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# Impact of heavy metals and Hsp Response

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## Abstract

Heavy metals are natural constituents of the earth's crust, but indiscriminate human activities have drastically altered their geochemical cycles and biochemical balance. Heavy metals such as Iron, copper, Zinc, Nickel, Molybdenum are essential for normal biological functioning. Heavy metals such as Mercury, Lead, and Cadmium are biologically non-essential, but are important metals for industrial applications. Prolonged exposure to heavy metals such as cadmium, copper, lead, nickel, and zinc can cause deleterious health effects in plants, fishes and humans. Higher concentrations of both essential and non-essential metals disturb normal biological functions and which evoke cellular stress responses. Prolonged exposure of heavy metals induces heat shock proteins in plants, animals and fishes. Heat shock proteins are expressed in response to a wide range of biotic and abiotic stressors. Heat shock proteins are a family of highly conserved cellular proteins present in all organisms including fish, plant and humans. This review focus the toxic effects of heavy metals and the significance of heat shock proteins in response to stress in plant, fish and human

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## Introduction

Heavy metals constitute a heterogeneous group of elements widely varied in their chemical properties and biological functions. Heavy metals are chemical elements with a specific gravity. Specific gravity is a measure of density of a given amount of a solid substance when it is compared to an equal amount of water (Lide, 1992). Heavy metals occur in environment from natural processes and anthropogenic activities (Connell *et al.*, 1999; Franca *et al.*, 2005). Heavy metal such as iron, chromium, nickel commonly known as trace elements play an important role in biological systems, yet they may become highly toxic when present in high concentrations (Ibok *et al.*,1989). Cadmium, mercury and lead are non-essential metals. They are toxic, even in trace amounts (Fernandes *et al.*, 2008). Pollution by heavy metals is a worldwide problem due to its persistency and continuing accumulation of metals in the environment. The fact that heavy metals cannot be destroyed through biological degradation and have the ability to accumulate in the organs of living organisms make these toxicants deleterious to living organisms and consequently to humans. Heavy metals accumulate in the tissues of aquatic animals and may become toxic when accumulation reaches a substantially high level. Heavy metal toxicity can result in damaged or reduced mental and central nervous function, lower energy levels, and damage to blood composition, lungs, kidneys, liver, and other vital organs. Toxic effects occur when excretory, metabolic, storage and detoxification mechanisms are no longer able to counter uptake. Long-term exposure may result in slowly progressing physical, muscular, and neurological degenerative processes that mimic Alzheimer's disease, Parkinson's disease, muscular dystrophy, and multiple sclerosis. Disruption of normal cellular processes may cause rapid increase in the synthesis of a group of proteins which belong to the HSP families. Heat shock proteins (HSP) are a family of proteins. This expressed in response to a wide range of biotic and abiotic stressors. Thus, they are referred to as stress proteins (George *et al.*, 1998). These proteins have been classified into several families based on their molecular weight such as Hsp90 ( 85-90kDa), Hsp 70 (68-73 kDa), Hsp 60, Hsp 47 and small hsps (12-43kDa) (Park *et al.*, 2007; Hallare *et al.*, 2004). The Hsp genes are highly conserved and have been characterized in a wide range of organisms. The heat shock response is an evolutionarily conserved heat shock response is an evolutionarily conserved mechanism for maintaining cellular homeostasis following sublethal noxius stimuli (Lindquist, 1986; Lindquist and Craig,1988). Heat shock proteins act as molecular chaperones, which mediate the correct assembly and localization of intracellular and secreted polypeptides. Heat shock protein stress response plays a role by enhancing the survival and health of the living organisms. These review focuses on the toxic effects of heavy metals stress tolerance of plants, humans and fish.

## Toxic effects of heavy metals in plants

Plants interact not only with climatic factors (such as irradiation, temperature, and drought) but also soil factors (such as salinity) and biotic factors (such as herbivores and pathogens). All these factors put the plant under interrelated stresses (Levitt, 1980). Moreover, the presence of heavy metals due to human activities could result in extra stresses on plants (Vierling, 1991). Heavy metals such as Cu and Zn are essential for normal plant growth and development since they are constituents of many enzymes and other proteins. However, elevated concentrations of both essential and non-essential heavy metals in the soil can lead to toxicity symptoms and the inhibition of growth of most plants. The toxicity symptoms seen in the presence of excessive amounts of heavy metals may be due to a range of interactions at the cellular/molecular level. Toxicity may result from the binding of metals to sulphydryl groups in proteins, leading to an inhibition of activity or disruption of structure, or from the displacing of an essential element resulting in deficiency effects (Van Assche and Clijsters, 1990).

Copper (Cu) is considered as a micronutrient for plants (Thomas *et al.*, 1998). Copper is concentrated in roots of plants and plays a part in nitrogen metabolism. It plays an important role in $CO_2$ assimilation and ATP synthesis and it is also an essential component of various proteins like plastocyanin of photosynthetic system and cytochrome oxidase of respiratory electron transport chain (Demirevska- kepova *et al.*, 2004). Excess of Cu in

soil plays a cytotoxic role. Exposure of plants to excess Cu generates oxidative stress and ROS in plants (Stadtman and Oliver, 1991). This leads to plant growth retardation and leaf chlorosis.

Nickel (Ni) is a transition metal. It is required for the enzyme urease to break down urea to liberate the nitrogen into a usable form for plants. Nickel is required for iron absorption. Seeds need nickel in order to germinate. Excess of Ni2+ in plants causes various diverse toxicity symptoms such as chlorosis and necrosis (Pandey and Sharma, 2002; Rahman *et al.*, 2005). Plants grown in high Ni2+ containing soil showed impairment of nutrient balance and resulted in disorder of cell membrane functions. High uptake of Ni2+ induced a decline in water content of dicot and monocot plant species. The decrease in water uptake is used as an indicator of the progression of Ni2+ toxicity in plants (Pandey and Sharma, 2002).

(Zn) is an essential nutrient for plant. Zinc is a component of enzymes or a functional cofactor of a large number of enzymes including auxins (plant growth hormones). It is essential to carbohydrate metabolism; protein synthesis and internodal elongation (stem growth). Excess of Zn in soil plays a phytotoxic role. High levels of Zn in soil inhibit many plant metabolic functions. Result in retarded growth and cause senescence. Zinc toxicity in plants limited the growth of both root and shoots (Ebbs and Kochian, 1997; Fontes and Cox, 1998) and also causes chlorosis in the younger leaves.

Selenium (Se) has shown positive effect on crop growth and show metabolic importance in agricultural plants. Stunting of growth, slight chlorosis, decreases in protein synthesis and dry matter production, and withering and drying of leaves are most often associated with selenium toxicity (Mengel *et al.*, 1987). Toxicity of selenium appears as chlorotic spots on older leaves that also exhibit bleaching symptoms. A pinkish, translucent color appearing on roots can also occur. Onions grown under extremely toxic Se concentrations showed sulfur-deficiency symptoms just before plant death (Kopsell and Randle, 1997b).

Mercury (Hg) is a unique metal due to its existence in different forms (HgS, Hg2+, Hg° and methyl-Hg). In agricultural soil, ionic form (Hg2+) is predominant (Han *et al.*, 2006). High level of Hg2+ is strongly phytotoxic to plant cells. Toxic level of Hg2+ can induce visible injuries, physiological disorders (Zhou *et al.*, 2007) and also interfere the mitochondrial activity in plants. This induces oxidative stress by triggering the generation of ROS. This leads to the disruption of biomembrane lipids and cellular metabolism in plants (Israr and Sahi, 2006).

Cadmium (Cd) is nonessential and potentially toxic for higher plants, animals and humans. Plants exposed to high levels of Cd causes reduction in photosynthesis, water uptake, and nutrient uptake. High levels of Cd show visible symptoms of chlorosis, growth inhibition, browning of root tips, and finally death (Wojcik andTukiendorf, 2004; Mohanpuria *et al.*, 2007).

Lead (Pb) is most abundant toxic elements in the soil. It exerts adverse effect on morphology, growth and photosynthetic processes of plants. High level of Pb causes inhibition of enzyme activities, water imbalance, alterations in membrane permeability and disturbs mineral nutrition (Sharma and Dubey, 2005). High Pb concentration also induces oxidative stress by increasing the production of ROS in plants (Reddy *et al.*, 2005).

Arsenic (As) tolerance has been identified in a number of plant species (Meharg, 1994; Sharples *et al.*, 2000). The Arsenic also undergoes transformation within plant cells to other less phytotoxic as species (Meharg, 1994).

Chromium (Cr) is a heavy metal. Excess of Cr causes inhibition of plant growth, chlorosis in young leaves, nutrient imbalance, wilting of tops, and root injury (Sharma *et al.*, 2003; Scoccianti *et al.*, 2006). Cr inhibits chlorophyll biosynthesis in terrestrial plants (Vajpayee *et al.*, 2000). Toxic effects of Cr on plant growth and development include alterations in the germination process as well as in the growth of roots, stems and leaves. Cr also causes deleterious effects on plant physiological processes such as photosynthesis, water relations and mineral nutrition. High Cr concentration

also induces oxidative stress by increasing the production of ROS in plants.

**Heat shock protein expression in plants**

Heavy metals are simultaneously acting on the plants causing cell injury and producing secondary stresses such as osmotic and oxidative ones (Wang *et al*., 2003). Heat stress as well as other stresses can trigger some mechanisms of defense such as the obvious gene expression that was not expressed under "normal" conditions (Morimoto, 1993; Feder, 2006). Heat shock proteins (Hsps) and other stress proteins have been known to protect cells against deleterious effects of stress. Hsps are also expressed in some cells either constitutively or under cell cycle or developmental control.

Heat-shock proteins are stress proteins involved in the protection, repair, and degradation of damaged cell components, especially proteins, during most abiotic stresses (Parsell and Lindquist, 1994; Hamilton and Heckathorn, 2001). Most heat shock proteins are molecular chaperones. Chaperones aid in the transport of proteins throughout the cell's various compartments. Heat shock proteins are classified by their molecular weight, size, structure, and function. They are divided into several families, namely: Hsp100, Hsp90, Hsp70, Hsp60 (or chaperonins), 17-to 30 kda small hsps (shsps) and ubiquitin (8, 5 kda) (waters et al., 1996). Heat shock proteins play various roles and reside in various locations within the cell (Table:1).

**Heat shock proteins response to heavy metals in plants**

Heavy metal stresses usually give rise to dysfunctional protein conformations. Molecular chaperones are stress proteins and many of them were originally identified as heat shock proteins (Hsps). According to current knowledge, Hsps facilitate protein refolding and stabilize polypeptides and membranes. Hsp70 has essential functions in preventing aggregation and assisting refolding of nonnative proteins under stress conditions. Wang et al).

Photosynthesis is typically decreased by increased level of heavy metals. The specific effects of heavy metal on photosynthesis vary among species (Patsikka *et al*., 2002; Vinit-Dunand *et al*., 2002). Heavy metals damages both membrane and soluble phases of chloroplasts through multiple mechanisms that include protein denaturation and oxidative damage (Hall, 2002). General response of plants to elevated levels of heavy metals appears to be increased synthesis of various heat-shock proteins (Hsps) (Barque et al., 1996; Hall, 2002). Heat-shock proteins are general stress proteins involved in protection of photosynthesis during heat, oxidative, and photoinhibitory stress, by protecting PSII or other aspects of thylakoids (Nakamoto *et al*., 2000). Chloroplast has small heat shock protein (smHsps). Chloroplast small heat-shock proteins protect photosynthesis during heavy metal stress (Scott *et al*., 2004). Which protect photosynthesis through more than one mechanism by preventing irreversible protein aggregation, stabilizing chloroplast membranes and by site-specific antioxidants.

**Toxic effects of heavy metals in fishes**

Massive amounts of domestic wastewater and industrial effluents are transported by rivers and discharged into the sea, contaminating rivers and coastal waters. Such anthropogenic pollutants are the main sources of heavy metal contaminants in the ocean. Heavy metals enter from contaminated water into fish body by different routes and accumulate in organisms (Olaifa *et al*., 2004; Surec, 2003).These contaminants entering the aquatic ecosystem may not directly damage the organisms; however, they can be deposited into aquatic organisms through the effects of bioconcentration, bioaccumulation and the food chain process and eventually threaten the health of humans by seafood consumption. Heavy metals such as iron, copper, zinc and manganese are essential for biological systems. Other heavy metals like lead, cadmium and mercury are toxic (Fernandes *et al*., 2008). Fishes take the essential metals from water, food or sediment for its normal metabolism. High concentration of heavy metals causes toxic effects (Tüzen, 2003).

**Table: 1.** HSP locations in Plants and its specific functions.

| Sl. no | Heat shock proteins in plants | Cellular Compartments | Functions |
|---|---|---|---|
| 1 | Hsp100 | Cytosol, mitochondria | Disaggregation,unfolding |
| 2 | Hsp90 | Cytosol, mitochondria, endoplasmic reticulam, chloroplast | Facilitating maturation of signaling molecules, genetic buffering. |
| 3 | Hsp70 | Cytosol, mitochondria, endoplasmic reticulam, chloroplast | Preventing aggregation, assisting refolding, protein import and translocation, signal transduction, transcriptional activation. |
| 4 | Hsp60(chaperonins) | Cytosol, mitochondria, chloroplast | Folding and assisting refolding |
| 5 | Small hsps | Cytosol, mitochondria, endoplasmic reticulam, chloroplast | Preventing aggregation, stabilizing non native proteins. |
| *6* | Ubiquitin | Cytosol, mitochondria, endoplasmic reticulam, chloroplast | Immunity, control plant growth and stress tolerance. |

**Table 2.** HSP locations in fish and its specific functions.

| Sl. No | Heat shock proteins in fish | Cellular Compartments | Functions |
|---|---|---|---|
| 1. | Hsp47 | Endoplasmic reticulum | Procollagen triple helix assembly |
| 2. | Hsp70 | Cytosol, mitochondria, endoplasmic reticulam | Preventing aggregation, protein folding. |
| 3. | Hsp90 | Cytosol, mitochondria, endoplasmic reticulam, | Signal transduction, transcriptional activation, protein folding, protein degradation |
| *4.* | sHSPs | Cytosol, mitochondria, endoplasmic reticulam | Prevent aggregation of proteins, stabilizing non native proteins. |

Copper (Cu) play a significant role in growth and development of fish. It is a key component of enzymes, compounds that act as catalysts in the metabolism of organisms adequate supply is necessary for normal metabolism, metalloenzymes and enzymes catalyze many different chemical reactions, enzymes are critical to the development of bone tissue and the production of red blood cells. Rask *et al.*,(1990) reported delayed spawning in perch, Perca fluvicetilis in acidified lakes due to decreased gonadal maturation. High concentration of copper may badly damage gills, adversely affect the liver and kidneys of fish or cause some neurological damage.

Nickel (Ni) activates the enzyme arginase and influences oxidative processes. Excess intake of nickel causes some morphological transformations in numerous cellular systems and chromosomal aberrations (Coen *et al.*, 2001).

Zinc (Zn) is one of the most important trace elements in the body, and participates in the biological function of

several proteins and enzymes (Maity *et al.*, 2008). Zinc is known for its essential role in growth, immunity, DNA replication, Body's defensive (immune) system, cell division, cell growth, wound healing, and the breakdown of carbohydrates. High Zinc intake leads to enfeeblement, retardation of growth and may bring about metabolic and pathological changes in various organs in fish (Ambrose *et al.*,1994; Sharma and Sharma,1994).

Selenium (Se) is an essential metal; it is anti-cancerous and powerful antioxidant properties (Ganther, 1999; Rayman, 2000; Surai, 2002). Excessive intake of selenium cause gastrointestinal upsets, fatigue, irritability, and mild nerve damage.

Mercury (Hg) is considering one of the most dangerous of the heavy metals because of its high toxicity, bioacummulative properties an on biota including genetic alternation or mutagenesis. Reproduction of fish is impaired by exposure to mercury. Methyl mercury induces apoptsis of steroidogenic gonadal cells in fish (Drevnick *et al.*, 2006b), resulting in suppressed sex steroid hormone levels that are linked to inhibited reproduction (Drevnick and Sandheinrich, 2003). Apoptosis often a symptom of oxidative stress(Holden, 2000) and other recent laboratory tests have reported that dietary MeHg causes oxidative stress in fish (Gonzalez *et al.*, 2005), which result in histopathological effects in liver and other tissues.

Cadmium (Cd) has a cumulative polluting effect and could cause serious disturbances in fish metabolism such as abnormal behavior, locomotor anomalies or anorexia (Woo et al., 1994; Bryan *et al.*, 1995). Cadmium may also affect the blood cells (Witeska, 1998). Metals interact with legends in proteins particularlty, enzymes and may inhibit their biochemical and physiological activities.

Lead (Pb), a non-beneficial and nonessential heavy metal to animals is capable of causing hypertension, atherosclerosis, nephropathy, hepatopathy, neuropathy and neoplasia among mammals (DeMayo *et al.*, 1982). Alter the hematological system by inhibiting the activities of several enzymes involved in heme biosynthesis. Once absorbed, it is distributed particularly to the liver, kidney, heart and male gonads as well as it affect the immune system (ATSDR, 2005)

Arsenic (As) exerts its toxic effects through an impairment of the cellular respiration by inhibition of various mitochondrial enzymes, and the uncoupling of oxidative phosphorylation. Arsenic toxicity results from its ability to interact with sulfahydryl groups of proteins and enzymes to substitute phosphorous in a variety of biochemical reactions (Patlolla *et al.*, 2005).

Chromium (Cr) exists in different oxidation states which have distinct biological effects (Richard, 1991). Hexavalent chromium [(Cr VI)] is a well known carcinogen metal form for animals and human beings. Cr at higher concentrations is mutagen, teratogen, and carcinogen (Sala *et al.*, 1995).

**Heat shock protein expression in Fish**

The heat shock proteins (HSPs) are a family of highly conserved and ubiquitous intracellular molecules that are critical for cellular functions in unstressed as well as in stressed cells (Kregel, 2002). In unstressed condition, heat shock proteins have constitutive function in protein metabolism (Morimoto *et al.*, 1994; Hightower *et al.*, 1999). Heat shock protein activation is triggered by the heavy metals in fish. Increased levels of various Hsps have been measured in tissues of fish exposed to several metals such as copper, zinc and mercury and arsenite. The functions of Hsps affect various aspects of fish physiology, including development and aging, stress physiology and endocrinology, immunology, environmental physiology, stress tolerance and acclimation (Basu *et al.*, 2003). Families of heat shock protein are classified based on their molecular mass (kDa). Heat shock proteins are also grouped according to function (e.g. chaperonin), DNA sequence, and antibody cross-reactivity (Morimoto *et al.*, 1994). Fish HSP has various functions and can reside in various locations within the cell (Table 2).

**Table 3.** HSP locations in Humans and its specific functions.

| HSP in humans | Chaperone members | Cellular compartments | Functions |
|---|---|---|---|
| HSP 100 | HSP 104 | cytoplasm | Thermotolerance |
| HSP 90 | HSP90<br>Grp94 | Cytoplasm<br>endoplasmic reticulum | Stabilize inactive forms of certain hormone receptors until hormone is present; interact with certain protein kinases to assist their transmit to plasma membranes; prevent aggregation of denatures proteins |
| HSP 70 | HSC70<br>HSP70<br>BipGRP78<br>Grp75 | cytoplasm/nucleus<br>cytoplasm/nucleus<br>ER<br>mitochondria | stabilize prefolded/ unfolded structures for translocation/folding; assembly of immunoglobins; target aged proteins to lysosomes for degradation; protein secretion; antigen presentation; thermo tolerance; interaction with certain immune suppressants |
| HSP60 | Hsp60 | mitochondria | stabilize prefoled structures for folding/ assembly; re-export of precursors to membrane space |
| HSP40 | HSP 40 | mitochondria<br>cytoplasm/nucleus | chaperone activity; essential co-chaperone activity with HSP70 to enhance ATPase rate and substrate release |
| Small HSP | HSP27<br>αA and αB crystallins | cytoplasm<br>cytoplasm | prevents polypeptide aggregation; thermotolerance through stabilization of microfilaments; possible roles in cell growth |

**Heat shock proteins response to heavy metals in fishes**

Heat shock proteins (Hsps) play an important role in protein homeostasis and cellular stress response within the cell (Multhoff, 2007; Keller *et al*., 2008). Currie and Tufts (1997), first suggested that Hsp70 in rainbow trout is regulated primarily at the level of transcription. Subsequently Airaksinen *et al*. (1998), reported that an HSF1-like factor was involved in the induction of hsp70 mRNA in rainbow trout. Hsp70 has been cloned from rainbow trout (Kothary *et al*., 1984), medaka (Arai *et al*., 1995), zebrafish (Lele *et al*., 1997), tilapia (Molina *et al*., 2000), and pufferfish (Lim and Brenner, 1999).

Environmental contaminants also elicit HSP expression in primary cultures. Environmental contaminants such as heavy metals, BKME, SDS and BNF all have been shown to induce HSP70 in fish tissues. Juvenile rainbow trout exposed to metals in the water or feed. This showed increased levels of HSP70 in the gill tissue (Williams *et al*., 1996). Comprehensive studies such as chinook salmon embryonic cell line- CHSE-214 (Gedamu *et al,* 1983; Misra *et al,* 1989), rainbow trout gonadal cell line- RTG-2 (Mosser and Bols, 1988), and rainbow trout hepatoma cell line -RTH-149 (Misra *et al,* 1989; Heikkila *et al,* 1982) have all shown increased expression of various Hsps in response to metal exposure.

**Toxic effects of heavy metals in humans**

Heavy metals are dangerous because they tend to bioaccumulate in vital organs. Trace elements such as copper, zinc and selenium are essential to maintain the metabolism of the human beings. Heavy metals such as Hg, Cd, Ni, As, Pb pose a number of hazards to humans. Humans are exposed to these metals by ingestion (drinking or eating) or inhalation (breathing). At higher concentrations this heavy metals lead to poisoning.

These metals are also potent carcinogenic and mutagenic. The high concentration intake of cadmium cause itai ita disease and mercury intake lead to minamita disease.

Copper is also essential for numerous enzymes and is a constituent of hair and of elastic tissue contained in skin, bone and other body organs. There are a number of important copper-containing proteins and enzymes, some of which are essential for the proper utilization of iron. Increase in copper ions inhibits synthesis of macromolecules and other enzymatic reactions (Company *et al.* 2004).

Nickel is believed to play a role in physiological processes as a co-factor in the absorption of iron from the intestine. The metal is not only anallergen but also a potential immunomodulatory and immunotoxic agent in humans (Das KK and Buchner, 2008). An increase in structural malformations was observed in infants of women who worked in a nickel hydrometallurgy refining plant 89 Nickel compounds are potent carcinogens and can induce malignant transformation of rodent and human cells. Inflammation in the bronchioles, alveolar congestion, alveolar cell hyperplasia, and sometimes congestion in the lumen was also noticed Inflammation in the bronchioles, alveolar congestion, alveolar cell hyperplasia, and sometimes congestion in the lumen was also noticed (Gupta *et al*., 2006).

Zinc is involved in numerous body functions, including enzymes involved in gene expression. Zinc also taking role in electrone transfer. Excessive intake may lead to toxic effect such as carcinogenesis, mutagenesis and teratogenesis as a result of its bioaccumulation.

Selenium is an essential trace nutrient. Selenium plays a role in the element functioning of the thyroid gland. Short-term oral exposure to high concentrations can cause nausea, vomiting, and diarrhea. Chronic oral exposure to high concentrations can produce selenosis. Major signs of selenosis are hair loss, nail brittleness, and neurological abnormalities (Sabine Martin and Wendy Griswold, 2009).

Mercury permanently damages the brain, kidneys, and developing fetuses. The nervous system is very sensitive to all forms of mercury. Effects on brain functioning may result in irritability, shyness, tremors, changes in vision or hearing, and memory problems. Short-term exposure to high levels of metallic mercury vapors may cause lung damage, nausea, vomiting, diarrhea, increases in blood pressure or heart rate, skin rashes, and eye irritation (Sabine Martin and Wendy Griswold, 2009). High intake of mercury lead to minamita disease

Cadmium is a known human carcinogen. Ingesting high levels severely irritates the stomach, leading to vomiting and diarrhea. Long-term exposure cadmium leads to a possible kidney disease, lung damage, and fragile bones (Sabine Martin and Wendy Griswold, 2009). The high concentration intake of cadmium cause itai itai disease

Lead severely damages the brain and kidneys and ultimately causes death. In pregnant women, high levels of exposure to lead may cause miscarriage. High level exposure in men can damage the organs responsible for sperm production (Sabine Martin and Wendy Griswold, 2009).

Arsenic is a known carcinogen. It can cause cancer to skin, lungs, liver and bladder. Lower level exposure can cause nausea and vomiting, decreased production of red and white blood cells, abnormal heart rhythm, damage to blood vessels and a sensation of pins and needles in hands and feet (Sabine Martin and Wendy Griswold, 2009).

Chromium compounds are toxins and are known human carcinogens. Breathing high levels can cause irritation to the lining of the nose; nose ulcers; runny nose; and breathing problems, such as asthma, cough, shortness of breath, or wheezing (Sabine Martin and Wendy Griswold, 2009).

**Heat shock protein expression in Humans:**

An important cellular alteration induced by heavy metal stress involves the synthesis of heat-shock proteins (HSPs). Heat shock proteins are important components of cellular networks. The dramatic up regulation of the heat shock proteins is a key part of the heat shock

response. It induced primarily by heat shock factor (HSF) (Wu C 1995). Heat shock proteins (hsps) are a family of highly conserved proteins playing an important role in the functioning of unstressed and stressed cells (Parsell and Lindquist, 1993). Heavy metal stresses usually give rise to dysfunctional protein conformations. Heat shock protein functions as molecular chaperone and crucial for protein functioning, facilitate protein refolding and stabilize polypeptides, intracellular localization, regulation, secretion, and protein degradation (Fink, 1999). It also functions as biochemical regulator to mediate cell growth, apoptosis, protein homeostasis and cellular targets of peptides. Each HSP has many documented functions and can reside in various locations within the cell (Table:3).

**Heat shock proteins response to heavy metals in humans**

Heavy metals cause changes in the pattern of cellular stress protein expression referred to as HSPs. Wagner *et al.*, (1999), compared the induction of heat shock proteins (HSPs) by heat and heavy metal ions in three different endothelial cell types. Human umbilical vein endothelial cells, human pulmonary microvascular endothelial cells, and the cell line EA.hy 926. Results showed that $Zn^{2+}$ and $Cd^{2+}$ are inducers of 70-kDa (HSP70), 60-kDa (HSP60), 32-kDa (HSP32), and 27-kDa (HSP27) HSPs. The strength of inducibility is specific for each HSP. $Ni^{2+}$ and $Co^{2+}$ only show an inducible effect at very high concentrations.

Heavy metals may exert their acute and chronic effects on the human skin through stress signals. 2DE-based proteomics was used to analyze the protein expression in human keratinocytes. This exposed to heavy metals-chromium and neodymium. 10 proteins with altered expression were identified. Among these proteins, small heat shock protein 27 (HSP27) was up-regulated significantly and the up-regulation was validated by Western blot and immunofluorescence. The mRNA expression level of HSP27 increased as detected by quantitative PCR. The ratio of phosphorylated HSP27 and total HSP27 significantly decreased in keratinocytes treated with the heavy metals. These findings suggested that heavy metals reduced the phosphorylation level of HSP27, and that the ratio of p-HSP27 and HSP27 may represent a potential marker or additional endpoint for the hazard assessment of skin irritation caused by chemical products Zhang *et al.*, (2010).

This review concludes that both essential and non essential heavy metals can lead to toxicity of living organisms. The toxicity result from the binding of metals to sulphydryl groups in proteins, leading to an inhibition of activity or disruption of structure. Heat shock proteins are the only molecular mechanisms that living organisms adopt to tolerate heavy metal stress, and these proteins have pleiotropic effects, interacting with multiple systems in diverse ways regulated by the endocrine system. Heat shock proteins are important in relation to heavy metal stress resistance and adaptation to the environment. Heat-shock proteins play an important role in regulating a range of effect or components, all of which contribute to survival under heavy metal stress by solving the problem of misfolding and aggregation, as well as its role as chaperones.

**References**

**Airaksinen S, Rabergh CMI, Sistonen L, Nikinmaa M.** 1998. Effects of heat shock and hypoxia on protein synthesis in rainbow trout (*Oncorhynchus myk*iss) cells. Journal of Experimental Biology **200**,2543- 2551.

**Ambrose T, Vincent S, Cyril L.**1994. Susceptibility of the freshwater fish, Gambusia affinis (Baird and Giard), Sarotherodon mossambicus (Peters) and Cirrhinus mrigala (Ham.) to zinc toxicity. J. Environ. Toxicol **4**,29-31.

**Arai A, Naruse K, Mitani H, Shima A.** 1995.Cloning and characterization of cDNAs for 70- kDa heat shock proteins (Hsp70) from two fish species of the genus Oryzias. Japanese Journal of Genetics **70**,423–433.

**ATSDR.** 2005. Draft toxicological profile for lead, US Department of health and human services. Atlanta, Georgia, USA, 102 – 225.

**Barque JP, Abahamid A, Chacun H, Bonaly J**. 1996. Different heat-shock proteins are constitutively overexpressed in cadmium and pentachlorophenol adapted *Euglena gracilis* cells. Biochemical and Biophysical Research Communications **223**,7-11.

**Basu N, Kennedy CJ, Iwama GK.** 2003. The effects of stress on the association between Hsp70 and the glucocorticoid receptor in rainbow trout. Comparative Biochemistry and Physiology **134**,655-663.

**Bryan MD, Atchison GJ, Sandheinrich MB**. 1995. Effects of cadmium on the foraging behavior and growth of juvenile bluegill, Lepomis macrochirus. Can. J.Fish. Aquat. Sci **52**, 1630-1638.

**Coen N, Mothersill C, Kadhim M, Wright EG.** 2001. Heavy metals of relevance to human health induce genomic instability. Pathol **195**,293 -299.

**Company R, Serafim A, Bebianno MJ, Cosson R, Shillito B, Fiala-medioni A**. 2004. Effect of cadmium, copper and mercury on antioxidant enzyme activities and lipid peroxidation in the gills of the hydrothermal vent mussel *Bathymodiolus azoricus*. Mar. environ. Res **58,**377-381.

**Connell D, Lam P, Richardson B, Wu R. 1999**. Introduction to Ecotoxicology. Oxford,UK: Blackwell Science Ltd,**71**.

**Currie S, Tufts BL, Moyes CD.** 1999. Influence of bioenergetics stress on heat shock protein gene expression in nucleated red blood cells of fish. American Journal of Physiology - Regulatory, Integrative, and Comparative Physiology **276**, 990-996.

**Das KK, Buchner V.** 2007**.** Effect of nickel exposure on peripheral tissues: Role of oxidative stress in toxicity and possible protection by ascorbic acid. Rev Environ Health **22**,133-49.

**DeMayo A, Taylor MC, Taylor KW, Hudson PV.** 1982. Toxic effects of Heat-shock proteins, molecular chaperones, and the stress response: evolutionary and ecological physiology. Annu. Rev. Physiol **61**, 243–282.

**Demirevska-Kepova KL, Simova-Stoilova Z, Stoyanova R.** 2004. Biochemical changes in barley plants after excessive supply of copper and manganese. Environ Exp Bot **52**,253-66.

**Drevnick PE, Sandheinrich MB, Oris JT.** 2006b. Increased ovarian follicular apoptosis in fathead minnows (Pimephales promelas) exposed to dietary methylmercury. Aquat. Toxicol **79**, 49–54.

**Drevnick PE, Sandheinrich MB.** 2003. Effects of dietary methylmercury on reproductive endocrinology of fathead minnows. Environ. Sci. Technol **37**, 4390–4396.

**Ebbs SD, Kochian LV.** 1997. Toxicity of zinc and copper to Brassica species: implications for phytoremediation. Journal of Environmental Quality **26**, 776–781.

**Feder ME.** 2006. Integrative biology of stress: molecular actors, the ecological theater, and the evolutionary play. International Symposium on Environmental Factors. Cellular Stress and Evolution, Varanasi, India, 21.

**Fernandes C, Fontainhas- Fernendes A, Cabral D, Salgado MA.** 2008. Heavy metals in water, Sediment and tissues of Liza saliens from Esmoriz-Paramos lagoon, Portugal. Environ. Monit. Assess **136**,267-275.

**Fink AL.** 1999. Chaperone-mediated protein folding. Physiol. Rev **79**, 425–449.

**Fontes RLS, Cox FR.** 1998. Zinc toxicity in soybean grown at high iron concentration in nutrient solution. Journal of Plant Nutritio **21**, 1723–1730.

**Franca S, Vinagre C, Cacador I, Cabral HN.** 2005. Heavy metal concentrations in sediment, benthic invertebrates and fish in three salt marsh areas

subjected to different pollution loads in the Tagus Estuary (Portugal). Marine Pollut. Bull **50**,993-1018.

**Ganther HE.** 1999. Selenium metabolism, selenoproteins and mechanisms of cancer prevention: complexities with thioredoxin reductase. Carcinogen **20(9)**,1657-1666.

**Gedamu L, Culham B, Heikkila JJ.** 1983. Analysis of the temperature-dependent temporal pattern of heat-shock protein synthesis in fish cells. Biosci. Rep **3,** 647-658.

**George K, Iwama, Philip T, Thomas, Robert B, Forsyt H, Mathilakath M, Vijayan.** 1998. Heat shock protein expression in fish. Reviews in Fish Biology and Fisheries **8**, 35-56.

**Gonzalez P, Dominique Y, Massabuau JC, Boudou A, Bourdineaud JP.**2005. Comparative effects of dietary methylmercury on gene expression in liver, skeletal muscle, and brain of the zebrafish (Danio rerio). Environ. Sci. Technol **39**, 3972–3980.

**Gupta, AD, Patil AM, Ambekar JG, Das SN, Dhundasi SA, Das KK**. 2006. L-ascorbic acid protects the antioxidant defense system in nickel-exposed albino rat lung tissues. J Basic Clin Physiol Pharmacol **17**, 87-100.

**Hall JL**. 2002. Cellular mechanisms for heavy metal detoxification and tolerance. Journal of Experimental Botany **53**, 1-11.

**Hallare AV, Kohler HR, Triebskorn R**. 2004. Developmental toxicity and stress protein responses in zebrafish embryos after exposure to diclofenac and its solvent, DMSO. Chemosphere **56**, 659-666.

**Hamilton III EW, Heckathorn SA.** 2001. Mitochondrial adaptations to NaCl stress: Complex I is protected by anti-oxidants and small heat shock proteins, whereas Complex II is protected by proline and betaine. Plant Physiology **126**, 1266–1274.

**Han FX, Su Y, Monts DL, Waggoner AC, Plodinec JM.** 2006. Binding, distribution, and plant uptake of mercury in a soil from Oak Ridge, Tennessee, USA. Science of the Total Environment **368**, 753–768.

**Heikkila JJ, Schultz GA, Iatrou K, Gedamu L.** 1982. Expression of a set of fish genes following heat or metal ion exposure. J. Biol. Chem **257**, 12000-12005.

**Hightower LE, Norris CE, Dilorio PJ, Fielding E.** 1999. Heat shock responses of closely related species of tropical and desert fish. American Zoologist **39**, 877-888.

**Holden PR.** 2000. Toxic mechanisms mediated by gene expression. In: Roberts, R.A. (Ed.), Apoptosis in Toxicology. Taylor and Francis, London, 187–211.

**Ibok UJ, Udosen ED, Udoidiong OM. 1989.** Heavy metals in fishes from some streams in Ikot Ekpene area of Nigeria. **Nig. J. Tech. Res 1, 61-68.**

**Israr M, Sahi S.** 2006. Antioxidative responses to mercury in the cell cultures of *Sesbania drummondii*. Plant Physiology and Biochemistry **44**, 590–595.

**Keller JM, Escara-Wilke F, Keller ET.** 2008. Heat stress-induced heat shock protein 70 expression is dependent on ERK activation in zebrafish (*Danio rerio*) cells. Comparative Biochemistry and Physiology (Part A) **150**, 307-314.

**Kopsell DA, Randle WM.** 1997b. Short-day onion cultivars differ in bulb Se and S accumulation which can affect bulb pungency. Euphytica **96**,385–390.

**Kothary RK, Burgess EA, Candido EPM.** 1984. The heat shock phenomenon in cultured cells of rainbow trout: Hsp70 mRNA synthesis and turnover. Biochimica et Biophysica Acta **783**,137-143.

**Kregel KC.** 2002. Invited review: Heat shock proteins: Modifying factors in physiological stress responses and acquired thermotolerance. J Appl Physiol **92(5),** 2177-2186.

**Lele Z, Engel S, Krone PH.** 1997. Hsp47 and Hsp70 gene expression is differentially regulated in a stressand tissue specific manner in zebrafish embryos.Developmental Genetics **21**,123-133.

**Levitt J. 1980.** Responses of Plants to Environmental Stresses: Water, Radiation, Salt and Other Stresses. vol. II. Academic Press Inc, New York, London.

**Lide D. 1992**. Selected values of chemical thermodynamic properties.CRC Handbook of Chemistry and Physics, 73rd. Boca Raton, FL: CRC Press, **270**(1-8).

**Lim EH, Brenner S.** 1999. Short range linkage relationships, genomic organization and sequence comparisons of a cluster of five Hsp70 genes in *Fugu rubripes*. Cellular and Molecular Life Sciences **55**,668-678.

**Lindquist S, Craig EA**. **1988**. The heat shock proteins. Annual Review of Genetics **22**, 631-677.

**Lindquist S. 1986.** The Heat Shock Response. Annual Review of Genetics **55**, 1151-1191.

**Maity S, Roy S, Chaudhury S, Bhattacharya S.** 2008. Antioxidant responses of the earthworm Lampito mauritii exposed to Pb and Zn contaminated soil. Environ. Pollut **151**,1-7.

**Meharg AA.** 1994. Integrated tolerance mechanisms – constitutive and adaptive plant - responses to elevated metal concentrations in the environment. Plant Cell Environ **17**, 989–993.

**Mengel K, Kirkby EA. 1987.** Principles of Plant Nutrition. International Potash Institute. Bern, pp: 687.

**Misra S, Zafarullah M, Price-Haughey J, Gedamu L.** 1989. Analysis of stress-induced gene expression in fish cell lines exposed to heavy metals and heat shock. Biochim. Biophys. Acta **1007**, 325-333.

**Mohanpuria P, Rana NK, Yadav SK.** 2007. Cadmium induced oxidative stress influence on glutathione metabolic genes of Camellia sinensis (L.) O. Kuntze. Environmental Toxicology **22**, 368–374.

**Molina A, Biemar F, Muller F, Lyengar A, Prunet P, Maclean N, Martial JA, Muller M.** 2000. Cloning and expression analysis of an inducible Hsp70 gene from tilapia fish. Federation of European Biochemical Societies Letters **474**,5-10.

**Morimoto RI, Tissieres A, Georgopoulos C.** 1994. The Biology of Heat Shock Proteins and Molecular Chaperones. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 155 .

**Morimoto RI**. 1993. Cells in stress: The transcriptional activation of heat shock genes. Science **259**, 1409–1410.

**Mosser DD, Bols NC.** 1988. Relationship between heat-shock protein synthesis and thermotolerance in rainbow trout ®broblasts. J. Comp. Physiol **158B**, 457-467.

**Multhoff G.** 2007. Heat shock protein 70 (Hsp70): Membrane location, export and immunological relevance. Methods **43**, 229-237.

**Nakamoto H, Suzuki N, Roy SK**. 2000. Constitutive expression of a small heat-shock protein confers cellular thermotolerance and thermal protection to the photosynthetic apparatus in cyanobacteria. FEBS Letters **483**,169-174.

**Olaifa FE, Olaifa AK, Adelaja AA, Owolabi AG.**2004. Heavy metal contamination of Clarias garpinus from a lake and fish farm in Ibadan. Nigeria. Afr. J. Biomed. Res **7**,145-148.

**Pandey N, Sharma CP.** 2002. Effect of heavy metals Co2+, Ni2+ and Cd2+ on growth and metabolism of cabbage. Plant Sci **163**, 753 -758.

**Park H, Ahn IY, Lee H**E. 2007. Expression of Hsp70 in the thermally stressed Antarctic clam *Laternula elliptica*. Cell Stres&Chaperons **12**, 275-282.

**Parsell DA, Lindquist S.** 1993. The function of heat-shock proteins in stress tolerance: degradation and reactivation of damaged proteins. Annu. Rev. Genet **27**, 437–496.

**Parsell DA, Lindquist S.** 1994. Heat shock proteins and stress tolerance. In R. Morimoto, A. Tissieres, and C. Georgopoulos ed. The biology of heat shock proteins and molecular chaperones. New York, USA: Cold Spring Harbor Press, 457-494.

**Patlolla, Anita K, Tchounwou, Paul B.** 2005. Serum Acetyl Cholinesterase as a Biomarker of Arsenic Induced Neurotoxicity in Sprague-Dawley Rats. Int.J. Environ. Res. Public Health 2**(1),** 80-83.

**Patsikka E, Kairavuo M, Sersen F, Aro EM, Tyystjarvi E.** 2002. Excess copper predisposes photosystem II to photoinhibition in vivo by outcompeting iron and causing decrease in leaf chlorophyll. Plant Physiology 129,1359-1367.

**Rahman H, Sabreen S, Alam S, Kawai S**. 2005. Effects of nickel on growth and composition of metal micronutrients in barley plants grown in nutrient solution. J. Plant Nutr **28**, 393 - 404.

**Rask M, Vuorinen PJ, Vuorinen M.**1990.Delayed spawning of perch, Perca fluviatilus (Linn.) in acidified lakes. J. Fish. Biol **36**, 317-325.

**Rayman MP.** 2000. The importance of selenium to human health. The Lancet **356**,233- 241.

**Reddy SG, Kumar G, Jyonthsnakumari S, Sudhakar C.** 2005. Lead induced changes in antioxidant metabolism of horsegram (*Macrotyloma uniflorum* (Lam.) Verdc.) and bengalgram (*Cicerarietinum* L.). Chemosphere **60**,97–104.

**Richard CF, Bourg CMA.** 1991. Aqueous geochemistry of chromium: A review. Water Res **25(7),** 807-816.

**Sabine Martin, Wendy Griswold PG.** 2009. Human Health Effects of Heavy Metals. Center for Hazardous Substance Research Kansas State University. **15**,785-532.

**Sala LF, Rizzoto A, Frascaroli MI, Palopoli CM, Signorella SR.**1995. Contamination ambiental por el metal de transition cromo. Estamos frente a un serio problema ecokjgico?. Quim Nova **18**,468-474.

**Scoccianti V, Crinelli R, Tirillini B, Mancinelli V, Speranza A.** 2006. Uptake and toxicity of Cr (Cr3+) in celery seedlings. Chemosphere **64**,1695–1703.

**Scott A, Heckathorn, Kathleen mueller J, Stephanie laguidice, Bin zhu,Tara barrett, Brian blair, Yan dong.** 2004. Chloroplast small heat-shock proteins protect photosynthesis during heavy metal stress. American Journal of Botany **91**, 1312-1318.

**Sharma A, Sharma MS**.1994. Toxic effect of zinc smelter effluent to some developmental stages of fresh water fish, Cyprinus carpio (Linnaeus). J. Environ. Biol **15**(3), 221-229.

**Sharma DC, Sharma CP, Tripathi RD** .2003.Phytotoxic lesions of chromium in maize. Chemosphere **51**, 63–68.

**Sharma P, Dubey RS.** 2004. Ascorbate peroxidase from rice seedlings: properties of enzyme isoforms, effects of stresses and protective roles of osmolytes. Plant Sci **167**, 541-550.

**Sharples JM, Meharg AA, Chambers SM, Cairney JWG.** 2000a. Mechanism of arsenate resistance in the ericoid mycorrhizal fungus *Hymenoscyphus ericae*. Plant Physiol **124,** 1327–1334.

**Stadtman ER, Oliver CN.**1991. Metal-catalyzed oxidation of proteins. J Biol Chem **266**,2005-8.

**Surai PF.** 2002. Selenium. In: Natural Antioxidants in Avian Nutrition and Reproduction. Nottingham University Press, UK,233-304.

**Surec B**.2003. Accumulation of heavy metals by intestinal helmints in fish: an overview and perspective. Parasitology **126**, 53-60.

**Thomas DJ, Avenson TJ, Thomas JB, Herbert SK.** 1998. A cyanobacterium lacking iron superoxide dismutase is sensitized to oxidative stress induced with methyl viologen but not sensitized to oxidative stress induced with norflurazon. Plant Physiology **116**, 1593–1602.

**Tuzen M.** 2003. Determination of heavy metals in fish Samples of the MidDame Lakee Black Sea (Turkey) by graphite furnace atomic absorption spectrometry. Food Chem **80**,119-123.

**Vajpayee P, Tripathi RD, Rai UN, Ali MB, Singh SN.** 2000. Chromium (VI) reduces chlorophyll biosynthesis, nitrate reductase activity and protein content in *Nymphaea alba* L. Chemosphere **41**,1075-1082.

**Van Assche F, Clijsters H.1990**. Effects of metals on enzyme activity in plants. Plant, Cell and Environment **13,**195–206.

**Vierling E. 1991**. The role of heat shock proteins in plants. Annu. Rev. Plant Phys **42**, 579–620.

**Vinit-dunand F, Epron D, Alaoui-sosse B, Badot PM.** 2002. Effects of copper on growth and on photosynthesis of mature and expanding leaves in cucumber plants. Plant Science **163**,53–58.

**Wagner M, Hermanns I, Bittinger F, Kirkpatrick CJ.** 1999. Induction of stress proteins in human endothelial cells by heavy metal ions and heat shock. Am J Physiol Lung Cell Mol Physiol **277,** L1026-L1033**.**

**Wang W, Vinocur B, Altman A.** 2003. Plant responses to drought, salinity and extreme temperatures: towards genetic engineering for stress tolerance. Planta **218**, 1–14.

**Williams JH, Farag AM, Stansbury MA, Young PA, Bergman HL, Petersen NS.** 1996. Accumulation of hsp70 in juvenile and adult rainbow trout gill exposed to metal-contaminatedwater and or diet. Env. Toxicol. Chem **15**, 1324-1328.

**Witeska M.**1998. Changes in selected blood indices of common carp after acute exposure to cadmium. Acta. Vet. Brno **67**, 289-293.

**Wojcik M, Tukiendorf A.** 2004. Phytochelatin synthesis and cadmium localization in wild type of Arabidopsis thaliana. Plant Growth Regulation **44**, 71–80.

**Woo PTK, Sin YM, Wong MK.**1994. The effects of short-term acute cadmium exposure on blue tilapia, Oreochromis aureus. Environ. Biol. Fish **37**,67- 74.

**Wu L.** 1994. Selenium accumulation and colonization of plants in soils with elevated selenium and salinity. In: W.T. Frankenberger Jr., S. Benson, eds. Selenium in the Environment. New York: Marcel Dekker 279–326.

**Zhang Q, Zhang L, Xiao X, Su Z, Zou P, Hu H.** 2010.Heavy metals chromium and neodymium reduced phosphorylation level of heat shock protein 27 in human keratinocytes. Toxico In Vitro **24**,1098-1104.

**Zhou ZS, Huang SQ, Guo K, Mehta SK, Zhang PC, Yang ZM.** 2007. Metabolic adaptations to mercury-induced oxidative stress in roots of *Medicago sativa*. L. Journal of Inorganic Biochemistry **101**, 1–9.