SELENIUM DEFICIENCY, TOXICITY AND ITS REQUIREMENT IN MARINE FISH: A RESEARCH REVIEW

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ABSTRACT

The necessity of selenium (Se) in maintaining normal growth and physiological functions have been demonstrated in fish due to its important role as a cofactor in glutathione peroxidase enzyme (GPx), protecting cell membranes against oxidative damage. The deficiency of Se can lead to reduced growth, feed utilisation and health status in farmed fish. Whereas fish fed elevated dietary Se levels results in reduced feed utilisation and adverse effects on physiological performance and impaired histology. Dietary Se requirements have been quantified for some marine fish species with varied results, probably due to the differences in bioavailability, sources of Se, protein ingredients as well as the interaction of Se with other nutrients in the diets. Besides, due to the narrow gap between deficiency, optimality and toxicity of Se level, it is imperative to find out the exact dietary Se requirement for any aquatic species. This review summarises the available information regarding dietary Se requirements in marine fish. The effects of Se deficiency and its toxicity in marine fish also are discussed.

Keywords: selenium, marine fish, toxicity, requirement

I. Introduction

The nutritional effects of selenium (Se) have gained attention due to its essential roles in growth and physiological functions (Watanabe *et al*., 1997). It serves as a cofactor in glutathione peroxidase-catalysed reactions, which are necessary for the conversion of hydrogen peroxide and fatty acid hydroperoxides into water and fatty acid alcohol by using reduced glutathione (GSH), thereby protecting cell membranes against oxidative damage. A deficiency of Se can cause negative effects on growth, feed utilisation and survival in many marine fish such as grouper *Epinephelus malabaricus*, cobia *Rachycentron canadum*, yellowtail kingfish *Seriola lalandi* (Le, Fotedar, 2013; Pham *et al*., 2018). Whereas, the beneficial effects of dietary Se supplementation on growth, feed utilisation and immune responses have been demonstrated in various fish species (Le, Fotedar, 2013; Le *et al*., 2014a; Le *et al*., 2014b; Pham *et al*., 2016; Pham *et al*., 2018). However, the excessive dietary Se may cause toxicity in fish. Signs of Se toxicity in fish include high mortalities, histopathological changes in liver tissues, diminished reproductive performance and reduced feed intake, growth response and haematocrit values (Arteel, Sies, 2001; Lin, Shiau, 2005; Liu *et al*., 2010) and reduced host defence function (Liu et al., 2010; Sweetman *et al*., 2010; Wang *et al*., 2013).

As the difference between beneficial and toxic effects of dietary Se is narrow, it is necessary to determine the beneficial and toxic levels of Se to optimise its inclusion concentration in the diet formulation. However, past investigations have also provided varied results on Se requirement in fishes, probably due to the differences in Se levels in the rearing water, the availability and bioavailability of Se sources, diet formulation and characteristics among fish species. Additionally, both Se and vitamin E act as biological antioxidants to protect cell membranes from oxidative damage (Rotruck *et al*., 1973), The peroxides formation can improve the functions of vitamin E, whereas Se is responsible for peroxide degradation, thus the dietary Se need in fish may vary, depending on the concentration of dietary vitamin E (Watanabe *et al*., 1997). The interaction between Se and other minerals such as copper, sulphur, mercury (Watanabe *et al*., 1997) may also alter the bioavailability of Se for fishes, making the investigation on Se requirement

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more complicated.

This review aims to summary the effects of Se deficiency and its toxicity in marine fish. It also compiles the dietary Se requirements to date in fish species. The possible reasons for the varied results in dietary Se requirements in fish also is discussed to provide future directions in evaluating Se and other mineral requirements in fish.

II. Dietary Se in marine fish

1. Se deficiency and toxicity

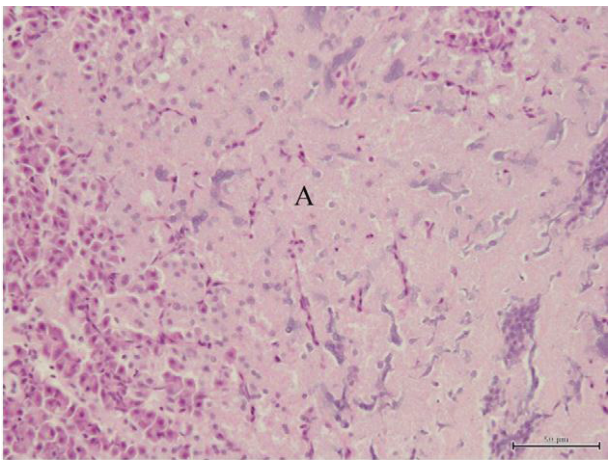
Although, Se is an essential trace element for normal growth and physiological function in fish (Watanabe *et al*., 1997), but can be harmful at higher dietary levels resulting in growth and feed efficiency reduction (Le, Fotedar, 2014a; Lee *et al*., 2010), histopathological alterations in digestive tissues such as livers, spleens, kidneys (Le, Fotedar, 2014a; Lee *et al*., 2008; Lee *et al*., 2010), reproductive teratogenesis (Lemly, 2002). Simultaneously, Se-deficiency can cause negative effects on growth and survival, and may lead to peroxidative damage to cells and membranes (Arteel, Sies, 2001; Lin, Shiau, 2005; Liu *et al*., 2010) and reduced host defence function (Liu *et al*., 2010; Sweetman *et al*., 2010; Wang *et al*., 2013). However, the deficient or toxic threshold of Se in fish considerably varies, depending on protein ingredients, Se sources and different species. The deficiency and toxicity of dietary Se are presented in Table 1 & 2.

Table 1. Effects of Se deficiency in fish

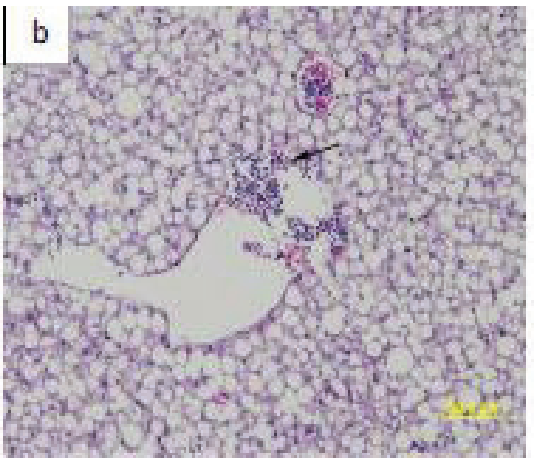
Species	Dietary Se (mg/kg)	Fish size (g)	Exposure period (weeks)	Signs of Se deficiency	References
Yellowtail kingfish *Seriola lalandi*	2.31	19.5	10	Reduced growth, feed intake and GPx activity	Le, Fotedar (2014a)
Cobia *Rachycentron canadum*	0.20	6.27	10	High mortality, reduced growth rate, feed efficiency and GPx activity	Liu *et al.* (2010)
Cobia	1.15	13.6	8	Reduced growth, feed utilisation	Pham *et al.* (2018)
Grouper *Epinephelus malabaricus*	0.21	12.2	8	Growth and feed depression, reduced GPx activity	Lin, Shiau (2005)
Grouper *Epinephelus malabaricus*	0.17	24.4	8	Reduced feed efficiency,	Lin (2014)

The interrelationship between dietary Se and histopathological alterations has been evidenced in fish, mainly due to the excessive Se concentrations in diets. However, the effects are variable, depending on different tissues, exposed Se concentrations and the species. Juvenile sacramento splittail *Pogonichthys macrolepidotus* exposed to 6.6 mg/kg Se diet for 9 months resulted in severe glycogen depletion and moderate fatty vacuolar degeneration in the liver tissues, whereas moderate eosinophilic protein droplets, mild fatty vacuolation and glycogen depletion were observed in liver tissues of fish fed 26.04 mg/kg Se diet for 5

months (Teh *et al*., 2004). The cell necrosis of hepatocytes (Figure 1) can be explained by the gradual deterioration in synthesis of new structural and metabolic component of the cell to restore the damages caused by toxic effects of Se, resulting in cell death (Teh *et al*., 2004). Besides, glycogen depletion induced by increasing glycogenolysis may also cause single cell necrosis and macrophage aggregates in the liver. The lipid vacuolar degenerations in livers may be results of the changing in protein turnover and lipid metabolism caused by Se toxicity, consequently, resulting in incapacitation of liver in metabolism and excretion of biochemicals (Teh *et al*., 2004).



Hepatocyte atrophy in livers of yellowtail kingfish fed 20.87 mg/kg Se diet (Le, Fotedar, 2014a)



Cobia fed the diet containing 3.14 mg/kg Se showed necrotic hepatocytes (arrow) (Pham et al., 2018)

Figure 1. Histopathological lesions in liver tissues of fish fed high dietary Se levels

However, the deficient and toxic concentrations of dietary Se have been a controversial topic for many years. Pham *et al.* (2018) proposed that cobia fed diet containing 1.15 mg/kg Se showed reduced growth and feed utilisation as signs of Se deficiency, whereas, the fish fed dietary Se of 3.14 mg/kg caused histopathological alternations in livers and reduction in growth rate as well as feed efficiency. The deficient Se signs were observed in juvenile grouper fed diets containing 0.17 mg/kg Se, while dietary Se level of 1.52 mg/kg could be toxic for this species (Lin, 2014). Whereas, Le, Fotedar (2014a) revealed that yellowtail kingfish fed dietary Se up to 15.43 mg/kg did not show any toxic effects, and suggested that the Se threshold level for this species is between 15.43 and 20.87 mg/kg. This could be attributed to their capacity in regulation Se through excretion to maintain Se levels below toxic concentrations, as seen in cutthroat trout *Oncorhynchus clarki bouvieri* (Hardy *et al*., 2010)

The erroneous replacement of Se for sulphur during protein synthesis could be a reason for the toxic effects of Se (Janz *et al*., 2010). In excessive Se supply, the triselenium linkage (Se-Se-Se) or a selenotrisulphide linkage (S-Se-S), instead of disulphide S-S linkages are formed which have key roles for the normal tertiary structure of protein molecules, resulting in the dysfunction of proteins (Maier, Knight, 1994). However, in the amino acid structure, the terminal methyl group can protect Se in SeMet form (Egerer-Sieber *et al*., 2006; Mechaly *et al*., 2000), whereas the selenocysteinyl-tRNA controls the incorporation of SeCys into proteins at the ribosomal level, consequently, the Se required for structure or function of protein is specifically incorporated in the polypeptide via the mRNA sequence. Thus, both SeMet

Table 2. Toxic levels of Se in fish

Species	Dietary Se and source (mg/kg)	Fish size (g)	Feeding period (weeks)	Signs of Se toxicity	References
White sturgeon *Acipenser transmontanus*	41.7	29.8	8	Reduction in growth and feed intake, histological damage in liver.	Tashjian *et al.* (2006)
Black seabream *Acathopagrus schlegeli*	12.3 Selenite	7.0	15	Reduced growth, feed utilisation. Increased histological damage in tissues	Lee *et al.* (2008)
Olive flounder *Paralichthys olivaceus*	7.38 SeMet	5.0	10	Reduction in growth and survival, histological lesions in liver tissues.	Lee *et al.* (2010)
Yellowtail kingfish *Seriola lalandi*	20.87 SeMet	19.5	10	Reduced growth and damage in liver and spleen tissues	Le, Fotedar (2014a)
Grouper *Epinephelus malabaricus*	1.52 Selenite	24.4	8	Growth and feed efficiency depression	Lin (2014)
Grouper *Epinephelus malabaricus*	1.49 SeMet	24.4	8	Reduced feed efficiency,	Lin (2014)
Cobia *Rachycentron cannadum*	Se-yeast	3.14	8	Reduced growth, feed efficiency, damage in liver	Pham *et al.* (2018)

and SeCys may not cause the dysfunctional proteins (Janz *et al*., 2010).

2. Dietary Se requirements in marine fish species

As important roles of Se in aquatic animal, dietary Se requirements have been quantified for grouper (Lin, 2014; Lin, Shiau, 2005), black seabream Acathopagrus schlegeli (Lee *et al*., 2008), cobia (Liu *et al*., 2010; Pham *et al*., 2018) and yellowtail kingfish (Le, Fotedar, 2013). However, these studies have provided varied results, probably due to the differences in Se sources and its bioavailability, protein ingredients, Se concentrations in rearing water as well as different growth rates among different fish species (Table 3).

In nature, selenite and selenate are inorganic forms, while organic Se forms comprise selenomethionine, selenium-methylselenomethionine (SeMet), selenocystine and selenocysteine (SeCys), which result in different pathways on absorption and metabolism in animal (Burk, 1976). Fish fed dietary Se in organic forms such as SeMet, SeCys and/or Se-yeast resulted in higher growth rate than those fed inorganic Se forms,

Table 3. Dietary Se Se requirements quantified for fish using different diet formulations

Species	Se source	Protein source	Optimum Se (mg/kg)	References
Black seabream *Acathopagrus schlegeli*	Selenite	Casein	0.21	Lee *et al.* (2008)
Grouper *Epinephelus malabaricus*	Se-Met	Casein	0.70	Lin, Shiau (2005)
Grouper *Epinephelus malabaricus*	Selenite	Casein	0.90	Lin (2014)
Grouper *Epinephelus malabaricus*	Se-Met	Casein	0.98	Lin (2014)
Cobia *Rachycentron canadum*	Se-Met	Casein	0.79 - 0.81	Liu *et al.* (2010)
Cobia	Se-yeast	Fishmeal	2.32	Pham *et al.* (2018)
Hybrid striped bass *Morone chrysops* × *M. saxatilis*	Selenite	Fishmeal	1.81	Cotter *et al.* (2008)
Hybrid striped bass *Morone chrysops* × *M. saxatilis*	Se-yeast	Fishmeal	1.61	Cotter *et al.* (2008)
Yellowtail kingfish *Seriola lalandi*	Se-yeast	Fishmeal	4.91 – 15.43	Le, Fotedar (2014a)
Yellowtail kingfish *Seriola lalandi*	Se-yeast	CD diet	5.56	Le, Fotedar (2013)

as reported in juvenile yellowtail kingfish (Le, Fotedar, 2014b) and grouper (Lin, 2014). This could be due to higher bioavailability of Se in organic form than inorganic compounds. Le, Fotedar (2014b) also demonstrated a higher muscle Se accumulations in yellowtail kingfish fed Se-yeast and SeMet than those fed inorganic Se. The reason for this difference is probably due to the different absorption and digestion pathways for Se. In animal, SeMet is metabolized following the methionine pathways, where it is readily assimilated into proteins and then accumulated in liver and muscle tissues (Terry, Diamond, 2012; Yeh *et al*., 1997), wherein selenite is converted to selenide before binding with albumin or hemoglobin and transported to liver for further processes (Haratake *et al*., 2008).

Another possibility for this observed variability in results might be the inconsistency in the diet formulation among the studies. Previous studies have used casein as a sole protein source in the purified or semi-purified diets to quantify optimum Se requirements

for aquatic species (Lee *et al*., 2008; Lin, Shiau, 2005; Liu *et al*., 2010). However, in a commercial farming environment, fishmeal rather than casein, is generally used as a major protein source in commercial feeds (Gatlin *et al*., 2007), though, Watanabe *et al*. (1997) stated that the Se concentration in fishmeal could provide adequate Se to meet Se demands of fishes. However, due to a significantly lessened Se uptake than from selenomethionine (SeMet) or Se-yeast (Bell, Cowey, 1989; Le, Fotedar, 2014b; Watanabe *et al*., 1997), fishmeal or plant-based diets may require additional dietary Se to meet the nutritional requirements of the species (Abdel-Tawwab *et al*., 2007; Le, Fotedar, 2013). For example, the dietary Se requirements estimated for juvenile cobia fed casein-protein based diet was 0.79 - 0.81 mg/kg (Liu *et al*., 2010), whereas cobia fed fishmeal-protein based diet required 2.32 mg/kg Se to optimise their growth performance and health status (Pham *et al*., 2018). The incorporation of plant-derived ingredients in aqua-feeds also puts increasing pressures on the dietary Se requirement due to its lessened concentrations in plant meals (Antony Jesu Prabhu *et al*., 2016; Welker *et al*., 2016). Barramundi *Lates calcarifer* fed either lupin kernel meal or soybean meal resulted in the growth and feed efficiency reductions, reduced GPx activity as well as histopathological damages in livers, corresponded with decreasing dietary Se level from 3.11 and 3.15 mg/kg in the fishmeal-based diet to 1.58 and 1.53 mg/kg in lupin-based diet and soybean-based diet, respectively (Ilham *et al*., 2016a; Ilham *et al*., 2016b). Interestingly, barramundi fed plant-based diet with supplemental Se showed improved growth, physiological and histological performances, as were those in fishmeal diets (Ilham *et al*., 2016a; Ilham *et al*., 2016b). Thus, the optimised dietary mineral requirements for fishes fed purified or semi-purified diets may not be met when formulated diets are used, as shown in barramundi and cobia.

The interaction between Se and other minerals such as copper, sulphur, mercury (Watanabe *et al*., 1997) and vitamin E (Le *et al*., 2014a; Lin, Shiau, 2009) may also alter the bioavailability of Se for fishes. The effectiveness of Se is through GPx activity, whereas vitamin E is a part of membrane antioxidant, thus the interaction of these nutrients is beneficial in protecting biological membranes against lipid oxidation (Watanabe *et al*., 1997). The peroxides formation can improve the functions of vitamin E, whereas Se is responsible for peroxide degradation, thus the dietary Se need in fish may vary, depending on the concentration of dietary vitamin E (Watanabe *et al*., 1997), as reported in grouper, where the dietary Se requirement was reduced from 1.6 to 0.4 mg/kg when dietary vitamin E increased from 50 to 200 mg/kg (Lin, Shiau, 2009).

Dietary Se requirement is also species dependant, but no research has explained the reasons behind species-specificity. Although, fishmeal-based diets can provide adequate amounts of Se to meet nutritional requirements in some fish (Watanabe *et al*., 1997), dietary Se supplementation in commercial or low-protein fishmeal diets is necessary to enhance growth, feed utilisation and physiological performances, as in yellowtail kingfish (Le, Fotedar, 2013; 2014a) and barramundi (Ilham *et al*., 2016a). Le, Fotedar (2013) and Liu *et al*. (2010) described higher Se requirements in yellowtail kingfish and cobia due to their higher growth rates. The higher metabolic rates associated with faster-growing fish require sufficient energy to maximize their growth potential (DeVries, Eastman, 1981), resulting in a need to uptake more nutrients, including Se to meet their nutritional requirements.

The effects of Se deficiency, toxicity and its requirements have been evaluated for some marine fish species with varied results, probably due to the bioavailability in different Se forms, Se concentration in rearing water, ingredient composition in the diet as well as the interactions between Se with other nutrients, which need to be concerned in evaluating dietary Se or other mineral requirements. Moreover,

recent studies have indicated that dietary Se requirements in fish evaluated using purified or semi-purified diets could not meet their needs when formulated diets are used. Besides, the changes in dietary formulations recently have resulted in alteration of ingredients fed to fish. The dietary Se requirements may need to be re-investigated due to changeability in the availability and bioavailability of Se in various protein sources.

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