CONTACT SENSITIZATION AND ALLERGENS IN THE COMPOSITION OF COSMETIC PRODUCTS – CURRENT KNOWLEDGE

KONTAKTNA SENZIBILIZACIJA I ALERGENI U SASTAVU KOZMETIČKIH PROIZVODA – POSTOJEĆA SAZNANJA

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Summary
Contact sensitivity is a latent state that lasts a lifetime with a clinically manifesting response in the form of allergic contact dermatitis that often has an unfavorable prognosis. In contact urticaria syndrome, one can cause anaphylactic reactions. Exposure to irritants or sensitizing factors represents a major risk. Age and gender are not risk factors for contact sensitivity in themselves. A recent meta-analysis has shown that the prevalence of contact sensitivity in the general population is 20.1% and that 4 allergens from cosmetic products are among the top 6 allergens that cause contact sensitivity in the general population. Cosmetics products are responsible for more than half of all allergic contact dermatitis which mainly affects adults of middle and older age, who generally do not have atopy and whose occupations have low academic requirements. It is possible for a cosmetic allergy to develop even after years of using a cosmetic product without previous problems. Beauty products to watch for. Just because a label says that something is "dermatologist tested", that is no guarantee that the product will be kind to your skin. There are no rules about these terms and criteria how to use them on a label. Ingredients that may cause allergy. Preservatives and fragrances are the most frequently detected allergens in those with an allergy to a cosmetic product. The future of allergen labeling. Allergens identified by the Scientific Committee on Consumer Safety need to be present on a label. Every cosmetic product placed on the European Union market must have a compliant product information and an International Fragrance Association certificate if contains fragrances. Conclusion. Because so-called “hypoallergenic” products are not necessarily less sensitizing, allergy departments should distribute lists of cosmetic products not containing the respective allergen(s) that consumers can use as safe alternatives.

Key words: Cosmetics; Dermatitis, Contact; Allergens; Risk Factors; Preservatives, Pharmaceutical; Odorants; Consumer Product Safety; Health Knowledge, Attitudes, Practice

Sažetak
Kontaktna senzibilizacija predstavlja latentno stanje koje traje doživotno. Najčešće se manifestuje u vidu alergijskog kontaktnog dermatitisa, koji neretko ima nepovoljnu prognozu. Ukoliko se manifestuje sindrom kontaktnih urtičarija, može izazvati anafilaksiju. Izloženost iritansima i/ili alergenima predstavlja veliki rizik. Starost i pol, sami po sebi, nisu faktori rizika. Nedavna metaanaliza je pokazala da prevalencija kontaktnih senzibilizacija u opštoj populaciji iznosi 20,1% i da se četiri alergena u sastavu kozmetičkih proizvoda nalaze na listi prvih šest alergena, najčešćih izazivača. Kozmetički proizvodi su odgovorni za više od polovine svih slučajeva alergijskog kontaktnog dermatitisa, koji najčešće tada pogađaju osobe srednjeg i starijeg životnog doba, koje uglavnom nemaju atopiju i čija zanimanja imaju niske akademske zahteve. Moguće je da se razvije i nakon prethodne višegodišnje bezbedne upotrebe kozmetičkog proizvoda. Kozmetički proizvodi na koje treba obratiti pažnju. samo zato što na etiketi proizvoda piše da je nešto "dermatološki testirano", to nije garancija da je bezbedno za primenu na svakoj koži. Ne postoje regulativna pravila kako i kada ovaj termin staviti na etiketu. Sastojci koji mogu izazvati alergiju. Konzervansi i mirisi su najčešće dokazane klase alergena kod osoba koje su razvile preosetljivost na kozmetičke proizvode. Budućnost označavanja alergena. Sve supstancije koje je Naučni komitet za bezbednost potrošača u Evropskoj uniji označio kao alergene, moraju biti prisutni na etiketi. Svaki kozmetički proizvod koji se plašira na tržište Evropske unije mora imati dostupnu datoteku u slučaju da sadrži mirise, neophodan je i sertifikat Međunarodnog udruženja za mirise koji potvrđuje da je proizvod bezbedan za upotrebu. Zakučak. Pošto tako označeni "hipoalergogeni" proizvodi nisu za sve osobe jednako bezbedni, odeljenja koja se bave dijagnostikom kontaktnih senzibilizacija treba da distribuiraju liste onih kozmetičkih proizvoda koji ne sadrže odgovarajući alergeni(e), tako da preosetljive osobe mogu da ih koriste kao bezbedne alternative. Ključne reči: kozmetologija; kontaktni dermatitis; alergeni; faktori rizika; farmaceutski konzervansi; mirisi; bezbednost konzumerskih proizvoda; znanje o zdravlju, stavovi, praksa

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Patients can hardly avoid it. For this reason, ACD often occurs where exposure to an allergen is on a daily basis and throughout the whole lifetime of the affected persons, particularly in situations involving skin contact allergy (ACD) [1]. The ACD significantly reduces the quality of life of those affected, and in severe cases it can cause chronic or recurrent dermatitis, often leading to the loss of workplace or school capacity due to recurrent courses of the disease [2]. In such cases, ACD should be included in the differential diagnosis [2]. The existence of CS is diagnosed by a positive epicutaneous patch test (PT), and in order to diagnose ACD, in addition to a positive PT, medical history data on exposure to the incriminated allergen is required. Epicutaneous testing is standardized procedure and if performed technically correctly, a positive test result indicates the presence of a specific sensitization [3]. Contact allergens are chemically reactive substances of low molecular weight (< 1000 daltons (Da)) and as haptens react with larger protein biomolecules in the skin to form immunogenic complexes. The ability of haptens to bind to proteins is the main predictor of its allergenic potential, while differences in the location and mode of protein binding are predictors of the type of allergic response, early or late [4]. In rare cases CS can result in the production of specific immunoglobulin E (IgE), whereas in contact urticaria syndrome it can cause signs and symptoms of severe anaphylaxis. The role of genetic predisposition for CS refers to the existence of polymorphisms for genes that encode the synthesis of enzymes necessary for metabolic transformation in the skin of contactors, the so-called prehapten into hapten. The number of these allergens is small [5, 6].

Contact sensitivity

Contact sensitivity (CS) is a latent state of specifically altered reactivity of the immune system that lasts a lifetime, caused by contact of the skin or visible mucous membranes with substances from the external environment, the so-called contact allergens. In most cases, CS is of the eczema type, and represents a late-cellular immune response in the skin. After the first contact with the antigen, in its first, induction phase, CS results in the formation of specifically preformed effector T-lymphocytes. After 10 refractory days on average, in the second elimination phase of CS, during the first reexposure, these cells recognize the allergen and within 48 hours respond with a specific immune inflammatory response. In both phases, epidermal dendritic Langerhans cells (LC) and dermal dendritic cells (DC) play a key role in antigen processing and presentation, by interaction with neighboring keratinocytes, migration to the local draining lymph nodes, and by priming of naive T-cells. During the process of migration, pinocytosis and the so-called internalization, DC translates the antigen protein into a peptide chain and binds it within itself to the molecules of the major histocompatibility class II molecules. The antigen in the complex thus formed is ready to bind to the receptors on the T-lymphocyte in the lymph node by stimulatory and costimulatory connections. These connections exist through inflammatory cytokines, chemokines and adhesion molecules. Antigen specific effector T-cells migrate into the skin upon contact with the same hapten, during reexposure (elicitation phase), primarily at the site of contact with the antigen. After activation by antigen-presenting skin cells, including LCs, DCs, keratinocytes, and macrophages, in the Th1 cytokine milieu, they reach an inflammatory, clinically manifesting response in the form of allergic contact dermatitis (ACD) [1]. The ACD significantly reduces the quality of life of the affected persons, particularly in situations where exposure to an allergen is on daily basis and patients can hardly avoid it. For this reason, ACD often has an unfavorable prognosis and a high tendency of recurrence and chronicity. In each case of recurrent dermatitis, ACD should be included in the differential diagnosis [2]. The existence of CS is diagnosed by a positive epicutaneous patch test (PT), and in order to diagnose ACD, in addition to a positive PT, medical history data on exposure to the incriminated allergen is required. Epicutaneous testing is a standardized procedure and if performed technically correctly, a positive PT has medico-legal significance [3]. Contact allergens are chemically reactive substances of low molecular weight (< 1000 daltons (Da)) and as haptens react with larger protein biomolecules in the skin to form immunogenic complexes. The ability of haptens to bind to proteins is the main predictor of its allergenic potential, while differences in the location and mode of protein binding are predictors of the type of allergic response, early or late [4]. In rare cases CS can result in the production of specific immunoglobulin E (IgE), whereas in contact urticaria syndrome it can cause signs and symptoms of severe anaphylaxis. The role of genetic predisposition for CS refers to the existence of polymorphisms for genes that encode the synthesis of enzymes necessary for metabolic transformation in the skin of contactors, the so-called prehapten into hapten. The number of these allergens is small [5, 6].

Surveillance of contact sensitivity

Clinical data, based on patient consultation and PT results, one can never directly interpret as estimates of disease incidence at the general population level. However, since relative changes we interpret, given that the selection process into the “clinical sample” is stable, surveillance of CS trends is validly possible. Thus, clinical surveillance provided the first data on the newly emerging methylisothiazolinone-induced epidemic of ACD and then on the reduction in disease incidence after preventive measures [7]. In this sense, population and clinical epidemiology complement each other [8, 9]. In order to examine e.g. the trend of CS by comparing the prevalence of sensitization over time, with the variable age and sex distribution of the tested patients and in combination with a negligible age gradient of sensitization risk, we should apply separate analyses for age and sex groups, e.g. population-adjusted frequency of sensitization (PAFS) method [10]. At the same time, the MOAHFA index (M - male; O - occupational; A - atopic dermatitis present or past; H - hand; L - leg; F - face; A - age of 40 years and above), indicates the presence of demographic characteristics in the examined population that can significantly affect the incidence of CS. By including these variables in a multifactorial analysis, it provides comparison of the results obtained from different sources and in different periods. The first, and according to the available literature, the only tests of CS and ACD in Serbia, in which these principles are used, came from our institution from Department of Allergy and Clinical Immunology at the Clinic of Dermatovenerology Diseases in Novi Sad [11–14]. It is difficult to interpret the distribution of occupations, age or gender, in a patient population without knowing the distribution of these characteristics in general population. The world sci-
.tifific literature, considering the results of multicenter studies on ACD and CS, originates from Information Network of Departments of Dermatology (IVDK) (https://ivdk.org), which is the most relevant for studying clinical epidemiology and its comparison with the results of population epidemiological studies. The IVDK represents a unique information database which gathers results from all dermatological centers in Germany and applies the principles of good epidemiological practice [2, 10, 15, 16]. However, the incidence of CS and ACD in the general population can be determined in cross-sectional studies conducted in recent years. The data indicate that female gender, young age, and ear piercing (before 1990), are the main risk factors for the development of CS to nickel, while the relative risk for the development of CS to fragrances that are the most important allergens in cosmetics, more than doubles in older groups, compared to younger ones. Fragrance allergy is the second most frequent cause of CS after nickel and it affects every 10th patient examined for CS [5]. Age-dependent immune reactivity seems to be less significant than differences in the degree and type of complexity that exist between age groups and between the sexes [17]. The prevalence studies strongly suggest that age and gender are not risk factors for CS in themselves, but that these characteristics are associated with exposure to occupational and everyday activities [2]. Exposure to irritants or sensitizing factors represents a major risk for the development of irritant CD (ICD) and ACD.

The CD is a common cause of morbidity with a lifetime prevalence of 15% and an incidence greater than 7.9 per 1,000 inhabitants [18]. A meta-analysis of relevant population epidemiological studies [19] has shown that the combined prevalence of CS in the general population is 20.1%, in children and adolescents (under 18 years) 16.5% and that it is significantly higher in females (27.9%) than in males (13.2%). The most common incriminated allergens were nickel (11.4%), fragrance mix (FM) (3.5%), cobalt (2.7%), Peru balsam (PB) (1.8%), chromium (1.8%), methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (1.5%) and para-phenylenediamine (PPD) (1.5%) [19]. It has also shown that 4 allergens from the composition of cosmetic products (FM, PB, MCI/MI, and PPD) are among the first 6 allergens that cause CS in the general population [18–20].

Cosmetic products

There is an increasing use of cosmetic products in the general population, since there are over 8,000 registered substances, available for incorporation into cosmetic products [21]. Through the relevant legislation, several countries and regions of Europe have adopted Article 2 of the European Union (EU) Cosmetics Regulation (No. 1223/2009). The Article 2 defines a cosmetic product as follows: “any substance or mixture intended to come into contact with various external parts of the human body (e.g. epidermis, hair system, nails, lips and external genitalia) or with the teeth and mucous membranes of the oral cavity, with the aim of exclu-

sively or mainly cleaning them, making them fragrant, changing their appearance and/or correcting body odors” [22]. Similarly, the United States Federal Food, Drug and Cosmetics Act defines cosmetic products as: “articles that are rubbed, poured, sprinkled, or sprayed, or otherwise applied to the human body to clean, beautify, promote attractiveness, or change in appearance” [23].

Explanation of research needs

Cosmetic products are among the most important products on the world market and their growth and diversification has become unstoppable [24, 25]. There is little data on the actual incidence of adverse reactions to cosmetics. The prevalence of 12% in the general population, reached 47% in patients referred for allergy testing. The ACD is of particular interest because of the severity of symptoms it produces, the need to identify the allergen and the risk of cross-reactions. Traditionally, ACD to cosmetic products and their ingredients in patients referred for epicutaneous testing was 2 – 4%, but recent studies indicate a progressive increase and a prevalence of 19 – 25% [24, 25]. About 16% of patients with eczema in Europe have sensitivity to odor components [26]. It is estimated that women on average use at least 9 – 15 cosmetic products every day, which contain 168 unique ingredients, while an average man uses 6 products every day for personal care with 85 unique ingredients [18]. Recent studies have shown that up to 10% of the population has some kind of reaction to cosmetics during their lifetime [27]. Today, cosmetic products are responsible for more than half of all cases of ACD. Female sex represents a risk factor. The ACD to cosmetics mainly affects adults of middle and older age (≥ 40 years), who generally do not have atopy and whose occupations have low academic requirements. Preservatives, fragrances and PPD are responsible for up to 80% of all CS to cosmetics, and this trend has remained stable over the last few decades [24–27]. The results of population epidemiological studies have shown the prevalence of CS to cosmetic products and their ingredients to be 1 – 3%. The prevalence of CS to fragrant ingredients is 1% and to all other substances 2 – 3% [18]. Recent clinical epidemiological studies showed that the ingredients of cosmetic products are responsible for 25 – 50% of all cases of ACD. Interestingly, the prevalence of CS caused by cosmetic products has become higher compared to topical pharmaceutical products, even though they are applied to diseased skin [24, 25]. A significant correlation exists between cosmetic ACD and female gender, but not atopy.

A review of the prevailing attitudes and understandings in the literature

In the United Kingdom, 51.4% of women and 38.2% of men believe they have sensitive skin. The Pons-Guiraud classification includes several entities, with a global prevalence of 38.4% of sensitive skin in the population. “Very sensitive” skin is reactive to a wide variety of endogenous and/or exogenous factors with both acute and chronic symptoms and a strong psychological component. “Environmentally sensitive” skin is clear, dry and thin skin with a tendency to flush or blush.
and it is reactive to primarily environmental factors. “Cosmetically sensitive” skin is transiently reactive to specific and definable cosmetic products [18]. Muizzuddin classification includes “delicate” skin characterized by easily disrupted barrier function not accompanied by a rapid or intense inflammatory response and “reactive” skin with a strong inflammatory response without a significant increase in permeability, while “stingers” skin has heightened neurosensory perception to minor cutaneous stimulation [18]. There is a subset of patients with a condition referred to as “status cosmetics”, since every cosmetic product or soap applied to the face produces itching, burning, or stinging sensation. These patients appear to have normal looking skin or a very faint erythema. They may end up having to avoid any facial cosmetics for 6 – 12 months and then slowly reintroduce some emollients [18]. The PT and repeat open application or use tests are in these cases mostly negative, although they can become positive after prolonged use due to irritation or low-grade sensitization. It is possible for a cosmetic allergy to develop even after years of using a cosmetic product without previous problems [20].

**Beauty products to watch for**

The beauty products most likely to cause skin reactions are bath soaps, detergents, antiperspirants, eye makeup, moisturizers, shampoos, long-wearing lip stains, nail polish (especially those that have formaldehyde), fingertip glue with methacrylate, as well as hair products containing p-phenylenediamine or ammonium persulfate used to lighten hair. Just because a label says something is “hypoallergenic”, “dermatologist tested”, “sensitivity tested”, or “non-irritating” that is no guarantee that the products will be kind to your skin. Some companies do the testing, others do not. There are no rules about these terms and criteria how to use them on a label [28].

**Ingredients that may cause allergy**

There are several categories of cosmetic ingredients: fragrances, preservatives (including antimicrobials and antioxidants), ultraviolet absorbers, excipients (vehicles), emollients, surfactants (including detergents and emulsifiers), hair styling products and dyes, nail products, and acrylates. Preservatives and fragrances are the most frequently detected classes of allergens in those with an allergy to a cosmetic product. Other important allergens include hair color p-phenylenediamine, nail polish resin (tosylamide formaldehyde resin), ultraviolet filters, and lanolin. The mixture of preservatives MCI and MI, FM and PPD are the most common causes of ACD, while acrylates are new allergens. In our Allergy Department at the Clinic of Demarovenology Diseases in Novi Sad, we came to almost the same results after inclusion of the standard cosmetic series of contact allergens (preliminary results).

**Fragrance** represents a category rather than an individual ingredient. There are more than 5,000 different fragrances used in cosmetics and skincare products [20]. Patients may develop reactions to the whole host of products, which contain fragrance as a constituent. Thus, a new fragrance-related allergen C12–15 alkybenzoate, present in sunscreen products, skincare creams, anti-aging and depigmentation products, deodorants as well as cleansing products causing ACD, appeared in the literature. It is unclear whether the reactions to benzyl benzoate and salicylate represent cross-reactivity with alkybenzoate or concomitant reactivity [18]. Product labeling can be incomplete or misleading, thus many essential oils are not labeled as fragrances. The EU Cosmetic Directive states that cosmetics sold in Europe containing the 26 specific fragrance ingredients known to cause ACD, must be declared on the ingredient lists of cosmetic products, if present at more than 10 ppm in leave-on products or more than 100 ppm in rinse-off products. The Cosmetic Directive also states that if a product contains other fragrances, this must also appear on the label as aroma, fragrance, or perfume (with individual e-labeling rather than labeling on the package) [18].

**Preservatives** are the second most common cosmetic contact allergens and belong to various groups such as antimicrobials that include formaldehyde, formaldehyde-releasing preservatives (FRPs), non-formaldehyde-releasing preservatives (NFRPs) and antioxidants. The latter include phenolic antioxidants, vitamins E, K, B5 and gallates. Phenolic antioxidants (e.g. butylated hydroxyanisole) that are ubiquitous food additives also present in foods containing fats or oils, as well as in cosmetics particularly in lipsticks and hair dyes, cause contact allergy. The EU Cosmetic Directive banned vitamin K in cosmetic products in the EU in 2009, although the still permitted oxidized form (phytonadione epoxide) can cause allergy when applied to treat bruising after laser therapy or in make-up for dark circles around the eyes. Gallates, esters of gallic acid (dodecyl, octyl, propyl), are antioxidant chemicals that are commonly used as preservatives in food products and cosmetics, but also in antibiotic creams, lipsticks, moisturizes, topical steroids, and eye cosmetics [18].

In the EU, the maximum formaldehyde concentration is limited to 0.2% (0.1% in oral hygiene products) whereas in the United States there are no specific regulations. Individuals allergic to formaldehyde may also react to products containing any of the FRPs. Between 30% and 50% of the cosmetic products released formaldehyde despite lacking a declaration of formaldehyde or formaldehyde releasers in the list of ingredients [18].

The NFRPs are also an important cause of contact allergy, including parabens, isothiazolinone (in cosmetics specifically MCI and MI)), methyldibromoglutaronitrile (MDBGN) and sodium metabisulphite among others. The EU Cosmetic Directive banned MDBGN in cosmetics since it first appeared in the mid-1980s. However, MDBGN is still present on the market, recently causing relevant contact allergy reported in the literature [18].

Methylisothiazolinone (MI) is a biocide used in cosmetics (e.g. hair care and personal hygiene products and facial cleansers, industrial and household products), either alone or in combination with MCI. In 2005, the
EU Cosmetic Directive banned MCI and approved MI use only as a stand-alone preservative in cosmetic products at a maximum concentration of 100 ppm, that is, considerably higher than the concentration allowed when it is in mixture with MCI (max. 15 ppm). This resulted in an epidemic of contact allergy. Initially, most cases were due to the use of wet wipes (moist toilet paper) for intimate hygiene (also for babies, causing hand dermatitis in their parents) but, later on, facial skin-care products, body lotions, deodorants, and even rinse-off products, such as shampoos and liquid soaps turned out to be important sensitization sources. Later on, there was a decline of contact allergy since its removal from leave-on cosmetic products in the EU in February 2017 and limitation to 15 ppm in rinse-off products [18]. However, it has not completely gone. The explanation lies in the fact that rinse-off products that contain MI/MCI concentrations of 15 ppm and leave-on products with concentrations of 7.5 ppm are unlikely to result in allergic contact dermatitis. Even in patients who are sensitive to MI/MCI, rinse-off products that contain MI/MCI concentrations of 15 ppm are unlikely to cause a reaction. The maximum concentration allowed in Europe was set to 15 ppm in both rinse-off and leave-on cosmetics (in the United States, the concentrations allowed are 25 ppm in rinse-off products and 7.5 ppm in leave-on cosmetics). Despite this change in legislation, there is an increase in the prevalence of sensitization to this preservative. The increased use of MI without MCI as a preservative has led to greater sensitization to MI and because of cross-reactivity, to an increase in positive reactions to MCI/MI. It remains an important allergen to look out for, especially in shampoos/conditioners, lotions and creams, wet wipes, and skin cleansers [18]. The MI is sometimes responsible for severe skin lesions and atypical clinical symptoms, leading to a delay in the correct diagnosis since respiratory problems may occur as well. Patients with suspected reactions to MI/MC, rinse-off products that contain MI/MCI concentrations of 15 ppm are unlikely to be diagnosed. The concentration of MI in the MI/MCI patch (25 ppm) is much lower than in the patch with the preservative by itself (75 ppm). Our preliminary results at the Clinic of Demarovenerology Diseases in Novi Sad have shown MDBGN, MI and MI/MCI as the top three preservatives causing positive P Ts in cosmetic series® (Chemotechnique Diagnostics, Vellinge, Sweden). Although the cosmetic industry advised its members to phase out the use of MI from leave-on products, there are still such products on the market and European authorities have urged MI to avoid this potential allergen. If sensitization to isothiazolinones is suspected, both the MCI/MI mixture and MI alone should be included in the patch test, because if only MCI/MI is included, approximately 40% of allergies to MI will not be diagnosed. This is because the concentration of MI in the MI/MCI patch (25 ppm) is much lower than in the patch with the preservative by itself (75 ppm). Our preliminary results at the Clinic of Dermatovenerology Diseases in Novi Sad have shown MDBGN, MI and MI/MCI as the top three preservatives causing positive P Ts in cosmetic series® (Chemotechnique Diagnostics, Vellinge, Sweden). Although the cosmetic industry advised its members to phase out the use of MI from leave-on products, there are still such products on the market and European authorities have urgency to bring up appropriate regulations [24]. It is also worth mentioning Triclosan used as an antiseptic in cosmetics, known to have low sensitizing potential but causes contact allergy in soaps [18].

A new generation of UV filters has appeared, thus octocrylene (a cinnamate) replaced para-aminobenzoic acid and became the most common cause of photocontact allergies [25]. Propylene glycol as a vehicle (excipient) of choice, despite being cause of allergy or irritation, tends to be favored over glycerin, which is a rare sensitizer and does not irritate the skin. Moreover, propylene glycol is also cheaper, more lipid-soluble, and is widely used vehicle for topical therapeutics and cosmetics including deodorants. The amount may be as high as 70% [18]. Although emollients rarely cause allergy, the prevalence of lanolin contact allergy has increased over a 12-year period. This raises the question of which lanolin products (e.g., acetylated lanolin, hydrogenated lanolin, or ointments such as eucerin), may also be patch test preparations. Inclusion of Amerchol™ L-101, which is a mixture of 10% lanolin alcohols and mineral oil, will increase the chance of detecting lanolin contact allergy.

Surfactants may act as detergents, wetting agents, emulsifiers, foaming agents, and dispersants. Emulsifiers rarely cause positive PTs, probably due to lack of commercial allergens and difficulties in finding these molecules. Since the 1990s, glucosides are present in both rinse-off products, but also in certain baby products such as wipes and cleansers. Although alkyl glucosides have low irritancy and sensitizing potency, recent studies showed that the prevalence of alkyl glucoside-induced ACD is relatively high. There are frequent concomitant reactions between different alkyl glucosides necessitating its inclusion in patch test cosmetic series. Octoxyglycerin, another widely used ingredient that also has antimicrobial properties (hence its use in preservative-free cosmetics), has been reported recently concerning its presence in sunscreens [24].

Regarding hair styling products and dyes, glyceryl monothioglycolate persists on permed hair for months and therefore re-exposes particularly the hairdresser to the allergen. It can penetrate rubber gloves. The older perms contain thioglycolic acid combined with ammonia and rarely cause contact allergy. Various follow-up chemicals for hair care often involve application of oils and moisturizers, which may contain fragrance, preservatives, and propylene glycol.

Regarding nail products and acrylates, tosylamide formaldehyde resin has been historically responsible for almost all the allergic reactions, accounting for around 10% of reactions and standing only behind preservatives, fragrances, and emulsifiers. The ACD caused by nail acrylates has become an increasing concern nearly rising to epidemic proportions [28]. Today, the main techniques are based either on acrylates that need UV curing (sculptured gel nails and long-lasting acrylate-based nail varnish), or on cyanacrylate (glued nail tips or dipping nails). The main agents responsible for ACD caused by these products are in particular, 3-metacrylates, ethylene glycol dimethacrylate, 2-hydroxyethyl methacrylate, and 2-hydroxypropyl methacrylate.

Natural substances, such as plant extracts, have become very popular, many of which have induced CD such as glycyrrhetinic acid and castor oil, propolis, which cross-reacts with bisabolol, and Myroxylon pereirea in Compositae plants [29, 30]. Sometimes they are present because of other properties than being fragrances, and as such even in “non-scented” products.
Besides delayed-type reactions, plant extracts and hydrolyzed proteins can also cause IgE-mediated anaphylactic reactions, such as oatmeal extract and hydrolyzed wheat proteins. High molecular weight wheat hydrolysates are more allergenic than the lower ones. Subjects may become sensitized through topical agents and subsequently, develop food allergies [24].

**Cosmetics regulations**

Many countries around the world have regulatory standards that ensure cosmetic products to be safe for the workers handling them, the environment, and for consumers. Thus, the United States have the Federal Food, Drug and Cosmetic Act, while Europe has the Cosmetics Directive at the European Commission for Consumer Affairs. In addition, the Commission relies upon the work of the European Food Safety Authority (ÉFSA), the European Medicines Agency, the European Centre for Disease prevention and Control, and the European Chemicals Agency. However, despite being subject to strict legislation (Directive 2003/15/EC of the European Parliament and Council of 27 February 2003, amending Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products - Off J Euro Union, 2003; L66:26-35), cosmetics are not free from adverse reactions [25]. All cosmetic products in the EU must comply with European Commission Regulation No. 1223/2009. Paragraph 49 of the Regulation restricts the use of any potential cosmetic allergens identified by the Scientific Committee on Consumer Safety (SCCS) [26]. They must be present on the product label. The Regulation also proposes a ban or restriction on concentrations and substances that are likely to cause allergies in a large number of people [26].

The declaration of all ingredients in cosmetic products has been mandatory for more than 35 years in the United States. However, only since 1997 the declaration of all ingredients in cosmetic products has been mandatory in Europe, while the nomenclature used in the EU, namely the International Nomenclature of Cosmetic Ingredients, is based on the American Nomenclature of Toiletries and Fragrances [18]. All cosmetic products are constituents of several categories. Thus, personal care products include shower gels, shampoos, soaps and toothpastes. Non-rinsing products include moisturizers, sunscreens and skin lightening creams. Scented products include perfumes, shavers and deodorants. Decorative products (make-up) include foundations, eye shadows and lipsticks. Products for hair care include dyes and styling agents, such as gels, waxes, sprays, shaving and hair removal creams. Nail care products include nail polishes, paint removers and acrylic nails. The Food and Drug Agency in the US has categorized the most common cosmetic allergens into fragrances, preservatives, dyes, rubber, and metals [20].

**Prevention of cosmetic allergy**

The best way to prevent allergic reactions is to know what you are sensitive to and how to avoid it [27]. Look for products that are hypoallergenic, fragrance-free and non-comedogenic. However, one must be aware that these may still cause reactions [27]. Almost any product that contains water must have some preservatives [28]. One way to accomplish this is by carefully reading the product ingredient panel. It is not enough to check for terms like “hypoallergenic”, “fragrance-free” or “for sensitive skin,” as there is no federal standard or definition to govern the use of these terms. Even products that say they are “unscented” can have a fragrance to cover up chemical scents [28]. To be sure, there is no perfume, look for products marked “fragrance-free” or “without perfume”.

The present request for SCCS is to recognize fragrance allergens the consumer needs to know, to indicate thresholds for their safe use and to consider possible modification of allergens by metabolism and autoxidation. The International Fragrance Association (IFRA), as a representative of the fragrance industry, provided relevant unpublished scientific data on fragrance ingredients and together with the up-to-date published scientific literature, critically prepared an opinion for the SCCS [5]. For a long time, there were insufficient scientific data for the determination of dose-response relationships and/or thresholds for these allergens. The limits of 0.01 and 0.001% were set, for rinse-off and leave-on products respectively [5]. Special fragrance database lists more than 2,587 fragrance ingredients used for perfuming. Fragrances are volatile and therefore it is known that they may exacerbate pre-existing asthma.

Contact allergy to fragrance ingredients is a common disease. In Europe, it affects about 1 to 3% of the general population and about 16% of eczema patients [18]. The ACD can significantly impair the quality of life. Thus, prevention of contact sensitization to fragrances, both in terms of primary prevention (limiting or eliminating exposure to allergens in the population) and secondary prevention (avoiding re-exposure to specific sensitizer in clinically diagnosed individuals), is an important objective of public health risk management measures. Primary prevention includes prohibition by regulatory measures; restriction of the maximum permissible concentration; substitution of the allergen; reformulation of the fragrance or fragranced product; deliberate avoidance of fragrances where they are not essential; providing information, e.g. labeling. In this context, the valid diagnostics of sensitization by PT with ingredient labeling represents secondary prevention. In the case of prehaptens, it is possible to prevent activation outside the body. In the case of prohaptensthe possibility of activation is inherent to the molecule and extrinsic measures cannot prevent activation. A prohapten is a chemical that by itself is non-or low-sensitizing, but may become a more potent hapten in the skin by transformation (‘bioactivation’) usually via enzyme catalysis. It is not always possible to know whether the chemical is a prohapten. Activation can thus increase the risk of sensitization. Limonene, linalool and linalyl acetate are prehaptens and form sensitizing compounds by air oxidation. For these substancese, the presence of the oxidized fraction represented by the peroxide content should not be higher than 10 ppm. The prevention of autoxidation using antioxidants
needs thorough investigation, because after their own oxidation, instead of the compound that they protect, antioxidants become skin-sensitizing derivatives. Citronen alcohol, eugenol, isoeugenol and isoeugenyl acetate are prohaptens and form sensitizing compounds by metabolic transformation. Geraniol and alpha-terpinene are both prohaptens and prohaptens. Geraniol (an isomer of citral) is a sensitizer without activation, but forms more potent sensitizing compounds by air oxidation and by metabolic transformation as well. Cross-reactivity exists between alcohols, esters and their corresponding aldehydes, and their parent alcohols [5].

**Fragrance allergen labeling requirements**

There are more than 2,587 fragrance ingredients used for perfuming. Based on available data, in 1999, the SCCS updated the list of the Scientific Committee on Cosmetic Products and Non-Food Products on fragrance substances. The substances are constituents of several categories namely category of established contact allergens in humans (82 substances) or animals (19 substances) with recommended labeling, than likely contact allergens (26 substances) with recommended labeling, and the category of possible contact allergens (48 substances) without recommended labeling. It is worth to know that if human evidence is negative, there is still a potential sensitization risk, as the number of (consecutive) patients tested was low [5].

The property of a chemical to react with and bind to proteins in the skin, either directly or after activation, determines the chemicals’ potential to be a skin sensitizer [4]. The relationship between molecular structure and protein reactivity is based on principles of mechanic organic chemistry. This provides the basis for identifying structural alerts of existing structure-activity relationship by computer modeling, but the computer-based methodology alone is not sufficient for the identification of skin allergens, thus structure activity relationship works in combination with human and animal data, if human and animal data are limited or missing. Up to now, based on elicitation levels in sensitized individuals, the SCCS could not establish thresholds of safe use for individual fragrance allergens but proposed a general level of exposure up to 0.8 µg/cm² (0.01%) to be tolerated by most consumers both the sensitized, as well as most of the non-sensitized consumers, protecting the later of developing contact allergy. However, some strong and extreme sensitizers may require lower individual thresholds. For very weak sensitizers, this generic threshold may be too conservative. The model providing a general threshold of 100 ppm includes single substances only. Dose-response studies have been performed with only 4 of these fragrance substances (hydroxyisohexyl 3-cyclohexene carboxaldehyde, isoeugenol, cinnamal and hydroxycitronellal). This general threshold does not preclude that the most sensitive part of the population may react upon exposure to these levels. Hence, it does not remove the necessity for providing information to the consumer concerning the presence of the fragrance substance in cosmetics. In cases where specific data on threshold levels for a specific allergen are available, these data can help to set an individual safe threshold. However, when such quality data are not available and a substance poses a high risk of sensitization to the consumer, a general threshold limit is operating. As data from human dose elicitation experiments are very limited, no levels that could be considered safe for the majority of allergic consumers could be established for individual substances. However, safe use concentrations of these 26 fragrances in cosmetic products had not yet been determined [5].

Clinical relevance (CR) is a concept used to describe the significance of a positive PT for an individual patient. It covers current and/or past relevance based on: 1) medical history; 2) results of PT and/or other tests; 3) ingredient labeling; or 4) chemical analysis. If the patient is weakly sensitized (e.g. by a low induction dose), and CR is “unknown”, the occlusive exposure during PT may have been the only exposure above the individual elicitation threshold capable of eliciting an unequivocal allergic contact reaction. That is why a lack of or unknown CR does not make future allergen avoidance unnecessary [5].

**The future of allergen labeling**

Cosmetic products in the EU have to comply with European Commission Regulation No 1223/2009; thus, the allergens identified by the SCCS have to be present on a label. Every cosmetic product placed on the EU market needs a compliant product information file (PIF). However, the labeling with “contains fragrances” or “fragrance-free”, does not provide sufficient information, leading to unnecessary avoidance of other fragrance substances and exposure to incriminated fragrance used for other purposes, e.g. as preservatives, respectively. In case when a cosmetic product contains fragrances, it is necessary for the PIF to include also the list of allergens and an IFRA certificate that conforms that the product is safe to use. In light of the SCCS opinion on fragrance allergens, in 2014 the European Commission proposed to amend Annex III to Regulation No 1223/2009, and added another 62 to the list of 26 allergens that need to be labeled individually and evoked a strong reaction from the industry. Due to space and readability of ingredient lists, e-labeling has been proposed, which requires access to the internet at the time of shopping. However, in terms of other ingredients labeling, when other uses are less problematic, as each ingredient is not used as a fragrance but e.g. as a preservative, they must be on the label [26].

**Conclusion**

Considering that so-called “hypoallergenic” products are not necessarily less sensitizing, allergy departments should distribute lists of cosmetic products not containing the respective allergen(s) that consumers can use as safe alternatives.
References

1. Fowler JF, Zirwas MJ, Fisher AA. Fisher's contact dermatitis. Phoenix: Contact Dermatitis Institute; 2019.
2. Uter W, Diepgen TL. Epidemiology of contact dermatitis and contact allergy. In: Johansen J, Mahler V, Lepoittevin JP, Frosh P, editors. Contact dermatitis. Cham: Springer; 2020. p. 195-216.
3. Lachapelle JM, Maibach HI, editors. Patch testing and prick testing: a practical guide: official publication of ICDRG. Cham: Springer; 2020.
4. Chipinda I, Hettick JM, Siegel PD. Haptenation: chemical reactivity and protein binding. J Allergy (Cairo). 2011;2011:839682.
5. Scientific Committee on Consumer Safety. Opinion on Fragrance allergens in cosmetic products [Internet]. 2012 [cited 2020 Jan 24]. Available from: https://ec.europa.eu/health/scientific_committees/consumer_safety/docs/scs_o_102.pdf
6. Karlb erg AT, Börje A, Duss Johansen J, Lidén C, Rastogi S, Roberts D, et al. Activation of non-sensitizing or low-sensitizing fragrance substances into potent sensitizers - prehaptens and prohaptens Contact Dermatitis. 2013;69(6):323-34.
7. Urwin R, Craig S, Latthe F, Wilkinson M. Methylisothiazolinone: the epidemic is declining - but not gone. Contact Dermatitis. 2017;76(5):301-2.
8. Schnuch A, Schubert S, Geier J, IVDK. Clinicians vs. epidemiologists: patch testing with methylbrom glutaronitrile as a controversial issue. J Eur Acad Dermatol Venereol. 2019;33(6):c242-4.
9. García Castro R, Velasco Tirado V, González de Arriba M. Should methylbrom glutaronitrile in the baseline series be tested? Results of the skin allergy unit of a fourth-level hospital in Spain. Contact Dermatitis. 2021;84(6):477-9.
10. Schnuch A, Geier J, Uter W, Frosh P, Lehmacher W, Aberer W, et al. National rates and regional differences in sensitization to allergens of the standard series. Population-adjusted frequencies of sensitization (PAFS) in 40,000 patients from a multicenter study (IVDK). Contact Dermatitis. 1997;37(5):200-9.
11. Jovanović M, Boža P, Karadagić D, Bukić S, Petrović A, Mimica-Dukić N, et al. Contact sensitivity in patients with psoriasis in Vojvodina. Int Arch Allergy Immunol. 2009;148(4):311-20.
12. Jovanović M. Manifestations of contact allergy. Srp Arh Celok Lek. 2012;140(11-12):786-91.
13. Jovanović M, Golubić Z, Stojanović M, Nišavić M. Immediate, delayed and dual-contact reactivity to common contact urti- cariogens in patients with chronic spontaneous urticaria: a study in Serbia. Iran Red Crescent Med J. 2019;21(9):e92416.
14. Vujanović Lj, Jovanović M, Matić M, Jakovljević S, Golubić Z. Contact sensitization in patients with chronic venous insufficiency in Vojvodina (Serbia) and the impact of disease duration on the risk of occurrence of contact sensitization. Vojnosanit Pregl. In press. Doi: https://doi.org/10.2298 VSP190820103V
15. Schäfer T, Böhler E, Ruhdorfer S, Weigl L, Wessner D, Filipiak B, et al. Epidemiology of contact allergy in adults. Allergy. 2001;56(12):1192-6.
16. Schnuch A, Geier J, Lessmann H, Arnold R, Uter W. Surveillance of contact allergies: methods and results of the Information Network of Departments of Dermatology (IVDK). Allergy. 2012;67(7):847-57.
17. Uter W, Schnuch A, Geier J, Pfähler B, Gefeller O; IVDK study group. Association between occupation and contact allergy to the fragrance mix: a multifactorial analysis of national surveillance data. Occup Environ Med. 2001;58(6):392-8.
18. Latheef F, Wilkinson M. Adverse skin reactions to cosmetics and skin care products. In: Johansen JD, Mahler V, Lepoittevin JP, Frosh P, editors. Contact dermatitis. Cham: Springer; 2020. p. 913-2.
19. Alinaughif B, Bennike NH, Egeberg A, Thysen JP, Johansen JD. Prevalence of contact allergy in the general population: a systematic review and meta-analysis. Contact Dermatitis. 2019;80(2):77-85.
20. US Food and Drug Administration. Allergens in cosmetics [Internet]. 2020 [cited 2021 Jan 24]. Available from: https://www.fda.gov/cosmetics/cosmetic-ingredients/allergens-cosmetics
21. Smith VM, Clark SM, Wilkinson M. Cosmetics. In: Johansen JD, Lepoittevin JP, Thysen JP, editors. Quick guide to contact dermatitis. Berlin: Springer; 2016. p. 257-73.
22. Corazza M, Amendolagine G, Toni G, Mantovani L, Borghi A. Side effects of tango: connubial contact dermatitis. Contact Dermatitis. 2019;80(4):241-2.
23. US Food and Drug Administration. Cosmetics and U.S. law [Internet]. 2020 [cited 2021 Jan 24]. Available from: https://www.fda.gov/cosmetics/cosmetics-laws-regulations/cosmetics-us-law
24. Goossens A. Cosmetic contact allergens. Cosmetics. 2016; 3(1):5.
25. Zaragoza-Ninet V, Blasco Encinas R, Vilata-Corell JJ, Pérez-Ferríols A, Sierra-Talamantes C, Esteve-Martínez A, et al. Allergic contact dermatitis due to cosmetics: a clinical and epidemiological study in a tertiary hospital. Actas Dermosifiliogr. 2016;107(4):329-36.
26. Grum T. Beauty labels: in-depth on 'crucial' regulations for cosmetic allergens [Internet]. 2020 [updated 2020 Feb 10; cited 2021 Jan 24]. Available from: https://www.cosmeticsdesign-europe.com/Article/2020/02/10/Cosmetic-allergens-EU-list-states-concentrations-and-banned-ingredients
27. Ngan V. Contact reactions to cosmetics [Internet]. 2020 [cited 2021 Jan 24]. Available from: https://dermnetnz.org/topics/contact-reactions-to-cosmetics
28. Jaliman D. Skin reactions to beauty products [Internet]. 2019 [cited 2021 Jan 24]. Available from: https://www.webmd.com/contact-reactions/cosmetics-and-banned-ingredients
29. Vujanović Lj, Džumic D, Butković M, Poljački M, Golušin Z. Contact dermatitis due to cosmetics: a clinical and epidemiological study in a tertiary hospital. Actas Dermosifiliogr. 2019;110(4):329-36.
30. Goossens A. Cosmetic contact allergens. Cosmetics. 2016; 3(1):5.
31. Zaragoza-Ninet V, Blasco Encinas R, Vilata-Corell JJ, Pérez-Ferríols A, Sierra-Talamantes C, Esteve-Martínez A, et al. Allergic contact dermatitis due to cosmetics: a clinical and epidemiological study in a tertiary hospital. Actas Dermosifiliogr. 2016;107(4):329-36.
32. US Food and Drug Administration. Allergens in cosmetics [Internet]. 2020 [updated 2020 Feb 10; cited 2021 Jan 24]. Available from: https://www.cosmeticsdesign-europe.com/Article/2020/02/10/Cosmetic-allergens-EU-list-states-concentrations-and-banned-ingredients
33. Ngan V. Contact reactions to cosmetics [Internet]. 2020 [cited 2021 Jan 24]. Available from: https://dermnetnz.org/topics/contact-reactions-to-cosmetics
34. Jaliman D. Skin reactions to beauty products [Internet]. 2019 [cited 2021 Jan 24]. Available from: https://www.webmd.com/allergies/cosmetics
35. Vujanović M, Poljački M, Compositae dermatitis. Med Pregl. 2003;56(1-2):43-9.
36. Zaragoza-Ninet V, Blasco Encinas R, Vilata-Corell JJ, Pérez-Ferríols A, Sierra-Talamantes C, Esteve-Martínez A, et al. Allergic contact dermatitis due to cosmetics: a clinical and epidemiological study in a tertiary hospital. Actas Dermosifiliogr. 2016;107(4):329-36.
37. Grum T. Beauty labels: in-depth on ‘crucial’ regulations for cosmetic allergens [Internet]. 2020 [updated 2020 Feb 10; cited 2021 Jan 24]. Available from: https://www.cosmeticsdesign-europe.com/Article/2020/02/10/Cosmetic-allergens-EU-list-states-concentrations-and-banned-ingredients
38. Ngan V. Contact reactions to cosmetics [Internet]. 2020 [cited 2021 Jan 24]. Available from: https://dermnetnz.org/topics/contact-reactions-to-cosmetics
39. Jaliman D. Skin reactions to beauty products [Internet]. 2019 [cited 2021 Jan 24]. Available from: https://www.webmd.com/allergies/cosmetics
40. Vujanović M, Poljački M, Compositae dermatitis. Med Pregl. 2003;56(1-2):43-9.