AIMS Environmental Science, 4(3): 386-402.
DOI: 10.3934/environsci.2017.3.386
Received: 14 December 2016
Accepted: 31 March 2017
Published: 10 April 2017

http://www.aimspress.com/journal/environmental

Review

Mercury and its toxic effects on fish

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Abstract: Mercury (Hg) and its derivative compounds have been parts of widespread pollutants of the aquatic environment. Since Hg is absorbed by fish and passed up the food chain to other fish-eating species, it does not only affect aquatic ecosystems but also humans through bioaccumulation. Thus, the knowledge of toxicological effects of Hg on fish has become one of the aims in research applied to fish aquaculture. Moreover, the use of alternative methods to animal testing has gained great interest in the field of Toxicology. This review addresses the systemic pathophysiology of individual organ systems associated with Hg poisoning on fish. Such data are extremely useful to the scientific community and public officials involved in health risk assessment and management of environmental contaminants as a guide to the best course of action to restore ecosystems and, in turn, to preserve human health.

Keywords: mercury; methylmercury; toxicity; oxidative stress; immunity; fish

1. Introduction

Mercury (Hg) is considered a devastating environmental pollutant, mainly after the environmental disaster at Minamata (Japan) and several other poisoning accidents due to the use of Hg pesticides in agriculture [1]. Hg exists as elemental form, inorganic (iHg) and organic Hg (primarily methylmercury, MeHg). In the environment, Hg is released from natural and anthropogenic sources [2]. iHg enters the air from mining ore deposits, burning coal and waste, or from manufacturing plants. It enters the water or soil from natural deposits, disposal of wastes, and the use of Hg containing fungicides. iHg is maintained in the upper sedimentary layers of water-beds and is methylated and thus transformed to the highly toxic species MeHg by sulphate-reducing bacteria.

Numerous toxicological studies have gained increasing interest in order to understand the impact of Hg on aquatic communities, which are particularly vulnerable. In this regard, fish have been used to assess pollution because they represent the most diverse group of vertebrates [3] and have genetic relatedness to the higher vertebrates including mammals. It is widely known that fish are a great source of Hg in our food and their accumulation could represent a serious risk for human beings [4]. Although fish have always been perceived as a healthy and nutritive food [5], the Environmental Protection Agency (EPA) has raised public concern as it claimed that the levels of Hg in certain fish species make them unsuitable or be restricted for children and pregnant women consumption [6]. Some data about the Hg concentration in common fish species are shown in Table 1. This data are worrying us if we consider that the projections show an increase in the demand for seafood products to year 2030.

Table 1. Mercury content in different fish. Values are presented as mean ± SD. Maximum allowable concentration in seafood is 1 ppm according to US Food and Drug Administration. Mercury levels in commercial fish and shellfish according to US Food and Drug Administration and US EPA Advisory EPA-823-F-04-009 (1999–2012).

Specie	Mercury content (ppm)	Safety
Anchovies	0.017 ± 0.015	Eco-good
Atlantic cod	0.095 ± 0.080	Eco-bad
Bass (saltwater, black, striped, rockfish)	0.167 ± 0.194	Eco-bad
Bass Chilean	0.354 ± 0.199	Eco-bad
Carp	0.140 ± 0.099	Eco-bad
Catfish	0.049 ± 0.084	Eco-good
Croaker Atlantic (Atlantic)	0.069 ± 0.049	Eco-good
Croaker White (Pacific)	0.287 ± 0.069	Eco-bad
Grouper (all species)	0.448 ± 0.287	Eco-bad
Mullet	0.05 ± 0.078	Eco-bad
Salmon, wild (Alaska)	0.014 ± 0.041	Eco-good
Sardines, Pacific (US)	0.016 ± 0.007	Eco-good
Shark	0.979 ± 0.626	Eco-bad
Swordfish	0.976 ± 0.510	Eco-bad
Tilapia	0.013 ± 0.023	Eco-good
Trout, rainbow (farmed, freshwater)	0.072 ± 0.143	Eco-good
Tuna species	0.415 ± 0.308	Eco-bad

In this regard, aquaculture is one of the most important food manufacturing industries in the coming decades trying to compensate the human consumption demand. Moreover, farmers have to know and control the impact of the environmental contaminants in the species produced for humans [7]. In this specific field, very little is known about the effects of Hg exposure in fish, and the comparison of any results is very difficult and sometimes contradictory because different investigators have used a variety of administration methods as well as concentrations of Hg. Moreover, the development of prominent trends in toxicity testing based on *in vitro* tests and especially *in vitro* mechanistic assays has gain considerable attention in recent years.

2. Toxicokinetics: absorption, distribution

In the aquatic environment, Hg speciation, uptake, bioavailability, and toxicity are dependent upon environmental parameters including hydrophobicity, pH, salinity, hardness (Ca^{2+} and Mg^{2+} concentration) and interaction of metals with biotic and abiotic ligands [8]. In teleost fish species, bioavailability of Hg depend not only on total chemical concentration in the environment but also on how readily the fish can absorb these different Hg forms at the gill, across the skin, and within the digestive tract and on how chemical speciation affects distribution throughout the organism [9]. Thus, the metal absorption and distribution occurs as follows: first, Hg crosses the epithelium; second, it incorporates into blood including binding to plasma proteins, transport via the systemic circulation or freely dissolved to various tissues; and finally, it is transported from blood into tissues. Gills, digestive system, and, to a lesser extent, the skin, are the major sites of metal uptake in fish [8].

Hg uptake can be passive or energy-dependent, depending on the Hg species [10]. Concretely, in plasma, MeHg binds reversibly to cysteine amino acid and therefore to sulphur-containing molecules such as glutathione (GSH). The cysteine-bound form is of particular interest because it is transported by an L-neutral amino acid transporter system into the cells of sensitive tissues such as brain [11]. In the gastrointestinal tract, ingested MeHg is efficiently absorbed and its distribution to the blood is complete within approximately 30 h, and the blood level accounts for about 7% of the ingested dose. The brain is the primary target site for MeHg and approximately 10% is retained in the brain with the remainder transported to the liver and kidney where it is excreted through bile and urine [12]. In rainbow trout (*Oncorhynchus mykiss*), however, 90% of whole-blood MeHg is bound to the beta-chain of hemoglobin in red blood cells [13]. In addition, MeHg readily binds to metallothioneins (MTs) and metalloproteins with cysteine residues displacing Zn^{2+} [10,14]. The primary mechanism of MeHg as well as its specificity has yet to be identified. MeHg-cysteine conjugates have shown increased cellular efflux, presumably due to the generation and involvement of glutathione.

Regarding its bioaccumulation, concentrations of MeHg are magnified within the food chain, reaching concentrations in fish 10,000- to 100,000-fold greater than in the surrounding water [2]. The primary target tissues for Hg are the central nervous system (CNS) [15] and the kidney, triggering loss of appetite, brain lesions, cataracts, abnormal motor coordination, and behavioural changes, alterations that lead to the fish to have impaired growth, reproduction, and development.

3. Systemic toxicological effects of mercury

3.1. Molecular mechanism of toxicity

Several studies have shown that Hg produce an imbalance between the reactive oxygen species (ROS) production and its clearance by the antioxidant system in the known oxidative stress response. Thus, in fish, it has been described the production of ROS after Hg exposure *in vivo* [16-21] or *in vitro* [22-26]. Indeed, Hg reacts with the thiol groups of GSH, which can induce GSH depletion and oxidative stress [19-21,27,28]. Thus, some studies have found alterations in the antioxidant system caused by Hg exposure including glutathione reductase (GR) and glutathione peroxidase (GPx) activities in zebra seabream (Diplodus cervinus) [29], modifications in superoxide dismutase (SOD), catalase (CAT), glutathione S-transferase (GST), and GPx activities in trahira species (Hoplias malabaricus) [30]. Very recently, MeHg exposure increased the ROS levels and decreased the

antioxidant potential of gilthead seabream (Sparus aurata) serum while increased the SOD, CAT and GR activities in the liver [18]. In addition, significant alterations in the expression of the antioxidant enzyme genes sod, cat, gst, gpx, and gr have been observed in the freshwater fish Yamú (Brycon amazonicus) after Hg exposure leading to oxidation of lipids and proteins [31]. In a set of studies conducted on wild golden grey mullet (Liza aurata) it has been demonstrated the depletion on reduced GSH, GPx, SOD and lipid peroxidation (LPO) and increment on total GSH, GST and CAT activities towards other metabolites indicating the potential of using metabolomics to determine and probe the Hg exposure and oxidative stress relations [19-21]. *In vitro* studies including fish cell lines [SAF-1, derived from gilthead seabream, and DLB-1, derived from European sea bass (Dicentrarchus labrax)] or primary fish cell cultures (leucocytes or erythrocytes) showed an increase in ROS levels after Hg exposure; however, an up- or down-regulation in the expression of some antioxidant genes (sod, cat, gr or prx) was observed [24-27,32-34].

MTs also play a protective role in response to Hg exposure. The mRNA expression of two *mt* genes was noted in the liver of common carp (*Cyprinus carpio*) from Hg contaminated river [35]. However, no significant correlations between total Hg content and MT levels were described in different fish tissues from a Hg contaminated area [36]. Thus, in *in vitro* studies, *mt* gene expression was enhanced after Hg exposure in SAF-1 [26] and DLB-1 [24] cell lines as well as in gilthead seabream or European sea bass peripheral blood leucocytes (PBLs) [33] and erythrocytes [34]; however, a strong down-regulation was observed in leucocytes derived from the head-kidney, the main hematopoietic tissue, from the same species [25,32]. Indeed, Hg bind easily to MTs [37,38] but an excess of metal could provoke a MT dysfunction leading to an increase of ROS levels as we have observed in some fish or fish cell lines before.

Furthermore, the ROS imbalance leads to cell death by apoptosis. Hg forms induce apoptosis by inhibiting mitochondrial function [39] and releasing cytochrome C from the mitochondria to the cytosol [40]. Moreover, p38 mitogen-activated protein kinase is activated by mercury resulting in apoptosis [41]. In addition, mitochondrial membrane permeability is regulated through a family of anti-apoptotic (Bcl-2, Bcl-xL, etc.) and pro-apoptotic (Bad, Bax, Bak, Bid, etc.) proto-oncogenes [42]. This cell death mechanism has been demonstrated in fish exposed to Hg [43-45] as well as in *in vitro* fish systems including cell lines [24,26] and primary cultures of head-kidney leucocytes [25,32], PBLs [33] and erythrocytes [34].

3.2. Immune system

Although the immunotoxicological effects of mercurial compounds have been well studied in mammals [46,47] far less is known concerning the effects in fish to date [7,48]. Moreover, due to the complexity and multifaceted of the immune system, recent articles show the difficulty to assess the immunotoxicological effects in fish and the challenge to select appropriate exposure and effect parameters out of the many immune parameters which could be measured [49]. Because of the immunotoxicological studies of Hg in fish have focused on almost exclusively on immunosuppressive effects, some aspects have been ignored. For instance, a range of scientific studies have attempted to investigate the role of Hg in mammalian autoimmunity [50] or hypersensibility [51,52].

MeHg exposure by dietary intake [53], injection [54] or waterborne [18] can trigger alterations of the fish immune system. Upon immune mediators, little is known about their regulation of

cytokines in fish. The freshwater fish snakehead (*Channa punctatus*) exposed to 0.3 mg/L $HgCl_2$ showed an up-regulation of pro-inflammatory cytokines such as tumour necrosis factor-α (*tnfα*) and interleukin-6 (*il6*) after 7 days of exposure [1]. *In vitro* models have shown a down-regulation of pro-inflammatory *il1b* gene expression after 2 or 24 h of MeHg exposure in gilthead seabream head-kidney leucocytes, while alterations were not observed in European sea bass leucocytes [25,32]. On the other hand, effects on soluble humoral factors of fish have been widely studied after Hg exposure. For example, lysozyme activity was enhanced in goldfish (*Carassius auratus*) [55] or rainbow trout [56] after exposure to different $HgCl_2$ concentrations but decreased in plaice (*Pleuronectes platessa*) [57]. Other humoral activities such as serum complement or peroxidase activities or total IgM levels were increased or impaired after MeHg exposure in diverse fish species [18,54,56]. Interestingly, waterborne MeHg significantly increased the immune responses in the gilthead seabream skin mucus including the microbicidal activity [18]. Upon the cellular innate immune response, MeHg increased the phagocytosis in gilthead seabream head-kidney leucocytes exposed *in vivo* by waterborne [18] and *in vitro* [25] whilst in European sea bass leucocytes the phagocyte functions (phagocytosis and respiratory burst) by *in vitro* exposure to Hg was reduced [22,32]. In addition, in the European sea bass leucocytes, *in vitro* treatment with $HgCl_2$ induced apoptosis in head-kidney macrophages as well as reduced the ROS production and the benefits of macrophage- activating factors (MAF) [22,58]. Thus, the presence of factors such as the serum levels of corticosteroids and catecholamines that do not operate *in vitro* could explain the differences observed between *in vitro* and *in vivo* studies [59]. However, the mechanisms by which metals alter the phagocyte functions are still poorly understood. Strikingly, few studies have dealt with the leucocyte death by Hg. Thus, an increase in the transcription of genes related to apoptosis was shown after MeHg exposure to gilthead seabream or European sea bass blood leucocytes (PBLs) [33]. However, Hg exposure promoted both apoptosis and necrosis cell death in gilthead seabream or European sea bass head-kidney leucocytes [25,32].

3.3. Respiratory and cardiovascular systems

Although exposure to some metals often disturbs normal metabolic processes in fish, including irritation of respiratory epithelium, changes in ventilation frequency, or inefficient oxygen delivery to tissues [60] considerably less is known regarding the effect of Hg on the respiratory system. Previous studies have shown that an exposure to dissolved Hg disrupts gill epithelium, potentially affecting gas exchange and permeability of cell membranes to cations [61,62]. Such disruptions may result in compensatory changes in ventilation frequency, increased energy demands, or altered gas exchange efficiency, possibly resulting in the increase in metabolic rate [63]. However, gill damage and a subsequent increase of metabolic rate did not occur in the mosquitofish (*Gambusia holbrooki*) fed with $HgCl_2$ probably due to the Hg accumulation via intestinal absorption from dietary sources [64]. More recently, $HgCl_2$ via food or diet decreases the plasticity of the cardiorespiratory responses reducing the survival chances of Yamú and trahira under hypoxic conditions frequently observed in theirs wild [65].

Upon histopathology studies, the gills is the organ to better study due to their function in the respiration process and since this organ is continuously and directly exposed to the external environment [62,66-70]. Moreover, a report shows an increase of the chloride cells (CCs) in the European sea bass gills after exposure to Hg [71], which is in concordance with another study using mosquitofish [62]. The CAT activity remained unchanged while GPx and GR activities showed a significant decrease in trahira gills after exposure to $HgCl_2$ [65]. In wild grey mullet from

Hg-contaminated areas, gill GPx and SOD activities were depleted while GST and CAT activities were increased indicating a massive GSH oxidation [20,21]. In *in vitro* conditions, gill cell suspensions exposed to $HgCl_2$ showed high rate of DNA breaks (single and double stranded) measured as the comet assay in common carp and rainbow trout [72,73].

Similarly, Hg accumulation in the heart is thought to contribute to cardiomyopathy. The mechanism by which Hg produces toxic effects on the cardiovascular system is not fully elucidated, but this mechanism is believed to involve an increase in oxidative stress [74]. In a recent study, trahira specimens exposed to $HgCl_2$ showed an anticipated bradycardia and lower heart rate probably due to damage in cardiac myocytes [65], which is in agreement with other studies in trahira [75,76] or in other tropical species [77].

3.4. Reproductive organs

Numerous studies suggest that the inhibitory effects of Hg on fish reproduction occur at multiple sites within the hypothalamic–pituitary–gonadal (HPG) axis [78]. Moreover, in most cases, studies have been carrying out in *in vivo* conditions due to the missing information of hormone release in *in vitro* assays. Thus, recent studies have reported a significantly lesser transcripts of gonadotropin-releasing hormone (GnRH) (*gnrh2* and *gnrh3*) in the brain of both male and female zebrafish (*Danio rerio*) after Hg exposure, suggesting that Hg could modulate hypothalamic production of GnRHs in fish and consequently disrupted production of gonadotropin hormones such as follicle stimulating hormone (FSH) and luteinizing hormone (LH) [81,82]. Furthermore, an alteration in expression of genes commonly associated with endocrine disruption and a decrease in the production of vitellogenin as a result of dietary MeHg exposure in fathead minnows (*Pimephales promelas*) was observed [83]. Similarly, by using cDNA microarray analysis in the cutthroat trout (*Salmo clarkii*), expression levels of *gnrh1* and *gnrh2* were down-regulated in the liver from those specimens containing high Hg levels compared to those with low Hg concentrations [84]. Moreover, down regulation of genes involved in early stages of the spermatogenesis (*fshβ, fshr, lhr* or *lhβ*) or genes involved in the synthesis of steroid hormones (*cyp17* and *cyp11b*) were observed in male zebrafish testis after exposure to 30 µg Hg/L [81] which results are concomitant with other studies in catfish (*Clarias batrachus*) [85]. Likewise, as in male, an impaired RNA transcription of genes involved in promoting follicular growth (*lhβ* and *lhr)* was observed in the ovary of zebrafish [81].

On the other hand, severe histological lesions in the gonad have been observed in fish after Hg exposure *in vivo*. In testis, exposure to $HgCl_2$ caused the thickening of the tubule walls and disorderly arranged spermatozoa in zebrafish [81] as well as in medaka (*Oryzias latipes*) after MeHg exposure [86], probably resulting in inhibition of spermatogenesis. Moreover, a disorganization of seminiferous lobules, proliferation of interstitial tissue, congestion of blood vessels, reduction of germ cells and sperm aggregation was induced after $HgCl_2$ injection in the tropical fish *Gymnotus carapo* [87]. In ovary, degenerative changes such as atresia (follicular degeneration) were found after $HgCl_2$ exposure in zebrafish [81] in agreement with other studies [88-90].

In recent years, research of reproductive effects such as spawning success, spawning behaviour, fertilization success and fecundity after Hg has highlighted their importance in fish [91]. A significant reduction of the spawning success and an increase time to spawn was observed in female fathead minnows after MeHg feeding [82]. Most recent studies have shown the maternal transfer as a significant route of exposure of MeHg diet for larval and juvenile fish. The cellular mechanisms by

which MeHg moves through the body is readily complexed with cysteine S-conjugates. This structure mimics that of methionine and can therefore be transferred across cell membranes to developing oocytes via methionine transporters [82]. It was originally thought that MeHg partitioned from stores in female tissues into developing oocytes [93]. However, recent research has shown that the diet of the maternal adult during oogenesis, rather than adult body burden is the principal source of Hg in eggs [94]. A study [93] employed the use of stable MeHg isotopes to investigate the sources of Hg transferred to eggs. Adult sheepshead minnows (*Cyprinodon variegatus*) were exposed to MeHg-spiked diets. The diets administered during the pre-oogenesis stage contained different MeHg isotopes than the diet administered during oogenesis, allowing us to characterize the proportion of Hg in eggs derived from maternal body burden versus maternal diet during oogenesis. The results indicate that a constant percentage of maternal body burdens were transferred to eggs across all treatments; however, the majority of total Hg found in eggs was from recent maternal dietary exposure. In another study, males of fathead minnow fed with MeHg had significantly higher gonad concentrations of MeHg than females, which may be attributed to losses of contaminants due to maternal transfer of dietary MeHg to eggs [95] and is in concordance with other studies [93,96]. Moreover, resulting embryos from the MeHg low-diet treatment displayed altered embryonic movement patterns (hyperactivity) and decreased time to hatch while embryos from the MeHg high-diet treatment had delayed hatching and increased mortality compared with the other treatments [95].

3.5. Nervous system

Notwithstanding that Hg neurotoxicity has been well reported in both human and mammalian models [15,97-99], information regarding its threat to fish nervous system and underlying mechanisms is still scarce. Both $HgCl_2$ and MeHg are able to easily cross the blood-brain-barrier (BBB), reaching the fish brain where it exerts toxicity [100-102]. Moreover, both forms of Hg share the same toxic chemical entity [103] and, thus, neurotoxicity may depend mainly on the external bioavailability. Only a few neurotoxicological endpoints have been employed to evaluate the biological effects of Hg in fish, both in laboratory experiments and under field exposures. For instance, high concentrations of MeHg were accumulated in the medaka brain after exposure to graded sublethal concentrations [86] or in European sea bass brain [104]. Changes in oxidative stress profiles of the Atlantic salmon (*Salmo salar*) [105] and European sea bass brain [101] or alterations in the protein expression in the marine medaka brain [106] have been reported after $HgCl_2$ exposure. Adult zebrafish exposed to dietary $HgCl_2$ showed induced *mt* production at gene level [107]; however, no changes in the expression of genes involved in antioxidant defences, metal chelation, active efflux of organic compounds, mitochondrial metabolism, DNA repair, and apoptosis were observed [108]. Moreover, histopathological examinations of fish brain was performed, revealing a widespread neuronal degradation [105] or for the first time a deficit in the number of the cells of the white seabream (*Diplodus sargus*) brain as an effect of Hg deposition [102]. Curiously, as in humans, the long-term effects of Hg were also disclosed by numerous alterations on motor and mood/anxiety-like behaviour after 28 days of recovery [102]. Concerning *in vitro* studies, only one report has dealt with Hg toxicity on the cell line DLB-1, derived from European sea bass brain. In particular, MeHg reduced the viability of the DLB-1 cells, failed to increase ROS, reduced the *cat* gene expression and increased the *mta* transcription. Furthermore, DLB-1 cells exposed to Hg elicited a rapid cell death by apoptosis [24].

3.6. Digestive system and excretory system

Although an effective barrier to iHg, the intestinal wall is permeable to Hg, due to the high lipid solubility of the compound [109]. Thus, the gastrointestinal tract represents a major route of entry for a wide variety of toxicants present in the diet or in the water that the fish inhabit [110-112]; nonetheless there is little information relating to the protective mechanisms adopted by the intestine epithelial surfaces of the fish against Hg uptake [113]. Light microscopy based investigations have demonstrated that there are alterations in the gut of snakehead and Stinging catfish (*Heteropneustes fossilis*) following Hg intoxication [110,112] but surprisingly no histopathological changes were described in the arctic charr (*Salvelinus alpinus*) following exposure to dietary $HgCl_2$ and MeHg [113]. In contrast, perturbations including the notable presence of vacuoles within the cytoplasm along with various inclusions, myeloid bodies and modifications to the endoplasmic reticulum and mitochondria on the intestinal epithelium of European sea bass exposed to Hg have been shown [71]. Moreover, the presence of MeHg in the intestine epithelial cells of trahira and, at a minor extent, in the extracellular matrix represents the main tissue targets [30]. Although epithelial cells from intestinal mucosa represent a biological barrier that selects the entrance of essential nutrients as well as contaminants, it should be remarked the fact that MeHg absorption can occur by passive diffusion through neutral amino acids carrier proteins [114] and accumulate in the epithelial cells or toward the connective tissue and transported via bloodstream to other target organs.

Unlike mammals, Hg can also be depurated by the kidney, liver, and, possibly, the gills of fish [116]. Small amounts of MeHg were detected in the urine of treated juvenile white sturgeon (*Acipenser transmontanus*) and high concentrations of MeHg were also found in the kidneys and gills [116]. Thus, the high concentration of Hg in the kidneys and gills may reflect a transient state before MeHg is eliminated from these organs. Moreover, liver registered the highest elimination percentages (up to 64% in the liver, 20% in the brain, and 3% in the muscle) in European sea bass exposed to MeHg during 28 days [104]. Surprisingly, it was verified that the concentration of MeHg in gilthead seabream liver was higher, approximately two-fold [18], than the amount detected in the muscle as it happened in other fish species such as goldfish [118], zebrafish [108] or European sea bass [117]. Furthermore, Hg can cause liver damage as demonstrated by some studies in gilthead seabream [18], the arctic charr [113] or in trahira [27].

The kidney of teleost receives a large portion of the cardiac output because of their extensive portal system. The role of kidney on Hg elimination depends on the mercurial form, preferably iHg form by urine [119]. Previous studies showed that after a 4-week exposure to dietary MeHg, the kidney of sturgeon species showed prominent degeneration of the renal tubules [120]. Similar changes were reported in guppy (*Poecilia reticulata*) [121] and Indian catfish (*Clarias batrachus*) [122] exposed to waterborne MeHg. The accumulation of MeHg in the renal tubes of trahira kidney has also demonstrated [30].

3.7. Blood system

Due to the affinity to conjugate reversibly to cysteine amino acid, Hg is transported by the blood to the rest of the organs [123]. However, there is little available information in the literature related to hematological responses in fish chronically exposed to Hg. Thereby, some reports have focused on the effect of Hg on fish blood cells, namely erythrocytes. Because of it is thought to compete with iron for

binding to haemoglobin, which can result in impaired hemoglobin formation, Hg exposure resulted in anemia in two fish species (*Channa gachua* and *Pleuronectes platessa*) [124,125]. However, dietary MeHg increased significantly the values of haematocrit after exposure in trahira [54] suggesting an increase in the blood oxygen capacity, in contrast to the not significantly changes observed in Nile tilapia (*Oreochromis niloticus*) exposed to sublethal concentrations of Hg [126]. [127] observed a decrease in membrane fluidity, change of internal viscosity, and internal protein conformation and hemolysis in erythrocytes of common carp subjected to Hg. Moreover, a differential sensitivity of fish species towards the induction of erythrocyte micronuclei (MN) and other nuclear abnormalities has been reported after intraperitoneal injection of Hg [128,129] or in olden grey mullet (*Liza aurata*) along an environmental Hg contamination gradient [130]. On the other hand, *in vitro* toxicological tests using human erythrocytes are gaining traction as alternatives to *in vitro* tests, however few studies are available in fish. For example, gilthead seabream or European sea bass erythrocytes exposed to Hg exhibited cytotoxicity and alteration in the gene expression profile of genes involved in oxidative stress, cellular protection and apoptosis death [34].

4. Conclusion

Although Hg is ubiquitous in the environment, it is considered one of the most toxic elements or substances on the planet that continues to be dumped into our waterways and soil, spilled into our atmosphere, and consumed in our food and water. Research indicates that Hg exposure can induce a variety of adverse effects in fish at physiologic, histologic, bio-chemical, enzymatic, and genetic levels. Certain fish species, however, appear to show more sensitivity to Hg toxicity than others. Hence, Hg-induced toxicological pathology in fish is influenced by such factors as species, age, environmental conditions, exposure time, and exposure concentration. The exact causes of fish death are multiple and depend mainly on time-concentration combinations. In-depth toxicodynamics and toxicokinetics studies are necessary to establish an exact cause-effect relation. The scientific data discussed in this review provide a basis for understanding the potential impact, as well as for advancing our knowledge of the ecotoxicology and risk assessment of Hg.

Acknowledgements

This work was partly supported by Fundación *Séneca* (*Grupo de Excelencia de la Región de Murcia* 19883/GERM/15).

Conflict of interest

All authors declare no conflict of interest in this paper.

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