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▶ To cite this version:

Andrea Rivero Arze, Catherine Mouneyrac, Amélie Chatel, Nicolas Manier. Comparison of uptake and elimination kinetics of metallic oxide nanomaterials on the freshwater microcrustacean Daphnia magna. Nanotoxicology, 2021, 10.1080/17435390.2021.1994668. ineris-03470734

HAL Id: ineris-03470734 https://ineris.hal.science/ineris-03470734

Submitted on 8 Dec 2021

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<u>Comparison of uptake and elimination kinetics of metallic oxide</u> nanomaterials on the freshwater microcrustacean *Daphnia magna*

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The Version of Record of this manuscript has been published and is available in Nanotoxicology, 2021, https://www.tandfonline.com/doi/full/10.1080/17435390.2021.1994668

Abstract

The widespread use and release of nanomaterials (NMs) in aquatic ecosystems is a concerning issue as well as the fate and behavior of the NMs in relation to the aquatic organisms. In this work, the freshwater microcrustacean D. magna was exposed to 12 different and well-known NMs under the same conditions for 24h and then placed in clean media for 120h, in order to determine their different uptake and elimination behaviors. The results showed that most of the tested NMs displayed a fast uptake during the first hours arriving to a plateau by the end of the uptake phase. The elimination behavior was determined by a fast loss of NMs during the first hours in the clean media, mainly stimulated by the presence of food. Remaining NMs concentrations can still be found at the end of the elimination phase. Two NMs had a different profile i) ZnO-NM110 exhibited increase and loss during the uptake phase, and ii) SiO₂-NM204 did not show any uptake. A toxicokinetic model was applied and the uptake and elimination rates were found along with the dynamic bioconcentration factors. These values allowed to compare the NMs, to cluster them by their similar rates, and to determine that the TiO₂-NM102 is the one that has the fastest uptake and elimination behavior, SiO₂-NM204 has the slowest uptake and CeO₂<10nm has the slowest elimination. The present work represents a first attempt to compare different NMs based on their uptake and elimination behaviors from a perspective of the nano-bio interactions influence.

Keywords: Daphnids, nanomaterials, uptake, elimination, toxicokinetics, modelling.

1. Introduction

From production to release, metal oxide nanomaterials (NMs) predominate in emissions to water according to the NMs estimated global mass flow (Keller and Lazareva, 2014). The applications of these NMs are widely spread. For example SiO₂ NMs have many application in industry as ceramic producing, glass making, cosmetic products, medicines, magnetic mixtures and to increase the strength and stability of industrial coverings (Shariati et al., 2020). Applications of TiO₂ NMs include food industry, personal care products, catalysis, purification agents, antimicrobial agents and numerous coatings of building materials (Tan and Wang, 2017). CeO₂ NMs have been used increasingly in ceramics, photosensitive glass, fuel catalysts, sunscreens and paints (Angel et al., 2015). ZnO NMs are being used in sunscreens, cosmetics, ointments (antimicrobial), paints, plastics and electronic semi-conductors (Bhuvaneshwari et al., 2018). Given this widespread use of NMs containing products and the augmented number of NMs applications, it is expected that the amount of metal-based engineered NMs released into the aquatic environment will continue to increase (Baek et al., 2019).

Aquatic organisms have to cope with this increasing presence of NMs in their ecosystems. The toxic effect of metallic oxide NMs in aquatic organisms has been widely observed during the last decades; from microalgae (Nguyen et al., 2020), passing through marine invertebrates (Canesi and Corsi, 2016) to fish (Handy et al., 2008). Concerning freshwater, *Daphnia magna* is a well-known ecotoxicological test organism that had already been used to test NMs effects (Juganson et al., 2015). The interest of this filer-feeding organism in the NMs uptake and elimination experiments is that the uptake capacity for the aquatic exposure is related to their normal feeding behaviors (Roberts et al., 2007), specially for low concentration exposures (Zhu et al., 2009). Uptake and elimination studies in *D. magna* already exist, as they represent a key

level in trophic chains while feeding on unicellular organisms and serving as prey for second

consumers (Petersen et al., 2019), but the experiments are always focused on one or two NMs at the time, *i.e.* TiO₂ NMs (Tan and Wang, 2017), CuO NMs (Wu et al., 2017), Ag NMs (Ribeiro et al., 2017) (Kalman et al., 2015) (Pakrashi et al., 2017), Au NMs (Skjolding et al., 2014), ZnO NMs (Danabas et al., 2020).

Modelling the NMs uptake in organisms is essential to reinforce experimental research, develop overarching theories, improve our fundamental understanding of NMs exposure and hazard, and thus to enable risk assessment of NMs (Baalousha et al., 2016). There are several publications concerning the exercise of modelling the exposure, uptake and elimination of NMs in aquatic organisms (Arini et al., 2020) (Garner et al., 2018) (Wray and Klaine, 2015) (Croteau et al., 2011). Specifically, D. magna has also been used in NMs modelling studies (Fan et al., 2016) (Khan et al., 2015) (Sakamoto et al., 2015). Nonetheless, in the NMs environmental risk assessment, there is uncertainty about the actual forms and environmental concentrations of NMs and exposure modelling, as well as the difficulty to determine which facets of the physicchemical properties of NMs are the most important to the hazard (Klaine et al., 2012). Understanding nanomaterial-biological (nano-bio) interactions, and organism responses to the NMs, is a crucial step in elucidating their environmental safety and facilitating their regulation (A. Ellis and Lynch, 2020). The nano-bio interaction, as understood for this study, is a set of multiple physical, chemical and biological interactions; that globally includes all possible interactions between an organism and a NM. The parameters that rule these interactions can depend on the NMs properties, the organism's characteristics and the combination of both.

The unique behavior of the NMs substances as particulate pollutants and their underlying physicochemical mechanisms that lead to the accumulation of different NMs into aquatic organisms are still not well understood, and they have been studied in a case-by-case basis as previously shown. To date, there are very few studies where different NMs are tested under the same experimental conditions, so comparison between different NMs uptake and elimination

behaviors is difficult, though essential, if we want to better understand the mechanisms that drive these phenomena.

Therefore, using the freshwater cladoceran *D. magna* and a set of 12 different and well-known metal oxide NMs, the authors present a systematic study that aims to answer the following questions: First, are the uptake and elimination behaviors of the tested NMs different? And which are the characteristics of these differences? Are these behaviors suitable for being modeled? And if so, how the model resulting parameters as the uptake and elimination rates can inform us about the different interactions of NMs and organisms? Finally, the possibility of clustering NMs with similar uptake and/or elimination characteristics is addressed.

2. Materials and Methods

2.1.Test organism

The test organism of this study is the freshwater cladoceran *Daphnia magna* Straus. The organisms are raised permanently in the laboratory facilities in an Elendt M4 media (composition in Supplementary Data). Temperature is at $20 \pm 2^{\circ}$ C with a day-night cycle of 16h of light (1000-1500 lux). They are fed daily with freshwater microalgae (*Chlorella vulgaris, Desmodesmus subspicatus* and *Raphidocellis subcapitata*) at 2 mg/L TOC and the offspring is daily removed.

2.2.Nanomaterials preparation and characterization

The set of the chosen nanomaterials for this study came from the JRC Nanomaterial Repository and are considered as reference nanomaterials as they are well known and characterized. The set consisted on 6 TiO₂ NMs (NM100, NM101, NM102, NM103, NM104 and NM105), 3 SiO₂ NMs (NM200, NM202 and NM204), 1 ZnO NMs (NM110) and the 2 CeO₂ NMs were named in relation to their diameter size as CeO₂<10nm (NanoBYK[®]) and CeO₂ <25nm (Sigma Aldrich nanoCeO₂). The description, preparation protocols and main characteristics of the NMs are detailed in a precedent work (Rivero Arze et al., 2020). NMs stock suspensions were prepared at 1 g/L in ultrapure water and added directly to the test containers with ISO media to arrive to the exposure concentration of 1 mg/L.

Stock and exposure suspensions were characterized (size distribution and zeta potential) by Dynamic Light Scattering (DLS; NanoZS, Malvern Instruments[®]). For each analysis, three measurements were done at 10 mg/L, directly after sampling. Noninvasive back scatter detection at 173° with a He-Ne laser ($\lambda = 633$ nm) as light source was used. The aggregates or agglomerates sizes were determined by the Non-Negative Least Squares (NNLS) analysis method at 25 °C, after an equilibration time of 60 s. Each measurement is an average of 13 runs of 10 s.

The dissolution of ZnO-NM110 was studied in three independent replicates under the same organisms' exposure conditions (1 mg/L) using centrifugal ultrafilters (3kDa NMWCO, Amicon[®] Ultra, Milipore). Samples were collected at 0, 2, 6 and 24h; centrifugated at 4000g for 40 minutes and dosed by ICP-OES as detailed below.

2.3. Uptake and elimination experiments

For each uptake and elimination experiment, 1100 neonates were put in 10 aquariums of 4 L of M4 media each one, distributing 110 organisms per aquarium. For one week the daphnids were fed with the freshwater microalgae *Raphidocelis subcapitata* at a concentration equivalent of 1 mg/L TOC. When the organisms arrived at their 8th day, the uptake phase started. Prior to the exposure, the daphnids were fed one last time, after one hour they were placed in clean ISO media for acclimatization and to clean their guts, where they remained for another hour. This time was chosen base on previous studies that showed that 15-30 minutes are necessary to clear the guts of daphnids from non-contaminated algae (Barata et al., 2002).

Then, the organisms were placed by groups of 50 individuals in 1L containers with ISO media spiked with NMs at a concentration of 1mg/L. This concentration was chosen based on a 'sublethal' effect concentration scale for the organisms and taking into account the results of (Zhu et al., 2010), where good delimitations of the uptake and elimination curves were obtained for nTiO₂. The sampling of the uptake phase was made in independent triplicates at 0, 1, 2, 4, 6 and 24 hours, each sample consisted on 25 individuals of each container, leaving the other 25 for the elimination phase (experimental design in Supplementary Data). The collected individuals were left to swim freely during 5 minutes in a clean media container to lose any weakly attached NMs to the carapace and to ensure that no additional NMs, coming from the media, were added to the samples. After 24h of exposure, the daphnids were collected, placed in other set of containers with clean ISO media and fed daily with *R. subcapitata* 1.7 mg/L TOC for the elimination phase. The sampling of this phase was done at 2, 6, 24, 48 and 120 hours. All samples were dried in an oven at 70°C for 24h in order to obtain their dry weight.

2.4. Acid digestion and ICP-OES analysis

Samples of TiO₂, ZnO and CeO₂ NMs exposed daphnids and media were digested in 50 mL Teflon reactors using 3 mL of ultra-pure HNO₃ and 2 mL of HBF₄. For the SiO₂ NMs samples HF was used instead of HBF₄ and they were neutralized with 20 mL of 55 g/L ultra-pure boric acid after digestion . The acid digestion was carried out using a microwave (Mars6, CEM), for the SiO₂ NMs samples, the process consisted on a 30 min temperature rise ramp until 205°C and hold for 30 min (1800 W). For the rest of the samples the digestion program had four temperature rise ramps, i) to 120°C for 15 min, ii) to 140°C for 5 min, iii) to 160°C for 5 min, iv) to 200°C for 10 min with a hold at that temperature for 20 min.

Water samples were taken at the middle of the water column. Each time 5 mL of media were sampled at the beginning and the end of the uptake and elimination phases respectively. The acid digestion process was the same as the one applied to the organisms.

After digestion, all samples were adjusted to a final volume of 50mL and analyzed using an inductively coupled plasma optical emission spectrometry (ICP-OES; Agilent Technologies 5110). For some water samples, an inductively coupled plasma mass spectrometry (ICP-MS Agilent Technologies 7500cx) was used to analyze the lower concentration points.

2.5.Modelling

Toxicokinetic (TK) models were obtained for each tested NMs with the uptake and elimination data obtained previously from the ICP-OES results. The analysis was made using the MOSAIC_{bioacc} web platform that is available on <u>http://lbbe-shiny.univ-lyon1.fr/mosaic-bioacc/</u>, hosted at the Rhône-Alpes Bioinformatics Center PRABI. MOSAIC_{bioacc} uses the JAGS (version 4.3.0) and R (version 4.0.2) software, and particularly packages RJags (version 4.10), jagsUI (version 1.5.1) and Shiny (version 1.6.0) (Ratier et al., 2020a).

The organisms are considered as single compartments for which a first-order kinetic bioaccumulation model can be applied, as showed in the equations (Eq1) and (Eq2). Models are fitted to bioaccumulation data using Bayesian inference via Monte Carlo Markov Chain (MCMC) sampling (Ratier et al., 2020b).

Equation 1.

$$\frac{dC_p(t)}{dt} = k_{uw} \times c_w - (k_{ee}) \times C_p(t) \quad for \ 0 \le t \le t_c$$

Equation 2.

$$\frac{dC_p(t)}{dt} = -(k_{ee}) \times C_p(t) \quad for \ t > t_c$$

With: t = time (hours); t_c = duration of the uptake phase (hours); $C_p(t)$ = internal concentration of the parent compound at time (µg.g⁻¹); k_{ee} = elimination rates of excretion (hours⁻¹); c_w = exposure concentration of water route (µg.g⁻¹); k_{uw} = uptake rate of water exposure (hours⁻¹). This model also provides data of the bioaccumulation factor (BCF_k) as a relationship between the uptake rate and the elimination rate (Eq3). BCF_k, k_{uw} and k_{ee} are given as a probability distribution and summarized with its median and its 95% uncertainty limits (95% credible interval delimited by the 2.5% and the 97.5% quantiles of the probability distribution) (Ratier et al., 2020a)

Equation 3.

$$BCF_k = \frac{k_{uw}}{k_{ee}}$$

Many criteria for a goodness of fit are given by the model: i) the posterior predictive check plot that inform about the fitting quality of the model, with the percentage of data in credible interval (expected to be >95%) ii) the comparison of prior and posterior distributions inform about the robustness of the inference process, iii) the potential scale reduction factor (PSRF) which is expected to be close to 1.00, checks the convergence of the MCMC chains. (Ratier et al., 2020a)

2.6. Statistical analysis

The significative differences between the non-contaminated daphnid samples (T0) and the uptake and elimination samples were analyzed with RStudio (version 1.3.1073). Preliminary tests of normality and variance homogeneity were carried out. And according to the results of those tests, the Kruskal-Wallis test for non-parametrical data was applied with significance of p < 0.05.

3. Results

3.1. NMs characterization

The applied NMs dispersion protocol has allowed to obtain the NMs stock suspensions that were diluted in the ISO media (pH 7.8 \pm 0.2) and then characterized by DLS. The results, illustrated in Table 1, show that the measured agglomerates size and surface charge vary between the different NMs. The smaller agglomerates are presented in SiO₂-NM202 in the order of 178 nm and the bigger were those of TiO₂-NM102, ZnO-NM110 and SiO₂-NM200 that had a size above 1000 nm. Regarding the NMs surface charge (Z potential), TiO2 NMs are not very charged and SiO₂ NMs are the most negatively charged ones with Z potential around -16 mV. Mostly all NMs are also negatively charged being only 2 positively charged (TiO₂-NM103 and TiO₂-NM104).

Table 1. Hydrodynamic diameter (Z-average in intensity, d.nm) and zeta potential (mV) measures for all the NMs suspensions in ISO media.

NMs	Hydrodynamic diameter (nm)	Z potential (mV)			
TiO ₂ -NM100	361.3 ± 14.7	-7.6 ± 0.87			
TiO ₂ -NM101	792.2 ± 46.6	-8.4 ± 0.78			
TiO ₂ -NM102	2279.3 ± 295.4 ^a	-5.5 ± 0.71			
TiO ₂ -NM103	889.7 ± 23.3	3.9 ± 0.02			
TiO ₂ -NM104	677.7 ± 97.1	4.7 ± 0.02			
TiO ₂ -NM105	844.4 ± 124.7	-1.9 ± 0.46			
ZnO-NM110	2468 ± 153.0 ^a	-2.1 ± 0.29			
SiO ₂ -NM200	1144.5 ± 307.8 ^a	-14.9 ± 1.10			
SiO ₂ -NM202	177.9 ± 5.6	-16.4 ± 0.79			
SiO ₂ -NM204	1027.1 ± 79.6 ^a	-16.9 ± 0.53			
CeO ₂ <10nm	684.5 ± 107.8	-13.3 ± 0.55			
$CeO_2 < 25nm$	987 + 42.8	-7.0 ± 1.15			

^aTo consider with care since size cannot be determined with precision by DLS above 1000 nm.

3.2. Uptake and elimination kinetics

D. magna individuals were exposed to 1 mg/L of each of the twelve NMs during 24 h of uptake and then they were kept in clean media for 120 h for elimination. Samples were taken and the content of metal were dosed. The results showed an uptake and elimination profile for each NMs as showed in figure 1. Once the exposure have started, all the points are significantly different from the non-contaminated daphnids all along the uptake and elimination phases except for some elimination points as follows: TiO₂-NM101-120h, ZnO-NM110-48h and 120h, SiO₂-NM200-24h, 48h and 120h; and SiO₂-NM204-48h.



Figure 1: Uptake and elimination profiles for the set of tested NMs at 1 mg/L exposure concentration in *Daphnia magna*. The figures show the body burden in g/Kg of dry weight, over time (h). Range bars show minimum and maximum values of the replicates. For ZnO NM110 the behavior profile is zoomed in the same graphic.

Similar behaviors were identified for 10 out of the 12 tested NMs, where the concentration in the organisms increased rapidly during the first 6 hours of exposure. After 6h the uptake behavior reaches slowly a plateau towards 24h, except for TiO_2 -NM103 and CeO₂<10nm for which the uptake is still increasing until the end of the exposure phase. SiO₂-NM204 showed a lower accumulation profile than the others. During the first hours of the elimination phase, NMs concentrations dropped drastically. After the 120h in clean media none of these 10 NMs was completely eliminated. The remaining NMs concentrations found at this point represent between 0.2% to 8.3% of the 24h uptake concentration.

The two different behaviors observed were firstly for ZnO-NM110, where the concentration in the organisms was 50 to 100 times smaller, and the organisms started accumulating the NMs for the first hour; then, the concentration kept dropping until 6h and finally it increased at the 24h measuring point. The organisms kept a 14.7% of the 24h Zn concentration at the end of the elimination phase. The second case of different behavior is for SiO₂-NM202 that showed no apparent uptake at any moment since all the samples concentrations, from all the three independent replicates, were under the quantification limit of the ICP-OES (50 μ g/L of Si).

The metal concentration in water was also followed, having measure points at the beginning and at the end of the two phases (uptake and elimination). Water samples were analyzed, and the results are showed on Table 2. The concentrations at the beginning of the experience showed that the looked-for concentration of 1 mg/L for the exposure was achieved (0.91 to 1.53 mg/L). The results of NM202 are in accordance with the no uptake by the organisms shown for this NMs, the initial and final concentrations are very similar and no increase of the SiO₂ water concentration was measured as release after the elimination phase. Similar behavior is showed for the NM110 NMs that had very little uptake. For the rest of the tested NMs, at the end of the uptake phase, the water concentration decays. A mass balance calculation was done to see how much of the lost concentration in water during uptake phase was found in the organisms. The results showed that between 55 to 100% of the metal decrease in water was found in the dosed organisms. The SiO₂ and ZnO NMs along with TiO₂-NM103 presented above 90% of the NMs difference in daphnids. For the beginning of the elimination phase, it was verified that the media was clean having all the dosed values under the quantification limit. Consequently, the elimination of NMs from the daphnids can be observed with the metal increase in the media at the end of the elimination phase.

Table 2. NMs concentration in water at the beginning and at the end of the uptake and elimination phases. And the percentage of the lost NMs concentration during the uptake phase found in the organisms.

NMs	Composition	Uptake to (mg/L)	Uptake t24 (mg/L)	% of the uptake difference (t ₂₄ -t ₀) found in the organisms	Elimination t ₀ (mg/L)	Elimination t ₁₂₀ (mg/L)
TiO ₂ -NM100	TiO ₂	1.11 ± 0.04	0.69 ± 0.03	87.4	$< lq^b$	0.11 ± 0.01
TiO ₂ -NM101	TiO ₂	0.91 ± 0.02	0.25 ± 0.01	59.3	$< lq^b$	0.20 ± 0.01
TiO ₂ -NM102	TiO ₂	1.14 ± 0.07	0.26 ± 0.10	62.8	$< lq^b$	0.32 ± 0.01
TiO ₂ -NM103	TiO ₂	0.96 ± 0.01	0.46 ± 0.06	90.7	$< lq^b$	0.18 ± 0.01
TiO ₂ -NM104	TiO ₂	1.01 ± 0.01	0.40 ± 0.03	66.0	$< lq^b$	0.24 ± 0.01
TiO ₂ -NM105	TiO ₂	1.13 ± 0.00	0.42 ± 0.12	74.2	$< lq^b$	0.28 ± 0.01
ZnO-NM110	ZnO	1.10 ± 0.00	1.10 ± 0.01	99.7	$< lq^b$	$< lq^b$
SiO ₂ -NM200	SiO ₂	0.95 ± 0.01	0.93 ± 0.31	125.5	$< lq^b$	0.22 ± 0.05
SiO ₂ -NM202	SiO ₂	1.53 ± 0.16	1.37 ± 0.23	_ ^a	$< lq^b$	$< lq^b$
SiO ₂ -NM204	SiO ₂	1.22 ± 0.04	0.94 ± 0.10	94.0	$< lq^b$	0.49 ± 0.22
CeO ₂ <10nm	CeO ₂	1.09 ± 0.02	0.40 ± 0.01	73.6	< lq ^b	0.27 ± 0.00
CeO ₂ <25nm	CeO ₂	0.95 ± 0.02	0.24 ± 0.01	55.1	$< lq^b$	0.34 ± 0.01

^a Calculation not possible since there is no uptake data for this NMs ^b Analytical quantification limits equivalency for TiO₂ is 0.08 mg/L; for ZnO is 0.06 mg/L; SiO₂ is 0.21 mg/L and CeO₂ is 0.03 mg/L

The dissolution profile of ZnO NMs was also studied. This NM present a high dissolution in these experimental conditions, showing already a $32.6\pm3.6\%$ of dissolved Zn at T0, $55.6\pm0.8\%$ at 6h and arriving at $84.1 \pm 3.9\%$ at 24h. The complete profile is presented in Supplementary Data.

3.3.Modelling

The obtained data from the ICP-OES dosing were used to fill the model on the MOSAIC_{bioacc} platform. SiO₂-NMs204 and ZnO-NMs110 were not considered for the modelling process since the first one was not accumulated at all and the second one had a profile not compatible with

the model because the uptake concentrations in the organisms dropped and resumed. The measured water concentration was used to fill the model.

The resulting values of the model showed similarities and differences in the uptake and elimination behaviors, as presented on Table 3. For the uptake, resemblances can be found in a group of low kuw (slower uptakes) for TiO₂-NM100, TiO₂-NM104, SiO₂-NM204 and CeO₂<10nm. Another group of intermediate uptakes is formed by TiO₂-NM101, TiO₂-NM103, TiO₂-NM105, SiO₂-NM200 and CeO₂<25nm. And TiO₂-NM102 differentiates itself from the others with a higher k_{uw} (53840 h⁻¹) representing the fastest uptake behavior. The same exercise for kee showed low elimination rates for TiO2-NM103 and CeO2<10nm. Intermediate lost rates for TiO₂-NM100, TiO₂-NM104, TiO₂-NM105, SiO₂-NM200, SiO₂-NM204 and CeO₂<25nm. And a fast elimination behavior for TiO₂-NM101 and TiO₂-NM102 ($k_{ee} = 0,74 h^{-1}$ and 0,79 h^{-1} respectively). The figures corresponding to the modeled curves and the validated goodness-ofa-fit criterion are detailed in Supplementary Data, as well as relationship figures between k_{uw}, kee and BCFk that showed a more extended distribution of the uptake values in relationship to the BCF_k.

tactor (BCF _k). The median va	The para lue is sho	own at th	re presen e 50% co	ted as a dolumn of	each para	on betwee ameter.	en the 2.5	% and th	ie 97.5%.
NMs	k _{uw} (h ⁻¹)			kee (h ⁻¹)			BCF _k		
	2.5%	50%	97.5%	2.5%	50%	97.5%	2.5%	50%	97.5%
T;O. NM100	0750	11050	1/050	0.370	0.475	0.615	22630	25122	27527

Table 3. Modelling results. Uptake rate (kuw), elimination rate (kee), kinetic bioaccumulation

NMs	k _{uw} (h ⁻¹)			k ee (h ⁻¹)			BCF _k		
	2.5%	50%	97.5%	2.5%	50%	97.5%	2.5%	50%	97.5%
TiO ₂ -NM100	9759	11950	14950	0.379	0.475	0.615	22630	25122	27527
TiO ₂ -NM101	28180	32090	36790	0.642	0.742	0.866	41089	43242	45442
TiO ₂ -NM102	45720	53840	63800	0.665	0.793	0.957	63553	67879	72137
TiO ₂ -NM103	22540	25860	29620	0.273	0.317	0.372	75056	81523	87941
TiO ₂ -NM104	11570	14000	17100	0.341	0.419	0.529	30192	33366	38539
TiO ₂ -NM105	25920	29510	33880	0.549	0.635	0.745	43915	46481	48978
SiO ₂ -NM200	24610	30150	37510	0.502	0.627	0.808	44095	48069	51832
SiO ₂ -NM204	6493	9395	14640	0.453	0.687	1.141	11839	13674	15563
CeO ₂ <10nm	9889	13600	18540	0.217	0.297	0.428	37150	45660	54022
CeO ₂ <25nm	17560	21210	26060	0.414	0.513	0.647	37695	41349	44957

4. Discussion

The uptake and elimination profiles of the 12 tested NMs have been obtained by dosing the metal concentration in the exposed daphnids during the 24h uptake phase and the 120h elimination phase. Most of the tested NMs presented a rapid uptake during the first hours of exposure, ingestion was identified as the main influx route to the organisms and along the strong external NMs adsorption to the carapace, they constitute the primary source of the detected total body burden concentration. This is corroborated by studies as (Wray and Klaine, 2015). The mass balance of the water concentration loss compared to the uptake concentration found in the daphnids at the end of the uptake phase, shows that between 55% to 100% is found in the organisms, therefore due to the ingestion and attachment. No differentiation of the NMs from ingestion and from attachment is made for this study as they are considered as the whole NMs quantity that the organisms take from their environment. The rest may be lost due to i) loosely attached NMs to the carapace that were missing during rising time, and ii) precipitation of big NMs agglomerates that became not available for the water sampling.

The fast loss of NMs during the first hours of the elimination phase can be due mainly to excretion; since the gut retention time of daphnids has been proven to be between 2 and 55 minutes (Rigler, 1961) (Schindler, 1968) (Mcmahon, 1970) (Gliwicz, 1986) (Cauchie et al., 2000). This process can be also stimulated by the food provided during this phase. Previous studies have found that the presence of food during the elimination phase increased the NMs depuration from the organisms (Petersen et al., 2009) (Zhu et al., 2010) (Skjolding et al., 2014). It has also been showed that the excretion of contaminated content inside the daphnids guts can take longer (3-6 hours) than non-contaminated food (15-30 min) (Barata et al., 2002). The NMs elimination behavior observed in our work is also in accordance with other studies as the one of (Gillis et al., 2005); where a significant drop in gut fullness occurs from 56% immediately after exposure to contaminated sediment to 17% after 4 h of gut-clearance. The observed

elimination behavior corresponds to a rapid initial clearance that likely represents elimination of the unabsorbed fraction (Wray and Klaine, 2015), followed by a much slower elimination phase that likely represents elimination of internalized material (Feswick et al., 2013). During the uptake phase it seemed that no excretion has been occurred and the guts of daphnids filled increasingly with NMs; and according to (Gophen and Gold, 1981), starved daphnids can retain feces in the mid-gut indefinitely.

Concerning the special profile cases, there was no detected uptake of the SiO₂-NM202, that has the smallest size of agglomerates in the ISO media. It is important to note that daphnids, as many other filter-feeding organisms, chose the size of their ingested food (Hessen, 1985). A study with TiO₂ NMs of different sizes (due to aging) showed that the preferable size of particles ingested by D. magna is around 500 nm (Seitz et al., 2015), because their filtering apparatus have a mesh size range of 240 - 640 nm (Geller and Müller, 1981). This could explain the lack of uptake, being the agglomerates size of SiO₂-NM202 smaller (178nm) than the preferable food size for these organisms. Accordingly, the tested NMs that had the hydrodynamic sizes between that branch of sizes were indeed the ones that showed an important uptake. The peculiar profile of the ZnO-NM110 can be explained by an uptake in the nano form during the first hours and a later ionic accumulation into the daphnids bodies, based on the high percentage of Zn dissolution measured for these experimental conditions. NMs of ZnO are known to be easily dissolved in aqueous media and there is evidence showing an ionic uptake of these NMs (Ma et al., 2013) along with the toxic effects attributable to the ionic form (Xia et al., 2008) (Heinlaan et al., 2008). In the present work, the uptake of ZnO-NM110 in the daphnids is very low compared to the other tested NMs. This can be explained by the natural process of zinc regulation that organisms can implement when an internal high concentration of zinc is detected (Adam et al., 2015). Studies that reported little or no measurable uptake of ZnO NMs as (Johnston et al., 2010) in zebrafish, attributed it to particle aggregation that reduces their bioavailability. Nonetheless, it seems to not be the case for our experiment, since the water samples showed similar concentrations in the exposure media at T0 and T24, meaning that there was no lack of exposure due to NMs sedimentation, even with the large size of agglomerates ($\sim 2\mu m$).

The model applied to the set of data is a toxicokinetic (TK) model, that considers uptake and elimination in one compartment. In particular, this model has a unified inference method that estimates parameters for both accumulation and depuration phases simultaneously and this innovative inference process makes it possible to incorporate the TK part into a complete TKTD model (Ratier et al., 2019). This model was found to be suitable to be used in the present study results of NMs uptake and elimination behavior, because the obtained curves of the model fitted very accurately with the raw measures and all the goodness criteria were fulfilled. These kinds of models are recommended to be used in time-dependent exposure conditions (Ockleford et al., 2018). Nevertheless, they should be used with care when derived dynamically in time resolved experiments; because accumulation, depuration, metabolization and excretion (ADME) processes related to the fate of nanomaterials in organisms may not always be resolved completely (Brink et al., 2019). Nonetheless, it must be mentioned that the chosen BCF for the present work is the kinetic bioaccumulation factor and not the BCF at steady state. The authors are aware of the limits of these kind of models and encourage a careful interpretation of the modelling data. In the case of the present study, the found k_{uw}, k_{ee} and BCF_k are intended to be used as comparison values that can inform about the differences in the uptake or elimination behavior of the tested NMs.

Having clarified this point, it is interesting to note that, if related the values of k_{uw} and k_{ee} to the BCF_k values, it is found that there is an extended distribution of the kuw related to the BCF_k, meaning that the uptake is the driving process that generate the main differences between the tested NMs. This can be related once again to the ingestion behavior of the NMs by the

daphnids. The obtained rates allowed to lump together some NMs by their similar uptake or elimination rate values. Since most of the authors that had published values of BCF are those calculated at the steady state, with a variety of different experimental conditions, comparison with our data is difficult, even when the same taxa and same type of NMs were tested. Additionally, the age of the organisms has a very important role in this kind of studies because of the different body morphometrics along their life cycle, which can impact the amount of NMs that can be retained in their guts (Petersen et al., 2019). Nonetheless, it is interesting to note that the values of some studies are close anyway, for example, the BCFs for the NMs "S2" from (Fan et al., 2016) equal to 79000 L/Kg, is similar to the BCF_k = 81523 from the TiO₂-NM103 that has similar characteristics. The results of (Zhu et al., 2010) are also in concordance with the obtained data in the present work. These authors worked with a TiO₂ NM (Degussa P25) that has similar characteristics as our TiO₂-NM105. Where their maximal body burden found was nearly 60 g/Kg and the body burden for the TiO₂-NM105 was 57.8 g/Kg. But the BCF found by these authors is much higher than the BCF_k found in our studies (118063 L/Kg and 46481 respectively).

Finally, in order to deepen into the understanding of the nano-bio interaction of the differentiated NMs uptake and elimination behaviors, new analytical techniques can be applied. A recent study combined single particle inductively coupled mass spectrometry (spICP-MS) and dynamic secondary ion mass spectrometry (dynamic SIMS) to be able to determine the number, size and biodistribution of NMs inside *C. elegans* (Johnson et al., 2021). Also, some complementary studies of their toxic effects can be made in the future. Subcellular and individual effects should be analyzed. And nowadays, there are many emerging methods that may help determine this interaction, as it has been showed by (Karatzas et al., 2020) that used Deep Learning applied to microscopic images of NMs exposed daphnids to detect possible malformations, to even recognize uncommon lipid concentrations and lipid deposit shapes.

5. Conclusion

The present study aimed at determining the differences between the uptake and elimination of a set of 12 different NMs on the model organism *D.magna*. An uptake phase of 24h and an elimination phase of 120h allowed to obtain the uptake and elimination profiles. Based on those results, it can be concluded that, most of the tested NMs are capable of undergo uptake and elimination processes by the daphnids at different rates and quantities, except for the SiO₂-NM202 that showed no uptake. A fast uptake as well as a fast elimination behavior can be noticed during the first hours of exposure and the first hours of elimination phases respectively. The presence of food during the elimination phase, plays an important role for this rapid NMs elimination. Nonetheless, between 0.2% to 14.7% of the accumulated NMs still remain in the organisms after 120h of elimination.

The toxicokinetic model of MOSAIC_{Bioacc} was found to be suitable to model the NMs uptake and elimination behaviors. The resulting values of K_{uw} , K_{ee} and BCF_k helped to compare the NMs and found that TiO₂-NM102 is the one that has the fastest uptake and elimination on daphnids, also that SiO₂-NM204 has the slowest influx and CeO₂<10nm has the slowest elimination. It was also found that the uptake is the determining process of the NMs bioaccumulation, which can be driven by some of the nano-bio interaction characteristics as the NMs agglomerates size in relationship with the daphnids preference for ingestion size. It can also depend on the NMs physic-chemical properties, as the NMs ionic dissolution which may be the process behind the intake, the loss and the anew intake of Zn from the ZnO-NM110 profile. The uptake and elimination rates allowed to cluster together some of the NMs by their similar behaviors. These similarities and differences based on the nano-bio interaction can enrich the understanding of the NMs hazard characteristics on the environmental risk assessment. Finally, we believe that the combination between the modelling uptake and elimination data, with innovative techniques as the "omics" studies for subcellular effects, can help to establish the links between exposure, intake and toxic effects of NMs in aquatic environments for future regulation.

Acknowledgements: The authors thank the support of the French Ministry for the Ecological and Inclusive Transition. A special recognition is given to Arnaud PAPIN, to Farid AIT-BEN-AHMAD and to Yohann BAILLON for the access and the assistance with the ICP-OES and ICP-MS instruments. And we express our gratitude for the counseling in the model application by Cléo TEBBY and Aude RATIER.

Disclaimer of interests: The authors declare that they have no competing interests.

Data availability statement: Data pertaining to this manuscript are deposited in figshare at https://doi.org/10.6084/m9.figshare.15098343.v1

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