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Review

A multidimensional concept for mercury neuronal and sensory toxicity in fish - From toxicokinetics and biochemistry to morphometry and behavior

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ABSTRACT

Background: Neuronal and sensory toxicity of mercury (Hg) compounds has been largely investigated in humans/mammals with a focus on public health, while research in fish is less prolific and dispersed by different species. Well-established premises for mammals have been governing fish research, but some contradictory findings suggest that knowledge translation between these animal groups needs prudence [*e.g.* the relative higher neurotoxicity of methylmercury (MeHg) *vs.* inorganic Hg (iHg)]. Biochemical/physiological differences between the groups (*e.g.* higher brain regeneration in fish) may determine distinct patterns. This review undertakes the challenge of identifying sensitive cellular targets, Hg-driven biochemical/physiological vulnerabilities in fish, while discriminating specificities for Hg forms.

Scope of review: A functional neuroanatomical perspective was conceived, comprising: (i) Hg occurrence in the aquatic environment; (ii) toxicokinetics on central nervous system (CNS)/sensory organs; (iii) effects on neurotransmission; (iv) biochemical/physiological effects on CNS/sensory organs; (v) morpho-structural changes on CNS/sensory organs; (vi) behavioral effects. The literature was also analyzed to generate a multidimensional conceptualization translated into a Rubik's Cube where key factors/processes were proposed.

Major conclusions: Hg neurosensory toxicity was unequivocally demonstrated. Some correspondence with toxicity mechanisms described for mammals (mainly at biochemical level) was identified. Although the research has been dispersed by numerous fish species, 29 key factors/processes were pinpointed.

General significance: Future trends were identified and translated into 25 factors/processes to be addressed. Unveiling the neurosensory toxicity of Hg in fish has a major motivation of protecting ichtyopopulations and ecosystems, but can also provide fundamental knowledge to the field of human neurodevelopment.

1. Introduction

1.1. Historical context

Mercury (Hg) neurological effects were first described in miners in ancient Rome (from last century BC to first century AC), in Venetian mirror workers (around 1700) and, throughout history, several cases of Hg poisoning were reported involving royals and celebrities (see description in Rao [1]). However, it is as uninventive as unavoidable to invoke the Minamata disaster (Japan) when addressing the issue of Hg-associated neurological and sensory disturbances. In the 1950s and early 1960s, this catastrophic mass poisoning showed the world the devastating effects of Hg, particularly methylmercury (MeHg), on the human nervous system and intrinsic sensory structures. Multiple neurological symptoms were reported, including paresthesia, constriction of visual fields, impairment of hearing and speech, cerebellar ataxia and psychiatric symptomatology [2,3]. In cases of severe intoxication, the victims became incapacitated and died [4]. Since then, the neuronal and sensory toxicity of mercurial compounds has been investigated in humans and mammals, thereby reflecting a focus on public health

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protection (e.g. [5,6]). Owing to the close bonds between the aquatic environment with the ontogeny and emergence of Hg threats, a shift of focus towards understanding the neuro-sensory disruptions induced in fish, the most prolific vertebrate group in terms of biomass and number of species [7], appears as obvious and mandatory. Nevertheless, there is disproportion in the scientific efforts and resources available for the field of fish toxicology, when compared to the equivalent activity developed in the human/mammalian context. This is translated into the knowledge degree and corresponding body of literature, as a bibliography search on the Web of Science Core Collection (carried out in September 2018) using the search terms"mercury neurotoxicity" returned more than 1000 references, of which only about one hundred involved fish (see Tables 2 and 3).

Here, a clarification is needed on the eventual ambiguity of the concept of "fish", since, currently, the term (also Pisces) is considered a typological description of an aquatic vertebrates group, convenient for communication purposes [8] but without a direct correspondence in the phylogenetic classification or in a systematic category or taxon. Hence, as referred by Keat-Chuan Ng et al. [8], "fish", as a collective term, primarily refers to Agnatha (jawless fishes; hagfishes and lampreys), Chondrichthyes (cartilaginous fishes; sharks and rays), Sarcopterygii (bony and lobe-finned fishes; lungfishes and coelacanths) and Actinopterygii (bony and ray-finned fishes). Although we share this more comprehensive assumption, it should be noted that, in the context of the literature analyzed for this review, the term "fish" is often used in a more restrictive perspective and, unless stated otherwise, it is tacitly assumed as referring to actinopterygians. This results from the fact that this taxon embraces the majority of fish species and has been, predictably, reflected in a piscine neurotoxicological research addressing almost exclusively actinopterygians (see Tables 2 and 3).

Anyhow, the bibliography search signalized that a considerable number of species has been used in the research of neurosensory effects of various Hg chemical species on fish. From the analysis of Tables 2 and 3, it can be easily concluded that the existing literature is dispersed over 60 species (and therefore, by several fish-related specificities), as well as different organism developmental stages, Hg chemical forms and exposure conditions (comprising dissimilar levels, routes and durations). This points out the existence of several pieces of the same puzzle that still needs to be fitted, but also denotes a wide representativeness of fish biodiversity on the research of the neuronal and sensory toxicity of Hg. Such a large number of fish species used will bring fragmentation between studies, hampering the emergence of patterns and mechanisms, but can also represent an added-value in a way that eventual risks for various species could be identified.

Zebrafish (*Danio rerio*) has been a valuable model organism, supporting many experiences on the scope of human neurotoxicology (*e.g.* [9–13]). While *D. rerio* is an excellent and extremely popular biomedical research model, an understanding of Hg neuronal and sensory toxicity on other fish species (non-model) has been also considered in studies with emphasis on protection of ichthyo-fauna and ecosystem health preservation. This will be the main framework of the current review article, even if findings with zebrafish obtained in biomedical contexts will be also described.

Historically, the relationship between different scientific areas has been marked by a vanguard position of human-centered and human-driven studies, often serving as inspiration and even guidance to non-human focused research in terms of technological/analytical tools, identification of problems, and approaching strategies. This triggering role involves a dominant risk associated to an anthropocentric thinking, giving rise to a "tendency to reason about other organisms by analogy to humans" [14]. An attempt to analyze critically the information available on fish (as well as the knowledge gaps), avoiding unsupported extrapolations, underlies this review.

Interestingly, it is perceptible that research on the neurosensory toxicity of Hg in fish has been mostly paced by the pre-existent large amount of scientific knowledge on humans and other mammals. This is consubstantiated by the chronological analysis of the scientific studies on this subject; for example, the first publication on humans (describing a fatal occupational MeHg poisoning, with a clinical picture marked by sensory disturbances) occurred in 1865 (Edwards [15] as stated by Grandjean et al. [16]), while the first article objectively reporting Hg-dependent neurosensory effects in fish (describing the interference of $HgCl_2$ with palatal chemoreceptors in the common carp *Cyprinus carpio*, affecting the taste sensitive area) came out more than 100 years later (in 1970) [17]. The fact that MeHg has been more investigated in fish for its neurosensory toxicity in comparison to Hg inorganic forms (iHg) also illustrates well the previous assumption (see Tables 2 and 3). The preponderance of studies investigating MeHg effects on fish is probably based on the assumption of its higher neurotoxicity in relation to iHg, at the light of what is widely known for humans. However, this apparent consensus has recently been called into question in what concerns to fish [18], as it will be explored below.

1.2. Fish nervous system, including sensory structures

A brief description of the fish central nervous system (CNS), consisting of the brain and spinal cord, including sensory centers, with emphasis on bony fishes, is opportune to provide a functional neuroanatomical basis for the following sections. Fish have a brain relatively small in comparison to other vertebrates (typically one-fifteenth the brain mass of a similarly sized mammal) [19]. The following conventional main divisions, extended rostrocaudally (examples of the respective minor divisions or structures are indicated in brackets), are considered [20,21] (Fig. 1): (i) telencephalon (*e.g.* bulbus olfactorius; mainly involved in olfaction) and diencephalon (*e.g.* epithalamus, thalamus and hypothalamus; mainly involved in the correlation of afferent and efferent impulses and modulation of the endocrine system), together representing the forebrain (prosencephalon); (ii) mesencephalon or midbrain (*e.g.* optic tectum and tegmentum; mainly involved in the vision and learning); (iii) metencephalon (cerebellum; mainly involved in the coordination of muscular activities during swimming) and myelencephalon (medulla oblongata; mainly involved in sensory functions such as gustation and audition), together representing the hindbrain (rhombencephalon). The medulla oblongata and the tegmentum are collectively referred as brainstem, diverging from human neurology [20]. The spinal cord has a uniform general structure and extends for the whole length of the fish body [22].

The CNS is referred to as "central" because of its pivotal role on the integration of information received from the entire body and the subsequent initiation of coordinated actions to modulate the activity of skeletal muscles (via somatic system), as well as smooth and cardiac muscles, and glandular epithelia (via autonomic system), and, ultimately, behavior and emotions (already demonstrated in fish; see *e.g.* [9,23–25]). It possesses a cytoarchitecture and a neuronal machinery finely designed for integrative tasks owing to complex and multimodal inputs. Cerebellum (motor learning and coordination, and, probably, cognition), optic tectum (orientation tasks, such as object identification and location) and telencephalon (olfaction) are examples of relevant integrative centers in fish [20] (Fig. 1).

Like other vertebrates, the peripheral nervous system (PNS) of fish comprises, besides ganglia and receptors, two groups of nerves - spinal and cranial, with origin in the spinal cord and in the brain, respectively. Cranial nerves (in a total of 10 pairs; Fig. 1) collect and send information between the brain and near body areas in head, and include, for instance, olfactory (from the olfactory lobes to the olfactory rosette), optic (arises from the optic tectum and reaches the retina of the eye), auditory (connects medulla oblongata and the vestibular system implicated in senses of equilibrium and hearing) and glossopharyngeal (connects medulla oblongata with gustation buds in the pharynx and with muscles of gill slits) nerves. Fish spinal nerves (in number depending on the fish length and number of vertebrae) connect the spinal cord to skin and internal organs, *viz.* body/cephalic/pharyngeal/fin

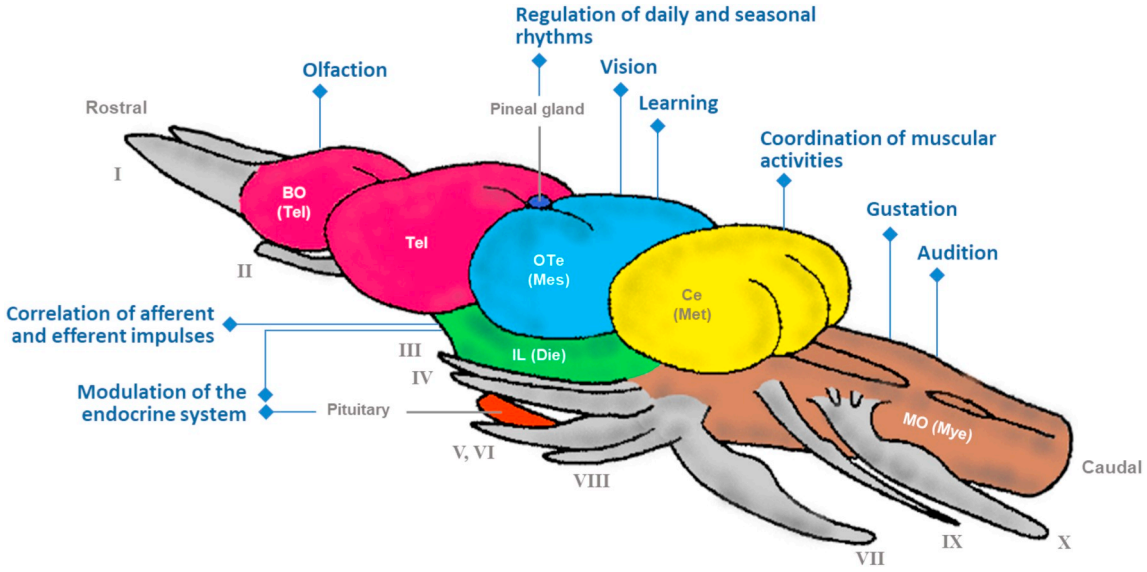

Fig. 1. Left lateral view of brain external morphology of actinopterygian fish (Japanese eel, *Anguilla japonica*), adapted from Mukuda and Ando [98]. Main areas/structures are colored: telencephalon (Tel), including bulbus olfactorius (BO); mesencephalon (Mes), including optic tectum (OTe); diencephalon (Die), showing specifically the inferior lobe of the hypothalamus (IL); cerebellum (Ce), corresponding to metencephalon (Met); medulla oblongata (MO), corresponding to myelencephalon (Mye). Pituitary and pineal gland are also represented. Cranial nerves, numbered from I to X, are depicted in gray. Examples of functions associated to each area/structure are indicated.

locomotor muscles and, except in Agnatha, are mixed nerves, meaning that they include different fibers carrying sensory (afferent conveyance) as well as motor and autonomic (efferent conveyance) signals [22].

Most fish possess highly developed sensory organs/structures, involving several types of receptors/sensors: (i) chemoreceptors (responsible, for instance, for gustation and olfaction); (ii) photoreceptors (visual information); (iii) nociceptors (detection of noxious tissue-damaging stimuli); (iv) mechanoreceptors (mechanosensory lateral line system); (iv) electroreceptors (electrosensory lateral line system). The mechanosensory lateral line, along with the auditory sense, constitute the mechanical sense system, also called vestibular system, involved in the control of fish body position and its static and dynamic equilibrium [26].

Neurotransmission is the basis of neuronal communication, including various stages and a set of biochemical processes, each one passible to be affected by environmental toxicants [27]. According to Kasumyan [26], comparative studies on the identity of neurotransmitters are often fragmentary but point to a similarity in their chemical nature among the different vertebrate classes. The major neurotransmitter systems identified in fish were thoroughly reviewed by Horzmann and Freeman [27] and are associated to the following classical transmitter substances: (i) glutamate (the primary excitatory neurotransmitter and the most common in the bony fish brain); (ii) gamma aminobutyric acid (GABA - the major inhibitory neurotransmitter in the CNS); (iii) catecholamine neurotransmitters [dopamine (DA), norepinephrine (NE) and epinephrine - modulatory neurotransmitters]; (iv) serotonin (5-HT – a modulatory neurotransmitter); (v) acetylcholine (ACh - the major neurotransmitter in the parasympathetic nervous system); (vi) histamine (a non-synaptic neuromodulator); (vii) glycine (an inhibitory neurotransmitter).

As stated by Wullimann [20], we are only at the beginning of fully understanding the differences and similarities in the functional organization of nervous system between fish and other major vertebrate groups. Several problems remain to be solved regarding the homology of particular nuclei, neuronal connections, neurotransmitter distribution, as well as sensory pathways. Remarkable progresses have been registered in this context thanks to the profuse neurobiological investigation in zebrafish (as reviewed by [28,29]). This model species shares the main neurotransmitter pathways with mammals and has similar neuroanatomy in many areas (*e.g.* spinal cord, hindbrain and retina), but some classical regions of the mammalian brain (*e.g.* hippocampus, amygdala, and substantia nigra) are not present as such [27]. The degree of homology is nevertheless of great functional interest but should be evaluated in each single case. For example, the circuitry of the optic tectum, cerebellum and telencephalon is similar in bony fish and mammals [20]. Differently, a remarkable feature distinguishes mammal and fish brain in terms of plasticity. Indeed, contrary to mammals, fish brain remains plastic throughout life, which makes them able to adapt their physiology and behavior to the challenges posed by the surrounding environment, such as avoiding predation, dealing with spatial complexity or finding a mate [30–32]. This is important to be taken into account when interpretations are made in the other way around, *i.e.*, when fish are used as model in human neurosensory toxicology. For a detailed description of specific features of fish neuroanatomy and neurophysiology, please see other reviews (*e.g.* [33–35].

1.3. Review outline

The emergence of signals of neuronal and sensory disruptions in fish causally associated to mercury (Hg) exposure can take place at various levels of biological organization and be determined by different variables and risk modifiers. Thus, the neurosensory toxicity of Hg has been investigated in fish by different approaches ranging from toxicokinetics, molecular/biochemical and physiological effects, to changes on structures morphology and behavior. Generally, to the best of our knowledge, the effort of bridging different approaches has not been made in the same work (see Tables 2 and 3) preventing the perception of an overview picture on this subject. The links from the lower to the higher levels of organization (*i.e.*, molecular to behavior) were seldom made in this context, and most studies tend to concentrate their work at a single approach. Looking at how different levels of biological organization relate to one another might light up both the mechanisms underlying the responses of the individual organisms to Hg neurosensory toxicity and their ecological consequences. For instance, few studies had investigated the effects of Hg on both brain morphology and behavior, but those existing [23,24,36] may provide an important insight into the mechanisms by which environmental levels of Hg may disrupt

behavior.

It has been assumed that the full picture of the mechanisms mediating the Hg neurotoxicity and subsequent neurological disorders at upper levels (*e.g.* neurocognitive) has yet to be unmasked, even within the framework of human-centered research [37]. In fact, to the greatest extent, this can be also an unsolved puzzle for fish. When facing a complex problem, it is a wise and rational decision to adopt a decomposition strategy, by breaking it down into more manageable parts. In line, this review addresses first the molecular mechanisms and subcellular processes that mediate Hg-induced neurotoxicity, pursuing a more attainable goal. Specifying, in mammalian CNS, some molecular targets, structures and mechanisms have been implicated in MeHg neurotoxic effects, namely: blood-brain barrier, cytoskeleton, axonal transport, neurotransmission, protein/DNA/RNA synthesis, respiratory and energy-generating systems [38]. In what concerns specifically to fish, recent advances in this direction have been accomplished through genomic, transcriptomic and proteomic approaches [39–41], though only focused on MeHg. It is worth highlighting that the toxicity of Hg on sensory fish organs has been poorly investigated so far (Tables 2 and 3). Since the sensory functions are key connections between an organism and the environment, if Hg exerts toxicity on the fish sense organs, repercussions on behavior may ultimately occur, as demonstrated for other trace elements [42].

Systematizing, as a first step, the present literature revision was governed mainly by a functional neuroanatomical perspective (Fig. 2), which was translated into an outline encompassing six sections (sections 2 to 7). The definition of these sections, though reflecting a less integrative perspective dictated by an organizational pragmatism, mirrors six main components/dimensions selected, viz. an overview of Hg occurrence in the aquatic environment, with particular emphasis on Hg forms, abundance and distribution (section 2), Hg toxicokinetics with focus on CNS and sensory organs (section 3), effects of Hg on neurotransmission (section 4), as well as at biochemical, physiological (section 5), and morpho-structural levels (section 6), together with Hg-induced behavioral shifts (section 7). Thereafter, pursuing the perception of an integrative picture, the available literature was critically analyzed with the final aim of providing, for the first time, a multidimensional conceptualization (section 8), delineating the "Rubik's Cube" of Hg neurosensory toxicity in fish and, hopefully, triggering a task force towards its resolution. Knowledge gaps as well as future research perspectives will be highlighted.

During the last decades of the 1990s, research on environmental neurotoxicology has been particularly focused on the interference of environmental pollutants (including Hg) with fish sense organs, which was the subject of two review articles [43,44]. Later, the neurobehavioral effects of pollutants [45] or, in a more restricted perspective, of MeHg [46] in fish were also reviewed. Recently, the role of zebrafish in the elucidation of mechanisms of metal toxicity on nervous system function was also subject of a literature revision [29]. Hence, the present review article emerges as timely and alternative in relation to the previous ones, by its specific focus on fish (therefore with an inherent aquatic environmental perspective) and on neuronal and sensory toxicity of Hg. It has also an added value for its completeness and integrative approach in terms of the set of factors/processes considered at both sub-organismic and organismic levels.

2. Mercury occurrence in aquatic systems

Mercury is widely present in the environment. Natural sources of the metal include active volcanoes, forest fires, cinnabar (ore) and fossil fuels such as coal and petroleum, though anthropogenic sources remain as the ones of most concern. Among them, discharges from hydroelectric, mining, pulp, and paper industries, incineration of municipal and medical waste and emissions from coal-using power plants contribute to high levels of anthropogenic mercury [47]. This element is naturally present in waters at very low levels. However, the concentrations in the aquatic compartments are dependent on the distance from sources of contamination (not necessarily anthropogenic)

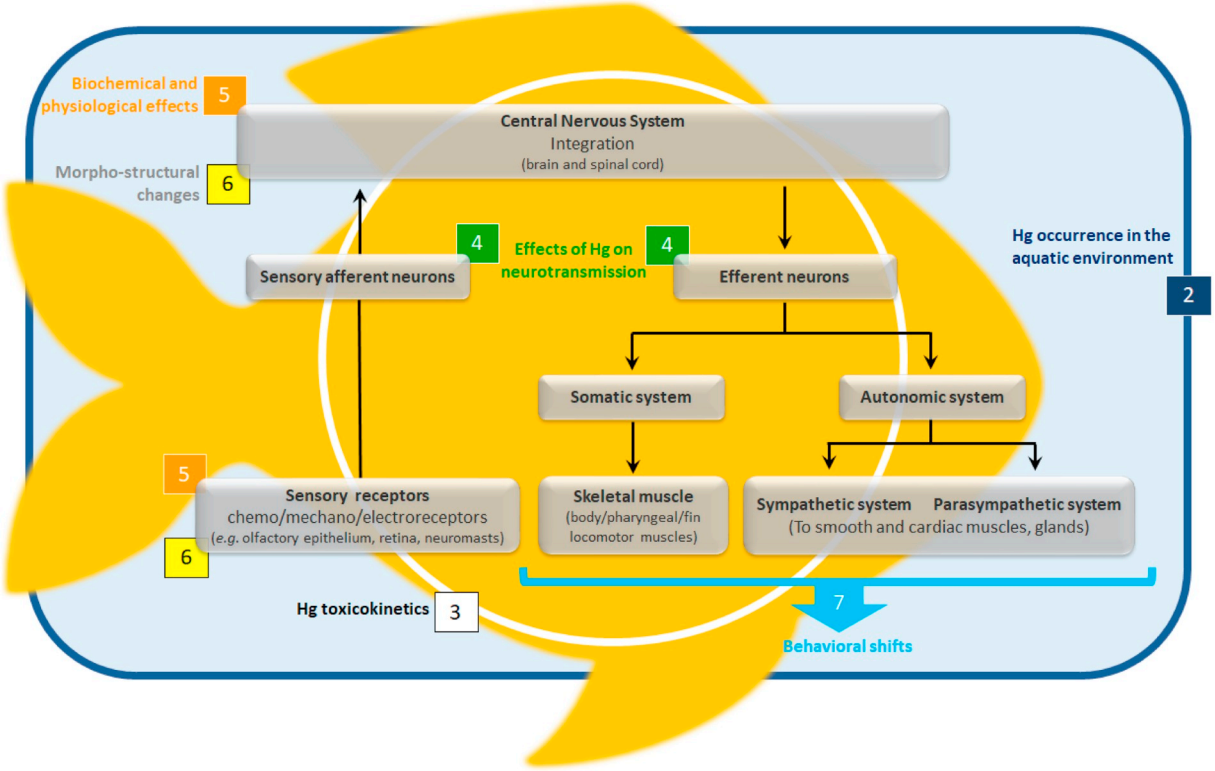

Fig. 2. Diagram of the underlying approach to the neurosensory toxicity of Hg in fish, which incorporates a functional neuroanatomical perspective, covering the selected dimensions/components and translated into corresponding article sections (depicted by the numbers).

Table 1
Ranges of concentrations of total mercury (tHg) and methylmercury (MeHg) recorded in the water and sediment of several aquatic ecosystems worldwide.

Water			
System, country	Total Hg (ng L^{-1})	MeHg (ng L^{-1})	Reference
Atlantic Ocean	0.20 – 0.94	-	Batrakova et al. [86]
Southern Ocean	0.13 – 1.23	0.09 – 0.31	Cossa et al. [87]; Canário et al. [88]
Pacific Ocean	0.08 – 0.18	-	Laurier et al. [107]
Pacific Ocean	0.10 – 0.52	0.01 – 0.20	Sunderland et al. [94]; Kim et al. [104]
Arctic Ocean	0.14 – 2.9	0.01 – 0.18	Kirk et al. [105, 106]
Chesapeake Bay, USA	0.1 – 12	5.4 – 216[a]	Mason et al. [89]
Gironde Estuary, France	1.24 – 31.6	0.04 – 2.3	Schafer et al. [93]
Minimata Bay, Japan	0.84 – 22.3	0.28 – 5.21	Tomiyasu et al. [90]
San Francisco Bay, USA	5.0 – 52.2	0.22 – 12.9	Choe et al. [92]
Tagus Estuary, Portugal	1.2 – 365	0 – 63	Monteiro et al. [97]; Cesário et al. [77, 76]
Aveiro Lagoon, Portugal	16 – 177	-	Ramalhosa [100]; Ramalhosa et al. [101]
Marano & Grado Lagoons, Italy	8.4 – 1200	0.19 – 2.40	Hines et al. [103]
Tagus Estuary, Portugal	3.2 – 330	-	Canário et al. [64]
Bohai Sea Coast, China	39 – 2700	0.046	Wang et al. [99]
Sediment			
System, country	Total Hg (μg g^{-1})	MeHg (ng g^{-1})	Reference
Bay of Fundy, Canada	0.5 – 50[b]	2.7 – 717[c]	O'Driscoll et al. [109]
Mainstem, Chesapeake Bay, USA	0.25 –1.0	2.2 – 10.8	Mason et al. [89]
Medway–Horrid Hill, UK	0.02 – 1.2	0.02 – 4.3	Ouddane et al. [67]
Seine–Vasière Nord, France	0.15 – 1.5	0.6 – 3.0	Ouddane et al. [67]
Marano & Grado Lagoons, Italy	1.22 – 4.57	1.03 – 2.39	Hines et al. [103]
Tagus Estuary, Portugal	0.01 – 66.7	0.31 – 43	Canário et al. [96, 108]
Bohai Sea Coast, China	0.5 – 64	0.12 – 35	Wang et al. [99]
Tagus, Portugal	0.24 – 126	0 – 201	Monteiro et al. [97]; Cesário et al. [77, 76]
Aveiro Lagoon, Portugal	0.26 – 245	5.84 – 46.4	Ramalhosa [100]; Ramalhosa et al. [101, 102]
Minamata & Fukuro Bay, Japan	0.61 – 6.63	0.7 – 36.7	Tomiyasu et al. [91, 90]
San Francisco Bay, USA	0.02 – 1.0	0.09 – 14.2	Choe et al. [91]

[a] Values in pg L^{-1}.
[b] Values in ng g^{-1}.
[c] Values in pg g^{-1}.

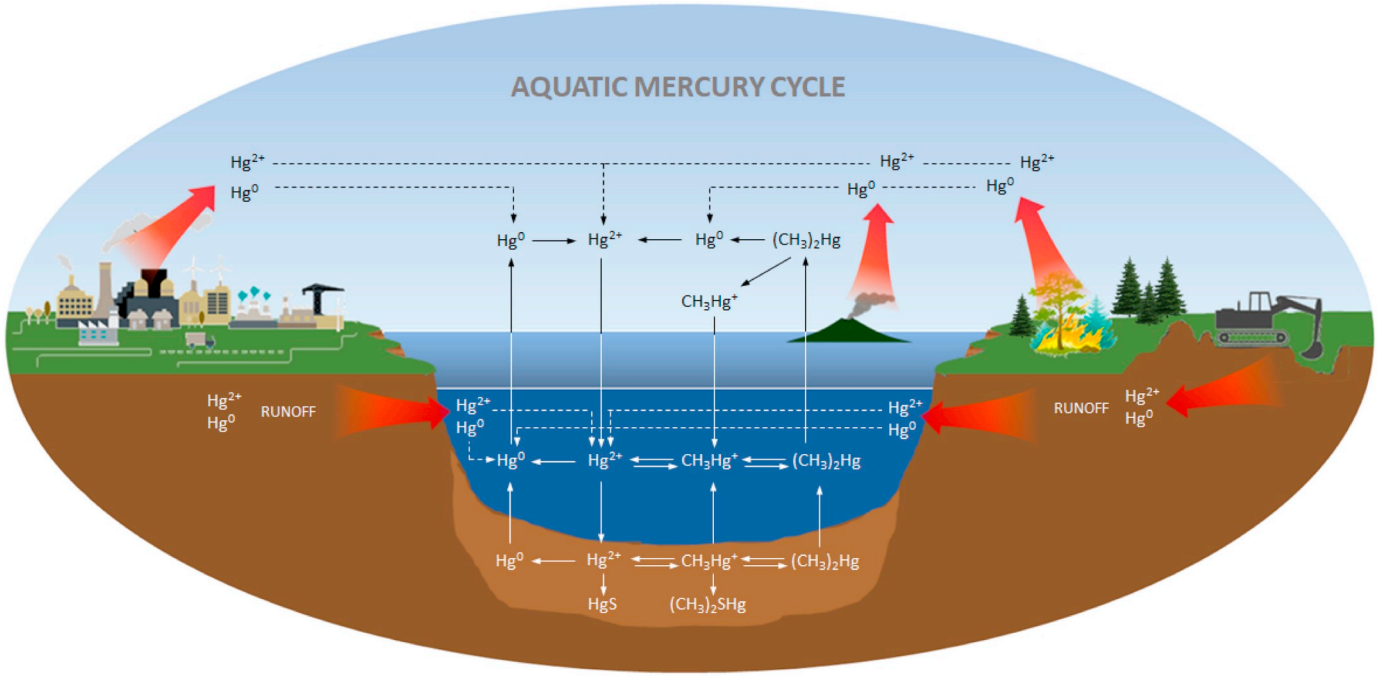

Fig. 3. Summary of the major transformations of mercury (Hg) in the environmental compartments (atmosphere, water and sediment) with emphasis on chemical states and fates of organic [$(CH_3)_2SHg$; CH_3Hg^+; $(CH_3)_2Hg$] and inorganic [Hg^0; HgS; Hg^{2+}] forms in aquatic systems. Cycling pathways involve biogeochemical processes within each compartment and inter-compartmental movements (*e.g.* deposition, runoff, volatilization, sedimentation and sediment diffusion/advection/resuspension). Natural (*e.g.* volcanoes and forest fires) and anthropogenic (*e.g.* hydroelectric, pulp/paper and mining industries, incineration of municipal waste) sources of Hg are depicted by the red arrows.

(Table 1). While the Hg levels are highly related with the sources, its speciation will depend on the biogeochemical characteristics of the environment. Mercury enters the water via anthropogenic discharges, atmospheric deposition and natural processes such as river runoff. Mercury in natural waters is present as Hg^{2+} and MeHg, either in dissolved or particulate forms [48] (Fig. 3), and as Hg^0 that, together with dimethylmercury (extremely volatile species), exist as dissolved gases. Mercurous mercury ion is only stable as a dimer (Hg_2^{2+}) in aqueous solution and is easily transformed into Hg^0 and Hg^{2+}. In surface waters, Hg^0 occurs from the reduction of Hg^{2+} compounds by aquatic organisms, as well as from abiotic reduction by humic substances and decomposition of organic Hg forms. Due to its relatively high volatility, elemental Hg is readily lost from the aquatic environment at normal temperatures (Fig. 3).

In natural waters, mercuric ion (Hg^{2+}) is the most stable form [49] and the main form that is methylated by a bacterially mediated process. It does not exist as free ion, but usually in complexes with hydroxide or chloride. The existence of these species depends on pH and chlorine concentrations [50]. Both the Hg^{2+} and CH_3Hg^+ (MeHg) have a high tendency to form complexes, in particular with soft ligands such as sulphur [51]. In the absence of sulphide, the speciation of inorganic Hg (iHg) in freshwaters is dominated by three uncharged complexes: $Hg(OH)_2$; HgOHCl and $HgCl_2$. As salinity increases, Hg^{2+} forms $HgCl^+$, $HgCl_2$, $HgCl_3^-$ and $HgCl_4^{2-}$ complexes, and, when the opposite occurs (decrease on Cl^- ion concentration), the formation of $HgCl_2$ is more favorable than $HgCl_3^-$ and $HgCl_4^{2-}$, which are the most present chlorine ions in seawater [51]. In spite of these characteristics, mercury speciation in freshwaters is dominated by organic rather than chlorine or hydroxide complexes. Strong associations are formed with humic matter, where Hg is most likely bound to thiol and carboxylic groups (*e.g.* [52]). However, in seawater, the proportion of Hg^{2+} bonds to humic substances is decreased due to chlorine ion competition (*e.g.* [53]). In freshwater, more than 90% of Hg is complexed by organic matter and most of the MeHg is also associated with dissolved organic carbon (DOC) [54]. Mercury complexation by dissolved organic matter (DOM) can facilitate the leaching of mercury from soils and sediments into the water column of lakes and streams [55] and, consequently, favors the transport of Hg within watersheds. Dissolved organic matter is also known to promote [56] or inhibit [57] the formation of bioaccumulative MeHg species. Complexation with DOM limits Hg^{2+} availability to methylating bacteria and CH_3Hg^+ availability for bioaccumulation [58].

In the water column, a large amount of Hg is associated to suspended matter [59]. Methylmercury is strongly adsorbed onto particles although to a less extent than iHg [51]. Consequently, suspended solids have a major role on the distribution of Hg forms in aquatic systems [60,61].

Sediments constitute the main reservoir of Hg in freshwater and estuarine systems [51] (Fig. 3). Sediments are constituted by a solid fraction of soil and organic matter derived from both the catchment and internal sources (*e.g.* decomposing estuarine plants and algae), pore waters and dissolved gases resulting from the diagenetic processes that occur within. These sediments can temporarily bind nutrients and other contaminants, such as Hg, or more permanently store these contaminants with burial (i.e., the formation of new sediments on the surface).

In several cases the sediment vertical profiles of total mercury have been related to historical evolution of mercury contamination in the area [62,63]. However, their chemical forms of occurrence, to a large extent, determine the behavior of Hg, in sediments. As a result, numerous processes, including sorption/desorption, precipitation/dissolution and complexation/decomplexation, govern Hg fate in sediments. Chemical forms of Hg in sediments are strongly influenced by redox and pH conditions, which control adsorption and retention in the sedimentary column, as well as the concentration of inorganic and organic complexing agents. Inorganic (Hg^{2+}) and methylated (CH_3Hg^+) Hg forms have high tendency to form complexes, particularly with soft ligands such as sulphur, by covalent and ionic bonds [49]. In solid sediments, Hg is associated with organic matter and sulphur compounds [64–66], and in interstitial waters is often significantly correlated with DOM [51]. Hg^{2+} appears to be more strongly sorbed by humic substances then MeHg, which may be the reason why it is less easily mobilized from sediments [51].

Sediments of aquatic environments are important sites of methylation, particularly at the interface with water. Recent studies have confirmed the sediments and porewaters in aquatic environments to be key locations of methylation and have elucidated how methylation potential may change in proportion to depth within the sediment. Higher %MeHg in mudflats [67], higher MeHg concentrations in lagoons [68], and higher potential methylation and demethylation rates in Gulf of Mexico sediments [69] were found in the surface sediment compared with deep sediment. These results have confirmed past research that suggested that methylation occurs primarily in the upper layers of sediment where there is significant microbial activity [70–72]. A similar effect has been observed in peatland porewaters, with higher MeHg concentrations found nearer to the surface [73]. Decreases in methylation potential with increasing distance from the sediment-water interface may be due to bacteria from the sediment moving into the water column once oxygen is depleted [74]. Sediments can be considered as significant sources of Hg and MeHg to the water column via processes that include advective transport (*e.g.* [75]), diffusion [76,77], resuspension [78] and/or bioturbation (e.g. [79]) (Fig. 3). On the other hand, they also act as a sink of Hg species [75,77] and, once contaminated, they provide pathways for rapid mercury-to-biota transfer, posing a risk to aquatic life (including fish) for many years [80]. Although sediments are the primary location of Hg methylation, this process may also occur, albeit to a lesser extent, in the water column of aquatic systems [51,81].

Since the sediment–water interface is pointed as the main site for methylation processes, the deposition and settling of particulate matter is an important mechanism [82]. Total Hg concentrations tend to be higher in pore waters than in the water column and the proportion of MeHg can reach between 30 to 85% (*e.g.* [77]). Although aquatic sediments efficiently retain mercury, water-level fluctuations may lead to the resuspension and short-term exposure of sediments to solar radiation [83,84]. On the other hand, Kim et al. [78] suggested that sediment resuspension affects Hg methylation by changing the association of Hg with sediment binding phases. In addition, sediment resuspension can play a large role in transferring sediment MeHg to organisms in shallow water systems (e.g. [82]). Additionally, biological processes (e.g. microbial reduction, sediment bioturbation) in wetland ecosystems may also lead to the mobilization of sediment-bound mercury [85].

Table 1 gives an overall perspective of Hg levels in water and sediment in multiple aquatic ecosystems worldwide, ranging from low impacted areas to highly contaminated ones. Mercury (including MeHg) in the water has been found all over the world, from open waters, such as the Atlantic [86], Southern [87,88], Pacific [94,104,107] and Artic Oceans [105,106] to more enclosed systems where highest levels have been reported. These concern bays (*e.g.* [89,92]), comprising also the Minamata bay [90], estuaries [64,75,77,93,97], and coastal lagoons [100,101,103]. Moreover, high levels of Hg have been documented in sediments of coastal areas related with past industrial discharges, such as in the Tagus estuary [66,75,77,96,97] or in Aveiro lagoon located in Portugal [100–102]. The sediments of Minamata bay still have high contamination levels, mostly of MeHg [90,91], as well as those in the Bohai Sea Coast (China) [99]. Lower levels of Hg were reported in the sediments of other systems worldwide where the impact of Hg seems to be less notorious [67,109].

3. Mercury toxicokinetics in the nervous system of fish, including sensory organs

Despite the well-documented and extensively studied Hg neurotoxicity in mammals (e.g Clarkson and Magos [110]), little is known about the uptake and accumulation of organic and inorganic Hg species in the nervous system of the fish. The majority of the laboratory and field studies on Hg toxicokinetics in fish focuses on liver, kidney, gills and muscle. The disposition of Hg in the central and peripheral nervous systems, including the sensory organs such as the eye, ear and olfactory bulb is rarely investigated; yet, there is increasing evidence of the detrimental effects of organic and inorganic Hg species on fish behavioral patterns and sensory responses, which could stem from the Hg accumulation in both the nervous system and sensory structures. In general, the toxicokinetics of Hg (uptake/assimilation and retention rates, as well as its distribution between different organs and tissues) strongly depends on the chemical form of Hg and the exposure pathway by which metal entered the fish [12,111,112]. Fish are generally exposed to organic (mainly as MeHg) and inorganic (i.e., Hg^{2+}) Hg either through diet or water. Among these two forms of Hg, it is frequently stated that the organic one (oHg) is more neurotoxic as it can crosses the blood-brain barrier and accumulate in the CNS [113,114]. However, several studies have demonstrated the ability of iHg to accumulate in the brain but at generally different tissue concentrations and deposition patterns [12,115,116].

Below, we will review the current knowledge on the uptake, accumulation and disposition of oHg and iHg in the nervous system (including sensory structures) of fish following environmental and laboratory exposures (Tables 2 and 3).

3.1. Central nervous system (CNS)

The pathway for Hg from the contamination source to the CNS of the fish depends on its chemical speciation and its points of entry to the fish body. Following water exposure, both Hg species (iHg/Hg^{2+} and oHg) are taken up across the gills to the fish bloodstream, where they are distributed to different organs [111]. The uptake across the skin or oral epithelia is likely less important, especially in adult fish, due to skin thickness, low surface area and limited blood perfusion [117]. In addition, the presence of mucus on the skin further decreases the uptake, especially for Hg^{2+}, by capturing almost 80% of the total accumulated Hg [118]. Consistently, Rouleau et al. observed strong labeling of oral mucosa and skin following waterborne $^{203}Hg^{2+}$ exposure in brown trout (*Salmo trutta*) (0.1 μg L^{-1}) and rainbow trout (*Oncorhynchus mykiss*) (2 μg L^{-1}) [119]. In fact, the strong binding of Hg^{2+} to the fish skin and oral mucosa prompted these authors to propose another pathway for waterborne Hg^{2+} to reach the brain, i.e., through water-exposed sensory cells on the fish skin and oral epidermis (e.g. mechanoreceptors of the lateral line system, cutaneous sensory cells and/or receptor cells of taste buds). The axonal transport would occur across primary nerve pathways and terminate at the synaptic junctions with the interconnected neurons [119]. More recently, Korbas et al. demonstrated accumulation of Hg in the skin and in the neuromasts of the lateral line system of the zebrafish larvae exposed in water to various inorganic and organic Hg species (Hg forms and exposure levels in Table 2), which implies that these sensory cells could be indeed the access sites to the brain, not only for Hg^{2+} but also for MeHg [12].

The mechanisms of the uptake of Hg^{2+} and MeHg species through dietary exposure have been summarized by Bradley et al. [120] in a review article. Following ingestion of Hg-contaminated food, Hg crosses the epithelia of the gut either through active or passive process (depending on the Hg chemical form) and is first carried with the blood to the liver via hepatic portal vein. As discussed by Bradley et al. [120], since liver is exposed to dietary Hg^{2+} or MeHg before other tissues, its ability to metabolize and sequester Hg will affect its concentrations and distributions in other organs including the brain.

Ultimately, following either water or diet exposure, both organic and inorganic Hg species, could reach the brain with the circulating blood. As a critical organ, the brain is well protected from the external toxicants through a specialized endothelial structure called blood-brain barrier (BBB). This protective system tightly controls the exchange of substances between the blood and the brain and is equipped with specialized transport proteins to allow access of nutrients. The ability of Hg to penetrate the BBB and accumulate in the brain is tightly connected to its molecular form in the blood. Due to strong affinity and lability of Hg^{2+} and MeHg to thiol and selenol groups, Hg metallomics is controlled by the biomolecules containing such chemical groups [121]. In blood, both oHg and iHg partition between red blood cells (RBC) and plasma depends on the RBC/plasma ratio and on the molecular form of Hg [122]. *In vivo* and *in vitro* rainbow trout (*Oncorhynchus mykiss*, formerly *Salmo gairdneri*) studies [123,124] showed MeHg almost exclusively bound to RBC fraction (> 89% of the whole blood Hg) whereas more than 90% of the total Hg^{2+} in blood was bound to plasma [124]. In RBC, the vast majority of MeHg was bound to hemoglobin (likely through its thiol groups) and the bond was labile as the RBC-bound MeHg was transferrable to other tissues [123]. Studies on mammalian RBC showed MeHg binding to both glutathione (GSH) and hemoglobin [125,126], with relative distribution between these two compartments dependent on the animal species. In plasma, Hg^{2+} is likely bound to thiol-containing molecules such as albumin, cysteine or glutathione [127], though the concentrations of the last two sulfhydryl components are generally low in comparison with RBC [122]. Since MeHg is mostly present in RBC, its passage to tissues, including the brain, likely involves transfer through plasma and ligand exchange as intermediate steps, as pointed out by Oliveira Ribeiro et al [128]. A recent study on MeHg binding in the serum of the rats exposed to MeHg showed the majority of Hg (73%) bound to selenoprotein P [129]. Previous studies demonstrated the uptake of MeHg-S(L-Cys) conjugate across the rat BBB and its accumulation in the brain [130]. Subsequent studies shed more light on the molecular mechanisms of the MeHg-S(L-Cys) trans-membrane transport revealing the conjugate to be the substrate for the L-type large neutral amino acid transporter [131,132], which is expressed in the mammalian BBB [133] and has been recently detected in the fish muscle and gut [134]. Significantly less research has been done on the molecular mechanisms of iHg uptake across the BBB, but similarly to MeHg, it has been postulated that thiol-conjugates of Hg^{2+} present in the blood could be actively transported across the membranes due to some form of molecular mimicry with endogenous molecules [135]. In fact, Bridges et al. [135] showed mercuric bis-cysteineate $Hg(Cys)_2$ to be actively transported by the amino acid transporter system $b^{0,+}$ in the proximal tubular cells [136]. Moreover, recent results on the effects of short-term Hg^{2+} exposure on Na^+/K^+-ATPase activity and osmoregulation in the fish brain indicate that iHg could potentially affect the integrity of the biological barriers (such as BBB) [137]. This hypothesis, if confirmed experimentally, could provide yet another plausible explanation for Hg^{2+} accumulation in the CNS.

To unfold the molecular mechanisms of Hg uptake and accumulation specifically in the fish brain, we reviewed multiple laboratory studies, which reported accumulation of Hg in the fish brain following Hg^{2+} or MeHg exposures, either through diet, water or injections (intraperitoneal or intravenous) (Table 2). In addition, several field studies, which reported Hg brain levels in fish were also identified (Table 3). In majority of the waterborne experiments, Hg concentrations in water were reached by dissolving either $HgCl_2$ or CH_3HgCl. Only in two studies [12,138] cysteine conjugates were also used for both iHg and oHg exposures. As shown by Korbas et al. [12], depending on the water chemistry, the speciation of Hg in water following these formulations could be different for the same compound, affecting the uptake of Hg across the membranes. Similarly, for most of the dietary exposures, the feeds were spiked with solutions of either $HgCl_2$ or CH_3HgCl. In general, independent from the chemical form of the Hg

Table 2
Summary of studies reporting the neuronal or sensory effects of inorganic and organic mercury (Hg) forms on several fish species exposed under controlled laboratory conditions. Levels of inorganic Hg (iHg) are presented both as μg L^{-1} or μg g^{-1} of Hg^{+}, weather exposure was through water or diet, respectively. Levels of MeHg are presented both as μg L^{-1} or μg g^{-1} of CH_3Hg^{2+} weather exposure was through water or diet, respectively. These levels were provided to better enable inter-studies comparisons, and thus, highlighted in bold, while the original ones (as presented in the article) are in brackets. In a few cases, when available at the article, the daily intake levels of iHg or MeHg per body weight (bw) were also provided. All the studies were reported to Actinopterygii fish.

Main approach	Species	Weight (g)	Length (cm)	Developmental state	Habitat type	Hg species	iHg chemical form	oHg chemical form	iHg exposure route	iHg exposure settings (μg Hg L^{-1} or μg Hg g^{-1} fish bw)	oHg exposure route	oHg exposure settings (μg CH_3Hg L^{-1} or μg CH_3Hg g^{-1})	Target organ	Reference
Toxicokinetics	Rainbow trout (*Salmo gairdneri*)	400	-	-	Freshwater	iHg	-	CH_3HgCl CH_3HgOH CH_3HgCys	-	-	Intragastrical or Injection	**4** μg g^{-1} bw (CH_3HgCl/ CH_3HgOH); **0.01** μg g^{-1} bw (CH_3HgCys) (levels correspond to Hg)	Multi-organ	Giblin et al. [123]
Toxicokinetics	Atlantic salmon (*Salmo salar L.*)	250	-	-	Multi-habitat	oHg or iHg	$HgCl_2$	CH_3HgCl	Water	**270** μg L^{-1} for 2, 6 or 12 h	Diet	**99** μg g^{-1} daily for 28 d [a]	Olfactory	Baatrup and Doving [166]
Toxicokinetics	Brown trout (*Salmo trutta*)	30	-	-	Freshwater	oHg or iHg	$HgCl_2$	CH_3HgCl	Water	**150** μg L^{-1} for 5 d	Gastric catheterization	**2.5** μg g^{-1} bw once a week for 4 w (levels correspond to Hg)	Inner ear	Skak and Baatrup [147]
Toxicokinetics	Pike (*Esox lucius*)	1700 - 2800	-	-	Freshwater	iHg	$HgCl_2$	-	Dose into naris or injection	**27** μg pippeted to each naris or **0.054** μg g^{-1} bw single iv injection	-	-	Olfactory	Borg-Neczak et al. [151]
Toxicokinetics	Catfish (*Trichomycterus zonatus*)	-	12 - 18	Adult	Freshwater	iHg	$HgCl_2$	-	Water	**15** μg L^{-1} for up 4, 12, 24, 48 and 96 h	-	-	Multi-organ	Ribeiro et al. [152]
Toxicokinetics	Arctic charr (*Salvelinus alpinus*)	48 ± 18	-	Juvenile	Freshwater	oHg or iHg	$HgCl_2$	CH_3HgCl	Diet	**0.26** μg g^{-1} bw single dose	Diet	**0.26** μg g^{-1} bw single dose (levels correspond to Hg)	Multi-organ	Ribeiro et al. [128]
Toxicokinetics	Brown trout (*Salmo trutta*) / Rainbow trout (*Oncorhynchus mykiss*)	3 - 6 (Brown) / 20 - 25 (Rainbow) 150 - 200 (Rainbow, intravenous)	-	Multi-stage	Freshwater	iHg	unspecified	-	Water or Injection	**0.1** μg L^{-1} (Brown) for 7 or 21 d or 2 μg L^{-1} (Rainbow) for 21 d or **100** μg in **0.3** mL saline (iv injection, Rainbow)	-	-	Multi-organ	Rouleau et al. [119]

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Table 2 (*continued*)

Main approach	Species	Weight (g)	Length (cm)	Developmental state	Habitat type	Hg species	iHg chemical form	oHg chemical form	iHg exposure route	iHg exposure settings (μg Hg L^{-1} or μg Hg g^{-1} fish bw)	oHg exposure route	oHg exposure settings (μg CH_3Hg L^{-1} or μg CH_3Hg g^{-1})	Target organ	Reference
Toxicokinetics	Zebrafish (*Danio rerio*)	-	-	Larvae	Freshwater	iHg	-	CH_3HgCys or Thimerosal	-	-	Water	**43.1** (0.2 μM), **431** (2 μM) and **21560** (100 μM) μg L^{-1} for up to 84 h (CH_3HgCys) or **21560** (100 μM) μg L^{-1} (Thiomerosal) for 20 h	Multi-organ	Korbas et al. [10]
Toxicokinetics	Zebrafish (*Danio rerio*)	0.88 ± 0.03	3.63 ± 0.05	Adult	Freshwater	oHg	-	CH_3HgCl	-	-	Diet	13.5 μg g^{-1} for 50 d[a]	Eye	Mela et al. [161]
Toxicokinetics	Marine medaka (*Oryzias melastigma*)	0.5 ± 0.05	-	-	Seawater	iHg	$HgCl_2$	-	Water	**1000** μg L^{-1} for 8 h	-	-	Multi-organ	Wang et al. [150]
Toxicokinetics	Zebrafish (*Danio rerio*)	-	-	Larvae	Freshwater	iHg	$HgCl_2$	-	Water	**10030** (50 μM) μg L^{-1} for 10 min	-	-	Eye and Brain	Bera et al. [163]
Toxicokinetics	Rohu (*Labeo rohita*)	30 - 40	15 - 20	Juvenile	Freshwater	iHg	$HgCl_2$	-	Water	**49** (66) μg L^{-1} or **98** (132) μg L^{-1} for 15 or 30 d	-	-	Olfactory	Ghosh et al. [168]
Toxicokinetics	Zebrafish (*Danio rerio*)	-	-	-	Freshwater	oHg	-	CH_3HgCys	-	-	Diet	**5.2** or **9.8** μg g^{-1} for up to 8 weeks[a]	Multi-organ	Amlund et al. [138]
Toxicokinetics	Zebrafish (*Danio rerio*)	-	-	Larvae	Freshwater	oHg or iHg	$HgCl_2$	CH_3HgCl	Water	**401** (2 μM) μg L^{-1} up to 48 hrs	Water	**216** (1 μM) μg L^{-1} for 24-36 h or **108** (0.5 μM) μg L^{-1} for 48 h	Multi-organ	MacDonald et al. [159]
Toxicokinetics	White seabream (*Dipodus sargus*)	146 ± 14	19 ± 1	Juvenile	Seawater	iHg	$HgCl_2$	-	Water	**2** μg L^{-1} for up 14 d	-	-	Multi-organ	Pereira et al. [116]
Toxicokinetics	European seabass (*Dicentrarchus labrax*)	19.2 ± 4	12.8 ± 0.7	Juvenile	Seawater	oHg	-	CH_3HgCl	-	-	Diet	**8** μg g^{-1} for 28 d [a]	Multi-organ	Maulvault et al. [146]
Toxicokinetics	Common carp (*Cyprinus carpio*)	47.67 ± 4.61	-	Juvenile	Freshwater	iHg	unspecified	-	Water	**0.5**, **1.5** and **3** μg L^{-1} for up to 14 d	-	-	Multi-organ	Pelcová et al. [149]
Toxicokinetics	Zebrafish (*Danio rerio*)	-	-	Adult	Freshwater	oHg	-	CH_3HgCys	-	-	Diet	**9.8** μg g^{-1} for 56 d [a]	Brain	Rasinger et al. [160]
Effects on neurotransmission	Rosy barb (*Puntius conchonius*)	-	5	Adult	Freshwater	iHg	$HgCl_2$	-	Water	**134** (181) μg L^{-1} for 2 d	-	-	Multi-organ	Gill et al. [181]
Effects on neurotransmission	Catfish (*Clarias batrachus*)	60 ± 5	-	Adult	Freshwater	oHg or iHg	$HgCl_2$	CH_3HgCl	Water	**37** (50) μg L^{-1} for 45, 90 or 180 d	Water	**34** (40) μg L^{-1} for 45, 90 or 180 d	Brain	Kirubagaran and Joy [190]
Effects on neurotransmission	Tilapia (*Oreochromis mossambicus*)	-	-	Juvenile	Freshwater	iHg	$HgCl_2$	-	Water	**11** (15) or **22** (30) μg L^{-1} for 180 d	-	-	Brain	Tsai et al. (1995) [191]

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Table 2 (*continued*)

Main approach	Species	Weight (g)	Length (cm)	Developmental state	Habitat type	Hg species	iHg chemical form	oHg chemical form	iHg exposure route	iHg exposure settings (μg Hg L^{-1} or μg Hg g^{-1} fish bw)	oHg exposure route	oHg exposure settings (μg CH_3Hg L^{-1} or μg CH_3Hg g^{-1})	Target organ	Reference
Effects on neurotransmission	Mummichogs (*Fundulus heteroclitus*)	-	-	Larvae	Multi-habitats	oHg	-	CH_3HgCl	-	-	Water	**10** μg L^{-1} for 7 or 14 d	Brain	Zhou et al. [193]
Effects on neurotransmission	Japanese medaka (*Oryzias latipes*)	0.58	3.89	Adult	Freshwater	oHg	-	CH_3HgCl	-	-	Water	**2.5**, **5**, **10**, **20** or **40** μg L^{-1} for 8 or 16 d [a]	Brain	Liao et al. [187]
Effects on neurotransmission	Zebrafish (*Danio rerio*)	-	-	Adult	Freshwater	iHg	$HgCl_2$	-	Water	**15** (20) μg L^{-1} for 1, 4 or 30 d	-	-	Brain	Richetti et al. [186]
Effects on neurotransmission	Fathead minnows (*Pimephales promelas*)	-	-	Adult	Freshwater	oHg	-	CH_3HgCl	-	-	Diet	**0.72** μg g^{-1} for 30 d [a]	Brain	Bridges et al. [195]
Effects on neurotransmission	Nile tilapia (*Oreochromis niloticus*)	57.5 ± 16.4	15.4 ± 1.33	Adult	Freshwater	iHg	$HgCl_2$	-	Water	**81** μg L^{-1} (0.3 μM) for 3 d or **8.1** μg L^{-1} (0.03 μM) for 30 d	-	-	Brain	Atli et al. [182]
Biochemical and physiological effects	Common carp (*Cyprinus carpio* L.)	700 - 1100	-	Adult	Freshwater	iHg	$HgCl_2$	-	Water	**20060** (10^{-4} M) μg L^{-1} for 10s	-	-	-	Hidaka et al. [235]
Biochemical and physiological effects	Atlantic salmon (*Salmo salar*)	-	15 - 18	Adult	Multi-habitats	iHg	$HgCl_2$	-	Water	**20060** (10^{-4} M) or **200600** (10^{-3} M) μg L^{-1} for 10 s	-	-	Olfactory	Sutterlin and Sutterlin [17]
Biochemical and physiological effects	Rainbow trout (*Salmo giardneri*)	-	18.5 - 26.5	-	Multi-habitats	iHg	$HgCl_2$	-	Injection	**0.05** μg L^{-1} for 1, 2, 3 or 4 h	-	-	Olfactory	Hara et al. [223]
Biochemical and physiological effects	Spotted snakehead (*Channa punctatus*)	60 ± 10	15 ± 2	-	Freshwater	iHg	$HgCl_2$	-	Water	**2.2** (3) μg L^{-1} for 15, 30 or 60 d	-	-	Multi-organ	Sastry and Rao [220]
Biochemical and physiological effects	Rainbow trout (*Oncorhynchus mykiss*)	-	15 - 20	-	Multi-habitats	oHg	-	CH_3HgCl	-	-	Injection	**4** (4.6) or **5.3** (6.2) μg g^{-1} (single injection)	Eye	Hawryshyn et al. [227]
Biochemical and physiological effects	Bronze featherback (*Notopterus notopterus*)	-	-	Adult	Freshwater	iHg	$HgCl_2$	-	Water	**13** (17.6) - **65** (88) μg L^{-1} for 30 d	-	-	Multi-organ	Verma et al. [205]
Biochemical and physiological effects	Mozambique tilapia (*Tilapia mossambica*)	-	7 - 11.8	-	Freshwater	iHg	unspecified	-	Water	**10** or **40** μg L^{-1} for 11 w	-	-	Multi-organ	Menezes and Qasim [228]
Biochemical and physiological effects	Spotted snakehead (*Channa punctatus*)	40 - 45	-	Adult	Freshwater	iHg	$HgCl_2$	C_3H_7ClHgO	Water	**148** (200) μg L^{-1} for 20, 40 or 80 d	Water	500 μg L^{-1} for 20, 40 or 80 d (as methoxy ethyl mercuric chloride)	Brain	Ram and Sathyanesan [196]

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Table 2 (*continued*)

Main approach	Species	Weight (g)	Length (cm)	Developmental state	Habitat type	Hg species	iHg chemical form	oHg chemical form	iHg exposure route	iHg exposure settings (μg Hg L^{-1} or μg Hg g^{-1} fish bw)	oHg exposure route	oHg exposure settings (μg CH_3Hg L^{-1} or μg CH_3Hg g^{-1})	Target organ	Reference
Biochemical and physiological effects	Catfish (*Heteropneustes fossilis*)	40 - 50	17 - 19	-	Freshwater	iHg	$HgCl_2$	-	Water	**148** (200) μg L^{-1} for 10, 20 or 30 d	-	-	Multi-organ	Bano and Hasan [210]
Biochemical and physiological effects	Zebrafish (*Danio rerio*)	0.88	3.63	Adult	Freshwater	oHg	-	CH_3HgCl	-	-	Diet	**5** or **13.5** μg g^{-1} for 7, 21 or 63 d [a]	Multi-organ	Gonzalez et al. [209]
Biochemical and physiological effects	Thraira (*Hoplias malabaricus*)	-	30	-	Freshwater	oHg	-	CH_3HgCl	-	-	Diet or Injection	**0.01** - **6.0** μg g^{-1} (injection); **0.75**, **0.075** or **0.0075** μg g^{-1} for 70 d	Eye	Tanan et al. [229]
Biochemical and physiological effects	Atlantic cod (*Gadus morhua*)	260 - 530	-	Juvenile	Seawater	oHg	-	CH_3HgCl	-	-	Injection	**0.4** (0.5), **1.7** (2) or **6.9** (8) mg kg^{-1} bw (half dose at 1st d and second half after 7 d)	Brain	Berg et al. [39]
Biochemical and physiological effects	Beluga (*Huso huso*)	102 ± 6	0.3 ± 0.06	Juvenile	Multi-habitats	oHg	-	CH_3HgCl	-	-	Diet	**0.8**, **8** or **16** μg g^{-1} for 32 d	Brain	Gharaei et al. [219]
Biochemical and physiological effects	Zebra-seabreams (*Diplodus cervinus*)	16 ± 5	10 ± 1	Juvenile	Seawater	oHg	-	CH_3HgCl	-	-	Water	**0.5**, **1** or **2** μg L^{-1} for 7, 14, 21 or 28 d	Multi-organ	Branco et al. [212]
Biochemical and physiological effects	Atlantic salmon *(Salmo salar)*	340 ± 17	-	Juvenile	Multi-habitats	oHg	-	CH_3HgCl	-	-	Diet	**5** μg g^{-1} for 84 d [a]	Multi-organ	Olsvik et al. [213]
Biochemical and physiological effects	Atlantic salmon (*Salmo salar*)	340 ± 17	-	Juvenile	Multi-habitats	oHg	-	CH_3HgCl	-	-	Diet	**5.2** or **5.7** μg g^{-1} for 90 d [a]	Eye	Remø et al. [233]
Biochemical and physiological effects	Zebrafish (*Danio rerio*)	0.43 ± 0.09	-	Adult	Freshwater	oHg	-	CH_3HgCl	-	-	Injection	**0.5** μg g^{-1} - total exposure 4 d	Brain	Richter et al. [208]
Biochemical and physiological effects	Atlantic salmon (*Salmo salar*)	340 ± 17	-	Juvenile	Multi-habitats	oHg	-	CH_3HgCl	-	-	Diet	**5.2 or 5.7** μg g^{-1} for 90 d [a]	Brain	Amlund et al. [218]
Biochemical and physiological effects	Zebra-seabreams (*Diplodus cervinus*)	29 ± 6	9.8 ± 0.6	Juvenile	Seawater	oHg or iHg	$HgCl_2$	CH_3HgCl	Water	**2** μg L^{-1} for 28 d	Water	**2** μg L^{-1} for 28 d	Multi-organ	Branco et al. [148]
Biochemical and physiological effects	Largemouth bass (*Micropterus salmoides*)	-	-	-	Freshwater	oHg	-	CH_3Hg	-	-	Injection	**2.5** μg g^{-1} - total exposure 4 d	Multi-organ	Richter et al. [41]
Biochemical and physiological effects	European seabass (*Dicentrarchus labrax*)	19.2 ± 4.0	12.8 ± 0.7	Juvenile	Seawater	oHg	-	CH_3HgCl	-	-	Diet	**8** μg g^{-1} for 28 d [a]	Multi-organ	Maulvault et al. [211]

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Table 2 (*continued*)

Main approach	Species	Weight (g)	Length (cm)	Developmental state	Habitat type	Hg species	iHg chemical form	oHg chemical form	iHg exposure route	iHg exposure settings (μg Hg L^{-1} or μg Hg g^{-1} fish bw)	oHg exposure route	oHg exposure settings (μg CH_3Hg L^{-1} or μg CH_3Hg g^{-1})	Target organ	Reference
Morpho-structural changes	Catfish (*Trichomycterus brasiliensis*)	-	6 - 11	-	Freshwater	iHg	$HgCl_2$	-	Water	**37** (50) and **74** (100) μg L^{-1} for 4 d	-	-	Olfactory	Ribeiro et al. [252]
Morpho-structural changes	Bleak (*Alburnus alburnus*)	-	-	-	Freshwater	iHg	unspecified	-	Water	**300** μg L^{-1} for 19 d	-	-	Oral cavity	Pevzner et al. [251]
Morpho-structural changes	Zebrafish (*Danio rerio*)	-	-	Embryo	Freshwater	oHg	-	CH_3HgCl	-	-	Water	**5**, **10**, **50** and **80** μg L^{-1} for 24 hpf	Brain neurons	Hassan et al. [247]
Behavioral shifts	Mosquitofish (*Gambusia affinis*)	-	-	-	Freshwater	iHg	$HgCl_2$	-	Water	**3.7** (5), **7.4** (10), **37** (50) and **74** (100) μg L^{-1} for 3 d	-	-	-	Kania and O'Hara [261]
Behavioral shifts	Lake Withefish (*Coregonus clupeaformis*)	-	12 - 17	-	Freshwater	iHg	$HgCl_2$	-	Diet	**37** (50) μg L^{-1} for 1 to 2 w	-	-	-	Kamchen and Hara [260]
Behavioral shifts	Mummichogs (*Fundulus heteroclitus*)	-	0.45 - 0.60	-	Multi-habitats	oHg or iHg	$HgCl_2$	CH_3Hg	Water	**7.4** (10) μg L^{-1} for 1 or 2 w / **15** (20) μg L^{-1} for 1 w	Water	**10** or **20** μg L^{-1} for 1 w / **10** μg L^{-1} for 2 w	-	Weis and Khan [256]
Behavioral shifts	Mummichogs (*Fundulus heteroclitus*)	-	-	Embryo or larvae	Multi-habitats	oHg	-	CH_3HgCl	-	-	Water	**5** and **10** μg L^{-1} [b]	-	Weis and Weis [262]
Behavioral shifts	Mummichogs (*Fundulus heteroclitus*)	-	-	Embryo	Multi-habitats	oHg	-	CH_3HgCl	-	-	Water	**5** or **10** μg L^{-1} [b]	-	Ososkov and Weis [265]
Behavioral shifts	Grayling (*Thymallus thymallus*)	-	-	Embryo	Multi-habitats	oHg	-	CH_3HgCl	-	-	Water	**0.16**, **0.8**, **4** or **20** μg L^{-1} [b]	-	Fjeld et al. [266]
Behavioral shifts	Mummichogs (*Fundulus heteroclitus*)	-	-	Embryo or larvae	Multi-habitats	oHg	-	CH_3HgCl	-	-	Water	**5**, **10** or **20** μg L^{-1}	-	Zhou and Weis [263]
Behavioral shifts	Mosquitofish (*Gambusia affinis*)	0.125 ± 0.005	-	-	Freshwater	iHg	$HgCl_2$	-	Water	**15** (20) μg L^{-1} for 28 d	-	-	Multi-organ	Jakka et al. [255]
Behavioral shifts	Zebrafish (*Danio rerio*)	-	-	Adult	Freshwater	oHg	-	CH_3HgCl	-	-	Injection	**1** or **5** μg g^{-1}	Brain	Maximino et al. [9]
Behavioral shifts	Zebrafish (*Danio rerio*)	-	-	Adult	Freshwater	oHg	-	CH_3Hg	-	-	Water	**2.2** - **65** (0.01 - 0.30 μM) μg L^{-1} (daily) for 2 w	-	Xu et al. [264]
Behavioral shifts	Zebrafish (*Danio rerio*)	-	-	Embryo	Freshwater	iHg	$HgCl_2$	-	Water	**1.5** - **50** (7.5 - 250 nM) μg L^{-1} (until hatching)	Water	-	Whole body	Bakar et al. [267]
Behavioral shifts	Zebrafish (*Danio rerio*)	0.5 – 0.8	-	Adult	Freshwater	iHg	$HgCl_2$	-	Water	**1477** (2000) μg L^{-1} for 30 min	-	-	Whole body	Biswas et al. [259]

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Table 2 (*continued*)

Main approach	Species	Weight (g)	Length (cm)	Developmental state	Habitat type	Hg species	iHg chemical form	oHg chemical form	iHg exposure route	iHg exposure settings (μg Hg L^{-1} or μg Hg g^{-1} fish bw)	oHg exposure route	oHg exposure settings (μg CH_3Hg L^{-1} or μg CH_3Hg g^{-1})	Target organ	Reference
Behavioral shifts	Zebrafish (*Danio rerio*)	-	-	Adult	Freshwater	oHg	-	CH_3HgCl	-	-	Water	**0.9** (1) or **13** (15) μg L^{-1} for 32 h	Whole body	Strungaru et al. [25]
Multi-approach	Atlantic salmon (*Salmo salar*)	-	-	-	Multi-habitats	oHg or iHg	$HgCl_2$	CH_3HgCl	Water	**2006** (10^{-5} M) μg L^{-1} for 5 min and 15 min	Water	**2156** (10^{-5} M) μg L^{-1} for 5 min and 15 min	Olfactory	Baatrup et al. [224]
Multi-approach	Arctic charr (*Salvelinus alpinus*)	-	-	Juvenile	Freshwater	oHg or iHg	$HgCl_2$	CH_3HgOH	Diet or Water	**15** μg L^{-1} for up 4, 12, 24, 48 and 96 h (water) or **0.26** μg g^{-1} bw (single dietary dose)	Diet	**0.26** μg g^{-1} bw single dose (levels correspond to Hg)	Multi-organ	Ribeiro et al. [253]
Multi-approach	Atlantic salmon (*Salmo salar*)	14.7 ± 3.8	20.8 ± 3.8	-	Multi-habitats	oHg or iHg	$HgCl_2$	CH_3HgCl	Diet	**7.4** (10) or **74** (100) μg g^{-1} for 120 d	Diet	**4.3** (5) or **8.6** (10) μg g^{-1} for 120 d	Multi-organ	Berntssen et al. [36]
Multi-approach	Fathead minnows (*Pimephales promelas*)		3.5 - 4	Juvenile	Freshwater	iHg	$HgCl_2$	-	Water	**1.2** (1.69), **5** (6.79), or **10** (13.57) μg L^{-1} for 10 d	-	-	Brain	Grippo and Heath [194]
Multi-approach	Golden shiner (*Notemigonus crysoleucas*)		0.5 - 0.7	Adult	Freshwater	oHg		CH_3HgCl	-		Diet	**0.46** or **0.96** μg g^{-1} for 90 d [a]	Brain	Webber and Haines [188]
Multi-approach	Thraira (*Hoplias malabaricus*)	342.09 ± 29.9 and 353.34 ± 36.69	-	Adult	Freshwater	oHg	-	CH_3HgCl	-	-	Injection	**1.7** (2) or **5.2** (6) μg g^{-1}	Eye	Bonci et al. [230]
Multi-approach	Common goby (*Pomatoschistus microps*)	-	2.5 - 3	Juvenile	Seawater	iHg	$HgCl_2$	-	Water	**3.1** - **200** μg L^{-1} for 4 d	-	-	Brain and whole head	Vieira et al. [184]
Multi-approach	Zebrafish (*Danio rerio*)	-	-	Larvae	Freshwater	oHg	-	CH_3HgCys	-	-	Water	**431.2** (2 μM) μg L^{-1} for 12 and 24 h	Eye	Korbas et al. [11]
Multi-approach	Zebrafish (*Danio rerio*)	0.88 ± 0.03	3.63 ± 0.05	Adult	Freshwater	oHg	-	CH_3HgCl	-	-	Diet	**13.5** μg g^{-1} (0.6 μg MeHg/fish/day) for 25 or 50 d	Brain	Cambier et al. [246]
Multi-approach	Zebrafish (*Danio rerio*)	-	-	Larvae	Freshwater	oHg or iHg	$HgCl_2$ or $Hg(Cys)_2$	CH_3HgCl or CH_3HgCys	Water	**201** μg L^{-1} ($HgCl_2$) or **40120** μg L^{-1} ($Hg(Cys)_2$) for 36 h	Water	**216** μg L^{-1} for 36 h (CH_3HgCl) or **431** μg L^{-1} for 36 hrs (CH_3HgCys)	Multi-organ	Korbas et al. [12]
Multi-approach	Thraira (*Hoplias malabaricus*)	158 ± 10.6	23 ± 0.5	Adult	Freshwater	oHg	-	CH_3HgCl	-	-	Diet	**0.075** or **0.75** μg g^{-1} for 70 d	Eye	Mela et al. [162]

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Table 2 (*continued*)

Main approach	Species	Weight (g)	Length (cm)	Developmental state	Habitat type	Hg species	iHg chemical form	oHg chemical form	iHg exposure route	iHg exposure settings (μg Hg L^{-1} or μg Hg g^{-1} fish bw)	oHg exposure route	oHg exposure settings (μg CH_3Hg L^{-1} or μg CH_3Hg g^{-1})	Target organ	Reference
Multi-approach	Zebrafish (*Danio rerio*)	-	-	Larvae	Freshwater	oHg	-	CH_3HgCl	-	-	Water	**108** μg L^{-1} for 48 h	Eye and Brain	Korbas et al. [13]
Multi-approach	Zebrafish (*Danio rerio*)	0.6 ± 0.1	0.3 ± 0.02	Adult	Freshwater	oHg or iHg	unspecified	fish food prepared from bycatch marine products	Diet	**11.92** μg g^{-1} for up to 62 d	Diet	≈ **11.58** μg g^{-1} for up to 62 d	Multi-organ	Gentès et al. [145]
Multi-approach	Marine medaka (*Oryzias melastigma*)	0.5 ± 0.05	-	-	Seawater	iHg	$HgCl_2$	-	Water	**0.7** (1) or **7.4** (10) μg L^{-1} for 60 d	-	-	Brain	Wang et al. [207]
Multi-approach	Zebrafish (*Danio rerio*)	-	-	Larvae	Freshwater	iHg	$HgCl_2$		Water	**401** (2 μM) μg L^{-1} for 3 d	-	-	Olfactory	MacDonald et al. [167]
Multi-approach	White seabream (*Diplodus sargus*)	146 ± 14	19 ± 1	Juvenile	Seawater	iHg	$HgCl_2$	-	Water	**2** μg L^{-1} for 7 and 14 d	-	-	Brain	Pereira et al. [23]
Multi-approach	White seabream (*Diplodus sargus*)	124 ± 11	18 ± 0.6	Juvenile	Seawater	oHg	-	CH_3HgCl	-	-	Diet	**8.7** μg g^{-1} for 7 or 14 d	Brain	Puga et al. [24]
Multi-approach	Flatfish (*Solea senegalensis*)	7.63 ± 2.08	8.73 ± 0.89	Juvenile	Seawater	oHg	-	CH_3HgCl	-	-	Water	**8.5** μg g^{-1} for 28 d	Brain	Sampaio et al. [258]
Multi-approach	White seabream (*Diplodus sargus*)	146 ± 14 and 124 ± 11	19 ± 1 and 18 ± 0.6	Juvenile	Freshwater	oHg or iHg	$HgCl_2$	CH_3HgCl	Water	**2** μg L^{-1} (0.265 μg g^{-1} bw) daily for 1, 3, 7 or 14 d	Diet	**8.7** μg g^{-1} (0.261 μg g^{-1} bw) daily for 1, 3, 7 or 14 d	Brain	Cardoso et al. [18]
Multi-approach	Yellowfin bream (*Acanthopagrus australis*)	-	0.07 - 0.12	Juvenile	Seawater	iHg	$HgCl_2$	-	Diet	**0.7**, **2.4** and **6** μg g^{-1} for 4, 8 or 16 d	-	-	Multi-organ	Harayashiki et al. [257]
Multi-approach	Peacock blennies (*Salaria pavo*)	23.2 ± 3.7	12.7 ± 1.3	Adult	Seawater	iHg	$HgCl_2$	-	Water	**49** (66) μg L^{-1} for 1, 4, 10 and 15 d	-	-	Brain	Naïja et al. [248]

[a] Levels correspond to total Hg levels measured in the fish feeds.
[b] Exposure during development.

Table 3
Summary of studies reporting the neuronal or sensory effects of inorganic and organic mercury forms (iHg and oHg, respectively) on several wild fish species from different areas worldwide. Maximum Hg levels reported for the water and sediment compartments were indicated. All the studies were reported to Actinopterygii fish, except the one of Bergés-Tiznado et al. [144] that was performed with a Chondrichthyes species.

Main approach	Species	Developmental state	Habitat type	Study location (system, country)	Hg hotspot area	Water Hg form	Maximum Hg level in water (ng L^{-1})	Sediment Hg form	Maximum Hg level in sediment (μg g^{-1})	Target organ	Possible interference of other contaminants	Reference
Toxicokinetics	Spotted seatrout (*Cynoscion nebulosus*)	Adult	Seawater	South Florida, USA	Yes	-	-	-	-	Multi-organ	Organic contaminants	Adams et al. [143]
Toxicokinetics	Multi-species	-	Seawater	Hokkaido/Chiba Prefectures (Pacific saury only), Japan	Unspecified	-	-	-	-	Multi-organ	-	Watanabe et al. [139]
Toxicokinetics	Bluefish (*Pomatomus saltatrix*)	Multi-stage	Seawater	New Jersey, USA	Unspecified	-	-	-	-	Multi-organ	-	Burger et al. [140]
Toxicokinetics	Golden grey mullet (*Liza aurata*)	Juvenile	Seawater	Aveiro lagoon, Portugal	Yes	Total Hg oHg/MeHg	4.4 1.0	Total Hg oHg/MeHg	2.9 0.029	Brain and Eye	Negligible	Pereira et al. [141]
Toxicokinetics	Multi-species catfish	Adult	Freshwater	Madeira River, Brazil	Unspecified					Brain	Negligible	Bastos et al. [142]
Toxicokinetics	Scalloped Hammerhead Shark (*Sphyrna lewini*)	Juvenile	Seawater	SE Gulf of California, Mexico	Unspecified	-	-	-	-	Multi-organ	-	Bergés-Tiznado et al. [144]
Effects on neurotransmission	Nile tilapia (*Tilapia nilotica*)	-	Freshwater	Alexandria, Egypt	-	-	-	-	-	Multi-organ	-	El-Demerdash and Elagamy [183]
Effects on neurotransmission	Mummichogs (*Fundulus heteroclitus*)	-	Multi-habitats	New Jersey, USA	-	-	-	-	-	Multi-organ	-	Smith et al. [192]
Biochemical and physiological effects	Golden grey mullet (*Liza aurata*)	Juvenile	Seawater	Aveiro lagoon, Portugal	Yes	-	-	Total Hg	6.8	Brain	Negligible	Mieiro et al. [215]
Biochemical and physiological effects	European seabass (*Dicentrarcus labrax*)	Juvenile	Seawater	Aveiro lagoon, Portugal	Yes	-	-	-	-	Brain	Negligible	Mieiro et al. [214]
Biochemical and physiological effects	Golden grey mullet (*Liza aurata*)	Juvenile	Seawater	Aveiro lagoon, Portugal	Yes	Total Hg oHg/MeHg	4.4 1.0	Total Hg oHg/MeHg	2.9 0.029	Eye	Negligible	Pereira et al. [189]
Biochemical and physiological effects	Yellow perch (*Perca flavescens*)	-	Freshwater	Nova Scotia, Canada	Yes	-	-	-	-	Multi-organ	Negligible	Graves et al. [216]
Morpho-structural changes	Golden grey mullet (*Liza aurata*)	Juvenile	Seawater	Aveiro lagoon, Portugal	Yes	Total Hg oHg/MeHg	- -	Total Hg oHg/MeHg	- -	Brain	Negligible	Puga et al. [250]
Multi-approach	Golden grey mullet (*Liza aurata*)	Juvenile	Seawater	Tagus estuary, Portugal	Yes	Total Hg oHg/MeHg	31.9 8.1	Total Hg	3.3	Brain and eye	Trace elements	Pereira et al. [249]

toxicant, all water and dietary exposures demonstrated Hg accumulation in the brain. However, Hg disposition between various organs, the Hg uptake levels and rates, as well as the severity of the detrimental effects in the brain, significantly differed between Hg^{2+} and MeHg exposures. Several field studies also reported the detectable levels of Hg in the fish (Chondrichthyes and Actinopterygii) brain following environmental exposures [139–144].

Following chronic (4 months) dietary exposure, Atlantic salmon (*Salmo salar*) parr accumulated higher levels of Hg in the brain when fed with MeHg-contaminated diet (4.3 and 8.6 μg g^{-1} of CH_3Hg^+) than with Hg^{2+}-spiked diet (7.4 and 74 μg g^{-1} of Hg^{2+}), reaching 1.16 μg g^{-1} (wet weight) in the brain after exposure to the lower concentration of MeHg. In addition, higher Hg levels in the MeHg-exposed fish were associated with more severe pathological injuries in the brain. Similar results were obtained by Gentès et al., who compared both oHg and iHg levels in the brain of zebrafish (*Danio rerio*) reared for up to 62 days on either MeHg- or Hg^{2+}-enriched diet (levels around 11 μg g^{-1} for both forms) [145]. Following MeHg exposure, the oHg levels in the brain were 49 times higher than those of iHg in the brain from the Hg^{2+} exposure. In addition, the final brain concentration of oHg from the MeHg-exposure was higher than the liver from the same exposure. For the Hg^{2+} exposure group, after 62 days of dietary intake, the levels of iHg in the brain were comparable to those in liver. The brain Hg concentrations were also found to be higher than liver and muscle following 8 weeks of dietary exposure to MeHg in zebrafish (*Danio rerio*) adults [138] and at 28 days of dietary exposure to MeHg (levels of total Hg in the feeds of 8 μg g^{-1}) in juvenile European seabass (*Dicentrarchus labrax*) [146]. Different distribution pattern of Hg bioaccumulation was reported by Skak and Baatrup, who investigated 4-week dietary exposure to MeHg (2.5 μg g^{-1} bw, levels correspond to Hg) in brown trout (*Salmo trutta*) and found Hg brain levels similar to muscle but only 30% of that in the liver and 20% of that in the spleen [147]. Bergés-Tiznado et al. evaluated Hg levels in the muscle, liver, kidney and the brain in juvenile scalloped hammerhead shark (*Sphyrna lewini*) from SE Gulf of California and found the lowest Hg in the brain [144]. Moreover, consistently with Skak and Baatrup [147], the levels in the brain correlated with those in the muscle. The dissimilarities among different studies in the Hg partition between target organs could, at least partially, be due to differences in the metabolic rates between fish species.

The exposures to waterborne Hg also led to higher brain accumulation in the exposure to MeHg than to Hg^{2+} [12,148]; however, in these exposures, Hg brain levels were generally lower than other target organs. For example, Pelcova et al. observed that the total Hg content in the brain of the juvenile common carp (*Cyprinus carpio*) following 14-day water Hg^{2+} exposure (0.5, 1.5 and 3 μg L^{-1}) was the second lowest among tested tissues (kidney, gills, scales, spleen, liver and skin) [149]. Similarly, Skak and Baatrup, also reported higher levels of Hg in the olfactory organ, kidney, gills, liver and spleen than in the brain following 5-day exposure to Hg^{2+} in water (150 μg L^{-1}) [147]. However, in adult medaka (*Oryzias melastigma*) acutely exposed to waterborne Hg^{2+} (1000 μg L^{-1}), the brain Hg levels were higher than the liver after a 8 hour exposure [150]. Using juvenile zebra seabreams (*Diplodus cervinus*) exposed to waterborne MeHg (2 μg L^{-1}), Branco et al. found higher values of Hg in the kidney and the liver than in the brain [148]. Interesting results were reported by Korbas et al. who found higher levels of Hg in the eye lens and the retina than the brain of the zebrafish larvae acutely exposed to relatively high concentrations of MeHg in water [216 μg L^{-1} for 36 h (CH_3HgCl) or 431 μg L^{-1} for 36 h (CH_3HgCys)] [12]. Using juvenile white seabreams (*Diplodus sargus*), Cardoso et al. contrasted the brain accumulation following dietary exposure to MeHg with Hg^{2+} exposure in water as a likely scenario for environmental exposures by using similar daily intake levels (around 0.260 μg g^{-1} bw), and found consistently higher levels of Hg in the brain upon exposure to MeHg than Hg^{2+} [18]. Overall, the results from various studies indicate higher accumulation of MeHg in comparison with Hg^{2+} in the fish brain, irrespective of the route of exposure. Similar result was reported by Pereira et al., who assessed total, organic and inorganic Hg levels in the brain of the golden grey mullet (*Liza aurata*) from a Hg contaminated site at Aveiro lagoon in Portugal, finding that the fish brain preferentially accumulated MeHg over iHg [141].

Interestingly, Hg was not detected in the brain following a single intravenous injection of $^{203}Hg^{2+}$(~500-667 μg kg^{-1} bw) in adult rainbow trout (*Oncorhynchus mykiss*) (up to 21 days post exposure) [119]. Borg-Neczak et al. reported low levels of Hg in the brain (significantly lower than the liver or the blood) following similar intravenous exposure at significantly lower exposure level (54 μg kg^{-1} bw $^{203}Hg^{2+}$) in adult pike (*Esox lucius*) [151]. Both groups compared the intravenous and the waterborne exposure, observing significantly higher Hg accumulation in the olfactory bulbs in the brain following exposure in water. This result led the authors to conclude that the BBB limited the penetration of Hg^{2+} into the CNS and that the axonal transport of Hg^{2+} could play an important role in the bioaccumulation of iHg in the specific areas of the fish CNS.

The toxicokinetics data for Hg uptake in the brain were mostly reported for dietary MeHg and waterborne Hg^{2+} exposures. Generally, irrespective of the route of exposure, the increase in brain Hg levels was linear in time [18,116,145,149]. For waterborne Hg^{2+} exposure, the accumulation rate of Hg in the brain was significantly slower than that reported for other target organs and especially for the detoxification and input tissues. Pelcova et al. found that the brain had lower accumulation rate than gills, spleen and scales [149]. Similarly, Oliveira Ribeiro et al. reported slower accumulation rate for waterborne Hg^{2+} in the brain than in the gills, liver, skin, muscle and gut upon exposure to 15 μg L^{-1} [152]. In addition, the Hg accumulation rate in the brain was one order of magnitude higher for dietary MeHg exposure (8.7 μg g^{-1}) than for the Hg^{2+} exposure in water (2 μg L^{-1}) [18]. Also, in contrast with Hg^{2+} exposure, the accumulation rate of MeHg in the brain was higher than in the muscle or liver [145]. Interesting result was reported by Maulvault et al., who investigated the effect of seawater temperature on the accumulation of MeHg through diet (8.0 μg g^{-1}) and found that fish exposed to warmer water (22 °C) exhibited in general higher MeHg contents in brain than fish exposed to lower temperature (18 °C) [146]. The chemical form of Hg had also affected its elimination rate from the brain. The Hg levels in the brain accumulated following Hg^{2+} water exposures were either unchanged [18,116] or slightly increased [149,152] following the post-exposure phase when the toxicant was no longer present in the external environment. Pereira et al. also found that Hg levels in the white seabream (*Diplodus sargus*) brain exposed to waterborne Hg^{2+} (2 μg L^{-1}) were negatively correlated with the blood Hg levels in the post-exposure period indicating that iHg could not be eliminated from the brain [116]. Following waterborne MeHg, the total Hg levels in the brain were either decreasing in the depuration phase [18,146] or increasing [148]. Maulvault et al. investigated the process of MeHg elimination (upon dietary exposure to 8.0 μg g^{-1}) from the brain at two temperatures (18 °C and 22 °C) and found that 14 days after cessation of exposure, the elimination factor was significantly higher for 22 °C than 18 °C (13.8% against 3.5%, respectively) [146]. However, after additional 14 days of depuration, the elimination factor increased to 20% at both temperatures. Also, the elimination of MeHg was more efficient for the liver than the brain (elimination factor of 64.2% *versus* 20%, at 18 °C) [146]. Overall, these studies confirmed that the brain is the primary target organ for MeHg but the persistence of iHg in the brain may lead to detrimental effects, despite its overall lower levels therein. Another significant finding is that warming environments may lead to significant changes in MeHg toxicokinetics [146].

Only few studies investigated spatial distribution of Hg in the fish brain. Using whole-body autoradiography following waterborne $^{203}Hg^{2+}$ exposure in adult rainbow (*Oncorhynchus mykiss*) and brown trout (*Salmo trutta*), Rouleau et al. were able to identify the preferential sites for Hg accumulation in the brain [119]. The highest radioactivity

levels were detected in the olfactory system (including the bulbus olfactorius in the brain) but labeling of this part of the brain was limited to the most anterior part. Slightly lower labelling was detected in the rhombencephalon and mesencephalon. A weaker labelling was observed in corpus cerebellum, eminent granulates and choroid plexus. The concentrations of Hg, as shown by the radioactivity levels, were very low in telencephalon, optic tectum and diencephalon [119]. Korbas et al. used a synchrotron-based X-ray imaging method (X-ray fluorescence imaging) to compare Hg distribution patterns (at the microscopic level) in zebrafish (*Danio rerio*) larvae acutely exposed to four different Hg formulations in water (details on levels and formulations on Table 2) [12]. This unique approach in toxicological studies allowed them to reveal dramatic differences in the accumulation of Hg in the brain following oHg and iHg exposures. Generally, oHg accumulation in the brain was more widespread and at overall higher levels than for the iHg exposures, which showed more localized distribution. This result is consistent with the demonstrated ability of MeHg-S(Cys) conjugate to cross BBB using the LAT transporter [132] and indicative of significantly less efficient transport of Hg^{2+} into the brain. In addition, the localized pattern of the iHg distribution does not support a passive diffusion of iHg across the BBB. Upon exposure to MeHg (independent from the bound ligand, as chloride and cysteine conjugates were used in this study), Hg was detected in the telencephalon, optic nerve, diencephalon and medulla oblongata with overall slightly higher levels in the white *versus* gray matter. Following exposures to Hg^{2+}, Hg was specifically localized in the ventricular regions of the brain, whereas the oHg was excluded from this region [12]. Inorganic Hg was also detected in the habenula. Interestingly, irrespective of the Hg species in water, all exposures resulted in the preferential accumulation of Hg in the fish pineal gland [12]. In the follow up study, by using sub-micron resolution X-ray fluorescence imaging, Korbas et al. were able to pinpoint the exact localization of Hg in the zebrafish pineal gland upon MeHg exposure as the outer segments of the pineal photoreceptors [13]. The pineal organ of bony fish is a directly photosensory organ and the pineal photoreceptors cells are similar to those in the retina [153]. The pineal gland secrets melatonin, which helps to regulate processes displaying daily or seasonal rhythms [154]. Thus, it could be hypothesized that Hg accumulation therein could potentially interfere with the fish circadian clock. Up to date, there is however no further evidence to support it.

Due to high affinity of Hg to selenols ($\sim 10^6$ higher than for thiols) and ability to form extremely strong Hg-Se bond [155], Hg metabolism is tightly linked with that of selenium (Se) [156]. This interaction becomes especially important in the brain as Se is required for maintaining the proper function of the brain [157]. The formation of the HgSe complexes in the nanoparticulate form in the human brain was revealed by Korbas et al. and could be connected with the initial uptake of methylmercury cysteineate to the brain and its subsequent demethylation leading to the HgSe deposition [158]. The interaction between Hg and Se has not been extensively studied and especially not in the fish CNS. Recently, MacDonald et al. reported formation of nano-sized co-localized deposits of Hg and Se $HgS_xSe_{(1-x)}$ in various tissues of the zebrafish (*Danio rerio*) larvae acutely exposed to Hg^{2+} in water (401 μg L^{-1} up to 48 h) [159]. Following the Hg exposure, the Hg-Se deposits could be located in the pronephric ducts, pigmented retinal epithelium, the pineal gland, the dorsal thalamus and the habenula. Interestingly, these spots could not be observed in the MeHg-exposed fish, likely due to much longer time scale of the demethylation of MeHg, which precedes the formation of the Hg-Se deposits, as shown by Korbas et al. [158]. In another study, dietary exposure to MeHg (5.2 or 9.8 μg g^{-1} for up to 8 weeks) did not affect endogenous Se levels in the muscles of the zebrafish (*Danio rerio*) but the Se concentrations in the liver and the brain could not be assessed as the they were close to the limit of quantification [138]. In the same study, 8-week co-exposure to dietary selenomethionine (SeMet) and MeHg resulted in the decreased accumulation of Hg in the zebrafish muscles after 8 weeks compared to fish on MeHg-only diet. In the follow up study, zebrafish fed both MeHg and SeMet had lower levels of Hg in the brain compared to those on the MeHg-only diet [160]. In addition, the SeMet supplementation along with the MeHg diet allowed the fish to maintain a brain proteome more similar to that of the control animals, thus providing some level of protection against the detrimental effects of MeHg. Similar result was reported by Branco et al., who found lower levels of Hg in the brain (and other organs as well) when zebra seabreams (*Diplodus cervinus*) were co-exposed in water to MeHg and selenite compared to the MeHg-only exposure [148]. However, in the fish co-exposed to Hg^{2+} and selenite, total Hg levels in the brain remained on the same level as in the Hg^{2+}-only group. In addition, exposure to MeHg led to a decrease of endogenous Se levels in the brain, whereas for the Hg^{2+} exposure, the endogenous Se was not affected, likely due to lower accumulation of Hg^{2+} compared to MeHg. The authors hypothesized that the decreased accumulation of MeHg in the presence of selenite in water could stem from increased production of selenoprotein P trapping MeHg and preventing its entry into the brain and other organs, or it could also be a result of increase secretion of MeHg in the presence of Se. These results show that Se can significantly alter Hg toxicokinetics in the fish brain but the underlying molecular mechanisms for this interaction are still poorly understood.

3.2. Eye

The accumulation of Hg in the fish eye has not been studied extensively as the eye has not been considered the primary target organ for Hg until recently. The eyes play crucial role in many aspects of fish behavior such as mating, ensuring adequate food supply and orientation in space. Thus, Hg uptake by this neurosensory organ may result in adverse effects on fish fitness and survival.

The deposition of Hg in the eye was confirmed following dietary exposure to MeHg [147,161,162], water exposure to either MeHg or thiomerosal [10,12] and water exposure to Hg^{2+} [12,116,119,149,163], as well as in a field study [141]. Following dietary exposure to MeHg (2.5 μg g^{-1} bw once a week for 4 weeks) in brown trout (*Salmo trutta*), low levels of Hg (lowest among all tested organs) were detected in the lens [147]. Hg accumulated in the lens also following Hg^{2+} water exposures in zebrafish (*Danio rerio*) larvae [163]. Also using zebrafish larvae, Korbas et al. compared distribution and levels of Hg in the lens following water exposures to either MeHg or Hg^{2+} (details on exposure levels and forms in Table 2), finding ~80-fold increase in the cellular Hg concentrations in the periphery of the lens from the MeHg-exposed fish as compared to the Hg^{2+}-exposed lens [12]. However, no Hg could be detected in the eye lens interior following Hg^{2+} water treatments [12]. The preference of MeHg for accumulating in the eye lens was unprecedented as the *in-situ* concentrations of Hg in the lens were higher than those in the brain, muscle, liver, kidney and olfactory system. A subsequent study identified the secondary lens fibres as the main site for the MeHg accumulation inside the zebrafish lens [13]. Interestingly, the accumulation of Hg in the lens continued after removal of the zebrafish larvae from the MeHg-contaminated waters indicating redistribution of Hg from the original target organs to the eye lens [11]. Using juvenile white seabreams (*Diplodus sargus*) Pereira et al. traced the toxicokinetics of waterborne Hg^{2+} (2 μg L^{-1}) separately in the eye lens and the eye wall [116]. Interestingly, the levels of Hg in the lens remain unchanged throughout the exposure and post-exposure period and, in general, no statistical difference was found between the lens Hg levels in the control and the exposed fish. In contrast, the eye wall Hg levels showed similar pattern to the brain, i.e., increasing with the exposure times and staying leveled in the post-exposure period. Interestingly, the levels of Hg in the eye wall did not correlate with the levels of Hg in the blood (opposite to the blood-brain levels) prompting the authors to conclude that blood-retina barrier (BRB) has lower permeability to Hg^{2+} than BBB [116]. The accumulation of Hg in the eye wall and specifically in

the eye retina was also reported for MeHg. The Hg uptake through water exposure into the retina was more efficient for MeHg as it resulted in ~10 times higher concentrations of Hg compared to Hg^{2+} treated fish [12]. Moreover, by using sub-micron resolution X-ray fluorescence imaging technique, Korbas et al. were able to identify the outer segments of the retinal photoreceptors and the outer plexiform layer as the main sites for Hg deposition following waterborne MeHg exposure in the developing zebrafish larvae [13]. However, lower levels of Hg were deposited across the whole retina. Mela et al. reported in an autometallographic study of Hg localization the retina following dietary exposure to MeHg (13.5 μg g^{-1}) in adult zebrafish by 50 days [161] and thraira (*Hoplias malabaricus)* (exposed to 0.075 or 0.75 μg g^{-1} for 70 d) [162]. Hg deposits were present in the photoreceptor layer of the retina (both fish species), inner and outer plexiform layer (thraira) and inner and outer nuclear layer (zebrafish). The mechanisms of MeHg transport into the lens or the retina are at present unknown but appear to involve an active transport rather than passive diffusion [12]. The eye retina is shielded from a direct access from blood by the BRB, which is composed of both the inner and the outer barrier [164]. The outer BRB is formed at the retinal pigmented epithelium and it regulates the access of macromolecules from the choroid to the outer segments of the photoreceptors. The inner BRB, more similar to BBB, is comprised of retinal endothelial cells, which line the retinal micro vessels providing the other retinal cells with the nutrients. Both human inner and outer BRB contains multiple transporters including LAT1 [165], which has been shown to actively transport MeHg-S(L-Cys) [132]. It is therefore possible that similar transporters are involved in regulating access of MeHg across the fish BRB. Consistently with the laboratory results, Pereira et al. found that the eye wall and the lens of the golden grey mullet (*Liza aurata*) from a Hg contaminated site (Aveiro lagoon, Portugal) preferentially accumulated MeHg over iHg in the eye wall and the lens. Additionally, MeHg levels in the eye wall were correlated with those in the brain, pointing out to a similar uptake system from the bloodstream for those two compartments [141].

3.3. Olfactory system

Olfaction allows fish to process critical environmental information to facilitate mating, homing, locating food and avoiding predators. The presence of toxic contaminants in waters can impair these behaviors by direct effect on the olfactory system [95]. Several studies reported the uptake of Hg into the olfactory system following either dietary MeHg [147,166], water Hg^{2+} [12,119,147,151,166–168] or water MeHg [12] exposures. Korbas et al. compared the localization and tissue concentrations of Hg in zebrafish larvae acutely exposed to either Hg^{2+} (chloride or cysteineate conjugates) or MeHg (chloride and cysteineate conjugates) (exposure levels detailed in Table 2) [12]. Similar levels of Hg in the olfactory epithelium were found in the fish exposed to either of the chemical forms of MeHg as well as mercuric chloride. However, in the case of the mercuric bis-cysteineate exposure, the olfactory epithelium had four times lower concentrations of Hg despite 200 times higher Hg concentration in the water as compared to other exposures [12]. MacDonald et al. used the sub-micron X-ray fluorescence imaging to study the cellular localization of Hg in the olfactory epithelium of zebrafish larvae exposed to waterborne Hg^{2+} (401 μg L^{-1} for 3 days) and found Hg distributed independently of the cell nuclei marked by P (phosphorus) in the elemental distribution maps [167]. In addition, tubuline immunofluorescence staining of the olfactory system revealed decreased immunoreactive tubuline levels in the olfactory pits possibly due to the cell death [167]. Bioaccumulation of Hg and histomorphological changes in the olfactory epithelium were also observed in *Labeo rohita* after 15-30 days exposure to waterborne Hg^{2+} (49 or 98 μg L^{-1}) [168]. Baatrup and Doving [166] studied the deposition of iHg (waterborne; 270 μg L^{-1} for 2, 6 or 12 h) and oHg (dietary; 2.5 μg g^{-1} bw once a week for 4 weeks) in the olfactory system of salmon (*Salmo salar*). Using autometallographic method for Hg detection in the fish tissues, they found silver-enhanced Hg deposits in the olfactory epithelium following iHg and oHg exposures. However, the Hg accumulation pattern differed between iHg and oHg treatments. Whereas for oHg exposure the Hg was predominantly detected within the receptor cells, it was mainly situated along the borders of the neighboring receptor and sustentcular cells in the iHg-exposed fish. Also, following dietary oHg exposure, Hg accumulated in Schwann cells and axons throughout their entire length (from the sensory epithelium to the bulbus olfactorius) [166]. In the case of the waterborne iHg exposure, the authors contrasted two routes of Hg^{2+} delivery to the olfactory system, i.e., (1) direct route from the water within the nasal cavity (one naris left open allowing free access to Hg^{2+} contaminated water with the other naris obstructed with vaseline) and (2) Hg^{2+} absorption through gills and distribution to the olfactory system in the bloodstream [166]. The quantitative analysis using $^{203}Hg^{2+}$ showed approximately 10 times lower deposition of Hg in the olfactory rosettes in the blocked naris than in the open one suggesting that the olfactory epithelium primarily received Hg from the water in the nasal cavity. In contrast, the staining of the olfactory nerves was reported the same for the blocked and unobstructed naris, which prompted the authors to conclude that the blood was the only source of Hg in the olfactory nerves. However, the results of the subsequent study on Hg^{2+} accumulation in the olfactory system by Borg-Neczak et al. challenged that statement [151]. Therein, Hg^{2+} was directly applied to the olfactory chambers of pike (*Esox lucius*) with both nares closed with latex seal after the application of the Hg^{2+} solution (27 μg pipetted to each naris). Such treatment resulted in labelling of the olfactory epithelium and the olfactory nerves up to the superficial zones of the bulbus olfactorius. When Hg^{2+} was applied to only one naris, the other side of the olfactory system including the respective olfactory nerves and the bulbus olfactorius remained unlabeled. In addition, when Hg^{2+} was applied intravenously (0.054 μg g^{-1} bw single injection), labelling of the olfactory rosettes and the olfactory nerves remained low. Based on these results, the authors concluded that, following Hg^{2+} application in the olfactory chamber, Hg that accumulated in the olfactory nerves and the olfactory bulbs did not originate from the blood, which was in contrast to the conclusion drawn by Baartrup and Doving [166]. Instead, Borg-Neczak et al. [151] attributed the accumulation of Hg in the olfactory nerves to the axonal transport of Hg^{2+} in the olfactory system, i.e., the anterograde movement of Hg species from the olfactory receptor cells in the olfactory epithelium to the axonal terminals in the bulbus olfactorius [151]. The presence of the axonal transport was also suggested by Rouleau et al. based on the Hg labelling of the olfactory system of rainbow trout and brown trout following waterborne Hg^{2+} exposures [119]. Similar transport was also suggested for the iHg uptake in the rat olfactory system [169]. By exposing rats to iHg trough intranasal instillation of $^{203}Hg^{2+}$ only in one nostril (similarly to Borg-Neczak et al. [151] in fish), strong labeling of the bulbus olfactorius and the olfactory nerve bundles (projecting to the olfactory bulb) was observed but only in the exposed nostril. The authors, similarly to Borg-Neczak et al. [151], concluded that their results could only be ascribed to the movement of Hg along the olfactory axons and not to circulatory uptake from the mucosal vasculature [169]. However, Hg axonal transport following uptake from the systemic circulation, as originally suggested by Baartrup and Doving [166], cannot be excluded and therefore it is likely that Hg accumulation in the olfactory bulb is a result of both Hg circulating in the blood and transported along the axons.

Little is known, especially in fish, about the mechanism for the uptake of Hg (either iHg or oHg) in the olfactory receptors and its subsequent transport along the axonal pathway, as most studies were focused on only reporting the presence of the retrograde axonal transport of Hg in rats [170–172] or mice [173]. Simple diffusion, endocytosis or uptake via sodium or calcium channels have been considered but no particular mechanism of uptake in the olfactory system has been confirmed by the experimental studies.

3.4. Inner ear

We were able to identify only one study that investigated the accumulation of Hg in the fish inner ear [147]. The authors measured the accumulation of both iHg and oHg in brown trout (*Salmo trutta*) and found differential accumulation of Hg in the inner ear following either dietary exposure for 4 weeks (2.5 μg g^{-1} bw once a week) or water exposure for 5 days (150 μg L^{-1}), respectively. Following both exposures, Hg deposits were found in the trout utriculi. In the MeHg-exposed group, the levels of Hg in the utriculi were significantly higher than those in the gut, the brain, the gills, the muscle and the olfactory organ. In contrast, the levels of Hg in the utriculi from the Hg^{2+}-exposed group were at the same level as in the brain but significantly lower than the levels in the kidney and the gills. The distribution of Hg deposits was also different for each exposure. In the fish exposed to MeHg, Hg deposited predominantly in the apical part of the sensory epithelium, inside both the sensory cells and the supporting cells. In contrast, when fish were exposed to waterborne Hg^{2+}, Hg was mainly found along the borders of neighboring cells throughout the depth of the epithelium. Both Hg distribution patterns in the inner ear sensory epithelium resembled those in the olfactory epithelium suggesting common mechanism for Hg deposition in the sensory epithelia.

3.5. Lateral line system

The mechanosensory line system, the so-called lateral line, is another sensory system that allows fish to detect changes in water flow and pressure and is composed of hundreds of superficial structures called neuromasts, spread across the fish body (head, trunk and tail fin). A single neuromast consists of a hair cell epithelium and a cupula that connects the ciliary bundles of the hair cells with the surrounding waters. The evidence for Hg accumulation in the neuromasts is scarce. Rouleau et al. implicated the mechanoreceptors of the lateral line could provide the entry for the waterborne Hg^{2+} axonal transport to the brain [119]. Korbas et al. reported Hg deposition in the neuromasts of the zebrafish (*Danio rerio*) larvae following acute waterborne exposures to 1 μM of either Hg^{2+} or MeHg [12]. The *in situ* tissue concentrations of Hg in the neuromasts from the MeHg-exposed fish were twice as high as those from the Hg^{2+} exposure, demonstrating more efficient uptake of MeHg into those structures [12]. However, no further studies of the effects of Hg exposure on the function of the neuromasts could be identified.

In summary, exposure to mercury leads to its accumulation not only in the fish CNS but also in the fish sensory systems (eye, olfactory system, inner ear, lateral line). Mercury accumulates in the fish brain following exposures to either iHg or oHg in water or through diet. However, the uptake of oHg is more efficient as it leads to overall higher levels of Hg, especially in the brain and the eye. Both iHg and oHg could access the brain trough blood circulation and/or direct uptake through sensory cells and subsequent axonal transport to the specific areas of the brain. The uptake rates for iHg and oHg in the CNS and sensory systems are different for various fish species and also depend on the water temperature. Interestingly, a similar pattern of iHg and oHg accumulation in the inner ear and olfactory epithelia indicates a common mechanism for Hg uptake in these sensory tissues. Overall, Hg deposition in the sensory systems indicates that direct effects on these tissues could play a role in the disruption of vision, olfaction and other sensory processes by Hg in fish.

4. Effects of mercury on neurotransmission processes in fish

The exposure to neurotoxic compounds can alter the nervous cells, fibers and myelin sheaths, compromising the neurotransmission processes and thereby impairing, more or less extensively, the nervous system functions. The neurotransmitters are essential for the correct transmission of nervous message along the synapse between nerve cells, or between the presynaptic cells and other type of cells (*i.e.*, muscles and glands). In fish, the lipophilic oHg exceeds the BBB and bioaccumulates in nervous system, causing biochemical, physiological and structural injuries [44], as explored in sections 5 and 6. Therefore, Hg can interfere with the synthesis and release of neurotransmitters, influencing the enzyme activity and interfering with receptors, with consequent accumulation of neurotransmitters in the synapse [174]. Because each neurotransmitter acts on multiple communication ways, the impairment of neurotransmission affects several functions in fish, such as response to external stimuli, behavior and reproduction. In fish, all these activities need the involvement of neurotransmitters, namely acetylcholine (ACh), serotonin (5-HT), dopamine (DA), norepinephrine (NE) and gamma aminobutyric acid (GABA).

It is well documented, in mammals as well as in fish, that Hg, both in its inorganic ($HgCl_2$) and organic (MeHg) forms, is able to interfere with the cholinergic nervous system, impairing choline acetyltransferase (ChAT) activity, choline uptake and acetylcholinesterase (AChE) activity [175]. The enzyme AChE hydrolyses ACh in the CNS, in the neuromuscular junction, and in the autonomic nervous system (parasympathetic and sympathetic synapses) of both vertebrates and invertebrates, and the evaluation of its activity is widely used as neurotoxicity biomarker in environmental monitoring studies [175–180]. Gill and co-workers [181] in a laboratory study with the freshwater fish rosy barbs (*Puntius conchonius*) evaluated the modulation of AChE activity after *in vivo* and *in vitro* exposure to $HgCl_2$. In details, after *in vivo* exposure of individuals for 48 h at 134 μg L^{-1} (as Hg^{2+}), the AChE activity was significantly decreased, in respect to the control, in the brain but not in the muscle. *In vitro* tests, using the homogenates added as $HgCl_2$ (at concentrations from 0.02 to 20,060 μg L^{-1} as Hg^{2+}), showed that the AChE activity was depressed at 200 μg L^{-1} Hg in all examined tissues [181]. The anticholinergic effect of iHg ($HgCl_2$) was also recently documented in the brain of the freshwater fish *Oreochromis niloticus* after acute (81 μg L^{-1} as Hg^{2+} for 3 days) and chronic (8.1 μg L^{-1} as Hg^{2+} for 30 days) exposures [182]. A field study with *Tilapia nilotica* from unpolluted and polluted sites in Egypt, showed a statistically significant inhibition of AChE activity in the brain of fish from the polluted area [183]. In the same study, an *in vitro* experiment highlighted that $HgCl_2$ (0.07 or 370 μg g^{-1} as Hg^{2+}) inhibits the brain AChE activity at all concentrations in a dose-dependent manner [183]. In line, a significant inhibition of AChE activity was recorded in juvenile specimens of the estuarine fish *Pomatoschitus microps* exposed to sub-lethal and ecologically relevant concentrations of $HgCl_2$ (3.125, 6.25, 12.5, 25, 50 μg L^{-1} as Hg^{2+}, nominal concentrations) for 96 h [184]. In this experimental study, it was also carried out the evaluation of AChE activity using two different approaches, the Ellman's method and the *o*-nitrophenylacetate assay, because it is possible that Hg reacts with the products of the Ellman's technique [185]. Both techniques showed a significant inhibition of enzymatic activity after exposure to Hg, but the *o*-nitrophenylacetate assay was effectively more sensitive reporting 54% of inhibition at 50 μg L^{-1}. In zebrafish brain, it was also documented the alteration of AChE activity after exposure to waterborne $HgCl_2$ (15 μg L^{-1} as Hg^{2+}), with a significant decrease after 24 h of treatment, followed by significant increase at 96 h, and normalization of the enzyme activity after 30 days of chronic exposure [186]. The reduction in AChE activity could be attributable to the binding of Hg to lipid-rich structural components of mitochondria, which may lead to ionic fluxes, differential membrane permeability and disturbed metabolic and nervous activity, or also be related to the decreased synthesis of the enzyme by the inhibitory nature of Hg.

In what concerns the organic Hg forms, similar findings were reported in the adult Japanese medaka *Oryzias latipes* after the exposure to sub-lethal concentrations of MeHgCl (2.5 to 40 μg L^{-1} as CH_3Hg^+), since inhibition of total ChE activity, including AChE and butyrylcholinesterase (BuChE), was detected in the brain (for 8, 16 and 24 days of exposure) [187]. In contrast, no differences in the brain AChE activity were observed in golden shiner (*Notemigonus crysoleucas*) fed

for 90 days with low-MeHg diet (0.455 μg g^{-1} Hg) or high-MeHg diet (0.959 μg g^{-1} Hg), among treatments and in respect to control [188]. The same authors [188] hypothesized that the results may be dependent on the Ellman's method applied, in terms of different sensitivity, enzymes, or forms of enzymes reacting with different substrates, as supported by other authors that used a modified Ellman's method by using *S*-acetylthiocholine iodide as the substrate [187].

In a recent field study, a depletion in the AChE activity was recorded in the eye wall of wild grey mullet *Liza aurata* environmentally exposed to Hg, concomitantly with elevated levels of iHg (0.029 μg g^{-1}) and MeHg (0.28 μg g^{-1}) accumulated in the same organ, clearly indicating that both Hg forms interfere with neurotransmission processes [189].

These results, all together, indicate that both Hg forms can act as cholinergic disruptor by binding the sulfhydryl group and inducing a conformational change in ChE, therefore depressing the AChE activity (although it depends on Hg concentrations and time of exposure) and leading to an overstimulation of the target cells, events that may threaten the vital functions of fish. However, a higher consensus is evident for iHg form.

The monoamine neurotransmitters include 5-HT and the catecholamines DA, NE and epinephrine. The 5-HT synthesis from amino acid tryptophan is catalysed to tryptophan-5-hydroxylase, and the serotoninergic system plays a crucial role in the fish, together with the dopaminergic system, in the control of physiological functions and behavior. Adult catfish *Clarias batrachus* exposed to sub-lethal concentrations of $HgCl_2$ (37 μg L^{-1} as Hg^{2+}) and CH_3HgCl (34 μg L^{-1} as CH_3Hg^+) displayed a significant reduction of 5-HT in the brain after 90 and 180 days, highlighting that oHg is more toxic in respect to the inorganic form [190]. In the same study, a significant increase of DA and NE was reported in the brain of catfish after 90 and 180 days of exposure to iHg and MeHg forms [190].

Tsai and co-workers [191] estimated the effects of iHg on 5-HT concentration in the brain of *Oreochromis mossambicus* from 7 days post-hatching for 6 months. During this experimental plan, fish were exposed to $HgCl_2$ (11 and 22 μg L^{-1} as Hg^{2+}) and the results showed a significant dose-dependent 5-HT reduction in the hypothalamus. No variations were observed in other brain regions such as telencephalon and optic tectum. These findings indicate that the serotonergic system may be mercurophilic, since iHg may mediate the cerebrospinal fluid to act directly on cerebrospinal fluid contacting serotonin neurons or diffuse to act on the hypothalamic serotonergic neurons. Additionally, numerous studies reported that mercurials affect the synaptic transmission by blocking the voltage dependent Ca^{2+} channel, depleting the release of neurotransmitters and inhibiting the binding of serotonin at its synaptic sites [191]. Moreover, a significant decrease of 5-HT concentration was recorded in the medulla oblongata of adult fish *Fundulus heteroclitus* from Piles Creek (PC; New Jersey, USA), a Hg polluted site (0.066 μg g^{-1} total Hg in the brain) in respect to the samples collected near Tuckerton (TK), a reference site (0.029 μg g^{-1} total Hg in the brain) [192]. Additionally, no differences were reported for DA concentration both in medulla oblongata and cerebellum [192]. Subsequently, an experimental study [193] carried out with embryos obtained from the adult *F. heteroclitus* sampled in the same sites showed, after exposure to 10 μg L^{-1} MeHg, a relevant increase of 5-HT levels in the entire head of 7- and 14-day larvae from TK, while a drastic reduction was reported after 14 days in the larvae from PC (in respect to the untreated larvae). However, there were no significant differences in 5-HT levels between untreated TK and PC larvae, at both time of development. In the same experimental study, a significant increase in DA and decrease in dopaminergic activity were recorded in TK larvae, while the DA level was considerably higher than the control at 7 days post-hatch (dph), and significantly lower at 14 dph in PC larvae. The different responses recorded for the larvae from TK and PC sites are, probably, due to the different pollution degrees and, consequentially, to the mixture of contaminants influencing the Piles Creek site [193]. Surprisingly, no significant difference was reported in the levels of the neurotransmitters 5-HT, DA and NE in the brain of adult fathead minnows *Pimephales promelas* immediately after 10 days of exposure to $HgCl_2$ (1.7, 6.8 and 13.6 μg L^{-1} as Hg^{2+}) and after 10 days of recovery in uncontaminated water [194]. Contrarily, the dietary exposure of fish of the same species to MeHg (720 μg g^{-1} Hg dw) over 30 days caused significant changes in DA concentrations in the telencephalon of adult fish and decreases in monoamine oxidase (MAO) activity in the whole brain [195]. However, these findings also suggest that whole brain quantification may mask the variations of neurotransmitters levels in specific brain areas, which may be associated with alterations in biological functions and behavior [194]. Nevertheless, these data support the hypothesis that MeHg could enter the brain by crossing the BBB and the chorion in fish embryos, exerting its neurotoxic and embryotoxic effects.

In the brain of *Channa punctatus* a reduced MAO activity, resulting in disturbances in the aminergic system, was also recorded after exposure to both organic (methoxy ethyl mercuric chloride; 500 μg L^{-1}) and inorganic mercurial ($HgCl_2$; 148 μg L^{-1} as Hg^{2+}) for 20, 40 or 80 days [196]. Accordingly, also the neurochemical investigations performed in Hg-contaminated wild spotted seatrout *Cynoscion nebulosus* revealed reduced levels of N-methyl-D-aspartic acid (NMDA) receptors (glutamate receptors) in the brain (0.24 μg g^{-1} wet weight total Hg concentration) as subclinical neurological damage associated with Hg exposure, though muscarinic cholinergic receptor levels as well as MAO and AChE activities remained unaltered [143].

Moreover, the impairment of monoaminergic neurotransmission due to Hg, induced neurological dysfunction during the embryo-larval development and an alteration on the reproductive axis, with consequent reduction of gametogenesis and reproductive rate in the adult fish [197].

Overall, the findings in mammalian models provide interesting clues in relation to Hg interference with neurotransmission processes, reporting, for instance, MeHg-related alterations on the transmission of nervous impulses along the cell membranes [198], Hg^{2+}-related impairments on the release of neurotransmitters [199] and disruption on binding to the receptors associated to both MeHg and Hg^{2+} [200].

5. Biochemical and physiological effects of mercury on fish central nervous system (CNS) and sensory structures

The effects of both iHg and oHg can be studied at various planes of biological organization, including biochemical levels, which precede functional and structural effects detectable at higher levels up to the individual. Therefore, biochemical effects can be considered as early warning signals, or precocious biomarkers of exposure or response to Hg [201]. To date, there is considerable knowledge about how Hg is taken up by actinopterygian fish, distributed among tissues, and bound to specific molecules (as described in section 3), as well as about the biochemical pathways and enzyme functioning affected by Hg exposure, as highlighted by several cutting-edge mechanistic studies [202,203]. However, from a toxicological perspective, it is crucial to distinguish between iHg and oHg forms because of discrepancies in absorption, body distribution and toxic effects [44].

Mercury and its derivatives are known to be strongly bonded to thiol groups and disulfides, and therefore, highly interact with phosphates, cysteinyl and histidyl side-chains of proteins, provoking structural and functional alterations of enzymes, as well as of purines, pyrimidines, nucleic acids, and other cellular components [204].

5.1. Effects on central nervous system (CNS)

In fish, most of the Hg-induced biochemical disorders were documented in the CNS, which is a main target for Hg, with consequent inhibition of key enzymes for neurological function. As a matter of fact, Verma and co-workers [205] reported an inhibition of brain Na^+/K^+-ATPase in *Notopterus notopterus* exposed to waterborne $HgCl_2$ (17.6 - 88

μg L^{-1}, corresponding to 13 - 65 μg L^{-1} of Hg^{2+}) for 30 days, whereas in the brain of the catfish *Ictalurus punctatus* a considerable depletion in the activity of Ca^{2+}-ATPase was recorded, suggesting a possible disruption of calcium metabolism, essential in the CNS [206].

Alterations in the protein profiles of the brain of marine medaka *Oryzias melastigma* chronically exposed for 60 days to different $HgCl_2$ concentrations (0.7 or 7.4 μg L^{-1} as Hg^{2+}) were also documented, indicating that iHg may cause neurotoxicity through the induction of oxidative stress, cytoskeletal assembly dysfunction and metabolic disorders [207]. Similar findings were also observed by using a proteomic approach in the brain of Atlantic cod *Gadus morhua* following intraperitoneal injection of MeHg (0.4, 1.7 or 6.9 mg kg^{-1} bw) exposure for two weeks, as mitochondrial dysfunction, altered calcium homeostasis, disruption of microtubules and oxidative stress were noticed [39].

Zebrafish (*Danio rerio*) has been recurrently adopted as model species to address the biochemical processes underlying Hg impact on fish CNS. Hence, in brain of zebrafish acutely exposed to 0.5 μg g^{-1} body weight (bw) to MeHg administrated by intraperitoneal injection for 96 h, a microarray analysis showed effects on protein structure and the involvement of oxidative stress in the mechanism of action of MeHg [208], whereas in zebrafish treated with a MeHg diet (9.8 μg g^{-1} total Hg concentration) for 8 weeks, the brain proteome was changed, indicating mitochondrial dysfunction, disruption of calcium homeostasis and oxidative stress [160]. Moreover, induction of metallothionein production was recorded in brain of adult zebrafish dietary exposed for 2 months to MeHg (11.58 μg g^{-1}) and iHg (11.92 μg g^{-1}) [145]. Surprisingly, in the brain of zebrafish, after dietary exposure to MeHg (5 or 13.5 μg g^{-1}, measured as total Hg levels in the diet) over 7, 21 and 63 days, no change on the expression of genes involved in the oxidative stress defence system were observed, although the brain accumulated the highest Hg concentration in respect to other organs [209].

In fact, oxidative stress is one of the best-studied causative factors associated to Hg neurotoxicity in fish, as demonstrated in other species. In what concerns to iHg, it is worthy to note that a significant increment in lipid peroxidative products and depletion of total lipids were detected in the brain of catfish *Heteropneustes fossilis* following waterborne exposure to $HgCl_2$ (148 μg L^{-1} as Hg^{2+}) [210]. Interestingly, the dietary exposure to higher doses of $HgCl_2$ (7.4 or 74 μg g^{-1} as Hg^{2+}) did not cause brain lipid peroxidation (LPO) in juvenile Atlantic salmon *Salmo salar* (even though the brain was found contaminated with Hg and some other neurotoxic effects were observed, such as astrocyte proliferation and reduced MAO activity) [36].

Considering oHg exposures, the brain of juvenile European sea bass *Dicentrarchus labrax* dietary exposed for 28 days to MeHg (8.0 μg g^{-1} feed dw) showed alteration in some antioxidant enzymes activities, specifically increased catalase (CAT) activity and inhibition of superoxide dismutase (SOD) activity [211]. In contrast, inhibition of endogenous antioxidant enzymes, namely SOD and glutathione peroxidase (GPx), was found resulting in a general break-down of the redox defence system in the brain of Atlantic salmon dietary exposed to MeHg (4.3 and 8.6 μg g^{-1} d.w. as CH_3Hg^+) for four months [36]. In parallel, oxidative injury occurred in salmon brain after oral $HgCl_2$ administration (10 and 100 μg g^{-1} d.w., corresponding to 7.4 and 74 μg g^{-1} of Hg^{2+}), as observed from the high augmentation in LPO levels (as thiobarbituric acid reactive substances - TBARS) [36]. Interestingly, in the brain of zebra seabream (*Diplodus cervinus*) exposed to waterborne MeHg (0.5, 1 or 2 μg L^{-1} for 7, 14, 21 or 28 days), an increased activity of glutathione reductase (GR) was recorded in combination with inhibition of the thioredoxin reductase (TrxR), suggesting a complementarity between antioxidant defence and thioredoxin systems [148,212], as also documented in the brain of the Atlantic salmon as an effect of dietary lipids modulating MeHg (5 μg g^{-1} for 84 days) toxicity [213].

Changes in oxidative stress profiles were also detected in the brain of wild European sea bass *Dicentrarchus labrax* environmentally exposed to Hg (levels of total Hg detected in fish brain ranged from 0.04 to 0.23 μg g^{-1} w.w.). Specifically, ambivalent antioxidant responses were revealed, with increased GR activity, as a sign of protective adaptation, and reduced CAT activity, indicating elevated susceptibility to oxidative stress challenge [214]. Though the risk of an overwhelming reactive oxidative species (ROS) production could not be excluded, brain appeared to possess compensatory mechanisms and was able to avoid lipid peroxidative damage [214]. As an effect of environmental Hg exposure, an antioxidant system break-down was instead noticed in brain of feral golden grey mullet *Liza aurata*, which exhibited a depletion of total glutathione (tGSH), CAT, GPx, glutathione-*S*-transferase (GST) and GR activities, and, unexpectedly, unaltered LPO levels, correlated with augmented total Hg levels in the brain (0.04, 0.10 and 0.15 μg g^{-1} w.w.) [215]. Wild female of yellow perch (*Perca flavescens*) from Kejimkujik National Park and National Historic Site located in Nova Scotia (Canada), that has been termed a “biological mercury hotspot” because of the unusually high concentrations of Hg in the fish and loons inhabiting the lakes, were investigated for Hg neurotoxicity. Fish from that area had displayed catalase mRNA levels significantly lower in fish brain with the higher level of MeHg (from 0.38 to 2.00 μg g^{-1} w.w.). However, other oxidative and general stress-related transcripts did not show differential expression in the brain of wild perch over the Hg gradient [216].

Recently, a study carried out by Cardoso et al. [18] allowed the comparison of the pro-oxidant potential of both iHg and oHg forms, as similar daily exposure levels (~260 μg day^{-1} kg^{-1} bw) were tested under realistic exposure conditions. It was demonstrated in the brain of juvenile white seabreams *Diplodus sargus* that waterborne exposure to $HgCl_2$ (2 μg L^{-1} as Hg^{2+}) for 14 days triggered oxidative damage (as protein oxidation) without a proportional and efficient activation of the antioxidant system, whereas the dietary exposure to CH_3HgCl (8.7 μg g^{-1} as CH_3Hg^+ in feed dw) in the same period increased antioxidant protection, preventing oxidative damage, thus displaying a reduced neurotoxic potential as compared to waterborne iHg [18]. These findings are somewhat in counter-current with a preconceived idea (not yet fully proven in fish) as they seem to challenge the dogma that MeHg has higher neurotoxic potential in comparison to iHg. This is in line with a contemporaneous publication reporting that lower concentrations of divalent inorganic mercury Hg^{2+} (20 μM mercuric acetate) blocked bulk cellular thiols and protein-associated thiols in *Escherichia coli* more completely than higher concentrations of monovalent organomercurials (40 μM phenylmercuric acetate, PMA and 160 μM merthiolate, MT) [217].

This highlights a concept central in toxicology that advises against *lato sensu* assumptions of harmfulness of a given agent (or comparisons of different agents), as if it depended exclusively on an intrinsic toxicity. There are several factors that play a role at determining adverse effects and toxicity extent, namely those related with the exposure profile (*e.g.* routes, frequency, duration, co-exposures) and the target organism (*e.g.* species, age, gender). Overlooking these factors can lead to misunderstandings and inaccuracies on risk extrapolations. In fact, this flaw can be found in the literature on Hg neurotoxicity, which has led to the propagation of some dogmas, with the inherent risk of maladjustment on the definition of research priorities.

Recently, the hypothesis that nutritional aspects may interfere with Hg neurotoxicity, via, for instance, the interaction between MeHg and marine fatty acids has been addressed [218]. Thus, Atlantic salmon was fed experimental diets based on fish oil (FO) or vegetal oil (VO), with or without the addition of MeHg (5 μg g^{-1} measured as total Hg in the diet) for 3 months. Different dietary lipid sources did not affect the accumulation of Hg, but dietary MeHg resulted in decreased levels of 20:4 *n*-6 (arachidonic acid; ARA) in phosphatidylinositol in brain of VO fed fish [218], disclosing a possibility of interference with brain function and metabolism.

Neurophysiological impairments associated with Hg exposure were also disclosed in fish. Evidences of neuroendocrine disruption were

observed in the hypothalamus of largemouth bass *Micropterus salmoides* injected with MeHg (2.5 μg g^{-1} bw), for 96 h, and a detectable overlap in gene expression changes between the hypothalamus of laboratory-exposed fish and the whole brain of wild fish from MeHg-contaminated habitats were also highlighted, mainly as a significant reduction in reproductive neuropeptides [41]. A down-regulation in the gonadotropin-releasing hormone (GnRH) signalling network was also observed in the whole brain of juvenile beluga *Huso huso* fed with dietary MeHg (0.76, 7.88, and 16.22 μg g^{-1}) [219]. Interestingly, waterborne iHg (2.2 μg L^{-1} as Hg^{2+}) exposure for 15, 30 or 60 days, has been shown to affect the activities of lactate, pyruvate and succinate dehydrogenases in the brain of *Channa punctatus* [220], as also supported by the exposure to iHg (5, 10, 15 and 20 μg g^{-1} as mercuric nitrate) for 4.5 h in nine freshwater actinopterygian fish that caused the elevation of glucose and lactate in fish brain [221].

5.2. Effects on sensory structures/receptors

Besides the CNS, also the sensory organs of fish can be greatly affected by Hg toxicity. A number of studies have dealt with the functional derangement of the olfactory system of fish caused by exposure to sub-lethal levels of Hg. At the receptor level, it was found an olfactory inhibition induced by waterborne $HgCl_2$ (200.6 μg L^{-1} as Hg^{2+} for 1h 45 min) in the coho salmon *Oncorhynchus kisutch* due to interferences with the binding of L-serine to its olfactory cell membrane [222]. Similarly, also in the olfactory epithelium of the Atlantic salmon *S. salar*, Sutterlin and Sutterlin [17] reported that waterborne $HgCl_2$ (20,060 μg L^{-1} or 200,600 μg L^{-1} as Hg^{2+} for 10 seconds) acts as a blocking agent of the receptor chemosensitivity to a number of odorants. In accordance with these findings, a marked but reversible depression of the olfactory bulbar electrical response to the standard stimulant L-serine was recorded in the rainbow trout *Oncorhynchus mykiss* (formerly *Salmo gairdneri*) after perfusion of the olfactory organs with a $HgCl_2$ (0.05 μg L^{-1} as Hg^{2+} for 1, 2, 3 or 4 h) solution with appreciable effects observed within 2 h, and a slower recovery of the olfactory response with higher Hg concentrations and longer exposure time [223]. Interestingly, in the olfactory system of the salmon *S. salar* it was observed that the exposure to waterborne $HgCl_2$ (2,006 μg L^{-1} as Hg^{2+} for 5 min, followed by additional 15 min after 30 min with fresh water, it was found mainly along the sustentacular cells) caused an immediate but partly reversible depression of the electra-olfactogram (EOG) responses upon L-alanine stimulations, whereas the exposure to MeHg (2,156 μg L^{-1} as Hg for 5 min, followed by additional 15 min after 30 min with fresh water, it was found mainly within the receptor cells) induced an EOG steady decline and an irreversible extinction of olfactory receptor function [224]. Successively, it was also reported in larval stage of zebrafish that waterborne $HgCl_2$ (401 μg L^{-1} as Hg^{2+} for 3 days) specifically accumulates in the sensory cells of the olfactory pits, targeting tubulin-rich cells and interfering with essential cellular processes, such as microtubule formation. Indeed, Hg interfered with tubulin polymerization by binding the β-tubulin guanosine triphosphate (GTP) binding region, probably forming a highly covalent and stable Hg-S bond with a cysteinyl thiol group in the active site, as demonstrated by the depleted immunoreactive tubulin in zebrafish olfactory sensory cells, likely dead after Hg exposure [167].

Also the visual system of fish is susceptible to the toxicological effects of Hg, since the fish eye has a wide surface area continuously in contact with the external medium, and therefore could be a major uptake route of Hg as well as a primary target for its accumulation [11,141,189]. The complex morphological and neural retinal organization of fish eyes has been described, as well as the spectral sensitivities of retinal and extraretinal photoreceptors. It is known that fish possess a duplex retina, with a scotopic system mediated by rods for achromatic, high sensitivity and low acuity vision, and a photopic system mediated by cones for color, low sensitivity and high acuity vision at higher light intensities [225]. In fish, the vision mediates various behaviors, such as feeding, orientation and schooling [226], and, consequently, the functional disruption of fish eyes due to toxicants could affect fish fitness and survival. Visual deficits (as scotopic spectral sensitivity) were reported in rainbow trout following single injections of MeHg (4 or 5.3 μg g^{-1} as CH_3Hg^+), which provoked significant spectrally uniform decrements in visual sensitivity, due to a possible accumulation of Hg and subsequent functional changes in cones and rods [227]. It was also documented that waterborne Hg (10 or 40 μg L^{-1} for 11 weeks) alters the electrophoretic pattern of eye lens proteins in the euryhaline fish *Tilapia mossambica* [228]. More recently, electrophysiological anomalous effects were reported on horizontal cells in the retina of the tropical freshwater fish *Hoplias malabaricus* after acute and sub-chronic MeHg intoxication (0.01 – 6.0 μg g^{-1} by injection, dietary exposure to 0.75, 0.075 or 0.0075 μg g^{-1} for 70 days) [229], as well as depletion of immunoreactivity in parvalbumin amacrine cells and α protein kinase C bipolar cells [230]. These findings clearly indicate that MeHg plays a direct action on eye sensory cells, where it may be responsible for subsequent visual disturbances or vision loss [11,13]. The presence of Hg within the retina could be explained through the complex system of blood vessels at the inner limiting membrane in direct contact with the Muller cells and ganglion cell layer [231], from which Hg can also reach the outer and inner plexiform layers (respectively the first and second synaptic site in the retina of fish), as found in *H. malabaricus* after sub-chronic dietary exposure to MeHg (0.075 or 0.75 μg g^{-1} for 70 days) [162]. As stated above, the neurotoxic effect of Hg can be attributed to non-specific reactions with any sulfhydryl groups in the cell membrane, causing its breakdown and interfering with its permeability, with a consequent access of Hg into the cells and disturbances to their structural integrity and function, as well as interferences with important intracellular processes [44,204]. Damage to the plasma membrane of photoreceptors can change ionic flow and therefore alter membrane potential. Atypical outer segment morphology may change the phototransdution efficiency due to a decreased probability that a photon will be absorbed by a cone or rod [232]. Changes in juxtaposed membrane of the double cones may impair polarized vision in *H. malabaricus*, since the elliptical cross section of the inner segments act as a birefringent, polarization-sensitive and dielectric waveguide [162,225]. In a recent field study, high levels of iHg (0.029 μg g^{-1}) and MeHg (0.28 μg g^{-1}) were recorded in the eye wall of wild grey mullet *Liza aurata* environmentally exposed to Hg, in combination with reduced CAT and SOD activities, in line with the occurrence of peroxidative damage [189]. During the summer season, an increment of tGSH, GPx and GR activities was observed in the eye wall of grey mullet collected from the same area, with prevention of LPO occurrence, clearly indicating that Hg, both in its inorganic and organic forms, could exert ocular toxicity by the promotion of oxidative stress [189]. The ability of Atlantic salmon lenses to withstand oxidative stress *ex vivo*, with focus on the nutritional lipid history and exposure to MeHg (5 μg g^{-1} measured as total Hg levels in the diet) as a relevant dietary contaminant, was recently investigated. However, although the lenses accumulated Hg in response to dietary uptake, neither the oxidative status nor any physiological responses were affected [233].

It is well known that the fish gustatory system provides the final evaluation in the feeding process, which may be adversely influenced by exposure to toxicants. Unlike other vertebrates, in fish, the gustatory system, characterized by abundance of taste buds, may be divided in the oral and extraoral subsystems, both of them mediating behavioral responses to food items brought in contact with the fish [234]. There have been few experimental studies conducted on the effects of Hg on the behavioral taste response in fish. Hidaka [235] documented a suppressed taste receptor activity in the palatal organ of the common carp *Cyprinus carpio* after short-time waterborne exposure to $HgCl_2$ (20,060 μg L^{-1} as Hg^{2+} for 10 sec). Similar results were also observed in the catfish *Ictalurus punctatus*, in which the mercuric ion (20,060 or 200,600 μg L^{-1} as Hg^{2+}) reduced the binding of L-alanine to taste

receptor sites irreversibly [236]. Contrarily, Kasumyan [237] demonstrated that the loss of taste responses in fish after exposure to $HgCl_2$ solutions (from 200.6 to 0.02 μg L^{-1} as Hg^{2+}) is reversible. Indeed, in common carp exposed for 3 h, the recovery of taste preferences to L-cysteine was recorded after 6-12 days, and a direct relationship between the duration of the exposure to a toxic compound and the duration of the recovery period was also highlighted.

The neurosensory system in fish includes also the ear, which is involved with complex analysis of signals, such as in sound discrimination and localization [238]. However, to the best of our knowledge, to date no studies investigated the effects of Hg forms on the auditory structures of fish, yet.

Another neurosensory system of fish is the mechanosensory lateral line, a mechanoreceptive system especially adapted for aquatic life that acts as an interface between the environment and the CNS, whose structure and functions were described in previous sections. It plays a vital role for various functions, ranging from schooling, reproductive and parental behavior, location of prey, escaping from predators, as well as balance and navigation. Additionally in many fish, like Chondrichthyes, the lateral line mechanoreceptors are modified to act as electroreceptors, namely the ampullae of Lorenzini [239]. Therefore, a compromise in the lateral line system, often associated to fish behavioral abnormalities, could have severe impact at both the individual and population level. Lateral line receptors are very sensitive to pollutants, and metal ions, including Hg, were found to exert the strongest effects on their function by blocking temporarily calcium channels in both free and canal neuromasts, provoking mainly an altered ability of the fish to orient itself in the water current [240,241]. For instance, it was reported that exposure to Hg provokes a degeneration of the anterior lateral line in the mummichog *Fundulus heteroclitus* [242]. More recently, following a waterborne $HgCl_2$ (401 μg L^{-1} as Hg^{2+}) treatment of zebrafish larvae, for 72 h, it was found accumulation of Hg in fish neuromasts and depletion of immunoreactive tubulin in these areas, attributable to the known interference of Hg with tubulin polymerization, causing disruption of cytoskeleton and consequent cell death [167].

Overall, it is also noteworthy to point out that very recently the mechanisms of Hg neurosensory toxicity were partially unveiled by application of the innovative environmental metabolomics approach, which demonstrated its effectiveness in uncovering tissue-specificities regarding Hg toxic effects in gills and liver of wild fish under realistic environmental conditions [243–245]. In detail, by identification of numerous metabolites, *i.e.*, amino acids, osmolytes, carbohydrates, nucleotides and neurotransmitters, metabolomics succeeded in unravelling the mechanisms underlying Hg-induced oxidative stress, and revealed also that Hg has multiple levels of impact, including membrane stabilization/degradation/repair processes, osmoregulation, energy metabolism, gene expression, antioxidant protection, and neurotransmission [243–245]. Therefore, it would be highly beneficial the use of environmental metabolomics in future studies in order to accurately address and better elucidate the biochemical and functional effects of Hg on CNS and sensory receptors of fish.

6. Morpho-structural changes induced by mercury on fish central nervous system (CNS) and sensory structures

There are only a few studies on morpho-structural changes in fish CNS upon exposure to Hg compounds (Tables 2 and 3). From these works, most consisted in alternated exposures to dietary MeHg or iHg [36], only to dietary MeHg [24,246] or waterborne MeHg [247], while a couple of studies investigated the effects of waterborne iHg forms in fish brain [23,248]. It is worth revisiting that the diet is the most relevant route of MeHg exposure in fish in the natural environment, while water has a higher preponderance for fish exposure to iHg, suggesting that conclusions provided by studies that did not used that binomial combination of exposure route and Hg form should be analyzed critically. There are also two studies that consisted in the brain morphometric analysis of wild fish from Hg contaminated areas located in Portugal [249,250], but effects of Hg in the brain were not very expressive, pointing out dissimilarity of field and laboratory findings that need to be clarified. Research on the morpho-structural effects of Hg on fish sensory organs is still missing, even if the first publication is from 1975 and reported effects on the olfactory organs and lateral line [242]. More recently, studies have been focused on the effects of Hg forms on the taste buds [251], olfactory epithelium [252,253] and eyes [162,230], while no information is available on fish ear.

6.1. Changes on central nervous system (CNS)

Berntssen and colleagues [36] performed a histopathological analysis of the Atlantic salmon (*Salmo salar*) brain after long-term dietary exposure (120 days) to MeHg (4.3 and 8.6 μg g^{-1} dw) and $HgCl_2$ (10 and 100 μg g^{-1} dw, corresponding to 7.4 and 74 μg g^{-1} of Hg^{2+}). MeHg exposure lead to vacuolation and necrosis in the medulla oblongata, ventral regions of the optic tectum and cerebrum with effects being more severe in fish exposed to the higher levels. A gross oedemous separation of the grey- and white-matter (even in the forebrain) and a diffuse necrosis throughout the brain was observed in fish exposed to 8.6 μg g^{-1} of MeHg. The severity of effects was not consistent with brain accumulation levels, which were higher after exposure to the lower dose of MeHg (1.16 μg g^{-1} in brain) in comparison to the higher exposure level (0.68 μg g^{-1} in brain). Authors hypothesised that the decline in brain Hg accumulation at the higher dose of MeHg exposure was probably related with the gross brain oedema, which would apparently decrease Hg tissue concentration when expressed on a wet weight basis. Effects of $HgCl_2$ in the salmon brain were much less severe (even at higher exposure concentrations) than those recorded for MeHg. Nevertheless, after 120 days of exposure to $HgCl_2$ as 7.4 μg g^{-1} of Hg^{2+} fish showed increased cellularity of astrocytes, especially in the dorsal regions of the optic tectum and throughout the medulla oblongata. The general level of necrosis was moderate after $HgCl_2$ exposure, when compared with the severe necrosis recorded in the MeHg exposed fish (at identical exposure levels of 8.6 μg g^{-1}). Interestingly, the increase of Hg^{2+} exposure levels from 7.4 to 74 μg g^{-1} was followed by a decrease in the severity of necrotic injury to occasional foci with a diffuse vacuolation rather than foci of massive oedema. A marked compensatory hyperplasia of astrocytes was hypothesized to explain reduced effects of $HgCl_2$, regardless the exposure concentration levels were 10 times higher. Moreover, salmon brain accumulated higher levels of Hg after exposure to 74 μg g^{-1} of Hg^{2+} than to 7.4 μg g^{-1}, contrarily to what was found for MeHg. Overall, at the light of these findings dietary MeHg was more neurotoxic than iHg to salmon. This study had also included the investigation of changes on biochemical parameters in salmon brain, as fully described in section 5. Bridging the data on biochemical and morpho-structural effects on the brain may shed some light on the neurotoxicity mechanisms of Hg forms. Biochemical alterations in the brain also pointed out to a higher toxicity of dietary MeHg [oxidative stress was perceived by the increase of lipid peroxidation (LPO), possibly related with a break-down of antioxidant defences], in comparison with iHg [no significant alterations on LPO were found]. This finding points out oxidative stress as a chief mechanism of MeHg neurotoxicity, as described for mammals (e.g. Farina et al. [37]).

An extensive stereological analysis of fish brain morphology (comprising volume and number of neurons plus glial cells in specific brain regions), upon exposure of juveniles of white seabream (*Diplodus sargus*) to dietary MeHg (8.7 μg g^{-1}), underpinned a significant decrease of the number of brain cells in the medial pallium and optic tectum after 7 days of exposure, together with an increase of the hypothalamic volume [24]. Despite a higher accumulation of total Hg was recorded after 14 days of exposure, no morphometric alterations were found in any of the analysed brain areas (i.e., lateral and medial pallium; hypothalamus; optic tectum; cerebellum), probably due to compensatory

mechanisms as described for dietary $HgCl_2$ by Berntssen et al. [36]. The recovery of the number of cells in medial pallium and optic tectum of *D. sargus* implies the formation of new cells, which can typical occur in teleost fish due to the great regeneration capacity of brain cells [33]. Moreover, although MeHg decreased almost two-fold in the brain during the post-exposure period that lasted 28 days, Hg accumulation levels were still higher than in control fish, leading to a loss of cells in the optic tectum [24]. In this study the optic tectum revealed to be particularly vulnerable to MeHg exposure in fish [24]. An impairment of the optic tectum integrity was also recorded in adult zebrafish (*Danio rerio*) with a decrease of the cell density after a long-term dietary exposure (50 days) to MeHg (13.5 μg g^{-1}) [246]. A preferential accumulation of MeHg in the fish optic tectum would explain the higher vulnerability of this brain region. While these studies did not assess Hg accumulation in different brain regions, Korbas et al. [12] reveled that MeHg is preferentially accumulated in the pineal gland (occurring also in the optic tectum) when mapping its distribution in zebrafish body.

D. sargus exposed to waterborne $HgCl_2$ (2 g L^{-1} as Hg^{2+}) in a similar daily intake of that considered in Puga et al. [24] for dietary MeHg, displayed a significant reduction in the number of cells in hypothalamus, optic tectum and cerebellum after 7 days of $HgCl_2$ exposure [23]. The decrease in the number of neurons and glia in the molecular layer of the cerebellum was accompanied by a contraction of its volume. As reported upon exposure to dietary MeHg for medial pallium and optic tectum [24], a recovery of hypothalamus and cerebellum occurred after 14 days of $HgCl_2$ exposure regardless of the higher accumulation levels [189]. This was put in evidence by the identical number of cells found in exposed and control fish, and similar volume of cerebellum, which was associated with an adaptive phenomenon of fish brain [23]. That recovery was not found in the optic tectum underpinning a higher vulnerability of this brain area to $HgCl_2$, which was maintained after 28 days of post-exposure. In fact, the optic tectum continued to show a decrease in the number of cells, 28 days after the end of the exposure, reinforcing a higher vulnerability of this region. Optic tectum findings were consistent with those described for the morphometric effects of MeHg in *D. sargus* brain [24], and can be related with the preferential accumulation of Hg^{2+} in this area of the brain, but this still needs confirmation. The higher vulnerability of this brain region to Hg forms is underpinned in these studies [23,24], eventually with repercussions for fish wellbeing and survival. In fact, the optic tectum receives information by the optic nerves and its large size in fish is related to the vision importance for a number of behaviors, such as food location, predator escape or reproduction [254]. A histological analysis of the peacock blennies (*Salaria pavo*) brain upon exposure to waterborne $HgCl_2$ (66 μg L^{-1}, corresponding to 49 μg L^{-1} Hg^{2+}) also revealed several damages in the optic tectum and the cerebellum, and 3 reaction patterns were identified for each brain area: circulatory disturbances, regressive and progressive changes [248]. Interestingly, these effects were not followed by a significant accumulation of Hg in the brain and authors claimed that brain of peacock blennies was able to detoxify iHg [248]. Moreover, iHg waterborne exposure did not affect the activity of AChE in the brain, suggesting that this enzyme was not directly related with morphological alterations described in the optic tectum and cerebellum.

A comparison of the neurotoxic potential of dietary MeHg and waterborne iHg is possible by the comparison of Pereira et al. [23] and Puga et al. [24] findings, since both studies considered a similar daily intake of both Hg forms (around 260 μg day^{-1} kg^{-1} bw), as recently described in Cardoso et al. [18]. Briefly, while dietary MeHg was on the basis of a reduction of the number of brain cells in the medial pallium and optic tectum after 7 days of exposure, together with an increase of the hypothalamic volume [24], waterborne $HgCl_2$ lead to a reduction in the number of cells in hypothalamus, optic tectum and cerebellum (volume reduction too) after the same exposure time [23]. Comparing morphometric effects of dietary MeHg and waterborne iHg in *D. sargus* brain does not clarify which combination of Hg form and route is more neurotoxic to fish, but pointed out both Hg forms as able to trigger brain morphological effects. These findings are not consistent with those of Bernstssen et al. [36] in salmon, where MeHg reveled to be more neurotoxic than $HgCl_2$.

Under realistic exposure conditions where a concomitant exposure to dietary MeHg and waterborne iHg occur, and also with waterborne MeHg and dietary iHg (although in much less extent), the effects of Hg on the brain morphometry were distinct from those earlier described for laboratory exposures. At Aveiro lagoon, that is almost exclusively contaminated by Hg at a confined area (Laranjo), Hg triggered a deficit in cell density of *Liza aurata* hypothalamus during the winter, while in the summer it promoted larger volumes of the optic tectum and cerebellum [250]. Differently, *L. aurata* caught at an impacted area of the Tagus estuary (Portugal), including by Hg, did not displayed any brain morphometric changes when assessed by cell density of the lateral pallium, hypothalamus, optic tectum and cerebellum [249]. The discrepancy between field and laboratory studies for the effects of Hg in the fish brain can be related with a number of factors, ranging from differences between fish species and its origin (wild *vs*. fish farm) to differences in exposure levels. Although Pereira et al. [23] study considered realistic levels of iHg in water for high contaminated areas (2 μg L^{-1} as Hg^{2+}), as adequately argued in that work, contamination concentrations detected in water (maximum total Hg levels [tHg]: 1.5 - 4.4 ng L^{-1}) of Laranjo were 1000 times lower than those used at Pereira et al. [23]. A 62 times difference was detected between levels reported at Barreiro area of the Tagus estuary for Hg (tHg in water: 32 ng L^{-1}) and those of Pereira et al. [23]. This discrepancy may have contributed for the preponderance of effects at laboratorial exposures in relation to observations in wild fish.

Previous findings were made in juvenile and adult specimens of seawater fish, namely: *S. salar* [36]; *D. sargus* [23,24]; *S. pavo* [248] and *L. aurata* [249,250]. Besides that, the ultra-structural effects of waterborne MeHg on embryonic zebrafish neurons were also investigated using transmission electron microscopy [247]. Neurons of embryos exposed to 50 and 80 μg L^{-1} of MeHg showed disrupted and degenerated nuclei, while some neurons exhibited different morphological patterns of cell death that may reflect either different stages of the cell death process or, possibly, different types of cell death [247]. The MeHg levels used in the study are much higher than those reported for heavily contaminated areas (Table 1), making almost implausible the translation of Hassan et al. [247] work conclusions to realistic exposure conditions.

6.2. Changes on sensory structures/receptors

Few studies had investigated the effects of Hg on the sensory structures morphology. Generally, that research has been considering very high levels of Hg in the water, much above those reported for contaminated areas worldwide (see Table 1). As far as our knowledge goes, no studies on morpho-structural changes of the fish ear have been performed, even if the deposition of Hg in the inner ear was already reported in the trout (see section 3) [147]. A single study from the 70s found morphological effects on the lateral line [242]. Exposure of mummichog to 500 μg L^{-1} of Hg (or higher levels) lead to severe cytoplasmic and nuclear degeneration of all cellular elements of the lateral line. The necrocytosis affected secretory cells of canal lining, squamous epithelium of canal walls, and canal's secretory and mucus cells [242]. In parallel, severe degenerative changes of olfactory organs were reported [242]. As similarly discussed by the end of section 6.1, such high exposure levels were never reported in the aquatic environment, which makes findings of the Gardner study [242] very improbable under a realistic exposure scenario.

A decade later, taste buds were investigated by scanning electron microscope on various parts of the oral cavity of the bleak (*Alburnus alburnus*) upon iHg exposure (300 μg L^{-1} as Hg^{2+}) [251]. Morphological alterations on the taste buds were recorded just after 3 days of

exposure, when the microridge system of the epithelial cells became damaged and the mucus secretion increased on the apical surface of the taste buds. Hg effects increased over time, since swollen microvilliar tips of the sensory cells were observed after 10 days of exposure, as well as damage of the epithelial microridge system. Degenerative changes were detected on the microvilliar system of both the supporting and receptor cells of taste buds after 19 days of exposure [251]. Exposure levels of this study are within the same range as the previous one. Therefore, the same criticism could be made in relation with the relevance of iHg levels that were considered, and thus on conclusions.

The deposition of iHg and MeHg on the olfactory epithelium of fish had been under study since the 90s [166] as previously detailed in section 3. Additionally, the surface of the olfactory epithelium of *Trichomycterus brasiliensis* was investigated with scanning electron microscopy upon exposure to two different concentrations of $HgCl_2$ (50 and 100 μg L^{-1}, corresponding to 37 and 74 μg L^{-1} Hg^{2+}, respectively) [252]. Within 24 hours, all fish died after exposure to the highest Hg levels, displaying significant damage of the olfactory epithelium. Morphological alterations of the olfactory epithelium were also considerable after exposure to the lowest levels, but the epithelial surface was able to recover after 96 hours of exposure [252]. Interestingly, when salmon was exposed to identical levels of $HgCl_2$ but through contaminated feeds (74 μg g^{-1} as Hg^{2+}), fish were able to survive and histopathology in the brain was even lower than that recorded for exposure levels one order of magnitude below (7.4 μg g^{-1}), as previously described [36]. More recently, Oliveira Ribeiro et al. [253] examined the histopathological effects of Hg on the olfactory epithelium of the arctic charr (*Salvelinus alpinus*) after a 96 h acute exposure to waterborne iHg (15 μg L^{-1} as Hg^{2+}), as well as those of a single dietary dose of iHg and MeHg (0.26 μg Hg g^{-1} body weight) after 30 days. Ciliated cells in the olfactory epithelium of *S. alpinus* were affected by waterborne iHg after a 24 h exposure, with cilia of type I cells being clearly thinner and shorter than those of control fish. An apparent complete recovery was observed after 96 h, with cilia presenting visual aspect similar to those of the control group [253]. This study highlighted a major effect of iHg on the olfactory epithelium of fish, while presenting MeHg as probably less harmful since it is less abundant in the water [253].

During a period of 70 days, adults of a freshwater fish species *Hoplias malabaricus* were fed with fish prey previously labeled with two different doses of MeHg (0.075 and 0.75 μg g^{-1}). The ultrastructure analysis of retina revealed a cellular deterioration in the photoreceptor layer, morphological changes in the inner and outer segments of rods, structural changes in the plasma membrane of rods and double cones, changes in the process of removal of membranous discs and a structural discontinuity [162]. In fact, it was detected that MeHg accumulates within the lens epithelia and optic nerve of *D. rerio* larvae [10]. Additionally, Bonci et al. [230] found that intraperitonial injection of MeHg (2 and 6 μg g^{-1}) reduced the density of amacrine cells within the retina of adult trahiras *Hoplias malabaricus*. As claimed by the authors, further studies are needed to identify the physiological impact of these findings on fish visual function.

7. Behavioral shifts on fish following mercury exposure

Biochemical, physiological and morpho-structural alterations of fish brain or sensory organs related to Hg exposure may ultimately change the performance of normal behavior. Thus, several studies on the behavioral effects of Hg forms on fish have been undertaken (see Table 2). Most of them have been focused on the locomotor activity, mainly by assessing the swimming activity performance from a motor status perspective (e.g. [23,24,36,184,255]) or as an expression of the fish fear/anxiety-like status [9,23,24]. Other studies had addressed the prey capture ability [194,256,257] or predator avoidance skills [188] of fish after Hg exposure. These behaviors are all critical to fish survival and have high ecological relevance, as reviewed by Weis [46]. Recently, fish memory and aggressiveness [25], as well as lateralization and habitat preference [258] were also addressed after MeHg exposure. In general, behavioral effects on larvae, juvenile and adult fish have been assessed after exposure to either iHg or MeHg forms, both via water or diet. Moreover, there are several studies where the behavior of fish was assessed later in life, even if Hg exposure was still during the neurodevelopment. Since the development of fish behavior and of nervous system occurs in parallel, embryonic exposures to Hg at concentrations that do not produce evident anatomical malformations may, even though, result in functional deficits at later stages in life [46]. Studies on the effects of MeHg on neurodevelopment, and particular on behavior, have been largely discussed on review articles [46], namely on the scope of the use of zebrafish as a model [29]. Therefore, these studies will be briefly reported in the current review that does not intend to fully cover the neurodevelopment effects of Hg in fish. It is worth of mentioning that most of research on the effects of Hg on fish behavioral development had gave particular importance to MeHg, while repercussions of iHg were seldom studied.

The evaluation of swimming performance is considered a paradigmatic endpoint of the fish motor status that is being widely used to evaluate neurobehavioral effects of aquatic contaminants, including Hg. Salmon exposed to dietary MeHg (10 μg g^{-1}) displayed lower swimming activity together with cellular damages in the brain, while no effects on swimming behavior were detected upon exposure to $HgCl_2$ contaminated feeds (100 μg g^{-1}, corresponding to 74 μg g^{-1} Hg^{2+}) even if moderate brain lesions were perceived [36]. Identically, after 7 days of exposure to dietary MeHg (8.7 μg g^{-1}), *D. sargus* swam for a shorter time, suggesting an impairment of motor activity [24]. Coincidently, this behavior shift occurred after 7 days of exposure to MeHg, the point in time where brain morphometric alterations were more pronounced in three different regions (i.e., loss of cells in medial pallium and optic tectum, and increase of hypothalamus volume). Interestingly, after 14 days of exposure to MeHg fish swam greater distances than controls, which was associated with a recovery from those morphometric alterations in all of the examined brain areas. This was observed despite the higher accumulation of Hg in the fish brain after 14 days of MeHg exposure. The enhancement of the total swimming distance by *D. sargus* exposed to dietary MeHg for 14 days was concomitant with the recovery of brain cells in medial pallium and optic tectum, and thus related to neurophysiological and structural compensatory mechanisms [24]. Swimming-related endpoints expressing the fear/anxiety-like status of fish (i.e., refuge latency, immobility latency, dragging latency) were not altered in *D. sargus* exposed to dietary MeHg [24]. Contrastingly, adult zebrafish treated acutely with MeHg (1.0 or 5.0 μg g^{-1}, intraperitoneal injection) exhibited a marked anxiogenic profile in both used tests (novel tank and light/dark preference) at the smaller exposure level, while fish showed hyper-locomotion in the novel tank test after exposure to 5.0 μg g^{-1} of MeHg [9]. These behavioral effects were followed by a decrease in extracellular levels of serotonin, and an increase in extracellular levels of tryptamine-4,5-dione, a partially oxidized metabolite of serotonin [9]. A marked increase in the formation of malondialdehyde, a marker of oxidative stress, accompanied these parameters [9]. It was suggested that MeHg-induced oxidative stress, produced mitochondrial dysfunction and originated tryptamine-4,5-dione, which could have further inhibited tryptophan hydroxylase. This study suggested that anxiety is an early effect of low-level MeHg exposure in zebrafish, which could be associated with changes in the serotonin system. Thus, fish anxiety-like symptoms could be used to detect early effects of MeHg exposure [9]. Recently, zebrafish was exposed to waterborne MeHg (1 and 15 μg L^{-1}) for a period of 32 hours, which lead to a reduced swimming performance [25]. For instance, fish traveled a lower distance and displayed a reduced swimming speed after MeHg exposure [25].

Waterborne $HgCl_2$ (2 μg L^{-1} as Hg^{2+}) corresponding to a daily intake of Hg similar to that used in Puga et al. [24] for dietary MeHg [18], triggered changes in hypothalamus, optic tectum and cerebellum

related to numerous modifications in both motor function and mood/anxiety-like status [23]. For instance, fish exposed to $HgCl_2$ swam a smaller distance in the first run than controls after 7 days of exposure, while exhibiting a lower velocity in the first run. In what concerns the assessment of mood/anxiety-like behavior, fish exposed to $HgCl_2$ for 7 days showed alterations in the time spent to take refuge on the dark area of the device, as they spent less time than controls to seek for protection. Also, mosquitofish (*Gambusia affinis*) aqueously exposed to $HgCl_2$ (20 μg L^{-1}, corresponding to 14.8 μg L^{-1} Hg^{2+}) showed altered swimming activity and decreased swimming speed [255]. Moreover, significant and concentration-dependent effects of $HgCl_2$ on swimming resistance of the estuarine fish *Pomatoschistus microps* were found within a range of waterborne iHg from 3.1 to 50 μg L^{-1} (as Hg^{2+}), as well as covered distance against water flow [184]. Swimming resistance and covered distance were lower for higher iHg levels in the water [184]. Recently, a significant change in the basic locomotor parameters of zebrafish was observed after 5 days of exposure to dietary iHg, including speed (43% reduction), meander (150% increment), and the number of freeze points (125% increment). Abnormal behavior was also recorded in color preference test and novel tank diving [259].

The normal preference response of the lake whitefish (*Coregonus clupeaformis*) to a food extract was reduced after exposure to 50 μg L^{-1} of $HgCl_2$ (37 μg L^{-1} as Hg^{2+}) for 1 to 2 weeks [260]. In addition, avoidance-preference assessment with $HgCl_2$ only (without a food extract) showed that the lake whitefish did not avoid iHg [260]. The role of olfaction was investigated in parallel, supporting speculation about the involvement of olfactory organs on the fish response to food extracts and, therefore, leading to the hypothesis of organs damage by Hg^{2+} [260]. Later, Weis and Khan [256] studied the effects of MeHg and Hg^{2+} (as $HgCl_2$) on the feeding ability of mummichog (*Fundulus heteroclitus*) from Piles Creek, a polluted ecosystem in New Jersey (USA). It was found that exposure to 10 μg L^{-1} of MeHg for one week had less impact on the prey capture rate than exposure to a similar concentration of Hg^{2+}. In this study, the fish were affected to a greater degree on their ability to capture preys by exposure to waterborne Hg^{2+} than to MeHg. By the time, authors stressed out that this was an uncommon pattern of neurotoxicity of Hg forms by making reference to a higher tolerance of Piles Creek fish to MeHg than to Hg^{2+} [256]. However, according to the previous studies on white seabream [23,24], waterborne iHg can potentially trigger a large extent of effects on swimming behavior than dietary MeHg (that did not changed fear/anxiety-behavior related endpoints). White seabream were juvenile naïf fish without any previous contact with Hg contamination before the experiment, probably contributing for the different patterns observed between the two species. Also, fathead minnows (*Pimephales promelas*) exposed to $HgCl_2$ (1.25, 5.0, and 10 μg L^{-1} as Hg^{2+}) over 10 days, showed performance deficits in foraging efficiency and capture speed at the highest exposure levels [194]. Recently, changes of the feeding behavior of yellowfin bream (*Acanthopagrus australis*) were investigated after ingestion of iHg (0.2, 0.7 and 2.4 μg g^{-1} as Hg^{2+}) over 16 days. After 4 days, exposed fish attempted feeding more often, and showed a significantly lower eating success than controls. Interestingly, these differences became less notable with longer exposure periods [257].

Kania and O'Hara [261] used a test system with a shallow water refuge area that allowed the mosquitofish (*Gambusia affinis*) to avoid predation by bass (*Micropterus salmoides*), which was limited to the deeper water of the test tank. After 24 h of exposure to iHg (10, 50 and 100 μg L^{-1} as Hg^{2+}), the ability of mosquitofish to avoid predation was impaired. Later, the effects of dietary MeHg on the predator avoidance behavior were examined in the golden shine (*Notemigonus crysoleucas*) exposed to 2 different levels (0.46 and 0.96 μg Hg g^{-1}). Fish were presented to an avian predator-model in order to assess their predator avoidance behavior [188]. Fish fed with the high-Hg diet had significantly greater shoal vertical dispersal following predator exposure, took longer to return to pre-exposure activity level, and had greater shoal area after return to pre-exposure activity than did fish of the other conditions. All these behavioral traits were hypothetically associated with a higher vulnerability of the fish to predation upon MeHg exposure [188]. In 2012, Weis and Candelmo [45] did a review on the effects of pollutants on fish predator-prey behavior where the previous findings had been emphasised [45].

There are other behavioral traits that have been less frequently assessed in fish after exposure to Hg forms. For instance, aggressiveness and memory were assessed in zebrafish upon waterborne MeHg exposure (1 and 15 μg L^{-1}) for 32 h [25]. The mirror test was used to address fish aggressiveness, revealing that MeHg exposure significantly reduced the aggressive behavior. Authors speculated that under realistic conditions less aggressive fish may have problems with predators' avoidance, territorial protection and competition [25]. In the same study, fish capacity to learn and to do associations between a negative or positive stimulus with a color was used to assess memory, concluding that waterborne MeHg may affect negatively fish memory [25]. Moreover, dietary MeHg exposure (8.5 μg g^{-1}) of juvenile *Solea senegalensis* lead to impaired lateralization [258]. In a T-maze device a left turning preference of the *S. senegalensis* population (i.e., relative lateralization) was observed under control conditions, while this pattern was disrupted in fish exposed to MeHg [258]. In addition, MeHg had altered habitat preference of flatfish with exposed individuals spending more time in the complex habitat, where they could neither bury nor match the background. Behavioral alterations were followed by a decrease of brain AChE activity [258], suggesting that neurotransmission changes involving the cholinergic system triggered behavioral impairments.

Interestingly, behavioral delayed effects of Hg in fish have been poorly described, so far. Only recently, more attention has been paid to this topic with a focus on the use of zebrafish as a neurodevelopment model for human toxicology [29]. In a more ecological perspective, Weis and Weis [262] examined the behavior of mummichog (*Fundulus heteroclitus*) larvae after embryonic exposure to waterborne MeHg (5 and 10 μg L^{-1}). Prey capture ability of early larvae was impaired, but approximately one week after hatching the prey capture skills were comparable to control fish, suggesting a temporary effect of MeHg on the larvae. Authors claimed that MeHg exposure might have caused retardation of neurological development, which was subsequently compensated and therefore no long-lasting effects were observed in larvae [262]. In parallel, the same authors found that mummichog larvae exposed as embryos to MeHg (5 and 10 μg L^{-1}) were also more susceptible to predation by the grass shrimp (*Palaemonetes pugio*) or adult mummichogs [262]. Indeed, larvae that had been exposed to MeHg as embryos generally had increased activity levels, which hypothetically can attract predators resulting in an increased capture [263]. Accordingly, observations in adult zebrafish hatched from embryos exposed to waterborne MeHg (2.2 - 65 μg L^{-1}) were described as hyperactive for frequently swimming back and forth [264]. Social behavior was assessed in mummichog larvae hatched from embryos collected at two sites (Hg polluted and reference) that were then exposed to MeHg (5 and 10 μg L^{-1}) [265]. MeHg exposure significantly increased the number of collisions by larvae from the reference site, while no effect was found on the larvae from the Hg polluted area. This effect disappeared 4 weeks after hatching, indicating that the damage to the developing nervous system was reversible [265], an effect that had been previously described by Weis and Weis [262]. Later, Fjeld et al. [266] found long-delayed effects of embryonic MeHg exposure. Embryos of grayling (*Thymallus thymallus*) were exposed to waterborne MeHg (0.16, 0.8, 4.0 and 20 μg L^{-1}) during the first 10 days of development. Three years later impaired feeding efficiencies and reduced competitive abilities were found in fish that had accumulated Hg levels of 0.27 μg·g^{-1} (or more) as yolk-fry. In the foraging efficiency experiments, these fish were 15-24% less efficient than controls. In the competitive ability experiments, the control group caught 2 to 6 times more preys than MeHg exposed fish. In 2009, Weis [46] reviewed most of the previous findings on the developmental effects of MeHg in fish

with repercussion on behavior. Interestingly, behavioral assessment after developmental exposure of fish to iHg has been poorly investigated. Abu Bakar et al. [267] investigated the effects of embryonic exposure to waterborne iHg on motor function and anxiety-like behavior in larvae. The embryos were exposed to a range of $HgCl_2$ levels (7.5 to 250 nM, corresponding to 1.5 and 50 μg L^{-1} Hg^{2+}) at 5 hours post-fertilization (hpf) until hatching (72 hpf). Embryonic exposure to low concentration of $HgCl_2$ (27 μg L^{-1} as Hg^{2+}) induces motor deficit, while disrupting the anxiety-like behavior by decreasing swimming speed, increasing the resting percentage and impairing the thigmotaxis and avoidance response. In parallel, biochemical analysis showed that iHg exposure alters proteins, lipids, carbohydrates and nucleic acids of the zebrafish larvae [267]. Authors argued that exposure to $HgCl_2$ could lead to the destruction of the biochemical molecules, causing developmental impairments in the developing zebrafish. These impairments may target different system in the body including the nervous, musculoskeletal system and visuomotor function that results in behavioral impairments.

8. Contribution to the definition of a multidimensional conceptualization of mercury neuronal and sensory toxicity and future perspectives

Notwithstanding the recent advances in the understanding of Hg neurosensory toxicity in different animal models, there are several central questions that remain unclear concerning fish. Anyway, assuming as starting point the literature available on this topic and taking advantage of the complementarity and interdisciplinarity of the co-authors, we took up the challenge to propose a multidimensional concept for Hg neurosensory toxicity in fish. Therefore, to delineate this conceptualization we had appealed to an academic analogy with the Rubik's Cube, as a multidimensional puzzle, where each one of its faces represents a component/dimension (and at the end a scientific puzzle) listed (corresponding to sections 2 to 7, as described above) (see Fig. 4). Each face of this paradigmatic Rubik's Cube is divided into 9 pieces, representing 9 key factors/processes within the dimension in equation. Each set of key factors was selected based on the existing knowledge within the fish framework, but also elected on the basis of the mechanisms described in other contexts, namely from human-driven research. In this way, knowledge gaps, as well as future research perspectives, will be highlighted.

It should be pointed out that the cube is depicted in its solved state (Fig. 4), which is far from reflecting the current state of the art. The resolution of this Rubik's Cube is a great challenge for environmental toxicologists, but an analytical capacity allowing the definition of its external architecture is an unavoidable step towards that ultimate goal. Reinforcing the analogical argumentation, it becomes clear that it is virtually impossible to move a given piece individually, and the rotation of the corresponding layer inevitably interferes not only with the pieces of the same face (dimension) but also with pieces of other faces (dimensions). This has a stimulating symbolism as it mirrors the variables interdependence into play. In the same direction, the internal pivot mechanism linking the different pieces is hidden, in the same way that the mechanistic explanations for the myriad of cross-linked processes, within and between dimensions (faces), are still obscure.

It is assumed that this conceptualization must be applied to a specific context concerning the target organism, *i.e.*, to a well-defined setting in terms of fish species, gender, developmental stage, etc. The exposure (dark blue face; Fig. 4), and the inherent features, represents the most upstream dimension, thus, determining all the other dimensions. Thereafter, the Hg toxicokinetics (white face) appears as a second set of determinants of the multiple planes of effects expected, from the

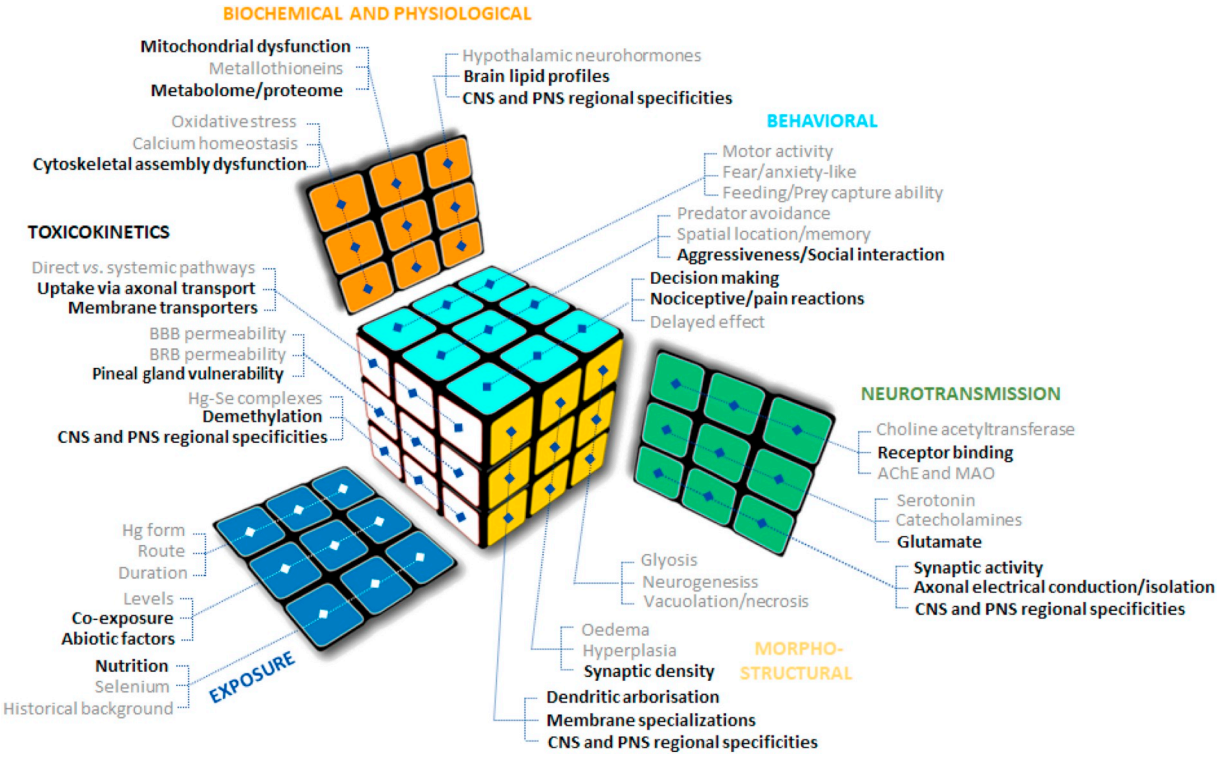

Fig. 4. Conceptual design of the multidimensional character of the neurosensorial toxicity of Hg in fish, adopting an analogy to the "Rubik's Cube", a multiple puzzle, where each one of its faces represents a component/dimension: (i) exposure; (ii) toxicokinetics; (iii) neurotransmission; (iv) biochemical and physiological; (v) morpho-structural; (vi) behavior. Each face of the cube is divided into 9 pieces, representing 9 key factors/processes that were selected for their demonstrated/potential role on the neurosensorial toxicity of Hg in fish. The factors/processes highlighted in bold are the ones uncovered or largely uncovered in fish (*i.e.*, knowledge gaps), while the others concern factors/processes that were already reported in fish studies, even if, in some cases, results just provide some insights on that direction.

most basal (biochemical; orange face) to the highest level (behavior; light blue face).

Along this review a number of limitations and shortfalls on the research of the neuronal and sensory effects of Hg in fish were identified. Although these restraints and gaps were already described in the specific sections, some will be briefly recalled along with the discussion of the most prominent factors/processes that were associated with each dimension of the Rubik's Cube designed for illustrating the state of the art of the neuronal and sensory toxicity of Hg in fish. A transversal aspect to the several dimensions of the current analyses is that research in the current subject has been implemented in a large number of fish species (around 60 different species were identified in the review; Tables 2 and 3) in different developmental stages (embryos, juveniles and adults). This contributes to a dispersion of the findings with results that are then difficult to compare, which at the end prevents the emergence of the mechanisms of Hg neurosensory toxicity in fish. In the future, knowledge could be consolidated by focusing research on a restricted number of fish species that should be representative from the different aquatic ecosystems (*e.g.* freshwater, estuarine, seawater). These species should be alternatives to zebrafish, which has been mostly used as a model for human neurotoxicology. Another gap that was identified and needs to be filled in further works is the lack of links between the several dimensions involved on the neuronal and sensorial toxicity of Hg in fish (represented here by the 6 phases of the Rubik's Cube). This is crucial to disclose the biochemical mechanisms of Hg neurosensory toxicity in fish, as well as the up-scaling repercussions (e.g. on behavior, fish fitness and survival). More investigation could be done *in vitro* by exposing, for instance, fish neuronal cells to Hg forms, as an approach to fully unraveling the biochemical mechanisms of Hg neurotoxicity in fish. Then, research could evolve to the association of biochemical and cellular changes, to better understand if neurons and glial cells have a differential vulnerability to Hg forms.

Next, it will be discussed each of the dimensions that give substance to the proposed concept.

8.1. Exposure

Neuronal and sensory effects of Hg in fish are from its onset determined by a number of exposure related key factors (Fig. 4). Firstly, it is strongly ruled out by the Hg form that fish are exposed to, either inorganic Hg (iHg) or organic Hg compounds (mainly MeHg). In fish, the Hg form and exposure route are closely related, since the water is the main via for iHg forms [in natural waters, the majority of Hg occurs in inorganic forms, while MeHg often contributes to less than 5% of the total waterborne Hg [268]], while the diet is preponderant for MeHg exposures. Realistically, fish are exposed to iHg mainly through water and to MeHg in the diet. Despite the relevance of both Hg forms for fish exposure associated more specifically with these routes, most studies (number in parenthesis) had investigated the neuronal or sensory toxicity of MeHg, either via contaminating water (22) or via food (24), as well as upon exposure to waterborne iHg (40). Besides that, iHg effects had been also addressed upon dietary exposure (6), which has less preponderance in realistic environmental conditions. So far, the research of the neurosensory toxicity of Hg upon a combined exposure to waterborne iHg and dietary MeHg (the most realistic condition) is still scarce. This is probably because studies combining exposure to two Hg forms/routes involve a more complex experimental design, as well as much advance technology for Hg quantification in the fish. For instance, a concomitant exposure to different forms requires the use of Hg isotopes in order to pinpoint the distribution of each chemical form in the fish organs. The high cost of Hg isotopes could explain the limited efforts towards this research option. The duration of exposure is also a key factor of Hg toxicokinetics and therefore on the effects at the neuronal and sensory systems of fish. In this context, many studies had exposed fish acutely (minutes/hours) to Hg forms (around 20), while others used a long-term exposure (raging from weeks to months) (59 studies). In both cases, iHg and MeHg compounds were associated with effects on neuronal and sensory systems, depending on a combination of exposure length and Hg contamination levels. However, it must be highlighted that in what concerns Hg neurotoxicity, a higher exposure dose was not always followed by an increase of brain damaging effects (see section 6). In laboratorial research the previous key factors associated with the exposure dimension of the designed conceptualization (i.e., Hg form, levels, exposure route and duration) are well controlled, allowing a more comprehensive understanding of Hg effects. Contrarily, interpreting the effects of Hg at neuronal and sensory levels is more intricate in field studies, due to limitations in fully characterizing those 4 key factors. In fact, while Table 2 included 84 laboratory studies, only 14 works investigated the neuronal or sensory toxicity of Hg in wild fish (Table 3). Moreover, field studies were almost exclusively a report of Hg accumulation in the brain (6), while just a couple addressed Hg effects, suggesting that more efforts need to be made towards the understanding of Hg neurosensory toxicity under realistic conditions. This would be particularly relevant for species that are critically endangered, such as the European eel (*Anguilla anguilla*).

While the previous key factors related with Hg exposure are relatively well established in relation to Hg toxicokinetics and toxicodynamics encompassing neuronal and sensorial levels, some other factors were seldom investigated, suggesting possible new lines of research under this context. An interesting topic is related with the influence of abiotic factors on Hg availability in water. As detailed in section 2, water and sediment chemistry play a major role on the bioavailability of Hg for aquatic organisms, including fish. Seawater and freshwater physical-chemical conditions have been under change related with climatic alterations. For instance, average ocean pH has already declining by 0.1 units since pre-industrial times because of absorption of additional carbon dioxide (CO_2) from the atmosphere. Presumably, ocean pH will decline another 0.3–0.4 units by 2100 [269], with some locations showing an even greater than predicted rate of decline [270]. In parallel, average seawater surface temperature has also been rising and a further increase of 2-4 °C is anticipated by 2100. Both seawater pH and temperature may influence Hg bioavailability and speciation, as occur for other physical-chemical parameters, such as salinity. To the best of our knowledge, a single study had investigated the combined effects of seawater pH reduction, temperature increase and MeHg contamination at the fish brain and behavior [258]. Authors concluded that current levels of MeHg in the aquatic environment might lead to a severe disruption of behavioral and neurological functions of flatfish, which combined with ocean warming and acidification could further jeopardize the species ecological fitness [258].

The neuronal and sensory effects of Hg in fish are probably shaped by the concurrent exposure with other contaminants, although this knowledge remains elusive. A recent study investigated the short-term toxic effects of microplastics and waterborne iHg exposures on the European seabass. Results indicated that microplastics likely sorbed iHg from the water and influenced the accumulation of Hg in the brain and muscle. Evidence of toxicological interactions between microplastics and iHg were found, including for neurotoxicity biomarkers [271]. While the interaction of Hg with other environmental contaminants has not been explored in fish regarding the neuronal and sensory toxicity yet, this topic is very well described in mammals under dietary exposure to contaminated fish. In this context, polychlorinated biphenyls (PCBs) have received most attention, as result of the potential for concurrent PCB exposure to influence the supposed effects of MeHg *in utero* exposure in a Faroe Islands study [272]. The relevance of considering co-exposures of Hg and other environmental contaminants is particularly important when aiming to unveil neuro-sensorial effects of Hg in wild fish, because under field conditions it is generally difficult to have exposures to a single contaminant. Fish from Aveiro lagoon (Portugal) have been largely investigated by the current co-authors [23,250], since this system has a confined area almost exclusively contaminated by Hg, offering an ideal environment to investigate

neuro-sensorial toxicity of Hg in wild fish and validate laboratorial findings.

A topic of considerable importance is the potential for nutritional constituents in fish to ameliorate the adverse effects of Hg neuronal and sensory toxicity. A single study was reported along this review related with this subject (section 5). Atlantic salmon was fed with a diet based on fish oil (FO) or in alternative vegetal oil (VO), with or without the addition of MeHg. While different dietary lipid sources did not affect the accumulation of Hg, dietary MeHg resulted in decreased levels of 20:4 *n*-6 (arachidonic acid; ARA) in phosphatidylinositol in brain of VO fed fish [218], disclosing a possibility of interference with brain function and lipid metabolism. Moreover, no information is available for the effect of nutritional status on the toxicity of iHg in fish. In mammals, two nutrients demonstrated to provide protection against MeHg neurotoxicity, namely: i) omega-3 fatty acids; ii) selenium [273]. Branco et al. [148] have demonstrated that selenite interaction with Hg *in vivo* depends on the Hg compound considered and the organ analyzed. MeHg accumulation in the brain was reduced by co-exposure to Se but its toxic effects over antioxidant enzymes remained. Even though Hg^{2+} accumulated less than MeHg, it exerted a comparable inhibitory effect, which was only counteracted by Se in the liver. At this light, more studies should be made to investigate the protective effect of Se in the fish brain upon Hg exposure.

Finally, the historical background of fish regarding contamination exposure may play a relevant role on the effects of Hg at the neuronal and sensorial levels of fish. Weis works with common killifish (mummichogs - *Fundulus heteroclitus*) illustrated well the relevance of this key factor, as detailed in section 7. In summary, fish from contaminated sites (Piles Creek) were less active and able to capture prey than those from a reference area. Then, fish from the reference area were exposed to Piles Creek conditions (food and sediment), resulting in a decrease of their ability to prey capture, as denoted by the Piles Creek fish, while Hg in their brains increased, reaching similar values to those of the Piles Creek population. Interestingly, when Piles Creek fish were maintained in clean water, sediments, and food for 6 weeks, prey capture ability increased slightly but not significantly, and their levels of Hg in the brain did not decreased (detailed in section 7). From a different perspective, a recent zebrafish study found that the trans-generational effects elicited by MeHg exposure could persist through the F3 generation [274], raising the alarming possibility that neurological disorders could persist in exposed fish populations several generations after the source of contamination is eliminated. This result is important to consider, for instance, in the context of fish aquaculture, where the elimination of dietary Hg exposure is virtually impossible due to the presence of residual Hg (mainly as MeHg) in aquafeeds.

8.2. Toxicokinetics

The review of the published results on the toxicokinetics of the iHg and oHg in the fish CNS and the sensory organs allowed some common patterns to emerge but also identified deficiencies in our knowledge of Hg neurotoxicity in fish. Mercury accumulation was observed not only in the fish brain but also in the fish sensory systems such as the eye, the olfactory, the inner ear and the lateral line. The main finding was that irrespective of the route of exposure (either water or diet) and chemical form of the Hg toxicant in the diet and/or water, Hg was taken up by the fish brain. However, its relative disposition between brain and other organs (also reflected in the tissue uptake rates) differed between Hg^{2+} and MeHg exposures. Moreover, the levels of Hg in the fish brain were generally higher for MeHg exposures than for the Hg^{2+} exposures. Similar pattern was observed in the fish eye upon the laboratory exposure to either waterborne iHg or oHg, and also during the environmental exposure, which showed preferential accumulation of MeHg over iHg in the eye wall and the lens.

The interesting aspect of mercury disposition, which was postulated several decades ago but never adequately studied, is the axonal transport of various Hg species from the surrounding waters to the CNS through access areas on the fish skin and oral epithelia. This type of direct pathway for Hg to the CNS has been proposed for iHg but cannot be excluded for oHg as well. More studies are needed to confirm the presence of such transport and to determine the molecular mechanisms involved in it. The counterpoint direct uptake (occurring, for instance, in sensory structures in direct contact with contaminated water) *versus* systemic distribution and indirect uptake (occurring, for instance in CNS), and the subsequent direct toxicity *versus* systemic toxicity, is something to keep in mind.

There are also insufficient studies regarding the membrane transporters for either Hg^{2+} or MeHg in fish and especially in the CNS. Whereas for mammals the transport of the MeHg cysteineate conjugate is now confirmed to take place through the L-system transporter, the same depth of knowledge is lacking for Hg^{2+}. The presence of LAT1 and LAT2 transporters in the fish gut and muscles have been recently confirmed but no research into their role in the MeHg transport in fish is available.

Since the uptake of iHg and oHg species in the fish brain and the eye involves crossing the BBB and the BRB barriers, more studies are also needed to shed light on the molecular mechanisms of the mercury transport across these barriers. Whereas LAT1 transporter have been detected in the mammalian BBB and BRB, it is not known if similar transporters are expressed by the fish endothelial cells forming these barriers, and if they actively transport MeHg to the fish brain and the eye.

Another interesting aspect is the accumulation of Hg in the fish pineal gland detected following waterborne iHg and oHg exposures. In view of the role of the pineal gland in regulating the fish circadian rhythm, more studies are needed to correlate the Hg accumulation in this organ with behavioral changes.

The toxicokinetics of mercury is tightly interconnected with that of selenium (Se) but in contrast with mammalian studies, little is known on the Se metabolism in the fish CNS and the Se role in MeHg demethylation. Co-localized spots of Hg and Se were detected in various fish organs but the origin of Se as well the pathways leading to their formation are not known at present. The source of Se used to form the HgSe deposits is crucial for verifying the Se depletion hypothesis, which attributes the detrimental effects of Hg to Se depletion. Studies on human brain confirmed demethylation of MeHg species ultimately leading to the formation of nanoparticulate HgSe therein. However, there is no evidence for similar detoxification pathway in the fish brain. The interesting question is, assuming the presence of these nanoparticles in the fish brain is indeed confirmed, are these HgSe nanodeposits benign due to low bioavailability of HgSe or does their small size renders them more neurotoxic than their bulk HgSe counterpart? This aspect deserves further research in fish brain.

Reviewed studies also suggest different patterns of the accumulation of Hg in the fish brain upon the Hg^{2+} and MeHg exposures. The limited data on the spatial distribution of Hg generally revealed a more widespread presence of Hg upon MeHg exposure and a more localized pattern upon the Hg^{2+} exposure, especially in the ventricular regions of the fish brain. This area of Hg toxicokinetics in fish clearly requires more studies as in the majority of the research reviewed, the brain has been treated as a single homogenous compartment when investigated for Hg accumulation. However, Korbas studies (e.g. [10]) revealed that the Hg deposition can vary by brain area with specific structures more prone to this metal, in line with what has been documented for mammals. The same shortfall is applicable to the eye and other neurosensory systems. The exact localization of Hg in these tissues and its speciation *in situ* is of vital importance to understand the molecular mechanisms underlying Hg neurotoxicity and to predict the impact of environmental Hg exposure on fish health.

Mercury can seriously harm human health, and it is a particular threat to the development of fetuses and young children. The most common pathway of human's direct exposure is through fish and

seafood contaminated with Hg (particularly MeHg). It was estimated that the human body absorbs 95% of this Hg form, once contaminated food is ingested [47], which has been associated with the occurrence of several disorders both in children and in adults namely at the neurological level (see section 1). In this context, advisory guidelines have been implemented to evaluate the risk associated with fish consumption, aiming to minimize Hg accumulation in consumer populations, but without compromising the many benefits of fish to human health. The World Health Organization and the Food and Agriculture Organization of the United Nations endorse a maximum of 0.5 μg g^{-1} of Hg in non-predatory fish and 1 μg g^{-1} in predatory fish, while the US Food and Drug Administration has established a maximum of 1 μg g^{-1} in fish, shellfish, and aquatic animals. Canada and the European Community set a limit of 0.5 μg g^{-1} in fishery products, while Japan allows up to 0.3 μg g^{-1} (reviewed by Chan et al. [275]). These values correspond to maximum levels in fish edible tissues, which mostly match to the muscle. Since the fish head (where the brain and most neurosensory structures are located) is not, in generally, consumed, Hg accumulation in this part of the body does not represent a direct risk to human consumption. Nevertheless, there are some ways of fish cooking that include the whole body boiling in water, which could lead to the hypothesis that Hg may be released to the cooking sauce. This problematic was investigated by Mieiro et al. [276] in three widely consumed fish species, with Hg being detected in the boiling water, supporting the hypothesis that to some extent (still undetermined) levels in the fish head may contribute to the Hg final budget that can be ingested.

From a different perspective, it could be interesting to investigate levels of different Hg forms in the brain to infer human health risk from exposure to mercury through fish consumption. This is due to the close relationship between Hg accumulation in the brain and muscle. Indeed, Mieiro et al. [277] found comparable ratios of total Hg levels in the blood and muscle with that of blood and brain, interpreting it as a symptom of an equivalent Hg uptake in the muscle and brain. Accordingly, MeHg levels in the brain correlated well with total Hg in the muscle of the wild yellow perch (Nova Scotia, Canada) [216]. Another important aspect on this discussion is that the fish brain is well protected by an epithelial barrier (BBB) that limits, to some extent, the transport of Hg to the brain (as discussed in section 3). The same occurs for the retina that is protected by the BRB. These biological barriers contribute to fish survival, particularly at highly Hg contaminated areas, by protecting highly sensitive organs. Alongside with blocking Hg passage to the brain and eyes, these barriers are determining a higher accumulation of this element in other tissues, including the muscle. The same possibly occurs with Hg scavenging compounds, such as selenium. The close association of Hg levels in brain and muscle further supports this speculation. Overall, it is plausible to hypothesize that physiological and molecular strategies that fish may have to counteract Hg accumulation in particularly vulnerable structures (like neuronal and sensory components) will promote their survival, and, ultimately, contribute to increase the human risk of fish consumption by promoting Hg storage in the edible tissues.

8.3. Neurotransmission disorders

The expression of Hg-induced neurosensory toxicity has a multifactorial ontogeny, with both extrinsic and intrinsic factors, being clear that it is underlined by more than one mechanism or disruptive pathway. Though the existence of multiple mechanisms of toxicity (in some instances occurring more or less simultaneously) makes difficult to reconcile with the specific pattern of neurological signs [278], it has been demonstrated (in fish and other animal models) that the interference with neurotransmitter systems plays a preponderant role, namely because it occurs at early time-points. Overall, the available literature pointed out neurotransmission as particularly vulnerable to Hg in fish.

Neurotransmission includes synaptic (also at myoneural junctions) and postsynaptic (related to nerve impulses and the propagation along the axon) events. The former can be divided into several stages, most of them passible to be impaired by intracellular Hg. Hence, as a first stage, the synthesis of neurotransmitters (at the cell body, axon, or axon terminal) showed to be affected in the fish cholinergic system by both iHg and oHg forms (present in contaminated sediment), as depicted by an impaired ChAT activity (responsible for the synthesis of the acetylcholine) in gills [175]. This study provided promising indications, but no other reports can be found on this neurotransmission stage, pointing out the need to reinforce this research.

The following stages involve the neurotransmitter storage (in granules or vesicles in the axon terminal), its release into the synaptic cleft, and then, binding (and activation) to the specific receptor in the postsynaptic membrane. No data are available on interference of Hg forms at these stages in fish neurotransmission, with the exception of a recent field study showing Hg interference with glutamate receptors. In fact, the intrusion of MeHg with the interaction neurotransmitter-receptor was clearly described in mammalian models [278], as well as concentration-dependent decreases in receptor levels [279]. For instance, it was suggested that MeHg acts at $GABA_A$ receptors to decrease tonic receptor-mediated inhibitory neurotransmission [280]. Therefore, this subject was clearly elected as a gap to be filled in future research on the neurotoxicology of Hg in fish.

The deactivation of neurotransmitters is the next step and represents the best-studied process in the context of neurotransmission impairments in fish generated by Hg exposure (as detailed in section 4). However, it is notorious a concentration of studies on acetylcholine-mediated neurotransmission, since most data available concerns ChE activity, including AChE and BuChE. A reduction of MAO activity was also reported in fish. As only the aminergic system (including 5-HT, NE, DA, and ACh) was addressed, a wider application of this approach, encompassing neurotransmitter inactivation in other systems, is recommended.

A considerable number of studies quantified the levels of specific neurotransmitters in the brain of fish following exposure to both iHg and oHg, *viz.* 5-HT, DA and NE. Surprisingly, no studies addressed the glutamate system, the most common excitatory neurotransmitter in the bony fish brain [27], which is a lacuna that should be suppressed. This is even more important at the light of mammals' findings where glutamate dyshomeostasis in the CNS represents a critical step in MeHg-induced neurotoxicity (for review see [37]). Moreover, a systematic quantification of the main neurotransmitters in the different regions of the CNS, as well as in afferent and efferent nerve fibers innervating sense organs, is still required.

The synaptic activity regarded, for instance, as Na^+ and Ca^{2+} fluxes and the function of several types of voltage-gated and ligand-gated ion channels, and the frequency and amplitude of synaptic currents, and axonal electrical conduction/isolation are also key processes that needs to be unmasked in fish.

Aspects related to the involvement of astrocytes and other glial cells on neurotransmission, recently disclosed in mammalian systems (e.g. [281,282]), is also a matter that should be addressed in fish under the future investigations of Hg neurosensory toxicity.

Though the investigation on the key processes above highlighted still needs a boost, the great challenge is the establishment of associations between specific vulnerabilities at the neurotransmission level, the occurrence of neuron/glia injury, axonopathies, and demyelination, and translations into motor, endocrine and behavior disorders in fish exposed to the different forms of Hg. In other words, the great challenge is to unveil the internal pivot mechanism of the Rubik's Cube articulating the links between the green, yellow and light blue faces.

8.4. Biochemical and physiological effects

The neurotoxicity of Hg (particularly MeHg) has been widely studied in mammals and the molecular mechanisms of cytotoxicity are

partially established, being associated with three main mechanisms: (1) perturbation of intracellular Ca^{2+} levels (for instance, exposure to MeHg has been shown to increase intracellular Ca^{2+} in several cell types); (2) induction of oxidative stress by overproduction of ROS or by reduced oxidative defense capacity; (3) interactions with sulfydryl groups with the formation of thiol-containing complex, by targeting proteins and peptides containing cysteine and methionine (reviewed at [4]). These mechanisms of Hg toxicity are probably common to fish due to cellular similarities, but a complete examination of their occurrence in fish is being done, for the first time, in the current review. MeHg exposure had altered Ca^{2+} homeostasis in the Atlantic cod, whereas in the brain of the catfish exposed to iHg a considerable depletion in the activity of Ca^{2+}-ATPase was recorded, suggesting a possible disruption of Ca^{2+} metabolism [206]. Moreover, levels of ROS had increased in fish brain after exposure to Hg forms, while changes in the activities of enzymatic and non-enzymatic antioxidants were found upon exposure to Hg, underpinning a convergence of molecular mechanisms of toxicity. Accordingly, an enhancement of lipid peroxidation and protein oxidation was also reported in the fish brain. These effects pointed out an induction of oxidative stress, as reported for mammals related with Hg exposure. Moreover, the binding of MeHg to GSH is known to decrease the availability of this antioxidant, exposing the cells to free-radical mediated damage [4]. Accordingly, a depletion of GSH was reported in fish brain upon environmental Hg exposure [215]. Also, brain mitochondrial dysfunction was reported in zebrafish. Likewise, the increased level of ROS induced by Hg had been related to alterations in mitochondrial functions in mammals [4]. Finally, the binding to SH-groups of peptides may also have several detrimental consequences due to modifications of proteins structure and/or inactivation of enzymes. For instance, binding of MeHg to tubulin and the subsequent disturbances of microtubule assembly/disassembly have been proposed as possible mechanisms responsible for cytoskeletal alterations [4]. Interestingly, Hg accumulation in fish neuromasts had led to a depletion of immunoreactive tubulin, attributable to the known interference of Hg with tubulin polymerization, causing disruption of cytoskeleton and consequently cell death (details in section 5). Metallothioneins (MTs) have been expressed in the brain of fish exposed to Hg [145], but not in sensory organs so far. Contradictory results were reported by Mieiro and co-workers [283] in wild fish, where MTs were not overexpressed in the brain of fish from a Hg contaminated area. MTs have a relevant role in reducing the availability of diffusible forms of Hg within cells, while decreasing its toxic potential and, therefore, their occurrence in fish CNS and sensory organs associated with Hg accumulation needs to be clarified.

Neurophysiological impairments associated with Hg exposure were also reported in fish, such as the neuroendocrine disruption recorded in the hypothalamus of largemouth bass exposed to MeHg, which was characterized by a significant reduction of the reproductive neuropeptides. This is a single study focused solely on MeHg, but it gives some insights on the impact that Hg forms may have on fish reproduction, with possible repercussions on population maintenance. Moreover, fish Hg exposure had led to changes of the brain lipid profiles, as well as on the brain proteome, while no studies had addressed effects at these levels on the sensory organs, so far. In this direction, a depletion of total lipid levels in the catfish brain was recorded upon waterborne exposure to iHg [210], while the proteome of zebrafish brain had changed upon MeHg exposure, indicating mitochondrial dysfunction, disruption of calcium homeostasis and oxidative stress. Investigating the effects of Hg forms on the CNS and sensory organs metabolome is a promising new line of research, which can make a valuable contribution to disclose the neurosensory toxicity of Hg in fish, at the light of what has been reported for other organs in wild fish from Hg contaminated areas, as detailed in section 5. Nevertheless, so far, no studies had addressed the effects of Hg forms on the brain metabolome. In this direction, the omics techniques emerge as very powerful approaches to disclose the neurosensory toxicity of Hg in fish, which remain completely underexplored in this context.

Reviewed studies regarding Hg toxicokinetics (section 3) suggested some specificity on Hg forms accumulation in the fish brain, where for instance the pineal gland seems to be a preferential area for Hg accumulation following waterborne iHg and oHg exposures. Nonetheless, the evaluation of biochemical and physiological effects had, in general, been made in the whole fish brain, while ignoring the specificity of Hg accumulation in some brain regions. These regions would be probably more vulnerable to Hg than others with lower accumulation levels. The same shortfall is common to Hg toxicokinetic studies, as described in section 8.2. Many other factors could also determine an increased vulnerability of some brain regions in comparison with others, namely the availability of Hg targeting thiols, such as GSH that is know to promote the excretion of MeHg conjugates from the cells [284]. While this remains to disclose in fish, it was found in rat that the GSH content varied within brain region in the following order: brain cortex > brain hippocampus > brainstem [285]. In the case of confirmation for fish, this would probably determine a distinct vulnerability of different brain regions to Hg forms.

8.5. Morpho-structural changes

The impact of Hg toxicity on the morphological shaping and structural organization of the CNS, along its neuroaxis, and peripheral nervous system (dorsal root ganglia, autonomic nervous system and peripheral sensory fibers) in fish is far from being uncovered. Mainly based on the well-established knowledge of the neurosensory effects of Hg forms in mammals, it is clear from the reviewed articles that the first five mechanisms (Fig. 4) are common to fish. These key factors/processes are: gliosis, neurogenesis, vacuolation/necrosis, oedema and hyperplasia (see section 6). For instance, MeHg exposure lead to vacuolation and necrosis in the medulla oblongata, ventral regions of the optic tectum and cerebrum of the Atlantic salmon, with effects being more severe in fish exposed to the higher levels [36]. A gross oedemous separation of the grey- and white-matter (even in the forebrain) and a diffuse necrosis throughout the brain was also recorded. It is worth highlighting that some brain regions of fish seem to be more vulnerable to Hg chemical forms than others, as a reduced number of cells (neurons and glial cells) were reported specifically for some areas. The optic tectum appeared as particularly vulnerable, both to iHg and MeHg. While there are some insights suggesting that this could be related with an elevated accumulation of Hg in optic tectum, this hypothesis still needs confirmation.

MeHg crosses the blood–brain barriers, and may affect critical neurodevelopmental processes including cell proliferation, migration, differentiation, synaptogenesis, myelination, and apoptosis, raising the hypothesis that they may also occur in fish. However, to the best of our knowledge, nothing is known on the impact of mercury in synaptic plasticity and density, and dendritic arborization (plasticity) of neurons in the CNS, and in sensory neurons of the periphery in fish. In the rat, changes in organism homeostasis, like chronic stress, resulted in decreased synaptic density and functional plasticity, and decreased dendritic arborization of neurons of specific brain regions, which may result in decreased or increased volumes of these areas (prefrontal cortex, amygdala, hypocampus) and cognitive impairment (e.g. [286]). Other types of challenges to the nervous system, like chronic pain, may result in decreased and increased volumes of the same or different brain regions in the rat [287] and humans (e.g. [288,289]). Future studies should evaluate if these types of morphological changes at the neuronal level also occur in fish brain areas more susceptible to Hg toxicity. Moreover, only a couple of studies had investigated the effects of Hg on the sensory organs morphology and structure (details in section 6). Generally, that research considered very high levels of Hg in the water, much above those reported for contaminated areas worldwide, giving no realism to conclusions. Future research should take this criticism into account, while mitigating the gap of understanding the

morphological alterations of very specialized sensory structures of fish, such as the neuromasts (specialized mechanoreceptors of the lateral line). The morphological and functional integrity of neuromasts appears as indispensable for the fish existence and survival.

8.6. Behavioral shifts as apical responses

The disruption of fish behavior by Hg exposure is still far from being completely achieved. Mitigating this knowledge gap is very important in the way that the preservation of complex behaviors provides the foundation for fish population structure and aquatic communities preservation [290]. The literature contains already several examples illustrating that Hg exposure can be on the basis of significant alterations on fish motor activity. A large set of endpoints had been associated with the evaluation of this key trait (raging from fish velocity to distance covered) with a similar number of studies being focused on iHg and MeHg forms. A more complex behavior was addressed, for the first time, in parallel with motor activity in studies of Pereira et al. [23] and Puga et al. [24], corresponding to some behavioral traits that were associated with an expression of fish fear/anxiety-like status. Waterborne iHg exposure revealed to alter that fish condition after 7 days, when it was observed that exposed individuals spent less time to seek for protection [23], while MeHg did not affect that condition in fish [24]. Further studies should work on the comparison of behavioral effects for both Hg forms at comparable conditions, which so far had been scarcely made. Maximino et al. [9] was the precursor study on the effects of MeHg on the anxiety status of zebrafish by using two behavioral promising tests of anxiety (*i.e.*, novel tank and the light/dark preference tests), pointing out to a new line of research on the neurobehavioral effects of Hg in fish.

The ability of fish for capturing preys or to avoid predators may be seriously compromised by Hg exposure. Studies were both focused on iHg and MeHg effects on these key behaviors. Recently, a couple of studies had demonstrated that Hg exposure can negatively interfere with fish memory and decision making related with habitat preference. An emerging aspect of Hg behavioral effects is related with the social interaction with conspecifics. A first insight was provided by the mirror test, while addressing fish aggressiveness. Results revealed that MeHg exposure significantly reduced the fish aggressive behavior, supporting speculation on fish survival at realistic conditions where less aggressive fish may have problems with predators' avoidance, territorial protection and competition [25]. The knowledge of the repercussions of Hg exposure on fish social behavior is still in its infancy and an effort should be made to overcome this gap. Hg effects on mammals' social behavior are being under research for decades. Just as an example, prenatal MeHg exposure in non-human primates negatively affected social play behavior [291]. At this light, social effects of Hg exposure in fish are highly expected and must be explored.

There have been several studies demonstrating behavioral delayed effects in fish upon Hg exposure, meaning that exposures during one life history stage can produce effects much later in life, as reviewed by Weis [46]. For example, exposures during sensitive embryonic periods can produce long-lasting effects that can be found in adult stages (details in section 7). Interestingly, in some cases effects disappeared over time, probably related with a possible recovery of the nervous system, although this association remains largely unknown. The existence of behavioral delayed effects in fish renders the practice of short-term toxicity evaluation particularly inadequate for understanding the effects of Hg at this level. Indeed, most of the studies that addressed Hg behavioral effects in fish (Table 2) had considered an exposure time that ranged between 2 and 3 weeks, while a single study exposed fish for 3 months. Recently, this topic is gaining more attention with a focus on the use of zebrafish as a neurodevelopment model for human toxicology [29]. However, we shared Weis [292] point of view when referring to the preferential use of zebrafish as a model organisms for the evaluation of early life neurotoxicity of Hg, which is mainly based on the knowledge of its genome. Several other species have been studied over a long time and it is also relevant to understand the neurosensory effects of Hg on a variety of species with different life histories, behaviors and ecology. Studies on these species have been developed in the aquatic toxicology context, with the big motivation of protecting the aquatic environment and its species.

The nociceptive system is a specific component of the CNS that is essential for organism survival, since it allows the detection of potential noxious and harmful stimuli and their avoidance. The importance of this mechanism is well patent by its preservation and presence in invertebrates and all types of vertebrates. In humans, nociception is the basis for the sensory-discriminative component of pain, where it is integrated with the pain motivational-affective (emotional and cognitive) dimension of pain. Bony fish are known to have nociceptors innervated by the trigeminal nerve and that these are physiologically similar to those found in higher vertebrates [293]. Nothing is known about the impact of Hg exposure on nociception in fish but in humans, abdominal and chest pain are reported in some studies following Hg poisoning [294]. For example, from five patients with Hg intoxication by exposure in a school laboratory either by inhalation or skin contact three developed neuropathic pain [295], which resulted from a lesion or disease of the somatosensory nervous system [296]. In MeHg intoxicated rats, it was reported a greater vulnerability of sensory nerve fibers and dorsal root neurons than of motor nerve fibers to MeHg-induced degeneration [297]. Dorsal root nerves are generally considered to be the primary target sites in rats intoxicated with organic mercury, and thin-myelinated Aα and large-myelinated Aβ fibers may be differentially affected by this compound [297]. The lack of studies at this level in fish, namely the eventual higher susceptibility of the sensory system to Hg, should foster attention in future research studies.

Future studies on Hg effects on behavior need to consider chronic exposures to low levels of Hg forms in order to mimicry realistic environmental conditions. So far, iHg levels ranged from 0.7 to 74 μg L^{-1}, and MeHg from 0.16 to 65 μg L^{-1}, with the higher levels much above the ones reported for the aquatic environment, even for contaminated areas worldwide (Table 1). Unfortunately, few studies have sought to integrate changes in behavior upon Hg exposure with CNS and sensory organs physiology or morphology, and this appears as a major flaw on the understanding of Hg neurobehavioral effects. Future research should strive towards the knowledge integration to better achieve the neuronal and sensory effects of Hg in fish.

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