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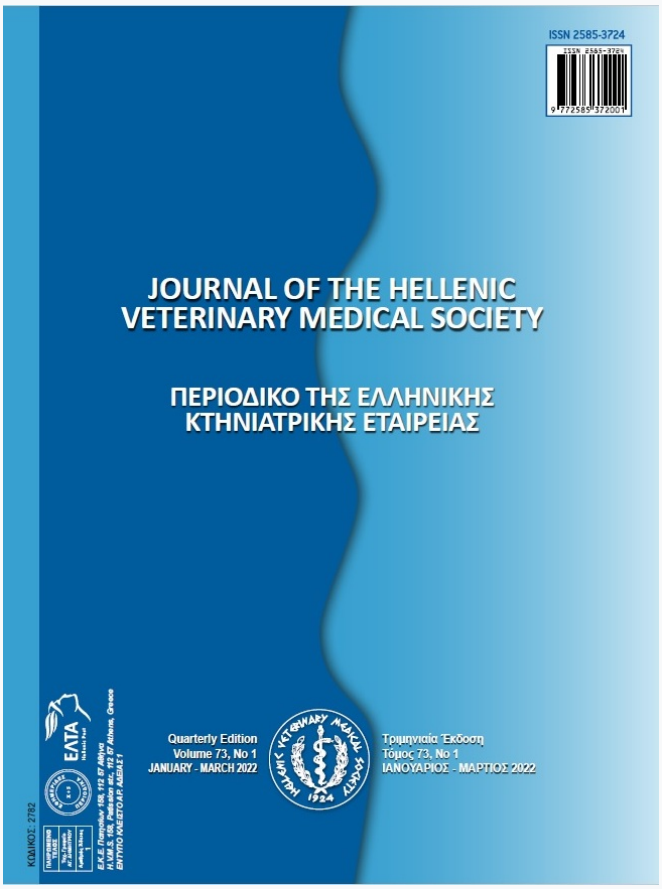

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Review article
Ανασκόπηση

A mini-review of toxicokinetics and toxicity of heavy metals in marine and freshwater fish

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ABSTRACT: The aquatic environment continues to be polluted by anthropogenic activities that cause heavy metal contamination of fish.These trace metal contaminants are present in abundance in the aquatic environment because their inputs also originate from several natural processes. In addition, they are bioaccumulative, persistent and non-biodegradable over time.Therefore the present mini-review aims to assess the bio-kinetics and known effects of the heavy metals and their toxicity in fish. Among the most toxic metals are arsenic (As), cadmium (Cd), lead (Pb) and mercury (Hg), and they have been the primary focus of many aquatic ecotoxicological studies in recent years. According to the previous studies analyzed; heavy metals bioaccumulate in the body of fish, whose kinetic activity depends on the metal and also varies from one fish species to another, and can cause irregular and sometimes devastating effects in different organs and systems of the body, acute or chronic, depending on the duration of exposure and the dose of metal assimilated through water or food. Metal uptake can affect all life stages of fish, and these effects are a function of the concentration of the metal in the surrounding environment, its chemical form and also the type of the water in which it lives; fresh or marine.

Keywords: Fish, Heavy metals, Bio-kinetics, Bioaccumulation, Toxicity

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INTRODUCTION

Fish consumption has increased in recent years because it is recognized as an important part of a balanced human diet containing high levels of many essential nutrients that are not present in other foods such as proteins of high biological value, vitamins (A, D, E, K and water - soluble vitamin B and C), iodine, selenium and calcium (Kara et al., 2020; Mehouel et al., 2019). Beneficial polyunsaturated fatty acids (omega-3 fatty acids) such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are found in large quantities in fish tissue. These polyunsaturated fatty acids have the ability to both prevent and cure certain diseases such as cancer, heart disease, rheumatoid arthritis and inflammation (Ayanda et al., 2019). For this reason, most European dietary guidelines recommend a minimum of two servings of fish per week to ensure the supply of essential nutrients (EFSA, 2014). However, many natural and anthropogenic activities pollute the environment with various chemical contaminants such as heavy metals and metalloids that accumulate in aquatic organisms, especially fish (Micheline et al., 2019).

Heavy metals are important components of a wide range of contaminants in the aquatic environment. This is due to their toxicity, accumulation and ability of some to biomagnify throughout the food chain (Ayanda et al., 2019). Lead, cadmium, arsenic, and mercury are the main non-essential elements that contribute to risks to human health through food consumption and especially in the case of drinking water for arsenic. And they are not required for the human body and their toxic effects have been recorded at extremely low concentrations; hence they are of primary concern on all lists of toxic substances (Ince et al., 2021; Ooi et al., 2015; Chahid et al., 2013).Hence the importance of monitoring their concentrations in fish and comparing them to international regulatory limits regulating the presence of these contaminants in fish to protect consumer health (ANZFSC, 2011; EU, 2006).

Exposure to metals can damage several organs in humans, even at low levels of exposure. Mercury can accumulate in the brain, the intestines, kidneys, liver and placenta and cause many dysfonctions and cancer. Prolonged exposure to cadmium is toxic to various tissues, including the kidneys, liver, bones, the central and peripheral nervous system, cardiovascular system, immune system and reproductive system whichcause irreversible damage and different types of cancer. Exposure to low doses of lead has been associated with neurological, immunological, cardiovascular, renal, digestive, reproductive and developmental effects. Exposure to arsenic causes a variety of complications in organ systems, *e.g.*the integumentary, nervous, respiratory, cardiovascular, hematopoietic, immune, nervous, endocrine, hepatic, renal and reproductive systems (Genchi et al., 2020; Tamele et al., 2020; Al-Saleh and Abduljabbar, 2017).

The aim of this global review is to investigate the most critical aspects of arsenic, cadmium, lead and mercury contamination of fish and examine their toxicokinetics and toxic effects based on experimental works.

HEAVY METALS

Arsenic in fish

Arsenic is a metalloid widespreadin the environment. Its presence in aquatic waters is due to anthropogenic sources such as industrial effluents, and to natural sources which are essentially volcanic eruptions, fluvial contributions and erosion of rocks. This element causes toxic effects in fish and other aquatic organisms via oxidative stress (Ince et al., 2018; Arslan-Acaroz et al., 2017; Kumari et al., 2017).

The concentration of arsenic is generally very high (1-10 μg/g) in marine fish (Zhang et al., 2016).Arsenite (As^{3+}) and arsenate (As^{5+}) are the inorganic forms, whereas monomethyl arsenic acid, dimethyl arsenic acid, arsenobetaine, arsenocholine and different arsenolipids and arsenosugars are the important organic forms (Jabeen and Javed, 2011). In fish arsenobetaine is the most dominant form and contributes 95% of the total arsenic which is non-toxic, while the more toxic inorganic forms contribute only 1-4% (Avigliano et al., 2020; ; Kollander et al., 2019; Amlund et al., 2006).

Toxicokinetics

Fish absorb inorganic arsenic via water and food whereas organic arsenic (arsenobetaine) is only accumulated from food (Hong et al., 2014). Arsenobetaine accumulates in the major organs (liver, kidney) and at a higher rate in muscle tissue (Amlund et al., 2006). In contrast, inorganic arsenic accumulates more in the liver and stomach and at low concentrations in the gills and muscle tissue (Ferreira et al., 2019). The principal routes of excretion are through the kidney (urine), liver (bile), gills and skin (Amlund et al., 2006; Özcan et al., 2006).

Toxicity

The toxicity of inorganic arsenic (As (III) and As (V)) is more toxic than the organic forms (Avigliano et al., 2020; Kim et al., 2018). Acute exposure to arsenic is usually generally fatal to most fish, while the chronic exposure is sublethal and can result in a multitude of molecular events (Chen et al., 2019; Kumar et al., 2019). Arsenic in aquatic organisms is highly dependent on the chemical form in which it occurs. Arsenic modulates antioxidant enzymes such as glutathione reductase (GR) and glutathione S-transferases (GST), it also leads to lipid peroxidation and loss of DNA integrity by inducing the generation of reactive oxygen species and by depressing the functions of the antioxidant defense system (Ince et al., 2018; Arslan-Acaroz et al., 2017; Ventura-Lima et al., 2009). The reduction of AsV to As III may allow the fixation of arsenic in the body through the interaction with thiol groups (Ince et al., 2018; Arslan-Acaroz et al., 2017). For higher trophic level species, sensitivity to arsenic is much less critical, and concentrations in the range of 100 to 500 µg/L are necessary to observe the first toxic effects on macro-algae, shrimp or fish (IFREMER, 1993). Toxicity manifests itself by affecting different systems and functions such as growth, reproduction, ion regulation, smoltification, gene expression, immune function, enzyme activities and histopathology of fish (Kumari et al., 2017).

Cadmium in fish

Cd is a non-essential metal widely present in the aquatic environment as a result of various industrial and mining activities (Renieri et al., 2017). It can be toxic to fish, even in trace amounts, of which free ions (Cd^{+2}) are the most bioavailable and toxic and are found either in free form or in a variety of complexes with suspended particles and in sediments (Renieri et al., 2017; Kovarova and Svobodova, 2009). Hence Cd is available for bioaccumulation by fish via a number of dissolved Cd and food ingestion pathways (Renieri et al., 2017; Kovarova and Svobodova, 2009).

Toxicokinetics

Metal ions dissolved in water are absorbed through the gills and other permeable surfaces of the body, while metals bound to solid particles are ingested and then detached from their carrier particles in the digestive system and absorbed through the intestinal epithelium (Kovarova and Svobodova, 2009). Cadmium is transported in the blood, where it is distributed mainly in the liver and kidneys, which are the main organs of accumulation during acute and chronic exposure, and to a lesser extent in the visceral mass (Ferain et al., 2018; Verge, 2006). The cadmium content in muscle tissue is generally very low (Bremner, 2002). In the cytoplasm uptake is supported by metallothioneins, which are proteins rich in sulfur amino acids and poor in aromatic amino acids, and they facilitate a stable bonding with cadmium ions (Cd^{+2}) (Verge, 2006). The elimination of cadmium is low and takes place mainly through the urine. This renal elimination seems to depend only on the intensity of exposure, in fact, it is independent of metabolic activity or the size of the individual (Le Croizier et al., 2019; Verge, 2006).

Toxicity

Even at low ambient concentrations, cadmium can accumulate in fish causing several toxic effects, particularly in the early life stages (Safari, 2015; Maunder et al., 2011). The acute toxicity of cadmium generally affects ionic homeostasis, in particular that of calcium, by concurrence on absorption sites (Dave and Kwong, 2020; Olsvik et al., 2016). Chronic toxicity can affect a wide variety of physiological processes and functions (Olsvik et al., 2016). Cadmium can indirectly generate oxidative stress all and free radicals that may be caused by overproduction of reactive oxygen species (ROS) or by depletion of cellular antioxidant levels; furthermore it can also lead to DNA damage and blocking of DNA repair (Zhang and Reynolds, 2019; Malarvizhi et al., 2018). In addition, cadmium is responsible for endocrine and ionoregulatory disruption, histopathology and depression of the immune system, all of which can affect the growth, reproduction and survival of fish (Le Croizier et al., 2019; Sierra-Marquez et al., 2019).

Lead in fish

Toxicokinetics

Ionic lead (Pb^{+2}) enters the body of fish through the gills, the surface of the body and also by direct ingestion. Absorption from contaminated water is more important than absorption from food (Macirella et al., 2019; Bibi and Ahmed, 2010). Bioaccumulation is well documented in skin, gills, stomach, muscles, intestines, liver, brain, kidney and gonads, however the main target organs are liver, kidney and muscles (Bibi and Ahmed, 2010).In contrast to inorganic lead compounds, tetra-alkyl lead is readily absorbed by fish and rapidly eliminated after the end of exposure (Casas and Sordo, 2011).

Toxicity

Exposure to lead causes a wide range of toxic effects on the physiological, behavioral and biochemical functions of fish. It also damages the central and peripheral nervous system, the immune, hematopoietic, and cardiovascular systems as well as organs such as the liver and kidneys (Lee et al., 2019).Lead also leads to reproductive disorders, growth and developmental problems (Lee et al., 2019; Kim and Kang, 2015). Exposure to this metal can be lethal, even at low concentrations, due to efficient bioaccumulation (Lee et al., 2019).

Lead is one of the most toxic metals in the aquatic environment because of its ability to mimic biologically important metals, mainly calcium, iron and zinc (Company et al., 2011). It can enter the cell because of its similarity to calcium by using calcium's transport pathways (Amadob et al., 2012). It can also reduce the unidirectional influx of sodium (Na^+), frequently correlating with the inhibition of Na^+/K^+ATPase, an enzyme essential for the maintenance of cell volume (Amadob et al., 2012). Lead can interact with a variety of cellular lipids by changing the composition of the cell membrane, a process which results in disruptions in membrane integrity, permeability and function thereby increasing the sensitivity to lipid peroxidation (Taylor and Maher, 2012). Lead accumulation can also cause the production of reactive oxygen species (ROS) which leads to depletion of cellular antioxidant defense systems, destabilization of cell membranes and DNA damage. Furthermore its accumulation in mitochondria and other organelles can cause serious disturbances in the energy balance of tissues and eventually cell death (Taylor and Maher, 2012).

Mercury in fish

Mercuryis a highly toxic chemical contaminant (Custódio et al., 2020). Its presence in the environment comes from both natural and anthropogenic sources. It can be released into the aquatic environment in its inorganic form where it can undergo various biochemical processes (oxidation, reduction, methylation and demethylation) which result in producing the more toxic methyl mercury species (Donadt et al., 2021; Kim et al., 2016). Elemental mercury, inorganic mercury and organic mercury are the three main forms of this metal found in the aquatic environment (Vasanthi et al., 2019). The total mercury content of fish may consist of a combination of its organic and inorganic forms, with methylmercury being the most toxic and abundant organic form. The latter is obtained by methylation of inorganic mercury via aquatic bacteria which makes it more bioaccumulatable in aquatic food chains, accounting for 75-100% of the total mercury in fish, and with the potential for biomagnification in certain fish species especially large predatory fish (Sadeghi et al., 2018; Bosch et al., 2016; Kim et al., 2016).

Toxicokinetics

The different forms of mercury that come into contact with aquatic organisms originate from the surrounding water, sediment and food (Cambier, 2009). Inorganic mercury crosses biological barriers less easily than methylmercury; it has an absorption rate through the intestinal barrier on the order of 10% when contamination occurs via the trophic route (Cambier, 2009). However, the intestinal barrier as well as the gill epithelium are highly permeable to methylmercury (Cambier, 2009). Methylmercury is absorbed and accumulated more than other forms, with 99% of the bioaccumulated mercury in this methylated form (methylmercury) (Bridges and Zalups, 2017). After contamination via the direct route (water), gills and muscle show the highest concentrations (Dominique, 2006) ; however, after trophic contamination, bioaccumulation in the gills is low, while the liver, brain and muscle tissue show high concentrations (Dominique, 2006). Inorganic mercury is mainly found in the liver and kidneys from where it is excreted (Dominique, 2006). Although aquatic organisms have mechanisms for intestinal and renal demethylation and excretion, the loss rate of methylmercury remains low compared to the entry velocity, thereby bioaccumulating over a lifetime of certain species, particularly in top trophic level predators (Amiard, 2011).

Toxicity

Exposure to mercury can cause a variety of adverse effects in fish at the physiological, histological, biochemical, enzymatic and genetic levels (Morcillo et al., 2017). Induced toxicity is influenced by various factors such as species, age, environmental conditions, concentration and duration of exposure (Morcillo et al., 2017). The chemical form of mercury plays an important role in its toxicity, for example, the methylated form is 50 to 100 times more toxic than the initial inorganic form of mercury (Meyer et al., 2004).

The acute toxicity of mercury following 24 h of exposure to 0.73 ppm leads to erratic swimming, ab-

normal posture, sluggishness, imbalance in posture, increase in surface activity, opercular movement, gradual loss of equilibrium and spreading of excess of mucus all over the surface of the body, and mortalities were also observed (Vasanthi et al., 2019). Chronic exposure to mercury especially affects the embryonic and larval stages which are the most sensitive periods of growth. By affecting the development of organs and also the metabolic activity of fish, it can also leads to slow development, morphological abnormality, dysfunction and eventually death. In general, this metal causes neurological, hepatological and reproductive damages that are always worrying even at low concentrations (*e.g.*0.02 ppm) (Zheng et al., 2019).

Summary

Given the large number of experimental studies which have addressed the problem of heavy metal contamination in both marine and freshwater fish, we have summarized in Table 1 the basic toxicokinetic data and ancillary information that has been produced from toxicokinetic experiments following exposures to As, Cd, Pb and Hg. The findings highlight the exposure times, tissue distribution of the metal, target organs and elimination routes in both juvenile and adult marine and freshwater fish.

With respect to aspects of metal toxicity, in Table 2 the toxic effects of the four contaminant metals are summarized for similar types of teleost fish following experiments using a wide range of different exposure doses of As, Cd, Pb and Hg. The results underscore the very different effects which arise from acute and chronic exposures.

CONCLUSIONS

In this overview we have examined the toxicokinetics and distribution and potential effects of four of the most toxic heavy metals (As, Cd, Pb, and Hg) in fish and, based on the results of previous experimental studies, the degree of toxicity of these metals is ordered as follows : As<Pb<Cd<Hg. Each metal has a specific affinity for certain organs and tissues.Previous studies on the toxicokinetics of heavy metals in fish have shown differences even for the same metal, and within the same species of fish variations are found according to the stage of development of the fish and the aquatic environment in which it lives, i.e. marine or freshwater. Their toxicity also depends on several factors; *e.g.* for a given metal certain chemical forms are more toxic than others and for fish, toxicity depend mainly on the exposure dose which can lead to either acute or chronic effects.Toxicity also depends on the stage of development of the fish and the physico-chemistry of the water in which it lives. It would therefore be of interest to conduct further detailed studies on both the toxicokinetics and toxicity of these metals for the most abundant physico-chemical forms of the metals and for the most toxic to freshwater and marine species, including investigating these aspects at all stages of development from hatching to adulthood. It would also be important to conduct toxicokinetics and toxicity studies of these metals based on the route of dietary or water exposure and especially to evaluate the degree of toxicity of these four metals for the same species of fish after acute and chronic exposure. Such information will be vital in improving and refining our assessments of the potential for biomagnification of Hg in various species of fish.

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CONFLICT OF INTEREST

None declared by the authors.

Table 1. Summary of toxicokinetic studies of heavy metals (As, Cd, Pb and Hg) in fish

Metals	Species	Develop-mental stage	Habitat type	Time of exposition	Distribution in Tissues	Target organ	Elimination	References
As	Tilapia (*Oreochromis mossambicus*)	Adult	Freshwater	7 days	Gill, liver, muscle, intestine, stomach, whole body	Stomach	Intestine	(Liao et al., 2004)
	Tilapia (*Oreochromis mossambicus*)	Adult	Freshwater	7 days	Gill, liver, alimentary canal, carcass	Liver, Aliment-ary canal	Liver Alimentary canal	(Tsai and Liao, 2005)
	Tilapia (*Oreochromis niloticus*)	Juvenile	Freshwater	7days	Gill, liver, stomach, muscle	Stomach, liver	Liver, stomach	(Ferreira et al., 2019)
Cd	Zebrafish (*Danio rerio*)	Adult	Freshwater	3 days	Gill, liver, intestine, gonad, carcass, brain	Liver	-	(Zhang et al., 2019)
	Rainbow trout (*Oncorhynchus mykiss)*	Adult	Freshwater	100 days	Gill, liver, kidney, Whole body	Kidney	-	(McGeer et al., 2019)
	Olive flounder (*Paralichthys olivaceus*)	Juvenile	Seawater	50 days	Gill, intestine, kidney, liver, muscle	Intestine	Intestine	(Kim et al., 2004)
Pb	Zebrafish (*Danio rerio*)	Adult	Freshwater	3days	Gill, liver, intestine, gonad, carcass, brain,	Gill	-	(Zhang et al., 2019)
	Prussian carp (*Carassius gibelio*)	Adult	Freshwater	24 months	Muscles, hepatopancreatic gland, kidney, intestine, gill.	Kidney	Kidney	(Łuszczek-Trojnar et al., 2013)
	Tilapia (*Coptodon zillii*)	Adult	Freshwater	10 days	Liver, gill, brain, muscle tissues	Gill	Gill and liver	(Kalay and Canli, 2000)
MeHg	White sturgeon (*Acipenser transmontanus*)	Juvenile	Freshwater	2 days	Gastro-intestinal tract, kidney, spleen, gill, heart, liver, brain, white muscle	Gastro-intestinal	Kidney	(Huang et al., 2012)
	Sheepshead minnows (*Cyprinodon variegatus*)	Adult	Freshwater	35 days	Intestine, blood, liver, gill, rest of body	Intestine	Kidney	(Leaner and Mason, 2002)
	Wild rabbitfish (*Siganus canaliculatus*)	Adult	Seawater	21 days	Gill, liver, intestine, muscle and whole body	Muscle	Intestine	(Peng et al., 2016)
Hg (II)	Wild rabbitfish (*Siganus canaliculatus*)	Adult	Seawater	21 days	Gill, liver, intestine, muscle and whole body	Gill, intestine	Gill	(Peng et al., 2016)
	Sea bream (*Diplodus sargus*)	Adult	Seawater	14 days	gills, eye wall, lens, blood, liver, brain and bile	Gill	gills, blood and liver	(Pereira et al., 2015)
	Flounder (*Platichthys Flesus*)	Adult	Seawater	4 months	Liver, kidney, muscle	Liver, kidney	Fillet	(Riisgård and Famme, 1988)

Table 2. Summary of toxic effects of heavy metals in fish experimentally exposed to selected concentrations of As, Cd, Pb and Hg

Metals	Fish species	Develop-mental Stage	Habitat type	Exposure dose of metal	Toxic effect		
					Actue toxicity	Chronic toxicity	
As	Tilapia (*Oreochromis mossambicus*)	Adult	Freshwater	328.05 mg/L	Lethargy, mouth and operculum wide open, body slimy, mortality after a few minutes of exposure		(Ahmed et al., 2013)
	Teleost fish (*Channa punctatus*)	Adult	Freshwater	5 mg/L		Distortions in the cell organelles, DNAfragmentation, activity enzymatic inhibited, fish survived more than 100 days after exposure	(Das et al., 2012)
Cd	Red sea bream (*Pagrus major*)	Juvenile	Seawater	3mg/L	Cardiac edema, degenerated, hooked tails, fin lesions, spinal curvature with skeletal deformities, mortality also observed.		(Cao et al., 2009)
	Sole (*Solea senegalensis*)	Adult	Seawter	25µg/g		Alteration of the whole-body	(Le Croiziez et al., 2019)
Pb	Rainbow trout (*Salmo gairdneri*)	Juvenile and adult	Freshwater	0.20 g/L	Mortality after 5 days of exposure		(Davies et al., 1976)
	Rainbow trout (*Salmo gairdneri*)	Juvenile and adult	Freshwater	64µg/L		Black tails noted, fish exhibited spinal curvatures and eroded caudal fins, paralysis and atrophy of the flexed portion of the body, little interest for food observed one month after exposition,	(Davies et al., 1976)
Hg	Nile Tilapia (*Oreochromis niloticus*)	Adult	Freshwater	0.1453 mg/L	Mortality after 72h of exposure, external abnormality : namely pale gills, anemic eyes, whitish body color, internal lesions affecting the gills, liver, and hepatopancreas also observed		Suhendrayatna et al., 2019
	Salmon (*Salmo salar*)	Adult	Freshwater	0.10 mg/ kg		Diverse abnormalities observed in kidney, brain and liver in the 4 months of exposure	(Berntssen et al., 2003)

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