

A narrative review of heavy metals in cosmetics; health risks

SOMAYE SAFAVI¹, RAHELEH NAJARIAN², MORAD RASOULI-AZAD³, SHAGHAYEGH MASOUMZADEH⁴, AMIR GHADERI^{5, 6}, RAZIE EGHTESEDI¹

¹Trauma Research Center, Kashan University of Medical Sciences, Kashan, Iran

²Emergency Medicine Specialist, Kashan University of Medical Sciences, Kashan, Iran

³Education and Psychology Department, College of Education, University of Raparin, Kurdistan Region, Iraq

⁴Student Research Committee, Kashan University of Medical Sciences, Kashan, Iran

⁵Department of addiction studies, Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran

⁶Clinical Research Development Unit-Matini/Kargarnejad Hospital, Kashan University of Medical Sciences, Kashan, Iran

Email id : Razieeghtesadi@yahoo.com (R. Eghtesadi). Tel: +98-31-55540021; Fax: +98-31-55463377.

Received: 22.07.19, Revised: 22.08.19, Accepted: 22.09.19

ABSTRACT

Cosmetics products since the dawn of civilization are considered a part of routine body care. The last few decades these products have had increasing and applied to the human body for beautification. Xenobiotics and heavy metals including chromium, copper, iron, mercury, cadmium, arsenic and nickel, classified as a light metal, are determinate in various types of cosmetics such as color cosmetics, face and body care products, hair cosmetics, herbal cosmetics. In cosmetic products was harmful when they occur in excessive amounts. Evidence studies determinate that in commercially available cosmetics toxic metals might present in amounts creating a danger to human health. The aim of this review is to assess identification of elimination, sources and control of sources, and monitoring countries marketed exposures and hazards can be used to prevent heavy metals toxicity.

Keywords: Heavy metals, Cosmetics, Toxicity

INTRODUCTION

The past decades the safety of cosmetic products and their ingredients has attracted increasing attention; so, their toxicological safety determination is a relatively young discipline, which evolved in the second half of the 20th century. It was generally shown that cosmetic products will always remain on the surface of the human body in up to the 1960s. Thus, local effects were the primary and secondary safety concern[1]. Cosmetics have been used as a part of routine body care by all classes of people throughout the world[2]. Xenobiotics and heavy metals (e.g., lead, Cadmium, Mercury, Arsenic, Nickel, Chromium, Copper, Iron) are not normally considered as a primary concern in cosmetics. There are concerns regarding the presence of harmful chemicals, including heavy metals, in these products. Although in most cases, cosmetics are applied by a category of a population, the use of toothpastes on a daily basis to maintain oral hygiene is cosmopolitan. Therefore, the daily constant ingestion of heavy metals raises safety issues[3-5]. Cosmetic can be defined as any preparation intended to be applied to the human body for purpose of cleansing, beautifying, promoting attractiveness or altering the appearance without affecting the body's function[6]. Cosmetic products are regulated for health and safety. There are concerns regarding the presence of harmful chemicals, including heavy metals, in these products. There have not been many studies on presence of

heavy metals in cosmetics in Iran. To assess the levels of heavy metals, pollution monitoring laboratory conducted a study on commonly available lipsticks, fairness creams, lip balms and anti-aging creams. Recent reported has demonstrated that these metals can easily cause many types of skin problems. The use of some heavy metals in cosmetic has been controversial due to the biological accumulation of those metals and their toxicity in human body. In most countries, it is legally prohibited to use lead, arsenic, and mercury in skin cosmetic products. In other hand, demonstrated that these metals can cause allergic contact dermatitis or other skin problems[2, 7-9]. Several toxic elements (e.g., lead, cadmium, etc.) have been shown as impurities in pigments of lipsticks, eye shadows, and face powders. In evidence study demonstrated that heavy metals including lead can be absorbed by women's and children's skin through using cosmetic products[5, 10-12]. The use of cosmetics by world women is an ancient tradition. In the study by Nourmoradi[13], Showed that the levels of lead and cadmium in the lipsticks was within the range of 0.08–5.2 µg /g and 4.08–60.20 µg/g, respectively. The eye shadow samples had a lead status of 0.85–6.90 µg/g and a cadmium level of 1.54–55.59 µg /g. The content range of the heavy metals in the eye shadows was higher than that of the lipsticks. There was significant difference between the averages of the lead content in the different

brands of the lipsticks and eye shadows in Iran. In another study, shown that all the brands of lipsticks and lipglosses submitted for analysis contains no lead and cadmium. It therefore assures safety in the use of these brands available in Yenagoa cosmetic stores in Nigeria[14]. Also, in the study by Ze'eviMa'or[15], demonstrated following exposure to Dead Sea mud, MoS (margin of safety) calculations for nickel and chrome showed no toxicological concern for systemic toxicity. Also, skin sensitization is not to be expected by exposure of normal healthy skin to Dead Sea mud. Topical application, however, is not recommended for already nickel or chrome-sensitized persons. In addition, Zakaria and Bin Ho showed that there was no significant difference of cadmium and chromium content in the lipsticks of different price categories. However, there was significant difference of lead content in the lipsticks of different price categories. There was no significant chronic non-carcinogenic health risk due to the exposure to these heavy metals through the ingestion of lipsticks[16]. Lead, which might an impurity, is a proven neurotoxin linked to learning, language, and behavioral problems. Also, young children and pregnant women are vulnerable because lead crosses the placenta and may enter the fetal brain[17, 18]. Cadmium and chromium found in body and hair creams are absorbed into the body through dermal contact[2, 17]. In addition, Mercury is linked to nervous system toxicity, as well as reproductive, immune, and respiratory toxicity. The investigated fairness creams were varied in their metal levels, and the estimated amounts of lead, cadmium, and chromium were shown to be higher than the respective maximum allowable levels, according to the WHO standard[2]. In the review evidence reported cosmetic products are not often linked to serious health hazards, this does not mean that they are always safe to use, especially with regard to possible long-term effects as the products may be used extensively over a long period of time. Cosmetics and skincare products might contain ingredients whose safety is not certain or which are known to cause health risks. Several of the cosmetics, particularly hair dyes and shampoos might contain ingredients classified as known or probable human carcinogens. Again, many of these products may contain penetration enhancers, enhancing penetration through the skin[19]. Also, the use of cosmetic product exposure users to low levels of toxic heavy metals which could constitute potential health risk to users since they are known to accumulate in biological systems over time[20]. Despite the existing published evidence on the association between heavy metals contamination and cosmetics, there are discrepant results regarding the different subsets of heavy metals contamination and studies on cosmetics still remain inconclusive. This review is focused on the heavy metals contamination in cosmetics. In this a narrative review, all papers

published about sources and hazards of heavy metals pollution and cosmetics during the past two decades have been gathered and criticized to reach a conclusion about exact risk of cosmetics and heavy metals contamination in a large country with highest rate of import and export.

METHODS

We looked up the terms heavy metals (lead, Cadmium, Mercury, Arsenic, Nickel, Chromium, Copper, Iron), cosmetics, toxicity, poisoning, toxicity, exposure, source and Iran in all bibliographical databases such as Google Scholar, Pub Med, and Scopus. This review includes relevant articles published between 1990 and 2019.

Lead

International limits have been established for metal impurities in cosmetics to prevent over exposure to heavy metal ions[21]. One of the major issues in the application of cosmetic products is their high contents of heavy metals, due to the industrial manufacturing process. Cosmetic products have been used by humans for thousands of years[22, 23]. Also, several evidence have explored the content of toxic elements in personal care and cosmetic products such as eye pencils, eyeliner, lipstick, skin whitening creams, mascara, body cream, face cream, powder, hairspray, liquid, spray perfumes, body wash, shampoo, and foundation[24-26]. Results demonstrated that in Nigeria, exposure sources include electronic waste, paint and batteries. In Mexico exposure sources include glazed ceramics, lead contaminated utensils and lead contaminated water, for India lead sources include cosmetics and traditional medicines. In France, exposure sources included lead paint from older homes, imported ceramics and cosmetics and industrial emissions[27]. Lead, the main elements of concern in terms of the popular consumption of cosmetics. Lead is toxic elements for the humans, and when they come into contact with vital organs, can cause hepatotoxicity, neurotoxicity, and nephrotoxicity[28]. Lead exposure has been associated with hormonal changes, miscarriage, reduced fertility in men and women, delays in puberty onset in girls. Lead compounds have been classified as a suspected carcinogenic to humans[29, 30]. Lipstick can become pollution with Lead via the use of contaminated raw materials or through the use of pigments that contain it. The use of leaded eye powders such as Surma, Kohl, and Alkol has been linked to enhancing blood Lead concentration in children and women[19, 29]. In the evidence reported that a significant difference of lead content in the lipsticks of different price categories[16]. In Bayelsa state, Nigeria reported the highest concentration of lead and cadmium was detected in the lipsticks while the lipglosses contain no lead and cadmium[14]. Eye shadows and lipsticks have been reported to contain relatively high concentration of heavy metals, kohl a customary

cosmetic used for beautifying the eyes in the Middle East is found to contain lead. Lead and cadmium were present in cosmetics products which include soap, face cream, shampoo, shaving cream and talcum powder[31-33]. In the study by Ali Zainy, reported the content of heavy metals including Al, Fe, Ti, Ag, As, Ba, Cd, Co, Cr, Cu, Mn, Ni, Pb, and Zn in twenty-two lipstick products of imported and locally manufactured at the local market in Jeddah, Saudi Arabia[34]. Also, the results of study in Khyber Pakhtunkhwa, Pakistan revealed that the levels of Fe, Zn, Pb and Cu in the samples within each class under investigation were higher[35]. It has several influences in early interventions of public health, although further studies on epidemiology and mechanism studies are recommended.

Cadmium

Despite the glittering appeal of cosmetics, their public health risk continues to mount. The Food and Drug Administration and European Union's Restriction on Hazardous Substances demonstrated that some cosmetic materials used by humans especially women contain hazardous substances[14]. These heavy metals have been indicted in varying concentrations in various cosmetics, also bearing in mind that some of these metals have been banned as intentional ingredients coupled with their known or probable negative effect[36]. Cadmium described as heavy metals which in their standard state have a density of more than about 5g/cm³ cadmium are essential in very low concentration for the survival of all forms of life, but, when present in higher concentration can cause metabolic disturbance[37]. Cadmium is a deep yellow to orange pigment and mostly present in lipsticks and face powders. The use of cadmium in cosmetics products are due to its color property as it has been used as a color pigment in many industries. In the study by Chauhan et al., reported among the different cosmetics products studied, the highest heavy metal (lead and cadmium) contamination was found in bathing soap[33]. Also, concludes that though in less amount but beauty cosmetic products are contaminate with heavy metals and hence may results in skin problems[38]. In addition, determination of cadmium ions in lipsticks, eye shadows, and hair dyes in Kermanshah[38]. However, evidence reported that the cadmium values in all cosmetic products were significantly lower than the limit set by the Protection and Food Safety of Germany [22]. The authors suggest further analysis of the toxic elements in cosmetics and better monitoring of both imported and contraband cosmetics.

Mercury

Mercury is a metallic element that is naturally occurring in the environment. Mercury can have several forms but is most often recognized as a shiny, silver-white, dense liquid. Metallic mercury finds many uses including in thermometers, electrical switches, dental amalgams and some industrial

manufacturing. In addition to metallic mercury, the element can exist in combination with other elements to form compounds. Mercury compounds are the most common form that exists naturally in the environment. As noted above, the use of such compounds in cosmetic products is strictly regulated by the FDA[39]. Since the dawn of civilization cosmetics have constituted a part of routine body care not only by the upper strata of society but also by middle and low class people. Last few decades have shown a big boost in cosmetic in industries, by the production of the various types of the cosmetics which are needed for the care and beatification of the skin, hair, nails, teeth, body comprises of creams, beauty soaps, etc[33]. Mercury in cosmetics exists in two forms: inorganic and organic. Inorganic mercury (e.g. ammoniated mercury) is used in skin lightening soaps and creams. Organic mercury compounds (thiomersal [ethyl mercury] and phenyl mercuric salts) are used as cosmetic preservatives in eye makeup cleansing products and mascara[40-42]. However, chronic exposure of the body to mercury at very low levels can cause long-lasting neurological and kidney disturbance. Mercury in bleaching preparations can be absorbed through the skin and accumulates in body organs giving rise to severe poisoning. A study conducted on Tanzanian gold miners who use mercury for amalgamation and people not engaged in gold mining activities revealed that the mercury found in their blood and urine was derived from cosmetic soaps and creams containing mercury. Also, Glahder and Appell demonstrated high concentration of mercury in imported soaps and creams bought in Tanzanian shops. In addition, an evidence of Kenyan women with damaged kidney revealed that they suffered severely from higher incidence of nephritic syndrome, which was attributed to the use of creams containing mercury. Depending on the form of mercury, exposure to sufficiently high concentrations can result in allergic reactions, skin irritation, or neurotoxicity. Chronic exposure and accumulation to mercury compounds can result in a variety of signs and adverse reactions (e.g., weakness, irritability, tremors, nervousness, fatigue, memory loss, changes in hearing, vision and taste, vomiting, nausea, diarrhea, kidney damage, and death[43-46]. Evidence studies shown on mercury levels in creams obtained from the Saudi Arabians market which originated from Asia and Middle East contained T-mercury levels above the US FDA limit[42]. Overall, Public awareness needs to be elevated regarding the types of products and the specific products that contain mercury and the risks linked to mercury exposure.

Arsenic

Many people believe that all cosmetics are safe but there are number of studies proving that majority of the cosmetics contains heavy metals or other chemicals. Arsenic, a redox inactive metalloid, is a

notoriously hazardous inorganic element and presents almost everywhere as a major contaminant in environment. It can bind sulfhydryl groups of proteins and deplete glutathione[47-51]. The higher contents of arsenic in contraband eye shadows and eyebrow pencils are an issue that should be taken into considerations by the relevant authorities[22]. The long-term exposure to arsenic can lead to hyperpigmentation, keratosis, various types of cancer and vascular diseases[52-54]. In the study by Tan et al., reported the arsenic contents in some of the studied brands exceed the maximum recommended value of 2.0 mg/kg⁻¹ set by China. These results lead to the conclusion that constant control of arsenic content in cosmetics should be seriously considered[47]. Also, the analysis of five commercial face-powders revealed the presence of all the considered metals in the range 0.06–8.0 µg/g in Italy[55]. In addition, all the samples (skin bleaching creams) analyzed contained significant amounts of Mercury and Arsenic and none of them can be considered safe for prolonged human use[56]. Currently, Arsenic is found in pigments used in cosmetics and is regulated by the USFDA[57]. Although past studies have demonstrated that arsenic is present in a range of cosmetic products such as eye shadows, lotions and lipsticks, only the European Union is known to have strict regulations against the metal, banning it from use in cosmetics. Neither the USFDA nor the WHO has defined acceptable levels for Arsenic in cosmetics[35, 56]. Further studies are needed to confirm findings.

Nickel

The health risk related to the usage of cosmetic has currently become an emerging public health problem, and the safety assessment of cosmetic products on inorganic elements has drawn great attention during the last decade[58-60]. Consumers have asked about "heavy metals" and "toxic metals" in cosmetics. FDA has surveyed a variety of cosmetics on the market, testing for arsenic, cadmium, chromium, cobalt, lead, mercury, and nickel. Nickel is present naturally in the earth. Chronic exposure of nickel may cause skin allergic reaction, skin rash, etc. in addition, IARC classified nickel compounds in Group 1 (carcinogenic to humans) and metallic nickel in Group 2B (possibly carcinogenic to humans)[61]. Nickel is an important cause of allergic contact dermatitis in the general population, both among children and adults, with a worldwide prevalence of around 8.6%. The prevalence among young females is even higher, around 17%[62-64]. There are currently no international standards for nickel impurities in cosmetics. Nickel elicitation studies have revealed that approximately 5% of a nickel-sensitized population will react to an occluded dose of 0.441g nickel/cm²/week. In addition, that the allergy and elicitation thresholds for skin-penetrating exposure are lower. Nickel levels were lower than 5

µg/g only in three samples, the highest concentrations were found in one eye shadow made in Italy with a nickel range of 169–3441 µg/g, in the other samples, six of which made in China, the nickel amounts went from 2.76 (pink) to 22.71 µg/g (yellow green)[37, 65, 66]. Naturally, lipstick is applied on the lips for the users to look more beautiful and attractive, but the price for these women to be beautiful is their exposure to heavy metals contained in the lipstick. Lipsticks are believed to contain heavy metals such as lead, nickel, aluminum, arsenic, cadmium, antimony, and chromium. Moreover, heavy metals can be released by the metallic devices used during the manufacturing of products[16, 67, 68]. Cosmetics often contain nickel and some products such as mascara and eye shadows might cause or aggravate allergic contact dermatitis, particularly in patients with eyelid involvement. "Nickel-free" cosmetics available in the market contain less than 1ppm of nickel and can be safely used by most sensitized patients[5, 69, 70]. Clinical features by exposure to nickel include involvement of previous exposed areas (flare-up of dermatitis and/or patch test sites), as well as unexposed areas (e.g., maculopapular exanthema, pompholyx, flexural eczema, "baboon syndrome", and vasculitis-like lesions) and general symptoms (e.g., headache, malaise, fever, arthralgia, pirosis, nausea, diarrhea and vomiting)[64]. In the study by Concetta Bruzzone et al., reported despite the wide range of metal levels (chromium, nickel, and cobalt) in the samples (e.g., pearly powder eye shadow), the amounts of bioaccessible elements were undetectable or very low (less than 0.4 mg/kg)[71]. However, the number of cosmetics on the market is unlimited and many cosmetics are used in combination and can have different exposure patterns and health effects, further evidence on the safety of cosmetics is mandatory in order to reduce an unnecessary exposure to toxic metals.

Chromium

Chromium can exist in multiple valence states, with trivalent being most common. Chromium is the most common form found in food-stuffs, nutritional supplements, and biological system and is associated with a very low degree of toxicity[72, 73]. The cosmetic industry is growing fast due to the high demand from the consumers especially female. Despite any age groups, it has become a trend that the consumers will apply cosmetics in their daily life[74, 75]. Several reported has demonstrated the potential toxic effects that result from chromium pollution in different exposure routes. These include (e.g., blood, liver, and kidney toxicity), and following oral exposure (e.g., lung cancer following inhalation exposure, and allergic contact dermatitis) following dermal exposure[76, 77]. In the reported by Filon et al. revealed that chromium is able to

permeate through intact human skin, and its levels was shown to be significantly higher in the damaged skin compared to that in the intact skin. Also, chromium can be easily absorbed by the skin probably due to its strong binding capacity to the skin proteins. Sweat enhances the absorption rate of chromium into the skin and cause sensitizing effects. Contact allergies are also observed in sensitive individuals via dermal contact with the chromium compound[78, 79]. Previous studies found a measurable level of heavy metals in facial cosmetics such as mascara, eye shadows, lipsticks, eye liners, foundation, and cream, as well as nail polish. The chromium mean levels in the eye shadow samples was $120.4 \pm 77.3 \mu\text{g kg}^{-1}$. The maximum chromium concentration was $197.2 \mu\text{g kg}^{-1}$, whereas the lowest concentration was $1.2 \mu\text{g kg}^{-1}$ [80-82]. Also, In the study by Lim et al., demonstrated lead and chromium concentrations were to be the highest in blue color category with the mean levels of $161.8 \pm 101.6 \mu\text{g kg}^{-1}$ and $149.4 \pm 53.1 \mu\text{g kg}^{-1}$, respectively. The chromium levels were higher in the shimmering shade[75]. In addition, evidence study chromium (VI) was undetectable in black iron oxide and present at very low levels (about 0.3 mg/kg) in pearly pigment and in the pearly powder eye shadow samples[71]. The results of Corazza study demonstrated that concentrations chromium exceeded 5 ppm in 28 out of 52 (53.8%) samples, with values over 1000 ppm in 3 eye shadows[83]. With these evidences, further studies are necessary.

Iron

Inorganic and iron compounds are demonstrated widely in the human environment. Iron compounds are used commercially in plastics, textiles and cosmetics, where advantage is taken of their colour range and the safety in use afforded by various ferrous and ferric salts. In other hand, iron is an important nutrient in the human body. Also, its major function in the metabolism of oxygen radicals, iron plays a central role in maintenance, the growth and normal physiology of the skin and its appendages. It is not clear to what extent iron in cosmetic formulations improves the health of the skin. However, the nature of the human skin and its excretions, or limitations in the so-called barrier function, can be expected to permit the absorption of some organic and inorganic substances applied to its surface, albeit at very low levels[84-88]. The high of Fe is most likely attributed to the established role of iron compounds as colorants in cosmetics[31, 34]. Even the essential metals when present in higher concentration become toxic[89]. In the study by Ullah[35], reported that the levels of Fe, Zn, Pb and Cu in the samples with in cosmetics products under investigation were higher. Also, Faruruwa and Bartholomew[80], demonstrated that in a total of 40 Samples consisting of 10 different types of facial cosmetics commonly used in Nigeria, Chromium, nickel, zinc and, iron were shown in varying levels in

all the samples. In addition, Ni was demonstrated in iron oxide brown pigments ($1.9\text{--}250 \text{ mg kg}^{-1}$) used for the production of eye cosmetics. Furthermore, an incident of a 44-year-old woman with persistent eyelid allergic contact dermatitis (lasting for 10 months) caused by 5% black ironoxide from a mascara has been noticed[90]. In the review evidence indicate metals necessary, but harmful when they occur in excessive amounts, elements (e.g., copper, iron, chromium and cobalt) are present in cosmetic products. Literature data show that in commercially available cosmetics toxic metals may be present in amounts creating a danger to human health[91].

Copper

Copper is a reddish metal that occurs naturally in (e.g., rock, soil, water, sediment, and, at low levels, air). Its average levels in the earth's crust is about 50 parts copper per million parts soil and, stated another way, 50 grams of copper per 1,000,000 grams of soil (1.8 ounces or 0.11 pounds of copper per 2,200 pounds of soil). Also, copper occurs naturally in plants and animals. It is an essential element for all known living organisms including humans and other animals at low levels of intake. At much higher concentration, toxic effects can occur. The term copper in this profile not only refers to copper metal, but also to compounds of copper that may be in the environment[92]. Metals (e.g., cadmium, lead and mercury) exist in cosmetics because of impurities in raw materials, release from manufacturing devices or intentional addition to cosmetics. The active center of tyrosinase, copper, can be replaced by mercury, which inhibits melanin production[21, 93]. Harmful heavy metals when occur in excessive amounts, elements including copper, iron, chromium and cobalt are present in cosmetic products[91, 94]. A calibration curve with different copper levels (0, 1, 1.5, and 2 mg/l)[20]. Small levels copper peptides have an excellent safety record and are widely used in cosmetic products. The most studied copper peptide is glycyl-L-histidyl-L-lysine, a small copper-binding peptide, naturally present in human plasma [95]. Mercury, cadmium, lead, nickel, chromium, and copper are the most common heavy metals detected in cosmetic products (e.g., shampoo, lipstick, cream, eye shadow, and powder)[68]. It has been suggested by Peled et al[96], that copper-free GHK promotes the survival of stem cells and possibly the de-differentiation of cells, while GHK with copper 2+ promotes cell differentiation. In the study by Sani et al[20], the cosmetics were digested and analyzed for heavy metals, the range of the levels in skin lightening creams is 4.24-8.48 for copper, the levels copper also in lipsticks are 4.24-12.71 in selected cosmetic products sold in kano metropolis, Nigeria. Also, copper detected in lipstick products marketed in Saudi Arabia[34]. Prolonged use of products containing these elements may pose a threat to human health and could damage the

environment[34]. The monitoring other heavy metals and chemicals used in the manufacture of cosmetics products which may cause health risks to users should be emphasized.

CONCLUSION

This narrative review investigated the concentration of heavy metals in cosmetic products of different countries marketed. However, recently there has been enhancing concern about their safety. Unfortunately, using these products in some cases is related to the occurrence of unfavorable effects resulting from intentional or the accidental presence of chemical substances, including toxic metals. Therefore, Identification of elimination, sources and control of sources, and monitoring countries marketed exposures and hazards can be used to prevent heavy metals toxicity. The data obtained clearly demonstrated that further evidence is needed of these heavy metals in cosmetic products of daily use. Acceptable limits of potential pollutions in cosmetics must be enforced. The principle of good manufacturing practice must be followed. There is need for a determination of human risk from the exposure to cosmetics which are highly pollutions with heavy metals.

REFERENCES

- Al-Dayel, O., J. Hefne, and T. Al-Ajyan, Human exposure to heavy metals from cosmetics. *Oriental Journal of Chemistry*, 2011. 27(1): p. 1.
- Alam, M., et al., Assessment of some heavy metals in selected cosmetics commonly used in Bangladesh and human health risk. *Journal of Analytical Science and Technology*, 2019. 10(1): p. 2.
- Łodyga-Chruścińska, E., A. Sykuła, and M. Wiśniewska, Hidden Metals in Several Brands of Lipstick and Face Powder Present on Polish Market. *Cosmetics*, 2018. 5(4): p. 57.
- Vafaei F, Abdollahzadeh F. Investigating the effects of Hydroalcoholic extract of jujube fruit (*Zizyphus vulgaris* L.) on second degree burn wound healing in Balb/c mice. *J Med Life*. 2015;8(Spec Iss 2):117-120
- Sainio, E.L., et al., Metals and arsenic in eye shadows. *Contact Dermatitis*, 2000. 42(1): p. 5-10.
- Oyediji, F., G. Hassan, and B. Adeleke, Hydroquinone and heavy metals levels in cosmetics marketed in Nigeria. *Trends Appl. Sci. Res*, 2011. 6(7): p. 622-639.
- Hostynek, J., Chromium, cobalt, copper and iron: metals in personal care products. *Dermatol Vic W*, 2000. 115: p. 52-65.
- Kerosuo, H., et al., Nickel allergy in adolescents in relation to orthodontic treatment and piercing of ears. *Am J Orthod Dentofacial Orthop*, 1996. 109(2): p. 148-54.
- Nesterenko, P.N. and P. Jones, Single-column method of chelation ion chromatography for the analysis of trace metals in complex samples. *Journal of Chromatography A*, 1997. 770(1-2): p. 129-135.
- Al-Saleh, I., et al., Determinants of blood lead levels in Saudi Arabian schoolgirls. *International journal of occupational and environmental health*, 1999. 5(2): p. 107-114.
- Al-Saleh, I.A. and L. Coate, Lead exposure in Saudi Arabia from the use of traditional cosmetics and medical remedies. *Environ Geochem Health*, 1995. 17(1): p. 29-31.
- Godt, J., et al., The toxicity of cadmium and resulting hazards for human health. *J Occup Med Toxicol*, 2006. 1: p. 22.
- Nourmoradi, H., et al., Assessment of lead and cadmium levels in frequently used cosmetic products in Iran. *J Environ Public Health*, 2013. 2013: p. 962727.
- Vafaei F, Nouri G, Razi A. Spontaneous Cholecystocutaneous Fistulae: A Case Report, *International Journal of Pharmaceutical Research*, 2018; 3; 344-345.
- Ma'or, Z., et al., Safety evaluation of traces of nickel and chrome in cosmetics: The case of Dead Sea mud. *Regul Toxicol Pharmacol*, 2015. 73(3): p. 797-801.
- Zakaria, A. and Y.B. Ho, Heavy metals contamination in lipsticks and their associated health risks to lipstick consumers. *Regul Toxicol Pharmacol*, 2015. 73(1): p. 191-5.
- Ayenimo, J.G., et al., Heavy metal exposure from personal care products. *Bull Environ Contam Toxicol*, 2010. 84(1): p. 8-14.
- Horowitz, Y., et al., Acro-dynia: a case report of two siblings. *Arch Dis Child*, 2002. 86(6): p. 453.
- Okereke, J., et al., Possible health implications associated with cosmetics: a review. *Sci J Public Health*, 2015. 3(5-1): p. 58-63.
- Sani, A., M.B. Gaya, and F.A. Abubakar, Determination of some heavy metals in selected cosmetic products sold in kano metropolis, Nigeria. *Toxicol Rep*, 2016. 3: p. 866-869.
- Chen, K.L., S.J. Jiang, and Y.L. Chen, Determining lead, cadmium and mercury in cosmetics using sweeping via dynamic chelation by capillary electrophoresis. *Anal Bioanal Chem*, 2017. 409(9): p. 2461-2469.
- Saadatzadeh, A., et al., Determination of heavy metals (lead, cadmium, arsenic, and mercury) in authorized and unauthorized cosmetics. *Cutan Ocul Toxicol*, 2019. 38(3): p. 207-211.
- Brown, V.J., Metals in lip products: a cause for concern? *Environ Health Perspect*, 2013. 121(6): p. A196.
- Sayed Saeed Mazloomi Mahmoodabad, Fereshteh Sohrabi Vafa, Ali Akbar Vaezi, Hamid karimi, Hosein Fallahzadeh, Explanation of the Perceptions of Women with Prediabetes Affecting Physical Activity: A Qualitative Study, *International Journal of Ayurvedic Medicine*, 2019, 10(1), 95-104.
- Alqadami, A.A., et al., Determination of heavy metals in skin-whitening cosmetics using microwave digestion and inductively coupled plasma atomic emission spectrometry. *IET Nanobiotechnol*, 2017. 11(5): p. 597-603.

26. Lim, D.S., et al., Non-cancer, cancer, and dermal sensitization risk assessment of heavy metals in cosmetics. *J Toxicol Environ Health A*, 2018. 81(11): p. 432-452.
27. Obeng-Gyasi, E., Sources of lead exposure in various countries. *Rev Environ Health*, 2019.
28. Karri, V., M. Schuhmacher, and V. Kumar, Heavy metals (Pb, Cd, As and MeHg) as risk factors for cognitive dysfunction: A general review of metal mixture mechanism in brain. *Environ Toxicol Pharmacol*, 2016. 48: p. 203-213.
29. Sprinkle, R.V., Leaded eye cosmetics: a cultural cause of elevated lead levels in children. *J Fam Pract*, 1995. 40(4): p. 358-62.
30. Agency of Toxic Substances and Disease Registry, "Toxicological Profile for Cadmium," <http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=48&iid=15>, 2008. Retrieved, March 10, 2015.
31. Basketter, D.A., et al., Nickel, chromium and cobalt in consumer products: revisiting safe levels in the new millennium. *Contact dermatitis*, 2003. 49(1): p. 1-7.
32. Bellinger, D.C., Teratogen update: lead and pregnancy. *Birth Defects Res A Clin Mol Teratol*, 2005. 73(6): p. 409-20.
33. Chauhan, A.S., et al., Determination of lead and cadmium in cosmetic products. *Journal of Chemical and Pharmaceutical Research*, 2010. 2(6): p. 92-97.
34. Zainy, F.M.A., Heavy metals in lipstick products marketed in Saudi Arabia. *Journal of Cosmetics, Dermatological Sciences and Applications*, 2017. 7(04): p. 336-348.
35. Ullah, H., et al., Comparative study of heavy metals content in cosmetic products of different countries marketed in Khyber Pakhtunkhwa, Pakistan. *Arabian Journal of Chemistry*, 2017. 10(1): p. 10-18.
36. Mathee, A., et al., Exposure to lead in South African shooting ranges. *Environ Res*, 2017. 153: p. 93-98.
37. Bocca, B., et al., Levels of nickel and other potentially allergenic metals in Ni-tested commercial body creams. *J Pharm Biomed Anal*, 2007. 44(5): p. 1197-202.
38. Ahmadi-Jouibari, T., et al., Determination of cadmium in cosmetics from Kermanshah, Iran by graphite furnace atomic absorption spectrometry. *New Journal of Chemistry*, 2017. 41(20): p. 11948-11954.
39. ATSDR (1999). Toxicological profile for mercury. Atlanta, GA, Agency for Toxic Substances & Disease Registry
40. Cain, A., et al., Substan(<http://www.atsdr.cdc.gov/toxprofiles/TP.asp?id=115&tid=24>).ce flow analysis of mercury intentionally used in products in the United States. *Journal of Industrial Ecology*, 2007. 11(3): p. 61-75.
41. Ladizinski, B., N. Mistry, and R.V. Kundu, Widespread use of toxic skin lightening compounds: medical and psychosocial aspects. *Dermatol Clin*, 2011. 29(1): p. 111-23.
42. al-Saleh, I. and I. al-Doush, Mercury content in skin-lightening creams and potential hazards to the health of Saudi Women. *J Toxicol Environ Health*, 1997. 51(2): p. 123-30.
43. Agorku, E.S., et al., Mercury and hydroquinone content of skin toning creams and cosmetic soaps, and the potential risks to the health of Ghanaian women. *Springerplus*, 2016. 5: p. 319.
44. Barr, R.D., B.A. Woodger, and P.H. Rees, Levels of mercury in urine correlated with the use of skin lightening creams. *Am J Clin Pathol*, 1973. 59(1): p. 36-40.
45. Dean, B.J., et al., Genetic toxicology testing of 41 industrial chemicals. *Mutat Res*, 1985. 153(1-2): p. 57-77.
46. Kahatano, J., S. Mnali, and H. Akagi, A study of mercury levels in fish and humans in Mwakitolyo mine and Mwanza town in the Lake Victoria goldfields, Tanzania. *Br Med J*, 1998. 2: p. 543-545.
47. Tan, X., et al., Safety Assessment of Arsenic in Cosmetic Face-creams by Inductively Coupled Plasma Atomic Emission Spectrometer. *American Journal of Applied Chemistry*, 2019. 7(1): p. 35-41.
48. Chung, J.-Y., S.-D. Yu, and Y.-S. Hong, Environmental source of arsenic exposure. *Journal of preventive medicine and public health*, 2014. 47(5): p. 253.
49. Tchounwou, P.B., A.K. Patlolla, and J.A. Centeno, Carcinogenic and systemic health effects associated with arsenic exposure--a critical review. *Toxicol Pathol*, 2003. 31(6): p. 575-88.
50. Jomova, K. and M. Valko, Advances in metal-induced oxidative stress and human disease. *Toxicology*, 2011. 283(2-3): p. 65-87.
51. Flora, S.J. and V. Pachauri, Chelation in metal intoxication. *International journal of environmental research and public health*, 2010. 7(7): p. 2745-2788.
52. Gibb, H., et al., Utility of recent studies to assess the National Research Council 2001 estimates of cancer risk from ingested arsenic. *Environmental Health Perspectives*, 2010. 119(3): p. 284-290.
53. Sun, H.-J., et al., Arsenic and selenium toxicity and their interactive effects in humans. *Environment international*, 2014. 69: p. 148-158.
54. Bhattacharjee, P., et al., Systems biology approaches to evaluate arsenic toxicity and carcinogenicity: An overview. *International journal of hygiene and environmental health*, 2013. 216(5): p. 574-586.
55. Capelli, C., et al., Determination of arsenic, cadmium, cobalt, chromium, nickel, and lead in cosmetic face-powders: optimization of extraction and validation. *Analytical Letters*, 2014. 47(7): p. 1201-1209.
56. Mohammed, T., E. Mohammed, and S. Bascombe, The evaluation of total mercury and arsenic in skin bleaching creams commonly used in Trinidad and Tobago and their potential risk to the people of the Caribbean. *J Public Health Res*, 2017. 6(3): p. 1097.
57. Hepp, N.M., et al., Survey of cosmetics for arsenic, cadmium, chromium, cobalt, lead, mercury, and nickel content. *J Cosmet Sci*, 2014. 65(3): p. 125-45.
58. Ruiz, L.R., et al., Investigation of the Presence of Heavy Metals and Other Contaminants in Labor Cosmetics and their Health Risks in General. *Health Science Journal*, 2019. 13(3): p. 1-3.

59. Malvandi, H. and F. Sancholi, Assessments of some metals contamination in lipsticks and their associated health risks to lipstick consumers in Iran. *Environ Monit Assess*, 2018. 190(11): p. 680.
60. Prasertboonyai, K., et al., Mercury(II) determination in commercial cosmetics and local Thai traditional medicines by flow injection spectrophotometry. *Int J Cosmet Sci*, 2016. 38(1): p. 68-76.
61. Ahlstrom, M.G., et al., Nickel allergy and allergic contact dermatitis: A clinical review of immunology, epidemiology, exposure, and treatment. *Contact Dermatitis*, 2019.
62. Thyssen, J.P., et al., The epidemiology of contact allergy in the general population--prevalence and main findings. *Contact Dermatitis*, 2007. 57(5): p. 287-99.
63. Nielsen, N.H. and T. Menne, Allergic contact sensitization in an unselected Danish population. The Glostrup Allergy Study, Denmark. *Acta Derm Venereol*, 1992. 72(6): p. 456-60.
64. Torres, F., et al., Management of contact dermatitis due to nickel allergy: an update. *Clin Cosmet Investig Dermatol*, 2009. 2: p. 39-48.
65. Fischer, L.A., T. Menne, and J.D. Johansen, Experimental nickel elicitation thresholds--a review focusing on occluded nickel exposure. *Contact Dermatitis*, 2005. 52(2): p. 57-64.
66. Contado, C. and A. Pagnoni, A new strategy for pressed powder eye shadow analysis: allergenic metal ion content and particle size distribution. *Sci Total Environ*, 2012. 432: p. 173-9.
67. Al-Saleh, I. and S. Al-Enazi, Trace metals in lipsticks. *Toxicological & Environmental Chemistry*, 2011. 93(6): p. 1149-1165.
68. Volpe, M., et al., Determination and assessments of selected heavy metals in eye shadow cosmetics from China, Italy, and USA. *Microchemical Journal*, 2012. 101: p. 65-69.
69. Diepgen, T.L. and E. Weisshaar, Contact dermatitis: epidemiology and frequent sensitizers to cosmetics. *J Eur Acad Dermatol Venereol*, 2007. 21 Suppl 2: p. 9-13.
70. Le Coz, C.J., et al., Allergic contact dermatitis from shellac in mascara. *Contact Dermatitis*, 2002. 46(3): p. 149-152.
71. Bruzzoniti, M.C., et al., Chromium, nickel, and cobalt in cosmetic matrices: an integrated bioanalytical characterization through total content, bioaccessibility, and Cr(III)/Cr(VI) speciation. *Anal Bioanal Chem*, 2017. 409(29): p. 6831-6841.
72. Hwang, M., et al., Safety assessment of chromium by exposure from cosmetic products. *Arch Pharm Res*, 2009. 32(2): p. 235-41.
73. Felter, S.P. and M.L. Dourson, Hexavalent chromium-contaminated soils: options for risk assessment and risk management. *Regulatory Toxicology and Pharmacology*, 1997. 25(1): p. 43-59.
74. Mansor, N., D.E.B.M. Ali, and M.R. Yaacob, Cosmetic usage in Malaysia: understanding of the major determinants affecting the users. *International Journal of Business and Social Science*, 2010. 1(3).
75. Lim, J.S.J., Y.B. Ho, and H. Hamsan, Heavy metals contamination in eye shadows sold in Malaysia and user's potential health risks. *Annals of Tropical Medicine and Public Health*, 2017. 10(1): p. 56.
76. Kang, E.K., et al., Determination of hexavalent chromium in cosmetic products by ion chromatography and postcolumn derivatization. *Contact Dermatitis*, 2006. 54(5): p. 244-8.
77. Hansen, M.B., J.D. Johansen, and T. Menne, Chromium allergy: significance of both Cr(III) and Cr(VI). *Contact Dermatitis*, 2003. 49(4): p. 206-12.
78. Filon, F.L., et al., In vitro absorption of metal powders through intact and damaged human skin. *Toxicology in vitro*, 2009. 23(4): p. 574-579.
79. Baruthio, F., Toxic effects of chromium and its compounds. *Biol Trace Elem Res*, 1992. 32: p. 145-53.
80. Faruruwa, M. and S. Bartholomew, Study of heavy metals content in facial cosmetics obtained from open markets and superstores within Kaduna metropolis, Nigeria. *Am. J. Chem. Appl*, 2014. 1(2): p. 27-33.
81. Monnot, A.D., et al., An exposure and health risk assessment of lead (Pb) in lipstick. *Food Chem Toxicol*, 2015. 80: p. 253-260.
82. Nnorom, I., J. Igwe, and C. Oji-Nnorom, Trace metal contents of facial (make-up) cosmetics commonly used in Nigeria. *African Journal of Biotechnology*, 2005. 4(10).
83. Corazza, M., et al., Measurement of nickel, cobalt and chromium in toy make-up by atomic absorption spectroscopy. *Acta dermato-venereologica*, 2009. 89(2): p. 130-133.
84. Giancola, G. and M.L. Schlossman, Decorative Cosmetics. *Cosmeceuticals and Active Cosmetics*, 2015: p. 191.
85. Riley, P., Colouring materials used in decorative cosmetics and colour matching, in *Poucher's Perfumes, Cosmetics and Soaps*. 2000, Springer. p. 151-165.
86. Sato, S., Iron deficiency: structural and microchemical changes in hair, nails, and skin. *Semin Dermatol*, 1991. 10(4): p. 313-9.
87. Lansdown, A., Action and interaction of metal ions in the physiology and toxicology of the skin. *CRC Current Reviews in Toxicology*, 1995. 25: p. 397-462.
88. Roe, D.A., *Nutrition and the skin*. 1986: Liss.
89. Al-Trabulsy, H.A., A.E. Khater, and F.I. Habbani, Heavy elements concentrations, physiochemical characteristics and natural radionuclides levels along the Saudi coastline of the Gulf of Aqaba. *Arabian Journal of Chemistry*, 2013. 6(2): p. 183-189.
90. Van Ketel, W. and D. Liem, Eyelid dermatitis from nickel contaminated cosmetics. *Contact Dermatitis*, 1981. 7(4): p. 217-217.
91. Borowska, S. and M.M. Brzóška, Metals in cosmetics: implications for human health. *Journal of applied toxicology*, 2015. 35(6): p. 551-572.
92. Flemming, C. and J. Trevors, Copper toxicity and chemistry in the environment: a review. *Water, Air, and Soil Pollution*, 1989. 44(1-2): p. 143-158.

93. Defense, E., Heavy Metal Hazard: the Health Risks of Hidden Heavy Metals in Face Makeup. Environmental Defence: Toronto, ON, 2011.
94. Michalek, I.M., et al., A systematic review of global legal regulations on the permissible level of heavy metals in cosmetics with particular emphasis on skin lightening products. *Environ Res*, 2019. 170: p. 187-193.
95. Pickart, L. and A. Margolina, Skin regenerative and anti-cancer actions of copper peptides. *Cosmetics*, 2018. 5(2): p. 29.
96. Pickart, L., et al., Growth-modulating plasma tripeptide may function by facilitating copper uptake into cells. *Nature*, 1980. 288(5792): p. 715-7.