

Cosmetics, chemical exposure and gender differences

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Summary. The use of cosmetic products has always played an important role in human society, and has reflected the social and cultural changes it has undergone throughout history. The natural ingredients that were used to manufacture cosmetics until the early twentieth century have now been largely replaced by synthetic chemicals used as emulsifiers, preservatives, thickeners, moisturizers, colouring agents or fragrances. Synthetic cosmetic ingredients may include sensitising substances or irritants such as parabens and para-phenylenediamine and other toxic substances, such as formaldehyde and heavy metals, may be present as contaminants, especially in illegal cosmetic products. Although the doses of potentially harmful chemicals present in cosmetics are generally low, due to their direct contact with the epidermis and mucous membranes, they can be readily adsorbed and reach the bloodstream, leading to significant internal exposure. The probability and intensity of adverse effects following exposure to hazardous substances in cosmetic products can be largely modulated by individual susceptibility factors, to which gender-related traits make a significant contribution.

This paper provides a short overview of cosmetics regulations, the manufacture of cosmetic products, and the potential effects on health, placing emphasis on the health implications of gender-related differences in chemical susceptibility and the use of cosmetics.

Key words: cosmetics, chemical agents, health, gender, consumer safety.

Cosmetici, esposizione chimica e differenze di genere

Riassunto. La storia dei cosmetici corre parallela alla storia dell'uomo e il suo uso, riflettendo il contesto storico e culturale, assume valenza sociale e psicologica. Prima del ventesimo secolo per la produzione di cosmetici venivano usate soltanto sostanze naturali, ma nel '900, soprattutto con l'affermarsi dell'industria del petrolio, che forniva prodotti chimici a basso costo, si sono iniziate ad usare (per la loro produzione) sostanze di sintesi. Attualmente gli ingredienti usati sono autorizzati e controllati, tuttavia possono essere presenti sostanze ad azione sensibilizzante o irritante, come i parabeni e la para-fenilendiamina, o sostanze tossiche, come i metalli pesanti e la formaldeide, contenute a volte nei cosmetici prodotti illegalmente.

Sebbene la quantità di queste sostanze sia generalmente bassa, poiché i cosmetici vengono a diretto contatto con

l'epidermide, il loro uso rappresenta un'importante via di esposizione a sostanze chimiche. Gli effetti avversi che possono manifestarsi sono spesso diversi tra uomini e donne a causa di differenze sia biologiche che comportamentali.

In questo articolo, dopo aver richiamato gli aspetti regolatori e di cosmetovigilanza, si discutono, in ottica di genere, i potenziali rischi per la salute associati all'uso di prodotti cosmetici.

Parole chiave: cosmetici, sostanze chimiche, rischi per la salute, genere, protezione dei consumatori.

Introduction

*"A woman without paint is like food without salt."
Plautus (254-184 BC)*

Humans have always striven to improve their appearance or to alter it in order to highlight their social status (as in the Egyptian, Greek, Roman and Chinese civilisations), and for religious and ritual purposes. To do so, they have used cosmetics i.e. substances or products able to modify the body's appearance or fragrance, since the earliest civilisations. The term *cosmetics* derives from the Greek κοσμητική τέχνη (*kosmetike tekne*), i.e. "technique of dress and ornament", from the terms κοσμητικός (*kosmētikos*), "skilled in ordering or arranging" and κόσμος (*kosmos*), which means both "order" and "ornament". However, the history of the use of cosmetics is merely a reflection of the history of mankind, as has been proven by archaeological evidence dating back to the emergence of *Homo sapiens*¹.

Over time, the use of cosmetic products has always played an important role in human society, reflecting the social and cultural changes it has undergone through history. In the past, cosmetics were artisanal products, made exclusively from natural ingredients. The development of industry and the progress of chemistry in 18th and 19th centuries led to significant advancements in the production of cosmetics and the birth of the modern cosmetic industry in the early 20th century, with the establishment of historical brands such as "Elizabeth Arden" (1910) and "L'Oréal Paris" (1909), which launched

the famous slogan “*Because you’re worth it*”. International fashion evolved rapidly after the 1930s, with the introduction of new styles that are continuously changing and moulding trends. Today, cosmetics are a global business and cosmetic advertising, which was previously directed primarily at women, is now targeting a wider population, including men.

As mentioned above, prior to the industrial era, cosmetics were prepared exclusively from natural ingredients, which nevertheless included potentially hazardous substances such as lead or belladonna. Today’s cosmetics industry employs a variety of synthetic chemicals, which are added to cosmetic products as emulsifiers, preservatives, thickeners, moisturisers, colouring and fragrances². The potential effects on health of these cosmetic ingredients depend on their intrinsic toxicity, as well as on the conditions under which the cosmetic product is used and individual susceptibility to the ingredients. In this sense, gender-related traits play an important role as determinants of individual susceptibility to chemical exposure.

Due to the potential health implications of the use of cosmetics, these products are subject to national surveillance and are governed in Europe by Regulation (EC) No 1223/2009³. This Regulation excludes medicinal products, medical devices or biocidal products, in accordance with the precise definition of cosmetic products, their scope and their purposes, provided in the Regulation. In Italy, responsibility for Cosmetic Vigilance lies with the Ministry of Health that, when it receives reports concerning undesirable effects due to the use of a cosmetic product, proceeds with a validation and evaluation procedure. The Italian Ministry of Health has launched a centralised computer platform for the collection and management of reports of serious and non-serious adverse effects, in order to glean new information on the quality and safety of the cosmetics available on the market and to provide corrective or preventive measures in order to protect public health.

At the current time, although the levels of potentially harmful chemicals found in cosmetics are generally low, chemical exposure through cosmetics is considered worthy of consideration in terms of public health⁴, because of the large number of individuals potentially affected. These are still primarily female consumers, despite the growing number of male users, which calls for greater consideration of gender-related differences in the assessment of cosmetic product safety.

This paper aims to provide a brief overview of the state of the art with regard to regulations, production, and the safety issues associated with the use of cosmetics, placing particular emphasis on the possible health implications of gender-related differences in chemical susceptibility and the use of cosmetics.

Cosmetics: definition, regulations and vigilance

A “cosmetic product” is any substance or mixture intended to be applied to the outer surface of the human body (epidermis, hair and hair, nails, lips, external genital organs) or mouth or mucous membranes, primarily to clean, scent and protect them, change their appearance, keep them in good condition, or correct unpleasant odours. A substance or mixture intended to be swallowed, inhaled, injected or implanted into the human body cannot be considered a cosmetic product.

According to Regulation (EC) No 1223/2009, cosmetic products include a great many products such as creams, emulsions, lotions, gels and oils for the skin, face masks, make-up and products to remove make-up, personal hygiene powders, bath soaps, deodorants, perfumes, bath and shower preparations, hair removal products, hair cleansing, conditioning and styling products, dental and oral hygiene product, for nail care and make-up, for external personal hygiene, sunscreens and self-tanning products and the like. Regulation (EC) No. 1223/2009 also governs the aspects of good manufacturing practice, the composition of cosmetics, their presentation (labelling, packaging and any other form of external representation of the product), safety assessment, the fulfilment of obligations concerning the marketing of cosmetic products and information regarding Serious Undesirable Effects.

Cosmetics are subject to Cosmetic Vigilance (CV), i.e. the various activities associated with the collection and reporting of undesirable effects connected with the use of a cosmetic product. CV facilitates post-marketing surveillance and protects health, since cosmetics are used by people of all ages. Nevertheless, undesirable effects can be experienced as a consequence of using a cosmetic product. In Regulation no. 1223/2009, an Undesirable Effect (UE) is defined as an “*adverse reaction for human health attributable to the normal or reasonably foreseeable use of a cosmetic product*”, whereas Serious Undesirable Effects (SUEs) are “*temporary or permanent functional incapacity, disability, hospitalisation, congenital anomalies, or an immediate vital risk or death*”. In this regard, the European Commission published its “SUE Reporting Guidelines” and Annex 1 “Causality assessment of undesirable effects caused by cosmetic products”. In Europe, the national vigilance systems cooperate by means of the rapid safety alert system called RAPEX (RAPid EXchange information system). This system is updated weekly and is based on the reporting of health risks associated with the use of a particular product excluding foods, medicines and medical devices. Using the RAPEX system, the national authorities notify the European Community of all those products, including cosmetics, that may pose a risk to consumers. In Italy,

any report regarding a dangerous product that is received by the *Carabinieri* Fraud Prevention Unit from citizens or Local Health Authorities, is swiftly forwarded to the Ministry of Health and the system is activated. Following risk assessment and precautionary seizure and analysis, if the risk is confirmed, the report is entered into the RAPEX system.

Some 8013 RAPEX reports were filed between 1 January 2014 and 31 December 2017. Of these, 269 (3.4%) concerned cosmetics, of which 29 were produced in USA (10.8%) and 28 (10.4%) in China. In Italy, 4 reports were filed, equal to 1.5% of the total. The chemical risk primarily involved irritants and sensitizing substances (142 reports, equal to 52.8% of the total), but also involved Substances of Very High Concern (SVHC) such as formaldehyde (5 reports, equal to 1.9% of the total)⁵.

Cosmetic chemicals: ingredients and contaminants

As the use of a cosmetic involves direct contact with the epidermis and/or mucous membranes, and the consequent easy absorption of its chemical ingredients, cosmetic products are strictly regulated in order to protect consumer health. Lists of the cosmetic substances considered are provided in Annexes II, III, IV, V and VI to Regulation (EC) No 1223/2009. These annexes lay down clear restrictions and requirements for the cosmetic substances concerned. More specifically, they set forth restrictions for certain substances, namely prohibited substances (Annex II of the Regulation (EC) No 1223/2009), restricted substances (Annex III), colourings (Annex IV), preservatives (Annex V), UV-filters (Annex VI), substances classified as CMR (Carcinogenic, Mutagenic or toxic to Reproduction) substances, nano-materials and traces of prohibited substances. Other important lists of cosmetic substances include the INCI (International Nomenclature of Cosmetic Ingredients) inventory (96/335/EC) or CIN (2009/1223/EC), which identify a great many substances with their possible functions in finished cosmetic products and with the nomenclature that needs to be used on the label of finished cosmetic products.

Sex/gender-related differences in cosmetic exposure and adverse effects

Although the gap in the use of cosmetics between men and women is currently shrinking due to increasing consumption amongst males, exposure to cosmetic products still represents a scenario in which sex and gender-related differences have a considerable weight. At least in

western countries, cultural habits and lifestyle differences mean that there is a distinct prevalence in the frequency and intensity of the use of cosmetics, body care products and jewellery amongst women. This increases the likelihood of women and girls being affected by potentially hazardous ingredients of cosmetic products, particularly when using counterfeited cosmetics. Moreover, the prevalence of female workers in professional activities such as hairdressing, beauty therapy and wellness, entails higher occupational exposure to the chemical ingredients of cosmetic products, including hair dyes, amongst women. According to the U.S. Breast Cancer Fund, the risk of breast cancer is five times greater amongst women employed in the hairdressing and cosmetics sectors⁷.

Indeed, although cosmetics are strictly controlled under European legislation, in the interests of consumer health, several ingredients of cosmetic products marketed in Europe or worldwide raise concern for their potential effects on health, especially for women of reproductive age⁸. The list of hazardous ingredients in cosmetics that are available on the legal and/or illegal market includes aromatic amines, which are suspected of being carcinogenic and mutagenic, heavy metals such as lead and mercury, the skin sensitiser para-phenylenediamine, and alleged endocrine-disrupting chemicals, such as bisphenol A, phthalates and parabens (Table 1).

The ultimate effect of exposure to these potentially harmful agents is modulated by sex-related differences in pharmacokinetics and pharmacodynamics, as well as by gender-related differences in social and lifestyle factors^{9,10}. As women's bodies have a different composition to men, characterised by a lower average body weight, higher proportion of fat deposits and lower plasma volume and organ blood flow, and given the differences in hepatic metabolism and their lower renal clearance, there may be certain differences regarding pharmacokinetics, and higher levels of internal chemical exposure in women, thereby exacerbating the consequences of xenobiotic exposure^{11,12}. In the case of dermal exposure, as is the case for most cosmetics, differences in skin thickness, the number of sebaceous glands, body hair, and the possible presence of shaving cuts, may also differentially affect individual internal exposure to cosmetic ingredients.

Pharmacodynamics, i.e. the way the body responds to chemical exposure, is also affected by sex-related factors, as shown by the dimorphic profile for adverse drug reactions in women and men (Nicolson et al, 2010), and by the higher prevalence of nickel-related allergies and hand eczema in women than in men¹³.

Table 1. Examples of potentially hazardous chemicals present in cosmetic products

Substance and class of contaminant	Use and source of exposure	Associated adverse health effects
4-aminobiphenyl (4-ABP)	<i>Cosmetics use</i> Black, red and blonde hair dyes	Human urinary bladder carcinogen
Bisphenol A (BPA) (EDC, Endocrine Disrupting Chemical)	<i>Cosmetics use</i> Nail polish, skin creams, bath lotions, cosmetic dentistry and fillings	Disturbs foetal development of reproductive and central nervous systems. Possibly associated with several common diseases. The developing child is more susceptible than adults. Endocrine active, estrogenic
Lead (Heavy metal)	<i>Cosmetics use</i> Traditional eye cosmetics (surma and kohl)	Adverse effects on nervous system and cognitive development (children are more susceptible than adults), kidney damage, reduced haemoglobin production, anaemia, reproductive effects
Mercury (Heavy metal)	<i>Cosmetics use</i> Skin lightening creams and soaps, eye make-up and eye make-up remover (phenyl mercuric salts)	Methyl mercury and mercury vapor is neurotoxic, possibly carcinogenic Metallic mercury and inorganic mercury compounds are nephrotoxic
Parabens (EDC)	<i>Cosmetics use</i> Personal care products, skin moisturisers, perfumes, lipstick	Some show effects on reproduction and development. Endocrine active, interfering with oestrogen and androgen hormones
Phthalates (EDC)	<i>Cosmetics use</i> Personal care products, skin moisturisers, perfumes, lipstick	Some show effects on reproduction and development. Endocrine active, interfering with oestrogen and androgen hormones
Para-phenylenediamine (PPD)	<i>Cosmetics use</i> Frequently used as hair dye substance in hair dye products. Used in black henna tattoos	Extremely potent skin sensitiser, asthma, renal failure

Modified from UNDP, 2011.

Cosmetics market: the weight of legal and illegal products

The international cosmetics industry has a value of over 260 billion euros, with a constant positive trend despite the economic crisis of the last decade, confirming the anti-cyclic characteristics of luxury goods. Although the main purchasers of cosmetic products on a global scale are China and Russia, followed by Japan and South Korea, Europe is the greatest producer of cosmetics, with an estimated market value in excess of 77 billion euros (Cosmetics Europe, 2017). In Europe, the cosmetics industry employs more than 190,000 workers, and indirectly involves more than 2 million workers employed in related sectors. 56% of these workers are women. Italy occupies a leading position in the cosmetic product sector, manufacturing 60% of the world's cosmetics and it generated estimated sales of 14 billion euros in 2017.

Cosmetic marketing primarily targets women. Women still consume the vast majority (70%) of cosmetic products, especially in the case of make-up products, although over the past decade the no-gender cosmetics market, or cosmetic market specifically devoted to males,

has steadily increased amongst men in the 20-40 years age range, also known as the next generation. Nevertheless, there are still clear gender-related differences in the use of cosmetics (Figure 1), which generate different exposure profiles with possible health implications as discussed below. In recent years, the illegal cosmetics market has grown steadily: counterfeit products labelled as original brands have flooded the cosmetics market, taking a heavy toll on the economy of the sector, with an estimated 10% loss in sales, and on consumer safety, due to the lack of regulatory compliance and the possible presence of hazardous ingredients. Heavy metals such as nickel, lead and especially chromium, all of which are forbidden by European legislation, are most frequently found in counterfeit lipsticks, eyeliners, and other make-up products imported illegally from non-UE countries. These contaminants may occur in concentrations high enough to cause dermatitis and severe allergies, which are more frequent among women, given both their greater use of these products and their greater susceptibility to allergic reactions.

It is therefore important for health authorities to inform consumers correctly regarding the potential hazards related to the use of illegal cosmetic products, as

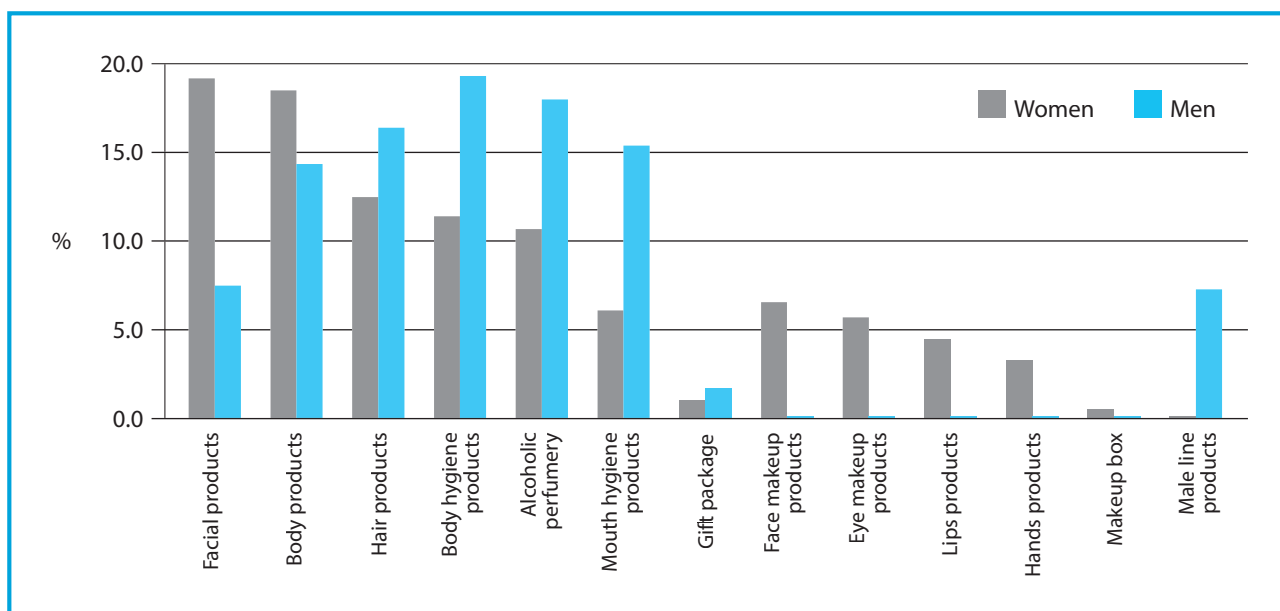


Figure 1. Percentage of use of different cosmetic products in women and men.

well as to improve the awareness amongst consumers and healthcare professionals regarding the need to report any adverse effect associated with the use of cosmetics, in order to implement an efficient health surveillance system for the protection of consumer safety.

Biocosmetics

The cosmetic industry, a rapidly growing industry that is continuously developing new active ingredients, recently began to provide scientific validation for the use of certain botanical ingredients as substitutes for chemicals. Indeed, public opinion trends show an ever-higher demand for natural or organic products among customers and people are increasingly demanding the use of organic and natural ingredients only for the production of many products, including cosmetics. At present, the “biocosmetics” sector lacks specific regulations, however, notwithstanding the lack of standardised guidelines establishing the requirements for their safety assessment, these “natural” products are gaining great popularity on the market. “Natural” generally means products produced using ingredients derived from nature, mainly plants, that have been enhanced by laboratory procedures to improve their ability to penetrate into the epidermis, to remain on the skin without any changes in their properties, and to guarantee their intended action. Botanical compounds for which dermatological and cosmetic applications have been emerging include olive oil, chamomile, colloidal oatmeal, oat kernel extract, feverfew, acai berry, coffee berry, curcumin, green tea,

pomegranate, licorice, paper mulberry, arbutin, and soy¹⁴. Many of these botanical sources provide biologically active ingredients that are employed for cosmetic use; however, only recently both clinical and industrial research have begun to provide scientific advice for the safe use of certain botanical ingredients^{15,16}. In some cases, the knowledge obtained regarding their biological mechanisms of action have been translated into clinical practice. However, the axiom that “a natural product” equates “a safe product” cannot be taken for granted, given the known toxic and pharmacological activity of many natural substances, and natural cosmetic ingredients also require appropriate scientific assessment, in order to make sure they are safe to use.

Conclusions

Cosmetics are among the most widely-used consumer products, and ensuring that they are used safely and healthily is a priority need. In most cases, the use of cosmetics entails exposure to multiple chemical ingredients that may elicit undesirable biological effects, especially in vulnerable subjects, depending on many factors including age, gender, health and nutritional status. The occurrence of gender-related differences in chemical susceptibility, and the possible presence in cosmetics of ingredients preferentially targeting the female sex, call for special consideration of gender-related differences in cosmetic risk assessment. Although, in principle, the assessment of the safety of consumer products and the related health risks is primarily the manufacturer’s re-

sponsibility, consumers can help to minimise the possible risks associated with the use of cosmetic products by complying with the prescribed conditions of use and by only using safe purchasing channels in order to avoid risks associated with illegal products. In this respect, it is the responsibility of health authorities to improve customer awareness regarding chemical risks in consumer products, through comprehensible but effective awareness campaigns.

Key messages

- The use of cosmetic products has always played an important role in human society, and has reflected the social and cultural changes it has undergone throughout history.
- Synthetic cosmetic ingredients may include sensitising substances or irritants such as parabens and parafenylenediamine and other toxic substances, such as formaldehyde and heavy metals, may be present as contaminants, especially in illegal cosmetic products.
- Although the doses of potentially harmful chemicals present in cosmetics are generally low, due to their direct contact with the epidermis and mucous membranes, they can be readily adsorbed and reach the bloodstream, leading to significant internal exposure.
- The probability and intensity of adverse effects following exposure to hazardous substances in cosmetic products can be largely modulated by individual susceptibility factors, to which gender-related traits make a significant contribution.

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