

Review

# Nutrition and Metabolism of Minerals in Fish

Santosh P. Lall<sup>1</sup>, Sadasivam J. Kaushik<sup>2</sup>

<sup>1</sup> Retired from National Research Council of Canada, Halifax, NS, Canada; santosh.lall13@gmail.com

<sup>2</sup> Retd. INRA, France; Former ERA Chair, Ecoaqua, Univ Las Palmas de Gran Canarias, Spain ;

[kjsachi@gmail.com](mailto:kjsachi@gmail.com)

Correspondence: [santosh.lall13@gmail.com](mailto:santosh.lall13@gmail.com)

**Simple Summary:** Our aim is to introduce the mineral nutrition of fish and explain the complexity of determining requirements as these elements, which are absorbed and excreted by the fish into the surrounding water. To date, only the requirement of nine minerals have been investigated. The review is focused on the absorption and the dietary factors that reduce their absorption from feed ingredients of plant and animal origin. Some of diseases such as cataracts, anaemia and bone deformity have been linked to dietary deficiency of minerals.

**Abstract:** Aquatic animals have unique physiological mechanisms to absorb and retain minerals from their diets and water. Research and development in the area of mineral nutrition of farmed fish and crustaceans have been relatively slow and major gaps exist in the knowledge of trace element requirements, physiological functions and bioavailability from feed ingredients. Quantitative dietary requirements have been reported for three macroelements (calcium, phosphorus and magnesium) and six trace minerals (zinc, iron, copper, manganese, iodine and selenium) for selected fish species. Mineral deficiency signs in fish include reduced bone mineralization, anorexia, lens cataracts (zinc), skeletal deformities (phosphorus, magnesium, zinc), fin erosion (copper, zinc), nephrocalcinosis (magnesium deficiency, selenium toxicity), thyroid hyperplasia (iodine), muscular dystrophy (selenium) and hypochromic microcytic anaemia (iron). An excessive intake of minerals from either diet or gill uptake causes toxicity and therefore a fine balance between mineral deficiency and toxicity is vital for aquatic organisms to maintain their homeostasis either through increased absorption or excretion. Release of minerals from uneaten or undigested feed and from urinary excretion can cause eutrophication of natural waters, which requires additional consideration in feed formulation. The current knowledge in mineral nutrition of fish is briefly reviewed.

**Keywords:** Minerals, Trace elements, Fish, Copper, Iron, Selenium, Manganese, Zinc, Calcium, Phosphorus, Magnesium

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## 1. Introduction

All aquatic animals require minerals for their vital physiological and biochemical functions and to maintain their normal life processes. Fish live in a wide range of salinity (0-35 ‰) in freshwater (FW), seawater (SW) and brackish water (BW) environments, and unlike other vertebrates absorb minerals from the diet as well as surrounding water. Most of the essential minerals required for animals and other vertebrates (Suttle, 2010) have been detected in fish tissues. The essentiality of macrominerals (calcium, phosphorus, magnesium, sodium, potassium and chloride) and certain trace elements (cobalt, copper, iodine, iron, manganese selenium and zinc) have been confirmed in fish (NRC, 1993; 2011). Other trace elements (arsenic, boron, chromium, fluorine, nickel, lithium, lead, molybdenum, silicon, and vanadium) considered essential for humans and animals based on the impairment of specific physiological functions have not been reported in fish. Mineral nutrition of fish has received limited attention as compared to other nutrients. The main focus of the current review is trace element nutrition and metabolism of fish with a brief discussion on major macrominerals. A significant amount of research has been directed

towards the physiological aspects of waterborne mineral toxicity and is the subject of comprehensive reviews (Wood et al., 2012a,b).

The biochemical mechanisms of mineral metabolism in fish are generally considered similar to those of terrestrial animals at the cellular level. The exchange of ions from across the gills and skin of fish in surrounding water complicates the determination of the quantitative dietary requirement (Lall, 2002). Gills comprise over 50% of the surface area of the fish and are considered the major route of uptake of waterborne minerals in FW. In SW fish exhibit obligatory drinking as part of their overall physiological osmoregulatory mechanism to maintain internal body fluids substantially hypotonic to the external salinity of seawater (Evans and Claiborne, 2009). Therefore, absorption of dietary minerals from the gastrointestinal tract is important in FW fish, whereas in SW fish, both dietary and waterborne minerals are absorbed. The life cycle of anadromous fish like salmonids consists of FW and SW, where they gradually adapt to a marine environment and acquire inorganic elements by drinking SW similar to marine fish.

In the past two decades, the number of crustaceans, FW and marine fish species have increased considerably (Tacon et al., 2021). Often generalization is made estimating their mineral requirements based on salmonids and certain freshwater species with proper consideration for the determination made on different types of diets (purified, semi-purified and practical diet) and use of inorganic supplements with high bioavailability. In addition, fish feeds have become increasingly comprised of alternate sources of plant-based feed ingredients as compare to widely used fish meal before due to the increase in global aquaculture production and its limited supply. Obviously there is a need to reassess the mineral requirements as well as their bioavailability from a wide range of plant feed ingredients as well as new alternate sources of feed ingredients to fish meal. The absorption of minerals may vary among fishes because of differences in gastric acid secretion in fish with stomach and agastric or stomachless fish (Lall, 2002) as well as uptake of minerals from water. There are also differences in the methodology used to measure the mineral requirements and response criteria (e.g., growth, feed utilization, whole body and/or vertebrae, plasma/serum and tissue mineral concentration, hematology and changes in specific enzyme activities).

Minerals are known to interact with other nutrients due to their lability and tendency to form chemical bonds. The term "interaction" for minerals was defined by O'Dell (1997) as "interrelationships among mineral elements as revealed by physiological or biochemical consequences". Such interactions are broadly classified as positive or synergistic, or negative or antagonistic. Direct positive interactions between elements in structural processes such as the requirement of copper (Cu) and iron (Fe) for hemoglobin formation, calcium (Ca), phosphorus (P) and magnesium (Mg) for formation of bone hydroxyapatite and an interaction of Mn with Zn for proper conformational shape of RNA molecules in the liver have been widely recognized. Antagonistic relationships occur when elements with a similar electronic configuration and ionic radius compete for binding sites, e.g., Zinc (Zn) and cadmium (Cd) in metallothionein, and Mg/manganese (Mn) substitutions at enzyme active sites. In the gastrointestinal tract, antagonistic relationships may occur by a simple mechanism, which involves a chemical reaction forming an insoluble complex between minerals such as Cu and sulphur (S) to form copper sulfide or a mineral and another dietary component such as Zn combined with phytic acid to form phytate (Erdman, 1979). A wide range of potential mineral-mineral and mineral-vitamin interactions in fish have also been reported (Hilton, 1989). Specific trace element interactions are discussed in appropriate individual sections.

Extensive research conducted on animals have clearly shown that mineral requirements are significantly affected by their bioavailability from different forms of feed supplements and feed ingredients. Bioavailability has been defined as the proportion of element consumed that is utilized for biochemical or physiological functions (O'Dell, 1997). Generally, the bioavailability reflects the absorption of the nutrient. From a practical standpoint, measurement of biochemical and physiological functions may not always be possible. Ammerman et al. (1995) suggested that more emphasis should be on the degree

to which an ingested element could be utilized for metabolism. Limited information exists on the utilization and metabolism of trace elements in fish. The following methods have been used to determine the bioavailability of trace minerals in animals (Ammerman, 1995; O'Dell, 1997, Spears and Hansen, 2008): a), growth, b) apparent absorption or digestibility, c) plasma or tissue mineral concentration, d) mineral retention or balance, e) specific enzyme activity (e.g., superoxide dismutase, glutathione peroxidase) or blood parameter (e.g., hemoglobin level), f), prevention of deficiency signs. Some of these methods have also been used in fish to estimate the bioavailability of Zn, Fe and selenium (Se) from chemically defined or practical diets based on fish meal and plant protein and are discussed later in individual sections.

Aquatic animals accumulate excessive minerals from water which can interact with as well as inhibit proteins that facilitate essential ion transport (Bury et al., 2003; Wood, 2012). Metal binding reactions include competition at the biotic ligand with other cations (e.g., Na<sup>+</sup>, H<sup>+</sup>, Ca<sup>2+</sup>) and competing complexation reactions for the metal by other ligands in solution including inorganic anions (e.g., chloride, hydroxide, sulfide) as well as organic ligands such as dissolved organic carbon (Brix et al., 2017). For example, accumulation of Cu or silver (Ag) at the fish gill interferes with Na<sup>+</sup> uptake, thereby disrupting ionic balance in the organism leading to toxicity (Grosell, 2012). Similarly, Cd and Zn interfere with Ca uptake at the fish gill, leading to hypocalcaemia and toxicity (Hogstrand, 2012). The ability of fish to regulate high concentrations of trace elements originating from water varies among different fish species. The major route of uptake for some metals, such as Se, mercury (Hg), and arsenic (As) is trophic transfer through the food chain. Certain fish are able to excrete high proportions of excessive metal intake and consequently regulate the concentration in their body at relatively normal levels (Handy, 1996). The soluble trace elements in water are considered more toxic than higher dietary intake of minerals such as Cu, Fe and Zn. The subject of aquatic toxicology to fish is beyond the scope of this review.

Minerals discharged from uneaten feeds, excretion of undigested material in feces and urine from hatcheries and aquaculture operations directly influence the aquatic environment (Lall and Milley, 2008a). These minerals excreted in soluble and particulate forms affect the water quality. The particulate form can settle to the bottom of the tank or accumulate in the sediment under fish cages. The breakdown of organically-bound minerals from feed and feces varies considerably due to differences in the chemical characteristics of feed ingredients and type of mineral supplements used, the environmental conditions (e.g., temperature, oxygen, pH and salinity, water current) and the type of micro-organisms in natural waters. Elevated levels of Zn and Cu have been found in sediments under the sea cages of salmon farms (Dean et al., 2007). Experimental studies have demonstrated that the concentration of these trace elements in sediments decrease to background levels after chemical remediation (Brooks et al., 2003). These studies indicate that metals complexed with free sulphides, particularly Cu and Zn are released to the water column during the chemical remediation process.

Copper, zinc and cadmium may be incorporated into the sediment from accumulated feed and faeces; however, these trace elements can also be associated with naturally occurring organic debris. The decomposition of organic material during early stages of diagenesis in the oxidized surface layers influences the pore water concentration of Cu, Zn and Cd, and results in elevated pore water levels. Organic particles associated with metals are remobilized into the dissolved phase, and soluble Cu, Zn and Cd form complexes with organic ligands in pore waters (Petersen et al., 1995; Ponce et al., 2000). Generally fish feeds are not supplemented with Cd, however, fishery by-products and other ingredients may contribute to a minor amount of Cd in the finished feed. Cadmium is relatively less soluble in reducing pore waters than toxic overlying waters (Sundby et al., 2004). Cadmium can be scavenged from the water column and ultimately deposited with organic particles (McGeer et al., 2012). Several countries have developed regulations to regulate the maximum limit of mineral supplementation in aquatic animal feeds to reduce their impact on the environment.

The main purpose of this review is to update current knowledge of mineral nutrition of fish and to identify areas that require future research particularly trace elements.

## 2. Microminerals

Optimum levels of essential macro-and microminerals are required for growth and maintenance of normal health of fish. Four broad biochemical functions of micro or trace elements are widely recognized: a) catalytic, b) structural, c) physiological and d) regulatory (Mertz, 1998). Trace minerals can act as catalysts in enzyme and endocrine systems, as integral and specific components of the structure of metalloenzymes and hormones or as activators (coenzymes) within those systems. More than one-third of all proteins require a trace element cofactor for normal function (Maret, 2010; Andreini et al., 2009). Numerous metalloenzymes are required for a wide range of metabolic activities such as energy production, protein digestion, cell replication and antioxidant activity, which are discussed in later sections. Deficiencies or suboptimum levels of the trace element may cause a decrease or loss of enzyme activities (Lall, 2010). Increased attention has been focused on certain micronutrients and immunostimulants to reduce susceptibility to various stressors and diseases, as well as enhance the overall health of humans, animals and fish (Lehmann et al., 2011; Richards et al., 2010; Mohan et al., 2019). The concept is based on understanding the contribution of minerals in reducing the detrimental effects of free radicals and toxic metabolites on immune processes in the animal's body. The knowledge in this area on the role of minerals in fish or shrimp as compared to animals and humans is scant.

### 2.1. Copper

It is widely accepted that Cu is an essential trace element required for cellular functioning of all living organisms. Copper ions have a unique chemistry due to their ability to adopt distinct redox states, either oxidized  $\text{Cu}^{2+}$  or the reduced state  $\text{Cu}^{3+}$ . Because of the high avidity of biological ligands, free ionic  $\text{Cu}^{2+}$  is present in physiological fluids at extremely low concentrations. Copper metalloenzymes are involved in Fe metabolism, cellular energy production (cytochrome c oxidase), protection of cells from free radical damage (superoxide dismutase), collagen synthesis (lysyl oxidase) in brain neurotransmitters (dopamine hydroxylase and peptidyl alpha amidating monooxygenase), and melanin production (tyrosinase) (Linder, 2002). Four Cu-containing enzymes, known as multi-copper oxidases (MCO) or ferroxidases oxidize  $\text{Fe}^{2+}$  to  $\text{Fe}^{3+}$  ion, the form of iron that can be incorporated onto the protein transferrin for transport to the site of red blood cell formation. The MCO family comprises the circulating and membrane bound ceruloplasmin and two other proteins (Prohaska, 2011). Metabolic changes in Cu requiring proteins or alterations in enzyme activities may cause pathophysiological conditions (Harris, 2003).

Fish absorb Cu via the gills and digestive tract; however, the diet is considered a major source of Cu for growth, development and essential physiological functions (Kamunde et al., 2002; Bury et al., 2003). The gill may contribute to a significant amount of Cu uptake depending upon the Cu concentration of the water (Taylor et al., 2003), particularly when dietary Cu intake is low (Miller, 1993). In rainbow trout fed Cu-deficient diet, waterborne Cu uptake contributed the major proportion (60 %) of the body's Cu; however, feeding high levels of Cu contributed to nearly 99 % of body Cu (Kamunde et al., 2002). Uptake of Cu from water and its toxicity has been extensively studied and reviewed (McDonald and Wood 1993; Grosell, 2012). Copper uptake is facilitated via two distinctive mechanisms: a) by a transmembrane protein (Cu transporter 1) and b) the apical  $\text{Na}^{+}$ -uptake pathways located at branchial epithelial cells. The former pathway is insensitive to external Cu concentrations, and the latter pathway involving  $\text{Na}^{+}$ -uptake is sensitive to Cu (Grosell and Wood, 2002). In gastrointestinal Cu transport, apical Cu uptake appears to be passive while basolateral transport is active and rate limiting (Clearwater et al., 2000; Handy et al., 2000). Copper is known to induce oxidative stress, olfactory

impairment, increased plasma ammonia and disturbed acid-base balance (Eyckmans et al., 2011; Grosell, 2012).

Maintaining Cu homeostasis demands a critical physiological orchestration between Cu uptake and distribution within cells, and detoxification and removal. In fish and terrestrial vertebrates, the liver is the main organ involved in Cu homeostasis and metabolism (Cousins, 1985; Grosell and Wood., 2002). Most studies on Cu homeostasis in fish have been conducted in FW fish. After gill uptake and absorption from the gut, Cu is cleared from blood by the liver and incorporated into ceruloplasmin for transport to extrahepatic organs, stored in Cu-protein complexes or excreted via the bile (Handy, 1996; Grosell et al., 1996).

#### 2.1.1. Requirement

The dietary Cu requirement has been reported for several freshwater and marine fish (Table 1). These requirements are relatively low as compared to other trace elements. It is necessary to know the concentration of Cu in water, feed ingredients and tissue levels prior to requirement studies, in order to properly estimate the quantitative Cu requirement (Suttle, 2010). Copper in the water alone cannot meet the requirements so oral administration of Cu is essential for aquatic animals (NRC, 2011). Dietary Cu requirement would also depend on the physiological state of the animal, Cu concentration in the water, and probably the level of elements that are metabolic antagonists of copper, such as Fe, Zn, Cd, and Mo (NRC, 2005; Suttle, 2010). A meta-analysis of published information on Cu requirement of several fish species showed relatively close estimates for the Cu requirement (mg kg<sup>-1</sup> diet) based on the following parameters: weight gain, 5; liver Cu concentration, 6; liver CuZn SOD activity, 4 (Antony Jesu Prabhu et al., 2016). In rainbow trout, the antagonistic effects of Zn and Cu have not been observed (Knox et al., 1982). An interaction between dietary Cu and Se was observed in Atlantic salmon, where liver Se was inversely related to dietary Cu concentration (Lorentzen et al., 1998).

As regards shrimp, Davis et al. (1993b) found that Pacific white shrimp (*P. vannamei*) would require no more than 34 mg total Cu/kg<sup>-1</sup> diet and that high levels of dietary Cu levels did not have any adverse effects on growth or survival. In black tiger shrimp, *P. monodon*, Lee and Shiau (2002) established the dietary Cu requirement to be 15–21 mg Cu kg<sup>-1</sup> diet. Based on immune response indicators, a dietary Cu requirement of about 10–30 mg Cu kg<sup>-1</sup> diet was established to elicit non-specific immune responses. When fed very high dietary Cu levels, an increase in dietary vitamin C improved growth, haemocyte respiratory burst response and prevented tissue Cu accumulation (Lee and Shiau, 2003).

#### TABLE 1 near here

#### 2.1.2 Deficiency

Copper deficiency is well recognized in domestic animals (Suttle, 2010); however, gross deficiency signs of Cu have not yet been reported for fish. Unlike terrestrial vertebrates, low amounts of Cu are supplied from water as well as feeds. Therefore, overt deficiency signs would only occur during a long period of Cu deprivation. To date, the response criteria used to detect the Cu deficiency and adequacy of this element are not consistent in studies conducted on 14 FW and marine fish species (Table 1). A decrease in growth, body and liver Cu concentration and ceruloplasmin and enzyme activities (liver CuZn SOD, heart cytochrome c oxidase) have been reported. In a long term study, carp fed diets containing white fish meal without Cu supplement showed reduced growth and cataract formation (Satoh et al., 1983a).

#### 2.1.3 Toxicity

Generally dietary Cu toxicity rarely occurs under practical feeding conditions except when there is an error in feed mixing or the use of Cu contaminated feed ingredients. Toxicity of Cu has been experimentally produced in rainbow trout, Atlantic salmon, rockfish (*Sebastes schlegeli*), Nile tilapia and African walking catfish (*Clarias gariepinus*),



however, the tolerance of Cu varies among fish species (Lanno et al., 1985; Baker, 1998; Berntssen et al., 1999a,b; Clearwater et al., 2002; Hansen et al., 2004; Kim and Kang, 2004; Kang et al., 2005; Shaw and Handy, 2006; Hoyle et al., 2007; Damasceno et al., 2016). Signs of oral Cu toxicity include reduced growth and feed utilization, changes in hematological parameters and tissue lipid peroxidation. Dietary copper toxicity measured as growth inhibition in rainbow trout was approximately 664-730 mg Cu kg<sup>-1</sup> feed corresponding to 44 mg Cu kg<sup>-1</sup> body weight per day (Lanno et al., 1985; Clearwater et al., 2002). Much lower concentrations of Cu (34 mg kg<sup>-1</sup>) in Atlantic salmon diet caused tissue lipid peroxidation (Berntssen et al., 2000). The estimated threshold of diet borne Cu toxicity for Atlantic salmon parr and fry, based on organ copper burden and reduced growth ranged from 15 to 17 mg Cu/kg body weight per day (Clearwater et al., 2002). EU commission authorized maximum content of Cu in complete feed for salmonid and other fish species is 25 mg kg<sup>-1</sup> (EFSA, 2016c).

Aquatic Cu toxicity in fish and other organisms has been the subject of extensive research for five decades (Grosell, 2012) and is briefly mentioned in this section. The mechanism of Cu toxicity differs in FW and SW. In FW, Cu toxicity varies with water hardness, pH, anions and dissolved organic carbon. Copper toxicity is more lethal in soft compared to hard waters rich in cations (e.g. Ca<sup>2+</sup> and Mg<sup>2+</sup>) as cations reduce bioavailability of Cu and thus accentuate toxic effects (Pagenkopf 1983). Copper is more toxic under acidic conditions (pH < 6). Anions and dissolved organic carbon bind to Cu and form compounds thus reducing the toxic effects (Niyogi and Wood 2004). In SW, waterborne Cu toxicity affects not only gills but also the intestine because marine fish drink to compensate for water loss into the surrounding water. The cause of reduced oxidative metabolism appears to be gill damage, manifested as either disruption of branchial structure, secretion of mucus that binds metals and impedes the rates of diffusion, inhibition of respiratory enzymes, and damage to gill oxygen receptors (Grosell, 2012). In addition to gill, Cu toxicity also affects liver, kidney, heart, brain and reproductive organs. In summary, an exposure to higher levels of Cu in water affects several physiological and biochemical functions affecting the performance of the whole organism by decreasing metabolic rate and causing oxidative stress (Beaumont et al., 2000; McDonald and Wood, 1993). Oxidative damage from Cu exposure has been observed as changes in biomarkers (e.g. protein carbonyls, lipid peroxidation, and DNA damage products) in the gill, liver and intestine of numerous fish species (McDonald and Wood, 1993). Low concentrations of waterborne Cu affected the hatching of fish eggs by inactivating chorionase activity that causes osmotic disturbances and also affects the muscular movements necessary to break the eggshell (Johnson et al., 2007; Jezierska et al., 2009). Other effects may include low pigmentation of the embryo, spinal cord deformation, cranial malformations, jaw underdevelopment, decreased length, increased time for complete yolk absorption, oedema and opaque yolk sacs (Jezierska et al., 2009).

#### 2.1.4 Bioavailability

Limited information exists on the availability of Cu from feed ingredients or Cu feed additives. Feed ingredients of plant and animal sources show a variable Cu content resulting from either contaminant originating from soil or during the processing of plant and animal products. Common Cu feed additives commercially available to supplement fish and animal feeds are, copper sulphate, cupric chloride; cupric carbonate; cupric acetate; cupric methionate; cupric oxide; cupric chelate of amino acid hydrate; copper lysine sulphate, cupric chelate of glycine hydrate, copper chelate of hydroxy analogue of methionine, dicopper chloride trihydroxide and copper bislysinate. In most fish studies, copper sulphate has been used as a dietary supplement or a standard for the evaluation of Cu bioavailability. To date, limited research effort has been made to measure the bioavailability of Cu from inorganic and organic forms or the residual Cu present in feed ingredients. A wide range of methods (e.g., plasma/liver Cu, erythrocyte SOD activity, plasma ceruloplasmin and bile Cu) have been used to estimate Cu bioavailability in animals (Spears and Hansen, 2008).

Studies conducted on bioavailability from different organic Cu sources in animal feeds show similar bioavailability while others show higher bioavailability relative to copper sulphate NRC (2005). Some of the differences have been attributed to species differences, age of animals, response criteria and the method used. In rainbow trout fed semi-purified diets, cupric sulphate Cu-protein, and Cu-lysine showed similar bioavailability (Kjoss et al., 2006). Recently, Cu-Met and nano-copper oxide were shown to be more bioavailable than copper sulphate in Russian sturgeon (Wang et al., 2016). Metal ion interactions with Cu-Zn have been observed in animal studies (Baker and Ammerman, 1995); however, no significant antagonism between Cu and Zn was observed in rainbow trout fed plant-based diets (Read et al., 2014).

## 2.2 Iron

Iron is one of the most investigated essential trace elements, which is present in all body cells of vertebrates. It is essential for the functioning of several biochemical processes, which include the electron transfer reaction, gene regulation, binding and transport of oxygen and regulation of cell growth and differentiation. The most important Fe-containing compounds are the heme proteins, hemoglobin, myoglobin and cytochromes. Enzymes containing non-heme Fe such as iron-sulphur cluster proteins (e.g., NADH dehydrogenase, succinate dehydrogenase, xanthine oxidase) are involved in energy metabolism. Another group of Fe-containing enzymes (e.g., hydrogen peroxidases) are well known to act on reactive molecules originating as the by products of oxygen metabolism. The formation of the reduced form of iron, Fe<sup>2+</sup> can produce highly reactive hydroxyl and lipid radicals, which can damage lipid membranes, nucleic acids and proteins. In mammals, iron homeostasis involves the regulation of its absorption into the body, regulation of iron entry into cells, the incorporation of iron into proteins, the storage of iron in ferritin, and the regulation of iron released for transport to other cells and organs.

Although there is relatively little information on absorption and metabolism of iron in fish, some studies suggest that mechanisms of iron absorption from the digestive tract, and storage and excretion may be similar to those in other vertebrates (Glover and Hogstrand, 2002; Bury et al., 2003). The uptake of Fe from natural waters is considered low. Fish gills play an important role in Fe acquisition (Bury and Grosell, 2003), particularly in developing fish when the digestive tract is not fully functional (Andersen, 1997). The gastrointestinal tract is considered the major site of Fe absorption (Cooper and Bury, 2007). In the acidic environment of the stomach, ferric ion is released from the ingested food materials and binds to mucin which may facilitate metal solubility in the small intestine of fish (Whitehead et al., 1996). It is proposed that epithelial mucus secretion may play an important role in maintaining metal solubility in fish (Bury et al., 2012; Glover and Hogstrand, 2003). The mechanism of Fe absorption in marine fish is not clear. They ingest significant amounts of Ca and Mg from SW and also secrete large quantities of bicarbonate (Wilson et al., 2002) that could potentially cause problems for intestinal iron uptake. It has been suggested that metal-mucus chelates that retain the metal in solution in the intestinal tract, reducing agents in foods (e.g. ascorbic acid) and other physiological factors in the gut may modify Fe solubility and enhance its absorption (Andersen et al., 1997; Bury et al., 2003). Food is regarded as the main source of Fe for metabolic purposes (Bury et al., 2003; Andersen et al., 1997). It is widely accepted that the control of body Fe status is mainly dependent on tight regulation of Fe uptake from the diet and water. A small amount of Fe is eliminated via the liver (i.e., bile) and to some extent by the kidney (Bury et al., 2012).

### 2.2.1 Requirement

The Fe requirement reported for certain fish species (Table 1) ranges from 30-170 mg kg<sup>-1</sup> diet with the exception to gibel carp which has an optimum requirement value of 202 mg kg<sup>-1</sup> diet. Response criteria used to estimate Fe requirement were weight gain, whole body, liver and plasma iron concentration, and hematological parameters (hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin). A meta-analysis

of published information on Fe requirement of several fish species showed estimates for Fe requirement ranging from 58.8-166.4 mg kg<sup>-1</sup> with a wide variation for all parameters tested (Antony Jesu Prabhu et al., 2016). It should be emphasized that weight gain alone may not provide a good estimate of Fe requirement. Most of the Fe body pool is in the form of hemoglobin in red blood cells. At later stages of growth and maturity, the Fe requirement is likely to change as the blood volume declines and a lower rate of iron deposition occurs in tissues (Suttle, 2010).

Even a dietary level of around 12 mg Fe kg<sup>-1</sup> was found to be sufficient in *P. vannamei* fed practical diets and with diets containing processed land animal proteins, which are rich in iron, there was no need for iron supplementation. High levels of dietary Fe did not appear to induce any adverse effects in *P. vannamei* (Davis et al. 1992; Morgan, 2013).

### 2.2.2 Deficiency and toxicity

Generally Fe deficiency causes anemia and tissue Fe depletion in fish and other vertebrates (Lall, 2010). A characteristic microcytic anemia has been detected in brook trout (Kawatsu, 1972), rainbow trout (Desjardins et al., 1987), Atlantic salmon (Bjornvic and Maage, 1993; Andersen et al, 1996), red sea bream (Sakamoto and Yone, 1976), yellowtail (Ikeda et al., 1973), eels (Nose and Arai, 1979) and carp (Sakamoto and Yone, 1978b) fed low iron diets. In most cases, semi-purified diet without Fe supplementation did not affect the growth of fish, except cobia, where fish fed a basal diet without Fe supplement (45.8 mg kg<sup>-1</sup>) showed a decrease in weight gain and feed efficiency (Qiao et al., 2013). In addition, a decrease in Hb and serum catalase activity was also observed. In catfish, Fe deficiency suppressed hematocrit, hemoglobin, and plasma iron levels and caused transferrin saturation (Gatlin and Wilson, 1986b).

Effects of Fe toxicity in fish and animals have been comprehensively reviewed (NRC, 2005; Bury et al., 2012) and are briefly mentioned in this section. Dietary Fe toxicity was experimentally produced in rainbow trout fed levels higher than 1380 mg Fe kg<sup>-1</sup> (Desjardins et al., 1987), a concentration far above the level found in ingredients used to formulate either practical or purified diets. The major effects of Fe toxicity were reduced growth, poor feed utilization, feed refusal, increased mortality, diarrhea and histopathological damage to liver cells. Iron toxicity occurs from excessive Fe exposure of fish in water, which interferes with Fe homeostatic regulation by causing Fe overload in tissues (Bury et al., 2012). Iron naturally exists as soluble ferrous (Fe<sup>2+</sup>) and insoluble ferric particulate iron (Fe<sup>3+</sup>). In oxygenated waters, soluble Fe<sup>2+</sup> oxidizes to Fe<sup>3+</sup> and in circum-neutral waters (pH > 6.5), Fe<sup>3+</sup>-ions are insoluble and rapidly precipitate as hydroxides and oxyhydroxides. Iron toxicity in water is closely related to Fe speciation and the interaction of Fe with body and gill surfaces. Excess Fe in the water is known to cause respiratory disruption due to physical clogging of the gills (Dalzell and MacFarlane, 1999).

### 2.2.3 Bioavailability

Iron in feeds is in two forms, heme iron and non-heme iron. Feed ingredients of animal origin (e.g., fish meal, animal meat and blood meal) are the major sources of heme iron. None heme iron refers to other sources of iron within feeds or inorganic contaminants from ingredient and/or feed processing. In cereal grains, a small proportion of Fe may be present as an iron phytin complex. Several factors are known to affect Fe absorption including, amount and chemical form of Fe, Fe status and age of animal, physiological conditions of gastrointestinal tract (e.g., pH) and other dietary components (e.g., phytic acid, ascorbic acid, citrate) (Henry and Miller, 1995). In juvenile animals, growth, hemoglobin concentration, plasma Fe and its retention may respond linearly to Fe supplementation; however, Fe repletion in deficient animals is considered the preferred method to estimate iron bioavailability (Spears and Hansen, 2010).

Little is known about the bioavailability of Fe from feed ingredients and inorganic /organic iron feed supplements for fish. Bioavailability of ferrous sulfate and ferric chloride are considered essentially the same (Lall, 2002). In red sea bream, ferrous and ferric chloride were more efficiently utilized than ferric citrate (Sakamoto and Yone, 1979a).



Biological availability of Fe measured by a hemoglobin regeneration assay in Atlantic salmon showed that the relative availability of Fe from ferric chloride, ferric oxide, blood meal and herring meal was 98.8, 17.8, 52.3 and 47.1%, respectively (Naser, 2000). However, higher bioavailability of iron from blood meal (Andersen et al., 1997), Fe-hydroxy methionine analogue (Huang et al., 2018) and Fe-methionine (Qiao et al., 2013) have been reported for Atlantic salmon, grouper and cobia respectively. The quality of blood meal varies widely in terms of protein quality. Whether the wide range of temperature and processing conditions used to produce blood meal affects the bioavailability of Fe remains to be investigated. There is also a need to standardize the method to predict the bioavailability of Fe in fish diets.

### 2.3 Manganese

Manganese plays an important role in protein and energy metabolism, bone mineralization, glycosaminoglycans synthesis, cellular defence against free radicals and metabolic regulation (Aschner and Aschner, 2005). The essentiality of Mn in the above biochemical processes is based on its function as an enzyme activator (e.g., oxidoreductases, lyases, ligases, hydrolases, kinases, decarboxylases) and constituent of several metalloenzymes (Leach and Harris, 1997). Many enzymes activated by Mn can be also activated by other metals particularly Mg with the exception of glutamine synthetase, glycosyltransferases, farnesyl pyrophosphate synthetase, phosphoenolpyruvate carboxykinase, which show specific Mn activation. Manganese metalloenzymes include arginase, pyruvate carboxylase, and Mn superoxide dismutase (MnSOD). Limited information exists on the physiological aspects of Mn uptake from both gills and intestine and its metabolism in fish. In mammals, gastrointestinal absorption and biliary elimination of Mn, are the two main regulatory sites of Mn homeostasis, which are influenced by the dietary Mn intake (Keen et al., 1999; Aschner and Aschner, 2005). Excretion of Mn in bile and feces has also been observed in Atlantic salmon (Antony Jesu Prabhu et al., 2019a). Manganese and Fe compete for absorption sites. A small fraction of biliary Mn excreted into the intestine may be reabsorbed. Manganese is efficiently absorbed from diet but the absorption may be reduced by high levels of Ca and P, fiber and phytate (Lall, 2002). Divalent Mn entering the circulation system is removed rapidly by the liver. Reduced intestinal absorption, enhanced liver metabolism, and increased biliary excretion are considered adaptive mechanisms during high dietary intake of Mn (Aschner and Aschner, 2005).

Manganese uptake from FW has been demonstrated from gills and gastrointestinal tract (Miller et al., 1980; Rouleau et al, 1995). Unlike other trace metals, the mechanisms of Mn uptake from gills, gut, skin and other tissues and toxicity are poorly understood. Brown trout (exposed to low concentration of Mn readily accumulated this metal in blood and other tissues (gills, epidermal mucus, liver, kidney, viscera, skeleton and brain) (Rouleau et al, 1995). The Mn toxicity was affected by water hardness and low pH and a higher risk of Mn toxicity to fish has been observed in acidic and Ca-deficient water (Rouleau et al, 1995; Peters et al, 2011). These conditions can markedly enhance the uptake and toxicity of Mn and other metals. High concentrations of Mn caused Na imbalance, reduced the absorption of Ca and P, affected carbohydrate metabolism and impaired the immune functions of fish (Partridge and Lymbery, 2008; Ye et al., 2009). It also caused oxidative stress, tissue damage, inflammation, neurodegeneration and disruption of other metals homeostasis in fish (Rouleau et al, 1995; Vieira et al. 2012;).

#### 2.3.1 Requirement

Manganese requirements of fish range from 2.5 to 25 mg kg<sup>-1</sup> diet (Table 2). Some of these differences are likely due to differences in Mn uptake in water and bioavailability of Mn in experimental diets. Different requirement values were found using three different forms of Mn additives for cobia, manganese sulphate, 15.4; Mn-glycine, 11.2; Mn-2-hydroxy-4-(methylthio) butyrate, 10.5 mg Mn kg<sup>-1</sup> (Nie et al., 2016). In addition to growth, several studies have shown that body and vertebrae Zn provide a good estimate of Mn requirement. Meta-analysis of Mn requirement on several fish species estimated 10.7, 13.4

and 18.4 mg Mn kg<sup>-1</sup> for weight gain, whole body Mn and vertebrae Mn content respectively (Antony Jesu Prabhu et al., 2016). It appears that broodstock fish require higher amounts of Mn than juvenile fish (Takeuchi et al., 1981). Other dietary (e.g., Ca, P, phytate) and physiological factors, particularly changes occurring in bone mineralization at various stages of development should also be taken into account for the estimation of Mn requirement of fish (Lall, 2002).

#### TABLE 2 near here

In shrimp, Kanazawa et al. (1984) suggested that a dietary supply of Mn was not required. Similar observations were also made by Fa-Yi and Lawrence (1997) who found that there was no need for dietary supplementation with Mn.

#### 2.3.2 Deficiency

The deficiency signs of Mn have been experimentally produced in several fish species. In addition to reduced growth, Mn deficiency causes skeletal abnormalities in rainbow trout, carp and tilapia (Ishak and Dollar, 1968; Ogino and Yang, 1980; Yamamoto et al., 1983). In studies designed to determine Mn requirement of certain fish species (Table 2), low intake of Mn caused reduced body and/or vertebrae Mn concentration, a sign of poor bone mineralization. Although Mn deficiencies have shown a decrease in the activity of several enzymes in mammals (Aschner and Aschner, 2005), to date decreases in the activity of liver Mn SOD activity have been reported in Atlantic salmon (Maage et al., 2000), tilapia (Lin et al., 2008b), cobia (Nie et al., 2016), gibel carp (Pan et al., 2008) and yellow catfish (Tan et al., 2012). Low levels of dietary Mn (2.4 mg kg<sup>-1</sup>) did not affect Mn SOD activity in catfish (Gatlin et al., 1984a). A decrease in cardiac muscle Cu-Zn SOD was also observed in rainbow trout fed Mn deficient diet (Knox et al., 1981). Mn deficiency in broodstock rainbow trout diets affected reproductive performance and poor hatchability of eggs (Takeuchi et al., 1981). Manganese is considered to be one of the least toxic of the essential elements (NRC, 2005). However, high concentrations of dietary Mn supplementation (1g kg<sup>-1</sup>) affected changes in feeding behavior, decrease in body Fe concentration and elevation of Zn concentration in body and vertebrae of grouper (Ye et al., 2009). Freshwater borne Mn toxicity in brown trout caused histological changes in their olfactory nerve and brain (Rouleau et al., 1995). The effects of dietary Mn toxicity on olfactory system and brain function of human and animals are well documented (Horning et al., 2015).

#### 2.3.3 Bioavailability

Dietary Mn absorbed from the gastrointestinal tract is generally low in monogastric animals (Spears and Hansen, 2010). Several manganese compounds are available for use in animal/fish feeds: manganous chloride (MnCl<sub>2</sub>·4H<sub>2</sub>O), manganous oxide (MnO), manganous sulphate (MnSO<sub>4</sub>·4H<sub>2</sub>O or MnSO<sub>4</sub>·H<sub>2</sub>O), manganese carbonate (MnCO<sub>3</sub>), manganese acetate, manganous hydrogen phosphate (MnHPO<sub>4</sub>·3H<sub>2</sub>O), manganese amino acid complex, manganese methionine complex, manganese amino acid chelate and manganese proteinate. However, the availability of only a few compounds have been tested and their availability may differ in various inorganic Mn salt supplements. Manganese in manganous oxide is poorly utilized by rainbow trout and Atlantic salmon (Watanabe et al., 1997; Lall, 2002). The most commonly used source of Mn in fish feeds is manganous sulphate, monohydrate. The availability of Mn is low in manganous carbonate for carp (Satoh et al., 1987b). Mn-glycine was effectively utilized by cobia, turbot and Atlantic salmon reared in SW (Ma et al., 2015; Nie et al., 2016; Antony Jesu Prabhu et al., 2019b). Mn-glycine was better utilized by cobia and turbot than manganous sulphate (Ma et al., 2015; Nie et al., 2016). Availability of Mn-methionine and Mn-2-hydroxy-4-(methylthio) butyrate were relatively high for turbot (Ma et al., 2015) and cobia (Nie et al., 2016) respectively. Phytic acid like other divalent ions (Zn<sup>2+</sup>, Cu<sup>2+</sup>, and Fe<sup>2+</sup>) binds inorganic Mn and reduces their bioavailability (Lall and Milley, 2008b). Recently, Antony Jesu Prabhu et al. (2019a,b) found that dietary supplementation of 15 mg kg<sup>-1</sup> of Mn-Gly lowered the digestibility of

Zn and Cu. The environmental impact of undigested Mn excretion in natural water is widely recognized so the upper limit has been set for Mn in complete feeds in certain countries. In Europe the maximum limit for fish feed is 100 mg kg<sup>-1</sup> (EFSA, 2016b).

#### 2.4 Selenium

Selenium as an essential micronutrient for salmonids as well as a toxicant in diets and water is widely recognized (Poston et al., 1976; Hilton et al., 1980; Hodgson and Hilton, 1983). Essentiality of Se for several farmed fish species grown in FW and SW is now widely recognized (Lall, 2002; NRC, 2011; Antony Jesu Prabhu et al., 2016). In nature, inorganic Se is present in four oxidation states: selenate, selenite, elemental Se and selenide. These forms are converted by all biological systems into more bioavailable organic forms, mainly as the two seleno-amino acids selenocysteine (SeC) and selenomethionine (SeMet). Selenoproteins are responsible for diverse biological functions and they all contain at least one SeC (Labunsky et al., 2014; Roman et al., 2014). A comprehensive study of the identification and comparative analysis of vertebrate selenoproteomes have shown more than 45 selenoproteins in mammals and among bony fishes as well as 38 selenoproteins in zebrafish (Mariotti et al., 2012).

SeC is present in vertebrates at the active sites of glutathione peroxidases, thioredoxin reductases, iodothyronine deiodinases, and selenophosphate synthetases, as well as an essential component of other selenoproteins, (Hesketh, 2008; Labunsky et al., 2014). The biochemical functions of many of these selenoproteins are poorly understood in fish. In several organisms, there are eight glutathione peroxidases (GPXs), five of them are selenocysteine enzymes (GPX1, GPX2, GPX3, GPX4 and GPX6), whereas the other three (GPX5, GPX7 and GPX8) have a cysteine at their catalytic site (Papp et al., 2007; Labunsky et al., 2014). Three best characterized groups of selenoproteins in fish include glutathione peroxidases, thioredoxin reductases and iodothyronine deiodinases. The GPXs are involved in the hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) signalling, detoxification of hydroperoxides, and maintaining cellular redox homeostasis. GPX1 is the most abundant selenoprotein, which is considered a potent antioxidant in the cell scavenging of toxic H<sub>2</sub>O<sub>2</sub>. This protection of cells from oxidative damage by degrading toxic H<sub>2</sub>O<sub>2</sub> has been closely linked to health and disease prevention in animals, humans and fish (Arthur et al., 2003; Fairweather-Tait, 2011; Choi et al., 2013; Roman et al., 2014; Khan et al., 2017; Dalgaard et al., 2018). Thioredoxin reductases are also important antioxidant enzymes that maintain cellular redox status. Selenium as an integral part of GPx and thioredoxin reductase interacts with certain micronutrients (e.g., a-tocopherol) that affect redox status (i.e. pro-oxidant and antioxidant balance). The third group of selenoproteins are iodothyronine deiodinases, which activate the prohormone thyroxine (T<sub>4</sub>) to the active thyroid hormone triiodothyronine (T<sub>3</sub>), and catalyze the inactivation of T<sub>4</sub> to reverse T<sub>3</sub> and T<sub>3</sub> to diiodothyronine (T<sub>2</sub>) (Labunsky et al., 2014).

Fish absorb limited amounts of Se from the environment via the gills and skin under certain conditions; however, the gastrointestinal tract is the primary site for Se absorption (Janz, 2012). Low concentrations of selenium are found extensively in aquatic ecosystems (Janz et al, 2019). The uptake of Se as selenite across gills is very efficient at low waterborne concentrations (Hodgson et al., 1983). Selenocysteine and selenomethionine are likely to be absorbed by an active amino acid transport mechanism, whereas selenite is absorbed by simple diffusion and selenate by a sodium-mediated carrier shared with sulfate (Burk and Hill, 2015). Absorbed Se is associated with proteins in the plasma and transported to tissues. After absorption from the diet Se is transported to the liver and metabolized to selenide and incorporated into selenocysteine for selenoprotein synthesis or converted to selenosugars or methylated metabolites for excretion. Fish and other vertebrates excrete Se via feces, but urine is the primary excretion route and likely plays a quantitatively important role in Se homeostasis (Janz, 2012; Burk and Hill, 2015).

Beneficial effects and toxicity of dietary Se supplementation in fish and animals are well documented (NRC, 2005, 2011; 2012; Suttle, 2010; Hosnedlova et al., 2017). The effects of dietary Se also show an increase in expression of selenoprotein P in rainbow trout and

zebrafish (Fontagné-Dicharry et al., 2015; Pacitti et al., 2015; Penglase et al., 2015; Wang et al., 2018). In Se-adequate animals, the kidney and liver have the highest Se content. Muscle has moderate levels of Se content but accounts for the largest pool of body Se. Retention and distribution of Se in tissues are affected by the body Se status and chemical form of Se (Berntssen et al., 2017). Selenium deficient animals retain Se more efficiently than Se-adequate animals. Dietary Se supplementation showed an increase in expression of selenoprotein P in rainbow trout and zebrafish (Fontagné-Dicharry et al., 2015; Pacitti et al., 2015; Penglase et al., 2015; Wang et al., 2018).

#### 2.4.1 Requirement

Selenium requirements (mg Se kg<sup>-1</sup> diet) of several fish species have been determined on the basis of different response criteria (growth, liver and plasma/serum GPx activities, and Se concentration of total body and tissues e.g., liver, muscle) and are summarized in Table 3. The lack of standard methodology and form of Se used makes it difficult to compare the results of different species or within species. The minimum Se requirement of fish varies with the form of Se (inorganic or organic) ingested, Se availability from different feed ingredients from the diet, vitamin E content of the diet, and concentrations of waterborne selenium. The estimated Se requirement based on weight gain, whole-body Se retention and of liver GSH-Px activities have shown different values for some fish species. Some studies have used a single or limited number (<3) to test the requirements, which have limited value in assessing the Se requirement properly. Published data on the Se requirement of farmed animals have demonstrated that growth alone does not reflect their Se requirement. A meta-analysis of published information on Se requirements of several fish species showed different estimates for the Se requirement (mg/kg-1) based on different parameters: weight gain, 0.35 ; enzyme activities of liver GPx, 0.78; serum GPx, 0.43; liver GR activity, 0.41 (Antony Jesu Prabhu et al., 2016). In a recent study, the estimated requirement of Atlantic salmon smolts based on available Se in a plant ingredient based-diet was much lower (0.27 mg/kg-1). Supplementation of SeMet as compared to sodium selenite showed lower Se requirements for Atlantic salmon smolts (Antony Jesu Prabhu et al., 2020) and gibel carp (Zhu et al., 2016). In addition to differences between the bioavailability of Se from the experimental diets, Se uptake from water, age, dietary vitamin E levels and Se bioavailability, and differences among fish species in the utilization of Se must be considered when published requirement values are applied in feed formulation.

#### Table 3 near here

Quantitative data on Se requirement for maximum growth was established to be about 0.6-0.7 mg Se kg<sup>-1</sup> diet (Kong et al. 2017) who also showed that higher dietary Se levels (>1.1 mg kg<sup>-1</sup>) were required to maximise body Se concentrations. A dietary supply of 0.45 mg kg<sup>-1</sup> was found sufficient for improving growth (Yu et al. 2021) and higher levels (0.8 mg kg<sup>-1</sup> diet) led to increased antioxidant enzyme activities but also led to stress and tissue damage in the same species. A supply of 0.43 to 0.45 mg kg<sup>-1</sup> of Se in the form of hydroxyl methionine selenium (HMSe) was likewise found to be effective (Wang et al. 2021) for maintaining high growth and an antioxidant response.

#### 2.4.2 Deficiency

Unlike other micronutrients, gross deficiency of Se alone has not been characterized due to its interaction with vitamin E, polyunsaturated fatty acids, and other dietary factors. Early clinical signs of deficiency caused by low dietary intake of Se have been detected in low enzyme activities in plasma and liver glutathione peroxidase of several fish species (Poston et al., 1976; Hilton et al., 1980; Gatlin and Wilson, 1984b; Bell et al., 1985; Wang and Lovell, 1997; Liu et al., 2010a; Han et al., 2011; Zhu et al., 2011; Zhu et al., 2016; Dominquez et al., 2019; Ning et al., 2020; Wang et al., 2019). Selenium deficiency caused growth depression in rainbow trout (Hilton et al., 1980), carp (Satoh et al., 1983b), and



catfish (Gatlin and Wilson, 1984b), but Se deprivation alone did not produce any pathological signs in these fish. Both Se and vitamin E were required to prevent muscular dystrophy in Atlantic salmon (Poston et al., 1976) and exudative diathesis in rainbow trout (Bell et al., 1985). Extensive research conducted on animals show that it is very difficult to produce or distinguish symptoms of Se deficiency alone from that of a Se-vitamin E deficiency (Suttle, 2010).

Although effects of selenium deficiency on reproduction of animals is well documented (Suttle, 2010; Hosnedlova et al., 2017), effects of Se on reproductive performance of fish are not clear. Recently, Wischhusen et al. (2019) found that Se-supplementation of diets based on a major proportion of plant ingredients enhanced the total number of spawning fish and higher levels of hydroxymethionine supplementation led to earlier spawning. There was no evidence of transfer of maternal Se to progeny and supplementation of organic Se increased activity of GPx activity and mRNA expression of other proteins involved in antioxidant protection at the cellular levels as well as elevated tissue vitamin C and E concentrations.

#### 2.4.3 Toxicity

Dietary Se toxicity has been extensively studied in farm animals and the following three possible mechanisms of toxicity have been proposed : a) substitution of Se for sulfur in important biochemical reactions and structures (e. g. disulfide bonds may disrupt normal function and cell integrity); b) reaction between selenite and glutathione depletes cellular free and protein-bound thiol levels thus affecting the activities of certain enzymes; c) free radicals such as superoxide anions produced by the reactions of certain forms of Se with tissue thiols may cause oxidative injuries to tissues (NRC, 2005; Suttle, 2010). In fish, both dietary and water borne Se toxicities have been experimentally produced (Hodgson and Hilton, 1983). The physiological mechanisms involved in the uptake of Se from water and its toxicity to fish and other aquatic organisms have been extensively investigated and are the subject of comprehensive reviews (Hamilton, 2004; Janz, 2012; Janz et al., 2019). Dissolved inorganic forms of Se (selenate and selenite) in water are oxyanions that are not absorbed appreciably through gill membranes (Pedersen et al., 1998) and ingestion of natural food organisms that accumulate Se from the aquatic environment appear to be more toxic (Janz et al., 2019). The susceptibility to Se toxicity and the mode of action of Se toxicity may differ among fish due to their diverse chemical properties, uptake and metabolism from diet and water. Coho salmon are more sensitive than chinook salmon to inorganic Se (Hamilton and Buhl, 1990). As in the case of trace element bioavailability, the relative toxicity of a given Se compound is affected by its chemical form and solubility. Highly insoluble elemental Se is much less toxic to many species than other more soluble forms such as selenite and selenate (NRC, 2005; Janz, 2012). Dietary Se-Meth was less toxic to chinook salmon, coho salmon and Atlantic salmon than selenite or selenate (Hamilton and Buhl, 1990; Berntssen et al., 2018). However, the Se-Meth caused Se toxicity in white sturgeon fed levels above 20.5 mg Se kg<sup>-1</sup>diet (Tashjian et al., 2006).

A relatively narrow range between dietary requirement and toxicity exists in fish and other vertebrates (Hilton et al., 1980; Janz, 2012; Hosnedlova et al., 2017). Selenium toxicity in rainbow trout and catfish occurs when dietary Se exceeds 13 and 15 mg kg<sup>-1</sup> dry feed, respectively (Hilton et al., 1980; Gatlin and Wilson, 1984b). Reduced growth, poor feed efficiency, and high mortality were observed as the major adverse effects of Se when concentration exceeded the dietary requirements of juvenile fish. In addition to reduced growth, several other adverse effects of feeding higher levels of selenite and SeMet in diets include decreased energy retention (De Riu et al. 2014; Zee et al. 2016), lower egg viability (Schultz and Hermanutz, 1990), decrease in swimming activity (Tashjian et al., 2006), reduced immunological functions (Choi et al. 2013), pathological changes in liver, kidney and ovaries (Hicks et al. 1984; Hamilton, 2004) and skeletal deformities (Kupsco and Schlenk, 2016; Berntssen et al., 2018).

For the assessment of early sublethal adverse effects of selenite and SeMet toxicity, several biomarkers such as tissue lipid peroxidation, reduced glutathione (oxidative stress



marker) and changes in lipid composition have also been proposed (Berntssen et al., 2017). Elevated Se levels for rainbow trout, chinook salmon, fathead minnow, striped bass, bluegill, and razorback sucker ranged from 2.4 to 70 mg Se kg<sup>-1</sup> in feed and 47 to 472 µg L<sup>-1</sup> of water (Hamilton, 2004). In most cases, reduced growth or survival occurred at dietary Se levels close to 3 mg Se kg<sup>-1</sup>. Atlantic salmon tolerated either 1–2 or 3 mg Se kg<sup>-1</sup> of selenite and SeMet supplementation respectively in a feed based on a high proportion of plant ingredients that contained 0.45 mg Se kg<sup>-1</sup> (Berntssen et al., 2018). Relative toxicity of different Se supplements may be largely related to their solubility in water and nutrient bioavailability, and can be modulated by dietary factors such as protein, sulfate, vitamin E, and a number of trace elements including As, Cu, and Hg. The maximum limit for total Se in animal feeds, including fish, has been set at 0.5 mg Se kg<sup>-1</sup> feed by the U.S. Food and Drug Administration and the European Union (EFSA, 2016a), which is considered low to meet the Se requirement of Atlantic salmon fed diets based on plant ingredients and low in fish meal (Anthony Jesu Prabhu et al., 2020).

The primary biochemical mechanism for chronic Se toxicity was initially considered to be linked to the substitution of Se for sulfur in cysteine and methionine, which affected the tertiary structure of protein and its function by altering disulfide linkages (Maier and Knight, 1994). More recently, oxidative stress has been proposed as a main cause for excess dietary Se intake or exposures in fish (Berntssen et al., 2017). In Atlantic salmon fed high levels of selenite and SeMet yeast, oxidative stress was a main driver for Se toxicity (Berntssen et al., 2017); however, white sturgeon and brown trout fed high levels of organic Se did not show oxidative stress (Knight et al., 2016; Zee et al., 2016). Altered liver lipid synthesis and metabolism have been shown to be the central mechanism in dietary organic Se toxicity in rainbow trout (Knight et al., 2016; Pacitti et al., 2016). Recent wide-scope pathway assessments by the application of metabolomics techniques show that disturbance in lipid metabolism is an important factor in inorganic and organic Se toxicity (Berntssen et al., 2017).

#### 2.4.4 Bioavailability

Feed sources of Se used in feeds are either in inorganic (selenite, SeO<sub>3</sub><sup>2-</sup> or selenate, SeO<sub>4</sub><sup>2-</sup>) or organic (selenized yeast, SeMet and analogues) forms and they differ significantly in bioavailability, metabolism and toxicity. The major proportion of Se in common feed ingredients occurs as seleno-amino acids with SeMet being the most predominant form (Suttle, 2010). In addition, other minor organic forms derived from plants or yeast metabolism such as Se-adenosylselenohomocysteine, methylselenocysteine, selenocystathionine and γ-glutamyl-Se-methylselenocysteine have been reported (Rayman et al., 2004; Schrauzer, 2006). The Se content of feed ingredients of plant origin varies in various geographical locations to a great extent, depending on the Se concentration of the soil and its uptake. In cereal grains, it may range from <0.1 to >0.8 mg kg<sup>-1</sup> (Scott and Thomson, 1972; NRC, 2011). Fish meals represent the best natural source of Se among the common feedstuffs with concentrations ranging from 1–2.4 mg kg<sup>-1</sup> with the exception of tuna and mackerel meals where concentrations may exceed 5 mg kg<sup>-1</sup> (Scott and Thomson, 1971; NRC, 2011). High concentrations of Se have also been reported in shrimp meal and crab meal (Scott and Thomson, 1972). Selenium is widely distributed in small concentrations in FW (0.1–0.3 µg L<sup>-1</sup>) and SW (0.05–0.2 µg L<sup>-1</sup>) (NRC, 2005). In certain regions of the USA with highly seleniferous exposed shale deposits, as high as 5–50 µg Se L<sup>-1</sup> in water have been reported (Canton and Van Derveer, 1997). Limited amounts of dissolved inorganic forms of Se as selenate and selenite in water is absorbed through gill membranes (Pedersen et al., 1998).

Several factors affect the bioavailability of Se including, form of Se, other dietary components, physiological status of Se in animals and species differences (Henry and Ammerman, 1995; Fairweather et al., 2010). The effects of the chemical form of Se in feeds and feed ingredients on the bioavailability and metabolism of this element have been extensively studied in animals (Henry and Ammerman, 1995) and humans (Thiry et al., 2012). Different criteria have been used to determine the bioavailability of Se including GSH-Px

activity, tissue Se concentration and prevention of Se deficiency. Activity of GSH-Px in plasma, red blood cells and a number of tissues respond to dietary Se concentration. Organic sources of Se supplements have shown a higher bioavailability as compared to inorganic forms for fish (Wang and Lovell, 1997; Rider et al., 2010; Sele et al., 2018; Le and Fotedar, 2014; Fontagné Dicharry et al., 2015; Mechlaoui et al. 2019; Antony Jesu Prabhu et al. 2020). Selenium enriched yeast showed higher bioavailability than sodium selenite (Godin et al., 2015). Nanoforms of Se also show high bioavailability in vertebrates (Hosnedlova et al., 2017); however, their bioavailability, metabolism and safety remain to be fully evaluated in fish (Khan et al., 2017).

The early work of Bell and Cowey (1989) showed higher bioavailability in Atlantic salmon and it follows the order from highest to lowest: selenomethionine > selenite > selenocysteine > fish meal (Bell and Cowey, 1989). Certain fish meals, e.g. tuna, may have poor biological availability because of heavy metal complexing of Se. A wide variation in Se availability (38.5-60%) of different batches of capelin meal measured using GSH-Px activity in a chick bioassay was observed (Gabrielsen and Opstvedt, 1980). Until the initiatives to reduce the amount of fish meal with plant ingredients, Se supplementation of farmed fish diets was not considered necessary. An increase in plant protein sources and reduction in fish meal in feeds has reduced the Se and bioavailability of Se (Sissener et al., 2013; Antony Jesu Prabhu et al., 2020; Godin et al., 2015; Fontagne-Dicharry et al., 2015; Betancor et al., 2016; Sele et al., 2018; Silva et al., 2019). Selenium supplementation of fish diets appears to be the most effective method to meet its requirement.

### 2.5 Zinc

Zinc is the second most abundant trace element, after Fe, essential to all cells in most living organisms (Vallee and Falchuk 1993). It has many diverse biochemical functions and is the subject of extensive studies to define the role of Zn at the subcellular level in nutrition and health of human and animals. Most knowledge related to the biochemical function of Zn has emerged from research on other vertebrates and this area is wide open for research from fish perspectives. The ubiquitous distribution of Zn among cells, coupled it being the most abundant intracellular trace element, have resulted in identification of three specific functions in biology of vertebrates and plants: a) catalytic, b) structural and c) regulatory. The catalytic role of Zn is essential for the biological function of all six classes of more than 300 enzymes (McCall et al., 2000). Some examples are RNA nucleotide transferases (RNA polymerase I, II and III), alkaline phosphatase, carbonic anhydrases. In the structural role of metalloenzyme, Zn ion stabilizes the tertiary structure of enzymes (e.g., CU-Zn superoxide dismutase). For this enzyme Cu serves at the catalytic site and Zn serves a role in structure. Zn fingers (where some histidine replaces cysteine) motif in protein represent an important structural role. The single Zn atom at the base of motif influences the binding of protein to DNA. The linking of these Zn fingers to the corresponding sites on DNA initiates the transcription factor and initiates gene expression. Approximately 3000 Zn proteins in human genome and fish genome carry the annotation Zn binding. (Passerini et al., 2007). Zinc is required for the structural and functional integrity of over 2000 transcription factors and almost every signalling and metabolic pathway is dependent on one or more zinc-requiring proteins (Maret, 2013). Also, Zn as an intracellular regulatory ion activates or inhibits transcription factors responsible for regulating gene expression. An example of this role is metallothionein (MT) or MT-like proteins.

The homeostasis of Zn is tightly controlled at the whole body, tissue, cellular, and subcellular levels by a number of proteins with zinc transporters playing key roles. Two Zn transporter families, Zn transporters (ZnT) and Zrt-, Irt-related proteins (ZIP) function in zinc mobilization of influx, efflux, and compartmentalization and sequestration across biological membranes (Kambe et al., 2015). ZnT and ZIP contribute to a wide range of physiological and cellular functions (e.g., immune, endocrine, reproductive, skeletal, and neuronal) by tightly controlling zinc homeostasis (Fukada and Kambe, 2011; Kambe et al., 2015). Biochemical roles for Zn transporters and regulation of specific genes have been

studied in zebrafish (Feeney et al. 2005; Zhao et al, 2014) and are beyond the scope of this review.

The two main routes of zinc uptake from water are through the gills and gastrointestinal tract in fish (Spry et al., 1988). However, the major absorption of Zn occurs primarily through the gut. Waterborne and dietary Zn is also a source of this mineral for salmonids and marine fish because they drink SW (Pentreath, 1973; Lall and Bishop, 1977). In FW fish, uptake across the gill can contribute significantly (~50%) to total Zn absorption if the Zn concentration in the water is high or that in the diet low. Zn may interfere with calcium homeostasis by competitive inhibition of Ca<sup>2+</sup> transfer across the apical membrane of the gill epithelial cells by Zn<sup>2+</sup> (Hogstrand et al., 1996). The accumulation of Zn in gills is also regulated through alteration in Zn uptake mechanisms limiting its excessive uptake (Bury et al., 2003). Zinc chelation with certain amino acids, such as histidine and cysteine that have a high affinity for this element, may enhance Zn distribution in various tissues of fish (Glover and Hogstrand, 2002). The gills in rainbow trout also play a major role in excretion of dietary Zn (Hardy et al., 1987).

Calcium may have an inhibitory or a stimulatory effect on Zn uptake from water depending on the concentration (Glover and Hogstrand, 2003; Ojo and Wood, 2007). Waterborne Ca is a competitive inhibitor of branchial Zn influx. Zinc inhibits the influx of Ca across gills thus Ca in water protects fish against Zn toxicity. The accumulation of Zn in gills is also regulated through alteration in Zn uptake mechanisms limiting its excessive uptake (Bury et al., 2003). The excretory mechanisms and control of gastrointestinal tract uptake may play important roles in maintaining Zn homeostasis. The Zn status of fish is tightly controlled and surplus Zn is excreted via bile, the sloughing of intestinal mucosa in feces and through gills (Handy, 1996). Information on the absorption of Zn from gut is limited. In the intestine, dietary Zn binds to the mucus of the intestinal epithelium, and is transported into the epithelial cells either as Zn ions or as ions bound to amino acids (Bury et al., 2003; Hogstrand, 2012). It is well known that high intakes of phytate and iron reduce the absorption of zinc (Lall, 2002). Development of enterocyte models show potential to investigate specific mechanisms involved in absorption of Zn from fish diets, which contain different forms of organic and inorganic Zn (Antony Jesu Prabhu et al., 2018b).

#### 2.5.1 Requirement

A dietary requirement for Zn (mg kg<sup>-1</sup>) has been reported for several juvenile fish species (Table 4). The minimum Zn requirement varies with age, sexual maturity, composition of diet, water temperature and water quality (NRC, 2011). The response criteria used to determine Zn requirement of fish in various studies include growth, feed efficiency, deficiency signs, whole body Zn concentration and retention, serum or plasma levels and enzyme activities. Most of the above criteria show responses to increasing dietary concentration, the major proportion of dietary Zn is retained in skeletal tissues particularly vertebrae. A meta-analysis of published information on Zn requirement of several fish species showed estimates ranging from 33.5-64.6 mg kg<sup>-1</sup> on the basis of different parameters tested (weight gain, 36; whole body Zn, 33.5; vertebrae Zn, 64.6; serum Zn, 53.4; serum ALP activity, 47) (Antony Jesu Prabhu et al., 2016).

#### Table 4 near here

Studies by Shiao and Jiang (2006) with tiger shrimp, *Penaeus monodon*, showed that for improved growth, a dietary level of 32-34 mg Zn kg<sup>-1</sup> diet was sufficient but an increased supply (35-48 mg Zn kg<sup>-1</sup> diet) led to beneficial effects in terms of non-specific immune responses. Shi et al (2021) showed that dietary organic zinc promoted growth, immune response and antioxidant capacity and the optimal dietary zinc level required was estimated to be 104.8 mg kg<sup>-1</sup> for juvenile Pacific white shrimp (*P. vannamei*) and that a higher dietary level (130.6 mg kg<sup>-1</sup>) led to increased tissue zinc concentrations. Davis et al. (1993a) showed that a dietary supplementation of 200 mg Zn/kg diet was required

to overcome the depressed bioavailability of zinc and to maintain normal zinc levels in the hepatopancreas.

#### 2.5.2 Deficiency

Overt signs of Zn deficiency are difficult to produce in short term experiments due the ubiquity of this trace element in water and feed ingredients. Early work of Ogino and Yang (1978) showed lens cataracts, erosion of fins, skin as well as growth depression and high mortality in juvenile rainbow trout fed semi-purified diet containing a low level of Zn. Later, Satoh et al. (1983b) observed short body dwarfism due to poor mineralization of trout vertebrae. In several fish species, low dietary Zn intake caused reduced growth, low serum, liver, scale, body and vertebrae Zn concentrations. Widespread occurrence of cataracts in salmonids fed diets based on high amounts of white fish meal in United States hatcheries were attributed to Zn deficiency (Ketola, 1979). Zinc is considered essential for normal eye development in juvenile fish and high levels of dietary Ca, P in fish meal and phytic acid in plant ingredients reduces Zn bioavailability resulting in lens cataracts (Ketola et al., 1979; Richardson et al., 1985; Satoh et al., 1983b; Welker et al., 2016). Dietary histidine has also been found to prevent development of cataracts in Atlantic salmon smolts (Waagbø et al, 2010). Zinc and multiple dietary, genetic and environmental factors may be involved in the pathogenesis of cataracts (Bjeerkåas and Sveier, 2004; Lall, 2010). Broodstock diets low in Zn reduced egg production and hatchability of eggs (Takeuchi et al., 1981). Caudal fin Zn concentration is considered a good indicator of Zn status in rainbow trout (Wekell et al., 1986).

#### 2.5.3 Toxicity

Excessive dietary zinc levels may become toxic to fish and compete for similar binding sites with other bivalent minerals such as Cu, Fe, Ca and Cd in the digestive tract during absorption (Clearwater et al., 2002; Luo et al., 2011; Moazenzadeh et al., 2017). Rainbow trout and carp can tolerate 1700 to 1900 mg zinc kg<sup>-1</sup> in diet without any apparent signs of toxicity (Wekell et al., 1983). Common carp accumulate higher concentrations of Zn in their tissues, particularly in the viscera than other fish studied, without any overt toxicity signs (Jeng and Sun, 1981). In rainbow trout, high concentrations of dietary Zn (500 to 1,000 mg Zn kg<sup>-1</sup>) caused reduced hemoglobin, hematocrit, and hepatic Cu concentrations in rainbow trout (Knox et al., 1982).

Effects of environmental pollution and heavy metal contamination of aquatic organisms have been the subject of intensive research particularly their accumulation in fish (Alsop and Wood, 1999). Uptake and toxicity of zinc and other metals from water are known to vary, depending on an organism's physiology and osmoregulatory mechanisms (Alsop and Wood, 1999; Bielmyer et al., 2012). The physiological toxic effects of Zn have been conducted mainly in FW, which show that hypocalcemia caused by Zn interferes with active Zn uptake at the gills (Hoagstrand, 2012). Sublethal Zn exposure of killfish in FW and SW caused pathological changes in both Ca and Na homeostasis and an increase in salinity exerted protective effects against sublethal and lethal Zn toxicities (Loro et al., 2014). Mineral sensitivity is highest during the larval stage, compared to other times in the life history of a fish. Zinc content of scales reflect environmental metal concentrations (Hoagstrand, 2012)

#### 2.5.4 Bioavailability

Dietary factors (e.g., form of Zn, protein source, phytic acid, and dietary Ca and P levels) are known to affect absorption and retention of Zn in fish (Gatlin and Wilson, 1983; Richardson et al., 1985; Wekell et al., 1986; Hardy et al., 1987; Satoh et al., 1987a; McClain and Gatlin, 1988; Satoh et al., 1989; Apines -Amar et al, 2004; Welker et al., 2016; Silva et al., 2019). In most Zn requirement studies (Table 4), zinc sulfate (ZnSO<sub>4</sub>·7H<sub>2</sub>O) has been used due its high bioavailability. Both zinc sulfate and zinc nitrate (40 mg kg<sup>-1</sup>) alleviated dwarfism and cataract problems in rainbow trout (Satoh et al., 1987a). The bioavailability of Zn oxide is low in Atlantic salmon and other fish species probably due to the lower



solubility of this compound (Lall, 2002). Recent studies on monogastric animals show high variability of zinc oxide feed supplements in color, texture and Zn content and manufacturing techniques, which affects their bioavailability (EFSA, 2016a). Organically complexed minerals (amino acid chelate, yeast complexes, etc.), including zinc, appear to be more readily available to rainbow trout compared with inorganic sources (Apines et al. 2003a,b; Apines-Amar et al. 2004; Rider et al. 2009, 2010). No apparent differences in the bioavailability of zinc sulphate and zinc methionine were observed in catfish (Li and Robinson, 1996).

Although fish meal produced from whole fish (e.g., herring and capelin meal) is considered a good source of Zn (80 to 130 mg Zn kg<sup>-1</sup>) and other minerals, the concentration of Zn varies in meals produced from processing discards containing partial fish parts. Feed ingredients of animal origin (meat and bone meal, poultry feather meal) contain high zinc levels (90–140 mg Zn kg<sup>-1</sup>). High levels of Ca and P in high ash fish meal and meat and bone meal affects the bioavailability of Zn (Hardy and Shearer 1985; Hilton, 1989; Watanabe et al. 1997; Lall 2002). Phytate in plant products, especially cereals and legumes, irreversibly binds zinc in the intestinal lumen and reduces their bioavailability. Furthermore, there are copper–zinc and calcium–phytate–zinc antagonistic interactions, which can decrease bioavailability of zinc to rainbow trout (Hilton 1989; Watanabe et al. 1997; Lall 2002). Fiber may interfere with Zn absorption but this may be attributed to the phytate content of high fiber plant feedstuffs. Amino acids, such as histidine and methionine, and other low-molecular-weight ions, such as EDTA and organic acids (e.g., citrate), are known to have a positive effect on zinc absorption (Lönnerdal, 2000). The removal or reduction of phytate by enzyme (phytase) treatment, fermentation or plant breeding/ genetic engineering markedly improves zinc absorption (Kumar et al., 2011). Increasing levels of Cd in foods associated with environmental contaminants and other factors have also been shown to reduce zinc absorption (Lönnerdal, 2000). A higher limit in fish feed has been set for salmonid (150 mg kg<sup>-1</sup> of diet) and other fish (100 mg kg<sup>-1</sup> of diet) in Europe (EFSA, 2015).

### 2.6 Iodine

Iodine is an essential constituent of the thyroid hormones, T3 (3,5,3'-triiodo-L-thyronine) and T4 (L-thyroxine; 3,5,3',5'-tetraiodo-L-thyronine) that regulate cell activity and growth in all tissues. The metabolism of thyroid hormones (TH) and iodine which mainly exists as inorganic iodide are closely linked, TH play a critical role in cellular oxidation, hematopoiesis, circulation, reproduction, neuromuscular functioning, and metabolism of major nutrients (Hetzl and Welby, 1997). T3 is the predominant hormone secreted by the thyroid gland and is regarded as an active precursor for T4. T3 is more biologically active than T4 in several fish species (Higgs et al., 1982; Cyr and Eales, 1996). The inhibition of extrathyroidal T4 -to-T3 conversion reduces the potency of thyroid hormone (Cyr et al., 1988; Lebel and Leloup, 1992); however, the mode of action of the less active T4 is not fully established. Thyroid has an established role in development and metamorphosis (Blanton and Specker, 2007; Power et al., 2008), and where TH metabolism could differ. Major differences exist between fish and mammals in the physiology of iodine and extrathyroidal metabolism of T4 and T3 and recently reviewed (Eales, 2019).

The branchial uptake of iodide by fish is widely recognized. Marine fish drink SW ensuring an adequate intestinal I absorption, which is supplemented by I in food and possible I uptake through body surfaces (Moren et al., 2008). FW fish drink negligibly, hence, dietary and gill uptake are both considered important sources of I (Geven et al., 2007; Higgs et al., 1982). Most research on I metabolism in fish has been focused on salmonids in the FW phase of their lifecycle. In rainbow trout, approximately 19% iodine is derived from diet, 80% from water, and less than 1% from recycling iodide originating from thyroid hormone degradation (Hunt and Eales, 1979). Salmonids undergo parr-smolt transformation, with established thyroid involvement (Specker et al., 2000). After the growth phase during sexual maturation and reproduction, some changes in thyroidal status occurs as well as interaction of TH with sex-related hormones (Cyr and Eales, 1996; Habibi



et al., 2012). Female fish transfer significant amounts of thyroid hormones to developing ova (Blanton and Specker, 2007; Brown et al., 2014) and the offspring may rely on parental iodine storage to complete their early development. Some of these physiological changes may affect the iodine metabolism and requirement at different stages of the life cycle of fish (Higgs et al., 1982).

Iodine enrichment of live food organisms such rotifers, copepod and *Artemia* to increase their I concentration has been tested with cod, halibut and Senegal sole larvae (Einarsdottir, et al., 2006; Ribeiro et al., 2012; Penglase et al., 2013); however, its retention was low in some species, probably due to differences in the bioavailability of I from water or the form of I compounds used to increase the I concentration (Hamre et al., 2013). Recent work of Penglase et al. (2013) has clearly demonstrated that rotifers could be successfully enriched with I. Feeding cod larvae, a high concentration of I enriched rotifers (129 mg I kg<sup>-1</sup> DW) caused I toxicity. Ozone treatment of sea water in recirculation systems oxidizes I to an unavailable IO<sub>3</sub> form, which has low bioavailability for fish (Sherrill et al., 2004). Nitrate (NO<sub>3</sub><sup>-</sup>) is considered goitrogenic for fish and as its build up in water may block iodide uptake by the sodium iodide symporter (Tonacchera et al., 2004), which causes goiter in sharks (Morris et al., 2011).

The relation of Iodine deficiency to enlargement of the thyroid gland or goiter in salmonid fish was first shown by Marine (1914). Senegalese sole larvae developed thyroid hyperplasia and hypertrophy (goiter) fed *Artemia* and grown in recirculation system (Ribeiro et al., 2012). In vertebrates, other deficiency signs of I includes goiter, cognitive and neuromuscular retardation, embryonal and postnatal mortality and impaired fertility (Delange, 1994). Excessive I intake can also negatively affect thyroid hormone production and produce goiter, termed I or colloid goiter in humans (Vanderpas, 2006). In most fish species, I requirement and deficiency remain to be investigated. Woodall and LaRoche (1964) found a higher iodine requirement for advanced parr compared to fingerlings due to increased thyroid activity during smoltification. Lall et al. (1985) observed that 4.5 mg I kg<sup>-1</sup> of diet was essential to protect Atlantic salmon from bacterial kidney disease infections. It is likely that I requirement is influenced by growth, sex, age, physiological status, environmental stress, disease, and iodine content of the water.

Few definitive studies on iodine bioavailability have been conducted due to high uptake of I from water and the problem with distinguishing absorption from water and dietary sources. Iodine concentration of marine fishes is relatively high (Julshamn et al., 2001; Lall, 1995); however, substantial amounts of iodine are lost during fish meal processing (Lall, 2002). Ingested inorganic iodine and iodate are reduced to iodide and absorbed almost completely from the gastrointestinal tract (Hetzl and Welby, 1997). Certain seaweeds also contain high levels of iodine (Teas et al., 2004). Goitrogenic substances in feed may increase iodine requirement depending on the amount and type of this natural toxicant (Bell, 1984). Glucosinolates (GLS) in rapeseed meal are known to impair thyroid function causing goiter in vertebrates (Mawson et al., 1994) and fish (Leatherland et al., 1987; Higgs et al., 1982). This effect is caused by their hydrolytic products (e.g., thiocyanate anions, visnyloxazolidinethiones, and isothiocyanates). The thiocyanate anions are competitors of iodine for active transport across the cell membrane and for binding to tyrosine residues of thyroglobulin. Burel et al. (2001) showed that dietary supplementation with T<sub>3</sub> or iodine induced an increase in plasma T<sub>3</sub> levels, as compared to fish fed rapeseed meal diets, and reduced the deleterious effect of rapeseed meal (RM) on growth. Processing methods have been developed to overcome these antinutritional factors in rapeseed products (Francis et al., 2001).

### 2.7 Chromium

Chromium is a transition metal that exists in food and the environment as Cr<sup>3+</sup> (trivalent) and Cr<sup>6+</sup> (hexavalent) forms. These naturally occurring oxidation states differ significantly in their bioavailability and toxicity. Trivalent Cr has been postulated to be involved in regulating carbohydrate and lipid metabolism by enhancing insulin's efficacy (Vincent 2000). No Cr-dependent enzymes have been identified. The precise biochemical

mechanism of Cr as an essential trace element is not clearly known; however, it has been shown that Cr binds to an oligopeptide to form chromodulin, a low-molecular-weight, chromium-binding substance that binds to and activates the insulin receptor to promote insulin action (Vincent, 2017). It may also have antioxidant effects. Recent research has suggested that although pharmacologic amounts Cr as a therapeutic agent might increase insulin sensitivity and affect lipid metabolism, it is not an essential mineral (Vincent, 2017; EFSA, 2014). Because, according to the definition of an “essential, trace element”, its absence or deficiency from the diet does not produce abnormalities that can be reversed with the addition of Cr. Molecular mechanisms have been proposed for the beneficial effects of Cr but have not been definitively shown to occur consistently in animals.

Several studies on the effect of Cr in fish have been related to its role in metabolism (Hertz et al., 1989; Shiau and Lin, 1993; Ng and Wilson, 1997; Shiau and Shy, 1998; Fernandez et al., 1999; Liu et al., 2010b; Giri et al., 2014; Wang et al., 2014; 2019), growth (Tacon and Beveridge, 1982; Jain et al., 1994) and toxicity (Calamari and Solbé, 1994). To date, many of these studies have provided some evidence that Cr has an effect on the metabolism of fish; however, Cr forms tested and their level as well as experimental conditions have been different in these reports. Chromium yeast appears to modulate the immune response of rainbow trout, and this effect was both dose- and time-dependent (Gatta et al., 2001). Information on the need for supplemental chromium in practical diets of certain animals including fish was too sparse to allow any conclusions (NRC, 2005). A need for research designed to create reproducible signs of chromium deficiency in animals, which would facilitate the establishment of dietary chromium requirements, was identified.

Chromium is absorbed across the gills and transported via blood to tissues but mechanisms of absorption from gills and the gastrointestinal tract, and excretion is not known. Studies on the uptake of Cr from water as it relates to physiology and toxicology have been reviewed (Reid, 2012). The toxic Cr<sup>6+</sup> readily passes cellular membranes and is then reduced to the trivalent form. This Cr<sup>3+</sup> combines with several macromolecules including genetic material inside the cytosol, and ultimately exposes the toxic and mutagenic alterations of Cr toxicity. Higher levels of Cr in diet and water caused histological changes in intestine, gills, liver and kidney but the mechanism of toxicity remains to be established (Reid, 2012; Bakshi and Panigrahi, 2018).

### 2.8 Cobalt

Cobalt is a component of vitamin B12, which is collectively called “cobalamins”. Methylcobalamin and 5-deoxyadenosylcobalamin are the metabolically active forms of this vitamin: however, two others form, hydroxycobalamin and cyanocobalamin are converted to the active forms methylcobalamin and 5-deoxyadenosylcobalamin. Microbiota in the digestive tract of ruminants and algae are known to synthesize vitamin B12 from inorganic cobalt sources. Monogastric animals and fish require vitamin B12 because they lack the ability to synthesize this vitamin from dietary Co in sufficient amounts by microbiota in their digestive tract. In certain warmwater fish, intestinal synthesis of vitamin B12 by microorganisms appears to satisfy the requirements of this vitamin for Nile tilapia (Lovell and Limsuwan, 1982) and hybrid tilapia (Shiau and Lung, 1993), but not for channel catfish (Limsuwan and Lovell, 1981). The estimated dietary Co requirement reported for *Tilapia zillii*, was about 100 mg Co kg<sup>-1</sup> of diet (Anadu et al., 1990). A lower concentration of Co (10 mg Co kg<sup>-1</sup>) in the diet promoted gastrointestinal bacterial synthesis of vitamin B12 in Malabar grouper and met the dietary requirement of this vitamin (Lin et al., 2010b).

Cobalt is absorbed by FW fish via the gills and gut as main routes of uptake (Baudin et al., 2000; Blust, 2012). Some uptake of cobalt occurred in rainbow trout eggs during embryonic development (Kuenze et al., 1978). The uptake routes, homeostasis and mechanism of Co toxicity has been reviewed (Blust, 2012). Cobalt normally present in common feed ingredients, and animal and fish diets are relatively low to cause toxicity (Suttle, 2010; NRC, 2005).

### 2.9 Boron

Boron is an essential nutrient for plants including algae, but biological functions required to establish its essentiality for humans and animals are not clearly identified. To date, boron has been found to be essential for only zebrafish to complete their life cycle (Eckhert and Rowe, 1999). It also stimulates embryonic growth in trout (Eckhert, 1998) and zebrafish (Row and Eckhert, 1998). Boron has beneficial effects on such functions as reproduction and development, calcium metabolism, bone formation, brain function, insulin and energy substrate metabolism, immunity, and the function of vitamin D and steroid hormones (Nielsen, 2014; Hunt, 2012). As compared to FW, the concentration of boron in the marine environment is relatively high (0.4 mM), which is efficiently taken up by algae (Miller et al., 2016). Acute toxicity of B to fry of Chinook salmon and Coho salmon has been reported (Hamilton and Buhl, 1990).

### 2.10 Cadmium

Cadmium is a heavy metal that does not have a clear physiological function as a nutrient and is considered a toxicant for fish by its uptake from the aquatic environment. The toxicity of Cd causes the disruption of Ca ion homeostasis and to some extent Na and Mg (McGeer et al., 2012). Cadmium enters the gill epithelium via the same pathway as Ca<sup>2+</sup>(apical Ca<sup>2+</sup> channel of the chloride cells) and inhibits basolateral Ca<sup>2+</sup> ATPase, thereby blocking active Ca<sup>2+</sup> uptake (Verboost et al. 1989). Atlantic salmon fed 25 mg Cd kg<sup>-1</sup> showed inhibition of ATP dependent Ca uptake measured as Ca<sup>2+</sup> and Na<sup>+</sup>/K<sup>+</sup>-ATPase in the intestine (Berntssen et al., 2003). Generally, the concentration of Cd in most feed ingredients is relatively low (Adamse et al., 2017).

### 2.11 Other trace elements

Biochemical functions of other trace elements (As, F, Li, Ni, Pb, Si and V) have been shown in animals and humans, but their essentiality based on the defined criteria of physiological impairment has not been widely accepted. These minerals in fish have been studied mostly from physiological aspects of their uptake from water and toxicity. Arsenic is naturally abundant in aquatic environments and is considered moderately toxic (McIntyre and Linton, 2012). Supplementation of rainbow trout diet with As, reduced growth and resulted in As accumulation in several tissues (Cockell et al., 1991; Erickson et al., 2011). A maximum tolerable limit for fish may be in the range of 5 mg As kg<sup>-1</sup> diet (NRC, 2005). Arsenic levels in algae and crustaceans are particularly high due to their uptake from water or consumption of aquatic organisms through the food web, but are relatively low in fish (Borak and Hosgood, 2007; Taylor et al., 2017). Marine fish accumulate higher levels of As than FW fish, presumably because of the higher levels of arsenobetaine in their prey. Approximately 90% of As in fish is organic As, with arsenobetaine being the dominant form in marine fish; which is virtually non-toxic (NRC, 2005). Some fish meals may contain high levels of total As, but their inorganic As concentration is low (Sloth et al., 2005). Arsenic is far less toxic to fish than are most metals (Spehar and Fiandt, 1986; Buhl and Hamilton, 1991).

## 3. Macrominerals

### 3.1 Calcium and phosphorus

Calcium and phosphorus play a major role in the development and maintenance of the skeletal system and perform many other physiological functions including the maintenance of acid base equilibrium. In skeletal tissue, Ca and P are deposited as tricalcium phosphate [Ca<sub>3</sub>(PO<sub>4</sub>)<sub>2</sub>], which then undergoes further crystalline changes to form hydroxyapatite, Ca<sub>10</sub>(PO<sub>4</sub>)<sub>6</sub>(OH)<sub>2</sub>, which is deposited in the organic matrix during mineralization. The ratio of Ca to P in bone may show some changes during development, however, their ratio reported in several fish species ranges from 1.6:1 to 2:1. Fish scale is also a calcified tissue and serves as an internal Ca reservoir during periods of increased Ca demand, such as sexual maturation and starvation (Persson et al., 1998). During the

reproductive period, the plasma Ca level increases in females, which is bound to vitellogenin, a major component of egg protein and a calcium-binding protein (Kwon et al., 1993).

Fish absorb Ca and P from the surrounding aquatic environment via gills, gastrointestinal tract and integument; however, the gills represent the major site of Ca uptake (Evans and Claiborne, 2009). The physiological aspect of Ca uptake at the gills is well established and is the subject of several reviews (Flik et al., 1995; Marshall 2002; Lin and Hwang 2016). The absorption and metabolism of Ca depends not only on its concentration in the surrounding water, but it is affected by species differences and their homeostasis by the endocrine system, biological availability from diet and P level (Lall, 2021). Osmoregulation allows them to control their Ca levels predominantly via the hypocalcemic hormones, stanniocalcin and calcitonin. Certain minerals (e.g., Cd, Cu, Mg, Sr, Zn) may reduce Ca absorption from gills or gastrointestinal tract (Berntssen et al., 2003; Baldisserotto et al., 2006; Zimmer et al., 2019). In vertebrates, vitamin D is known to play an essential role in Ca metabolism. Although, limited research has been conducted on fish, the function of the endocrine system and metabolites identified appears similar in fish and terrestrial vertebrates (Sundell et al., 1992; Graff et al., 1999; Fraser, 2018).

In addition to skeletal tissue metabolism, P as phosphate ( $\text{HPO}_4^{2-}$ ) plays a major role in the function of all cells. It is a major signaling molecule, and structural component of cell walls, essential for nucleic acid helical structure (i.e., RNA and DNA), and a component of high-energy compounds (i.e., AMP, ADP, and ATP). Food is the main source of P for fish because FW and SW are low in phosphate. Thus regulation of phosphate is considered more critical than that of Ca because fish must effectively absorb, and conserve phosphate in both FW and SW environments. Dietary P concentration is a major regulator of P metabolism in fish (Coloso et al. 2003). The amount of phosphate absorbed from the food is affected by the level of phosphate in the blood (Lall, 2002). The serum concentration of phosphate and the total body content of phosphate are highly regulated and movement into cells is mediated by sodium-phosphate co-transporters (Hernando and Wagner et al., 2018).

Information on the endocrine regulation of P homeostasis in fish is limited. The hormones involved in phosphate regulation include ST, prolactin and parathyroid like hormones (Pth1h). With the rise in serum Ca, stanniocalcin is secreted by the corpuscles of stannius to inhibit gill and intestinal Ca transport and to promote P reabsorption in the kidney to maintain normal physiological serum Ca and P levels (Wagner, 1993; Wagner et al., 1998). Parathyroid hormone-like hormone, Pth3 and Pth4 play an important role in functions related to P and bone mineral homeostasis (Potts 2005; Guerreiro et al. 2007). It is also not clear whether the effect is mediated by the vitamin D metabolites as happens in terrestrial vertebrates (Wendelaar Bonga and Flick, 1995). Although intraperitoneal injection of vitamin D metabolites influence P homeostasis (Fenwick and Vermette, 1989), dietary intake of cholecalciferol had no clear effect on P absorption and retention in rainbow trout (Vielma et al., 1999).

### 3.1.2 Requirement

The Ca requirement of fish is affected by dietary factors (e.g. bioavailability, P level), uptake from water and species differences (NRC, 2011; Hossain and Yoshimatsu, 2014). Generally, a large part of Ca requirement of most fish is met by its absorption through gills in FW and by drinking SW. A low concentration of calcium (0.34 % or less) is required in the diet of carp, red sea bream, striped bass, tilapia, catfish and chum salmon (Sakamoto and Yone, 1973; Ogino and Takeda, 1976; Lovell, 1978; Nakamura, 1980; Robinson et al., 1984; Dougall et al, 1996). Catfish and tilapia reared in water with a low calcium concentration (< 1 mg Ca/L) required 0.45 % and 0.7 % calcium in the diet, respectively (Robinson et al., 1986, 1987). Atlantic salmon absorb Ca from SW, thus making dietary supplementation unnecessary (Lall and Bishop, 1977). There is a relatively low requirement (0.1-0.25 %) of Ca for farmed marine fish (NRC, 2011). Other details related to Ca utilization



and requirements of certain fish species have been reviewed (Hossain and Yoshimatsu, 2014; Lall, 2021).

The P requirement (g/100g) of a wide range of fish species reared in fresh, brackish and SW have been reported. Requirement in FW: Atlantic salmon, 0.6-1.0 (Ketola, 1975; Vielma and Lall, 1998; Åsgård and Shearer, 1997), rainbow trout, 0.34-0.8 (Ogino and Takeda, 1976; Rodehutscord, 1996; Ketola and Richmond, 1994); chum salmon, 0.5-0.6 (Watanabe et al., 1980); channel catfish, 0.33-0.8 (Andrews et al., 1973; Lovell et al., 1978; Wilson et al., 1988) milkfish, 0.85 (Borlongan and Satoh, 2001); blue tilapia, 0.5 (Robinson et al., 1987); Nile tilapia, 0.65-0.86 (Yao et al., 2014; Carvalho et al., 2017); common carp, 0.6-0.7 (Ogino and Takeda, 1976); gibel carp, 0.67-1.07 (Xie et al., 2017); grass carp, 0.85 (Liang et al., 2012); crucian carp, 0.78-0.83 (Sun et al., 2018); stinging catfish, 0.9-1.1 (Zafar and Khan, 2018); African giant catfish, 1.23 (Nwana et al., 2009); walking catfish, 0.58-0.73 (Yu et al., 2012); Chinese sucker, 0.83-0.86 (Yuan et al., 2011); hybrid striped bass, 0.5 (Brown et al., 1993); snakehead, 0.96 (Shen et al., 2016); tambaqui, 0.7 (Araujo et al., 2016); Japanese eel, 0.29 (Nose and Arai, 1979). Requirement in brackish water (salinity, 5-6 ‰): red drum, 0.86 (Davis and Robinson, 1987). Requirement in SW: Atlantic salmon, 0.6 (Lall and Bishop, 1977); red sea bream, 0.68 (Sakamoto and Yone, 1978a); gilthead seabream, 0.75 (Pimental-Rodrigues and Olivia-Teles, 2001); black seabream, 0.55 (Shao et al., 2008); haddock, 0.96 (Roy and Lall, 2003); Japanese seabass, 0.86-0.90 (Zhang et al., 2006); European seabass, 0.65 (Olivia-Teles and Pimental-Rodrigues, 2004); orange spotted grouper, 1.09 (Ye et al., 2006); Yellow croaker, 0.89-0.91 (Mai et al., 2006); Japanese flounder, 0.6-1.5 (Choi et al., 2005; Wang et al., 2005; Uyan et al., 2007).

The requirement estimates above are mainly based on juvenile fish studies and there were differences in dietary sources of P and their bioavailability, fish size and response criteria selected. Anthony Jesu Prabhu et al. (2013) used a meta-analysis approach to estimate the P requirements based on published information on P utilization for 40 different fish species where requirement values were determined using differences in the response criteria. They found that requirement based on weight gain, and P concentration of whole-body and vertebrae were 0.35, 0.47 and 0.52 g available P/100 g diet (dry matter basis) respectively. Some of these estimates differed from NRC recommendation on P requirement (g/100g) for major farmed fish species: Atlantic salmon, 0.8; rainbow trout, 0.7; Pacific salmon, 0.6; channel catfish, 0.33; common carp, 0.7; tilapia sp., 0.4; hybrid striped bass, 0.5; red drum, 0.8; European seabass, 0.65; Japanese flounder, 0.6 P/100 g diet. Obviously, there is a need to better define the P requirement of fish taking into account the stage of development, bioavailability of P from the test diet and feed supplement used to fortify the experimental diets. Studies conducted on other animals show that the maximum growth rates are not necessarily adequate for maximum bone mineralization and they may need higher levels of P in their diet (NRC, 2012).

### 3.1.3. Deficiency

Calcium deficiency has not been detected in carp and catfish in FW (Andrews et al., 1973; Ogino and Takeda, 1976) or in Atlantic salmon in SW (Lall and Bishop, 1977) fed low Ca diets. Generally, uptake of Ca from water and absorption from dietary feed ingredients supplies sufficient calcium to meet the requirements of most finfish. Studies conducted on the P requirement of several fish species have shown reduced weight gain, feed utilization and bone mineralization when the P content of the diets were low, with certain exceptions, gibel carp (Xie et al., 2015), red drum (Davis and Robinson, 1987), gilthead bream (Pimental-Rodrigues and Olivia-Teles, 2001) and European seabass (Olivia-Teles and Pimental-Rodrigues, 2004). Other P deficiency signs experimentally produced in fish included increases in liver or body fat, reduced blood phosphate levels and poor mineralization of scales. Fish fed diet containing either mineral deficient or low P diet mobilize minerals including Ca and P to maintain normal physiological functions (Lall, 2021) and fish scales appear to be the most sensitive indicator of P deficiency in young fish (Skonberg et al., 1997; Vielma and Lall, 1998a). The cause of low dietary P-induced skeletal deformities in salmonids and certain marine fish have been the subject of intensive research and



several reviews have been published in this area (Sugiura et al., 2004; Lall and Lewis-McCrea, 2007; Lall, 2010; Baeverfjord et al., 2019). Common skeletal deformities with low intake of P include curved spines and soft bones in Atlantic salmon (Baeverfjord et al., 2019), cephalic deformities in the frontal bones of common carp (Ogino and Takeda, 1976), and compressed vertebral bodies resulting in scoliosis in haddock (Roy and Lall, 2003) and halibut (Lall and Lewis-McCrea, 2007). Recent studies of bone tissues have revealed that mobilization of minerals during low intake of dietary P does not fully explain the biochemical mechanism involved in the demineralization process (Witten et al., 2016, 2019; Drabiková et al., 2021). A decrease in dietary P content in a practical diet of Atlantic salmon smolts showed vertebrae without any significant changes in organic matrix and demineralization of bone (Fjelldal, et al. 2007; Witten et al., 2019). Several nutrients support skeletal growth including bone and scale matrix mineralization, and interactions between P and other nutrients in skeletal tissue biomineralization are poorly understood (Lall, 2010).

#### 3.1.4 Bioavailability

The bioavailability of P by fish differs markedly among feed ingredients and inorganic P supplements as well as among other dietary factors (e.g., chemical form, digestibility of diet, particle size, interaction with other nutrients, feed processing and water chemistry) (Lall, 1991; NRC, 2011). Most of the P in cereal grains and oilseed meals present in the form of an organic complex, phytic acid or phytate (myo-inositol 1, 2, 3, 4, 5, 6-hexakis dihydrogen phosphate) is not available to fish because their intestinal tract does not have sufficient extracellular phytase like other nonruminant vertebrates. Phytate depresses protein and amino acid digestibility and utilization efficiency in fish and other higher animals. Phytate interactions with proteins are also pH-dependent (Cheryan, 1980). Several reviews have considered various aspects of phytates in fish nutrition and potential strategies to improve the bioavailability of phytates in feed ingredients of plant origin (Cao et al., 2007; Kumar et al., 2012; Dersjant-Li et al., 2015; Lemos and Tacon, 2015). The hydrolysis of phytic acid can be achieved by enzymatic and nonenzymatic degradation. Development of phytases and optimization of their catalytic features has been a promising strategy for efficient reduction of phytate in animal feeds. Phytate also forms complexes with lipid and derivatives along with other nutrients (Vohra and Satnarayana, 2003) but this aspect of chelate formation has not been investigated in fish. The preferable method of phytase application in feeds is coating a liquid form of the enzyme after extrusion and drying which prevents loss of enzyme activity during processing (Verlhac-Trichet et al., 2014).

Phosphorus in fish meal is mainly in the form of an insoluble Ca-P complex, hydroxyapatite which varies with the source of fish used and its bioavailability varies among fish species (NRC, 1993; 2011). Acid hydrolysis of fish bone by-products appears to increase P availability of the hydroxyapatite in bone (Albrektsen et al, 2017). There are significant differences in the availability of P from a variety of inorganic salts: the more soluble the salt, the higher the availability of P, thus P is more readily available from mono- or dicalcium phosphates than from tri-calcium phosphate (NRC, 1993; 2011). Salmonids utilize P present in fish meal more efficiently than carp, tilapia and channel catfish (Lovell, 1978; Ogino et al., 1979; Watanabe et al., 1988; Köprücü and Özdemir, 2005).

#### 3.2 Magnesium

Magnesium is a critical intracellular divalent cation that plays an essential physiological role in many functions in the body. It forms a key complex with ATP and plays a key role in many important biological processes such as protein synthesis, cell replication, and energy metabolism. Magnesium is a regulator of ion channels, an important intracellular signaling molecule, involved in nerve conduction, muscle contraction, potassium transport and a modulator of oxidative phosphorylation. Extracellular Mg is vital to normal nerve conduction, muscle function, and skeletal tissue metabolism. It plays an important role in the respiratory adaptation of FW fish (Houston, 1985). The major

proportion (50-70%) of Mg in the body of fish is located in skeletal tissues and scales (Bijwelds et al., 1998). The remainder is found within the cells of soft tissues. In muscle, it comprises approximately 20% of the total body Mg pool (Knox et al., 1981).

Dietary Mg is considered the main source for growth and development of fish (Cowey et al., 1977; Lall, 2002). When dietary Mg concentration was low in FW, part of its requirement was met by uptake from water via gills (Shearer and Asgard, 1992; Dabrowska et al., 1991). However, in most fish species studied, Mg uptake from FW was insufficient to meet their dietary Mg requirement (Lall, 2002; NRC, 2011). There is some evidence that excess Mg is excreted renally by fish in FW (Oikari and Rankin, 1985). In SW, fish absorb Mg by drinking (Hickman and Trump, 1969) and the major part of the Mg requirement of Atlantic salmon and other marine fish could be met by absorption of SW (Lall and Bishop, 1977).

### 3.2.1 Requirement

Magnesium requirements of most farmed fish species have ranged from 0.4 to 0.6 g kg<sup>-1</sup> diet (NRC, 2011; Lall, 2021). Hybrid tilapia showed the Mg requirements of 0.2 and 0.02 % in FW and SW respectively. No requirement of Mg for yellow croaker and red mullet has been reported (El-Zibdeh et al., 1996). A meta-analysis of Mg requirement reported for several fish species showed relatively close estimates for the Mg requirement (g kg<sup>-1</sup> diet) based on the following parameters: weight gain, 0.34; whole body Mg, 0.49; vertebrae Mg, 0.42; plasma Mg, 0.5 (Antony Jesu Prabhu et al., 2016). In SW, Mg requirement for Atlantic salmon and red seabream was not observed (Lall and Bishop, 1977; Sakamoto and Yone, 1979b). Unlike terrestrial animals, Mg requirement of rainbow trout was not influenced by an increase in dietary Ca and P levels (Knox et al., 1981).

### 3.2.2. Deficiency

Magnesium is mobilized from bones and scales when dietary Mg intake is low (Cowey et al., 1977). Deficiency signs of Mg in carp, catfish, hybrid tilapia, eel, and rainbow trout may include one or more of the following deficiency signs: anorexia, reduced growth, sluggishness, high mortality, and reduced magnesium content (NRC, 2011; Lall, 2010). In rainbow trout, Mg deficiency also causes calcinosis of kidney, vertebrae deformity, and degeneration of muscle fibers and epithelial cells of the pyloric cecum and gill filaments (Cowey et al., 1977; Ogino et al., 1978). A low concentration of Mg in water reduced the Mn concentration of eggs in carp, which reduced the hatchability of egg and survival of offspring and also caused deformities and tissue necrosis (Van der Valden et al., 1991).

### 3.2.3 Bioavailability

Information on Mg bioavailability from feed ingredients and inorganic supplements for fish is scarce. Generally, Mg concentration in natural feed ingredients of plant and animal origin contain moderate levels of Mg. Inorganic Mg feed supplements include magnesium sulfate, magnesium chloride, magnesium oxide and magnesium acetate. Magnesium sulfate is more water soluble than magnesium oxide and therefore more available for absorption. Magnesium present as Mg acetate was more efficiently used by tilapia than either Mg oxide or sulfate (Dabrowska et al., 1989).

## 4. Concluding remarks

Many gaps exist in the knowledge of mineral nutrition of fish and shrimp related to their dietary requirements, physiological functions, absorption from gastrointestinal tract and bioavailability from feed ingredients. Information on animal and human nutrition has been useful to confirm the biochemical functions of certain inorganic elements including skeletal tissue metabolism, cellular respiration, oxygen transport, regulation of acid-base equilibrium as well as important components of hormones, enzymes and enzyme activators. Extensive research on farm animals has demonstrated that mineral requirements differ at various stages of their production cycle, certain trace elements play important role

in immune functions and disease prevention and application of specific methodologies are useful to predict the bioavailability of minerals from feed ingredients; however, the research in these areas on fish is limited. Another issue specific to aquatic animals is that there is a need to consider the impact of water-borne minerals from both the nutritional and environmental points of view.

Aquaculture is now the fastest growing food production system globally with many new challenges to address the nutritional problems of more than 40 major farmed fish species. Early studies on mineral nutrition were conducted on salmonids and some warm water fishes using semi-purified diets and trace element supplements of high bioavailability. Most known mineral requirements (Ca, P, Mg, Cu, Zn, Mn, Se) were determined for young fish. NRC (1993, 2011) requirement values for certain minerals for about 10 fish species have been used as guidelines and as a starting point to establish recommendation allowances for new fish species. Many studies were short term and gave little consideration to the dietary intake or mineral status prior to the experimental period and to the effect of the previous diet may have on body stores at the commencement of the study. Some minerals take longer period, depending on the water temperature to reach a steady state following a change in their dietary intake. A shift from the use of fish meal as a major source of protein and minerals in feeds to proteins of plant origin and land animal products, now requires better assessment of mineral bioavailability for improving feed formulation more precisely. There are also new trace element supplements available which require proper assessment of their rate of absorption and potential impact on fish performance.

Because an animal's requirement for any nutrient is affected by many factors, limited data on nutrient requirement values (e.g., NRC, 2011) should not be regarded as fixed quantities. Instead of solely relying on these values, changes in animal performance with alterations in nutrient intake should be determined as dynamic responses, to derive requirement estimates that are appropriate to the particular fish species under different culture conditions and dietary regimes. This should start with the units of expression of data on mineral requirements. Meta analyses of existing data on requirements provide some general guidelines on recommendations. Factorial models are now being applied to estimate nutrient requirements and metabolism of farmed animals and fish; however, additional reliable new data on mineral requirements of major farmed fish species is needed to generate reliable information for use in feed formulation.

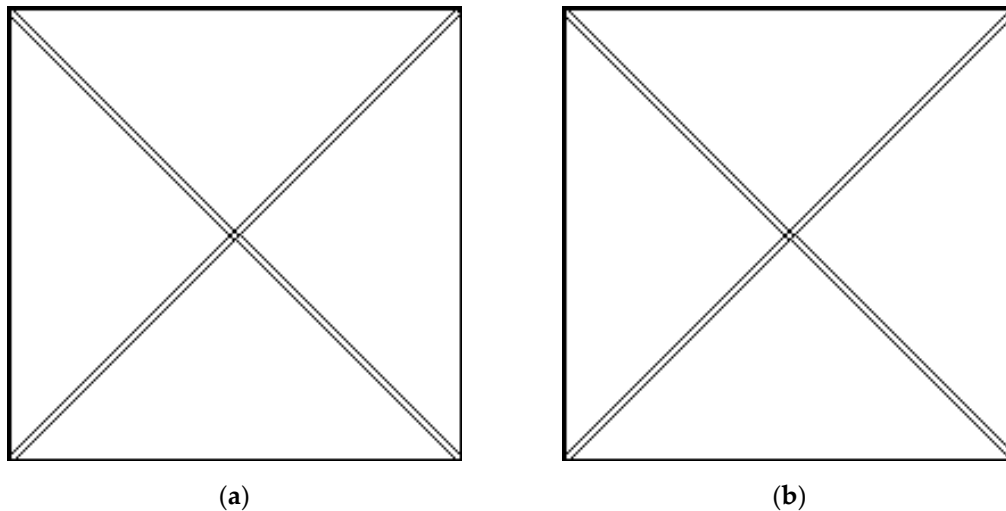
This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

**Table 1.** This is a table. Tables should be placed in the main text near to the first time they are cited.

Title 1	Title 2	Title 3
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<sup>1</sup> Tables may have a footer.

The text continues here (Figure 2 and Table 2).



**Figure 2.** This is a figure. Schemes follow another format. If there are multiple panels, they should be listed as: (a) Description of what is contained in the first panel; (b) Description of what is contained in the second panel. Figures should be placed in the main text near to the first time they are cited. A caption on a single line should be centered.

**Table 2.** This is a table. Tables should be placed in the main text near to the first time they are cited.

Title 1	Title 2	Title 3	Title 4
entry 1	data	data	data
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entry 4	data	data	data
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**Table 1.** Iron and copper requirement of fish

Fish species	Copper <sup>a</sup>			Iron <sup>e</sup>		
	mg kg <sup>-1</sup>	Main response criteria	Reference	mg kg <sup>-1</sup>	Main response criteria	Reference
Atlantic salmon	5-10	Liver Cu	Lorentzen et al., (1998)	60-100 60	H <sup>f</sup> , Liver Fe Weight gain, H <sup>f</sup> , Liver Fe	Andersen et al., (1996) Naser (2000)
Rainbow trout	3	Body, vertebrae, liver Cu	Ogino and Yang (1980)			
Channel catfish	5	Liver Cu-Zn SOD	Gatlin and Wilson (1986b)	30	WG, H <sup>f</sup>	Gatlin and Wilson (1986a)
Yellow catfish	3.1-4.2	WG <sup>b</sup> , Cu retention	Tan et al., 2011a	55.7		Luo et al., (2017)
Common carp	3 <sup>c</sup>	Body, vertebrae, liver Cu	Ogino and Yang (1980)	147.4	Serum Fe	Ling et al., (2010)
				202	Hematocrit, liver Fe	Pan et al., (2009)
Grass carp	4.7-5	WG, plasma ceruloplasmin activity	Tang et al., (2013)			
Hybrid tilapia	4	WG, body Cu retention	Shiau and Ning (2003)	150-160 <sup>g</sup> 85 <sup>e</sup>	Weight gain, hemoglobin, Liver Fe	Shiau and Su, 2003
Japanese eel				170		Nose and Arai (1979)
Asian stinging catfish	5.2-5.7	WG, plasma ceruloplasmin activity	Zafar and Khan (2020)			
Russian sturgeon	7-8	WG, whole-body Cu, liver Cu-Zn SOD, serum ceruloplasmin activity	Wang et al. (2016)			



Red sea bream				150		Sakamoto and Yone, (1978c)
Tongue sole	11-12	WG, serum Cu-Zn SOD activity	Wang et al., 2015			
Malabar grouper	4-6	WG, Liver Cu-Zn SOD activity, body Cu retention	Lin et al., (2008a)	100 <sup>h</sup>	Liver Fe	Ye et al., (2007)
	2-3 <sup>d</sup>	WG, Liver Cu-Zn SOD activity, body Cu retention	Lin et al., (2010a)			
Yellow croaker	3.4-7	Serum Cu-Zn SOD activity, body and vertebrae Cu	Cao et al., (2014)			
Cobia				80.5-94.7 <sup>e</sup> 71.3-75.1 <sup>i</sup>	WG, serum catalase activity	Qiao et al., (2013)

<sup>a</sup>Unless specified CuSO<sub>4</sub>·5H<sub>2</sub>O used as Cu supplement ; <sup>b</sup>Weight gain; <sup>c</sup>CuCl<sub>2</sub> used as Cu supplement ; <sup>d</sup>Copper peptide used as Cu supplement; <sup>e</sup>Unless specified FeSO<sub>4</sub>·6H<sub>2</sub>O used as Fe supplement ; <sup>f</sup>Hematology; <sup>g</sup>Ferric citrate used as Fe supplement; <sup>h</sup>Requirement for orange-spotted grouper (*Epinephelus coioides*); <sup>i</sup>Iron methionine used as Fe supplement

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**Table 2.** Manganese requirement of certain fish<sup>a</sup>

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Fish species	mg kg <sup>-1</sup>	Main response criteria	Reference
Atlantic salmon	15 7.5-10.5	Body and vertebrae Mn Body Mn	Lorentzen et al., (1996) Maage et al., (2000)
Rainbow trout	12-13	WG <sup>b</sup>	Ogino and Yang (1980)
Channel catfish	2.4	WG	Gatlin and Wilson (1984a)
Yellow catfish	5.5-6.4	WG, vertebrae Mn, liver Mn-SOD <sup>c</sup>	Tan et al., (2012)
Common carp	12-13	Growth rate	Ogino and Yang, (1980)
Gibel carp	13.8	WG, body and vertebrae Mn	Pan et al., (2008)
Hybrid tilapia	7	Body Mn, Liver Mn-SOD	Lin et al. (2008b)
Grouper <sup>d</sup>	15	Body and vertebrae Mn	Ye et al., (2009)
Yellow croaker	16.4	Growth rate, liver Mn-SOD	Zhang et al., (2016)
Cobia	21.7-24.9 10.5-15.4 <sup>e</sup>	WG, Body and vertebrae Mn Specific growth rate, liver Mn-SOD	Liu et al., (2012) Nie et al. (2016)

<sup>a</sup>Unless specified MnSO<sub>4</sub>·H<sub>2</sub>O used as Mn supplement; <sup>b</sup>Weight gain; <sup>c</sup>Liver Mn-SOD activity; <sup>d</sup>Orange spotted grouper (*Epinephelus coiodes*) ; <sup>e</sup>MnSO<sub>4</sub>·H<sub>2</sub>O, manganese glycine and manganese 2-hydroxy-4-(methylthio)butyrate showed Mn requirement of 15.4, 11.2 and 10.5 mg kg<sup>-1</sup> respectively

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**Table 3.** Selenium requirement of certain fish

Fish species	Requirement, mg kg <sup>-1</sup>	Selenium source	Main response criteria	Reference
Atlantic salmon	0.27 <sup>a</sup> (0.65)	Na <sub>2</sub> SeO <sub>3</sub> or SeMet <sup>b</sup>	Body and tissue Se	Antony Jesu Prabhu et al.,(2020)
Rainbow trout	0.15-0.38	Na <sub>2</sub> SeO <sub>3</sub>	Plasma GPx	Hilton et al., (1980)
Channel catfish	0.25 0.28, 0.17 0.09, 0.12 0.11, 0.12	Na <sub>2</sub> SeO <sub>3</sub> Na <sub>2</sub> SeO <sub>3</sub> SeMet Se-yeast	Liver and plasma GPx WG <sup>c</sup> , GPx WG, GPx WG, GPx	Gatlin and Wilson, (1984b) Wang and Lovell, (1997)
Gibel carp	1.18 0.73-1.19	SeMet SeMet	WG, Liver GPx, tissue Se Liver Se, Liver SOD, T-AOC	Han et al., (2011) Zhu et al.,(2016)
Nile tilapia	0.57	SeMet	WG, Liver GPx	Ning et al., (2020)
Largemouth bass	1.60-1.85	Na <sub>2</sub> SeO <sub>3</sub>	Liver GPx	Zhu et al., (2011)
Gilthead sea bream	0.94	Na <sub>2</sub> SeO <sub>3</sub>	Growth. Liver Se	Dominguez et al.,(2019)
Black sea bream	0.86	Se-polysaccharide <sup>d</sup>	Liver SOD and GPx	Wang et al., (2019)
Malabar grouper	0.7 0.9 0.98	SeMet SeMet Na <sub>2</sub> SeO <sub>3</sub>	WG. Se retention WG, Flesh Se	Lin and Shiau, (2005) Lin, (2014)
Cobia	0.8	SeMet	Liver and serum GPx, Whole body Se	Liu et al., (2010a)

<sup>a</sup>Based on available Se ; <sup>b</sup>Se-methionine used as Se supplement; <sup>c</sup>Weight gain ; <sup>d</sup>Se-polysaccharide used as Se supplement

Table 4. Zinc requirement of certain fish<sup>a</sup>

Fish species	Requirement, mg kg <sup>-1</sup>	Main response criteria	Reference
Atlantic salmon	37 - 67	Body and serum Zn	Maage and Julshamn (1993)
Rainbow trout	15-30 30.1	WG <sup>b</sup> , vertebrae Zn WG	Ogino and Yang (1978) Welker et al., (2016)
Channel catfish	20	WG, vertebrae Zn	Gatlin and Wilson (1983)
Yellow catfish	17.1-20.9	WG, PER <sup>c</sup>	Luo et al., (2011)
Common carp	15	WG, vertebrae Zn	Ogino and Yang (1979)
Jian carp	43.2-48.7 <sup>d</sup>	WG, serum, Zn	Tan et al., (2011b)
Grass carp	55	WG, whole body, vertebrae, scale and tissue Zn	Liang et al., (2012)
Indian major carp	47.8-52.9	WG, vertebrae, scale serum and liver Zn	Musharraf and Khan (2019)
Hybrid tilapia	26-29 105-115 <sup>e</sup>	WG, whole body Zn WG, whole body and plasma Zn	Lin et al., (2008c) Li and Huang, (2016)
Blue tilapia	20	Scale and vertebrae Zn	McClain and Gatlin (1988)
Nile tilapia	30 37.2-52.1	WG, vertebrae and serum Zn WG, bone Zn	Eid and Ghonim (1994) Huang et al., (2015)
Russian sturgeon	28.2-34.6	WG and Liver Zn	Moazenzadeh et al., (2017)
Red drum	20	WG, serum and bone Zn	Gatlin et al., (1991)
Blunt snout sea bream	52.1 <sup>f</sup> , 86.2 <sup>f</sup>	WG, whole body Zn	Jiang et al., (2016)
Malabar grouper	28.9-33.7	WG, vertebrae and scale Zn	Huang-Yung et al., (2014)
Cobia	42.9	WG, vertebrae Zn	Xu et al., (2007)

<sup>a</sup>Unless specified ZnSO<sub>4</sub>·7H<sub>2</sub>O used as Zn supplement ; <sup>b</sup>Weight gain; <sup>c</sup>Protein efficiency ratio; <sup>d</sup>Zinc lactate (C<sub>6</sub>H<sub>10</sub>O<sub>6</sub>Zn); <sup>e</sup>Diet based on soybean meal ; <sup>f</sup>Requirements based on weight gain and whole body Zn respectively

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