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## Food chain exposure to heavy metals (cadmium and arsenic), effects on Plasma, tissue triglyceride concentration, experimental rats, a model study

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### Abstract

This study determined the effect of cadmium and arsenic acid containing diet on plasma and tissue triglyceride concentration using albino rats as model, monitoring its effect on body weight, organ/body weight ratio, respectively. Twenty eight albino rats weighing 150 - 200g were used for the study. Diets containing cadmium or arsenic significantly decreased ( $P > 0.05$ ) the body weight gain of rats. No significant difference ( $P > 0.05$ ) was observed in the liver/body weight ratio of rats in all the experimental groups. Significant change was not observed in the kidney or heart to body weight ratio in all the experimental groups. A significant increase was observed in plasma triglyceride level in rats fed cadmium containing diet as compared to the control group but no significant change was observed in plasma triglyceride of rats fed either arsenic or arsenic plus cadmium in diet. The liver triglyceride of the rats shows a significantly ( $P < 0.05$ ) increase relative to control in rats fed cadmium, arsenic and cadmium plus arsenic. A similar trend was observed in the heart of rats fed with cadmium and arsenic as the tissue glyceride was significantly increased as compared to control. Parallel analysis in the kidney shows significant ( $P < 0.05$ ) increase in triglyceride concentration in rats fed cadmium and cadmium plus arsenic containing diet. However, no significant change was observed in those fed arsenic-containing diet relative to control. Importantly, the study, contribute to the toxicity of these metals and brings to the fore, role of food chain in mammals exposure.

**Keywords:** Cadmium, Arsenic, heavy metals, pollution, food contamination

### 1. Introduction

Cadmium (Cd) is a relatively rare element that occurs naturally in ores together with zinc, lead and copper or is emitted into the air through the process of volcanic emission. It lies between zinc and mercury in the periodic table with atomic number 48. It became commercial in the 20<sup>th</sup> century due to agricultural and industrial applications (WHO, 2000; Jarup, 2003) [52, 21].

Occupational exposure to cadmium, such as working with cadmium containing pigment, glass, metal alloys and electrode material in nickel-cadmium batteries, and non-occupational exposure such as food, water cigarette smoke induces uptake of cadmium from the environment into the body through pulmonary and enteric pathways (Warsberg *et al.*, 2003) [49]. Cadmium has no known biological function in higher organisms, however, a cadmium-dependent carbonic anhydrase has been found in marine diatoms (Roman, 2010) [36]. Cadmium absorbed and accumulates mainly in the kidney and liver, and then it is bound to the apoprotein metallothionein (Morales *et al.*, 2006) [29].

According to Koizumi *et al.* (1991) [26]. Cadmium toxicity has a chronic effect on the sodium molybdate cofactor of sulphite oxidase in mammals. The intracellular release of cadmium is responsible also for the generation of reactive oxygen species, glutathione depletion, lipid peroxidation, protein cross-linking, DNA damage, culminating ultimately in oxidative-induced cell death (Brennan, 1996, shaikh *et al.*, 1999, Jurezuk *et al.*, 2004; Babu *et al.*, 2006) [10, 41, 23, 5]. Some components of cadmium include cadmium carbonate, cadmium sulphite cadmium oxide etc.

Cadmium has been shown to decrease the activity of some drugs metabolizing enzymes such as cytochrome p450-dependent mono-oxygenase system by decreasing the concentration of cytochrome p450 and cytochrome 5 and inhibiting the activity of their corresponding reductase (Frias *et al.*, 2008; Plewka *et al.*, 2004) [16, 35]. Arsenic is a metalloid. It is rarely found as a free element in the natural environment, but more commonly as a component of sulphur-containing

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ores in which it occurs as metal arsenide. Arsenic occurs in natural waters in oxidation states iii and v, in the forms of arsenous acid ( $H_3AsO_3$ ) and its salts, and arsenic acid ( $H_3AsO_5$ ) and its salt, respectively (Sawyer *et al.*, 2003) [40].

The toxic effects of arsenic depend specially on the oxidation state and chemical species, amongst others. Inorganic arsenic is considered carcinogenic and is related mainly to lung, kidney, bladder and skin disorders, Agency for Toxic Substance and Disease Registry (ATSDR, 2003) [4]. The toxicity of arsenic in its inorganic form has been known for decades under the following forms; acute toxicity, sub chronic toxicity, genetic toxicity, developmental and reproductive toxicity (Ali and Ali, 2010) [3]. immuno toxicity (Sakurai, 2003, Okoh MP, 2015) [39, 34]. Drinking water is one of the primary routes of exposure to inorganic arsenic (Saha *et al.*, 1999.) [38]

## 2. Material and Methods

### 2.1. Experimental Animals and design

Twenty-eight (28) adult male albino rats of Wistar strain weighing between 150-200g were procured from the animal house, College of Health Science, Delta State University, Abraka, Nigeria. The animals were housed in standard animal cage, at room temperature with access to water in accordance with the international guide for the care and use of laboratory animals (Committee for update of the guide for the care and use of laboratory animals, 2011). They were maintained under controlled environmental condition with a 12 hour dark: light cycle.

These twenty-eight (28) male albino rats of Wistar strain were, divided into four (4) groups and, seven (7) rats in a group (**group A –D**). **Group A(Control)**: In this group, animals were fed with normal diet and water daily for four (4) weeks. Animals in, **group B (cadmium)** - were fed with cadmium treated diet for four (4) weeks. Those in **group C (arsenic)**- were fed with diet containing arsenic and water daily for four (4) weeks. In **group D (cadmium + arsenic)**- Animals in this were fed with cadmium + arsenic treated diet and water daily for four (4) weeks.

### 2.2. Dietary Preparation

Sixty (60) live catfishes were purchased from a local market, enabling, compounding the diets for the experimental animals used. The fishes were divided into four (Group A-D) groups and left to acclimatize for two (2) weeks in a pound. For group A (control) - fishes in this group were housed in fresh water. Those in, group B (cadmium) – were in water contaminated with known concentration (0.4 mg/100 mL) of cadmium. The water, changed every 24 hours maintaining constant concentration of cadmium, for four (4) weeks. Similarly, group C (Arsenic) – had water containing (0.4 mg/100 mL) arsenic, and changed every 24 hours for four (4) weeks with constant concentration of arsenic. The group D (cadmium + arsenic)-water had cadmium and arsenic (0.4mg/100ml of each pollutant. The water was changed but maintaining constant concentration of the pollutants, every 24hours for four (4) weeks. All fishes received normal feeding for the duration after which they were killed, dried in an oven and used as protein source in the diet for the experimental animals. The diet administered, constitute: Catfish prepared as above, serve as source of protein, Corn-starch serve as carbohydrate source. Vegetable oil served, as the fat sources. Laboratory cellulose served as the fibre source. Granulated refined sugar doubled as source of sugar. Vitamins and mineral mix (Hebei Vsyong Animal Pharmaceutical Co. Ltd, China). The minerals and

vitamins were used according to manufacturers recommendation.

### 2.3. Collection of Tissues and Blood Samples

At the end of the treatment periods, the experimental rats from both, acute and sub-chronic studies were weighed and sacrificed under anaesthetized chloroform (May and Baker, England) saturated chamber. Blood samples were collected from the animal by heart puncture, using Lithium heparin as anticoagulant and stored at  $-20^{\circ}C$  until required. The liver, Kidney and lungs were dissected out, washed in ice cold 1X phosphate buffer saline (PBS) solution (137 mM NaCl, 10 mM phosphate, 2.7 mM KCl pH 7.4).

The dissected liver, Kidney and lungs after washing, were, blotted individually on ash free filter paper, patted dry and weighed. The weighed tissues were stored in separate containers, labeled and immediately transferred to ice packs awaiting homogenization.

### 2.4. Preparation of Blood and Tissue Samples

The blood samples collected in lithium heparin bottles were centrifuged at 3000g for 15 minutes to separate the plasma and stored in  $-20^{\circ}C$  pending, biochemical analysis.

Ten percent homogenates of liver, Kidney and lungs were prepared in 1 X PBS containing (0.9% NaCl) using pre-chilled mortar and pestle. The homogenates were centrifuged at 5000g for 10 minutes and the supernatants stored in  $-20^{\circ}C$  preparatory for biochemical analysis.

### 2.5. Statistical Analysis

The results were expressed as Mean $\pm$ SD, following similar study (Nwachukwu *et al.*, 2014). Each parameter was analyzed using one-way analysis of variance (ANOVA) followed by Duncan's multiple range test using SPSS 10.0 computer software package (SPSS Inc., Chicago, U.S.A), for the group means. The least significant difference or probability were carried out when:  $F_{cal} > F_{tab}$ ; using the equation:

$$LSD = (Sx_1 - x_2)t$$

$$Sx_1 - x_2 = \sqrt{\frac{2S^2P}{n}} = \sqrt{\frac{2S^2}{n}}$$

where

t = tabular or critical  $t_{0.05, df}$  (error)

$Sx_1 - x_2$  = standard error of difference between means

N = Number of replicates per treatment

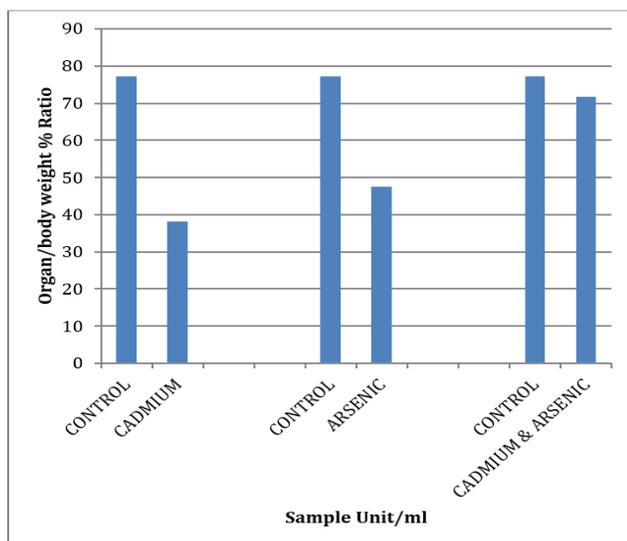
$S^2$  = error mean square

This was calculated and significance between mean values was determined using the critical values of p at 0.05 being the Pearson correlation coefficient and test of significant level of probability.

## 3. Results

To corroborate different exposure route to these toxicant in higher mammals, this study was design, specifically, to determine the effect of cadmium (Cd) and arsenic (As) following food chain contamination on plasma and tissue triglyceride concentration with, experimental albino rats as model.

Fig 1 and (Table 1) shows results of the effects of cadmium and arsenic containing diet on body weight gain and organ/body weight ratio of rats. The rats feed with diets containing cadmium or arsenic only significantly decreased ( $P > 0.05$ ) the body weight gain of rats (Fig 1). However, those feed with diet made up of cadmium and arsenic had no significant difference on the weight gain of the rats, as the level was comparable to the control (Fig 1).



**Fig 1:** Effect of cadmium and arsenic containing diet on body weight gain

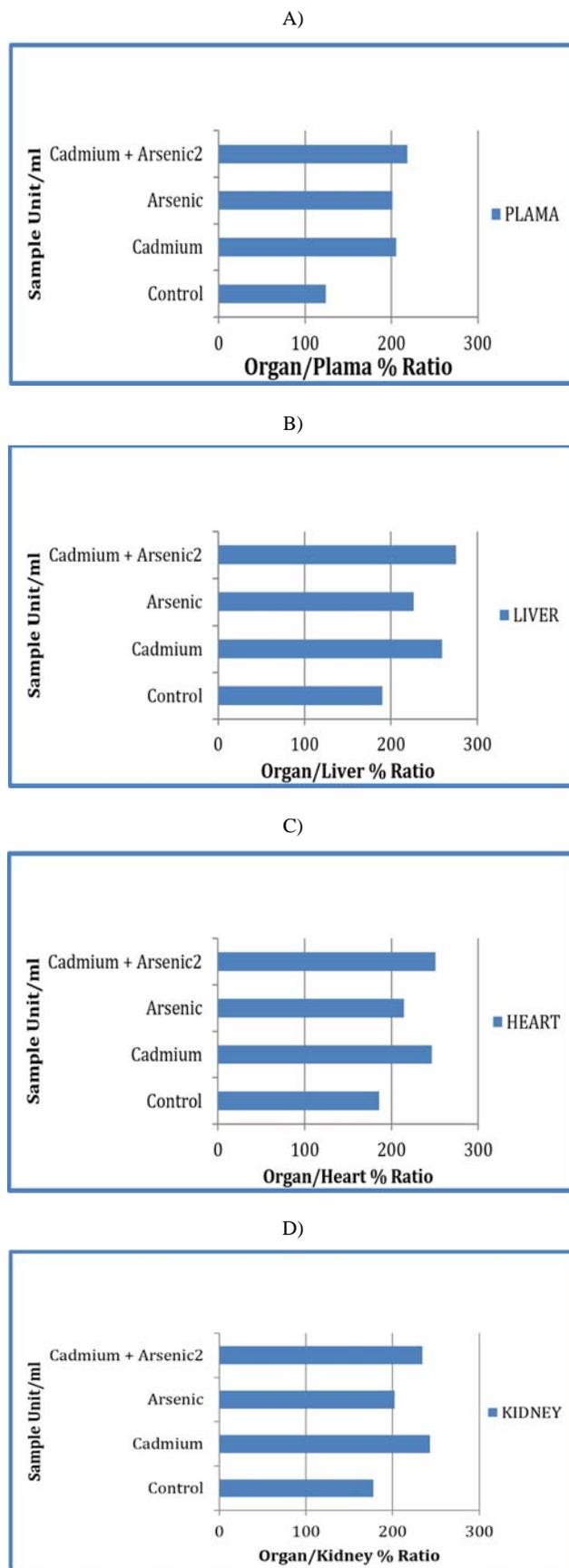
Further, there seems no significant differences ( $P > 0.05$ ) observed in the liver/body weight ratio of rats in all the experimental groups. Similarly no significant change was observed in the kidney or heart to body weight ratio in all the experimental groups (Table 1).

**Table 1:** Effect of cadmium and arsenic containing diet on organ/body weight ratio of rats

	Control	Cadmium	Arsenic	Cadmium and arsenic
Liver/ Body weight	0.034±0.003 <sup>a</sup>	0.033±0.007 <sup>a</sup>	0.035±0.001 <sup>a</sup>	0.034±0.006 <sup>a</sup>
Kidney/ Body weight	0.006±0.000 <sup>a</sup>	0.007±0.001 <sup>a</sup>	0.009±0.001 <sup>a</sup>	0.008±0.002 <sup>a</sup>
Heart/ Body weight	0.004±0.001 <sup>a</sup>	0.004±0.001 <sup>a</sup>	0.004±0.001 <sup>a</sup>	0.003±0.001 <sup>a</sup>

Results are expressed as mean ± SEM. Means on the same row with different letters as superscript are significantly different ( $P < 0.05$ )

The effects of cadmium and arsenic containing diet on the level of plasma and tissue triglyceride concentration of rats is presented in Fig 2. A significant increase was observed in plasma triglyceride level in rats fed cadmium, containing diet (Fig 2 A) as compared to the control group but no significant change was observed in plasma triglyceride of rats fed either arsenic or arsenic plus cadmium in diet. The liver triglyceride of the rats showed a significantly ( $P < 0.05$ ) increase relative to control (Fig 2 B) in rats fed cadmium, arsenic and cadmium plus arsenic. A similar trend was observed in the heart of rats fed with cadmium and arsenic (Fig 2 C) as the tissue glyceride was significantly increased as compared to control. Parallel analysis in the kidney showed significant ( $P < 0.05$ ) increase in triglyceride concentration in rats fed cadmium and cadmium plus arsenic containing diet (Fig 2 D). However, no significant change was observed in those fed arsenic-containing diet relative to control.



**Fig 2:** Effects of cadmium and arsenic containing diets on plasma and tissue triglyceride concentration of rats A (Plasma), B (Liver), C (Heart), D Kidney)

#### 4. Discussion

The objective of this study was to examine the effects of cadmium and arsenic containing diets on plasma and tissue triglyceride in experimental rats. Changes in the body weight and organ/body weight ratio have often been used as indices of toxicity (Timbrell, 1991; Nwachukwu *et al* 2014) [42, 33]. The significant alteration (Fig 1) observed in these parameters in the rats are, indicative of toxicity, which is in agreement with earlier reports (Bhatia *et al.*, 2001) [8], Robert *et al.* (2013) [37], studying the effects of nickel on triglyceride, observed that nickel was a potent metal, which can cause significant changes in the levels of blood and tissue triglyceride. Thus, results of this study showing alteration of triglyceride levels in the organs of rats fed diets containing cadmium, arsenic and cadmium plus arsenic is indicative of interference in metabolism of lipid by these metals.

Information relating to the toxic effects of most metals is established. For instance, exposure to some heavy metals e.g. cadmium, mercury, lead etc. are known to induce a variety of toxic symptoms in both the environment (Biossette *et al*, 1978; Agbadah *et al*, 2015 submitted) [9, 1], experimental animals and exposed human populations (Herman and O'leary 2014) [18]. It is known that most of these metals like organic pollutants e.g. polychlorinated biphenyl (PCB) and other persistent organic pollutants (POPs) bio-accumulate up in the food chain because of their solubility in organic solvent (Holoubek I, 2000; Okoh MP, 2015; UNEP 2012, 2013a,b,c) [44, 45, 47], informing, our dietary design (Fig 3).

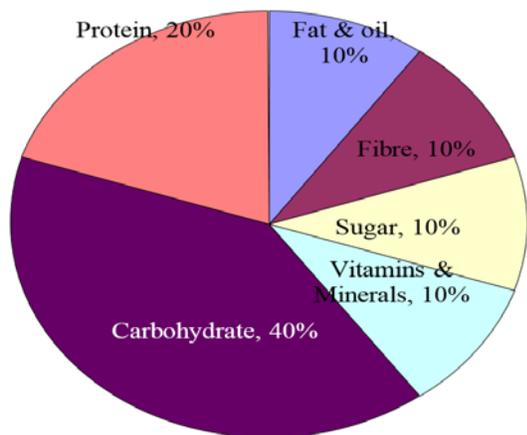


Fig 3: Dietary design

Attention to heavy metal toxicity has grown in recent times following the occurrence of “itai-itai” and minimata disease in Japan leading to minimata convention, a legal binding instrument develop to mitigate mercury (Hg) usage (UNEP, 2013) [45]. Available data in literature indicate that adverse effects due to chronic exposure to heavy metal occur mainly in the liver, kidney and bone (Åkesson *et al.*, 2005) [2].

#### 4.1. Biochemical Assays and biological importance of triglyceride

To assay for triglycerides, enzymatic hydrolysis with lipases is important, being the committed step. The quinoneimine, formed from hydrogen-peroxide, 4-aminophenazone and 4-chlorophenol under the catalytic influence of peroxidase serve as an indicator.

A triglyceride is an ester of glycerol and other three fatty acids. It is known to be a blood lipid and, helps in the transference of adipose fat and blood glucose from the liver

(Nelson and Cox, 2000) [30]. There are different types saturated and unsaturated.

Saturated compounds are “saturated because hydrogen are available in places where hydrogen atoms ought to be bonded, carbon atoms”. Unsaturated compounds on the other hand have double bonds (C=C) between carbon atoms, reducing the number of places where hydrogen atoms can bond to carbon atoms. Saturated compounds have single bonds (C-C) between the carbon atoms, and the other bond is bound to hydrogen atoms (for example =CH-CH=, -CH<sub>2</sub>-CH<sub>2</sub>- etc.). Unsaturated fats have a lower melting point compared to saturated fat with a higher melting temperature.

Triglycerides form the major components of vegetable oil (unsaturated) and animal fats (saturated) (Nelson and Cox, 2000) [30]. They are a major component of the human skin (Lampe *et al.*, 1983) [27].

Chemically, triglycerides, consist joining the hydroxyl groups of glycerol with the carboxyl groups of the fatty acid to form ester bonds. E.g. CH<sub>2</sub>OH(OH)CH<sub>2</sub>CHO + RCO<sub>2</sub> + R'CO<sub>2</sub>H + R"CO<sub>2</sub>H



The three fatty acids (RCO<sub>2</sub>H, R'CO<sub>2</sub>H, R"CO<sub>2</sub>H in the equation) are usually different, and many forms of triglycerides are known. The chain lengths of fatty acids triglycerides, mostly contains even numbers (16, 18 or 20), carbon atoms. Hence, natural fatty acids in plants and animals are composed of mostly even numbers of carbon atoms, bearing their biosynthesis pathways using, two-carbon atom from acetyl CoA as building block. However, because bacterial, possess the ability to synthesize both odd- and branched- chain fatty acids, ruminant animal fat (e.g. goat) contains unsaturated numbered fatty acids. Reflecting action of bacteria in the rumen.

In humans, high concentration of triglycerides in the bloodstream have been linked to atherosclerosis and the risk of heart disease (Drummond *et al.*, 2014) [13].

#### 4.2. Reduction of Triglyceride Levels

Evidently, carbohydrate foods with a high, glyceric index causes insulin over production with concomitant increase triglyceride levels, atleast in women (Coulston *et al.*, 1983) [11]. Adverse changes due to high food consumption resulting in increase triglyceride levels also, tends to have stronger risk factors for heart disease in women than in men (Coulston *et al.*, 1983) [11]. Triglyceride levels can reduced by moderate exercise (Koutsari *et al.*, 2001) [25], consuming omega-3 fatty acids (Davidson *et al.*, 2008) [12]. Carnitine has also been shown to have ability to lower blood triglyceride levels (Batch, 2006) [7]. However, heavy alcohol consumption, are thought to elevate triglyceride levels (Hemat, 2003) [19].

#### 4.3. Source of Environmental Exposure to these metals

Numerous human activities result in the release of significant quantities of cadmium or arsenic to the environment. At the global level, the smelting of non-ferrous metal ores has been estimated to be the largest human source of cadmium release to the aquatic environment (Nriagu and Pacyna, 1988) [32]. Atmospheric fallout represents a major input of cadmium at the global level. Cadmium II ion (Cd<sup>2+</sup>) is the form of uptake of cadmium by terrestrial organism and the uptake is affected by some environmental factors such as temperature, as uptake increase with increase in temperature (Nriagu and Pacyna, 1988) [32].

Iron production, fossil fuel combustion, cement manufacture release cadmium into the atmosphere, being a natural constituent of the raw materials.

In the body, cadmium is widely distributed, with the major portion of the body burden, located in the liver and kidney (WHO, 1992)<sup>[51]</sup>. Liver and kidney cadmium concentrations are comparable after short-term exposure, but the kidney concentration exceeds the liver concentration following prolonged exposure (WHO, 1992)<sup>[51]</sup>.

The concentration of cadmium in the liver of occupationally exposed, workers generally increases in proportion to intensity and duration of exposures. The concentration of cadmium in the kidney is thought to rise more slowly than in the liver after exposure and, begins to decline after the onset of renal damage (Flamagan *et al.*, 1978)<sup>[15]</sup>, with critical concentration suggested at 160-285µg/g/body weight. However, most non-occupationally exposed people are exposed to cadmium primarily through their diet (Nriagu and Pacyna, 1988)<sup>[32]</sup>.

Cadmium uptake by humans and mammals generally, occurs via absorption from inhalation, through the intestinal tract, skin, and by trans-placental transfer (Neumann *et al.*, 1975)<sup>[31]</sup>. The most dangerous characteristic of cadmium is that it accumulates in the liver, kidneys and has a long biological half-life, from 17-30 years in man.

Cadmium, upon binding to albumin is preferentially taken up by the liver (Klassen, 1978)<sup>[24]</sup>. In the liver, it induces the synthesis of metallothioneins, proteins whose purpose is to metabolize and regulate metals. It has been shown that metallothionein plays a role in cadmium transporting and detoxification (Klassen, 1978)<sup>[24]</sup>. It is rich in cysteine but contains no aromatic amino acids or histidine (Klassen, 1978)<sup>[24]</sup>.

## 5. Chronic Effects of Cadmium

The kidney is the critical organ in human that could be exposed for long period to relatively small amounts of cadmium. Experiments have shown in humans, for example, that exposure to cadmium causes type of proteinuria. Further, its effects on the immune system, are due to decrease in the number of antibody forming cell in the spleen with concomitant decreased in antibody production, documented in experimental mice after long term exposure to cadmium in drinking water (WHO, 2004)<sup>[51]</sup>. Moreover, chronic oral administration of cadmium compounds to rat induced statistically significant elevation of blood pressure (WHO, 2004)<sup>[51]</sup>. Cadmium exposure also caused effects on bones and calcium metabolism (WHO, 1992)<sup>[51]</sup>. However, some of the findings in experimental animals are yet to be fully documented in higher mammals as, their remain a serious gap e.g. humans. For instance, cadmium has been associated with reproductive disorder in rats. As fertilized eggs obtained from black rat (*Rattus rattus*) exposed to cadmium fail to develop to the blastula stage (Frias *et al.*, 2008)<sup>[16]</sup>. Hence, cadmium is thought to be important endocrine disrupter that may alter a broad range of genetic programmes controlled by oestrogen (Frias *et al.*, 2008)<sup>[16]</sup>. Cadmium inhibits estradiol receptor transcriptional activity in *Rattus rattus* (Frias *et al.*, 2008)<sup>[16]</sup>. It is probable, also, that cadmium may be involved in disruption of the lysosomal components of these (some) receptors, following, similar characteristic hypothesize for PCB (Okoh MP, 2015)<sup>[34]</sup>. However, experimentation are needed for validation hence, their remain gaps in, available evidence.

Reducing the toxic effects of cadmium, antioxidant e.g. vitamin C and E have shown to be effective. These,

antioxidant reduces the biochemical changes induce by cadmium. Moreover, selenium significantly decreases the toxicity cause by cadmium, whilst, zinc pretreatment caused a reduction in cadmium genotoxicity in cultured liver cells (WHO, 2004)<sup>[51]</sup>. glutathione has been reported to ameliorate cadmium-induced injury in isolated hepatocytes (WHO, 2004)<sup>[52]</sup>. And ethanol confers protection on the brain accumulated with cadmium (WHO, 2004)<sup>[53]</sup>.

## 5.1. Sources of Environmental Exposure to arsenic

Naturally occurring pathways of exposure include volcanic ash, weathering of arsenic-containing minerals and ores and dissolved in groundwater. It is also found in food, water, soil and air. Arsenic is absorbed by all plants, but is more concentrated in leafy vegetables, rice, apple and grape juice and seafood (FAO, 2011)<sup>[14]</sup>. An additional route of exposure is through inhalation. Occupation exposure and arsenic poisoning may occur in persons working in industries involving the use of inorganic arsenic and its compounds such as wood preservation, glass production, non ferrous metal alloys and electronic semi conductor manufacturing. Inorganic arsenic is also found in oven emissions associated with the smelter industry.

The chronic health effects of As exposure from consumption of As-contaminated water and food includes; skin lesions, skin cancer, internal malignancies, neurological effects, hypertension, peripheral vascular disease, cardiovascular disease, respiratory diseases, and diabetes mellitus. Skin lesions are one of the most common features of chronic As poisoning and hence, are used as a diagnostic criteria of endemic As poisoning. There are several reports that discuss the relative risk or prevalence rate of chronic health effects in As-exposed populations, although few papers attempt to define dose-response relationships between As exposure via drinking water and chronic toxicity, because of the difficulty in the estimation of individual exposure.

At the molecular level, arsenic poisoning leads to genetic-toxicity, which involves inhibition of DNA repair and DNA methylation (Wilcox *et al.*, 2013)<sup>[50]</sup>. The carcinogenic effect of arsenic arises from the oxidative stress induced by arsenic (Wilcox *et al.*, 2013)<sup>[50]</sup>. However, arsenic oxide is an approved and effective chemotherapeutic drug for the treatment some form of cancer e.g. used in treatment of acute promyelocytic leukemia (APL) (Gibaud *et al.*, 2010; Wilcox *et al.*, 2013)<sup>[17,50]</sup>.

Recent *In vitro* studies also suggest that arsenic trioxide (As<sub>2</sub>O<sub>3</sub>) inhibits the proliferation of myeloma cells via cell cycle arrest as well as triggering cell death (Gibaud *et al.*, 2010)<sup>[17]</sup>. These results suggest arsenic trioxide may be clinically useful for treatment in patients with multiple myeloma or leukemia (Lungi *et al.*, 2004)<sup>[28]</sup>.

## 6. Conclusions

Cadmium and arsenic are notoriously poisonous to multicellular life, however, a few species of bacteria are able to use arsenic compounds as respiratory metabolites. These metals are important in many respects, including, manufacturing of certain important products of human use. However, the bio-toxic effects, a consequence of, unduly exposure, is potentially life threatening hence, cannot be neglected. These metals are though, in many ways indispensable, however, good precaution and adequate occupational hygiene should be taken in handling them. Heavy metal poisoning can be clinically diagnosed and medically treated, however, the best option is to prevent heavy metal

pollution and the subsequent human exposure. The current study, added value on the mechanism of toxicity of these metals, and also, reveal the role of food-chain in metal uptake, leading to toxicity in human population. The, results showing alteration of triglyceride levels in the organs of rats fed diets containing cadmium, arsenic and cadmium plus arsenic is indicative of interference in metabolism of lipid by these metals.

**Conflicts of Interests:** We declare that there are no conflicts of interests.

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