TOXICOLOGY OF HEAVY METALS USED IN COSMETICS

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ABSTRACT

Cosmetics have been used by humans since the start of human civilization. Initially, it was typically consisting of natural products but to get prompt results, heavy metals were frequently added to cosmetics to accelerate the affects. Heavy metals such as mercury (Hg), lead (Pb), cadmium (Cd) and chromium (Cr) are detected in various cosmetic products; most frequently in color cosmetics, hair cosmetics, face-body care products and beauty cosmetic products. These metals are included in toxic metals. The application of cosmetics to different body parts leads to the absorption of metals through the stratum corneum into the blood, accumulate or replace essential elements of different biomolecules which triggers the unfavorable mechanism. Reported data shows that in some common cosmetic products toxic metals are being used greater than permissible limit. The United States Food and Drug Administration (FDA) and World Health Organization (WHO) have established the highest permissible limit of exposure for heavy metals in different cosmetic products. However, commonly in developing world no care is taken for permissible limit set by FDA and WHO and to obey cosmetic production legislations which resulted in fatal health consequences. Thus, in this review article we are focusing on the permissible limits, hazardous effects of the toxic metals and mechanisms associated with the hazardous effects related to heavy metals found in cosmetics. Owing to the growing usage of cosmetics it is necessary to explore the possible sources and routs of metals toxicity to fix the hazardous effects related to heavy metals found in cosmetics.

Keywords: Cosmetics, Heavy metals, Mercury, Lead, Cadmium, Chromium.

1. INTRODUCTION

Beauty consciousness cannot be tagged with modern era. In ancient time the people had also been practiced beauty tips for appearing glowing and attractive. Consciousness to improve physical appearance, however is gaining ample intention in present era of globalization regardless of the gender [1]. According to the Cosmetic Europe (CE) – The Personal Care Association (PCA), approximately 450 million people of Europe use on daily bases a wide variety of different cosmetic products (COLIPA, 2015). Innovation is one of the basic principles in this field. According to FDA and European legislation cosmetics are the products that are applied to various body parts such as hairs, face, eyes, lips, hands, nails and feet for multi functions – commonly for attractiveness and as anti-aging [2]. Make-up is described as subset of cosmetics that is used to accentuate or change a person's appearance and to enhance natural features [3]. The application of these products are carried out to the areas where absorption is very high such as pre-ocular areas and facial skin [4]. Metals gradually take the place as essential gradient of cosmetics. Greeks, Egyptians and Romans used Pb and white Hg based cosmetics [3]. The potential due to which metals are used as components of cosmetics either to impart different colors to cosmetic products or for UV absorbers and emollients [4, 5].

In current era, cosmetic industrialization played vital role in human's exposure to various toxic metals through cosmetics. Exposure to metals beyond permissible limit set by FDA-WHO may produce complications. Most of the developing countries, according to the reported data on toxic effects of metals, give little attention to metal contamination of cosmetic products. According to Health-Canada, in Nigeria and most sub-Saharan African countries, all the cosmetic products 100% tested positive for Ni, >90% tested positive for Pb and beryllium (Be) and found at least 4 metals out of Cd, Pb, Hg, Ni, Be, arsenic (As), selenium (Se) and thallium (Tl) on the average. Environment Defense Canada (EDC) also tested about 49 different cosmetic products out of which more than 90% contained Pb and about 40% contained As [6].

FDA (USA) allowed 10 to 20 mg/kg of Pb in cosmetics. Health-Canada has set safe limit lower than 10 mg/kg for Pb and 3 mg/kg for Hg. German federal government has set 20 mg/kg permissible limit for Pb and 5mg/kg for Hg [7]. In USA the concentration of heavy metals in cosmetics raw materials and finished products are strictly monitored by FDA [8, 9]. In developing countries, the monitoring system is very poor or even absent which lead to the violation of international standards.

In these circumferences, reported studies showed that various health problems are associated with cosmetic metal ingredients [10-12]. Female are at greater risk for birth defects, reproductive and developmental impairments, cancer and respiratory issues [3, 13-17]. The other reported events of heavy metal poisoning using beauty products are Hg poisoning using Mexican beauty creams and soaps in Mexico, Kenya and Hong Kong. At cellular level changes in membrane permeability and macromolecular structure are quite hazardous effects [7, 18].

Epidemiological studies revealed variety of potential hazards of heavy metals on humans by using beauty products which are necessary to update. In this review we are focusing on physiological disorders and mechanisms associated with the hazardous effects related to heavy metals found in cosmetics.

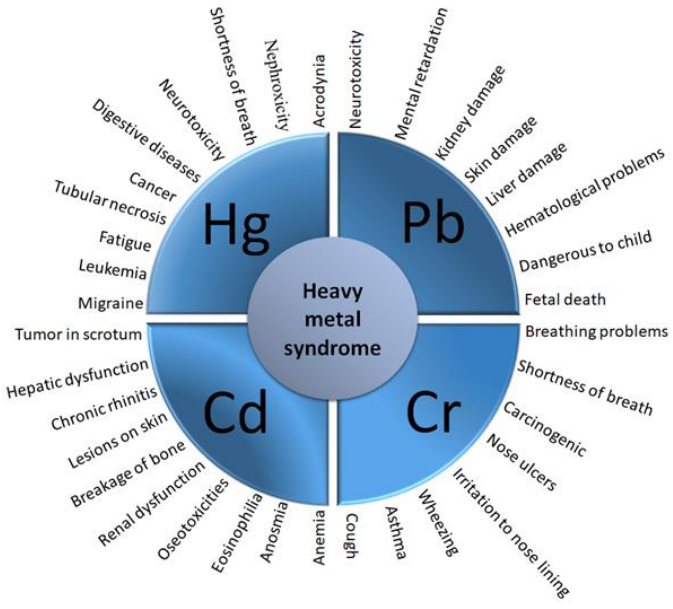

Figure 1. Health risks caused by mercury, lead, cadmium and chromium in human body.

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2. Mechanism of heavy metals absorption

Remarkable route for penetration of cosmetic ingredients is skin dermas which primarily protect sub-dermal and internal body organs [19]. The application of cosmetics products on external skin reach the cell environment through hair follicles, sweat pores and finally blood capillaries for the function for which to be chosen [20]. Although raptness through the skin is a slow process but continuously long term use of cosmetics increases the concentration. However, inclusion of heavy metals to contaminant level accelerate the accumulation and also cause toxicity in the form of different disorders. The electrophilic substitution of heavy metals with essential elements in key biomolecules appear more threatening to human body [5, 19]. The following sections will explain the hazardous effects and mechanisms associated with the hazardous effects due to Hg, Pb, Cd and Cr; found in cosmetics.

Mercury – Melanin inhibitor cosmetic ingredient

Mercury is a common but dangerous ingredient found in cosmetic products. It is generally existing in three different forms; metallic, organic and inorganic. These forms differ in their poisonous effects on different body systems mainly lungs, central nervous system, skin and kidneys [4]. The most often Hg recognized as a shiny, silver-white, dense order-less liquid which transfer to gas on heating. Mercury is reported as highly toxic and exceedingly bio accumulative. Anthropogenic activities (industrial and municipal waste water discharges, mining, incineration, and agriculture) are reported the major source of mercury contamination in environment. However, marine life is known to effect badly with mercury due to the formation of methyl mercury which undergo bio-magnification which is a real cause of disturbance in aquatic life [21]. In cosmetics the use of mercury salts, based on its potential to inhibit the formation of melanin which results in skin-lightening [22]. Many Africans, Asian, Caribbean and dark-skin population of Europe commonly use mercury-added soaps, creams and lotions to light the skin tone. The *Minamata Convention* on Hg establishes a limit of 1mg/kg (1ppm) for skin-lightening products [23]. Despite having been banned in many countries; to accelerate the whitening effect many skin-whitening products brands are sold containing Hg greater than permissible limit [24]. It is difficult to eliminate the Hg containing beauty products as it is rapidly growing sector of cosmetics industry and is estimated to be worth 31.2 billion US$ business by 2024 [25]. The most common symptoms of over accumulation of Hg are dizziness, migraine, weakness, fatigue, anxiety, irritability, limb and joint pain with signs of insomnia and short term loss of memory and acrodynia [26].

Mechanism and hazardous effect associated with Hg absorption

A brief step wise transformation of Hg after applying over skin is shown in sketch **Figure 2**. It is difficult for inorganic mercury to cross the blood barrier to enter the central nervous system, gastrointestinal tract or multiple organs, however prolonged application over skin lead to the accumulation in central nervous system as a consequence induce various behavioral and neurological impairments [18]. Gastrointestinal damage causes nausea, gingivostomatitis, metallic taste and hyper salivation. According to WHO over accumulation of Hg can cause leukemia, liver damage and kidney cancer.

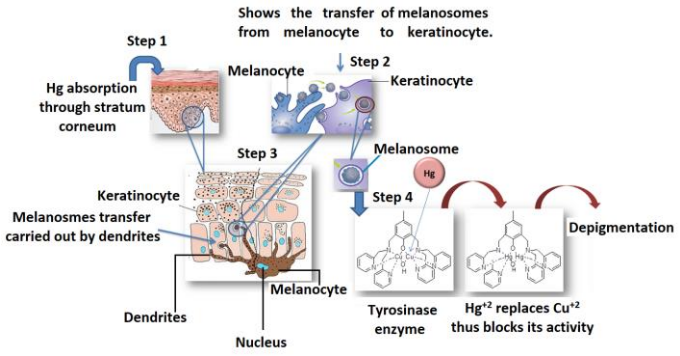

Figure 2. Shows the mechanism of de pigmentation. Step 1: shows absorption of mercury through stratum corneum. Step 2: depicted the transfer of melanosome from melanocytes to keratinocytes. Step 3: shows the involvement of dendrites in the transfer of melanosomes. Step 4: shows depigmentation.

As said earlier Hg is fundamental element to accelerate the skin-whitening effect of beauty products. Typically, it blocks the melanin production in the body. Melanin is a natural shield for DNA to protect from ultraviolet (UV) radiations. Melanosomes are produced in dendritic melanocytes as less as 2% of the epidermal cells. As melanin produced in melanosomes it is carried to adjacent keratinocytes through dendrites. It settles down as supranuclear caps in the perinuclear area in melanocytes and keratinocytes to protect DNA from UV radiations. Continuous and over use of Hg-salts added beauty product considerably reduce the production of melanin by replacing Cu in tyrosinase enzyme to stop producing pigmentation and consequently dark complexion [27].

The absorption of mercury takes place at quite high rate, particularly when stratum corneum (outermost layer of skin) is hydrated via intercellular and transcellular routes. After absorption it distributes to different tissues. It has low lipid solubility, so only a small amount of mercury can cross the blood barrier. Therefore, the mercury exposure to cellular level may lead to DNA damage; it has affinity to sulfhydryl and thiol groups of DNA and other molecules thus cause variations in macromolecular structure and also results in the alteration of permeability of membrane [28].

It was reported that about 5.9% by weight of mercurous chloride was found in facial creams resulting in elevated urinary mercury of up to 1.88 mg/g creatinine in Mexico [29]. The recommended treatment in such scenario is antidotes and chelation therapy using unithol (2, 3-dimercapto-1-propane sulphonic acid) and succimer (dimercaptosuccinic acid), meso-DMSA and D-penicillamine. DMPS and meso-DMSA are more useful than other chelators [30-33]. FDA in the Minamata Convention on Hg cut the upper limits at 1 ppm in beauty creams [34] and Drug and Cosmetics Act 1940 banned the use of mercury in skin lightening creams but yet available in number of countries. US Federal law in 1973 also banned the use of mercury beyond 1mg/kg limit in beauty products [35]. European Union also banned the distribution of mercury containing cosmetics including soaps, creams, lotions, shampoos and skin bleaching products. However, it is in documents but most companies especially local industries use heavy metal contents without caring the legislations passed [18]. Following are the most reported toxic effects of Hg which is accumulate in different regions of the body either through beauty product use or through other sources contaminated with Hg.

Nephrotoxicity

Mercury is the only heavy metal that is liquid at room temperature. In addition to absorption through skin by applying Hg-added cosmetics, respiratory-tract and digestive-tract also pave the way to blood stream which lead to poisoning. In skin whitening and anti-freckle creams mercury is commonly used in the form of $HgCl_2$, ammoniated mercury (ClH_2HgN), mercurous oxide (Hg_2O), largely show hydrophilicity due to which predominantly accumulated in tubules and nephrons leading to chronic tubular necrosis and nephropathy [40]. Nephrotic and neurotic syndrome however, are two major Hg-poising abnormalities. Numerous reports are available which describe the Hg-poisoning by suction of Hg-vapors, filling a tooth, and use of Hg contaminated food or drugs. Least attention was given to very common source of Hg which play critical role in increasing Hg-level in human body. A nephrotic syndrome case report of 28-years old female was published who used Hg-added skin lightening cream for a long term. Study indicated that Hg contents in blood and urine gradually increased. On discontinuing the use of cream and treating with sodium dimercaptosulfonate and glucocorticosteroid, her symptoms were relieved after 6-months [36, 37]. Membranous nephropathy and minimal change disease (MCD) have also been reported due to mercury-induced nephrotic syndrome [38]. The syndrome was induced in 1 to 60-months after exposure to Hg. All subjects showed heavy proteinuria and biopsy test showed 67% minimal change disease or 23% membranous nephropathy [39].

In case of Proteinuria the inorganic mercury from the blood get entered to the intracellular compartments in the kidneys, bonds to thiol containing proteins inactivates them because of its greater affinity to them; hence enhance the sensitivity of lysosome towards Hg^{+2} ions lead to the fusion of primary lysosomes with the cytotic and cytosolic vesicles containing the Hg^{+2} bonded sulfhydryl protein [40].

Neurotic syndrome

Other key disorder which is associated with Hg exposure is neurotic syndrome that occurs when mercury leads to accumulate in the central nervous system [41]. Neurotoxicity is concerned to sulfhydryl and selenium (Se) containing enzymes and proteins. Mercury attacks thiol and selenium groups containing proteins in the neuroglia (See graphic abstract); blocks the activity of these neuro-proteins in the cellular membranes and the intracellular environment. Specifically, neuronal microtubules (the constituents of neuronal cytoskeleton) are composed of a polymer of tubulin protein (containing 15 thiol groups in each tubulin monomer) are more vulnerable to mercurial attack. Selenium containing enzymes acts as a guarding agent to neuronal toxicity by triggering different processes like detoxification of Hg-complexation, prevents oxidation of mercury to mercuric or mercurial ions by increasing the production of Se-proteins; but when mercuric ions concentration exceeds than Se-enzymes complex, it leads to severe toxicity like tremors, lethargy, confusion, headache, migraine, dysarthria, seizures, decreased cognitive functions and ataxia [42].

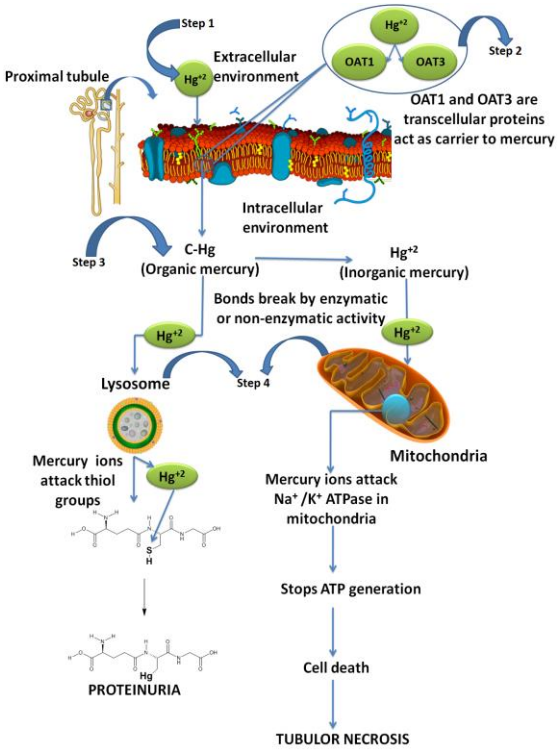

Figure 3. Shows the general mechanism of nephrotoxicity. Step 1: shows the intake of mercury through cell wall. Step 2: shows Oat1 and Oat3 act as carrier to organic mercury to the intracellular environment. Step 3: which converts to inorganic mercuric ions by enzymatic activity, as a consequence it ceases the enzymatic reaction in the cell. Step 4: causes severe nephropathy and proteinuria in mitochondria and lysosomes respectively.

Tubular necrosis

Organic anion transporter 1 (Oat1 – a gene involved in kidney transporter) and Organic anion transporter 3 (Oat3 – a gene identified as reduced in osteosclerosis transporter (Roct) are the transcellular proteins composed of amino acids, localized in epithelia of the body and endothelium of all cells, basic function is to transport various substances (including drugs and toxins) between the body fluids (blood, urine, bile and intestinal fluids) and various organs of the body, bonded to the organic mercury and excretes it through urine, but inorganic mercury (Hg^{2+}) is accumulated in the cells at faster rates which appear ten times more dangerous than organic Hg. Kidneys primarily targeted by toxins released from other organs, however it filters to remove all the noxious materials from the body fluids and excrete out from body. When mercuric ions bonds to the organic anion 1 and 3 and enter the cell, there various enzymes like glutathione (GHS), albumin, metallothionein (MT) competes for the mercuric ions (due to promising affinity of Hg^{+2} for thiol groups), Hg^{+2} forms thermodynamically stable complexes at full range of pH, disturbs various oxidation reduction reactions in the cell; as a result, cell losses homeostatic conditions. One can assume the severity of Hg^{+2} as it also bonds to the Na^+, K^+-ATPase enzymes disturbs the Na^+ gradient for the normal transport of solutes from extracellular to intracellular environment, which leads to cease the ATP generation. As a consequence cell death occurs, the condition known as tubular necrosis or nephropathy [40, 43-45]. Detailed mechanism is Hg absorption and cell death is explained in **Figure 3**.

Lead – A color additive in cosmetics

Typically, color shades of cosmetics are the key factors to accelerate the cosmetic industry. Different color additives are used to produce broad spectrum of color tones. However, misuse of color additives make the cosmetics adulterated and marketing of such products are against the law. Therefore, before their use in cosmetics, there is a need of FDA approval. The approved color additive then included in FDA "listing regulation" which describes that on what bases the permission was given and limit of impurities.

Lead is a soft and malleable heavy metal with atomic number 82. It is denser than most common metals. According to reported data, annual global production of lead in average is about ten million tons which make it inexpensive and its ionization energy (715.6 kJ/mol) which resembles to many color imparting metals such as Mg, Mn and Ni make it a good choice to use as color additive in cosmetics, food, drugs and many medical devices. Typically, the limit of lead as color additives in cosmetic set to 10 to 20 ppm by USFDA. Lead is frequently used as a color additive ingredient in lipstick, other cosmetic lip products, and eyeliners (kohl, kajal, al-kahal, surma, tiro, tozali, or kwalli) and externally applied cosmetics [13]. In Middle East, kohl which is a form of customary product is used for eyeliner containing more than 50% of lead. The use of such products by breast feeding and pregnant women appear more drastic for infants – a published report revealed 39 μg/dL concentration of lead in a blood of seven-month baby because his mother used kohl continuously [30, 46].

The FDA funded projects data revealed that the lip cosmetic products such as lipstick and lip-glosses contain Pb below the detection-limit of inductively coupled plasma (ICP) that was 7 ppm. But the ICP analysis of hundreds of other externally used cosmetics such as blushes, shampoo, eye shadows and body lotions showed the level of Pb below the detection-limit to 14 ppm. Lead was also included in hair dyes in the form of lead acetate for progressive coloring effect and in 1980 lead acetate was listed as color additive however due to number of reports on the toxicity of lead acetate in hair dyes, on October 30, 2018, the FDA banned the use of lead acetate in hair dyes under the amended rules entitled "color additive regulations". The non-biodegradable nature and reactivity of lead is the main reason for its prolonged persistence in environment and in living body.

The leading targets to Pb-toxicity are the thiol-containing antioxidants, heme synthesis enzymes, and variety of enzymes including glutathione peroxidase, catalase, antioxidant molecules like GSH, superoxide dismutase, and glucose 6-phosphate dehydrogenase. The high accumulation of Pb is not needed to inhibit the activity of all these enzymes; low blood lead levels can inhibit the activity of enzymes which accelerate the generation of ROS and intensify the oxidative stress. Oxidative stress is the leading pathway to pathogenesis of Pb-toxicity[47]. However, the central nervous system is the primary target of Pb-toxicity which accomplished in body through different cellular, intracellular and molecular mechanisms: such as induction of oxidative stress, intensification of apoptosis of neurocites, interfering with Ca(2+) dependent enzyme like nitric oxide synthase [48, 49]. The other drastic Pb-induced toxicity is to develop autoimmunity, in which a person's immune system assault its own cells; mental retardation and learning disability, intrauterine fatal death and hearing problems [50]. Further, published population studies demonstrate direct link between Pb exposure and subsequent development of hypertension and cardiovascular disease. Vascular endothelium are also reported the main target for Pb-induced toxicity [51]. Following section will explain the mechanisms associated with Pb-toxicity in main Pb targets.

Oxidative Stress induced disorders

Oxidative stress is known to behind the chronic disorders of human. Increased blood level of Pb (Pb-BL) impose oxidative stress mainly in two ways which are interrelated to each other: the first mechanistic rout involves the triggering the production of ROS such as hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), hydroxyl radicals (OH°), and reactive nitrogen species (RNS), i.e. nitric oxide

(NO) while the second mechanism involve the quenching of cellular antioxidant pool [52]. Production of ROS and RNS are primarily initiated with the inhibition of δ-aminolevulinic acid dehydratase (ALAD, enzyme for heme biosynthesis) by increased Pb-BL, which leads to the accumulation of δ-aminolevulinic acid (ALA) that accelerate the generation of ROS [53]. Pb-induced toxicity also promoted by effecting on antioxidant cellular defense system (ACDS). ACDS works through variety of enzymes to protect body from ROS such as glutathione peroxidase (GPx), catalase (CAT), glucose-6-phosphate dehydrogenase (G6PD), and superoxide dismutase (SOD). All these enzymes contain thiol (-SH) group for which Pb has promising affinity. Increased Pb-BL significantly inhibit the activities of these enzymes [52, 54]. Due to its divalent nature, it replaces number of essential divalent elements i.e. Zn, Mg, Se, etc., from different biomolecules rendering adverse consequences. It also play role in decreasing the glutathione (GSH) level, a tripeptide component of antioxidant non-enzymatic protection [52].

Renal Diseases

It is well reported that Pb is a nephrotoxic agent, particularly in the renal cortex [55]. Increased Pb-BL causes renal tubular necrosis in kidney [56]. Glycosuria, aminoaciduria, phosphaturia, cause acute lead toxicity in proximal tubule. Approximately, 90% of Pb binds to erythrocytes protein called as albumin. It also associated with oxidative damage to cell and tissues in kidneys. Pb(+2) competes with Ca(+2) and cause malfunctioning of Ca(+2) homeostasis. As a result Ca(+2) release from mitochondria is stimulated, starts the mitochondrial permeability transitional pore opening and cause it to damage by mitochondrial swelling and cell death by apoptosis which also alters the lipid metabolize [57]. Further, exposure of HEK293 kidney cells to Pb causes to decreased cell distortion, cell viability, cohesion loss, lipid per-oxidation and production of superoxide anion [58]. Pb-induced cellular damage is most probable in proximal tubules by apoptosis. Studies on rat proximal tubules suggested that it increases systolic, mitochondrial calcium concentration and depletes endoplasmic reticulum [57].

Alpha thalassemia – mental retardation

Different studies were reported to see the relation with Pb-BL and Alpha thalassemia. The females are more prone to Pb through daily use Pb-added cosmetics which proved as a silent poison. Low exposure of Pb (0.01mg/g) proves to be toxic to brain. Histopathological evidence showed that Pb exposure to mice exhibited Pb-induced structural lesions as seen with a light microscope after 30 days of Pb-dose [56, 59]. Mild increase in brain cytochrome concentrations in young animals exposed to Pb may be affected in two ways, i.e. either specific inhibition of heme-synthesis or by affecting brain development by more general processes (e.g. inhibition of protein synthesis) [60]. Change in the chromatin regulator gene ATRX X-linked syndrome (ATR-X) causes mental retardation due to epigenetic modifications [61]. This syndrome causes normal to severe disabilities, characteristic facial gestalt during infancy, expressive language disorder , and hematological symptoms [62]. An outline of action of Pb is shown in Figure 4. Investigation to a study reported that high Pb exposure in nursing rat pups causes an increase in ADP-independent respiration in brain, mitochondria and delayed development of brain dicarboxylic amino acid metabolism. Epidemiological studies have also found correlative evidence of modestly increased exposure to Pb with mental retardation [63].

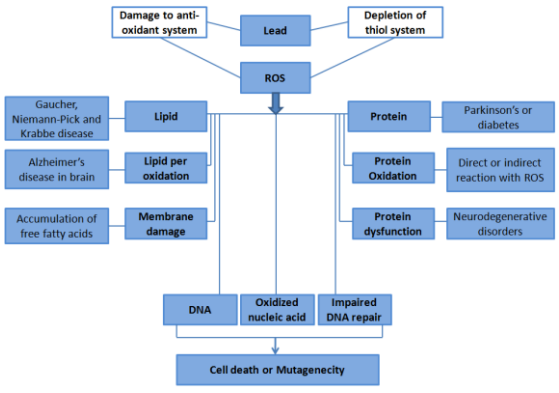

Figure 4. Lead induced oxidative stress.

Placental Exposure

Lead is a heavy metal that crosses the placenta and blood barriers which continue to deposit in fetal tissues. It was seen that the use of Pb-added externally used cosmetics may affect developing fetal: at this stage the blood barrier is not mature and exposure or intake of Pb leaving fetus vulnerable to critical neurological development. Main reason of lead poisoning is that lead substitute for calcium in neurological system causing hippocampus mediated learning and memory impairment [64]. By direct or indirect interaction with hormones through hypothalamic; pituitary glandular axis Pb causes poisoning of the reproductive organs [65]. Epidemiological studies showed adverse birth outcomes from either maternal or paternal lead exposure, including low birth weight (LBW), spontaneous abortion, minor malformations and preterm birth [66]. A considerable increase in the risk of premature births was associated with the elevated urinary Pb fertile after adjusting for confounders with odds ratio (OR) of 1.96. 25-36 years old mothers with OR of 2.03 were more pronounced with this association [67].

Lead accumulation in tissues or organs leads to activate different mechanisms that cause the neuronal cell death by apoptosis and necrosis[68]. It inhibits Na^+/K^+ ATP'S cell membrane interfering with impairment of calcium release from mitochondria and energy metabolism and cause formation of reactive oxygenated species which initiate s apoptosis cascade. Cellular breakdown occurs by malfunctioning of mitochondria, nuclear shrinkage, chromatin condenses, DNA fragmentation and membrane blabbing. During fetal development increase in apoptosis can result in poor learning and memory in children. In addition, it penetrates in CNS and affects the fetal growth by disrupting normal functions of cell and cause abnormal skeleton growths of fetus [69]. It also suppresses activity of thyroid stimulating hormone leading to decrease of soft tissue growth and decrease birth weight and impaired transport of nutrients to fetus as shown in figure 5. New-born Epigenetic Study obtained at gestation 12 weeks hypothesize that prenatal Pb exposure distorts DNA methylation of imprinted genes resulting in rapid growth and lower birth weight. Inductively coupled plasma mass spectrometry (ICP-MS) measured, Pb in peripheral blood of 321 women. Pb exposure also induce poorer cognitive function in childhood and adolescence [70].

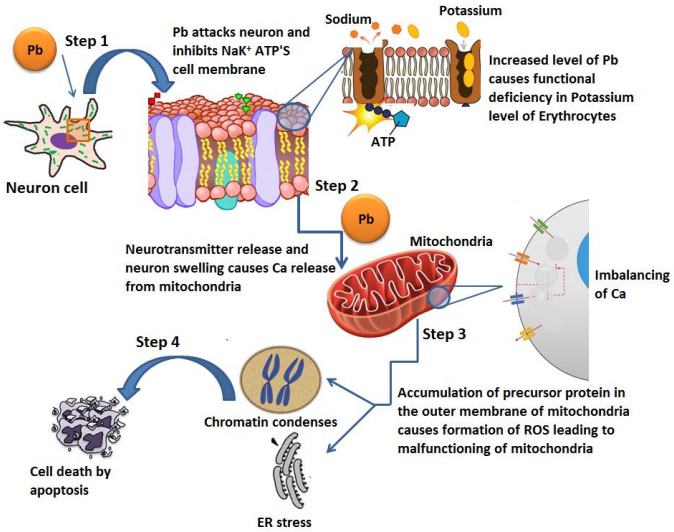

Figure 5. Mechanism of lead toxicity to fetus. Step 1: Shows how Pb attacks a neuron cell. Step 2: Shows neuron release from mitochondria. Step 3: Formation of ROS. Step 4: Cell death by apoptosis.

Cadmium – A color pigment in cosmetics

Cadmium was discovered in 1817 having atomic number 48, it is a soft silvery white metal. The average concentration in Earth's crust is 0.1 – 0.5 ppm. It is refined and consumed in variety of industrial applications such as in batteries, as fuel rods in fission reactors, pigments, stabilizer for plastics, photovoltaic devices coating and paintings, and many others. It was recognized by FDA as toxic metal in late 20th century that can induce severe intoxications. In Japan Cd-induced intoxications with dramatic outcomes was reported in the form of Itai-itai disease

[71]. Cadmium is best known for its color pigment characteristics; commonly the Cd-compounds are found in yellow, orange and red pigments. Cadmium sulfide is used for yellow color whoever, doping of selenium intensify the tone to black. It also mixed with chromium oxide to produce light green tone. So all the cosmetics products used externally for varying the color tone on face use Cd, however the use of Cd is not left without taking precautionary measure to keep it within the limit defined by FDA. These are being added in externally used cosmetics for developing different color tones. Therefore, these are the manufacturers, who should follow the good manufacturing practices (GMPs). It is one of the most toxic metal found in eye liners , lip gloss, beauty creams and lip pencils having adverse effects such as significant proteinuria [19]. As cosmetics are applied over face skin, two possible mechanisms are reported to facilitate Cd absorption through the skin: binding of free Cd-ions to sulfhydryl radicals of cysteine in epidermal keratins or induction and complexing with metallothionein [72]. Then the Cd is released into blood pool where it is distributed throughout the body through binding with erythrocytes membranes, blood-albumin or MTs. It mainly accumulates in liver on short-term exposure; however, on long-term exposure it binds to small proteins which transported to kidneys where filtration in glomerular tubules and re-absorbance into proximal tubular cell takes place. Thus the accumulation in kidneys gradually impose threatening symptoms [9]. The females, who continuously use Cd-added cosmetics can pass Cd to kids during pregnancy, or through mother feeding. Cadmium can accumulates in placental tissues and may disturb nutrient passage along with steroid hormone synthesis [33]. It is found to be associated with carcinogenicity of pancreas, lungs, prostate and kidney cancer [73, 74]. In bathing soaps 0.03 ppm to 0.04 ppm Cd was reported [26]. No Observed Adverse Effect Level (NOAEL) reported for cadmium is 0.005 mg/kg [19]. Thus, in the following sections the diseases triggered by Cd-exposure are discussed.

2.1 Renal malfunctioning

Following the absorption, the Cd through blood mainly accumulate in kidney and liver. Therefore, kidneys are at great risk if the exposure to Cd is continue for long term either due to environment of cosmetic products. Cadmium exposure in Population-based women's health survey in southern Sweden (Women's Health in the Lund Area, WHILA), in relation to tubular and glomerular function in 820 women (71% participation rate) of 53–64 years age, showed 0.38 µg/L cadmium in blood, 0.52 µg/L in urine to be significantly associated with renal tubules disorder [75]. It has also been found that in women, Cd concentrations are generally higher than men [56]. Extremely small amount of Cd is excreted in urine after deposition in kidney due to a lack of excretory mechanism. Further, Cd accumulates in the kidney as a consequence of its preferential uptake by receptor-mediated endocytosis of Cd-bound metallothionein (Cd-MT) and freely filtered cadmium in the renal proximal tubule. Internalized Cd-MT is degraded in lysosomes and endosomes, releasing free Cd into the cytosol where it activates cell death pathways and generate ROS. Heavy cadmium and continued exposure can progress to the clinical renal fanconi syndrome, and leads to renal failure [76].

There are three main thresholds for Cd concentration in urine, the first threshold at approximately 2mg/g creatinine causes biochemical alterations. The second causes cytotoxic signs and the development of high-molecular-weight proteinuria and approximately 4mg/g creatinine is present. The commonly used marker of glomerular malfunctioning is concentrated albumin in urine. An increased urinary excretion of alanine aminopeptidase (AAP) and N-acetyl-b-d-glucosaminidase (NAG) has been attributed to chemical-induced renal tubule damage. The third threshold is associated with tubular proteinuria resulting from an impaired tubular reabsorption of low-molecular-weight proteins along with around 10mg/g creatinine [77].

2.2 Osteoporosis

Osteoporosis is defined as low bone mass and micro-architectural deterioration of the skeleton which causes fragility and increased risk of fractures [78]. Osteomalacia and renal deterioration associated with Cd poisoning was first noted in Japan in late 1940s. Itai-itai disease is considered to be the most severe Cd-intoxication and cause bone and kidney damage [79]. In Itai-Itai disease patients urine concentration of cadmium was found to be in range of 20-30 µg/g creatinine [80]. Extensive epidemiological studies have recently exhibit increased cadmium exposure correlating significantly with competitive replacement of Ca with Cd rendering increased fracture incidence in humans and decreased bone mineral density at lower exposure levels. Cadmium at low concentrations acts directly on bone cells in bone culture system and cause both increases in bone resorption and decrease in bone formation, independent of its effects on circulating hormone concentration, intestine or kidney. The effects of Cd poisoning in bone mineral content of the femoral bone and lumbar spine were measured in a male rat model. Bone damage in these male rats was estimated by dual-energy X-ray absorptiometry (DEXA) [81]. Extreme renal excretion of calcium is an indicator of the loss of bone minerals and in relation to tubular malfunctioning. In addition, it can also reduce the generation of active vitamin D in kidney and results in lack of active vitamin D which delays active calcium reabsorption in the distal convoluted tubule and calcium uptake in the duodenum. This is the main cause of osteomalacia and osteoporosis, especially in the old age. On the other hand, cadmium may also act directly on bone turnover, declining both their production of collagen and ability to mineralize [79].

Three main pathway of Cd acting on bone are: first disturbance of the normal activation process of renal tubular injury followed by vitamin D; second the action of Cd in interference with calcium; however, the mechanism of osteoporosis by Cd has not been completely elucidated, and the third is the direct action of Cd on bone metabolism which does not induce renal injury [82].

3. Chromium – Color additive

Chromium is steely-grey, lustrous and brittle metal with atomic number 24. It is a key ingredient of stainless-steel as anti-corrosive agent. It was considered the essential element, however in 2014, the European Food Safety Authority (EFSA) concluded that there were not sufficient evidence for Cr to be recognized as essential [83]. The most common allergen found in soaps, lip products, eye makeup products and foundations its purpose is to add variety of colors in them [19, 76]. Its color level is in the range of 0.50 to 2.70 ppm; however, toxicity depends on its valence state. Trivalent Cr (Cr(III) is found naturally and it is documented as essential element required for normal energy metabolism [76], while the hexavalent Cr (Cr(VI) not found naturally and toxic for human health i.e. genotoxic, carcinogenic and toxins [19, 84]. The process is typically associated with reduction processes inside the cells which produce ROS and Cr metabolites that generate various genotoxic effects; such as changes in somatic cells as a result of which develop tumors, basically the mechanism of chromium carcinogenicity is based on the exposure of cancer stem cells to hexavalent chromium[85]. Chromium in its hexavalent state is more permeable to skin; cleansing enhances its absorption. However, both Chromium states also act as haptens to develop contact allergy [86]. Typically, its function is mediated by reduction of Cr(VI) to Cr(III) in cell which generate ROS and react with cell protein and DNA. Chromium (III) also make adduct with DNA which initiate mutation [87, 88].

Many oxides of Cr are being used in cosmetics especially in soaps as hydrated chromium and chromium oxides. Different studies were carried out to know the level of Cr in different cosmetics, their exposure rate to consumers and effect on health. According reported data; application of cosmetic product containing Cr from 0.1 – 3.2 µg/g, over face skin showed exposure between 0.0002 µg/Cm^2 and 0.003 µg/Cm^2, which quite less than Cr(VI) which was 1 µg/Cm^2. It can cause Irritation to lining of nose, nose ulcers, running nose, breathing problems (asthma), cough, shortness of breath, wheezing, skin ulcers, severe redness swelling of the skin if breathed in massive amounts [33]. Prolonged exposure to Cr, can cause severe damage to kidney liver circulatory, nervous system, and allergic contact dermatitis when accumulated in stratum cornea [5, 26]. Chromium found in small amounts in makeup cosmetic products which has also been reported recently which describes the level of different metals in cosmetics, and found value of human No Observed Effect Level (NOEL). At this level Cr cannot pose serious health risks to humans, however if it is continuously used then it may cause severe health problems or triggers cancer processes in association with risk factors originated from environment [89]. The elevated amount of Cr was generally found in eye shadows marketed almost in most countries [90-94]. In all type of eye shadows present in toy make-up kits contained Cr at levels above 10 µg/g with a maximum of 3620 µg/g [95]; while makeup kits sold in Egypt contained high Cr-contents i.e. 16.05 – 29,800 µg/g. However, minimal risk factor associated with chromium which is discussed in the following section.

Cr-induced toxicity

In externally applied cosmetics chromium hydroxide green and chromium oxide greens are both allowed to add as color additives. Due to its least-toxicity

profile, even by its maximum possible use as color pigment in cosmetics, FDA has not constituted regulation for Cr that limit its use in cosmetic. The skin allergy is the most commonly reported toxic effect that was induced by Cr. Different studies reported the minimal eliciting threshold (MET, *minimal concentration of Cr(VI) that gives a positive patch test in an individual*) for Cr(VI) ranged from 1770 – 9 µg/g and in another study by the same author reported that 36% patients reacted to a Cr(III) at ≤ 8850 µg/g, while 64% to 17700 µg/g [96, 97]. Currently, no toxicology data available that reflects some serious consequences; a very recent study was reported by Alam et. al., in which they calculated the carcinogenic risk factor for mercury, lead, cadmium and chromium. For chromium the cancer risk was found to be 1.32×10^{-7} in beauty cream sample [98]. According tom the reported limits the carcinogenic (cancer) risk between 10^{-6} and 10^{-4} is considered to be acceptable[99]. The calculated value far lower than the acceptable cancer risk value which indicating no cancer risk from chromium by using in externally used cosmetics.

CONCLUSION

Our approach to discuss the mechanism associated with most frequently used heavy metals i.e. mercury, lead, cadmium and chromium in cosmetics. In general, many study reported the varied amount of concentration of these metals in different cosmetics. Typically, the trend was found in the order of Pb > Cd > Cr > Hg. FDA survey/analysis on cosmetic products being sold in US and Europe markets indicates controlled use of these metals, whoever many African, Asian and developing countries seldom follow the FDA regulations for the use of color additives in cosmetics. Most of the markets such as in 2-Riyal market of Saudi Arabia selling cheaper cosmetics which contain excessive amount of color additives. Similarly, may Chinese cosmetic products also contain color additives more than permitted values. In lieu of this article, reader will be aware about the possible consequences to use lack-of-standard cosmetic products and what type of risks they may face if they use continuously sub-standard cosmetic products. However, there is prime responsibilities of food and drug regulatory authorities in each region of world to make sure that manufacturers are following GMPs.

CONFLICT OF INTEREST

All authors disclose; no conflict of interest exist

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