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The development of a kinetic biotic ligand model to predict acute toxicity of Gadolinium for *Daphnia magna*

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ABSTRACT

The metal Gadolinium (Gd) is a member of the lanthanide (Ln) group and is recognized as an emerging pollutant due to its widespread application in modern technology. Its acute toxicity depends on its free ion concentrations (Gd^{3+}), which is directly related to chemical speciation. The Biotic Ligand Model (BLM) is a valuable tool for risk assessment which predicts the metal bioavailability and toxicity to specific organisms. However, studies developing BLM for any Ln species are rare. Consequently, this study aimed to develop a kinetic BLM to predict the acute toxicity of Gd to the freshwater crustacean *Daphnia magna*. A series of 48-hour toxicity tests were conducted using different major cation concentrations, in order to estimate their affinity constants for the biotic ligand (BL). The model was then validated, first in the presence of dissolved organic matter (DOM), and then with water samples collected from lakes, rivers, and estuaries in France and Germany. The outcome revealed that three major cations (potassium, magnesium, and calcium) act as strong competitors. The model was successfully validated in the presence of organic matter and in the majority of surface freshwater samples (9 out of 13 samples). In this case, the predicted survival had a strong fit with the observed data. However, this was reduced when applying the model to samples of elevated electroconductivity and a pH below 6.8, when survival was consistently overestimated, potentially a multistressor effect. The kinetic BLM predicted 48 h measured EC_{50} ranging from 4 to 30 mg L^{-1} which agreed with the data from the literature. The model could also predict chronic effect of Gd by estimating the no-effect concentration (NEC) under prolonged exposure time ranging from 0.1 to 1 mg L^{-1}.

1. Introduction

Metals represent a significant class of environmental pollutants, capable of causing sublethal and lethal effects on aquatic organisms (Tchounwou et al., 2012). However, their toxicity is directly influenced by their bioavailability, which, in turn, is determined by their chemical speciation (Adams et al., 2020). This is particularly the case for lanthanides (Ln), a group of 15 metals which have become of increasing concern in recent years due to their increased use in modern technology (Paul and Campbell, 2011). These metals, now considered as emerging pollutants, are typically found in surface waters at low concentrations (measured in μg L^{-1}) (Bau and Dulski, 1996). However, within Ln mining regions, concentrations ranging from 1 to 10 mg L^{-1} were measured (Liang et al., 2014; Liu et al., 2019). Once in the water, Ln can cause impacts on aquatic organisms such as lethal effects, oxidative stress or cytotoxicity by perturbing calcium (Ca) homeostasis due to the similar ionic radius between Ln^{3+} and Ca^{2+} (Dubé et al., 2019; Zimmer et al., 2019; Blinova et al., 2020; Malhotra et al., 2020). Depending on the composition of the exposure media, the speciation chemistry of Ln can lead to strong deviations in the lethal or effect concentrations (LC_{50} or EC_{50}). For instance, the presence of dissolved organic matter (DOM) increases metal complexation causing a decrease of Ln bioavailability and therefore toxicity (Lachaux et al., 2022). The Ln are also found to be significantly more toxic for *Hyalella azteca* in soft water compared to in tap water, due to the presence of major cations capable of competing with Ln^{3+} (Borgmann et al., 2005). Recently, Revel et al. (2023)

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revealed that under acute exposure conditions, only the soluble fraction of Ln can affect the freshwater crustacean *Daphnia magna* by biodistributing in its tissues. This observation aligns with the fundamental principles of the Biotic Ligand Model (BLM), which suggests that the bioavailability and subsequent toxicity of metals are due to the interactions of free metal ions with the site of action of the organism (biotic ligand) (Di Toro et al., 2001).

The BLM is a conceptual framework in ecotoxicology that aims to predict the bioavailability and toxicity of metals in different aquatic environments, providing a tool for risk assessment that takes into account water chemistry and biota characteristics. BLMs have only been developed for few metals including cadmium (Cd) (Clifford and McGeer, 2010), copper (Cu) (Arnold et al., 2005; De Schamphelaere and Janssen, 2002), and zinc (Zn) (Heijerick et al., 2002; Santore et al., 2002), silver (Ag) (Paquin and Di Toro, 2008) and nickel (Ni) (Santore et al., 2021) in water samples. To predict metal bioavailability, these models take into account the metal complexation with aqueous ligands (e.g., PO_4^{3-}, HCO_3^- or dissolved organic matter (DOM)) and the protective effect of major cations (e.g., Ca^{2+}, Mg^{2+}, H^+, Na^+ and K^+) which compete for the same BL as the target metal. Compared to other technologically important metals, very little work has been carried out to date on the development of BLMs for lanthanides: A free-ion model for lutecium (Lu) was developed by Weltje et al. (2004), using the bacterium *Vibrio fischeri*. This model demonstrated that Lu toxicity varies with the presence of organic ligand and is closely linked to the free ion concentration, aligning with the principles of the BLM. Similar affinity constants for the biotic ligands of the green alga *Chlamydomonas reinhardtii* have been derived for different Ln, suggesting that these metals share a common transport site (Yang et al., 2014; Aharchaou et al., 2020). These affinity constants (log *K*) were found to be pH-dependent (El-Akl et al., 2015) however, no major cations seemed to affect Ln bioavailability in single-cells.

At the moment, only one study has developed a more complete BLM for Ln, studying the acute toxicity of dysprosium (Dy) on the aquatic invertebrate *Hyalella azteca* (Vukov et al., 2016). In this study, calcium (Ca) and sodium (Na) effectively reduced acute Dy toxicity, with log *K* estimated at 3.95 and 4.10 respectively. However, log *K* value for magnesium (Mg) could not be calculated due to the absence of effects of Mg on Dy toxicity. Furthermore, the potential effect confounding factors on Dy toxicity were noted when pH levels were modified, making the calculation of log *K* for H^+ impossible. No validation of that model is currently available, which limits its application in risk assessment.

Given these limitations, an approach to define a comprehensive BLM was developed for a representative Ln: gadolinium (Gd), chosen due to its classification as a middle Ln and its widespread applications in technology and medicine (i.e. as contrast agent in magnetic resonance imaging (MRI), in nuclear reactors as neutron absorber or in magnets for magnetic refrigeration) (Rogowska et al., 2018). The stability constants for all five major cations (Ca^{2+}, Mg^{2+}, Na^+, K^+, and H^+) and the metal were estimated for the BL of the freshwater crustacean *Daphnia magna*, a widely recognized model organism in the field of aquatic ecotoxicology.

A series of acute exposures of *D. magna* were performed according to the method of Liang et al. (2021). This method offers a novel approach by integrating the BLM into a toxicokinetic-toxicodynamic (TK-TD) framework, leading to a significant reduction in toxicity testing (up to 60–70 % less compared to traditional methods) while allowing more flexible predictions over different exposure times. The evolution of the organism's survival over time was measured to parametrize the kinetic BLM with the primary objective of estimating the affinity of Gd^{3+}, Ca^{2+}, Mg^{2+}, K^+, Na^+, K^+ and H^+ to the biotic ligand in form of a stability constant. Then, BLM was validated in the presence of dissolved organic matter (DOM) and in natural water samples. The EC_{50} and NEC (no effects concentration) were predicted by the model and compared with the available acute EC_{50} data from the literature.

2. Material and methods

2.1. Model

Developing a BLM usually requires a large number of bioassays and test organism data. Furthermore, traditional BLMs are limited to one exposure time and one specific toxicity reference value (e.g., LC_{50} or EC_{50}). The recent development of a new kinetic BLM by Liang et al. (2021), integrating the BLM into a TKTD framework offers a more flexible approach that is appropriate for the conditions of prediction (exposure time and toxicity reference value can be chosen). It requires significantly fewer toxicity bioassays for the estimation of the stability constants (Liang et al., 2021).

In this model, the stability constants of each cation for the BL are integrated in a Michaelis-Menten equation following the equation of Slaveykova and Wilkinson (2005), with J(t) the metal uptake rate in the organism (μg g^{-1} h^{-1}) (Eq. 1).

$$J(t) = \frac{J_{\max} \bullet K_{\mathrm{GdBL}} \bullet [\mathrm{Gd}^{3+}](t)}{1 + \quad K_{\mathrm{GdBL}} \bullet [\mathrm{Gd}^{3+}](t) + \sum K_{\mathrm{C}_i\mathrm{BL}} \bullet [\mathrm{C}_i^{z+}](t)} \tag{1}$$

This equation is incorporated into a toxicokinetic and toxicodynamic framework with the internalization flux leading to an internal concentration of metal in the organism over time (C_{int}) (μg g^{-1}), and k_e being the elimination rate constant (h^{-1}) (Eq. 2).

$$\frac{dC_{\text{int}}(t)}{dt} = J(t) - \quad k_e \quad . \quad C_{\text{int}}(t) \tag{2}$$

The toxicity of the metal is considered to be related to the internal metal concentration in the organism. When reaching an internal threshold concentration (C_{IT}, ug g^{-1}), the hazard (*H,* dimensionless) of the metal will be higher than the background effect (h_0, h^{-1}) (Eq. 3). This hazard is proportional to the killing rate k_k (g μg^{-1} h^{-1}) and is directly related to the probability of survival *S*(*t*) of the organisms (Eq. 4).

$$\frac{dH(t)}{dt} = k_k . \quad (C_{\text{int}}(t) - C_{IT}) + h_0 \tag{3}$$

$$S(t) = \quad e^{-H(t)} \tag{4}$$

Despite the use of TK-TD, bioaccumulation data were not necessary to calibrate the model, as the bioaccumulation dynamics, described by the Eq. 2 could be predicted from survival data. Daphnid survival over time was sufficient to estimate the parameters of the kinetic model (Liang et al., 2021).

2.2. Experimental design

As in the method of Liang et al. (2021), the following procedural steps were applied: (1) tests for estimating BLM parameters; (2) model validation tests in the presence of dissolved organic matter (DOM); (3) model validation with natural water samples.

All of the toxicity tests were performed according to ISO 6341 in 6-well plates (VWR International, 734–1599). M4 media was used as the test medium (for the two first test series) and was prepared in accordance with ISO 6341. However, Na was added as NaCl rather than $NaHCO_3$ to reduce the precipitation of Gd-carbonate. The pH was kept at 7.00 + /- 0.2, and the oxygen concentration was maintained at more than 3 mg L^{-1}. Neonates less than 24 hours old were exposed to 10 mL of medium per well in 6-well plates for 48 hours. Five organisms were introduced to each 10-mL well, with three wells acting as a replicate for each concentration. Only three replicates were possible to ensure optimal visibility with the camera system for tracking daphnid mobility. To compensate for the reduced sample size, five independent repetitions of the experiment were conducted, resulting in a total of 75 organisms (5 repetitions x 3 vessels x 5 neonates). The mobility of *D. magna* was measured every 8 h over 48 h using Motic Images Plus 3.0 as a camera system. A program was built on UiPath Studio (version 21.4.3) in order to activate the camera for four minutes every eight hours after one minute of gentle agitation of the test plates (RO-OS 5, Phoenix Instrument). The videos were watched on VLC media players. As slight movement of the limbs was not visible on the videos, only clear changes in the position of the organism in the well plate over four minutes was considered as signs of survival. After 24 and 48 h, the mobility was verified directly in the laboratory to confirm the results obtained by video. Tests were considered valid when the control survival was over 90 %.

2.2.1. Estimation of the BLM parameters

First, the Gd effect on the *D. magna* survival was studied over a gradient of six concentrations of Gd (0–30 mg L^{-1}). Then, to evaluate the effect of different cations, five test series were performed to study the toxicity of 15 mg L^{-1} of Gd with varying concentrations of individual cations (Ca^{2+}, Mg^{2+}, Na^{+}, K^{+} and H^{+}). The specific cation gradient details can be found in supplementary data S1. This constant nominal concentration of 15 mg L^{-1} of Gd was chosen as it is close to the LC_{50} of Gd, therefore clearly affected the daphnid survival without leading to significant metal precipitation. These tests permitted the parametrization of the model in order to measure the stability constants of each cation for the biotic ligands of *D. magna*.

2.2.2. Validation of the model in the presence of DOM

The effect of complexation by dissolved organic matter was studied by observing the toxicity of 15 mg L^{-1} of Gd under different concentrations of commercial humic acid (0.17, 1.11, 2.23, 4.42, 8.6, and 17.4 mg of carbon L^{-1}) (HA, VWR, SIALH16752). Commercial DOM is often used as an alternative to natural organic matter for the development of BLM as it is better characterized and its generic stability constants usually provide a satisfactory prediction of metal speciation and bioavailability (U.S. U.S. U.S. Environmental Protection Agency, 2003; De Schamphelaere and Janssen, 2004; Liang et al., 2021). A stock solution of HA was prepared by dissolving 100 mg of HA in 500 mL of pure water at pH 10. After 24 h of agitation, this solution was filtered through glass fiber filter (GF/F, Whatman, WHA1825047) then to 0.45 µm polycarbonate filter (Whatman, 7060–2504). The carbon concentration remaining in the stock solution was measured with OCT-L 8-Port Autosampler (Shimadzu). The final carbon concentration was at 45.31 mg L^{-1}. This step permitted to validate the kinetic BLM in the presence of DOM.

When HA solution was added to M4 media, pH was adjusted before exposure. Major cation and anion concentrations, as well as conductivity, were measured at the end of the test to take into account any dilution effects during speciation modeling.

2.2.3. Validation of the model with natural water samples

The toxicity of 15 mg L^{-1} of Gd was studied in different natural surface freshwater samples in order to validate the model. Water samples were taken upstream of the estuaries, in rivers and in lakes from Germany and France throughout the years of 2021 and 2022 (Fig. 1, Supplementary data S3–5 -). The water samples were filtered through glass fiber filter and then through 0.45 µm polycarbonate filter and stored at 4°C in the dark before use. On the day of the experiment, samples were spiked with 15 mg L^{-1} of Gd. As adding acidified Gd stock solution strongly affects the pH in the solution, an aliquot of 4.19 g L^{-1} of MOPS buffer solution (Roth, 6979.3) was added in order to stabilize the pH. While all samples were initially spiked with 15 mg L^{-1} of Gd, the actual free ion concentration is expected to vary due to interactions with anions, pH, and the presence of organic matter. These factors influence the speciation of Gd, which explains the variations observed in the soluble metal concentration (Supplementary data S4).

Most of the pH of the natural water was originally higher than 7.7 which caused strong precipitation of Gd. Therefore, the pH was changed

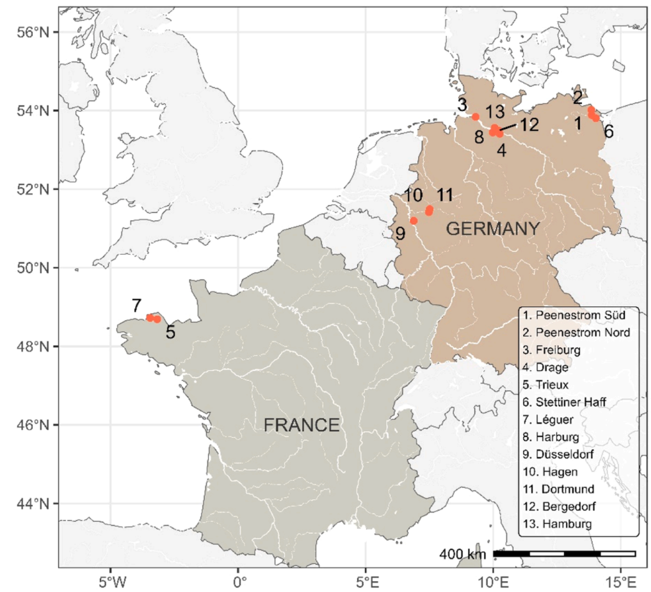

Fig. 1. Natural water samples collected in France and Germany for the validation of the kinetic BLM.

to the range of 5.80–7.05 (Supplementary data S4). This pH was measured at both the beginning and the end of each test, and the variation did not exceed 0.2 units throughout the experiment. The modified pH was then used for speciation modelling.

2.3. Chemical measurements

At the end of 48 h of exposure, replicates of each water sample were collected into one sample, mixed together, and filtered through 0.2 µm cellulose nitrate filter (Whatman, 7182–004). Filtrates were acidified with 0.2 % HNO_3 (Roth, 4989.1) in polyethylene (PE) sample tubes (Roth, TT13.1) and stored at 4°C until analysis. Dissolved major cation (Ca^{2+}, Mg^{2+}, Na^{+} and K^{+}) and Gd concentrations were quantified by Inductively Coupled Plasma Mass Spectrometry at the UMR 6249 of Chrono Environment, Besançon (France). At the same laboratory, the concentration of dissolved anions (Cl^{-}, SO_4^{2-}, NO_3^{-}, PO_4^{3-} and CO_3^{2-}) in the filtered natural water samples were also measured using a Thermofisher Scientific integrion ion chromatography system. This system was in combination with AS19 anion exchange column, an electrolytically generated hydroxide (KOH) eluant and suppressed conductivity detection. pH of each solution was measured with a pH meter (FiveEasy Plus FP20, Mettler-Toledo) and the DOC was quantified using a total organic carbon analyzer (TOC-L, Shimadzu). Due to the large volume of water required for these measurements, only a single measurement was possible for each chemical, limiting the ability to assess potential variability in the measurement.

2.4. Data treatment and statistics

Chemical equilibrium speciation modelling was performed using Visual MINTEQ (version 3.1) to calculate the free ion activity of Gd^{3+} and the major cations (Ca^{2+}, Mg^{2+}, Na^{+}, K^{+} and H^{+}) at CO_2 atmospheric pressure of 4.1×10^{-4} atm. To evaluate the interaction of humic acid, two models were used and compared: NICA (non-ideal competitive adsorption)-Donnan and the Stockholm humic model (SHM).

The free ion activity of Gd and the cations from the first test series was used to estimate the kinetic BLM parameters from a Markov chain Monte Carlo fitting. The detailed steps of MCMC fitting using OpenModel is provided in the Note S2 of Liang et al. (2021) Once the maximum likelihood values of the BLM and TKTD parameters were obtained, the free ion activity of Gd and the cations from the test series using DOM and natural water samples were applied in order to predict the daphnid survival over time, using OpenModel (version 2.3.2) software. The predicted survival was then presented graphically and compared with the observed data using R software (v.4.3.0) and the package “ggplot2”.

3. Results and discussion

3.1. Observed mortality

The points in Fig. 2 show the observed impact of Gd on daphnid survival, as well as the influence of major cations on the toxicity of Gd at a concentration of 15 mg L^{-1}. Increasing the nominal Gd concentration reduced the survival of *D. magna*, from 100 % to 25 % at the highest Gd concentration (30 mg L^{-1}) after 48 h of exposure. Speciation modelling indicate that the decrease in survival is due to an increase of free Gd ions in the media, able to bind to the biotic ligand (BL) of the organisms (Supplementary data S2).

The effects of major cations on Gd toxicity were studied by varying the respective cation concentration at the same nominal Gd concentration of 15 mg L^{-1} of Gd. This Gd concentration was close to the LC_{50} as the survival rate was reduced to approximately 50 % (Revel et al., 2023). The increase in concentration of K^{+}, Mg^{2+} and Ca^{2+} decreased the toxicity of Gd, indicating competitive binding for the same BL as Gd^{3+}. Indeed, after 48 h of exposure to 15 mg L^{-1} of Gd, the survival was between 70 % and 75 % at the highest concentrations of these three cations. In contrast, survival rates showed comparable development over time and remained close to 50 % after 48 h of exposure despite varying Na^{+} concentrations.

The increase of H^{+} on the other hand, strongly elevated the toxicity of Gd. Indeed, at the lowest pH (5.5), survival was reduced to approximately 25 % after 48 h in the Gd spiked media. At a pH higher than 7, 15 mg L^{-1} of Gd did not affect the organisms as the observed survival remains at 100 %. The solubility of Ln is strongly dependent on the pH and Ln easily precipitate with carbonates and hydroxides at pH higher than 7 (Smith et al., 2004). In the experiment, this led to a reduced

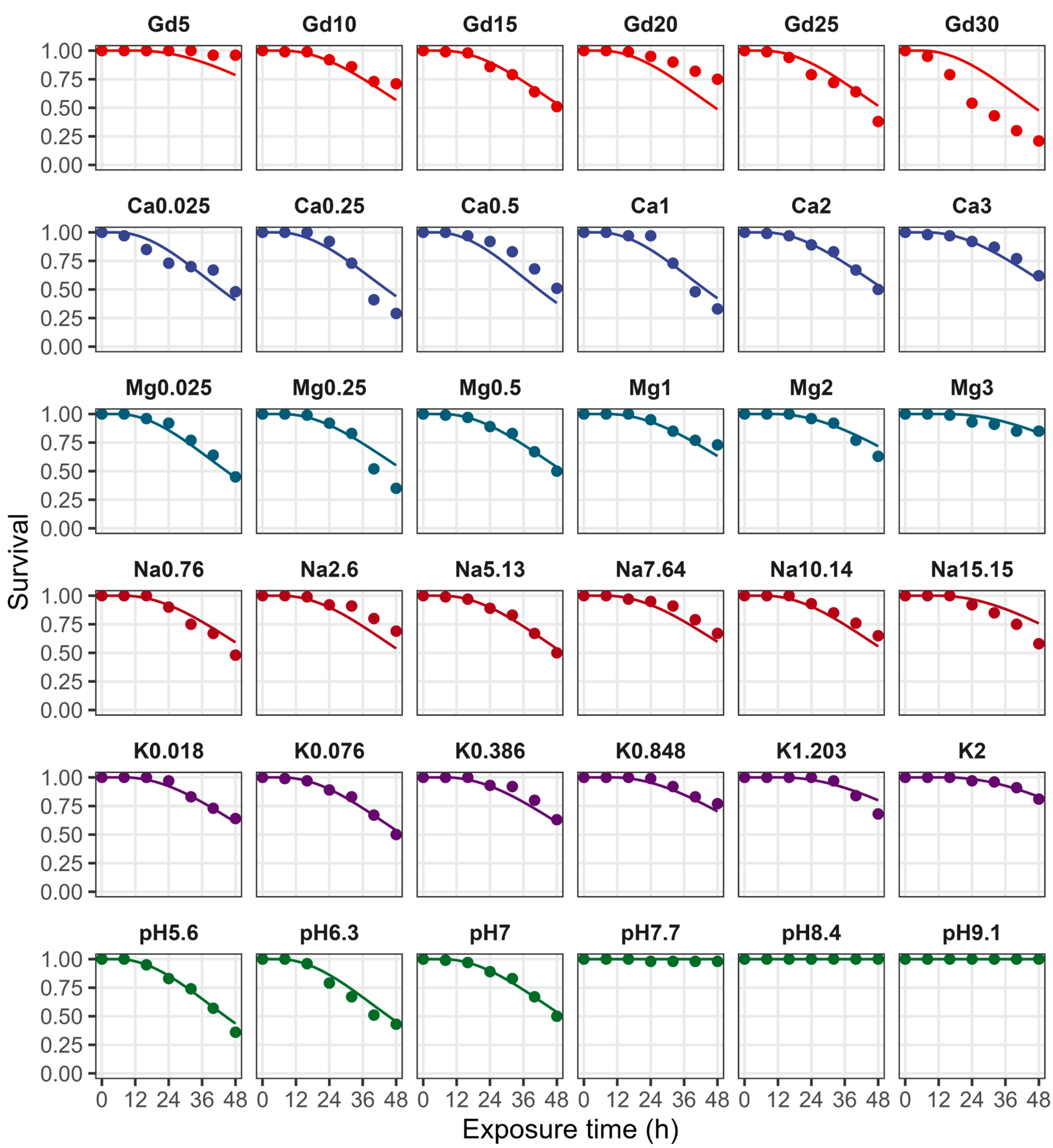

Fig. 2. Survival of *D. magna* during the 48-h exposure to Gd under various conditions. Points are observed survival; lines are BLM predicted survival using parameters listed in Table 1. Gd, Ca, Mg, Na and K values are in mg L^{-1}.

concentration of Gd ion concentration and lowered bioavailability of Gd for the organism. Lower pH led to an increase of the free ion Gd concentrations available to interact with the BL, explaining the higher Gd toxicity. Therefore, the observed changes in Gd toxicity with varying pH levels are primarily due to the effect of pH on metal solubility (Suzuki et al., 1986), rather than the competition between H^+ and Gd^{3+}.

3.2. Parametrization of the model

As no BLM or TKTD models are currently available for Ln on *D. magna*, the initial values of each parameters were set using Cd^{2+} as a reference from Liang et al. (2021) (Supplementary data S6). The Log K_{GdBL} was however increased by an order of magnitude and J_{max} was decreased by an order of magnitude, as suggested by Tan et al. (2017). Indeed, that previous study estimated such a difference between for these two parameters for samarium (Sm), another Ln, compared to Cd.

The affinity constant for each cation and the target metal for the BL were estimated by the model from the Markov chain Monte Carlo fit (Table 1). From the cations studied here, log K_{GdBL} has the highest value with 8.28 L mol^{-1}. Therefore Gd^{3+} has the highest affinity to the BL of *D. magna*. The other cation binding constants were K^+ (7.03), Mg^{2+} (6.89) and Ca^{2+} (6.04). The log K of H^+ and Na^+ were significantly lower ranging 5.11 and 5.47 L mol $^{-1}$ respectively.

From the estimation of these parameters, the survival of daphnids was predicted by the model for each experimental condition (Fig. 2, lines). This prediction in most cases fitted closely to the observed data (Fig. 2, dots). Slight overprediction of the survival was observed at the highest Gd concentrations, which could due to the formation of metal precipitates that can be ingested by the organisms (Blinova et al., 2018b; Zhou et al., 2019). However, according to Revel et al. (2023) ingested Gd should not cause any toxicity to daphnid under acute exposure. Alternatively, this overprediction may result from inaccuracies in cation and anion quantification, as only a single measurement was possible for each sample. Further analysis is required to verify the ability of the model to predict Gd toxicity at high nominal concentrations.

The estimated binding constant of Gd remains close to the log K estimated for Cd^{2+} on *D. magna* (7.96 L mol^{-1}) (Liang et al., 2021) or on fish such as in *Oncorhynchus mykiss* (8.0) (Niyogi et al., 2008) and in *Pimephales promelas* (8.6 L mol^{-1}) (Playle et al., 1993). Similar data were also found for Cu^{2+} with a log K between 7.40 and 8.02 L mol^{-1} on *D. magna* (Ardestani et al., 2014).

The only other BLM available for a lanthanide, Dy^{3+}, developed for the freshwater invertebrate, *Hyalella azteca* (Vukov et al., 2016), calculated a log K_{DyBL} of 7.75 L mol^{-1} which is relatively close to the log K estimated for Gd^{3+} on *D. magna*. Vukov et al. (2016) also demonstrated the presence of a protective effect of Ca^{2+} on Dy^{3+} toxicity (log K of 3.95 mol L^{-1}). In the present study, the high affinity constant of K^+, Mg^{2+} and Ca^{2+} signify that the three major cations have a protective effect on *D. magna* when exposed to Gd as they can probably bind to the same site of action as the metal. The high binding constant of Ca^{2+} and Mg^{2+} for the BL were expected as they are known to have similar ionic radii compared to Ln^{3+} (Herrmann et al., 2016). Their capacity in reducing metal toxicity has been demonstrated for other metals such as for Cu^{2+} or Dy^{3+} (De Schamphelaere and Janssen, 2002; Vukov et al., 2016). For K^+, however, most studies have not measured any protective effect against metal toxicity (Ardestani et al., 2014). In contrast to those studies, K^+ had a particularly high protective effect with an estimated log K of 7.03 mol L^{-1} in this study. Gd^{3+} has been shown to block the delayed rectifier potassium channel in nerve cells of guinea pigs (Hongo et al., 1997). This type of potassium channel has also been found in other organisms such as crayfish (Lin and Rydqvist, 2001). It may thus be possible, that Gd^{3+} competes with K^+ for action sites connected to certain channel proteins.

The difference between the log K value of the metal and the major cations were smaller than for other Ln (Clifford and McGeer, 2010; Vukov et al., 2016; Liang et al., 2021). The accuracy of log K is directly dependent on the dissolved Gd concentration measured and the chemical speciation modeling of Gd. The chemical speciation modelling relies on the reliability of available thermodynamic constants and introduces potential uncertainties. Any uncertainties could lead to an overestimation of the log K of Gd and, consequently, an overestimation of log K for competing cations (*e.g.*, Ca^{2+}, K^+, Mg^{2+}). In the case of H^+, the strong sensitivity of the chemical speciation of Gd to pH complicates the prediction of log K_{HBL}. Nevertheless, the calibrated set of log K values is self-consistent and satisfactorily describes the experimental results (Fig. 2). It provides an explanation for the protective effects of cations against Gd toxicity. Therefore, this set of log K values in our opinion is useful for the prediction of environmental risks.

Table 1
The maximum likelihood parameter values of the Gd Biotic Ligand Model for *Daphnia magna* are obtained from the Markov chain Monte Carlo fitting. 95 % credible intervals are represented in brackets.

Parameters	Unit	Best-fit values and 95 % CI
log K_{GdBL}	L mol^{-1}	8.28 (7.76–8.57)
log K_{HBL}	L mol^{-1}	5.11 (4.64–5.25)
log K_{CaBL}	L mol^{-1}	6.04 (5.74–6.28)
log K_{MgBL}	L mol^{-1}	6.89 (6.71–7.04)
log K_{KBL}	L mol^{-1}	7.03 (6.86–7.12)
log K_{NaBL}	L mol^{-1}	5.47 (5.34–5.56)
J_{max}	μg g^{-1} h^{-1}	158 (53.7–285)
k_e	h^{-1}	5.73×10^{-6} (3.01×10^{-6}–8.52×10^{-6})
C_{IT}	μg g^{-1}	222 (91−478)
k_k	g μg^{-1} h^{-1}	2.42×10^{-5} (8.19×10^{-6}–4.34×10^{-5})

3.3. TK-TD parameters

The four TKTD parameters estimated by the model are presented in Table 1. In the case of TK, the maximum uptake rate of Gd^{3+} (J_{max}) and its elimination rate constant (k_e) were optimized to 158 μg g^{-1} h^{-1} and 5.73×10^{-6} h^{-1}, respectively. In comparison to Cd, the estimated TK parameters were significantly different for Gd. J_{max} was higher by two orders of magnitude while k_e was lower by three orders of magnitude. This differs from the finding of Tan et al. (2017) for freshwater microalgae that calculated a lower J_{max} for samarium (Sm) compared to Cd. However, this difference could be biological species dependent as microalgae and crustacean will have different BL.

The TD parameters were as well different from the one calculated by Liang et al. (2021). Compared to Cd, the internal threshold concentration of Gd was two times higher in magnitude while the killing rate was lower by two orders of magnitude. These TKTD parameters suggest a lower toxicity of Gd compared to Cd which agrees with the predicted LC_{50} for the model (Fig. 5a) being higher for Gd than Cd.

3.4. Validation of the model

3.4.1. With dissolved organic matter

The validation of the kinetic BLM was first performed in the presence of six different DOM concentrations (0.17–17.4 mg C L^{-1}). Increasing the concentration of humic acid increased the survival of the exposed daphnids (Fig. 3). Therefore, humic acid has an important protective effect against Gd probably because it decreases its free ion concentration by increasing metal complexation.

Other studies have found a nonlinear effect on metal bioavailability and toxicity (Gao et al., 2022). For instance, Gao et al. (2022) observed a decrease of Cd toxicity under low concentration of hydrophilic acidic compounds (<3.55 mg L^{-1}), while higher concentrations increased Cd toxicity. This finding does not agree with the present study where DOM had a linear effect on the toxicity of Gd. This inconsistency may be due to different kinds of DOM used in the studies, as this term covers a methodically defined group of very different substances (Zhao et al., 2018; Gao et al., 2022).

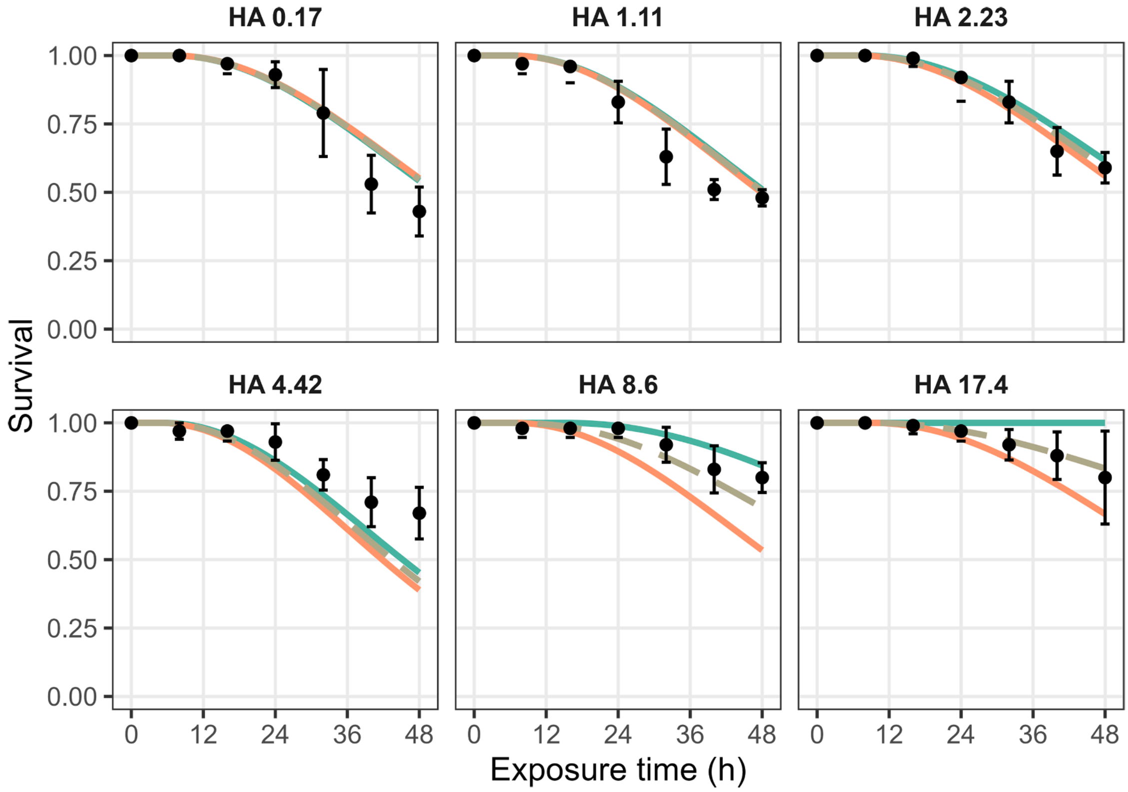

Fig. 3. Comparing observed vs. predicted survival of *D. magna* in media containing 15 mg L^{-1} of Gd (nominal concentration) and different humic acid (HA) concentrations (0.17–17.4 mg C L^{-1}). Black dots: observed survival, green line: survival predicted using SHM to model chemical speciation with HA, orange line: survival predicted using NICA-Donnan to model chemical speciation with HA. Brown dashed line: Average of the two survival predictions. Error bars represent the standard deviation calculated from five experimental repetitions, each containing three replicates of 5 daphnids.

Two distinct speciation models were used to predict the metal and cation free ions. The Stockholm Humic Model (SHM) permitted a good prediction of survival except at the highest humic acid concentration (17.4 mg C L^{-1}), where an overprediction of survival occurred. In contrary, the model underpredicted survival at 4.43 mg C L^{-1} due to a higher soluble Gd concentration measured at the end of the exposure time which led to an increase of free Gd ions (Supplementary data S2). This elevated concentration may be attributable to measurement variability in major cation quantification by ICP-MS measurement. Additionally, the methods for Gd and major cation quantification allowed for only a single measurement, limiting the ability to assess that potential variability.

Conversely, the non-ideal competitive adsorption (NICA)-Donnan model seemed to underpredict survival at the three highest DOM concentrations (4.42–17.4 mg C L^{-1}). The underprediction of survival indicates that the predicted toxicity was higher than the measured one. This difference may be attributed to the model's potential overestimation of free Gd ions in the media, leading to deviations from the observed survival values. These observations emphasize the importance of selecting an appropriate chemical speciation model, as limitations of available chemical speciation databases can result in uncertainties when predicting the bioavailability and consequently toxicity of Gd.

The third prediction, which combines the average predictions of the two models (Fig. 3; represented by the brown dashed line), provides the closest match with the observed survival. This alignment was particularly close at the highest concentrations of DOM. Therefore, the prediction of survival in natural water samples will also be compared using geochemical speciation models with two organic matter variants and their average prediction.

3.5. With natural water samples

Finally, the effect of 15 mg L-1 of Gd was studied for different natural surface freshwater samples collected in France and Germany (Figs. 1 and 4). The toxicity observed for Gd varies across the different water samples. In all cases the initial Gd effects emerged after approximately 12 hours of exposure.

As observed in the validation of the model in presence of organic matter, the survival was predicted using two different DOM models: NICA-Donnan and the SHM. Both models predict metal speciation with DOM but differ in approach. The NICA-Donnan model estimates metal binding via partitioning between bulk solution and the humic gel Donnan phase (Kinniburgh et al., 1999), while the SHM models electrostatic interactions at specific DOM binding sites (Gustafsson, 2001). The models use different affinity constants which may lead to a different in the estimation of Gd^{3+} concentration.

For most samples, the evolution of the survival was clearly predicted by the fit of the two models with the observed data. However, in two samples (Trieux (site 5) and Hagen (site 10)), the NICA-Donnan predicted a stronger decrease of survival, in comparison with the SHM model. This was specifically the case in the sample from Trieux (site 5) collected in France where only the NICA-Donnan model permitted a good prediction of the Gd toxicity. In that sample, the SHM model overpredicted the survival by underpredicting the Gd^{3+} activity. This difference could be explained by a relatively high DOM concentration (approximately 5 mg C L^{-1}) in the sample that seem to affect the quality of the metal speciation prediction by the SHM model. The average model (Fig. 4; brown dashed line) offered a better prediction only in the sample collected in Hagen (site 10). In contrast, the NICA-Donnan model was considered to be a more conservative model as it consistently predicted the greatest impact on daphnid survival.

No mortality was observed in the Peenestrom Süd 1 (site 1),

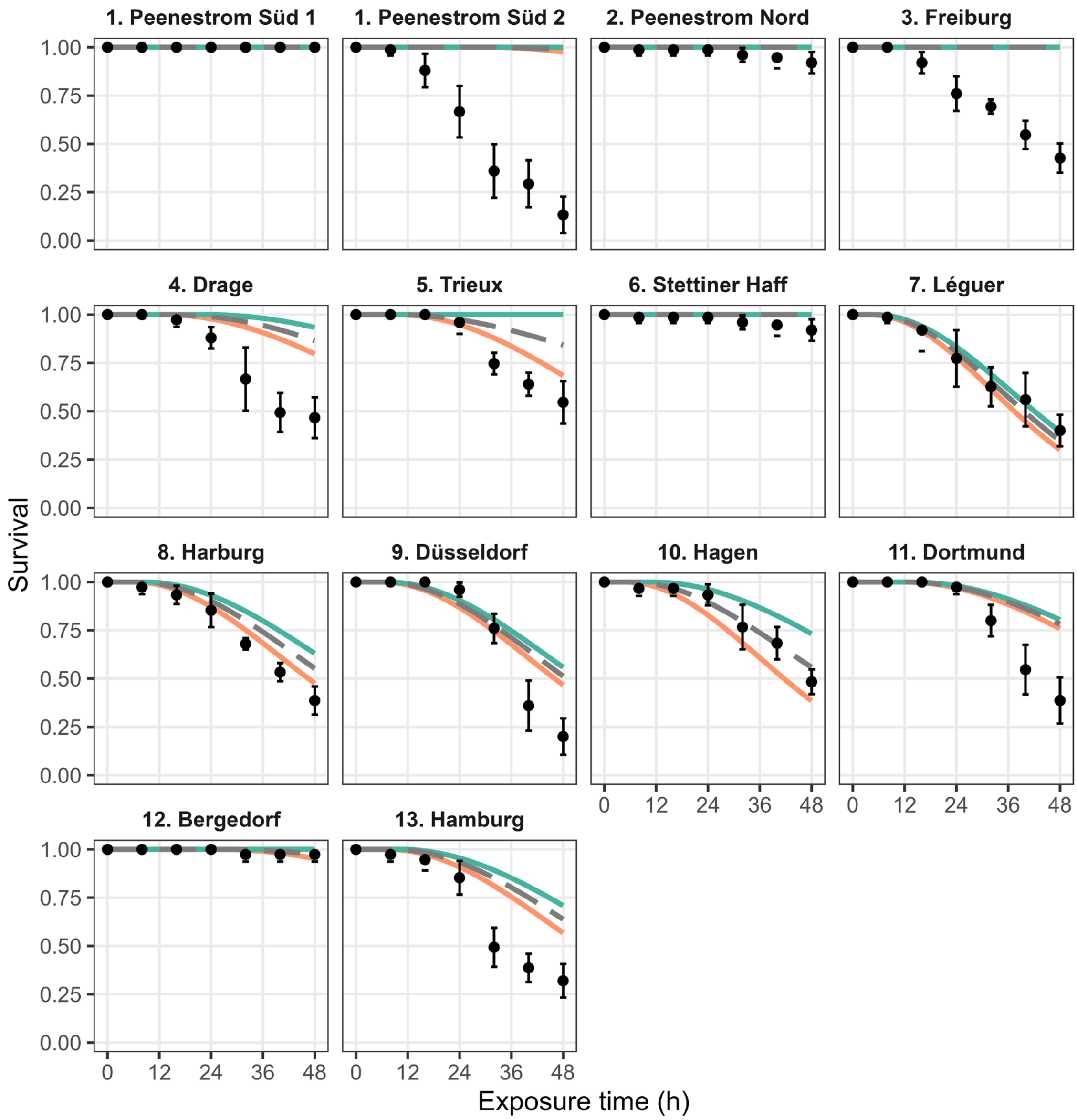

Fig. 4. Comparison of observed vs. predicted survival of *D. magna* in natural waters containing Gd: Effects of 15 mg L^{-1} (nominal concentration). Numbers correspond to the location site presented in Fig. 1. Black dots: observed survival, green line: survival predicted using SHM to model chemical speciation with HA, orange line: survival predicted using NICA-Donnan to model chemical speciation with HA. Brown dashed line: Average of the two survival prediction models. Error bars represent the standard deviation calculated from five experimental repetitions, each containing three replicates of 5 daphnids.

Peenestrom Nord (site 2) and Bergedorf (site 12) samples, due to a pH higher than 6.5 (6.85–7), leading to strong metal complexation and precipitation. Therefore, the free Gd ion concentration, bioavailable for the BL, was too low to affect the survival of *D. magna*. The variation in Gd toxicity observed between the two Peenestrom Süd samples (site 1) can be attributed primarily to differences in pH. Initially, both samples collected at the same location had a pH of 8. To assess the effects of Gd, the samples were randomly acidified to prevent metal precipitation. Consequently, Peenestrom Süd 1 was adjusted to a pH of 6.85, while Peenestrom Süd 2 was set at a pH of 5.85. The lower pH in Peenestrom Süd 2 is likely to have resulted in an increased concentration of free Gd ions and, consequently, elevated toxicity.

In samples from Freiburg (site 3), Peenestrom Süd 2 (site 1), the predictions did not fit with the observed data. According to the chemical speciation modelling, high concentration of Gd and major cations was bioavailable at equilibrium. The high amount of major cations led the BLM to calculate an important protective effects against Gd toxicity, leading to an absence of predicted toxicity after 48 h. However, the experimental work determined significant effect of the metal on *D. magna* with more than 50 % of reduction in survival. These two samples showed higher electroconductivity than the other locations (Supplementary data S4). This discrepancy between the modelled and observed data could be due to limitations in the prediction of metal-DOM-interaction as shown for areas of high salinity by Arnold et al. (2005). Furthermore, elevated salinity (> 5 PSU) leads to osmotic stress in freshwater organisms such as *D. magna* which could increase their sensitivity to any other stressors like metal exposure (Grosell et al., 2007; Chen et al., 2017). Indeed, while higher salinity levels (<5 PSU) were observed to reduce metal bioaccumulation in *Potamocorbula laevis*, their sensitivity to Cu increased when salinity concentrations exceeded their optimal physiological range (Chen et al., 2017). Thus, the increased mortality unpredicted by the model may be due to increase of sensitivity due to multi stressors effect. This multi stressors effect due to the presence of possible other chemicals (e.g., pesticides or micro-plastics) may as well explain the model's overprediction of the survival in site 4, 11 and 13. Indeed, sites 11 and 13 are in urbanized areas, where pollutant levels are likely elevated, while site 4 is situated upstream of the Elbe River, an area potentially impacted by industrial and agricultural runoff. Quantifying additional pollutants would be necessary to verify the potential role of multi-stressor effects on Gd toxicity.

3.6. EC_{50} and NEC prediction

Median effective concentration (EC_{50}) after 48 h of exposure and the no-effect concentration (NEC) of Gd were predicted by the model in the different test conditions used for its parametrization (Fig. 5). For the experiments with different concentrations of humic acid (HA), the SHM speciation model was used rather than the NICA-Donnan model, as the latter may overestimate the free Gd ion concentrations. As shown in Supplementary data S7, this overestimation results in the prediction of similar EC_{50} and NEC values for all HA concentrations.

Most of the EC_{50} ranged from 4 to 30 mg L^{-1}. These concentrations increased with the increase of the major cation concentrations which was particularly visible with Mg^{2+} and K^{+}. These two major cations are considered as the most protective according to the current kinetic BLM. Strong variation of EC_{50} appeared when pH or DOC increased, due to an increase of metal precipitation at pH higher than 7.7, and of metal complexation with organic matter.

The predicted EC_{50} agreed with the Gd EC_{50} available in different available literature (Fig. 3c) (Blinova et al., 2018a; Lachaux et al., 2022; Revel et al., 2023). When comparing with six other Ln, nominal EC_{50} remains higher than the dissolved EC_{50}. However, all EC_{50} remained in a similar range as predicted once. Even though contradictory conclusions are available in the literature, several studies suggested that Ln toxicity is similar among the group due to their similar properties (Tai et al., 2010; Joonas et al., 2017; Rucki et al., 2021). In that case, the present kinetic BLM could potentially serve as a general tool for risk assessment of Ln in aquatic environments.

The NEC was calculated using the kinetic BLM (Liang et al., 2021) and gives further information on the possible chronic effect of Gd on *D. magna*. NEC is considered to be the maximum concentration causing no effect on the survival of *D. magna* under longer exposure time. Therefore, the internal concentration of Gd must remain lower than the internal threshold concentration (C_{IT}) (Tan et al., 2019). With the exposure considered to be constant, the maximum internal Gd concentration is reached at the steady state meaning that $dC_{int}(t)/dt = 0$ in Eq. 2, leading to the Eq. 5:

$$C_{IT} = J/k_e \tag{5}$$

However, the estimated elimination rate of the present study is lower than the growth rate of the organisms. Therefore, to avoid an overprediction of the chronic toxicity of Gd, the elimination rate was replaced by the growth rate constant (g). As suggested by Guan and Wang (2006), this constant is equal to 0.009 h^{-1} (Eq. 6) (see Supplementary data S8 for further explanation).

$$C_{IT} = J/g \tag{6}$$

Chronic toxicity data for Ln on invertebrates remains rare and to date, no NEC is available for comparison. The estimated NEC for Gd ranged 0.1–1 mg L^{-1}, which is two order of magnitude higher than the NEC predicted for Cd by Liang et al. (2021). This observation confirms the lower toxicity of Gd compared to Cd on *D. magna*. However, it is important to note that the use of the kinetic BLM is suitable when only free ion metals impact the organism. Recent research challenges this assumption for lanthanum (La) and Gd with *D. magna* under sub-chronic exposure (Revel et al., 2024). In fact, a recent study revealed that over extended exposure time, both metals accumulated in the organisms' intestines due to particle ingestion while causing lethal effects. Furthermore, while the NEC predicted by the model is derived from the DEB-toxicity model, it currently lacks experimental validation to support its estimation. Therefore, the present kinetic BLM might need some improvement and further validation process in order to better predict the chronic toxicity of Gd on freshwater crustaceans.

Nevertheless, establishing a BLM approach marks a significant advancement in risk assessment of Ln in allowing the considering of water quality factors, such as water hardness. With further validation and refinement—such as improving chemical concentration quantification and exploring potential effect of metal precipitates and combined stressors on daphnid survival —this model can become a valuable tool for enhancing our understanding of Ln toxicity mechanisms.

4. Conclusion

The development of a BLM for Gd on *D. magna* represents a significant advance in ecotoxicology and risk assessment for Ln. By using the

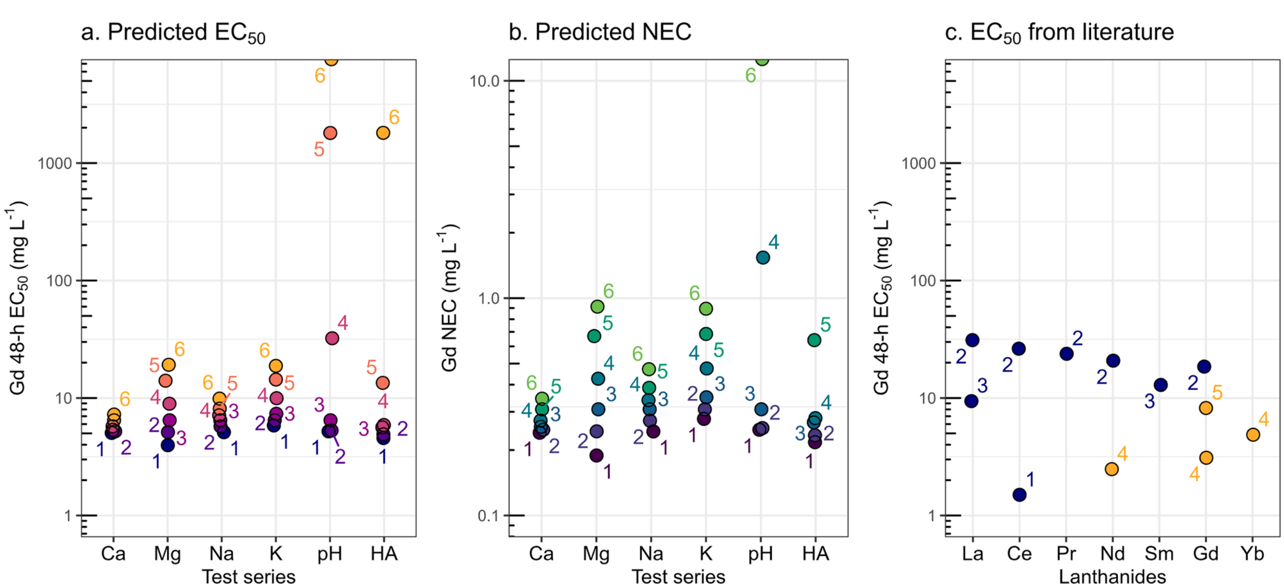

Fig. 5. Gd 48 h EC_{50} (a) and NEC (b) estimated by the kinetic BLM in the different test series compared to EC_{50} from the literature. Numbers from 1 to 6 represents the different level of Gd, major cations and DOM used in each test series (Supplementary data S1) (c) EC_{50} of different Ln on *D. magna* available from the published literature. Dark blue: nominal EC_{50} and Yellow: dissolved EC_{50} calculated after exposure. Letters represents the different publications; a: Ma et al. (2016), b: Blinova et al. (2018a), c: Bergsten-Torralba (2020), d: Lachaux et al. (2022), e: Revel et al. (2023).

framework established by Liang et al. (2021), this model successfully estimated the binding constants between Gd and major cations with the biotic ligand. The results showed that potassium, magnesium, and calcium were strong competitors for the biotic ligand of Gd. This finding raised questions about the potential for Gd^{3+} to interact with a number of different biotic ligands.

The model prediction of the survival was validated, first in the presence of humic acid as organic matter and subsequently with Gd spiked natural water samples collected in rivers, lakes, and estuaries. However, a noteworthy difference was observed in samples with elevated electroconductivity, where the model overpredicted survival. This discrepancy highlights the complex interplay of high electroconductivity and Gd toxicity and the role that multiple stress factors can have on the sensitivity of organisms.

From these observations, the present kinetic BLM can be used for risk assessment in freshwater environments. The EC_{50} values predicted by the model were in the range of available data from the literature (4–30 mg L^{-1}). Due to the similar properties among Ln elements, the current kinetic BLM might be applicable to assess the risk of Ln in aquatic environments, but validation with other elements of this group will be necessary.

Using a kinetic BLM enables the prediction of toxicity of Gd under various exposure times. Therefore, NEC were estimated to fall in the range of 0.1–1 mg L^{-1}, which is three magnitudes higher than that for Cd. However, recent studies on the bioaccumulation of Gd in *D. magna* under sub-chronic exposure suggested that ingested metal particles can cause lethal effect (Revel et al., 2024). The results of this last study suggest that the current kinetic BLM may require improvements to better predict the chronic effects of Gd on *D. magna*.

Author contribution

Marion Revel was responsible for conducting the bioassays with *Daphnia magna*, preparing the water samples for chemical analysis and for the analysis of the data.

The parametrization, validation and interpretation of the kinetic BLM was performed by Marion Revel and Qiao-Guo Tan.

The first draft of the paper was written by Marion Revel. It was then verified and modified by Qiao-Guo Tan, Susanne Heise and Andrew Hursthouse.

CRediT authorship contribution statement

Susanne Heise: Writing – review & editing, Supervision, Conceptualization. **Qiao-Guo Tan:** Writing – review & editing, Visualization, Methodology, Formal analysis. **Andrew Hursthouse:** Writing – review & editing, Supervision. **Marion Revel:** Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2024.117486.

Data availability

Data will be made available on request.

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