NanoImpact 8 (2017) 38–47

Contents lists available at ScienceDirect

NanoImpact

journal homepage: www.elsevier.com/locate/nanoimpact

Review article

Evaluation of environmental exposure models for engineered nanomaterials in a regulatory context

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A B S T R A C T

Exposure modeling is an important tool in the risk assessment process because it can provide information on predicted environmental concentrations (PEC values) even in the absence of analytical data. A suite of different models has been used in the last years to predict environmental flows and concentrations of engineered nanomaterials (ENM). These models can be separated into material flow models that track the flows of ENM from production and use to end-of-life processes and finally to the environment, and environmental fate models that describe the behavior within and the transfer between environmental compartments. This review presents the existing material flow and fate models for ENM and evaluates them within a regulatory context. The reliability of the models and their relevance to the regulatory process is discussed, knowledge gaps are identified and recommendations are made about the use of the models for regulation. Some of the available fate models for nanomaterials are built on concepts that are accepted by regulators for conventional chemicals, thus those nanomodels are also likely accepted. A critical issue for all models is the missing validation of PEC values by analytical measurements; however, validation on a conceptual level is possible. It is recommended that the material flow models should also include information on the material characteristics, e.g. form, size distribution, and if the material has already been transformed, because this constitutes very important input information for fate models.

1. Introduction

Environmental exposure models are essential tools for the assessment of contaminants in the environment (MacLeod et al., 2010). These models can aid in the understanding of fate and behavior and are essential to the regulatory risk assessment process. Models are especially important for emerging contaminants such as engineered nanomaterials (ENM) for which much information needed for a proper risk assessment is not yet available from experimental or analytical studies. The specific detection of ENM at trace concentrations in natural samples is in most cases not yet possible (Montano et al., 2014). Currently, a major issue with detecting these particles is that a multitude of nanomaterials are present naturally in environmental systems but only a small fraction are ENMs; various other particles of natural origin are abundant in the same systems. The available analytical tools are not yet capable of distinguishing the natural from engineered nanomaterials at the low ENM concentrations expected in complex environmental matrices (Wagner et al., 2014). In this situation, environmental exposure modeling has been used extensively in recent years to obtain estimates of flows of ENM through the technosphere and into the environment (Dale et al., 2015a; Baalousha et al., 2016). These flows have also been used to calculate environmental concentrations and to model the environmental fate of ENM (Gottschalk et al., 2013). Two very different types of exposure models exist:

- Material flow analysis (MFA) to predict releases from products, fate in technical systems and final release to the environment and
- Environmental fate models (EFM) that describe the fate of the ENM in the environment and distribution within environmental compartments.

Fig. 1 shows the relationship between these two types of models. The general MFA principle is to track material flows throughout the entire life cycle: production; incorporation into products; release from products during use; transport and fate within wastewater treatment plants, waste incineration plants, landfills and recycling processes (technosphere); and finally transfer from technosphere to air, soil, water and sediments (ecosphere). In EFM the input into the environmental compartments is needed as starting point for the mechanistic description of fate processes to predict the form of ENM, e.g. particle size distribution and to quantify the transport between environmental compartments. The EFM models therefore rely on the input of MFA

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http://dx.doi.org/10.1016/j.impact.2017.06.005
Received 28 March 2017; Received in revised form 13 June 2017; Accepted 29 June 2017
Available online 05 July 2017

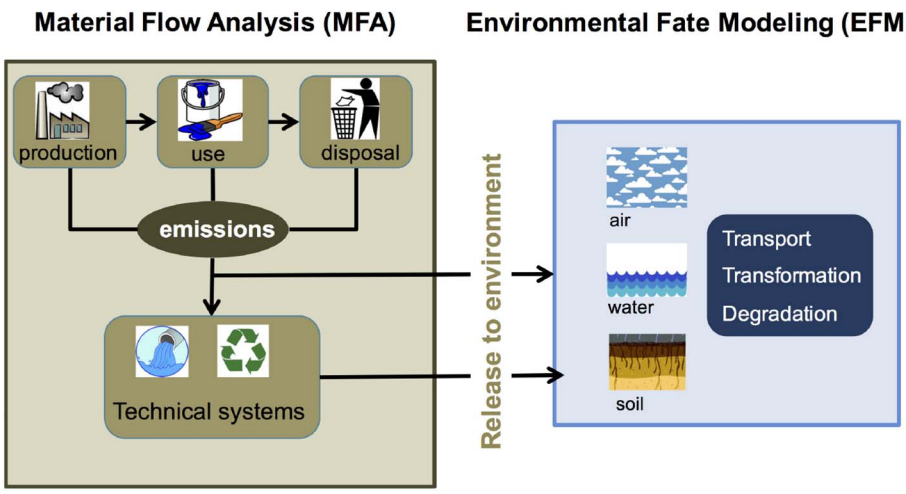

Fig. 1. The relationship between material flow analysis (MFA) and environmental fate models (EFM).

models or simple estimates of input.

The aim of this review is to evaluate MFA and EFM models for nanomaterials within a regulatory context. The published MFA and EFM models are presented and described. A strong focus is set on the description of release of ENM during use as this represents an important source of ENM. The reliability of the models and their relevance for the regulatory process is discussed, knowledge gaps are identified and recommendations are made about the use of the models for regulation.

2. Modeling of flows of nanomaterials over the whole life cycle (material flow analysis)

2.1. Model presentation

MFA models track the materials from production and manufacturing to use, followed by end-of-life stages and finally disposal. At each stage the MFA models identify how much materials are released into different technical or environmental compartment. A decisive step in the MFA models is the distribution of the total produced mass to different product categories. The life cycle of the different products then determines the potential for release. In a majority of cases, the released flows are first entering technical compartments such as wastewater treatment plants or waste incineration plants. The resulting MFA models then predict the final releases to the environment.

Many nanomaterial models rely on a MFA approach, in particular the probabilistic MFA models (PMFA) (Gottschalk et al., 2009; Sun et al., 2014; Caballero-Guzman et al., 2015; Gottschalk et al., 2015; Sun et al., 2015; Bornhöft et al., 2016; Sun et al., 2016) and the LearNano model (Keller et al., 2013; Keller and Lazareva, 2013; Liu et al., 2015) as well as a variety of other models (O'Brien and Cummins, 2010a, 2010b; O'Brien and Cummins, 2011; Arvidsson et al., 2012, 2014a, 2014b; Wigger et al., 2015). Some models are only valid for certain materials in selected applications, while others have the aim to be comprehensive, such as PMFA and LearNano. These models are currently reference models and also rely partially on each other. The main difference is that PMFA is probabilistic and as result produce probability distributions, while LearNano works with scenarios and parameter uncertainty.

The latest development are dynamic MFA models which consider that many ENM are first “locked” in products during their use phase before release and that release can occur over many years (Bornhöft et al., 2016; Sun et al., 2016). This results in a delay in the release which is important in a situation with a rapidly increasing production. This dynamic model called DPMFA is an extension of the PMFA (Gottschalk et al., 2010). In order to calculate the amounts accumulated in environmental sinks such as soils, it is important to have knowledge on historic inputs. The dynamic model therefore also includes a module to estimate past emissions of ENM. This dynamic model is currently the most comprehensive model to provide flows of ENM into the environment. Table 1 presents an overview of the MFA models for ENM that have been published so far, including some of their characteristics and application materials and studies. The table contains for each model the basic paper describing the model as well as all further applications of the respective model.

It is important to distinguish between “the model” and the specific application of the model that has been published. “The model” represents the basic model structure and the mathematical modeling approach, e.g. whether it is probabilistic or deterministic. The application of this basic model structure to a specific case is then determined by the system boundary that is chosen in a specific study and the parameterization. This includes in particular which compartments are included in the evaluation and how the input parameters are obtained. In order to predict the most significant exposures, one needs to have a model case study that contains all input flows and considers all relevant compartments and flows between the compartments. The specific application of a model within a case study therefore needs to be distinguished from the capability of the model itself. It is thus rather the availability of experimental studies that allow the parameterization of a case study than the basic model structure that limits the potential to describe ENM fate and exposure.

While the underlying models are robust, the parameters to run the models might be uncertain. The PMFA/DPMFA models collect all available information and produce probability distributions, thus have a greater likelihood to catch the real situation. The input data with the highest uncertainty are the production volume and especially the distribution of the nanomaterial mass to different product categories – these data are notoriously difficult to get and are mainly based on reports or informal data. Table 2 gives an overview of the basic input data needed for MFA models. This table also presents an evaluation of the data uncertainty on a relative scale. There is a high uncertainty for data that are largely missing and for which no read-across from other data is possible (e.g. product distribution), whereas there are other cases of missing data where estimates can be made based on knowledge of the system (e.g. release during recycling). In several models scenarios are used to deal with the uncertainty in input parameters – often a realistic and a high production/high release scenario are formulated.

The type of input parameters needed in MFA are depicted in Fig. 2. The main type of information that is requested are the transfer factors from one compartment to other down-stream compartments, both technical and environmental. Depending on the place in the life cycle, different types of transfer factors are needed that are based on product-specific or compartment-specific data and that are either nano-specific (e.g. release from products) or are a property of the system (e.g. the distribution of sewage sludge on soils). For some transfer factors, e.g.

Table 1
Overview of published material flow models (MFA) for nanomaterials.

Model name	Reference	Model type	Uncertainty consideration	Covered ENM	Additional applications
PEC-estimation	Boxall et al. (2007)	Single equations	3 scenarios	Ag, Al_2O_3, Au, CeO_2, fullerenes, hydroxyapatite, latex, silica, organo-silica, TiO_2, ZnO	Tiede et al. (2010)
MFA	Mueller and Nowack (2008)	Excel-based MFA	2 scenarios	TiO_2, CNT, Ag	Mueller et al. (2013)
PMFA	Gottschalk et al. (2010)	Probabilistic model in R	Probabilistic	TiO_2, ZnO, Ag, CNT, fullerenes, SiO_2, Au, Fe-oxides	Sun et al. (2014), Gottschalk et al. (2015), Mahapatra et al. (2015), Sun et al. (2015), Wang et al. (2016a, 2016b)
NanoPOLL	O'Brien and Cummins (2010a)	Excel with add-on packages	Probabilistic	TiO_2, Ag, CeO_2	O'Brien and Cummins (2011)
PFA	Arvidsson et al. (2011)	Implemented in Excel	Scenarios	Ag, TiO_2	Arvidsson et al. (2012)
LeanNano	Keller et al. (2013), Liu et al. (2015)	Integrated in RedNano, web-based	High and low estimates, coefficient of variation	TiO_2, SiO_2, ZnO, CeO_2, Al_2O_3, Ag, Cu, Fe, CNT, nano-clay	Keller and Lazareva (2013)
DPMFA	Bornhöft et al. (2016)	Dynamic probabilistic model in Python	Probabilistic	TiO_2, CNT, Ag, ZnO	Sun et al. (2016), Sun et al. (2017)
PMFA Version 1.0.0	SUN (2016)	Probabilistic model in R with GUI	Probabilistic		

Abbreviations: PEC: predicted environmental concentration; MFA: material flow analysis: PMFA: probabilistic MFA; PFA: particle flow analysis; DPMFA: dynamic probabilistic MFA; GUI: graphical user interface.

behavior in technical systems, experimental data are available to directly parameterize them whereas for other transfer factors, e.g. for release, the available experimental data can only be used to guide the derivation of the transfer factors.

2.2. Estimation of releases of ENM to the environment

The quantification of release during all stages of the life cycle is the most important data input which defines exposure in environmental compartments. Although the literature on ENM release is growing (Froggett et al., 2014; Wohlleben and Neubauer, 2016; Koivisto et al., 2017), coverage of exposure scenarios is still limited. Only 20% of the ENMs used industrially and 36% of the product categories involved have been investigated in release studies and only a few relevant release scenarios have been described (Caballero-Guzman and Nowack, 2016). Furthermore, the information provided is rather incomplete concerning descriptions and characterization of ENMs and the released materials. Current MFA studies rely to a large extent on extrapolations, authors' assumptions, expert opinions and other informal sources of data to parameterize the models.

Results documenting releases from consumer products are quite abundant, mostly detailing release from nano-Ag textiles by garment washing and release of TiO_2 during sunscreen use, as reviewed in Mitrano et al. (2015). Whereas some experimental data are available about release from nano-products, it is often difficult to use the results for MFA modeling (Caballero-Guzman and Nowack, 2016). The experiments were often not designed in a way that transfer factors can be estimated over the full lifetime of a product – and this is what would be needed for MFA models. However, the release during use can be very relevant with up to 40% of silver being removed in the first washing of nano-Ag textiles (Geranio et al., 2009; Lorenz et al., 2012); therefore, constituting one of the main release pathways for silver from textiles. For most other consumer articles besides textiles and sunscreens, very little data actually exist (Mitrano et al., 2015; Caballero-Guzman and Nowack, 2016). Release from paints during weathering constitutes another important process that can result in direct release of ENM into the environment from outdoor paints. Several studies have investigated release of TiO_2, Ag and SiO_2 from paints, as reviewed in Mitrano et al. (2015). Again, it is difficult to use the data obtained in these studies to formulate transfer factors that can be used in MFA modeling (Caballero-Guzman and Nowack, 2016). The last category of products where a lot of release data are available are polymer nanocomposites. Most of these studies are mechanistic studies and the results are difficult to incorporate in MFA.

The estimations of release from technical compartments are based on estimated flows into these compartments, combined with transfer factors through the system that are based on experimental data. In these experiments the input into the technical system is known and compared to the measured outflow. By combining different studies ran under different conditions, an average transfer factor or a probability distribution of a transfer factor can be obtained. Transfer factors are only available for certain materials, e.g. for waste incineration plants (WIP) only for CeO_2 and TiO_2 and for wastewater treatment plants (WWTP) for Ag, SiO_2, TiO_2, ZnO and CeO_2. For other ENM the models usually chose the transfer factor of an ENM with similar properties, most based on composition (e.g. TiO_2 is used for other insoluble oxides). The further flows of ENM out of the WWTP are then governed by the disposal of the sludge which varies from country to country. In some countries the sludge is incinerated or landfilled and thus no direct transfer to the environment is possible. In other countries land application of sludge is still allowed and all models agree that this process constitutes one of the main ENM flows to the environment (Sun et al., 2015).

Releases during end-of-life processes have so far received only passing attention (Boldrin et al., 2014). The flows of ENMs into WIP and landfills have been quantified in the existing models, e.g. (Gottschalk et al., 2009; Keller et al., 2013; Mueller et al., 2013; Sun

Table 2
Input data usually required for material flow analysis (MFA).

Parameter	Comment	Uncertainty
Production volume within the system boundary	Directly available or scaled up/down from other regions	Depending on the material the uncertainty is medium to very high
Distribution of mass to product categories	The most critical parameter in MFA	Very high: quantitative data are largely absent
Release from products/applications	Transfer factor needs to be estimated based on release studies or expert knowledge	Real-world studies using real products are mostly missing, therefore quite high uncertainty. Often worst-case assumptions are used.
Transfer factors for technical compartments	Data for WWTP are abundant, for WIP only few available, almost nothing for landfills	Low uncertainty for WWTP and WIP, high for landfills
Transfer factors during recycling	Only considered in some models, no quantitative data available	Uncertainty medium
Transfer factors for environmental compartments	Although transfer between environmental compartments is part of EFM, some MFA models include limited transfers	Uncertainty medium, especially because processes are only considered to a limited extent

Abbreviations: WWTP: waste water treatment plant; WIP: waste incineration plant.

et al., 2014; Heggelund et al., 2016). Depending on the type of ENM, the materials either survive the incineration process intact, are transformed or combusted (Roes et al., 2012). What has so far only received very little attention is the release from these waste-handling processes. One experimental study about the fate of CeO_2 in a WIP is available (Walser et al., 2012; Walser and Gottschalk, 2014) and one report about TiO_2 behavior in a German WIP has recently been published (Börner et al., 2016).

Landfills as final sink are an important compartment where most of the ENM end up (Mueller et al., 2013) but so far almost no work has dealt with possible releases from landfills. Three main types of landfills exist: reactive landfills receiving municipal waste, landfills for residues from waste incineration and landfills for inert materials, e.g. construction waste. Additionally, landfills for hazardous waste exist but so far they have never been considered in nano-modeling. However, hazardous waste is either incinerated or treated with physicochemical methods and the residues are disposed of safely. One experimental study reports the release of nanosized TiO_2 from construction waste landfills (Burkhardt et al., 2015) and the presence of nanosized materials has been investigated in reactive landfills (Hennebert et al., 2013) and landfills for incineration wastes (Mitrano et al., 2017). Since modeling studies have shown that a large fraction of many ENM will end up in landfills, a better understanding of possible releases from the various types of landfills that exist is urgently needed.

Recycling as other important end of life (EoL) process has received almost no attention in flow modeling. The PMFA models considered to some extent flows into recycling but did not model the further fate during recycling processes. One modeling study evaluated the possible releases during recycling (Caballero-Guzman et al., 2015) and these data were then considered in the latest PMFA model application so that also flows out of recycling could be modeled (Wang et al., 2016a).

The waste incineration process not only affects the ENM but also produces fly ash particles that are partially in the nano-range. The mass-based fraction of the fraction below 100 nm was at most 0.07% in one study from Switzerland, the number-based fraction was 5–22% (Buha et al., 2014). Modeling has shown that ENM could represent an important part of this smallest fraction of fly ash (Buha et al., 2014). Also in wastewater the ENM will be present together with natural nanoparticles and also with the same material in conventional form. Sun et al. (2014) have compared modeled ENM concentrations in wastewater to the total concentration of the respective material for TiO_2, Zn and Ag. The total concentrations of the metals are 1–3 orders of magnitude larger than the corresponding ENM.

The direct release to the environment – without passing through a technical compartment – could form a very relevant pathway for environmental exposure. However, whether this pathway is actually of importance depends on the applications of ENM that are currently on the market. In an analysis of possible exposure from various applications, those with a direct release to the environment scored very high on an exposure scale, even if the release was unintended as in the case of abrasion of tires (Nowack et al., 2013). One application with a very direct release to the environment is the use of CeO_2 in diesel fuels (Johnson and Park, 2012). It was concluded that the Ce-concentrations in soils would only marginally increase upon use of CeO_2 in fuels

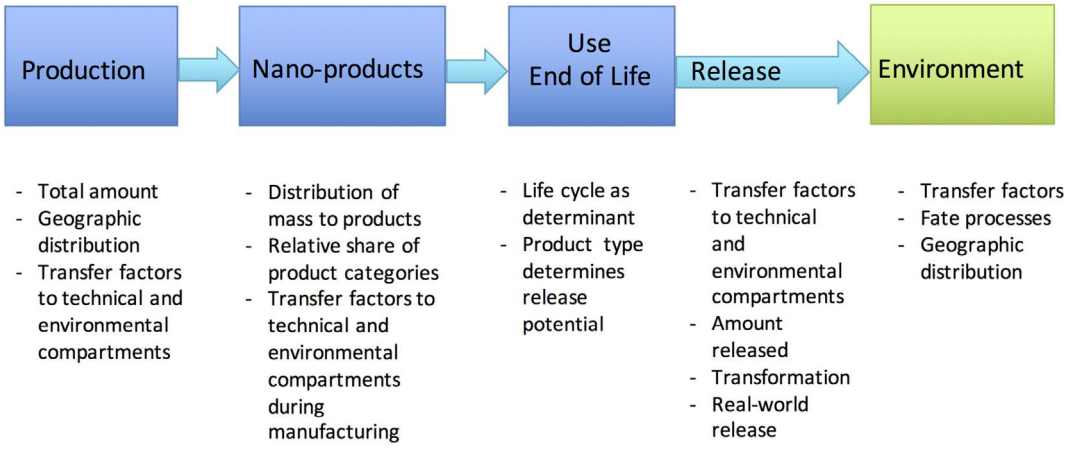

Fig. 2. The different types of input parameters needed for material flow analysis (MFA).

(Johnson and Park, 2012). In addition, the use of diesel particulate filters would eliminate almost all releases to air (Ulrich and Wichser, 2003). The further flows of the trapped CeO_2 would then be determined by the disposal/recycling of the used filters. Several models include in their parameterization direct releases to the environment, for example swimming in lakes after sunscreen application or wear and tear during use. These flows can easily be identified in the mass flows diagrams provided in the articles about the PMFA-model, e.g. (Gottschalk et al., 2009; Sun et al., 2014; Sun et al., 2016).

Applications with intended release, for example soil or groundwater remediation or applications in agriculture, are other areas with high exposure potential. However, currently the use in agriculture is very limited (Gogos et al., 2012; Kah et al., 2012; Kah, 2015) and no model includes it. In the EU pesticide regulation 1107/2009 no nano-specific provisions are included. Therefore, numbers on the use of ENMs as active ingredients, encapsulates or composites are not known, but are currently presumed to be low, if any. An application can be included in a model if the basic input parameters are available, e.g. the tonnage used in this application.

The release of nano zero-valent iron (nZVI) into groundwater clearly constitutes one of the largest point sources of environmental release at the moment (Mueller et al., 2012). However, no exposure models for nZVI are currently available.

It is not possible to give a general conclusion on the most important sources of releases to the environment. The release is determined by the uses of the ENM and for different ENM different uses are important. For some ENM such as TiO_2 the release into wastewater and further with the sludge onto soils is important, however, for others such as carbon nanotubes (CNT) the direct release from abrasion might be more important (Sun et al., 2014). Only an analysis using a life-cycle perspective can identify for which ENM which release pathway is the most relevant.

2.3. Current acceptance by regulators

MFA is a standard method to quantify flows of materials from production to the environment (Brunner and Rechberger, 2004). The MFA-approach has been used by all models predicting flows to the environment, although this is not always explicitly mentioned. EUSES, the European Union System for the Evaluation of Substances (https://ec.europa.eu/jrc/en/scientific-tool/european-union-system-evaluation-substances), also bases the exposure estimation for chemicals on a life-cycle based model, although the term MFA is not used. The general approach to track the flows of chemicals from production over manufacturing and use to disposal can be implemented in various ways. MFA is the most formalized and complete approach but simpler versions adhere to the same concept. The MFA concept is therefore well accepted by regulators in the registration of chemicals to quantify the inputs into the model. The MFAs of ENM are by no means different to MFA for conventional chemicals. There are no nano-specific parameters used in MFA models. All parameters either just track the mass flows from production to use and disposal, and quantify the mass released without any characterization. Also the removal during WWTP for example is based on pilot-scale experiments, using an observed aggregated parameter that integrates all possible processes during the treatment that has no “nano-specific” issues.

In the current EUSES system for chemicals, (https://ec.europa.eu/jrc/en/scientific-tool/european-union-system-evaluation-substances), uncertainty in production/release is not really considered. Single values are often used (best guess/worst-case). However, there is a push towards probabilistic assessments in environmental risk assessment (US EPA, 2014).

3. Modeling the fate in the environment (EFM models)

Pure MFA models that quantify only the release to the environment do not model the further fate of the materials in the environment. For this, we need environmental fate models (EFM) that use a mechanistic description of fate processes to model the behavior in environmental compartments. In MFA only transfer factors are used that describe the amounts of mass flowing from one compartment into another. These factors are based on observations (e.g. measurement of inflow/outflow to a wastewater treatment plant) but don't model any processes. Nevertheless, many nano-MFA models do provide environmental concentrations, e.g. (Gottschalk et al., 2013; Keller et al., 2013; Sun et al., 2014). In these models the flows to the environment are simply transformed to environmental concentrations by assuming standard sizes of environmental compartments and complete mixing. This approach is based on the concept as given in the European Chemicals Agency (ECHA) guidance for chemical risk assessment (ECHA, 2010), therefore constituting an accepted way to derive average environmental concentrations, the so-called PEC values (predicted environmental concentrations). These extended MFA models are therefore a simplified version of an EFM model.

Two reviews about the fate modeling ENM in natural systems have recently been published (Dale et al., 2015a; Baalousha et al., 2016). These reviews discuss the trade-offs between the complexity of the models and the availability of data for aquatic, terrestrial and bio uptake models. Both articles make recommendations for future directions and research priorities and conclude that the major aim should be placed on focusing on parameterizing the models and generating lab and field data to validate the models.

EFM models can be separated into three tiers:

- Tier 1: equilibrium models
- Tier 2: steady-state models
- Tier 3: dynamic and spatially resolved models

Almost no EFM based on equilibrium models have been formulated for ENM. However one example is a model describing removal of ENM during waste water treatment that is based on equilibrium partitioning coefficient K_d (Hendren et al., 2013). Most EFM models include agglomeration reactions that cannot be modeled with an equilibrium approach (Praetorius et al., 2014b).

A steady-state approach (Tier 2) is often used to calculate a situation where all input and output flows (e.g. sedimentation) are balanced. In truly dynamic models the influence of fluctuating input parameters can be quantified over time. When coupled to spatially-resolved models, the behavior of ENM over time and within a watershed can be predicted (Tier 3). Such information may be not needed for the European legislation on “Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)” with its generic approach but may be helpful for further applications, e.g. within the Water Framework Directive.

The first fate model for ENM was published by Praetorius et al. (2012). At that time the model could not be parameterized due to a lack of experimental data on heteroagglomeration and only scenarios were given. Since then several complete nano-EFM models were published: the SimpleBox4Nano (SB4N) (Meesters et al., 2014), based on the SimpleBox model used in REACH/EUSES for conventional chemicals, the nanoDUFLOW model (Quik et al., 2015) which is spatially explicit and includes river flow, and the RedNano model (Liu et al., 2015) that is a further development of the MendNano model Liu and Cohen, (2014). In RedNano and nanoDUFLOW the transfers between compartments are modeled by rate constants for chemical and physical processes. The models include agglomeration, heteroagglomeration, sedimentation, dissolution and transformation reactions in addition to transport processes affecting the ENM bound to particulate matter. Dissolution and transformation are by no means nano-specific and models are available for metals and minerals, only the parameters describing the reactions for the nanoparticles need to be derived.

A spatially-resolved fate model for a river system considering changes in stream flow and sediment transport has been developed for

Table 3
Overview of published environmental fate models (EFM) for nanomaterials.

Model	Reference	Model type	Main fate processes	Uncertainty	Applied to
Rhine model	Praetorius et al. (2012)	Spatially explicit, watershed	Heteroagglomeration, sedimentation, sediment transport	Scenarios	TiO_2
SimpleBox4Nano	Meesters et al. (2014)	Compartment-model, steady-state	Heteroagglomeration, sedimentation, dissolution	None	TiO_2
MendNano	Liu and Cohen (2014)	Compartment-model, dynamic	Heteroagglomeration, sedimentation, dissolution	Scenarios	TiO_2, SiO_2, ZnO, CeO_2, Al_2O_3, Ag, Cu, Fe, CNT, nano-clay
WSM/WASP7	Dale et al. (2015c)	Spatially explicit, watershed	Sedimentation, dissolution, transformation, sediment transport	None	Ag, ZnO
RedNano	Liu et al. (2015)	Compartment-model, dynamic	Heteroagglomeration, sedimentation, dissolution	Scenarios, probabilistic assessment possible	TiO_2, SiO_2, ZnO, CeO_2, Al_2O_3, Ag, Cu, Fe, CNT, nano-clay
Rhone model	Sani-Kast et al. (2015)	Spatially explicit, watershed	Heteroagglomeration, sedimentation, sediment transport	Cluster analysis	TiO_2
SimpleBox4Nano	Meesters et al. (2016)	Compartment-model, steady-state	Heteroagglomeration, sedimentation, dissolution	Probabilistic	TiO_2, ZnO, CeO_2
nanoDUFLOW	Quik et al. (2015), de Klein et al. (2016)	Spatially explicit, watershed	Heteroagglomeration, sedimentation, dissolution	Scenarios, probabilistic	Ag, CeO_2

ZnO and nano-Ag (Dale et al., 2015c). Other spatially-explicit models have been published that distribute the emitted mass of ENM to different regions and river networks but include only a limited description of environmental processes (Gottschalk et al., 2011; Dumont et al., 2015; Sun et al., 2015). Table 3 below presents an overview of the published EFM models for nanomaterials. Some "model families" can be recognized such as the Rhine and Rhone models that build on each other or the MendNano and RearNano models. SimpleBox4Nano is listed twice, recognizing the significant advancement in the way the model is used in a probabilistic way in the second iteration.

3.1. Fate predictors

Important fate predictors for conventional chemicals are vapor pressure and the octanol-water partitioning constant K_{OW}. These predictors are not used in any nano-model, since the discussion on their usefulness for fate modeling of ENM has been closed (Westerhoff and Nowack, 2013; Praetorius et al., 2014b). The discussion is ongoing whether a K_d value describing distribution between a solid and solution makes sense or is useful for ENM (Praetorius et al., 2014b; Cornelis, 2015; Dale et al., 2015b). However, none of the models described in Table 3 uses such a parameter.

There is still an open discussion on what is the best way to measure the heteroagglomeration. The fate models rely on colloid behavior and on the attachment coefficient (α_{hetero}) that needs to be determined for each ENM and natural particle type. There have been some approaches published in the last years how to measure this parameter (Barton et al., 2014; Praetorius et al., 2014a; Quik et al., 2014a) and to apply the results in fate models (Meesters et al., 2014; Praetorius et al., 2017).

In the current fate models there is a common agreement about how to consider environmental fate of ENM: there is no discussion anymore on which parameters to base the modeling. It is clear that heteroagglomeration is the main process to include, with the attachment efficiency as main parameter. The way in which this is solved in the models differs. There are even models that assume all ENM to be bound completely to larger natural particles – the fate of the ENM is then determined by the fate of the larger particles (Dale et al., 2015c; de Klein et al., 2016). The limitation of such an approach is that no information can be gained on the free nanoparticle concentration that, even if small, might be an important species for the interaction with biota. Other important processes that are included in the models are dissolution and transformation reactions.

3.2. The assumption of equilibrium conditions

There is an ongoing discussion among scientists about the rigorousness with which the dynamic nature of ENM interactions should be incorporated into models and which fate descriptors should be used (Praetorius et al., 2014b; Cornelis, 2015; Dale et al., 2015b). Both SB4N and RedNano don't use equilibrium constants but model (homo)agglomeration, heteroagglomeration and sedimentation as dynamic processes. However, SB4N is modeling an equilibrium condition where the inputs into the system equal the outputs such that steady concentrations are achieved. This is different in RedNano that can model the ENM concentrations over time, e.g. after a perturbation of the system or with intermittent rain events. The SB4N approach follows the SimpleBox model that is accepted by ECHA for the risk assessment of standard chemicals. The SB4N therefore provides results that are comparable to those in the standard chemical risk assessment and delivers results for a hypothetical "equilibrium" state that does not exist but is representative for a standard world. A dynamic and spatially resolved model is suitable for in-depth investigations in specific regions and incorporating dynamic changes over time and would follow as a next level of assessment when evaluating a specific production site or a river catchment.

3.3. Predictions made by environmental fate models

Once the ENM have reached the environment, there are two major sinks: soils and sediments and all models agree on this. The transfer from water to sediments is driven by the strong interactions of ENM with suspended matter, resulting in efficient scavenging and sedimentation (Quik et al., 2012; Praetorius et al., 2014a; Quik et al., 2014b; Dale et al., 2015c). None of the existing models includes a modeling of the transport in soils or the subsurface but this is also not asked for in the current chemical risk assessment. Recent reviews have shown possibilities of how transport models in porous media could be advanced (Goldberg et al., 2014; Goldberg et al., 2015).

Both the SB4N (Meesters et al., 2014) and the RedNano (Liu et al., 2015) fate models only include dissolution as transformation process. No transformation into other phases or other aging processes are included (except if heteroagglomeration is also considered as an aging process – this process is included in both models). The stream-flow model by Dale et al. (2015c) includes chemical transformations; thus it's the only model so far that considers this fate process but the model is specific to two ENM (nano-Ag and ZnO). The need for inclusion of fate processes in EFM has been identified but quantitative experimental data that can be used to parameterize the processes are still largely missing (Dale et al., 2015a; Baalousha et al., 2016).

The fate models provide data on the size distribution of the ENM and the distribution to larger particles (heteroagglomerates). With respect to the properties of the transformed ENM, the models therefore currently provide only limited information. Dissolution removes the ENM and transforms it into a dissolved metal that then has to be considered in the context of metal risk assessment. However, a comparison between total metal concentrations in environmental compartments and the contribution that ENM can make, revealed that the ENM do not influence to any significant degree the total concentrations of metals (Sun et al., 2014).

3.4. Current acceptance by regulators

The EFM models are clearly very relevant in a regulatory framework where the estimation of environmental concentration (PEC values, predicted environmental concentrations) is a crucial step in the risk assessment process (ECHA, 2010). PEC values are needed and are either estimated by simple algorithms or modeled using MFA and EFM models. Those models that determine PEC values based on the procedures used for standard chemicals (ECHA, 2008b) are therefore currently preferred in a regulatory context. This applies especially to SimpleBox4Nano that is an adaptation of SimpleBox, the model accepted by ECHA to predict environmental behavior. Because SimpleBox is unable to make any prediction for nanomaterials, it is either necessary to use the nano-adapted SB4N or another more advanced MFA/EFM approach.

The SB4N calculates a steady-steady concentration at equilibrium. This is the same approach as used by ECHA for the registration of conventional chemicals and is thus accepted by regulators. One can therefore assume that SB4N will be accepted by regulators because they are familiar with the underlying concept and because the nano-specific reactions that are incorporated are widely accepted in the scientific community. The SB4N approach identifies the ultimate environmental sinks at equilibrium, even if the time scale needed to reach equilibrium can be millions of years (Meesters et al., 2016). When more detailed information is needed, the application of models which provide time- and spatially resolved information should be accepted by regulators.

4. Reliability, availability and validation of the models

All models are based on three parts: the concepts, the codes and the input parameters. All publications about models always suffer the same problem that the underlying concepts can easily be described but that the codes are actually the basis. However, without a well-written manual, codes are often difficult to understand if they are not developed with the aim to be published – and the current codes are mainly developed within research programs and not with the intention to be published. Two models are available online: RedNano (http://nanoinfo.org) and SB4Nano (http://www.rivm.nl/SimpleBox). The code of the DPMFA model can be downloaded from a Python code repository (Bornhöft et al., 2016). The other models are not freely available and have so far not been used outside a scientific context. Input parameters are normally given as extended Supporting Information but the way the input parameters are obtained is sometimes unclear (especially for MFA models) where the transfer factors are often the result of best guesses or based on qualitative expert knowledge.

All current models have the problem that the PEC values that are the main outcome of the models cannot be validated so far (Nowack et al., 2015). Mathematical models of environmental systems always require experimental validation by analytical data, either to prove that the model is accurately capturing the main components and reactions of the system or to show that significant deficiencies in the model still exist. Validation means determining the extent to which the model results are accurate representations of the real world by comparison with measurements. Given the many assumptions that current models for ENM are required to make, performing a model validation is clearly appropriate.

However, analytical methods need to be available for a model validation. A variety of different nanomaterials are present in the environment, but natural nanoparticles outnumber the engineered nanomaterials. The analytical methods currently available are not yet able to distinguish natural from engineered particles at trace concentrations in complex environmental matrices. No validation of modeled concentrations is therefore possible at the moment. However, both modeling studies and analytical data are able to provide an orthogonal view on nanomaterials (Nowack et al., 2015): modeling is able to yield estimates of the presence of ENMs in different environmental compartments while analytical methods can provide data on the physical characterization of ENMs in these systems with hints towards the total nanomaterial concentration (sum of natural and engineered particles). While we need to make strides to improve the two approaches separately, using the results for both approaches together in a mutually supportive way will advance the field of ENM risk assessment.

However, even in the absence of a model validation by analytical measurements, the models can still be validated on a conceptual level, which means showing that the underlying assumptions of the conceptual model and the mathematics are correct (Sargent, 2011). Such models that could not be fully validated are useful for providing either prospective estimations or because they allow statements to be made about current exposure even in the absence of analytical data. Most of the models contain, at least in some of the parameters, worst-case assumptions (e.g. don't consider sedimentation for the prediction of surface water concentration) and the PEC values therefore represent in many models worst-case scenarios. The methods used in most of the models are based on the procedures formulated in the chemicals risk assessment (ECHA, 2008a) and thus the PEC values derived by them are based on methods that are accepted by the regulatory authorities.

In a validation of the processes, the underlying physical and chemical processes are validated, which means, that model results are compared to experimental or analytical measurements. If an assumption of the model is that ENM are associated with sediments (Dale et al., 2015c) or suspended particles (Praetorius et al., 2012), a validation of sediment or particle behavior can serve as a validation for the prediction of the fate of ENM. This is the approach that de Klein et al. (2016) used to validate the nanoDUFLOW model.

5. Methodological and knowledge gaps

There is one issue central to all models: experimental data to

parameterize the models are scarce or even missing. For MFA models the most critical parameters are the distribution of the produced mass to different product categories and the quantification of release. For EFM models the parameterization of the agglomeration is a key issue. Whereas there are numerous studies on homoagglomeration available, there are very few on heteroagglomeration which is the most relevant process in natural waters. Chemical transformation of nanomaterials, except dissolution, is so far not considered in any EFM model although it might be very important for certain materials. Several ENMs (e.g. Ag, CeO_2, CuO and ZnO) are highly reactive and may undergo different transformation reactions, e.g. redox reactions, dissolution and interaction with other ions and re-precipitation as new nanomaterials. Systems which initially contain no nanomaterials but only bulk forms of a given metal, may eventually produce nanoparticles similar to ENM over time (Ma et al., 2014; Mitrano et al., 2014). This shows us both that, i) ENMs cannot be assessed in their pristine composition in the environment, and ii) that many conventional compounds can also exist at the nanoscale in the environment.

EFM models also need input data for size distribution of the ENM. So far the models use some standard values - however, nobody knows what the size distribution is of those ENM that actually enter the environment. All current MFA and EFM models assume that the form of ENM released is the same as the pristine form – however we know that this is mostly not the case. The released ENM are often present as "chunks" of the matrix with embedded ENM and not as free ENM (Froggett et al., 2014). Nobody has yet tried to include this real size distribution or characterization of released particles in any model due to a severe lack of experimental data to parameterize the models (Caballero-Guzman and Nowack, 2016).

Another issue with all models is that they consider a generic ENM, for example "TiO_2" irrespective of the mineralogical form, coating and functionalization. Especially for MFA models almost no quantitative information about production or use of different forms of ENM is available. Without these flows the EFM models are only able to calculate scenarios and not the actual concentrations. A first step into separating generic ENM flows has been done for TiO_2 where the flows for photocatalytic and photostable TiO_2 were separated into two MFA-models (Gottschalk et al., 2015).

6. Recommendations

6.1. MFA models

In MFA, the type of model that is used is less important than the setting of the system boundaries and the quality of the input data. The main missing data are the production/use volume in a certain region and especially the distribution of this mass to the different product categories. A major issue here is the definition of a "nanomaterial" that is used in a data source. Many ENM also exist in a similar form as bulk or pigment material (e.g. TiO_2, SiO_2, iron oxides, aluminum oxides). Depending on the source, production volume estimations can therefore vary a lot if the underlying definitions what a nanomaterial is are different. Because many of the production volume estimates are based on "grey sources", e.g. reports with unknown source of the raw data, it is difficult or even impossible to identify what kind of material is actually considered in a source. Even using a mandatory reporting scheme such as the French registry (ANSES, 2013) does not solve this problem. The production/import volume reported for nano-silica for example is the highest of all nanomaterials, caused by the inclusion of colloidal and fumed silica in the values – materials that have been in use since many decades and were usually not considered as "engineered nanomaterials" (Bosch et al., 2012). The use of a specific definition can therefore affect the production volume enormously if for example another source does not count colloidal or fumed silica as an ENM. The production volume as primary input parameter is of course enormously affecting any modeling of actual ENM concentrations in the environment. There are some ENM such as fullerenes or CNT that are novel materials and where it is clearer whether a certain material is an ENM or not. For these materials the spread of reported production values is much smaller (Piccinno et al., 2012). Thus, it is recommended to use only sources for production/use data that have been collected using the standard EU definition or – in the best but improbable case – report the actual size distribution of the produced amount. It is also recommended to use probabilistic assessments to incorporate the uncertainties in these values into the environmental risk assessment.

Quantitative information on the use of ENM products would be even more important to obtain than production volumes because the life cycle of the products determines the potential for release. Whereas qualitative information is easily available ("Nanomaterial x is used in applications X, Y and Z"), the quantitative information about the distribution of the total mass to different product categories is largely absent. It is urgently needed to obtain more accurate data on this mass distribution based on products and applications that are currently on the market. It would also be important to get information that goes beyond consumer products such as those in the NanoDB (Nanodatabase, 2015) and also include industrial uses or non-advertised applications in products. A life-cycle based view on the ENM flows is needed and the life cycle starts with production and use – and thus quantitative knowledge on uses of ENM has to be at the start of any ENM risk assessment.

The MFA models should also include information on the material characteristics, e.g. form, size distribution, and if the material has already been transformed. So far some models do not include any transformation but just assume that for example "nano-Ag" remains a "nano-Ag" throughout product use, release into technical systems and finally release to the environment (Keller et al., 2014; Liu et al., 2015). This is of course an oversimplification and the mass flows should be separated into different forms of the ENM. The PMFA model e.g. (Gottschalk et al., 2009; Sun et al., 2014; Sun et al., 2015) include dissolution of ENM as flow into an elimination compartment, also sulfidation of nano-Ag or nano-ZnO is considered as a removal during wastewater treatment. No other transformations during use or release are considered in any model. It is recommended that in addition to basic flow data, MFA models should also include information on the chemical and physical characteristics of materials that are released and transported through the compartments of the system.

6.2. EFM models

Because the input of fate models is determined by MFA, an improved characterization of the ENM flows in MFA models will enable also a much better parameterization of the EFM models. This is especially important with respect to the initial size distribution of the ENM that is crucial for predicting the (hetero)agglomeration behavior. An intensification of the collaboration between MFA and EFM developers is therefore highly recommended with respect to the parameters that are needed in one model (EFM) and those that are practically possible to estimate (MFA). The current input to EFM that consists solely of a mass of ENM per unit time needs to be further specified:

- Distribution to already dissolved ENM, ENM contained in matrix fragments, free ENM, and transformed ENM
- Size distribution of all forms
- Separation of a generic ENM, e.g. "TiO_2" into different forms with different chemical identities or coatings (if this affects their fate processes).

The parameters needed for EFM modeling, e.g. dissolution rates or heteroagglomeration constants, need to be provided by experimentalists in a form that is useful for the models. This aspect should also be considered during standardization of methods for these parameters. An important issue is that experiments should be conducted

under conditions relevant for real environmental systems, e.g. with respect to the concentration of ENM or the ratio ENM/natural organic matter or ENM/natural particles.

Because a true validation of modeled values by analytical studies is not yet possible, the EFM models should be validated in controlled small-scale tracer studies using mesocosms (Auffan et al., 2014; Baalousha et al., 2016). In order to distinguish the ENM from natural particles, labelled ENM could be used in small-scale field experiments. These experiments would allow the validation of the basic processes of the models and increase the acceptability of the models in a situation where the model predictions about PEC values cannot be validated.

It is also recommended that regulators should accept models that go beyond equilibrium conditions and are able to provide time- and spatially resolved information, features that are important to describe the fate of reactive ENM in natural systems.

Acknowledgements

This research was funded by the EU H2020 project ProSafe (promoting the implementation of Safe by Design), grant agreement 646325. The author thanks Klaus Günter Steinhäuser and Phil Sayre for critical comments and input on earlier version of this manuscript.

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