Chapter

Review of Health Hazards and Toxicological Effects of Constituents of Cosmetics

John Kanayochukwu Nduka, Henrietta Ijeoma Kelle and Isaac Omoche Odiba

Abstract

Cosmetic products are designed for use on human body for beautifying and promoting attractiveness and appearance; for these reasons, cosmetics are in high demand especially among women of all ages in every country. Despite many vulnerabilities associated with cosmetic usage, the cosmetic and 'makeup' continues to enjoy wide acceptability irrespective of age and sex. This is made possible by massive advertising employed by producers and marketers of cosmetics. Advertising is the link between manufactured products and would-be consumers; it plays a crucial role in determining the product that is mostly patronised and vice versa. Therefore, ethical advertising that promotes utilitarian benefits of cosmetics should be encouraged over and above emotional advertisement that lowers self-esteem of consumers and offers such products as solution to their low self-esteem. Despite the ban in many countries of poisonous substances in cosmetic products, inexhaustive list of substances, such as lead, chromium, nickel, mercury, arsenic, cadmium, hydroquinone, steroids, nitrosamine, etc. are still present in many cosmetic products. In most cases, above regulatory values, cancers, renal disorders, thinning and easy brushing of the skin, dermatophyte infection with lesions, macular hyper pigmentation, pityriasis vesicular, diabetes mellitus, micropapular eruption, hypertension, etc. are possible toxicological and health hazards that may be associated with continuous cosmetic application.

Keywords: cosmetics, hazardous constituents, toxicological effects, public health issues, continuous cosmetic usage

1. Introduction

Body and personal care products (cosmetics) are designed to be applied on body parts for the purpose of enhancing cleaning, protecting, beautifying, healthy and young looking appearance or altering appearance without changing the body's operational nature [1, 2]. Body care products are of different kinds like skin moisturizers, perfumes, lipsticks and lip glosses, finger nail polishes, eye and facial makeup preparations, shampoo, hair colours and deodorant [3, 4]. A distinction that is made between cosmetics and drugs is that the latter is described as substances used as medicine or used in medicine. That is, drugs are intended to be used to treat or prevent ailments or diseases upon reaction with the human system. In addition, unlike cosmetics, drugs must be subjected to and pass premarket

screening test(s) where they are proven to be safe and effective before they are marketed [3]. Certain chemicals that are part of cosmetic formulations have been found to be harmful, and the usage of cosmetic products containing such chemicals portends danger for human health. Inexhaustive list include heavy metals, hydroquinone, steroids, phenols and nitrosamines, etc. [1, 2, 5–9]. Surprisingly, in spite of the regulations put in place to prevent or minimize the presence of such ingredients in cosmetic brands, heavy metals, organic and inorganic chemical substances are still very much in them. A reason given for this is that such substances may be a major component of the raw materials used in cosmetic manufacture or are deliberately included in cosmetics [1, 6].

Cosmetic products appear not to be subjected to clinical trials or laboratory testing(s) by regulatory authority in Nigeria before premarket approval. This is evident from legal document setting up the Nigerian National Agency for Food and Drug Administration and Control (NAFDAC). Guidelines stating the necessary requirement for registration of imported cosmetics in Nigeria are the attachment of certificate of analysis to the application for registration. This implies that safety and quality of products are monitored through post-market surveillance (PMS) activity. The implication is that laboratory/clinical testing of cosmetic products by NAFDAC takes place only when a victim of hazardous effect of cosmetic is reported or an end user discovers it to be defective or have side effects on the consumers. The guidelines prohibit mercury and its compounds, including corticosteroids. The reason is that mercury is a known cause of dermatitis and kidney damage which could manifest as hypertension. Continuous and possible excessive application of corticosteroids through cosmetics on the skin is reported to cause recalcitrant acne, red striae, excessive hairiness, proneness to infections, insulin related ailments and cataract [10]. Creams with hydroquinone at a concentration higher or in amount in excess of two percent (2%) are under prohibition because their side effect manifests as exogenous ochronosis which is depicted as a dirty brown pigmentation or colouration on areas of the body exposed to the sun followed by the skin's loss of elasticity [10].

The cosmetic market in Nigeria is currently flooded with a variety of cosmetic products in response to the high demands for such products [7]. Nigeria with a conservative population estimated at 154,774,091 people as in February 2010 [11] whose citizens are regarded as being highly fashionable and glamorous provides an ever increasing market for cosmetic product manufacture, marketers and importers. Cosmetic manufacturers and marketers/distributors selling products containing mercury and corticosteroids usually violate fair packaging and labelling requirements by not always listing them as ingredients of the products. Furthermore, dark-skinned African populace use cosmetic majorly in an attempt to change their skin colour in response to social pressures [7]. Society tends to associate affluence (social and professional success) with physical attractiveness [12]. This may suggest the rationale behind the advertising strategy of most cosmetic manufacturers and marketers whereby their products are promoted majorly by exposing the populace to pictures of good-looking and even slightly above-average-looking females [3, 12]. It may also suggest the reason why Nigerian women were ranked high on a list of African countries known for patronizing skin lightening products [6].

Nigeria, irrespective of their social-economic background, attach a lot of importance to their looks and actively seek to improve such regardless of the cost or implications [7].

Although skin lightening products alter the body's structure and function by inhibiting and/or reducing melanogenesis [2, 6, 9, 13], they are classified as cosmetics rather than drugs and can be readily purchased over the counter at roadside non-pharmaceutical stores. As a result, these products are much more readily available, and since some of them come very cheap, anybody, regardless of

socio-economic background would always find a product that is affordable [7]. The choice of product usage is compounded by ignorance, illiteracy and make-believe lifestyle. According to the Nigeria's National Literacy Survey [11] carried out by Nigeria's National Bureau of Statistics, the study revealed that the adult literacy level rate in English language stands at 57.9%. This makes it difficult for a large segment of the population (42.1%) to even read and comprehend the inscriptions on the label of cosmetic product, leaving them ignorant of the actual benefits and risks associated with the cosmetics they have decided to use. That aside, the quest for survival makes even the literate populace to pay little attention to information on content and instruction on direction of use that are contained on the product labels. A huge chunk of the cosmetic brands found in Nigeria are imported from America, Europe and Asia. It is not surprising, as Nigerians view products tagged 'foreign' as being of superior quality and therefore attach greater value to such products than locally manufactured ones. In order to maintain a clean and healthy environment that is free of pollution as well as protects public health, potential public health and environmental pollutant such as cosmetics must have their contents carefully and properly scrutinized and continuously monitored. The aim of this review is to X-ray the toxicological profile and effects of toxicants contained in cosmetic brands in Nigerian market and elsewhere.

2. Types of cosmetics

Many cosmetic products exist in Nigerian market and elsewhere across the globe; some are locally made, while others are imported. They may occur in liquid, semi-liquid, solid, granular and volatile form; examples include skincare creams, hair creams, toothpaste, soaps, perfumes, lipsticks, fingernail and the toe polish, eye and facial makeup, towelettes, permanent waves, hair colours, hair sprays and gels, deodorants, hand sanitizer, etc. [3]. A 'make-up is a micro aspect of cosmetics', which ordinarily can refer to colouring products intended to improve the user's appearance.

3. Harmful substances in cosmetics

The presence of some substances in cosmetics constitutes imminent danger to the users. Such substances that may cause damage to the users of cosmetics include but not only:

3.1 Inorganic-heavy metals

These are metals having a specific gravity greater than four (4). Sulphides of such metals are insoluble in water. Examples of heavy metals are cadmium, lead, nickel, mercury, manganese, chromium, thallium, etc. [14].

3.2 Arsenic (As)

Arsenic occurs in many minerals, in conjunction with sulphur and other metals, and also as a pure elemental crystal. Arsenic is a metalloid. It can exist in various allotropes, although only the grey form has important use in industry [15]. It is notoriously poisonous to multicellular life, although a few species of bacteria are able to use arsenic compounds as respiratory metabolites. Arsenic contamination of groundwater is a problem that affects millions of people across the globe [16].

3.3 Cadmium (Cd)

Cadmium belongs to group IIB (group 12) of the periodic table and is used in nickel-cadmium storage battery where it enhances long service life and a wide operating range. It occurs in nature mostly in zinc deposits in the mineral greenockite (CdS) and otavite ($CdCO_3$). Its abundance in the earth's crust is estimated to be 0.15 mg/kg and in sea water 0.11 μg/L [17].

3.4 Lead (Pb)

Lead belongs to group IVA (group 14) of the periodic table. It is one of the oldest metals known to civilization. It is rarely found in nature in its native form but can be found in several minerals such as galena (PbS), angelsite ($PbSO_4$) and cerussite ($PbCO_3$). Its concentration in the earth's crust is 12.5 mg/kg and in sea water, 0.03 mg/L [17]. Lead and its alloys such as solder can be used in the construction of pipelines, plumbing fixtures, wires, ammunition, containers for corrosive acids and shield against short wavelength radiation.

3.5 Nickel (Ni)

Nickel is a transition metal, the most common oxidation state is +2, abundance in the earth crust is 84 μg/kg, and its average concentration in seawater is 0.56 μg/mL. It occurs in nature as in pentlandite $(NiFe)_9S_{16}$, limonite $(FeNi)O(OH).nH_2O$ and garnierite $(NiMg)_6Si_4O_{10}(OH)_8$ [17]. Nickel metal is used in numerous alloys that are used to construct various equipment such as reaction vessels, plumbing parts, missiles and aerospace components. It is also used in catalysis [15].

3.6 Chromium (Cr)

Chromium belongs to group VIB (group 6) in the periodic table as a transition metal [15]. Chromium occurs in the mineral chromite, $(FeO.Cr_2O_3)$, and its abundance in the earth's crust is estimated to be near 0.01%, and its concentration in sea water is 0.3 μg/L [17]. Its most important application is in the production of nickel-based alloys. Trace amounts of Cr are necessary in the diet of mammals. Cr^{3+} and insulin are both involved in maintaining the correct level of glucose in the blood. In cases of Cr deficiency, glucose is only removed from the blood half as fast as normal. Some cases of diabetes may reflect faulty metabolism of Cr [15].

3.7 Manganese (Mn)

Manganese is distributed widely in nature, mostly as oxide, silicate and carbonate ores. It is the 12th most abundant element in the earth's crust. Its earth crust concentration is estimated to be 0.093%; average concentration in sea water is 2 μg/L. Most important industrial use is in ferrous metallurgy yet an essential element for plants and animals [17].

3.8 Mercury (Hg)

Mercury is the only liquid metal at standard temperature and pressure (STP), with a freezing point of −38.83°C and boiling point of 356.73°C; mercury has one of the narrowest ranges of its liquid state of any metal [18–20]. Mercury poisoning results from exposure to water-soluble forms of mercury (such as mercuric chloride or methylmercury), inhalation of mercury vapour, or eating seafood contaminated with mercury [15].

It is used in the manufacture of industrial chemicals, in electrical and electronic applications and in thermometers, especially when high temperatures are required. Larger proportions of gaseous mercury are used in fluorescent lamps, but its other applications are gradually replaced considering health and safety implications and in some applications totally substituted with less toxic but highly expensive Galinstan alloy [21].

Compounds of mercury have found extensive application in medicine but are much less utilized nowadays than previously intended, since its toxic effects are more widely understood. The element mercury is an ingredient in dental amalgams. Thiomersal (called Thimerosal in the United States) is an organic compound used as a preservative in vaccines, though it has declined remarkably [22]. Another mercury compound merbromin (mercurochrome) is a topical antiseptic used for minor cuts and scrapes and is still in use in some countries. In the 1930s, some vaccines were preserved with thiomersal, which can convert to ethyl mercury on degradation or metabolism. Although it was generally speculated that this mercury-based compound (preservative) can cause autism in children, scientific proof to support the speculation was lacking (Parker et al., 2004). But as a precautionary measure, the US government has removed or drastically reduced thiomersal in all US vaccines recommended for children 6 years of age or below, with the exception of inactivated influenza vaccine [22].

Cinnabar, a mercury compound, was utilized in traditional Chinese medicines. When its safety considerations were reviewed, it was found that it can cause serious mercury intoxication on application of heat, taken in more required concentration or on continuous exposure time, and can have adverse effects at therapeutic doses, though this is typically reversible at therapeutic doses. Despite the fact that mercury in this form may be less toxic than others, its utilization in traditional Chinese medicine can be justified as the therapeutic basis for the use has not been proved [23]. Presently, its application in medicine has slowed greatly in all aspect, especially in developed countries. Some over-the-counter drugs such as topical antiseptics, stimulants, laxatives, diaper-rash ointment and eye drops contain mercury compounds. The FDA has inadequate data to establish general recognition of the safety and effectiveness of the mercury ingredients in these products [22].

Thiomersal is widely used in the manufacture of mascara. In 2008, Minnesota in the United States became the first state to ban intentional use of mercury in cosmetics [24]. A study of mean concentration of mercury in urine samples shows skincare products as a major exposure route to inorganic mercury among New York City residents. Population-based bio-monitoring confirms sea food and fish meals as a major source of mercury [25]. Mercury can be absorbed through the skin and mucous membranes, while the vapours can be inhaled, so containers of mercury are securely sealed to avoid spills and evaporation. Literature has shown that the most toxic forms of mercury are its organic compounds, such as dimethylmercury and methylmercury. Inorganic compounds are highly toxic by ingestion or inhalation [26].

3.9 Nitrosamines

Nitrosamines are compounds of the chemical structure R_1N (—R_2)—N = O, most of which are carcinogenic. They are formed when secondary amines react with nitrous acid (generated by action of dilute acid on nitrites) in an environment with pH values below 7 [27]. They are used in the manufacture of some cosmetics, in pesticides and in most rubber products. In 1956, two British scientists, John Barnes and Peter Magee, reported that dimethylnitrosamine produced liver tumours in rats. Research was undertaken, and approximately 90% of nitrosamine compounds were deemed to be carcinogenic [28]. In the 1970s, increased frequency of liver cancer was found in Norwegian farm animals that were fed on herring meal that

was preserved using sodium nitrite. The sodium nitrite had interacted with dimethylamine in the fish and produced dimethylnitrosamine [28].

3.10 Nitrite

Nitrite is the univalent radical NO_2^- with a molecular weight of 46 g/mol or a compound containing it, such as a salt or an ester of nitrous acid [29]. The nitrite ion NO_2^- has a V-shape that is based on a plane triangular structure; with nitrogen [N] at the centre, two corners are occupied by oxygen [O] atoms, and the third corner occupied by a lone pair. As a result, the N atom is sp^2 hybridized [15]. Nitrite is a weak oxidizing agent that oxidizes Fe^{2+} to Fe^{3+} and I^- to I_2, while it is reduced to N_2O or NO.

4. Organic substances

4.1 Hydroquinone

Hydroquinone, known as benzene-1,4-diol or quinol, is an aromatic organic compound that is a type of phenol. Its chemical structure features two hydroxyl groups bonded to a benzene ring in a para position. In a substituted form, the derivatives of the compound can still be referred to as hydroquinone.

Hydroquinone (R = H)
Hydroquinone bis(trimethylsilyl ether) (R = $Si(CH_3)_3$)

Since it is weakly acidic, the reactivity of O—H groups of these compounds compares well with other phenols. Its conjugate base can easily undergo O-alkylation as to produce mono- and diethers. In the same way, hydroquinone is highly susceptible to ring substitution by Friedel-Crafts reactions such as alkylation. This reaction is used to produce much known antioxidants such as 2-tert-butyl-4-methoxyphenol ('BHA'). A very important dye quinizarin is produced by diacylation reaction of hydroquinone with phthalic anhydride [30], but the most important reaction is the conversion of hydroquinone to produce mono- and diamino derivatives—methylaminophenol, used in photography.

$$C_6H_4(OH)_2 + CH_3NH_2 \rightarrow C_6H_4(OH)(N(H)CH3) + H_2O \quad (1)$$

Also diamines, useful in the rubber industry as antiozone agents, can be produced from aniline:

$$C_6H_4(OH)_2 + 2C_6H_5NH_2 \rightarrow C_6H_4(N(H)C_6H_5)_2 + 2H_2O \quad (2)$$

The compound is variously used, mainly with its action as a reducing agent that dissolves in water. It is widely used in most photographic development for film and paper. It can act as an inhibitor by preventing polymerization of acrylic acid, methyl methacrylate, cyanoacrylate and other monomers that can respond to free radical-initiated joining. This reaction utilizes the antioxidant properties of hydroquinone to undergo mild oxidation and convert to the compound parabenzoquinone, $C_6H_4O_2$, often called p-quinone or quinone. This reaction is reversible as reduction

of quinone reverses this reaction back to the original form. Some biochemical compounds in nature have this sort of hydroquinone or quinone section in their structures, such as coenzyme Q, and can undergo similar redox interconversions. Hydroquinone can lose an H^+ from both hydroxyl groups to form a diphenolate ion.

4.2 Steroids

This is an organic compound in which four cycloalkane rings are joined with each other; dietary fat cholesterol, the sex hormone—estradiol, testosterone and the anti-inflammatory drug dexamethasone are common examples. The steroid centre consists of 20 carbon atoms which are bound together where they exhibit the structure of 4 fused rings composed of 3 cyclohexane rings and 1 cyclopentane ring. They vary by the functional groups attached to this four-ring core and by the oxidation state of the rings [31]. All steroids are made in cells either from the sterol lanosterol (animals and fungi) or from cycloartenol (plants). Both lanosterol and cycloartenol are derived from the cyclization of the triterpene squalene [32].

Corticosteroids are a class of chemicals that includes steroid hormones naturally produced in the adrenal cortex of vertebrates and are involved in a wide range of physiological processes, including stress and immune response, and regulation of inflammation, carbohydrate metabolism and catabolism of protein. Synthetic glucocorticoids are used in the treatment of joint pain or inflammation, temporal arthritis, dermatitis, allergic reactions, asthma, hepatitis, systemic lupus erythematosus, ulcerative colitis, Crohn's disease and sarcoidosis and for glucocorticoid replacement or other forms of adrenal insufficiency (Higashi et al., 2009).

5. Bibliographies that prove cosmetic brands are in continuous use and contain poisonous toxicants

An epidemiological survey was conducted by Adebajo [7] on the use of skin lightening cosmetics among traders in Lagos, Nigeria, using 450 traders from three major and popular markets (Tejuosho, Balogun and Mushin) in Lagos metropolis between May and July 1998 using stratified sampling method. Information on their socio-demographic characteristics, knowledge and attitudes to and the patterns of use of skin lightening cosmetics were elicited from the respondents with the application of questionnaire-based interview. The result obtained showed that for socio-demographic characteristics of the respondents that participated, 28.9% were males and 71.1% females. 51.6% were aged between 20 and 29 years with a mean of 30.8 years and about 49.3% were married. Over 95% of the respondents had some form of formal education with 31.1% who had at least primary school education and 119 post-secondary school education. Most of them (82.2%) were traders, while the remaining operated small-scale business such as hairdressing, barbing, tailoring and chemist. Many of them (45.6%) earned less than N1, 000.00, while 18 (4.0%) earned above N5, 000.00 per month. For patterns of use of skin lightening cosmetics, 348 respondents (77.3%) made up of 96 male traders (27.6%) and 252 female traders (72.4%) admitted using skin lightening cosmetics. Sex did not have any effect on the pattern of use of these cosmetics ($p > 0.05$). Hydroquinone-based cosmetics were the most widely used by the respondents, and the least use was the mercury-based ones; female traders generally tended to use more corticosteroid-based cosmetics much more than male traders. The modal duration of the use of the skin lightening cosmetics was 1–3 years, although 29 respondents (8.3%) had used them for less than 6 months and 44 (12.6%) for 5 years. Many of the respondents (45.7%) who admitted using the cosmetics spent between N250 and N500 per month on the cosmetics, while some

(12.4%) spent between N500 and N1000. Over half of the respondent claimed that they discovered the skin lightening cosmetics themselves, while, 123 (35.3%) were influenced by their friends. Other sources of influence include health workers (2.3%), chemist (5.5%), parents (1.4%) and the media (1.4%). One hundred and nine respondents (31.3%) commenced the use of skin lightening cosmetics to treat skin blemishes. Almost one-third of the respondents (30.2%) indulged in the use of these cosmetics because they felt that being fair complexioned made them more attractive. Others use them to cleanse or tone their faces and bodies (21.0%), and the rest used them simply because they felt it was trendy to be fair complexioned. Only 14 respondents indulged in the use of skin lightening cosmetics to satisfy the desires of the opposite sex. Although the level of the use of skin lightening cosmetics increased with the level of education of the respondent, this was weakly significant ($p = 0.05$). One hundred and sixty seven (73.2%) Christians compared with 181 (81.5%) Moslems used bleaching creams. This difference was statistically significant ($p < 0.05$). On how respondents felt about their new look, most of the respondents (64.1%) felt they were more attractive; hence, they were more confident about their new look. Only 46 (13.2%) claimed they were relieved of their skin blemishes, while 33 (9.5%) were better appreciated by their spouses. About 50% of 348 respondents (made up of 44 males and 130 females) who use skin lightening cosmetics developed side effects. Respondents were more likely to develop side effects as duration of use increased from 6 months to 3 years. Beyond 3 years, however, fewer respondents developed side effects. The respondents reported several side effects, the commonest being yellowish brown colouration of the skin (23.9%). Others were skin rashes, multiple stretch marks, thinning and easy brushing of the skin. Twenty-five of the participants had worsening of their existing skin conditions, and on observing some of the side effects, 79 respondents (45.4%) just simply ignored the side effects, while only 35.6% stopped using the cosmetics. To mitigate against these problems, clinical trials should be conducted to ascertain the safety levels acceptable for the Nigerian skin types and climate.

Nnorom et al. [8] analysed the content of trace metal of several cosmetics in Nigeria for the presence of lead, cadmium, zinc and iron; three groups of facial cosmetics were used, such as eye pencil, eye liners and mascara, lipstick and lip gloss and native eyeliner (tiro and uhie) which were purchased from retail outlet and open market in Umuahia, Southeast Nigeria. The result from this study showed that the range of Pb levels for lipsticks is higher in concentration than that for local eyeliners, with the geometric mean value for the local eyeliners being 120.5 μg/g. Comparative amounts of Pb were found in the local eyeliners and pencil. Cd was generally low, being much less than 3 μg/g, while chromium was much higher than the corresponding levels of nickel and cadmium in each sample group. Cr, Fe and Zn were much higher in the samples than those of the non-essential metals, Pb, Ni and Cd. Zinc and Fe were in the highest concentration. The research concluded that the continuous use of these cosmetics could result in an increase in the trace metal levels in human body beyond acceptable limits.

Nnoruka and Okoye [9] studied topical steroid abuse to document the prevalence, motives and observed complications of steroid use as depigmenting agent among African Blacks of Southeast Nigeria; consecutively new patients are attending the dermatological clinic of the University of Nigeria Teaching Hospital, Enugu. Nigeria, from June to December 2004, was recruited. All the participants were adults (males and females) and were recruited only if they use depigmenting agents. These was ascertained by obtaining information from the back of the containers or packets of waste containers; leaflets containing useful information concerning active ingredients were used to ascertain that the products contained well-known active lightening substances such as hydroquinone, mercury compounds and steroids. Questionnaire was used to obtain information on the most frequently

used cosmetic and mode of application with full consent of the patients. Relevant information such as age, sex, occupation, demographic information as well as names and types of products utilized within the last three months; length of and regularity of application and body parts involved; amount or volume utilized monthly and cost involved were determined. Also medical history of the patients, if they have had other medical conditions such as hypertension, diabetes mellitus or renal disorders, and the duration of such problems. Manner and method of presenting the problem and clinical examination already are carried out in the affected areas. Where adequate information were not obtained or unsatisfactory, relevant laboratory tests like mycological studies, venereal disease research laboratory (VDRL), blood urea electrolytes, creatinine, urinalysis or skin biopsy were performed on the patients.

The results they obtained showed that there were 547 (58.7%) patients utilizing depigmenting agents who met the criteria for the study, out of the 931 consecutive new patients recruited for the study. Of these, 414 (75.7%) were females and 133 (24.3%) were males within age range of 18–71 years. Traders (22.7%) accounted for the most affected, followed by businessmen and women. The duration of such practice varied from 3 months to 30 years. Utilization of topical steroid amounted to 57.2% (313) patients for depigmenting cosmetic agents. 5.9% (32) of participants agreed they were utilizing them as medication for various skin or surface body conditions such as eczema, papulosquamous disorders, sycosis barbae and connective tissue disorders. More than 21 different steroid-containing products were utilized, mostly class 1 steroid in 89.6% cases. These products include Topifram®, Topicort®, Topgel®, Topsyn®, Movate®, Dermovate®, Diprosone®, Visible Difference®, Betadine®, Bio Claire®, Betnovate–N, Neomedol®, Synalar®, Locacorten®, Palmer's Spot Remover®, Top Clear Skin®, Betnovate–C®, Neutone®, etc. Skin disorders documented during dermatologic/systemic examination included widespread dermatophyte infections with lesions, and diagnosis was frequently delayed or missed (tinea incognito). The distribution among the participants were, on the body in 191 (34.9%), macular hyper pigmentation of the face accounted for 204 (37.3%) cases, and these caused observable inflamed pustules and micropapular eruption masking the entire face. Pityriasis versicolor was very noticeable and situated at unusual sites, like the medial aspect of the upper and lower limbs among 31 (5.7%) patients. They had deep depigmentation and are linked with superficial atrophy; three patients among them had been associated with diabetes mellitus which is in early stage. Other disorders and complications observed were widespread striae in 161 (28.3%) cases, telangiectasia in 117 (21.3%), easy bruisability in 95 (17.4%) and hypertrichosis in 73 (13.3%) cases. The study concluded that cosmetic use of topical steroids exposes the users to several cutaneous complications alongside medical and aesthetic problems.

Amit et al. [33] determined lead and cadmium in cosmetic products, like soap, face cream, shampoo and shaving creams, using atomic absorption spectrophotometer. In samples consisting of a total of three different brands (coded A–C) of each product and total five samples of one brand of each sample collected from various retail shops from local market of Gwalior, India, the highest concentration of lead was detected in soap with brand code B (1.59 mg g^{-1}), while face cream, brand code C (0.07 mg g^{-1}) and talcum powder and brand codes B and C (0.24 and 0.25 mg g^{-1}) showed lowest lead content. For comparison between same products with different brands, mostly brand A showed the highest concentration (soap, 4.63 mg g^{-1}; face cream, 0.03 mg g^{-1}; shampoo, 1.49 mg g^{-1}; shaving cream, 0.69 mg g^{-1}; and talcum powder, 0.38 mg g^{-1}) followed by brand B (soap, 4; face cream, 0.05; shampoo, 1.59 mg g^{-1}; shaving cream, 0.66 mg g^{-1}; and talcum powder, 0.25 mg g^{-1}). The highest concentration of cadmium was detected in

shampoo with brand code A (0.042 mg g^{-1}) followed by soap with A and B brand (0.04 and 0.037 mg g^{-1}). The findings showed that lead is a major toxic heavy metal in cosmetic products.

Oyelakin et al. [34] assessed the level of mercury in soaps by the use of cold vapour fluorescence spectrophotometric analysis in Gambia; a total of 16 brands of soaps were analysed. These brands of soap were grouped under four categories: medicated, toilet, skin lightening and laundry soaps. The soaps, purchased from different supermarkets in the Gambia, were used for analyses. They showed that all 16 soap brands contained mercury with concentration ranging from 2.87ng/g to 12.61 ng/g.

The World Health Organization [6] review on mercury in skin lightening products revealed that mercury is a common ingredient found in skin lightening soaps and creams as well as other cosmetics such as eye makeup, cleaning products and mascara. It stated that skin lightening soaps and creams are more commonly used in certain Africa and Asian nations and also among dark-skinned populations in Europe and North America. It further stated that mercury salts inhibit the formation of melanin, resulting in lighter skin tone. The review showed countries of greatest cosmetic use in Africa, Mali, Senegal, South Africa, Togo and Nigeria in order of increasing usage by women as 25, 27, 35, 59 and 77% are reported to use skin lightening products on a regular basis. Close to 40% of women surveyed in China, Malaysia, the Philippines and Republic of Korea in the year 2004 were reported to have used skin lighteners, while in India, 61% of the dermatological market were made of skin lightening products. The result also showed that skin lightening products are manufactured in many countries such as the Dominican Republic, Lebanon, Mexico, Pakistan, the Philippines, Thailand and the United States, and mercury-containing skin lightening products are available for sale over the internet, while individuals from Brazil, Kyrgzstan, Mexico, and the Russian Federation believe that mercury-containing skin lightening products are easy to obtain. Furthermore, the result revealed that skin lightening products come in different forms, including soap and creams, with the soap containing approximately 1–3% mercury iodide, and the cream is composed of 1–10% mercury ammonium (some soap products tested contained mercury at concentrations of up to 31 mg/kg, whereas cream products had mercury at concentration as high as 33,000 mg/kg).

Oyedeji et al. [2] ascertained hydroquinone, chromium and aluminium levels in cosmetics are marketed in Nigeria with the aim of proving that they contained poisonous substances at levels harmful to the populace; 80 cosmetic emulsions were purchased from a wholesale supermarket in Ibadan, Southwest Nigeria. The various cosmetic emulsions country of manufacture were determined by inspection of labels on the cosmetic packaging. The concentration of hydroquinone (HQ) was determined using a UV spectrophotometer. Heavy metals in the emulsion were determined by atomic absorption spectrophotometer. The study concluded that most of the cosmetic emulsion did not contain hydroquinone at levels that are detrimental to the skin, while the heavy metals were within acceptable values.

Nduka et al. [35, 36] assessed the cancer and no cancer risk of heavy metals, steroids, hydroquinone, nitrosamines and nitrites in 42 cosmetic brands purchased from cosmetic shops in Southeastern Nigeria through dermal exposure pathway; the total cancer risk value for both the cosmetic products manufactured in Nigeria and the cosmetic products manufactured outside Nigeria was less than the regulatory purpose acceptable or tolerable risk level of 10^{-6} to 10^{-4} set by USEPA [37]. This implies that the low levels of these carcinogenic elements to which users of these cosmetics are continually exposed to through the dermal exposure pathway alone over their lifetime are unlikely to pose a non-cancer and cancer risk. This therefore confers a measure of safety and no toxicological concern, but the values for total cancer risk and non-cancer risk subsist entirely on the risk contributed

by the heavy metals and do not contain any risk that may be contributed by other hazardous substances as well as from other more common exposure pathways such as inhalation and ingestion.

6. Toxicological effect of harmful substances in cosmetics

Minimal exposure level to arsenic can lead to serious illness or death [38]. Result from Chile establishes a dose-dependent relation between chronic arsenic exposure and various forms of cancer, especially when other risk factors, such as cigarette smoking, are joined. The effect is established to persist below 50 ppb of arsenic [39]. Studies on inorganic arsenic exposure suggest a small but measurable risk increase for bladder cancer at 10 ppb [40]. The acute poisoning effects of cadmium are nausea, vomiting, diarrhoea, headache and shock; inhalation of its dust and fumes can cause cough, respiratory distress, congestion of lungs and broncho-pneumonia [41]. The metal accumulates in the liver and kidneys, damaging these organs when the exposure is chronic. Biological half-life of cadmium in humans is estimated at 20–30 years. Cadmium is listed by the United States Environmental Protection Agency [42] as one of the priority pollutant metal [43]. Absorption of lead into the skin is governed by chemical structure; therefore, skin organic lead absorption into the body tissues is more rapid than with inorganic lead compounds because of greater lipid solubility; large amounts of lead gain access to nerve tissue [44]. Acute effects of lead intake are ataxia, headache, vomiting, stupor, hallucination, tremors and convulsions. Chronic cases include weight loss, anaemia, kidney damage and memory loss. Lead bioaccumulates in bones and teeth, and it is classified as an environmental priority pollutant by the US EPA. The safe level for drinking water is 15 μg/L [41].

Skin contact with nickel can cause dermatitis, and a type of chronic eczema known as 'nickel itch' is caused by hypersensitivity reactions of nickel on the skin [45]. Oral toxicity of nickel is very low, but ingestion results to hyperglycerine and depression of the central nervous system. Large dose inhalation of nickel dust can cause lung and sinus cancer in humans. Nickel and certain of its compounds are listed by International Agency for Research on Cancer (IARC) under group 2B carcinogens as possibly carcinogenic to humans [45].

Cr^{6+} is regarded as cancer-causing agent and is toxic [17]. It is corrosive to skin and causes denaturation and precipitation of tissue proteins. Chronic exposure may lead to cancer of the respiratory tract [17] and should be controlled in such a manner that no person is exposed to carcinogenic chromium (VI) at concentrations greater than 25 mg/m^3 of air, determined as the time-weighted average (TWA) concentration limit for up to a 10-hour workday or a 40-hr work week, over a working lifetime [44]. Chronic inhalation of manganese dust or fumes can cause manganism, a nonfatal disease which affects the central nervous system. The symptoms are mental disorder and disturbance in speech [45].

Mercury can cause both chronic and acute poisoning. Case control studies have shown effects such as tremors, impaired cognitive skills and sleep disturbance in workers with chronic exposure to mercury vapour even at low concentrations in the range 0.7–42 $\mu g/m^3$ [46, 47]. A study has shown that acute exposure (4–8 hours) to calculated elemental mercury levels of 1.1–44 mg/m^3 resulted in chest pain, dyspnoea, cough, haemoptysis, impairment of pulmonary function and evidence of interstitial pneumonitis [48]. Occupational exposure has resulted in broad-ranging functional disturbance, including erythrism, irritability, excitability, excessive shyness and insomnia. In regular and consistent use, a fine tremor develops and may escalate to violent muscular spasms. Long-term, low-level exposure has been

associated with more subtle symptoms of erythrism, including fatigue, irritability, loss of memory, vivid dreams and depression [49, 50].

In 2006, the United States Food and Drug Administration revoked the approval of the use of hydroquinone and proposed a ban on all over-the-counter preparations [51], because it felt that hydroquinone cannot be ruled out as a potential carcinogen. The reason was based on the absorption in humans and the incidence of neoplasm in rats shown by several studies in which adult rats showed increased rates of tumour development [51].

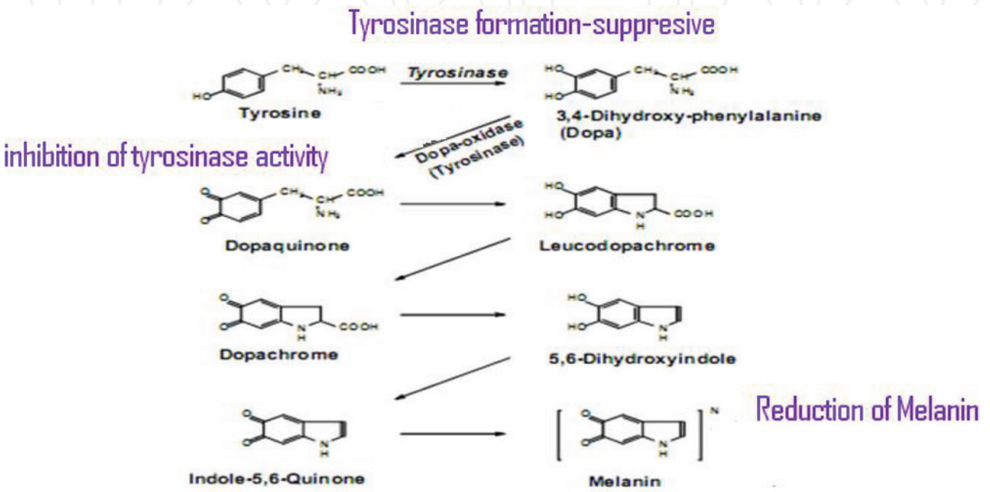
Extensive literature documentation reveals that hydroquinone can cause exogenous ochronosis, a disease that deposits blue-black coloration on the skin, if taken orally; but skin preparations containing the ingredient are administered topically [51, 52]. Although proper use of hydroquinone as skin lightening agent can be effective, it causes skin sensitivity. The effect can be minimized by daily use of sunscreen with a high persistent pigment darkening (PPD) rating. Hydroquinone can be combined with alpha hydroxy acids which exfoliate the skin to quicken the lightening process. In the United States, skin creams usually contain up to 2% of hydroquinone, but higher amounts up to 4% or above should be prescribed and used with caution.

The most trending research and publication shows that minor constituents of other chemicals such as phthalates, parabens and phenols in personal care products (shampoos, toothpaste, soap, etc.), though not extensively discussed, can cause early puberty in young girls and boys. The chemicals can enter the body by cutaneous penetration through the skin, inhalation or accidental ingestion. A worrisome aspect is that exposure is very much possible through mothers during pregnancy and breastfeeding [53].

6.1 Skin depigmentation

In human medicine, hydroquinone is used as a topical application in skin whitening to reduce the colour of skin by decreasing the production of melanin pigment in the skin. Since hydroquinone lightens the skin by reducing melanin, it simultaneously increases exposure of the skin to UV rays, thereby increasing skin cancer risks due to UV exposure [54]. It does not have the same predisposition to cause dermatitis as metals do. This use is banned in some countries, including the member states of the European Union under Directive 76/768/EEC: 1976 [55].

6.2 Mechanism of whitening agent



Clinical trials and experimental results prove that corticosteroids can cause permanent eye damage by inducing central serous retinopathy (CSR) or central serous

chorioretinopathy (CSC) [56]. Different steroid medications, from anti-allergy nasal sprays (Nasonex, Flonase) to topical skin creams, eye drops (Tobradex) and prednisone, have been implicated in the development of CSR [57].

Corticosteroids have been applied on people with traumatic brain injury. In a systematic study in which the authors recommended that people with traumatic head injury should not be routinely treated with corticosteroids [58], side effects, such as cutaneous addiction with the development of uncomfortable and unsightly dermatoses, can occur with just one 15 g tube of moderate steroid over a period of 1 year [59].

The use of corticosteroids have severe side effects such as steroid psychosis [60], hyperglycaemia, insulin resistance, diabetes mellitus, osteoporosis, cataract, anxiety, depression, colitis, hypertension, ictus, erectile dysfunction, hypogonadism, hypothyroidism, amenorrhoea and retinopathy [61]. Evidence for corticosteroids causing peptic ulceration is relatively poor except for high doses taken for over a month [62]; majority of doctors as of 2010 still believe this is the case and would consider protective prophylactic measures [63]. Corticosteroids have a low but significant teratogenic effect, causing a few birth defects per 1000 pregnant women treated. Corticosteroids are therefore contraindicated in pregnancy [64].

Nitrosamine has been established to cause cancer in animal species, which suggests that it may also be carcinogenic in humans. Available prove from case-control studies on nitrite and nitrosamine intake implicates it in gastric cancer (GC) risk and oesophageal cancer (OC) [28].

According to Lautenschläger [27], there is no hard evidence on carcinogenic effect of nitrosamine-contaminated products applied on the skin. The study suggests that it is limited to nitrosamines inhaled with cigarette smoke or those formed by sodium nitrite from nitrite cured food reacting with secondary amines from vegetables or other food components. The study stated that although there is no 100% protection, as secondary amines and nitrite also occur in the natural environment, however, as far as cosmetic products are concerned, it should be taken care that nitrosamines and their co-chemicals such as secondary amines and nitrites are not used in the formulation. It may be a fact that health risk involved with contaminated surface body care products may be ignored as they are not supposed to remain on the skin. Also, consumers can now hive a sign of relief by drawing attention to the fact that the human system is equipped with its own secondary amines; therefore the skin can fight off any so as to protect itself with its natural moisturizing factor (NMF) which mainly contains amino acids. Chemical constituents of these amino acids are regarded as primary amines that can interact with NO_2, but when the molecule is destroyed in the process, nonhazardous nitrogen is normally formed.

Nitrite is approximately 10 times more toxic than nitrate [65], and interaction of nitrite with haemoglobin occurs in the blood as methaemoglobin is formed; this compound drastically lowers oxygen carrying capacity of the blood; when this happens, it results to methaemoglobinemia or 'blue baby syndrome' in infants; this is caused by lack of acidity condition in the intestinal walls of infants that is supposed to kill or reduce the bacteria; as a result these bacteria convert nitrate into nitrite. The most outstanding symptom of methaemoglobinemia is the appearance of a bluish colouration on the skin around the eyes and mouth as evidence of shortage of blood. The medical condition is treatable on early detection using methylene blue injection, which changes methaemoglobin back to haemoglobin, but death is sure when over 70% of the body's haemoglobin has been replaced by methaemoglobin [29].

Exposure to heat can cause damage to any cosmetic or makeup products. It changes the chemical formula, evaporates water and separates oil composition from other ingredients (an occurrence referred to as creaming) [66]. It also encourages the emergence of a culture medium for bacteria. The effect of these changes on the skin is harmful as such cosmetic product would no longer satisfy its optimal role [67].

7. Conclusions

We conclude that apart from mercury, steroids and hydroquinone, a variety of other poisonous chemicals which are prohibited by many country's regulatory authorities are still present in many cosmetics. In many cases, cosmetic product manufacturers, importers and marketers conceal the real constituent of cosmetics by not listing them in the product label. Cosmetic and skin lightening products are in high usage in every country of the world, especially among women of all ages, even with the knowledge of hazardous effect it possess to human health. Skin rashes, multiple stretch marks, yellowish brown colouration, hypertension, diabetes mellitus, renal failure and cancer are some of the toxicological and health hazards associated with cosmetic product usage and are linked to poisonous substances used in cosmetic preparation.

Author details

John Kanayochukwu Nduka[1*], Henrietta Ijeoma Kelle[2] and Isaac Omoche Odiba[3]

1 Environmental Chemistry and Toxicology Research Unit, Pure and Industrial Chemistry Department, Nnamdi Azikiwe University, Awka, Nigeria

2 Department of Pure and Applied Science, Faculty of Sciences, National Open University, Abuja, Nigeria

3 Department of Chemistry, Alvan Ikoku Federal College of Education, Owerri, Nigeria

*Address all correspondence to: johnnduka2000@yahoo.co.uk

References

[1] Adepoju-Bello AA, Oguntibeju OO, Adebishi RA, Okpala N, Coker HAB. Evaluation of the concentration of toxic metals in cosmetic products in Nigeria. African Journal of Biotechnology. 2012;**11**(97):16360-16364

[2] Oyedeji FO, Hassan GO, Adeleke BB. Hydroquinone and heavy metal levels in cosmetics marketed in Nigeria. Trends in Applied Science Research. 2011;**6**:622-639

[3] Hill JW. Chemistry for Changing Times. 6th ed. New York: Macmillan Company; 1992. pp. 610-615

[4] Odumosu PO, Ekwe TO. Identification and spectrometric determination of hydroquinone levels in some cosmetic creams. African Journal of Pharmacy and Pharmacology. 2010;**4**(5):231-234

[5] Scientific Committee on Consumer Safety (SCCS). Opinion on Nitosamines and Secondary Amines in Cosmetic Products. 27 March 2012

[6] WHO. Mercury in Skin Lightening Products. Geneva: World Health Organization; 2011. Available from: http://www.who.int/ipcs/assessment/public_health/mercury/en /index.html [Retrieved: 10-10-2013]

[7] Adebajo SB. An epidemiological survey of the use of cosmetic skin lightening cosmetics among traders in Lagos, Nigeria. West African Journal of Medicine. 2002;**21**(1):51-55

[8] Nnorom IC, Igwe JC, Oji-Nnorom CG. Trace metal contents of facial (make-up) cosmetics commonly used in Nigeria. African Journal of Biotechnology. 2005;**4**:1133-1138

[9] Nnoruka E, Okoye O. Topical steroid abuse: Its use as a dipigmenting agent. Journal of National Medical Association. 2006;**98**:934-939

[10] Nigeria Nursing World. Alert notice on banned products. 2012. Available from: http://www.nursingworldnigeria.com/.../nafdac-alert-notice-on-banned-products [Retrieved: 10-10-2013]

[11] National Literacy Survey. The National Literacy Survey. 2010. Available from: http://www.nigeriastat.gov.ng/pages/download/43. [Retrieved: 15-09-2013]

[12] Apaolaza-Ibanez V, Hartmann P, Deihi S, Terlutter R. Women satisfaction with cosmetic brands: The role of dissatisfaction and hedonic brand benefits. African Journal of Business Management. 2011;**5**(3):792-802

[13] Briganti S, Camera E, Picardo M. Chemical and instrumental approaches to treat hyperpigmentation. Pigment Cell & Melanoma Research. 2003;**16**:101-110

[14] Environmental Defence. Heavy Metal Hazard—The Health Risks of Hidden Heavy Metals in Cosmetics: Toronto. 2011;**1**:3-10

[15] Lee JD. Concise Inorganic Chemistry. 5th ed. London: Blackwell Science Ltd; 1996

[16] Klassen RA, Douma SL, Ford A, Rencz A, Grunsky E. Geoscience Modeling of Relative Variation in Natural Arsenic Hazard in Potential in New Brunswick. Geological Survey of Canada; 2009 [Retrieved: October 14, 2012]

[17] Patnaik P. A Handbook of Inorganic Chemicals. 1st ed. New York: McGraw Hill Publishers; 2003. pp. 140-609

[18] Lide DR. CRC Handbook of Chemistry and Physics (86th ed). Boca Raton, FL: CRC Press; 2005. pp. 4.125-4.126. ISBN: 0-8493-0486-5

[19] Norrby LJ. Why is mercury liquid? Or, why do relativistic effects not get

into chemistry textbooks. Journal of Chemical Education. 1991;**68**(2):110. DOI: 10.1021/ed068p110 [Retrieved: 10-10-2013]

[20] Senese F. Why is mercury a liquid at STP? General Chemistry Online at Frostburg State University; 2007 [Retrieved: 10-10-2013]

[21] Surmann P, Zeyat H. Voltammetric analysis using a self-renewable non-mercury electrode. Analytical and Bioanalytical Chemistry. 2005;**383**(6):1009-1013. DOI: 10.1007/s00216-005-0069-7

[22] FDA. Thimerosal in Vaccines. Center for Biologics Evaluation and Research, U.S. Food and Drug Administration. 2007 [Retrieved: 10-10-2013]

[23] Liu J, Shi JZ, Yu LM, Goyer RA, Waalkes MP. Mercury in traditional medicines: Is cinnabar toxicologically similar to common mercurials? Experimental Biology and Medicine (Maywood). 2008;**233**(7):810-817. DOI: 10.3181/0712-MR-336

[24] CIDPUSA. Mercury in your eye. 2008. Available at: http://www.cidpusa.org/mercury.htm [Retrieved: 10-10-2013]

[25] McKelvey W, Jeffery N, Clark N, Kass D, Parsons PJ. Population-based inorganic mercury biomonitoring and the identification of skin care products as a source of exposure in New York City. Environmental Health Perspective. 2011;**119**(2):203-209. DOI: 10.1289/ehp.1002396

[26] Oxford University. Safety Data for Mercuric Sulphide. Oxford University; 2009 [Retrieved: 2009-07-07]

[27] Lautenschläger H. Nitrosamines in cosmetic products—Risk of skin problems. Kosmetische Praxis. 2006;**2**:12-14

[28] Jakszyn P, Gonzalez CA. Nitrosamine and related food intake and gastric and oesophageal cancer risk: A systematic review of the epidemiological evidence. World Journal of Gastroenterology. 2006;**12**(27):4296-4303

[29] Genentech. Hazardous Substances. 2014. Available from: http://www.lenntech.com/hazardous substances/nitrite.htm [Retrieved: 06-12-2014]

[30] Phillip MH. Ullmann's Encyclopedia of Industrial Chemistry. Weinheim: Wiley-VCH; 2002, 2005. DOI: 10.1002/14356007.a13_499

[31] Moss GP. Nomenclature of steroids (recommendations 1989). Pure & Applied Chemistry. 1989;**61**(10):1783-1822. DOI: 10.1351/pac198961101783. [Retrieved: 10-10-2013]

[32] International Union of Biochemistry and Molecular Biology. Lanosterol biosynthesis. In: Recommendations on Biochemical & Organic Nomenclature, Symbols & Terminology. 1989

[33] Amit SC, Rekha B, Atul KS, Sharad SL, Dinesh KC, Vinayak ST. Determination of lead and cadmium in cosmetic products. Journal of Chemical and Pharmaceutical Research. 2010;**2**(6):92-97

[34] Oyelakin O, Saidykhan J, Secka P, Adjivon A, Acquaye HB. Assessment of the level of mercury present in soaps by the use of cold vapour fluorescence spectrometric analysis—A Gambian case study. Ethiopian Journal of Environmental Studies and Management. 2010;**3**(1):8-12

[35] Nduka JK, Odiba IO, Aghoghome EI, Umedum LN, Nwosu MJ. Evaluation of harmful substances and health risk assessment of mercury and arsenic in cosmetic brands in Nigeria. International Journal of Chemistry. 2016;**8**(1):178-187. DOI: 10.5539/ijc.v8n1p178

[36] Nduka JK, Odiba IO, Orisakwe OE, Ukaegbu LD, Sokaibe C, Udowelle NA. Human health risk assessment of heavy metals in cosmetics in Nigeria. Journal of Cosmetic Science. 2015;**66**(4):233-246

[37] US EPA. Section 2.4.1.1, pp. 51589-51590 of the HRS rule. 2011. Available from: http://www.epa.gov/superfund/training/hrstrain/htmain/s2411.htm [Retrieved: 08-10-2014]

[38] Kozul CD, Ely KH, Enelow RI, Hamilton JW. Low dose arsenic compromises the immune response to influenza A infection in vivo. Environmental Health Perspectives. 2009;**117**(9):1441-1447. DOI: 10.1289/ehp.0900911

[39] Ferreccio C, Sancha AM. Arsenic exposure and its impact on health in Chile. Journal of Health and Population Nutrition. 2006;**24**(2):164-175

[40] Chu HA, Crawford-Brown DJ. Inorganic arsenic in drinking water and bladder cancer: A meta-analysis for dose-response assessment. International Journal of Environmental Research and Public Health. 2006;**3**(4):316-322. DOI: 10.3390/ijerph2006030039

[41] Patnaik P. A Comprehensive Guide to the Harzadous Properties of Chemical Substances. 2nd ed. New York: John Wiley and Sons; 1999. pp. 56-60

[42] Environmental Protection Agency (EPA). Health Assessment Document for Chromium. Vol. 60. Washington, USA: Environmental Protection Agency; 1984. pp. 301-305

[43] Manahan S. Toxicological Chemistry. 1st ed. Chelsea, Michigan: Lewis Publishers; 1989. pp. 43-48

[44] Sharma JL, Garg NK, Buldini PL. Condensed Chemical Dictionary. 1st ed. New Delhi: CBS Publishers; 2002

[45] International Agency for Research on Cancer (IARC). IARC Monograph 49. Geneva; 1990. pp. 3-7

[46] Liang YX, Sun RK, Sun Y, Chen ZQ, Li LH. Psychological effects of low exposure to mercury vapour: Application of computer-administered neurobehavioral evaluation system. Environmental Research. 1993;**60**(2):320-327. DOI: 10.1006/enrs.1993.1040

[47] Ngim CH, Foo SC, Boey KW, Keyaratnam J. Chronic neurobehavioral effects of elemental mercury in dentists. British Journal of Industrial Medicine. 1992;**49**(11):782-790

[48] McFarland RB, Reigel H. Chronic mercury poisoning from a single brief exposure. Journal of Occupational and Environmental Medicine. 1978;**20**(8):532. DOI: 10.1097/00043764-197808000- 00003

[49] Friberg L. Inorganic Mercury, Environmental Health Criteria 118. Geneva: World Health Organization; 1991. ISBN: 92-4-157118-7

[50] WHO. Environmental Health Criteria 1: Mercury. Geneva: World Health Organization; 1976. ISBN: 92-4-154061-3

[51] United States Food and Drug Administration (US FDA). Skin Bleaching Drug Products for Over-the-Counter Product Use. Proposed Rule (Report). 2006. 1978N-0065

[52] Olumide YM, Akinkugbe AO, Altraide D, Mohammed T, Ahamefule N, Ayanlowo S, et al. Complications of chronic use of skin lightening cosmetics. International Journal of Dermatology. 2008;**47**(4):344-353. DOI: 10.1111/j.1365-4632.2008.02719.x

[53] Harley KG, Berger KP, Kogut K, Parra K, Lustig RH, Greenspan LC, et al. Association of phthalates, parabens and

phenols found in personal care products with pubertal timing in girls and boys. Journal of Human Reproduction. 2019;**34**(1):109-117

[54] Jimbow K, Obata H, Pathak MA, Fitzpatrick TB. Mechanisms of depigmentation by hydroquinone. Journal of Investigative Dermatology. 1974;**62**:436-449

[55] EEC. Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products. 1976. Available from: http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31976L07 68: EN: HTML. Example of a product recall in Ireland. [Retrieved: 10-10-2013]

[56] Shamsiah NS. Determination of hydroquinone and arbutin in whitening cosmetic skin care by using high performance liquid chromatography (HPLC). Malaysian Journal of Public Health Physicians' Association. 2011;**11**(4):18

[57] Carvalho-Recchia CA, Yannuzzi LA, Negrão S, Spaide RF, Freund KB, Rodriguez-Coleman H, et al. Corticosteroids and central serous chorioretinopathy. Ophthalmology. 2002;**109**(10):1834-1837. DOI: 10.1016/S0161-6420(02)01117-X

[58] Alderson P, Roberts I. Corticosteroids for acute traumatic brain injury. Cochrane Database of Systematic Reviews. 2005. DOI: 10.1002/14651858.CD000196.pub2

[59] Kenneth PF, David JE. Tortured tube sign. Western Journal of Medicine. 2001;**174**(6):383-384. DOI: 10.1136/ewjm.174.6.383

[60] Hall R. Psychiatric Adverse Drug Reactions: Steroid Psychosis. Massachusetts: Director of Research Monarch Health Corporation Marblehead; 2002

[61] Donihi AC, Raval D, Saul M, Korytkowski MT, DeVita MA. Prevalence and predictors of corticosteroid-related hyperglycemia in hospitalized patients. Endocrine Practice. 2006;**12**(4):358-362

[62] Pecora PG, Kaplan B. Corticosteroids and ulcers: Is there an association? Annals of Pharmacotherapy. 1996;**30**(7-8):870-872

[63] Martínek J, Hlavova K, Zavada F. A surviving myth—Corticosteroids are still considered ulcerogenic by a majority of physicians. Scandinavian Journal of Gastroenterology. 2010;**45**(10):1156-1161. DOI: 10.3109/00365521.2010.497935

[64] Shepard TH, Brent RL, Friedman JM, Jones KL, Miller RK, Moore CA, et al. Update on new developments in the study of human teratogens. Teratology. 2002;**65**(4):153-161. DOI: 10.1002/tera.10032

[65] Schneider NR. Overview of Nitrate and Nitrite Poisoning. 2012. Available from: http://www.merckmanuals.com/vet/toxicology/nitrate_and_nitrite_poisoning/overview_of_nitrate_and_nitrite_poisoning.html [Retrieved: 06-12-2014]

[66] Lautenschläger H. Shelf Life and Preservation. Leichlingen: Kosmetik Konzept KOKO GmbH & Co. KG; 2007. Available from: www.dermaviduals.de [Retrieved: 11-11-2014]

[67] Ioana C. How to Properly Store Cosmetics. 2010. Available from: www.metrolic.com/how-to properly-store-cosmetics-100056/ [Retrieved: 10-10-2013]