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Concerns for Human Health Relating to Methylmercury (MeHg) Toxicity in Aquatic Environment: A Systematic Literature Review

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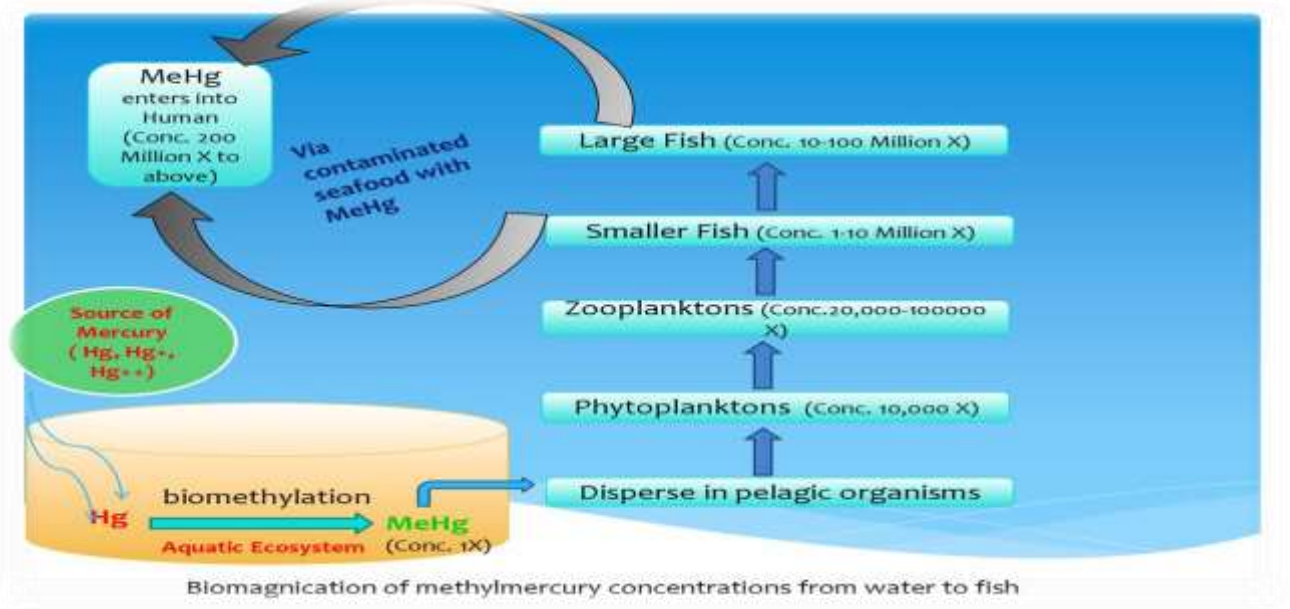
Abstract

Mercury poses serious health risks to people, and during the last century, its contamination of the ocean's surface has more than doubled. As a result, authorities and organizations have taken measures to shield people from exposure to this dangerous substance. Mercury pollution mainly comes from many anthropogenic activities, such as burning coal and other industrial processes. In addition to polluting food chains in marine and coastal ecosystems, these operations released mercury into the environment, which subsequently accumulated in fish and was ingested by people. Fish eating from marine, estuarine, and freshwater sources is to blame for more than 90% of MeHg (methylmercury) exposure in the United States and most other regions of the world. This systematic review describes the biotransformation of Hg into MeHg, the entry of MeHg into the aquatic food chain/food web, and the bioaccumulation process of MeHg. This article also describes MeHg toxicity in fish. It focuses on the effects of exposure to MeHg on biochemical, histological, and neurological outcomes in humans, as evident from various epidemiological sources.

Keywords: *Methylmercury, Biomagnification, Mercury Toxicity, Fish Consumption, Human Health.*

1. Introduction

Graphical Abstract



This Hypothetical Diagrammatic Representation Describes the Methylation of Inorganic Mercury (Hg, Hg^{++}) Into Organic Mercury (Mehg) Along with The Bioaccumulation, Biomagnification, And

Increase In Methylmercury Concentration At Different Trophic Levels (Aquatic Ecosystem) As Well As In Humans (Terrestrial Ecosystem).

Mercury is a well-known heavy metal ubiquitously present in the environment and is mainly found in three basic forms, i.e., elemental mercury (liquid form), inorganic mercury, and organic mercury (methylmercury). All three forms of mercury impart noxious effects on various species, including mammals [1]. Mercury is a natural and anthropogenic contaminant of considerable ecological concern, having the property to be converted into methylmercury and dimethylmercury by a simple biomethylation process through microorganisms present in an aquatic ecosystem where it is consumed by a large number of smaller fish and biologically biomagnified in the aquatic food chain and food web so that the highest concentration occurs in large and long-lived top predators such as fish and marine mammals [2, 3]. Methylmercury (MeHg) can exert its detrimental effects on various organisms, including humans, under certain exposure concentrations, but the mechanism is still unknown [4-6]. Being hydrophobic, MeHg can penetrate an organism's plasma membrane and easily cross the blood–brain barrier (BBB) [7]. It is biologically available to various aquatic organisms and can be easily bioaccumulated in a step-by-step manner in the ecological food chain and food web up to humans [8, 9]. Fish and other kinds of seafood play a major role in human vulnerability to MeHg in freshwater and marine food chains, and the contamination of MeHg is the main reason for fishing advisories in the USA [10]. Fish, being a rich source of various important nutrients, provide advantageous effects for brain development and help prevent various diseases, thereby obscuring the harmful effects of MeHg [11]. The content of Hg may vary among the different taxa of fish species, which means that all fish have varied proportions of Hg contamination, as MeHg biologically accumulates at different levels throughout the aquatic food chain.

Background

Bioaccumulation/biological magnification is a natural process in which the concentration of various toxins and other manufactured contaminants increases per unit of biomass with increasing trophic levels. Generally, all organisms can easily take up toxic materials through their skin, lungs, gills, or other direct points of transfer to the environment, depending upon the nature of the toxicant. The major source of toxins in predators is the population of their prey. The prey population is the major source of toxins in the predator population (mechanism of toxicokinetics). Mercury is atmospherically generated as a highly stable and least reactive uncharged gaseous form (Hg0) in the Northern Hemisphere due to the continuously populated industrial area gaseous Hg reached at higher latitudes by areal transport, where it is either oxidized to form the inorganic divalent ion Hg++ or combined with other substances that settle on aquatic or terrestrial surfaces [12-18]. Inorganic mercury (Hg+ and Hg++) is methylated in anaerobic microorganism marine sediments by different types of reducing bacteria, such as iron- and sulphur-reducing bacteria, and reaches back into the bottom layer of the aquatic ecosystem and internal soil horizon. Methylmercury (MeHg) is known to be easily absorbed by aquatic flora, fauna, and microbes. In the open ocean, where the environment is anaerobic, anaerobic bacteria such as sulphur and iron-reducing bacteria are activated and cause the formation of methylmercury from inorganic mercury [19-22]. It has been proven by in vitro experiments and confirmed that mercury could be actively absorbed through the plasma membrane by bacteria in their cytosol and methylated by a simple methylation mechanism, with some traces of this methylmercury released back into the ocean system [23]. Due to the lipophilic nature of MeHg, it is actively absorbed by phytoplankton and enters the cytoplasmic stream, and this absorbed MeHg is more easily transferred through the food chain than inorganic Hg [24-27]. Once MeHg enters the ecosystem, it generally increases concentration from a lower trophic level to a higher trophic level, a process called biomagnification, and hence reaches the highest concentrations of MeHg in top predators. This natural trophic phenomenon may have resulted from 3 to 20-fold increase in the load of atmospheric mercury since the mid-1800s of the Industrial Revolution [28]. The main interest in mercury is the biomethylation and biomagnification of MeHg in the aquatic food web and its potential for toxicity in humans who regularly consume fish and other kinds of seafood [29-30].

Methylmercury Exposure

A. Source of Exposure

Fish and seafood play a major role in MeHg exposure in humans in freshwater as well as the marine food chains, and in the United States, MeHg contamination has now become the main reason for the advisories needed for fishing. A variety of edible fish, however, also contain essential nutrients, such as omega-3 fatty acids, polyunsaturated fatty acids (PUFAs), proteins, selenium, calcium, and phosphorus, and a good source of minerals, such as Fe, Zn, I, Mg, and K, which are beneficial for the proper development of the human brain along with preventing cardiovascular diseases, thereby

concealing the adverse effects of MeHg in fish. Nutrient and Hg ratios vary from species to species because MeHg biomagnifies through the various trophic levels in the aquatic food web [31]. Methylmercury concentration in freshwater fish species tissue samples depends mainly on the species, location, body weight, and length. (Figure 1). In farmed fish, MeHg is also detected, and the concentration of MeHg solely depends on the presence of a concentration of MeHg in their feed [32]. According to the European Food Safety Authority, there are no significant differences in wild and farmed fish welfare [33], but the MeHg concentration in farmed fish can be lowered by checking and controlling the quality of fish feed. The MeHg concentration in the human diet is also dependent on rice cultivation in the mercurycontaminated zone, the organ-specific meats of different animals, and eating chicken and pork, using fish meals as livestock feed [34-36]. In the rice field, mercury is converted into MeHg by anaerobic microflora, and hence MeHg accumulates in the rice field.

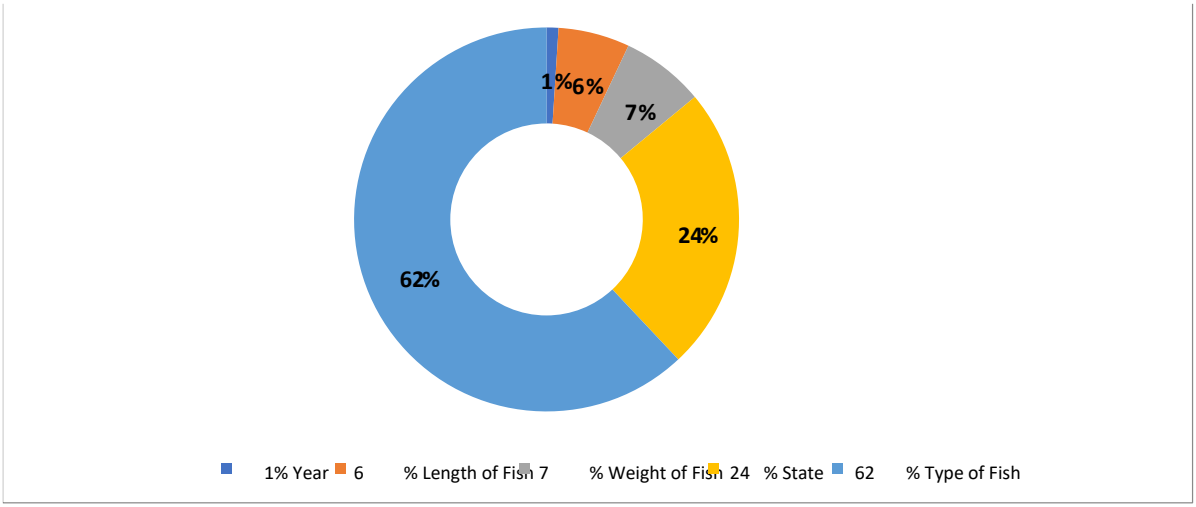


Figure 1: Factors that affect MeHg in fish tissues are fish species; 62%, locality (24%), fish body weight (7%), fish length (6%), and year (1%), which was not significant here (Data was taken from Jianping Xue et al., 2015)

B. Exposure Profiles

The levels of Hg exposure have been increasing continuously in fish and seafood-eating populations. Gaskin et al., 1979; and Honda et al., 1983 observed MeHg contents in different tissues between males and females in freshwater fish species in the 10 ng/mL group after 24 days of exposure, µg Hg/g (w.w.) and found that there was no significant sex difference ($P>0.05$) (Figure 2). The median concentrations of Hg observed in maternal hair of the Faroe Islands and Seychelles were 4.5 µg g−1 (with 27% above 10 µg g−1) and 5.8 µg g−1, respectively [37,38]. The freshwater fish-eating population in Amazon communities has 5 to 15 µg g−1 median hair Hg levels [39,40]. In the population where the fish consumption rate is very low, [41-43] the mean hair Hg levels range from 0.1 to 1.0 µg g−1, and average blood Hg levels range from 1.0 to 5.0 µg L−1[41,45]. Recently, the national health research of the USA found that in women's hair, the mercury geometric mean is 0.20 µg/g (geometric mean of regular fish consumers was three times higher 0.38 µg/g than the non-consumers of fish 0.11 µg/g), and in children below the age of 13 ± 1, the mercury geometric mean is 0.12 µg/g (geometric mean two times higher 0.16 µg/g of hair mercury of fish consumers than the non-fish consumers 0.08 µg/g) [46-48]. Likewise, the blood mercury concentration's geometric mean was 0.34 µg/L and 1.02 µg/L in women who ate 3 to 4 servings of fish in the last 30 days. The geometric mean of mercury was nearly 4 times higher than that of non-consumers (1.94 µg/L vs. 0.51 µg/L) [49]. These results concluded that in 5-10% of females at motherhood age, mercury levels in hair exceeded 1.0 µg/g and in blood vessels above 5 µg/L. in Japan, the ratio of mercury exposure is very high due to excess fish consumption, and 73.3% of women have mercury levels in the hair above 1.0 µg/g, and 1.7% above 5 µg/g [50]. Mercury exposure depends not only on fish intake frequency and the size of each diet but also on the nature of the fish species being consumed. Organic mercury biomagnifies in the aquatic food chain, which is why the concentration of MeHg can be highest at top trophic levels in fish and top predators, including mammals. Shark, tuna swordfish, and tilefish are major predatory fish with high MeHg concentrations [51]. Recent studies in Chinese adults and children found elevated blood and hair mercury levels. In the Chinese population, shark fin soup is a major source of MeHg exposure [52].

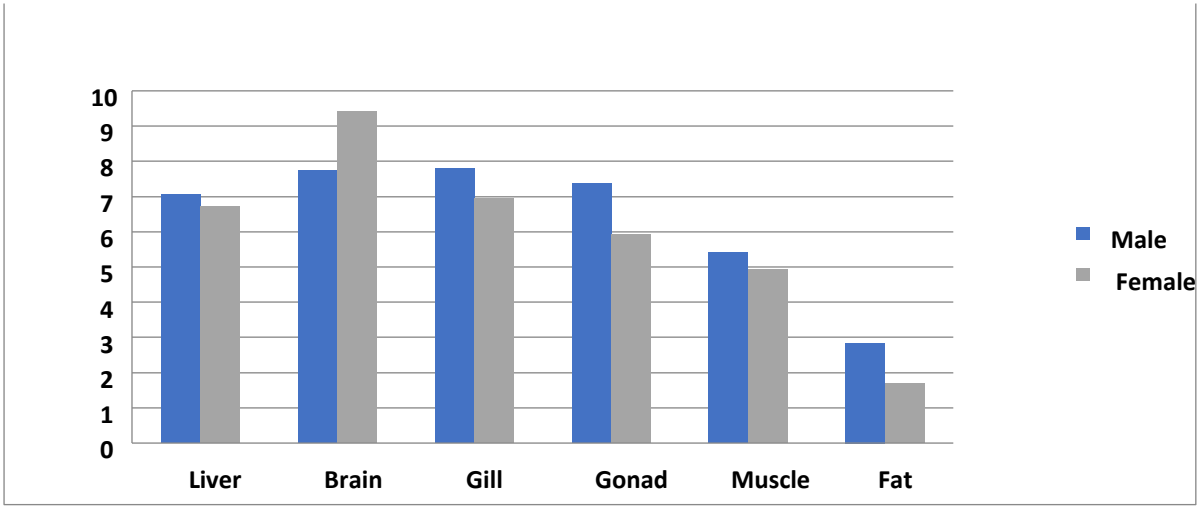


Figure 2: Comparative analysis of MeHg contents in different tissues between males and females in freshwater fish species in the 10 ng/mL group after 24 days of exposure, µg Hg/g (w.w.).

C. Biomarkers of Exposure

Mercury analysis has been performed in various samples, such as blood and tissues of the umbilical cord and parental hair (mother especially). A maternal diet survey was also used to obtain information on the regularity of Hg consumption from fish and different seafood, but the blood samples provided the most recent Hg exposure. In the blood, the half-life of MeHg is 50-70 days only, whereas, from the external body part, it is hair that may provide a schedule of mercury exposure [38]. Approximately 80-98% of the total Hair mercury is predominantly MeHg. Hg in hair is more concentrated than Hg in the blood (250-300 times) [53]. However, Hg concentration shows variability in external contamination, such as hair colour, hair types, and leaching, as a permanent solution for hair treatment [54-56]. All these factors may be imprecise biomarkers. In the same way, Hg concentration in blood may also be subject to possible variation; the concentration of Hg in the blood is considered a more relevant indicator of the amount of available dose and amount of absorbed dose of Hg. Dry weight base analysis of Hg concentration in the cord tissue gives more accurate Hg information than the wet weight Hg concentration [57]. In assessing exposure biomarkers, Grandjean and Budtz-Jørgensen reported that umbilical cord blood provides accurate information on prenatal MeHg exposure [58]. The effect of mercury on different cardiovascular abnormalities has used Hg concentrations in the nails of the toe and finger as Hg exposure biomarkers, although the extent to which these reflect organic or inorganic Hg exposure is still not clear [59,60]. Dentists also showed increased total mercury concentrations because of mercury exposure to salts in dental amalgam, but they also found it a useful biomarker. Few studies have reported inorganic Hg excretion in urine and its concentrations are considered a biomarker of MeHg toxicity [61,62].

Pharmacotoxicokinetics of Mehg

1. Absorption

The absorption rate of inorganic mercury (Hg or Hg++) is nearly 2% to 30%, respectively; however, organic mercury (methyl mercury, ethyl mercury, and dimethylmercury) can easily cross the plasma membrane and is almost completely absorbed in the vascular system [63]. When consumers ingest MeHg through contaminated seafood, it is separated by gastric acid in the digestive tract. In the digestive tract, MeHg combines with the SH- group (sulfhydryl group) of cysteine amino acids and forms the CH3Hg-SH-Cys complex, similar to methionine amino acids, and nearly 100% of it is absorbed. The blood vascular system binds with hemoglobin of RBCs in the circulatory system and subsequently accumulates in the portal vein and induces various disorders [64].

2. Distribution

MeHg, when ingested in the human body, strongly binds with tripeptide glutathione and forms the MeHgglutathione complex, and this whole complex is administered to different organs and tissues through the blood vascular system [65,66]. It can simply cross the blood–brain barrier (BBB) and the placental barrier so that it can accumulate excessively in the brain of the developing foetus [67]. It has been reported that if MeHg is injected into pregnant mice, the chance of its accumulation in the foetal brain increases up to 1.7 - 4.8 times higher than in the mother. Compared to inorganic Hg-containing compounds, MeHg crosses the placenta at an approximately 10 times higher rate; however, the passage

of MeHg from the blood vascular system to breast milk is reported to be higher than inorganic mercury [68].

3. Excretion

Bile and faeces are the main excretion pathways of MeHg. It is excreted mainly in the bile, but low amounts of MeHg are reabsorbed through the enterohepatic circulatory system and flow back to the liver by demethylation, methylmercury is demethylated and converted into inorganic mercury that is easily excreted by faecal matter. Therefore, the mercury concentration in urine would not be a good biomarker for estimating MeHg accumulation in various body organs. On the other hand, breast milk is the major excretory route of organic mercury excretion, as the half-life of MeHg in lactating females is much less than that in nonlactating females [69].

Table 1. Classification of toxicological endpoints and relative severity in fish exposed to dietary MeHg

SEVERITY RATING	CLASSIFICATION OF ENDPOINT	CONSIDERATION OF ENDPOINTS
Moderate	Adverse effects with poor ecological consequences	Altered biochemistry of blood/plasma, altered neurochemistry, changes in gene transcription, changes in cell physiology, pathological damage to different organs and tissues, and altered behavior have also been observed.
Acute	Adverse effects related to reproductive success	Reduced growth (weight or length), Emaciation, reduced spawning success, Reduced fecundity, gonadosomatic index, altered spawning behavior, altered sex steroids
Chronic	Severe adverse effects (SAEs)	Acute or chronic lethality observed.

Health Effects of Methylmercury

Dietary MeHg can affect fish through genetic variations, morphological and physiological changes in their tissues, and survival, growth, and overall development (Table 1). The consequences can directly affect the health of humans who regularly consume contaminated fish. (Figure 4)

1. Neurotoxicity

MeHg is a well-defined neurotoxin even when exposed to its lowest concentration. It is a potent toxin that may affect many enzymatic processes, functioning of the cell membrane, and neuron delivery substances that ultimately cause oxidative damage, mitochondrial dysfunction, and lipid peroxidation and distract many functions, such as microtubule composition, synapse transmission, transportation of amino acids, and cell movement, in developing brains [70]. It has been documented that disturbance in motor neurons causes various neurological disorders, such as ataxia, trembling, and dysesthesia. It was reported that MeHg had fatal effects on neurogenesis during embryonic development by poisoning the effect of Hg in the Minamata disaster, Japan, in the 1950s [71]. Neuropathological studies have helped monitor neuronal injury sites, and there have been documented reports on a large number of cases of Minamata disease in Japan. MRI reports also demonstrated the involvement of asymmetrical lesions present in the cerebral cortex and cerebellum part of the brain [72].

2. Reproductive Effects

The reproductive toxicity of MeHg is well documented. A large number of studies correlate chromosomal abnormality with the exchange of sister chromatids as per the degree of MeHg exposure [73]. It has been reported from an in vivo study carried out in experimental animals that exposure to high concentrations of MeHg for a short period leads to testicular atrophy, oligospermia, reduced size, an increase in the mortality rate of the fetus, and other fetal deformities [74]. Another study reported that the developing embryos showed that when mice were injected with 400-800 µg/kg of MeHg dicyandiamide into their peritoneum at the 7th, 9th, and 12th day of the gestation period, the highest sensitivity to MeHg toxicity. The effects of MeHg on adult females were not prominent, but it was found that a fetus in the uterus is more sensitive to exposure to MeHg because of its lipophilic nature having the capability to cross the placenta and behave as a teratogen and hindering organogenesis of the fetus compared to newborns fed milk after parturition [75]. However, more studies on human reproductive toxicology exposed to even a low concentration of MeHg are needed.

3. Immunotoxicity

MeHg-induced immunotoxicity is still not very clear in humans. An animal study in which mice were fed a MeHg concentration of 3.2 mg per kg did not show any physiological changes in body weight or

the weight of different organs, such as the spleen, liver, and kidney, but the reported weight of the thymus was observed to be reduced by 22% and thymocytes by 50%. The lymph cell proliferation response against T cells and B-cell mitogens increased in the thymus and spleen, and the activation of natural killer cells in blood was reduced by 44% and 75% in the spleen and blood, respectively [76]. MeHg-induced toxicity has also been reported in the malfunctioning of mast cells in rodents [77]. Recently, the research found that a high Hg concentration increases the risk of atopic dermatitis/Eczema [78]. However, considering that the results from in vitro experiments revealed the possibility of immunotoxicity of MeHg inside the human body should not be avoided, further studies of the impact of MeHg on humans should be performed over a broad spectrum.

4. Carcinogenicity

There is no experimental evidence to prove that MeHg induces carcinogenicity in human beings. Although a report has shown the possibility of hematological malignancy (leukemia) due to methylmercury exposure, there could not be a well-defined relationship between mercury exposure and blood-related disorders because of the limited population [79]. A study on factory workers in Sweden's chloralkali plant reported two times higher risks of being affected with different types of cancers, viz., lung, brain, and kidney cancers, but the difference was not statistically significant. The International Agency for Research on Cancer concluded adequate evidence of methylmercury chloride (MeHgCl) on the carcinogenicity of experimental animal models. MeHg is designated as a material of Group 2B (possibly carcinogenic to human beings), while MeHg is designated as a Group C material (possible human carcinogen) by the American Environmental Protection Agency (EPA) because it believed that evidence of MeHg carcinogenicity in humans was insufficient. The rationale of the carcinogenicity was restricted in experimental animal models [80].

5. Cardiovascular Effects

Limited studies have been carried out to clarify the relationship between methylmercury exposure and cardiovascular toxicity, and the exact mechanism of its involvement in cardiovascular disorders is still unknown. It is well known that mercury induces free radical formation. It also decreases antioxidants such as catalase and glutathione peroxidase, as it has a strong affinity with thiol groups (SH group) and causes lipid peroxidation, mercury-induced sclerosis of the arteries, blood coagulation, and an increase in blood pressure. Aggregation of platelets has been reported [81]. Therefore, it can be stated that there is a high probability of myocardial infarction and mortality risk due to cardiovascular diseases following exposure to mercury [82]. An expert panel from the Environmental Protection Agency in the US (2011) concluded that MeHg is directly involved in myocardial infarction and various cardiovascular-associated risk factors, such as atherosclerosis, oxidative stress, a decrease in heart rate variability, and hypertension, to some extent [83,84]. A systematic review published in 2017 also showed that MeHg enhances free radical generation, which affects the parasympathetic activity of the heart, resulting in hypertension, myocardial infarction (MI), and ultimately death, which has been confirmed in many studies [85,86]. However, there is a paucity of studies to prove any association between mercury toxicity and cardiovascular events. Figure 3 describes the MeHg-associated abnormalities in humans.

Figure 3: Different types of MeHg-induced toxicity in humans, such as neurotoxicity, immunotoxicity, carcinogenicity, and many other adverse effects, viz., cardiovascular disorders and reproductive disorders.

4. Conclusion

This systematic review outlines substantial scientific evidence on the biotransformation of mercury into methylmercury, bioaccumulation of methylmercury, the entrance of MeHg into the food web, and various disorders related to its exposure in fish as well as in humans. Even at very low exposure, Mercury can not only affect the morphology, physiology, genetic mutation, and behavior of marine and freshwater fish but can also affect their growth, survival, reproductive strategy, and development. A large number of marine products have now become an important global issue due to the accumulation of mercury that must be addressed. The key research target should be the proper tracking of all mercury sources and establishing a good understanding of the mechanism of Hg circulation in aquatic ecosystems. It is well documented that different orders of mercury poisoning occur in fish tissue. However, further studies are required to assess mercury concentrations in different organs after exposure. Fish, along with other seafood, contain large amounts of essential vitamins, minerals, and amino acids that may be good for health, but fish and other seafood are also a main route for exposure to various toxicants in humans, such as MeHg. A large number of studies in this area focused on either the nutritional benefit of seafood or the risk associated with MeHg. A future study that might be needed in this field should focus on the advantageous and adverse effects of MeHg-contaminated fish and other seafood in our diet in a wider range of fish species. Various advisories should emphasize MeHg exposure to determine whether the contamination of MeHg is highest in those fish that originate from contaminated water, especially in fish with higher trophic levels in the food chain and food web. Hence, regulatory agencies should be needed to develop risk communication strategies for consuming different species of fish and seafood, which are the major routes of MeHg toxicity in humans.

Declarations

All authors have read, understood, and have complied as applicable with the statement on "Ethical responsibilities of Authors" as found in the Instructions for Authors and are aware that with minor exceptions, no changes can be made to authorship once the paper is submitted.

Compliance With Ethical Standards

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2. **Conflicts Of Interest:** All authors declare that he/she has no conflict of interest.

3. **Ethical Approval:** This article does not need approval from the ethics committee, as the study was not performed on human/animal samples.

4. **Informed Consent:** This study does not require informed consent.

5. **Authors' Contributions:** Ramesh Mani Tripathi and Sandeep Pandey created the manuscript, gathered information from the authentic database, organized the content, produced the final product, and also gave several resources to assist with the literature. Abbas Ali Mahdi made revisions to the book while offering conception and general direction during the preparation process. The concepts and general support for the article design were produced by Mohammad Serajuddin. Mohd. Kaleem Ahmad and Kalpana Singh provided oversight and assistance in verifying the accuracy of the completed manuscript.

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