Nickel essentiality and homeostasis in aquatic organisms

B.T.A. Muyssen, K.V. Brix, D.K. DeForest, and C.R. Janssen

Abstract: It has been well established that a number of trace metals are essential for various biological functions and are critical in many of the enzymatic and metabolic reactions occurring within an organism. The essentiality of nickel is now generally accepted, based on the numerous symptoms caused by nickel deficiency (mainly in terrestrial vertebrates) and its essential role in various enzymes in bacteria and plants. The information on optimal and deficient concentrations of nickel, however, is limited and the essentiality of nickel to aquatic animals is not established. The purpose of this review is to synthesize the available information on nickel essentiality and homeostasis in aquatic organisms. There is less information on these topics compared to that for other essential metals. Nickel essentiality to aquatic organisms can only be confirmed for plants and (cyano)bacteria due to the documented role of nickel in the urease and hydrogenase metabolism. Deficiency levels ranged from 10^{-12} M to 2×10^{-6} M Ni in different species. No studies were identified that had the explicit objective of evaluating homeostatic mechanisms for nickel in aquatic life. However, inferences could be made through the evaluation of nickel bioconcentration and tissue distribution data and a comparison to other metals that have been more thoroughly studied. Data suggest active regulation and therefore nickel essentiality, since there are no known examples of active regulation of non-essential metals in invertebrates.

Key words: nickel, essentiality, homeostasis, bioconcentration, regulation.

Résumé : Il est bien connu qu'un certain nombre d'éléments traces sont essentiels pour diverses fonctions biologiques, et jouent un rôle déterminant dans plusieurs réactions métaboliques et enzymatiques survenant dans un organisme. Aujourd'hui, on accepte généralement que le nickel est essentiel, sur la base des nombreux symptômes causés par une déficience en nickel (surtout chez les vertébrés terrestres) et de son rôle essentiel dans des activités enzymatiques, chez les bactéries et les plantes. Cependant, l'information dont on dispose sur les concentrations optimales et déficientes sont limitées et l'essentialité du nickel pour les plantes aquatiques n'a jamais été établie. Les auteurs se proposent de synthétiser l'information disponible sur l'essentialité du nickel et l'homéostasie chez les organismes aquatiques. Il y a moins d'information à ces sujets, comparativement à celle qui existe pour les autres éléments essentiels. L'essentialité du nickel pour les organismes aquatiques ne peut être confirmée que pour les plantes et les (cyano)bactéries, compte tenu du rôle documenté du nickel dans le métabolisme de l'uréase et de l'hydrogénase. Les seuils de déficience vont de 10^{-12} à 2×10^{-6} M en Ni, chez différentes espèces. On ne retrouve aucune étude ayant pour objectif l'évaluation des mécanismes homéostatiques pour le nickel, dans la vie

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B.T.A. Muyssen[1] and C.R. Janssen. Ghent University, Laboratory of Environmental Toxicology and Aquatic Ecology, J. Plateaustraat 22, B-9000 Gent, Belgium.
K.V. Brix. EcoTox, 721 Navarre Ave, Coral Gables, FL 33134, USA.
D.K. DeForest. Parametrix, Inc., 5808 Lake Washington Blvd Ste 200, Kirkland, WA 98033, USA.

[1]Corresponding author (e-mail: brita.muyssen@ugent.be).

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aquatique. Cependant, on peut faire des inférences via l'évaluation de la bio-concentration en nickel et des données de distribution dans les tissus, ainsi que les comparaison avec d'autres métaux qui ont été étudiés plus à fond. Les données suggèrent une régulation active et conséquemment l'essentialité du nickel, puisqu'il existe des exemples de régulation active pour des métaux non-essentiels chez les invertébrés.

Mots clés : nickel, essentialité, homéostasie, bio-concentration, régulation.

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Introduction

It has been well demonstrated that a number of trace metals are essential for various biological functions, often at very low concentrations. They are critical in many of the enzymatic and metabolic reactions occurring within an organism. Many metals are components of prosthetic groups in proteins (e.g., copper, iron) or cofactors in enzymes (e.g., manganese, molybdenum, selenium) (Depledge and Rainbow 1990). The essential nature of an element is established when: (1) it is present in living matter; (2) it is able to interact with living systems; and (3) a deficiency results in a reduction of a biological function, preventable or reversible by physiological amounts of the element (Mertz 1974).

Nickel has been shown to be essential for a wide variety of animal species including chickens, rats, pigs, cows, sheep, and goats (for a review on terrestrial organisms see Phipps et al. 2002). The effects of nickel deficiency include delayed gestation period, fewer offspring, anaemia, skin eruptions, reduced hemoglobin and hematocrit values, and reduced activity of several enzymes (WHO 1991). Although a deficiency disease for nickel in humans has not been identified, probably because the nickel supply in diets exceeds its requirement, there is substantial circumstantial evidence for the essential status of nickel (Anke et al. 1995; Nielsen 1996). The essentiality of nickel has also been demonstrated for many bacterial and plant species, where eight nickel-containing enzymes present in one or more of these species have been identified (e.g., Van Baalen and O'Donnell 1978; Gordon et al. 1978; Eskew et al. 1983; Pederson et al. 1986; Price and Morel 1991; Ragsdale 1998; Watt and Ludden 1999). However, the information on optimal and deficient nickel concentrations is limited. The essentiality of nickel to aquatic animals (invertebrate as well as vertebrate species) remains unknown, as a nickel-containing metalloenzyme has yet to be recovered from animal tissues (Goyer and Clarkson 2001).

Given the essential biological function of many metals, aquatic biota have developed a variety of homeostatic control mechanisms to regulate their concentrations in vivo. Aquatic biota have extremely diverse physiology and metabolic requirements and, accordingly, mechanisms by which metal concentrations are regulated vary widely between organisms (George and Pirie 1980; Mason and Nott 1981; Rainbow et al. 1980; Simkiss 1981; White and Rainbow 1984; Rainbow 1988; Viarengo 1989; Depledge and Rainbow 1990). In general, aquatic organisms are classified as regulators, partial regulators, or non-regulators (Phillips and Rainbow 1989). However, these terms are a misnomer as all organisms regulate metals, rather it is the mechanisms by which they do so that distinguishes them. Consequently, the following terms will be used to describe the mechanisms by which nickel, as well as other metals, are regulated: (1) active regulation, (2) active regulation in combination with storage, and (3) storage.

Much of the research on metal homeostasis in aquatic biota has focused on a limited number of metals, including cadmium, copper, and zinc (e.g., Rainbow et al. 1980; Brown 1982; White and Rainbow 1982). However, a number of other metals are known to be regulated by various storage mechanisms. For example, mercury and silver are sequestered by metallothioneins (Viarengo 1989) while lead is stored in granules (Phillips and Rainbow 1989). There do not appear to be any examples of non-essential metals being actively regulated by aquatic invertebrates (Rainbow 1996), although there is evidence that cadmium is pumped out of Gram-positive microorganisms using an ATPase (Simkiss and Taylor 1995).

Recently, it has been recognized that the risk assessment of essential elements requires a different approach compared to non-essential metals and organic chemicals. Standard procedures for deriving

environmental quality criteria may not be appropriate to accurately assess their true impact on ecological quality of terrestrial and aquatic ecosystems (Bergman and Dorward-King 1997; Janssen et al. 2000; Muyssen and Janssen 2001). In order to use proposed approaches such as the no risk area (NRA) concept (Van Assche et al. 1997), toxicity as well as deficiency data on as many organisms as possible are needed.

The purpose of this paper is to synthesize the available information on nickel essentiality and homeostasis in aquatic organisms. Information on these topics is limited compared to other essential metals, such as copper and zinc. However, as the available data indicate that nickel behaves in a similar manner to other metals, inferences specific to nickel are made where necessary from an understanding of metal homeostasis in general.

A comprehensive literature search was conducted to compile information on nickel essentiality–deficiency and homeostasis–regulation in aquatic organisms. Relevant studies identified in the literature search were compiled into the following general data categories:

- Related to essentiality and deficiency
  - General information: These studies mainly presented data on human health and nutrition
  - Nickel essentiality in vertebrates (mainly rats, cattle, or chicken), higher plants, bacteria and fungi
  - Nickel essentiality in aquatic organisms, other than bacteria
- Related to homeostasis and regulation
  - Water-based bioconcentration – bioaccumulation data: Studies that presented data for calculating bioconcentration and bioaccumulation factors (BCFs–BAFs)[2]
  - Sediment-based bioccumulation data: Studies that presented data for calculating biota-sediment accumulation factors (BSAFs)[3] for nickel in aquatic biota, but did not explicitly evaluate homeostatic control mechanisms
  - Tissue distribution data
  - Mechanistic data: Studies that evaluated or discussed at the sub-organismal level how homeostatic control is maintained in aquatic organisms

A very limited number of studies on essentiality and deficiency was related to aquatic organisms, while the literature related to homeostasis and regulation is largely of studies focusing on BCF–BAFs, BSAFs, and tissue distribution data. Very little information was identified specific to nickel homeostatic mechanisms. Before summarizing the studies on nickel essentiality and homeostasis, some general information is provided concerning concentrations of nickel in the aquatic environment, its metabolic role and the interactions with other elements.

Nickel in the aquatic environment

Nickel is ubiquitous in the biosphere and ranks 24th in crustal abundance of all elements (Eisler 1998). Furthermore, nickel is one of the most common metals in surface waters (USEPA 1986). Nickel enters surface waters naturally from three primary sources: (1) particulate matter in rain water, (2) the

[2]The BCF is the ratio of a chemical's concentration in an organism's tissue to its concentration in the water to which the organism was exposed. The BAF is calculated the same as the BCF, but the organism was also exposed to the chemical via its diet.

[3]The BSAF in this paper is the ratio of a chemical's concentration in an organism's tissue to its concentration in the bulk sediment to which the organism was exposed.

dissolution of primary bedrock materials, and (3) secondary oil phases (Eisler 1998). Given the many industrial and commercial uses of nickel, including stainless steel, electroplating, as pigments, and in ceramics, nickel also enters aquatic systems from anthropogenic sources. In streams with minimal anthropogenic disturbance, nickel concentrations are typically below 10 μg/L. Dissolved nickel concentrations in estuaries also tend to be less than 10 μg/L, while concentrations in the open ocean tend to be less than 0.7 μg/L (Jenkins 1980; Eisler 1998). Input from mixed industrial urban sources may increase these values to 10–50 μg/L (Moore and Ramamoorthy 1984). Historic records of highly-contaminated lakes, e.g., near the nickel smelter at Sudbury (Ontario), indicate that nickel concentrations up to 3000 μg/L may be measured (Stokes et al. 1973). Within aquatic systems, nickel typically occurs as soluble salts adsorbed onto, or associated with, clay particles, organic matter, and other substances (Eisler 1998). Nickel may be deposited in sediment by precipitation, complexation, adsorption on clay particles, and via uptake by biota. Because of microbial activity or changes in physical and chemical parameters, including pH, ionic strength, and particle concentration, sorption processes may be reversed, leading to release of nickel from the sediment (Di Toro et al. 1986).

Nickel metabolism

Studies on nickel metabolism in aquatic organisms are limited to phytoplankton and cyanobacteria and are related to the role of nickel in urease and (cyano)bacterial hydrogenase metabolism. Ragsdale (1998) describes four additional nickel-containing microbial enzymes. They are superoxide dismutase (isolated from a *Streptomyces* species), methyl-coenzyme M reductase (from methanogenic bacteria), carbon monoxide dehydrogenase (from *Rhodosprillum rubrum*), and acetyl-coenzyme A synthase (from acetogenic and methanogenic bacteria). Glyoxalase I and isomerase are reported by Watt and Ludden (1999) as two additional nickel-containing enzymes from *Escherichia coli*.

Urease plays a key role in nitrogen metabolism of plants and microbial populations by metabolizing urea to ammonium and carbon dioxide:

$$H_2N\text{-}CO\text{-}NH_2 + 2H_2O \rightarrow 2\ NH_3 + H_2CO_3$$

$$(2NH_3 + 2H_2O \rightarrow 2NH_4^+ + 2OH^-)$$

The first indication of the biological role of nickel was its identification as a constituent of Jack bean (*Canavalia ensiformis*) urease (Dixon et al. 1975). Urea can serve as a sole source of nitrogen for many unicellular algae. In algae grown on urea, two enzymes involved in urea catabolism have been described: urease and ATP–urea amidolyase. All the algae examined by Leftley and Syrett (1973) that are unequivocally classified as Chlorophyceae, contained ATP–urea amidolyase but not urease. All the other algae contained urease but no ATP–urea amidolyase. As ATP–urea amidolyase is not a nickel-containing enzyme, organisms using this enzyme to metabolize urea are not dependent on nickel for urea metabolism. One exception was reported for a nickel-requiring *Chlorella* that lacks urease (Soeder and Engelmann 1984). Considering the comparatively simple reaction performed by the enzyme, ureases are structurally complex and unlike most enzymes, additional urease specific gene products are required for the production of a catalytically active holoenzyme (Ragsdale 1998; Colpas and Hausinger 2000; Olson et al. 2001).

Hydrogenase catalyses the oxidation of hydrogen (H_2):

$$2H^+ + 2e^- \leftrightarrow H^+ + H^- \leftrightarrow H_2$$

In many nitrogen fixers, hydrogen (produced as a consequence of the mechanism of nitrogenase) is efficiently recycled by means of the hydrogenase enzyme. The latter has been assumed to enhance nitrogenase function by recouping ATP and reductant that would otherwise be wasted. By preventing

the build-up of inhibitory H_2 at the nitrogenase enzyme and by lowering the oxygen tension at the site of nitrogenase, inactivation is minimized (Pederson et al. 1986). Hydrogenases can be divided into four types: NiFeSe, NiFe, Fe-only enzymes, and one that lacks metals (Hartmann et al. 1996). As for urease, accessory proteins are involved in the processing of nickel before a catalytically active enzyme is obtained (Maier and Bock 1996).

In mammals and humans nickel metabolism has been described in great detail (Eisler 1998; WHO 1991). As reported in the Introduction, symptoms of nickel deficiency in these animals are numerous. Specific metabolic roles of nickel, however, remain largely unknown (Spears 1999). A hypothesis for the biochemical action of nickel is the CO_2-fixation of propionyl-CoA to form D-methylmalonyl-CoA (Nielsen 1991). Other studies suggest that nickel may serve as a cofactor for activation of calcineurin, a calmodulin-dependent phosphoprotein phosphatase, that has importance as a brain and skeletal muscle enzyme regulator (Sunderman and Oskarsson 1991; Nielsen 1993). Additionally, it might be involved in cyclic nucleotide gated channel functions (Gordon and Zagotta 1995) and recent evidence suggests that there is a collaborative relationship between vitamin B-12 metabolism and nickel (Stangl et al. 2000).

Interaction with other metals

Among animals, plants, and microorganisms, nickel interacts with at least 13 essential elements (Ca, Cr, Co, Cu, I, Fe, K, Mg, Mn, Mo, Na, P, and Zn). Competitive interactions have been reported with Ca, Co, Cu, Fe, Mg, Mn, and Zn (Nielsen 1980; WHO 1991). In most cases it is not known whether competition occurs at the cell-surface uptake sites or at intracellular metabolic sites (Bruland et al. 1991). However, competition at both sites is likely to occur because metal-chelating functional groups found in both membrane transport proteins and intracellular enzymes are never completely specific for one metal (Sunda 1988).

The effect of nickel–zinc interactions in amphibian embryos (*Bufo arenarum*) were dependent on the zinc concentration, ranging from no effect on nickel toxicity at low zinc concentrations (0.5 mg Zn^{2+}/L), a synergistic effect at intermediate concentrations (2 to 20 mg Zn^{2+}/L), to a beneficial effect at the highest concentrations (30 mg Zn^{2+}/L) (Herkovits et al. 2000). A synergistic effect of copper and nickel was demonstrated by Hutchinson (1973) for several algal species. Mixtures of metals (arsenic, cadmium, copper, chromium, mercury, lead, zinc) containing nickel salts are more toxic to daphnids and fish than are predicted on the basis of individual components (Enserink et al. 1991). Chromium-nickel mixtures produced a more-than-additive deleterious effect in 96-h toxicity tests with guppies (*Poecilia reticulata*) (Khangarot and Ray 1990).

Gordon et al. (1978) reported that it is possible that Co^{2+} may play the same role as Ni^{2+} in urea metabolism of the duckweed *Lemna paucicostata*. Nickel deficiency symptoms in *Chlorella emersonii* (lacking urease) were partially reversible by cobalt addition (Soeder and Engelmann 1984). Gerendas et al. (1998), however, stated that cobalt does not replace nickel with respect to functional urease in zucchini and soybean. Manganese, cobalt, zinc, molybdenum, copper, and iron were not able to prevent the repression of hydrogenase synthesis by EDTA as nickel did (Papen et al. 1986).

Nickel essentiality and deficiency

Nickel is not unequivocally considered essential to aquatic organisms, mainly because the nickel requirements of many species have not been studied. Nickel has been reported as “toxic” and “not an algal nutrient” (Gray et al. 2001), “less metabolically essential” (Alikhan and Zia 1989) or classified as essential but with no further reference to its metabolic role (Catsiki et al. 1994). Zauke et al. (1996) and Ritterhoff and Zauke (1997) mention this lack of information on metal requirements for copepods. The essentiality of nickel has been studied in cyanobacteria, algae, and aquatic plants. An overview of the main results described for these organisms is given below and summarized in Table 1. No studies were found describing nickel essentiality and deficiency in aquatic invertebrates and fish, although some indirect indications might be found in the accumulation and regulation data (see further below).

Table 1. Summary of aquatic species in which the nickel requirements are reported and their deficient and optimal nickel levels.

				μM Ni		
	Species	Enzyme tested	Endpoint	Deficiency	No deficiency/optimal	References
Cyanobacteria	*Anabaena cylindrica*	Hydrogenase	H_2 consumption	<0.002	0.68	Daday et al. (1985); Pederson et al. (1986)
	Anacystis nidulans	Hydrogenase	H_2 evolution and H_2 uptake	<2	8–12	Papen et al. (1986)
	Mastigocladus laminosus	Hydrogenase	H_2 consumption	<0.002	0.68	Pederson et al. (1986)
	Oscillatoria sp.	—	Cell dry weight	<0.02	0.05	Van Baalen and O'Donnell (1978)
Algae and aquatic plants	*Cyclotella cryptica*	Urease	Growth (optical density)	<0.004	0.1–1	Oliveira and Antia (1984)
	Thalassiosira weissflogii	Urease	Growth rate (Price and Morel 1991; Peers et al. 2000) , growth (OD) (Oliveira and Antia 1986)	10^{-6} (Price and Morel 1991; Peers et al. 2000), ≤0.05 (Oliveira and Antia 1986)	0.0001 (Price and Morel 1991; Peers et al. 2000), 0.01 (Oliveira and Antia 1986)	Price and Morel (1991); Peers et al. (2000), Oliveira and Antia (1986)
	Thalassiosira pseudonana	Urease	Assay optimization	—	0.006	Peers et al. (2000)
	Thalassiosira nordenskioldii	Urease	Growth (OD)	≤0.05	0.1	Oliveira and Antia (1986)
	Phaeodactylum tricornutum	Urease	Urease activity	Not added	1 (Syrett and Peplinska 1988), 10 (Rees and Bekheet 1982)	Syrett and Peplinska (1988); Rees and Bekheet (1982)
	Tetraselmis subcordiformis	Urease	Urease activity	Not added	10	Rees and Bekheet (1982)
	Emiliania huxleyi	Urease	Chlorophyll fluorescence	Not added	0.1	Palenik and Henson (1997)
	Chlorella emersonii	—	Cell number and dry matter	0.009	0.04	Soeder and Engelmann (1984)
	Rhodomonas sp.	Urease	Growth (OD)	≤0.005	0.01–0.1	Oliveira and Antia (1986)
	Achnanthes brevipes	Urease	Growth (OD)	≤0.005	0.01–0.1	Oliveira and Antia (1986)

Table 1. *Concluded.*

	Species	Enzyme tested	Endpoint	μM Ni		References
				Deficiency	No deficiency/optimal	
Algae and aquatic plants	*Amphidinium carterae*	Urease	Growth (OD)	≤0.005	0.01	Oliveira and Antia (1986)
	Skeletonema costatum	Urease	Growth (OD)	≤0.005	0.01	Oliveira and Antia (1986)
	Pavlova lutheri	Urease	Growth (OD)	*	<0.005*	Oliveira and Antia (1986)
	Chaetoceros gracilis	Urease	Growth (OD)	*	<0.005*	Oliveira and Antia (1986)
	Prymnesium parvum	Urease	Growth (OD)	*	<0.005*	Oliveira and Antia (1986)
	Hymenomonas elongata	Urease	Growth (OD)	≤0.005	0.01	Oliveira and Antia (1986)
	Porphyridium cruentum	Urease	Growth (OD)	≤0.005	0.01	Oliveira and Antia (1986)
	Olisthodiscus luteus	Urease	Growth (OD)	*	<0.005*	Oliveira and Antia (1986)
	Lemna paucicostata	Urease	Multiplication rate	<2	50	Gordon et al. (1978)
	Spirodela polyrrhiza	Urease	Multiplication rate	<2	50	Gordon et al. (1978)
	Wolffia globosa	Urease	Multiplication rate	<2	50	Gordon et al. (1978)

Note: —, not reported; OD, optical density.

*Owing to the toxicity of nickel at all concentrations tested, the optimal nickel concentration is expected to be lower than that shown, if nickel is at all required for growth on urea.

Cyanobacteria

Daday et al. (1985) studied the effect of nickel on hydrogen metabolism and nitrogen fixation in the cyanobacterium *Anabaena cylindrica*. Four sets of growth conditions were used, and in each case nickel-containing cells had an active hydrogen uptake capacity, whereas nickel-depleted cells (cultured in <1.7 nM) did not. Maximum hydrogenase activity was measured in the 0.68 μM nickel treatment. Pederson et al. (1986) demonstrated the nickel dependent hydrogenase activity of *A. cylindrica* and *Mastigocladus laminosus*. In *Anacystis nidulans*, maximum H_2-evolution and H_2-uptake were observed at nickel concentrations ranging from 8 to 12 μM (Papen et al. 1986). However, the importance of hydrogenase activity on growth and nitrogen content of free-living nitrogen fixers, including cyanobacteria, has not been demonstrated (Pederson et al. 1986). Also in the study by Daday et al. (1985), no advantages of increased hydrogenase activity to the organism in terms of growth and nitrogen fixation could be observed. Under the conditions tested, neither hydrogenase nor urease were in any way essential for cell growth of *A. cylindrica*. Possibly the significance of these enzymes for the organism is only apparent under certain stress conditions. Indeed, at elevated temperatures a definite protective effect of nickel–hydrogenase was observed compared to nickel-deficient cells (Pederson et al. 1986). On the other hand, Van Baalen and O'Donnell (1978) did isolate an *Oscillatoria* sp., taken from a marine mud sample, which had an absolute requirement for nickel. Nickel (Ni^{2+}) concentrations lower than 0.05 μM drastically reduced growth of the blue green alga.

Algae and higher plants

In the absence of added nickel, *Thalassiosira weissflogii* failed to grow in urea medium. This effect was reversed when the nickel concentration was increased from 10^{-12} to 10^{-9} M. Urea-grown cells grew at half their maximum rate at $10^{-10.5}$ M and reached a maximum growth rate at concentrations higher than 10^{-10} (Price and Morel 1991). Peers et al. (2000) added 63 nM Ni to the culture medium of *T. weissflogii* and *T. pseudonana* for the development of an in vitro urease enzyme assay. Also for another diatom, *Cyclotella cryptica*, the importance of nickel for urease activity was demonstrated (Oliveira and Antia 1984). Urease activity in the marine unicellular algae *Phaeodactylum tricornutum* and *Tetraselmis subcordiformis* deprived of nickel was restored by adding 10 μM nickel (Rees and Bekheet 1982). It is suggested that during nickel starvation both algae synthesized a non-functional urease protein that required the insertion of nickel at the active site to restore activity. Syrett and Peplinska (1988) added 1 μM Ni to the culture medium in order to differentiate between Ni-deprived and non-deprived *P. tricornutum*. Palenik and Henson (1997) demonstrated the nickel-dependent growth of most *Emiliania huxleyi* strains (eukaryotic marine phytoplankton) by comparing differences in growth between nickel-depleted cells and cells to which 0.1 μM nickel was added to the culture medium. *Chlorella emersonii*, lacking urease, was demonstrated to be dependent on nickel for growth (Soeder and Engelmann 1984). After transfer to nickel deficient medium containing only 8.5×10^{-9} M Ni, biomass production dropped and cells became chlorotic. A concentration of 3.8×10^{-8}M Ni appeared to be in the optimal range. Oliveira and Antia (1986) reported optimal Ni concentrations for 12 marine microalgae. For most species this optimum was approximately 0.01 μM. For *Thalassiosira nordenskioldii* this optimum was a factor of 10 higher, while for four other species the optimum was expected to be lower than 0.005 μM, due to the fact that nickel was toxic at all concentrations tested. If a nitrogen source other than urea is present (e.g., NH_4^+), urease metabolism will not be compromised in urease dependent eukaryotic phytoplankton when nickel is limiting (Morel et al. 1991; Price and Morel 1991).

Gordon et al. (1978) presented the first confirmation in an intact higher plant (the duckweed *Lemna paucicostata)*, based on enzymology and tissue culture responses, of the role of Ni^{2+} in urea metabolism. Although, *L. paucicostata* does grow on urea as a sole nitrogen source both in the presence and absence of added nickel, nickel levels above 2 μM significantly promoted growth of *L. paucicostata* grown on 10 mM of urea. It indicates that the pathways of urea utilization with and without added nickel may be substantially different. Other duckweed species (*Spirodela polyrrhiza* and *Wolffia globosa*) responded to nickel and urea in a similar manner.

Nickel accumulation, regulation, and homeostasis

Nickel bioconcentration factors

As discussed above, studies were identified that presented BCF and BAF data for nickel. This paper focuses on BCF data, i.e., nickel uptake from water only, because exposure via the diet is normally poorly characterized in BAF studies and may lead to improper interpretation of study results. Additionally, the available data suggest very limited uptake of nickel via the diet (Watras et al. 1985).

Nickel BCF data were identified for a wide variety of aquatic organisms including bacteria, algae, aquatic plants, invertebrates, and fish (Riley and Roth 1971; Friedrich and Filice 1976; Lind et al. 1978 [4]; Calamari et al. 1982; Hall 1982; Watling 1983; Wilson 1983; Zaroogian and Johnson 1984; USEPA 1986; Alikhan and Zia 1989; Alikhan et al. 1990; Azeez and Banerjee 1991; Samecka-Cymerman and Kempers 1996; Wong et al. 2000). As shown in Fig. 1*a*–1*e*, an inverse relationship between the BCF and exposure concentration in water is consistently observed across a variety of organism types (i.e., the BCF decreases as the water concentration increases). This same pattern has previously been described for several other divalent metals (e.g., Cd, Cu, Pb, Zn) and most organisms for which sufficient BCF data are available (McGeer et al. 2003).

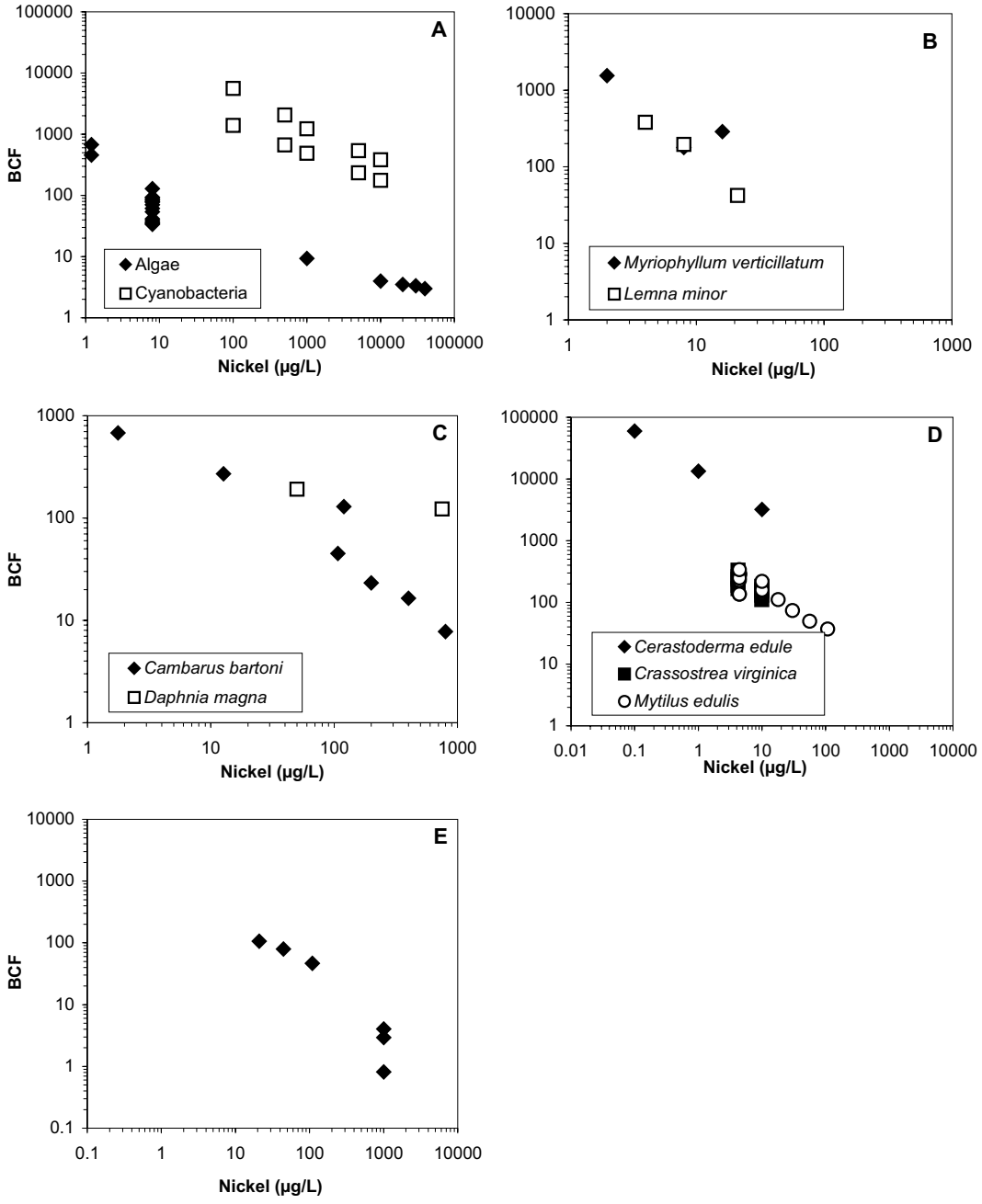
There are two main mechanisms that drive the inverse relationship usually observed between metal BCFs and water concentration. First, unlike many organics, uptake and elimination of metals and other inorganics is not by simple diffusion processes. Rather, uptake occurs via physiological mechanisms that exhibit saturable kinetics (e.g., Simkiss and Taylor 1989; McDonald and Wood 1993). Similarly, elimination is not a diffusion process but is controlled by physiological processes, usually renal, biliary or branchial and, additionally, detoxification and storage can occur (Mason and Jenkins 1995; McDonald and Wood 1993). Nickel is also eliminated by shedding the carapaces in some zooplankton (Hall 1982). The degree of uptake and ultimate internal fate of metals is strongly influenced by ligand binding and receptor site competitive interactions that control metal availability and (or) transfer processes at the level of (1) the aquatic or sediment medium, (2) the biological membranes, (3) the vascular and intercellular transfer mechanisms, and (4) the intracellular matrix (e.g., Campbell 1995; Mason and Jenkins 1995). Given all of these compounding factors, metals typically do not bioconcentrate in organisms in a concentration dependent fashion.

Second, using the active transport mechanisms described above, homeostatic control of metal bioaccumulation is accomplished over a wide range of environmental exposure conditions. Aquatic biota regulate internal concentrations of metals through (1) active regulation, (2) storage, or (3) a combination of active regulation and storage. Active regulators are organisms that maintain stable tissue concentrations by excreting metal at rates comparable to the intake rate. Other biota store metals in detoxified forms, such as in inorganic granules or bound to metallothionein-like proteins. Some organisms use a combined regulatory strategy. Depending on the organism, any one of these regulatory mechanisms may explain the relationship observed between the BCF and exposure concentration. The inverse relationships observed for algae, aquatic plants, and crustaceans may be due to active regulation of nickel by these organisms (Fig. 1*a*–1*c*). Given the demonstrated essentiality of nickel for some algae and aquatic plants, it is likely that these organisms have developed mechanisms for maintaining their internal nickel concentrations over a range of external (aqueous) nickel concentrations. The inverse relationships observed for crustaceans may also be reflective of active regulation, as Hall (1978) suggested that *Daphnia magna* may be able to actively regulate nickel uptake, excretion, or both. However, the possibility of active nickel regulation by *D. magna* suggests but does not prove essentiality and further research is necessary to confirm these hypotheses.

The basis for the inverse relationships observed for bivalves and fish (Fig. 1*d*–1*e*) is even more

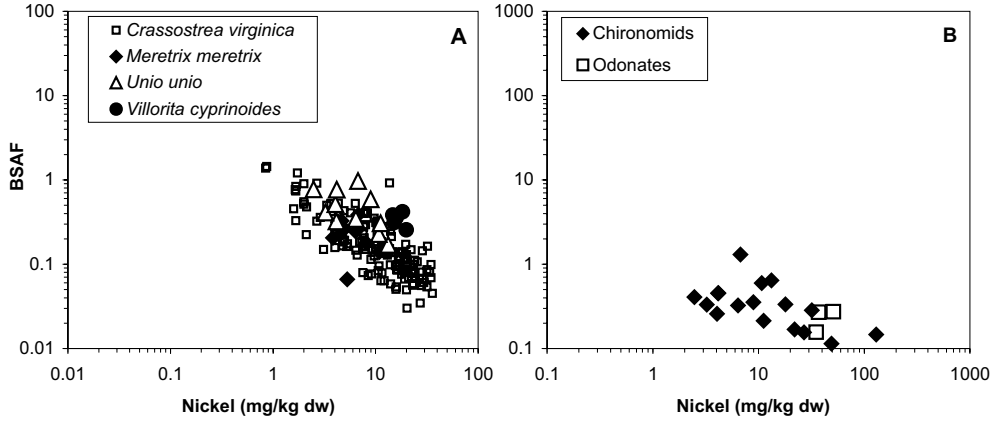
[4]D. Lind, K. Alto, and S. Chatterton. 1978. Regional copper-nickel study; aquatic toxicology study. Minnesota Environmental Quality Board, Minnesota. Unpublished report.

Fig. 1. Relationship between nickel BCFs and concentrations in water for (*a*) algae–cyanobacteria, (*b*) aquatic plants, (*c*) crustaceans, (*d*) bivalves, and (*e*) fish.



uncertain because it is unknown whether these organisms actively, or partially, regulate nickel. If nickel behaves similar to other divalent metals, such as zinc, it is likely that bivalves store excess nickel in detoxified forms. For example, oysters accumulate high concentrations of zinc in detoxified granules (George et al. 1978), while mussels excrete zinc-rich granules from the kidney (George and Pirie 1980). Magnesium–calcium (Mg–Ca) phosphate-pyrophosphate granules can contain a number of different

Fig. 2. Relationship between nickel BSAFs and concentrations in sediment for (*a*) bivalves and (*b*) insects.



metals, including nickel, and appear to be linked with metal detoxification (Viarengo and Nott 1993). Further, these insoluble granules are often present in cells from which they can be eliminated by exocytosis or complete cell disintegration. Such a mechanism could contribute to the inverse relationship observed for nickel and bivalves, but nickel-specific research also is necessary to evaluate this hypothesis. Similarly, the basis for the inverse relationship observed for fish is uncertain. However, if nickel behaves like other essential metals in fish, it is likely that the inverse relationship is due to active regulation by fish (or combination of active regulation and storage) (Phillips and Rainbow 1989). Further research on the homeostatic mechanisms of nickel in fish is also needed.

Nickel biota-sediment accumulation factors

A number of studies were identified that could be used to calculate BSAFs for nickel (Mudroch and Capobianco 1979; Knapton et al. 1988; Sadiq et al. 1992; Lambing et al. 1994; Babukutty and Chacko 1995; Klavins et al. 1998; Mussel watch[5]). As defined previously, the BSAF for metals is calculated as the ratio of a chemical's concentration in an organism to its concentration in bulk sediment. Similar to the pattern observed for BCFs, BSAFs for various benthic biota appear to be inversely related to sediment concentration (Fig. 2*a*–2*b*). This perhaps is not surprising since dietary exposure (i.e., sediment ingestion) does not appear to be important for nickel. Watras et al. (1985) measured the uptake of nickel from the alga *Scenedesmus obliquus* by *Daphnia magna* and observed that ingested nickel is either not incorporated through the gut or is rapidly eliminated. Consequently, most nickel uptake was found to be a function of soluble nickel. Accordingly, nickel bioaccumulation by benthos is likely driven more by pore water nickel concentrations than other exposure routes, such as sediment and detritus ingestion (hence, a similar pattern to BCFs that are based on water only exposures).

This suggestion is also supported by the BSAFs for nickel, which are almost always less than 1.0 (i.e., nickel concentrations in benthos are lower than concentrations in sediment to which they are exposed). It should be clarified, however, that further research on nickel bioaccumulation pathways by benthos is necessary to confirm the mechanistic basis for the observed patterns.

Nickel tissue distribution data

A number of studies were identified that measured the distribution of nickel in individual organs of various aquatic species. These data provide clues to homeostatic mechanisms for nickel based on whether organisms tend to store nickel in specific organs and whether organisms regulate a range of

[5] Mussel Watch. http://ccmaserver.nos.noaa.gov/data.html.

nickel concentrations differently (e.g., actively excrete nickel at lower concentrations and store excess nickel at higher concentrations). The following summarizes examples of nickel distribution data within biota.

Alikhan and Zia (1989) measured aqueous nickel uptake by the crayfish *Cambarus bartoni* and its distribution in the gill, digestive gut, hepatopancreas, abdominal muscles, exoskeleton, and viscera. Crayfish were exposed to nickel concentrations of either 107, 200, 400, and 800 μg/L for 28 d. In general, the highest nickel concentrations were measured in the gill and digestive gut of the crayfish, while the lowest concentration was measured in the viscera. The authors conducted a regression analysis of whole body nickel concentrations with exposure time for those organisms exposed to nickel concentrations of either 400 or 800 μg/L. The analysis showed a third degree polynomial relationship, suggesting that *C. bartoni* undergoes a 2 week cycle of active uptake followed by a 2 week cycle of active excretion of nickel that could not be accommodated in various tissues (it was not reported whether nickel excretion was correlated with the ecdysis cycle). It did not appear that nickel induced metallothionein in crayfish since an increase in mass of the hepatopancreatic tissue was not observed (the hepatopancreas is the site of metallothionein production) (Alikhan and Zia 1989).

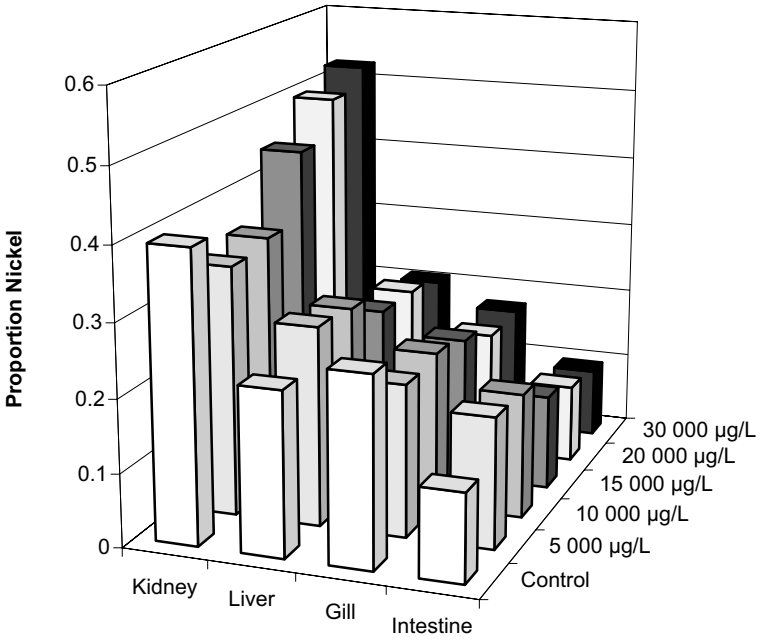
Ray et al. (1990) exposed the catfish *Clarias batrachus* to nickel concentrations of 5, 10, 15, 20, and 30 mg/L for 30 d. Nickel concentrations in the kidney, liver, gill, and intestine were measured (Fig. 3). Nickel concentrations followed the general pattern kidney > liver > gill > intestine. In general, nickel concentrations increased in the kidney with increasing nickel exposure concentrations, while concentrations in the other organs remained relatively stable. Comparing organ nickel concentrations as a percent increase with time demonstrated that the greatest percent increase was observed in the kidney from day 4 to day 30 at the highest concentrations (15, 20, and 30 mg/L). However, it should be noted that for all organs, the bioaccumulation rate tended to decrease with increasing exposure concentration. In fish, metals are often excreted via the kidney or chloride cells of gills (Brown and Depledge 1998). Accordingly, the data from Ray et al. (1990) suggest the catfish may be eliminating excess nickel via the kidney. Tjalve et al. (1988) exposed brown trout (*Salmo trutta*) to nickel concentrations of 0.1 and 10 μg/L (within reasonable background levels for nickel) for 7 d and, like Ray et al. (1990), the highest proportion of nickel concentrations were measured in the kidney.

Tissue distribution data are mostly limited to crayfish and fish species. As summarized above, the available data for these organisms suggest that nickel may be actively regulated. Alikhan and Zia (1989) directly measured what appears to be active uptake and excretion of nickel in the crayfish *Cambarus bartoni*, while nickel concentrations in the kidney of fish, a common organ for excretion of metals, appear to contain proportionally more nickel than other organs (Ray et al. 1990; Tjalve et al. 1988). These data support the idea that the inverse relationships observed between BCF and water concentration for crustaceans and fish (Figs. 1*a* and 1*e*) may at least be partially explained by some level of active nickel regulation by these organisms.

Nickel homeostatic mechanisms

No studies were identified with the explicit objective of evaluating homeostatic mechanisms for nickel in aquatic life. As discussed above, inferences can be made through (1) evaluation of nickel bioconcentration and tissue distribution data and (2) comparison to other metals that have been more thoroughly studied. First, BCF and BSAF data demonstrate an inverse relationship with exposure concentration. The basis for these relationships can result from a number of factors, including saturable uptake kinetics, active regulation, and growth dilution. Accordingly, these data alone provide little information on homeostatic mechanisms for nickel. However, consideration of these data along with tissue distribution data provide corroborative evidence of nickel regulation strategies. For example, elevated nickel concentrations in fish kidneys suggest that they, in some part, actively regulate nickel concentrations. Similarly, the data from Alikhan and Zia (1989) were used by the authors to suggest that crayfish actively take up and excrete excess nickel.

Fig. 3. Proportional distribution of nickel in organs of the catfish *Clarias batrachus* (data from Ray et al. 1990).



Second, the data presented above for nickel are consistent with other essential metals, such as copper and zinc (although the essentiality of nickel in aquatic animals has not been demonstrated). Copper and zinc, both essential metals, are known to be actively regulated by a number of aquatic crustacean species, including the shrimp *Palaemon elegans*, the lobster *Homarus gammarus*, the crab *Carcinus maenas*, and the shrimp *Crangon crangon* (Rainbow and White 1989). In addition, like Ni, Cu and Zn BCFs tend to be inversely related to exposure concentration (McGeer et al. 2003). This supports the concept that the inverse relationships observed for nickel for some species may also be due to active regulation. Active regulation of nickel in animals would suggest that nickel may be essential to at least certain animals since there are no known examples of active regulation of non-essential metals in invertebrates (Rainbow 1996). Rayner-Canham et al. (1985) suggested the essentiality of nickel and cobalt for the marine tunicate *Halocynthia pyriformis*. However, their evidence is only based on the observed correlation between nickel and cobalt concentrations (resulting in a fixed 7:1 nickel:cobalt ratio) in the organism. The authors refer to the fact that also in many plant species and in two scallop species, consistent nickel–cobalt ratios were found. They also found a negative correlation between mass of the tunicates and the nickel and cobalt concentrations indicating that the organism contains a fixed concentration of each of the metals. However, further research is necessary to demonstrate whether nickel is essential to aquatic animals.

Ultimately, depending on the species, it is likely that homeostatic mechanisms for nickel reflect all regulatory strategies, ranging from active regulation to storage. It is clear that research is lacking in this area for nickel and further research will be necessary to evaluate the hypotheses and comparisons to other metals presented in this paper.

Conclusions and future research needs

From this review it is clear that studies on nickel essentiality and homeostatic mechanisms in aquatic organisms are few, and in the case of nickel, evidence of essentiality is limited to cyanobacteria,

phytoplankton, and a few higher plants. Indications of active regulation in different types of aquatic organisms suggest that nickel is essential, since there is no evidence of non-essential metals being actively regulated by invertebrates.

The majority of studies cited in this review have focused on the marine environment. Research exploring nickel essentiality to freshwater organisms has hardly been reported. Nevertheless, studies with terrestrial animals (e.g., rats) indicate many nickel deficiency symptoms such as depressed haematological parameters, altered activities of the citric-cycle enzymes in the liver, and increased activities of aspartate, aminotransferase, alanine aminotransferase, and glutamate dehydrogenase in serum (Stangl and Kirchgessner 1996) that are thus not related to urease or hydrogenase. These effects are probably not restricted to terrestrial vertebrates and similar nickel deficiency symptoms may possibly also occur in aquatic organisms. To the best of our knowledge no metal has been identified of which the essentiality is limited to terrestrial organisms.

The study of the metabolic role of nickel in aquatic invertebrates, fishes and mammals in marine and freshwater environments is one of the important future fundamental research needs concerning nickel essentiality. From an applied point of view, e.g., for risk assessment and water quality criteria derivation, the importance of nickel essentiality is possibly limited to the fact that test organisms have to be cultured under non-deficient and environmentally relevant (background) nickel concentrations.

Secondly, it needs to be investigated whether nickel deficiency is an environmental reality. Evidence suggests that nickel limitation may be an oceanographic reality where phytoplankton obtain from 20% to 50% of their nitrogen from urea (McCarthy et al. 1977; Harrison et al. 1985). Calculations by Price and Morel (1991) show that although the supply of nickel to surface ocean water by advection and diffusion from depth is sufficient to meet the needs of urease in phytoplankton, limitation may result from the low surface concentration of nickel and its slow reaction rate. Biological uptake of nickel by cyanobacteria and phytoplankton for the nickel-dependent hydrogenase and urease may be an additional mechanism of nickel removal from seawater. Any complexation of nickel by organic ligands would further limit nickel availability. In some coastal waters, 30–40% of the dissolved nickel is organically complexed (Nimmo et al. 1989). In freshwater, assuming that ionic nickel represents between 0.1% and 100% of the total nickel concentrations, nickel concentrations ranging from $10^{-9.5}$ to $10^{-6.5}$ M seem reasonable for natural systems (Watras et al. 1985). Not enough information on freshwater organisms is available to conclude if nickel deficiency may occur in this environment.

Thirdly, the interaction of nickel with other essential metals in aquatic organisms needs more attention. Bruland et al. (1991) point out the importance of metal antagonisms of potential biolimiting metals for the biological productivity in areas of the open ocean. As Price and Morel (1991) have shown that nickel is potentially biolimiting, the interaction with iron, manganese, zinc, and especially copper should be considered. In terrestrial organisms it is demonstrated that nickel may alter the magnesium and zinc status, possibly leading to deficiency of these elements (Anke et al. 1995). Nickel also interacts with iron in rat nutrition and metabolism (Nielsen 1980). Studies with chicks indicate that nickel deficiency impairs the absorption of iron from the intestine and thus reduces iron concentrations in these animals (Nielsen 1975).

Finally, additional research on many aspects of nickel regulation and homeostasis in different types of organisms is necessary. Explicit studies to evaluate homeostatic mechanisms will reveal if the inverse relationship between bioconcentration factors and water concentrations is caused by active regulation or other mechanisms (such as storage in granules followed by exocytosis). Further research needs to include the confirmation of the relation between active regulation and essentiality, the investigation of nickel bioaccumulation pathways by benthos, and the generation of nickel tissue distribution data for species other than fish and crayfish.

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