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Challenges in Exposure Modeling of Nanoparticles in Aquatic Environments

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ABSTRACT

Managing the potential environmental risks of nanoparticles requires methods to link nanoparticle properties with macro-scale risks. This study outlines challenges in exposure modeling of nanoparticles in aquatic environments, such as the role of natural organic matter, natural colloids, fractal dimensions of agglomerates, coatings and doping of particles, and uncertainties regarding nanoparticle emissions to aquatic environments. The pros and cons of the exposure indicators mass concentration, particle number concentration, and surface area are discussed. By applying colloid chemistry kinetic equations describing particle agglomeration and sedimentation for the case of titanium dioxide nanoparticles, a limited exposure assessment including some of the factors mentioned is conducted with particle number concentration as the exposure indicator. The results of the modeling indicate that sedimentation, shear flows, and settling are of less importance with regard to particle number based predicted environmental concentrations. The inflow of nanoparticles to the water compartment had a significant impact in the model, and the collision efficiency (which is affected by natural organic matter) was shown to greatly affect model output. Implications for exposure modeling, regulation and science are discussed. A broad spectrum of scientific disciplines must be engaged in the development of exposure models where nano-level properties are linked to macro-scale risk.

Key Words: fate modeling, environmental risk assessment, nanoparticles, titanium dioxide.

INTRODUCTION

In a report from the European Environmental Agency (2001) case studies show several examples of how early calls for precautionary measures regarding emerging technologies have been neglected. There is a possibility that the case of nanoparticles (NPs) will become yet another of these unheard calls (Hansen *et al.* 2008). Many studies outline NPs as a potential environmental risk, and the importance of understanding the fate and exposure routes of NPs has been stressed (Sweet and Strohm 2006; Klaine *et al.* 2008; Colvin 2003; Maynard *et al.* 2006). The lack of knowledge is often highlighted in these studies; production volumes, emissions to the environment, environmental fate and exposure, and toxic effects are stated as highly uncertain. Issues related to fate and exposure modeling of NPs in water are addressed in this study. One main difficulty in exposure modeling of NPs lies in vertical system integration, that is, linking properties on a nano-scale to macroscopic risks. In our terminology, “macro-scale risks” is the outcome in terms of potential effects on defined endpoints, such as specific impacts on human health or environmental endpoints such as fish or crustacean populations. Previous exposure and risk assessments of NPs have not modeled fate processes at the nano level, but at much higher system levels (Mueller and Nowack 2008; Boxall *et al.* 2007; Blaser *et al.* 2008). In those studies NPs are treated as bulk material and material flow analysis is applied, without acknowledging the particulate nature of the material. For instance, fate processes such as agglomeration[1] and sedimentation have not been considered, despite the fact that agglomeration has been pointed out as an important fate mechanism that could affect the exposure and bio-availability of NPs (Velzeboer *et al.* 2008; Klaine *et al.* 2008; Handy *et al.* 2008; Baun *et al.* 2008), and sedimentation was suggested to be an important sink for NPs in Baun *et al.* (2008).

Other important properties that affect NP fate and exposure in the water compartment include the presence of natural organic matter (NOM), the concentration and type of natural colloids (NCs), the fractal dimension of agglomerates and break-up of agglomerates (Christian *et al.* 2008). These properties are nano-level properties that have an impact on particle concentration and size distribution; that is, they are examples of vertical system integration where the nano level affects the macro level. Also, these properties are not covered by the procedures of chemical risk assessment under REACH (Hassellöv *et al.* 2009).

Chemical risk assessment, however, has a long tradition of relating small-scale molecular properties to macro-scale risks. In chemical risk assessment it is normal to calculate a risk quotient (RQ) using the predicted environmental concentration (PEC) of a substance and the predicted no-effect concentration (PNEC) of the same substance (European Chemicals Bureau 2003; van Leeuwen and Hermens 2004). The RQ is calculated according to the formula:

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[1] Note that sometimes the words “coagulation” or “aggregation” are used instead of “agglomeration” in the colloid chemistry literature. Recently, however, an ISO standard has suggested that “aggregation” should denote when the particles are bound together by tight covalent bonds (sintered) and “agglomeration” should denote when particles are held together by weaker attractive forces such as van der Waals forces (ISO 2008). See also Jiang *et al.* (2009) for a more detailed discussion.

$$RQ = \frac{PEC}{PNEC} \tag{1}$$

A risk quotient greater than 1 indicates risk. The PEC is often estimated using exposure models, where molecular properties such as Henry's law coefficient, the octanol-water partition coefficient and molecular mass, and environmental properties such as water volumes, wind speed, and soil density are inserted into models based on thermodynamically founded natural science theories (van Leeuwen and Hermens 2004; Mackay *et al.* 1996; Mackay *et al.* 1992). Recently, environmental scientists have been encouraged to turn to colloid chemistry to create analogous models of the environmental fate and exposure of NPs (Velzeboer *et al.* 2008; Klaine *et al.* 2008; Handy *et al.* 2008; Christian *et al.* 2008). A reason is that colloids are often defined as particles with a diameter between 1 nm and 1 µm (Elimelech *et al.* 1995; Shaw 1992) while NPs are often defined as particles ranging in diameter from 1 to 100 nm (Royal Society and Royal Academy of Engineering 2004; ISO 2008; Oberdorster *et al.* 2005; Swedish Chemicals Agency 2007). Even with the broad definition of NPs of up to 500 nm suggested by Handy *et al.* (2008), NPs are well within the colloid size range.[2] Therefore it seems reasonable to apply colloidal physical chemistry theories for modeling NP exposure.

This study outlines the possibilities and difficulties in modeling fate and exposure of NPs in water in order to derive a PEC by applying colloid chemistry, using titanium dioxide NPs (TiO_2 NPs) as an example. TiO_2 NPs are among the most frequently used nanomaterials in consumer products according to the Project on Emerging Nanotechnologies (2009), and the risk associated with TiO_2 NPs has been stressed in particular by Mueller and Nowack (2008). Thus TiO_2 NPs provide a relevant case study. The main question investigated in this study is whether a PEC for NPs in water can be derived from colloid chemistry models. Therefore a model is presented, together with some results, which form the starting points for a discussion on the further need for research and development of exposure models for risk assessments of NPs. Also, difficulties in choosing an appropriate exposure indicator for risk assessments of NPs have been discussed (Handy *et al.* 2008). This study thus discusses the pros and cons of three different exposure indicators and the importance of finding indicators relevant to both exposure and effect, that is, of identifying which common unit the PEC and PNEC should have. Suggestions are also given for future studies and possible regulation based on the results from this study.

THE KINETIC MODEL

A kinetic model supporting fate and exposure estimations for NPs can, in principle, be constructed since a colloidal dispersion is never thermodynamically stable, but could be stabilized

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[2] Note, however, that there exist other definitions of colloids, depending on the scientific field (Gustafsson and Gschwend 1997).

kinetically (Handy *et al.* 2008). The kinetic laws that describe changes in particle concentration in a homogenous fluid have been described by Smoluchowski (1917) and Friedlander (1977), which include both sedimentation and three agglomeration mechanisms: (1) perikinetic agglomeration caused by Brownian motion; (2) orthokinetic agglomeration caused by shear flows; and (3) differential settling caused by sedimentation. A collision efficiency[3] α is included to take into account the electrostatic potential barriers surrounding the NPs due to the electric double layer surrounding particles in a fluid, and it obtains values between 0 and 1, with $\alpha = 1$ meaning that all collisions lead to a merging of the NPs and $\alpha = 0$ meaning that no collisions lead to a merging. A continuous inflow of particles I_j is also added, see Equation 2.

$$\frac{dn_j}{dt} = \frac{1}{2}\sum_{i=1}^{i=j-1} \alpha_{i,j-i} K_{i,j-i} n_i n_{j-i} - n_j \sum_{i=1}^{i=\infty} \alpha_{i,j} K_{i,j} n_i - \frac{v_s}{d} j^{\beta} n_j + I_j \tag{2}$$

Equation 2 is based on the assumptions that all particles are approximately spherical and that merging of two particles is an irreversible reaction. In Equation 2, n_j is the particle number concentration of particle j (if j equals three, then particle j consists of three primary particles that have agglomerated), $\alpha_{i,j}$ and $\alpha_{i,j-i}$ are collision efficiencies, $K_{i,j}$ and $K_{i,j-i}$ are rate constants, v_s is the sedimentation rate of primary particles, β describes the increase in sedimentation rate due to increased cluster size (2/3 for spherical particles), d is the depth of the water compartment and I_j is the inflow of particles. The first term on the right side of Equation 2 describes the formation of particle j through agglomeration of particles i and j-i. The second term describes the loss of particle j through agglomeration with other particles i. The third term accounts for the sedimentation, and the last term for the inflow of particles. A particle number based PEC can be derived from Equation 2 by solving the differential equation and summing the particle concentrations n_j at a time when the system has reached steady state. An expression for the agglomeration rate constant, which includes perikinetic agglomeration, orthokinetic agglomeration and differential settling respectively, is shown in Equation 3:

$$K_{i,j} = \frac{2k_B T}{3\mu}\frac{\left(a_i + a_j\right)^2}{a_i a_j} + \frac{4}{3}G\left(a_i + a_j\right)^3 + \left(\frac{2\pi g}{9\mu}\right)\left(\rho_p - \rho_w\right)\left(a_i + a_j\right)^3\left(a_i - a_j\right) \tag{3}$$

where k_B is the Boltzmann constant, T is the temperature, μ is the fluid viscosity, a_i and a_j are the radii of particles i and j respectively, G is the shear rate, g is the gravitational acceleration and ρ_p and ρ_w are the densities of the particles and water, respectively. The sedimentation rate in Equation 2 is calculated according to Grant *et al.* (2001):

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[3] Note that the collision efficiency is sometimes referred to as the sticking probability or the stickiness coefficient.

$$v_s = \frac{2a^2\left(\rho_p - \rho_w\right)g}{9\mu} \tag{4}$$

where *a* is the radius of the primary particle. In Equations 2–4 above, most parameters, for example the water viscosity and the gravitational acceleration, are easy to determine. However, some parameters are more difficult to assign a value to and several relevant factors are not included in Equation 2.

In the following, some model parameters and factors are discussed, and then an initial sensitivity assessment illustrating their relative importance is presented. The two most notable parameters that raise difficulties are the collision efficiency and the shear rate. Also, assigning a value to the inflow has been difficult due to lack of information regarding NP production volumes. Equation 2 assumes spherical particles, which is doubtful especially after agglomeration when fractal agglomerates are often formed. The importance of including not only synthetic NPs but also NCs is discussed, and finally the assumption that the agglomerates do not undergo break-up is treated along with the effect of coatings and doping. These parameters and processes are discussed in more depth below. The conceptual model describing the fate of NPs in water that has guided the model construction can be seen in Figure 1.

Collision Efficiency and Natural Organic Matter

Assigning a value to the collision efficiency (α) is not a trivial matter. Approximate equations exist where the collision efficiency depends on pH, point of zero charge, ion valence, concentration, and temperature (Reerink and Overbeek 1954), but they only take into account the electrostatic forces between pure particles in water without NOM and are generally not supported by experimental observations (Wiesner 1992; Ryan and Elimelech 1996). In natural waters the existence of NOM creates a different situation. Several studies have shown that NOM interacts with NPs and it is clear that NOM can affect the collision efficiency of particles significantly, both with regard to electrostatic forces and steric hindrance (Sander *et al.* 2004; Baalousha *et al.* 2008; Buffle *et al.* 1998).

The effect of NOM on the collision efficiency is complex, since it can both enhance and reduce agglomeration. Buffle *et al.* (1998) suggest that agglomeration of natural inorganic colloids is enhanced by rigid biopolymers (*e.g.*, peptidoglycans, hemicelluloses, and microbial cell walls) due to the attachment of particles to the polymers and by bridging flocculation, and decreased by fulvic compounds due to electrostatic and/or steric stabilization. The decreased agglomeration in the presence of fulvic acid was also reported by Domingos *et al.* (2009). Further, the effects of NOM are also interconnected with other parameters such as pH and salt concentration (Sander *et al.* 2004; Baalousha *et al.* 2008; Domingos *et al.* 2009) and the exact composition of the NOM differs between different waters (Buffle *et al.* 1998).

However, the vast majority of natural particles are negatively charged due to NOM coatings (Loder and Liss 1985; Beckett and Le 1990). Loux and Savage (2008) showed that NPs coated with organic matter have a more negative surface charge than uncoated NPs. According to Fang *et al.* (2009), TiO_2 NPs were stabilized by NOM in soil suspensions. In summary, the physiochemistry behind the collision efficiency is not yet fully understood and currently no precise equations exist for calculating the collision efficiency, and this is especially true in the presence of NOM.

Since the interaction between NOM and NPs is not well enough understood, model estimations of the collision efficiency are limited. The collision efficiency must thus be determined experimentally in order to get a reliable value (Wiesner 1992; Ryan and Elimelech 1996), which creates additional problems from an exposure modeling point of view. First, many experimental studies on the effect of NOM on NP fate do not estimate the collision efficiency as output. Instead, other properties such as the size distribution, electrophoretic mobility, mean particle diameter, diffusion coefficient, and zeta potential are the output of many experimental studies (*e.g.*, Baalousha *et al.* (2008), Domingos *et al.* (2009)). Second, several studies do not perform measurements at conditions close to the conditions in relevant environmental compartments, but at pH values or ion concentrations that are very rarely found in nature. For instance, Buffle *et al.* (1998) studied the interaction between hematite NPs and a NOM called polyacrylic acid derivatives, with the collision efficiency as output. The pH in the experiment was 3, which is much lower than normally found in the environment, which is typically from 5 to 8 (Swedish University of Agricultural Sciences 2008). Furthermore, reference to Figure 5 in Buffle *et al.* (1998) shows that the collision efficiency is very sensitive to the concentration of NOM, changing almost four orders of magnitude for a change in NOM concentration from 0.03 to 0.04 mg/l. These values are, however, much lower than the average total organic carbon content in Swedish waters, which is 12 mg/l (Swedish University of Agricultural Sciences 2008).

Assigning a value to the collision efficiency is difficult from a modeling perspective: The complicated dependence of the collision efficiency on NOM and other parameters makes calculation impossible at the present state of knowledge. Furthermore, few empirical studies exist where collision efficiencies have been determined under relevant environmental conditions. Based on current knowledge the only thing that can be said about the numeric value of the collision efficiency in general is that it often varies between 0.001 and 1 (Buffle *et al.* 1998; Chen and Elimelech 2007; Elimelech 1994).

Shear Rates and Differences between Waters

The shear rate G in Equation 3 represents laminar flow, which is unusual under natural conditions. Camp and Stein (1943) developed an equation that takes into account theturbulent flow by estimating the mean velocity gradient G_m. Note also that even more refined expressions exist, for example, Peddocchi and Piedra-Cueva (2005). However, a major problem is the large variations in shear rate due to weather conditions and whether the water is running or not. For instance, a still, deep lake should normally have a much lower shear rate than a river. In lakes the shear rate is normally about 0.1-3 s^{-1}, and it is 0.01-10 s^{-1} in oceans (Colomer *et al.* 2005). No shear rates representative for rivers have been found, but they are likely >10 s^{-1}, and thus the shear rate varies at least four orders of magnitude in natural aquatic systems. Hence, although the shear rate in principle can be determined, it is still difficult to assign a general value that is representative for the whole water compartment (contrary to other properties such as water density, which can be assumed to be roughly the same throughout the freshwater compartment).

Fractal Dimension

Synthetic primary NPs can often be regarded as spherical. However, during rapid agglomeration fractal agglomerates are often formed (Meakin 1987). Fractal agglomerates are characterized by their mass fractal dimension d_F, which varies between 1 and 3 for three-dimensional objects (Wiesner 1992). An aggregate so compact that it had no pores would coalesce with a sphere, having a fractal dimension of three. More open aggregates have a fractal dimension closer to 1. The difference in bioavailability and toxicity of primary NPs and particle agglomerates is largely unknown, although it has been suggested that agglomerates are less toxic (Velzeboer *et al.* 2008). However, creation of oxygen radicals has been pointed out as a potential toxicity mechanism for TiO_2 NPs (Hund-Rinke and Simon 2006) and fractal agglomerates may also be able to generate significant amounts of oxygen radicals. The mass fractal dimension is difficult to estimate since it depends on material and fluid properties in a complex way, and must be determined experimentally, similar to the collision efficiency (Elimelech *et al.* 1995). However, Wiesner (1992) showed that neglecting agglomerate porosity could cause an error of less than 10 percent in the collision efficiency, and due to this low impact compared to the range of 0.001-1 as has been reported for the collision efficiency, along with modeling difficulties, the fractal dimension has not been included in the model calculations of this study.

Inflow and Production Volumes

For TiO_2 nanomaterials, approximately 58,800 kg/year enter the Swiss water compartment according to Mueller and Nowack (2008). This figure is based on a company survey stating the amount of several different NPs produced in Switzerland (Schmid and Riediker 2008). Unfortunately such information is not available for most regions. Another source of NP production data in Mueller and Nowack (2008) is a report from the United Nations Environment Program

(UNEP 2007). That report, in turn, states that the data originates from “NanoroadSME, a research project founded by the European Commission, 2006.” However, no information regarding production volumes can be found on the project web page (Project NanoRoadSME 2008), and thus it is unclear where the data originate. A report from the Royal Society and Royal Academy of Engineering (2004) also reports figures for global production of nanomaterials, for instance TiO_2, stating as reference “chemical journals and reviews (2003–2004), and market research BCC (2001).” However, no information on production volumes of specific NPs or nanomaterials can be found in the proceedings of the conference mentioned, that is, BCC (2001). A report from BCC Research gives some information, but it includes no references (BCC 2008). This illustrates the difficulties in finding reliable information about the inflow of NPs to the water compartment, and even if the emissions of NPs to the water compartment could be specified in terms of mass, the input unit in Equation 2 is particle number concentration. If production volumes were well known it would still be a problem that the fate of NPs from the product to the water compartment is not fully understood, such as the fate of NPs in waste incineration plants and in sewage treatment plants. Thus the annual produced mass of a certain NP is not equal to the inflow to the water compartment. The same difficulties described here for TiO_2 NPs apply for other NPs as well.

Natural Colloids

Another important factor with regard to NP fate is the role of NCs that are likely to interact with synthetic NPs (Sweet and Strohm 2006; Klaine *et al.* 2008; Handy *et al.* 2008). Measurements performed by Gallego-Urrea *et al.* (2010) suggest that the amount of natural NPs in water is in the range of 10^{14} particles/m^3, a result that was similar to those found in other studies. Very few particles larger than 500 nm were found. The effect of NCs can be included mathematically into Equation 2 by adding a term describing the heteroagglomeration:

$$\frac{dn_j}{dt} = \frac{1}{2}\sum_{i=1}^{i=j-1} \alpha_{i,j-i} K_{i,j-i} n_i n_{j-i} - n_j \sum_{i=1}^{i=\infty} \alpha_{i,j} K_{i,j} n_i - \frac{v_s}{d} j^{\beta} n_j + I_j - n_j \sum_{i=1}^{i=\infty} \gamma_{i,j} H_{i,j} c_i \qquad (5)$$

where γ is the collision efficiency and H is the rate constant for collisions between NCs and synthetic NPs, and c_i is the concentration of an agglomerate with i primary NCs.

The problem here lies in the diversity of NCs with regard to shape and chemistry. For instance, both organic and inorganic colloids can be found in natural waters. According to measurements performed, the average diameter of these is close to 200 nm for many natural waters, although the size distribution is wide (Gallego-Urrea *et al.* 2010). Besides the diversity of the NCs themselves, they may also be partly or fully covered by NOM, which affects the collision efficiency as described above. To our knowledge, no measurements of the collision efficiency between NPs and NCs have been conducted. Another important question in this context concerns how agglomerates consisting of both natural and synthetic NPs should be classified. Such a heteroagglomerate of a naturally occurring substance and synthetic NPs, outlined as a potential hazard, is indeed difficult to conceptualize from a risk perspective. Are they to be seen as NPs, as NCs, or as something else?

Break-Up and Limiting Size

In Equation 2 the agglomeration is regarded as irreversible in that no agglomerate break-up occurs. Zhang *et al.* (2008) showed that it was very difficult to disaggregate metal oxide NPs below 500 nm, which indicates that break-up may not be of importance, at least not for metal oxide NPs. However, Wiesner (1992) showed that break-up could be of importance and that it is partly controlled by the fractal dimension. Different studies have tried to estimate the maximum size of agglomerates, but these estimations are difficult to confirm experimentally and can be highly system-specific (Elimelech *et al.* 1995). One possibility mentioned by Wiesner (1992) was to model break-up as a reduced agglomeration rate, but to our knowledge no simple expression that can be implemented into Equation 2 exists.

Coatings and Doping

“Coatings” sometimes refers to a layer of NOM surrounding the NPs, as discussed above. More often, however, it refers to a coating that is synthesized along with the particles or right after particle synthesis. Surface properties of particles are important since it is a particle’s surface that can interact with the surroundings, and thus coatings can affect NP fate and effects (Nel *et al.* 2006; Handy *et al.* 2008). For instance, the TiO_2 and zinc oxide NPs in sunscreen are normally coated with silicon oils, SiO_2 or Al_2O_3 in order to improve dispersibility and reduce reactive oxygen species generation in sunscreen (Nohynek *et al.* 2007). The exact extent to which the properties are modified is not known. Whether a TiO_2 NP coated with Al_2O_3 adopts exactly the same properties as an Al_2O_3 NP, or just more Al_2O_3-like properties, is currently unknown. “Doping” refers to the process of purposely introducing impurities into the NPs, which can be done to enhance the UV absorption of TiO_2 NPs (Wakefield *et al.* 2004). The effect of doping on NP behavior is largely unknown.

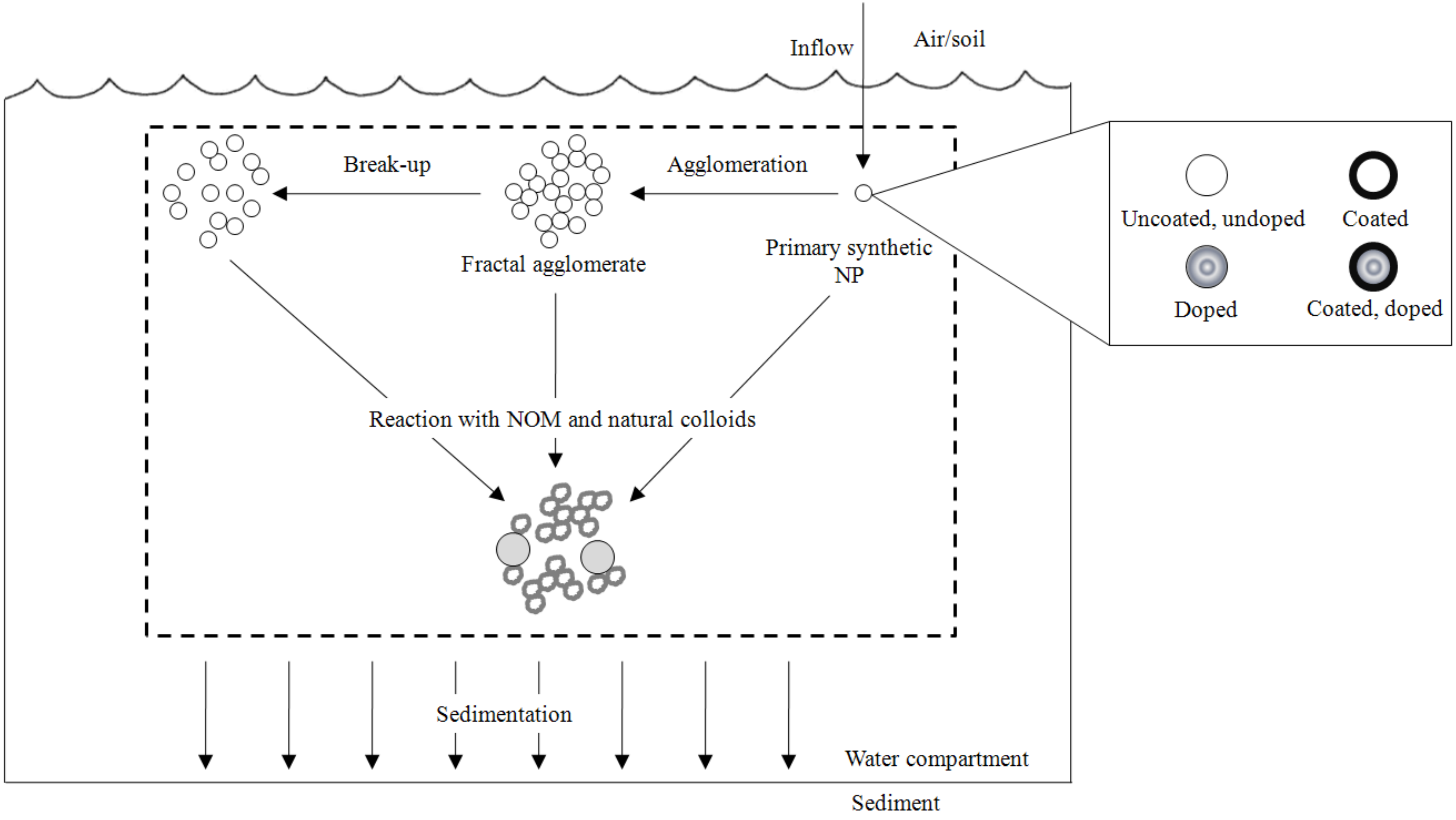

Figure 1. The conceptual model describing NP aquatic fate mechanisms, which have guided the mathematical modeling.

Table 1. A description of the model scenarios tested in this study along with model input and output variables.

Scenario	**Shear rate, *G*** **[s^{-1}]**	**Collision efficiency, α**	**Primary particle size, *a*** **[nm]**	**Temperature [K]**	**Particle density, ρ_p** **[kg/m^3]**	**Water density, ρ_p** **[kg/m^3]**	**Water depth, *d*** **[m]**	**Inflow relative to baseline case inflow**	**Output (PEC) relative to baseline case**
Baseline case	0.01	1	21	277	4200	1000	3	1	1
High shear rate	10	1	21	277	4200	1000	3	1	1
High shear rate and larger particles	10	1	500	277	4200	1000	3	1	1
Differential settling excluded and larger particles	0.01	1	500	277	4200	1000	3	1	1
Low collision efficiency	0.01	0.001	21	277	4200	1000	3	1	10
Sedimentation excluded	0.01	1	21	277	4200	1000	3	1	1
High inflow	0.01	1	21	277	4200	1000	3	10	2

MODEL CALCULATIONS

Some limited model calculations were performed for the case of TiO_2 NPs in order to estimate the importance of the collision efficiency (α), shear rate (G), differential settling, sedimentation and inflow rate (I_j), of which all except differential settling and sedimentation have been discussed above. The material TiO_2 NP is chosen as an example since it is one of the major nanomaterials produced today and has been shown to constitute a potential environmental risk (Mueller and Nowack 2008). Break-up, NCs, fractal dimensions, coating and doping were not included in the model due to insurmountable modeling difficulties and lack of data. The model (Equations 2–4) was implemented in MATLAB® along with input values from the literature for the different parameters.

Input Assumptions

A temperature of 277 K was applied, since the temperature at the bottom of lakes is 4°C or 277 K, and it is also a common water temperature during winters in many places in the northern temperate zone. The viscosity of water at 277 K is about 1.5 mPa·s. The NP modeled was selected to be a TiO_2 NP with a primary particle diameter of 21 nm (same diameter as the commercial TiO_2 NP AEROXIDE® P25 from Degussa/Evonik). This is a smaller particle size than the primary particles found in sunscreen and the particles emitted from painted facades, for instance (Nohynek *et al.* 2007; Kaegi *et al.* 2008). The density of water was set to 1000 kg/m^3 and the density of the TiO_2 NPs was set to 4200 kg/m^3. The depth of the water compartment was set to 3 m according to the guidelines of the European Chemicals Bureau (2003). Since no reliable figures for the inflow have been found in the literature, the inflow was set to a random value in Equation 2. This can be done since this study does not seek to determine a PEC, but rather to investigate the feasibility of such models and the importance of some parameters and factors.

Besides the input values listed above, a shear rate of 0.01 s^{-1} and a collision efficiency of 1 have been applied for the baseline case. Regarding shear rate, two additional assumptions were tested: One with the shear rate increased to 10 s^{-1}, and one with the shear rate increased to 10 s^{-1} along with an increased size of the primary particles in the inflow from 21 nm to 500 nm, but with the same number of particles entering the water compartment. The size of 500 nm was chosen since it is the highest suggested upper limit for the definition of NPs known to the authors; see Handy *et al.* (2008). The complete exclusion of the differential settling factor was tested in one case, combined with increasing the primary particle size from 21 nm to 500 nm but with the same number of particles entering the water compartment as for the baseline case, to see the influence on the result. In order to estimate the effect of lower collision efficiency, in one simulation it was decreased to 0.001. One case with the sedimentation term excluded was also tested. Besides the baseline inflow, the impact of a 10-fold increase or decrease in inflow was investigated since existing estimations of annual TiO_2 nanomaterial production vary roughly by a factor of ten or one hundred (Royal Society and Royal Academy of Engineering 2004; Mueller and Nowack 2008). See Table 1 for a summary of the scenarios and assumptions. The results are given as the changes relative to the baseline case.

Model Calculation Results

The low effect of an increased shear rate in the model for the case where a particle size of 21 nm was assumed is not surprising since the orthokinetic agglomeration was shown to be of less importance for small particle sizes (Handy *et al.* 2008). Not even at a primary particle size of 500 nm was the orthokinetic agglomeration significant in the model. The same was true for differential settling as well; not even for 500 nm particles was that effect significant in the model, which was also suggested by Handy *et al.* (2008). The sedimentation term also had a negligible impact on the calculated PEC even for larger 500 nm particles. For all these model parameters, the changes in parameter values or exclusion of factors resulted in a change in PEC at least smaller than 10^{-4} compared to the baseline case. However, significantly lower collision efficiency could increase the PEC by more than a factor of ten according to the model. Also, a 10-fold increase in the model inflow resulted in a twice as high PEC compared to the baseline case, and a 10-fold decrease of the inflow resulted in a reduction of the PEC by a factor of four. It can thus be concluded from the model calculations that for the case of TiO_2 NPs the collision efficiency and the inflow seem to be the most influential parameters of the ones tested. See Table 1 for a summary of the results.

According to Mueller and Nowack (2008) the inflow of TiO_2 NPs to the Swiss water compartment is 58.8 ton/year and the Swiss water compartment is 3.7 km^3. If that inflow is recalculated into primary AEROXIDE® P 25 particles and a total and instant mixing of the water compartment is assumed, the inflow *I* in Equation 2 is $2.47 \cdot 10^7$ particles$\cdot s^{-1} \cdot m^{-3}$ of P 25. Inserting this value into Equation 2 for our baseline case gives a PEC of approximately $2.5 \cdot 10^{12}$ particles/m^3, which is two orders of magnitude lower than the concentration of NCs reported by Gallego-Urrea *et al.* (2010). However, due to the many uncertainties in the model and especially in inflow data, the authors hesitate to present this figure as a realistic PEC.

EXPOSURE INDICATORS

In the calculation above, particle number based PEC was used as the exposure indicator, leading to the risk quotient indicator. This is because the processes of agglomeration and sedimentation according to Equation 2 are described by the unit particles per volume and also because studies have suggested particle number concentration to be a relevant exposure indicator for NPs (Handy *et al.* 2008). In previous risk assessments, however, mass concentrations have been used for both the exposure and effect assessment (Mueller and Nowack 2008; Boxall *et al.* 2007; Blaser *et* *al.* 2008). This is similar to chemical risk assessment, where mass concentrations are often used in both exposure and effect assessments (van Leeuwen and Hermens 2004). For the case of chemical risk assessment, the choice between mass and molar concentration is not that crucial, since there is an easy way to convert mass to amount of substance using the molar mass. For particles, this is different. For the case of TiO_2, the estimated PEC from Mueller and Nowack (2008) was 16 µg/l, which can correspond to either one particle per liter with a diameter of 200 µm, or 1 million particles per liter with diameters of 2 µm, or 10^{12} particles per liter with diameters of 20 nm and so on.

Toxicological studies have had difficulties confirming the dose-response relationship for mass concentration that applies for many NPs; sometimes dose-response relations are obtained and sometimes not, and in some studies particle and agglomerate size were found to affect the toxicity (Baun *et al.* 2008). Oberdörster *et al.* (2005) found that particle surface area was a better dosimetric exposure indicator than mass, making dose-response curves understandable. Not knowing the proper exposure indicator is a difficulty when performing exposure assessments. The model described in Equations 2-4 can, however, be used to obtain not only particle number concentrations but also mass concentrations, since the amount of particles in each agglomerate (j) is known. Surface area is more complicated to calculate, and is related, for example, to the fractal dimension of the agglomerate.

Mass concentration is a convenient indicator of risk in exposure assessments due to the law of mass conservation and to experimental ease, but problematic for NPs since is cannot discriminate between many small particles and fewer larger particles. Surface area or even bio-active surface area might be more relevant as an exposure indicator, but it would be difficult to make operational since it is difficult to calculate or measure. Changes in surface area along exposure pathways would thus be difficult to monitor. One benefit with particle number concentration, as has been mentioned, is that it is the unit used in agglomeration kinetics equations, although it is also somewhat difficult to monitor along exposure pathways. There is a possibility that an exposure indicator that is suitable from an exposure assessment perspective will prove to be less accurate from an effect assessment perspective, and vice versa. Whether and when mass concentration, particle number concentration, surface area or other indicators of risk are most appropriate is an issue that needs to be addressed by further research.

IMPLICATIONS FOR EXPOSURE MODELING

It is important to notice that an exposure model is not meant to be a perfect representation of reality, but is instead meant to provide a reasonable and conservative estimate of the exposure. An exposure model should include only relevant properties and exclude factors that do not have a large effect on the outcome. Besides the fate processes described above, additional ones of presumed less importance can be added, see for example Elimelech *et al.* (1995). The question posed here thus concerns which of the processes described in this paper and elsewhere are of relevance to the exposure modeling. The calculations above indicate that the orthokinetic agglomeration can be excluded for NPs that enter the aquatic environment. This is convenient considering the variety in shear rate for different waters. Also, differential settling and sedimentation seem to be of less importance. Note, however, that the low impact of the sedimentation is in large part due to the choice of particle number as exposure indicator, and thus the impact of different factors depends partly on the exposure indicator (see discussion above). Changes in collision efficiency related to the amount and type of NOM can increase the PEC of TiO_2 NPs 10-fold according to the model calculations above. Changes in the inflow also had a significant impact, although a 10-fold increase of the inflow only resulted in a doubling of the PEC. The influence of other aspects such as the fractal dimension, the presence of NCs, agglomerate break-up, coatings and doping should be evaluated by models and measurements in order to achieve a reasonably accurate exposure model able to predict environmental concentrations of NPs. The first steps would be to evaluate the importance of break-up, agglomerate fractal dimension and NCs. Here the complexity and diversity of NCs provide perhaps the greatest challenge. In parallel, modeling efforts to estimate current and future inflows (*i.e.*, emissions and leakage from society) are of great importance for an appropriate risk assessment of nanoparticles.

Although the calculations above show that the collision efficiency is an important parameter for exposure modeling, its complex dependence on type and amount of NOM, pH, salt concentration and valence, *etc*. makes it difficult to calculate using existing equations. Thus more accurate equations should be developed. Until then, experimental collision efficiencies relevant for environmental conditions must be derived. However, if the collision efficiency varies greatly within the water compartment, only emissions that are clearly localized, such as peak emissions or point sources, can be modeled with high certainty. For diffuse emissions that are emitted in low amounts to several types of waters, reliable exposure modeling will be more difficult. Unfortunately, many of the known emissions of NPs that have been outlined in the literature are diffuse. Some examples are TiO_2 NPs from ordinary paint (Kaegi *et al.* 2008), TiO_2 and zinc oxide NPs from sunscreen, silver NPs from textiles, iron NPs for soil remediation (O'Brien and Cummins 2008), silica NPs in polishing products and cerium oxide NPs as fuel additives (O'Brien and Cummins 2008). Even if the collision efficiency could be calculated by modeling, the question of exposure indicator is urgent and requires communication between toxicologists, colloid chemists, and risk analysts. It is important to agree on which indicators are relevant for linking exposure and toxic effects. These indicators must also be possible to derive from exposure models. The difficulty in modeling changes in surface area for NPs in the environment in contrast to the presumed merits of surface area as effect indicator (Handy *et al.* 2008) illustrates this great challenge.

Considering the challenges, it is not surprising that previous exposure assessments of NPs have not included specific particulate or colloidal behavior and have used mass concentration as the exposure indicator for a more convenient exposure modeling. However, although excluding the particulate nature of the material makes exposure modeling more feasible, there is no guarantee that the results are relevant and they may offer limited guidance (Wiesner *et al.* 2009). It is thus suggested that scientists working at different system levels relevant for exposure modeling of NPs be given resources to co-operate to develop integrated models where nano-level properties are linked to macro-scale risk.

IMPLICATIONS FOR REGULATION

The problems in exposure modeling of NPs of course lead to regulatory challenges. Several ways to deal with the potential risk of NPs have been suggested. Reinert *et al.* (2006) suggested voluntary information programs similar to the current voluntary program for nanotechnologies established and maintained by the U.S. Environmental Protection Agency. Under this program the producer of nanotechnology can report material characterization, hazard information, use and exposure potential, and risk management practice. However, considering the high uncertainties in exposure modeling of NPs discussed above, it seems unlikely that producers of nanotechnology or NPs could give reliable information about the potential exposure of their products, especially if the products give rise to diffuse emissions. Also, Köhler and Som (2008) showed that innovators of nanotechnology in general did not perceive ecotoxicity of NPs to be a major risk and that they were not sensitive to early scientific warnings regarding risks of nanotechnology. Another option mentioned in Reinert *et al.* (2006) is to create new precautionary regulations, and Köhler and Som (2008) suggested that risk preventive measures should not be postponed until more information about NPs is available. The discussion above about the difficulties in exposure modeling of NPs supports the conclusion that precautionary measures may be the best way to prevent NPs from becoming yet another late lesson.

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