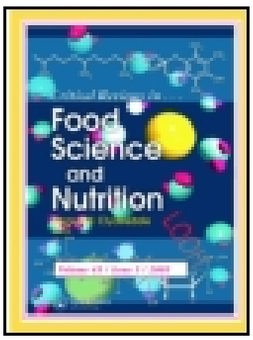

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Hazardous properties and toxicological update of mercury: From fish food to human health safety perspective

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ABSTRACT

The mercury (Hg) poisoning of Minamata Bay of Japan widely activated a global attention to Hg toxicity and its potential consequences to the aquatic ecosystem and human health. This has resulted to an increased need for a dynamic assembly, contextualization, and quantification of both the current state-of-the-art and approaches for understanding the cause-and-effect relationships of Hg exposure. Thus, the objective of this present review is to provide both hazardous toxic properties and toxicological update of Hg, focusing on how it ultimately affects the aquatic biota to potentially produce human health effects. Primarily, we discussed processes that relate to Hg exposure, including immunological aspects and risk assessment, vulnerability, toxicokinetics, and toxicodynamics, using edible fish, swordfish (Xiphias gladius), as a model. In addition, we summarized available information about Hg concentration limits set by different governmental agencies, as recognized by national and international standardization authorities.

KEYWORDS

Mercury; swordfish; immunotoxicology; aquatic environment; human health; regulatory standards

Introduction

Despite that some trace metals such as iron (Fe), copper (Cu), zinc (Zn), and manganese (Mn) play essential function in biological systems, the aquatic environment is perceived to be at risk, due to the large amount of chemical substances released into it (Altindağ and Yiğit, 2005; Bosch et al., 2016; Islam and Tanaka, 2004; Sivaperumal et al., 2007). Mercury (Hg), cadmium (Cd), lead (Pb), and arsenic (As) are nonessential heavy metals that could exert toxic effects at trace amounts (Castro-González and Méndez-Armenta, 2008; Türkmen et al., 2005). In particular, Hg has been in the environment since the beginning of time, as it has been used by many cultures for a variety of symbolic and useful purposes, such as good luck charms, to ward-off evils, material for ceremonial objects (Egyptians), and as colorants/cosmetics (Kojadinovic et al., 2006). In the 19th century, Hg is reported to have played a predominant role in alchemy and used for medicinal purposes such as curing syphilis (Kojadinovic et al., 2006).

The widely reported Hg poisoning of Minamata Bay in Japan largely resulted in a global emphasis for undertaking Hg studies and never to underestimate the dangers associated with Hg poisoning with respect to the environment, aquatic food chain, and human health (D'Itri, 1991; Harada, 1995). Several reports have shown that Hg from natural and anthropogenic sources increasingly contributes to the global concerns for human health, aquatic ecosystem, and food chain, thus elevating the attention about environment contamination by Hg (Bosch et al., 2016; Jinadasa et al., 2013; Kim et al., 2016). Further, there are clear indications that human activities have been contributing significantly to Hg levels in the atmosphere, land, and aquatic ecosystems (Asare-Donkor and Adimado, 2016; Driscoll et al., 2013; Jinadasa et al., 2013; Kojadinovic et al., 2006; Oppong et al., 2010). In this context, the presence of Hg in seafood products has captured the interest of public health officials, scientists, and general public (Burger and Gochfeld, 2012; Gibb and O'Leary, 2014; Mozaffarian, 2009).

The numerous redox states of Hg make it an interesting compound for biophysical reactions, which may result in biogeochemical cycling and trace retention in fish tissues (Bosch et al., 2016; Jinadasa et al., 2013; Voegborlo et al., 2008). The ability of Hg to accumulate and be excreted from aquatic species and humans largely depends on its chemical form (Bosch et al., 2016). Thus, Hg is predominantly found in the organic form where marine microorganisms promote its contamination in seafood (Bosch et al., 2016; Hajeb et al., 2014). For example, methylmercury (MeHg) bioaccumulates and biomagnifies in aquatic species and food chain, respectively, and are widely regarded as the most toxic form of Hg (Branco et al., 2007; Kojadinovic et al., 2006). In addition, fish contains essential polyunsaturated fatty acid (PUFA)/omega-3 fatty acids with wide range of human benefits such as development of brain cells and visual system in infants, as well as risk reduction for certain forms of heart disease in adults (Daviglus et al., 2002; Driscoll et al., 2013; Rasmussen et al., 2005). Given the trophic transfer property of MeHg, edible fish species that occupy high aquatic trophic positions and characterized with long lifespans are susceptible to contain high MeHg burdens (Kojadinovic et al., 2006).

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Table 1. Summary of previous reviews conducted on mercury (Hg) and involving either fish and/or humans.

References	Purpose of review/synthesis	Key sections/remarks
Kim et al. (2016)	Route of Hg in humans, health impacts, associated risks, and treatments based on recent findings	Hg in various media, sources, occupational risks, and exposure-led health effects
Bosch et al. (2016)	Shortcomings in current knowledge and research on accumulation of metal contaminants such as Hg in commercially consumed marine fish	Hg as a toxic metal, and its presence in seafood
Renieri et al. (2014)	Summary of biomonitoring studies on metal levels such as Hg in fish tissue, analytical methods, and its accumulation in fish, with some calculations in Mediterranean populations comparing other representative data	Methods structured review; Hg-biomonitoring and risk assessment
Gibb and O'Leary (2014)	Evaluation of Hg-health effects among those working in artisanal small-scale gold mining (ASGM) in developing countries.	Hg-vapor exposed population include workers up to families/residents that consume fish heavily contaminated by methylmercury
Driscoll et al. (2013)	Hg dynamics, human–environment health effects, and implications for control policies are synthesized	Hg exposure to human health on land, fresh water, and oceans
Hsu-Kim et al. (2013)	State of knowledge regarding the mechanisms regulating microbial Hg methylation, Hg-speciation in environments where methylation occur, and Hg- bioavailability control processes	Sources and transformations of mercury in the environment; microbial methylation of mercury
Mousavi et al. (2011)	Occurrence and speciation of Hg in natural waters to address toxicological concerns in aquatic ecosystems and preventive regulations	Toxicity as well as preventive regulations of Hg in natural waters, occurrence and release
Bernhoft (2011)	State of knowledge regarding published clinical evidence of Hg toxicity and treatment	Hg sources, pharmacokinetics, toxicity, clinical presentation, laboratory assessment, and safety practices.
Li et al. (2010)	Human MeHg exposure and the related health effects.	Pathways of human exposures, impacts of nutrition and cocontaminants on MeHg intoxication
Grandjean et al. (2010)	The extent to which environmental methylmercury research has manifested and health implications	Early evidence of human toxicity, unexpected exposure pathways, diagnostic difficulties up to regulatory concerns
Mozaffarian (2009)	Evidence and relative magnitudes of effects of Hg- fish consumption in adults	With focus on Hg, fish and cardiovascular risk and its interaction
Myers et al. (2009)	Postnatal MeHg exposure in children and its association with children's development with respect to maternal consumption of fish	Postnatal MeHg exposure and poisoning following fish consumption by mothers
Rasmussen et al. (2005)	Understanding current issues of Hg in seafood	Background Hg information and large-scale poisonings, epidemiology studies and risk assessment, and Hg studies in tuna in different geographical locations
Chan and Egeland (2004)	Hg-toxicity on human health and some epidemiological evidence (of that time)	From elemental Hg, its exposure effects on heart development and synthesis of various conducted studies
Wang et al. (2004)	Sources of Hg contamination in aquatic systems	Major Hg contamination sources
Ullrich et al. (2001)	Behavior of Hg in aquatic systems and factors essential in methylmercury formation in the environment	Hg in aquatic environment, and Hg methylation in the aquatic environment
Sweet and Zelikoff (2001)	Toxicological and immunomodulatory effects of Hg to fish and humans in field and laboratory settings	Concepts in Hg toxicology, concepts in mercury immuno-toxicology in fish and human
Spry and Wiener, (1991)	(1) How burdens of metals such as Hg in fish differ by level of alkalinity in waters, (2) what mechanisms of metal accumulation such as Hg by fish in low-alkalinity waters, and (3) toxicological significance of aqueous concentrations of such metals in low-alkalinity waters to fish populations	Characteristics of low-alkalinity lakes and how it affects Hg toxicity and bioaccumulation, Hg in low-alkalinity lakes and its toxicity
Eisler (1987)	Responding to request on chemical contaminants such as mercury levels found in natural environment	Sources of Hg in environment and properties; Hg in Minamata, Japan; background, concentrations, toxicity, and effects of Hg in aquatic ecosystem
Dallinger et al. (1987)	Relative contributions of water and food to uptake of metal such as Hg by fish.	Hg bioavailability in water and take-up pathways by fish, food as a source of Hg, role of aquatic food chains in Hg toxicity and accumulation in fish, ecological constraints and the food chain effect
Tollefson and Cordle (1986)	Hg fish consumption risks on infants, prenatal life, especially in large quantities	Toxicological evaluation of Hg with respect to fish consumption and residues, FDA data on Hg concentration in fish on the U.S. market

Previous reviews conducted on Hg concentrations in fish and humans, during the past three decades are summarized in Table 1. It was shown that the current state-of-the-art have largely focused on areas that include Hg as a contaminant and its exposure (Bosch et al., 2016; Eisler, 1987; Renieri et al., 2014; Spry and Wiener, 1991; Wang et al., 2004), knowledge about Hg accumulation in fish and its effects on populations (Dallinger et al., 1987; Hsu-Kim et al., 2013; Spry and Wiener, 1991; Ullrich et al., 2001), and Hg bioavailability/methylation and corresponding environmental speciation (Dallinger et al., 1987; Mousavi et al., 2011). Hg toxicity concerns in aquatic ecosystems and preventive regulations (Eisler, 1987; Mousavi et al., 2011; Sweet and Zelikoff, 2001), as well as human (child, adult, and pregnant women) exposure with associated health implications due to consumption of contaminated fish species have been reported (Li et al., 2010; Mozaffarian, 2009; Myers et al., 2009; Rasmussen et al., 2005). The increase in global attention on Hg contamination and how it relates to fish products, human consumption, and its health implications (Li et al., 2010; Mozaffarian, 2009; Renieri et al., 2014) are also presented in Table 1. Other conducted reviews have echoed the increasing global attention associated with Hg toxicity and effects to

human populations (Castro-González and Méndez-Armenta, 2008; Driscoll et al., 2013; Kim et al., 2016). All the above-mentioned studies have advocated the need for steady assembly of state-of-the-art information, which synthesizes published relevant reviews together with contextualization and quantification of emergent published relevant data, with ultimate aim of supplementing existing information(s). Thus, the objective of this present review is to provide hazardous properties and toxicological update of Hg starting from its exposure processes, up to applicable perspectives of immunological effects and risk assessment, as well as vulnerability, toxicokinetics, and toxicodynamics. Essentially focusing on how Hg in edible fish may ultimately lead to Hg poisoning, together with relevant human health concerns will be discussed using swordfish (*Xiphias gladius*) as a reference aquatic species. Further, Hg concentration limits set by governments and recognized (international) standardization authorities around the world will also be summarized.

Toxicological properties of elemental mercury

The ecotoxicological effects of Hg have been of increasing societal and scientific interests (Castro-González and Méndez-Armenta, 2008). Depending on its chemical state, Hg is a natural element that can neither be created nor destroyed (Kim et al., 2016; Ullrich et al., 2001) and without documented roles in biological systems (Olmedo et al., 2013). Hg is present in the geosphere mainly as a mineral known as cinnabar (Red Sulphide) that is largely deposited in areas of volcanic activity (Greenwood and Earnshaw, 1984; Mousavi et al., 2011). It can also be found at the Mediterranean basin around countries such as Spain, Italy, and former Yugoslavia, as well as in Canada, China, Japan, Mexico, Russia, and USA (Rasmussen et al., 2005; Renzoni et al., 1998). As a trace element, the detectability of Hg in the environment makes it different from other environmental contaminants (Chan and Nriagu, 2011; Kehrig et al., 2013). In the aquatic environment, the toxicity variation of Hg is dependent on different physicochemical properties, dosage, and rate of exposure (Kim et al., 2016; Ullrich et al., 2001). The three major oxidation states of Hg form toxic compounds (Jinadasa et al., 2013; Rasmussen et al., 2005), permitting biological actions on multiple targets, strengthens toxicokinetics and toxicodynamics, and interactions with other elements (Burger and Gochfeld, 2013). Apart from being the only volatile metal at room temperature, Hg is also capable of volatilization (Allen-Gil et al., 2003; Baldi et al., 1993; Compeau and Bartha, 1984; Laurier and Mason, 2007). Hg(0) (i.e., the metallic form) is present in the atmosphere in gas phase (Driscoll et al., 2013; Mousavi et al., 2011). Hg^{+} (mercurous form) can precipitate into ionic Hg^{2+} (mercuric form), permitting binding with other elements such as chlorine (Cl), sulfur (S), oxygen (O_2) to inorganic compounds, as well as organic compounds with one or two carbon atoms to produce a more hydrophobic compound that is ready to bond with proteins (Rasmussen et al., 2005).

Inorganic compounds such as mercuric chloride ($HgCl_2$), mercurous chloride (Hg_2Cl_2), mercuric acetate ($HgC_4H_6O_4$), and HgS (mercuric sulfide) are common Hg-forms found in nature (Bosch et al., 2016). These compounds undergo transformation to organic Hg in the environment (Driscoll et al., 2013). Besides, the binding of mercuric form to a single methyl, two carbon atoms or ethyl group, result in the formation of MeHg—the most toxic form of Hg, dimethylmercury [$(CH_3)_2Hg$], and ethylmercury ($CH_3CH_2Hg^{+}$), respectively (Branco et al., 2007). Linking inorganic and organic compounds in the environment underpins "methylation," in a process that is characterized, either by photochemical reaction (photomethylation) and/or catalyzed process involving aquatic microorganism such as sulfate-reducing bacteria in sediments, as well as gills and gut of fish (Beijer and Jernelöv, 1979; Bernhoft, 2012; Bosch et al., 2016; Callister and Winfrey, 1986; Monperrus et al., 2007; Mousavi et al., 2011). It should be noted that, while dimethylmercury is considered as nonbioaccumulative, it is the bioactive monomethylmercury that plays a role in Hg bioaccumulation and biomagnification in aquatic food web (Bodaly et al., 1997; Cai et al., 2007; Cossa et al., 2009; Gentès et al., 2013; Mason et al., 1995; Watras et al., 1998).

Major processes leading to mercury hazard

Hg emission processes and sources

The increase in human activities, including industrialization and urbanization within the past two decades has resulted to increases in the environmental concentration of trace metals such as Hg (Bastami et al., 2014; Bosch et al., 2016; Piazzolla et al., 2015). Hg belongs to a group of persistent and toxic heavy metals in the environmental (Ikem and Egiebor, 2005; Vizzini et al., 2010). Whether temporal or spatial, the transport of Hg and subsequent distribution in aquatic and terrestrial environment has direct link with its chemical and physical properties (Driscoll et al., 2013). In terms of Hg transport, the emitted particles can be carried either short or long distance through aquatic waterways such as rivers and streams, and atmospheric media. For example, long distance atmospheric processes are able to transport and deposit Hg(0) element from local and regional sources to Artic and Antarctic region (Allen-Gil et al., 2003; Bernhoft, 2012; Bosch et al., 2016; Driscoll et al., 2013). During the transport, elemental Hg can thrive for months and up to a year during which it oxidizes into mercuric form (Hg^{2+}) with reduced atmospheric residence time (hours to days). This can be due to dry particle deposition or scavenging by precipitation. On one hand, the land–ocean Hg processes involve the (re)-distribution via freshwater-, marine-, and terrestrial ecosystem (Driscoll et al., 2013). On the other, they result to the production of MeHg (Bosch et al., 2016; Driscoll et al., 2013). The primary (natural and anthropogenic) and secondary Hg emission sources and associated effects are shown in Table 2. Natural sources can range between sediment bacteria of deep oxygen-deficient areas and volcanic activities (Anderson et al., 2008; Kim et al., 2016; Mousavi et al., 2011), whereas agrochemical and chloralkali industries, coal-fired power utilities and metal mining remain potential anthropogenic sources of Hg input to the aquatic environment (Chan and Nriagu, 2011; Pacyna et al., 2006a; Pacyna et al., 2006b; Pacyna and Pacyna, 2005; Türkmen et al., 2005). While these human activities might neither solely increase the environmental Hg deposition nor be completely responsible for

Table 2. Major mercury (Hg) emission types, sources and some environmental effects.

Emission types	Sources	Description of source	Effects	References
Primary emission	Natural	Geogenic erosion Volcanic activities Burning biomass Vegetation Soils and snow Bacteria of sediment	Increase the global pool of Hg(0) in surface reservoirs	Anderson et al., 2008; Bosch et al., 2016; Driscoll et al., 2013; Kim et al., 2016; Kojadinovic et al., 2006; Mousavi et al, 2011; Pacyna and Pacyna, 2005; Pacyna et al., 2006a; Pacyna et al., 2006b;
	Anthropogenic	Coal-fired power station Coal-fired electricity generation Coal and municipal waste burning Residential coal burning (heating/cooking) Industrial processes Chloralkali industry Industrial/hazardous waste site Mining (gold extraction) Military sector Implemented control technologies Fuel combustion Pesticides (farms/orchards)	Increase the global pool of Hg (0) in all environments	
Secondary emission		Reemission processes of deposited Hg (reduced to Hg(0))	Redistribution of Hg(0) among and within ecosystems	

other biochemical situation(s) exemplified by increased net Hg-methylation rates, bioavailability, or exposures (Chan and Nriagu, 2011; Chan and Egeland, 2004), the natural fate of Hg may include lithosphere reservoirs up to land and oceans (Mousavi et al., 2011).

Moreover, the primary anthropogenic and secondary reemission processes can transport Hg directly to the environment (atmosphere, land, rivers, oceans, and lakes). In addition, secondary reemission process involves Hg^{2+} to Hg(0) elemental deposits through the atmosphere as vehicle exchanges among surface reservoir and ecosystems (Driscoll et al., 2013). The regional and global Hg atmospheric impact on ecosystem health have been well documented, and include, the recorded amounts of between 6500 and 8200 mg/year (Kim et al., 2016). Whether in remote or impacted environment, the major steps of Hg methylation in aquatic food chain involves biomethylation, as well as abiotic methylation that results in methylated products and reductive processes of Hg demethylation (Jinadasa et al., 2013). In addition, some key factors affecting methylation process cut across the dissolved O_2, presence of microbial entities, environmental temperature, prevailing pH condition, presence of organic material, redox conditions, presence of sulfides and salinity (Jinadasa et al., 2013; Ullrich et al., 2001).

From bioaccumulation to biomagnification

Schematic illustration of Hg–MeHg increasing by bioaccumulation and biomagnification in fish food chain within water body to result in human health effects incorporating EPA advise for (fish) consumption is shown in Figure 1. Generally, Hg-bioaccumulation is underpinned by ratio of total Hg or MeHg in biota against concentration in aquatic media, whereas Hg biomagnification is underpinned by Hg concentration in aquatic predator relative to the prey (Watras et al., 1998) in fish. The food chain is important for Hg processes, where Hg is taken up through either food or passive (surface) absorption. Although autotrophic organisms have passive absorption as the only Hg exposure route, the resultant quantity is likely not to pose much harm. On the other hand, and via food intake, it is the Hg exposure at toxic concentrations in fish products (heterotrophs) that pose greater harm (Mercury and Environment: www.ec.gc.ca/mercure-mercury/accessed on December 31, 2016). Primarily, it is the non-soluble and nonexcreted MeHg that accumulates in muscle tissue and viscera (Chen et al., 2005; Cocoros et al., 1973; Liu and Wang, 2014; Watras and Bloom, 1992). Therefore, the bioavailability and uptake of Hg and MeHg in aquatic environments has been previously studied (Baeyens et al., 2003; Cheng et al., 2011; Choy et al., 2009; Costa et al., 2012; Gentès et al., 2013; Ordiano-Flores et al., 2012; Qiu et al., 2011; Sundeland, 2007; Tomasello et al., 2012; Ullrich et al., 2001; Watras et al., 1998). The presence of Cl^-, dissolved organic carbon (DOC), $OH-$, and sulfides readily permit absorption of some of these Hg complexes through large surface area (Liu et al., 2011). While MeHg concentration in seawater appears to be low at the surface, it increases with depth of >100 up to 1000 m, depending on location (Choy et al., 2009). Moreover, such high MeHg concentration can occur in zones where sinking organic matter is rapidly remineralized (Driscoll et al., 2013). In particular, the high volatility of elemental Hg at ambient temperature coupled with low oxygen concentration, especially in subthermocline waters might facilitate the increase in Hg-methylation (Choy et al., 2009). Such conditions are typical of deep ocean waters that are characterized by reduced water circulation and low oxygen levels (Choy et al., 2009). These conditions create high bioavailability of Hg, and because of the microbial loop, the bioavailable Hg further accumulates within aquatic organisms inhabiting higher depths and deepwater predators (Bernhoft, 2012; Kim et al., 2016; Rice et al., 2014). Another aspect of Hg bioavailability is bioconcentration, which is an integral factor for introducing Hg to the food web (Watras et al., 1998). High Hg level would have a strong impact on aquatic environment as demonstrated by natural and anthropogenic activities and should not be underestimated (Bernhoft, 2012; Grandjean et al., 2010; Oken et al., 2005). Further, the US Environmental Protection Agency (US-EPA) advised that Hg levels in human and its associated frequency of consumption of contaminated fish food has strong association with the food chain, as depicted in Figure 1.

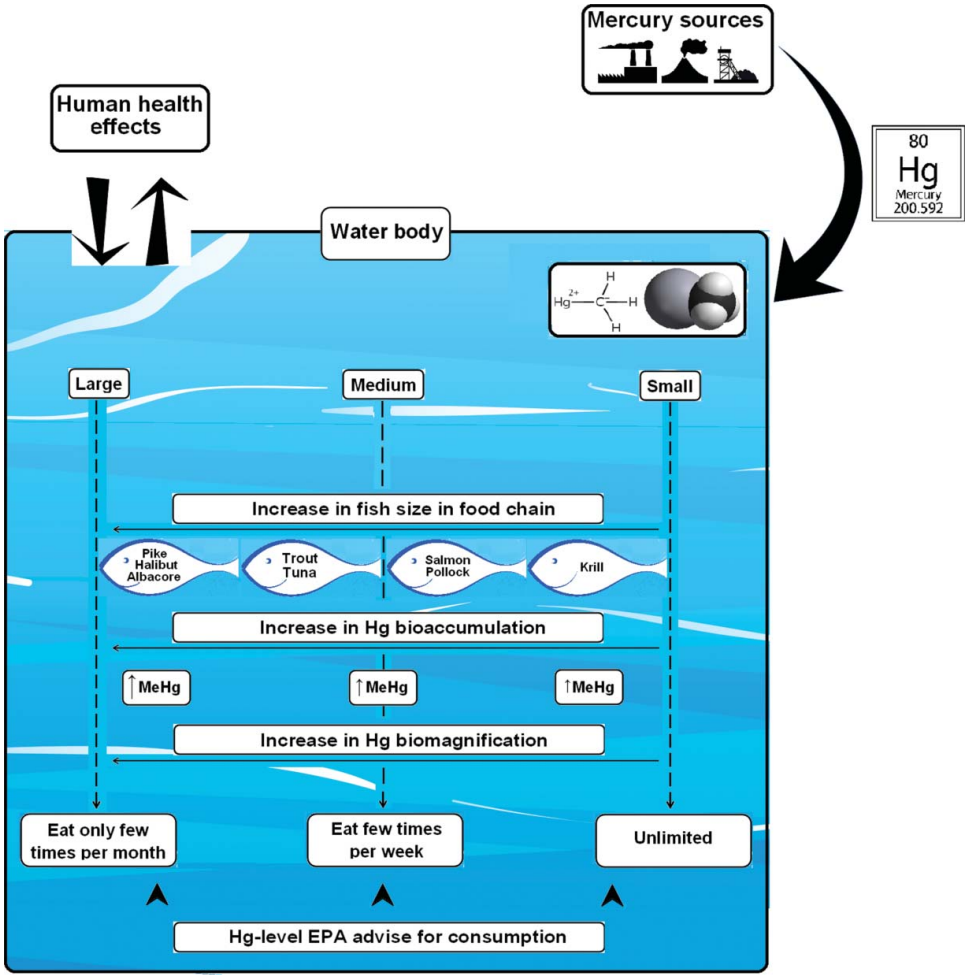

Figure 1. Schematic illustration of mercury (Hg)-methylmercury (MeHg) increasing by bioaccumulation and biomagnification in fish food chain within water body to result in human health effects incorporating EPA advise for (fish) consumption.

Therefore, to define the potential Hg bioaccumulation levels, factors such as the chemistry of the aquatic environment, nature of the occupied ecosystem, as well as abundance of prey have to be considered (Chan and Nriagu, 2011). Resultant Hg-bioaccumulation is understood to build-up in the adipose tissue of successive trophic levels, from small to large fish, as showed in Figure 1. The older the fish, the more Hg would get potentially absorbed. Demonstrated by predatory fish types, such consumption produces higher levels of Hg accumulation within the food chain. It is this process that underpins the crux of Hg biomagnification (EPA, 1997), whose ramifications are increasingly investigated (Clayden et al., 2015; Omara et al., 2015; Poste et al., 2015). From a holistic perspective, the mobility and toxic nature of MeHg facilitates its bioaccumulation properties within the (aquatic) food chain (Tadiso et al., 2011). Particularly, in large fishes, the biomagnification of MeHg has been as a result in more rapid and efficient absorption and accumulation rate, compared to its release from prey to predator (Liu et al., 2011). Subsequent to methylation, the consumption of MeHg-containing bacteria allows for plankton absorption and further transfer to higher trophic level (Mousavi et al., 2011) such as anchovy, mackerel, sardine, and apex predators such as swordfish (Renzoni et al., 1998; Varghese et al., 2013). The structure of both trophic levels and foodweb can be used to characterize the extent of Hg transfer patterns within the aquatic ecosystem (Driscoll et al., 2013; Tadiso et al., 2011). Apart from predator activities at Hg polluted waters that may produce high exposure, rate of their longevity makes them effective candidates for accumulation and transfer of Hg (Monteiro and Lopes, 1990). Consequently, all these factors in turn represent increased health risk to fish consumers (Branco et al., 2007; Kojadinovic et al., 2006; Tadiso et al., 2011). Total Hg level appears to be strongly influenced by dietary Hg concentrations (Harris et al., 2007). In this context, the accumulation of metals such as Hg in aquatic species are dependent on their age, ambient concentration, biomagnification tendencies, foraging methods, growth cycle, and trophic position (Barone et al., 2015). The ubiquitous nature of Hg to undergo bioaccumulation and biomagnification in aquatic food chain remains an issue of scientific and societal relevance (Burger and Gochfeld, 2013; Kehrig et al., 2013).

Immunological effects and risk assessment perspectives

Hg remains a potent immune modulator and/or suppressor across range of vertebrate species. Specifically, the modulation of immune function/system operates via inhibition/suppression

of immune competence, hypersensitivity, and/or by stimulation (Hawley et al., 2009; Sweet, 1999; Sweet and Zelikoff, 2001). Approaches to determine the immune-toxicity testing of chemicals in fish is widely considered as mechanistic, but unfortunately, very limited. In addition, and at molecular level, immune-toxicity testing is mostly conducted via *in vitro* mechanistic assays using chemical immune-toxicants. By examining chemical toxicity on immune system in exposed fish, the immune cell population can be assessed (Hawley et al., 2009). However, the sensitivity of these tests can depend on how immune cells respond to toxic agent, which underscore the mechanistic processes exemplified by chemically induced effects at cellular level and subsequent molecular validation (Sweet and Zelikoff, 2001). Given that immune-suppression at *in vitro* and *in vivo* levels/stages, such sensitivity test can also help to define the degree of adverse effects of chemicals (Sweet and Zelikoff, 2001), such as Hg exposure, on overall functionality of the immune system.

The broad nature of Hg distributions and levels in fish tissue by type and associated conditions of exposure has been dependent on biological, environmental, and physicochemical factors (Lenartova et al., 1997; Romeo et al., 1999; Sweet, 1999). Serum C-reaction protein in fish systems can undergo transformation in response to chemical exposure such as $HgCl_2$, which underscores the immune responses such as altered complement activation and opsonization (Paul et al., 1998). $HgCl_2$ can also inhibit acetylcholinesterase activity, probably due to altered ionic fluxes, membrane permeability, and/or preferential binding to lipid-rich structural components of mitochondria (El-Demerdash and Elagamy, 1999; Sweet and Zelikoff, 2001). Because fish (and human) serves as useful models for independent investigation, there is comparative immunological evidence that fish immune cells biochemically, functionally, and morphologically resemble that of human (Smith, 1999; Sweet and Zelikoff, 2001; Zelikoff et al., 1991).

Hg-induced immunotoxicity in fish, for example, can be assessed based on abundance of immune cells and ease of maintenance at low cost, as well as variability in fish size considering that availability of immune cell population in whole blood and that vertebrate immune system remains useful for evaluating chemical toxicity (Zelikoff et al., 1991). On this premise, many researchers (Fisher et al., 1996; Mikryakov and Lapirova, 1997; Sweet, 1999) have investigated immunomodulatory effects of Hg on fish, to establish dose and effect relationships. Schematic illustration of immune parameters in fish exposed to Hg is shown in Figure 2. For example, Hg exposure can induce immunotoxic effects such as decreased hematopoetic viability, leucopoiesis, osmoregulation, and serum lysozyme, and apoptotic increases in thymocytes, leading to enhanced cell death (Daoust et al., 1984; Fisher et al., 1996; Fletcher, 1986; Jagoe et al., 1996; Mikrayakov and Lapirova, 1997; Sweet, 1996). Sublethal Hg exposure of fish can induce immunotoxic impact on hematologic tissue and disrupting carbohydrate metabolism, ion balance, seasonal adaptation, and stress hormones (Alvarez et al., 1998; Moiseenko, 1998; Sweet and Zelikoff, 2001). Therefore, immune assays in fish can be useful candidate to evaluate Hg immunotoxicity in humans. This might contribute to the growing use of fish species for immunotoxicological risk assessments. In addition, the

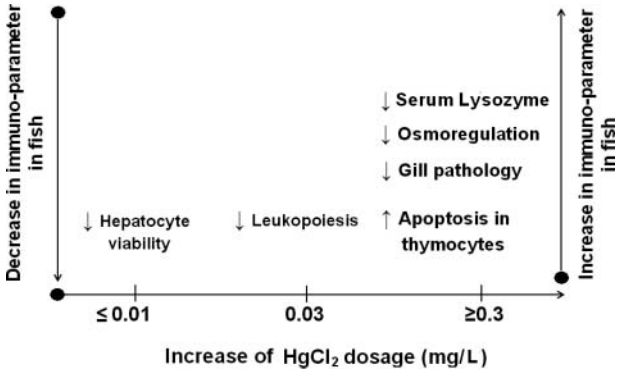

Figure 2. Schematic illustration of decrease/increase in immuno-parameters in fish as impacted by $HgCl_2$ dosage, which is based on data provided by Daoust et al. (1984), Fisher et al. (1996), Fletcher (1986), Jagoe et al. (1996), Mikrayakov and Lapirova (1997), and Sweet (1999).

sensitivity of immunological end points and specific cell types and tissues can help in the extrapolation across species. Either *in vitro* or *in vivo* Hg exposure warrants due considerations, cautious interpretation is pertinent given the corresponding effects arising due to differences in genetics, pharmacokinetics, metabolism, DNA repair, age, gender, and nutritional status (Gogal et al., 1999; Kakkar et al., 1996; Olin et al., 1997; Sweet and Zelikoff, 2001). By comparing and contrasting the Hg immunotoxicity in fish and human, Sweet and Zelikoff (2001) considered *in vitro* evidence that connects with Hg exposure that produces immunomodulation. On the other hand, and identifiable by geographical locations, the use of histopathological biomarkers has helped to detect bioaccumulated and biomagnified Hg in fish tissue, which probably contributed to the rationale used by Schwindt et al. (2008) to study Hg concentration in Brook salmon from Western U.S. National Parks. The authors established that whole-body Hg concentration can exceed consumption criteria and at several sites, indicating Hg exposure not only by geographical extension, but also as an ecological problem.

Risk assessment can be either chemical or fish-oriented. Chemical-oriented risk assessment aims to address and control the pollution source. On the converse, fish-oriented risk assessment looks at how to protect the health of fish and corresponding ecosystem (Couillard et al., 2008). As an evolving process, risk assessment should not only be based on toxicology of chemicals, but also on broader knowledge, ranging from chemistry to physiology, cellular and molecular biology, and from environmental transport processes to applied statistical approaches. Under specific conditions, risk assessment is expected to produce quantitative(s) estimate of relative risk (Fan, Howd, and Davis, 1995) posed by a particular contaminant, such as Hg. Further, risks can be determined by the lowest dose effect for a given exposure duration, assuming that the lowest dose effects were to be protected against, preventing all other effects (Fan, Howd, and Davis, 1995). Thus, in order to identify potential hazard(s), the estimation of chemical risks is required with respect to acute (single dose), subchronic (few doses), or chronic exposures toward potential toxic end points (Fan, Howd, and Davis, 1995). From a geographical standpoint, a prediction of any increases in immune-modulation arising from Hg exposure,

would require a set of wide range of risk assessment strategies (Couillard et al., 2008).

Vulnerability, toxicokinetics, and toxicodynamics perspectives

Due to its complex immune system, fish is considered to be vulnerable to Hg exposure. In this context, toxicological responses (of fish exposed to Hg, as an example) may be affected by environmental variability that may influence optimal risk assessment. Thus, toxic responses would require careful consideration of both exposure and vulnerability, as these may in turn help to establish processes such as toxicokinetics and toxicodynamics, as well as damage repair and/or recovery processes (Fig. 3a). Exposure to toxic chemical such as Hg would not only directly affect the immune system, but will inevitably reduce its resistance to infectious disease and produce indirect effects through environmentally induced stress and affecting proliferation/survival of pathogens (Couillard et al., 2008).

The vulnerability to chemicals has been considered to be higher for less resilient organisms, more exposed either as a result of their behavior or life history, and more sensitive individuals (Turner et al., 2003; US EPA, 2003). Besides, a wide range of ecological (from individual fish to population, metapopulation, communities, ecosystems, and/or habitats) and geographical scales (from local to regional) may also be used to assess vulnerability (Smith et al., 2000). Life-history is another determinant of vulnerability for aquatic species to toxic chemicals (Chapman and Riddle, 2005; Couillard et al., 2008). However, the severity of toxic injury may depend on the genetic make-up, gender, capacity to recover, concentration and duration of the active toxic compound(s) at target site, as well as the number of available target sites (Collier et al., 1992; Couillard et al., 2008; Heinrich-Hirsh et al., 2001). Thus, exposure to organic contaminants such as Hg can, therefore, be influenced by process-altered biotic factors such as olfaction, foraging, and swimming behavior, migratory clock and developmental rate, and abiotic factors such as temperature, oxygen, and salinity (Couillard et al., 2008). The vulnerability of an aquatic organism to Hg-exposure can, not only vary among different chemicals but also, change over time with seasonal reproductive cycles. In a changing environment, vulnerability can be altered as an individual responds to or is injured by chemical or other environmental stressors (Couillard et al., 2008). The increase in vulnerability of, for example, fish exposed to Hg, against the lifetime period of affected fish sample is shown in Figure 3b. Chemical exposure is considered to peak at organogenesis compared to other life stages. Although adult stage may show

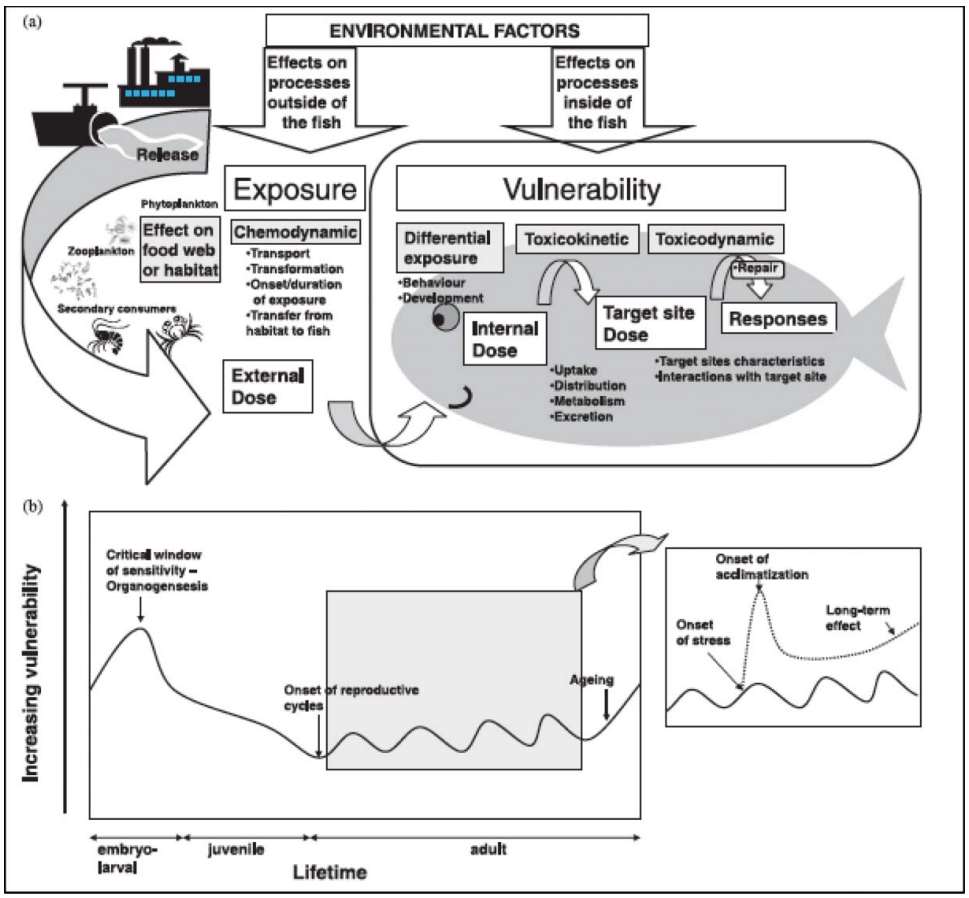

Figure 3. (a) The effects of environmental factors on exposure and vulnerability of organisms, to toxic chemicals. (b) The dynamic changes in vulnerability of fish to toxic chemicals over their lifetime. Vulnerability of an aquatic organism changes over time as the organism ages and undergoes seasonal reproductive cycles (solid line). This pattern of vulnerability will vary among different chemicals. In a changing environment, vulnerability is further altered as the individual responds to or is injured by chemicals or other stressors (dotted line in inset, hypothetical example of one possible change in vulnerability in response to environmental stressors). Reproduced from Couillard et al. (2008) with permission from NRC Press.

fluctuating trend in vulnerability, the onsets of acclimatization and stress could occur simultaneously prior to any or anticipated long-term effects of contaminant exposure, such as Hg.

Applicable to Hg exposure, toxicokinetics (absorption, distribution, excretion, and metabolism) depend highly on the form and type of molecular targets such as receptors (Pavlogeorgatos and Kikilias, 2002). Largely, toxicokinetics can incorporate processes such as biotransformation and excretion, tissue distribution followed by uptake. With respect to biotransformation and excretion, while oxygen, salinity, and temperature affect enzymatic activities (El-Alfy et al., 2002; Lange et al., 1998; Paterson et al., 2007; Prasch et al., 2004) and phototransformation of chemicals to accumulate in tissues (Couillard et al., 2008), xenobiotic or natural toxins have been shown to also affect biotransformation and excretion of contaminants (Smital et al., 2004; Van der Oost et al., 2003). With respect to tissue distribution, while climate and environmental changes can affect metabolic rate and mobilization of fat reserves (Couillard et al., 2005; Debruyn et al., 2004; Jørgensen et al., 2006), temperature has been shown to equally affect lipid partitioning in organisms (Van Wezel and Jonker, 1998). Further, habitat degradation, intensive fishing, invasive species, oxygen, and temperature will also affect growth rate and lipid content in aquatic species (Boeuf and Payan, 2001; Gordon, 2005; Swanson et al., 2006). With respect to uptake, while chemicals, temperature, and oxygen may affect ventilation rate (Heugens et al., 2001; Pierron et al., 2007), infectious disease, or chemicals may also affect gills and skin permeability (Black and McCarthy, 1990; Hallare et al., 2005). In addition, salinity would affect drinking rate and integument permeability (Bervoets et al., 1995; Hall and Anderson, 1995; Wood et al. 2004). Relevant to Hg exposure, toxicodynamics may involve both interactions with receptors and repair capability. While interactions with receptors may affect genetic adaptation, as temperature affects mitochondrial function (Cherkasov et al., 2006; Couillard et al., 2008; Pollenz, 2002), hypoxia can produce endocrine disrupting effects (Sures, 2006; Wu et al., 2003). For repair capability, changes in quality and quantity of food resources, invasive species, exposure to other toxic compounds may induce antioxidant responses and nutritional deficiencies (Couillard et al., 2008; Hennig et al., 2004; Liess et al., 2001, 2008), and extreme environmental conditions and diseases may produce energy expenditure and/or stress response (Lemly, 1996; Sures, 2006).

Mercury in edible fish: A swordfish case study

The role of fish in human diet cannot be overemphasized, accounting for why Hg in fish is of societal and scientific interests. Several studies on Hg have involved highly consumed fish species such as bluefish (*Pomatomus saltatrix*) (Burger, 2009), swordfish (*X. gladius*) (Kojadinovic et al., 2006; Lambert et al., 2012; Monteiro and Lopes, 1990), sailfish (*Istiophorus* spp.) (Barber and Whaling, 1983), billfish (*Makaira* spp.) (Shomura and Craig, 1974), yellowfin (*Thunnus albacares*), skipjack (*Katsuwonus pelamis*), big-eye tuna (*Thunnus obesus*) (Boush and Thieleke, 1983; Kojadinovic et al., 2006; Lambert et al., 2012; Licata et al., 2005), canned fish (Ashraf et al., 2006), anchovy, mackerel, sardine, salmonids and herrings species (Baldi et al., 1978; Ikem and Egiebor, 2005), and golden grey mullet (*Liza aurata*) (Filazi et al., 2003). Since a number of the above-mentioned fish species are large sized and at the same time, top predators on the pelagic food webs, determining Hg burdens in such fish species of high commercial value is of integral importance. The reason for this is the potential concerns of food contamination on human health, as well as legal thresholds that have been set for local consumption and exportation (Kojadinovic et al., 2006). In addition, there is evidence that the general public and scientific community have demonstrated significant attention to organic Hg in pelagic fish species of commercial importance such as tunas, sharks, swordfish, and billfishes (Choy et al., 2009).

Swordfish is of special interest, not only because it is among major consumed fish species in EU pelagic long-line or less by troll line fleets (Branco et al., 2007; Varghese et al., 2013), but also because it has high concentration of Hg, compared with other top predator of the pelagic ecosystems such as marlin, shark, and tuna (Forsyth et al., 2004). The human populations consuming this fish has recorded relatively high Hg intake (Lambert et al., 2012). For example, countries such as the USA and Spain have recorded Hg intake among 10% and 20% of their studied populations, respectively (Lambert et al., 2012; Sahuquillo et al., 2007; Sundeland, 2007). This phenomenon may likely explain why swordfish has been globally ascribed as long-term quantitative indicator for Hg contamination in monitoring programs (Monteiro and Lopes, 1990). In fact, swordfish is an aggressive, voracious, and opportunistic apex predator of mainly benthic (epipelagic [within the upper 200 m], upper mesopelagic [from 200 to 600 m], and lower mesopelagic [from 600 to 1000m]) species, feeding throughout the water column and migrating depths down to 1000 m (Choy et al., 2009; Renzoni et al., 1998). Swordfish is also understood to have phenomenal growth of up to 3–4.5 m and >400 kg, and with an average lifespan of about 25 years (FishBase, 2000; Jinadasa et al., 2013). Further, swordfish also shows sex differences in Hg accumulation pattern (Monteiro and Lopes, 1990). Given that the females grow faster than males, the differences in Hg accumulation with age is also associated with gonad growth and Hg affinity, resulting to either loss of residues through gamete production or total amount of sperm and ova shed (Monteiro and Lopes, 1990). Kojadinovic et al. (2006), measured Hg concentration in the muscle of 183 individuals of five (5) commercially important fish species from tropical zone of Indian Ocean, where the highest Hg levels (3.97 ± 2.67 μg/g at dry weight) were noted in swordfish. These authors found that the size of the fish served as a determinant factor for Hg burden, while sex appeared not to influence Hg levels. The authors suggested that consumers from Western Indian Ocean should limit themselves to one swordfish meal/per week. Comparable Hg values measured in muscle tissues of the corresponding species studied in other areas such as Reunion Island, North of the Mozambique Channel is shown in Table 3 (Barone et al., 2015; Branco et al., 2007; Chen et al., 2007; Jinadasa et al., 2013; Kim et al., 2016). Using size-specific Hg concentration, Kojadinovic et al. (2006), demonstrated that Hg levels positively correlated with fish length (L) (Fig. 4), which was best fitted by regression model $[\mathrm{Hg}] = a \times L^b$ where "a" and "b" are equation parameters estimated from the data given for

Table 3. Concentration of mercury (Hg) by location, in Swordfish (*Xiphias gladius*).

Location (nation/sea)	Values	Measurement units	References
USA	0.99	Ppm	Barone et al., 2015;
USA/ Sweden[f]	1.05	mg/kg	Bosch et al., 2016;
USA[g]	1.40[c]	ppm	Burger and
Canada	0.85	ppm	Gochfeld, 2006;
	1.82		Castro-Gonzalez
Canada[f]	1.82	mg/kg	and Mendez-
Atlantic Ocean	1.20[e]	μg/g	Armenta, 2008;
	0.62	μg/g	Chen et al., 2007;
	0.93[d]		Jinadasa et al.,
	1.30		2013; Kim et al.,
	1.30[a]	mg/kg	2016 Kojadinovic
	0.93[b]		et al., 2006;
	0.62		Lambert et al.,
Indian Ocean	1.47[e]	μg/g	2012; Miedico
Indian and Atlantic Ocean	1.30	mg/kg	et al., 2015; Plessi et al., 2001
Sri Lanka	0.90	mg/kg	
Indian/ South Pacific/ Atlantic Ocean	0.82	mg/kg	
Fiji Islands	1.81	mg/kg	
Reunion Islands	3.97[d]	μg/g	
	1.24	mg/kg	
Mozambique Channel	1.61[d]	μg/g	
Mauritius	0.65[c]	mg/kg	
Pakistan	0.97	ppm	
Mediterranean Sea	0.49	mg/kg	
Adriatic Sea	0.80[c]	μg/g	
	0.46[c]	μg/g	
Tyrrhenian/ Adriatic Sea	1.95[c]	μg/g	
Italy[h]	2.89	μm/kg	
Italy[i]	0.80	mg/kg	
Spain	0.93	mg/kg	
Catalonia, Spain	2.22[c]	mg/kg	
United Kingdom	1.36[c]	mg/kg	
France[j]	0.78[c]	mg/kg	
Cyprus	0.54[c]	mg/kg	

[a]male;
[b]female; ppm = parts-per million;
[c]w/w = wet weight;
[d]d/w = dry weight;
[e]f/m = flesh mass;
[f]fish market;
[g]USA specific to Chicago (Illinois);
[h]Italy specific to Modena;
[i]Italy specific to Puglia/Basilicata;
[j]Fish caught in English Channel, Baltic and North Sea, Atlantic Ocean.

each species situated in locations of Mozambique Channel and Reunion. With respect to swordfish, those of Mozambique Channel obtained statistically significant effects ($r^2 = 0.57$, $p < 0.001$) between fish length and Hg levels. Overall, the fitted regression was significantly better than constant models, except for Reunion swordfish, probably because of small sample size (Kojadinovic et al., 2006). Given that swordfish showed higher muscle Hg concentration above World Health Organization (WHO) recommended threshold of 1 μg/g for human consumption, consumers of this type of fish species were advised to limit their consumption to one swordfish meal/week (Kojadinovic et al., 2006). Although, there is ongoing debate that fish sex may not necessarily influence Hg concentration, since the males and females have different feeding habits, the concept of fish size still remains an important factor in the determination of Hg burden (Kojadinovic et al., 2006; Kraepiel

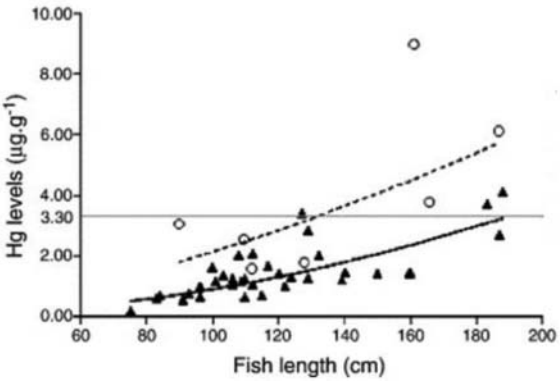

Figure 4. Mercury levels (μg/g d.w.) against fish length (cm) of Swordfish, where Mozambique and Reunion data have been represented by symbols ▲ and ◯, respectively. Corresponding regression curves have been represented by full and dotted lines, respectively. The threshold level for human consumption set by WHO is represented by gray horizontal line. Reproduced from Kojadinovic et al. (2006) with permission from Elsevier B.V.

et al., 2003). In line with the concept of fish size, Jinadasa et al. (2006) studied the relationship between total Hg (T-Hg) concentration with length and weight of swordfish. The most suitable linear model for weight (T-Hg $= a + bW$) and power fit model for length ($Y = aL^b$) were elucidated, where W = weight of fish, L = length of fish, and "a" and "b" are parameters related to the fitted equation. Model analysis showed positive correlation between T-Hg level and swordfish weight ($r = 0.69$, $p < 0.001$) and length ($r = 0.70$, $p < 0.001$). For correlation between Hg concentration and weight, $a = 2.26$ and $b = 1.37$, respectively. For correlation between Hg concentration and length, $a = 5.36$ and $b = 1.50$. Because of the unclear correlation between Hg levels and parameters such as fish age, trophic level, and presence of exoskeleton in swordfish, there is need for further studies in this area of research in order to better understand these relationships.

Apart from its ample geo-distribution and water column range, compared to other species, swordfish occupies a wide spatial water latitudes of between 45° North and South of the Equator (FAO Species Fact Sheet, http://www.fao.org/fishery/species/2503/en; Accessed 10/07/2016). In addition, it can tolerate water temperatures in the range 5°C to 27°C (Jinadasa et al., 2013; Varghese et al., 2013). The Hg concentrations reported in swordfish by different countries is summarized in Table 3. Different countries have reported wide variations in Hg concentration and by different standard units, for this fish species, making direct comparison a painstaking process. For example in Canada (1.82 ppm), Indian Ocean (1.47 μg/g w/w), Reunion (3.97 μg/g d/w), Chicago-USA (1.40 ppm w/w), Indian, South Pacific, and Atlantic Ocean (5.20 mg/kg), Atlantic Islands (9.80 ppm), Tyrrhenian and Adriatic Sea (1.95 μg/g w/w). Further, Hg concentration of 0.97 μg/g d/w in swordfish at an unidentified location has been reported (Jinadasa et al., 2013; Kojadinovic et al., 2006). In fact, due to its higher affinity to sulfur-containing proteins and amino acids such as cysteine, MeHg is capable of penetrating across cell membranes and hence, a stable organometallic compound (Liu et al., 2011; Rasmussen et al., 2005). This is facilitated by MeHg binding ability with thiol group complexes, particularly in muscle tissues (Bosch et al., 2016). In general, the liver and kidney can contain

high concentrations of T-Hg, whereas muscle is the main storage compartment for MeHg (Liu et al., 2011). Negative health effects may result in fish products if Hg bioaccumulation in swordfish reaches >1 μg/g (Chen et al., 2007), and when Hg concentration is above 0.3 and 0.5 μg/g in whole body and muscle tissue, respectively (Driscoll et al., 2013). In addition, predators such as swordfish may experience negative physiological and health effects due to high Hg exposure through prey organisms. Effects in fish due to Hg toxicity in muscle include loss of appetite and emaciation, decreased coordination, and eventual mortality (Driscoll et al., 2013). Apart from the inevitable cell and tissue damages, the reproductive capacity in human may be compromised, exemplified by differences in biochemical process and retarded embryonic development (Driscoll et al., 2013). Because fish is an important source of protein and essential fatty acids (FAs) for human diet, it is therefore not surprising that Hg concentration in large predatory fish have been of key research interest (Driscoll et al., 2013; Kojadinovic et al., 2006). According to the WHO, the toxic effects of MeHg may produce damages, not only to the fish, but also top predators, including humans (Burger and Gochfeld, 2013; Kehrig et al., 2013).

Mercury poisoning and human health concerns

Hg poisoning and subsequent harm to human population have been attributed to the consumption frequency of high Hg concentration in fish food (Björnberg et al., 2005; Booth and Zeller, 2005; Bosch et al., 2016; Burger and Gochfeld, 2006, 2012; Burger and Gochfeld, 2013; Chan and Nriagu, 2011; Copat et al., 2012; Mozaffarian, 2009; Park et al., 2011). Hg concentration in tissues of migratory, long-lived, and slow-growing marine fish species is assumed to be above recommended consumption limits for humans (Branco et al., 2007). The toxicity effects of Hg are explained by duration, frequency, and quantity reaching exposure pathways, as well as age and vulnerability of exposed subjects (Kim et al., 2016). Further, the chemo-toxicity of Hg compounds such as CH_3Hg^+ affects accumulation and excretion, probably accounting for between 75% and 100% of total human Hg exposure through fish (Bosch et al., 2016; Hajeb et al., 2014; Rasmussen et al., 2005). Organic forms of Hg such as CH_3Hg^+ are believed to be the most hazardous due to its capacity to penetrate biomembranes of gastrointestinal tract by binding to THO-SH protein group that can result to a breakdown of the central nervous system (Mousavi et al., 2011). In particular, MeHg is stable and readily accumulated in fish and human, whereas the inorganic Hg compounds such as $HgCl_2$ appear nontoxic due to low accumulation in fish and high human excretion rate (Bosch et al., 2016). On the other hand, it is important to mention that, there could be other sources of Hg exposure to human, such as consumption of contaminated foodstuffs, household products such as fluorescent light bulbs, thermostats, and occupational routes such as manufacturing of electrical equipment, chemical processing plants, dental amalgams, and Hg-containing vaccines (Hajeb et al., 2014; Kim et al., 2016).

The major human health implications of Hg in organs and associated symptoms are summarized in Table 4. Affected human systems may include, but not limited to, cardiovascular, immunological, genetic, muscular, nephrological, neurological, reproductive, and respiratory systems (Bosch et al., 2016; Castro-González and Méndez-Armenta, 2008; Kim et al., 2016). In particular, cardiovascular effects may include high blood pressure, myocardial infarction, and cardiomyopathy, whereas immunological effect is due to the high capacity of Hg as either immuno-stimulant, immuno-suppresant, or lymphoproliferant (Kim et al., 2016). Genetic problems and molecular signaling may involve microtubular disruption, increase of intracellular Ca^{2+}, which may produce alterations of neurotransmitter function due to the binding capacity of MeHg to

Table 4. Major human health implications of mercury (Hg) with respect to organs and symptoms.

Organ/System	Symptoms	References
Brain	Deficit on test of cognitive function	Bosch et al., 2016; Burger and Gochfeld, 2006; Castro-Gonzalez and Mendez-Armenta, 2008; Driscoll et al., 2013; Kim et al., 2016; Voegborlo et al., 2008
	Headaches	
	Memory loss	
	Epilepsy	
	Depression	
	Sudden burst of anger/rage/violence/ self-effacement/suicide thoughts/ lack of strength/anxiety/resist obsession and compulsion	
	Erethism	
	Infectious disease	
	Schizophrenia	
	Bipolar disorder	
	Neurological effects in early childhood	
	Neurobehavioral harm	
	Disturbance of neurotransmitter function	
	Dementia	
	Parkinson	
	Twitching	
	Visual dysfunction	
Kidney	Dysfunction (exposition during prenatal period)	
Immune system	Immunostimulant	
	Immunosuppressant	
	Lymphoproliferation	
	Hypergammablobulinemia	
	Total systemic hyper/hyporeactivities	
Heart	Arrhythmias	
	Cardiomyopathy	
	Chest pains	
	Rapid hearth beat	
	Hearth palpitation	
	High blood pressure	
	Risk of hypertension	
	Myocardial infarction	
	Coronary dysfunction	
	Atherosclerosis	
Muscles	Fatigue	
	Loos of coordination	
	Muscle atrophy	
	Movement difficulties	
Reproductive organs	Impotency	
	Reduction of sperm mobility and sperm count	
	Reduction in libido	
	Major rate of spontaneous abortion	
	Impair fertility/pregnancy/newborn development	
	Menstrual cycle disorder	
Lungs	Necrotizing bronchitis	
	Pneumonitis	
	Respiratory failure	
Genetic/ molecular	Inhibition of protein synthesis	
	Microtubule disruption	
	Increase of intracellular Ca^{2+}	
	Block of enzymes/cofactors/hormones	
	Teratogenesis	

thiol or sulfhydrl groups, leading to the activation of sulfur to block related enzymes, cofactors, and hormones (Castro-González and Méndez-Armenta, 2008). Nephrological effects in human can occur by Hg exposure at prenatal periods such as kidney dysfunction, whereas reproductive effects may include infertility (reduction of sperm count and motility), impaired fertility and pregnancy, and possible cause of menstrual cycle disorder (Bosch et al., 2016; Kim et al., 2016). In addition, at early childhood, Hg may impact neurological effects up to visual dysfunction, headaches, memory loss, depression, epilepsy, and cancer as well as respiratory effects, including pneumonitis and overt respiratory failure (Burger and Gochfeld, 2006; Castro-González and Méndez-Armenta, 2008; Driscoll et al., 2013; Kim et al., 2016). Moreover, some researchers believe that, following Hg poisoning (potential single dose of CH_3Hg^+) in human and gastrointestinal absorption, MeHg finds its way through blood stream (red blood cells) allowing for wider distribution to tissues and target organs probably within a day or two, which may be eventually excreted via feces and urine (Bosch et al., 2016; Castro-González and

Table 5. Mercury (Hg) concentration limits with bio-features by regulatory authorities.

Authorities/regulatory bodies	Concentration limits	Biofeatures	References
World Health Organization (WHO)	Blood level over 200 μg Blood level over 40–50 μg Hair safe limit approximately to 10–14 ppm ADI[a] of 0.71 μg/kg /bwt ADI[a] limit is restricted to 0.35 in some cases	Harmful effects for adults Harmful effects for pregnant women Harmful effect for adult Harmful effects for Pregnant women/ nursing mothers/children of less 10 years/fetus	Barone et al., 2015; Bosch et al., 2016; Burger and Gochfeld, 2006; Chen et al., 2007; Di Leo et al., 2010; Kojadinovic et al., 2006; Plessi et al., 2001; Rasmussen et al., 2005; Renieri et al., 2014; Romeo et al., 1999;
Joint Expert Committee on Food Activities (FAO/WHO)	PTWI[b] of 1.6 μg/kg bwt/wk Daily intake of 0.2 μg/kg bwt TDI[c] of 0.23 μg/kg bwt	Pregnant women	
UN Food and Agriculture Organization (FAO)	MALs[d] of 0.5 mg/kg for other fish and 1 mg/kg for large predatory fish		
European Commission (EC)	MALs[d] of 0.5 mg/kg for other fish and 1 mg/kg for large predatory fish	Consumption safety of fish meat	
European Food Safety Society (EFSA)	PTWI[b] of 1.6 μg/kg bwt MRLs[e] of 0.5 mg/g w/w for other fish and 1.0 mg/g w/w for large predatory fish		
US Food and Drug Administration (FDA)	Should avoid fish with level close to or exceeding 1.0 ppm		
US Environmental Protection Agency (EPA)	Reference dose of 0.1 μg/kg bwt/day		
US Agency for Toxic Substances and Disease Registry (ATSDR)	MRL[f] of 0.3 μg/kg bwt/day		
Health Canada	PTWI[b] of 1.4 μg/kg bwt /wk	Harmful effects for pregnant women and children	
	PTWI[b] of 3.3 μg/kg bwt /wk Daily exposure of 0.2 μg/kg bwt/day	Harmful effect for the rest of population	
Canadian Food Inspection Agency (CFIA)	Limit of 0.05 ppm with exception for some pelagic fish	Consumption safety of fish meat	
German Commission on Human Biomonitoring	Level $\geq$15 μg/L Levels of 4–5 ppm	Level in blood/hair that indicate risk for pregnant woman and children	
	Level in excess of 5 μg/L Levels of 1.5 ppm	Level in blood/hair that indicates high Hg concentration in woman	
UK Food Standard Agency (FSA)	Intake level of 1.6 μg/kg bwt /wk, equivalent to daily intake of 0.2 μg/kg bwt	Suggested level for pregnant women within a year	
	Intake level of 3.3 μg/kg bwt /wk, equivalent to daily intake of 0.5 μg/kg bwt	Suggested level for nursing women	
	Daily intake of 0.2 μg/kg bwt	Suggested level for breast-fed infant	
Conseil Superieur d'Hygiene Publique de France (CSHPF)	Level of 2.5 μg/g dwt	Suggested level in fish muscle for human consumption	
Agence Française de Securite Sanitaire des Aliments (AFFSA)	Same guideline with WHO	Suggested level for human consumption	
Italian Legislation (Gazz. Uff. n. 21 del 27 gennaio 1994)	Concentration limit of 0.5 mg/kg for other fish and 1 mg/kg for large predatory fish	Suggested level for edible fish	
Turkish Legislation (Turkish Food Codex Notification)	Maximum level of 0.5–1.0 mg/kg	Suggested level for human consumption	
Department of Health (Taiwan)	Standard level of 2.0 μg/g	Low level due to small amounts of fish meat consumed in Taiwan	
China Legislation	Concentration limit of 0.5 mg/kg for other fish and 1 mg/kg for large predatory fish	Suggested level for edible fish	

[a]ADI, acceptable daily intake;
[b]PTWI, provisioned tolerable weekly intake;
[c]TDI, tolerable daily intake;
[d]MALs, maximum allowable limits;
[e]MRLs, maximum residue levels;
[f]MRL, minimum risk level; bwt = body weight; w/w = wet weight; d/w = dry weight; wk = week; ppm = parts-per million.

Méndez-Armenta, 2008; Hightower and Moore, 2003). Nonetheless, some authors have reported that MeHg readily crosses the blood–brain barrier to significantly accumulate in the human brain (Bosch et al., 2016) and that might probably account for the accumulation in organs such as brain, kidney, and muscles (Table 4). Thus, the reported CH_3Hg^+ residues in the blood stream at respective 70, 46 and 90 days in adults, lactating mothers, and children (Hightower and Moore, 2003), is of significant concern.

Hg concentration limits and biohazards proposed by regulatory authorities of different countries and synergy between Hg contamination, fish, and human health is summarized in Table 5. The WHO and JECFA (Joint FAO [Food and Agriculture Organization]/ WHO Expect Committee on Food Activities), Food and Agriculture Organization (FAO), European Food Safety Authority (EFSA), and European Commission (EC) have set limits for Hg concentration in consumed fish species. These limits are for the safety of humans (adults, pregnant women, nursing mothers, children less than 10 years of age), providing safe consumption limits of contaminated fish products that should not exceed acceptable daily intake (ADI), maximum residual level (MRL), PTWI (provisional tolerable weekly intake), TDI (tolerable daily intake), and MALs (maximum allowable limits) (Barone et al., 2015; Bosch et al., 2016; Chen et al., 2007; Di Leo et al., 2010; Rasmussen et al., 2005; Renieri et al., 2014). For example, PTWI refers to the permissible human weekly exposure to heavy metal contamination associated with the consumption of otherwise whole and nutritious foods, whereas MALs refers to the limit above which consumers are likely to be exposed to harmful contaminant levels specific to food products. Further, ADI has also been set in particular to pregnant mothers by WHO due to increased sensitivity of fetus to T-Hg toxicity (Kojadinovic et al., 2006). In the USA, there are regulatory authorities such as US Food and Drug Administration (US-FDA), USEPA, and Agency for Toxic Substances and Disease Registry (ATSDR) that have set Hg contaminated fish standards for human consumption, within the frameworks of reference dose and minimum risk level (MRL). For example, FDA have stipulated that Hg contaminated fish exceeding above certain reference MRL values should be avoided, especially by pregnant women and young children. This regulation is in accordance with the Hg concentration guideline in fish consumption standards by regulatory bodies such as Health Canada and Canadian Food Inspection Agency (CFIA) (Table 5). Other regulatory bodies such as Food Standard Agency (FSA) and Scientific Advisory Committee on Nutrition (United Kingdom), German Commission on Human Biomontoring (Germany), *Conseil Superior d'Hygiene Publique de France* (CSHPF), *Agence Française de Securite Sanitaire des Aliments* (AFSSA), and governmental legislative bodies of Italy, China, and Turkey, including Department of Health in countries such as South Africa and Taiwan, are applicable to other representative authorities at other parts of the globe, have comparable standards for Hg concentration in fish for human consumption (Bosch et al., 2016; Burger and Gochfeld, 2006; Chen et al., 2007; Di Leo et al., 2010; Plessi et al., 2001; Rasmussen et al., 2005; Renieri et al., 2014).

Concluding remarks and future perspectives

In this review, we have discussed that the increases in Hg concentrations in the aquatic environment and fish food ultimately affects both aquatic ecosystems and human health. Essentially, the location and trophic level dependency of such contaminated aquatic species and resultant variability can be considered among limiting factors for effective Hg exposure effect data interpretations. Based on the synthesis of relevant information provided in this review, there is need for further studies on the short- to long-term interactive effects of Hg exposures versus dynamics of fish population and habitat, as this will help to supplement existing information. The data from such studies will immensely contribute in improving the understanding about other potential vulnerabilities and toxicological aspects of fish species exposed to varying concentration of Hg. Considering the dynamic environmental trends, including climate changes, there is also need for additional baseline studies to monitor Hg concentration limits in fish food species of commercial importance, in order to continually update the database of international and national regulatory standards. This database will also complement and provide for robust risk assessment strategies. Nonetheless, there appears to be a persistent cycle occurring between Hg, fish, and humans. In this context, some questions still remain unanswered, these include the following: (i) Where is the actual starting point, or better to say, the root cause of this persistent cycle? (ii) Why has this cycle that occurs between Hg, fish, and humans persisted amidst global efforts? (iii) Who should actually take full responsibility of the increasing global Hg hazard? (iv) What could be done to reduce the anthropogenic impact in the cycle? and (v) What problem-solving approaches should be adapted to prevent Hg contamination in the aquatic food chain? A substantive answer to any or all these unanswered questions will require both collaborative and integrative efforts between responsible national and international regulatory authorities and the scientific community.

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