Directions in QPPR development to complement the predictive models used in risk assessment of nanomaterials

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Words: 6424

Tables: 5

Figures: 1

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Abstract

There is an increasing need for predictive risk assessment of nanomaterials (NMs) using methods that are rapid, accurate and resource efficient. To fulfill this need, the development and use of Quantitative Property Property Relationships (QPPRs) for estimating the hazard of NMs and NM-related parameters in exposure modelling seems eminent. In this study, we analyze a selection of models used for hazard and/or exposure assessment of NMs. This analysis was done by identifying all the NM-related properties used in these models related to three categories of data: (i) Intrinsic properties specific to the NM, matrix or experimental conditions, (ii) Extrinsic NM properties related to interaction between the intrinsic properties and (iii) Measured hazard or exposure data. This analysis is combined with the current state of QPPR development to recommend further development of QPPRs for predictive risk assessment of NMs. In particular, the use of descriptors related to the interaction between a NM and its surroundings, e.g. the attachment efficiency is proposed.

Key words: nanomaterial, modelling, in silico, QPPR, QNAR, risk assessment

1 Introduction

With the increasing rate of new nanomaterials (NMs) being developed and applied, an increase in knowledge gaps is expected for assessing the hazard, exposure and risk of NMs to the environment and to human health. NMs are expected to be applied in a vast number of variations in e.g. size, shape, coating and chemical composition. It is not feasible to generate information for every nanomaterial on the routes of exposure and uptake, and potential bioaccumulation in biota and in the human body. In addition, generating information on the main interactions with biological systems, requiring animal testing, may be regarded as unethical in terms of animals use and wasteful in terms of resource use (Russell and Burch, 1959). Therefore, it is important to develop *in silico* approaches to aid in the prediction of NM safety based on their physico-chemical properties. *In silico* methods traditionally refer to the application of computational modeling techniques for predicting the activity or effects of a chemical based on its chemical structure (Reisfeld and Mayeno, 2012). This includes Quantitative Structure-Activity Relationships (QSAR) which are more widely used in pharmacology (Dearden, 2003; Fujita and Winkler, 2016), and are already finding application in the safety regulation of molecular or ionic substances (European Commission, 2006; ECHA, 2008). QSARs have already been successfully used in relating structural characteristics to chemical properties and biological effects of molecular substances in order to fill data gaps (Chen et al., 2014; Singh et al., 2014; Modarresi et al., 2007). According to REACH, data derived from QSARs may support the waiving of laboratory testing or serve as a trigger for proposing further testing or used instead of testing data when certain required conditions are met (ECHA, 2008). A well-known example in this respect is the *in silico* approach used in the exposure models that are included in REACH, allowing to predict the solids-water partition coefficient on the basis of the octanol-water partitioning coefficient (K_{ow}) of organic compounds in combination with the fraction organic matter (f_{oc}) of solids (Sabljić et al., 1995). Similarly, the K_{ow} can be used as a descriptor to calculate the acute toxicity (LC50) of certain compounds for mice (Dearden, 2003).

These relationships, although strictly not addressing 'activity' in the pharmacological sense, are usually named QSAR; more properly, they should be named QSPR (Katritzky et al., 1997) or QPPR (de Jongh et al., 1997), Quantitative Structure-Property and Quantitative Property-Property Relationships, respectively. For nanomaterials, such QSARs, QSPRs or QPPRs are still in the early stages of development, and are often named Quantitative Nanostructure-Activity Relationship (QNAR) or nano-QSPR; these include advanced statistical methods using machine learning (González-Durruthy et al., 2017). In this paper, we will use the term QPPR, which relates to all kinds of predictive relationships that use nanomaterial properties as descriptor. To date, a number of attempts have been made to correlate the characteristics of NMs to their biological responses

(Tantra et al., 2014; Raies and Bajic, 2016; Chen et al., 2017; Sizochenko and Leszczynski, 2017). Those reviews showed the tantalizing possibility that the QPPR method may indeed be feasible and useful in predicting the biological activity profiles of novel NMs. However, it also revealed that nano-QPPR is now still in its infancy and further challenges in this field need to be overcome. One issue standing out on this background relates to the comprehensive representation of NM structures. As known, NMs often exist as populations of materials varying in structural characteristics, e.g. composites, sizes, shapes, functional groups. The structural ambiguousness of NMs makes it difficult for experimentalists to provide precise information on NM characterization which consequently hinders the calculation of representative descriptors for NMs (Tamm et al., 2016).

Another issue of importance in this context concerns the dynamics of NMs in media. NMs often strongly interact with constituents in the medium and undergo dramatic changes to their surface properties, and dissolution and aggregation behavior (Winkler, 2016). These changes consequently alter the mobility, bioavailability, and ultimately the toxicity of NMs. Therefore, in some cases the toxicity information of NMs can be poorly correlated to the NMs' characteristics without considering the dynamics of NMs in the media. Thus QPPRs, predicting toxicity, based on initial structural features of NMs are now also extended to incorporate experimental descriptors like zeta-potential (Fourches et al., 2010; Liu et al., 2011; Singh and Gupta, 2014) and aggregate size (Sayes and Ivanov, 2010; Sizochenko et al., 2014; Pan et al., 2016). The fact that these dynamics play a role in NM risk assessment was previously made clear in several studies focused on environmental exposure assessment (Westerhoff and Nowack, 2013; Cornelis, 2014; Hendren et al., 2015a; Baun et al., 2017). These studies suggest the use of empirical parameters for predicting risk, which include the effects of experimental conditions, such as pH, ionic strength and Natural Organic Matter content. Although several possibilities exist, an early study indicated that global descriptors for NM fate and transport need to include information on at least these experimental conditions (Westerhoff and Nowack, 2013).

Just as for molecular or ionic chemical substances, other methods than QPPRs are available as well for predicting the safety of NMs. These alternatives include mechanistic models, tools which implement these models and overarching frameworks (Hristozov et al., 2016; Liguori et al., 2016; Sanchez Jimenez et al., 2016; Baun et al., 2017; Boyes et al., 2017; Nowack, 2017). These methods range from models based on commonly applied regulatory accepted approaches, predominantly in the area of exposure assessment, to more novel approaches such as used for hazard banding. The aim of all these tools, models and frameworks is to reduce the burden of testing NMs case by case and to focus on predicting risks based on the physico-chemical properties of a NM and on its application and use. The tools and models have NM properties as input parameters. Often the parametrization of the models is based on assumptions related to the processes that are deemed relevant based on the mechanistic understanding of the system and more pragmatic choices, e.g. based on data availability. This leads to differences but also to commonalities in processes and parameters used between the currently available models. In this respect the ‘age’ of a model is also an issue as it takes a considerable effort to keep them up to date with the most recent mechanistic understanding, with newer versions being developed almost continuously (Hristozov et al., 2016).

The key question with regard to the applicability of QPPRs in NM specific risk assessment is how QPPRs can be used to predict model parameters instead of requiring empirical data for each unique NM. To answer this question, we analyzed a selection of currently available mechanistic models and their parametrization related to nanomaterial properties. As such, we did not aim to include an exhaustive review of all available tools, models and methods for risk assessment, but we intended to include as many processes and parameters deemed relevant for risk assessment in order to provide a novel insight on the future of predictive risk assessment and the use of *in silico* methods in combination with mechanistic modelling.

The analyzed models predict hazard and/or external and internal exposure concentrations for humans and for the environment. For hazard assessment, only a few hazard banding tools could be analyzed as this is still almost solely based on (eco)toxicity testing. Although in hazard assessment other developments and discussions play an important role in reducing animal testing (e.g. in vitro-in vivo extrapolation), our analysis focuses on available hazard banding tools and *in silico* methods.

In the analysis of model parameters and QPPR descriptors a classification is introduced using three categories loosely based on the strategy for nanomaterial risk forecasting as presented by Hendren et al. (2015a), see Figure 1. The first category consists of the intrinsic properties of either the NM, the matrix or the (experimental) conditions of the system. The second, affected by the first, are the extrinsic NM properties that are based on the interaction of NMs with their surrounding matrix and the conditions affecting that system, e.g. a process rate constant or the attachment efficiency. The hazard concentrations (no effect, effect or lethal concentrations) or exposure concentrations (measured or otherwise estimated) make up the third category. These hazard and exposure concentrations are the regulatory basis for assessing risks. The division into these categories is used in the discussion and recommendations to assist in finding better descriptors for use in development of QPPRs and in silico methods with a basis in empirical data. For that reason the subcategorization of the intrinsic properties, relates to the fact that this metadata should be reported together with the main experimental outcome (Marchese Robinson et al., 2016). This is because the intrinsic NM, matrix and experimental system properties inherently affect the extrinsic NM properties and eventually risk, in this sense the categorization is hierarchical (Figure 1). For example, an intrinsic NM property is size, an intrinsic matrix property is pH or ionic strength and an intrinsic experimental condition is temperature or mixing rate, these likely affect an extrinsic NM property such as the dissolution rate.

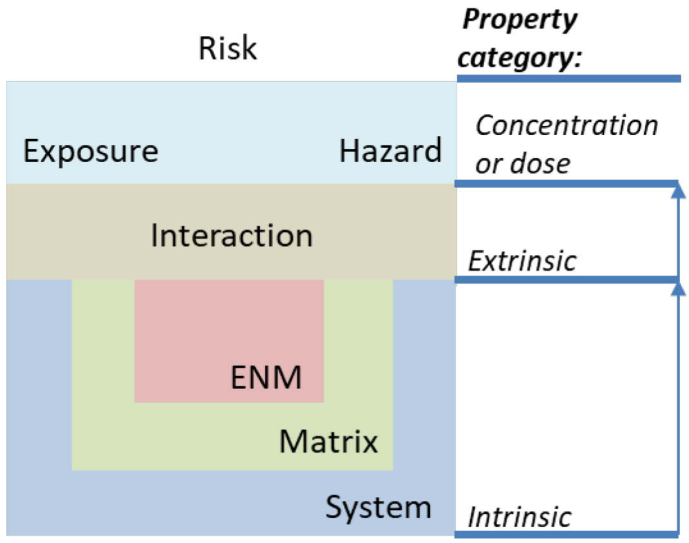

Figure 1. Schematic representation of property categories and types of data required for predicting the risk of engineered nanomaterials (NMs) based on quantitative relationships. These are (i) intrinsic properties of the ENM, the matrix and the overall experimental System, (ii) Extrinsic properties that are dependent on the interaction between ENM, Matrix and System conditions. (iii) Exposure and hazard concentrations used for risk assessment.

2 Nanomaterial related properties in environmental exposure models

Several environmental exposure models have been developed describing transport and transformation processes of nanomaterials (Praetorius et al., 2012; Liu and Cohen, 2014; Meesters et al., 2014; Dale et al., 2015a; Quik et al., 2015; Garner et al., 2017). We have analyzed the processes reported in these fate models specifically affecting NM transport or transformation, to evaluate the dependency of these models on intrinsic NM properties or extrinsic NM properties related to interaction with the intrinsic matrix or system conditions (Table 1). Although numerous properties affect NM fate, not all of them are related to intrinsic or extrinsic NM properties (Table S1 in supporting information). For example, the description of dry and wet deposition and resuspension of aerosols is mainly based on atmospheric characteristics such as the rain rate, wind speed and aerosol properties (Nho-Kim, 2004; Wang et al., 2010). Runoff from soil to water and leaching out of the soil are processes primarily related to soil characteristics and the rain rate (Renard et al., 1997). In the aquatic compartment, sedimentation and resuspension can also be considered processes already taken into account in multimedia modelling of conventional chemicals (Hollander et al., 2016). The process rates are thought to be largely based on the characteristics of the sediment and natural suspended particulate matter characteristics rather than on properties of the NM (Quik et al., 2012; Dale et al., 2015b).

In practice, the effects that nanomaterials have on these processes cannot be fully neglected. It is clear from experimental and modelling studies that hetero-agglomeration between soil, sediment or suspended particles and NMs is an important process affecting their transport (Praetorius et al., 2012; El Badawy et al., 2013; Quik et al., 2014; Therezien et al., 2014; Bouchard et al., 2015; Quik et al., 2015; Ghosh et al., 2016). The mechanistic approach to including this process in models is to estimate the hetero-agglomeration rate, which is dependent on the hetero-agglomeration rate constant, which equals the product of the collision frequency and attachment efficiency (also called attachment affinity or attachment factor, and α) (Lyklema, 2005). There are theoretical approaches to calculate these properties (Lyklema, 2005; Petosa et al., 2010), but they mostly apply to relatively simple colloidal systems, e.g. not taking into account more complex behavior due to the presence of natural organic matter or protein corona's. For this reason the hetero-agglomeration rate or attachment efficiency is mostly measured empirically (Westerhoff and Nowack, 2013; Barton et al., 2014; Garner et al., 2017).

In addition to hetero-agglomeration affecting NM transport, the NMs are transformed into a new form, being the hetero-agglomerate. Several other transformations of NMs are deemed relevant in the natural environment, such as changes in the surface chemistry, disintegration due to chemical reactions and dissolution (Dale et al., 2015a). However, only dissolution and sometimes an overall process rate for additional degradation processes are included in the current models (Table 1).

Table 1. The nanomaterial related parameters used for the reported parameterization methods commonly applied in nanomaterial fate models: Praetorius (Praetorius et al., 2012), MendNano (Liu and Cohen, 2014), SimpleBox4nano (Meesters et al., 2014), NanoDUFLOW (Quik et al., 2015) and NanoFate (Garner et al., 2017).

Fate process	Model	Reported parametrization	Nanomaterial related properties
Dry deposition	MendNano	Theory for interception due to surface resistance combined with Stokes' Law	Size and density
	SimpleBox4nano	Theory for interception due to aerodynamic and surface resistance combined with Stokes' Law	Size and mass
	nanoFate	Stokes' law	Size and density
Wet deposition	MendNano	Below cloud rain scavenging ratio	No parameter, defined by size class
	SimpleBox4nano	Rain collection efficiency calculated from Brownian, Interception and gravitational impaction	Size and density
	nanoFate	Below cloud rain scavenging ratio	No parameter
Sedimentation	Praetorius, MendNano SimpleBox4nano, NanoDUFLOW, nanoFate,	Stokes' Law	Size, density
Hetero-agglomeration (air)	MendNano	Fixed attachment and weighing factor	Attachment factor
	SimpleBox4nano	Coagulation coefficient and transitional correction coefficient or attachment efficiency	Size, density, attachment efficiency
	nanoFate	Empirically estimated hetero-agglomeration rate for freshwater adjusted based on lower collision frequency	Hetero-agglomeration rate constant
Hetero-agglomeration (water)	Praetorius, NanoDUFLOW, SimpleBox4nano	Smoluchowski theory on particle aggregation based on collision frequency and attachment efficiency	Size, density and attachment efficiency
	MendNano	Fixed attachment and weighing factor	Attachment factor
	nanoFate	Empirically estimated hetero-agglomeration rate	Hetero-agglomeration rate constant
Hetero-agglomeration (soil)	MendNano	Fixed attachment and weighing factor	Attachment factor
	SimpleBox4nano	Smoluchowski theory on particle aggregation and particle filtration theory with the attachment efficiency estimated empirically or using the interaction force boundary layer approximation	Size, density, attachment efficiency, surface potential, Hamaker constant
	nanoFate	Partitioning between solids and water fraction of soil based on empirical estimate of NM retention in soil.	NM-Soil retention fraction
Dissolution	MendNano	Based on solubility, mass transfer coefficient and available surface area of NMs	Concentration, size, density, fractal dimension
	NanoDUFLOW, SimpleBox4nano, nanoFate	Empirical	Dissolution rate constant
Agglomerate breakup	Praetorius, nanoDUFLOW,	No, assumed irreversible	No parameter

	MendNano, SimpleBox4nano, nanoFate		
Degradation and other transformation processes	Praetorius, MendNano, nanoFate	No	No parameter
	SimpleBox4nano, NanoDUFLOW	No	Degradation rate constant

From Table 1, it becomes clear that size and density are the only intrinsic NM properties used for modelling the transport processes, deposition and sedimentation. The transformation processes do not include other purely intrinsic nanomaterial related descriptors, except for the fractal dimension of homo-aggregates in MendNano where homo-aggregates can be defined as the form of ENM under consideration. The Hamaker constant, attachment efficiency, attachment factor, hetero-agglomeration rate constant and dissolution rate constant are extrinsic properties not only related to the nanomaterial, but also to the environmental compartment under consideration, including the natural colloids and particulates.

3 Nanomaterial related properties in human exposure models

Human external exposure modelling traditionally largely depends on the application scenario of a consumer product (in the case of consumer exposure) or on a worker's activity scenario (in case of occupational exposure). For the former the calculation of the load of a NM based on the concentration in a product and the frequency and amount of use are the relevant variables (RIVM, 2016) (see table S2 in supporting information), while for the latter the activity and the duration mainly determine the exposure.

Although several models exist that take into account consumer exposure to chemicals and particles due to inhalation from consumer products (sprays), only the well established Multiple-Path Particle Dosimetry (MPPD) model and recent extension of ConsExpo nano (https://www.consexponano.nl/)(RIVM, 2016) take specific nanomaterial properties into account (Table 2). In both models the size and density, shape only in Consexpo nano, of a NM are taken into account for assessing the deposition of the NM in the lung. The NM dissolution rate is used to estimate the clearance rate for soluble particles in Consexpo-nano, for other particles both Consexpo-nano and MPPD use a particle independent clearance rate constant.

The main concern in relation to estimating human occupational exposure of NM is related to inhalation (Schneider et al., 2011). For occupational exposure several risk control banding tools (e.g. Stoffenmanager Nano, NanoSafer CB, Control Banding Nanotool) also include an estimate of the exposure to nanomaterials (Liguori et al., 2016). The exposure estimate in these tools is largely based on the application scenario and dustiness is the only NM related property used (Table 2). Dustiness is measured using standard testing methods and is thought to be primarily related to the coating and agglomeration of NM (Jensen et al., 2008; Schneider and Jensen, 2009).

This shows that although dustiness of a powder is related to intrinsic physico-chemical properties of the NM, the attractive and repulsive forces affecting agglomeration are also dependent on the systems conditions and matrix, e.g. moisture decreases dustiness and statically charged systems increase dustiness, meaning that this is an extrinsic parameter describing an interaction (Jensen et al., 2008; Schneider and Jensen, 2009; Koivisto et al., 2015; Levin et al., 2015).

Table 2. Nanomaterial related properties used in estimating worker and consumer exposure to NM using a selection of control banding tools (Zalk et al., 2009; Duuren-Schuurman et al., 2011; Jensen et al., 2014) and quantitative consumer exposure models (Anjilvel and Asgharian, 1995; Asgharian and Price, 2007; RIVM, 2016).

Process	**Model**	**Reported parametrization**	**Nanomaterial related properties**
Exposure at room level due to worker handling	Stoffen manager nano	Application scenario, dustiness, moisture	Dustiness
	NanoSafer CB	Application scenario, dustiness	Dustiness
	CB NanoTool	Application scenario, dustiness, mistiness	Dustiness
Inhalation of spray product	ConsExpo nano	Similar to (conventional) ConsExpo model	Not reported
Deposition of NM in lungs	ConsExpo nano	ICRP deposition model	Size, density and shape
	Multiple-Path Particle Dosimetry (MPPD)	Semi-emperical relationship using the molecular diffusion coefficient and effective diffusion coefficient in combination with lung dimensions	Size, density
Clearance of NM from lungs	ConsExpo nano	ICRP clearance model for non-soluble particulates using clearance rate constants First order removal due to dissolution for soluble nano materials.	Dissolution rate constant
	MPPD	Semi empirical relationship using clearance rate constants.	Not reported

4 Nanomaterial related properties in internal exposure/kinetic models

Although modelling of internal concentrations of compounds has been applied in risk assessment of chemicals, its use is often limited by availability of sufficiently generic data on the required input parameters. As internalization of NMs is an important driver for NM toxicity, these types of models are promising. Furthermore, this area of research contributes to future risk assessment methods that depend less on *in vivo* studies. From data on the external exposure and intake of NMs, the internal concentration in relevant organs in the human body can be calculated using physiologically based pharmacokinetic (or PBPK) models (Lankveld at al. (2010), Bachler et al. (2013, 2014), Van Kesteren et al. (2015), Heringa et al. (2016), Li et al. (2017) and references cited herein (Lee et al., 2009; Péry et al., 2009; Li et al., 2012)). Currently, most PBPK models depend on NM specific parameters that were fitted from experimental data. The main process parameters are related to the absorption and distribution of NMs to different organs, the metabolism and the excretion of NMs (Table 3).

The absorption of NMs to the skin, lungs and intestines is commonly modelled using an absorption fraction that is fitted using experimental data (Table 3). So, no clear relationship with any intrinsic physico-chemical NM property is used, although it is expected that several intrinsic NM properties will affect the absorption fraction or rate, such as NM chemical composition and coating, but also the intrinsic characteristics of the biological surface will play a role. This is similar to how in environmental exposure modelling, the attachment affinity is based on both the NM and the other surface to which the NM will be attached (or in this case: absorbed).

The distribution of NMs via the blood to the different organs is based on organ uptake and release rates which are dependent on the formation of the protein corona, particle size, surface charge, and dissolution, speciation (Lankveld et al., 2010) and the crystalline form (van Kesteren et al., 2015; Heringa et al., 2016) of the NM (Table 3). However, one of the main processes governing this distribution is related to the ability of NMs to cross the capillary wall of the organs and by uptake by macrophages in the mononuclear phagocyte system (MPS) (Bachler et al., 2013, 2014). These macrophages are primarily located in the liver, lung and spleen. The former process of crossing the capillary wall was reported as size independent for the size range from 15 to 150 nm, whereas the latter (uptake by macrophages) is dependent on the size of the particle. The minor influence of size (for silver and TiO_2)(Bachler et al., 2013, 2014), of the surface charge, of coating (for silver) (Bachler et al., 2013), and of the crystalline structure of the particles (TiO_2)(Bachler et al., 2014) on the passing of the capillary wall of the organs may be explained by the formation of a protein corona. Thus, the extrinsic property of a protein corona may have a stronger influence on the distribution than the intrinsic NM properties (Bachler et al., 2013).

The metabolism of NMs is related to the dissolution of NMs (Table 3). For silver, the formation of silver sulfide particles was the main metabolic process. The formation of silver sulfide complexes caused storage of these particles in the different organs. For each organ the relative complexation capacity was estimated using the glutathione (GSH) content of the organs (Bachler et al., 2013).

The excretion of NMs is considered size independent, although different mechanisms are used for Ag or TiO_2 NMs (Bachler et al., 2013, 2014). The Ag NM excretion was due to the biliary endocytosis of silver-GSH complexes and for TiO_2 NMs this was due to the trans- capillary pathway.

In summary, estimating the internal concentration of nanomaterials is largely based on the physical and biological characteristics of the bloodstream and different organs of the human body in combination with NM characteristics. NM size and crystalline structure are found to be the only intrinsic NM properties, and the other parameters are all extrinsic, related to the interaction of the NM with the matrix and blood or organ system. In particular, the surface chemistry and the formation of a protein corona could play an important role, e.g. in estimating the absorption to skin, lungs and intestines. In environmental and colloid sciences, the attachment affinity is an important similar property both related to the interaction of a NM and another surface with which the NM interacts, e.g. sediment or soil particulates. It was also shown that the NM characteristics itself could be of lesser importance compared to the interaction with proteins contained in the blood which result in formation of a protein corona (Li et al., 2017). This means that these proteins should be included in estimating any parameter related to absorption or attachment to biological surfaces.

Table 3. Processes and nanomaterial related properties as reported in studies on pharmacokinetic models using nanomaterials: Lankveld et al.(Lankveld et al., 2010), Bachler et al. (Bachler et al., 2013, 2014) and references cited herein (Lee et al., 2009; Péry et al., 2009; Li et al., 2012).

Process	Studied organ/compartment	Nanomaterial related properties
Absorption	Skin, lung, intestine	Absorption fraction to skin and intestine. Absorption rate to lung
Distribution	Blood and all organs	Size, surface charge, surface coating and protein corona, crystalline structure
Metabolism	Liver, lung, other organs	Dissolution rate, sulfidation rate
Excretion	Bile, kidney (urine), intestine	No reported dependencies

5 Nanomaterial related parameters in hazard banding tools

Although modelling is currently not common in estimating the hazard of chemicals in a regulatory context, several control banding tools are available to perform a first risk screening of a NM application in order to prioritize further assessment (Zalk et al., 2009; Duuren-Schuurman et al., 2011; Höck J. et al., 2011; Jensen et al., 2014). The approaches of these authors to estimating NM hazard are briefly, although not exhaustively, analyzed here. For a more thorough review see e.g. Liguori et al. (2016), Sanchez Jimenez et al. (2016) or Hristozov et al. (2016).

In general, all the considered tools distinguish some parameter that indicates whether the NM is expected to be persistent, often related to solubility. However, in the case of the Precautionary Matrix, a more general classification based on a nanomaterial half-life is used. In this sense, dissolution reflects the potential for degradation of NMs by an organism and not the potential toxicity related to a transformation product, such as the dissolved ion. The second and most important aspect in estimating NM hazard is classifying the potential toxicity of a NM based on either physico-chemical characteristics and/or the toxicological characteristics of the NM (toxic potential, Table 4). Several tools also include the toxicological characteristics of either bulk, larger sized particulates or of the parent chemical compound for estimating the toxic potential. Although there is some variation between the intrinsic physico-chemical characteristics considered, 3 out of 4 tools use shape to classify the toxic potential of a NM. They consider fibrous or tubular particles with a high aspect ratio to coincide with a high toxic potential following the fibre paradigm (Poland et al., 2008). Furthermore, 3 out of 4 tools include NM surface chemistry, for which the parametrization ranges from classifying the catalytic or redox potential to identifying the presence of surface coatings/modifications. Only one of the tools considers size a driver for toxic potential. For the eventual risk assessment, NanoSafer CB and ConsExpo use the specific surface area, based on NM size and density, to scale the exposure limits and exposure potentials.

This analysis shows that empirical toxicity data are a main component of hazard assessment, also in these hazard banding tools (hazard concentrations in Figure 1). Although it is clear that several inherent relationships between adverse effects and intrinsic NM physico-chemical properties are taken into account, only a few parameters relate to the interaction between a NM and the matrix or system, e.g. solubility or half-life.

Table 4. Nanomaterial related properties included in processes affecting hazard estimation used in risk control banding tools.

Process	Model	Reported classification method	Nanomaterial related properties
Biopersistence	Stoffenmanager nano	Soluble/insoluble	Solubility
	NanoSafer CB	Soluble/insoluble	Solubility
	Precautionary Matrix	NM stability	Half-life
	CB NanoTool	Soluble/insoluble	Solubility
Toxic potential	NanoSafer CB	Occupational exposure limit or risk sentence of conventional analogue compound, shape and coating	Dimension of primary particle, presence of coating/surface modification, hazard data
	Stoffen manager nano	Fiber aspect ratio, Hazard band NM and/or parent material based on hazard classification for either carcinogenicity, mutagenicity, reproduction toxicity or sensitisation.	Fiber aspect ratio, hazard data
	Precautionary Matrix	Classification of catalytic & redox activity	Catalytic & redox activity
	CB NanoTool	Mutagenicity, carcinogenicity, dermal, and reproductive effects of parent and micron-size	Surface activity, solubility, shape, size, hazard data

		or NM, surface activity, particle shape, particle diameter	
Hazard concentration	n-SSWD	Ecotoxicological data corrected for Species relevance, trophic level abundance and data quality	Hazard data

6 Discussion

6.1 Role of QPPRs in risk assessment

Based on the models and assessment methods currently used for prognostic risk assessment as presented here, it should be clear that QPPRs have different goals in exposure assessment on the one hand and hazard assessment on the other. Whereas exposure assessment uses quantitative mechanistic modelling techniques, hazard assessment mainly depends on measuring toxicity or using tools for a more qualitative hazard assessment. This means that, for hazard assessment, *in silico* methods, such as QPPRs, are most useful for predicting hazard concentrations (see supporting info table S4). On the other hand, for the exposure models - based on intrinsic and extrinsic NM properties - QPPRs and in silico methods in general are valuable for the estimation of extrinsic input parameters. Several of such hazard QPPRs have been developed, either classifying NMs into hazard categories or quantitatively predicting toxicity, which provide useful output for hazard band tools and hazard assessment in general. Only a few exposure-related nano-QPPRs have been developed, such as those for predicting the zeta-potential (Mikolajczyk et al., 2015; Wyrzykowska et al., 2016). Most other currently available QPPRs predict parameters that are not used for risk assessment of NMs, e.g. related to adsorption of compounds to NMs (Heidari and Fatemi, 2016; Toropova and Toropov, 2016; Urbaszek et al., 2017) or the K_{ow} of carbon nanotubes (Toropov et al., 2007). Here lies an opportunity to develop new *in silico* methods to predict different interactions of NM and natural and biological surfaces, such as the attachment efficiency, whereas it is more logical to use a modelling approach when the full mechanistic functioning of a system is understood. The strength of using nano-QPPRs here lies in bridging the gap between a NM property and a model parameter when this relationship is not (easily) quantifiable. This is for example the case for predicting the attachment efficiency. As mentioned above, the attachment efficiency can be calculated based on measurements of the zeta-potential, the Hamaker constant and NM radius (Petosa et al., 2010; Meesters, 2017). However, this is only valid for ideal systems where complexities due to the presence of proteins or natural organic matter and variable properties of natural and biological surfaces do not play a role (Petosa et al., 2010). This makes mechanistic modelling less relevant for environmental or biological systems. For this reason, development of a QPPR predicting the attachment efficiency, based on data gathered using a range of empirical data, appears a more beneficial approach. In addition, it is to be noted that use of empirical data on other transformation processes, such as dissolution, should be considered for QPPRs and other types of *in silico* methods, such as material modelling. Material modelling, for example, has been used for predicting dissolution kinetics of active pharmaceutical ingredients (Elts et al., 2016).

A major drawback in current efforts of developing any *in silico* method based on empirical data, is the present low availability and quality of data. For this reason, current activities have shown very limited success due to data scarcity, non-standardized testing methods and incomplete reporting of the NM, of the matrix used, and of experimental conditions (Hendren et al., 2015b; Marchese Robinson et al., 2016). Such development will only work when standardized assays are used in order to combine datasets for QPPR development and thus to allow for optimal use of data from different studies. Additionally, data curation systems need to be used, such as those developed for the Nanomaterials Registry (Guzan et al., 2013) and the NanoInformatics Knowledge Commons (https://ceint.duke.edu/research/nikc).

Based on the current understanding of NM behavior in the environment and in humans and organisms, it should be clear that their interaction with the surroundings is an important aspect to consider. Extrinsic parameters are the drivers of most exposure models (see Table 1, 2 and 3). Only few of these extrinsic parameters such as the sedimentation velocity can be estimated based on a quantitative theory using solely intrinsic parameters. These intrinsic parameters (such as size, shape and density) reported in earlier studies on pristine particles can be used for mechanistic modelling, although, as stated earlier, curation of reported data needs attention (Hendren et al., 2015b). Most parameters need to be estimated empirically in the relevant systems (Westerhoff and Nowack, 2013; Hendren et al., 2015a; Geitner et al., 2016). These extrinsic parameters which describe the interaction between the nanomaterial, the matrix in which they are present and the system's conditions (Figure 1) are inherently dependent on more than the properties of the nanomaterial alone. This means that any QPPR aimed at predicting extrinsic parameters should include intrinsic descriptors related to the matrix and system characteristics. This can be done using 'easily' measured extrinsic descriptors, e.g. zeta-potential or aggregate size, or by using intrinsic descriptors that also include system and matrix characteristics.

In the analysis of the environmental exposure models we have identified the most important extrinsic input parameters to be the attachment efficiency or the hetero-agglomeration rate constant, the dissolution rate constant, and rate constants related to transformation or degradation. In human exposure models dustiness is a key parameter, whereas also the absorption rate, surface charge and coating affect the internal exposure concentration (Table 5). These properties can all be empirically estimated, but this often requires a significant monetary investment. For this reason, further mechanistic understanding is needed on the interactions between NMs, the matrix and systems conditions, in order to find easily measured descriptors or parameters that can function as a basis for estimating these input parameters. This is the focus of the current efforts to develop specific standardized assays for these relationships between an input parameter and readily available characteristics of the experimental system, commonly called functional assays (Hendren et al., 2015a). In addition to using such standardized empirical methods or functional assays, the resulting data should be available so that they can be used to create *in silico* methods such as QPPRs. Eventually this will lead to a link between the extrinsic process parameters or interaction descriptors and intrinsic descriptors based on the NM, matrix and system. In this way, input parameters used for mechanistic exposure modelling can be estimated without the need for further functional assays. These input parameters can rather be estimated using much simpler measurements of specific properties, similar to how K_{ow} is used for organic compounds. This relationship between different types of descriptors and relevant input parameters is important to realize in further development of nano-QPPRs and other *in silico* models.

6.2 Descriptors in hazard assessment

From analyzing the current state-of-the-art of QPPRs for metal-based NM as reviewed in Chen *et al.* (2017), it is clear that hazards of NMs are dependent on a variety of intrinsic NM properties, some experimental conditions such as NM concentration, and on extrinsic characteristics of the interaction of the NM with the target organism or exposure matrix. These extrinsic characteristics include zeta-potential, agglomerate size in the exposure media or water and in one case the overlap of conduction band energy levels with the cellular redox potential and solubility. It is clear that these types of characteristics of the interaction of NM with organisms are important and the search for better descriptors (Tamm et al., 2016; Toropova et al., 2016) should include them in addition to intrinsic NM descriptors (Chen et al., 2017; Shityakov et al., 2017).

Given the analysis of the parametrization of hazard assessment models, we conclude that mainly hazard data itself, based on dose response relationships are important in assessing the toxic potential of NMs (Table 4). Furthermore, the intrinsic NM properties such as fiber aspect ratio, size, coating, and surface activity are used as drivers for this toxic potential. In only one tool, solubility is included in relation to the toxic potential, and all the tools otherwise use solubility or half-life only to estimate the persistence. In most cases this means that NM with high solubility would not be considered according to the NM specific toxic potential estimate, but related to the conventional compound.

In comparison with the hazard band tools, none of the QPPRs takes the fiber aspect ratio or shape into account. Although QPPRs are developed for high aspect ratio NMs, such as carbon nanotubes, they are only applicable to these types of NM and also do not include size or aspect ratio as a descriptor (González-Durruthy et al., 2017). Overall, both the hazard band tools and nano-QPPRs have descriptors related to the surface activity of NMs. Most currently available QPPRs have rather narrow applicability domains, e.g. limited to one core material with different coatings or different cores, but similar shape and coating, see table S3 in supporting info. Using a broader set of descriptors based on the known NM toxicity mechanisms could extend this applicability domain.

In addition to the different NM related properties that affect the toxic potential, the eventual adverse effects are also related to the kinetics of the uptake and internal distribution processes of the NM in humans and organisms. This means that any important parameter or descriptor identified in those studies (Table 3) is likely to also drive the hazard of an NM. This shows that three important interactions likely play a role in hazard assessment, but have until now not been commonly parameterized in hazard banding tools or as descriptors in QPPRs. The first of these is the interaction of NMs with organs, such as absorption to skin and lungs affecting internalization. Empirically estimating the attachment efficiency could prove useful here. The biological relevance of this parameter has recently been shown in a study on the trophic transfer of NMs through the food chain of aquatic organisms (Geitner et al., 2016). The second interaction of importance is the formation of a protein corona affecting several processes related to the distribution of NMs between blood and organs. This interaction is related to the first key interaction identified, but the focus here is on the formation and stability surrounding a protein corona and the NM itself. Formation of a protein corona affects the attachment efficiency, but other descriptors are likely to be relevant in this respect as well. The third interaction is the degradation of NM to other forms, e.g. dissolved ionic species (Waalewijn-Kool et al., 2013; Schwabe et al., 2014) or metabolites (Levard et al., 2011; Hou et al., 2015).

6.3 Conclusion

In conclusion, there is a big difference in the models and tools available to predict exposure or hazard of ENMs. This is mainly due to the more qualitative approach commonly applied to predicting hazard compared to the quantitative estimates of exposure. However, the currently used set of parameters for both exposure and hazard assessment is limited in nature, and consists of intrinsic and extrinsic parameters related to the dynamic interactions between NMs and the exposure media or biological kinetics (Table 5). These often complex interaction processes related to hazard or exposure can inherently be described using descriptors for the intrinsic characteristics of the NM, matrix and system conditions or by simpler extrinsic descriptors of interaction. This could for example be relationships between the aggregation rate and pH, organic matter concentration and ionic strength (Liu et al., 2013) or between the zeta-potential, an easily measured interaction type parameter, and the attachment efficiency (Wang and Keller, 2009). These relationships should be quantifiable using *in silico* methods, such as QPPRs and other modeling approaches, based on empirical datasets from standardized functional assays. This also means that the required data should be made available for the *in silico* modeling research field. These data should consist not only of the measured parameter, such as NM size, attachment efficiency or hazard concentration, but include meta-data that covers the relevant intrinsic properties of the NM, matrix and experimental conditions (Figure 1).

Table 5. Overview of nanomaterial related model parameters used in the analyzed models to predict nanomaterial risk. Italic parameters are likely to be useful endpoints for QPPRs and underlined parameters are likely descriptors for QPPRs. This should not be seen as a limitative list, specifically for the ENM intrinsic properties.

Hazard concentration	NM extrinsic property	NM intrinsic property
ECx, LCx, NOEC	*Attachment efficiency*	Size
	NM-Soil retention factor	Density
	Hetero-agglomeration rate	Shape
	Absorption rate	Coating
	Dustiness	
		Surface activity
	Dissolution rate	Catalytic & redox activity
	Sulfidation rate	
	Degradation rate	Isoelectric Point
		Crystalline structure
	Zeta potential	
	Surface Charge	
	Hamaker constant	

Given the inherent relationship between NM properties and the interaction with the relevant matrix or organism it can be hypothesized that even though changes of NM properties could occur in the exposure media, the characteristics of the pristine NMs may still be linked to the observed adverse biological effects or transformation and behavior. However, the current understanding of these complex interactions requires the use of descriptors related to the interaction of NM and the relevant exposure matrix. Although several descriptors are identified here based on the parameters used in modelling (Table 5), further steps are needed in finding relevant descriptors and developing better QPPRs in general. These steps include (i) availability of standardized methods for measuring the interaction parameters. The methods need to include proper characterization of NM properties and proper reporting of the matrix and of the experimental conditions; (ii) improvement of the availability of new and existing data for modeling, e.g. using the current state-of-the-art data systems including data curation to improve data quality (Thomas et al., 2013; Hastings et al., 2015; Hendren et al., 2015b). Overall, this should lead to novel risk assessment tools, which incorporate improved in silico models. These novel tools should be validated with high quality data so they can be accepted for regulatory use.

7 Acknowledgements

We thank Keld Alstrup Jensen, Walter Brand, Ilse Goosens, Minne Heringa, and Dick de Zwart for their contribution as well as numerous other colleagues for the many fruitful discussions. This work is supported by funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 686239 "caLIBRAte" and by NanoNextNL, a micro- and nanotechnology consortium of the Government of The Netherlands and 130 partners.

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