Fish and Cardiometabolic Concerns: A Link through Lead and Mercury

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Abstract

Conditions characterizing the cardio metabolic syndrome (CMS) including obesity, dyslipidemia, diabetes, insulin resistance, and hypertension are considered significant health problems worldwide. CMS is the product of the interplay between genetics and environment of which dietary factors are the main effectors. Fish consumption is recommended due to its good nutritional value especially omega-3 fats which have profound cardio protective effects. Heavy metals particularly lead and mercury contained in fish makes it difficult to clearly establish its health role. Henceforth, these metals are identified as potential risk factors for CMS development; though the mechanisms of their pathogenesis remain poorly understood. This article evaluates current literature linking among fish, lead, mercury, and pathogenesis of CMS components. In contrast to humans, evidence from animals supports the presence of associations between fish, lead and mercury and the emergence of obesity, insulin resistance, diabetes, and atherosclerosis. Randomized controlled trials that investigate the effects of fish, lead and mercury on the key CMS biomarkers are suggested.

Keywords: Cardio metabolic concerns, diabetes, dyslipidemia, fish, insulin resistance, lead, mercury, obesity.

1. Introduction

Cardiometabolic syndrome (CMS) is a complex of interconnected factors that increase the risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (Ahmad & Haddad, 2015). Obesity and its related disturbances including insulin resistance, dyslipidemia, hypertension, pro-inflammatory and pro-thrombotic states are the key components that characterize the CMS. It is well documented that CMS is the product of the interaction between genetic and environmental factors; however, the underlying mechanisms of its pathogenesis remain poorly understood (Ahmad & Haddad, 2015). The prevalence of CMS has increased considerably over the past two decades posing one of the greatest public health challenges worldwide (Meier et al., 2019). In 2016, CVD contributes to more than 30% of global deaths (>17 million people) and more than half of these deaths (9.1 million) are attributable to the risks associated with lifestyle changes particularly dietary habits and patterns (Meier et al., 2019). In this regard, evidence has accumulated indicating substantial concerns of fish, lead and mercury in nutrition and health with a major focus on their possible role in the pathogenesis of CMS (Ceja- Galicia et al., 2017; Leff et al., 2018; Zuliani et al., 2019; Liu, et al., 2019).

Fish consumption is well known to associate with reduced risks of many diseases particularly CVD (Zárate et al., 2017; Meier et al., 2019; Kannaiyan, et al., 2019). Recently, this notion has been viewed with some health concerns. This is especially important in view of the great ability of fish to accumulate chemical contaminants and heavy metals such as mercury and lead (Abarshi et al., 2017; Zuliani et al., 2019; Liu, et al., 2019), a matter that might weaken the positive health effects of fish (Jayabrakash et al., 2015). In essence, evidence has emerged linking these metals to CMS development (Sun et al., 2018; Lee, 2018; Liu, et al., 2019; Baranowska-Bosiaka et al., 2019). Although relations between heavy metal toxicity including mercury and lead and adipogenesis and obesity risks have been suggested, the evidence is not consistent. Several studies, with considerable controversy, are available which link increased obesity prevalence with heavy metal exposure including mercury and lead (Ceja-Galicia et al, 2017; Park et al, 2017; Simić et al., 2017; Lee, 2018). The evidence that links diabetes and insulin resistance with heavy metal exposure is relatively limited and inconsistent (Feng et al., 2015; Fan et al., 2017). Although a direct association between lead and mercury with dyslipidemia has been recorded (Feng et al., 2015; Baranowska-Bosiaka, et al., 2019), no associations with other CVD risk factors have been observed (Zuliani et al, 2019).

The evidence that links mercury and lead with inflammatory responses (Gardner et al, 2009) or hypertension (Kosik-Bogacka et al., 2017, Bilandžić et al., 2018) is limited, whereas that relates to inflammatory biomarkers is unavailable. Controlled human or animal studies that investigate possible links between feeding mercury and lead, incorporated freely into diets or given naturally in the form of foods, and obesity indices, insulin resistance, inflammatory responses, and other CVD risk factors are generally lacking. Thus, the aim of the present article is to evaluate the current literature dealing with the link among fish, lead, mercury, and CMS pathogenesis and its components, and suggesting future avenues of investigation.

2. Scientific Evidence: Literature Search

An up-to-date literature review was conducted on the relationships among fish and its contents of lead and mercury, cardio metabolic risks. The search was limited to English publications from a 15-year period (2005–2019). Relevant articles were principally identified through an online search of the PubMed, Science Direct, Google Scholar and other available databases. The search was performed using the following keywords or their combinations: fish, canned tuna, canned sardines, lead, mercury, cardio metabolic risks, diet, insulin resistance, obesity, dyslipidemia, diabetes, and CMS. Included articles were mainly original observational, experimental, and clinical, case study, intervention and cross-sectional researches in humans or animals. For further search accuracy, the reference lists of works were checked for additional publications from the major databases.

3. Role of Fish in Nutrition and Health

Worldwide, fish consumption has been growing rapidly due to potential health benefits that are related to its distinctive nutritional value as indicated by high-quality proteins, low saturated fat and high vitamins, mineral elements and omega-3 fatty acids contents (Bosch et al., 2016). Nutritionally, fish is mainly rich in vitamins A, D, E, B_{12}, $B_{6,}$ and niacin, in addition to calcium, phosphorus, iron, magnesium, zinc, sodium, potassium and selenium, as well as the omega-3 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Bosch et al., 2016). These nutritional characteristics of fish signify its role in fighting hunger and malnutrition mainly in developed and middle-income countries that face food and nutrition insecurity (FAO, 2016). The global per capita per year fish consumption has risen from 9.9 kg in 1960 to 19.2 kg in 2012, and above 20 kg in 2016 (FAO 2016). More than 3.1 billion people depend on fish for at least 20% of their total animal protein intake, and a further 1.3 billion people for 15% of animal protein intake. Fish may serve a solution to many health problems like goiter which can be solved only by fish consumption that contains natural iodine in cases of unavailable iodized salts, and CVD (Kannaiyan et al.,2019).

In many cases, canned fish is regarded as more convenient and affordable cost and nutritious as compared to fresh or frozen fish (Bosch et al, 2016). This is especially important in fisheries-poor countries like Jordan where fresh marine foods are generally scarce due to short length of coastline and narrow continental shelf which limits the fishing process to artisanal methods so that local fish production does not exceed 1% of total consumption (Al-Zibdah et al., 2006). In fact, in Jordan, the overall per capita fish consumption is just approaching 3.63 kg a year and about 50% of it is contributed by canned tuna and canned sardines (DoS, 2013).

White muscle meats in fish are known to have a unique lipid composition that is rich in omega-3 long-chain poly-unsaturated fatty acids particularly EPA and DHA (Kannaiyan et al., 2019; Mehouel et al., 2019). In this regard, fish contains an appropriate high ratio (4:1) of two opposing properties fatty acids; the multi-beneficial omega-3 α-linolenic acid (ALA) to the pro-inflammatory omega-6 linoleic acid (LA). This ratio shapes the genetics of human nutrition saving DNA from mutations (Zárate, et al., 2017). Cellular desaturase and elongase system compete for both types of fatty acids, however, the system has a higher affinity for ALA than to LA, due to the much higher dietary content in fish (Zárate, et al., 2017). This system metabolizes ALA to EPA and DHA, and LA to arachidonic acid (AA) that act as precursors of many bioactive mediators such as resolvins, protectins, and maresins (Mehouel et al., 2019). These mediators help the body to return to homeostasis and resolution of inflammation (Zárate et al., 2017). EPA and DHA are the precursors of the 3-series anti-inflammatory eicosanoids and the 5-series leukotrienes, whereas AA is the precursors of the 2-series pro-inflammatory eicosanoids and the 4-series leukotrienes (Mehouel et al., 2019).

It is well known that omega-3 fatty acids have vasodilatory, vasoprotective, anti-atherogenic, anti-thrombotic and anti-arrhythmic effects; they tend to improve blood pressure and lower atherogenic lipids and may slightly improve those antiatherogenic (Kannaiyan et al., 2019). They are incorporated into the phospholipids of cellular membranes and have a wide range of demonstrated physiological effects particularly those related to electrophysiology such as favorable changes to cardiac ion channel function, β-adrenergic and other receptors, cell signaling pathways and gap junction communication, as well as increased membrane fluidity (Zárate et al., 2017). Consumption of seafood-containing omega-3 fatty acids has been associated with other electrophysiological indexes, including lower heart rate, slower atrioventricular

Conduction, and a lower likelihood of abnormal repolarization and optimal values of many heart rate variability components (Kannaiyan et al., 2019). Moreover, increased dietary intake of these fatty acids has been shown to enhance arterial elasticity by increasing endothelium-derived vasodilators including 3-series prostacyclins, nitric oxide, and endothelium-dependent hyperpolarizing factor. Flow-mediated dilation is a measure of the brachial artery after shear stress that induces nitric oxide-dependent responses and resultant vasodilatation (Kannaiyan et al., 2019).

Omega-3 metabolites particularly EPA and DHA are essential components of cell membranes (Zárate et al., 2017). Their levels are especially high in the retina, brain, and sperm cells. They are also important in promoting the growth, development, and health of infants, improving the cognitive function and lessening Alzheimer's disease dementia and rheumatoid arthritis (USDA, 2017). Dietary Guidelines for Americans recommend the consumption of 8 oz. per week (≈2 servings) of seafood, which would provide about 250 mg/day of EPA and DHA (Kannaiyan et al., 2019; Mehouel et al., 2019). The American Heart Association's Strategic Impact goal through 2020 and beyond policy suggests consuming more than two times of 3.5-oz fish servings per week as fish (Zárate et al., 2017; Rimm et al., 2018). The American Heart Association's Strategic Impact goal through 2020 and beyond recommends more than two times of 3.5-oz fish servings per week as an intervention approach to reduce the risk of CVD (Meier et al., 2019).

4. Mercury and Lead in Fish

Fish are known to be good indicators of heavy metals contamination in aquatic systems (Abarshi et al., 2017). Heavy metals such as lead, mercury, cadmium, aluminum, and zinc are considered very important pollutants in biological systems with potential toxicity to humans (Hamida et al., 2018). In essence, lead and mercury are at the top of heavy metals in terms of the degree of contamination, fish bioaccumulation and toxicity concerns (Abarshi et al., 2017; Bilandzic et al., 2018). Aquatic systems heavy metals pollution is brought in by various natural or external sources particularly weathering of soil and rocks, volcanic eruptions and from a variety of human activities involving mining, processing and use of metal contaminants and or substances containing them (Jayaprakash et al., 2015; Hamida et al., 2018). After entering the aquatic medium, metals are transformed, transported and often got precipitated in water, changing the environment by various geochemical processes. Fish bioaccumulates metals by being exposed to the surrounding water as a direct consequence of biomagnifications, sedimentation and from the diet (Jayaprakash et al., 2015; Zuliani et al., 2019).

Table 1: Documented mercury and lead contents of selected commercial fish types (Means or ranges)

Fish type	Mercury (mcg/g)	Lead (mcg/g)	Reference
Pink salmons	36.1	0.00	Ikem & Egiebor, 2005
Red salmons	32.8	0.00	
Mackerel	36.4	0.2	
Tuna	28.5	1.1	
Sardines	10.7	0.2	
Herring	59.8	1.7	
Mackerels	0.01- 0.08	0.01- 0.69	Okyere et al., 2015
Sardines	0.01- 0.04	0.01-1.44	
Pilchards	0.01- 0.03	0.01	
Tuna	0.12 - 0.20	0.01- 0.30	
Thunnus species	0.140 ± 0.021	0.036 ± 0.03	Torres et al., 2016
Skipjack tuna	0.014 ± 0.012	0.152 ± 0.03	
Mackerel	0.050 - 0..490	0.000 - 0.040	Olmedo et al., 2013
Salmon	0.000 - 0.004	0.040 - 0.019	
Sardines	0.009 - 0.067	0.004 - 0.034	
Tuna	0.298 - 0.770	0.004 - 0.040	
Swordfish	0.177 - 1.227	0.004 - 0.064	
Mackerel	0.500 ± 0.000	Not available	Burger et al., 2012
Canned Skipjack	0.373 ± 0.249	0.239 ± 0.205	Abolghait & Garbaj, 2015
Canned tuna	0.044 - 0.402	0.00 - 0.0592	de Paiva et al., 2017
Canned tuna	Not available	2.8 ± 0.11	Massadeh et al., 2018
Canned sardines	Not available	2.5 ± 0.09	
Thunnus species	0.898 ± 0.466	Not available	Chen et al.,2011
Canned tuna	0.777 ± 0.320	Not available	Gerrstenberger et al., 2010

Table 1 shows documented mercury and lead levels in selected commercial fish types. Compared to other species, tuna fish is well known to accumulate substantial amounts of mercury (Ikem & Egiebor 2005), whereas lead predominates in sardines (Bilandzic et al., 2018). However, there is a great variability in the reported content of these heavy metals among the different fish types and species (Ikem & Egiebor 2005; Olmedo et al., 2013; Okyere et al., 2015; Abolghait & Garbaj, 2015; Torres et al., 2016; de Paiva et al., 2017; Massadeh et al., 2018). Mercury and lead levels range from zero in salmon (Ikem & Egiebor 2005; Olmedo et al., 2013) to as much as 59.8 mcg mercury/g in herring (Ikem & Egiebor 2005) and 28.5 mcg lead/g in canned tuna (Massadeh et al., 2018). In tuna, mercury levels range from 0.044 mcg/g (de Paiva et al., 2017) to 28.5 mcg/g (Ikem & Egiebor 2005), whereas lead levels range from zero (de Paiva et al., 2017) to 2.8 mcg/g (Massadeh et al., 2018). In sardines, mercury levels range from 0.009 mcg/g (Olmedo et al., 2013) to 10.7 mcg/g (Ikem & Egiebor 2005), whereas lead levels range from 0.004 mcg/g (Okyere et al., 2015) to 0.2 mcg/g (Ikem & Egiebor 2005). In Jordan, it has been shown that the mean lead levels in canned sardines and canned tuna are 2.50 mcg/ g and 2.80 mcg/ g respectively ((Massadeh et al., 2018). However, the highest lead concentrations have been found in canned sardines among 11 fish types (Alcala-Orozco et al., 2017). Variabilities of mercury and lead levels in various types of fish can be attributed to several biotic and abiotic factors, such as differences in fish age and genotype, conditions and types of aquatic systems, pollution sources, and fish handling and storage conditions and methods of analysis (Abarshi et al., 2017; Bilandzic et al., 2018; Zuliani et al., 2019). In essence, the European Commission (2015/1005) has set a safe level of lead in fish by 0.3 mg/kg and that of mercury by 1 ppm (EC, 2015).

5. Toxicity of Mercury

Mercury occupies the third position in the priority list of hazardous substances published by the US Agency for toxic substances and disease registry (ATSDR, 2013). This is attributed to its persistence, ability to enter biological systems through ingestion and inhalation of contaminated food, water and environment, and its high toxicity even at very low concentrations (Liao et al., 2016). It may cause brain and kidney defects in infants leading to neurological changes, especially if it exceeds the European dietary limits of (0.5 mg/kg) of fresh weight (Ikem & Egiebor, 2005; Bilandžić et al., 2018). In fact, fish intake is the most significant source of methyl mercury exposure and accumulation in the human body (Burger et al., 2012). In aquatic systems, 80-90% of methyl mercury is accumulated in fish with a high degree of absorption from the gastrointestinal tract (95–100%) mostly deposited in the brain (Alcala-Orozco et al., 2017). However, mercury level differs from one fish species to another due to several biotic and abiotic factors (Bilandzic et al., 2018; Zuliani et al., 2019). It is estimated that the mean dietary mercury exposure is (8.2 µg/d) and (8.6 µg/day) for females and males respectively, assuming that the amount obtained by fish intake as (0.66±0.05 µg/g) wet weight (ATSDR, 2013; Alcala-Orozco et al., 2017).

Table 2: Documented proposed mechanisms of action of mercury toxicity

Bio-level	Proposed mechanism of action	Reference
Cellular level (Mitochondrial oxidative stress)	Fe^{++} and Cu^{++} displacement in cytochrome C and NADH dehydrogenase	Valko et al., 2005
	Increased hydrogen peroxide, depletion of mitochondrial glutathione by 50%, increased lipid peroxidation markers' thiobarbituric acid reactive substances by >70%, oxidation of pyridine nucleotides NADPH and alteration of Ca homeostasis	Chen et al., 2006
	Depolarization , auto oxidation and lipid peroxidation of inner mitochondrial membrane	Zhang et al., 2009; Gardener et al., 2009
	Increased 8-hydroxy-20-deoxyguanosine, a marker of oxidative DNA damage and decreased serum antioxidant levels	Shenker et al., 2008
Molecular level	Defective enzymatic thiol or sulfhydryl groups, inhibited protein synthesis, caused microtubule disruption and disturbed intracellular Ca^{2+} with disturbed neurotransmitters	Chen et al., 2006
	Overproduction of free radicals	Valko et al., 2005
	Induction of oxidative- mediated apoptosis in human T cells and monocytes and inactivation of several antioxidant mechanisms	Kim & Sharma, 2004
	Induction of stress-related apoptotic signal by phosphorylation and activation of c-Jun N-terminal kinases and p38.	Sun et al.,2018
Liver and pancreas	Increased oxidative stress of β-cell that progress to inhibition of insulin receptors through: activation of phosphoinositide 3-kinase, depletion of γ-Glutamyl-cysteinyl glycine and blocking the protein kinase B signaling pathway	Fillion et al., 2008; Chen et al., 2006; Fan et al., 2017

	Interference with transcription and translation processes, disappearance of ribosomes and eradication of endoplasmic reticulum, apoptosis in human T lymphocytes and general apoptotic pathways activation	Kim and Sharma, 2004
	Increased serum thiobarbituric acid reactive substances levels leading to decreased serum insulin, hepatic insulin resistance, and hyperglycemia	Shenker et al.,2008
Cardiovascular system	Mitochondrial dysfunction, lowered ATP-synthesis, increased phospholipid, protein and DNA peroxidation resulting in vascular oxidative stress and inflammation, inactivated paraoxonase causing dysfunctional HDL and defective hepatic reverse cholesterol transport and interference with antioxidant proteins and DNA enzymes	Takahashi & Shimohat , 2019
	Increased pro-oxidant NADPH oxidase, lessened nitric oxide levels, increased vasoconstrictor cyclooxygenase -2 prostanoids production, raised angiotensin converting enzyme activity affecting rennin angiotensin system and body fluids	Ceja-Galicia et al., 2017
	Endothelial cells dysfunction, reducer their formation and migration, increased platelet aggregation and increase coagulation factor XIII activity causing hyper-coagulation	Takahashi & Shimohat , 2019
Nervous system	Binding to sulfhydryl end of tubulin in microtubule, defective gamma-amino butyric acid and N-methyl-d-aspartate receptor system, oxidation of neurons, polarization of microglial cells damaging neurons and impairment of blood brain barrier endothelial cells	Takahashi & Shimohat , 2019

Table 2 presents the documented proposed mechanisms of action of mercury toxicity. At the cellular level, mercury has a major role to induce mitochondrial dysfunction and oxidative stress (Zhang et al., 2009). The primary mitochondrial dysfunction occurs at the ubiquinone-cytochrome-b region and with NADH dehydrogenase triggering displacement of Fe^{++} and Cu^{+} ions in the a3Cub center of cytochrome- C (Valko et al., 2005). This results in depolarization and auto-oxidation of the inner mitochondrial membrane with lipid peroxidation and severe mitochondrial dysfunction (Zhang et al., 2009). Physiologic consequences comprise increasing of hydrogen peroxide, depletion of mitochondrial glutathione by more than 50%, increasing lipid peroxidation markers such as thiobarbituric acid reactive substances (TBARS) by more than 70%, oxidation of pyridine nucleotides such as NADPH, and alteration of calcium homeostasis (Cheng et al., 2006). This severe mercury-induced mitochondrial dysfunction increases the pro-oxidant NADPH oxidase, raises angiotensin-converting enzyme (ACE) activity that affects the renin angiotensin system and body fluids, lessens the antioxidant defenses like nitric oxide and vasoconstrictor cyclooxygenase -2 (COX-2) prostanoids production which have enormous health implications (Cheng et al., 2006; Ceja-Galicia, et al., 2017). This oxidative stress is identified by the increase in 8-hydroxy-20-deoxyguanosine "a marker of oxidative DNA damage" (8-OH-dG) and a decrease in antioxidant levels in the serum (Cheng et al., 2006; Shenker et al., 2008; Ceja-Galicia, et al., 2017).

Moreover, methyl mercury toxicity can act at the molecular level. It has been suggested that methyl mercury may inhibit protein synthesis causing microtubule disruption or increasing intracellular Ca^{2+} levels with disturbances of neurotransmitter function mainly by binding to thiol or sulfhydryl groups resulting in activation of sulfur and blockage of the related enzymes, cofactors and hormones (Valko et al., 2005; Chen et al., 2006). Oppositely, the indirect interactions of methyl mercury at critical cellular sites and as a consequence of the inhibition of the protective mechanisms may cause overproduction of free radicals (Valko et al., 2005). Indeed, the formation of reactive oxygen species (ROS) in the kidney, liver, and brain has been observed following administration of methyl mercuric chloride to rodents, fish and in vitro cells ((Valko et al., 2005; Chen et al., 2006).

Mercuric ions are broadly sulfhydryl reactive and modulate ROS. It has been reported that mercury regulates redox status (Shenker et al., 2008) that results in the induction of apoptosis in human T cells and monocytes inducing oxidative stress and inactivate several antioxidant mechanisms (Kim and Sharma, 2004). Oxidative stress induces activation of mitogen-activated protein kinases and results in caspase activation that would impede calcium metabolism that affects bone health (Liu et al., 2019). Oxidative stress also induces activation of the c-Jun N-terminal kinases (c-JNK) and p38 via phosphorylation triggering stress-mediated apoptotic signals (Sun et al., 2018).

Mercury is reported to cause the formation of glutathione–mercury complexes on the cysteine residue of the glutathione that reduces the cellular defense system against oxidative stress impairing the activity of glutathione peroxidase and stimulating lipid peroxidation, and thus atherosclerosis (Cheng et al., 2006; Liu et al., 2019). In several animal experimental studies, it has been reported that intraperitoneal or subcutaneous injections of methyl mercury or mercuric chloride result in intensified lipid and phospholipid peroxidation in various brain and renal regions (Shenker et al.,2008). Lipid peroxidation is shown to occur by free radicals degradation of phospholipids in the low-density lipoprotein cholesterol (LDL-C) molecules. Mercury exposure is suggested to induce production of free radicals, mitochondrial dysfunction, lowered ATP-synthesis and increased peroxidation of phospholipids, proteins and DNA resulting in vascular oxidative stress and inflammation (Takahashi & Shimohat, 2019)

Increased free radicals production may inactivate paraoxonase that causes dysfunctional high-density lipoprotein, thus reducing reverse cholesterol transport to the liver. It may also interfere with the active site of repair proteins for the DNA and cell homeostasis (Takahashi & Shimohat, 2019). By binding to the thiol groups present in the platelets membrane Na^+- K^+- ATPase, mercury can induce changes in platelet aggregation. It inhibits adenylate cyclase and stimulates phosphodiesterase activity that is associated with the elevation of platelet aggregation, a matter that is suggestive of a specific role of cellular cyclic AMP in this biochemical event (Takahashi & Shimohat, 2019).

In pancreatic β-cells, increased ROS production due to mercury exposure causes alteration of intracellular Ca^{2+} homeostasis; this results in dysfunction of these cells or evenly cell death leading to reduction in insulin secretion or an eventual autoimmune attack as in type 1 diabetes (Chen et al., 2006). Moreover, mercury causes disruption of phosphoinositide 3-kinase, depletion of γ-glutamyl cysteinyl glycine and blocking the protein kinase B signaling pathway (Chen et al., 2006; Fillion et al., 2008; Fan et al., 2017). Dysfunctioning of pancreatic β-cells and apoptosis in murine models, increased lipid peroxidation and NADPH oxidase, a reduction in antioxidant defenses, lessening in nitric oxide, raised vasoconstrictor Cox-2 prostanoids production and ACE activity have recently been reported (Fan et al., 2017). On the other hand, mercury exposure has been shown to cause phosphorylation of c-JNK that leads to serine phosphorylation in insulin signaling pathways resulting in inhibition of peroxisome proliferator-activated receptor γ expression and disrupting the pre-adipocyte differentiation, maturation, and adipokines secretion, thus increasing risks of obesity related problems (Kim & Sharma, 2004).

6. Toxicity of Lead

Lead is the second potent occupational toxicant with widespread use especially in marine foods (Hamida et al., 2018). It is thought that lead toxicity is responsible for the collapse of the Roman Empire due to their use of lead components in wine production, a matter that leads to dementia in many emperors (Wani et al., 2015). Once absorbed, lead accumulates in high levels in bones, teeth, liver, lungs, kidneys, brain, and spleen; then it goes through the blood brain-barrier and the placenta (Wani et al., 2015). The most sensitive targets for lead toxicity are the developing nervous, cardiovascular and hematological systems. The allowable level of lead in fish set by the European Commission guideline and FAO is 0.04 mc/g (EC, 2015).

Lead causes cell toxicity by ionic mechanisms of oxidative stress. The production of ROS is increased after lead treatment in vitro studies (Ahmad & Siddiqui, 2007). In vivo studies, it has been suggested that lead exposure causes the generation of ROS and alteration of antioxidant defense systems in animals (Hsu et al., 2002). The mechanisms for lead-induced oxidative stress include cellular structural damage of membranes proteins and lipids, nucleic acids and antioxidant defense systems through generation of highly ROS such as superoxide and hydroxyl radicals, and hydrogen and lipid peroxides (Mathew et al., 2011; Flora et al., 2012; Taylor et al., 2012). The ionic mechanism of lead toxicity occurs mainly due to the ability of lead metal ions to replace other bivalent cations mainly Ca^{2+}, Mg^{2+}, Fe^{2+} and monovalent cations particularly Na^+, K^+ which ultimately disturbs the biological metabolism of the cell (Hsu et al., 2002; Ahmad & Siddiqui, 2007). The ionic mechanism of lead toxicity possibly causes significant changes in various biological processes such as cell adhesion, intra- and inter-cellular signaling, protein folding, maturation, apoptosis, ionic transportation, enzyme regulation, and release of neurotransmitters (Taylor et al., 2012). Lead can substitute calcium even in picomolar concentrations affecting protein kinase C, which regulates the neural excitation and memory storage (Mathew et al., 2011).

Table 3 shows the documented proposed mechanisms of action of lead toxicity. At the cellular level, lead has a high affinity for sulfhydryl groups in enzymes of the antioxidative defense systems such as superoxide dismutase, catalase, glutathione peroxidase, and glucose-6-phosphate dehydrogenase, and subsequently inhibits their activities (Ahmad & Siddiqui, 2007; Flora et al., 2012). Lead has a higher affinity than calcium for calmodulin and can activate some calmodulin-dependent processes, inhibit Ca-ATPase and sodium-potassium and calcium bombs and channels and replace calcium in several of its receptors by calcium-mimicking effects (Flora et al., 2012).

In essence, lead may cause frank anemia as its absorption is inversely related to dietary calcium, thus the low dietary intake of calcium can lead to higher levels of lead in the circulation (Castro-González et al., 2008).

Table 3: Documented proposed mechanisms of action of lead toxicity

Bio-level	Proposed mechanism of action	Reference
Red blood cells	Inhibited δ-aminolevulinic acid dehydratase I in heme synthesis and accumulation of δ-aminolevulinic inducing reactive oxygen species	Taylor et al., 2012; Hsu et al., 2002; Flora et al., 2012
	Binding and inhibiting activity of antioxidant defense enzymes: Superoxide dismutase, catalase, glutathione peroxidase and glucose-6-phosphate dehydrogenase	Flora et al., 2012
	Activated calmodulin-dependent processes inhibiting Ca bombs and channels and replacing Ca in several of its receptors	Castro-González et al., 2008
	Disturbed porphobilinogen synthase and ferrochelatase, halted porphobilinogen formation and inhibited iron incorporation into protoporphyrin IX	Wani et al., 2015
Liver	Upregulation of gluconeogenic gene expression, disruption of hepatic energy metabolism, reduced levels of glycogen and elevated liver alanine aminotransferase and triglyceride leading to fatty liver	Castro-González et al., 2008; Tyrrell et al., 2017; Leff et al., 2018
Muscles and adipose tissue	Increased reactive oxygen species promoting insulin resistant by inhibiting insulin receptor substrates (1and 2) required for downstream signaling by addition of serine/threonine kinases phosphorylation	Leff et al., 2018
Nervous system	Calcium substitution in protein kinase C, neural excitation and memory storage defect, fluid movements into blood brain barrier interstitial spaces, disrupted intracellular second messenger systems and altered functioning of central nervous system, mental retardation, birth defects, psychosis, autism, allergies, dyslexia, weight loss, hyperactivity, paralysis, muscular weakness and brain damage	Mathew et al., 2011; Tyrrell et al., 2017; Castro-González et al., 2008
Pancreas	Defective antioxidant enzymes causing reduced β-pancreatic cells insulin secretion	Leff et al., 2018
Cardiovascular system	Stimulated oxidative stress mechanism causing: Defective renin-angiotensin system; nitric oxide down-regulation, reduced soluble guanylate cyclase and declined glomerular filtration rate	Feng et al., 2015; Nawrot et al., 2002
	Increased oxidation, accumulated foam cells in macrophages and stimulated lipids oxidation leading to esterified cholesterol and fatty acids participation	Baranowska et al., 2019

On the other hand, lipid peroxidation in red blood cell membranes causes its fragility and decreases their lifespan as a consequence of lead-induced oxidative stress (Flora et al., 2012). This type of stress causes hemolysis and restraining hemoglobin synthesis via inhibition of δ-aminolevulinic acid dehydratase (δ-ALAD), an important enzyme in heme biosynthesis which leads to the accumulation of δ-ALA (Ahmad & Siddiqui, 2007; Flora et al., 2012; Tyrrell et al., 2017). These oxidative events eventually induce the generation of ROS in the hematopoietic system resulting in lead-induced hemolytic anemia (Ahmad & Siddiqui, 2007; Tyrrell et al., 2017).

The central nervous system is the most sensitive organ to lead toxicity (Tyrrell et al., 2017). Chronic exposure of lead can result in mental retardation, birth defects, psychosis, autism, allergies, dyslexia, weight loss, hyperactivity, paralysis, muscular weakness, brain damage, kidney damage and may even cause death. In addition, elevated serum lead concentrations have negative effects on a persons' intelligence quotient (Castro-González et al., 2008). Although lead poisoning is preventable, it still remains a dangerous disease that can affect most organs (Burger et al., 2012). Edema-induced encephalopathy results from increased serum lead concentrations in which lead moves into the interstitial spaces of the blood-brain barrier (Tyrrell et al., 2017), replaces Ca^{+2} ions and accumulates in the astroglial cells and disrupts the intracellular second messenger systems and alters the functioning of the central nervous system by oxidative stress mechanisms (Burger et al., 2012; Tyrrell et al., 2017).

7. Mercury and Cardio metabolic Concerns

Evidence is now arising on the possible role of toxic heavy metals particularly mercury and lead in the pathogenesis of CMS and its associated diseases. They are accumulated in vital body organs such as liver, heart, kidneys, and brain disturbing normal biological functioning and possibly increasing the susceptibility of infection, inflammatory reactions, oxidative stress, hypertension, dyslipidemia, diabetes type 2, CVD, and thus CMS (Ceja-Galicia, et al, 2017; Park et al, 2017; Simi´c, et al, 2017; Lee, 2018). In addition, the development of CMS due to oxidative stress, endoplasmic reticulum stress and inflammatory reaction as a result of the environmental exposure to mercury and lead has been well documented (Lee, 2018). It has been suggested that CVD mortality could be reduced by decreasing or eliminating exposure to environmental pollutants such as heavy metals. The cardiovascular system is considered sensitive to acute or chronic exposure of low doses of mercury or lead exposure (Lee, 2018).

Blood mercury concentrations have been reported to associate with the CMS components mainly obesity and weight phenotype in a dose-dependent manner (Park et al., 2017; Lee, 2018). In animals, it has been shown that blood mercury concentration is associated with obesity which is the main risk factor for CMS (Kosik-Bogacka et al., 2017). On the other hand, in humans, the link between blood mercury level and adiposity is a matter of controversy. A possible role of mercury in the induction or exacerbation of chronic metabolic diseases such as diabetes mellitus and CVD and hence CMS has been postulated (Lee et al., 2018). Inorganic mercury is a well-established immunotoxin that might force the induction of oxidative stress, inactivation of several antioxidant mechanisms and generation a chronic low-grade inflammation leading to increased risk of CMS development (Liao et al., 2016). Furthermore, mercury might impudence calcium metabolism and affect bone health (Kosik-Bogacka et al., 2017). In animals, the development of systemic autoimmune diseases has been accelerated by inorganic mercury exposure (Sun et al., 2018).

There is a marked interrelation among heavy metal exposure, the pathogenesis of obesity and other related diseases (Sun et al., 2018). A tight relationship between CMS components and oxidative stress has been demonstrated. To our knowledge, the effect of environmental exposure to metallic elements on obesity development is still unclear (Sun et al., 2018). Some epidemiological studies have suggested that trace heavy metals may play key roles in the development of obesity as well as CVD, type 2 diabetes, hypertension and dyslipidemia (Okyere et al., 2015; Simić et al., 2017). It is known that the adiposeness process involves a complex and high orchestrated program of transcriptional factors, cofactors and signaling intermediates from numerous pathways. As heavy metals have long half-lives of several decades, they would accumulate persistently in the human body when ingested and absorbed (Simić et al., 2017) .

It is well known that insulin resistance and pancreatic β-cell dysfunction can occur several years before the development of type 2 diabetes. This heightens the risk of CMS sufferers who will become pre-diabetics and ultimately diabetics (Fan et al., 2017). In experimental studies, it has been shown that hyperglycemia is induced by orally treating rats with doses of methyl mercury of 20 μg/kg for 2 weeks leading to β-cell damage (Shenker et al., 2008; Fan et al.,2017). It is supposed that mercury is involved in the etiology in type II diabetes by a toxic mechanism affecting oxidative stress which may elaborate in the progression of insulin resistance and of pancreatic β-cell dysfunction (Fan et al., 2017). In addition, mercury induces apoptosis in human T lymphocytes. Both aforementioned theories suggest that the affected organelle is the mitochondrion and that inducing oxidative stress activates apoptotic pathways (Kim & Sharma 2004). These findings possibly indicate that methyl-mercury induces oxidative stress, regulated pancreatic β-cell cytotoxicity through a mitochondrial apoptotic pathway which activates caspase3 in response to the mitochondrial release of cytochrome C (Shenker et al., 2008).

Few human studies have investigated the association between blood mercury concentrations and the adipogenesis process in several points. Mercury level and adiposity which is measured by body mass index and waist circumference (Fan et al., 2017), although these are not direct measures of adiposity, the results have been inconsistent. Blood mercury concentration has been found to be related to waist-hip ratio, which is a cardiovascular risk factor via an obesity-related mechanism (Zárate et al., 2017). The mechanism of obesity by mercury exposure is not yet clear, although a possible relationship between dysregulation of lipid metabolism and glucose metabolism has been suggested (Fan et al., 2017), beside the higher content of omega -3 polyunsaturated fatty acids metabolites, that serve as anti-inflammatory agents (Zárate et al., 2017).

In humans, a tight relationship among the serum, hair, urine, and toenails mercuric concentrations in diabetic patients has been reported (Bilandžić et al., 2018). Furthermore, serum mercuric chloride and methyl mercury have been found to associate with lower levels of serum insulin, hyperglycemia, glucose intolerance and higher levels of serum TBARS concentrations (Shenker et al., 2008). In contrast, an inconsistent evidence for diabetes incidence as a result of high fish intake has been documented (Lee, 2018; Baranowska-Bosiaka et al., 2019). It has been assumed that the high antioxidant selenium content in fish may lessen the oxidative toxicity of mercury. In a cross-sectional study, it has been shown that methyl mercury blood levels are associated with hepatic insulin resistance (Shenker et al., 2008).

Controversially, in a nested case-control study, no evidence for mercury exposure from regular fish consumption to increase CVD risk in a population of Spanish adults with high CVD risk and high fish consumption has been found (Bilandžić et al., 2018). Although fish is a source of beneficial DHA and EPA for the cardiovascular system, their protective effect is expected to diminish by the presence of mercury in fish and products (Zhang et al., 2009).

8. Lead and Cardiometabolic Concerns

It has been revealed that exposure to low levels of lead can influence the development of diabetes (Feng et al., 2015). The urinary lead levels have been shown to be positively and significantly associated with impaired fasting blood glucose among the general adult Chinese population (Dapul et al., 2014). High-dose exposure to lead also causes acute symptomatic poisoning characterized by colic, anemia, and depression of the central nervous system that may result in coma, convulsions, and death Moreover, the immune, reproductive and cardiovascular systems are adversely affected (Dapul et al., 2014).

In an animal experiment, Tyrrell et al. (2017) have demonstrated that lead exposure in the obese rat model can disrupt glucose metabolism and lead to hyperglycemia and impaired glucose tolerance independently of body weight or food consumption. The suggested mechanisms include the promotion of insulin resistance in key peripheral tissues mainly skeletal muscle and adipose, the reduction of β-cell insulin secretion, or by dysregulation of glucose production in the liver leading to elevated hepatic glucose output (Castro-González et al., 2008). This may also induce an increase in hepatic glucose production which would contribute to both fasting hyperglycemia and glucose intolerance exacerbating impairments and metabolic abnormalities associated with diabetes (Lee, 2018). Additionally, the liver is the target organ in animals exposed to lead which leads to disruption of hepatic energy metabolism with the reduced level of glycogen and elevated triglyceride (Castro-González et al., 2008). At the same time, lead consumption induced upregulation of gluconeogenic gene expression which caused fatty liver, a condition associated with hepatic insulin resistance and diabetes (Lee, 2018).

Chronic exposure to lead has been linked to atherosclerosis and increased cardiovascular mortality in men; positive associations between serum lead and serum fasting glucose, body mass index, serum triglycerides, LDL-C, cholesterol, and insulin have been reported. Lead intoxication has been shown to promote atherosclerosis in experimental animals. It acts at multiple sites within the cardiovascular system and may affect systemic lipid metabolism (Ahmad & Siddiqui, 2007; Baranowska-Bosiaka et al., 2019).

Dose-response relationships as a result of lead exposure with blood pressure have been identified in numerous studies. The cardiovascular effects of lead are not limited to increased blood pressure and hypertension but also boost the incidence of clinical cardiovascular endpoints such as coronary heart disease, stroke, and peripheral arterial disease (Nawrot et al., 2002; Feng et al., 2015). Several suggestions for the mechanisms for lead toxicity as hypertensive effectors include oxidative stress mechanism that stimulates the renin-angiotensin system, down-regulation of nitric oxide and soluble guanylate cyclase that increases vascular tone and peripheral vascular resistance (Feng et al., 2015). In a general population study, inverse associations between estimated glomerular filtration rate and blood lead have been observed at blood lead levels less than 5 μg/dl indicating that lead-induced reductions in renal function could play a major role in hypertension (Nawrot et al., 2002).

Lead might be associated with obesity, Park et al. (2017) have observed correlations among lead exposure and risk of low birth weight infants, followed by rapid adiposity gain that is a consistent risk factor for childhood obesity, cardiovascular and metabolic impairment later in life. The suggested mechanism of lead resulting in obesity may involve the effects of metal neurotoxicity on brain function and signaling related to dysregulated appetite and satiety response (Coretes et al., 2016; Park et al., 2017). A higher risk of attention-deficit or hyperactivity disorder as a result of lead toxicity has been shown and linked with increased food intake and obesity (Coretes et al., 2016).

9. Conclusions

Worldwide, CMS presents a serious health problem and is closely associated with lifestyle and dietary factors. Fishes are an essential part of the human diet deeming their good nutritional value and cardioprotective effects. Fishes particularly tuna and sardines contain detectable amounts of mercury and lead that could seriously affect health. This makes it difficult to ascertain the role of fish in the healthy diet. Mercury and lead are especially identified as potential risk factors for CMS development. Nonetheless, the underlying mechanisms of their pathogenesis are poorly understood. In animals, the available evidence indicates the presence of associations between fish, lead and mercury and emergence of obesity, insulin resistance, diabetes, and atherosclerosis. In humans, the evidence is less clear and is highly controversial and no causal relationship is yet established. Randomized controlled trials are suggested that investigate direct clinical and longitudinal effects of fish, lead and mercury on the key biomarkers of CMS.

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References

Abarshi, M., Dantala, O. & Mada, S., (2017). Bioaccumulation of heavy metals in some tissues of croaker fish from oil spilled rivers of Niger Delta region, Nigeria, *Asian Pacific Journal of Tropical Biomedicine,* 7(6), 563-568.

Abolghait, S. & A. Garbaj. (2015). Determination of cadmium, lead and mercury residual levels in meat of canned light tuna (Katsuwonus pelamis and Thunnus albacares) and fresh little tunny (Euthynnus alletteratus) in Libya. *Open Veterinary Journal*, 5(2), 130-137.

Ahmad, M.N. & Haddad, F.H. (2015). Suitability of visceral adiposity index as a marker for cardio-metabolic risks in Jordanian adults. *Nutrición Hospitalaria*, 32, 6, 2701-2709. DOI: 10.3305/nh.2015.32.6.9543.

Ahmad, M. & Siddiqui, M. (2007). Low level lead exposure and oxidative stress: Current opinion. *Clinica Chemica Acta*, 383, 57–64. DOI: 10.1016/j.cca.2007.04.024.

Alcala-Orozco, M., Morillo-Garcia, Y., Gallardo, K. & Olivero-Verbel, J. (2017). Mercury in canned tuna marketed in Cartagena, Colombia and estimation of human exposure. *Food Additives and Contaminants*, DOI: 10.1080/ 19393210.2017.1323803.

Al-Zibdah, M., Khalaf, M., & Odat, N., (2006). The fishery status in Jordan's Gulf of Aqaba, Red Sea, *Dirasat, Pure Sciences*, 33(1): 127-137.

ATSDR (2013). Summary data for 2013: Priority list of hazardous substances, Agency for Toxic Substances and Disease Registry, Atlanta, USA. http://www.atsdr.cdc.gov/spl/resourced/ATSDR2013SPLDetailedDataTable.

Baranowska-Bosiaka, I., Olszowski, T., Gutowska, I., Korbecki, J., Rebacz-Maron, E., Barczack, K., Lubkowska, A. & Chlubek, D. (2019). Fatty acid levels alterations in THP-1 macrophages cultured with lead (Pb). *Journal of Trace Elements in Medicine and Biology*, 52(3), 222-231.

Bilandzic, N., Sedak, M., Calopek, B., Dokic, B., Varenina, I., Kolanovic S., Luburic, B., Varga, I., Benic, M. & Roncarati, A. (2018). Element contents in commercial fish species from the Croatian market, *Journal of Food Composition and Analysis*, DOI: 10.1016/j.jfca.2018.02.014

Bosch, A., O'Neill, B.,OSigge, G., Kerwath, S. & Homan, L., (2016). Heavy metals in marine fishmeat and consumer health: A review. *Journal of Science of Food and Agriculture*, 96, 32–48.

Burger, J., Gochfeld, M., Jeitner, C., Donio, M., & Pittfield, T. (2012). Interspecific and intraspecific variation in selenium:mercury molar ratios in saltwater fish from the Aleutians: potential protection on mercury toxicity by selenium. *The Science of the Total Environment*, 431, 46–56.

Castro-González, I. & Méndez-Armenta, M. (2008). Heavy metals: Implications associated to fish consumption, *Environmental Toxicology and Pharmacology*, 26, 263–271.

Ceja-Galicia, Z., Daniel, A., Salazar, A., Panico, P., Ostrosky-Wegman, P. & Diaz-Villasenor, (2017). Effect of arsenic on adipocyte metabolism: Is arsenic an obesogen? *Molecular and Cellular Endocrinology*, 452 (5), 25-32.

Chen, Y., C.F. Huang, C., K.S. Tsai, R.S. Yang, C.C. Yen, C.Y. Yang, S.Y. Lin-Shiau, & S.H. Liu, (2006). Methyl mercury induces pancreatic beta-cell apoptosis and dysfunction. *Chemistry Research, Toxicology*, 19, 1080-85.

Commission of European Communities. (2015). Commission Regulation (EC) No.221/2002 of 6th February 2002 amending regulation (EC) No.466/2002 setting maximum levels for certain contaminants in foodstuffs. *Official Journal of the European Communities*, Brussels.

Cortese, S., Moreira-Maia, R., Fleur, D., Morcillo-Penalver, C., Rohde, A. & Faraone, V. (2016). Association between ADHD and obesity: A systematic review and meta-analysis. *American Journal of Psychiatry*, 173(1), 34–43.

Dapul, H. & Laraque, D. (2014). Lead poisoning in children. *Advances in Pediatrics*, 61(1), 313-333.

Department of statistics. (2013). Average annual consumption of household member from food items and tobacco by Governorates, Urban and Rural, Jordan.

de Paiva, E., Morgano, M. & Milani, R., (2017). Cadmium, lead, tin, total mercury, and methyl mercury in canned tuna commercialized in São Paulo, Brazil. *Food Additives and Contaminants: Part B Surveillance*, 10(3), 185-191.

Fan, Y., Zhang, C. & Bu, J., (2017). Relationship between selected serum metallic elements and obesity in children and adolescent in the U.S. *Nutrients*, 104(9), 1-12. DOI: 10.3390/nu9020104.

FAO. (2016). Fisheries and aquaculture department statistics unit. FISHSTAT+ Databases and Statistics, Rome.

Feng, W., Cui, X., Liu, B., Liu, C., Xiao, Y. & Lu, W. (2015). Association of urinary metal profiles with altered glucose levels and diabetes risk: a population-based study in China. *PLoS One*, 10(4), e0123742. DOI:10.1371/journal.pone.0123742.

Fillion, M., Mergler, D., Sousa Passos, C., Larribe, F., Lemire, M. & Guimarães, R. (2006). A preliminary study of mercury exposure and blood pressure in the Brazilian Amazon. Environmental health. *A global Access Science Source*, 5: 29.

Flora, G., Gupta, D. & Tiwari, A. (2012). Toxicity of lead: A review with recent updates. *Interdisciplinary Toxicology*, 5(2), 47-58.

Gardner, R., Nyland, J., Evans, S., Wang, S., Doyle, K., Crainiceanu, C. & Silbergeld, E. (2009). Mercury induces an unopposed inflammatory response in human peripheral blood mononuclear cells in vitro. *Environmental Health Perspectives*, 117(12), 1932–1938.

Gerstenberger, S., Martinson, A. & Kramer, J. (2010). An evaluation of mercury concentrations in three brands of canned tuna. *Environmental Toxicology and chemistry*, 29(2), 237-242.

Hamida, S. Ouabdesslam, S. Ladjel, Escudero M. & Anzano, J. (2018). Determination of cadmium, copper, lead, and zinc in pilchard sardines from the Bay of Boumerdés by atomic absorption spectrometry. *Analytical Letters*, DOI: 10.1080/00032719.2018.1434537.

Hsu, P. & Guo, L. (2002). Antioxidant nutrients and lead toxicity. *Toxicology*, 180(1), 33-44.

Ikem, A., & Egiebor N. (2005). Assessment of trace elements in anned Fishes (mackerel, tuna, salmon, sardines and herrings) marketed in Georgia and Alabama (Unites States of America). *Journal of Food Composition and Analysis*, 18, 771-787.

Jayaprakash, M., Kumar, S., Giridharan, L., Sujitha, S., Sarkar, S. & Jonathan, M. (2015). Bioaccumulation of metals in fish species from water and sediments in Macro-tidal Ennore Creek, Chennai, SE Coast of India: Metropolitan city effect. *Ecotoxicology Environment Safety*, 120, 243-255.

Kannaiyan, S., Bagthasingh, C., Vetri, V., Aran, S. & Venkatachalam, K. (2019). Nutritional, textural and quality attributes of white and dark muscles of little tuna (Euthynnus affinis), *Indian Journal of Geo Marine Science*, 48 (02), 205-211.

Kim, S. & Sharma, R. (2004). Mercury-induced apoptosis and necrosis in murine macrophages: role of calcium-induced reactive oxygen species and p38 mitogen-activated protein kinase signaling. *Toxicology and Applied Pharmacology*, 196, 47-57.

Kosik-Bogacka, D., Lanocha-Arendarczyk, N., Kot, K., Ciosek, Z., Zietek, P., Karaczun, M., Pilarczyk, B., Tomza-Marciniak, A., Podlasinska, J., Kalisinska, E. & Pyzia, J. (2017). The effect of biological factors and health conditions on mercury and selenium concentrations in the cartilage, meniscus and anterior cruciate ligament. *Journal of Trace Elements in Medicine and Biology*, 44, 201-208.

Lee, K. (2018). Blood mercury concentration in relation to metabolic and weight phenotypes using the KNHANES 2011–2013 data. *International Archives of Occupational and Environmental Health*, 91(2): 185–193.

Leff, T., Stemmer, P., Tyrrell, J., & Jog, R. (2018). Diabetes and exposure to environmental lead (Pb). *Toxics*, 6(3), 54.

Liao, P., Liu, W. & Liu, Y. (2016). Bioaccumulation of mercury and polychlorinated dibenzo-p-dioxins and dibenzofurans in salty water organisms. *Environmental Monitoring and Assessment*, 188(1), 1-15.

Liu,H., Liu, G., Yuan, G. Ge,M., Wang, S., Liu, Y. & Da, C.(2019). Occurrence, potential health risk of heavy metals in aquatic organisms from Laizhou Bay, China, *Marine Pollution Bulletin*, 140, 388-394.

Massadeh, A., Al-Massaedh, T. & Kharibeh, S. Determination of selected elements in canned food sold in Jordan markets. (2018**).** *Environmental Science and Pollution Research*, 25, 3501. DOI: 10.1007/s11356-017-0465-5

Mathew, B., Tiwari, A. & Jatawa, S. (2011). Free radicals and antioxidants: A review. *Journal of Pharmacy Research*, 4(12), 4340-4343.

Mehouel, F., Bouayad, L., Hammoudi, A., Ayadi, O. & Regad, F. (2019). Evaluation of the heavy metals (mercury, lead, and cadmium) contamination of sardine (Sardina pilchardus) and swordfish (Xiphias gladius) fished in three Algerian coasts, *Veterinary World*, 12(1), 7-11.

Meier, T., Gräfe1, K., Senn, F., Sur, P., Stangl, G., Dawczynski, C., März, W., Kleber, M. & Lorkowski, S. (2019). Cardiovascular mortality attributable to dietary risk factors in 51 countries in the WHO European Region from 1990 to 2016: A systematic analysis of the Global Burden of Disease Study. *European Journal of Epidemiology***,** 34, 37–55.

Nawrot, T., Thijs, L., Den, E., Roels,H. & Staessen, A.(2002). An epidemiological re-appraisal of the association between blood pressure and blood lead: A meta-analysis. *Journal of Human Hypertension*, 16, 123–131.

Okyere, H., Voegborlo, R. &Agorku, S. (2015). Human exposure to mercury, lead and cadmium through consumption of canned mackerel, tuna, pilchard and sardine. *Food Chemistry*, 179, 331-335.

Olmedo, P., Pla, A., Hernandez, A., Barbier, F., Ayouni, L. & Gil, F., (2013). Determination of toxic elements (mercury, cadmium, lead, tin and arsenic) in fish and shellfish samples. Risk assessment for the consumers. *Environment International*, 59, 63-72.

Park, J., Ha, H., He, K. & Kim, D. (2017). Association between blood mercury level and visceral adiposity in adults. *Diabetes and Metabolism Journal*, 41, 113-120.

Shenker, B., Maserejian, N., Zhang, A. & McKinlay, S. (2008). Immune function effects of dental amalgam in children: A randomized clinical trial. *Journal of American Dentist Association*, 139(11), 1496-1505.

Simi´c, A., Hansen, A., Asvold, B., Romundstad, P., Midthjell, K., Syversen, T. & Flaten, T. (2017). Trace element status in patients with type 2 diabetes in Norway: The HUNT3 survey. *Journal of Trace Elements in Medicine and Biology*, 41, 91-98. DOI: 10.1016/j.jtemb.2017.03.001

Sun, Y., Li, Y., Rao, J. & Liu, Z. (2018). Effects of inorganic mercury exposure on histological structure, antioxidant status and immune response of immune organs in Yellow Catfish (Pelteobagrus fulvidraco*). Journal of Applied Toxicology*, DOI: 10.1002/jat.3592.

Takahashi, T. & Shimohat, T. (2019). Vascular dysfunction induced by mercury exposure, *International Journal of Molecular Science*, 20(10), 2435.

Taylor, P., Winder, C. & Lanphear, B. (2012). Eliminating childhood lead toxicity in Australia: A call to lower the intervention level. *The Medical Journal of Australia*, 197(9), 493.

Torres, P., Rodrigues, A., Soares, L. & Garcia, P. (2016*).* Metal concentrations in two commercial tuna species from an active volcanic region in the Mid-Atlantic Ocean*. Archives of Environmental Contamination and Toxicology*, 70(2), 341-347.

Tyrrell, J., Hafida, S., Sremmer, P., Adhami, A. & Leff, T. (2017). Lead exposure promotes diabetes in obese rodents, *Journal of Trace Elements in Medicine and Biology*, 39,221-226.

US Department of Health and Human Services, (2017) Dietary Guidelines for Americans, 2015-2020 Washington, DC: USDA.

Valko, M., Morris, H. & Cronin, M. (2005). Metals, toxicity and oxidative stress. *Current Medicinal Chemistry*, 12(10), 1161-1208**.** DOI: 10.2174/0929867053764635

Wani, A., Ara, A. & Usmani, J. (2015). Lead toxicity: A review, *Interdisciplinary Toxicology*, 8(2), 55-64.

Zárate, R., El Jaber-Vazdekis, N., Tejera, N., Pérez, J. A., & Rodríguez, C. (2017). Significance of long chain polyunsaturated fatty acids in human health. *Clinical and Translational Medicine*, 6(1), 25.

Zhang, P., Xu, Y., Sun, J., Li, X., Wang, L. & Jin, L. (2009). Protection of pyrroloquinolinequinone against methyl mercury-induced neurotoxicity via reducing oxidative stress. *Free Radical Research*, 43(3), 224-33. DOI: 10.1080/10715760802677348.

Zuliani, T., Vidmar, J., Drincic, A., Scancar, J., Horvat, M., Necemer, M., Piria, M., Simonovic, P., Paunovic, M. & Milacic, R. (2019). Potentially toxic elements in muscle tissue of different fish species from the Sava River and risk assessment for consumers. *Science of the Total Environment, 650(1)*, 958-969.