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Critical Review

An Assessment of Applicability of Existing Approaches to Predicting the Bioaccumulation of Conventional Substances in Nanomaterials

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Abstract: The experimental determination of bioaccumulation is challenging, and a number of approaches have been developed for its prediction. It is important to assess the applicability of these predictive approaches to nanomaterials (NMs), which have been shown to bioaccumulate. The octanol/water partition coefficient (K_{OW}) may not be applicable to some NMs that are not found in either the octanol or water phases but rather are found at the interface. Thus the K_{OW} values obtained for certain NMs are shown not to correlate well with the experimentally determined bioaccumulation. Implementation of quantitative structure–activity relationships (QSARs) for NMs is also challenging because the bioaccumulation of NMs depends on nano-specific properties such as shape, size, and surface area. Thus there is a need to develop new QSAR models based on these new nanodescriptors; current efforts appear to focus on digital processing of NM images as well as the conversion of surface chemistry parameters into adsorption indices. Water solubility can be used as a screening tool for the exclusion of NMs with short half-lives. Adaptation of fugacity/aquivalence models, which include physicochemical properties, may give some insights into the bioaccumulation potential of NMs, especially with the addition of a biota component. The use of kinetic models, including physiologically based pharmacokinetic models, appears to be the most suitable approach for predicting bioaccumulation of NMs. Furthermore, because bioaccumulation of NMs depends on a number of biotic and abiotic factors, it is important to take these factors into account when one is modeling bioaccumulation and interpreting bioaccumulation results. *Environ Toxicol Chem* 2018;9999:1–17. © 2018 SETAC

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INTRODUCTION

Bioaccumulation is defined as the net consequence of uptake, biotransformation, and elimination processes in an individual through all possible routes (e.g., digestive, integumentary, and respiratory; Newman 2014). High bioaccumulation raises concerns about the possibility of long-term adverse effects because chemicals that persist and build up may cause long-term chronic health effects (Dimitrov et al. 2005).

The definition of bioaccumulation is closely related to bioconcentration and biomagnifications. Bioconcentration is defined as the process that causes an increased concentration of a chemical in an (aquatic) organism, compared with that of the surroundings (usually water), due to the uptake of a chemical by absorption from the surroundings via the respiratory surface and/or the skin (Voutsas et al. 2002). Biomagnification is defined as the increase in the concentration of a contaminant from one trophic level (e.g., primary producers) to the next (e.g., primary consumers) that can be attributed to accumulation from food (Newman 2014).

Measuring bioaccumulation through the experimental determination of a bioaccumulation factor (BAF), bioconcentration factor (BCF), or biomagnification factor (BMF) is often challenging because it depends on many abiotic (such as water pH, salinity, and concentration of organic compounds) and biotic factors (such as lipid content, age, and/or sex of an organism; Glenn and Klaine 2013; Schäfer et al. 2015). When there are no experimentally determined BAF, BCF, or BMF values, the partitioning of a chemical between aqueous and organic phases is often used as a surrogate measure of its bioaccumulation

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potential. In addition, there are a number of modeling tools for predicting BAF, BCF, and BMF for humans and other living organisms (Pavan et al. 2006).

Bioaccumulation may be important for nanomaterials (NMs), defined as materials that have structural components <100 nm in at least one dimension (Buzea et al. 2007). Due to their many industrial applications, the potential may exist for the trophic transfer and bioaccumulation of NMs. Examples include the bioaccumulation of carbon nanotubes (CNTs) in *Daphnia magna* (Roberts et al. 2007), selenide quantum dots in a microbial food chain (Werlin et al. 2010), and gold nanoparticles (AuNPs) in a terrestrial food chain (Judy et al. 2011). Because these studies have confirmed the potential of NMs to bioaccumulate, an overview and critical analysis of the methods used for assessment and/or estimation of bioaccumulation are warranted.

BIOACCUMULATION OF NMs: CONCEPTUAL AND METHODOLOGICAL ISSUES AND CHALLENGES

A number of conceptual and methodological challenges hamper the study of bioaccumulation of NMs. The first challenge exists in relation to the definition of bioaccumulation: in some cases, the bioaccumulation of metal-based NMs has been envisaged to include both metal ions as well as the particulate form of NMs (Luoma et al. 2014), whereas in other cases assessment of bioaccumulation has only considered the particulate forms (Bouldin et al. 2008; Waalewijn-Kool et al. 2014; Jensen et al. 2017; Velicogna et al. 2017). These divergent views have many significant implications in the study of bioaccumulation of metal-based NMs (not carbonaceous NMs), particularly in terms of the methodological approaches utilized in the determination of accumulated species as well as the calculation and the subsequent interpretation of bioaccumulation. For example, when bioaccumulation included both ionic and particulate species, determination of accumulated NMs has been made using nondiscriminating methods such as inductively coupled plasma–mass spectrometry (Shoults-Wilson et al. 2011; Judy et al. 2012; Croteau et al. 2014) or radiometric analysis (Buzulukov et al. 2014). In contrast, bioaccumulation studies of NMs that distinguish particulate and ionic forms have been performed using analytical methods that often involve use of imaging techniques (Bouldin et al. 2008; Waalewijn-Kool et al. 2014; Jensen et al. 2017; Velicogna et al. 2017). Because risk assessment of NMs is primarily concerned with bioaccumulation of nanoparticulate forms, bioaccumulation results derived using the nondiscriminating approaches need proper interpretation because they include nonparticulate species. Otherwise, the risk assessment of NMs that only bioaccumulate in the ionic form will follow the pattern of conventional substances (Luoma et al. 2014).

The scope and definition of bioaccumulation of NMs have also been discussed in relation to bioavailability and biodistribution, especially regarding accumulation of NMs in the gut, as was the case for ferric oxide (Fe_2O_3) in *Ceriodaphnia dubia* (Hu et al. 2012), TiO_2 in *D. magna* (Zhu et al. 2010a), silver NPs (AgNPs) in *Nereis diversicolor* (García-Alonso et al. 2011), and CNTs in *Eisenia fetida* (Petersen et al. 2008a) and *Lumbriculus variegatus* (Petersen et al. 2008b), as well as AuNPs in *D. magna* (Jensen et al. 2017). Nanomaterials have similarly been observed to be trapped in gills of fish (Handy et al. 2008; Chen et al. 2011; Shaw and Handy 2011). The accumulation of NMs in the gut or gills may not be regarded as bioaccumulation because they do not enter the systemic circulation, so bioaccumulation studies may have to disregard the NM mass that accumulates in these organs. Failure to account for this behavior has resulted in large BCF values for *D. magna*, values that may not have toxicological significance (Luoma et al. 2014). Indeed, as a comparison, a correction for the material accumulated in the gut is often made in the bioaccumulation measurement of conventional substances, for which organisms are often purged of gut contents (Kukkonen and Landrum 1995). Therefore, in a similar manner, study of the NMs that do not penetrate epithelial surfaces requires a similar correction, to distinguish between NMs that have been merely ingested and those that have undergone the uptake process (Bjorkland et al. 2017).

However, another view would regard the gut or gills as parts of the physiology of these species that may in the long term be impaired by the bioaccumulation, as was observed in the midgut of *D. magna* following exposure to copper oxide NPs (Heinlaan et al. 2011). Similarly, bioaccumulation of TiO_2 NPs in the gut of *D. magna* is expected to interfere with food intake and digestion, ultimately affecting growth, reproduction, and survival (Zhu et al. 2010a), whereas accumulation of NMs in the gills may impair the efficiency of the gills as respiratory organs (Chen et al. 2011).

Another challenge in the study of bioaccumulation of both metal-based and carbonaceous NMs involves the expression of concentration in the equation used to calculate BAF, BCF, and BMF terms, because NMs exist not in a dissolved state but in a dispersed (colloidal) state (Utembe et al. 2015). Because the concentration terms do not represent dissolved states, there are inevitable concerns over maintaining the NMs homogeneously suspended in the respective phases. Approaches for maintaining homogeneity are important for obtaining accurate results and have been discussed elsewhere (Crane et al. 2008).

Concerns have been raised on the applicability of BAF, BCF, and BMF to NMs, especially regarding the attainment of equilibrium of NM concentrations in 2 phases that are in contact (Kühnel and Nickel 2014). Concerns may also be raised on the implications of an anticipated inverse relationship between exposure and BAFs/BCFs of NMs, as has been observed for metals (McGeer et al. 2003; DeForest et al. 2007). This concern arises from one of the most important theoretical conditions of the BAF/BCF approach: the BAF/BCF should be independent of exposure concentration. Where this condition is met, differences in BAFs/BCFs among substances will only result from variations in their bioaccumulation and not exposure concentration (McGeer et al. 2003). This is not the case for organic substances, where BAFs/BCFs are independent of the exposure concentration because the mechanism of their uptake is passive diffusion.

On the other hand, with metals, active transport plays a significant role in the uptake and subsequent accumulation, resulting in the dependence of BAF/BCF on exposure concentration (McGeer et al. 2003; DeForest et al. 2007). Similarly, uptake of NPs has been shown to occur via active transport processes such as endocytosis (Iversen et al. 2011), depending on the composition, size, and surface charge as well as surface coating. Therefore, a dependence of BAF/BCF on the exposure concentration may be anticipated. Consequently, similar to metals, use of BAF/BCF for NMs may require an understanding of uptake and regulatory mechanisms in various species. Furthermore, use of multiple BAF/BCF values for a specific NM may be recommended because no single BAF/BCF can be used to express bioaccumulation and/or trophic transfer without consideration of the exposure concentration (Chapman et al. 1996; DeForest et al. 2007). Furthermore, there is a need to ascertain the applicability to NMs of the maximum allowable limits of 5000 for BAFs and BCFs. Despite these concerns, BAFs, BCFs, and BMFs have been determined experimentally for various NMs including silver (Park et al. 2018), TiO_2 (Zhu et al. 2010b; Yeo and Nam 2013), fullerenes (Li et al. 2010a), CNTs (Petersen et al. 2008a), and gold (Judy et al. 2012).

FACTORS THAT AFFECT BIOACCUMULATION OF NMs

Just as the bioaccumulation of conventional substances depends on many biotic and abiotic factors (Luoma and Rainbow 2005), the bioaccumulation of NMs may also depend on a number of factors, the most prominent of which is the type or composition of NMs. In this regard, different NMs are expected to bioaccumulate to different extents because of differences in the levels of their internalization, dissolution, and other pharmacokinetic processes (Luoma et al. 2014).

In addition to the composition of NMs, pharmacokinetic processes are known to be affected by their functionalization (Li and Huang 2008; Riviere 2009), leading to differences in bioaccumulation. For example, functionalization has been shown to affect bioaccumulation of zinc oxide NPs (ZnONP)s, in which greater bioaccumulation was observed in 40-nm hexametaphosphate-stabilized NPs than in the <20-nm polyacrylic acid (PAA)-stabilized ZnONPs as well as in the 20-nm nonfunctionalized NPs (Merdzan et al. 2014). The lower bioaccumulation for the nonfunctionalized NPs and ZnO-PAA NPs was attributed to faster dissolution rates. On the other hand, functionalization was shown to have insignificant effects on the bioaccumulation of some NMs. For example, functionalization did not affect bioaccumulation in *E. fetida* of AgNPs (~50 nm) functionalized with oleic acid and polyvinylpyrrolidone (Shoults-Wilson et al. 2011), nor did it affect bioaccumulation in *D. magna* of 407-nm-long multiwalled CNTs (MWCNTs) functionalized with various polyethyleneimine surface coatings (Petersen et al. 2011).

Functionalization can also be utilized to confer a charge on the NPs that may affect their bioaccumulation NMs. For example, 4-nm dextran-coated CeO_2NPs were either functionalized with diethylaminoethyl groups (diethylaminoethyl dextran) to confer a net positive charge or with carboxymethyl groups (carboxymethyl dextran) to confer a net negative charge (Collin et al. 2014). The positively charged CeO_2NPs were shown to have greater bioaccumulation in the soil organism *Caenorhabditis elegans* than the neutral and negatively charged CeO_2NPs. Charge has also been shown to affect the uptake and the overall pharmacokinetics/toxicokinetics of NMs (Li and Huang 2008); for example, neutral 200-nm liposomes have been shown to have a decreased rate of uptake in the mononuclear phagocyte system and prolonged blood circulation compared with the charged liposomes (Levchenko et al. 2002).

In addition to type, composition, and surface functionalization of NMs, bioaccumulation has been shown to be affected by size. For example, a size-dependent bioaccumulation was demonstrated for AuNPs (5, 15, and 40 nm) in the Tellinid clam *Scrobicularia plana* (Pan et al. 2012), in which a greater accumulation was confirmed for larger NPs. Similarly, longer half-lives ($T_{1/2}$s) and mean residence times that may lead to greater bioaccumulation were observed for larger AuNPs than smaller AuNPs (Han et al. 2015). Although a greater accumulation was also observed for larger bovine serum albumin–stabilized 7.8-, 15-, and 46-nm AuNPs in filter-feeding bivalves (*Corbicula fluminea*; Hull et al. 2011), a greater accumulation in the tilapia species *Oreochromis niloticus* was observed for smaller ZnONPs (10–30 nm) than for larger NPs (100 nm; Kaya et al. 2015). On the other hand, size has also been shown to have no effect on absorption, distribution, metabolism, and excretion (ADME; and consequently bioaccumulation) of 10- and 25-nm AgNPs (Song et al. 2013). These studies have shown that the relationship between size and bioaccumulation may not be easily predicted, and must therefore be determined on a case-by-case basis.

Bioaccumulation of NMs has also been shown to be affected by shape. Shape was shown to have an effect on the bioaccumulation of CuO NMs in the deposit-feeder species, *Capitella teleta*, in which higher bioaccumulation was observed for 7- × 40-nm nanorods compared with 1140- × 270- × 30-nm nanoplatelets and 7-nm nanospheres (Dai et al. 2015). On the other hand, whereas in agreement with that study it was reported that rod-like NMs are preferentially internalized, leading to their higher bioaccumulation (Gratton et al. 2008), lower bioaccumulation was reported for 8- × 40-nm CuO nanorods in the deposit-feeder snail *Potamopyrgus antipodarumas,* in comparison with 7-nm nanospheres and nanoplatelets (1.14 nm in length and 270 nm axial width; Ramskov et al. 2014). Lower accumulation was also reported for Au nanorods than for spherical AuNPs in mammalian fibroblast, HeLa, and brain tumor cells (Chithrani et al. 2006). Influence of shape on bioaccumulation was also reported for TiO_2 (of unknown size), with higher levels of bioaccumulation and trophic transfers for TiO_2NPs in paddy microcosms than for TiO_2 NTs (Yeo and Nam 2013). On the other hand, shape has been shown not to have any significant effect on the bioaccumulation of 6, 71-, and 139-nm CuO nanospheres, 7-, 73-, and 126-nm CuO nanorods, and 7-, 56-, and 133-nm CuO nanospindles in the estuarine sediment-dwelling polychaete *N. diversicolor* (Thit et al. 2015).

Concentration of certain NMs has also been shown to have significant effects on bioaccumulation. For example, whereas bioaccumulation was observed to increase with concentration for some metal oxide NPs (ZnO, CuO, and nickel oxide [NiO]) in *Leptocheirus plumulosus* (Hanna et al. 2013) as well as 20- to 40-nm Fe_2O_3NPs in *C. dubia* (Hu et al. 2012), the bioaccumulation of TiO_2NPs (50–300 nm) was observed to be lower at higher concentration (López-Serrano Oliver et al. 2015), and the bioaccumulation of AgNPs (~50 nm) in *E. fetida* was not affected by concentration (Shoults-Wilson et al. 2011). Similarly, the lung clearance of AgNPs following 12-wk subchronic exposure showed similar clearance $T_{1/2}$s at low and high concentrations, but longer clearance $T_{1/2}$s at moderate concentrations (Song et al. 2013).

For a particular concentration or ranges of concentrations, bioaccumulation was dependent on mode of exposure, with higher bioaccumulation observed in biofilms, quillworts (*Isoetes japonica*), duckweeds (*Spirodela polyrhiza*), and Chinese muddy loaches (*Misgurnus mizolepis)* following exposure to sequentially lower 20-nm TiO_2NP concentrations than after exposure to a single high concentration (Kim et al. 2016). Moreover, bioaccumulation was also dependent on route of exposure. For example, greater assimilation of quantum dots was observed in *L. plumulosus* through dietary exposure than exposure via the water column (Jackson et al. 2012). Higher bioaccumulation of TiO_2NPs (<25 nm; Dalai et al. 2014) and 80-nm AgNPs (Ribeiro et al. 2017) was also observed under combined waterborne and dietary exposure compared with either exposure alone, whereas accumulation of 20- to 75-nm CuO and 16- to 50-nm ZnONPs in goldfish (*Carassius auratus*) through waterborne exposure alone was found to be 10 times higher than accumulation through the diet (Ates et al. 2015).

Similar effects of route of exposure on bioaccumulation were also observed for terrestrial animals. For example, in rodents, oral exposure (by gavage) resulted in little accumulation for few layer graphene in mice (Mao et al. 2016a) and intratracheal instillation and stomach intubation (gavage) resulted in low bioaccumulation of CNTs in mice, whereas intravenous (i.v.) exposure resulted in longer $T_{1/2}$s for the CNTs in the same organisms (Deng et al. 2007). Moreover, oral administration of AgNPs to rats produced longer $T_{½}$s (Lee et al. 2013) than those exposed to i.v. administration, indicating greater accumulation from the former than in the latter route of administration (Lee et al. 2018). These studies show that the effect of route of exposure on bioaccumulation depends on the type of NM as well as the species.

A number of environmental factors have also been shown to affect bioaccumulation. For example, environmental salinity was shown to have a dramatic effect on the bioaccumulation of AgNPs in rainbow trout (*Oncorhynchus mykiss*), in which at similar concentrations, the bioaccumulation of AgNPs was significantly greater at higher than at lower salinity (Joo et al. 2013). Bioaccumulation also depends on the pH, as was shown for magnetic Fe_2O_3NPs in *C. dubia* (Hu et al. 2012) and for AuNPs in aquatic macrophytes (Glenn and Klaine 2013). It was also shown to be dependent on ionic strength and water hardness, as was demonstrated for AuNPs in aquatic macrophytes (Glenn and Klaine 2013).

The interaction of NMs with organic compounds in the environment as well as in vivo has recently attracted particular interest. For example, humic acids and environmental organic matter were shown to affect the bioaccumulation of CeO_2NPs in *C. elegans* (Collin et al. 2014). On the other hand, proteins released by *D. magna* were shown to create a corona around polystyrene NPs, resulting in their increased uptake and accumulation in the gut (Deng et al. 2009). Similarly, when *Limnodrilus hoffmeisteri* were exposed to few layer graphene, the proteins secreted by the organisms during the exposure period coated the few layer graphene and therefore affected the bioaccumulation of few layer graphene in other organisms (Mao et al. 2016b). Moreover, apparently similar metal oxide NMs such as TiO_2 and ZnO have been shown to undergo differential plasma protein binding, even though they have similar surface charges (Deng et al. 2009). Therefore, different environments could result in different surface coatings on NMs, resulting in significant implications for the assessment and/or prediction of bioaccumulation, as well the interpretation of bioaccumulation results.

Bioaccumulation has also been observed to be affected by a number of species-specific biological factors such as physiology, phylogeny-influenced traits, gender (sex), functional ecology (Luoma et al. 2014), and other specific characteristics like pregnancy (Semmler-Behnke et al. 2014). For example, differences in the uptake and bioaccumulation of 4-, 18-, and 30-nm AuNPs were observed among 3 morphologically distinct aquatic macrophytes: the AuNPs were absorbed into the tissues of only 2 of the 3 species (Glenn and Klaine 2013). Differences in bioaccumulation were also observed in different aqueous mesocosms, with clams and biofilms bioaccumulating the most Au nanorods (65-nm length and 315-nm diameter) compared with other species (Ferry et al. 2009). Higher BMFs were also calculated for Chinese muddy loaches than for river snails following exposure to 10- to 20-nm TiO_2NPs (Kim et al. 2016).

Not only is bioaccumulation different among organisms of different species but also ADME behavior has been shown to be different in different organs of the same organism, depending on certain unique characteristics of the physicochemical properties of the NMs under consideration. For example, whereas AuNPs barely distributed to or accumulated in the brain and testis of Sprague-Dawley rats (Lee et al. 2018), the accumulated AgNPs showed much longer clearance $T_{1/2}$s and mean residence times in the same organs of the same species due to the existence of biological barriers such as the blood–brain and blood–testis barriers (Lee et al. 2013). On the other hand, accumulation of AuNPs has also been reported in the lungs and kidneys, with significant gender-related differences in the AuNP content in kidneys (Sung et al. 2011).

From the foregoing discussions, it can be seen that bioaccumulation of NMs is evidently a multifactorial process in which various factors are expected to have different concurrent effects on bioaccumulation. A summary of some of the studies conducted on the factors that affect bioaccumulation of NMs is presented in Table 1.

TABLE 1: Summary of factors that affect bioaccumulation of nanomaterials (NMs)

Factor	NM	Species	Impact	Reference
Physiochemical characteristics of NMs				
Functionalization	ZnONPs	*Chlamydomonas reinhardtii*	Greater bioaccumulation for ZnO–HMP than ZnO–PAA and naked ZnONPs	Merdzan et al. 2014
	AgNPs	*Eisenia fetida*	No difference in bioaccumulation between AgNP–OA and AgNP–PVP	Shoults-Wilson et al. 2011
	CNT	*Daphnia magna*	No difference in bioaccumulation for CNTs coated with various polyethyleneimine molecules	Petersen et al. 2011
Charge	CeO_2NPs	*Caenorhabditis elegans*	Greater bioaccumulation for positively charged NPs than for neutral and negatively charged NPs	Collin et al. 2014
Size	AuNPs	*Scrobicularia plana*	Greater accumulation for larger NPs	Pan et al. 2012
	AuNPs –BSA	*Corbicula fluminea*	Greater accumulation for larger NPs	Hull et al. 2011
	ZnONPs	*Oreochromis niloticus*	Greater accumulation for smaller NPs	Kaya et al. 2015
Shape	CuONPs	*Capitella teleta*	Higher bioaccumulation for nanorods compared with nanoplatelets and nanospheres	Dai et al. 2015
	CuONPs	*Potamopyrgus antipodarumas*	Lower bioaccumulation for nanorods compared with nanoplatelets and nanospheres	Ramskov et al. 2014
	TiO_2NPs	Algae, nematodes, white butterfly larva, mud snail, rice fish	Higher bioaccumulation for NPs than nanotubes	Yeo and Nam 2013
	CuONPs	*Nereis diversicolor*	No significant differences in the bioaccumulation of NPs	Thit et al. 2015
Exposure characteristics				
Concentration	ZnO, CuO, and NiO	*Leptocheirus plumulosus*	Higher accumulation at higher concentrations	Hanna et al. 2013
	Fe_2O_3	*Ceriodaphnia dubia*	Higher accumulation at higher concentrations (≥20 mg/L)	Hu et al. 2012
	AgNPs	*E. fetida*	Bioaccumulation similar at all concentrations	Shoults-Wilson et al. 2011
Route of exposure	QDs	*L. plumulosus*	Higher bioaccumulation through dietary exposure than through water	Jackson et al. 2012
Environmental factors				
pH	Fe_2O_3 NPs	*C. dubia*	Highest bioaccumulation at pH 7–8	Hu et al. 2012
	AuNPs	*Myriophyllum simulans, Egeria densa, Azolla caroliniana*	The presence of dissolved organic carbon resulted in a decrease of NP absorption by the aquatic plants	Glenn and Klaine 2013
Salinity	AgNPs	*Oncorhynchus mykiss*	Bioaccumulation greater at higher than at lower salinity	Joo et al. 2013

BSA = bovine serum albumin; CNT = carbon nanotube; HMP = hexametaphosphate; NP = nanoparticle; OA = oleic acid; PAA = polyacrylic acid; PVP = polyvinylpyrrolidone; QD = quantum dot.

PREDICTING BIOACCUMULATION FROM DISTRIBUTION COEFFICIENTS

The octanol/water distribution coefficient (K_{OW}; Kenaga and Goring 1980) is often used in bioconcentration, biomagnification, and bioaccumulation studies. Generally, substances with high K_{OW}s (or log K_{OW}s) are lipophilic (or hydrophobic) and expected to be bioaccumulative whereas substances with low K_{OW}s (especially those with negative log K_{OW}s) are hydrophilic and are expected not to bioaccumulate (French National Center for Scientific Research 2007). In Europe, for example, a limit of log $K_{OW} > 3$ is used for agricultural pesticides (European Commission 2002), log $K_{OW} \geq 4$ for veterinary medicines (European Medicines Agency 2004), and log $K_{OW} \geq 4.5$ for human pharmaceuticals (European Medicines Agency 2006).

A number of methods exist for determining K_{OW} experimentally, including the shake-flask method, column generator techniques, the slow-stirring method, and high-performance liquid chromatography (Finizio et al. 1997). Furthermore, theoretical methods have been developed to deal with challenges encountered in the determination K_{OW}s of compounds that have very low solubilities in either one or both of the aqueous and organic phases. For example, because fluorinated organic compounds are shown to be immiscible in aqueous and organic phases (Lewandowski et al. 2006), their K_{OW}s cannot be determined experimentally. Therefore, theoretical models based on quantitative structure–activity relationship (QSAR) approaches, which are discussed in detail later (in the *Predicting Bioaccumulation Using QSAR Models* section) have been utilized to estimate K_{OW}s for these compounds. For example, QSAR models have been developed to predict K_{OW} from free energy calculations (Endo and Goss 2014; Hidalgo and Mora-Diez 2016), as well as from molecular structure (Arp et al. 2006).

Applicability of the distribution coefficient to predict the bioaccumulation of NMs

A few applications of K_{OW} to the bioaccumulation of NMs have been described in the literature. For example, because the log K_{OW} of fullerenes was measured to be 6.67 (Jafvert and Kulkarni 2008), the C_{60} NMs would be expected to be hydrophobic (lipophilic), and thus also be expected to bioaccumulate. Similarly, because CNTs are hydrophobic, they are expected to bioconcentrate and bioaccumulate (Dunphy Guzman et al. 2006). On the other hand, the log K_{OW}s for polyamidoamine dendrimers with amidoethylethanolamine end groups were reported to range from –2.54 to –1.39 (Giri et al. 2009). Negative log K_{OW} values ranging from approximately –2 to approximately –10 have also been reported for polyglycerol dendrimers (Silva and Queiroz 2012). Such negative log K_{OW}s would indicate that they are not lipophilic and thus will not bioaccumulate, if indeed K_{OW}s for NMs correlate very well with experimentally determined bioaccumulation.

Attempts have therefore been made to measure and correlate the K_{OW}s of NMs to their bioaccumulation. For example, the phase distribution behaviors of MWCNTs between water and octanol were studied and compared with their bioaccumulation in earthworms (*E. fetida* and *L. variegatus*; Petersen et al. 2010). In that study, the MWCNTs accumulated between water/octanol interfaces and did not transfer between the 2 phases, a behavior that differs substantially from that of typical organic compounds. The accumulation of MWCNTs at the interphase between the 2 layers indicates a lack of affinity/preference of MWCNTs for both layers. Consequently, an apparent K_{OW} could only be obtained after vigorous mixing of the phases using sonication. Even though there were substantial differences in the apparent K_{OW}s of the purified or 3:1 MWCNTs and the acid-modified MWCNTs, there were no differences in their bioaccumulation by either the earthworms or the oligochaetes, with minimal uptake for both types of nanotubes. These findings show that the apparent K_{OW}s for the CNTs do not correlate with their experimentally determined bioaccumulation. Therefore, K_{OW} may not be applicable for predicting CNT bioaccumulation. The CNTs were also found to "not follow equilibrium partitioning behaviour as the nanotubes measured in the organisms were not absorbed into their tissues but rather associated with soils or sediments remaining in their guts" (Petersen et al. 2010). Similar results have been reported elsewhere, confirming further that K_{OW}s may not be directly applicable for the prediction of CNT bioaccumulation (Ferguson et al. 2008; Petersen et al. 2008a, 2008b).

On the other hand, K_{OW}s for fullerenes could be determined in a manner analogous to those for conventional organic compounds (Jafvert and Kulkarni 2008). The log K_{OW} for C_{60} was estimated to range from 6.54 to 6.75, indicating that C_{60} would be very bioaccumulative. Indeed, studies have demonstrated that C_{60} bioaccumulates in *E. fetida* (Li et al. 2010a). In addition, it is important to note that functionalization can have a large effect on K_{OW}s and can consequently affect the hydrophilicity or hydrophobicity of fullerenes (or any type of NP). For example, the log K_{OW}s of fullerenes functionalized with either 1, 2, or 3 different diserinol groups as well as 1, 2, or 3 quarternary pyrrolidinium groups ranged from –1.61 (hydrophilic) to 2.15 (less hydrophilic; Mroz et al. 2007). Therefore, there can be a large variation in log K_{OW}s of NMs of the same class depending on their surface properties.

The preceding paragraphs have shown the potential for utilizing K_{OW} in the prediction of bioaccumulation for fullerenes and polyamidoamine dendrimers, but they have also shown the serious challenges in using the same method for other NMs such as CNTs. For this reason the Organisation for Economic Co-operation and Development has stressed the need for more data, including the replacement of K_{OW} with so-called nano-relevant endpoints, as well as more studies on additional species such as crustaceans or bivalves (Kühnel and Nickel 2014). Nevertheless, even conceptually, the use of K_{OW} for NPs is difficult to understand under the fundamental definition of an equilibrium partition coefficient, which is expressed as the ratio of equilibrium concentrations of the NPs in 2 solvents. It has been observed that even though "nanoparticle dispersions can be kinetically stable for a long period of time (typically through electrostatic or steric stabilization), they do not reach thermodynamic equilibrium

and can consequently not be equilibrated with an additional phase" (Praetorius et al. 2014).

However, even if equilibria were to be established, many NMs prefer to partition at the water/octanol interface (Giri et al. 2009; Hristovski et al. 2011; Xiao and Wiesner 2012). This distribution at the interface probably occurs because some NMs are not dispersible in any of the 2 phases. Whatever the reason, characterization of distribution of NMs must therefore account for their accumulation at the octanol/water interface (Hristovski et al. 2011). However, K_{OW} is by definition a coefficient of distribution in 2 phases, and is therefore not able to account for this phenomenon; thus the development of a new distribution coefficient involving the interfacial region has been suggested (Hristovski et al. 2011). The development of such new distribution coefficients should, however, take into consideration the size of the NMs investigated: for example, citrate-stabilized AuNPs (Au-CiNPs) measuring <30 nm were observed to mainly remain in the bulk water phase whereas the majority of Au-CiNPs measuring approximately 100 nm accumulated near the water/octanol interface (Xiao and Wiesner 2012).

As an alternative to the use of the partition coefficient K_{OW}, a new parameter called the tissue "distribution coefficient" has been proposed to describe the partitioning behavior of NMs (Lin et al. 2008). The method, which is often used in physiologically based pharmacokinetic (PBPK) modeling. calculates the distribution coefficient as the ratio of the affinity of the NMs to a given tissue to the affinity of the NMs to blood. The affinity to tissues is expected to be governed by many factors including the type and nature of the tissue site, binding with proteins, and others. Although the distribution coefficient appears to be a viable option to the use of equilibrium partitioning coefficients, this approach, may require data on the affinity of NMs to various media and tissues, information that is currently not available for many NMs.

A lipid bilayer/water distribution coefficient (K_{LIPW}) involving distribution of NMs between water and lipid bilayers has also been studied and proposed (Hou et al. 2011, 2012). To elicit a biological effect, NMs need to first interface with lipid bilayers, the layers that surround most living cells and organelles and act as barriers to the transport of the NMs. Lipid bilayers more closely represent actual biological membranes than the octanol that is used in the determination of K_{OW}. For this reason, the lipid bilayers can be used as replacements for octanol in partitioning studies (Westerhoff and Nowack 2013). The K_{LIPW} is reported to be a more appropriate descriptor than K_{OW} for the uptake of hydrophobic substances such as polychlorinated biphenyls (PCBs; Dulfer and Govers 1995) and endocrine-disrupting chemicals (Kwon et al. 2006). Lipid bilayer/water distributions for fullerenes (Hou et al. 2011) and functionalized AuNPs (Hou et al. 2012) have been observed to reach equilibrium. The issue of partitioning at the phase interface appears to be nonexistent in these systems. The lipid/water distribution data for fullerenes were found to be qualitatively consistent with *Daphnia*/water distribution values from the literature. The lipid bilayer/water distribution for AuNPs could not be compared with actual BCF values for AuNPs because of the lack of BCF values for AuNPs in the literature. Nevertheless, even though K_{LIPW} may suffer under the same thermodynamic conceptual and technical challenges as K_{OW}, these studies seem to show the potential value of lipid bilayer/water distribution as method for predicting the bioaccumulation potential of NMs. Therefore, more studies on the correlation between K_{LIPW} for other forms of NMs and bioaccumulation in a variety of organisms are warranted.

PREDICTING BIOACCUMULATION USING QSAR MODELS

The QSAR approach is based on the assumption that the structure of a molecule contains the features responsible for its physical, chemical, and biological properties (Sabljic 2001). In this approach, "if molecular descriptors have been calculated for a group of compounds, but experimental data on the activity of those compounds are available for only part of the group, it is possible to interpolate the unknown activity of the other compounds from the molecular descriptors using a mathematical model" (Puzyn et al. 2011). Formulation of descriptors involves the transformation of chemical structure into mathematical information at various levels of molecular structure, including 0-, 1-, 2-, 3-, or 4-dimensional levels derived from the molecular formula, bulk properties (such as K_{OW}), the molecular topology, geometrical molecular (space) representation, and differences among conformers of the same compound, respectively (Puzyn et al. 2009). The QSAR bioaccumulation models use regression models based on either K_{OW} or other descriptors, such as molecular connectivity indices (Beek et al. 2000; Pavan et al. 2006). Most of the K_{OW} regression bioaccumulation models are comprised of linear regression models between the log transformations of BCF and K_{OW}, as shown in Equation 1:

$$\log BCF = a \log K_{OW} + b \quad (1)$$

where a and b are empirically determined coefficients (Esser and Moser 1982; Mackay 1982). Examples of QSAR bioaccumulation models based on K_{OW} include models by Arnot and Gobas (2003) and Papa et al. (2007).

Regression equations of the form given in Equation 1 have been shown to give fair approximations of BCF for nonionic, nonmetabolized substances with log K_{OW} in the range of 1 to 6. However, the relationship between BCF and K_{OW} may not be applicable for more hydrophobic substances or substances that are more easily metabolized (Mackay 1982; Meylan et al. 1999; Verhaar et al. 1999; Dimitrov et al. 2002). Suggestions have also been made that size affects the bioaccumulation potential of conventional chemicals (Sakuratani et al. 2008). For example, chemicals with an effective cross-sectional diameter of 0.95 nm were not expected to penetrate cell membranes, because 0.95 nm corresponds to the pore diameter of a cell membrane (Opperhulzen et al. 1985).

In addition to K_{OW}, other descriptors, including molecular connectivity indices (Sabljic et al. 1993; Lu et al. 2000; Gramatica and Papa 2005; de Melo 2012), quantum chemical (mechanical) descriptors (Chen et al. 2001; Wei et al. 2001), linear solvation energy relationship descriptors (Hawker 1990; Park and Lee 1993), fragment constants, and other theoretical descriptors, are

utilized in QSAR bioaccumulation models, when measured values of K_{OW} are not available (Pavan et al. 2006). In addition to the direct prediction of bioaccumulation (BCF, BMF, or BAF), these descriptors are used in QSAR models for the prediction of K_{OW}, if measured values are not available (Chen et al. 2001; Yu et al. 2016). The predicted K_{OW} can either be used directly to estimate bioaccumulation, as discussed earlier in the section, or it can be used as a descriptor in a QSAR model to estimate BAF or BCF (Pavan et al. 2006).

Applicability of QSAR models to predict the bioaccumulation of NMs

Similar to conventional molecules, size has been shown to play a role in uptake, biodistribution, and clearance of NMs (Lynch et al. 2014). Consequently, size (shape and other attributes) of NMs should play a definite role in the prediction of bioaccumulation. To this effect, a need has already been recognized to supplement the existing set of molecular descriptors of the existing QSAR models by new, so-called nanodescriptors that can represent the size- and shape-dependent properties of NMs (Puzyn et al. 2009, 2010). However, the development of nano-QSARs has been affected by a lack of data and knowledge of NM mechanisms of toxicity that make development and validation of computational models very challenging (Fourches et al. 2010, 2011; Puzyn et al. 2010). Most importantly, there are challenges in developing modeling procedures to describe structural and morphological properties of NMs such as size and shape in numerical terms. As a way forward, there have been proposals to convert images from scanning electron microscopy, transmission electron microscopy (TEM), and atomic force microscopy into matrices in which the numerical values correspond to individual pixels of the original pictures (Puzyn et al. 2009). Indeed, as a move in that direction, in one study surface morphological parameters were successfully extracted from TEM images of NPs through the use of digital image processing methods for subsequent application in QSAR models (Bigdeli et al. 2014).

As an alternative to size- and shape-dependent descriptors, optimal descriptors have also been calculated from available eclectic data using innovative tools such as quasi-simplified molecular input line entry system (SMILES), which represents features (conditions and circumstances) related to the behavior of NMs, and not the molecular structure (Toropov and Toropova 2015b). For example, QSAR models for the prediction of the mutagenicity of MWCNTs and fullerenes were developed through the use of quasi-SMILES based on the representation of conditions such as concentration as well as presence or absence of S9 mix (Toropov and Toropova 2015a). Furthermore, a computer program (NanoBRIDGES 2011) was developed to assist in the calculation of descriptors for NMs based on such physicochemical information as atomic number, ionization potential, electronegativity, and van der Waals radius (Ambure et al. 2015).

In addition to these approaches, QSAR models have also been developed based on quantum-chemical (mechanical) descriptors (for the cytotoxicity of metal oxide NPs [Gajewicz et al. 2015] and phototoxicities of CNTs; Betowski 2017), as well as regression of some parameters such as chiral vectors (for the estimation of K_{OW}s for CNTs; Toropov et al. 2007) and physicochemical properties such as enthalpy of formation (ΔH_f) and ionization potentials (for the cytotoxicity of metal oxide NPs; Puzyn et al. 2011; Mu et al. 2016).

It is also important to derive nanodescriptors based on surface chemistry parameters such as surface charge and functionalization, which have been shown to play significant roles in the biological activity of NMs (Asati et al. 2010; Lu et al. 2010; El Badawy et al. 2011). In this regard, nanodescriptors based on the biological surface adsorption index were derived by measuring adsorption coefficients using solid-phase microextraction and gas chromatography–mass spectrometry for potential application in QSAR modeling (Lu et al. 2010).

Despite the challenges involved in generating descriptors for NMs, QSAR models have been developed for prediction of various toxicological endpoints based on various descriptors, as presented in Table 2. The development of these models demonstrates the potential for utilizing QSAR models in the prediction of bioaccumulation of NMs in the future.

PREDICTING BIOACCUMULATION FROM WATER SOLUBILITY

Water solubility is used as a descriptor of bioaccumulation in that it is inversely proportional to lipid solubility, where substances with high water solubilities are expected to have low bioaccumulation potentials (European Centre for Ecotoxicology and Toxicology of Chemicals 1996).

Regression equations for estimating BCF from water solubility (S) for various classes of chemical compounds are in the form:

$$\log BCF = a + b \log S \tag{2}$$

Bioaccumulation models based on water solubility have been reported to be as accurate as those based on K_{OW} (Davies and Dobbs 1984; Isnard and Lambert 1988), and a number of correlations between BCF and water solubilities have been published in the literature (Briggs 1981; Kenaga and Goring 1980; Veith et al. 1980; European Centre for Ecotoxicology and Toxicology of Chemicals 1996). Nevertheless, water solubility is less often used as a predictor of BCF than K_{OW}.

Applicability of water solubility to predict the bioaccumulation of NMs

There are a few challenges in the application of the concept of solubility to NMs of low solubilities (Utembe et al. 2015). The NMs are dispersed in a solvent, and when dissolution is considered, it implies that the ions or molecules disintegrate from the NM surface. With that understanding of solubility, NMs that have a high dissolution rate in water will also most likely have a high dissolution rate in living systems. In this regard, the dissolution rate may be of some use for predicting the bioaccumulation potential of NMs: those that have a short $T_{½}$

TABLE 2: Examples of quantitative structure–activity relationship (QSAR) models developed for nanomaterials (NMs)

NM	QSAR model descriptors	Endpoint	Reference
CNTs	Chiral vector	K_{OW}	Toropov et al. 2007
SiO_2	Size and concentration	Cytotoxicity	Toropova et al. 2014
Metal oxides	ΔH_f	Cytotoxicity	Puzyn et al. 2011
Metal oxides	ΔH_f and polarization force	Cytotoxicity	Mu et al. 2016
TiO_2, ZnO, CeO_2, SiO_2, Ag, polystyrene latex beads, carbon black, CNTs, C_{60}, and diesel exhaust	Particle size and size distribution, surface area, morphology, metal content, reactivity, free radical generation, and zeta potential	Cytotoxicity	Wang et al. 2014
TiO_2-based Pd, Au, and bimetallic NPs	Size and specific surface area	Cytotoxicity	Mikolajczyk et al. 2017
Metal oxides	Hydrodynamic radius, mass density, the Wigner–Seitz radius, and the covalent index	Cytotoxicity	Sizochenko et al. 2017
SiO_2	Particle size, concentration, and cell exposure time	Cytotoxicity	Manganelli et al. 2016
CNTs	Raman spectra descriptors	Cytotoxicity	González-Durruthy et al. 2017
ZnO, CuO, Co_3O_4, and TiO_2	Quasi-SMILES–generated descriptors	Bioavailability	Toropova et al. 2017
C_{60}	Monte Carlo–generated optimal descriptors	Mutagenicity	Toropov and Toropova 2014
Various metallic and metal oxide NPs	Molar volume, electronegativity, polarizability, and particle size	Ecotoxicity	Kleandrova et al. 2014
Various metal and semimetal oxides	Quantum-mechanical descriptors, image descriptors, and periodic table descriptors (metal electronegativity, charge on the metal cation, atomic number, and valence electrons)	Cytotoxicity	Kar et al. 2016
Metal oxide	Quantum-chemical descriptors	Cytotoxicity	Gajewicz et al. 2015

ΔH_f = enthalpy of formation; CNT = carbon nanotube; NP = nanoparticle; SMILES = simplified molecular input line entry system.

in water are not likely to bioaccumulate in organisms. We therefore suggest that water solubility can be used as a screening tool in a tiered approach, with NMs that have short $T_{½}$s being exempt from further assessment of bioaccumulation.

PREDICTING BIOACCUMULATION FROM FUGACITY-BASED MODELS

The tendency of a chemical to migrate or escape to another phase can be expressed in a property called fugacity, which is described as the pressure that a chemical exerts when present in a medium (Gobas and MacLean 2003; Kilic 2008). Fugacity has been applied to conventional chemicals, which are categorized into a number of types or categories based on partitioning behavior (Webster et al. 2005). The concept has been used to predict bioaccumulation of organic compounds in food webs (Campfens and Mackay 1997; Arnot and Gobas 2009) and food chains (McLachlan 1995), as well as in the development of a number of commonly used models such as Optimal Modeling for EcotoxicoloGical Applications and CalTOX (Glorennec et al. 2005; Smitkova et al. 2005).

The fugacity approach is feasible for chemicals with appreciable vapor pressure or a nonzero air/water partition coefficient. However, for nonvolatile inorganic chemicals such as metallic ions, the fugacity approach is not feasible, and an analogous equilibrium criterion termed aquivalence is used (Diamond et al. 1992). The main difference in the 2 approaches is that the definition of fugacity is based in the vapor phase whereas that for aquivalence is based in the water phase (Diamond et al. 1994). Nevertheless, the mass balance equations in both approaches are identical and the main steps are essentially similar. The aquivalence approach has been applied to predict the fate of metals and other nonvolatile species such as lead, zinc, and mercury (Ling et al. 1993; Diamond 1999) and a fugacity/aquivalence model known as the Quantitative Water Air Sediment Interaction was used to estimate the concentrations of cadmium, arsenic, copper, and zinc in Lake Ontario (Diamond et al. 1994). However, there seems to be no indication that an aquivalence model has been used to assess the bioaccumulation/bioconcetration of metals.

Applicability of fugacity-based models to predict the bioaccumulation of NMs

Fugacity or aquivalence as developed for organic and inorganic substances may not be applicable to NMs, because studies seem to indicate that the transport of NMs in the environment is influenced by size, charge, and agglomeration rate (Darlington et al. 2009). Consequently, efforts have been made to adapt fugacity models (including SimpleBox) for NMs by placing the NMs into size bins as well as by the use of time-independent partitioning ratios for the different environmental compartments such as water and soil (Liu and Cohen 2014). In this model, termed MendNano, the transport behavior of NMs in the environment was said to be governed by physical transport mechanisms of particulate matter, where the rates of intermedia transport processes for the NMs depend on particle size distribution. A similar multimedia model known as SimpleBox4-Nano was also developed using a similar approach as MendNano (Meesters et al. 2014). Models developed in this manner can be designed to have a biota component that could give some insights on the bioaccumulation potential of NMs.

PREDICTING BIOACCUMULATION USING KINETIC MODELS

Risk assessment is often based on (eco)toxicological tests that employ constant exposure concentrations and fixed durations. Similarly, the equilibrium methods for predicting bioconcentration/bioaccumulation that are discussed in the sections *Predicting Bioaccumulation From Distribution Coefficients* and *Predicting Bioaccumulation From Fugacity-Based Models*, employ constant concentrations at equilibrium. However, concentrations of many pollutants may significantly fluctuate over time, and risk assessment of such substances requires assessment of toxicity that may result from such fluctuating exposures (Ashauer et al. 2011). Prediction of fluctuating concentrations requires the use of mechanistic models such as kinetic bioconcentration/bioaccumulation models that describe the exchange of chemicals between organism and water based on rates of chemical uptake, metabolism, and elimination (Arnot and Gobas 2004, 2006). Kinetic bioconcentration/bioaccumulation models range from simple kinetic models to more complex PBPK models.

A simple illustration of kinetic modeling is the use of kinetic rate constants to estimate bioconcentration, proposed by Arnot and Gobas (2006). In this illustration, the competing uptake and elimination processes that result in bioconcentration can be presented by an organism/water 2-compartment model, where the organism is considered to be a single compartment in which the chemical is homogeneously mixed. This model is mathematically presented as:

$$\frac{dC_B}{dt} = (k_u C_{WD}) - (k_2 + k_E + k_M + k_G) C_B \quad (3)$$

where C_B is the chemical concentration in the organism in g/kg, t is the unit of time (1/d), k_u is the chemical uptake rate constant from the water at the respiratory surface (L/kg/d), and C_{WD} is the freely dissolved chemical concentration in water (g/L). The k_2, k_E, k_M, and k_G values arerate constants representing chemical elimination from the organism via the respiratory surface, fecal egestion, metabolic biotransformation, and the reduced tissue concentration of a contaminant that results from rapid growth (i.e., growth dilution), respectively.

Under steady state conditions,

$$BCF = C_B/C_{WD} = k_u/(k_2 + k_E + k_M + k_G) \quad (4)$$

Equation 4 can simply be presented as:

$$BCF = k_u/k_T, \quad (5)$$

where $k_T = k_2 + k_E + k_M + k_G$ (Arnot and Gobas 2006).

An assessment of the reliability of utilizing uptake and elimination kinetics for estimating BCFs has, however, showed potential uncertainties that arise from the decreasing trends of uptake rates over time (Miller et al. 2016).

For bioaccumulation, BAF can also be calculated using the kinetic approach (Arnot and Gobas 2006):

$$\frac{dC_B}{dt} = (k_1 C_{WD} + K_D C_D) - (k_2 + k_E + k_M + k_G) C_B \quad (6)$$

where the various components are the same as for bioconcentration above, k_D is the chemical uptake rate constant in the diet (kg/kg/d), and C_D is the chemical concentration in the food (g/kg). At steady state the rate of change of the concentration in the organism is 0. Rearranging Equation 6 can yield C_B/C_{WD}, which is the same as BAF:

$$BAF = \frac{C_B}{C_{WD}} = \frac{\left[k_u + k_D\left(\frac{C_B}{C_{WD}}\right)\right]}{(k_2 + k_E + k_M + k_G)} \quad (7)$$

In addition to these simple 2-compartment models, other mechanistic kinetic bioconcentration/bioaccumulation models have been developed based on mass balance principles. Generally most of them utilize similar biological and chemical parameters (Barber 2003), but some may be adopted to suit their specific needs. Furthermore, more complex models are generally required when factors other than simple diffusion (for example, metabolism and uptake from food) are important in determining rates of uptake and loss (Walker 1987, 1990).

Bioaccumulation has also been studied using more complicated PBPK models, which use physiologic properties of organisms and the biophysical properties of substances to describe the ADME of substances in organisms (Yang et al. 2004). Parameters that are needed for the development of PBPK models include physiological and anatomical descriptors, partition coefficients of the compound between various media, and ADME data (Brown et al. 1997). Physiological and anatomical descriptors are species specific, whereas partition coefficients and ADME data are compound specific. Consequently, partition coefficients and metabolic and transport data must be determined for each substance.

Some PBPK models have been developed to study bioaccumulation in living organisms including humans. As examples, PBPK models were developed to study uptake and deposition of waterborne organic chemicals in fish (Nichols et al. 1990), bioaccumulation of PCBs in rats (Emond et al. 2005) and porpoises (Weijs et al. 2010), and bioaccumulation of lipophilic organic pollutants in humans (Czub and McLachlan 2004).

Applicability of kinetic models to predict the bioaccumulation of NMs

The development of kinetic models for the prediction of bioaccumulation of NMs requires a mechanistic understanding of the properties that influence uptake, accumulation, and elimination rates of NMs in different matrices. With such knowledge being increasingly available in the literature, kinetic models will most likely be used to assess bioaccumulation behavior of NMs. For example, steady-state kinetic equations such as Equation 4 have been used in various formats, including bioaccumulation models by Spacie and Hamelink (1985) and Luoma and Rainbow (2005), and adopted for the assessment of NM bioaccumulation in sediment-dwelling organisms (Dai et al. 2015; Ramskov et al. 2015a, 2015b). These steady-state equations were used to calculate a BCF of approximately 50 L/kg and a BAF of approximately 5×10^{-3} L/kg for iron (Fe)

NPs in *C. elegans* exposed to waterborne and foodborne FeNPs, respectively (Yang et al. 2017).

Using parameters published in the literature and implementing simple kinetic modeling as shown in Equation 5, we could calculate the BCFs as a measure of bioaccumulation for a number of NMs. In these calculations, it should be emphasized that C_B and C_{WD} do not represent the concentrations of dissolved NMs but rather the concentrations of suspended NMs in these media. The results, shown in Table 3, indicate that ZnONPs and AgNPs have very low BCF values, and thus would not be expected to be bioaccumulative, whereas AuNPs and fullerenes would be expected to be bioaccumulative.

The predicted BCFs for AgNPs (1.2 L/kg in *Folsomia candida* and 2.7 L/kg in *Peringia ulvae*), as we have calculated (Table 3), are of a similar magnitude to the value of 7.30 L/kg that was experimentally determined after exposure of *Misgurnus mizolepis* to AgNPs (Park et al. 2018). Furthermore, a good agreement between measured and predicted BCFs was also reported for TiO_2NPs, with TiO_2NPs shown to be nonbioaccumulative in zebrafish eleutheroembryo (López-Serrano Oliver et al. 2015). However, TiO_2NPs were shown to be bioaccumulative in *D. magna* in another kinetic modeling study in which the BCFs ranged from 2.40×10^5 to 1.52×10^6 L/kg. Larger NPs were associated with a lower BCF at a lower exposure concentration (Fan et al. 2016). Our predicted BCF values for *D. magna* were also analogous to those predicted by others (Wray and Klaine 2015), who have implemented a similar kinetic approach producing BCF values ranging from 1460 to 47 700 L/kg in the same species.

In addition to the use of simple kinetic models to predict bioaccumulation, there have been attempts to use more complicated PBPK models for NMs. The greatest challenge in PBPK modeling of NMs is that the NMs have different pharmacokinetic behavior compared with conventional molecules, with the result that new approaches are needed (Li et al. 2010b). For example, we have already discussed the challenges of defining and determining (equilibrium) partition coefficients for NMs, in the section *Predicting Bioaccumulation From Distribution Coefficients*.

TABLE 3: Uptake and elimination rate constants and bioconcentration factors (BCFs) for a number of nanomaterials (NMs)

NP	K_U (L/kg/h)	K_T (1/h)	BCF (L/kg)
ZnONP	24 500[a]	3800[a]	6.44
ZnO–octyl	38 200[a]	1100[a]	34.0
10 nm Au-MUDA	4112–27 720[b]	0.26[b]	15 815–106 615
30 nm Au-MUDA	35[b]–306[b]	0.03[b]	1167–10 200
10 nm Au citrate	339[b]–2911[b]	0.02[b]	16 950–145 550
30 nm Au citrate	409[b]–2275[b]	0.01[b]	40 900–227 500
Fullerene	1660[c]	0.11[c]	15 090
AgNP	0.106[d]	0.095[d]	1.2[d]
AgNP	0.074[e]	0.027[e]	2.74
AgNP	0.1[f]	0.1	1
CuO nanospheres	0.086[g]	0.332[g]	0.259
CuO nanorods	0.309[g]	0.423[g]	0.730
CuO nanoplates	0.212[g]	0.363[g]	0.584

[a]Skjolding 2015.
[b]Skjolding et al. 2014.
[c]Tervonen et al. 2010.
[d]Waalewijn-Kool et al. 2014.
[e]Khan et al. 2012.
[f]López-Serrano et al. 2015.
[g]Dai et al. 2015.
NP = nanoparticle; MUDA = mercaptoundecanoic acid.

Despite these challenges, a number of PBPK models have been developed for various NMs. For example, PBPK models were successfully developed and applied to study the ADME of nano-TiO_2 (Bachler et al. 2015b), AgNPs (Bachler et al. 2013), polyethylene glycol–coated polyacrylamide NPs (Li et al. 2014), and AuNPs (Bachler et al. 2015a). The predicted data from these models were reported to fit well with experimentally determined data. As a demonstration of the potential for wide application of PBPK principles to a variety of NPs and scenarios, the PBPK model by Li et al. (2014) was extended to polyacrylamide, Au, and TiO_2, despite the extensive differences in physicochemical properties (Carlander et al. 2016). The rapid clearance of TiO_2 from blood circulation ($T_{1/2}$ of 6 min), as indicated by the model, could be independently verified through in vivo studies (Shinohara et al. 2014).

In addition to ADME, the principles of PBPK modeling can be extended to model the bioaccumulation behavior of NMs, because bioaccumulation is essentially the difference between uptake and clearance processes. As an example, the model of Lankveld et al. (2010) was able to show accumulation of AgNPs in all organs, with most accumulation occurring in the lungs (for 80- and 110-nm NPs), kidneys (for 20-nm NPs), and liver (for 20-nm NPs). At dose levels of 26.4 and 27.6 μg/injection (translating to ~88 and 92 μg/kg/d), the model indicated that the times required for the concentration of 110-, 80-, and 20-nm AgNPs in blood to be reduced to 0 were 17, 11, and 11 d, respectively, whereas the times required for AgNPs in the brain, liver, lungs, heart, testes, kidney, and spleen to be reduced to 0 were all shown to be >17 d. The time required for the 20-nm AgNPs in blood to be reduced to 0 was slightly higher than the in vivo mean residence times of 3.75 and 5.53 d obtained for 25-nm AgNPs in male and female rats, respectively, at a relatively similar dose. Similarly, the mean residence times measured in vivo for AgNPs in the brain, kidney, liver, spleen, and testis were, respectively, 55.06, 25.80, 22.40, 30.75, and 55.34 d in male rats, and 5.53, 58.57, 34.33, 33.89, and 48.11 d in female rats. Therefore, with the exception of the mean residence time of AgNPs in the brain of female rats, all the mean residence times were >17 d, indicating some agreement with the model (Song et al. 2013).

It is important to note the discrepancies between the results of the PBPK model of Lankveld et al. (2010), which show NP accumulation in various organs, and the BCF values calculated in Table 3, which indicate no potential for bioaccumulation. These discrepancies may have resulted from the simplicity of the BCF approach: it does not take into account the formation of secondary particles such as AgCl and Ag_3PO_4, which are accounted for in the quasi-empirical approach used in the PBPK model. Therefore, prediction of BAF/BCF from the steady-state kinetic equations may be improved by addition of the formation of secondary particles.

Accumulation and identification of potential target organs for such accumulation were also assessed by murine PBPK models for zinc oxide (Chen et al. 2015), as well as for

superparamagnetic iron oxide NPs (SPIONPs; Silva et al. 2017). In the model of Chen et al. (2015), improvement in the fitness of simulation could only be obtained by replacing partition coefficients of ZnONPs with those of $Zn(NO_3)_2$, where it could be shown that smaller ZnONPs (<10 nm) accumulated in the body for a relatively longer time than both larger ZnONPs (71 nm) and $Zn(NO_3)_2$. In the model of Silva et al. (2017), the simulated pharmacokinetics for SPIONPs were also in good agreement with the in vivo experimental data, with higher accumulation predicted in the spleen, lung, and liver. Unfortunately, the manner in which they assessed the levels of these NMs could not differentiate between the accumulated species (ionic or particulate) in these various organs. Although these examples confirm the applicability of PBPK modeling for the prediction of bioaccumulation in experimental animals, there is as yet no indication for its applicability to aquatic organisms due to insufficient physiological and physicochemical parameters (Chen 2016).

CONLCUSIONS AND THE WAY FORWARD

In summary, the present review has shown the inherent conceptual and practical challenges as well as the prospects of the applicability of different approaches for the prediction of NM bioaccumulation. With the exception of fullerenes and dendrimers, the use of equilibrium partitioning for prediction of bioaccumulation appears to be fraught with insurmountable shortcomings and challenges. However, K_{LIPW} as a partitioning coefficient seems to hold some potential as a predictor of bioaccumulation.

The prospects of using QSAR models to predict bioaccumulation will most likely depend on the development of appropriate nanodescriptors, with recent efforts appearing to focus on the conversion of NM images into numerical matrices using digital image processing methods as well the conversion of surface chemistry parameters and interactions of NMs with the biomolecules into adsorption indices.

Water solubility can be useful as a predictor of bioaccumulation in a tiered strategy whereby NMs with short $T_{½}$s may be adjudged to have low bioaccumulation potential and to be exempt from further assessment.

Because the concept of partitioning based on fugacity/aquivalence does not appear to be feasible for NMs, there have been successful efforts to adapt fugacity models for the prediction of NM environmental behavior using such parameters as size, charge, and agglomeration. These models can be designed to give some insights into the bioaccumulation potential of NMs through the addition of a biota component.

Kinetic models, especially PBPK models, appear to have the greatest promise for prediction of bioaccumulation. However, more studies are recommended on the uptake, accumulation, and elimination behaviors of NMs for the development of such models, especially in ecotoxicology. The design and applications of appropriate PBPK models will also require the derivation of maximum allowable bioaccumulation values for specific NMs, depending on exposure concentration. Furthermore, because the bioaccumulation of NMs depends on a number of biotic and abiotic factors, it is important to take these factors into account.

In conclusion, the present review has presented the complexities, challenges, and prospects as well as the state-of-the-science for the prediction of NM bioaccumulation. Most importantly, the review has underlined the importance of assessing such bioaccumulation, because the potential for the trophic transfer, bioaccumulation, and biomagnification of NMs in different organisms has already been demonstrated.

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