A review of mercury pathological effects on organs specific of fishes
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\textbf{ABSTRACT}

Rapid development has been associated with mercury pollution in the aquatic environment, leading to mercury toxicity in fish and other aquatic organisms. Histopathological abnormalities such as hyperplasia, inflammation, and necrosis have been observed in various fish tissues as a result of mercury contamination based on organic mercury (methylmercury) and inorganic mercury (mercuric chloride) exposure via dietary or water exposure, respectively, with different duration doses of mercury. Knowing that tissue changes occurred at an important part of each organ that played various critical roles in the normal physiological actions of fish, it is critical to understand how fish respond to mercury contamination and how this heavy metal element affects their general well-being. This review paper focuses on major tissue histopathology changes in response to mercury toxicity and their potential use as a mercury contamination indicator in fish.

\textbf{1. Introduction}

Mercury is a global pollutant that can be found in both freshwater and marine ecosystems [1] which is harmful to all organisms, even at an extremely low concentration of 0.05 μg/g [2]. In aquatic ecosystems, mercury exists in three forms [3]. Firstly, in an elemental form such as mercury vapor (Hg\textsuperscript{0}), as a liquid at room temperature [4–6]. Secondly, in an inorganic form such as mercuric chloride (HgCl\textsubscript{2}), mercurous chloride (Hg2Cl\textsubscript{2}), mercuric sulfide (HgS), and mercuric acetate (C4H6O4Hg) [5–7]. Thirdly, in an organic form such as methylmercury (MeHg), dimethylmercury ((CH3)\textsubscript{2}Hg), and mercury complexes with organic matter [5,6]. Environmentally, mercury is released by both natural and anthropogenic sources [8] through the air, water, and soil [9]. A volcanic eruption is the main natural source of mercury being released into the environment [10]. Meanwhile, gold mining, combustion of coal, fuel, and chemical waste are the anthropogenic sources of mercury contamination [11].

In the past, the excessive contamination of mercury that leads to the MeHg poisoning had caused the major human health disaster in Japan and Iraq [12]. The exposure of mercury contamination can be detected through the human clinical test on hair, blood, or urine [13]. For the record, in the late 1940s, the Minamata disease that occurred in Japan had caused almost 200,000 lives to be exposed to MeHg poisoning. This was because of the acetaldehyde application as an intermediate by-product in plastic manufacturing [14] and MeHg as a disposal product that was released into Minamata Bay [12]. At the beginning of 1970, the Minamata disease instigated the effort of the United States and Canada to recognize industrial sources of mercury to minimize the mercury disposal into surface waters [15]. In Japan, wide application of fungicide paddly culture has contaminated the Agano River in Niigata Prefecture with lethal mercury contamination which caused severe Niigata-Minamata disease outbreak [16,17]. Around the winter of 1971–1972 in Iraq, approximately 40,000 people were reported poisoned with organic mercury compounds due to the mercury consumption of homemade bread with mercury polluted seed grains [12].

Mercury contamination is declared as a dangerous environmental contaminant that can accumulate in aquatic food chains with an acute threat to living things safety [18,19]. Organic mercury such as MeHg is a critical concern to the environment due to its bioaccumulation and potent neurotoxicity [20]. In the aquatic environment, MeHg is spread widely in marine and freshwater fish [21] either from natural or anthropogenic processes of mercury circulation in the environment [9].
inorganic mercury will be transformed into a highly toxic form of MeHg via microbial activity through the methylation process [1]. Then, it will merge into the food web cycle and contribute to the increase of MeHg accumulation in aquatic animals [22]. Specifically, fish acts as an excellent example of a mercury accumulation medium through the food chain cycle [23]. According to Soares et al. [24], up to 98% of MeHg form was found to accumulate in fish. MeHg in fish represents the main source of mercury pollution to human health from the biomethylation of mercury compounds discharged [25]. Besides that, MeHg is also highly lipophilic to the environmental pollutant that leisurely crosses the barrier which exists into the blood and brain [26]. Mercury pollution from oil spills can give effect to goiath grouper [27] at the uptake of the small doses of MeHg that is known to induce high metabolic activity in the liver cells that can lead to lipid reduction and loss of cytoplastic membrane [28]. There is a high potential risk for the consumers who consume the fish to be exposed to MeHg toxicity [29]. Thus, this leading to numerous studies regarding mercury contamination in exposed fish specifically in histopathology as it can be used as an excellent indicator to check the health of fish based on the anomalies of cells in organs. This also became the starting point for more comprehensive study by elucidating on how mercury contamination can cause damages to fish organs that included histopathological changes in the fish tissues. Based on the study by Fathi et al. [30], the increasing level of tissue damages severity and occurring of lamellar fusion in the gill of exposed fish to mercury was the mechanism of protection against pollutants. Apart from that, fish that are constantly exposed to a long period of mercury tend to show a higher mortality rate due to gill epithelium damages [31]. Histopathology study on the liver can detect the abnormalities in lipid metabolism that can cause failure in the functions of metabolizing and excreting biochemicals [32]. In the kidney, tissue lesions in the renal can significantly increase the stress in fish’s physiology and general health [33]. Mercury contamination in the intestine can cause tissue injuries such as degeneration, necrosis, and erosion as well as responsible for increasing and swelling goblet cells [30]. The increase of goblet cells will increase mucin production thus, it also can increase the probability of bacteria binding onto the intestinal tract which can cause disease to occur [34]. In the brain, mercury contamination impact in the central nervous system was studied to check whether it can affect the normal function of the brain [35]. Despite that, not many reviews were being made to differentiate between those histopathological anomalies in different tissue of different fish species for a better understanding of fish tissue damages. Thus, in this review paper, we aim to evaluate the histopathological anomalies on the different tissue of various fish species due to mercury contamination.

2. Overview on journal resources

The journals used in this review were from the year of 1999 until 2020. Numerous journals based on the histopathological anomalies of different species of fish as well as their tissues were organized and showed in Table 1. The histology changes found in fish tissues were based on the studies regarding chronic exposure via feeding and acute toxicity via water-borne mercury from the long-term and short-term mercury exposure respectively. The duration of the experiment taken for the chronic exposure through methylmercury for short term and long term can be reached up to 0 (12 hours (h)) to 4 weeks [28] and 2.7 to 8 weeks [32], respectively. For acute toxicity, 96 h of lethal concentrations at 50% (LC50) were determined with the average duration for short-term of inorganic mercury exposure were between average of 4 to 96 h [28,36,37] and long term that up to 3 weeks [37,38]. Besides, a study on tissue changes due to mercury contamination of wild fish from the natural environment that was exposed to mercury was also included in this review [27,39].

3. Histological alterations as an indicator to detect mercury contamination

Histopathology is a clinical assessment tool used to detect specific lesions on biological tissue damages or changes [28]. That is widely applied in forensic investigations, autopsy, diagnosis, education [40], and medical [41], caused by disease, infection, or exposure of pollution [27,33,36,37]. A major concern in marine food fish is mercury contamination via long food chain intake accumulate in the body [42]. In this case, the mercury contamination in the fish body will be carried into the bloodstream and accumulates in the peritoneal cavity [43]. Mercury contamination can affect the behavior of the fish by stimulating oxidative damage [44] and damaging organs alteration that depletes fish health status [45]. These pathological signs are used as a reference to evaluate the quality of the aquatic environment and fish health status [46]. The severity of lesions in different organs of fish can be calculated based on the qualitative measurement in the same lesion score. Lesion score can be assessed by using a score ranging from 0 to 6, according to the degree and extent of lesions. For examples: (0) unchanged; (2) mild occurrence; (4) moderate occurrence; and (6) severe occurrence (diffuse lesions) and intermediate values are also considered [47]. In addition, the severity of lesion scoring also was calculated based on: 0 = absent or rarely observed, + = mild (affected less than 10%), + + = moderate (affected greater than 10% but less than 50%), + + + = severe (affected greater than 50%) [32].
Table 1. Summary of the lesion on the different organs of different species due to several types of mercury contamination.

| Organ   | Species                     | Source of contamination | Quantity of mercury used | Lesions                                                                                     | References |
|---------|-----------------------------|-------------------------|--------------------------|---------------------------------------------------------------------------------------------|------------|
| Gill    | Epinephelus itajara (Goliath grouper) | MeHg                    | n.a                      | Fusion (secondary lamellae), edema at the base of secondary lamellae, mild laminar telangiectasis, tubular necrosis and hyalinisation, interstitial, and mononuclear cell infiltrates | [27]       |
|         | Oreochromis niloticus (Tilapia) | HgCl₂                   | 0.3 mg/L & 0.03 mg/L     | Lesion in the epithelial, focal proliferation, edema, mucous secretion, vacuolization, or almost empty, congestion and hemorrhage | [37]       |
|         | Oreochromis niloticus (Tilapia) | Trace elements          | n.a                      | Hyperplasia and hypertrophy of the gill epithelium, blood congestion, dilation of the marginal channel, epithelial lifting of the lamellae, fusion, disorganization, aneurysm of lamellae, complete fusion of all the lamellae, and rupture of pillar cells, lamellar epithelium as well as epithelial cells with hemorrhage | [51]       |
|         | Danio rerio (Zebrafish)      | HgCl₂                   | 7.7 & 38.5 μg/L          | Degeneration of epithelium, folded lamellae, lamellar fusion, hypertrophy of epithelial cells, hypertrophy of endothelial cells along with blood vessel congestion as well as aneurysms, detachment of epithelium from connective tissues, necrosis, macrophage infiltration, vacuolation, swelling and wrinkling lamellae, wrinkling filament and lamellar hyperplasia | [36]       |
|         | Salvelinus alpinus (Arctic char) | MeHg and HgCl₂          | 0.26 ± 0.05 mg/g body weight | Exfoliation, vacuolation and blood congestion, unorganized chloride and mucous cells at secondary lamellae base | [28]       |
|         | Acanthopagrus auratus (Seabream) | HgCl₂                   | 10, 20, 35 & 50 μg/L     | Extensive epithelial lifting and edema of the lamellae with enlarged sub-epithelial spaces, hyperplasia, partial lamellae fusion, club shaping of gill lamellae, lamellae with the marginal channel dilated, blood congestion, lamellar aneurysm, lamellar disorganization, hypertrophy of the lamellar epithelium, leukocytes infiltration, increase of mucosal cells and epithelium rupture | [38]       |
|         | Gymnotus carapo (Banded knifefish) | HgCl₂                   | 0.6 μg/g                 | Gill filament epithelium hypertrophy and hyperplasia; lamellar epithelium hypertrophy; and lamellar fusion | [43]       |
|         | Acipenser medirostris (Green sturgeon) and Acipenser transmontanus (White sturgeon) | MeHg                    | 25, 50 and 100 mg MeHg/kg diet | Areas with focal proliferation, fusion of adjacent secondary lamellae and vacuolization of epithelial cells | [32]       |
|         | Carassius auratus (Goldfish) and Cyprinus carpio (Common carp) | metal-doped titanium dioxide nanoparticles | 5.10, 20, 30, 40, 50, 60, 70, 80, 90, 100 mg/L | curvature, oedema, hyperplasia, dilated marginal channel, lamellar fusion, dilated and clubbed tips, epithelium shortening, aneurism, necrosis, increasing of mucous secretion, and haemorrhage at secondary lamellae | [53]       |
|         | Cyprinus carpio (common carp) | copper oxide nanoparticles and titanium dioxide nanoparticles | 15, 20, 25, 30, 35, 40, 45, 50, and 55 mg/L | Gills hyperplasia, oedema, curvature, fusion of lamellae, dilated and clubbed tips, aneurism, hypertrophy and proliferation in the erythrocytes of cartilaginous core, epithelium shortening, lamellar epithelium proliferation, dilated marginal channel, hypertrophy, vacuoles, and necrosis | [54]       |
|         | Cyprinus carpio (common carp) | titanium dioxide and copper oxide | 15, 20, 25, 30, 35, 40, 45, 50, and 55 mg/L | Dilated and clubbed tips, mucus secretion, edema, hyperplasia, lamellar fusion, synchiea of lamellae, epithelium shortening, aneurism, and necrosis | [55]       |
|         | Capoeta fasca (Blackfish)     | iron oxide nanoparticles and iron salts | 3.23, 1.6, 3.3, and 5.2 mg/L | Lamellar fusion, curvature, aneurism, hyperplasia, oedema, the fusion of lamellae, lamellar synchiea, and dear signs of necrosis | [58]       |
| Liver   | Cyprinus carpio (Common carp) | MeHg                    | 0.63 ± 0.26/0.34 ± 0.13 μg/g | Single boci necrosis/pyknosis, interstitial inflammation, bile duct hyperplasia, prevalence of liver, renal lesions and zonal steatosis/glycogen cytoplasmic deposits | [33]       |
|         | Epinephelus itajara (Goliath grouper) | MeHg                    | 2.87 ± 4.70 μg/g         | Steatosis or accumulation of glycogen, karyolysis, nuclear loss, necrosis (hyaline bodies formed), multifocal mono-nuclear cell infiltrates, mild portal fibrosis and multifocal melanomacrophage centers | [27]       |
|         | Oreochromis niloticus (Tilapia) | HgCl₂                   | 0.3 mg/L & 0.03 mg/L     | Disorganization of hepatic cells, severe degradation of the liver parenchyma, leucocytic infiltration, necrosis and micronecrosis | [37]       |
|         | Danio rerio (Zebrafish)       | HgCl₂                   | 15 and 30 mg/L           | Mild and severe parenchyma disorganization, pyknotic nucleus and vacuolation | [62]       |
|         | Serrasalmus rhombeus (Piranha) | Hg                       | n.a                      | Disorganization of hepatocyte cord, cellular hypertrophy, leukocyte infiltration, circulatory disorders, steatosis and necrosis | [39]       |
|         | Oreochromis niloticus (Tilapia) | Trace elements          | n.a                      | Melanomacrophages aggregates, eosinophilic granules in the cytoplasm, cellular and nuclear hypertrophy, irregular shaped cells and nucleus, nucleus in a lateral position, cytoplasmic vacuolation, eosinophilic granules in the cytoplasm, nuclear vacuolation, degeneration of cytoplasmic and nuclear, cell rupture, hyperemia, pyknotic nucleus, bile stagnation, necrosis and hepatic neoplasms | [51]       |
|         | Salvelinus alpinus (Arctic char) | HgCl₂ and MeHgOH         | 0.26 ± 0.05 μg/g         | Loss lipid, heterochromatin in nuclei and necrosis | [28]       |
|         | Hoplias malabaricus (Wolf fish) | MeHg                    | 0.075 μg MeHg/g          | Presence of necrosis area, melanomacrophages centers (MMCs) and pre-necrotic lesions (leukocytes infiltration). | [26]       |

*Continued*
| Organ          | Species                          | Source of contamination | Quantity of mercury used | Lesions                                                                                       | References |
|---------------|----------------------------------|-------------------------|--------------------------|-----------------------------------------------------------------------------------------------|------------|
|               | **Acanthopagrus latus** (Yellowfin seabream) | Hg                      |                          | Onotic necrosis, apoptic necrosis, focal necrosis, massive necrosis, centrilobular necrosis, enlarged nuclei, lateral necrosis, nuclear degeneration, nuclear vacuolation, atrophy, lipidosis, megalocytosis, hydroid swelling, cloudy swelling and oval cell proliferation and periporal necrosis. | [63]       |
|               | **Gymnotus carapo** (banded knifefish) | HgCl₂                   | 0.6 μg/g                 | Disorganization of the hepatic tissue, changes in hepatocytes nucleus, congestion of blood vessels, and areas of severe degradation of liver parenchyma. | [43]       |
|               | **Poecilia reticulata** (Guppy)    | CH₃CH₂Hg                | 1 μg/g                   | Presence of lipid droplet, glycogen depletion, vacuolar degeneration and single cell necrosis.   | [64]       |
|               | **Acipenser medirostris** (Green sturgeon) and **Acipenser transmontanus** (White sturgeon) | MeHg                    | 25, 50 and 100 mg/MeHg/kg diet | Moderate to severe glycogen depletion (Fig. 4B), characterized by decreased size of hepatocytes, loss of the 'lacy', irregular, and poorly demarcated cytoplasmic vacuolation typical of glycogen, and increased cytoplasmic basophilia. | [77]       |
| Kidney        | **Cyprinus carpio** (common carp larvae) | titanium dioxide and copper oxide | 15, 20, 25, 30, 35, 40, 45, 50, and 55 mg/L | Hepatocyte necrosis, hemorrhage, dilated sinusoids, blood sinusoids, and melanomacrophage aggregates | [55]       |
|               | **Cynoscion nebulosus** (spotted seatrout) | MeHg                    | 1.12 ± 0.69/0.44 ± 0.12 μg/g | Renal interstitial inflammation, glomerular lesions (dilatations, mesangial and basement membrane thickening, adhesions between the visceral and parietal layers of the Bowman’s capsule, and deposits of hyaline material in Bowman’s spaces), and tubular lesions (degeneration and necrosis) | [33]       |
|               | **Epinephelus itajara** (Goliath grouper) | Hg                      | 1.78 ± 3.12 μg/g         | Glomeruli lesion (necrosis, adhesions to the Bowman’s capsule or thickening of basement membrane/dilatations and contracture). Tubularcrosis/hyalinization, interstitial mononuclear infiltrates and multifocal melanomacrophage centers | [27]       |
|               | **Salvelinus alpinus** (Atlantic salmon) | HgCl₂ and MeHg           | 0.26 ± 0.05 μg/g         | Swelling of hepatocytes, loss of lipids reserves                                           | [28]       |
|               | **Haplochilus malabaricus** (wolf fish) | MeHg                    | 0.075 μg MeHg/g/25, 50 and 100 mg/MeHg diet | Presence of necrotic areas and dead cells with macrophage digestion of apoptotic bodies | [26]       |
|               | **Acipenser medirostris** (Green sturgeon) and **Acipenser transmontanus** (White sturgeon) | MeHg                    | 25, 50 and 100 mg/MeHg/kg diet | Tubular epithelium degeneration; renal corpuscle disintegration; and interstitial tissue degeneration including necrosis | [32]       |
| Intestine     | **Cyprinus carpio** (common carp larvae) | MeHg                    | 11.7 μg/g                | Moderate kidney tubular dilatation                                                        | [77]       |
|               | **Salvelinus alpinus** (Arctic char)   | HgCl₂ and MeHg           | 0.26 ± 0.05 μg/g         | Inorganic mercury found in epithelial tissue and intestinal villi; ciliated cells also were affected; organic Hg was apparently absorbed in many distinct regions of the intestinal epithelium at days 4 and 14 | [28]       |
|               | **Carassius auratus** (Goldfish) and **Cyprinus carpio** (Common carp) | metal-doped titanium dioxide nanoparticle and copper oxide | 5.10, 20, 30, 40, 50, 60, 70, 90, 100, and 100 mg/L | Increasing in goblet cells amount, swelling of goblet cells, the number of lymphocyte, integration of villi, and expansion at villi structure as well as necrosis-erosion | [53]       |
|               | **Cyprinus carpio** (Common carp)      | copper oxide nanoparticles and titanium dioxide nanoparticles | 15, 20, 25, 30, 35, 40, 45, 50, and 55 mg/L | Intestine degeneration, vacuolation, swelling of goblet cells, inflammation, and necrosis – erosion | [54]       |
|               | **Cyprinus carpio** (Common carp)      | titanium dioxide and copper oxide nanoparticles | 15, 20, 25, 30, 35, 40, 45, 50, and 55 mg/L | Degeneration, integration of villi; expansion at villi structure, increase in the number of blood cells, and necrosis – erosion | [55]       |
|               | **Cyprina fasciata** (Blackfish)       | iron oxide nanoparticles and iron nanoparticles | 32, 16, 33, and 5.2 mg/L | Increases in the number (and swelling) of goblet cells, higher blood cell counts higher numbers of lymphocyte and expansion of the villi structure | [58]       |
| Brain         | **Danio rerio** (Zebrafish)            | MeHg                    | 0.8 and 13.5 μg/g        | Effect on granular cells - reduce in cell density, nuclear area and condensation of chromatin. | [35]       |
|               | **Salmo salar** (Atlantic salmon)      | CH₃HgCl and HgCl₂        | 1, 10 & 100 mg/kg        | Vacuolation, necrotic cell, presence of tissue edema caused damage of gross architectural damage and oxidative injury | [71]       |

n.a. no available data; Hg: mercury; HgCl₂: mercuric chloride; MeHg: methylmercury; CH₃CH₂Hg: methylmercuric chloride; CH₃HgCl: monomethylmercury.
The effect of mercury contamination in the fish tissues can be primarily found in the liver followed by kidney, muscle, gonad, and brain [27]. The liver is one of the organs that take precedence in the uses for the histopathology assessment. This is because the liver is found to accumulate the highest level of mercury compared to other organs [37]. The effects of mercury exposure resulted in tissue lesions in the different organs of fishes are summarized in Table 1.

3.1. Tissue lesions in fish gill

Gill is a complex organ in both morphology and physiology with multifunction in osmoregulation, exchange site for the gas, regulation of acid-base, a site for nitrogenous waste excretion, and detoxification [36,48–50]. The gill also acts as a main route to the entrance of waterborne inorganic mercury in fish [36]. With those functions of the gill, it poses highly sensitivity changes to water quality, where the gill contains large surface area that directly and continuously contact with water contaminant [38]. There are two types of lesion patterns found on gills tissue with several classifications used to describe the effect of mercury pollution to the gills. The first one is based on the location of lesions found such as at epithelium lamellae whether at the base or secondary lamellae. The second classification is on associated changes in; mucous and/or chloride changes; blood vessel changes and; terminal stages [38].

Mercury contamination may cause fish gill respiration deficiency, where HgCl₂, in the concentration of 0.01 and 0.02 mg/L can deplete the ability of gas exchange in yellowfin seabream [38]. Based on previous studies, the severity of the lesions that occurred in fish gill can be varied depending on the duration and concentration of mercury exposure [36,37] as well as the size of the fish [30]. Two different concentrations of HgCl₂ that were used and exposed to tilapia which are 0.3 mg/L for short exposure and 0.03 mg/L for long exposure [37]. This resulted in cell modification in the gill that consists of focal proliferation and sometimes resulting in the fusion of adjacent secondary lamellar after 24 to 96 hours exposure to median lethal HgCl₂ at the concentration of 0.3 mg/L. Results showed that tilapia gill will undergo lesions in the epithelial cell, hypertrophy, and vacuolation for 10 days exposure of 0.03 mg/L of sub-lethal HgCl₂. Then, for the finding of 0.03 mg/L of sub-lethal HgCl₂ exposure to tilapia for 21 days, edema was presented in the epithelial cell with an increase in size but a decrease in number of cells noticed. The symptom of edema usually will occur in the epithelial cells at the base of lamella or secondary lamella with exposure to HgCl₂ and MeHg [27,37].

Another common symptom caused by the effect of mercury was the presence of fusion between lamellae caused by hyperplasia and hypertrophy [27,37,43,51]. Lamellar fusion also frequently reported to occur in fish secondary lamellae due to toxicants [52–55]. The fusion of lamellae occurred due to the severe proliferative lesions with increasing size of the cell [56]. This is known to be caused by hyperplasia with enlargement of tissue due to cell increase without change in cell volume [57]. Similarly, secondary lamellar fusion was also found in wild goliath grouper that was exposed to MeHg [27] as well as in sturgeon exposed to 100 mg/kg of MeHg diet for 4 weeks [32]. The ability of gills of yellow seabream in gas exchange efficiency will also be reduced because of the presence of lamellar fusion, extensive lamellar lifting, and hyperplasia caused by HgCl₂ at concentration of 0.05 mg/L [38]. But if the mercury exposure is at critical level, fish will increase the gill ventilation and cardiac output to support basal metabolic needs which may lead to that resulted in high living cost [32]. In addition, some studies reported that, some abnormalities in secondary lamellar occurred as clubbed tips and slight curvature of lamellae were seen that indicated the fish was in stress condition [53–55,58]. The symptom of edema will occur in the epithelial cells at the base of lamella or lamellae [38]. Serious injuries secondary lamella showed by Oliveira Ribeiro et al. [28] consisting of the exfoliative epithelial with detachment, vacuolation of epithelial cells, and aneurysm after 12 hours exposure to waterborne HgCl₂, at concentration of 0.015 mg/L. However, slight recovery was noticed with some alterations of the epithelial cells and changes in the shape of red blood cells indicated in an enduring of inorganic mercury effects on gill circulation.

The symptom of mercury exposure also included the swelling or rupture of either blood vessels or veins. This can cause hemorrhage and blood congestion in cells [36,37,51]. The gill hemorrhage with the rupture of secondary lamella epithelium, aneurysms, and stasis can lead to circulatory disturbances in whitefish [56]. Another symptom of mercury pollution to fishes was excessive mucus secretion as primary defense strategy which occurs in tilapia [37] and zebrafish [36]. This can lead to the problem arising at the lamellae of the fish which in certain cases, can cause the increase of mucus cells at the secondary epithelium [41]. Those lesions in the gill of fishes are based on Table 1.

3.2. Tissue lesions on fish liver

Liver also plays a crucial role in metabolism regulation, synthesis of plasma proteins, energy storage, certain vitamins, trace metals, steroids, hormone production and more importantly degradation of metabolic products with antioxidant protection as well as
detoxification [48,59–61]. Thus, this leads to a tendency of mercury accumulation because of its roles in detoxification and waste excretion. The hepatocytes are the cell of liver and it covered about 80% of liver areas. Thus, majority of the lesions in liver because of mercury contamination usually will take place around hepatocytes areas [39,62]. The increasing of mercury concentration during exposure will increase the accumulation of liver lesions. Nevertheless, the tendency of inorganic mercury to accumulate differs based on the gender with male zebrafish accumulating more mercury than females during HgCl₂ exposure [62].

The lesions in the liver of fish due to mercury pollutant are shown in Table 1. Pathological sign in liver caused by mercury contamination includes necrosis, lipidosis, nuclei change, swelling, degeneration, cytoplasmic vacuolization of the hepatic cells, bile stagnation, dilation of sinusoid, atrophy, and pre-necrotic lesions within many hepatocytes [55,63]. The degree of pathological index is depending on time and dose of exposure [62]. Oliveira Riberio et al. [28] showed the changes in liver cell of Arctic char after 12 hours of MeHg dietary intake at concentration of 0.26 ± 0.05 mg/kg body weight. Such as lipid loss occurred in hepatocyte cytoplasm, increase of heterochromatin quantity in nuclei and barely the presence of cytoplasmic membranes than in control but not leading to mortality and behavior changes. Mela et al. [26] stated that after wolf fish was exposed to the concentration of 0.075 mg/kg of MeHg in the diet for 70 days, the most significant damage was shown in the liver are pre-necrotic lesions and necrosis areas. However, based on the study by Mok et al. [64], the liver of guppies that were fed with 1 mg/kg of MeHg through fish diet showed the major formation of lipid droplets in the cells. Lipid accumulation can lead to the presence of slight hyperemia and high or higher vacuolization that is caused by hypertrophy of hepatocytes [65]. The loss of stored lipid substances in hepatocytes during the immature fish is exposed to the mercury is a primary response of the cells to support the increasing of metabolic needs [28,66]. The liver of wild European perch with metal exposure showed single hepatocytes and small sections of the liver parenchyma will be affected by the morphological changes due to necrotic alterations in that is related to the presence of karyopyknosis, karyorrhexis, and karyolysis [61].

Based on the previous studies, vacuolization usually appeared in zebrafish because of HgCl₂ contaminated liver tissue [62]. Vacuolization of hepatocytes lesion can be divided into two types, which are diffuse and focal vacuolization [51]. The symptom of vacuolization due to heavy metal contamination occurs when a few small vacuoles appeared in the cellular cytoplasm. Then fuse with large vacuole that will cause the cytoplasm and nucleus straining toward the periphery of the cell. The changes in the nucleus such as condensing of chromatin and increasing in optical density of the nucleus were documented [51].

### 3.3. Tissue lesions on fish kidney

Kidney plays an important role in regulating body fluid homeostasis, excessive metabolic waste is to be secreted, eliminated as urine, which important nutrients, and other essential metabolic will be reuptake into body [60,67].

Lesions occurred because of mercury contamination on the fish’s kidney are summarized in Table 1. In the kidney, mercury exposure can cause inflammation [68], interstitial inflammation, bile duct hyperplasia, and necrosis in the kidney tissue [33]. Furthermore, tilapia that exposed to 2 mg/kg of HgCl₂ for 3 days was found with severe tubulonephrosis and the presence of hyaline droplets in the kidney tissue [69]. Changes in the structure of renal and glomerular were observed as glomeruli lesion, tubularenecrosis/hyalinization, interstitial mononuclear infiltrates, and multifocal melanomacrophage centers in goliath grouper exposed to MeHg with the average concentration of 2.87 ± 4.70 mg/kg [27]. In addition, clinical signs such as hepatocytes swelling, loss of lipid reserves [28], necrotic, and dead cells with macrophage digestion of apoptotic bodies [26] was also observed.

The symptoms of kidney lesion also differ based on the species-specific. Whereas, (i) methymercury exposure of 25 mg MeHg/kg diet for 8 weeks, kidney of green sturgeon showed symptom of moderate tubular epithelium hydropic degeneration and Bowman’s capsule thickening while kidney of white sturgeon showed mild alterations or uncertain cellular limits on tubular epithelium. Whereas (ii) for exposure of 50 mg MeHg/kg diet for 8 weeks, kidney of green sturgeon showed symptoms of severe tubular epithelium degeneration, corpuscular disintegration, and Bowman’s space loss while kidney of white sturgeon showed Bowman’s capsule thickening and; (iii) for exposure of 100 mg MeHg/kg diet for 4 weeks, kidney of green sturgeon showed symptom of extensive tubular epithelium degeneration while kidney of white sturgeon showed necrotic cells or pyknosis and Bowman’s space enlargement [32]. Similarly, the increasing of Bowman’s space also been reported in other studies [55].

### 3.4. Tissue lesions on fish brain

Waterborne mercury can reach the brain of fish via water exposed of sensory cells through fish skin and oral epidermis such as mechanoreceptors of the lateral-line system, cutaneous sensory cells, and/or receptor cells of taste buds [70]. The organic and inorganic mercury can cause damage to Central Nervous System (CNS) of the brain in teleost fish via blood barrier [71].
Mercury affecting CNS by interfering in key enzymes like Na⁺/K⁺ - ATPase for neurological function [70]. Mercury exposure also affects brain functions including sensory perception and central processing that cause behavioral responses differently which is known to cause neurotoxic effects such as decline in the heart rate variability and normal motor speed [21].

The lesions on the fish brain due to mercury exposure are shown in Table 1. According to [35], 13.5 mg/kg of MeHg dietary that fed on the zebrafish can cause brain complications such as optical changes that resulted in impaired vision that lowers the adaptability of fish to the environment. The zebrafish fed by 13.5 mg/kg of MeHg (equivalent to 0.6 mg/kg of MeHg/fish/day) for 25 days was diagnosed to accumulate 30.2 ± 4.2 mg/kg of mercury compared to control with only 0.19 ± 0.03 mg/kg. Whereas at day 50, the level of mercury accumulation was up to 46.2 ± 7.3 mg/kg and the control fish was found only at 0.96 ± 0.08 mg/kg. On day 50 also, several lesions can be found in the cell of the brain consisting of the reduction of cell density, depletion of nuclear area, and condensation of chromatin in the granular cell were found [35]. Similarly, vacuolation, necrotic cell, presence of tissue edema that caused gross architectural damage, and oxidative injury also occurred [71].

### 3.5. Tissue lesions on fish gut

The fish gut consists of the fore-, mid-, and hindgut that came with the several of digestive organs. Where (i) the foregut that starts from the beginning of the posterior edge of gills included esophagus, stomach, and pylorus, (ii) mid gut consists of pyloric ceca that plays priority in digestion, and (iii) hindgut consists of distal intestine and anus [72]. Table 1 provides the information on lesions occurred in the intestine of fish contaminated by mercury. The study by Oliveira Ribeiro et al. [28] showed that lesion on the gut wall of Arctic char with tiny and black/silver grains when exposed to HgCl₂ and large black spots when exposed to MeHg under microautoradiography examination. The experiment showed that, the effect of the MeHg on the intestine is more severe than the HgCl₂ because of the efficiency of MeHg absorption in specific areas on epithelial cell membranes [28]. Histopathological anomalies in intestine that exposed to pollutant also can cause lesions such as the increase of goblet cells quantity, the amount of lymphocyte, swelling of goblet cells, integration, and expansion at villi structure as well as necrosis-erosion [53]. Some studies reported that, the histopathological anomalies such as degeneration, integration, and expansion involving the structure of villi as well as increase in the number of blood cells, vacuolization, and inflammation can also occur [54,55].

### 3.6. Mercury contamination alterations on gill, liver, kidney, intestine and brain

The effect of the mercury contamination in different organs can differ according to the organic and inorganic mercury exposure. The water-borne inorganic mercury with 96 h acute exposure can cause tissue anomalies such as exfoliation, vacuolation, and blood congestion in gills; hepatocytes swelling and lipid loss in the liver as well as; interregional gland lesion and cellular hemolysis in the kidney to occur [28]. For the organic mercury consisting of MeHg dietary (30 days), several tissue damages will occur in the liver such as the decreasing of lipid reservation, heterochromatin in nuclei, severe necrosis, and presence of small necrotic sites [28]. Other studies reported that, after MeHg and Hg (II) exposure, around 46.9% to 59.5% of MeHg and 42.3% to 64.9% of Hg (II) were found accumulated in gill and almost 41.9% of Hg (II) was recorded in the intestine [73]. However, the time of mercury exposure will cause the concentration of mercury in the intestine to increase linearly, contrarily in gill that will decrease steadily. The exchange of MeHg between blood and internal organs are slow with maximum uptake in the liver and gill are happening at 1.5 day during exposure of mercury dietary [74]. The highest mercury accumulation for inorganic mercury was found in the gill and intestine as these organs were the primary entrance for mercury to enter the fish body; then, mercury will be distributed to other fish organs via the bloodstream [75].

Mercury contamination due to the MeHg and HgCl₂ can also cause the same lesions but different levels of severity despite in different organs and cells involved. The mercury contamination in the fish can cause a lesion such as vacuolization represents by large and empty vacuoles with sharp borders that almost filled up most of the cytoplasm [76]. Vacuolization can occur in different organs and cells. For examples, in hepatocytes structure in the zebrafish’s liver caused by HgCl₂ [62] and in medulla, cerebellum, ventral regions of the tectum, and cerebrum of Atlantic salmon’s brain by MeHg [71]. But in the gill, the vacuolization was identified as edema that are occurring at epithelial cells of both the base of lamellae and in the secondary lamellae of goliath grouper because of MeHg [27]. MeHg contamination showed symptoms such as swollen and necrotic on epithelial cell on the gill cells of Sacramento splittail larvae that was contaminated with 11.7 mg/kg of MeHg [77]. Besides, necrotic areas and dead cells with macrophage digestion of apoptotic bodies also found in kidney of 1.78 mg/kg MeHg and necrosis in cell also happened in liver of wild goliath grouper followed by nuclear loss, multifocal mono-nuclear cell infiltrates, mild portal fibrosis, and multifocal melanomacrophage centers [27]. Likewise, necrotic cell
Table 2. Summary on effect of lesions on the different organs of fish due to mercury contamination.

| Organ       | Effect on fish                                                                                                                                                                                                 | References |
|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Gill        | Reddish gills and breathing problem due to major morphological alterations on respiratory lamellae by decreasing their gas exchange capability. Damage of tissue and cell will cause insensitivity of water quality detection. Decline of gas exchange capability. Gas exchange reduce and gill ventilation rate or cardiac output increase. | [36] [28] [38] [32] |
| Liver       | Severe stress as part of the cold-related mortality event, starvation and direct hypothermal effects. Increase of metabolism as a quick and primary response of the cells. Failure of normal liver functions such as metabolizing and excreting biochemicals. | [27] [28] [32] |
| kidney      | Severe stress as part of the cold-related mortality event, starvation and direct hypothermal effects. An increase in the kidney filtration rate as a countering mechanism against toxicant stress, accumulation of circulating Hg and subsequent cell damage. | [27] [32] |
| brain       | Injury to posterior region of the brain resulted in the loss of pyramidal cells, Purkinje cells and proliferation of astrocytes. | [71] |

Hg: mercury; HgCl₂: mercuric chloride; MeHg: methylmercury; Ch3CH2Hg: methylmericcuric chloride; CH3-HgCl: monomethylmercury.

also showed in the brain of Atlantic salmon due to contamination of HgCl₂ [71].

Mercury contamination in fish organs will show different lesions depending on the organs involved. Based on the current studies, the lesions caused by the mercury contamination in gill can be seen through primary and secondary lamella as the most suitable structure to detect lesions compared to the liver, kidney, gut and brain that need more details into the cell structure. For example, the most common lesion that can be found in gill, is lamellar fusion that will occur at the secondary lamella of the gill [27] caused by hyperplasia and hypertrophy on gill epithelium [51]. The lesion that occurred at lamella of gill can be easily identified compared to the one that is found in the liver, kidney, intestine and brain as if the hyperplasia and hypertrophy occurs in secondary lamellar, the effect on cell can be easily identified such as fusion but in other organs, we need to focus more into cell that was involved nucleus changes or loss. However, based on the current studies, the similarity on the lesions between the gill, liver, kidney, brain, and gut of the contaminated fish found, can be caused by different reasons but with same effect on tissue cell. The cell arrangement in the liver and gill (base of lamella) of the goliath grouper, both can be affected by the mononuclear cell infiltrates, but the glucogen accumulation and melanomacrophage center can also change the condition of cell structure of the liver as well as the same case that happens in gill when the vacuolization or severe edemas occurred [27].

The problem regarding the cells is also closely related to the changes in nuclear such as enlarged nuclei, lateral nuclei, nuclear degeneration, and vacuolization of nuclear [63]. In addition, the blood congestion (rupture of blood vessels) can easily be found at the lamellae of the gill [36] and the epithelial cell of liver [43] of the contaminated fish. The blood congestion as well as hemorrhage are occurring due to the damage of lamellae or epithelial cells or curled lamellae [37]. This will also lead to the blood coagulation that will cause the fusion at the lamellae that can be seen clearly in the contaminated gill of staked prochilod [45], but there is a different effect on the liver of banded knifefish whereas the presence of the swollen blood vessel had been found around the blood congestion [43]. According to Oliveira et al. [28], organic mercury was found started to absorb into many regions of the intestinal epithelium at day 4 exposure. The organic mercury was found accumulated in the epithelial tissue and microvilli along intestinal, thus cause lesions to ciliate cells.

4. Effect of lesions of changes in fish system

The effects of mercury contamination on fish are summarized in Table 2. Hyperplasia in the gill of sturgeon due to MeHg contamination will lead to the decrease of gills efficiency resulting in gas exchange depletion with the mild lesion, the sturgeon will atone the problem by increasing the gill ventilation rate and cardiac output to keep up with vital gas exchanges [32]. A previous study have shown that the exposure of MeHg in the gill and kidney caused negative effects on reproduction and other subclinical endpoints on biochemical, histological, and organonomic to goliath groupers [27]. This action occurs as the mononuclear cell infiltrates and gill edema leads to severe stress in the forms of cold-related mortality events, starvation, and direct hypothermal effects on goliath grouper. Other than that HgCl₂ exposure (10 and 20 µg/L) can lead to major gill structural modification in yellowfin seabeam by declining the capability of gas exchange in fish [38]. Besides, the loss of lipid substances in hepatocytes of the liver because of the HgCl₂ can alter metabolism cost due to a quick and primary response of the cells as well as physiological processes such as an active period of vitellogenesis in females [28]. The kidney filtration rate will increase to
withstand against toxicant stress and resulting in dilution of the glomerulus [32].

5. Importance of chelating agents to reduce mercury contamination

There are numerous pathological impact caused by mercury contamination on the gill, liver, kidney, and brain of fishes have been discovered. Histopathology examination plays an important role to determine the lesions on the fish tissue exposed to different concentrations and time exposure of mercury. Histopathological changes because of prolonged exposure to mercury will cause damage to respiratory, osmoregulatory, circulatory systems, slowdown the metabolic process, hematological changes, and reduction in fertility and survival of fish [18]. Thus, the new findings on the chelating agents that can be used to reduce the effect of mercury to fish are also being studied. The mercury chelating agents such as hydrochloric acid, sodium hydroxide, cysteine, EDTA, and salt (NaCl) were studied for the consumers’ health risk assessment [78]. Mercury concentration in the internal organs such as the liver or kidney was usually higher than in the muscle [27]. Thus, if the chelating agent can be used to reduce the mercury concentration in those internal organs, automatically, the mercury concentration in muscle also can be reduced along the process. Then, there will be less hg in a fish muscle that will be consumed by consumers. Cysteine and EDTA are recognized as good potential chelating agents for mercury decreasing in contaminated fish than others [78]. Cysteine is a hydrophobic amino acid consisting of a thiol group that can occur in most proteins even in a small amount [79]. It has been proven as an effective agent that can be used to remove the mercury concentration in mackerel fillet [78]. Besides that [64], it has also proven that the additional cysteine in the guppy diet can be used to reduce the mercury concentration in fish. In addition, trace minerals such as selenium can also act as a good potential chelating agent to decrease the toxicity of MeHg [80]. However, an organism that fed with MeHg only or MeHg with selenium showed no effect in reducing MeHg toxicity unless vitamin E was added together with selenium supplement, then the effective effect in reducing MeHg toxicity can be seen [81].

6. Suggestion

Nowadays, studies on the mercury exposure of the different species of fish are common. Usually, the studies can be differentiated from each other based on different species, types, concentrations of mercury, and exposure ways such as based on dietary or waterborne mercury contamination. However, just a few studies on mercury-related on the method of the mercury concentration reducing by using the reducing agent such as cysteine. Thus, the study on cysteine can be as important as mercury study because of the massive mercury contamination to the wild fish by human activities. The predator fish that feed on the other smaller fish also showed higher mercury content. Thus, if the method of mercury reduction in fish can be found, it will be beneficial to human health. The physiology state of fishes can also be used as a valuable measurement to strengthen the proof on lesions that occur in the fish internal organs due to mercury contamination. The abnormalities on fish can be observed according to the physical or behavior changes, swimming pattern, number of fish ventilation based on the opening of operculum, and mucus production on the fish body. In culturing condition, when fish exposed to mercury via either dietary contamination or water pollution, they will gasp for air in order to obtain oxygen. When this symptom was occurring, it can indicate that the gill is experiencing malfunction or dysfunction because of the mercury contamination. Mercury absorption can start at the epithelium of the gill, transverse via the blood vessel to all parts of the fish body, including systematic circulatory or internal organs and skin as the lesser affected area. The histology can be done to confirm if the fish gill is already started to show damages on lamellae due to fusion or excessive mucus production that cause slow oxygen intake. But, the other internal organs such as the liver, kidney, intestine, and brain can also be used as an indicator for histology. This is because the other factor such as high ammonia content in water also has potential to affect the histopathological study on the gill. But, the most important internal organs used to check the effect of mercury contamination on the tissue lesions are in the liver and kidney due to high mercury content that can be found in those two organs than the others.

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