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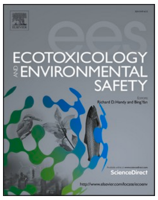

Chemodynamic features of nickel(II) and its complexes: Implications for bioavailability in freshwaters

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ABSTRACT

A robust description of the bioavailability of Ni(II) in freshwaters is fundamental for the setting of environmental quality standards. Current approaches assume that bioavailability is governed by the equilibrium concentration of the free metal ion in the bulk aqueous medium. Such strategies generally have limited predictive value: a suite of empirical fitting parameters is required to deal with variations in water chemistry. Herein we compile data on Ni(II) speciation under typical freshwater conditions and compute the lability of Ni(II) complexes with typical molecular and nanoparticulate components of dissolved organic carbon. In combination with an analysis of the kinetic setting of Ni(II) biouptake by freshwater organisms, we assess the potential contribution from dissociation of Ni(II) complexes to the diffusive supply flux of free Ni^{2+}. The strategy takes into account the absolute and relative magnitudes of the Michaelis-Menten bioaffinity and bioconversion parameters for a range of freshwater organisms, together with dynamic chemical speciation descriptors under environmentally relevant conditions. The results show that the dissociation kinetics of Ni(II) complexes play a crucial role in buffering the free metal ion concentration at the biointerface. Our results highlight the need to couple the timescales of chemical reactivity with those of biouptake to properly identify the bioavailable fraction of Ni(II) in freshwaters.

1. Introduction

Nickel is used in a variety of industrial and commercial materials, e.g. stainless steel, electroplating, batteries, and pigments. The potential for Ni(II) from such products to be released into the environment has led to great interest in the setting of environmental quality standards (EQS) for Ni(II) in freshwaters, as evidenced by a recent flurry of papers (Garman et al., 2020; Croteau et al., 2021; Gauthier et al., 2021; Peters et al., 2021; Santore et al., 2021; Stauber et al., 2021). The Ni(II) oxidation state is the only important one in natural waters. Due to its transition metal character, Ni(II) has affinity for both hard and soft donor atoms (Turner et al., 1981) and can form complexes with a variety of coordination numbers and geometries (Hausinger, 1993). Thus Ni(II) is expected to bind with various components of dissolved organic carbon (DOC) in natural waters. DOC comprises a wide range of compounds from well defined small molecules such as amino acids, to heterogeneous nanoparticles such as humic substances (HS) (Buffle, 1988).

Ni(II) is essential for aquatic plants (Gordon et al., 1978) and microorganisms (Price and Morel, 1991), but there is debate about its essentiality for aquatic animals (Blewett and Leonard, 2017). Based on evidence that the Ni(II) is homeostatically regulated by aquatic animals, some authors propose that it is an essential element (Muyssen et al., 2004; Chowdhury et al., 2008). In any case, once the concentration of Ni (II) exceeds a certain threshold, adverse effects are observed for a wide range of organisms, such as fish (Blewett et al., 2016), various invertebrates (Leonard and Wood, 2013) including oligochaetes (He and van Gestel, 2013) and snails (Niyogi et al., 2014), and microalgae (Deleebeeck et al., 2009). Current strategies for assessing the bioavailability and potential toxicity of Ni(II) rely on equilibrium based approaches such as the biotic ligand model (BLM) which assume that the equilibrium concentration of the free hydrated ion in the bulk aqueous exposure medium is the only relevant chemical species. Some exceptional cases have been noted, namely lipophilic metal complexes which cross the plasma membrane intact, e.g. Cd(II)-xanthates (Block and Glynn, 1992) and metal complexes that form ternary complexes with the biological surface, e.g. Al(III)-fluoride (Wilkinson et al., 1990). In any case, equilibrium-based approaches do not take into account the rate at which free metal ions are released from their complexed forms in the exposure medium (Paquin et al., 2002). Such assumptions are only valid if certain kinetic criteria are met, i.e. the *unsupported* diffusive flux of the free metal ion from the bulk solution to the biointerface is much greater

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Nomenclature

Latin

a	"Best" bioaffinity parameter (dimensionless).
a_g	geometrical center-to-center distance between a metal ion and a multi-site ligand (m).
a_i	center-to-center distance between a site i and a metal ion in an outer-sphere associate (m).
b	"Best" bioconversion parameter (dimensionless).
BLM	biotic ligand model.
c_L^*	concentration of free L in the bulk medium (mol m^{-3}).
c_M^0	concentration of free M at the biointerface (mol m^{-3}).
c_M^*	concentration of free M in the bulk medium (mol m^{-3}).
c_{ML}^*	concentration of ML in the bulk medium (mol m^{-3}).
$c_{M,t}^*$	total concentration of M in the bulk medium (mol m^{-3}).
$\bar{c}_S^\lambda$	average (smeared-out) concentration of nanoparticulate binding sites, S, in the operational reaction layer zone at a macroscopic reactive interface (m).
D_M	diffusion coefficient of M (m^2 s^{-1}).
D_{ML}	diffusion coefficient of ML (m^2 s^{-1}).
$\bar{D}$	mean diffusion coefficient of M and ML (m^2 s^{-1}).
DOC	dissolved organic carbon.
D_p	diffusion coefficient of particle (m^2 s^{-1}).
e	elementary charge (C).
HS	humic substances.
J_{dif}	diffusion controlled flux (mol m^{-2} s^{-1}).
J_{kin}	kinetically controlled flux (mol m^{-2} s^{-1}).
$J_{M,f}^*$	limiting diffusive supply flux of free metal ion (mol m^{-2} s^{-1}).
J_u	actual biouptake flux (mol m^{-2} s^{-1}).
J_u^{max}	maximal biouptake flux (mol m^{-2} s^{-1}).
k_a	association rate constant (m^3 mol^{-1} s^{-1}).
$k_{a,p}$	rate constant for diffusive supply of M to a particle (m^3 mol^{-1} s^{-1}).
k_B	Boltzmann constant (J K^{-1}).
k_d	dissociation rate constant (s^{-1}).
k_{int}	biointernalization rate constant (s^{-1}).
k_w	dehydration rate constant of free metal ion (s^{-1}).
K	stability constant for ML (m^3 mol^{-1}).
K^{os}	stability constant for an outer-sphere associate (m^3 $mol^{-1+)}$.
K_M	characteristic bioaffinity parameter (mol m^{-3}).
$\mathscr{L}$	lability parameter (dimensionless).
M	metal ion.
N_{Av}	Avogadro constant (mol^{-1}).
Q	"Best" normalized flux (dimensionless).
t	time (s).
T	temperature (K).
U^{os}	electrostatic potential between a metal ion and sites in an outer-sphere associate (J).
z_M	charge number of a metal ion.
z_i	charge number of ligand site i.

Greek

$\bar{\delta}$	mean diffusion layer thickness (m).
$\varepsilon_0\varepsilon_r$	permittivity of the aqueous medium (F m^{-1}).
θ_M	ratio of concentrations of bound metal ion and binding sites.
κ^{-1}	Debye screening length (m).
λ	reaction layer thickness (m).

than the biouptake flux and there is no bulk depletion. The BLM literature generally does not mention, let alone verify, compliance with these criteria. For predictions of toxicity, BLMs correlate the amount of metal ions bound to the so-called "biotic ligands" with toxicological endpoints (Paquin et al., 2002). Various empirical correction factors are used as fitting parameters in BLMs to account for the effects of pH, hardness, and dissolved organic carbon (DOC) on toxicological endpoints (Peters et al., 2018; Santore et al., 2021), and typically their applicability is limited to the range of conditions over which they have been developed (Nys et al., 2016). Furthermore, the free metal ion concentration is often not directly measured but rather computed from equilibrium speciation codes which themselves have serious limitations in their description of metal ion binding by natural organic matter (Town et al., 2019).

Herein we address the mechanistic links between chemical speciation dynamics in the aqueous exposure medium, bioavailability and biouptake. In doing so, we revisit concepts for coupling diffusive transport and lability of metal species in the exposure medium with biouptake kinetics (van Leeuwen, 1999, 2000; Jansen et al., 2022). The potential contribution of metal complex dissociation kinetics to the diffusive supply flux is explicitly considered for simple molecular ligands as well as nanoparticulate complexants. Literature data for Ni(II) speciation and biouptake are compiled and critically considered in light of dynamic considerations. Specifically, we (i) analyse experimental data on Ni(II) speciation in freshwaters to identify the range of free Ni^{2+} concentrations and assess the lability of typical Ni(II) complexes with representative molecular and nanoparticulate components of DOC, and (ii) compile Michaelis-Menten bioaffinity, K_M, and maximal biouptake flux, J_u^{max}, values for a range of organisms. By combining this information we identify the conditions under which the dissociation of Ni(II) complexes is essential to meet biouptake demand.

2. Theory

We consider the situation where the biouptake from water is the primary exposure route. Uptake of Ni(II) by aquatic organisms is primarily via the water phase (Watras et al., 1985) although diet can be relevant in some cases (Brix et al., 2017).

2.1. Ni(II) complexes and their labilities

Metal ion complexation by simple ligands in aquatic systems can be described by the Eigen mechanism (Eigen, 1963). That is, complexation involves two successive steps, namely (1) formation of an outer-sphere associate between the hydrated metal ion and the reactive site on the ligand, followed by (2) dehydration and inner-sphere coordination. For simple ligands, dehydration of the metal ion, with rate constant k_w, is often the rate limiting step in the overall complexation reaction. In the case of nanoparticle complexants, the particle size, reactive site density and charge density as well as k_w for the reactant metal ion determine which step in the overall process is rate limiting (van Leeuwen et al., 2011, 2013; Town et al., 2013). The dehydration rate constant, k_w, for Ni(II) is 3×10^4 s^{-1}, which is orders of magnitude lower than that for other trace metal ions such as Pb(II) ($k_w = 7 \times 10^9$ s^{-1}), Cu(II) ($k_w = 1 \times 10^9$ s^{-1}), and Cd(II) ($k_w = 3 \times 10^8$ s^{-1}) (Morel and Hering, 1993). This has the consequence that in the case of soft charged nanoparticles, such as humic substances (Duval et al., 2005), the rate constants for association and dissociation of Ni(II) complexes are usually limited by inner-sphere processes rather than by mere diffusive transport (Town et al., 2012). Accordingly, for both molecular and nanoparticulate Ni(II) complexes, the association rate constant, k_a, is given by k_wK^{os}, where K^{os} is the stability constant for the outer-sphere ion associate between the hydrated metal ion and the ligand which derives from the electrostatic pair interaction energy (Fuoss, 1958). It follows that the dissociation rate constant, $k_d = k_a/K$, where K is the stability constant for ML.

In the following we summarise a theoretical framework that has been developed for describing dynamic metal speciation. In brief, the approach applies to the situation shown in Fig. 1 where a metal ion is consumed at a (bio)reactive interface. Ongoing removal of metal ions from solution at the reactive interface results in a locally lower metal ion concentration which invokes diffusion of metal ions from the bulk solution towards the reactive interface and the establishment of a diffusion layer with thickness $\bar{\delta}$ (Fig. 1). The flux of free metal ions may be buffered by the dissociation of metal ions from metal complexes, ML, depending on the relative magnitudes of their rates of dissociation (expressed in terms of a kinetic flux, J_{kin}) and the timescale of their transport through the diffusion layer (expressed in terms of a diffusive flux, J_{dif}). The overall situation can be described quantitatively by invoking the concept of lability, as outlined below.

We consider the typical practical case in which there is sufficient excess ligand over metal such that the association reaction is quasi-monomolecular and the association rate constant, k_a, can be written as $k_a^{'} = k_a c_L^*$, where c_L^* is the concentration of free L in the bulk medium (superscript * denotes bulk concentration). In terms of the volume reaction in the bulk solution, a metal complex is sufficiently dynamic to maintain bulk equilibrium within a given timescale, t, if t is much larger than the characteristic lifetimes of the free metal ion M (given by the reciprocal of the association rate constant, $1/k_a^{'}$) and the metal complex ML (given by the reciprocal of the dissociation rate constant, $1/k_d$), i.e.:

$$k_a^{'} t >> 1 \text{ and } k_d t >> 1 \tag{1}$$

At the other extreme, a complex is inert if:

$$k_a^{'} t << 1 \text{ and } k_d t << 1 \tag{2}$$

Lability refers to the extent to which a metal complex can maintain equilibrium with the free metal ion in the context of an ongoing interfacial process that consumes the free metal ion, e.g. biouptake (van Leeuwen et al., 2005). The flux of free M towards the reactive interface is determined by the coupled diffusion and interconversion kinetic between M and ML as shown schematically in Fig. 1.

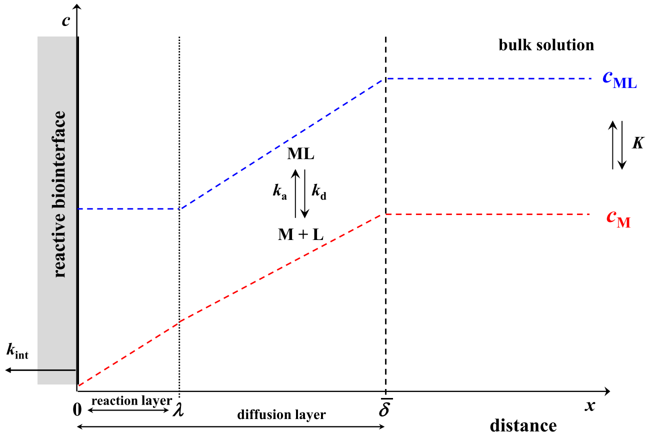

Fig. 1. Schematic representation of the contribution of dynamic chemical speciation processes to biouptake from an aqueous medium containing metal complexes. For simplicity, the case of a molecular complex, ML, is shown under limiting flux conditions. The concentration profiles for the free metal ion and the metal complex are indicated by the red and blue dashed lines, respectively. Arbitrary thicknesses are shown for the reaction layer (λ) and the mean diffusion layer for M and ML ($\bar{\delta}$); K is the stability constant for ML, k_a and k_d are respectively the association and dissociation rate constants for ML, and k_{int} is the biointernalization rate constant. The Koutecký-Koryta approximation specifies that equilibrium between M and ML is maintained from the bulk solution until $x = \lambda$. See text for details.

The lability parameter, $\mathscr{L}$, is given by the ratio of the kinetic flux, J_{kin}, and the diffusive flux, J_{dif} (van Leeuwen et al., 2005):

$$\mathscr{L} = J_{kin}/J_{dif} \tag{3}$$

In the case of labile complexes, $\mathscr{L} >> 1$ and there is frequent interconversion and coupled diffusion of M and ML during their transport through the diffusion layer. At the other extreme, $\mathscr{L} << 1$, complexes are nonlabile and the flux of M corresponds to the kinetically controlled limit originating from dissociation of the complexed species. Quantification of the extent to which metal complex dissociation contributes to the diffusive supply flux of free M is facilitated by use of the so-called Koutecký-Koryta approximation which divides the diffusion layer into a labile and nonlabile region (Brdička and Wiesner, 1947; Koutecký, 1953; Heyrovský and Kůta, 1966). Within the so-called reaction layer, the contribution of the complex is purely kinetic. The expression for the kinetic flux is thus given by:

$$J_{kin} = k_d c_{ML} \lambda \quad [\text{mol m}^{-2}\text{ s}^{-1}] \tag{4}$$

where λ (m) is the reaction layer thickness (Heyrovský and Kůta, 1966) which derives from the mobility of free M (D_M) and its mean free lifetime ($1/k_a c_L^*$) together with the mobility of the complex (D_{ML}) and its mean free lifetime ($1/k_d$). For the case of molecular ligands (Zhang et al., 2007):

$$\lambda = \left(\frac{k_a c_L^*}{D_M} + \frac{k_d}{D_{ML}}\right)^{-1/2} \quad [\text{m}] \tag{5}$$

where D_M and D_{ML} are the diffusion coefficients for M and ML respectively (mol m^{-2} s^{-1}). In the case of nanoparticulate ligands a mean reaction layer thickness, $\bar{\lambda}$, is operative (Duval et al., 2017, 2018):

$$\bar{\lambda} = \left(\left(k_{a,p}\bar{c}_S^{\lambda}/D_M\right) + k_d/D_p\right)^{-1/2} \quad [\text{m}] \tag{6}$$

where $k_{a,p}$ is the rate constant for diffusive supply of free M to the nanoparticle surface (m^3 mol^{-1} s^{-1}), k_d is the composite rate constant for dissociation (s^{-1}) (van Leeuwen et al., 2017), $\bar{c}_S^{\lambda}$ denotes the average (smeared-out) concentration of the nanoparticulate binding sites, S, in the operational reaction layer zone at the macroscopic reactive interface (mol m^{-3}) and D_p is the diffusion coefficient for the particulate complex (m^2 s^{-1}). In the case of nanoparticulate complexants, such as humic substances, partial exclusion of the particle body from the reaction layer must be taken into account (Duval et al., 2017, 2018).

The maximal diffusive flux, J_{dif} for a fully labile system is given by:

$$J_{dif} = \bar{D}\, c_{M,t}^* / \bar{\delta} \quad [\text{mol m}^{-2}\text{ s}^{-1}] \tag{7}$$

where $\bar{D}$ is the mean diffusion coefficient of free M and its complexed forms (m^2 s^{-1}), $c_{M,t}^*$ is the total concentration of M in the bulk solution, and $\bar{\delta}$ is the mean diffusion layer thickness (m).

The various physicochemical parameters involved in the preceding expressions are either independently measurable and/or can be derived from measured values by well-established expressions. For example experimentally-determined k_w values are available (Morel and Hering, 1993) which for Ni(II) lie in the range ca. 3×10^{-4} to 4.5×10^{-4} s^{-1} (Connick and Stover, 1961; Desai et al., 1969; Grant et al., 1970; Ducommun et al., 1980); similarly, metal ion diffusion coefficients at different temperatures have been measured (Li and Gregory, 1974) and their temperature dependence can be computed via the Stokes-Einstein equation (Simpson and Carr, 1958). Expressions are available to estimate $\bar{\delta}$ for given geometric and flow conditions (Levich, 1962).

The above-described framework has been shown to be a powerful tool for interpreting dynamic metal speciation data in a wide range of lability situations including molecular complexes involving protonated species (van Leeuwen and Town, 2009) and higher order complexes, ML_2 (van Leeuwen and Town, 2006) as well as nanoparticulate complexes (Duval et al., 2017). Furthermore, the relative contributions of metal species to the flux towards a biointerface has been shown to be proportional to their lability and independent of the bioaffinity for the metal ion and the internalization rate constant (Zhang et al., 2011).

2.2. *Michaelis-Menten kinetics and the "Best" equation*

Biouptake is usually described by Michaelis-Menten kinetics, i.e. fast Langmuirian adsorption of the free metal ion at the biosurface, e.g. the gills in the case of aquatic exposures, followed by a first-order rate-limiting internalization step. The expression for the steady-state biouptake flux, J_u, is given by (Michaelis and Menten, 1913):

$$J_u = J_u^{max}\frac{c_M^0}{K_M + c_M^0} \quad \left[\mathrm{mol\ \ m^{-2}\ \ s^{-1}}\right] \tag{8}$$

where J_u is the actual biouptake flux (mol m^{-2} s^{-1}), J_u^{max} is the maximal biouptake flux obtained for $K_M/c_M^0 << 1$ (mol m^{-2} s^{-1}), c_M^0 is the concentration of the bioactive M species at the biointerface (mol m^{-3}), i.e. at $x = 0$ (Fig. 1), and K_M is the characteristic bioaffinity parameter (mol m^{-3}; equal to c_M^0 for $J_u = \frac{1}{2}J_u^{max}$). K_M should be determined relative to the concentration of free M in the exposure medium, cf. many studies use total dissolved metal concentrations (Lebrun et al., 2011; Leonard and Wood, 2013; Leonard et al., 2014; Blewett et al., 2016). In practice, the Michaelis-Menten parameters K_M and J_u^{max} are obtained from measurements of biouptake as a function of time over a range of exposure concentrations until saturation is reached. A plot of the resulting J_u values as a function of the free metal ion concentration yields K_M and J_u^{max}. Often the necessary suite of measurements is not performed, i.e. a single time point and/or single exposure concentration is used and uptake is assumed to be linear over the entire exposure period (Leonard and Wood, 2013; Leonard et al., 2014; Niyogi et al., 2014). The validity of this assumption depends on the exposure time, exposure conditions, chemical speciation dynamics, and prevailing biouptake kinetics.

In reality, K_M is a composite function of several rate constants, and there is potential for bias in the determination of K_M when a significant concentration gradient in the exposure medium is present (Winne, 1973, 1977; Wilkinson and Buffle, 2004). Furthermore, when a concentration gradient of free M is present at the biointerface, metal complexes will tend to dissociate within the diffusion layer and thereby contribute to the diffusive supply of free M towards the organism. The contribution of metal complex species to the diffusive supply of free M depends on the rates of interconversion between M and ML, and the diffusion rates governed by the respective diffusion coefficients. D_M and D_{ML}, together with the characteristics of the biouptake process. The "Best" equation provides the means to analyse the bioavailability of metal complexes by coupling c_M^0 in the Michaelis-Menten expression with the supply of free M from the bulk medium containing free and complexed metal species at concentrations c_M^* and c_{ML}^*, respectively (van Leeuwen, 1999, 2000).

For the case of inert metal complexes, or when the free metal ion is the only form present, the diffusive flux of the free metal ion, $J_{M,f}$, is given by:

$$J_{M,f} = \left(D_M/\delta_M\right)\left(c_M^* - c_M^0\right) \quad \left[\mathrm{mol\ \ m^{-2}\ \ s^{-1}}\right] \tag{9}$$

which approaches its limiting value $J_{M,f}^*$ as c_M^0 approaches zero. The combination of Eqs. (8) and (9) yields the so-called "Best" equation (Best, 1955; Koch, 1990; Bosma et al., 1997) which can be written in normalized form as (van Leeuwen, 1999, 2000):

$$Q = \frac{(1 + a + b)}{2b}\left\{1 - \left[1 - \frac{4b}{(1 + a + b)^2}\right]^{1/2}\right\} \tag{10}$$

where Q is the normalized flux (J_u/J_u^{max}), a is the normalized bioaffinity parameter (K_M/c_M^*), and b is the limiting flux ratio ($J_u^{max}/J_{M,f}^*$). Depending on the relative magnitudes of a and b, J_u may be limited by the biointernalization step or by the diffusive supply of free M from the medium. That is for low bioconversion capacity ($b << 1$) and low bioaffinity ($a >> 1$), $J_u = J_u^{max}c_M^*/K_M$, whilst for high bioconversion capacity ($b >> 1$) and high bioaffinity ($a << 1$), $J_u = J_{M,f}^*$.

In the presence of (partially) labile metal complexes, Eq. (10) still holds, albeit that dissociation of complexed species may contribute to the diffusive supply of free M. The bioaffinity parameter retains its meaning with respect to the free metal ion concentration, i.e. $a = K_M/c_M^* = K_M(1 + K')/c_{M,t}^*$, where $K' = Kc_L^*$ with K being the stability constant for the complex ML. The flux of free M is now supported by dissociation of complexed species within the diffusion layer at the consuming biointerface. For fully labile complexes, the limiting diffusive flux of M (for $c_M^0 \rightarrow$ zero) corresponds to:

$$J_M^* = \overline{D}\, c_{M,t}^* \big/ \overline{\delta} = \overline{D}\left(1 + K'\right)c_M^* \big/ \overline{\delta} \quad \left[\mathrm{mol\ \ m^{-2}\ \ s^{-1}}\right] \tag{11}$$

where $\overline{D}$ is the mean diffusion coefficient of M and all complexed species ML, and $\overline{\delta}$ is the corresponding mean diffusion layer thickness.

The extent to which the dissociation of metal ions from (partially) labile complexes is relevant for determining the rate of biouptake depends on the relative magnitude of the diffusive flux of the free metal ion (expressed through $1 + K'$) and the biouptake flux (as governed by the magnitude and ratio of the "Best" equation parameters a and b). An overview of the various limiting situations is given in Table 1 (van Leeuwen, 1999).

3. Methods

3.1. *Ni(II) speciation in freshwaters*

We compiled literature data on direct measurements of free Ni^{2+} concentrations in the presence of different types and concentrations of DOC (Worms and Wilkinson, 2008; Kalis et al., 2006, 2007; Doig and Liber, 2007; Mueller et al., 2012; van Laer et al., 2006).

Table 1

Limiting cases for the normalized flux, Q, and the potential contribution of (partially) labile complexes to biouptake (adapted from van Leeuwen, 1999).

"Best" bioaffinity term, a	"Best" bioconversion term, b	Degree of complexation relative to b	Contribution from dissociation of metal complexes to flux of free M	"Best" Q, Eq. (10)
High, $a < < 1$	High ($b >> 1$)	immaterial	Yes	$1/b$
High, $a < < 1$	Low ($b << 1$)	$b(1 + K') < < 1$	No	1
		$b(1 + K') > > 1$	Yes	1
Low, $a > > 1$	High ($b >> 1$)	$a/b < < 1$	Yes	$1/b$
		$a/b > > 1$ and:		
		$a/b > > 1 + K'$	No	$1/a$
		$a/b < < 1 + K'$	Yes	$1/a$
Low, $a > > 1$	Low ($b << 1$)	$b(1 + K') < < 1$	No	$1/a$
		$b(1 + K') > > 1$	Yes	$1/a$

3.2. Lability of Ni(II) complexes with DOC

The expressions given in the Theory section were used to compute the lability of Ni(II) complexes with typical nanoparticulate (HS) and molecular (amino acid) components of DOC at environmentally relevant Ni(II)/DOC ratios. In the following we detail the derivation of the various parameters employed in the computations.

In the case of HS, their chemically heterogeneous nature means that their metal ion complexation parameters are distributed. The stability constants and rate constants for M-HS complexation are typically characterized as a function of the degree of binding site occupation ($\theta_M = c_{M,bound}/c_L^*$): metal ion binding occurs preferentially at the most strongly available binding sites, thus the mean thermodynamic stability constant increases with decreasing θ_M(Buffle, 1988). For the case of Ni(II)-HS complexes, the rate constants for association and dissociation have been estimated from collated literature data (Town et al., 2012). The rate of Ni(II)-HS association is governed by the rate of inner-sphere complex formation with $k_a \approx 10^{2.2}$ m^3 mol^{-1} s^{-1} being practically independent of θ_{Ni}. The rate constant for Ni(II)-HS dissociation, k_d, is θ_M-dependent (Town et al., 2012), and for the typical θ_{Ni} ranges in freshwaters (see Results and Discussion), k_d is in the range 10^{-3} to 10^{-1} s^{-1}. The applicable concentration of ligand, c_L^*, for computation of θ_{Ni} and the lability parameter refer to the physicochemical form which is involved in the complexation reaction, e.g. the fully deprotonated species. For HS at pH 7 to 8, c_L^* is taken as being equal to the concentration of carboxyl groups, which for aquatic HS is ca. 10 meq per g of C (Ritchie and Perdue, 2003). Thus, DOC concentrations in the range 2 to 30 mg dm^{-3} correspond to c_L^* values in the range 2×10^{-5} to 3×10^{-4} mol dm^{-3}. The diffusion coefficient for aquatic HS is ca. 2.5×10^{-10} m^2 s^{-1} (Lead et al., 2000) and that for free Ni^{2+} at 20 °C is 6×10^{-10} m^2 s^{-1}.

Using the above range of values for each of the parameters, the operational reaction layer thickness, $\bar{\lambda}$, Eq. (6), is found to lie in the range 3.5×10^{-6} m (for $k_d = 0.1$ s^{-1}, $c_L^* = 3 \times 10^{-4}$ mol dm^{-3}) to 1.4×10^{-5} m (for $k_d = 10^{-3}$ s^{-1}, c_L^*. 2×10^{-5} mol dm^{-3}). Since $c_{Ni,bound} \approx c_{Ni,total}$ (see above), the lability parameter, $\mathscr{L} = k_d \lambda \bar{\delta}/\bar{D}$. The applicable diffusion layer thickness, $\bar{\delta}$, depends on the size of the consuming interface and the hydrodynamic conditions. For a macroscopic interface, $\bar{\delta}$ ranges from ca. 10^{-4} m under mild convection to ca. 10^{-5} m under high flow conditions (Levich, 1962). For a planar surface, $\bar{\delta}$ is proportional to the square root of the flow velocity (Levich, 1962), thus for the typical 1 order-of-magnitude range in flow rates over a fish gill (Randall et al., 1991), $\bar{\delta}$ varies by a factor of ca. 3. For microscopic interfaces with dimensions much smaller than $\bar{\delta}$, e.g. microalgae, the pertaining diffusion distance is the radius of the micro-object.

For the case small molecular complexants, we take the example of free amino acids for which the stability constant for 1:1 complexes with Ni(II) is of the order of $10^{5.3}$ dm^3 mol^{-1} at ionic strengths relevant for freshwaters (Pettit and Powell, 2001). For simple ligands, the association rate constant, $k_a = k_w K^{os}$, where K^{os} is the stability constant for the outer-sphere ion associate between the hydrated metal ion and the ligand which derives from the electrostatic pair interaction energy (Fuoss, 1958). In the case of amino acids at pH ca. 8, the carboxyl group is fully deprotonated whilst the amino group remains protonated. For this case, where the ligand contains sites carrying different charges, the interionic potential U^{os} corresponds to the sum of all the electrostatic interactions between the hydrated metal ion and the charges on the ligand. The applicable expression for U^{os} comprises a primary Coulombic term and a screening factor (van Leeuwen et al., 2007):

$$U^{os} = \frac{z_M e^2}{4\pi\varepsilon_0\varepsilon_r} \sum_i^n \frac{z_i}{a_i}\left[1 - \frac{\kappa a_i}{1 + \kappa a_i}\right] \quad [\mathrm{J}] \tag{12}$$

where z_M is the charge number of the metal ion, z_i is the charge number of site i, e is the elementary charge (1.6×10^{-19} C), $\varepsilon_0\varepsilon_r$ is the permittivity of the aqueous medium, n is the total number of charged sites on the ligand, a_i is the center-to-center distance between site i and the metal ion, and κ^{-1} is the Debye screening length (4×10^{-9} m at $I = 5$ mM). Following previous work (van Leeuwen et al., 2007), the distance between the 2 + metal ion and the 1- site on the ligand is taken as 0.45 nm and that between the 2+ metal ion and the 1+ site is taken as 0.75 nm. The ensuing K^{os} is given by (van Leeuwen et al., 2007):

$$K^{os} = \frac{4\pi}{3} N_{Av} a_g^3 \exp(-U^{os}/k_B T) \quad [\mathrm{m}^3 \ \mathrm{mol}^{-1}] \tag{13}$$

where N_{Av} is the Avogadro constant (6.022×10^{23} mol^{-1}), a_g is the geometrical center-to-center distance between the metal ion and the ligand, k_B is the Boltzmann constant (1.38×10^{-23} J K^{-1}) and T is the temperature (K). Application of Eqs. (12) and (13) for the case of Ni^{2+} interacting with a simple amino acid under freshwater conditions yields $K^{os} = 1.15 \times 10^{-3}$ m^3 mol^{-1}, hence $k_a = 34.5$ m^3 mol^{-1} s^{-1}, and $k_d = 0.17$ s^{-1}. These parameters are used in the expressions given in the Theory section to compute the lability parameter for Ni(II) complexes with free amino acids (see Results and Discussion).

3.3. Relevance of Ni(II) complex lability for biouptake

To identify the conditions under which the dissociation of Ni(II) complexes contributes to biouptake, we compute the "*a*" and "*b*" parameters in the "Best" equation.

4. Results and discussion

4.1. Free Ni(II) concentrations in freshwaters

Knowledge of the free Ni^{2+} ion concentration in the exposure medium is fundamental for determination of the bioaffinity parameter, K_M, as well as for ascertaining the potential contribution of complexed metal species to the biouptake flux. In the vast majority of literature reports on biouptake of Ni(II), the concentration of free Ni^{2+} is computed using speciation codes, typically VMINTEQ or WHAM. These codes employ physicochemically poor descriptors for metal-DOC binding and fail to capture the heterogeneity of the intrinsic binding affinity (Town et al., 2019). Indeed, direct measurements of free Ni^{2+} generally show that such codes overestimate the free Ni^{2+} concentration at equilibrium in the bulk exposure medium (Unsworth et al., 2006; Kalis et al., 2006, 2007; Doig and Liber, 2007; Mueller et al., 2012). These observations cast doubts on BLM models which rely on such concentrations.

Several studies have measured the concentration of free Ni^{2+} in the presence of different types of DOC (whole natural waters and isolated humic substances) using a Donnan membrane technique (Kalis et al., 2006, 2007; van Laer et al., 2006) and ion exchange (Doig and Liber, 2007; Worms and Wilkinson, 2008; Mueller et al., 2012). The results are collated in Fig. 2.

The data shown in Fig. 2 can be used to estimate the concentration of free Ni^{2+} in other natural waters or in the presence of isolated humic substances for a given concentration of dissolved Ni(II) and DOC. In freshwaters, the typical concentration of dissolved Ni(II) is in the range ca. 1×10^{-8} to 1.5×10^{-7} mol dm^{-3}, DOC is in the range 2 to 30 mg dm^{-3}, and the pH is mostly in the range 7–8. (Deleebeeck et al., 2008; Van Regenmortel et al., 2017). For this range of conditions, the fraction of free Ni^{2+} (based on direct measurements) is in the range 0.02–0.15, i.e. ca. 0.2×10^{-9} to 25×10^{-9} mol dm^{-3}.

4.2. Lability of Ni(II) complexes with DOC under environmentally relevant conditions

Using the expressions given in the Theory section, the lability of Ni(II)-DOC complexes can be estimated at typical Ni(II)/DOC ratios (see Methods section). In the following we analyse the kinetic features of Ni(II) complexes with HS and with free amino acids under conditions

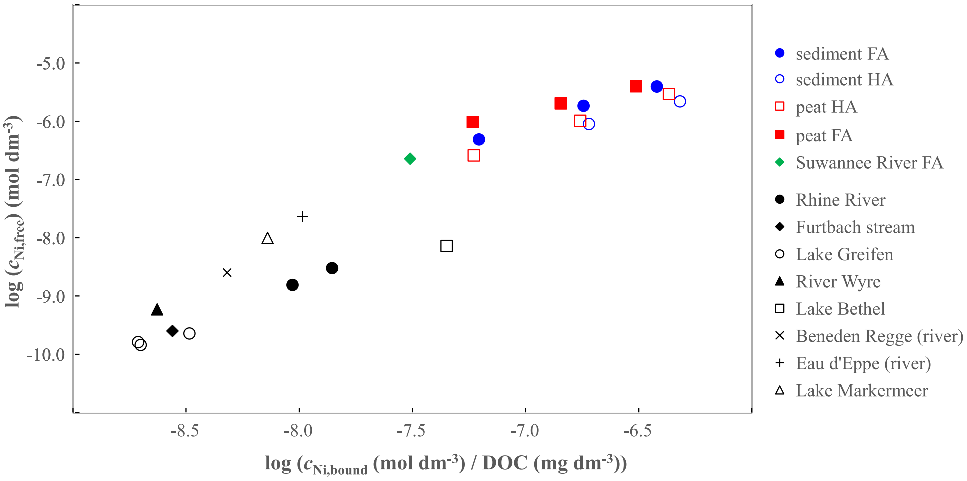

Fig. 2. Concentration of free Ni^{2+} as a function of the ratio of bound Ni/DOC. Data correspond to direct measurements of free Ni^{2+} in natural waters (Kalis et al., 2006; van Laer et al., 2006; Mueller et al., 2012), and isolated humic substances (Doig and Liber, 2007; Kalis et al., 2007). pH ca. 8 in all cases.

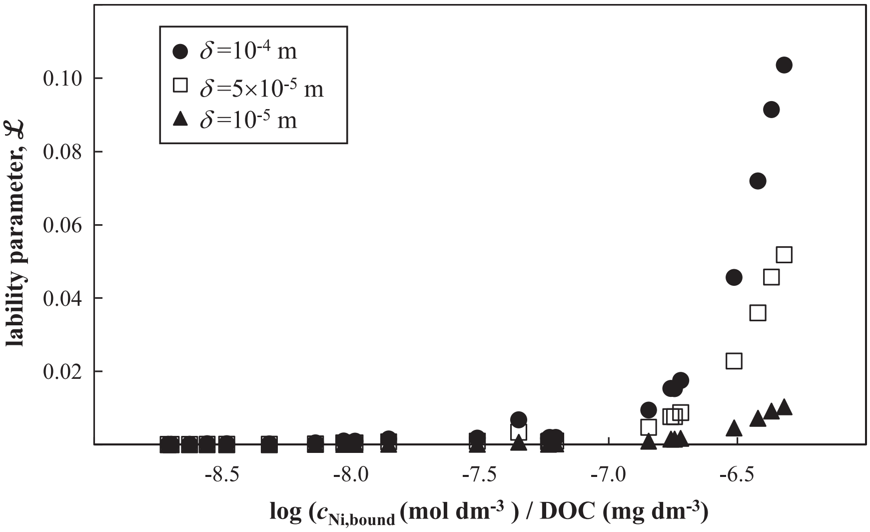

Fig. 3. Lability of Ni(II)-HS complexes as a function of the degree of binding site occupation for a diffusion layer thickness, δ, of 10^{-4} m (●), 5×10^{-5} m (□), and 10^{-5} m (▲). Points correspond to the samples reported in Fig. 2. See text for details.

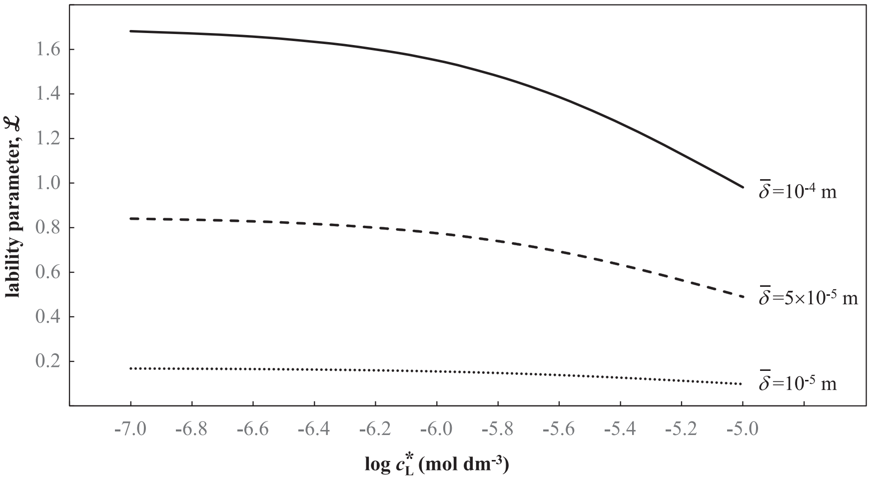

Fig. 4. Lability of Ni(II) complexes with amino acids as a function of ligand concentration for mean diffusion layer thicknesses, $\bar{\delta}$, of 10^{-4} m (solid curve), 5×10^{-5} m (dashed curve), and 10^{-5} m (dotted curve). Data are calculated for $K = 10^{5.3}$ dm^3 mol^{-1}, $k_a = 34.5$ m^3 mol^{-1} s^{-1}, and $k_d = 0.17$ s^{-1}. See text for details.

typical of freshwaters.

For HS, the lability parameter values calculated for the conditions applicable to the data presented in Fig. 2 are shown in Fig. 3 as a function of θ_{Ni}. Since the actual binding site concentrations were not reported in all cases, θ_{Ni} is expressed relative to the measured DOC. The results show that the lability, and thus potential bioavailability of Ni(II)-HS complexes depends on both the ratio $c_{\mathrm{Ni,bound}}/\mathrm{DOC}$ (which determines the applicable K and k_{d}; see Methods) and the applicable $\bar{\delta}$. At a given $\bar{\delta}$, lability increases with increasing θ_{Ni} because K decreases and k_{d} increases. Under the range of conditions considered in Fig. 3, the Ni(II)-HS complexes are partially labile and will thus make a kinetic contribution to the diffusive flux of free M towards a reactive (bio)interface, the magnitude of which increases with increasing θ_{Ni} and increasing $\bar{\delta}$. This finding highlights the limitations of empirical bioavailability corrections for DOC which consider only the absolute value of the DOC concentration and not the Ni(II)/DOC ratio (Peters et al., 2021; Stauber et al., 2021).

In terms of small molecular complexants, free amino acids are a significant component of DOC, with typical concentrations in the range 10^{-7} to 10^{-5} mol dm^{-3} in freshwaters (Jørgensen, 1987; Buffle, 1988; Thomas, 1997). Although the amino acid composition of natural waters varies seasonally and across water bodies (Jørgensen, 1987; Thomas, 1997), the stability constant for 1:1 complexes of Ni(II) with many amino acids is rather similar and of the order of $10^{5.3}$ dm^3 mol^{-1} at ionic strengths relevant for freshwaters (Pettit and Powell, 2001). Using the relevant expressions given in the Theory section together with the parameters derived in the Methods section, the lability parameter for Ni(II) complexes with a typical free amino acid is plotted in Fig. 4 as a function of the ligand concentration, for several $\bar{\delta}$ values.

The above analysis for nanoparticulate and molecular components of DOC demonstrates that Ni(II) complexes with DOC components will be at least partially labile on typical timescales of biouptake under freshwater conditions. In the following section we consider the potential contribution of such complexes to biouptake by various organisms.

4.3. Michaelis-Menten parameters

As detailed in the Theory section, the extent to which the dissociation of metal complexes contributes to biouptake of the free metal ion depends on the bioaffinity and bioconversion capacity of the organism as well as the degree of metal ion complexation in the aqueous medium (Table 1). The preceding sections detail the typical equilibrium and dynamic Ni(II) speciation conditions in freshwaters. This information, together with the Michaelis-Menten parameters (K_{M} and $J_{\mathrm{u}}^{\mathrm{max}}$) reported for various freshwater organisms identifies the conditions under which dissociation of Ni(II) complexes contributes to biouptake (Table 2 and Table S1, Supplementary Information). The biouptake data were measured under conditions where exposure to Ni(II) was solely via the aqueous phase. [In passing we note that the same strategy holds for cases in which dietary uptake is relevant: the applicable Michaelis-Menten parameters are then those for the gut interface together with the chemical speciation dynamics prevailing in the gut environment.] The value of a $(=K_{\mathrm{M}}/c_{\mathrm{M}}^{*})$ depends on the free metal ion concentration, which in freshwaters is typically in the range 0.2×10^{-9} to 25×10^{-9} mol dm^{-3} (see above). For comparative purposes, a free Ni^{2+} concentration of 10^{-9} mol dm^{-3} was used to compute the values given in Table 2 which are presented in order of increasing a/b ratio.

For all organisms shown in Table 2, Ni(II) biouptake is characterised by a fairly high bioconversion capacity $b > (>) 1$ coupled with fairly low bioaffinity, $a > (>) 1$. In such case, the ratio a/b determines the relevance of complex lability for biouptake. In most cases shown in Table 2, $a/b >> 1$, and thus the dissociation of Ni(II) complexes will be essential for buffering the concentration of free Ni^{2+} at the biointerface when $(a/b)/(1+K') << 1$ (Table 1). The relevance of this criterion for freshwater conditions is illustrated by a plot of $(a/b)/(1+K')$ as a function of the fraction of free Ni^{2+} over the typical range of 0.02–0.15 (see above); Fig. 5. At unity on the y-axis, a/b is equal to $(1+K')$; below unity the dissociation of Ni(II) complexes is essential to meet the biouptake demand. The term $(1+K')$ equals $c_{\mathrm{M,t}}/c_{\mathrm{M}}^{*}$, thus for given exposure conditions, the critical fraction of free Ni^{2+} below which dissociation of complexed forms contributes to the biouptake flux simply corresponds to $(a/b)^{-1}$. Thus the higher is the ratio a/b, the lower is the free Ni^{2+} concentration at which dissociation of complexed species is called into play.

Table 2
"Best" parameters for Ni(II) biouptake at a free Ni^{2+} concentration of 10^{-9} mol dm^{-3}. [a]

organism	Bioaffinity parameter, a	Bioconversion parameter, b	a/b
Gastropod, pond snail, *Lymnaea stagnalis*[b]	8.9	112	0.08
Gastropod, pond snail, *Lymnaea stagnalis*[c]	126	167	0.75
Gastropod, pond snail, *Lymnaea stagnalis*[d]	250	87	2.9
Crustacean, *Daphnia pulex*[d]	1840	120	15.3
Crustacean, *Daphnia pulex*[d]	5650	157	36.1
Cyprinid, Atlantic killifish, *Fundulus heteroclitus*[e]	11800	175	67.4
Crustacean, *Gammarus pulex*[f]	5100	61.7	82.7
Gobiiformes, round goby, *Neogobius melanostomus*[g]	1780	18.3	97.1
Dipteran, *Chironomus riparius*[d]	362000	1170	310
Dipteran, *Chironomus riparius*[d]	177000	417	425
Salmonid, rainbow trout, *Oncorhynchus mykiss*[f]	8640	16.7	518
Oligochaete, *Lumbriculus variegatus*[d]	12800	5.17	2480
Oligochaete, *Lumbriculus variegatus*[d]	13400	2.67	5020

[a] for organisms with gills, the diffusion layer thickness was taken as 5×10^{-5} m, for all others 10^{-4} m was used; exposure conditions: pH 7 to 8, range of hardness values (see Table S1).
[b] Niyogi et al. (2014).
[c] Crémazy et al. (2019).
[d] Leonard and Wood (2013).
[e] Blewett et al. (2016).
[f] Lebrun et al. (2011).
[g] Leonard et al. (2014).

A notable exception in Table 2 is the case of the pond snail *Lymnaea stagnalis* for which $a/b < 1$. In this case, dissociation of Ni(II) complexes is essential to meet the biouptake demand *irrespective* of the magnitude of $(1+K')$. Apparent discrepancies in the literature regarding the sensitivity of *Lymnaea stagnalis* towards Ni(II) may be due to the failure to properly account for dynamic chemical speciation. Whilst differences in *modelled* equilibrium chemical speciation and laboratory practices could not explain the observed discrepancies (Crémazy et al., 2020), we note that the exposure conditions in two apparently disparate studies (Niyogi et al., 2014; Crémazy et al., 2019) cover somewhat different ranges of Ni(II)/DOC ratios and thus the extent to which dissociation of Ni(II)-DOC complexes contributed to the biouptake flux may have been different in each case (cf. Fig. 3). Insufficient information precludes a more in-depth analysis.

Whilst our analysis focusses on the relationship between chemical speciation dynamics and bioavailability, it is noteworthy that the magnitude of a/b is in general agreement with the relative sensitivity of freshwater organisms to Ni(II) (European Community, 2008). Furthermore, since K_{M} and J_{u}^{*} are conditional values, their magnitude inherently takes into account the effect of water quality parameters such as pH and Ca^{2+} concentration on the biouptake kinetics. At an order-of-magnitude

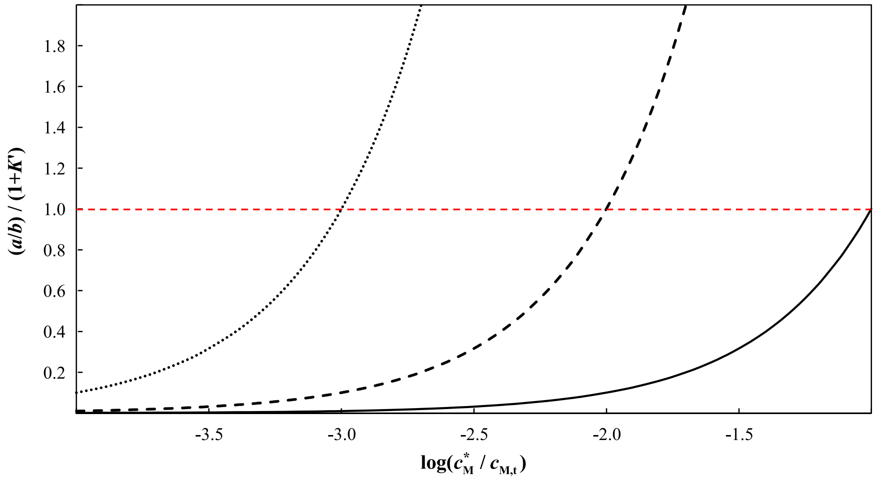

Fig. 5. Relationship between the "Best" equation parameters and the degree of metal ion complexation in solution. The curves correspond to $a/b = 10$ (solid curve), 100 (dashed curve), and 1000 (dotted curve). The computations apply to the case of low bioaffinity, $a > > 1$, and high bioconversion capacity, $b > > 1$. See text for details.

level, our approach provides a useful tool for identifying conditions under which the *kinetic* features of Ni(II) complexes in the exposure medium must be considered in interpretation and prediction of Ni(II) bioavailability.

5. Conclusions

Under typical freshwater conditions only a small fraction (0.02–0.15) of the dissolved Ni(II) concentration is present as the free metal ion. Our theoretical analysis shows that Ni(II) complexes with nanoparticulate and molecular components of DOC are (partially) labile under typical biouptake timescales. Available experimentally-derived biouptake descriptors for freshwater organisms show that the dissociation of Ni(II) complexes is expected to be essential for meeting the biouptake demand at environmentally relevant free Ni^{2+} concentrations. Our kinetic analysis of the chemical speciation and bioavailability of Ni(II) enables empirical equilibrium based approaches to be put in proper dynamic context. The absolute and relative magnitudes of the bioaffinity and bioconversion parameters, together with the dynamic chemical speciation descriptors, determine the kinetic setting of the biouptake process and the potential contribution from metal complexes to the diffusive supply flux of the free metal ion. The total exposure experienced by an organism corresponds to the *integral* of the biouptake flux over the exposure time. Proper consideration of the dynamics of chemical speciation and of biouptake is fundamental for interpretation and prediction of the true exposure conditions experienced by organisms. Further research on chemical speciation dynamics *within* organisms, i.e. the nature, magnitude, and timescale of internal biotic handling processes, including subcellular fractionation of Ni(II) species, and the coupling of such information with the sensitivities of responses across biological species is needed to advance environmental risk assessment beyond the current equilibrium-based empirical correlation strategies.

CRediT authorship contribution statement

Raewyn M. Town: Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing, Visualization, Funding acquisition. **Herman P. van Leeuwen:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Member of International Editorial Board of Ecotoxicology and Environmental Safety, RMT.

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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.2022.113840.

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