



New and emerging cosmetic allergens

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Abstract Human skin is exposed to a large variety of cosmetic allergens. Most allergic contact dermatitis occurs after exposure to fragrance, preservatives, and hair dyes. Such reactions can often be occult. As a result, a high index of suspicion is needed in assessing the patient with facial or cosmetic dermatitis. This contribution looks at why such a large number of chemicals are in everyday usage, at how dermatologists monitor trends in allergy to cosmetics, and at a number of new and emerging allergens to consider in the assessment of suspected cosmetic allergy.

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Introduction

Allergic contact dermatitis (ACD) is a T-cell-mediated delayed-type hypersensitivity reaction that occurs upon a specific hapten challenge in previously sensitized individuals. The inflammatory response in classical ACD requires an initial sensitization phase as a result of hapten penetration of the epidermal skin barrier. This is followed by an elicitation phase that is responsible for the recruitment and activation of specific T cells at the site of the hapten skin challenge.¹

The importance of the stratum corneum barrier function, as well as the signalling pathways that allow keratinocyte proliferation and generation of proinflammatory factors, is increasingly recognized.² The association between filaggrin null mutations in ichthyosis vulgaris and atopic dermatitis,³ together with protease and lipid defects, highlights the primary role of barrier disruption in allowing increased access of environmental toxins, microbes, and allergens.

The clinical appearance of ACD can be very similar if not identical to other types of dermatitis. Redness, scaling, and

vesiculation can be present, with only the distribution giving a clue to an allergic etiology. Some allergens regularly produce clinically atypical reactions: acute facial swelling due to type IV hypersensitivity to the black hair dye paraphenylenediamine (PPD) is one of the most dramatic illustrations of how facial swelling may not always be a type I reaction.⁴

Human skin is exposed to a large variety of cosmetic allergens. Most ACD reactions occur after exposure to fragrance, preservatives, and hair dyes. Such reactions can often be occult. As a result, a high index of suspicion is needed in assessing the patient with facial or cosmetic dermatitis.⁵ A review of patients patch tested in the US reported that of women with a positive patch test reaction, 24% were due to a documented cosmetic source.⁶

So why is such a wide range of these potentially allergenic compounds necessary?

To improve usability for the consumer, cosmetics often have high water content. This leaves the preparation at a risk of being contaminated by pathogenic microorganisms such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Bacterial contamination can alter the composition of the

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product or pose a health risk to the consumer. To prevent this, preservatives, including biocides, are added to cosmetic products. Varying concentrations of the same preservative are found in related products, posing the question of whether some of these preparations are over-preserved. Because the development and elicitation of ACD is dose-dependent,⁷ over-preservation of cosmetics potentially leads to an increased incidence of contact allergy.⁸

By collating patch test databases, dermatologists can track changes in the incidence of ACD to specific cosmetic allergens. Legislation in Europe or the US restricting or outlawing the use of specific allergens occurs as a consequence of this data; however, it takes some time for these allergies to clinically manifest, so there is a lag period after the introduction of a new preservative and the clinical assessment of the resultant ACD.

As the use of a new agent increases, subsequent reports of allergy increase, legislation again decreases its use, and allergy decreases. This process is then repeated all over again for the replacement allergenic cosmetic chemical, a phenomenon known as the Dillarstone effect.⁹

Dermatologists respond to this dynamic situation by the addition of emerging contact allergens to standardized patch testing series. In the UK, allergens with an incidence of positive reactions greater than 1% are added to the British Contact Dermatitis Society (BCDS) standard series, to which nearly all patients are tested. Allergens with a lower prevalence of positive reactions (less than 1%) are included in additional specialized and specific series. This contribution reviews important new cosmetic allergens identified in the last few years and also those allergens that have reemerged due to their introduction into modern cosmetic products.

We searched Medline from February 1995 to February 2009 using the terms *allergic contact dermatitis*, *propolis*, *sodium metabisulfite*, *dicaprylyl maleate*, *benzophenone 4*, *Lyrar*, *limonene*, and *iodopropynyl butylcarbamate*.

Sodium metabisulfite

The sulfites are a ubiquitous group of chemicals. Sodium metabisulfite is present in food and drink as a preservative and antioxidant, where it is labelled as E223.¹⁰ In addition, it is found as a component of photographic chemicals, is used in rubber manufacture, in leather tanning, in mineral extraction, and as a bleaching agent in fabric treatments.¹⁰ Sodium metabisulfite is present in certain local anaesthetic preparations to prevent oxidation of adrenaline and has been described as causing local anesthetic reactions.¹¹

Initial investigations of the ability of sulfites to cause skin sensitization were inconclusive. A Danish study in 1992 described 1762 consecutive patients patch tested with sodium sulfite in addition to the standard battery. Although 25 (1.4%) were positive, the authors were frequently unable to elicit a history indicating the clinical relevance of the

positive result and therefore did not recommend continued testing.¹² Expanding on this work in 1994, an Italian group patch tested 2894 patients to potassium metabisulfite, sodium metabisulfite, and sodium sulfite. They found 50 patients (1.7%) were positive to both potassium metabisulfite and sodium metabisulfite, whereas only 2 patients were positive to sodium sulfite. Seven of the 50 who were positive to sodium metabisulfite were identified as having an occupational exposure, but again, only 5 of the remaining 43 positive results were thought to be clinically relevant.¹³

More recently, it has been noted that sodium metabisulfite is present in some ketoconazole-containing products, as well as in Trimovate® and Timodine® creams,¹⁴ and accounts for relevant positive results when ACD develops in patients while using these products.¹⁵ Sodium metabisulfite has now been identified as a component of cosmetic creams,¹⁴ hair colors, and bleaching agents, and in false tanning products.¹⁰ In 2007, a 6.8% patch test positivity to sodium metabisulfite was described in a consecutive series of 117 patients in Ireland.¹⁴ As a consequence of these high rates of allergy, sodium metabisulfite was incorporated into the BCDS standard series of allergens in 2007.

Propolis

Propolis is a resinous substance collected from poplars and processed by honeybees to use as a sealant to maintain the structure of the hive. It is a well-recognized cause of occupational contact dermatitis in apiarists.¹⁶ Propolis has a variable chemical composition and is regarded as a potent skin sensitiser.¹⁷ Cases of ACD to propolis began to emerge in the 1970s; indeed, Petersen predicted that cases of ACD to propolis would increase with the increasing use of propolis in self-medicating patients.¹⁸ Owing to its purported antibacterial and antiinflammatory properties, propolis is now contained in a number of “natural” over-the-counter products such as cough syrups, lozenges, shampoo, conditioner, lipsticks, lip balms, lotions, toothpastes, and cosmetics.¹⁹ The predicted increase in ACD appears to have occurred. Between 1997 and 2002, a Finish center observed an increase in positive patch test reactions to propolis from 0.5% to 1.4%.²⁰ Propolis became part of the standard battery in Germany and Austria in 2004, and an average of 3.5% positive reactions were observed.²¹ Propolis was therefore also included in the BCDS standard series in 2007.

Dicaprylyl maleate

Dicaprylyl maleate (DCM), also known as dioctyl maleate, is a good example of an emollient and solvent in which original chemical testing indicated that the compound did not cause ACD.²² Ten years after it was introduced into

cosmetic products, it has been found to cause ACD in selected patients. DCM has been used as an ingredient in fake tanning lotions, moisturizers, foundations, and sunscreens.²³ Recently, a series of 22 patients who were suspected of having DCM contact allergy were tested to both freshly manufactured DCM and deliberately aged DCM. Only eight patients did not have a positive DCM patch test, and of these eight, a positive reaction to the aged DCM developed in six.²² This phenomenon occurs with other contact allergens (see Limonene section) and is thought to occur due to chemical degradation (autoxidation) producing allergenic by-products.²⁴ Ironically this may be seen to support the cosmetic industry's argument for the increased use of further newer preservatives in cosmetic products. As a result of this study, Boots, a major UK cosmetic manufacturer, withdrew DCM from its product lines (personal communication from S Kirk, March 2009); however, we continue to see patients with ACD in our practice who are using DCM-containing products and developing ACD.

Benzophenone 4

Many facial moisturizers, make-up, and hair care products²⁵ now incorporate ultraviolet light (UV) filters to protect the skin against photoaging and also to protect the product itself from UV degradation to prolong shelf life. Historically, benzophenone 3 was widely used in sunscreen for its UVA filter properties. In a retrospective series of 2715 patients undergoing photopatch testing between 1983 and 1998, benzophenone 3 was the most common UV filter photoallergen.²⁶ Benzophenone 4 (2-hydroxy-4-methoxybenzophenone-5-sulphonic acid: sulisobenzene) is a chemical UVA filter whose spectrum of action extends into the UVB range.²⁷ For this reason, benzophenone 4 is increasingly being used in cosmetics. Benzophenone 3 and 4 do not appear to cross-react.²⁵ A 2005 UK multicenter group photopatch tested 1155 patients with a history of a photodermatitis or a history consistent with a sunscreen allergy. Benzophenone 3 and 4 were each responsible for 9% of contact allergic reactions.

Between 2003 and 2005, 553 patients with a history of facial dermatitis or a possible cosmetic contact allergy were tested to an extended facial/cosmetics series. Benzophenone 4 was one of the allergens, and 2.3% of patients had a relevant positive patch test to benzophenone 4. This prompted the authors to call for inclusion of benzophenone 4 in the facial/cosmetics series of patch test allergens.²⁷

Artificial fragrances

Considering the ubiquitous occurrence of fragrance materials, the risk of allergy is small. In absolute numbers,

however, fragrance allergy is common,²⁸ and the prevalence of ACD due to fragrance in the general population has been estimated as 1.8% to 4.2%.²⁹ Fragrance is the second most common cause of ACD after nickel.³⁰ The distribution is classically axillae, facial (including the eyelids) and neck, although well-circumscribed patches in areas of "dabbing-on" perfumes (wrists, behind the ears) and aggravation of hand eczema is also described. The degree of sensitivity and therefore severity of dermatitis varies considerably. In the worst cases, ACD to fragrance can cause disseminated dermatitis beyond the site of application and erythroderma. In addition, patients with profound sensitivity are affected by airborne or "connubial" fragrance usage.²⁸

The BCDS standard series of allergens contains an original mix of fragrance allergens (Fragrance Mix I) that was introduced in 1977. By the mid-1990s, it became apparent that this mix missed an estimated 15% of fragrance allergies.³¹ Between 2002 and 2003 a Fragrance Mix II was trialled.³² This mix consisted of Lylal, citral, farnesol, citronellol, α -hexyl-cinnamic aldehyde, and coumarin. Six centers tested 1701 patients, and 7 patients with a strong history of fragrance allergy were identified with Fragrance Mix II and not Fragrance Mix I. The number of false-positive results was also lower with Fragrance Mix II. As a result, Fragrance Mix II entered the BCDS British Standard series in 2007.

Lylal (hydroxyisohexyl 3-cyclohexene carboxaldehyde) bears a lilylike odor and is commonly used in deodorant, shampoo, soap, and fine fragrance.³³ European contact allergy rates to Lylal vary between 1.5% and 3%.^{34,35} This rate is much higher than the US rate of 0.4%,³⁶ possibly due to higher concentrations of Lylal in European deodorants.³⁴ As a result of its high rate of contact sensitization, Lylal has been included in the BCDS standard series both on its own, dissolved in 1% petrolatum, and as part of the new Fragrance Mix II.³⁴

Limonene is widely used as a fragrance in cosmetics. It is present as a component of certain essential oils (rosemary, peppermint, lemongrass, lavender, eucalyptus, and caraway) and in tea tree oil.³⁰ Owing to its solvent capacity, it is used in domestic cleaning products and also in industry as a metal degreaser, where it can occur in concentrations up to 95%.³⁷ Limonene first appeared for industrial use in the late 1980s and became widely used because it was regarded as more environmentally friendly than its organic solvent equivalents; however, on exposure to air it easily oxidizes to products with considerable sensitizing capacity, such as limonene oxide, *l*-carvone, and the limonene hydroperoxides.³⁸ A Swedish group patch tested 2800 patients to varying concentrations of fresh and aged *d*-limonene. The highest rate of contact allergy (5.1% of patients) was found when 5% *d*-limonene was exposed to air for 10 weeks.³⁸ More recently, a multicenter study patch tested consecutive patients with dermatitis to both *R*-limonene and *S*-limonene and found that 2.6% of patients reacted to one or both preparations.³⁰

Iodopropynyl butylcarbamate

Iodopropynyl butylcarbamate (IPBC) is a biocide originally developed for use in an industrial context, initially in metalworking and subsequently as a wood preservative, where concentrations of up to 4% are permitted.³⁹ ACD to IPBC in these industrial settings is well described.⁴⁰ In a series of 251 German metalworkers with suspected ACD, 0.5% had a positive reaction to IPBC.⁴¹ Because of its usefulness as a biocide, IPBC has more recently been incorporated into cosmetic products and cleansing wipes,⁴² where the maximum permitted concentration is 0.1%. Reports of ACD appeared only a few years after it was introduced as a cosmetic ingredient.⁴³

Although IPBC is only thought to be weakly allergenic, it is a small lipophilic molecule that may readily penetrate the skin,⁴⁴ and as reports of ACD from IPBC exposure in cosmetics have increased, it is now incorporated into the Cosmetic Series of patch test allergens.

Conclusions

Contact allergy is an ever-changing area of dermatology due to the evolving nature of the chemical, and more specifically, cosmetics industry. Links between dermatology and industry have become increasingly important to allow early identification of allergenic compounds and to enable patch testing of chemicals not yet commercially available. Links between dermatologists and legislators have strengthened significantly,⁸ especially in the European Community. This has led to the publication of the European Community Cosmetics Directive.⁴⁵ In 2004, this dynamic legislation mandated the publication of ingredients on all cosmetics products. This has made it significantly easier for consumers and their physicians to identify and avoid the ever-increasing numbers of allergenic chemicals added to cosmetics and applied to the skin. ACD due to cosmetics can be occult and has a variable and sometimes dramatic clinical presentation, including acute facial swelling. Owing to improved product labelling, it should now be possible for patients to avoid the causative allergens identified on patch testing.

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