

Patterns of Cosmetic Contact Allergy

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KEYWORDS

- Contact dermatitis • Cosmetic • Toiletries
- Personal care product • Facial • Eyelid • Neck • Cheilitis

The use of toiletries is a long-standing practice that extends worldwide and reaches virtually one and all. Practically everyone uses some form of toiletry in daily life, from common items, such as soap, toothpaste, or deodorant, to elaborate facial cosmetics and glamorous fragrances. It has been estimated that approximately 800 raw materials, vehicles, and fragrance ingredients are used in making toiletries,¹ and although most ingredients are safe to use by the majority of consumers, a significant minority of people experience adverse reactions to personal care products.²

In the United States, toiletries regulation falls under the governance of the Food and Drug Administration (FDA), which defines the term “cosmetic” as “articles intended to be rubbed, poured, sprinkled, sprayed on, introduced into, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance.”³ Among the products included in this definition are skin moisturizers, perfumes, lipsticks, fingernail polishes, eye and facial makeup, shampoos, permanent waves, hair colors, toothpastes, and deodorants, as well as any material intended for use as a component of a cosmetic product—with the interesting exception of soap, which is legislated as a separate category. (In this article, the terms *cosmetic*, *toiletry*, and *personal care product* will be used interchangeably).

ADVERSE REACTIONS TO COSMETICS

Cosmetics are widely used, and yet, given the massive volume of sales and the range of product availability, there is remarkably little information on

the exact incidence and prevalence of their detrimental effects.⁴ Potential adverse reactions to cosmetics comprise a broad spectrum of cutaneous reactions that include irritant reactions, delayed-type hypersensitivity, contact urticaria, photosensitization (phototoxic or photoallergic), pigmentary disorders, damage of hair and nails, paronychia, acneiform eruptions, folliculitis, and worsening of preexisting dermatoses.⁵

The exact frequency of adverse reactions to toiletries in the general population is difficult to estimate,⁶ mainly because most people who experience such reactions seldom consult a physician and simply discontinue using the product suspected of triggering the reaction.⁷ (In an Italian poll published in 2006, more than 50% of the people who experienced an adverse reaction to a cosmetic did not seek medical advice.)⁸ A recent survey of a non-selected population in the United Kingdom revealed that 23% of women and 13.8% of men experience some sort of adverse reaction to a personal care product over the course of a year, with an increase in overall rates of 51.4% and 38.2% over a lifetime.⁹ Although they are quite common, only a minority of adverse reactions to cosmetics in the general population have been shown to be allergic in origin^{10–12} highlighting that despite the widespread use of personal care products, the rates of allergic reactions to their ingredients are relatively low. Several studies in Europe and the United States have found a prevalence rate of cosmetic allergy of less than 1% among the general population.^{1,13–19}

When looking at selected patients seen by a dermatologist and referred for patch testing for suspected allergic contact dermatitis (ACD), the

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prevalence rates of cosmetic allergy vary significantly from those seen in the general population and range from 2.4% to 36.3%, with most studies reporting prevalence rates between 4% and 9%.^{1,13–16,19,20} In a 2006 review of ACD to cosmetics, Biebl and Warshaw²⁸ identified a weighted prevalence rate of 0.4% for the general population and 9.8% for patients referred for patch testing.

In the latest and largest US-based study of selected patients with suspected ACD, the North American Contact Dermatitis Group (NACDG) patch tested a total of 10,061 patients (6621 females and 3440 males) over a period of 7 years.²¹ From the total of patients studied, 1582 females (23.8%) and 611 males (17.8%) had at least 1 allergic patch test reaction associated with a cosmetic source. Although slightly higher than the figures found by Biebl and Warshaw, the numbers are consistent with most major reviews. This and other studies also identified, not surprisingly, that the population most affected with cosmetic sensitivity are females^{14–16,22} between 20 to 55 years of age.^{1,13–15}

Most adverse reactions to cosmetics are irritant in nature, which can be further subdivided into subjective and objective reactions. Subjective irritation consists of the sensation of burning or stinging without visual changes, associated with the application of cosmetics.^{5,23} Although most often patients do not seek medical attention for such reactions, they are believed to be the most common source of dissatisfaction with cosmetics.²⁰ Objective irritation, on the other hand, is defined as nonimmunologically mediated skin inflammation with visible skin changes.²⁰ The development of delayed type sensitization and ACD to cosmetics is less common,^{12,24} and depends on several factors that include the product composition and concentration of potentially allergenic ingredients, the inherent sensitizing potential of an allergen, the application site, the amount of product applied, the frequency and duration of the exposure, the presence of penetration-enhancing factors, and finally the integrity of the skin barrier function.^{25–27} Sensitization often occurs after repeated applications or application to damaged skin.²⁸

When considering ACD to cosmetics, reactions can be classified according to the body region affected (site of dermatitis) and the likely allergens encountered at such region; or by the type of cosmetics (ie, eye cosmetics, nail cosmetics, hair cosmetics) and the possible allergens contained within.¹² Most of the available literature approaches the topic by type of cosmetic; in an attempt to provide a broader perspective, this

article overviews ACD to cosmetics with a combined approach, but with special focus on the patterns of dermatitis that cosmetics might incite, followed by a brief description of the potential culprit allergens.

PATTERNS OF ALLERGIC CONTACT DERMATITIS CAUSED BY PERSONAL CARE PRODUCTS

Cosmetic contact allergy manifests when an offending allergen is directly applied, airborne, or transferred (often from the hands). The sites most commonly involved in cosmetic contact allergy include the face, eyelids, lips, and neck.

FACIAL DERMATITIS

The face is a common site for ACD. Schnuch and colleagues analyzed the data of 18,572 patients patch tested in the Information Network of Departments of Dermatology (IVDK) between 1995 and 2007, and found that the face was the main anatomic site involved.²⁹ Among patients with facial dermatitis, females were more predominant than men, and were most commonly affected by cosmetic-associated allergens such as fragrance mix (10.8% vs 8.3%), paraphenylenediamine (PPD) (4.0% vs 2.8%), lanolin alcohols (3.0% vs 2.2%), and Lyril (3.1% vs 2.0%).²⁹

Allergens can be transferred to the face not only by direct contact but also indirectly from airborne or hand-to-face exposure. Facial cosmetic dermatitis is bilateral; however, even when a product is directly applied to the whole face, eczematous manifestations are often patchy, and therefore contact dermatitis might not be suspected because the involvement is not of the whole face. In addition to allergens found as ingredients in cosmetics, products used to apply them, such as cosmetic sponges, are reported to produce facial dermatitis in patients sensitive to rubber.³⁰ A similar situation is seen with nickel-plated objects used on the hair, such as bobby pins and curlers that may produce scalp and facial dermatitis in patients sensitive to nickel.³¹

Allergens applied to the scalp most often produce “run-off” patterns of dermatitis on the forehead and lateral face, eyelids, ears, neck, and hands, whereas the scalp remains uninvolved, suggesting that the scalp is particularly resistant to contact dermatitis.³¹ Nevertheless, patients exquisitely sensitive to hair preparations such as PPD or glyceryl thioglycolate may show a marked scalp reaction with edema and crusting. PPD is 1 of the most potent sensitizers known and is widely used as an ingredient in hair dyes. PPD sensitization manifests on the face and scalp of female

adult patients who had contact with a hair dye.^{32–35} In a small Brazilian study, Duarte and colleagues³² identified that in patients with positive patch test reactions to PPD (mostly females between 41 and 60 years of age), 70% had face or scalp involvement, and 48% had hair dye as the agent responsible for the sensitization.

EYELID DERMATITIS

The eyelids are one of the most sensitive skin areas, and they are highly susceptible to irritants and allergens. This does not mean that every case of eyelid dermatitis is allergic or irritant in origin, and other diagnoses, such as seborrheic dermatitis, atopic dermatitis, psoriasis, and nonspecific xerosis, should also be considered.³⁶ The particular vulnerability of eyelids to contactants might be because of the thinness of the eyelid skin, 0.55 mm, as compared to the rest of the facial skin, measuring approximately 2.0 mm.³¹ Transfer of small amounts of allergens used on the scalp, face, or hands might be enough to cause an eczematous reaction of the eyelids, whereas the primary sites of contact remain unaltered. Volatile agents may affect the eyelids first and exclusively, causing airborne eyelid contact dermatitis.

Cosmetic sources of contact dermatitis of the eyelids include mascara, eye liners and eye shadows, adhesive in fake eyelashes, and nickel and rubber in eyelash curlers. Furthermore, marked edema of the eyelids is often a feature of hair dye dermatitis. Eyelids are also characterized for being a typical site for “ectopic contact dermatitis.” Alexander A. Fisher coined this concept to describe the dermatitis caused by nail lacquer, since the allergic reaction does not occur in the periungual area, but on “ectopic” areas where fingernails touch, particularly the eyelids but also the neck, lips, and face.³⁷

In 2007, the NACDG published the results of 5145 patients routinely tested with a 65-allergen screening series over a 2-year study period (2003–2004).³⁸ In 5.2% (n = 268) of the patients studied, eyelid dermatitis was the sole site of involvement and ACD was the final diagnosis of the cause of the dermatitis. Sixty-five percent of the cases were caused by 1 of 26 clinically relevant contact allergens identified in the study. The NACDG suggested in conclusion that these top 26 allergens would constitute “a potential screening series for the evaluation of patients with eyelid dermatitis, without other areas of involvement” (Box 1). This list includes mostly allergens found as ingredients in cosmetics, but

Box 1

NACDG suggested screening series for the evaluation of patients with only eyelid dermatitis

Allergen

1. Gold sodium thiosulfate 0.5% pet
2. Fragrance mix I 8% pet
3. *Myroxylon pereirae* (balsam of Peru [BOP]) 25% pet
4. Nickel sulfate 2.5% pet
5. Neomycin 20% pet
6. Methylidibromo glutaronitrile 2% pet
7. Quaternium-15 2% pet
8. Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) 100 ppm aq
9. Cobalt chloride 1% pet
10. 3'-Demethoxy-3o-Demethylmatairesinol (DMDM) hydantoin 1% aq
11. Amidoamine 0.1% aq
12. Cocamidopropyl betaine (CABP) 1% aq
13. Thiuram mix 1% pet
14. Bacitracin 20% pet
15. Cinnamic aldehyde 1% pet
16. d- α -Tocopherol acetate 100%
17. Tosylamide formaldehyde resin (TSFR) 10% pet
18. Propylene glycol 30% aq
19. Tixocortol pivalate 1% pet
20. Formaldehyde 1% aq
21. Colophony 20% pet
22. Ylang ylang oil 2% pet
23. Lanolin 30% pet
24. Ethyl acrylate 0.1% pet
25. Methyl methacrylate 2% pet
26. Budesonide 0.1% pet

Abbreviations: aq, aqueous; pet, petrolatum; ppm, parts per million.

Data from Rietschel RL, Warshaw EM, Sasseville D, et al. Common contact allergens associated with eyelid dermatitis: Data from the North American Contact Dermatitis Group 2003–2004 study period. *Dermatitis* 2007;18(2):78–81.

also topical antibiotics and certain metals such as gold. An interesting feature of gold allergy is the propensity for facial and eyelid dermatitis to occur.³⁹ In the NACDG analysis, gold was the most common allergen that accounted for pure eyelid dermatitis. It has been observed that upon contact with hard particles such as titanium dioxide (which is used to opacify facial cosmetics and is used in sunscreens as a physical blocker of ultraviolet [UV] light), gold found in jewelry may abrade, encouraging the release of gold particles that can then make occasional contact with facial and eyelid skin, causing dermatitis.⁴⁰ Aside from gold, fragrances and preservatives have been

found to be the main cosmetic allergens to cause pure eyelid dermatitis in NACDG and other series.^{38,41}

NECK DERMATITIS

The neck is also a highly reactive site for ACD. Cosmetics applied to the face, scalp, or hair often initially affect the neck.³¹ Nail polish is also a common culprit in this region. Lazzarini and colleagues recently studied ACD from nail varnish according to the site of dermatitis and found that the most affected sites were the face and neck. Toluenesulfonamide formaldehyde resin, presently tosylamide formaldehyde resin (TSFR), the chemical added to nail polish to facilitate adhesion to the nail, was the most common allergen in the group studied.⁴² Furthermore, as a cultural practice, perfumes are sprayed on the neck. In fragrance-sensitized people, this practice of repeated application of fragrances to the anterior neck may result in the appearance of a dermatitic plaque in that particular region, which has been coined the “atomizer sign.”⁴³ Such a sign can be a particularly useful clue to the diagnosis of fragrance-based ACD, and its recognition may allow for early initial therapeutic intervention, notably fragrance avoidance.

ALLERGIC CONTACT CHEILITIS

Cheilitis is an inflammatory condition of the lips that can manifest as itching, burning, dryness, erythema, fissuring, crusting, and edema.⁴⁴ The factors contributing to this condition may be endogenous to the individual, like an atopic diathesis; exogenous to the individual, like allergens and irritants; or a combination of both.⁴⁵

Allergic contact cheilitis (ACC) has been reported to result from the use of a wide array of products, including foods, metals, and cosmetics (such as lip balms, lipsticks, lip glosses, moisturizers, sunscreens, nail products, and oral hygiene products [mouthwashes, toothpastes, and dental floss]).^{46,47}

A notable feature among patients with cheilitis is the evident female predominance, with most studies reporting a range of 70.7% to 90% female patients.^{48–50} In a recent Greek study, Katsarou and colleagues studied a group of 106 patients with eczematous cheilitis of whom 75.5% (n = 80) were females.⁵¹ Similarly, of 10,061 patients patch tested from 2001 to 2004 by the NACDG, 196 (2%) patients had lips as the sole involvement site, and females accounted for 84.2% of the cheilitis population.⁴⁵ (This is likely explained by the assumption

that women wear more cosmetics and lip products than men do).

Approximately one-third of the patients with cheilitis are typically found to have an allergen as a contributing factor.^{48,49} In accordance with this trend, 38.3% (n =75) of the 196 patients studied for cheilitis by the NACDG, were diagnosed with ACC after patch testing. Most of the studies on cheilitis have reported fragrance mix as the most common cause of allergy in patients who were patch tested.^{48,49,52} In the NACDG cheilitis study, fragrance mix was the most common allergen identified, followed by *Myroxylon Pereirae* (balsam of Peru [BOP]) and nickel (**Box 2**). Overall, the most common sources for the top allergens causing ACC are cosmetics (including lip products).^{45,48,49,52} Sources for nickel might include jewelry (causing ectopic dermatitis), metal lipsticks casings, or habitual sucking of metallic objects.⁵¹

An interesting contrast to the general patch test population is that patients with only lip involvement have few patch test reactions to preservatives. This might be as a result of the innate formulation of lip products, which are mostly waxy, water-free

Box 2
Top 18 clinically relevant allergens identified in patients with ACC patch tested to the NACDG standard series

- Allergen
- 1. Fragrance mix I 8% pet
 - 2. *Myroxylon pereirae* (BOP) 25% pet
 - 3. Nickel sulfate 2.5% pet
 - 4. Gold sodium thiosulfate 0.5% pet
 - 5. Neomycin sulfate 20% pet
 - 6. Cobalt chloride 1% pet
 - 7. Propylene glycol 30% aq
 - 8. Lanolin 30% pet
 - 9. Cinnamic aldehyde 1% pet
 - 10. Bacitracin 20% pet
 - 11. Benzophenone-3 3% pet
 - 12. Methylidibromo glutaronitrile/phenoxy ethanol 2% pet
 - 13. Tea tree oil, oxidized 5% pet
 - 14. Budesonide 0.1% pet
 - 15. Mercaptobenzothiazole 1% pet
 - 16. Formaldehyde 1% aq
 - 17. Potassium dichromate 0.25% pet
 - 18. TSFR 10% pet

Abbreviations: aq, aqueous; pet, petrolatum.
Data from Zug KA, Kornik R, Belsito DV. Patch testing North American lip dermatitis patients: Data from the North American Contact Dermatitis Group 2001–2004. *Dermatitis* 2008;19(4):202–8.

mixtures, consequently requiring fewer and lower concentrations of preservatives.⁴⁵ Another particularity is the presence of some uncommonly reported allergens relevant to the lip location, namely benzophenone-3 and gallates. Benzophenone-3, a major constituent in many sunscreens, is also a common ingredient in many lip products and is increasingly reported as a culprit for ACC. Schram and colleagues recently reported a patient with severe cheilitis who had a strong patch test reaction to both benzophenone-3 and his own lip balm.⁵³ Similarly, Nedorost⁵⁴ and Aguirre and colleagues⁵⁵ reported 1 patient each with cheilitis who reacted to irradiated and nonirradiated benzophenone-3 patches. Notably, benzophenone-3 was an ingredient in the lip products used by both patients. Gallates, on the other hand, are antioxidants used in waxy or oily products, such as lip balms, lipsticks, and lip glosses, and have also shown to play a potential role in ACC.⁵⁶

PERIORAL DERMATITIS AS A MANIFESTATION OF ALLERGIC CONTACT DERMATITIS

Perioral dermatitis (POD) is a distinct condition that usually presents as a persistent acneiform eruption composed of tiny (2–3 mm) erythematous papules or papulopustules distributed primarily around the mouth and sparing the vermillion border of the lips.⁵⁷ POD predominantly affects women between 16 and 45 years of age, with constitutionally dry skin or a history of mild atopic dermatitis. Without treatment, POD tends to run a fluctuating course. Its pathogenesis remains unclear; however, a number of factors have been implicated, including atopy, infective agents, contact allergens and irritants, occlusive topical cosmetic products, hormonal factors (premenstrual period, pregnancy, oral contraceptives),⁵⁸ glucocorticosteroids, and ultraviolet (UV) light. POD might represent a localized form of rosacea.⁵⁹ If rosacea-type POD and atopic dermatitis are ruled out by history or examination, or if appropriate treatment fails, ACC should be suspected and patch testing should be pursued.⁵⁹ In a medical pearl for the evaluation of POD, Nedorost recommended patch testing with a standard and bakery series in addition to photo patch testing to a sunscreen series, when ACD is the suspected cause of POD.⁵⁹ Such series would allow the identification of potential relevant allergens such as topical antibiotics (neomycin and bacitracin), cinnamic aldehyde (the flavorant used in most commercially available toothpastes), benzophenone-3,

and propolis (both frequently found as ingredients of lip products).

CONNUBIAL/CONSORT DERMATITIS

ACD may not be caused by direct exposure of a patient to an allergen, but by passive exposure via social contacts (partners, family members, friends, or coworkers). This phenomenon has been termed “consort” or “connubial” dermatitis, to describe the skin reaction as a result of a substance used by someone other than the person affected. Connubial dermatitis is most commonly a result of fragrances,⁶⁰ however, various case reports have proven that many other cosmetic-related allergens could be potentially involved. These include a case of compositae-mix contact allergy from exposure to a consort’s “natural” cosmetics;⁶¹ a case of facial dermatitis in a mother following face-to-face contact with her benzoyl peroxide-treated son;⁶² and a case of severe hand dermatitis as a result of PDD in a man that regularly helped his wife color her hair with a PPD-containing hair dye,⁶³ among many others.

OCCUPATIONAL CONTACT ALLERGY TO COSMETIC-RELATED ALLERGENS

In cross-sectional data of 2193 patients with at least 1 allergic patch test reaction associated with a cosmetic source, the NACDG identified 125 patients with occupationally related allergic reactions associated with a cosmetic.²¹ Cosmetics “not otherwise specified,” hair care products, and moisturizers were the most common product categories which were occupationally related. For both men and women, the most common occupation which relates an allergic reaction to a cosmetic source is hairdressing (including barbers and cosmetologists). Up to 50% of hairdressers develop dermatitis of the hands (either irritant or allergic in origin) within 3 years of starting work.⁶⁴ Common culprits include allergens found in hair care products such as dyes (mainly PPD), permanent wave solution (glyceryl monothioglycolate), hair bleaches (ammonium persulfate), preservatives, surfactants, and fragrances.

In a 2008 Finnish study, Aalto-Korte and colleagues reported on occupational contact allergy to formaldehyde and formaldehyde releasing preservatives in people that come in contact with cosmetics in their working environment; these include masseurs, hairdressers, and workers in various fields that are required to use barrier creams or liquid soaps at work.⁶⁵

POTENTIAL CULPRITS OF COSMETIC CONTACT ALLERGY

There are many allergens in cosmetics, and although this article concentrates on giving a brief description of the most common allergens⁴ (**Box 3**), it is important to keep in mind that virtually any ingredient found in a cosmetic can have the potential to cause a contact allergy. As a group, the preservatives are the most common allergens, closely followed by fragrances.⁶⁶

Preservatives

Formaldehyde

Formaldehyde is a colorless gas with preservative and disinfectant properties. The first mass commercial use of formaldehyde was in medical embalming, and soon after, it started to be used as a preservative for laboratory specimens. Currently there is a wide range of uses for formaldehyde (cleansing products, plywood, bonded leather, waterproof glues, fertilizers, biocides, and photographic developers), yet it is rarely used in cosmetics because it is a frequent sensitizer.²⁸ Formaldehyde is an irritant and an allergen,

and patch testing with it is important as it can serve as a marker to identify individuals allergic to formaldehyde related preservatives.

Formaldehyde releasing preservatives

Many manufacturers have replaced the use of formaldehyde with formaldehyde-releasing preservatives (FRPs) in an attempt to decrease contact sensitization to personal care products.⁶⁷ FRPs include: quaternium-15, imidazolidinyl urea (Germall), diazolidinyl urea (Germall II), 3'-deme-thoxy-3o-demethylmatairesinol (DMDM) hydan-toin (Glydant), 2-bromo-2-nitropropane-1, 3-diol (Bronopol), and tris nitromethane (Tris Nitro).⁶⁸ (Tris Nitro is an industrial biocide and is not usually found in cosmetic products.) FRPs are added to many skin, hair, and makeup products; mouth-washes; baby wipes; and topical medications. Allergic reactions to FRPs may be caused by the preservative per se, by formaldehyde, or by both.⁶⁹ The rate of cross-reactivity between FRPs and formaldehyde varies, and allergy to 1 FRP may not necessitate a restriction of the entire class. Herbert and Rietschel have suggested that it is only necessary to avoid the specific preserva-tives to which an individual tests positive.⁷⁰

Quaternium-15 deserves special mention since it is the most common cosmetic preservative allergen.^{1,14} It was the fourth most frequently positive allergen (10.3%) in the most recent NACDG patch test results study (2005–2006 period), after nickel sulfate, *Myroxylon pereirae*, and fragrance mix I.⁷¹ Quaternium-15 had a statistically significant higher prevalence rate of allergic reactions in the 2005–2006 cycle compared with the prior 10 years (1994–2004) ($P<.05$), showing that the frequency of positive patch tests to this preservative in the population tested by the NACDG continues to increase over time.

Parabens

With the exception of water, parabens are the most commonly used ingredient in cosmetic preparations; and are also the most widely used preservative in cosmetic products.^{68,72} There are 5 types of paraben esters of which methylparaben and ethylparaben are the most frequently used. Despite their widespread use, allergic reac-tions to parabens are rare, with most studies showing a prevalence that ranges from 0% to 4.2%.^{73–75} ACD to parabens has been most commonly reported when products containing parabens are used on damaged skin, for example in patients with long-standing dermatitis or leg ulcers.⁷⁶ Although frequently found in cosmetics, parabens are considered weak sensitizers in

Box 3

Most frequent sensitizers in cosmetics

- Preservatives:
 - Formaldehyde
 - Formaldehyde releasing preservatives:
 - Quaternium-15
 - Imidazolidinyl urea
 - Diazolidinyl urea
 - DMDM hydan-toin
 - Bronopol
 - Parabens
 - Methyl-dibromo glutaronitrile/phenoxy ethanol (MDGN/PE)
 - MCI/MI
 - Iodopropynyl butylcarbamate
- Fragrances
- Lanolin
- Cocamidopropyl betaine
- Antioxidants
- UV absorbers
- PPD
- Glyceryl monothioglycolate
- TSFR
- Propylene glycol

Not in order of frequency.

Data from White IR, de Groot AC. Cosmetics and skin care products. In: Frosch PJ, Menné T, Lepoittevin J-P, editors. Contact dermatitis. 4th edition. Berlin: Springer Verlag; 2006. p. 493–503.

these formulations; and patients sensitive to parabens are often able to tolerate paraben-containing cosmetics when applied to normal intact skin. Sites of resolved dermatitis occasionally flare when paraben-containing products are applied to healthy skin that does not react.⁷⁷ This unique aspect of paraben sensitivity was termed the “parabens paradox” by Alexander Fisher more than 35 years ago.⁷⁸

Methyldibromo glutaronitrile/phenoxyethanol

Methyldibromo glutaronitrile/phenoxyethanol (MDGN/PE) is a preservative commonly referred to in the literature as Euxyl K400. It is a combination of 2 active ingredients, 2-phenoxyethanol and 1,2-dibromo-2,4-dicyanobutane in a ratio of 4:1.²⁰ Shortly after being introduced to the market in the mid 1980s, MDGN/PE was labeled as an emerging and increasingly important sensitizing agent⁷⁹ and unleashed what has been considered an “epidemic of allergic contact dermatitis.”⁸⁰ This was followed by a ban in the European Union (EU) countries, first from stay-on cosmetics in 2005, and later from rinse-off cosmetics in 2007, in an attempt to decrease the rates of contact allergy. Following the regulatory intervention, a significant decreasing trend in the frequency of positive patch tests to MDGN/PE was found, from 4.6% in 2003 to 2.6% in 2007 ($P < .001$).⁸⁰

Earlier, the vast majority of allergic reactions to MDGN/PE came from cosmetics, especially creams, lotions, and liquid soaps. MDGN/PE is not banned in cosmetics produced outside the EU, and therefore cosmetics bought outside of the EU may still contain MDGN/PE. Of 4437 patients patch tested to MDGN/PE (2.5% pet) by NACDG in the 2005–2006 study period, 5.8% had a positive patch test reaction to this allergen, of which 3.9% were considered of definitive and 44% of probable clinical relevance.⁷¹

Methylchloroisothiazolinone/methylisothiazolinone

Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) is a broad-spectrum antimicrobial that consists of a mixture of 2 isothiazolinones. It is commonly referred to in the literature as Kathon CG. It can be found in many cosmetic products including rinse-off and leave-on products. The first reports of ACD to this preservative appeared in Europe in the mid 1980s, and many cases of ACD to this preservative resulted from the use of moisturizing creams. Sensitivity patterns to MCI/MI have followed a somehow similar pattern in the United States and in Europe, with an increase from the 1980s to the 1990s, followed by a decrease in the

first part of this decade. MCI/MI is patch tested at 100 ppm aqueous, but the amount actually used in products is much lower.²⁸ Studies have suggested that concentrations of 15 ppm MCI/MI in rinse-off products and 7.5 ppm in leave-on products are unlikely to produce sensitization to this agent.⁸¹

Iodopropynyl butylcarbamate

Iodopropynyl butylcarbamate (IPBC) is a relatively new preservative and biocide used in many personal care products. It is currently used in shampoos, lotions, powders, makeup, creams, and baby products including cleansing wipes.⁸² Structurally, it is a small, lipophilic molecule that potentially leads to sensitization after extensive and prolonged exposure.^{83,84} However, there are only a few reported cases of ACD from IPBC in cosmetics, despite its increasingly widespread use.

Thimerosal

Thimerosal is a mercury derived preservative. Exposure sources vary widely between different populations (eg, Europe vs America) and include contact lens solutions, otic and ophthalmic solutions, solutions for intradermal testing, antiseptics (eg, merthiolate), and certain cosmetics; however, it is believed that most sensitization cases originate from its presence in vaccines.^{85–87} While patch testing with thimerosal may indicate a positive test, relevance these days to the presenting dermatitis is uncommon. Because of this regular lack of identified relevant sources, the majority of US-based patch test experts have removed thimerosal from their standard screening trays.^{88,89}

Fragrances

Fragrances are aromatic compounds that impart a smell or odor. They can be natural (from botanic or animal products) or synthetic in origin. In 2007, fragrances were named “Allergen of the Year” by the American Contact Dermatitis Society (ACDS) to recognize the importance of these allergens.⁹⁰ It has been estimated that between 1% and 4% of the general population is allergic to fragrances.^{91,92} Fragrance allergy is 1 of the 2 top causes of contact allergy to cosmetics, and the typical sites of involvement include the face and hands, as well as behind the ears, neck, and axillae in addition to generalized contact dermatitis.^{93,94}

Three main substances are currently used by most patch test groups for screening of subjects with suspected fragrance sensitivity. The first substance, fragrance mix I (8.0% in petrolatum),

is a mixture of 8 fragrance allergens (cinnamic alcohol 1.0%, cinnamic aldehyde 1.0%, eugenol 1.0%, hydroxycitronellal 1.0%, isoeugenol 1.0%, geraniol 1.0%, oak moss absolute, and alpha-amyl cinnamic aldehyde 1.0%).

The second material, *Myroxylon pereirae* (MP), also known as balsam of Peru (BOP), is a substance derived from *Myroxolon balsamum*, a tree that is native to El Salvador. Given that many of MP components are fragrance ingredients,⁹⁵ it is considered to be a good marker for fragrance allergy, and able to identify approximately 50% of fragrance allergic individuals.⁹⁶ MP smells of vanilla and cinnamon because it contains 60% to 70% cinnamoin, a combination of cinnamic acid, benzoyl cinnamate, benzoyl benzoate, benzoic acid, vanillin, and nerodilol.⁹⁷ These are all potential allergens, making MP one of the 5 most prevalent allergens detected by the Thin-layer Rapid Use Epicutaneous (TRUE) test.⁷⁵ In addition to pharmaceutical preparations and cosmetic products such as perfumes, lotions, and lip products, MP-related substances can also be found in toothpastes and mouthwashes, as well as in scents and flavorings for foods and drinks. This explains the frequent association between MP and ACC.^{52,98} Cross-reactions may occur between MP and other chemicals such as colophony (rosin), wood and coal tars, resorcinol monobenzoate, coniferyl benzoate, Tolu balsam, storax, propolis, turpentine, and benzoin.³¹ Certain foods, such as tomatoes and tomato-containing products, citrus fruit peel/zest, chocolate, ice cream, wine, beer, vermouth, dark colored sodas, and spices such as cinnamon, cloves, curry, and vanilla, have chemical ingredients related to BOP.⁹⁹ In 2001, Salam and Fowler⁹⁹ drew attention to the ability of orally ingested balsam-related substances to induce systemic contact dermatitis; and they reported that almost half of the subjects with positive patch tests to MP who followed a BOP reduction diet in their study had a significant to complete improvement of their dermatitis.

It was originally estimated that over 90% of individuals allergic to fragrance would be detected by patch testing to fragrance mix I and MP;¹⁰⁰ however, fragrances used by the industry are evolving constantly, and more recent studies have suggested that these 2 testing substances now pick-up only 60% to 70% of individuals allergic to fragrances.¹⁰¹ In answer to this, an additional mixture called fragrance mix II has been added to many screening series. Fragrance mix II (14% in petrolatum) is a mixture of 6 fragrance allergens (citronellol 0.5%, Lyril (hydroxyisohexyl 3-cyclohexene carboxaldehyde) 2.5%, hexyl

cinnamal 5.0%, citral 1.0%, coumarin 2.5%, and farnesol 2.5%).

Regulation of fragrance ingredients in cosmetics is a complicated topic and differs widely between countries. The Fair Packaging and Labeling Act, for example, requires that every cosmetic product in the United States list all of its ingredients following the International Nomenclature of Cosmetic Ingredients (INCI). Fragrance formulas; however, are exempted from this rule, because they often constitute “trade secrets” or proprietary formulas.¹⁰² Therefore, most products found in the United States simply list either “fragrance” or “perfume” on their ingredient list, whereas there is the possibility that hundreds of different fragrance ingredients were mixed together to form that final fragrance in any given product.

A recent seventh amendment to the European Cosmetic Directive regulates cosmetic products in the EU. This amendment establishes that 26 distinct fragrance allergens are now required to be disclosed on the labels of cosmetic products that contain them. (A list of the 26 fragrance ingredients can be found in **Box 4**.)¹⁰³

Although some manufacturers do not consider essential oils to be fragrances, these plant extracts are natural sources of various fragrance ingredients, and therefore possible sources of fragrance contact allergy.¹⁰⁴ *Melaleuca alternifolia* oil (tea tree oil), *Cananga odorata* oil (ylang-ylang oil), *Jasminum officinale* oil (jasmine flower oil), *Mentha piperita* oil (peppermint oil), *Lavandula angustifolia* oil (lavender oil), and limonene (citrus oil) are all examples of essential oils known to cause contact allergy.

Another tricky aspect of fragrance allergy is the existence of so-called “covert fragrances.” Covert fragrances are aromatic chemicals which can be used for purposes other than imparting an aroma, for example, they can be used as preservatives, and therefore they can be added to a “fragrance-free” product. Examples of covert fragrances include benzaldehyde, benzyl alcohol, bisabolol, citrus oil, and unspecified essential oils.

Vehicles, Emulsifiers, and Surfactants

Lanolin

Lanolin (or wool wax alcohols) is the sebaceous excretion from sheep; it is extracted from wool and used as an emollient for skin barrier protection and repair. It is often added to a variety of cosmetics including lip products (lipsticks, lip balms), moisturizers, powders, shaving creams, shampoos, and soaps, and it may be a source of allergy from cosmetic products.^{105,106} Ointment

bases for topical medicaments are another common source of lanolin exposure.

Patients with chronic dermatitis, especially lower-extremity venous stasis dermatitis, have been identified as a high-risk population for the development of contact dermatitis from lanolin.¹⁰⁷ Based on this, Wolf concluded that lanolin is a weak sensitizer in normal skin, whereas damaged skin is easily sensitized, and Wolf named this phenomenon the “lanolin paradox.”¹⁰⁸

Box 4

List of the 26 fragrance ingredients requiring labeling on cosmetic products in Europe

INCI name

Amyl cinnamal
Benzyl alcohol
Cinnamyl alcohol
Citral
Eugenol
Hydroxycitronellal
Isoeugenol
Amylcinnamyl alcohol
Benzyl salicylate
Cinnamal
Coumarin
Geraniol
Lylal
Anise alcohol
Benzyl cinnamate
Farnesol
Butylphenyl methylpropional
Linalool
Benzyl benzoate
Citronellol
Hexyl cinnamal
Limonene
Methyl 2-octynoate
Alpha isomethyl ionone
Evernia prunastri (Oak moss) extract
Evernia furfuracea (Tree moss) extract

Data from IFRA. Skin reactions to fragrances. Procedures for promptly supplying fragrance information to dermatologist. Available at: http://www.ifraorg.org/binarydata.aspx?type=doc/FinalProcedure_Dermatologists-Requests.pdf. Accessed January 30, 2009.

Sorbitans

Sorbitol-based emulsifiers are commonly used in personal care products and topical medicaments (corticosteroids, antibiotics, antifungals, and retinoids).¹⁰⁹ Sorbitan sesquioleate (SSO) is a water-in-oil emulsifier that allows oil and water to blend together into a homogeneous mixture that does not separate.¹¹⁰ It is widely used in cosmetics such as moisturizers, cleansers, conditioners, eye makeup removers, exfoliating products, sunscreens, makeup, and baby products. ACD from sorbitol derivatives is uncommon. Cosmetics and topical medicaments have been reported as the most common sources for ACD in patients allergic to SSO. Closely related emulsifiers such as Span 20 (sorbitan monolaurate), Span 40 (sorbitan monopalmitate), span 60 (sorbitan monostearate), span 65 (sorbitan tristearate), span 80 (sorbitan monooleate), and Span 85 (sorbitan trioleate) can cross-react with SSO and therefore should be avoided in patients sensitive to SSO.¹¹⁰

Cocamidopropyl betaine

Cocamidopropyl betaine (CAPB) is derived from coconut oil and is a commonly used surfactant in foaming cleansers that appears in many shampoos, bath foams, and soaps.¹¹¹ Recently, there is evidence that impurities from the CAPB preparation, such as amidoamine^{112,113} and 3-dimethylaminopropylamine,^{114,115} may be the true sensitizers. With improved (less contaminated) manufacturing, sensitization to products containing CAPB may be reduced in the near future.¹¹⁶ Currently, contact sensitization prevalence rates are between 3.0% and 7.2%.¹¹⁷

Antioxidants

Gallates

Gallates (propyl gallate, octyl gallate, and dodecyl gallate) are chemical compounds used as antioxidant preservatives. They are added to food or cosmetic products to prevent spoilage as a result of the oxidation of fats and oils.¹¹⁸ In cosmetics, gallates are primarily found in waxy or oily products such as lip balms or lip sticks, but can also be found in creams. Because of its more frequent inclusion in cosmetic products since 1947, propyl gallate should be kept in mind when evaluating patients, especially women, presenting with cheilitis, and in consumers of creams and topical medicaments that contain these chemicals. Hausen and Beyer determined that the gallate with the most sensitizing potential is dodecyl gallate.¹¹⁹ The exact prevalence of gallate allergy in the United States is not known because screening for gallate sensitivity is not done routinely. These

chemicals are not included in the NACDG screening tray or in the TRUE test.

Because of the similarity of the base compounds, cross-reactions between gallates can occur. In general, if a patient is tested with only 1 gallate and has a positive reaction, he or she should avoid all gallates. However, if the patient is tested with all 3 gallates and reacts to only 1 of them, the patient needs to avoid only the specific gallate to which he or she reacted.¹¹⁸

Ultraviolet Absorbers

Benzophenone-3 (oxybenzone)

Benzophenone-3 (2-hydroxy-4-methoxy-5 acid benzophenone) is the most common sunscreen allergen.¹²⁰ Synonyms for benzophenone-3 include oxybenzone, Eusolex 4360, Uvinul M 40, and diphenylketone. In addition to its use in sunscreens, benzophenone-3 may be added to toiletries, cosmetics, perfumes, and other products to prevent color degradation.¹²¹ It is also an ingredient in many lip products, and patients may be unaware of any sunscreen exposure when using a product such as a shampoo or a lip balm. Occupational hand dermatitis to benzophenone in hair products has been reported in a hairdresser,¹²² and multiple cases of cheilitis as a result of benzophenone-3 are reported in the literature.

Compared with other contact allergens, the prevalence of oxybenzone allergy is relatively low. Between 2005 and 2006, only 0.7% of more than 4000 patients with suspected ACD patch tested by members of the NACDG reacted to benzophenone-3.⁷¹ Oxybenzone can cause both immediate and delayed-type hypersensitivity reactions that can be photoallergic and non-photoallergic, and therefore regular patch testing and photo patch testing may be necessary to evaluate patients with a suspected sunscreen allergy.

Allergenic Ingredients Found in Hair Products

Paraphenylenediamine

PPD is an oxidizing agent commonly used as a permanent hair dye. More recently it has gained notoriety for its use in adulterating natural henna to make "black henna," a substance increasingly used to make temporary tattoos.^{123,124} Hair dye, however, remains the main source of exposure to PPD.

Contact allergy to PPD often presents as facial dermatitis near the hairline, but it may also involve the eyelids and the neck, whereas the scalp may or may not be spared.¹²⁵ Both consumers and hairdressers who are exposed to PPD are at risk for sensitization. PPD has the potential to

cross-react with other para-amino group chemicals such as para-aminobenzoic acid, sulfonyleureas, hydrochlorothiazide, benzocaine, procainamide, and certain azo and aniline dyes.^{126–128}

Glyceryl monothioglycolate

Glyceryl monothioglycolate (GMT) is a chemical substance used in permanent wave (perming) solutions. Known as an acid perm, GMT works by altering the disulfide bonds of hair keratin so that the hair may be curled or waved. The scalp is generally resistant to ACD, and reactions to hair care products often involve the forehead, eyelids, ears, and neck, sparing the scalp. GMT reactions, however, frequently manifest as intense scalp reactions with scaling, edema, and crusting.¹²⁹ As an occupational cosmetic allergen, reaction to GMT can be seen on the hands, forearms, face, and neck of hairdressers. GMT persists on the permed hair for months, and therefore a sensitized hairdresser may react while cutting or styling permed hair.¹²⁹

Allergenic Ingredients Found in Nail Products

Tosylamide formaldehyde resin

TSFR is a chemical added to nail varnish to facilitate adhesion of the varnish to the nail. Despite the name, there is only a small amount of free formaldehyde in TSFR, and it is the actual resin that constitutes the allergen.¹³⁰ Allergic reactions to TSFR generally develop at sites that are remote from the fingernails, such as the eyelids, face, and neck. The prevalence of ACD to TSFR has been on a decrease for the past 20 years,¹³¹ and although this allergen is still traditionally considered in the evaluation of eyelid dermatitis, it has been found to be a minor factor.³⁸ In the NACDG study of common contact allergens associated with eyelid dermatitis, TSFR represented only 1% of the cases (n = 4 of 268 patients),³⁸ whereas other studies done outside the United States, like the one from Duarte and colleagues, have reported a rate as high as 12%.¹³²

Artificial nail products

Artificial nails are often used when natural nails are not of the desired length or shape. Preformed plastic nails may be glued over the natural nail using ethyl cyanoacrylate (the ingredient found in Super Glue), which has been reported as a potential sensitizer.¹³³ On the other hand, sculptured nails are usually made of acrylic created from a liquid monomer and a powder polymer that is cured with an accelerator, often benzoyl peroxide.¹² Sensitization to artificial nail products has been reported in both beauticians and their

clients, and includes nail fold, fingertip, facial, and neck dermatitis, as well as paresthesia.¹² Some authors advocate screening for suspected contact allergy to artificial nail products, with an acrylate series containing methyl methacrylate 2%, bisphenol A 1%, tetraethylene glycol dimethacrylate 2%, ethylene glycol dimethacrylate 2%, dimethyl-p-toluidine 2%, and benzoyl peroxide 1%.¹³⁴

Other Cosmetic Allergens

Propolis

Propolis, also known as “bee glue,” is a wax-like resinous substance made by honeybees. Resins collected by the bee from a variety of tree buds and barks (particularly conifers and poplars) are partially digested by the bee and then combined with beeswax to form a complex mixture of approximately 180 to 300 constituents, primarily resins (45% to 55%) consisting of free aromatic acids (ie, benzoic and cinnamic); waxes (30%); essential oils (10%); vitamins A, B, C, and E; flavonoids; and various minerals.^{135,136} Human uses of propolis are extensive and include cough syrups, lozenges, ointments, vitamins, and cosmetics, such as shampoos, conditioners, lip balms, lotions, and toothpastes.¹³⁶

Cases of ACD¹³⁷ and ACC^{138,139} have been reported in association with propolis, and most cases result from use of propolis-containing products either applied topically (cosmetics) or ingested orally.¹³⁵ The main allergen found in propolis is LB-1, which consists of 2 distinct allergens: 3-methyl-2- butenyl caffeate and phenylethyl caffeate.¹⁴⁰ 1.2% to 6.6% of patients who are patch tested for dermatitis are sensitive to propolis.¹³⁶

Colophony

Colophony, also known as rosin, is a natural resin obtained from the pine tree. In cosmetics, it is used in lip products as well as eye makeup (mascara, eye shadows, and eye liners).⁵ Cases of eyelid dermatitis, cheilitis, and perioral dermatitis have been reported, albeit uncommonly, in association with colophony. Abietic acid and dihydroabietyl alcohol have been determined as the allergens present in colophony.^{5,141}

Propylene glycol

Propylene glycol is a solvent and humectant with antibacterial properties, widely used in cosmetics. It is a frequent cause of both irritant contact dermatitis and ACD, yet it is predominantly an irritant. In view of its propensity to cause irritation, the high prevalence rates of sensitization have been questioned.¹⁴² The NACDG found that sensitization to propylene glycol 30% aqueous was 2.9% in 4439 patients patch tested from 2005 to

2006.⁷¹ Notably, in another study by the same group, Zug and colleagues identified propylene glycol as 1 of the most frequently relevant positive contact allergens in patients with a scattered generalized distribution of dermatitis.¹⁴³

Diagnosis

The first step in the diagnosis of ACD to cosmetics is a careful medical history, including a meticulous investigation of the products used by the patient (both in the household and working environments). This should be followed by a thorough physical examination, with special attention to the pattern of the dermatitis, because clinical signs can provide vital information regarding the precipitating factors.¹⁴⁴ Patch testing is considered the “cornerstone” procedure in the diagnosis of ACD and should be performed when there is a substantial clinical suspicion and a suggestive history. In patients presenting with dermatitis in sun exposed areas it may also be necessary to consider performing photo patch testing—even more now that UV filters are increasingly being introduced as ingredients in cosmetics. It is fundamental that all likely allergens are included in the patch test, and dermatologists should be aware of national differences in the formulations of products for particular populations. It is also necessary to continually update the patch test series according to changes in product formulation.

When considering cosmetic allergy, it is of foremost importance to include the patient’s own products in the testing. Most types of leave-on products (products that are meant to stay on the skin for a prolonged period of time, such as lotions, creams, sunscreens, makeup, and deodorants) can be patch tested “as-is,” but rinse-off products and products that contain obvious irritants (eg, shampoos, cleansers, bubble baths, toothpastes) need to be diluted. The appropriate dilution and the dilutional vehicle for each product should be estimated based on the product’s composition, solubility, and pH.¹⁴⁵ Other types of cosmetic products with volatile solvents (eg, hairsprays, mascara), can be patch tested “as-is,” but only after the product has been allowed to dry.¹²

The diagnosis of cosmetic allergy is usually based on a positive patch test; yet sometimes it can be based on a positive use test and/or repeated open application test (ROAT test).¹⁵ In a ROAT test, potentially allergenic leave-on products are applied twice daily to the upper arm on a marked 1 cm × 1 cm area for 7 days and evaluated for an eczematous skin reaction.¹⁴⁶ In a use test, a patient uses the suspected substance in the same way as when the dermatitis

developed,¹⁴⁷ for example, by applying a suspected facial cream to a small marked area (1 cm × 1 cm) on the face for 1 week. As with the ROAT test, if an eczematous skin reaction occurs during the test period, the test is considered positive. Both the ROAT test and the use test can also be helpful in determining clinical relevance of a particular patch test positive reaction. (Diagnostic pearls for cosmetic contact allergy are summarized in **Box 5**.)

General therapeutic strategy

Because allergen identification can be achieved through proper patch testing, there is a good potential for a sustained remission. Therefore identification and removal of the inciting agent (allergen avoidance) should always be the mainstay of treatment.¹⁴⁸

Waiting for patch testing, patients are helpfully provided with what Dr. K.A. Zug has coined the “Lo.C.A.L. (Low Contact Allergen) Skin Diet.” The Lo.C.A.L. Skin Diet consists of a list of topical products devoid of the most commonly identified contact allergens in patients with ACD, including fragrances, formaldehyde releasing preservatives, MCI/MI, MDGN/PE, lanolin, CAPB, and benzophenone-3. The list is short and does not eliminate all contact allergens; however, based on experience from interviewing and testing many allergic patients, the list does a good job eliminating the most common allergens.

Once patch testing has isolated the causal allergen(s), avoidance compliance generally requires the substitution of safe alternatives. A good tool to provide the patient with such safe alternatives is the Contact Allergen Replacement Database

(CARD).¹⁴⁹ The CARD was developed by James A. Yiannias, MD, at the Mayo Clinic in Scottsdale, Arizona, and consists of a regularly updated database with over 2000 over-the-counter and prescription personal care products available in the United States, which enables the creation of an individualized list of allergen-free products that the allergic patient can use. It has been shown that patients’ compliance rates of avoidance increase when the CARD is used.¹⁵⁰ Access to CARD is a benefit of membership in the ACDS.

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Box 5

Diagnostic pearls for cosmetic contact allergy

Persistent itching and swelling may be indicative of allergy versus solely cosmetic irritation.

Facial, eyelids, lips, and neck patterns of dermatitis should raise the suspicion of a cosmetic-related contact allergy.

Facial, eyelid, lip, and neck dermatitis can be caused by ectopic allergens.

Keep in mind the possibility of airborne and occupationally-related ACD to cosmetics.

In addition to screening series (including a routine and cosmetic tray), patients should be patch tested to their own cosmetics.

Both ROAT test and use test can be helpful when patch tests give negative results, or when the relevance of a positive reaction is in question.

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