automotive industry, carbon nanotubes (CNTs) can improve tire performance in terms of durability, fuel efficiency and traction control (Felix and SivaKumar, 2014). In addition, engineered nanoparticles (ENPs) can be used in water treatment and environmental remediation due to their catalytic and photocatalytic properties (U.S. EPA., 2010; Lu et al., 2016). Moreover, they are also very useful in the energy sector. Carbon-based nanomaterials, such as carbon nanotubes, graphene, and fullerenes, allow for improved solar cell efficiency and stability due to their unique electrical and mechanical properties (Deshmukh et al., 2021). The use of nanotechnology in agriculture is also primed to increase, with important environmental implications (Usman et al., 2020). The growing number of ENP-containing products demonstrates the enormous value of nanotechnology to the global economy. The global nanotechnology market is growing exponentially with millions of tons of production volume (Future Markets Inc, 2021a). Such high volume indicates that nanotechnology and nano-products have become part of our daily life (Hansen et al., 2020).

The widespread use inevitably leads to the release of ENPs to the environment, resulting in environmental exposure, which can occur at all stages of their life cycle: production, manufacturing, use and end-of-life disposal and recycling (Wigger et al., 2020). For example, during the manufacturing stage of nano-enabled products, small amounts of ENPs are released into the environment when the products are structurally modified using high-energy and high-temperature procedures (Martínez et al., 2020). According to the results of material flow models, most ENPs are released during the usage of products (Sun et al., 2016). For example, ENPs in sunscreen applied when people swim in open water can be released directly into surface water (Keller, 2023). Washing textiles with ENPs added can cause them to be released into the sewer system. Mass flow studies show that the majority of ENPs will be treated in wastewater treatment plants (WWTPs), waste incineration plants (WIPs) and landfill before reaching the environment (Sun et al., 2016; Keller and Lazareva, 2014). Once in the environment, ENPs can be further transported by wind, rainwater or surface water (Lead et al., 2018a; Garner and Keller, 2014; Garner et al., 2017).

Once released, ENPs can reach the environmental compartments of water, soil, and air and may undergo a wide variety of physicochemical transformations (e.g., homo- and hetero-aggregation/agglomeration, formation of organic corona, dissolution, sulfidation or other transformations) (Garner and Keller, 2014; Gregory et al., 2012b; Zhou et al., 2012; Wang et al., 2015; Nowack and Bucheli, 2007; Praetorius et al., 2020a; Tomak et al., 2022; Hadjidemetriou and Kostarelos, 2017; Quik et al., 2014). It has been also shown that even before reaching the environment, many ENP have undergone significant transformation, either during product use or withing technical compartments such as WWTP (Mitrano et al., 2015). The physicochemical properties of ENPs, particularly after their transformations, are critical to understanding their fate and behavior in the environment, the interactions of the ENPs with other pollutants, as well as their uptake and biodistribution in organisms. The behavior and fate of ENPs in the environment depends not only on the conditions in the medium (temperature, flow rate, pH, ionic strength, presence of organic matter, etc.), the so-called extrinsic parameters, but also the inherent properties of ENPs (size, shape, solubility, reactivity, etc.), the so-called intrinsic properties, which are modulated by the transformations (Lead et al., 2018b).

From a regulatory perspective, data on environmental release and exposure for ENPs are essential to estimate their environmental risk (Svendsen et al., 2020). ENP emissions only pose a risk if both exposure and hazard are observed (Aschberger et al., 2011). However, current analytical methods for ENP detection in environmental samples are still very limited (Gondikas et al., 2018; Yi et al., 2020; Wagner et al., 2014). Although some studies have characterized and quantified the release rates of nanoparticulate materials from specific products or waste treatment compartments, they do not give a complete picture of ENP exposure in the environment (Hagendorfer et al., 2010; Kaegi et al., 2017; Kaegi et al., 2010; Cervantes-Avilés and Keller, 2021; Mitrano et al., 2012; Nabi et al., 2021a; Laborda et al., 2016; Hadioui et al., 2013; Peters et al., 2018; Montaño et al., 2016). Therefore, environmental exposure modeling for determining predicted environmental concentrations (PECs), useful to calculate exposure dose, remains an indispensable tool for assessing the human and ecological health risk posed by ENPs.

The general scheme of environmental risk assessment consists of combining exposure with hazard assessment. As one pillar of any environmental risk assessment, exposure models cover the flows from production, manufacturing, use, and end-of-life to the environment (material flow analysis, MFA) and further describe their fate and distribution in the environment (environmental fate modeling, EFM) (Garner et al., 2017; Meesters et al., 2014; Quik et al., 2015a; Klein et al., 2016; Besseling et al., 2017; Praetorius et al., 2012; Nowack, 2017). The general framework of any MFA model contains the mass amounts of ENP production, product allocation and transfer coefficients between compartments as input and ENP releases to the environment as output. MFA models can be coupled with tools for EFM and enable a more accurate description of the actual form and concentration of the ENPs in the environment by considering material transport, transformation, and degradation processes. ENP behavior is, i.e., dependent on particle size distribution. In addition, uptake and bioaccumulation models are used to further link external exposure with adverse effects often observed in lab studies, commonly referred to as toxico- kinetic and dynamic models (Fig. 1).

Chemicals can pose potential toxicity if they bioaccumulate in organisms and are transported to target sites within the body (Charles et al., 2022). Followed by exposure modeling, the next step in environmental risk assessment could be to relate external concentrations (PEC) to internal concentrations within the organism, considering various processes within the organism such as absorption, distribution, metabolism, and excretion (ADME). Metabolic transformation of ENPs within the organisms is a complicating factor, since the internal exposure may be to an ENP with a different composition, or to dissolution products (Zhu et al., 2013; Wang et al., 2013). This part is denominated toxicokinetic (TK) or biokinetic modeling (Fig. 1). Biokinetic models are commonly used to calculate bioaccumulation metrics from experimental data collected in standard bioaccumulation tests (*OECD*, 2012). For bioaccumulation of ENPs in aquatic organisms, the simplest one-compartment biokinetic model is commonly used, where the organism is considered as one whole compartment. The chemicals enter the compartment at rate k_u and be eliminated by the organisms at rate k_e. Next, toxicodynamic (TD) models relate the damage suffered by an organism due to internal bioaccumulation concentrations to observed

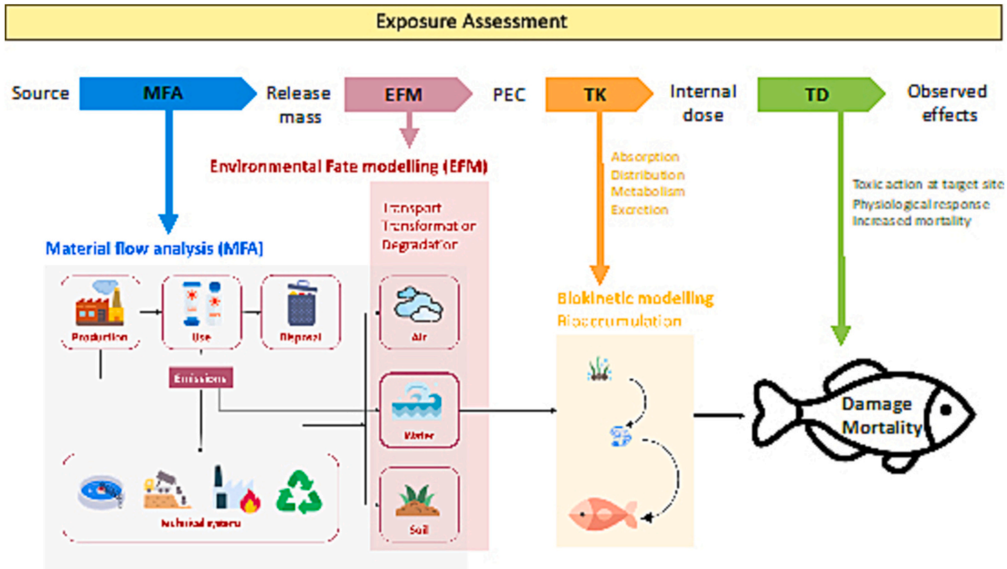

Fig. 1. Framework for modeling of exposure to support environmental risk assessment of ENPs. MFA: material flow analysis, EFM: environmental fate modeling, PEC: predicted environmental concentration, TK: toxicokinetic modeling, TD: toxicodynamic modeling.

effects, such as increased mortality or reduced growth. The European Food Safety Authority (EFSA) recommends the use of the combined TK-TD models to refine Tier-2 risk assessment (European Commission, 2013).

For this review we will cover the evolution of each of these steps within exposure assessment, highlighting the major advances, identifying the gaps, and providing some suggestions for the future of ENP exposure estimates.

2. Material flow analysis

The first MFA framework applied to ENPs was developed by Boxall et al. (2007). The MFA modeling in this study was based on assumptions and a high market penetration scenario. It did not provide realistic PEC values but aimed at providing a possible upper limit of concentration. Müller and Nowack (2008) then published the first PEC values for the three most used ENPs (nano-Ag, nano-TiO_2 and CNT) that were employed in several further studies (Mueller and Nowack, 2008). They substituted hypothetical calculations with more realistic scenarios based on the best available knowledge. MFA-modeling was then extended to a probabilistic material flow analysis (PMFA) by applying Bayesian statistics (Gottschalk et al., 2010). Bayesian modeling includes the propagation of incomplete knowledge and uncertainty analysis of all model parameters. Instead of single point values, model inputs and outputs are expressed as probability distributions. Another example of an MFA, developed by Keller and colleagues, estimated ENP releases at global, regional and US scales (Keller and Lazareva, 2013). They also estimated dynamic ENP release at U.S. and global scales (Song et al., 2017).

A further improvement was made by extending the probabilistic approach to a dynamic MFA modeling (Bornhöft et al., 2016), resulting in the dynamic, probabilistic, material flow analysis (DPMFA). The main purpose of dynamics is to quantify material flows over time and to create robust scenarios using historical patterns of development of physical stocks and flows. ENPs are produced and embedded in products in many different forms, and these forms can be altered during the life cycle (Sun et al., 2017). Studies showed that these forms of ENPs can affect their release, fate and toxicity in the environment (Lowry et al., 2012a; Gottschalk et al., 2015; Hendren et al., 2013). Considering this, Adam et al. (2018) developed a form-specific MFA, considering pristine, matrix-embedded, transformed, dissolved, and product-embedded forms (Adam et al., 2018a). Combining all the advancements from previously mentioned individual models, Adam et al. provided the IDPMFA model which is the most advanced model to predict the mass flows of ENP to the environment (Adam et al., 2021). Most recently, Zheng modified the DPMFA to consider the ENP particle-size distribution in addition to their form (Zheng and Nowack, 2021a).

A key input for all MFAs is an estimate of the production of ENPs for the region of interest. Some MFAs rely on commercial market studies (Future Markets, Inc, 2012; Future Markets Inc, 2021b), others have considered national databases such as the mandatory French registry of all nanomaterials produced in or imported to France (MTES, 2020), others have used or considered voluntary product registries such as the Nanodatabase (www.nanodb.dk) in Europe, the Wilson Center Project on Emerging Nanotechnologies Consumer Product Database, and the Nanomaterial Registry in the USA (http://www.nanomaterialregistry.org/), while others have used patent data and company proxy information to estimate production amounts (Hendren et al., 2011). One recent update on production has used the location of specific production sites to distribute the total European production to specific countries (Kuenen et al., 2020). While all sources of production data have considerable uncertainty, given that companies consider it proprietary information, it is estimated that in 2020 nanomaterial production was over 1.6 million metric tons, and will likely more than double by 2031, to nearly 3.5 million metric tons (Future_Markets, _Inc, 2021). These estimates do not include carbon black, with an estimated production of 14 million tons in 2021 and growing at a compounded annual rate of 3.4% (https://www.chemanalyst.com/industry-report/carbon-black-market-440). Thus, carbon black dwarfs the ENP market. Another major nanomaterial not considered in the previous estimates is nano calcium carbonate ($nCaCO_3$). The annual production of calcium carbonate is around 8.7 million tons (https://www.chemanalyst.com/industry-report/calcium-carbonate-market-687), but the fraction produced as nano is unknown. However, both carbon black and $nCaCO_3$ are considered nanomaterials in the French nanomaterial registry (MTES, 2020). Also missing from the market studies are mixed composition and most 2-D nanomaterials, likely due to their low sales volume, despite potential environmental implications (Parviz et al., 2020).

Coatings, paints, and pigments represent the dominant application, particularly if one considers that over 60% of carbon black is used as pigment in tires, 20% in other rubber (e.g., hoses, gaskets), 11% in paints, and 4% in printing inks, and 25% of calcium carbonate is used in paints and coatings. While many of the products in which ENPs are used in coatings and paints or as pigments are used directly in the environment (e.g., tires, automotive paints, building paints), most of the release is in composite materials (i.e., rubber and other polymeric matrices), with only a small fraction likely to be released in the nanoscale. Personal care products (e.g., sunscreens, cosmetics) are the application with the most significant load to the environment, given the release to wastewater, with a potential release via treated effluent to waterbodies, and via biosolids to the terrestrial environment, mainly to agriculture (Fig. 2). Overall, air emissions are expected to be small.

ENP production is mostly centered in developed countries (Fig. 3) in Asia, Europe, Oceania, and the Americas, with minimal production in Africa and less developed countries in Europe, Southeast Asia, and South America. Commodity nanomaterials are more likely to be produced in China and selected countries in Western Europe and North America, while specialties are more likely to originate from the US and a few Western Europe countries. While production is likely to shift to other countries by 2031, the current production centers are likely to continue to dominate. However, nanomaterial consumption is spread more widely incorporated into consumer and industrial products. Although the size of the nanomaterial market is small in comparison to other materials, there is a considerable transportation footprint, as nanomaterials are exchanged between continents for incorporation into products that are then shipped further to the rest of the world.

3. Multimedia (Box) models

3.1. Evolution

Multimedia fate models are useful for understanding the distribution of ENPs among different environmental compartments (i.e., air, soil, water, and sediments), considering the processes that determine the behavior of the nanoparticles within each compartment and their transfer from one compartment to another. In contrast, atmospheric or watershed models only focus on the fate of the ENPs within a more limited set of compartments (e.g., water and sediments), but with greater spatial representation. Multimedia fate models have existed for several decades for organic and metal compounds (van de Meent, 1993; Mackay and Paterson, 1991; Harvey et al., 2007). However, given the significant differences in behavior between organic compounds or even metals from those of ENPs, it was determined that these multimedia models needed major adjustments (Praetorius et al., 2012; Arvidsson et al., 2011; Meesters et al., 2013; Quik et al., 2011). The first to publish an adapted fate model were Arvidsson et al. (2011) and Praetorius et al. (2012) in which the Smoluchowski theory on particle agglomeration and Stokes Law on particle settling were included in an aquatic fate model (Arvidsson et al., 2011; Praetorius et al., 2012). The first two full multimedia fate models for ENPs, Mendnano (Liu and Cohen, 2014) and SimpleBox4nano (Meesters et al., 2014) followed after and primarily focused on estimating the environmental distribution of ENPs at steady

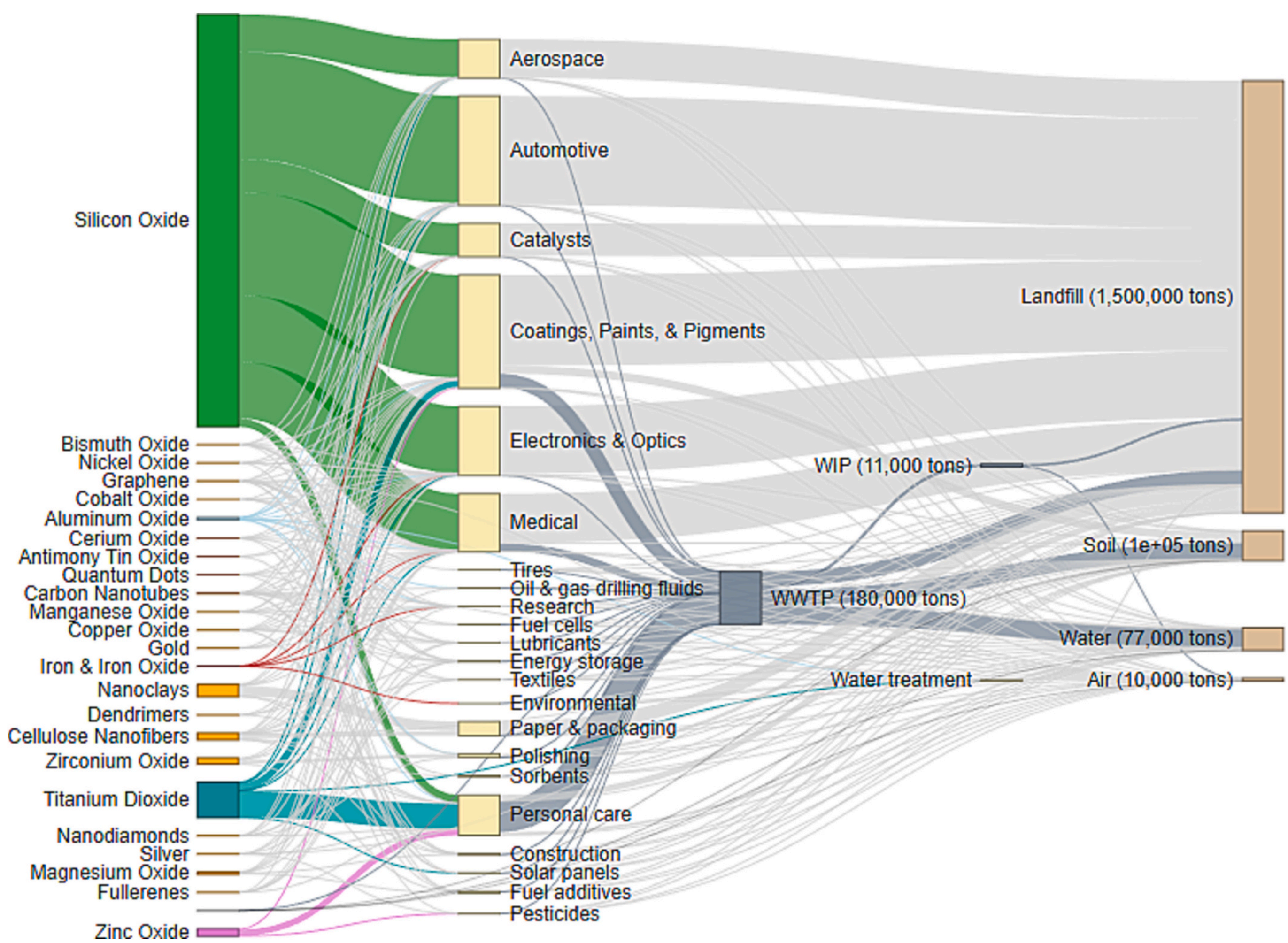

Fig. 2. Flow of nanomaterials in 2020 through the global economy, from production (left side) to applications (mid yellow boxes), to final compartments (right side, in brown), with some ENPs passing through wastewater treatment plants (WWTP) and waste incineration plants (WIP). Carbon black and $nCaCO_3$ are not considered. Data from ref. # 70. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

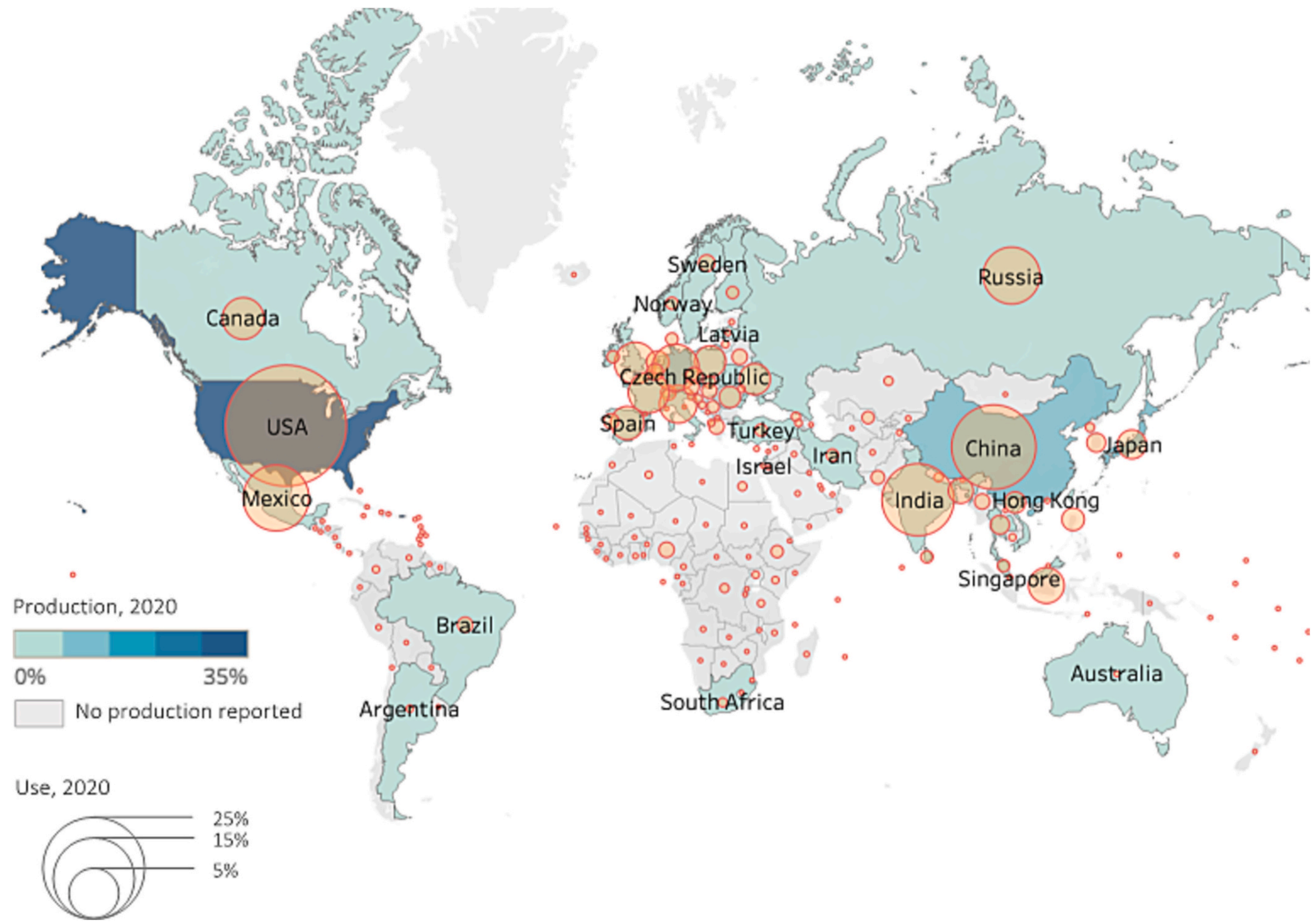

Fig. 3. Global nanomaterial production (blue scale) and use (size of circles for each country) estimates for 2020. Data from Reference (Future_Markets, _Inc, 2021) for regional production and sales. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

state. In 2017, the nanoFate model introduced a greater number of compartments and high-resolution temporal dynamics related to weather and nanomaterial release events (Garner et al., 2017). More recently, the NanoFase model was developed, with much higher spatial resolution for soil and water compartments, making it a hybrid between multimedia and watershed models (Lofts et al., n.d.).

3.2. Characteristics

To make fate models fit for use with ENPs, the relationship between ENP properties and their effect on transport or transformation processes in the environment needs to be explicitly incorporated. The relationship must consider intrinsic and extrinsic ENP properties (Hendren et al., 2015; Quik et al., 2018). Intrinsic properties include ENP composition, size, coating, and density among others. Extrinsic properties are related to the interaction between the ENPs, their surrounding matrix (e.g., air, water, soil), and the conditions of the overall system. Extrinsic properties are dependent on the environmental matrix (i.e., air, freshwater, seawater, groundwater), the ionic strength (i.e., salt concentrations), concentration and nature of natural organic matter (NOM), and pH. Important properties for the system include temperature, UV irradiation, concentration of suspended particles and aerosols, as well as soil characteristics such as cation exchange capacity (Garner et al., 2017). The coating of an ENP is a function of time and exposure pathway: initially, the ENP may be coated by the manufacturer to increase stability or provide specific functional properties, making it an intrinsic property (Cartwright et al., 2020). Later, as the particle travels through various matrices, it can be coated by organic matter (eco-corona) and/or proteins (Casals et al., 2010; Natarajan et al., 2021; Barbero et al., 2021), resulting in changes in extrinsic properties such as the attachment efficiency for homo-/heteroaggregation and in some cases the dissolution rate. For example, the dissolution rate is dependent on the chemical composition of the ENP, its coatings, pH of the water matrix (e.g., freshwater, seawater, soil pore water), aggregation state, and temperature (Amde et al., 2017) (Fig. 4). Another example is the transformation of ENPs by the microbiome, which can significantly alter their fate (Couvillion et al., 2023). Below we briefly discuss the prevalent ENP-related physico-chemical properties included in ENP fate models, the landscape and spatial aspects they consider and their temporal resolution.

3.3. Processes considered in multimedia models

Fate processes (e.g., dry and wet deposition, dissolution, homo- and hetero-aggregation, sedimentation) implemented in the currently available nanomaterial multimedia models are presented in Table 1, along with relevant ENP properties. Although the coating is a very important property, it is not considered explicitly in any of these models; it is taken into account implicitly via its effect on attachment efficiency and dissolution rates. MendNano is the only multimedia model that has implemented a size-dependent diffusion model for estimating the ENP-environmental medium mass transfer coefficient, to be used when no measured dissolution rate constant is available (Liu and Cohen, 2014). MendNano also utilizes the fractal dimension for estimating porosity of

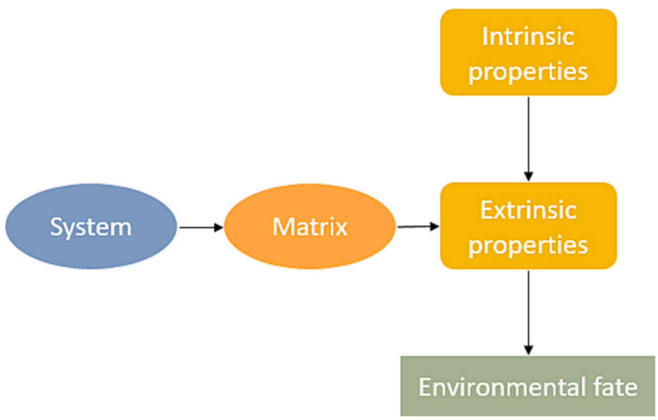

Fig. 4. Extrinsic properties reflect the change in parameter values of intrinsic properties (e.g., dissolution rate, attachment efficiency) depending on the matrix (e.g., freshwater, seawater, groundwater) and its characteristics (e.g., pH, NOM, ionic strength), and the pathway that the ENP may take through the System (i.e., within the nano-enabled product, through wastewater, in agricultural or stormwater runoff, etc.).

Table 1
Nanomaterial properties in relation to fate processes.

Nanomaterial property	Linked fate processes	Model(s)
Size	Dry air deposition	nanoFate, MendNano, SimpleBox4nano
	Wet air deposition	SimpleBox4nano
	Sedimentation	nanoFate, MendNano, SimpleBox4nano
	Hetero-agglomeration	SimpleBox4nano
	Dissolution	MendNano
Density	Dry air deposition	nanoFate, MendNano, SimpleBox4nano
	Wet air deposition	SimpleBox4nano
	Sedimentation	nanoFate, MendNano, SimpleBox4nano
	Hetero-agglomeration	nanoFate, SimpleBox4nano
	Dissolution	MendNano
Attachment efficiency/ factor	Hetero-agglomeration	nanoFate, MendNano, SimpleBox4nano
Hamaker constant	Hetero-agglomeration	SimpleBox4nano
Fractal dimension	Dissolution	MendNano
Dissolution rate constant	Dissolution	nanoFate, SimpleBox4nano
Degradation rate constant	Degradation	SimpleBox4nano
NA*	Wet deposition Porous media transport Advection	nanoFate, MendNano, SimpleBox4nano

* The fate models include these processes, but without a direct relationship with ENP related properties. References: MendNano (Liu and Cohen, 2014), nanoFate (Garner et al., 2017), SimpleBox4nano (Meesters et al., 2014).

ENP homo-agglomerates (Liu and Cohen, 2014). Given that the dissolution rate and the attachment efficiency or attachment factor are a function of the evolving ENP coating (a dynamic extrinsic property), it presents a major challenge, and thus it has not yet been explicitly incorporated into any multimedia model. SimpleBox4nano and nanoFate both explicitly consider ENP transport in porous media, either as free nanoparticles or heteroaggregated to clay particles. Both models also track the concentrations of free nanoparticles, hetero-agglomerates, and dissolved ions when applicable. Given their dependence on intrinsic properties, environment and system, these extrinsic properties need to be measured for specific relevant conditions (see Section 6, data needs).

3.4. Spatial and temporal resolution of multimedia models

Somewhat different approaches are considered by the multimedia models mentioned above with regards to landscape and spatial variability. There are two main differences in approaches. In the most common, the landscape is divided into relevant water and soil types representative of the spatial distribution. For instance, the landscape can be subdivided into agricultural soils (with and without the application of biosolids), natural soil and urban soil (Garner et al., 2017; Meesters et al., 2014). NanoFate and SimpleBox (Casals et al., 2010) also considers different water body compartments, for example a flowing river and a lake, estuary, or sea water. Most often these types of models consider a single well-mixed air compartment. SimpleBox also considers three nested scales at the regional, continental and global level simultaneously. In the second approach, utilized by NanoFase, the fate model considers a grid and grid cell characteristics have to be determined for each fraction of water and soil in that cell (Lofts et al., n.d.). Application of multimedia models to different spatial scales is dependent on the goal of each model. For instance, local air concentrations related to a point source are not represented adequately using a single well mixed air compartment (Poikkimäki et al., 2022).

Most multimedia models used for ENPs consider a daily temporal resolution for the emission of ENPs and in some cases also the weather (e.g., nanoFate, MendNano, NanoFase). Dynamic emissions patterns can be used to model increasing release as new products incorporate more ENPs, decreasing due to a phase-out, seasonal events (e.g., summer sunscreen application), and accidental spills. Weather events have a significant influence on wet deposition from air and runoff from soil. nanoFate also considers the daily streamflow through the flowing river, as well as discharge from groundwater into the river or other water bodies. The SimpleBox model differs markedly from the other models since only dynamic emission patterns at a monthly or yearly temporal resolution are considered (Parker and Keller, 2019).

Models such as SimpleBox are considered screening level and have particular applications in lower tiers of risk assessment, for instance in the context of European Chemicals legislation (REACH) (Hansen et al., 2017), or to calculate generalized fate factors for life-cycle assessment. The models with higher spatial or temporal resolution (e.g., nanoFate, NanoFase) are a better fit for higher tier risk assessments, including regional PECs (see also section 4).

3.5. Applications of multimedia models

The primary application of the multimedia fate models is for predicting the concentrations of ENPs in different environmental media over time, as part of an exposure assessment to estimate the risk ENPs may pose. Garner et al. (2017) showed that in temporal peaks of run-off and emission acute risk limits can be exceeded for TiO_2 and ZnO in freshwater, highlighting the importance of including interaction with the soil compartment for assessing aquatic exposure to ENPs (Garner et al., 2017). nanoFate has also been used to predict ENP concentrations in different cities, depending on their local characteristics (landuse, weather, emissions patterns) (Parker and Keller, 2019), and also within the broader ChemFate framework, to compare the concentrations and exposure of ENPs to other types of chemicals (e.g., ionizable and non-ionizable organics, dissolved metals) (Tao and Keller, 2020). SimpleBox is the basis for the EUSES model suite (Vermeire et al., 1997) to estimate background exposure concentrations to chemicals. As such SimpleBox4nano can be applied for these more general exposure assessments. Local scale environmental concentrations are also possible, provided the model is parameterized for a specific area (Lofts et al., n.d.; Poikkimäki et al., 2022; Domercq et al., 2022).

An additional application of multimedia fate models is estimating fate factors for life cycle impact assessment. One important tool for these assessments is UseTox, which uses SimpleBox4nano for the nano-specific fate factors (Salieri et al., 2019), and others have included their own implementation for derivation of ENP-specific fate factors (Ettrup et al., 2017). These nano-specific multimedia models can be applied in any assessment where the fate of ENPs is relevant. For instance, SimpleBox is used in socio-economic analysis of mitigation measures (Gabbert et al., 2023), where distinguishing between persistence and mobility of different chemicals and nanomaterials is relevant.

4. Watershed models

Freshwater environments are a major receiving compartment for ENPs, both via point sources such as WWTPs and via diffuse sources such as run-off from agricultural fields or urban landcover (e.g., roads, buildings). In the absence (or limited availability) of monitoring data for ENPs, PEC values in freshwaters and sediments play an important role in informing risk assessment. In contrast to unit world type multimedia fate models, where surface waters and sediments are each represented by one bulk compartment (box), watershed models are spatially resolved and can therefore predict concentration profiles as a function of the distance to their point of emission (Williams et al., 2019; Dale et al., 2015a). This enables the investigation of ENP concentration hotspots and their potential for long-range environmental transport. In watershed models the most relevant ENP-specific processes are heteroaggregation, sedimentation (and resuspension from surface sediments), dissolution and other (surface) transformations for reactive ENPs.

One of the first models to assess ENP fate in a river considered the case of silver originating from silver nanoparticle-containing products in the Rhine River (over 700 km from Basel (CH) to Lobith (NL)). (Blaser et al., 2008) The Rhine River was represented by a multimedia mass-balance model with well-mixed surface water, stagnant water and surface sediment compartments. Spatial resolution was achieved by subdividing the river into 70 boxes of equal length. Emissions were estimated using a silver MFA from biocidal plastics and textiles. No ENP-specific transformation or transport processes are included in the model, but the dominant form of silver was assumed to be silver sulfide and both dissolved and particle-bound silver concentrations were modelled. The model predicted a downstream accumulation of silver sulfide, with an earlier concentration maximum in water than in sediment.

The previous model by Blaser et al. was further developed by (Praetorius et al., 2012) to represent the ENPs in 5 distinct size classes and include ENP-specific processes, in particular heteroaggregation with suspended particulate matter (SPM) and size- and density-dependent settling (Praetorius et al., 2012). The impact of different ENP sizes, heteroaggregation attachment efficiencies, and SPM properties on downstream transport of TiO_2 NPs in the Rhine River was evaluated in selected scenarios. Additionally, higher spatial resolution was achieved in this model by reducing the length of the river boxes, in particular close to the emission source to prevent overestimation of downstream transport by numerical diffusion. The importance of using higher spatial resolutions was confirmed by Gao et al. (2022) when adapting the Rhine river model to assess the fate and transport of nanoAg in the Xiangjiang River (China) and comparing model outputs at high and low spatial resolution (Gao et al., 2022). Sani-Kast et al. (2015) presented an adaptation of the Rhine model to the Rhone River and incorporated spatial variability in the environmental conditions (aquatic chemistry, SPM concentration and size) (Sani-Kast et al., 2015). Thereby, the importance of the water characteristics, especially close to the emission source, on the downstream concentration profiles was demonstrated.

The strengths of the above-mentioned multimedia box models compared to these watershed models lie in their modularity with respect to introducing ENP-specific process descriptions, their comparatively low computational demands (especially when solved at steady-state) and the ability to adapt the models easily to represent different landscapes, including rivers or watershed. This is possible, because the representation of environmental conditions – in terms of river morphology, hydrodynamics of water and sediment flow, water quality and their temporal/seasonal variations typically – are greatly simplified. However, this simplicity is also their weakness.

Stream dynamics have a strong influence on ENPs transport and transformations in rivers and watersheds (Dale et al., 2015b). Dale et al. (2015) demonstrated this by using a spatially-resolved environmental fate model, the James River Basin portion of the Chesapeake Bay Watershed Model (WSM) coupled to the US EPA's water quality modeling suite WASP7 (Dale et al., 2015b). The stream hydrology in the model was previously calibrated to monitoring data from the modelled region and represented daily variations in streamflow, sediment transport and stream loads. The model results showed that in watersheds with high sediment mobility, sediment accumulation of ENP is less relevant than previously assumed and that using average sediment resuspension rates underestimates the distance that ENP can be transported in a watershed. Transformation reactions for ZnO and Ag NPs were represented in the model to assess the speciation of these reactive NPs (as speciation will influence toxicity). However, heteroaggregation was not modelled explicitly, as this was not possible in version 7 of the WASP model. Instead, complete heteroaggregation of the NPs in all media was assumed, which may represent the overall behavior reasonably well, but also makes it impossible to identify locations or scenarios where free NPs may remain in the environment.

The Water Quality Simulation Program WASP was further developed to include heteroaggregation, as well as photo-transformation as ENP-specific transformation processes. The updated WASP8, with its Advanced Toxicant module, is presented in detail in Knightes et al. (2019). In WASP8, chemical solutes, solid particles and nanoparticles can be simulated and particle attachment kinetics, as well as the environmental factors (e.g., ionic strength, pH, NOM, SPM) influencing them, are well described. By combining ENP-specific process descriptions with a spatially-resolved mass balance framework, that can represent different surface waters (i.e., lakes, streams, branched estuaries) at high level of hydrological detail (e.g. by linking to hydrological models), WASP8 represents an important milestone in the development of watershed models for ENPs. It was applied to several cases, (e.g., multi-wall CNTs, graphene oxide (GO) and reduced graphene oxide) in different aquatic ecosystems in the USA, ranging from a seepage lake, to a coastal plain river, a piedmont river and an unstratified, wetland lake (Bouchard et al., 2017; Avant et al., 2019; Han et al., 2019); and more recently also to CuO-NPs released from nano-copper-based antifouling paints on boats in a large lake (Lake Waccamaw, North Carolina, USA) (Ross and Knightes, 2022).

A similar approach of linking ENP-specific process description to a spatially explicit hydrological model was introduced by Quik et al. (2015b). The NanoDUFLOW model, which is parameterized in its default scenario for the Dommel River (NL), represents ENPs in 5 size classes. In the model, an explicit link is made between key hydrological characteristics of the river and ENP fate processes. For example, the heteroaggregation, sedimentation and resuspension rates are linked to water flow rate and shear stress. This makes it possible to model feedbacks between local flow conditions and the fate of ENPs and predict time- and place-dependent ENP hotspots. A major challenge faced by all ENP watershed models is the limited availability of monitoring data of ENPs needed for model validation. Klein et al. (2016) made first steps towards validation of the NanoDUFLOW model by comparing model outputs to measured concentrations of <450 nm-sized particles containing Ce, Al, Ti or Zr, measured by Asymmetric Flow-Field-Flow Fractionation (AF4) coupled to ICP-MS (Klein et al., 2016). They found good agreement between modelled CeO_2 NP concentrations and the measured concentration profile of Ce smaller than 450 nm, whereas for Al, Ti and Zr the model results were in line with measured trends, but with some underestimation, in particular further downstream.

Other approaches to model ENPs at the watershed level include the use of the Global Water Availability Assessment Model (GWAVA) to model monthly Ag-NP and ZnO-NP concentrations in surface waters across Europe (at 5' by 5' spatial resolution) by Dumont et al. (2015). Here ENP-specific processes are represented in first-order loss terms for sedimentation and dissolution. Another example is the incorporation of ENP-specific fate processes (homo- and heteroaggregation, sedimentation, but no dissolution) into an existing hydrological model (SOBEK-River) and water quality model (DELWAQ) to assess the fate of metallic NPs along the Rhine River (DE/NL) by Markus et al. (2016). Different scenarios were assessed, which, among other things, revealed the importance of the initial state of the ENPs entering the model on their distribution in the river. Similar to (Dale et al., 2015b), the study by Markus et al. (2016) reveals limited net sedimentation of ENPs in a fast flowing river like the Rhine, but the potential for long range transport up to the North Sea. The Markus et al. (2016) approach was adapted by Williams et al. (2019) to model Ag NPs in the River Isar (Wimmer et al., 2019). Model outputs matched well with measured data in the modelled area, except for load peaks near WWTP effluents areas.

Broadly, existing watershed models fall into two categories: (1) spatially-resolved multimedia box models (Praetorius et al., 2012; Gao et al., 2022; Sani-Kast et al., 2015) and (2) hydrological models adapted to include (selected) ENP fate processes (Dale et al., 2015b; Quik et al., 2015b; Markus et al., 2016; Wimmer et al., 2019). Models in category 1 are more easily adaptable to different rivers or watersheds, often include more ENP-specific processes (as their structure is more modular) and have a lower computational demand. Conversely, models in category 2 represent stream and sediment dynamics with higher environmental realism, making them better suited to predict ENP transport patterns in highly dynamic watersheds and to derive site-specific PECs. Yet, they are typically calibrated for a very specific river or watershed and cannot be easily adapted to a different geographic location. The recently updated WASP8 model (Knightes et al., 2019) is a very promising development, as its advanced toxicant module includes detailed ENP process descriptions and the model can be linked to different hydrodynamic and sediment transport models, thereby combining the advantages of most models described above.

4.1. Material Flow Analysis-Environmental Fate Model coupling

As depicted in Fig. 1, the EFMs (both multimedia as well as the watershed models), rely on environmental release data of ENPs as input. Three types of information are needed: 1) the amount released, 2) the form released and 3) the characteristics of the released materials. The amount released into the different environmental compartments is the direct output of all MFA models and the current EFMs have made use of these data. For example the multimedia model SimpleBox4nano (Meesters et al., 2014) used the release data from Müller and Nowack (2008) (Mueller and Nowack, 2008), the watershed model by Dale et al. (2015b) was based on the release data by Gottschalk et al. (2009), Dumont et al. (2015) used release data by Sun et al. (2017). The nanoFate model (Garner et al., 2017) used the results of the nanoRelease model (Keller and Lazareva, 2014). The watershed model by Dumont et al. (2015) used population as proxy to distribute the estimated released mass to different countries (Dale et al., 2015a). However, as Adam and Nowack (2017) have clearly shown there are large differences between the ENP flows to the environment for different European countries caused by very different water and waste treatment systems (Adam and Nowack, 2017). Kuenen et al. (2020) have further updated the releases in different countries but, so far, their data have not been used for modeling ENP concentrations in whole watersheds (Kuenen et al., 2020). The nanoFate model (Garner et al., 2017) does consider watershed-specific release, as shown in several examples for different regions in the USA and Europe (Garner et al., 2017; Parker and Keller, 2019; Tao and Keller, 2020; Keller and Parker, 2019).

Fate processes of ENP in the environment such as dissolution, (hetero)agglomeration, deposition from air or sedimentation in rivers and lakes are governed by particle size, among other factors (Garner and Keller, 2014; Meesters et al., 2014; Liu et al., 2011). The published fate models have used number-based size distributions (Meesters et al., 2014), average primary diameter or the average aggregate radius in freshwater (Garner et al., 2017) as their input of the size distribution. Yet these models did not specify the actual data sources used to obtain the size distribution. nanoFate relies on the modeler to provide the average particle radius, based on the available experimental data for the ENP in consideration, and the water quality (i.e., ionic strength, pH, NOM concentration) (Garner et al., 2017). The size-specific DPMFA is able to provide for all release flows also the particle size distribution used in a range of products (Zheng and Nowack, 2021b), however, so far the model has only been parameterized for TiO_2 (both pigment and nano-TiO_2), and additional calculations may be needed to consider the actual particle size in the discharge (e.g., wastewater effluent). The coupling of the release data from this model with a fate model would allow for the first time to predict the behavior of a nanomaterial based on the actual size distribution of the released particles.

5. Bioaccumulation models

Bioaccumulation studies are used to describe the body burden of the organism in relation to contaminant concentration in the surrounding environment. This allows estimation of the potential for exposure to contaminant concentration levels that may not be harmful upon short-term exposure but may be upon long-term exposure due to the continued uptake and accumulation, leading to the exceedance of critical body concentrations (Ribeiro et al., 2017).Bioaccumulation is a critical factor to make regulatory decisions on the potential environmental risks of ENPs (Petersen et al., 2019). Bioaccumulation describes the internal concentration of contaminants in the organisms in relation to the environmentally-relevant external concentration in the surrounding medium, e.g., soil or water. In bioaccumulation studies, different bioaccumulation metrics are used, which depend on the exposure routes: the bioconcentration factor (BCF), the bioaccumulation factor (BAF), and the biomagnification factor (BMF). A more detailed explanation of these terms and the experimental approaches is provided in the Supporting Information.

In a critical review of tools for modeling uptake and bioaccumulation of ENPs, van den Brink et al. (2019) underlined that the physiologically based pharmacokinetic (PBPK) model, or biodynamic model, was shown to be applicable to ENPs (van den Brink et al., 2019). Garner et al. (2018) developed the nanoBio model to predict short- and long-term bioaccumulation of metal-based ENPs (e.g., nano-CuO, nano-TiO_2, and nano-ZnO) across four trophic levels in an aquatic system, using first-order uptake and elimination, with no storage fraction (Garner et al., 2018). Seven aquatic species were chosen to understand exposure pathways, accumulation through trophic levels, and the potential for biomagnification. Uptake, elimination, and dissolution of the ENP were the only processes modelled, though different routes and rates were considered for each species. The nanoBio model considers uptake of free nanoparticles, heteroaggregated ENPs, as well as the dissolved metal ions, which are predicted by the nanoFate model on a dynamic basis, considering possible daily fluctuations in ENP loading (e.g., seasonal use of sunscreens with ENPs), and atmospheric and hydrologic conditions (e.g., precipitation, runoff). Dietary exposure was also considered, calculated internally by nanoBio, based on the uptake and accumulation of ENPs by lower trophic levels. Given the higher loading of nano-TiO_2, the highest overall biomagnification was predicted for nano-TiO_2 within the highest trophic level species. ENP dissolution decreased total biomagnification; however, the released metal ions may still cause toxicity. Predicted biomagnification factors, including free ENP, particulate-ENP, and metal ion) were ENP specific, and lower for daphnids and planktivorous fish, higher for bivalves and copepods, and much higher for the longer-lived omnivorous fish considered in the model (*O. mykiss*). Although this early modeling effort was based on very limited experimental data, important findings are the trophic levels at potentially higher risk of bioaccumulation, the temporal peaks in bioconcentration for different species; and the processes which require more experimental data to reduce uncertainty. Based on a sensitivity analysis, the most significant parameters include uptake rates from multiple exposure routes, and assimilation efficiency which has a substantial impact on biomagnification.

Van den Brink et al. (2019) reviewed several conventional modeling approaches to ENP uptake and accumulation (van den Brink et al., 2019). The analysis focused on ENP uptake and accumulation in soil and aquatic invertebrates, because they comprise >99% of all animals, are the most diverse group of organisms, and are key for several ecological functions (e.g. soil structure and maintenance, nutrient cycling). The authors determined that using a storage fraction would improve model performance, when considering nano-Ag ingested by daphnids. An alternative approach would be to consider two compartments within the organisms, with different kinetic rates for accumulation and elimination. However, this would require measuring ENP concentrations in the storage tissues, which adds complexity to the experimental studies. For ENPs with significant dissolution, the authors indicated that the bioconcentrations factor must consider both the ENP and the dissolved ion, once they reach a steady state. Using a case study of earthworms (*Enchytraeus crypticus*) exposed to nano-Ag, the authors found that increasing the complexity of the model by considering more processes improved the fit to experimental data, although the significance of the regression decreased due to lower degrees of freedom.

Most recently, Zheng and Nowack (2023) compared five biokinetic models for non-dissolvable ENPs in freshwater (Zheng and Nowack, 2023), using 34 datasets for nano-TiO_2, nano-SiO_2, nano-Au, fullerene, graphene, graphene oxide, and carbon nanotubes, including first-order models with and without storage fraction and growth dilution, as well as a model based on Michaelis-Menten kinetics for uptake and first-order elimination for depuration, with no storage fraction. Most studies were based on daphnids (*D. magna*, $n = 26$), 7 on zebrafish (*D. rerio*), and one on phytoplankton (*S. obliquus*). From their comparison, they determined that the Michaelis-Menten model with exponential depuration performed best compared to the observations, and the first-order model with storage fraction during uptake and depuration, performed second best. Rates of uptake were much greater for daphnids (k_u ranged from 1500 to 130,000 L kg^{-1} h^{-1}) than for zebrafish (k_u from 0.00027 to 130 L kg^{-1} h^{-1}), while depuration rates varied less (k_e from 0.001 to 3.9 h^{-1}) with no clear trend for the two trophic levels. There was no clear pattern in terms of daphnid uptake rates for different ENPs, but for zebrafish had a much greater rate of uptake of C_{60} (13-130 L kg^{-1} h^{-1}) compared to $nTiO_2$ (0.00027-0.62 L kg^{-1} h^{-1}). The storage fraction ranged from 0.002 to 0.69 with no clear pattern for ENPs or species. The authors concluded that the Michaelis-Menten model with exponential depuration was most appropriate when the uptake phase has not stabilized, and the first-order model with storage fraction during uptake and depuration would be most appropriate when a storage fraction was observed. Growth dilution would be important if the organisms are at early developmental stages.

A direct comparison of the models is challenging, since they have different attributes. The nanoBio model is focused on the aquatic environment and considers four trophic levels; it employs only first-order equations without storage (Garner et al., 2018). The models reviewed by Van den Brink et al. focused on soil and aquatic invertebrates; these models are based on first-order equations with storage (van den Brink et al., 2019). The analysis by Zheng and Nowack (2023) focused on determining which equations best reflect the experimental observations, although only consider a single trophic level (Zheng and Nowack, 2023).

While there has been considerable progress in modeling the biokinetics of ENP and metal ion accumulation, there are still many open questions, including the ENP characteristics (as synthesized and once in the environment) that result in higher uptake or decreased elimination, the differences in species response to exposure to ENPs which is a function of internal ENP processing (van den Brink et al., 2019), and trophic transfer. Just as in EFMs, ENP characteristics needed for modeling uptake and internal processes need to take into account the environmental system (i.e., the extrinsic property values dominate the behavior), but these are seldom available.

Bioaccumulation models rely on either observed ENP concentrations, or PECs from the EFMs, as their input. For a single species analysis, this involves observed or predicted concentrations in the media in which the organism is exposed (e.g., soil, water, sediments). However, for the more complex modeling of trophic transfer, as in nanoBio, this requires the calculation of the ENP and dissolved metal ion concentrations within each trophic level (Garner et al., 2018).

6. Data needs and challenges

As in almost every modeling study, the most significant limitation is the availability of abundant, high-quality data, to obtain the range of parameter values necessary for implementing the model, perform calibration against observed data, and then validate using additional observations. Standardized testing protocols are necessary to make valid comparisons between different models. The OECD has taken the lead on establishing protocols for nanoparticle characterization, nanoparticle dispersion stability (OECD, 2017), nanotoxicology, and bioaccumulation studies, in collaboration with USEPA and European agencies, but many studies in the literature have yet to follow these protocols. In every meta-analysis, tens to hundreds of studies must be discarded due to inadequate characterization, incomplete information, or major differences in testing protocols.

Starting from the production rates, even the information from the Market Studies for 2020 has a large estimated uncertainty (+/- 75%), and even for commodity (high production) ENPs such as nano-SiO_2 and nano-TiO_2. Validation is challenging, since only France maintains a mandatory registry of all nanomaterials produced in or imported to France (MTES, 2020), and it does not account for ENPs that are incorporated into imported products. Projected production into the future assumes constant growth rates, which cannot consider major disruptions to the global economy (e.g., pandemics, electronic chip manufacturing supply chain disruptions, very high inflation that leads to recession, etc.), or even major policy changes such as the accelerated investment in renewable energy, energy storage, electric vehicles, driven by tax and other incentives.

For MFAs, the transfer coefficients used to allocate ENPs to various processes and compartments are based on a handful of studies, with very limited replication. For some transfers with very significant implications for the environment (e.g., release of ENPs from coatings), major assumptions must be made, with scant data to validate estimates. Differences in product use, environmental conditions that increase or decrease release (e.g., rainfall patterns, solar radiation), and end-of-life management practices throughout even a single region (e.g., USA, EU) are often difficult to consider, given the limited available data. Caballero-Guzman and Nowack (2016) reviewed the strategies implemented by MFA models to use release data in determining transfer coefficients which form one of the basic parameters needed for MFA (Caballero-Guzman and Nowack, 2016). It was identified that MFA studies rely to a large extent on assumptions, expert opinions, extrapolations, and informal sources of data to parameterize the models. At the time of that review, the coverage of all relevant exposure scenarios was limited; only 20% of the ENPs used industrially and 36% of the product categories where ENP are used have been investigated in release studies and only few relevant release scenarios have been described. Overall, the lack of process data emphasizes even more the need for including the uncertainty and variability of the different processes and input applied in MFA's, by doing them probabilistically. A number of available MFA models are indeed based on probabilistic approaches and are able to handle those uncertainties (Wigger et al., 2020).Furthermore, assessing risk should if data is lacking be based on worst case assumptions following the precautionary principle.

Fate models require vast amounts of data, including intrinsic and extrinsic physicochemical characterization, and in particular the transformations that occur as the particles age in the environment (e.g., eco- and bio-corona, dissolution, heteroaggregation) (Vignardi et al., 2022; Jośko et al., 2020; Praetorius et al., 2020b). In addition to the change in ENP behavior during aging, the rate of change is key for determining which processes will dominate. ENP behavior is strongly linked to environmental conditions (pH, concentration of organic matter and specific biomolecules, ionic strength, concentration and nature of suspended sediments, etc.), which may be dynamic. There is a lack of robust analytical techniques for quantifying ENP properties in complex matrices; machine learning may be able to fill this gap (Duan et al., 2020; Winkler et al., 2014). However, data sets for these dynamic environmental conditions are rarely available; they may not even be available for a static condition. Most importantly, datasets with a spatiotemporal pattern of ENP and metal ion concentrations for a given location are extremely limited, making calibration and validation of models extremely challenging. Datasets are needed for model parameterization as well as for model evaluation. Monikh et al., (2018) discussed strategies to test ENP stability in a testing scheme designed to represent different environmentally relevant condition, which would serve to parameterize EFMs (Monikh et al., 2018). An additional challenge is determining whether the concentrations of a given nanoparticle in the environment reflect introduced (manufactured/engineered) or natural or incidental particles. For most major ENPs, the concentration of natural particles is significant, introducing a high degree of uncertainty with regards to the interpretation and use for model calibration or validation. For example, a study of Ti nanoparticles collected in stormwater treatment infrastructure detected total Ti in soils from 1300 to 2500 mg kg^{-1}, but the amount most likely due to Ti ENPs was between 555 $\pm$ 13 mg kg^{-1} and 1792 $\pm$ 203 mg kg^{-1} (Baalousha et al., 2020). Nanoscale Ti was found in stormwater runoff at 50 to 300 μg L^{-1} Ti (Nabi et al., 2021b), but natural soils were more likely the source, and a small fraction from paints and coatings, rather than from sunscreen and other personal care products. Deconvoluting the sources of nanoparticles in surface waters is certainly complex. A recent study focused on the estuary of the Yellow River in China detected Ti, Zn, Cu, Ag, and Au based nanoparticles, tracking 24 stations (Li et al., 2023). A recent field study provided very valuable information on the concentrations of Ti, Ce, and Ag ENPs in a wide range of surface waters and precipitation (Azimzada et al., 2021). Studies like these that provide rich datasets will be useful in the future to evaluate and validate the various nano fate and transport models.

So far, most MFA models assume that “nanoparticle A" remains “nanoparticle A" throughout product use, release into technical systems and finally release to the environment. Advanced MFA models have included the form of the released material, e.g., the crystal form in the case of TiO_2 (anatase vs. rutile) (Wigger and Nowack, 2019) and the released form (e.g., pristine, transformed, dissolved and matrix-embedded) (Adam et al., 2018b). These models have shown that for some materials only a small fraction of the initial ENP is actually released in pristine form and this information should also be reflected in the fate models using release data. Similarly the environmental transformations, such hetero-agglomeration and forming of eco-corona should be considered in the predicted PECs. However, these PECs should be defined in a way that they align with the effect concentration, PNECs, as required for environmental risk assessment. Similar to microplastics, there is often a limited range in ENP characteristics considered in effect studies, where the environmental distribution of ENPs and their characteristics is multidimensional. Some lessons could be learned from the alignment approach, recently introduced for microplastics (Koelmans et al., 2020).

While the number of laboratory bioaccumulation and trophic transfer studies continues to grow, they are still relatively limited and narrowly focused, with only a few species and ENPs represented. Continued efforts need to expand the bioaccumulation experiment to phytoplankton, zooplankton other than filter feeders, and some fish tissues, such as the stomach, heart, spleen, kidney, and blood. Information on the biodistribution in fish tissues could be relevant for the development of PBPK modeling in the future. In addition, an in-depth interpretation of bioaccumulation tests will depend heavily on a comprehensive description of the ENPs used, in particular their properties (hydrodynamic size, aggregation state and surface charge) in the test medium. It is found that the particle characterization reported is rarely sufficient in bioaccumulation studies. Typically, only primary particle size and nominal concentration are disclosed, lacking information on particle behavior and concentration within the test medium during exposure. This means that there is an urgent need for standardized procedures for the operation and reporting of bioaccumulation experiments specifically for nanomaterials. Existing guidelines for conventional chemicals place greater focus on the material's chemical attributes, whereas it is the physical properties of nanomaterials that may predominantly influence their interactions with living organisms. For this reason, specific guidance and guidelines for nanomaterials are available or being developed (OECD, 2023a), such as the test guideline for estimating ENP size (OECD, 2023b) and hydrophobicity index (OECD, 2023c). The hydrophobicity index is not currently applied in EFMs, but in future might become applicable as a proxy for Heter agglomeration process, similar to how K_{ow} is for organic compounds.

Another challenge is keeping the EFMs operational and up to date. For example, the DUFLOW hydrological model framework on which nanoDUFLOW is based is not officially supported anymore. In addition, it has a Windows 10 user interface to manually build up the catchment based on stream cross sections and relative slope, to define characteristics of sections connected by nodes, which may no longer be supported in future versions of the operating system. Boundary conditions can also be added using the user interface. But this all can be labor intensive for a large catchment. Thus, models can become obsolescent as the underlying software changes. Very few modelers can continue to support their models indefinitely.

7. Future of exposure modeling for nano

Clearly, the most important issue for the future is the generation of robust datasets of observed ENP concentrations in various compartments, over a sufficiently long period of time to be able to evaluate the various models. With these datasets, one can then compare the accuracy of the various models, and determine how useful they are for predicting environmental concentrations. (Couvillion et al., 2023; OECD, 2023d; Hou et al., 2021)

Almost all of the models to date have only considered metal-based ENPs. Carbon-based ENPs do exhibit hydrophobicity, and thus partitioning/adsorption to organic phases is an important process, requiring the consideration of their hydrophobicity index (OECD, 2023d; Hou et al., 2021). These carbon-based ENPs also degrade over time, which is not a process commonly considered for metal-based ENPs (Shams et al., 2019). Two-dimensional nanomaterials (e.g., GO and MoS_2 nanosheets) are becoming more common, again introducing additional considerations in terms of their transport (Lee et al., 2019; Li et al., 2016).

While it is tempting to use these models directly to model nano- and microplastics (Mitrano et al., 2021), there are important differences, for example the buoyancy of most plastics would require additional considerations. Nanoplastics are distinguished from ENPs because of the high heterogeneity of the particles (shape, composition) and their potential for rapid further fragmentation under environmental conditions (Gigault et al., 2021). A significant fraction of the plastic particles are fibers, with a very elongated dimension, very different from the common aspect ratios of ENPs, which is likely to result in additional retention in soils and sediments. Nevertheless, there are already models addressing this new class of contaminants. The Rhine River multimedia box model has been used as basis for Full Multi Model Framework (Domercq et al., 2022) and SimpleBox4nano has evolved to SimpleBox4plastics (Quik et al., 2023), to assess the PECs of these particles. NanoDUFLOW has also been used to estimate microplastic PECs in freshwater systems

(Besseling et al., 2017). While the full understanding of the fate processes for these materials is still an area of active research, these frameworks provide useful PECs for risk assessment.

8. Conclusions

The past fifteen years have seen tremendous progress in our ability to predict environmental concentrations of ENPs, as we understand better their production rates, their flow through our global, national, and even regional economies, their likely release pathways and processes, their transport through various environmental media to their ultimate fate, and even their potential accumulation in exposed organisms. There are several modeling frameworks for each stage of the process, with differing degrees of complexity in their representation of the environment and ENP characteristics. The comparisons that have been made to date between observed and predicted environmental concentrations indicate that most of the models can provide adequate estimates within an order of magnitude. However, there are a number of important challenges that need to be overcome to continue to improve the accuracy of PECs:

- Datasets for evaluation of the accuracy of the models, with enough detail in terms of the spatiotemporal patterns and in various compartments (i.e., water, soils, air) to capture hotspots;
- Datasets for accurate representation of the extrinsic properties of ENPs in a wide range of conditions and approaches to simplify estimating them;
- More accurate information on the production and use of ENPs at different levels (global, continental, country, and eventually local);
- Information on the form of the ENPs as produced (e.g., crystalline structure), and as used in various ENP-enabled products (i.e., as free ENPs, within a liquid or solid matrix), and the form as exposed to organisms (i.e., attached to SPM) after environmental transformation, to be linked to effects;

Ensuring the safe use of nanotechnology will require accurate estimates of PECs, and while there are many tools to perform the exposure assessment, their quality will rely on meeting these challenges.

CRediT authorship contribution statement

Arturo A. Keller: Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Formal analysis, Conceptualization. **Yuanfang Zheng:** Writing – review & editing, Writing – original draft, Visualization. **Antonia Praetorius:** Writing – review & editing, Writing – original draft. **Joris T.K. Quik:** Writing – review & editing, Writing – original draft, Conceptualization. **Bernd Nowack:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Joris T. K. Quik reports financial support was provided by European Union.

Data availability

No data was used for the research described in the article.

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