Chapter 30

Cosmetics and Skin Care Products* 30

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* In this chapter, the nomenclature used is according to the International Nomenclature of Cosmetic Ingredients (INCI), as required for ingredient labeling in Europe.

Contents

30.1 What Are Cosmetics?

In European legislation, a "cosmetic product" is any substance or preparation intended to be placed in contact with the various external parts of the human body (epidermis, hair system, nails, lips, and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance and/or correcting body odors and/or protecting them or keeping them in good condition (**Cosmetics Directive 76/768/EEC; article 1**).

Included within the definition of a cosmetic are the following:

- Soaps, shampoos, toothpastes, and cleansing and moisturizing creams for regular care
- Color cosmetics, such as eye shadows, lipsticks, and nail varnishes
- Hair colorants and styling agents
- Fragrance products, such as deodorants, aftershaves, and perfumes
- Ultraviolet light (UV light) screening preparations

30.2 Epidemiology of Side-Effects from Cosmetics

30.2.1 The General Population

Everyone uses cosmetics and, given the enormous volume of sales and the range of products available, there is remarkably little information on the incidence of adverse reactions to them. Most individuals who experience an adverse reaction to a cosmetic have a mild reaction and simply change to another product. Only rarely is an adverse reaction reported to a manufacturer, unless discomfort is marked or significant. In Europe, the industry is required to record adverse reactions reported to it and make the

register available to the appropriate "competent authority." Individuals are also unlikely to present to a dermatologist for evaluation, unless an adverse reaction is severe, as in the case of contact allergy to a hair dye, or persistent.

Several thousand substances are available to the cosmetic scientist for incorporation into cosmetics. The European Commission publishes an indicative but not exhaustive list of general ingredients and fragrance substances – known as the Inventory [1]. Many of these ingredients have had a long and established use, and are recognized as being safe or having a low toxicological profile. Some substances, however, pose a significant risk of causing adverse reactions, and, for these other substances, little is known about their safety. Regulatory aspects are discussed in Chap. 45.

In the general population, a questionnaire survey of 1,022 individuals in the United Kingdom found 85 people (8.3%) who claimed to have experienced an adverse reaction related to the use of a cosmetic [2]. Of these 85 individuals, 44 were patch tested and in 11 (1.1%), a significant reaction was obtained to a cosmetic ingredient. In Holland, a survey of 982 individuals attending beauticians found 254 (26%) who claimed to have experienced an adverse reaction to a cosmetic [3]. Evaluation of 150 cases of this group by patch testing demonstrated 10 individuals, 1% of the total, with an allergic reaction attributable to a cosmetic ingredient. These and other studies give an idea of the proportion of the population who may have experienced an allergic contact reaction to a cosmetic ingredient at some time. An estimated 1% is allergic to fragrances [4] and 2–3% are allergic to substances that may be present in cosmetics and toiletries [5].

30.2.2 Patients Seen by Dermatologists

Detailed information is available regarding the prevalence of contact allergy to some cosmetic ingredients amongst individuals who have been patch tested as an investigation for their dermatitis (of whatever type). The European standard series of contact allergens includes the following substances which may be used in cosmetics: fragrance mix, balsam of Peru (INCI name: Myroxylon pereirae; not used as such in cosmetics, but included as an indicator of fragrance sensitivity), formaldehyde, quaternium-15, methylchloroisothiazolinone (and) methylisothiazolinone (MCI/MI), parabens, lanolin (wool alcohols), colophonium (colophony), and *p*-phenylenediamine. Many centers also routinely test with the preservatives methyldibromo glutaronitrile, imidazolidinyl urea, and diazolidinyl urea, and some include iodopropynyl butylcarbamate and others. A European study of the frequency of hypersensitivity to some of these agents in a patch-tested population totaling 20,791 individuals showed the incidence of reactions as listed in Table 1 [5]. Of dermatological patients patch tested for suspected allergic contact dermatitis, about 10% are allergic to cosmetic ingredients [5].

Table 1. Frequency of reactions (mean from all centers and range) to cosmetic ingredients in the standard series (n=20,791) [5]

Substance	Mean (%)	Range (%)
Fragrance mix	7.0	6.4–9.4
Balsam of Peru (*Myroxylon pereirae*)	5.8	4.0–6.7
Colophony (colophonium)	3.4	1.7–4.7
p-Phenylenediamine	2.8	0.3–4.9
Wool wax alcohols (lanolin alcohol)	2.8	1.2–3.9
Formaldehyde	2.2	1.4–5.2
Parabens	1.1	0.5–2.6
Quaternium-15	0.9	0.3–2.2

Women are more at risk of acquiring hypersensitivity to cosmetic ingredients than men, due to their greater product use. Variability in the frequency of reactions reported is partially attributable to different patient selection between centers. True temporal and geographical variations in the frequency of hypersensitivity to cosmetic ingredients occur because of differences in ingredient use. These differences involve marketing strategies, local product preference, and preferred ingredient usage by manufacturers. Additionally, changes in legislation, recommendations on ingredient use, and availability are further important factors. Dillarstone [6] has pointed out the phasic nature of the prevalence of contact allergy to preservatives that results from these latter factors.

30.3 Clinical Picture

Sometimes, allergic contact dermatitis from cosmetic products can easily be recognized. Examples include reactions to deodorant, eye shadow, perfume dabbed behind the ears or on the wrist, and lipstick. In more than half of all cases, however, the diagnosis of cosmetic allergy is not clinically suspected [7].

The clinical picture of allergic cosmetic dermatitis depends on the type of products used (and, consequently, the sites of application), exposure, and the patient's sensitivity. Usually, a cosmetic contains only weak allergens or stronger ones present at low dilution, and the dermatitis resulting from cosmetic al-

lergy is mild: erythema, minimal edema, desquamation, and papules. Weeping vesicular dermatitis rarely occurs, although some products, especially the permanent hair dyes, may cause fierce reactions, notably on the face, ears, and scalp. Allergic reactions on the scalp may be seborrhö dermatitis-like with (temporary) hair loss.

Contact allergy to fragrances may resemble an endogenous eczema [8]. Lesions in the skin folds may be mistaken for atopic dermatitis. Dermatitis due to perfumes or toilet water may be "streaky." Allergy to tosylamide/formaldehyde resin in nail polish may affect the fingers [9], but most allergic reactions are located on the eyelids, in and behind the ears, on the neck, and sometimes around the anus or vulva. Eczema of the lips and the perioral region (cheilitis) [10] may be caused by toothpastes [11], notably from the flavors contained therein [12].

The face itself is frequently involved, and often, the dermatitis is limited to the face and/or eyelids. Other predilection sites for cosmetic dermatitis are the neck, arms, and hands. However, all parts of the body may be involved. Most often, the cosmetics have been applied to previously healthy skin (especially the face), nails, or hair. However, allergic cosmetic dermatitis may be caused by products used on previously damaged skin, for example, to treat or prevent dry skin of the arms and legs or irritant or atopic hand dermatitis.

30.4 The Products Causing Cosmetic Allergy

Most allergic reactions are caused by those cosmetics that remain on the skin: "stay-on" or "leave-on" products such as skin care products (moisturizing and cleansing creams, lotions, milks, tonics), hair cosmetics (notably hair dyes), nail cosmetics (nail varnish), deodorants and other perfumes, and facial and eye make-up products [13–15]. "Rinse-off" or "wash-off" products, such as soap, shampoo, bath foam, and shower foam, less commonly elicit or induce contact allergic reactions. This is explained by the dilution of the product (and, consequently, of the [potential] allergen) under normal circumstances of use, and because the product is removed from the skin by rinsing after a short period. An exception to this general rule was allergy to a fraction in some commercial grades of the surfactant cocamidopropyl betaine, which caused reactions to shampoo in consumers and occupational dermatitis in hairdressers, and to shower gels [16–18].

Trends in cosmetic usage, e.g., the expansion of the cosmetic market for men and the targeting of products specifically for children, may influence the situation.

30.5 The Allergens

Although there are numerous publications on contact allergy to the ingredients of cosmetics, the systematic investigation of the allergens in such products has been rare [7, 15]. Fragrances and preservatives (and in recent years, the preservative methyldibromo glutaronitrile [18–20] has emerged as an important cosmetic allergen) are the most common causative ingredients in allergic cosmetic dermatitis. Other important allergens are the hair color *p*-phenylenediamine (and related permanent dyes), the nail varnish resin tosylamide/formaldehyde resin [21], and uncommonly to UV filters, lanolin and other substances.

30.5.1 Fragrances

Adverse reactions to fragrances in perfumes and in fragranced cosmetic products include allergic contact dermatitis, irritant contact dermatitis, photosensitivity, immediate contact reactions (contact urticaria), and pigmented contact dermatitis [22]. Reviews of the adverse effects of fragrances (and essential oils) are available [14, 23]. The history of fragrances has been well described [24, 25].

Considering the enormous use of fragrances, the frequency of contact allergy to them is relatively small. In absolute numbers, however, fragrance allergy is common. In a group of 90 student nurses, 12 (13%) were shown to be fragrance allergic [26]. In a group of 567 unselected individuals aged 15–69 years, 6 (1.1%) were shown to be allergic to fragrances, as evidenced by a positive patch test reaction to the fragrance mix [4].

In dermatitis patients seen by dermatologists, the prevalence of contact allergy to fragrances is between 6–14% [27]; only nickel allergy occurs more frequently. When tested with 10 popular perfumes, 6.9% of female eczema patients proved to be allergic to them [28] and 3.2–4.2% were allergic to fragrances from perfumes present in various cosmetic products [29].

When patients with suspected allergic cosmetic dermatitis are investigated, fragrances are identified as the most frequent allergens, not only in perfumes, aftershaves and deodorants, but also in other cosmetic products not primarily used for their smell [21, 30]. Occupational contact with fragrances is rarely significant [14].

Contact allergy to fragrances usually causes dermatitis of the hands, face, and/or axillae. Patients appear to become sensitized to fragrances, particularly from the use of deodorant sprays and/or perfumes, and, to a lesser degree, from cleansing agents, deodorant sticks, or hand lotions [31]. Thereafter, eczema may appear or be worsened by contact with other fragranced products: cosmetics, toiletries, household products, industrial contacts, and flavorings in foods and drinks.

Over 100 fragrance chemicals have been identified as allergens [14]. Most reactions have been identified as the substances in the standard perfume mix, and of these, *Evernia prunastri* (oak moss), iso-eugenol, and cinnamal are the main sensitizers. Most recently, hydroxyisohexyl-3-cyclohexene carboxaldehyde (Lyral) has been identified as an important fragrance allergen [32]. An exhaustive review of fragrance allergens is available [33] and was the tool used by the European Commission in evaluating the need for the introduction of fragrance ingredient labeling.

Contact allergy to a particular product or chemical is established by means of patch testing. A perfume may contain as many as 200 or more individual ingredients. This makes the diagnosis of perfume allergy by patch test procedures complicated. The fragrance mix, or perfume mix, was introduced as a screening tool for fragrance sensitivity in the late 1970s [34]. It contains eight commonly used fragrance substances:

- Amyl cinnamal
- Cinnamyl alcohol
- Cinnamal
- *Evernia prunastri* (oak moss)
- Eugenol
- Geraniol
- Hydroxycitronellal
- Iso-eugenol

Between 6% and 14% [27] of patients routinely tested for suspected allergic contact dermatitis react to it. It has been estimated that this mix detects 70–80% of all cases of fragrance sensitivity; this may be an overestimation, as it was positive in only 57% of patients who were allergic to popular commercial fragrances [28]. Testing with the components of the mix is required when a positive reaction to the mix is found.

Although the fragrance mix remains an extremely important tool for the detection of cases of contact allergy to fragrances, it is far from ideal: it misses 20–30% of relevant reactions or more, and may cause both false-positive (i.e., a "positive" patch test reaction in a non-fragrance-allergic individual) and false-negative (i.e., no patch test reaction in an individual who is actually allergic to one or more of the ingredients of the mix) reactions. The routine testing with hydroxyisohexyl-3-cyclohexene carboxaldehyde (Lyral) and/or a second fragrance mix developed by Frosch [35] should improve the rate of detection.

In addition to patch testing, another useful test in cases of doubt (for example, with weakly positive patch test reactions, which are difficult to interpret) is the repeated open application test (ROAT; see below).

The finding of a positive reaction to the fragrance mix should be followed by a search for its relevance, i.e., is fragrance allergy the cause of the patient's current or previous complaints, or does it at least contribute to it? Often, however, correlation with the clinical picture is lacking and many patients can tolerate perfumes and fragranced products without problems [14]. This may sometimes be explained by irritant (false-positive) patch test reactions to the mix. Alternative explanations include the absence of relevant allergens in those products or a concentration too low to elicit clinically visible allergic contact reactions.

Between 50% and 65% of all positive patch test reactions to the mix are relevant. There is a highly significant association between the occurrence of self-reported visible skin symptoms to scented products earlier in life and a positive patch test to the fragrance mix, and most fragrance-sensitive patients are aware that the use of scented products may cause skin problems [36].

For perfume-mix-allergic patients with concomitant positive reactions to perfumes or scented products, interpretation of the reaction as relevant is highly likely. For such patients, the incriminated cosmetics very often contain fragrances present in the mix and, thus, the fragrance mix appears to be a good reflection of actual exposure [37]. Indeed, one or more of the ingredients of the mix are present in nearly all deodorants [38], popular prestige perfumes [28], perfumes used in the formulation of other cosmetic products [29], and natural-ingredient-based cosmetics [39], often at levels high enough to cause allergic reactions [40, 41]. Thus, fragrance allergens are ubiquitous and virtually impossible to avoid if perfumed cosmetics are used.

Determination of relevance has now been made easier by ingredients listing of well recognized fragrance allergens when present at 10 ppm or more in leave-on cosmetic products and at 100 ppm or more in rinse-off products:

- Amyl cinnamal
- Cinnamyl alcohol
- cinnamal
- *Evernia prunastri* (oak moss)
- *Evernia furfuracea* (tree mass)
- Eugenol
- Geraniol
- Hydroxycitronellal
- Iso-eugenol
- Alpha-isomethyl ionone
- Amylcinnamyl alcohol
- Anisyl alcohol
- Benzyl alcohol
- Benzyl benzoate
- Benzyl cinnamate
- Benzyl salicylate
- Citral
- Citronellol
- Coumarin
- d-limonene
- Farnesol
- Hexyl cinnamal
- Hydroxyisohexyl-3-cyclohexene carboxaldehyde (Lyral)
- Butylphenyl methylpropional (lilial)
- Linalool
- Methyl heptine carbonate

30.5.2 Preservatives

Preservatives are added to water-containing cosmetics to inhibit the growth of non-pathogenic and pathogenic micro-organisms, which may cause degradation of the product or be harmful to the consumer. After fragrances, they are the most frequent cause of allergic cosmetic dermatitis. Important review articles on the subject of preservative allergy have been published [42–44].

30.5.2.1 Methylchloroisothiazolinone (and) Methylisothiazolinone

Methylchloroisothiazolinone (and) methylisothiazolinone (MCI/MI) is a preservative system containing, as active ingredients, a mixture of methylchloroisothiazolinone and methylisothiazolinone. The most widely used commercial product contains 1.5% active ingredients; the methylchloroisothiazolinone moiety is the prime allergenic fraction. This highly effective preservative remains an important cosmetic allergen in most European countries. Allergic reactions on the face to cosmetics preserved with MCI/MI can have unusual clinical presentations that are very similar to seborrheic dermatitis and other dermatoses [45]. In the United States, a prevalence rate of 3% [27] has been observed. The concentration of MCI/MI used is usually between 3 ppm and 15 ppm, which is normally far below the threshold for the detection of allergy with patch tests, indicating that most allergic patients will not react to the cosmetic product upon patch testing. Therefore, MCI/MI is tested separately at 100 ppm in water in the European standard series (but tested at 200 ppm in Sweden). Currently, MCI/MI is primarily used in rinse-off cosmetic products at low concentrations, which infrequently leads to the induction or elicitation of contact allergy [46]. As a consequence, prevalence rates in Europe are static. The subject of contact allergy to isothiazolinones has been reviewed [47, 48]. Methylisothiazolinone itself is now permitted as a cosmetic preservative; it is, however, a much weaker allergen than methylchloroisothiazoline.

30.5.2.2 Methyldibromo Glutaronitrile

Methyldibromo glutaronitrile (synonym: 1,2-dibromo-2,4-dicyanobutane) is a preservative that has been widely used in cosmetics and toiletries. It was thought to be a suitable alternative to the MCI/MI, but, unfortunately, soon proved to be a frequent cause of contact allergy to cosmetics [19] and, in the Netherlands, to moistened toilet tissues [20]. Prevalence rates of sensitization in patients routinely investigated for suspected allergic contact dermatitis were 4% in the Netherlands [20], 2.9% in Italy [49], 2.3% in Germany [50], and 2% [27] to 11.7% in the United States [51]. Between 23% and 75% of positive patch test reactions are considered to be relevant.

Although there is some controversy as to the optimal patch test concentration, 0.5% pet. [52, 53] has been recommended, but 0.3% is also used [54]. False-negative and false-positive reactions may occur [52].

In Europe, methyldibromo glutaronitrile is now only permitted in rinse-off products at a maximum of 0.1%, but even this use may be curtailed.

30.5.2.3 Formaldehyde

Formaldehyde is a frequent sensitizer and ubiquitous allergen, with numerous non-cosmetic sources of contact. Routine testing in patients with suspected allergic contact dermatitis yields prevalence rates of sensitization of 3% [5] to as much as 9% in the United States [27]. Because of this, the cosmetic industry uses small but effective concentrations, with the

amount of free formaldehyde not exceeding 0.2% and its use is restricted almost exclusively to rinse-off products. In recent years, it has largely been replaced by other preservatives (such as MCI/MI); the literature on formaldehyde allergy has been reviewed [43, 44].

30.5.2.4 Formaldehyde Donors

Formaldehyde donors are preservatives that, in the presence of water, release formaldehyde. Therefore, cosmetics preserved with such chemicals will contain free formaldehyde, the amount depending on the preservative used, its concentration, and the amount of water present in the product. The antimicrobial effects of formaldehyde donors are said to be intrinsic properties of the parent molecules and are not related to formaldehyde release. Formaldehyde donors used in cosmetics and toiletries include quaternium-15, imidazolidinyl urea, diazolidinyl urea, 2-bromo-2-nitropropane-1,3-diol, and DMDM hydantoin. In anionic shampoos, the amount of formaldehyde released by such donors increases in the order: imidazolidinyl urea < DMDM hydantoin < diazolidinyl urea < quaternium-15 [55]. Contact allergy to formaldehyde donors may be due either to the preservative itself or to formaldehyde sensitivity [43, 44].

30.5.3 Quaternium-15

Patients sensitized to formaldehyde may experience cosmetic dermatitis from using leave-on preparations containing quaternium-15. The threshold for eliciting allergic contact dermatitis in the axillae is approximately 30 ppm formaldehyde. At a concentration of 0.1% (1,000 ppm), quaternium-15 releases about 100 ppm of free formaldehyde. Routine testing with quaternium-15 in the United States yielded a prevalence rate of 9.2% in patients suspected of allergic contact dermatitis [27]. Half of these reactions may have been caused by formaldehyde sensitivity [56]. In Europe, sensitization to quaternium-15 is less frequent [57].

30.5.4 Imidazolidinyl Urea

Imidazolidinyl urea releases only small amounts of formaldehyde, and, consequently, poses little threat to formaldehyde-sensitive subjects. Contact allergy to imidazolidinyl urea occurs occasionally [58]. In 1,175 patients tested with the preservative 2% aq. in Belgium, only eight (0.7%) positive reactions were observed, of which, one was accompanied by a reaction to formaldehyde [58]. In the United States, where imidazolidinyl urea is part of the routine series, 3.1% of patients patch tested reacted to the preservative [27]. Cross-reactions to and from the structurally related diazolidinyl urea may be observed [57].

30.5.5 Diazolidinyl Urea

Diazolidinyl urea is the most active member of the imidazolidinyl urea group, and a number of case reports of cosmetic allergy from diazolidinyl urea have been published [59]. In a Dutch study of 2,142 patients with eczema, patch tested with diazolidinyl urea 2% aq, 12 (0.6%) reacted. In 5 of these 12 cases, the patients were also allergic to formaldehyde and formaldehyde donors [60]. The members of the North American Contact Dermatitis Group tested 3,085 patients with diazolidinyl urea 1% in water, and obtained 3.7% positive reactions [27]. Of 58 individuals with diazolidinyl urea sensitivity seen at the Mayo Clinic, 47 (81%) also reacted to formaldehyde [61]. Cross-reactions to and from imidazolidinyl urea occur [59, 61]. Diazolidinyl urea appears to be a stronger sensitizer than imidazolidinyl urea.

30.5.6 2-Bromo-2-Nitropropane-1,3-Diol (Bronopol)

2-Bromo-2-nitropropane-1,3-diol is not a frequent cause of contact allergy in Europe [17, 62]. In the United States, however, it was found to be such a common cause of cosmetic allergy in one cosmetic cream [63], that the manufacturer decided to replace it. Recently, 2.3% of patients routinely tested in the United States were allergic to it [27]. Because interaction with amines and amides can result in the formation of nitrosamines or nitrosamides, suspected carcinogens, there is restriction in the formulations that may contain this preservative.

30.5.7 DMDM Hydantoin

DMDM hydantoin itself is probably not an allergen, but may cause reactions in formaldehyde-allergic individuals by virtue from the release of formaldehyde. Routine testing with DMDM hydantoin 3% aq. in 501 patients resulted in four positive reactions; all four were also allergic to formaldehyde [64]. Subsequent testing in patients allergic to formaldehyde resulted in positive reactions to DMDM hydantoin at concentrations as low as 0.3% [65]. Also, repeated open ap-

plication to the skin of a cream containing 0.25% w/w DMDM hydantoin elicited a positive response in some patients. Consequently, patients sensitized to formaldehyde may experience cosmetic dermatitis from using leave-on products preserved with DMDM hydantoin. In the United States, a prevalence rate of 2.3% positive reactions has been observed [27].

30.5.7.1 Parabens

The paraben esters (methyl, ethyl, propyl, butyl) are widely used preservatives in cosmetic products. Parabens have had an unwarranted reputation as sensitizers. However, most cases of paraben sensitivity are caused by topical medicaments applied to leg ulcers or stasis dermatitis. Routine testing in the European standard series yields low prevalence rates of sensitization [66]. At the usual concentration of 0.1–0.3% in cosmetics, parabens rarely cause adverse reactions. Parabens are not included in the North American standard series of contact allergens as the allergen causes problems only rarely [27].

Sensitized individuals may be able to tolerate products containing parabens, a phenomenon which has been called the *paraben paradox* [67]. Tolerance is related to concentration, duration and site of application, and skin status. The subject of paraben sensitivity has been reviewed [44].

30.5.7.2 Iodopropynyl Butylcarbamate

This preservative was popular in many skin care and hair care products, and contact allergy to it from cosmetic use has been reported [68, 69]. The recommended patch test concentration, based on an analysis of concurrent testing with several dilutions, is 0.2%. However, because of concerns about the bioavailability of iodine, there has been considerable reduction in its use in cosmetics.

30.5.7.3 Miscellaneous Preservatives

Preservatives used in cosmetics that have occasionally caused allergy include benzyl alcohol, chloroacetamide, chlorphenisin [70], phenoxyethanol, and triclosan.

30.5.8 Tosylamide/Formaldehyde Resin

Contact allergy to the main allergen in nail varnish, tosylamide/formaldehyde resin, is common [9, 71–75]. Up to 6.6% of women habitually or occasionally using nail cosmetics and presenting with dermatitis are allergic to it [71], and the prevalence in patients routinely tested in the United States was 1.6% [27]. Eighty percent of all reactions are observed as a dermatitis of the face and neck, with many cases manifesting as an eyelid dermatitis. Occasionally, other parts of the body are involved, including the thighs, the genitals, and the trunk; generalized dermatitis is rare. Periungual dermatitis may be far more common (60%) than previously thought [9]. Desquamative gingivitis was the sole manifestation in a compulsive nail-biter [76]. Partner ("connubial") dermatitis has been observed. Other, but rarely reported, allergens in nail lacquers include formaldehyde, nitrocellulose [77], polyester resin, phthalates, and *o*-toluenesulfonamide [72, 73].

Important sociomedical consequences of nail varnish allergy have been reported [9]. Allergic patients should stop using nail varnishes or use varnishes free from tosylamide/formaldehyde resin. However, some products claiming not to contain the resin may still do so [78]. Also, such nail varnishes may contain other sensitizers, such as methyl acrylate and epoxy resin [79]. Useful review articles on adverse reactions to nail cosmetics [80, 81] and sculptured nails [82] are available.

30.5.9 *p*-Phenylenediamine and Related Hair Dyes

p-Phenylenediamine and related hair dyes are very common and important sensitizers. Safer permanent dyes with a lower risk of contact allergy, but with the same technical qualities, are not available. Many cases of sensitization were reported in the 1930s, and sensitization was considered so great a hazard that the use of *p*-phenylenediamine in hair dyes was prohibited in several countries. Currently, its incorporation in cosmetic products is allowed in the European Union up to a maximum concentration of 6% (as free base), which equates, after mixing with the oxidizing agent, to 3%; in practice, the maximum level to which the consumer is exposed is 2%.

p-Phenylenediamine remains an important cause of cosmetic allergy, with a 6.8% prevalence rate of sensitization in routinely tested patients in the United States [27]. The clinical features of hair dye allergy are discussed in Chap. 29.

These oxidation dyes are also an occupational hazard for hairdressers and beauticians [83]. The chemistry of, and adverse reactions to, oxidation coloring agents have been reviewed [84]. Semi-permanent and temporary dyes rarely cause allergic cos-

Table 2. Examples of hair colors that have caused cosmetic allergy

1-Hydroxy-3-nitro-4-aminobenzene
1-Hydroxyethylamino-3-nitro-4-aminobenzene
2-Nitro-*p*-phenylenediamine
Basic blue 99
Henna
m-Aminophenol
N-(b-Hydroxyethyl)-2-nitro-4-hydroxyaminobenzene
Naphthalenediol
N-Phenyl-*p*-phenylenediamine
p-Aminophenol
p-Phenylenediamine
Pyrocatechol
Resorcinol
Toluene-2,4-diamine
Toluene-2,5-diamine

metic dermatitis. Examples of hair colors that have caused cosmetic allergy are listed in Table 2.

30.5.10 Cocamidopropyl Betaine

Cocamidopropyl betaine is an amphoteric surfactant, which is widely present in shampoos and bath products, such as bath and shower gels [16–18]. Residues in some commercial grades, dimethylaminopropylamine [85] and cocamidopropyl dimethylamine ("amidoamine") [86], were responsible for prevalence rates of sensitization to cocamidopropyl betaine in a range from 3.7% to 5% [85, 87, 88]. Due to its presence in shampoos, cocamidopropyl betaine was an important occupational hazard to hairdressers. Consumers became sensitized to shampoos and a variety of other hygiene products, such as liquid shower soaps and facial cleansers [85]. Since the allergenic fractions were removed, the problem has disappeared.

30.5.11 UV Filters

Ultraviolet light filters (UV filters) are used in sunscreens to protect the consumer from harmful UV irradiation from the sun and are also incorporated in some cosmetics, notably facial skin care products, to inhibit UV photo-degradation of the product and protect the skin of the user. The main classes of sunscreens are PABA and its esters (amyl dimethyl, glyceryl, octyl dimethyl), cinnamates, salicylates, anthranilates, benzophenones, and dibenzoylmethanes [89]. The latter have become very popular, since they absorb mainly in the UVA range (315–400 nm).

The most frequent adverse reaction to sunscreen preparations is irritation, which occurs in over 15% of users [90]. UV filters have also been identified as allergens and photoallergens, but such reactions are uncommon. Patients who regularly use sunscreens because they suffer from the photosensitivity dermatitis/actinic reticuloid syndrome may have an increased risk for developing allergic side effects to sunscreens [91]. (Photo)allergic reactions can easily be overlooked, as the resulting dermatitis may be interpreted by the patient or consumer as failure of the product to protect against sunburn or as worsening of the (photo)dermatosis for which the sunscreen was used.

Currently, the most frequent cause of (photo)contact allergy to UV filters is benzophenone-3 (oxybenzone) [92]. Cross-reactions between benzophenones appear to be rare [93]. A number of UV filters are reported to have caused (photo)contact allergy [13, 89, 93–96] and these are discussed further in Chap. 27.

30.5.12 Lanolin and Derivatives

Lanolin and lanolin derivatives are used extensively in cosmetic products as emollients and emulsifiers. However, the majority of individuals have been sensitized by using topical pharmaceutical preparations containing lanolin, especially for treating varicose ulcers and stasis dermatitis (a similar situation to that of parabens) [97].

Additionally, many "positive" patch test reactions are not reproducible [98]. Thus, it appears that the currently used test allergen (30% wool wax alcohols) may cause false-positive, irritant, patch test reactions [98, 99]. Possibly, the same applies to the lanolin derivative Amerchol L-101, which is often used in addition to patch testing [100].

The presence of lanolin or its derivatives in cosmetics may cause cosmetic dermatitis in lanolin-sensitive individuals, but the risk of sensitization from using such products is small [101]. In the general population, contact allergy to lanolin is considered to be rare [98, 99].

30.5.13 Glyceryl Thioglycolate

Glyceryl thioglycolate, a waving agent used in acid permanent waving products, occasionally sensitizes consumers [102], but it is usually an occupational hazard for the hairdresser [83]. Patients allergic to glyceryl thioglycolate infrequently react to ammonium thioglycolate, also a contact allergen, used in "hot" permanent wave procedures.

30.5.14 Propylene Glycol

Propylene glycol is widely used in dermatologic and non-dermatologic topical formulations, including cosmetics, as well as in numerous other products [103–105]. Propylene glycol may cause irritant contact dermatitis, allergic contact dermatitis, non-immunologic immediate contact reactions, and subjective or sensory irritation [103].

Allergic contact dermatitis is uncommon and its clinical significance has been overestimated. In earlier studies, higher concentrations of propylene glycol may have induced many irritant patch test reactions. Currently, a concentration of 1–10% [105] is advised in order to avoid such irritation, but cases of contact allergy are probably missed as a result (false-negative reactions). A diagnosis of allergic contact dermatitis should never be made on the basis of one positive patch test alone. Testing should be repeated after several weeks. In addition, repeat tests with serial dilutions down to 1% propylene glycol helps in discriminating between irritant responses and true allergic ones. Repeated open application tests (ROAT) and/or provocative use tests (PUT) can be conducted to verify the allergic basis of a positive patch test result.

30.5.15 Antioxidants

Antioxidants are added to cosmetics to prevent the deterioration of unsaturated fatty acids and are an occasional cause of cosmetic allergy [7, 15], though the actual prevalence may be underestimated [106]. Antioxidants that have caused cosmetic allergy include: BHA (butylated hydroxyanisole) [106], BHT (butylated hydroxytoluene) [106], *t*-butylhydroquinone [106, 107], gallates (dodecyl, octyl, propyl) [108], tocopherol (vitamin E), and its esters [109, 110].

30.5.16 Miscellaneous Allergens

Examples of other, infrequent causes of cosmetic allergy include oleamidopropyl dimethylamine [111], ceteayl alcohol [112], maleated soya bean oil [113], dicapryl maleate [114], diisostearyl malate [115], triethanolamine, and methyl glucose dioleate, castor oil [116], ricinoleates [117], polyvinylpyrrolidone (PVP) eicosene copolymer [118], polyvinylpyrrolidone triacontene copolymer [119], polyoxyethylene lauryl ether [120], tetrahydroxypropyl ethylenediamine, 1,3-butylene glycol [121], shellac [122], phthalic anhydride/trimellitic anhydride/glycols copolymer [123], colophonium [124], propolis [125], colors [126], and botanicals [127].

The depigmenting agent kojic acid is a common allergen in Japan [128].

A comprehensive literature survey on cosmetic allergy has been published [13, 129].

30.6 Diagnostic Procedures

The diagnosis of cosmetic allergy should strongly be suspected in any patient presenting with dermatitis of the face, eyelids, lips, and neck [13, 130]. Cosmetic allergic dermatitis may develop on previously healthy skin of the face or on already damaged skin (irritant contact dermatitis, atopic dermatitis, seborrheic dermatitis, allergic contact dermatitis from other sources). Also, dermatitis of the arms and hands may be caused or worsened by skin care products used to treat or prevent dry skin, irritant, or atopic dermatitis. Patchy dermatitis on the neck and around the eyes is suggestive of cosmetic allergy from nail varnish or hardeners. More widespread problems may be caused by ingredients in products intended for general application to the body. Hypersensitivity to other products, such as deodorants, usually causes a reaction localized to the site of application. A thorough history of cosmetic usage should always be obtained.

When the diagnosis of cosmetic allergy is suspected, patch tests should be performed to confirm the diagnosis and identify the sensitizer. Only in this way can the patient be counseled about their future use of cosmetic (and other) products, and the prevention of recurrences of dermatitis from cosmetic or non-cosmetic sources. Patch tests should be performed with the European (or other national) standard series, a "cosmetics series" containing established cosmetic allergens, and the products used by the patient.

The European routine series contains a number of cosmetic allergens and "indicator" allergens: colophonium, *Myroxylon pereirae* (balsam of Peru), fragrance mix, formaldehyde, quaternium-15, methylchloroisothiazolinone (and) methylisothiazolinone, lanolin, and *p*-phenylenediamine.

Although the patient's products should always be tested (for test concentrations, see Table 3 and Chap. 50), patch testing with cosmetics has problems. Both false-negative and false-positive reactions occur frequently. False-negative reactions are due to the low concentration of some allergens and the usually weak sensitivity of the patient. Classic examples of false-negative reactions have occurred with methylchloroisothiazolinone (and) methylisothiazolinone [47, 48] and paraben sensitivity. False-positive reactions may occur with any cosmetic product, but especially with products containing detergents or surfac-

Table 3. Recommended test concentrations for cosmetic products [130]

Cosmetic product	Test concentration and vehicle
Depilatory	Thioglycolate 1% pet.
Foaming bath product	1% water
Foaming cleanser	1% water
Hair bleach	Ammonium persulfate 1% pet.
Hair dyes	2% water
Hair straightener	Individual ingredients
Mascara	Pure (allow to dry)
Nail cuticle remover	Individual ingredients
Nail glue	Individual ingredients
Nail varnish remover	Individual ingredients
Nail varnish	Pure (allow to dry)
Permanent wave solution	Glyceryl thioglycolate 1% pet.
Shampoo	1% water
Shaving lather or cream	1% water
Skin lightener	Hydroquinone 1% pet.
Soap or detergent	1% water
Toothpaste	2% water

Most cosmetics not mentioned in this table can be tested undiluted

tants, such as shampoos, soaps, and bath and shower products. As a consequence, these products must be diluted (1% in water) before testing. Even then, mild irritant reactions are observed frequently, and, of course, the (necessary) dilution of these products may result in false-negative results in patients actually allergic to them. Testing such products is, therefore, highly unreliable.

In many cases, testing with the European standard series, suspected products, and a cosmetics screening series will establish the diagnosis of cosmetic allergy and identify one or more contact allergens. The label on the incriminated product will indicate whether or not the product actually contains the allergen(s). If not, the possibility of a false-positive reaction to the product should be suspected. The test should be repeated and/or control tests on non-exposed individuals should be performed. If an allergy is confirmed, an ingredient not included in the European series or the cosmetics screening series may be responsible. In such cases, the manufacturer should be asked for samples of the ingredients, and these can be tested on the patient after proper dilution [131].

In certain cases, an allergy to cosmetics is strongly suspected, but patch testing remains negative. In such patients, ROAT and/or usage tests can be performed. In the ROAT, the product is applied twice daily for a maximum of 14 days to the antecubital fossa. A negative reaction after 2 weeks indicates that sensitivity is highly unlikely. This procedure should be performed with all suspected products, except detergent-containing cosmetics, such as soap, shampoo, and shower products.

During the usage test, the use of all cosmetic products is stopped until the dermatitis has disappeared. The cosmetics are then reintroduced as normally used, one at a time, with an interval of 3 days for each product, until a reaction develops. Photopatch testing should be performed whenever photo-allergic cosmetic dermatitis is suspected. When all tests remain negative, the possibility of seborrheic dermatitis (scalp, eyelids, face, axillae, trunk), atopic dermatitis (all locations), irritant contact dermatitis (also from cosmetic products), and allergic contact dermatitis from other sources should be considered.

30.7 Ingredient Labeling in the European Union

Cosmetic ingredient labeling (introduced voluntarily in the United States in the 1970s) was a constant demand of European dermatologists for years. On 1 January 1997, the 6th Amendment to the Cosmetics Directive (76/768/EEC) in Europe became effective. This directive requires all cosmetic products marketed in the European Union to display their ingredients on the outer package or, in certain cases, in an accompanying leaflet, label, tape, or tag. The primary purpose of ingredient labeling is to allow dermatologists to identify specific ingredients that cause allergic responses in their patients, and to enable such patients to avoid cosmetic products containing the substances to which they are allergic.

The mandatory nomenclature used throughout the European Union for labeling is the International Nomenclature of Cosmetic Ingredients (INCI), based on the American Cosmetic, Toiletry, and Fragrance Association (CTFA) system. Most CTFA terms have been retained unchanged. However, all colorants are listed as color index (CI) numbers, except hair dyes, which have INCI names. Plant ingredients are declared as genus/species names using the Linnaean system. The source of information on ingredients is the European Inventory [1] published by the European Commission. Provided are the INCI names (in alphabetical order), CAS number, EINECS/ELINCS numbers, chemical/IUPAC names, and functions.

Patients allergic to certain ingredients of cosmetics must be supplied with the INCI names of their allergens, otherwise, they may fruitlessly seek for well-known names such as Kathon CG, oxybenzone, balsam of Peru, Amerchol L-101, dibromodicyanobutane, or orange oil. Dermatologists should be familiar with the INCI nomenclature. However, the relevant names are sometimes difficult to find, but a list of

substances which can be present in cosmetics and have been described as allergens has been generated and their names [CTFA, Merck Index, names provided by the producers of commercially available allergens (e.g., Chemotechnique, Trolab), "common names," and commonly used trade names] compared with those of the INCI [132].

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