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Influence of natural organic matter on the aquatic ecotoxicity of engineered nanoparticles: Recommendations for environmental risk assessment

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ABSTRACT

In this study, we investigate whether the influence of natural organic matter (NOM) on the aquatic ecotoxicity of engineered nanoparticles (ENPs) can be described quantitatively for the purpose of risk assessments based on existing ecotoxicity studies. A review of the literature studying the aquatic ecotoxicity of ENPs in the presence of NOM identified 66 studies in total, covering the metal and metal oxide ENPs most commonly used in consumer products. It was found that 80% of the studies show a reduction in ENP ecotoxicity in the presence of NOM. Analyses of ecotoxicity data based on 50% effect/inhibition/lethal concentrations (collectively referred to as XC50) were conducted. Correlations of XC50 values with the concentrations of NOM were investigated through Spearman's rank correlation coefficient as well as linear, power law, polynomial, exponential and logarithmic correlations. Furthermore, multiple linear regression (MLR) analyses, including also the pH in the reviewed ecotoxicity test systems (mainly in the range pH 7.0–8.5), were conducted. While none of these statistical approaches provided strong empirical correlations between XC50 values, NOM concentration and pH, an empirical rule of thumb was discovered for the ratio between XC50 values with and without NOM over an environmentally realistic concentration range for NOM (0.1–10 mg/L): XC50 values obtained in experiments with NOM present tended to be a factor of 1–10 higher than those without NOM. Until more accurate correlations are provided, a pragmatic approach for environmental risk assessments of ENPs might therefore be to use observed XC50 values from experiments without NOM present as reasonably conservative proxies for XC50 values with NOM present. Further studies are needed to confirm or falsify this rule of thumb for different ENPs, environmental conditions and metrics.

1. Introduction

The research on environmental risks of engineered nanoparticles (ENPs) has to date largely been about pristine particles, i.e. as they are when manufactured, which are usually bare or coated with some stabilising substance. However, increasing evidence suggests that ENPs do not appear as pristine in the environment but rather undergo a number of transformations (Lowry et al., 2012; Pradhan et al., 2018; Pulido-Reyes et al., 2017). One such important transformation is interactions with natural organic matter (NOM). NOM has a very differentiated and complex composition consisting of different macromolecules, such as lignin, cellulose, hemicellulose, tannic acid, fulvic acid and humic acid – the latter two often referred to as humic substances, which account for about 50% of the NOM in natural aquatic environments (Wang et al., 2016b). One way of interaction between ENPs and NOM is the adsorption of NOM onto ENPs, which can occur through different mechanisms: hydrophobic interaction, electrostatic interactions, van der Waals forces, ligand exchange, chelation, cation bridging and hydrogen bonding (Philippe and Schaumann, 2014). In this context, the eco-corona (also called environmental corona) concept has emerged as an analogy to the bio-corona (also called protein corona), which is a (possibly partial) layer of proteins formed around ENPs (Cedervall et al., 2007; Fadeel et al., 2013; Ke et al., 2017). The eco-corona is similar to the bio-corona, but formed in the environment rather than within organisms, and typically consists of organic macromolecules (Xu et al., 2020). Studies of how the adsorption of NOM onto ENP surfaces influences the environmental fate, subsequent exposure and ecotoxicity of ENPs have been ongoing since before the term eco-corona was coined, see for example the reviews by Wang et al. (2016b), Grillo et al. (2015), Yu et al. (2018), Philippe and Schaumann (2014), Arvidsson et al. (2011), Hartmann et al. (2014) and references within. The eco-corona is thus effectively a new term for adsorption of NOM onto ENPs,

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acknowledging its importance for the environmental fate and effects of ENPs. In addition, NOM can interact with ENPs in other ways depending on the type of NOM, for example by forming larger aggregates (Buffle et al., 1998).

Several experimental studies report that an eco-corona of NOM reduces or mitigates the ecotoxicity of different ENPs, such as zinc oxide (Kteeba et al., 2017, 2018), carbon nanotubes (Lawrence et al., 2016), zero-valent iron (Li et al., 2010), copper oxide (Zhao et al., 2013), silver (Cáceres-Vélez et al., 2018) and titanium dioxide (Lüderwald et al., 2019). However, whether such reduction in ecotoxicity is prevalent over a wide range of ENPs has not yet been shown. How such as potential reduction in ecotoxicity can be quantitatively considered when assessing ecotoxicity as part of environmental risk assessments of ENPs have not yet been shown either. In existing environmental risk assessment approaches for ENPs, ecotoxicity assessments have been based on pristine ENPs. This goes for both the effect assessment part of quantitative risk assessments (Blaser et al., 2008; Boxall et al., 2007; Coll et al., 2016; Gottschalk et al., 2013a; Gottschalk et al., 2009; Kjølholt et al., 2015; Mueller and Nowack, 2008; Wang et al., 2016a; Wigger and Nowack, 2019) and for screening, semi-quantitative risk assessment approaches in which some form of toxicity assessment is included (Arvidsson et al., 2018; Hansen et al., 2014; O'Brien and Cummins, 2010).

The aim of this study is to investigate the influence of NOM on the ecotoxicity of ENPs. More specifically, the aim is to identify possible empirical correlations which allow for a pragmatic inclusion of the influence of NOM on ENP ecotoxicity in environmental risk assessments. Considering the increasing number of nanoproducts on the market (Hansen et al., 2016; Vance et al., 2015), such risk assessments are important for providing guidance to decision making at national and international levels. Our study is centred around the following research questions:

1. Can an empirical correlation between NOM and reported 50% effect concentrations (EC50), 50% lethal concentrations (LC50) and/or 50% inhibition concentrations (IC50) be established for a relatively wide range of ENPs?
2. Can that correlation be quantitatively described for the purpose of risk assessments?

Throughout the study, the general abbreviation “XC50” will be used to refer to any of those three toxicity measures, where X stands for either of E, L or I.

The research questions are addressed through statistical analyses of data obtained in a literature review of studies quantifying the influence of NOM on ENP ecotoxicity. The review is focussed on reported XC50 values, which traditionally are regarded as the most robust and model-independent measures of toxicity, from ecotoxicity tests. Such values are today used for classification and labelling of chemicals substances and ENPs as well as in quantitative risk assessment to estimate predicted no-effect concentrations using assessment factors or species sensitivity distributions (European Chemicals Agency, 2011; European Commission, 2008). Furthermore, the XC50 values are also an integrated part of some screening risk assessment methods that have been proposed for ENPs in the literature (Arvidsson et al., 2018; Hansen et al., 2014).

2. Method and materials

Considering the common use of XC50 values in environmental risk assessments of ENPs, correlations between reported XC50 values and NOM were sought in the form of empirical equations of the type:

$$XC50 = f(NOM) \tag{1}$$

This is in accordance with correlations suggested by van Hoecke et al. (2011). It should be noted that a number of previous studies have developed other estimation methods for ECx values and various inherent properties of ENPs (Cai et al., 2019; Mu et al., 2016; Puzyn et al., 2011). However, these are specific to some type or groups of ENPs (e.g. metal oxides) and none of these empirical correlations include the consideration of NOM, which several of the reviewed studies (see Section 3) report is of high importance for ENP toxicity.

2.1. Review procedure

As indicated in Section 1, adsorbed NOM can go by several names, such as NOM coating, eco-corona, environmental corona and organic corona. Therefore, a broad search string was used in the search engine Scopus (www.scopus.com, 2020-08-29):

TITLE-ABS-KEY((*corona* OR (organic AND coating*) OR (natural AND organic AND matter) OR nom OR “fulvic acid” OR “humic acid”) AND (nanoparticle* OR (nano-sized AND particles)) AND *toxic*).

In order to ensure environmental relevance, only ENPs with existing or near-term applications were considered, meaning that ENPs with a currently low probability of becoming released to the environment were omitted. This was operationalized so that the study had to consider ENPs known to be produced at significant amounts in society (Furberg et al., 2016; Keller and Lazareva, 2013; Keller et al., 2013; Piccinno et al., 2012) in order for it to be included in the review. Consequently, we omitted a very limited number of studies, for example of one about nano-sized diamonds (Mensch et al., 2017). As an exception to this general rule, one study on silver sulphide NPs was included in the review as those NPs were formed from manufactured silver nanoparticles (Liu et al., 2018). This resulted in 66 toxicity studies being identified as relevant to include (see Table S1 in the Supplementary material (SM) for a full list of the 66 studies). Once identified, the 66 studies were carefully examined and available XC50 values, both with and without NOM present, were extracted. The concentration of NOM ([NOM]), in the unit mg carbon per litre, was sometimes reported as total organic carbon (TOC), sometimes as dissolved organic carbon (DOC) and sometimes as concentration of NOM. Besides the NOM concentration, additional parameters such as pH, media composition (in terms of micro- and macro-ions), water conductivity, salinity and ionic strength in the test system were reviewed in order to try to enable more complex empirical correlations involving other parameters than NOM itself. Unfortunately, pH was the only additional test medium-related parameter consistently reported in all studies reporting XC50 values.

2.2. Statistical analyses

In order to investigate potential empirical correlations between the gathered XC50 values and [NOM], Spearman's rank correlation coefficient r was calculated according to:

$$r = 1 - \frac{6\sum d^2}{n^3 - n} \tag{2}$$

where d is the difference in rank between XC50 and corresponding [NOM] values and n is the number of data points. A coefficient value of 1 means high positive correlation, a value of -1 means high negative correlation and 0 means no correlation.

Quantitative empirical correlations between XC50 and NOM were furthermore investigated by regression analysis (linear, power law, polynomial, exponential and logarithmic) plotting XC50 against [NOM]. Previous studies have suggested a linear correlation between ecotoxicity and [NOM] (specifically a linear reduction), at least for some species and within certain [NOM] ranges (Gao et al., 2012; van Hoecke et al., 2011; Wormington et al., 2017). However, according to van Hoecke et al. (2011), not only [NOM] but also pH influenced the EC20 values of TiO_2 ENPs, the reason being that pH influences the adsorption of NOM onto particle surfaces. Since corresponding pH values were available for all XC50 values in the dataset, a multiple linear

regression (MLR) analysis was also conducted, investigating the possible linear correlation of XC50 (as output parameter) with both [NOM] and pH (the two input parameters). These calculations were carried out for all ENPs as one single set, but also for the individual ENPs for which there were enough data points to render such calculations feasible, i.e. silver (Ag), titanium dioxide (TiO_2), copper and copper oxide (Cu/CuO) and zinc oxide (ZnO). Because of the low number of data points (three and two, respectively), no separate calculations were conducted for silicon dioxide (SiO_2) and cerium dioxide (CeO_2). Finally, the ratio between "XC50 with NOM present" and "XC50 without NOM present" was plotted against [NOM] in order to see if the relative *change* in XC50, rather than the XC50 values themselves, showed any correlation with [NOM].

3. Results and discussion

Of all 66 studies reviewed, 53 (80%) concluded that NOM reduced effects. Ten (15%) of the studies reported no influence or unclear influence. Only three (5%) studies reported that toxicity was increased by NOM: two studies about TiO_2 ENPs (Farkas et al., 2015; Yang et al., 2013) and one about CuO ENPs (Wang et al., 2011). There is thus strong evidence that NOM reduces toxicity of ENPs in most cases. This finding is in agreement with that of the recent review by Xu et al. (2020) about biological effects of environmental coronas, where they write that "[i]n most cases, NOM and [extracellular polymeric substances] coronas were reported to alleviate the […] hazards of [engineered nanomaterials] to aquatic organisms.

Several possible explanations for this reduction have been proposed, for example that the adsorbed NOM forms a soft "cushion" which physically hinders the ENPs from getting into contact with the organism (Chen et al., 2011; Li et al., 2010; Liu et al., 2018). Another common explanation proposed is that the NOM captures and pacifies reactive oxygen species in the test system, which might otherwise have caused toxicity to the organism (Gao et al., 2012; He et al., 2017; Lawrence et al., 2016). Many of the studies also propose that the NOM forms complexes with dissolved ions released from ENPs, resulting in a decrease in toxicity (Angel et al., 2013; Cáceres-Vélez et al., 2018; He et al., 2017; Kteeba et al., 2018; Li et al., 2011; Noventa et al., 2018). This is consistent with the classical view on the influence of speciation of metal ions with NOM resulting in a toxicity decrease (Aiken et al., 2011) and the requirement of using media with low content of organic carbon in the standard OECD guideline tests for ecotoxicity of metals (OECD, 2004, 2019).

For photoactive ENPs specifically, one cause of toxicity mitigation might also be a shading influence caused by NOM lowering the photocatalytic activity of the ENP and leading to formation of less reactive oxygen species that may cause toxicity (e.g. Tong et al., 2013; Zhang et al., 2018). Finally, some studies propose that the NOM might also serve as a source of nutrients for some organisms, thereby improving their conditions and making them less susceptible to harm, thereby reducing toxicity (e.g. Binh et al., 2014; Cerrillo et al., 2016). In the few cases where an increased toxicity was observed, one frequently proposed explanation is that the presence of NOM stabilizes the ENP dispersion, ensuring that the particles remain suspended and due to their small size can cause harm (e.g. Wang et al., 2011).

The review also resulted in the identification of a dataset of 91 XC50 values from experiments with NOM added, along with corresponding [NOM] and pH values. For 82 of those values, corresponding XC50 values from non-NOM experiments were also reported. The full dataset is provided in Table S2 in the SM. Of the 91 XC50 values with NOM present, 31 was for Ag ENPs (34%), 32 for TiO_2 ENPs (35%), 15 for Cu/CuO ENPs (16%), 8 for ZnO ENPs (9%), 3 for SiO_2 ENPs (3%) and 2 for CeO_2 ENPs (2%). The organisms tested represent a wide range of different species often used in ecotoxicological studies, including bacteria (19% of XC50 values), most often *Escherichia coli*, different algal species (21%), crustaceans (55%) (*Daphnia magna* and *Ceriodaphnia dubia*), as well as zebrafish (3%) and diatoms (2%). Note that some studies include multiple species. However, there do not seem to be any organism type-specific trends in the XC50 values obtained from the studies (Fig. S1, SM).

Table 1
Spearman's rank correlation coefficients for a ranking analysis of the concentration of NOM and the XC50 values reported in ecotoxicity studies of a range of engineered nanoparticles (ENPs). Ag = silver. TiO_2 = titanium dioxide. Cu/CuO = copper/copper oxide. ZnO = zinc oxide.

Stressors	Rank correlation coefficient	Significance level
All ENPs	−0.037	< 75%
Ag ENPs	0.42	97.5%
TiO_2 ENPs	0.52	99.75%
Cu/CuO ENPs	−0.095	< 75%
ZnO ENPs	0.23	< 75%

Based on this input data, analyses were conducted to describe this general reduction in toxicity quantitatively in Sections 3.1 and 3.2 below, with the aim of making recommendations for how this can be embedded in environmental risk assessments of ENPs.

3.1. Correlation between toxicity and concentration of NOM

The concentration of NOM ([NOM]) was the only NOM-related parameter which was frequently and consistently reported alongside with the XC50 values. This allows for a ranking analysis of the data and Table 1 shows rank correlation coefficients between XC50 and [NOM]. The only ENP for which both a high (> 0.5) correlation coefficient and a high (> 95%) significance level was achieved was for TiO_2: 0.52 and 99.75%, respectively. This points at TiO_2 ENPs having the strongest correlation between XC50 and [NOM]. For Ag ENPs, the coefficient had a significance level of 97.5%, but the coefficient value of 0.42 does not indicate a strong rank correlation. For the Cu/CuO and ZnO ENPs, the correlation coefficients were low, which was also the case when all ENPs were considered as a totality.

Plots of XC50 against [NOM], investigating different possible empirical correlations, were then conducted. These plots generally showed no obvious correlation visual to the naked eye (Fig. 1). When all ENPs were considered together, the best fit was a power law correlation ($y = bx^a$), still achieving an R^2 value of 0.0096 only and an almost horizontal line (Fig. 1a). The fits were generally better when the specific ENPs were considered one by one. As indicated by the Spearman's rank correlation coefficients, the best fit was obtained for TiO_2 ENPs, for an increasing second-order polynomial correlation ($y = ax^2 + bx + c$) with an R^2 value of 0.81 (Fig. 1b), implying a reduction of toxicity with higher [NOM] as reported in most ecotoxicological studies. For Ag ENPs, the best fit was also obtained with a power law correlation, giving an R^2 value of 0.18 (Fig. S2, SM). For Cu/CuO ENPs, an exponential correlation ($y = be^{ax}$) gave the best fit with an R^2 of 0.13 (Fig. S3, SM), and for ZnO ENPs, a second-order polynomial correlation gave the best fit with an R^2 of 0.71 (Fig. S4, SM). However, for the latter two ENPs, there were relatively few datapoints to substantiate the correlations. Overall, even the best fits performed rather poorly, showing no strong empirical correlation between XC50 and [NOM] for the standard ones tested here (linear, power law, polynomial, exponential and logarithmic).

An MLR analysis was then conducted to investigate whether the inclusion of pH as an input parameter would result in stronger empirical correlations. The MLR analysis gave low (< 0.3) R^2 values when conducted on the entire set of ENPs as well as on Ag ENPs and Cu/CuO ENPs separately. The exact values can be found in Table S3 in the SM. However, for TiO_2 ENPs, when also taking pH into account, an R^2 value of 0.72 (with an adjusted R^2 of 0.70) was obtained. This is in line with results from the Spearman's rank correlation coefficient and the plotting of XC50 against [NOM], both showing comparatively higher

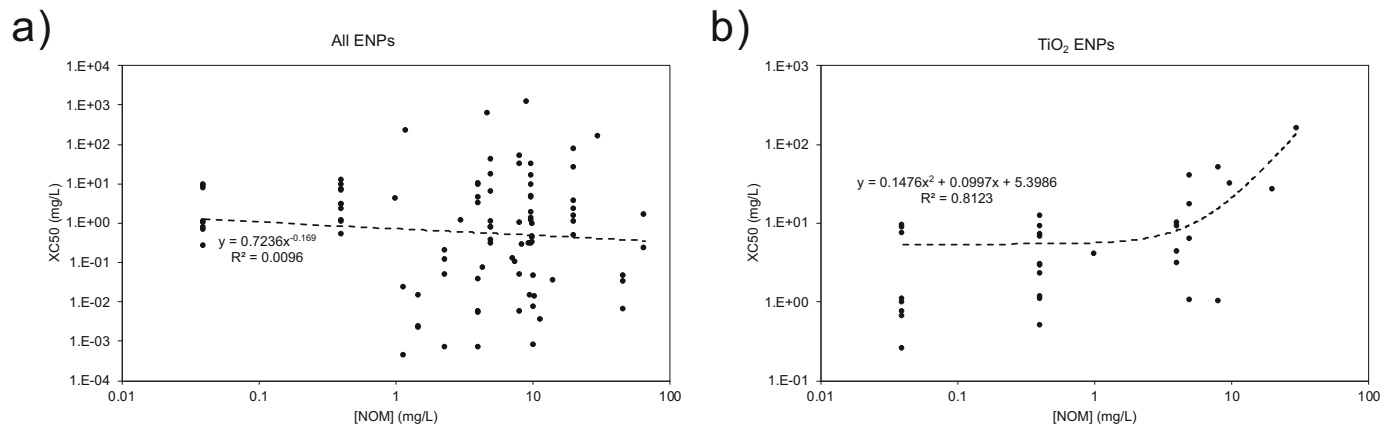

Fig. 1. Plots of XC50 against [NOM] with logarithmic scales for (a) all ENPs and (b) TiO_2 ENPs. Dashed lines show power law and second-order polynomial correlations, respectively.

correlations for TiO_2 ENPs than for the other ENPs. However, it should be noted that the MLR results for TiO_2 ENPs are highly sensitive to a certain datapoint with high XC50 value (156 mg/L). If this datapoint is removed, the R^2 value drops from 0.72 to 0.28. This heavy dependency on one datapoint means that the MLR results for TiO_2 ENPs are not robust. In the MLR analysis for ZnO ENPs, a relatively high R^2 value was also obtained (0.71, with an adjusted R^2 of 0.59) for the following empirical correlation:

$$XC50_{ZnO} = 6.56 + 0.0836[NOM] - 0.809pH \quad (3)$$

where XC50 and [NOM] are measured in mg/L. Fig. 2 shows the eight experimental, raw data XC50 values for ZnO ENPs compared with XC50 values calculated using Eq. (3). Although there is some agreement between the experimentally measured and calculated XC50 values, the modest R^2 value still means that this empirical correlation cannot be considered strong. It is also important to stress that Eq. (3) has a domain for which it is valid. For example, different combinations of [NOM] and pH might result in negative XC50 values, also under environmentally realistic conditions with lower [NOM] values (e.g. ≤1 mg/L) and higher pH values (e.g. > 8). In addition, Eq. (3) is based on experimental input ranges of [NOM] and pH beyond which the validity of the equation cannot be guaranteed, i.e. 3–20 mg/L for [NOM] and 7.0–8.5 for pH. Although these ranges roughly cover environmentally relevant ranges, this means that Eq. (3) might not apply to extreme values of [NOM] and pH. Environmentally realistic examples might be an acidic lake with a pH of about 6.0 and a clear mountain lake with [NOM] < 1 mg/L.

This analysis shows that the empirical correlations obtained from the MLR analysis only have modest explanatory power given certain validity domains in terms of [NOM] and pH. Similarly, for CeO_2 NPs, the algae *Pseudokirchneriella subcapitata* and NOM of natural origin, van Hoecke et al. (2011) derived an empirical correlation considering [NOM] and pH based on multivariate experiments:

$$EC20 = -1626.4pH + 109.45pH^2 + 116.49[NOM] - 14.317pH[NOM] + 6007.2 \quad (4)$$

This correlation found by van Hoecke et al. (2011) could explain 93.7% of the variability in the experimental data and shows the same general trend as Eq. (3), that for pH in the normal testing range for guideline ecotoxicity tests (pH 7.0–8.0), increasing [NOM] leads to higher EC20 values and hence lower toxicity. The ranges of [NOM] and pH in the experiments were 0–10 mg/L and 6.0–9.0, respectively, which is similar to the ranges in the literature reviewed in the present study. Although the empirical correlation in Eq. (4) has stronger explanatory power (R^2 = 0.937) than those obtained in the present study, it thus also suffers from the drawbacks of being limited to a certain ENP and certain validity domains.

3.2. Change in observed XC50 due to the concentration of NOM

In Fig. 3, the ratio between XC50 values with and without the presence of NOM in ecotoxicity tests ($XC50_{NOM}/XC50_{no\ NOM}$) is plotted

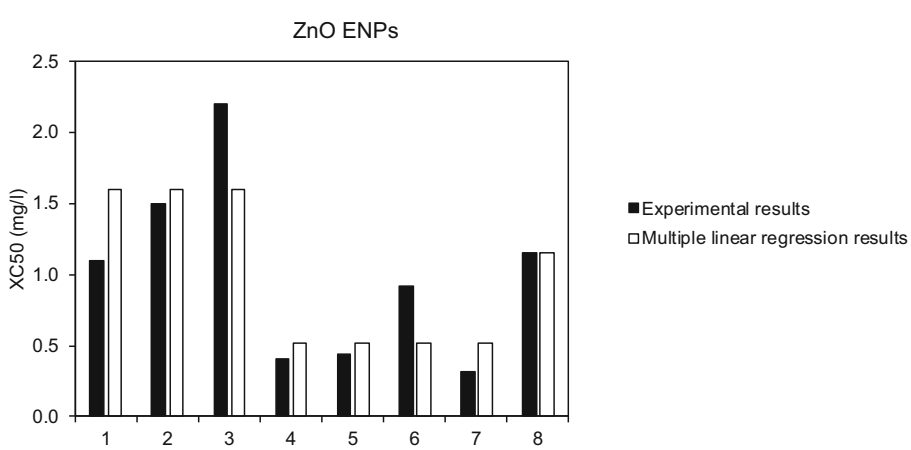

Fig. 2. Experimental XC50 values (black) compared with XC50 values calculated using the MLR analysis correlation in Eq. (3) (white) for ZnO ENPs.

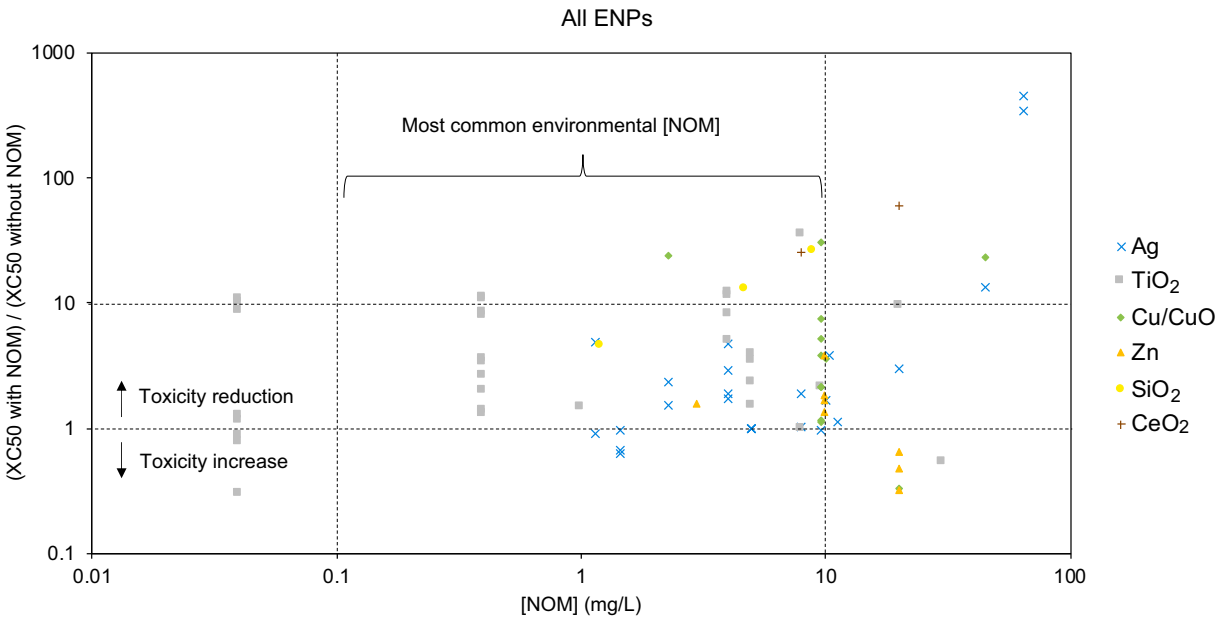

Fig. 3. Ratio between observed XC50 values in aquatic ecotoxicity tests with and without the presence of NOM plotted against the concentration of NOM [NOM]. The dashed lines on the horizontal axis show the most common [NOM] range in the environment. The dashed lines on the vertical axis show (i) no toxicity reduction/increase due to the presence of NOM and (ii) a tenfold toxicity reduction due to the presence of NOM.

against [NOM]. The trend that NOM reduces toxicity shows clearly, in accordance with the reports of most (80%) of the studies reviewed. There is also a trend that the higher [NOM] results in reduced toxicity. When interpreting Fig. 3, it is important to note that the [NOM] in the environment approximately ranges between 0.1 and 10 mg/L (Philippe and Schaumann, 2014), which is why this range is highlighted in Fig. 3. This means that ratio values outside this [NOM] range may be of less relevance from an environmental risk assessment point of view, since they represent more unusual environmental conditions. It can be noted that most [NOM] values reported are within this range (65 out of 91, corresponding to 78%), sometimes explicitly to ensure environmental relevance (e.g. Liu et al., 2014) or because natural water with natural [NOM] in this range was used (e.g. Joonas et al., 2019).

When focusing on the data points within the 0.1–10 mg/L range for [NOM], it is clear that most studies report a reduced toxicity due to NOM. Only a few data points (5) in this range, notably only for Ag ENPs, report an increased toxicity. However, these cases do not report a large increase; at most, the XC50 value reduction was by a factor of 0.63. For most data points (43) in the 0.1–10 mg/L [NOM] range, the reduction in toxicity due to the presence of NOM is between a factor of 1 to 10. Seven studies report reductions larger than factor of 10 in this range. For this reason, it seems reasonable to suggest that the presence of NOM under environmentally realistic concentrations generally increases the XC50 with up to a factor of 10 compared to tests with no presence of NOM:

$$XC50_{NOM} \leq 10XC50_{no\ NOM} \tag{5}$$

Based on available data, the probability of this correlation being true is 43/58 = 74% within the [NOM] range of 0.1–10 mg/L. If the reduction ratio range is extended somewhat from 1–10 to 0.63–14, only five data points within the environmentally relevant [NOM] range are outside this ratio range, which means that 53/58 = 91% of the data points are within this reduction ratio range:

$$XC50_{NOM} \in [0.63XC50_{no\ NOM} 14XC50_{no\ NOM}] \tag{6}$$

These two correlations (Eqs. (5) and (6)) seem to apply for the whole [NOM] range of 0.1–10 mg/L, although there are notably more data points towards the higher end of the range to substantiate the correlation. It can be noted that there was no notable difference between the toxicity reduction found for soluble ENPs (Ag, Cu/CuO and ZnO) and poorly soluble ENPs (TiO_2, SiO_2 and CeO_2) under the testing conditions and/or environmentally realistic conditions, see Fig. S5 and S6. In both cases, within the environmentally common [NOM] range of 0.1–10 mg/L, most data points fall roughly between a factor of 1 and 10 toxicity reduction. Thus, there does not seem to be any strong reason to differentiate between soluble and poorly soluble ENPs in this case. This is in line with the previous results from the Spearman's rank correlation, the plotting of XC50 against [NOM] and the MLR analyses (Section 3.1), which did not generally show stronger correlations for soluble ENPs.

3.3. Recommendations for inclusion of the toxicity mitigation of NOM in risk assessments of ENPs

A number of empirical correlations between the influence of the presence and concentration of NOM on the observed toxicity of ENPs in aquatic toxicity tests have been investigated throughout this study, including a polynomial correlation between XC50 of TiO_2 ENPs and [NOM] (Fig. 1b) and a multiple linear correlation between XC50 of ZnO ENPs, [NOM] and pH (Eq. (3)). However, these correlations only cover two ENPs and the R^2 values were only 0.81 and 0.71, respectively. This can be compared to the explanatory power in the study by van Hoecke et al. (2011), where NOM explained 93.7% of the variance in their equation for EC20 values (Eq. (4)). In addition, the correlations derived in the current study only provide the option of XC50 values for two types of ENPs and are only valid for certain domains of pH and [NOM]. In order to provide more useful recommendations for environmental risk assessments, we instead turned to the analysis of the relative change in XC50 due to the addition of NOM (Section 3.2). From this analysis, it is clear that most of the XC50 values observed in tests in the presence of NOM are higher than XC50 values without NOM. This means that applying XC50 values from tests without NOM as a proxy for XC50 with NOM generally does not seem to underestimate the toxicity. In addition, most (74%) of the XC50 values in the environmentally relevant [NOM] range are a factor of 1–10 higher than corresponding XC50 values without NOM (Eq. (5)). This means that applying XC50 values without NOM as proxy for XC50 values with NOM generally does not seem to overestimate the risk tremendously either. As a pragmatic and reasonably conservative approach in environmental risk

assessments of ENPs, we therefore suggest that XC50 values obtained in aquatic ecotoxicity tests of ENPs without NOM present can be used as a proxy for XC50 in the presence of NOM. This will be simple and feasible to apply since XC50 values without NOM are readily available for many ENPs, for example in the NanoE-Tox database (Juganson et al., 2015). However, while this empirical correlation might be applied as a pragmatic proxy for the time being, there are some data points below 1 and above 10 in Fig. 3, also in the [NOM] range of 0.1–10 mg/L. This shows that further research efforts to decipher the correlation between XC50 values and NOM are still needed.

In this respect, the perhaps most important question to answer is whether NOM will *not* have a mitigating influence on toxicity for certain ENPs or under actual environmental conditions. Regarding certain ENPs, it can be noted that the XC50 values reported in the review studies are only for metal and metal oxide ENPs, but not for other groups of ENPs, such as carbon-based ENPs. These were not omitted from this study due to the composition or use of carbon-based ENPs, but the reviewed studies covering carbon-based ENPs simply did not express the results in terms of XC50 values. To broaden the available data for correlation analyses, we recommend that future studies also for carbon- and polymer-based ENPs (and other ENPs not covered in Fig. 3 and Table S2 (SM)) focus on deriving XC50 values. Regarding actual environmental conditions, some of the reviewed studies considered [NOM] values > 60 mg/L, which constitutes relatively high concentrations compared to what is generally found in the environment. Also, in currently ecotoxicity tests, concentrations of ENPs tend to be in the μg/L-mg/L range, whereas measured and predicted concentrations of ENPs in the actual surface waters are generally 1–2 orders of magnitude lower, i.e. in the ng/L-μg/L range or even lower (Gottschalk et al., 2013b). Testing at environmentally relevant concentrations regarding both NOM and ENPs is recommended in order to provide knowledge and data relevant for environmental risk assessments. Alternatively, another way to achieve environmental relevance might be to conduct ecotoxicity tests at [NOM]/[ENP] ratios similar to what may be encountered the environment. These ratios will be dependent on the ENP in question and will rely on accurate estimates of environmentally relevant ENP concentrations. Based on the numbers above, a wide range between 1 (for [NOM] = 0.1 mg/L and [ENP] = 100 μg/L) and 10^7 (for [NOM] = 10 mg/L and [ENP] = 1 ng/L) is possible. However, the [NOM]/[ENP] ratios may be included as design criteria for future ecotoxicity studies of ENPs by clearly stating the assumptions going in to establishing these. We also recommend characterizations of the composition of the NOM used in experiments, especially in cases where non-standardized NOM is used, since this might enable the unrevealing of correlations between the NOM composition and ecotoxicity. Such characterizations are rarely conducted in the reviewed studies. A notable exception is the study by Seitz et al. (2016), which found that NOM high in aromatic and hydrophobic components had a stronger mitigating influence on the toxicity of TiO_2 ENPs.

A final comment can be made regarding the choice of dose metric (i.e. unit) for the XC50 values, which are reported in terms of mass in all reviewed ecotoxicity studies. Suggestions of different metrics have been made, such as particle number (Handy et al., 2008), surface area (van Hoecke et al., 2008) and recently also volume (Verschoor et al., 2019). Since the measurements in the reviewed papers rarely allow for a scientifically justified extrapolation beyond mass as metric, we were here bound to mass as the only possible metric to base the analyses on. However, we consider it highly relevant to investigate whether other dose metrics can give stronger correlations between aquatic ecotoxicity and NOM.

4. Conclusions

The main conclusion from this study is an empirical correlation between XC50 values and [NOM], which might be used as a pragmatic proxy until further research have provided more reliable correlations. Currently available data show that in most environmentally relevant cases, applying XC50 values without NOM – i.e. XC50 values for pristine ENPs without an eco-corona – provides a reasonably conservative estimate of XC50 values with NOM present. A recommendation for risk assessments based on our study of the currently available literature is therefore that applying XC50 values for ENPs generated in aquatic toxicity tests without the presence of NOM will result in conservative, but not overly conservative, safety assessments. However, we recommend further studies to investigate whether this empirical rule of thumb holds, e.g. for different organism species and ENPs under environmentally realistic conditions. In particular, it would be important to know if the rule of thumb provides misleading and/or non-conservative toxicity assessment results given some particular conditions.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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