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Exposure and Possible Risks of Engineered Nanomaterials in the Environment—Current Knowledge and Directions for the Future

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Abstract The consequences that engineered nanomaterials (ENMs) may cause in the environment have been under investigation for more than 15 years. Hundreds of millions of euros/dollars have been invested into safety issues of ENMs, and much progress has been made in the understanding of their fate and effects in the environment. After an initial phase of “observing the effects,” research has shifted toward elucidating the mechanisms of fate and ecotoxicological effects. This also included a stronger focus on exposure issues and the development of analytical methods and computational models to predict exposure. First environmental risk assessments for ENM were performed, and much progress has been achieved on the way to nanospecific and material-specific assessments. The release of ENM from products and their transformation in technical and natural compartments profoundly affect the form in which the ENMs are present in the environment. A crucial aspect in all areas is *if* there are truly nanospecific issues of the novel-added functionalities of ENM that are different from dissolved metals, larger particles, or natural particles. This review outlines progress in understanding the environmental dimensions of ENMs and areas that merit further investigation: To what extent are ENMs different from their natural counterparts and how “long” do we need to track them in natural and technical systems? A major challenge will be in developing methods for studying particle-mediated processes and their effects on ecosystems and organisms in a more general sense, going beyond just ENM, for example, to natural nanoparticles, microplastics, and extracellular vesicles.

Plain Language Summary The consequences that engineered nanomaterials may cause in the environment have been under investigation for more than 15 years, and hundreds of millions of euros/dollars have been invested into their safety issues. After an initial phase of “observing the effects,” research has shifted toward elucidating the mechanisms of fate and ecotoxicological effects. This review outlines the progress in understanding the environmental dimensions of nanomaterials and areas that merit further investigation: The release of engineered nanomaterials from products and their transformation in technical and natural compartments profoundly affect the form in which they are present in the environment. To what extent are engineered nanomaterials different from their natural counterparts and how “long” and in what form do we need to track them in natural and technical systems? A major challenge will be in developing methods for studying particle-mediated processes and their effects on ecosystems and organisms in a more general sense, going beyond engineered nanomaterials, for example, to natural nanoparticles, microplastics, and extracellular vesicles. A crucial aspect in all areas is *if* there are truly nanospecific issues of the novel-added functionalities of engineered nanomaterials that are different from dissolved metals, larger particles, or natural particles.

1. Introduction

Engineered nanomaterials (ENMs) are a group of anthropogenic compounds that have received much attention by scientists, regulators, and the general public in the last 15 years. All over the world, governments and funding agencies have invested a lot of time and efforts into their potential environmental health and safety aspects. ENMs are defined by ISO (2008) as materials designed for a specific purpose or function with any external dimension in the nanoscale or with an internal surface structure at the nanoscale which is between 1 and 100 nm. According to the European Union (EU) recommendation for a definition, a nanomaterial is a

material where 50% of the particles are between 1 and 100 nm (Bleeker et al., 2013). ENMs have, in many cases, novel properties as a consequence of their small size and thus can be used to add new or improved functionalities to materials and products (Roduner, 2006).

These “novel properties” raised early on questions if together with these properties also novel risks emerge. Maynard et al. (2006) suggested that responsible nanotechnologies can be tackled through a series of grand challenges within the next 15 years. Wiesner et al. (2006) stated challenges remain for future research on the environmental risks of nanomaterial although some progress had already been made toward understanding the health and environmental consequences of these materials. At that time, studying behavior and effects of nanomaterials in the environment was a field where the research was done based on a precautionary approach: What would happen if nanomaterials get into the environment? How would they behave there and how would they affect organisms? The occurrence of ENM in the environment has been assumed because “given the increasing production of nanomaterials of all types, the potential for their release in the environment and subsequent effects on ecosystem health is becoming an increasing concern” (Klaine et al., 2008). This assumption was based on the experience obtained with other pollutants in the past (Koehler et al., 2008) and has governed the field of environmental effects of nanomaterials in these early years. Maynard and Aitken (2016) called these early years the “turbulent times in the history of safe and beneficial nanotechnology” because on the one side, there was a growing interest in the possible benefits of nanomaterials, whereas on the other side, there was increasing concern about novel risks to human health and the environment. Maynard and Aitken (2016) state that there has been substantial progress in the last 10 years in some areas of nanosafety research and critical shortfalls in others that potentially limit the development of safe and beneficial uses of nanotechnology. They showed that we can learn from what has not worked well. For example, the nanosafety research has become increasingly unbalanced over the past 10 years, with toxicological studies by far exceeding research on exposure. Some materials such as silver and titanium dioxide have been studied a lot while others have received much less attention.

Several reviews have been published in the last 15 years on environmental aspects of ENM, and exposure has been increasingly in their focus. In 2013, the environmental concentrations of ENM were reviewed for the first time, and available analytical and modeling studies were critically presented (Gottschalk, Sun, et al., 2013). Several other reviews and book chapters presented the analytical and modeling methods in detail (Baalousha et al., 2016; Brar Satinder et al., 2015; Lead & Smith, 2009; von der Kammer et al., 2012; Xing et al., 2016).

Progress has been made in the last years on several aspects of environmental exposure of ENM. The aim of this review is therefore to critically evaluate the current knowledge on environmental exposure of ENM. Exposure covers the release of ENMs to the environment, their transformation reactions, their analysis in natural and engineered environments, and the prediction of exposure by modeling. The knowledge on exposure in combination with toxicity data can then be used to quantify the environmental risks of ENM. An important aspect covered in this review is to give the bigger picture and place ENM in the context of particles in the environment.

2. Flows of ENM to the Environment

Different to occupational or consumer exposure assessments, the estimation of environmental exposure has to consider a large set of different release scenarios (Gottschalk & Nowack, 2011). The potential for release to the environment exists during all life cycle stages: ENM production, ENM incorporation into products, the use of the nanoproducts, and their disposal and recycling. Figure 1 presents the life cycle steps where information has to be collected to understand and quantify the flows of ENM to the environment. The starting point for any assessment is the amount of ENMs that are produced because this represents the maximum amount that could possibly flow to the environment. Despite this importance, information on production amounts is difficult to obtain, and numbers from different sources may diverge a lot. This is especially true for materials that are outside the nanosized range and where the distinction between nanoform and conventional form is not clear and varies from source to source (Piccinno et al., 2012). Recently, Wigger et al. (2018) have shown that comparing the reported nanoproduction volumes in France (ANSES, 2013) with the total volume of the same material allowed to identify some materials where the nanoproduction actually matches the total production. This means that for these materials, the “conventional form” and the nanoform are

Figure 1. The life cycle steps where information has to be collected to understand and quantify the flows of ENM to the environment. The lower parts refer to assessments used in material flow analysis to assess the mass flows of materials (“mass based”); the orange boxes represent transformations occurring in different life cycle steps which may lead to a loss of nanospecific properties of the ENMs (“fate based”). Figure modified after Nowack et al. (2016).

identical, and thus, information on the production volume of the total material can be used. This is especially true for nano-SiO₂ but also for several organic pigments (Wigger et al., 2018).

Regionalization of production amounts has been considered in some assessments, as ENM production is distributed very unevenly around the globe (Keller & Lazareva, 2013). Release in this life cycle step can occur during synthesis of the ENM or the manufacturing of nanoenabled products (Gottschalk & Nowack, 2011). The knowledge about the distribution of the total ENM mass to nanoproducts is one of the most relevant steps in the assessment of release as the life cycle of the nanoproducts drives their potential release (Som et al., 2010). The required information is the relative share of ENM that the different product categories obtain. This information is even less available than the production amounts, and different approaches have been used to obtain this information, in many cases based on product inventories (Foss Hansen et al., 2016; Vance et al., 2015), on market research reports, or on surveys (Piccinno et al., 2012). Depending on the product, there can be intentional or unintentional release during the use phase (Gottschalk & Nowack, 2011).

Figure 2. The environment is integrating all releases of ENM from production, manufacturing, the product-use phase, and the end-of-life stage.

Intentional release occurs, for example, during groundwater remediation using nanozero-valent iron (nZVI) (Mueller et al., 2012), whereas unintentional release can occur through weathering or abrasion (Froggett et al., 2014). These unintentional release processes have received a lot of attention in the last years, and much progress has been made in combining the knowledge that affects the release of ENM (Harper et al., 2015; Mitrano et al., 2015; Wohlleben & Neubauer, 2016). Quantifying the amount of ENM that are released throughout the life cycle of nanoproducts forms the basis to quantify the release of ENM for exposure models (Caballero-Guzman & Nowack, 2016). The release of ENM during end-of-life processes has received much less attention although the potential for release is very high during this life cycle stage as products are often exposed to mechanical stress (Boldrin et al., 2014; Heggelund et al., 2016).

The environment is finally integrating the releases during all life cycle stages of all applications in use (Figure 2). Only a complete assessment of all release flows of all applications of a specific ENM can therefore yield information on the overall pollution of the environment. Often studies have only targeted a selected range of applications, for example, cosmetics (Musee, 2011) or paints, food packing, and fuel additives (O'Brien & Cummins, 2010), but these release estimates cannot be used to perform a full risk assessment. Caballero-Guzman and Nowack (2018) have shown that a comparison of release from a single application with the complete release from all applications can provide useful information on the contribution of selected applications to the overall release.

3. Transformations of ENM in Engineered Systems Before Being Released Into the Environment

Depending on the specific application (e.g., indoor, outdoor, cosmetics, medical, industrial, building material, electronic, and catalyst) and depending on the type of ENM (e.g., TiO_2 , SiO_2 , Ag, CeO_2 , CuO, and ZnO), different pathways leading to the release of ENMs to the environment are relevant. Results from mass flow analyses revealed that only a very limited amount of ENMs will directly be discharged into the environment and the vast majority first passes through various managed waste facilities, including wastewater systems (sewer and wastewater treatment plants [WWTPs]), waste incinerators, and landfills (Gottschalk, Sun, et al., 2013; Keller et al., 2013; Sun et al., 2014). The transformations of ENMs already start during their use, and Mitrano et al. (2015) have reviewed the most important aging reactions occurring in consumer products. Detailed discussions on physical, chemical, and biological processes leading to the transformations of (pristine) ENMs in different environmental compartments including soils, surface waters, and the atmosphere can be found in recent review papers (Abbas et al., 2020; Cornelis et al., 2014; Hedberg et al., 2019; John et al., 2017; Peijnenburg et al., 2015; Pulido-Reyes et al., 2017). Wagner et al. (2014) is discussing the similarities (and the differences) between the behavior of engineered and natural nanoscale materials especially highlighting the fact that the same processes act at both types of nanoscale materials, and Sharma et al. (2015) focuses on the formation of nanoparticles in the environment (“natural nanoparticles”) with a special focus on natural AgNP and AuNP. Motivated by promising applications of ENMs in the field of nanomedicine, the importance of the interaction between proteins and ENMs leading to the formation of a protein corona has been highlighted more than a decade ago (Lundqvist et al., 2008; Lynch et al., 2007; Lynch & Dawson, 2008). These authors suggest that the ENM-protein complex rather than the bare ENMs should be seen as a biological entity, driving the fate and impacts of nanoparticles in biological systems. These concepts were later transferred and applied to environmental systems and referred to a bio- or eco-corona (Ke et al., 2017; Lin et al., 2017) instead of a protein corona. Louie et al. (2016) specifically addressed the interaction between ENMs and macromolecules and discussed its impact on the fate and behavior of ENMs in the environment. More recently, specific proteins from activated sewage sludge were identified on the surface of TiO_2 and ZnO NPs, adding new information about the formation and importance of a protein corona in WWTPs (Zhang et al., 2018).

In summary, a wealth of knowledge on the transformation of (pristine) ENMs in the environment has been generated and reviewed over the last decades; however, transformations in managed waste facilities occurring before ENM are released into the environment received considerably less attention. Part et al. (2018) compiled the available data on the release of ENMs from products and briefly reviewed their fate and behavior during composting, recycling, incineration, and landfilling. To complement the available information, we provide additional data specifically focusing on the physical (agglomeration) and chemical (speciation)

changes of ENMs with a focus on managed waste facilities. We use the term “agglomerate” and “aggregate” following the ISO (2015) definitions. Agglomerates refer to weakly or medium strongly bound particles where the resulting external surface area is similar to the sum of the surface areas of the individual components, and aggregates refer to strongly bonded or fused particles where the resulting external surface area is significantly smaller than the sum of surface areas of the individual components.

Agglomeration trends of ENMs in aqueous systems are controlled by the water chemical properties, most importantly ionic strength, valence of the electrolytes, and pH. These parameters largely determine the surface charges/zeta potential of the particles. The interaction between particles can generally be predicted based on the DLVO theory (Derjaguin & Landau, 1941), taking electrical double layer interactions and van der Waals forces into account. Furthermore, surface coatings of the ENMs, either deliberately added during the ENM synthesis (engineered coating) or acquired after the release from respective products (bio- or eco-corona), additionally affect the stability of ENMs, for example, through electrosteric effects or hydrophobic interactions (Lin & Wiesner, 2012; Phenrat et al., 2008). Thus, the agglomeration of ENMs and the formation of a surface coating, which, depending on the surrounding matrices, dynamically evolves over time, are closely linked.

Initial research efforts on the stability of ENMs were directed toward a detailed understanding of the homoagglomeration of ENMs under variable water chemical conditions and especially on the impacts of organic compounds (Delay et al., 2011; Louie et al., 2013; Ottofuelling et al., 2011; Philippe & Schaumann, 2014; Piccapietra et al., 2012; Surette & Nason, 2016). These studies helped to explain the agglomeration behavior of ENMs in simplified lab-scale systems. However, in environmental systems, natural nanoscale particles and colloids will greatly outnumber ENMs, and thus, heteroagglomeration rather than homoagglomeration will determine the agglomeration state of ENMs. Therefore, recent studies aimed at describing the process of heteroagglomeration in more detail (Barton, Auffan, et al., 2014; Barton et al., 2015; Espinasse et al., 2018; Geitner et al., 2017, 2019; Labille et al., 2015; Praetorius et al., 2014, 2017; Yu et al., 2002). The formation of heteroagglomerates strongly affects the fate of ENMs in technical compartments. High removal efficiencies of mostly >95% were reported in WWTPs for different types of ENMs, such as Ag, Au, and TiO₂ (Kaegi et al., 2011; Ma et al., 2014; Westerhoff et al., 2011, 2013). The amount of ENMs discharged to the surface water following the wastewater treatment was positively correlated with the total suspended solids in the effluent suggesting an efficient incorporation of the ENMs into sludge flocs (heteroagglomeration). Comparable results were obtained for different core materials (Au, Ag) of different sizes (10 nm, 100 nm) and with different coatings (e.g., citrate). These results suggested that in complex (wastewater) matrices with ample of particulate compounds present, ENM cannot sufficiently be stabilized against heteroagglomeration (Kaegi et al., 2013). However, unexpectedly low removal efficiencies for very small (<10 nm) Ag₂S particles were observed recently indicating a size-dependent attachment efficiency and thus removal efficiency in the lower nanosized range (Tuoriniemi et al., 2017). However, this size dependence would equally apply for any nanoscale precipitates in the respective size range and cannot be assigned to a specific engineered property. High temperatures occurring during the incineration process (~900°C for sewage sludge combustion in a fluidized bed reactor and ~1200°C in a municipal solid waste incinerator) will inevitably destroy any engineered (organic) coatings that may be present on ENMs, and the agglomeration behavior of ENMs during incineration can be predicted from aerosol science (Hinds, 2011). The flue gas cleaning of modern waste incineration facilities very efficiently captures submicron particles (Burtscher et al., 2002), and thus, the release of ENMs from combustion facilities equipped with modern off gas treatment systems seems rather unlikely. This is consistent with recent finding that the majority of the ENM will be accumulated in the bottom ash (Vejerano et al., 2014), drawing the interest toward the potential release of ENMs from landfill sites. Only few studies have addressed the release of ENMs from landfill sites (Hennebert et al., 2013; Mitrano et al., 2017), and only one single study also documented that TiO₂ NP from a construction and demolition landfill site is actually discharged into surface waters (Kaegi et al., 2017). Thus, more detailed studies addressing the release mechanisms of ENMs from different types of landfilled materials are required to assess the importance and impacts of ENMs released from different types of landfills. In addition to the direct release of ENMs from combustion residues, the presence of ENMs in combustion goods may affect particulate emissions during the combustion (Motzkus et al., 2012). For example, Singh et al. (2017) reported altered emissions of polycyclic aromatic hydrocarbons (PAH) caused by the presence of nanofillers in thermoplastic materials.

The *chemical transformation* of different types of ENMs in different wastewater systems has been investigated at various scales. Due to the elevated concentrations of bisulfides in wastewater systems, ENMs made of chalcophile elements such as Ag, Cu, and Zn are very efficiently transformed to corresponding metal sulfides (Brunetti et al., 2015; Doolette et al., 2013; Kaegi et al., 2011, 2013; Lombi et al., 2012; Ma et al., 2014). Half-life times of the sulfidation reactions, referring to the time required to transform half of the mass of the metal into the corresponding metal sulfide, are in the order of minutes and thus considerably shorter than the average residence time in wastewater systems (Gogos et al., 2017, 2018; Liu et al., 2011; Thalmann et al., 2014, 2016). Thus, a near-complete sulfidation of chalcophile metals in wastewater systems (sewers and WWTP) can be expected. Sulfidation reactions of Ag and CuO NPs were also reported from experimental studies conducted on constructed wetlands (Auvinen et al., 2017) and freshwater mesocosms (Lowry et al., 2012; Stegemeier et al., 2017). Contrary to the sulfidation, Impellitteri et al. (2013) and Meier et al. (2016) reported the formation of nanoscale Ag(0) particles during sewage sludge incineration from Ag₂S precursors.

In addition to sulfidation reactions of ENM made of chalcophile elements, the partial reduction of CeO₂ (reduction of Ce (IV) to Ce (III)) was reported during the activated sludge process, during anaerobic digestion, and from freshwater mesocosm studies (Barton et al., 2015; Barton, Therezien, et al., 2014; Geitner et al., 2018). Walser et al. (2012) reported that CeO₂ NPs sprayed to the combustion goods were not affected by the combustion process, and based on electron diffraction, Vejerano et al. (2014) concluded that crystallographic phase of CeO₂ NP remained unaltered. Based on combustion experiments conducted with freeze-dried CeO₂ nanopowders in a muffle oven, Auffan et al. (2017) reported a significant increase of the crystallite size during combustion but no indication for a possible reduction of Ce (IV) to Ce (III). Results from experiments conducted with CeO₂-spiked sludge in a pilot fluidized bed reactor, however, revealed the size-dependent reduction of CeO₂ NP during the incineration process (Gogos et al., 2019). These results highlighted the importance of conducting experiments in sufficiently complex matrices. Most recently, the complete dissolution of Au NP (12 nm in diameter) has been reported, challenging the general assumption that Au NP can be used as conservative tracer (Avellan et al., 2018). Due to the stability of TiO₂ in aquatic systems, TiO₂ NPs are expected to behave conservative and remain as (aggregated) TiO₂ NP. Roes et al. (2012) suggested that TiO₂ particles also behave as inert components during the combustion process; however, Vejerano et al. (2014) reported a phase transformation from anatase to rutile, and Massari et al. (2014) revealed that TiO₂ (nano)particles transformed into calcium titanate during the combustion of paint residues.

In summary, in complex environmental media, where natural nanoscale particles and colloids with plenty of positive and negative charged moieties are present, heteroagglomeration of ENMs is the dominant process, and a stabilization of ENMs under such conditions seems unlikely. Thus, heteroagglomerates rather than homoagglomerates or freely dispersed ENMs are expected under environmentally relevant conditions. The activated sludge process during wastewater treatment accumulates the ENMs in the sludge phase. ENMs are efficiently removed from the flue gas during waste combustion. The majority of ENMs is accumulated in the bottom ash (municipal solid waste incineration) and fly ash (sewage sludge incineration), and both type of ashes are currently landfilled or used as additives in building materials/road construction. To what extent the presence of ENMs in combustion goods may lead to the emission of toxic byproducts is not clear. Chemical transformations of ENMs are element specific and dictate by the conditions in the surrounding media. Although a surface coating (engineered or acquired during the transport of the ENMs in sewer systems, in WWTPs, or in the environment) may modify the transformation rates, the transformation reactions will remain unaffected. Experimental facilities therefore have to be sufficiently complex to mimic conditions in environmental or engineered systems as an oversimplification may not capture the full complexity of the ENM interactions with the surrounding media and may hamper specific transformation processes.

4. Exposure in the Environment

The determination of environmental concentrations is the key for understanding the potential exposure to ENMs in the corresponding compartment. Generally, the environmental concentration is the potential dose to that an organism (or biota) can be exposed. Therefore, studies for understanding the environmental quantities as well as fate and behavior are relevant for the environmental risk assessment of any substances. Two

main approaches are at hand that are applied to determine environmental concentrations: The experimental analytics and the *in silico* models both are applied at different spatial scales from local measurements to larger system boundaries, respectively. The approaches complement each, and in the following, both approaches will be described in more detail considering the state and challenges that are related to ENMs.

4.1. Analytics

Over the last decades, several analytical techniques have been developed to investigate materials at the nanoscale. Developments were driven by disciplines in material science with the aim to fundamentally understand (changing) material properties at the nanoscale, in pure systems with plenty of materials available with well-described properties. Colloidal sciences first benefited from these analytical achievements which were also increasingly applied to detect engineered nanoparticles in complex matrices, as reflected in several review articles and book chapters (Hodoroaba et al., 2019). However, the original goal of the analytical developments was to understand nanoscale properties of (well-defined) materials, and the requirements for the sample properties were often not fulfilled when analyzing environmental samples, questioning the significance of the obtained results. An example is the dynamic light scattering technique, which is one of the most often used techniques to derive particle size distributions also on very complex suspensions, although the limitations of the techniques have been discussed more than 20 years ago (Filella et al., 1997).

Despite intensive research efforts, the unambiguous identification and quantification of ENMs in complex (natural) matrices, however, remained very challenging, and risk assessments related to the projected future increase in the production and use of nanomaterials largely remained on modeling studies (Giese et al., 2018; Gottschalk, Sun, et al., 2013; Keller et al., 2013; Sun et al., 2014). This, in turn, stimulated the development of dedicated nanoanalytical devices, resulting in novel techniques capable of detecting particles in the nanoscale range that became commercially available. Examples include nanoparticle tracing analyses (Gallego-Urrea et al., 2011), tunable resistive pulse sensing (Kozak et al., 2012), and hyperspectral imaging combined with dark field microscopy (Badireddy et al., 2012; Mortimer et al., 2014). Although these systems are very powerful when applied to systems of limited complexity, they are not specific enough to exclusively target the broad range of ENM in a variety of complex matrices. Other techniques that were around for considerable amount of time also strongly benefited from the increased need to detect particles at the nanoscale and were further developed. Examples include electron microscopy, where automated solutions for particle analysis in the transmission electron microscope have recently been presented (Uusimäki et al., 2019), and single particle inductively coupled mass spectrometry (sp-ICPMS) techniques. The fundamentals of the sp-ICPMS measurement technique have already been developed more than a decade ago (Degueldre & Favarger, 2003), but it needed further instrumental developments (e.g., reduced dwell times) which enabled the breakthrough of the method in the field of nanoanalytics and nanometrology (Laborda et al., 2016; Pace et al., 2012; Peters et al., 2014). Most recent achievements along this line include the development of methods based on time-of-flight mass spectrometry, allowing a simultaneous recording of virtually all elements of the periodic table on a single particle basis (Borovinskaya et al., 2013). The combination with advanced data evaluation algorithms allowed the unambiguous identification of spiked Ce NPs against a much higher background of naturally occurring nanoscale Ce particles present in the soil matrix (Praetorius et al., 2017). Further instrumental developments including the integration of an online microdroplet calibration system even allowed compensating for matrix effects on a single particle level (Hendriks et al., 2017, 2019).

Interferences caused by natural and incidental (unwanted byproducts such as diesel soot) (nanoscale) particles, as well as the presence of larger particles of up to 1 μm and above, limited the application of several well-established detection techniques in complex matrices. To remove such interferences and to enable a quantification of particles in the nanoscale, “size” separation of the particles prior to their quantification therefore increased in popularity. Examples include analytical ultracentrifugation (Wohlleben, 2012) and flow field flow fractionation coupled to various detecting systems, including ICP-MS to obtain elemental specificity (von der Kammer et al., 2012). A prerequisite for the successful separation of ENMs from the host matrices is that they are present as individual (freely dispersed) particles. The ubiquitous formation of heteroagglomerates in the environment requires an additional sample preparation step to break down the heteroagglomerates and liberate individual ENMs. Several standard operation procedures, including the

Figure 3. The main aspects covered by material flow analysis and environmental fate models to predict the environmental concentration. Please note the linkage between both is the environmental release of ENMs. WWTP = wastewater treatment plant; WIP = waste incineration plant.

addition of dispersant agents and the use of ultrasound treatments, have been developed for that purpose, for example (Mech et al., 2020).

Despite promising (nano)analytical developments over the last decade, only very limited data on the presence of ENM in complex matrices are available. The unambiguous detection of ENMs in complex (environmental) matrices, thus, remains wishful thinking to a large extent and the (quantitative) measurement of nanoscale particles in consumer products far from being routine.

4.2. Predicting Environmental Concentrations of Nanomaterials—Basic Principles

As an alternative to analytical methods, *in silico* modeling approaches are applied to estimate the potential environmental concentration of substances in a given region. So far, two main modeling approaches are at hand for predicting environmental release and concentrations of ENMs: material flow analysis (MFA) models and environmental fate models (EFMs) (Nowack, 2017). Figure 3 illustrates the main aspects that are regarded in both modeling approaches as well as their bilateral link through environmental release. The starting point of MFA models is usually the life cycle of nanoenabled products covering production, formulation, and manufacturing, usage, and end of life (either disposal or different types of recycling) assuming both transfer to the next process/life cycle step and potential release to the environment. The MFA model structure consists of several boxes that constitute processes in which input and output flows are balanced and if applicable potential releases determined (emission/release in period “p” = input – output).

The objective of EFMs is to predict the environmental concentration by considering key transport and transformation processes of a substance in or in between different environmental compartments. Due to the complexity of the environmental transport and transformation processes, several single compartmental EFMs exist (Dale et al., 2015; Praetorius et al., 2012; Quik et al., 2015), but also multicompartamental models were developed for this purpose considering intercompartmental transfers of ENMs with SimpleBox4Nano (Meesters et al., 2014), RedNano (Liu et al., 2015), and nanoFate (Garner et al., 2017), for instance. The available models for specific environmental compartments have been reviewed by Baalousha et al. (2016) for the aquatic and terrestrial compartment (including uptake by biota) and by Williams et al. (2019) for the aquatic compartment. So far, the models do not consider processes leading to transport into groundwater, although some MFA models do include release processes into the subsurface, for example, by leakage from sewers. The first model about uptake into biota has been published and was linked to a fate model (Garner et al., 2018).

The evaluation of the “true” predicted environmental concentration (PEC) value is challenging as it is influenced by several basic settings of the model being applied. It has to be noted that models and their results are not correct or incorrect per se, they can only be adequate according to the model purpose stated. Therefore, it belongs to the “good modeling practices” always to communicate the model purpose and its objectives and

Figure 4. Relation and influence of the key parameters (in bold) on the predicted environmental concentration (PEC) in EFM and MFA models. The numbers refer to the explanation in the subsection. Black circle = parameter has an influence; “±” = parameter can increase or decrease the PEC; red circle = key parameter for estimating the PEC; “+” = parameter increases the PEC; “−” = decreases the PEC.

transparently describe the underlying assumptions or data being used for the model parameterization. For the evaluation of different models, the model purpose has to be considered to enable comparisons due to the different setups. Models are always an abstract of the reality, and their structure as well as parametrization depends on the model designers' experience/background.

In the context of PEC calculation for ENMs, several studies have been published using different models based on MFAs or EFMs. For comparison reasons, we have assessed the models and summarized their main parameters and their influence on the PEC value. Figure 4 illustrates these interdependencies for MFA and EFMs. MFAs strongly depend on the production volume (cf. 1 in Figure 4) as the main input parameter determining the total potential ENM quantity in the system investigated. Unlike other key parameters, the production volume influences the PEC values, because ENMs are usually incorporated in products that are used during their lifetime and thereby determine the release quantity and location.

The second key parameter of the MFA models is the allocation of the production volume to product categories (cf. 2a in Figure 4) determining the release potential of the product category, accordingly. Depending on the product type, the ENM incorporation (i.e., amount of ENM and incorporation approach as, e.g., matrix bound or liquid), the usage during the product life span determine environmental release (cf. 2b in Figure 4) in the period considered. Although production volume is considered as the most important parameter, its allocation is as relevant as the product type triggers the environmental release and release points. The third key parameter of MFA models is the transformation of the released ENM in technical compartments (cf. 3 in Figure 4). ENMs can undergo transformation processes in WWTPs, and such transformation processes decrease the release quantity of ENMs and so the PEC. The fourth key parameter regards the solid waste treatment of nanoenabled products in which still residues of ENMs remain after their product life span (cf. 4 in Figure 4). Generally, it can be assumed that well-regulated waste management systems (i.e., collection, sorting, and treatment) are designed as closed system.

EFMs are linked to MFA models at the release event to the specific compartment using the release data as main input parameter (cf. Figure 3). The main purpose of EFMs is to describe the fate and behavior of ENMs considering the intrinsic material properties (i.e., ENM) and the extrinsic properties of the environmental compartment to determine the PEC. Similarly to MFAs, the PEC value links to the compartmental

volume and the geographic region with its local conditions (cf. Figure 4). The local conditions determine, together with ENM characteristics, the transformation and transport behavior of the ENM considered. Transformation processes (cf. 5 in Figure 4) decrease the PEC value, because homoaggregation/heteroaggregation, sedimentation, and dissolution reduce the originally released ENMs and thus the PEC.

4.3. Use of MFA Models to Obtain Mass Flows to the Environment

4.3.1. MFA—Overview

In the last decade, several MFA models have been developed differing in the purpose and consequently in the model setup (Furberg et al., 2016). Gottschalk, Sun, et al. (2013) published a review in a chronological order considering the MFA studies in the period 2008–2013. Therefore, our review will focus on the period 2013 to March 2019 considering the substantial progress made in the past years. Nevertheless, it has to be noted that some of the studies had investigated the potential release of less often studied ENMs as described in Boxall et al. (2007) (e.g., latex or hydroxyapatite) or Gottschalk et al. (2009) (e.g., fullerenes). Table 1 shows an overview on the MFA models available and summarizes for each model the key parameters considered.

The literature search identified 35 studies in the period from 2008 to February 2019 that deal with the estimation of environmental release of ENMs. We analyzed these studies with respect to ENM type, geographical boundary, key parameters assumed (production volume and release fractions), and model type (static, dynamic, and hybrid) and PEC estimation considered. The overview of the investigated ENM types is shown in Table 2 and Figure 5. Nano-Ag, nano-TiO₂, carbon nanotubes (CNTs), ZnO, and SiO₂ were the five most investigated materials in the period considered. Other ENMs were less often subject of studies.

The geographical systems under investigation were also very various complicating the comparison of different results. Figure 6 shows the relative share of geographical area and the model type applied in the study. Out of all identified studies, the most investigated geographical boundary was the European Union followed by the category “others” that summarizes several single studies of different areas.

4.3.2. Model Comparison

A comparison of the different models is quite challenging since the results and the underlying assumptions/model setups are not in line at a one-to-one basis. In the following, we will shed some light on the differences in MFA models that are relevant in the interpretation of the available modeling results. Most of the MFA studies focused on Europe or the European Union as geographical boundary (Sun et al., 2014, 2017) mainly determining potential releases. Other studies have shown that regional and local MFA models can better reflect the prevailing local system conditions, for example, for waste management systems and recycling processes (Adam & Nowack, 2017; Heggelund et al., 2016; Wang & Nowack, 2018a; Wigger et al., 2015) and also for wastewater treatment processes (Lazareva & Keller, 2014). MFA studies examined different regional system boundaries such as the United States of America (Keller et al., 2014), United Kingdom (Mahapatra et al., 2015), Germany (Filser et al., 2013; Giese et al., 2018), Australia (Sun et al., 2015), Japan (Suzuki et al., 2018), Denmark (Gottschalk et al., 2015), and the Hunan Province in China (Ding et al., 2019). As an alternative, Wang and Nowack (2018a) proposed the WWTP connection as suitable parameter to cluster countries of the European Union. It has to be noted that a switch from global to local MFA models generally requires more detailed data on the local production volume, products used, and end of life (Caballero-Guzman & Nowack, 2018; Keller & Lazareva, 2013), even though local MFA models mostly focus on single materials, selected applications, or environmental compartments. Parker and Keller (2019) combined the nanoRelease MFA model with subsequent nanoFate model to determine the potential environmental concentration for different local and regional locations. They have shown that depending on the local conditions and use of ENMs, the resulting concentration can vary up to 3 orders of magnitude.

Furthermore, the MFA models differ in the amount of selected applications considered ranging from single product uses (Caballero-Guzman & Nowack, 2018) such as textiles (Wigger et al., 2015) and contrast agents (Filser et al., 2013). The MFA focus can also include specific industrial sectors as, for example, construction and building (Suzuki et al., 2018) and nanomedicine (Mahapatra et al., 2015) or attempt to estimate the complete market using market reports or other product repositories, for instance (Keller et al., 2013; Wang, Kalinina, et al., 2016; Wigger et al., 2018).

4.3.3. Dynamic Models

The implementation of time-dependent processes in dynamic MFA models enabled a significant advancement of the modeling of ENM releases to the environment. Static models usually assume a steady-state

Table 1
Overview on the MFA Models Published in the Years 2013–2019 Including an Evaluation of Key Parameters Considered

Reference	Model type	Production volume (base year)	Number of product categories	Product life span/ dynamics	Waste and end-of-life treatment	Transformation in technical systems	Release fractions	Environmental transformation	PEC provided	Comments
Filser et al. (2013)	MFA	2009	1	–	±	–	+	±	+	Special application in medical uses → intended exposure
Keller et al. (2013)	MFA	2012	16	–	±	±	+	–	–	
Keller and Lazareva (2013)	MFA	2012	20	–	±	±	+	–	+	
Keller et al. (2014)	MFA	2012	21	–	±	–	+	–	–	Focus on personal care products
Sun et al. (2014)	PMFA	2012	5–17	–	±	±	+	±	+	
Sun et al. (2015)	PMFA	2012	9–19	±	±	±	+	±	+	
Caballero-Guzman et al. (2015)	PMFA	2012	1–5	–	+	±	+	–	–	Focus on waste management and recycling of selected ENMs
Wigger et al. (2015)	MFA	2012	1	±	+	–	+	–	+	Specific focus on textiles and the use/end-of-life stage
Mahapatra et al. (2015)	PMFA	2013	16	–	±	±	+	±	+	Special application in medical use
Gottschalk et al. (2015)	PMFA	2012	2–14	–	±	±	+	±	+	First nanoform differentiated assessment for TiO ₂ NP in Denmark
Sun et al. (2016)	DPMFA	2012	8–19	+	±	±	+	±	+	
Wang, Kalinina, et al. (2016)	PMFA	2014	20	–	±	±	+	±	+	
Wang, Deng, et al. (2016)	PMFA	2014	13	–	±	±	+	±	+	
Sun et al. (2017)	DPMFA	2012	8–19	+	±	±	+	±	–	
Song et al. (2017)	sd-MFA	2012	7	+	+	±	+	–	–	Production volume extrapolated to 2016
Giese et al. (2018)	DPMFA	1996	35	+	+	±	+	±	+	Production volume has been confirmed by a questionnaire being in the same range of 1996
Adam and Nowack (2017)	PMFA	2012	28	–	+	+	+	–	–	
Wang and Nowack (2018a)	DPMFA	2014	10–22	+	±	±	+	±	+	
Suzuki et al. (2018)	sd-MFA	2013	2	+	+	–	+	–	–	
Wigger et al. (2018)	PMFA	2014	30	–	±	–	+	±	+	
Caballero-Guzman and Nowack (2018)	PMFA	2012 and 2014	1–6	–	±	±	+	±	+	
Adam et al. (2018)	PMFA	2012	11–15	–	±	+	+	+	–	
Ding et al. (2019)	PMFA	2013	7	–	±	±	+	±	+	
Wigger and Nowack (2019)	PMFA	2012 and 2014	8–18	–	±	±	+	±	+	First study that separated the production volume into different nanoforms and allocated it to specific applications
Parker and Keller (2019)	sd-MFA + EFM	2012	12	±	±	±	+	+	+	

Note. “+” = considered; “±” = partially considered; “–” = not considered; EFM = environmental fate model; sd-MFA = stochastic dynamic material flow analysis; DPMFA = dynamic probabilistic material flow analysis; PMFA = probabilistic material flow analysis; MFA = material flow analysis; PEC = predicted environmental concentration.

Table 2
Amount of Data Points and Studies Used for the Reported Predicted Environmental Concentrations

ENM	Water ($\mu\text{g/L}$)		Sediment ($\mu\text{g/kg}$)		Sludge (mg/kg)		Sludge treated soil ($\mu\text{g/kg}$)		Soil ($\mu\text{g/kg}$)	
	No. of studies	No. of data points	No. of studies	No. of data points	No. of studies	No. of data points	No. of studies	No. of data points	No. of studies	No. of data points
Ag	6	8	6	7	4	5	5	7	3	4
Al_xO_y	2	3	2	3	2	3	2	3	2	3
Au	1	2	1	2	1	2	1	2	1	2
Ce_xO_y	3	3	3	3	3	3	3	3	1	1
CNT	4	5	4	5	4	5	4	4	4	4
Fe_xO_y	4	5	3	4	3	4	3	4	3	4
Fullerenes	1	2	1	2	1	2	1	1	1	2
QD	2	2	2	2	2	2	2	2	1	1
SiO_2	5	6	5	7	4	4	5	6	5	5
TiO_2	5	19	5	19	3	5	5	17	3	5
ZnO	3	4	3	4	2	2	3	3	3	4

Note. ENM = engineered nanomaterial; CNT = carbon nanotubes; QD = quantum dots.

balance in a period, often a year, assuming the balance of the inputs and outputs of the system considered. The crucial assumption here is that all product applications have a life span of 1 year and, consequently, the complete production volume is distributed to the final sinks (i.e., the point at which no further transformation or transfer is considered) in the period considered. In contrast, dynamic MFA models generally span over several periods and implement time-dependent parameters (e.g., changing production volume, different product life spans, or environmental release) that allow to “store” potential releases in so-called stocks that ought to be released in later periods (van der Voet, 2002). The results of such dynamic models are that some periods may have lower environmental release but others can have high peaks of release due to the interplay of stocks of older periods and flows of the current period. This is quite relevant for exposure assessments, as exposure strongly is time dependent. On the downside, dynamic models usually are more data demanding (van der Voet, 2002) or require additional assumptions leading to a higher uncertainty as well as the results are more complex to interpret than the results of static MFA models.

In the context of ENMs, several dynamic models were published that addressed different aspects of the beforehand framed context. Sun et al. (2015) implemented a partial dynamic MFA model considering the spatiotemporal dynamics of biosolid production and its application as fertilizer showing the influence of different biosolid and wastewater application rates on the environmental concentrations that varied by a factor

Figure 5. Number of predictions for environmental concentrations available for ENMs investigated by material flow analyses from 2008–2019. Raw data are given in Table S2.

Figure 6. Relative share of geographical boundaries (left) and model type used (right) in studies identified in the time period 2008–2019. Local boundaries refer to single locations in a region, that is, Johannesburg City (Musee, 2011), waste water treatment plants (New York, London, and Shanghai; Lazareva & Keller, 2014), and six watersheds (Los Angeles, New York, Des Moines, Rome, London, and Zürich; Parker & Keller, 2019). Regional models comprise counties or other smaller boundaries than national ones (e.g., Australian counties, Sun et al., 2015; Chinese province, Ding et al., 2019; and seven regions defined in the European Union according to their percentage of wastewater treatment plants connected to the population, Wang & Nowack, 2018a). The category other includes any study that did not match to the proposed categories. Raw data are given in Table S3.

of 2. Bornhöft et al. (2016) set up a complete dynamic MFA framework for ENMs, which is freely available in the python repository. It has been applied by Sun et al. (2016) for Europe and Wang and Nowack (2018a) for seven European regions both showing the increasing relevance of in-use stocks compared to the production volume in the period considered. This is mainly caused by the consideration of product life spans and time-dependent releases. Both authors could track the historical environmental concentration and project future environmental concentration. Sun et al. (2017) extended this work by implementing three “what if ...” scenarios prospectively analyzing the impact of business-as-usual, ENM product-ban, and ENM-hype scenarios. They were able to show considerable differences in these prospective scenarios leading to varying environmental concentrations. In contrast, Song et al. (2017) developed the nanoRelease tool focusing on the dynamic modeling of environmental release throughout the complete product life cycle. This tool was exemplified by the case study “nano-TiO₂ in paints and coatings” and was applied to different product groups with varying product life spans. It was shown that potential environmental concentration stemming from long life products are especially overestimated by static models in the first years of use. Wigger et al. (2015) dynamically modeled the use of textiles and showed the need to consider products (i.e., textile) with short life spans in the context of international waste management systems. Similarly, Giese et al. (2018) stressed the relevance to consider life cycle stage use and end of life separately as both can considerably differ depending on ENM type and product applications. The dynamic model of Suzuki et al. (2018) focused in the Japanese construction sector and emphasized the relevance of the in-use stock as temporary sink as well as recycled materials and landfills as final sinks that influence the environmental release.

4.3.4. Considering Different Nanoforms

An important simplification of MFA models generally is the fact that nanoforms and their transformations are not or if only very roughly considered in the model design. The term “nanoform” is characteristically used in the nanotechnology research field as well as in the European Chemical Regulation and refers to the different physicochemical identities of an elemental parent material (ECHA, 2019). Therefore, first attempts were made to improve the input and output data that specifically consider nanoforms and their potential environmental transformations. For the production volume as the most relevant input parameter, Wigger et al. (2018) used available data on ENM production from regulatory registries and compared them to bulk/ENM market reports. It was shown that some bulk materials such as SiO₂ or the organic pigment Diketopyrrolopyrrole (DPP) was redefined into ENMs, which gives the opportunity to use also data on bulk materials to improve the MFA models. Furthermore, Wigger and Nowack (2019) extended the work of Gottschalk et al. (2015) and improved the allocation of generic ENMs to product categories to nanoform-specific products as, for example, TiO₂ NP used in paints and sunscreens makes use of different crystal forms and coatings. Based on a functionality driven approach, a full environmental risk assessment

was presented indicating to differences in environmental concentration for different nanoforms of the same parent ENM. Adam et al. (2018) dedicated their effort to the environmental release and potential transformations and also underlined the relevance for considering environmental transformations in MFAs that can be used for more specific EFM. This work split the flows of “ENM” into product-embedded, matrix-embedded, pristine, transformed, and dissolved forms. While these adaptations discussed above consider specific properties of various nanoforms, these are not “nanospecific” but rather form-specific considerations because there are no special “nanoproperties” per se that are taken into account in the MFA modeling. It is, however, important to treat different nanoforms separately if they either have very different applications and release scenarios or if they have different environmental fate and toxic effects.

4.4. Estimated PEC Values

When evaluating the PEC values derived, one is challenged by the manifold of different models and their underlying assumptions as it was discussed in the previous subsection. Additionally, the meta-analysis of different studies is aggravated due to the nature of scientific publications in which often aggregated results are presented and less often the original raw data are reported. The raw data would be required for a sound statistical analysis that was not accessible at the point of time of this review. For example, if probability distributions of PECs were calculated, different statistical measures were used describing the main characteristics of the data, which do not allow the interstudy comparison. Consequently, we had to focus on the data retrievable from the articles, which are summarized in Figure 7. The figure is based on the reported means and modes in the MFA studies, which have derived a PEC value for the corresponding environmental compartment water, soil, sludge-treated soil, sludge (as input parameter for soil), and sediments published in the Years 2013 to 2019. The ranges reported for each ENM considerably differ between the compartments. AgNP shows the widest range in the water compartment compared to the other ENMs investigated. The main reasons are the different underlying assumptions, which mainly are the geographical system borders (Germany, Denmark, and Europe) and environmental transformation processes considered (none vs. full sedimentation/dissolution). Iron oxide nanoparticles (Fe_xO_y) similarly have wide range due to the different underlying assumptions, particularly regarding the geographical system borders, productions volume/number of product applications, and environmental transformation processes. Also, the value range for TiO_2 NP in sediments is surprising, because it does not dissolve in water as, for example, AgNP and should have a narrower range since actually five different studies were included. The highest values were reported by Parker and Keller (2019), who consider a local release model including environmental transformation processes based on the nanoFate model. The reasons for the wide range are the system boundaries, production volume, applications, and environmental transformations selected. Depending on the models and their assumptions considered, the PEC results vary across several orders of magnitude, which stress the required transparency for comparing similar model purposes. Particularly, the environmentally released fractions (i.e., the overall released quantity of ENMs throughout their life cycles) often are not given but would be required to understand the model mechanics and the differing results in comparison to other studies.

However, the PEC ranges give an orientation for the environmental risk assessment and decision-makers, who should thoroughly check which kind of PEC value is required. Critical parameters for deriving PECs are the production volume, released quantity in a given region, and environmental transformation, which is why these parameters should be at least reported and cross-checked for age (i.e., if possible, assumptions/data on key parameters preferably not older than 5 years), suitable geographical region (local vs. global), and life cycle stage considered. Even if environmental transformations are not considered, the PEC values can give an orientation to the worst case of environmentally released amount of an ENM.

Furthermore, the recently published dynamic models are only included as quantities being released in the reference year (Bornhöft et al., 2016; Song et al., 2017; Sun et al., 2016; Wang & Nowack, 2018a). Potential future releases (and in-use stocks) are neglected in Figure 7. Future studies should improve the current practices by including temporal aspects in exposure aspects and also for hazard assessments as both are dependent on this factor.

5. Environmental Risk Assessment

There are many reviews available that describe the best risk assessment strategy for nanomaterials and how one has to deal with the special properties of ENM, for example (Grieger et al., 2012; Hristozov et al., 2016;

Figure 7. The ranges of the reported predicted environmental concentrations for different compartments considering the lowest and the highest reported value out of the studies reviewed from 2013–2019. Please note the values refer to the mode and/or mean reported by different studies, which are shown in Tables 2 and S4.

Scott-Fordsmand et al., 2017). Many models exist that can be used to qualitatively or quantitatively assess environmental risks (Sørensen et al., 2019). These models need to cover hazard and exposure assessment that are then combined in the final risk assessment. There is an intense discussion in the literature about the best strategy to assess the hazards of nanomaterials, how to include nanospecific properties, and especially which modifications of existing test systems are necessary so that results that are reproducible and acceptable for regulators can be obtained (Holden et al., 2016; Hund-Rinke et al., 2016; Petersen et al., 2015).

The standard approach in environmental risk assessment is to derive for exposure the PEC and for hazard the predicted no effect concentrations (PNEC) and then derive the risk characterization ratio (RCR) = PEC/PNEC. This approach has been followed by a suite from published studies from 2008

Table 3
Overview of Quantitative Environmental Risk Assessment Studies for ENM Based on Comparison of PEC and PNEC

ENM	Exposure assessment	Hazard assessment	Comments	References
TiO ₂ , Ag, and CNT	MFA	PNEC	Uncertainty covered by different scenarios	Mueller and Nowack (2008)
TiO ₂ , ZnO, Ag, CNT, and fullerenes	PMFA	PNEC		Gottschalk et al. (2009)
Ag and TiO ₂	MFA	PNEC	Only for cosmetics	Musee (2011)
TiO ₂ , ZnO, Ag, CNT, and fullerenes	PMFA	PSSD	Risk probability given but no RCR	Gottschalk, Kost, et al. (2013)
TiO ₂ , ZnO, Ag, CNT, and fullerenes	PMFA	PSSD		Coll et al. (2016)
Au	PMFA	PSSD	Only for medical uses; RCR not provided	Mahapatra et al. (2015)
SiO ₂	PMFA	PSSD		Wang, Kalinina, et al. (2016)
Iron oxides	PMFA	PSSD		Wang, Deng, et al. (2016)
TiO ₂	PMFA/SB4N	PSSD	Uncertainty from fate processes included	Jacobs et al. (2016)
CeO ₂ , CuO, TiO ₂ , and ZnO	Fate model	PNEC	Visual comparison of PEC and PNEC; no RCR given	Garner et al. (2017)
Nano-SiO ₂ , nano-iron oxides, nano-CeO ₂ , nano-Al ₂ O ₃ , and quantum dots	DPMFA	PSSD	Different European regions	Wang and Nowack (2018b)
TiO ₂ (anatase and rutile), Al-ox (α - and γ -form), and CNT (MWCNT and SWCNT)	PMFA	PSSD	Form-specific risk assessment	Wigger and Nowack (2019)
Ag	PMFA	PNEC	Regional assessment for one Chinese province	Ding et al. (2019)
TiO ₂	Fate model	PNEC	Local risk assessment; only days of exceedance but no RCR provided	Parker and Keller (2019)
nZVI	Measurements	PNEC	Local risk assessment around groundwater injection well	Weil et al. (2019)
Nanocellulose	DPMFA	PSSD	Including prospective risk assessment	Stoudman et al. (2019)

Note. MFA = material flow analysis; PNEC = predicted no effect concentration; PMFA = probabilistic material flow analysis; DPMFA = dynamic probabilistic material flow analysis; PSSD = probabilistic species sensitivity distributions; SB4N = SimpleBox4Nano; RCR = risk characterization ratio.

onward (Arvidsson, 2018), constantly increasing in completeness and incorporation of more and more advanced hazard and exposure assessment methods and making use of the increased database on ENM. Table 3 summarizes these studies and lists the exposure and hazard assessment methods that have been used. Most RCRs are available for TiO₂ (8), followed by Ag (5), CNT (4), ZnO (3), fullerenes, SiO₂, CeO₂, iron oxides and Al-oxides (2 each), and, finally, QD, Au, CuO, nZVI, and nanocellulose (1 each).

The first exposure assessments were based on MFA, while in later studies, also probabilistic MFA was used. In 2018, the first exposure assessment using dynamic probabilistic MFA was published (Wang & Nowack, 2018b). These material flow models do not consider environmental fate processes for ENM but predict a worst-case scenario in an average region. The first assessments based on environmental fate models that consider environmental processes such as agglomeration and sedimentation have also been carried out recently (Garner et al., 2017; Parker & Keller, 2019).

The hazard assessment was initially performed based on PNEC values derived from the most sensitive end-points and this approach is still used in some recent studies. More often, species sensitivity distributions (SSD) are used in later studies, allowing to fully consider the large variability in toxicities for the same species in different studies in a probabilistic approach (Gottschalk & Nowack, 2013). For nZVI which is injected into groundwater, a local risk assessment could be performed based on measured values of nZVI present in groundwater (Weil et al., 2019). For most of the other assessments, regional PEC values were used, and thus, the occurrence of local hot spots was not considered.

Table 4 presents the risk characterization ratios derived using SSDs for ENM in surface waters. Values are available for 11 ENMs. The highest predicted value is for ZnO with 0.09. Also TiO₂ and nano-Ag have values above 0.01, whereas all other materials have values much lower than 0.01. A first risk assessment based on specific crystallographic forms of a material (TiO₂, Al-oxides, and CNT) has also been performed (Wigger & Nowack, 2019). The RCR for TiO₂ varies from 0.004 to 0.03 depending on the nanoform (anatase vs. rutile), caused by different toxicities of the two forms but also different PEC values.

The RCR shown in Table 4 were all derived from MFA models and so did not consider any fate processes in natural waters. The PEC values were derived assuming one well-mixed continental water compartment as specified in the REACH guidance (ECHA, 2008). The inclusion of fate processes, for example,

Table 4
Risk Characterization Ratios (RCR) for ENM in Surface Waters Derived Using Species Sensitivity Distributions (SSDs)

ENM	RCR	References
TiO ₂	0.03 ^{a,b} , 0.03 ^a	Coll et al. (2016) and Jacobs et al. (2016)
TiO ₂ (anatase)	0.004 ^a	Wigger and Nowack (2019)
TiO ₂ (rutile)	0.03 ^a	Wigger and Nowack (2019)
TiO ₂ (P25)	0.02 ^a	Wigger and Nowack (2019)
Ag	0.053 ^a , 0.038 ^a	Coll et al. (2016) and Ding et al. (2019)
CNT	<0.01 ^a	Coll et al. (2016)
MWCNT	0.000003 ^a	Wigger and Nowack (2019)
SWCNT	0.000009 ^a	Wigger and Nowack (2019)
ZnO	0.09 ^a	Coll et al. (2016)
Fullerenes	<0.01 ^a	Coll et al. (2016)
CeO ₂	0.00005–0.0002 ^c	Wang and Nowack (2018b)
SiO ₂	0.0003–0.001 ^c , 0.0001 ^a	Wang, Kalinina, et al. (2016) and Wang and Nowack (2018b)
Al-ox	0.0003–0.002 ^c	Wang and Nowack (2018b)
α-Al-ox	0.0001 ^a	Wigger and Nowack (2019)
γ-Al-ox	0.0001 ^a	Wigger and Nowack (2019)
Fe-ox	0.0001 ^a , 0.0004 ^c	Wang, Deng, et al. (2016)
QD	1e-8–2e-7 ^c	Wang and Nowack (2018b)
Nanocellulose	0.00007 ^c	Stoudman et al. (2019)

Note. Mean values are shown.

^aBased on static MFA. ^bBased on fate model. ^cBased on dynamic MFA.

agglomeration and sedimentation, would lower the PEC for the water compartment and thus the RCR. The current RCR takes a precautionary approach and is based on the assumption of complete suspension of the ENM in the water compartment. On the other hand, local RCR can also be higher because the ENM can have locally elevated concentrations, and thus, much higher risks can be expected. This was shown to be the case by Parker and Keller (2019) who showed that in a local situation downstream, a WWTP ecotoxicological threshold values can be exceeded several times a year.

Table 5 shows the available data for RCR of ENM in soils. Much less information is available for soil than for freshwaters because there are fewer toxicological studies available that can be used to derive PNEC values. Although PEC values for soils have therefore been published, fewer comparisons with hazard data have been performed. Those that exist have calculated RCR for soils in general but also for sludge-treated soils. In sludge-treated soils, RCR are much higher and can reach 0.3 for nano-TiO₂. This is one of the highest RCRs reported so far and clearly calls for a more in-depth analysis of the potential effects of nano-TiO₂ on soil organisms. However, it also has to be noticed that this value was published in 2009 when much less information of exposure and hazard of ENM was available.

Sediments are missing so far almost exclusively in the risk assessments, mainly caused by the absence of enough hazard data that could be used to derive PNEC values or even construct a SSD. Table 6 lists the

Table 5
Risk Characterization Ratios (RCR) for ENM in Soils and Sludge-Treated Soils

ENM	RCR	Comments	References
TiO ₂	0.013	SSD, sludge-treated soil	Coll et al. (2016)
TiO ₂	0.004	PNEC	Gottschalk et al. (2009)
TiO ₂	0.3	PNEC, sludge-treated soil	Gottschalk et al. (2009)
Ag	<0.01	SSD, sludge-treated soil	Coll et al. (2016)
Ag	0.000002	PNEC	Ding et al. (2019)
CNT	<0.01	SSD, sludge-treated soil	Coll et al. (2016)
CNT	<0.0005	PNEC, sludge-treated soil	Gottschalk et al. (2009)
ZnO	<0.01	SSD, sludge-treated soil	Coll et al. (2016)
Fullerenes	<0.01	SSD, sludge-treated soil	Coll et al. (2016)
Fullerenes	<0.0005	PNEC, sludge-treated soil	Gottschalk et al. (2009)

Note. Mean values are shown.

Table 6
Risk Characterization Ratios (RCR) for ENM in Sediments

ENM	RCR	Comments	References
CNT	<0.0005	Based on PNEC	Gottschalk et al. (2009)
CNT	0.03	Based on SSD	Coll et al. (2016)

Note. Mean values are shown.

two RCRs that have been predicted so far, both for CNTs. The PEC values in both assessments are based on the worst-case assumption of 100% sedimentation of the nanomaterials. The inclusion of fate processes could affect the sediment concentrations, as locally higher concentrations could be reached after point sources and rapid removal from the water column.

Based on the current knowledge, none of the ENM poses an environmental risk to surface waters as none of the RCR is above 1. However, we need

to consider that all reported RCRs are based on regional assessment and therefore have a limited spatial resolution and that local hot spots may occur. The RCR is also very much related to the total amount of an ENM that is produced, and increasing the production (and subsequently also release) will increase the RCR.

6. Putting ENM Into Perspective

The above discussion highlights some of the observations of toxicity, transformation, and risk assessment methods for ENMs. It has now been nearly 20 years since the question was first raised as to whether the “novel” properties, which emerge when the size of a material reduced to the nanoscale (Auffan, Rose, Bottero, et al., 2009; Roduner, 2006), translate to novel pathways of toxicity and risk materials that differ from the then known mechanisms for either solutes or fine particulates (Wiesner, 2000). To date, no such general mechanism of nanoderived toxicity has been observed. The toxicity of known toxic materials, such as silver, may be increased, or CNTs of a precise length may produce inhalation risks similar to other persistent fibers. But the underlying *general* mechanisms of *how* toxicity is created, distinct from exposure or absorption, distribution, metabolism, and excretion (ADME) effects that determine *where* toxic materials may come into contact with organisms or tissues, have not yet been elucidated that would indicate that reducing size changes the underlying manner in which these materials produce a biotic response. CNTs may be the next asbestos, but nanomaterials, as a general class of materials, do not appear to be a new emerging class of contaminants identifiable by size *alone*.

The nanotoxicology literature is swollen with studies using a relatively small group of ENMs such as nano-Ag, CNTs, and TiO₂. The acute toxicity of these latter three materials, determined by the LD50 from oral doses to rats or mice, is typically reported to be greater than 2,000 mg/kg, values similar to aspirin (1,000 mg/kg) and considerably less toxic than caffeine (130 mg/kg) (Buell & Girard, 1994). Where chronic effects have been observed, generally, at least one of three conditions apply: (1) Experiments were done at very high doses; (2) experiments were performed in vitro rather than in vivo, and/or (3) the nanomaterials in question were composed of known toxic materials (e.g., Ag, Cd, Cr, Cu, Zn, and persistent fine particles or fibers in inhalation studies). The toxicity of known toxic materials in the nanoform has been confirmed in several high throughput analyses (e.g., Farcas et al., 2015; George et al., 2011; Liu et al., 2014) and, in the case of mineral nanoparticles, confirms predictions by Auffan, Rose, Wiesner, et al. (2009) that toxicity of these materials should be largely predictable from the redox couples presented by the nanomaterial and common biomolecules.

However, due to the exquisite precision of ENMs, experiments with these materials have revealed the ubiquity of nanophase interactions with organisms and in ecosystems. Using ENMs as visible tracers against an otherwise complex background of materials, we now know that nanoparticles are readily bioavailable (Meyer et al., 2010) that they are subject to trophic transfer (Unrine et al., 2008, 2012) and maternal transfer (Blickley et al., 2014; Kim et al., 2013). Subtle ecosystem-level effects have been observed (Colman et al., 2013; Simonin et al., 2018) that are not predictable based on single species toxicity tests. In some sense, these results should not be surprising in that life is composed of, has evolved in the presence of and, as we are now more readily appreciating, uses nanophases as the basis for much intercellular and interspecies communication.

However, the relative importance of engineered nanophases in potentially disrupting or mediating these processes appear to be miniscule. Hochella et al. (2011) estimate that the production of nanoparticles from natural sources alone is over 5 orders of magnitude greater than that from engineered sources. Some ENMs, such as fullerenes, may be virtually indistinguishable from nanoscale materials of incidental or natural origin. ENMs should therefore not be evaluated in isolation but in context of natural particles and the dynamic processes that transform carbon, dissolved metals, and particles, including nanoparticles, into each other (Figure 8).

Figure 8. ENMs need to be evaluated in a larger context together with dissolved metals and the bulk form. In the environment ENM, other particles and metals can transform into a suite of different forms. Nanoparticles can also be formed from dissolved metals.

The significance of these natural and incidental nanophases as potential vehicles for the transport of known toxic compounds has received considerably less attention than the potential toxicity of ENMs (Wiesner et al., 2011), and yet there is rich literature on as facilitated transport of contaminants, Trojan horse effects in drug delivery, and other related topics. These topics, as well as the role of nanophase versions of known contaminants such as metals, in altering the exposure potential and effect doses of these materials can be explored using the tools of nanotechnology developed during the last 20 years. Methods developed for investigating possible ENM effects and transport processes can applied to a host of other particle-based problems including microplastics/nanoplastics, inhalation toxicology, and the transport and impacts of biologically derived nanophases.

Data Availability Statement

No new data were collected for this publication. All data collected from the literature are provided in supporting information Tables S1–S4.

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