Toxics in cosmetics: chemical properties, impact mechanism and clinical cases derived from major chemical components

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Abstract. From pure natural ingredients to synthetic product, cosmetics have been used for centuries. To pursue beauty, the appearance of cosmetics is almost as old as the appearance of civilizations. People use various cosmetics, like nail products, hair products, perfumes, lipsticks, face creams, which could contain toxic substances that are detrimental to human health. Modern society drives people to pay more attention on their appearance, brings more concern about how to balance the perusing beauty with cosmetics between the potential harmful side effects along the use of cosmetics. Therefore, toxin substances from cosmetics should be understood when purchased by consumers. Current study talks about the four major types of toxic substances in cosmetics focusing on the precise chemical properties, biological mechanism as well as the following damages these toxins could cause. People should be reasonably alarmed and aware the potential risks when using cosmetics containing these toxins.

Keywords: Toxics, Cosmetics, Clinical case, Chemical components.

1. Introduction

Cosmetics are increasingly used in people's daily life. Cosmetics are everywhere in our life, like shampoo, lipsticks, suncream, perfumes, et.al. They all have purposes of making consumer cleaner, more beautiful and attractive. However, while cosmetics enlighten the appearances of consumer along with various cosmetics product brands and new products appeared, more and more cases have been continuously reported as to have skin disorder, organ issues when using cosmetics. These cases are mainly due to two reasons. First, there aren't any safety substitution with the same or even better performances than the toxic enteritis to be used in cosmetics. A well-known example is that although hydroquinone causes skin problem, it is the most efficient compound to reduce black dot at present. And heavy metal is critical to be used for coloring in cosmetics even it has high toxicity. Second, many cosmetic companies are keen to reduce their production cost. In manufacture process, they using cheaper synthetic substances which are harmful for people's health instead of expensive natural ingredients. There are several toxics involved in cosmetics that could induce severe damage to human body. Damages can be categorized in two major types: outside the body and inside the body. For outside damage, paraben, the preservative, increases the risk to have skin cancer. Hydroquinone induces ochronosis. Toluene leads to allergies. For inside damage, paraben disrupts endocrine systems. Heavy metals increase possibilities of cell mutation which further leads to cancer and cause irreversible damages to organs including liver, lung, kidney. Toluene inhibits nervous system and harms important organs. Thus, it is critical for consumers to be alarmed about the potential risk when using cosmetics in daily life.

2. Parabens

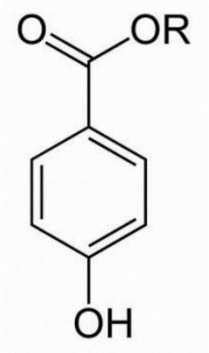


Figure 1. Structure of parabens

Parabens are esters of 4-hydroxybenzoic acid, and methylparaben, propylparaben are the most frequent parabens. They are a group of chemicals that use their antimicrobial abilities to work as preservatives in cosmetics, like sunscreen, facial moisturizer, and shaving gels. As result, it prolongs the time that consumers can use, which increases their benefit. Most of parabens used in cosmetics are synthesized. The European Union has limited the number of parabens used in cosmetics due to their negative effect including endocrine disruption of skin cancer.

Table 1. Contact allergen management program data (Fransway et al 2019)

Product Type/Family	Eye care products	Facial products	Hair care products	Lip products	Oral care products	Nail care products
No.Containing Parabens	107	107	79	21	13	13
% Contaiing Parabens	31.3	31.8	9.5	14	9.4	17.3

2.1. Paraben's absorption

Parabens enter the body via two main routes: transdermal penetration and oral ingestion.[1] While people apply cosmetics to their skin, parabens penetrate the skin against different skin integrity and barrier function. Compared with the integrity of normal skin, wounds have a larger surface area of capillary vessels that are exposed to parabens, which dramatically enhance the penetration. Paraben diffusion depends on the volatility of the solvent.[2] For example, ethanol and acetone increase the penetration by serving as the vehicle to transport parabens. On the other hand, due to consumers ' frequent daily usage' of cosmetics, when they wash off cosmetics that contain parabens, some parabens turn back into bottled water after a huge loop of water recycling system, which gives them other opportunities to get into the human body through oral drinking.

2.2. Parabens and endocrine disruption

Parabens increase endocrine disruption due to their interaction with estrogen hormones. [3,4] Estrogen is the sex hormone that regulates female reproductive system function and develops secondary sex characteristics. Estrogen mainly uses 17β-HSD1 and 17β-HSD2 to catalyse the conversion between estrone and estradiol. Estrone is a type of weak estrogen, which is categorized as a minor sex hormone. And estradiol is a female hormone that is used to mitigate menopause symptoms. However, parabens inhibit enzymes which disrupt the equilibrium between estrone and estradiol. The inhibition of the 17β-HSD1 reduces the rate of conversion of weakly active estrone into more potent estradiol, which causes ati-estrogenic ability. In contrast, the inhibition of 17β-HSD2 decreases the opposite reaction to reduce active estradiol, which severely breaks up the normal stable level of sex hormones.

Figure 2. Conversion between estrone and estradiol

2.3. Parabens and skin cancer

Parabens not only have the oestrogenic biological ability to cause endocrine disruption but also have the risk of increasing skin cancer. [5] When people apply paraben-containing creams to their faces or bodies, parabens affect the epidermis and dermis of the skin. Methylparaben severely reduces the keratinocytes 'proliferation. Keratinocytes produce keratin to protect against environmental change, including UV light, viruses, parasites, bacteria, heat. While parabens inhibit keratinocytes, they cause UV-induced damage and reactive oxygen species, nitro oxide production, and lipid peroxidation damage. [6] These damages further lead to the genotoxic effect of paragons in specific cosmetics like sunscreens. By interfering ERβ and keratinocytes, parabens might also lead to the development of melanoma cancer.

3. Hydroquinone

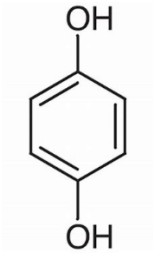


Figure 3. Structure of hydroquinone

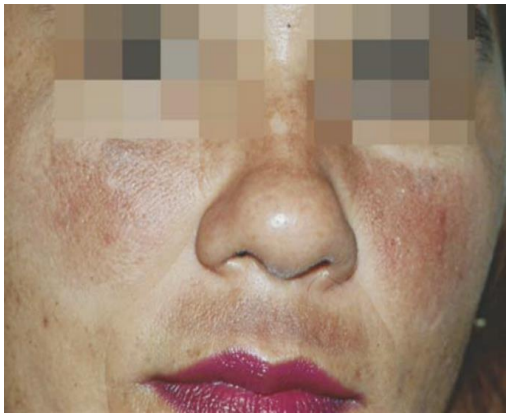
Hydroquinone is an organic compound that has two hydroxyl group bonded to the benzene ring, which with a chemical formula C6H6O2. [7] It often works as skin lightening agents through depigmenting dark spots on the skin and let skins appear smoother and brighter. To achieve this, hydroquinone inhibits tyrosinase, which is the particular enzyme responsible for the production of melanin, thus generate black dots. By producing free radicals to apply cytotoxicity to the melanocytes and interfering melanosomes, hydroquinone acts as an effective agent for depigmentation. Although hydroquinone is functional and effective in cosmetics, it is banned by Europe Union since March in 2000 due to its severe side effects to organisms.

3.1. Hydroquinone ad skin diseases

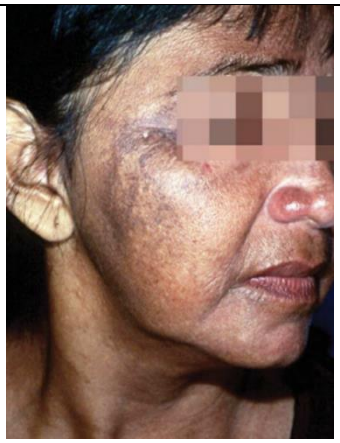
At the concentration of 2% to 5%, hydroquinone causes various detrimental effects, including dermatitis, pigmentation, nail discoloration, and most severely the ochronotic. [8] There are two types of ochronosis: endogenous and exogenous. Hydroquinone mainly induces exogenous ochronotic. The resulted symptoms include skin problems that depositing pigment throughout skins, eye problems with hyperpigmentation of corneas, and cartilage problems that ear cartilage is hardened and darkened. [9] Ochronosis is induced because of the deposition of hydroquinone or homogentisic acid one cartilage. By getting incorporated with elation and collagen fibers, these compounds' pigments change the fiber structure through curling and enlargement. And these pigments further accumulate fibers. Moving on, these pigments and pigments that positioned in fibers that decrease the elastic recoiling produce cross linkages. As a result, the elastic structure increases the rigidity and becomes

hardened. While this structure is ruptured, pigments expose and further lead to the reaction with inflammation follows.

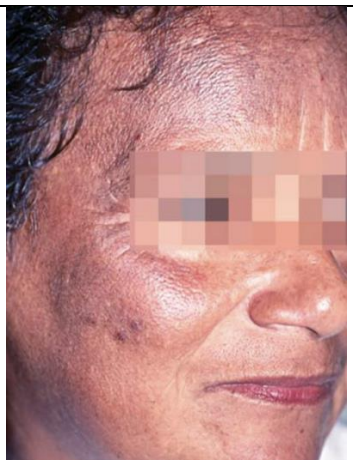
3.2. Hydroquinone related clinical cases



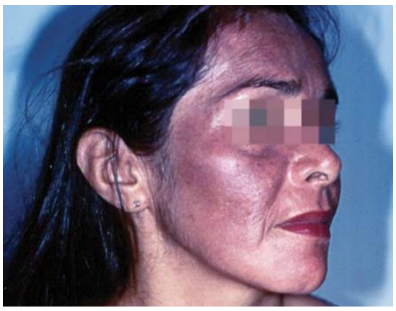
Case 01. Damages in malar and supralabial (Ribas 2010)



Case 02. Grey, brown damages in lateral regions and depigmented lesions (Ribas 2010)



Case 03. Black-blue damages in lateral regions and the forehead (Ribas 2010)



Case 04. Brown-purple damages in lateral regions and malar regions (Ribas 2010)

Figure 4. Reported cases of skin damage caused by using hydroquinone containing cosmetics

Experiments were conducted to further discover the relationship between hydroquinone and exogenous ochronosis. Experiments results showed that the inhibition of the enzyme that oxidized by hydroquinone, leading to the accumulation of homogentisic acid which transforms into ochronotic pigment. [10] In Riba's paper in 2010, there were 4 specific clinical reports which shows how hydroquinone affects skins. In case 01, a 36-year-old female patient who was treated with 2% concentration of hydroquinone for 5 years got facial melanoma appeared in molar region, and symmetrically on dorsal of the supralabial and nose (for 8 years??). And it further led to hyperpigmentation. In case 02, due to use different clarifying creams which contained the concentration of hydroquinone from 2% to 6%, a 56-year-old female patient presented more than 10 years grey brownish macula on her face while also had depigmentation in the center of the lesions. In case 03, a 58-year-old female patient used 2% to 5% hydroquinone to treat her 22 years facial melasma. Although it responded positively at the beginning, worsened hyperpigmentation occurred in the last 4 months. Dermatological detection indicated fuliginous blueish-black molecules were appeared on bilateral region of her face. In case 04, a 38-year-old patient who had brownish macula one lateral region of face and malaria used hydroquinone-containing facial cream which has concentration from 2% to 4%. As a result, she had hyperpigmentation on the last 6 months in the

treatment. Above experiments clearly shows that using hydroquinone product increases skin problem including hyperpigmentation and ochronosis, which severely threats people's health conditions.

4. Heavy metals

Heavy metals are basic elements exist in the earth, including lead, zinc, cadmium, aluminum. [11] These elements are also widely and commonly appeared in cosmetics product. In 2010, the investigation of the FDA showed that in 400 tested lipsticks, there were lead ranging from 0.026 ppm to 7.19 ppm while having the average value of 1.11 ppm. One year later, the Canadian Environmental Defense found the presence of cadmium, nickel, lead, mercury, arsenic, various kinds of heavy metals, in 49 face makeup products from six pedestrians. Heavy metals are used in cosmetics due to their splitting *d* orbitals. Five *d* orbitals in these metal elements split into high and low energy level. While electrons absorb different amount of energy and excite from lower energy level to higher and then drop back, this process emits different wavelength of light, which offers metals various colors. Thus heavy metals are used as colorants in cosmetics. However, heavy metals could induce all kinds of toxic effects to human body while putting them onto skins, which severely threats consumers' health.

4.1. Heavy metals and cancer

Generally, heavy metals increase the risk to induce carcinogenic effect. [12] They target cellular regulatory and signaling proteins, which inhibits normal DNA repair, DNA methylation, cell cycle regulation, cell growth, and apoptosis. The activation of redox-sensitive transcription is the factor that relates to carcinogenic effect induced by heavy metal. For example, in MAP (mitogen-activated protein) kinase pathway, it is detected that heavy metals signaled AP-1, which is charged in cell growth and cell differentiation, and NF-kB, which is involved in controlling inflammatory responses. After signaling, heavy metals produce free radicals into cells which increases the risk to expose the above activities to the carcinogenic metals. Specifically, each heavy metal has its own toxicity mechanism and side effects to human body.

4.2. Arsenic

Arsenic causes the biotransformation process that converts inorganic arsenic substances into methylated arsenicals. The final methylated products are mainly MMA and DMA. MMA, monomethylarsonic acid, isn't excreted and left in cells while being highly toxic and increases the risk for arsenical induced carcinogenesis. Short term exposure to arsenic could cause vomiting, nausea, abnormal heartbeat, erythrocytes and leukocytes inhibition and vessel pressure. Long term exposure to arsenic induces skin lesions, neurological diseases, internal cancer, pulmonary problem, peripheral vascular diseases, diabetes mellitus, and cardiovascular disease. And it also further leads to irreversible damages to organs and increases mortality rate. [13]

4.3. Lead

Lead shows toxicity through ionic mechanism which further causes oxidative stress. [13] Oxidative stress is the result of the imbalance between the production of ROS (reactive oxygen species) or the production of free radicals and the biological system's capability to detoxify reactive intermediates or to repair damages. During this ionic mechanism, lead metal ion substitutes other metal cations including, magnesium ion, iron ion, and calcium ion, which causes biological metabolism disruption, like cell adhesion, protein folding, apoptosis, maturation, and enzyme regulation. Furthermore, when the blood brain barrier is expose to high concentration of lead, the plasm membrane will move to the interstitial spaces, which causes edema. This process severely harms the human body by disrupting intracellular second messenger systems and the normal function of nervous system.

4.4. Cadmium

Cadmium toxicity is reflected through its interaction with cells. [12] When cadmium gets into the body and binds with cysteine-rich protein, its concentration rises 3000-fold. The cystein-metallothionein complex has hepatotoxicity in the liver. Cadmium plays the role of free radical robber by substituting zinc in metallothionein by having the identical positive charge in ion states. Due to its ability to bind with glutamate, histidine, and cysteine, it reduces the concentration of iron in blood. Cadmium causes damage to several important organs in human bodies. Cadmium is toxic to kidney because it gets easy to bioaccumulate in proximal tubular cells by its relatively high solubility in water while retaining in a very high concentration. [13] And it would result morpho pathological conversion in kidneys after log time interactions. Being exposed to low concentration of cadmium in long term, it not only causes bone mineralization through renal dysfunction but also leads to severe lug damages. If people ingest high level of cadmium accidentally while using cosmetics, it would lead to irritation in stomachs which further induces diarrhea and vomiting.

4.5. Mercury

Mercury has the nature of toxic and bioaccumulative. [13] For example, methyl mercury behaves as a neuro-toxic substance that causes mitochondrial damage, lipid peroxidation and microtubule destruction. Methyl mercury reacts with endohydric and sulfhydryl groups, which results the destruction of tertiary and quaternary protein structure. It also disrupts the transcription and translation process, which reduces ribosome and eradicates endoplasmic reticulum. The main target organ of mercury is the brain, is also harms other important organs' normal functions including kidneys, muscles and nerves. Exposure to high concentration of mercury eliminates cellular selenium which is required for the biosynthesis of thioredoxin reductase that is used to prevent and reverse oxidations. If the inhibition of this biosynthesis is severe, it would cause brain cell dysfunctions which further leads to physical death. Besides, mercury disrupts intracellular calcium homeostasis and membrane potential.

5. Toluene

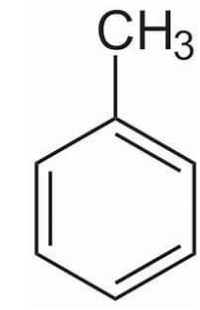


Figure 5. Structure of toluene

Toluene, methylbenzene, is a group of substances that are used in cosmetics for dyeing hairs and nail product. [14] Toluene-2,5-diamine and toluene-3,4-diamine are two typical isomers of toluene that applied in cosmetics. Toluene-2,5-diamine is soluble in water while being colorless. And toluene-3,4-diamine is a colorless crystal that also soluble in water. The International Cosmetics Ingredient Dictionary and Handbook shows that toluene-2,5-diamine and toluene-3,4-diamine are primary intermediates used as the oxidative in the hair colorants. These substances form colored materials inside the hair through oxidation and coupling reaction. And these two isomers form black, warm brown, blond and gray. Furthermore, due to its high solubility in different liquids, toluene is used as solvent to dissolve substances into nail product which can be smoothly and easily applied onto nails.

5.1. Toluene related syndromes

When toluene enter body through inhalation or penetration through skin, it goes through blood-brain-barrier and produces sedative-hypnotics.[15] Toluene influences central nervous system and further results headache, dizziness, memory damage, and eye irritation. Especially for pregnant women, if they were exposed to high concentration of toluene, they would have fetal solvent syndrome. Major effects for infants are the retardation growth and microencephaly and follow by appearance that has low set ears, deep set eyes and obvious deficits. [16] When people are exposed to toluene in long time, they would have chronic encephalopathy known as the toluene leukencephalopathy. And this syndrome can be compared to the white matter injury in the brain. As a result, toluene becomes a typical brain white matter neurotoxin. This damage is irreversible and cannot be cured with current clinical conditions.

5.2. Experiments related to toluene

In animal experiments, after being exposed to 1500ppm toluene for 4 hours per day and for 7 days, experiment rats have larger Arenal gland weight, bigger size of adrenocortical cells, which suggests exposure to toluene results adrenocortical hypertrophy. [17] In another experiment, rats that are treated with toluene have changes in catecholamine levels in hypothalamus, which is the higher center of the nervous system. Meanwhile, in an in vivo study, when exposed to solvents mainly contained toluene, participants had nervous system related symptoms like capitation, bound bowels, irritation, and nausea. Considering this, toluene could cause severe damage to human's nervous system.

6. Conclusion

Cosmetics products offer people better appearances through providing smoother skins, brighter faces, less wrinkles, sexier lips. On the flip side, toxics contained in these cosmetics induce health risks and side effects. Even though many regulations and controls are applied through polices in order to limits the concentration of these toxics, people should eliminate these damages through the origin — the demand of cosmetics. While using cosmetics, consumers need to check the ingredient table and rationally balance the damage it could bring with the beauty one pursue. With more and more cosmetics appear, it is critical for people to aware the potential risk of cosmetics. Cosmetics' consumers must pursue the beauty while having a good health body. The society also must rise public health strategies to increase people's awareness about the disadvantages of cosmetics to prevent the risks of turning individual toxic compounds damage into serious public health problems.

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