Cadmium toxicity and its harmful effects on human health via fish consumption

Qazi Muhammad Abuzar Iqbal[*], Aamna Shahzadi[*], Wajid Siraj[**], Sammar Sultan[*], Maryam Mazhar[***], Sundas Asghar[*]

[*] Institute of molecular biology and biotechnology, The University of Lahore, Pakistan
[**] Department of Agriculture and Agribusiness Management, University of Karachi, Pakistan
[***] Department of Psychology, Government College University, Lahore, Pakistan

Correspondence Authors email: qazi.abuzar025@gmail.com

Abstract- Modern industrialization is helping human beings in many ways by enhancing our lifestyle and comfort, but this comfort is coming at a heavy cost and that cost is the pollution. Industrial waste is dumped into different water bodies which are causing severe water pollution and damage to aquatic life particularly fish. Among water pollutants, the most dangerous pollutants are the heavy metals that are being dumped into water bodies by industries like paint, metallurgical, cigarette, fertilizers, and PVC. Cadmium (Cd) is such a heavy metal that is being produced in tons in different industries worldwide and dumped into water bodies and it settles down at the bottom. Cadmium can cause different types of cancers because it is a known carcinogenic metal. It can mimic different hormones in the human body. Cadmium is produced in industries like paint, PVC, and nickel-cadmium batteries. Fishery is a fast-growing industry that fulfills the needs of human daily protein intake worldwide and fish is a very important aquatic organism and an important part of the food chain. Fish, on the other hand, are extremely vulnerable to heavy metal pollution because of the presence of heavy metals in the water, which they consume in the form of aquatic plants, sediments, and other fish. Heavy metals can easily accumulate in the body of fish because fish is in direct contact with contaminated water and when this contaminated fish comes in contact with humans via fish consumption it can easily transfer to humans and can cause lethal effects to human health.

Keywords- Cadmium toxicity, Fish consumption, Human health, Modern industrialization.

I. INTRODUCTION

Any metallic synthetic component with a generally higher mass than water is harmful or deadly at low concentrations is referred to as heavy metal. Mercury, cadmium, chromium, and lead are some of the heavy metals that are present in the environment. Heavy metals dissolved in water are easily accessible to aquatic organisms and can have significant health consequences. Many biological systems have been harmed by the rapid growth of industry, notably the aquatic environment, which is contaminated with a diverse array of contaminants, moreover, a variety of synthetic chemicals are used in aquaculture that includes heavy metals at some point. Their inescapable application in industry and in agriculture, has spurred wider acceptance in the climate, raising worries about their possible influence on human well-being and the environment.

Cadmium (Cd):

Cadmium compounds are employed as stabilizers in PVC products, colorants, certain composites, and nickel-cadmium batteries. Many health issues are associated with the heavy metal cadmium such as renal failure, bone loss, and cancer (So *et al*., 2020; Ebrahimi *et al*., 2020). In humans, the rate of ingested cadmium retention is estimated to be 5% of total consumption. Cadmium consumption was predicted to be 25-60 micrograms/day for a 70kg person living in uncontaminated locations, although values could range from 10 to 61 micrograms per day. If the Cadmium accumulates at a higher level then it can cause chronic toxicity of the kidney, poor reproduction prospects, and body tumors (Olmedo *et al*., 2013). As per the (FAO/WHO 2002) expert panel, the Cd ingestion that is a provisional tolerated

weekly intake (PTWI) for an average adult of 70KG is 7μg/kg. Heavy metal cadmium show 2 different types of mimicry at the cellular level one is ionic and the second is molecular. In ionic mimicry, unbounded ions mimic other ions while in molecular mimicry cadmium takes place other molecular (Bridges & Zalups 2005). Molecular mimicry starts original transduction pathways which may result in cytotoxicity. The replacement of Cd^{2+} leads to the release of important metals, changes in the target molecular structure. Cadmium ion gets entry to cell via transporters and channels which are special for divalent ion like Ca^{2+}, Fe^{2+}. Production of reactive oxygen is the most common response of organisms when cadmium enters (Wang *et al*., 2011). These ROS leads to lesions and membrane breakage which leads to disturbance of homeostasis (Scandalios 2002). The overproduction of ROS due to cadmium ends up in increased NADPH oxidase and changes in mitochondria (Chou *et al*., 2012).

Acute and chronic toxicity of Cadmium:

Acute toxicity of Cadmium:

Chemical pneumonitis and pulmonary edema can result from acute exposure to cadmium fumes in welders (Yates and Goldman 1990). As a late result of acute poisoning, a Parkinsonism-like neurological condition has also been documented (Okuda *et al*., 1997).

Chronic toxicity of Cadmium:

Chronic cadmium poisoning has the greatest impact on the kidney, bones, and lungs. Toxicology studies have shown that persons exposed to cadmium fumes experience upper respiratory tract and lung symptoms, which can be likened to the symptoms of chronic bronchitis and emphysema (Hendrick 1996).

Cadmium root of exposure in humans:

Cadmium has long been applied in metallurgy. Its severe toxicity was discovered by scientists in the mid-twentieth century (Godt *et al., 2006*). When heavy metal like cadmium is dumped into rivers via different sources fish absorb them (Alamdar *et al*., 2017). Water continuously flows through the gills of fish cadmium accumulates there (Fatima & Usmani 2013). The heavy metal cadmium enters the body in 3 ways that are gastrointestinal, pulmonary, and dermal pathways.

Respiratory system:

Most of the absorption of cadmium occurs when people smoke cigarettes, which accounts for 40-60% of all inhaled cadmium. An average human who does not smoke shows a cadmium burden of 15mg at age of 50 years while the amount is twofold with the lifelong smoke which are 30mg and the cadmium exposure can cause acute respiratory distress syndrome (ARDS).

Dermal system:

There are two ways cadmium can get absorbed by skin one is by binding free cadmium ion to sulfhydryl radical of cystine in epidermal keratins and the second way is via induction and complexing with metallothionein.

Digestive system:

About 5% of the cadmium ingested is absorbed by the human body which depends on the composition of dose. The iron deficiency may also contribute towards cadmium absorption and the people having low iron levels in their bodies showed a 6% higher uptake of cadmium.

Handling of Cadmium in the body:

When cadmium enters the bloodstream, it is linked to proteins like albumin and metallothionein. First of all, it goes to the liver via blood and in the liver, this cadmium induces the assembly of metallothionein when cadmium causes hepatocyte necrosis and apoptosis, the Cd-Metallothionein complex is released into sinusoidal circulation. Cadmium that has been absorbed now reaches the entero-hepatical cycle via restoration into the biliary system in the form of Cd-Gultahione conjugates. The cadmium gets entry into the small intestine via the biliary tree when it is enzymatically degraded to Cadmium-cysteine. Cadmium has a very long half-life in the kidney and it is almost 10 years therefore accumulation in the kidney can lead to tubular cell necrosis hence recent exposure can be seen in the liver while the urinary tract shows us past exposure to cadmium. The cadmium excretes out from the body via feces and urine.

Cadmium carcinogenesis:

Cadmium's ability to induce lung cancer, toxicologists have categorized it as a human carcinogen, and the International Agency for Research on Cancer and the National Toxicology Program (NTP) confirmed it (IARC, 1993; NTP, 2000).

Occupational exposure, cadmium has been related to lung cancer, which provides the strongest evidence for cadmium's carcinogenicity in humans. The liver, pancreas, and stomach are considered problematic sites for cadmium carcinogenesis. Cadmium exposure has been linked to an increased risk of pancreatic cancer, which is the leading cause of cancer death in affluent countries (Schwartz and Reis 2000). Cadmium can generate a variety of molecular lesions in several cellular model systems that are relevant to oncogenesis. Oncogene activation and cell death suppression may be the primary mechanisms through which cadmium affects cells, according to the majority of research (Waalkes 2003). One of the ways cadmium contributes to the genotoxicity of other substances is by suppressing DNA repair processes. Cadmium's effect on E-cadherin cell-cell adhesion may be a factor in the development of cancer (Waisberg *et al*., 2003).

Initiation of apoptosis:

It has been demonstrated that cadmium cause apoptosis in rat organs in-vivo (programmed cell death) (Xu *et al*., 1996), together with several cell systems from other mammalian species (Lohmann and Beyersmann, 1993). C6 rat glioma cells and leukemia cells treated with cadmium showed activation of caspase-9, which is associated with apoptosis, in response to cadmium treatment. (Kondoh *et al*., 2002). Apoptosis in normal human lung cells, on the other front, is triggered by cadmium, but this process is triggered by mitochondria and is not dependent on caspase activation (Shih *et al*., 2003). The antiapoptotic protein Bcl-2's defense against cadmium-induced apoptosis provides more evidence for mitochondrial mediation (Biagioli *et al*., 2001) and cadmium's activation of the proapoptotic protein Bax in primary epithelial lung cells (Lag *et al*., 2002).

Inhibition of DNA repair:

Key mechanism contributing to cadmium's genotoxicity is the suppression of DNA repair (Hartwig and Schwerdtle, 2002). There are several ways evolved by organisms to repair DNA damages caused by endogenous and exogenous (genotoxic substances or radiation). Base-excision repair is slowed in mammalian cells by modest concentrations of cadmium, which does not cause oxidative base changes (Dally and Hartwig, 1997). Cadmium interfered with the earliest phase of the repair process, namely the incision at the DNA lesion, preventing the removal of UV-irradiated thymine dimers. At modest dosages, zinc restored the ability of repair proteins to selectively bind to damaged DNA. Cadmium's direct mutagenicity is quite mild, but it may be enough to cause cancers when combined with other unfavorable effects induced by this metal. Replication mistakes, other mutagenic substances, or oxidative reactions caused by cadmium interference with antioxidative enzymes might lead to gene mutations. Furthermore, by inducing proto-oncogenes, cadmium may boost the proliferation of cells with essential gene mutations, hence encouraging carcinogenesis in a multi-stage paradigm.

Cadmium in estrogen mimicry and ovarian cancer:

Fibroids and leiomyomas make for around 95 percent of all benign uterine neoplasms in women over 30. A monoclonal tumor derived from the intrauterine vascular system or myometrium itself is referred to as a myometrial tumor. In most cases, fibroid growth is slow and its neoplastic potential is unclear. Myometrium cells express the estrogen receptor (ER) and progesterone receptor (PR) to identify the effects of steroid hormones on fibroid development (Maruo *et al*., 2004). Cadmium, a known carcinogen, has lately been found to display estrogen-like qualities and to be an endocrine disruptor (Brama *et al*., 2007). In an in-vitro investigation, (Brama *et al*., 2007) and (Choe *et al*., 2003) found that cadmium had an estrogenic effect, although (Silva *et al*., 2006) said divergent cadmium impacts outcomes are most likely due to variation in cadmium concentrations employed in the in-vitro experiments.

Cadmium and breast cancer:

Toxins such as cadmium and nickel have been linked to breast cancer growth by attaching to estrogen receptors and emulating the actions of estrogen. Any substance that mimics the effects of estrogen, which is a proven risk factor for breast cancer, would virtually certainly induce the disease. Breast cancer is due to the process of bioaccumulation of heavy metals which interfaces with normal function of hormones. Cadmium duplicates the functions of estrogen, which makes them endocrine disruptors. Breast cancer is amplified by the combination of cadmium and estrogen. Exposure to 2.5M cadmium for 40 weeks resulted in the transformation of normal human breast epithelial cells MCF–10A into basal-like cells (Benbrahim–Tallaa *et al*., 2009).

Role of Cadmium in prostate cancer:

There is significant evidence to support the hypothesis that cadmium may directly affect the human prostate epithelium in-vitro, indicating that the metal's carcinogenic effects may directly affect human prostate epithelial cells. Prostate cancer is induced by a variety of etiological variables, including selenium, lycopene, vitamin D, and cadmium exposure. Nonsmokers are more likely to be exposed to cadmium through food but by smoking cigarette cadmium is greatly absorbed about 50% as compared to a food source. International Agency of Research on Cancer (IARC) in 1993 termed the cadmium & cadmium based compounds as carcinogens so when LNCaP was exposed to cadmium, there was a 2.4-fold increase in the number of dividing cells on day 4, and a 2.7-fold rise on day 8 (Martin *et al*., 2002).

Cadmium in bone deformities:

Cadmium ingestion has a serious impact on bone metabolism. Apoptosis and differentiation are crucial in Cd-induced osteoporosis. Cd-induced chondrocyte destruction may be linked to the development of osteoarthritis (OA). Cadmium toxicity to teeth is largely concerned with the formation of enamel and the development of dental cavities. As a result, cadmium poisoning has the greatest impact on bone cell activity and tooth formation. Osteoporosis, osteoarthritis, and osteomalacia have been related to exposure to cadmium, a common environmental toxin. Bone marrow mesenchymal stem cells (BMSCs) are inhibited by cadmium, which directly increases BMSC (Bone marrow mesenchymal stem cells) apoptosis. Cadmium predominantly affects osteoclast activation and bone resorption in osteoporosis. DNA damage and mitochondrial malfunction result from Cd-induced osteoblast injury, and endoplasmic reticulum stress cause cell death in the cells they are in (Ma *et al*., 2021). Cadmium poisoning has been classified as "Itai-Itai" disorder (Inaba *et al*., 2005), which is characterized clinically by neuralgia, bone pain, mobility problems, and respiratory discomfort. In the last stages of the condition, bone fragility, degeneration, malformed limbs, spinal deformity, weak bones, and even coughing can cause fractures (Järup *et al*., 1998).A common side effect of cadmium toxicity is osteoporosis; however, it was previously thought that cadmium toxicity on bones was indirect since it accumulates in the kidneys after entering blood circulation, causing damage to the kidneys and impairing vitamin D activity, which prevents normal calcinations and storage in bone, ultimately leading to osteoporosis (Uchida *et al*., 2010).

Bone marrow mesenchymal stem cells (BMSCs) and Cadmium toxicity:

Addition to being able to grow into osteoblasts (Hu *et al*., 2018), adipocytes (Lu *et al*., 2015), and chondrocytes (Gao *et al*., 2020), BMSCs are also effective for controlling inflammatory response and promoting tissue regeneration (Gao *et al*., 2020). Osteoblasts, the cells responsible for bone tissue metabolism and remodeling, cannot function normally without BMSCs (Mehranjani and Mosavi 2011). One cause of osteoporosis is environmental cadmium exposure (Lv *et al*., 2017). Osteoblast generation might be hindered if BMSC viability drops, further impeding bone growth. In the end, long-term exposure to cadmium (0.75–2 M) reduced BMSC cell survival and bone matrix calcification (Mehranjani and Mosavi 2011). Researchers discovered that cadmium inhibited osteoblast differentiation of BMSCs while boosting adipocyte differentiation (Rodrguez and Mandalunis 2016). Cadmium (3–14 M) triggered BMSC mortality via forkhead box O3 (FOXO3a)-dependent autophagy, which was unexpected (Yang *et al*., 2016). This might be exploited to develop a treatment for Cd-induced bone toxicity, as demonstrated by the work of (Pi *et al*., 2019), cadmium also trigger autophagy in BMSCs through modulating the PPP3/calcineurin-AKT-TFE3 signaling pathways. At different concentration levels, and for short and long durations, cadmium has a significant impact on BMSC function (Ma *et al*., 2020) as a result, BMSCs are extremely vulnerable to cadmium poisoning.

Cadmium toxicity toward chondrocytes:

For cartilage tissue and bone metabolism to function properly, chondrocytes, the only living components of cartilage, must be present (Ortega *et al*., 2004). Even though bone growth is directly linked to chondrocyte proliferation and differentiation, extracellular matrix secretion serves as a platform for osteoblast-mediated bone growth (Kronenberg 2003). Articular cartilage degeneration, the production of osteophytes, hyperosteogeny and hypertrophy, and bone remolding in the subchondral bone are all hallmarks of osteoarthritis (OA) (Bozkurt and Bagcier 2020). A recent study found that exposing synovial and chondrocytes to 3M cadmium chloride for 12 hours dramatically reduced their viability (Fernández-Torres

et al., 2020). A similar effect on the absorption ratios of essential trace elements by articular cartilage was shown by (Martinez-Nava *et al.*, 2020), who hypothesized that cadmium exposure might hasten cartilage degeneration, as a result, the significance of cadmium in the development of OA may be exaggerated. Exposure to cadmium (5M) enhanced the expression of enzymes linked to articular cartilage breakdown while decreasing the expression of collagen type II alpha 1 chain (COLl2A1) and aggrecan, as well as glycosaminoglycans. This suggests that cadmium's cytotoxicity may influence the development of osteoarthritis.

Cadmium in Renal Toxicity:

It is the kidney that is most affected by long-term exposure to cadmium and its toxicity. The renal proximal tubule filters free cadmium and metallothionein-bound cadmium (Cd-MT), resulting in receptor-mediated endocytosis in the kidney. Endosomes and lysosomes release free Cd2+ into the cytoplasm, which can lead to ROS production and cell death. The development of chronic kidney disease may be influenced by cadmium exposure when other co-morbidities such as diabetes or hypertension are present; hence, actions to reduce cadmium exposure require more attention (Johri *et al.*, 2010). In the proximal tubule, megalin-dependent, receptor-mediated endocytic uptake is the way through which both b2M and RBP are entirely reabsorbed (Wolff *et al*., 2006). Urine with b2M and RBP levels are a fairly sensitive signs of proximal tubular cell failure. The existence of elevated levels of b2M in the bloodstream may also lead to an increased urinary b2M concentration, which can be caused by a variety of non-renal conditions, these include cancers, amyloidosis, and autoimmune diseases such as rheumatoid arthritis, where the presence of high b2M concentrations in the bloodstream can lead to an increased urinary b2M concentration (Davey and Gosling 1982), consequently, RBP is seen as a more precise biomarker for proximal tubular dysfunction.

Importance of fish and transfer of Cadmium from fish to humans:

The fisheries sector is playing a critical role in addressing the food crisis by providing an abundant source of protein along with very important nutrients like omega-3 fatty acid, and different important vitamin & mineral-like Vitamin-D, zinc, iron, etc. About 25% of the population in third world countries suffers from hunger and medical problems, making fish flesh an ideal dietary source and solution to food-related problems as fish is the best source of different nutrients which are very important to human health but due to industrial waste production, this natural resource is not good for humans. Toxic heavy metals accumulate in fish's bodies due to their increasing usage in industry across the world (Chezhian *et al*., 2010). Heavy metal's environmental concern is the long-term persistence of metals in water because of their nonbiodegradability and ability to accumulate in the body (Gupta *et al*., 2015). Metal gets entry in fish via the surface of the gills (water contact) and the gastrointestinal system (food exposure) (Ptashynski *et al*., 2002). Pollutants from industry alter the chemistry of water, causing aquatic biota to suffer. Heavy metals interact with the aquatic biota in either a synergistic or antagonistic manner and may reduce biotic diversity in some situations. Heavy metals levels that are toxic can be found in agricultural, industrial, and mining operations these pollutants are harmful to fish, and their presence raises concerns about their influence on human health. Fish are remarkable bioindicators of the aquatic climate's ecotoxicological state due to their ability to gather persistent toxins. Fish and other aquatic species tend to acquire heavy metals and other contaminants because aquatic reservoirs are generally contaminated with them and when these contaminated fish are ingested by humans, they cause major health problems in the humans. Liver, kidney, gills, and body tissue of fish can be found to contain elevated amounts of heavy metals (Adhikary *et al*., 2019). Heavy metals that are ingested by fish can be transported by the blood to various organs, such as the liver, gills, kidneys, body tissue etc (Dural 2007). Metal accumulation in different fish types is caused by membrane permeability, which varies by species as a result, different fish species have varying amounts of metal deposited in their bodies (Kousar *et al*., 2014). Metal-contaminated fish is responsible for about 90% of the human health concerns associated with fish-eating (Demirak *et al.*, 2006). More than a dozen heavy metals including cadmium and chromium cause kidney failure, genotoxicity, hypertension, and infertility in humans (Al-Busaidi *et al*., 2011).

II. CONCLUSION

Heavy metals are being discharged into aquatic bodies by different industries like paint, metallurgy, fertilizers, cigarettes, etc and because fish is a source of protein and omega 3-fatty acids, it has great importance in the human diet and fish is a very important component of a food web. Cadmium is a heavy metal that is being used in the paint industry, nickel-cadmium batteries, PVC, these industries are dumping their waste in aquatic bodies without any processing. Cadmium is also produced while cigarette smoking so it is air exposure also. Heavy metals settle down in the river, canals, etc, and come to contact with fish via gills and feed. Cadmium can gain entry into the human body via 3 ways; Respiration, Dermal, and Digestion. Cadmium is nominated as a carcinogen by different organizations worldwide. Cadmium toxicity can have acute as well as chronic effects and it depends on the amount and time of exposure. Cadmium can cause different types of cancers like breast cancer, renal cancer, prostate cancer, and bone cancer. Cadmium enters the respiratory system and can cause acute respiratory distress syndrome (ARDS). Cadmium is a category-1 carcinogen it can induce apoptosis and inhibition of DNA repair. Cadmium can also mimic the estrogen hormone and can cause ovarian cancer and breast cancer. Exposure to cadmium can also lead to a deadly disease of prostate cancer. Chronic cadmium exposure has a detrimental impact on the kidney due to the receptor-mediated endocytosis of Cd-MT in the renal proximal tubule. Humans consume fish for taste as well as for nutrients like protein then heavy metals can easily gain entry into the human body. This is an alarming situation for human health as well as for aquatic life. Waste water from the industry should be treated before dumping into the aquatic bodies so that health risk can be minimized for fish as well as for humans.

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AUTHORS

First Author – Author name, qualifications, associated institute (if any) and email address.
Second Author – Author name, qualifications, associated institute (if any) and email address.
Third Author – Author name, qualifications, associated institute (if any) and email address.

Correspondence Author – Author name, email address, alternate email address (if any), contact number.