

Review Article

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A Review on Metals Induced Oxidative Stress in Fish

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ABSTRACT

Oxidative stress results from an imbalance between the production of reactive oxygen species and the antioxidants defences, in favour of the former. In recent years, the association between oxidative processes, environmental change and life histories has received much attention. Metals are important inducers of oxidative stress in aquatic organisms, promoting formation of reactive oxygen species through two mechanisms. Redox active metals generate reactive oxygen species through redox cycling, while metals without redox potential impair antioxidant defences, especially that of thiol-containing antioxidants and enzymes. Elevated levels of reactive oxygen species lead to oxidative damage including lipid peroxidation, protein and DNA oxidation, and enzyme inactivation. Antioxidant defences include the enzyme system and low molecular weight antioxidants. Metal-binding proteins, such as ferritin, ceruloplasmin and metallothioneins, have special functions in the detoxification of toxic metals and also play a role in the metabolism and homeostasis of essential metals. Antioxidative compounds are found in all fish species to protect their lipids and other compounds that contain double bonds, against damage caused by reactive oxygen species.

Keywords

Reactive oxygen species,
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Introduction

Molecular oxygen is a necessary compound for all aerobic organisms, since this element is critical for energy production; however, is a potent oxidant, which can lead to oxidative stress. The reactive oxygen species (ROS) produced and the resulting free radicals are results of normal cell metabolism, and many of these compounds play a key role in various metabolic pathways. Many of these

components are essential in the organism defense and their byproducts are considered potent bactericides that act actively in the destruction of invasive pathogens (Cross *et al.*, 1987; Dong *et al.*, 2017; Biller-Takahashi *et al.*, 2015). Oxidative stress occurs when there is an imbalance between the production of oxidant and antioxidant components. The organism during its normal metabolism produces several ROSs, however, it has an antioxidant defense system that keeps the

levels of these oxidizing compounds at an acceptable level. In some situations the oxidants production is very high and the cells can suffer serious damage and die (Dong *et al.*, 2017; Finkel, 2011; Kiley and Storz, 2004; Li *et al.*, 2016). Antioxidant enzymes and important indicators of oxidative stress. Reduced glutathione (GSH) and oxidized glutathione disulphide (GSSG) play a key role in non-enzymatic antioxidant defence. Metal-binding proteins such as ferritin, ceruloplasmin, and metallothioneins (MTs) have special functions in the detoxification of toxic metals, and also play a role in the metabolism and homeostasis of essential metals (Kelly *et al.*, 1998). Studies of the fish free radicals production are preliminary, but there are two factors that positively influence the oxidative stress studies in this species; one of them is that fish are considered biological indicators of pollution, which is a factor that promotes the generation of free radicals by the aquatic organism. Second is that many fish are considered biological models for metabolic pathways evaluation, so, due to the importance of the theme, other studies should be carried out to evaluate the ROS effects on fish, including their beneficial effect against pathogens and deleterious impact on the oxidation of cellular components (Ahmad *et al.*, 2000).

Metals, especially heavy metals, are important contaminants of aquatic environments worldwide. Metal pollution has increased with the technological progress of human society. Industry, mining, advanced agriculture, household waste, and motor traffic is all among the activities considered to be major sources of metal pollution. Metals can accumulate in aquatic organisms, including fish, and persist in water and sediments (Luoma and Rainbow, 2008a). Metals are well-known inducers of oxidative stress, and assessment of oxidative damage and antioxidant defences in fish can reflect metal

contamination of the aquatic environment (Livingstone, 2003). Speciation of metals, their solubility and complexation, are important factors that influence the toxicity of metals in the aquatic environment. The amount of dissolved metal strongly depends on water pH. The interaction of metals can alter their toxic effects on aquatic organisms both positively and negatively (Jeziarska and Witeska, 2001). Different modes of exposure to metals also play a role in metal toxicity. Fish take up metals through the gills, digestive tract and body surface (Tao *et al.*, 2001; Kamunde *et al.*, 2002). Various metal ions are involved in oxidative stress in fish.

Oxidative Stress

Oxidative stress is a condition that refers to the imbalance between levels of reactive oxygen species (ROS) and their antioxidants. Reactive oxygen species may be increased and damage lipids, proteins and DNA. Oxidative stress has been linked to a wide variety of diseases; however, ROS molecules also act on immune defense, as well as signaling molecules and on the maintenance of physiological processes (Figure 1) (Wood *et al.*, 2003; Schieber and Chandel, 2014). They may also be classified as free radicals, since chemical properties give them reactivity to different biological targets, and when in excess they can cause peroxidation of membrane lipids, impairment of proteins in tissues, membranes, enzymes, carbohydrates and DNA. Free radicals are highly reactive atoms or molecules that have an unpaired electron in their last electron layer.

Reactive oxygen species are produced mainly in the mitochondria, peroxisomes, cytoplasm and plasma membrane. Oxygen is a biradical that has two radicals in the orbitals, which makes it little reactive, however, the electron transfer or energy absorption processes can promote the ROS formation from molecular

oxygen. ROS include oxygen free radical (FR), such as the hydroxyl radical (HO^\bullet), superoxide anion ($\text{O}_2^{\bullet-}$), peroxy (ROO^\bullet) and alkoxy (RO^\bullet), nitric oxide (NO), but also non-radical compounds, such as oxygen, hydrogen peroxide (H_2O_2), hypochlorous acid (HClO), and transition metals (Cu and Fe) (Sorg, 2004; Barreiros *et al.*, 2006). The FR have a different degree of reactivity and half-life, but most of them are very unstable and can promote the non-enzymatic oxidation of biomolecules (proteins, carbohydrates, lipids and nucleic acids) (Halliwell, 2009; Buonocore *et al.*, 2010; Hamanaka and Chandel, 2010).

Among the ROS, the hydroxyl radical (HO^\bullet) is the most harmful, because there is great difficulty in its sequestration out of the cells due to its very short half-life. This free radical is formed in the body by reaction of H_2O_2 with transition metals and by homolysis of water by exposure to ionizing radiation. There is no antioxidant capable of preventing the HO^\bullet action, it is only possible to inhibit its formation or repair the damage caused by it (Halliwell *et al.*, 1992; Barreiros *et al.*, 2006). The superoxide anion radical ($\text{O}_2^{\bullet-}$) is usually inactive, and in aqueous media produces a hydrogen peroxide molecule and an oxygen molecule by dismutation. This free radical is part of several chemical reactions with important biological functions, such as HO^\bullet radical production, by reducing Fe chelates, as well as Fe^{2+} released from storage proteins (ferritin and aconitase) and iron-sulfoproteins, in addition to reacting with the HO^\bullet radical producing singlet oxygen ($^1\text{O}_2$) and reacting with nitric oxide (NO^\bullet) producing peroxynitrite (ONOO^-) (Babor, 1997; Halliwell, 2000; Barreiros *et al.*, 2006). The superoxide radical, in spite of its deleterious effects, has important function for immune defense, because in phagocytic cells, lymphocytes and fibroblasts, the $\text{O}_2^{\bullet-}$ has the capacity to destroy pathogens.

Hydrogen peroxide is a poorly reactive non-radical compound that can easily diffuse through cell membranes, and consequently promote the formation of the HO^\bullet radical after binding with transition metals, which are usually present within the cell. This FR is generated by the dismutation of the superoxide anion by oxidases enzymes, or even through the oxidation of fatty acids. Hydrogen peroxide in the mitochondrial matrix is produced in abundance during the O_2 reduction process but can be partially eliminated by the catalase, glutathione peroxidase enzymes and peroxidases bound to thioredoxin, or it may be further released into the cell cytoplasm. In phagocytes, H_2O_2 is a precursor of hypoalogen acids that are strong oxidants against pathogens, but also acts deleteriously on molecules of the organism itself (Husain *et al.*, 1987; Halliwell, 2000).

Antioxidant Defense System

Oxidative stress is an unavoidable aspect of aerobic life. It is the result of an imbalance between the production of reactive oxygen species (ROS) and antioxidant defences in living organisms (Nishida, 2011). Elevated production of ROS can cause oxidation of proteins and lipids, alterations in gene expression, and changes in cell redox status (Livingstone, 2003). Mechanisms of antioxidant defences in fish include the enzyme system and low molecular weight antioxidants, similar to those in mammals, although the specific isoforms of enzymes in various fish species have not been well identified (Di Giulio and Meyer, 2008). The organism, in the face of the imbalance of free radical production, presents a strategy to inhibit its formation or to promote chemical reactions to reduce the high reactivity of these compounds through antioxidant components, such as enzymes or cofactors, obtained by the cell itself (endogenous source) or through diet (exogenous source). Antioxidants are

substances that significantly delay or prevent the oxidation of an oxidizable substrate (Franco and Martínez-Pinilla, 2017; Sorg, 2004; Wang *et al.*, 2013). Many studies have been conducted on fish to evaluate their antioxidant compounds to determine a database for comparative studies on the effects of natural environment, diet, seasonal variation, xenobiotics and others (Mattos *et al.*, 2017; Moura *et al.*, 2017; Winston, 1991; Halliwell *et al.*, 1995; Pietta, 2000; Li *et al.*, 2016). The antioxidants produced by the body act enzymatically by decreasing the excess of FR, through enzymatic components, such as the superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) enzymes and through non-enzymatic components such as glutathione (GSH), histidine peptides, iron-bound proteins (transferrin and ferritin), dihydrolipoic acid and ubiquinone (CoQH₂). And some dietary antioxidants such as α -tocopherol (vitamin-E), β -carotene (pro-vitamin-A), ascorbic acid (vitamin C), micronutrients (selenium) and phenolic compounds, such as flavonoids and polyflavonoids (Albuquerque *et al.*, 2017, 1995; Pietta, 2000). Fish present a complex antioxidant defense system that comprises several enzymes, among them SOD is widely found in the cytosol (Cu²⁺-SOD and Zn²⁺-SOD) and in the mitochondria (Mn²⁺-SOD), that acts on the superoxide anion transforming in H₂O₂, avoiding the accumulation of O₂^{•-}, which is highly reactive and deleterious to the cell. The produced H₂O₂ can be eliminated by catalases, GPx and peroxidases bound to thioredoxin, or it may be further released into the cytoplasm of cells (Lambeth, 2004; Brand, 2010; Schieber and Chandel, 2014; Li *et al.*, 2016). CAT (derived from mitochondria and peroxisomes) catalyzes the decomposition of H₂O₂ into H₂O and O₂, which is produced in abundance by phagocytes, and maintains the ideal balance of ROS formation and elimination, essential for the functioning of the innate defense system. Modulation of CAT

production is important for many processes, such as proliferation, differentiation, cell migration and apoptosis (Underhill and Ozinsky, 2002; Oost *et al.*, 2003, Malhotra and Kaufman, 2007; Veal *et al.*, 2007; Zamocky *et al.*, 2008, Wang *et al.*, 2013). Hydrogen peroxide can also be neutralized by cytosolic or mitochondrial GPx in the presence of GSH. GSH also contributes to the removal of electrophilic components through the reaction with glutathione-S-transferase. The antioxidant system based on GSH acts in the presence of selenium, which is a very important micronutrient and widely studied in fish. GPx plays an important role in the prevention of lipid peroxidation, since it removes H₂O₂, consequently protects the membranes from peroxidation damage (Sies, 1986; Gaté *et al.*, 1999; Oost, *et al.*, 2003; Scandalios, 2005; Monteiro, *et al.*, 2006). Antioxidants from diet are important to avoid the ROS effects (Lambeth, 2004; Brand, 2010). Ascorbic acid or vitamin C normally appears in the body as ascorbate form and is an excellent antioxidant *in vivo*, as it can be oxidized by most of the FR in aqueous solution, and converted into poorly reactive substances. Vitamin C acts by binding to ROS present in the body and restoring the FR through H⁺ donation, in cell membranes it acts together with vitamin E, regenerating the Vit E after ROS interaction. Vitamin C also acts as a reductor agent, mainly decreasing transition metals such as Fe and Cu ions that react with H₂O₂ to form the hydroxyl radical (Buettner, 1993; Babior, 1997). Vitamin E, *in vivo*, is a potent inhibitor of lipid peroxidation. It acts as an H⁺ donor for the peroxy radical, interrupting the FR formation chain reaction. The H⁺ donation leads vitamin E loss of function, however, it can be regenerated with vitamin C. The impact of the vitamin E on fish immune system have been extensively studied (Storey, 1996; Theriault *et al.*, 1999; Monteiro *et al.*, 2006). Selenium (Se), an essential micronutrient, is an integral part of several

selenium-enzymes, among them GPx, iodothyronine deiodinase, thioredoxin reductase and selenophosphate synthetase. Selenium-enzymes is included on antioxidant defense system compound, as well as on metabolism of thyroid hormones, spermatogenesis and other biological processes, and it has been the subject of many studies on fish immune system. Some studies have demonstrated an improvement of humoral and cell-mediated immune responses following the selenium incorporation into the diet of fish (Hsu and Guo, 2002; Biller-Takahashi *et al.*, 2015; Chien *et al.*, 2003).

Enzymatic and non-enzymatic antioxidants are essential to maintain the balance between production and elimination of FR from fish cells. Antioxidants are an important biological defense against OS involved in cell detoxification, and are very important for understanding the deleterious effects of FR (Bainy, 1996; Doyotte *et al.*, 1997; Ahmad *et al.*, 2000).

Mechanisms of metal-induced oxidative damage

The involvement of metals in oxidative damage is multi-faceted. In general, metals produce free radicals in two ways. Redox active metals such as iron, copper, chromium, and vanadium generate ROS through redox cycling. Metals without redox potential, such as mercury, nickel, lead, and cadmium, impair antioxidant defences, especially those involving thiol- containing antioxidants and enzymes (Stohs and Bagchi, 1995). A third important mechanism of free radical production is the Fenton reaction, by which ferrous iron (II) is oxidized by hydrogen peroxide to ferric iron (III), a hydroxyl radical, and a hydroxyl anion (Valko *et al.*, 2005). The superoxide radical can reduce iron to its ferrous form. Copper, chromium, vanadium, titanium, cobalt, and their complexes can also

be involved in the Fenton reaction (Lushchak, 2011). Activation of redox sensitive transcription factors such as AP-1, p53, and NF- κ B is another mechanism by which metals can participate in producing oxidative stress. These transcription factors control the expression of protective genes which repair DNA and influence apoptosis, cell differentiation, and cell growth (Valko *et al.*, 2005)

Metals involved in oxidative stress in fish

Redox – active metals

Iron

Iron is an essential element required for many physiological functions, and its homeostasis is strictly regulated by various mechanisms. In bio-logical systems iron exists in three oxidation states (II, III, and IV). The majority of iron in the organism is bound to haemoglobin, transferrin, ferritin, and iron-containing enzymes. Therefore, only a trace amount of free iron is present (Valko *et al.*, 2005). Excessive uptake of iron or disturbances in its regulation can be toxic which is related to its ability to catalyze ROS formation via the Fenton reaction. Elevated production of superoxide anions increases the release of free iron (Emerit *et al.*, 2001). The deleterious effects of iron include DNA damage, lipid peroxidation (LPO), and oxidation of proteins (Valko *et al.*, 2005). Lipid peroxidation and alterations in antioxidant enzyme activity in embryonic and adult medaka *Oryzias latipes* exposed to nano-iron was reported by Li *et al.*, (2009). According to Baker *et al.*, (1997), an iron-enriched diet in the African catfish *Clarias gariepinus* induced LPO in the liver and heart. Significant increases in SOD activity and higher levels of LPO were observed in erythrocytes of cichlid fish from a metal-contaminated river, with the highest levels in

spring, when the concentration of iron in water was elevated (Ruas *et al.*, 2008).

Copper

Copper plays an essential function in a variety of metabolic processes. It is a component of many enzymatic and structural proteins, including Cu-Zn SOD, cytochrome oxidase, and ceruloplasmin. Copper occurs naturally in soil and water. Mining, industrial discharges, and copper-based pesticides, especially algaecides, are sources of water contamination (WHO, 1998). Copper toxicity to fish and its bioavailability in water vary with physicochemical properties of water, i.e., pH, alkalinity, suspended solids, organic compound content, and hardness (Di Giulio and Meyer, 2008). The concentration of free copper, cupric ion (II), increases with water acidity. Copper hydroxide predominates in water of pH 8.0 and higher (Tao *et al.*, 2001). Calcium, as a contributor of water hardness, was shown to reduce the harmful effects of copper on the growth of Nile tilapia (Abdel-Tawwab *et al.*, 2007). The cellular toxicity of copper can be explained through its participation in the Fenton reaction. Gravato *et al.*, (2006) observed an increase in copper associated LPO and DNA damage in the European eel *Anguilla anguilla* pre-exposed to β -naphthoflavone (BNF). This study suggests a synergistic relationship between copper and BNF. Copper binds thiol-containing molecules such as glutathione. The inhibition of total GSH was observed in the livers of three-spined sticklebacks *Gasterosteus aculeatus* exposed to copper sulphate. Concurrent with the depletion of GSH, enzymatic biomarkers such as CAT, SOD, and GPx increased within the first week of exposure and then recovered, concomitant with copper accumulation in the liver. The recovery of GSH and a return of antioxidant enzymes to basal levels suggest that metallothioneins play a role in detoxification

(Sanchez *et al.*, 2005). Gravato *et al.*, (2006) attribute the de-pletion of GSH to direct copper interference with GSH synthesis, inhibition of glutathione reductase, and the participation of GSH as a substrate in detoxification reactions. The depletion of GSH in fish muscle after copper sulphate exposure has also been reported (Jena *et al.*, 2009).

Redox – inactive metals and metalloids

Cadmium

Cadmium is a non-essential metal with no known biological function. The source of cadmium in the aquatic environment is industrial activity (Stohs and Bagchi, 1995). Cadmium does not generate ROS directly, but can alter GSH levels and influence cell thiol status, inducing the expression of metallothioneins in the liver. Changes in GSH and MTs can lead to LPO of the cell membrane. Cadmium enters the electron transport chain in mitochondria, leading to accumulation of unstable semiquinones which donate electrons and create superoxide radicals. Cadmium also affects antioxidant enzymes, especially SOD and CAT, and is able to displace copper and iron in various proteins, freeing these metals to then participate in the Fenton reaction (Ercal *et al.*, 2001). This decreased activity was explained by the authors as the direct binding of cadmium to CAT. Metallothioneins play a major role in the detoxification of cadmium, and this process is clearly organ-specific (De Smet *et al.*, 2001). The induction of *de novo* synthesis of MTs following cadmium exposure has been described in several studies (Jebali *et al.*, 2006; Ghedira *et al.*, 2010). According to De Smet *et al.*, (2001), MT induction following intraperitoneal injection of cadmium, as described by Ghedira *et al.*, (2010), is evidence of a genetic ability to synthesise MTs. Contradictory results were reported from a field study conducted by

Kovarova *et al.*, (2009), where no significant correlation between cadmium liver content and MT concentration was observed. The effects of cadmium exposure on GSH levels vary with fish species, duration of exposure, and the chemical involved. Both increases and decreases in GSH have been observed, depending on field and experimental conditions (Kovarova *et al.*, 2009; Cao *et al.*, 2010; Jia *et al.*, 2011).

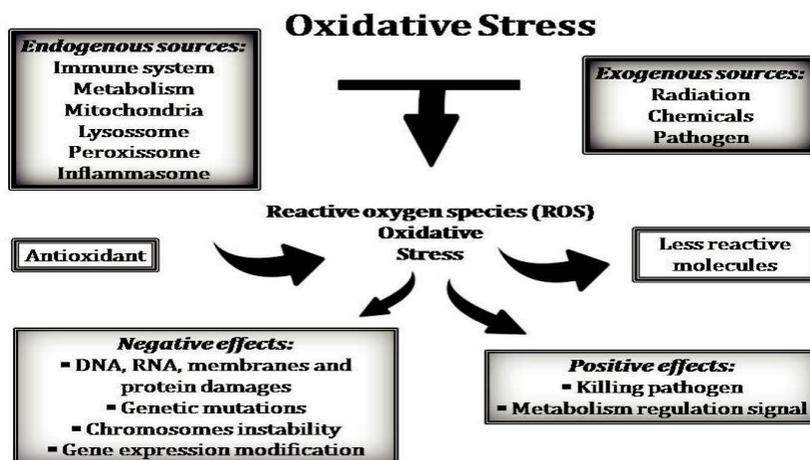
Mercury

Mercury is an important pollutant of water world-wide. A variety of human activities are connected with mercury pollution (silver and gold mining, coal combustion, dental amalgams) (Luoma and Rainbow, 2008b). Organic methylmercury and inorganic (mercurous, mercuric) forms exist in nature. Organic forms are the result of methylation of inorganic mercury by microorganisms in sediments and water. Methylmercury is generally more toxic to fish than the inorganic forms (Houserova *et al.*, 2006). Mercury reacts with the thiol groups of GSH, which can induce GSH depletion and oxidative stress in tissue (Stohs and Bagchi, 1995). Monteiro *et al.*, (2010) described changes in biomarkers of oxidative stress following exposure to inorganic mercury. Methylmercury was shown

to induce oxidative stress in several field studies (Larose *et al.*, 2008; Miei-ro *et al.*, 2010). The data presented in these studies suggest that both organic and inorganic forms of mercury participate in the formation of ROS. Metallothioneins also play a protective role in response to mercury exposure. The mRNA expres-sion of two MT genes was noted by Navarro *et al.*, (2009) in the liver of feral carp *Cyprinus carpio* from a mercury -contaminated river. No biochemical evidence of oxidative damage associated with these changes was found in the tissue. This suggests that quantitative analysis of the mRNA expression of MT genes can be a suitable biomarker of subtoxic metal exposure in cases of elevated levels of metals and no evidence of oxidative damage in fish tissue.

The authors have observed increases in GSH levels following mercury exposure (Rana *et al.*, 1995; Elia *et al.*, 2000). Depletion of GSH was reported by Elia *et al.*, (2003) and Miei-ro *et al.*, (2010). Metal-induced decreases in GSH levels could be the result of direct binding of the metal to GSH through its SH group (formation of metal-SG complexes) or of enhanced oxidation of this thiol (Elia *et al.*, 2003). Collectively, these data suggest that GSH has a key role in oxidative-induced toxicity caused by mercury.

Fig.1 Oxidative stress



Lead

Lead is a major environmental pollutant. Paint, cosmetics, human medicines, food supplements, and petroleum-based fuels are sources of lead pollution (Stohs and Bagchi, 1995). Lead accumulation in sediment is of significance for aquatic organisms. Lead is not a transition metal and cannot readily undergo valence changes. Lead can induce oxidative damage through direct effects on the cell membrane, interactions between lead and haemoglobin, which increase the auto-oxidation of haemoglobin, auto-oxidized δ -aminolevulinic acid, interactions with GR, or through the formation of complexes with selenium, which decrease GPx activity (Ercal *et al.*, 2001). An intraperitoneal injection of lead was administered to the toadfish *Halobatrachus didactylus* and its effects on aminolevulinic acid dehydratase (ALA-D) activity, MT levels, and LPO in the liver, kidney, and blood were investigated over seven days (Campana *et al.*, 2003). The results showed an increase in MT levels, suggesting that lead can induce the synthesis of MTs, although to a lesser degree than some other metals. The authors proposed that lead is not a good inducer of LPO, because a decrease in MDA levels was measured in the liver, and the induction of LPO observed in the kidney was ambiguous. No significant variations in ALA-D as a result of lead exposure were reported. Maiti *et al.*, (2010) described elevated MDA levels in the brains of walking catfish *Clarias batrachus* following a 60-day exposure to waterborne lead. These results suggest that the manner and duration of exposure are important factors in lead-induced oxidative stress.

Arsenic

Arsenic is a known carcinogen in human. Arsenic forms inorganic and organic complexes in the environment. Arsenite (III)

and arsenate (V) are inorganic forms that can be methylated. The trivalent arsenite is biologically more active than pentavalent arsenate. Glutathione plays a key role in the cell redox status induced by arsenic. Glutathione is an electron donor in the reduction of arsenate to arsenite. Arsenic cell metabolism generates ROS, although the mechanisms are not clear. Reactive nitrogen species are also involved in oxidative damage associated with arsenic (Bhattacharya and Bhattacharya, 2007). The central role of GSH in arsenic toxicity was described in several studies. The induction of LPO, an increased GSSG/GSH ratio, and excess production of hydrogen peroxide were observed in the Indian catfish *Clarias batrachus* exposed to nonlethal doses of arsenic for 10 days (Bhattacharya and Bhattacharya, 2007). The authors explained the elevated concentration of hydrogen peroxide as arsenic-induced alterations of peroxisome. Oxidative stress-induced apoptosis was suggested by Seok *et al.*, (2007) as a possible mechanism of arsenic toxicity in a zebrafish *Danio rerio* liver cell line. Arsenobetaine and arsenocholine are non-toxic organic forms of arsenic present in fish. According to Ciardullo *et al.*, (2010), the majority of total arsenic in fish tissue is present as arsenobetaine. This is similar to the conclusions of Harkabusova *et al.*, (2009). The data presented suggest that an assessment of arsenic speciation needs to be included in studies dealing with arsenic pollution, especially in field conditions, taking into consideration the risk to humans of fish consumption.

Selenium

Selenium as an essential element plays a role in anti-oxidant defences and is a cofactor for GPx. Preventive effects of selenite on heavy metal-induced stress in rainbow trout *Oncorhynchus mykiss* were described by Ates *et al.*, (2008). Selenium can be toxic to fish at

high doses. A source of selenium is coal mining from Se-rich rocks; selenate is the main form of Se originated from industrial discharges and selenium accumulates to toxic levels in the aquatic environment. Plants transform selenate to selenite and organo-selenide. Various mechanisms have been suggested for Se toxicity, one of which is the generation of ROS (Miller *et al.*, 2007).

Other metals

Apart from the above mentioned metals and metalloids, other metals are also connected with oxidative stress (nickel, vanadium, and cobalt) (Stohs and Bagchi, 1995) and can be detected in aquatic environments (Kandemir *et al.*, 2010). Tributyltin and aluminium are widespread pollutants. The induction of oxidative stress may also play some role in the mechanisms of their toxicity in fish, but more studies need to be performed to explore this possibility (Wang *et al.*, 2006; Garcia-Medina *et al.*, 2010; Ternjej *et al.*, 2010).

Oxidative stress is a very important issue considering the problem of the aquatic environment contamination with pesticides. The above mentioned studies document that oxidative stress induced by metals is an important issue in aquatic ecosystems. The response of fish to oxidative damage after acute and also chronic metal exposure is evident under laboratory conditions as well as in field studies. The components of antioxidant defences are diversely influenced by metals. Both increases and decreases in enzyme activities and also enhanced and reduced levels of non-enzymatic components have been described after metal exposure. Metallothioneins (MT) seem to be a suitable biomarker of metal exposure, especially under laboratory conditions. In field studies the applicability of MT content in fish tissues as a biomarker is questionable following chronic metal exposure. The experimental conditions

in field studies vary with a season and weather, and the physicochemical properties of water play an important role in metal solubility. Organic substances in water influence the availability of metal to fish and reduce metal toxicity. Some metals are rapidly bound to organic substances and thus cannot be detected in water; however, they can later become accessible in fish food. It should be borne in mind that fish of different species, sex, size, and age are involved in field studies. Another factor that can influence a representative sampling is fish migration. Therefore, field studies should be designed in such a way as to take into account the complexities of the aquatic environment. Fish can be used as bioindicators of metals in the environment by studying the induction of oxidative stress; however, the specific forms of biomarkers and mechanisms of their action still need to be investigated.

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