

'New' contact allergens

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Purpose of review

Due to the continuously changing environmental conditions, it is necessary to regularly monitor and update the spectrum of contact allergens that elicit contact dermatitis. New contact allergens and known contact allergens with currently increasing importance need to be identified for diagnostic and preventive purposes.

Recent findings

Within the last few years, allergic contact allergy to a number of substances derived from plants and other materials was reported for the first time. Furthermore, it has become obvious that dyes, especially paraphenylenediamine-related dyes, and fragrances are sources of contact allergens with increasing frequency. It is likely that within these groups of substances some as yet unidentified agents are relevant allergens.

Summary

It is an ongoing challenge for clinicians to meticulously explore the exposure of eczema patients to possible new allergens. Dyes and fragrances, in particular, are of increasing significance not only because of their known ingredients but also because of new allergenic compounds.

Keywords

cosmetics, dyes, fragrances, medicaments, paraphenylenediamine, plants

Introduction

Contact sensitization may occur in susceptible individuals following appropriate exposure to potential contact allergens. The clinically relevant spectrum of contact allergens keeps changing due to the emergence of new allergenic substances and to changing exposure to known contact allergens. This review will cover both of these aspects but it will concentrate on issues that are likely to attain a more general importance in the future.

Recently detected allergens

Nature, with its plants and other materials, is still a source of allergens that have not previously been identified. Miconidin and miconidin methyl ester were isolated from *Primula obconica*. Miconidin 0.01% in petrolatum and miconidin methyl ether 0.1% in petrolatum showed positive patch test reactions in patients sensitive to primin [1]. Parthenolide was identified as a compound of feverfew that can be distributed via volatile particles and elicit airborne contact dermatitis [2]. Triethanolamine polyethylene glycol-3 (TEA-PEG-3) cocamide sulphate was found to be an allergenic compound of coconut oil [3].

Cosmetics are complex formulations with various ingredients, and recently, attention has been drawn to copolymers. Copolymers are composed of two different types of monomers. Constituents like polyvinylpyrrolidone/hexadecane copolymer and other copolymers with and without polyvinylpyrrolidone are important ingredients of cosmetics because they help to define the consistency of a formulation. Due to their high molecular weight, they are usually not considered to be likely contact allergens, but they are widely used and can cause unexpected allergic reactions [4]. Further unexpected allergenic compounds of cosmetics (facial creams, moisturizers, shampoos, gels, etc.) are hydrolysed wheat proteins. Hydrolysed wheat proteins can induce immediate allergic reactions like urticaria or even anaphylaxis when applied to the skin of sensitized individuals [5]. Luckily, normal wheat proteins do not cross-react with such hydrolysates, and bread can be consumed without adverse reactions by individuals sensitized to wheat hydrolysates.

Many substances in topical formulations can induce contact sensitization. Fusidic acid has been found to be a rare sensitizer, but a recent report [6] illustrates that systemic contact dermatitis can occur in individuals following oral therapy with this antibiotic after preceding topical treatment with fusidic acid. Similarly, triclosan has now been recognized as a possible allergen [7], and

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due to the widespread use of this antibacterial agent, more allergic reactions can be expected in the future. Despite its nature as an immunosuppressive agent, pimecrolimus can also cause contact allergy by topical application [8,9]. Some chemical ultraviolet filters have long been known as contact allergens, and benzophenone 4 may need special attention in the future [10].

Paraphenylenediamine and related dyes

Paraphenylenediamine is certainly not a new substance or one that was only recently detected as an allergen, but the current literature provides evidence that its importance as a contact sensitizer is increasing considerably [11]. A rising rate of paraphenylenediamine patch test frequency and a continuously high proportion of positive reactions were found in a study from London [12[•]]. The authors discuss the use of permanent hair dyes as a likely explanation; hair dyes were previously found to be common sensitizers in Denmark [13]. Paraphenylenediamine was also identified as the relevant allergen in a permanent eyelash dye [14]. Not surprisingly, paraphenylenediamine was found to be the leading contact allergen in hairdressers with hand dermatitis [15], and in a prospective study the application of PPD-containing hair dyes was shown to result in an unacceptably high percentage of sensitization in users as well [16^{••}]. The observation that after repeated application of 0.3% paraphenylenediamine to the same skin area, it can accumulate at this site [17] may be of practical relevance for future usage limitations. 'Black henna' can be a source of paraphenylenediamine; the substance is added to this henna formulation because of its properties to darken the colour. If used for tattoos, paraphenylenediamine can trigger severe bullous contact dermatitis [18]. Finally, it is really alarming that even children can suffer from allergic reactions to hair dyes severe enough to require hospitalization [19] and that immediate hypersensitivity to paraphenylenediamine can occur [20]. In addition to paraphenylenediamine, other ingredients of hair dyes appear to be good sensitizers as well [21–23], leading to the suggestion of a special hair dye patch test series [24]. It was shown that a 24 h patch test with an appropriate hair dye reliably elicits a positive reaction in paraphenylenediamine-sensitized individuals [25]. Users of oxidative hair dyes are not only exposed to the dye itself but also to considerable amounts of precursors and couplers that are ingredients of the hair dye formulations. The amounts of such substances that remain unconsumed after the developments of the dyes are sufficient to trigger allergic reactions as well [26].

It is noteworthy in this context that, compared with other patch test allergens, paraphenylenediamine often causes late reactions that may indicate active sensitization [27,28[•]]. The threshold value to elicit a positive paraphenylenediamine reaction in 10% of persons who pre-

viously had at least a weak positive patch test reaction to paraphenylenediamine was 38 ppm, which is well below concentrations permitted for hair dyes [24]. It must be discussed whether the commonly used patch test concentration of paraphenylenediamine (1% in petrolatum) is safe [29] or needs to be redefined [30].

Allergic reactions to textile dyes were found in patients with eczema of arms, face, neck and axillary folds [31,32]. In a study from Sweden [31], patch tests with a textile dye mixture in consecutive patch test patients gave positive reactions in 1.5%, which is similar to the frequency observed in southern Europe.

Fragrances

Fragrances undoubtedly are very common allergens and obviously they still continue to gain importance as contact allergens. Fragrances now belong to the most frequent problematic allergen types in topical medicaments used by elderly patients [33[•]]. There is reason to be aware of the possibility that well known fragrance allergens are increasingly substituted by other perfume constituents that do not belong to the 26 agents that have to be declared as ingredients in Europe [34]. Concentration of fragrances in perfumes may even be higher than considered safe by the EU Scientific Committee [35^{••}]. The importance of new fragrances is supported by the high frequency of positive patch test reactions to the recently introduced fragrance mix II (FM II) [36,37], which is still increasing in 2007 (A. Schnuch, for the Information Network of Dermatological Clinics in Germany, personal communication). Due to the rapidly changing compositions of perfumes, it is advisable to test the patient's own perfumes. This can lead to the detection of allergens that otherwise would be missed [38[•]]. Correspondingly, a study from North America revealed that with the fragrance mix and balsam of Peru alone, sensitizations to, for example, jasmine absolute, ylang ylang oil or lylal are missed that can cause relevant problems [39].

Oxidized limonene was found to elicit positive patch test reactions in 2.6% of dermatitis patients in a European study, leading to the suggestion to screen dermatitis patients with oxidized limonene [40]. Modified colophonium derivatives like glyceryl rosinat should be considered as a cause of allergic contact dermatitis in cases suggestive of colophonium-related reactions and negative colophonium tests [41]. Although positive reactions to balsam of Peru often indicate fragrance allergy, there are many perfume oils that do not cross react with this mixture but can trigger allergic reactions in exposed individuals [42]. Extracts of Peru balsam are used in perfumeries that contain different constituents depending on the technique of preparation [43]. Lichen acids

like D-usnic acid were detected as relevant allergens in natural deodorants [44].

Conclusion

The spectrum of contact allergens that have a high relevance with regard to the general population shifts more and more from industrial chemicals to ingredients of cosmetic and medical products. Legislative regulations and preventive measures limit the contact with sensitizers via industrial processes, and the relevance of industrial sensitizers is mostly restricted to very limited groups of persons. In contrast, the use of cosmetics is increasingly widespread and many cosmetics and medical formulations are by intention stay-on products that are directly applied to the skin. Due to this intensive exposure, even ingredients with a rather moderate sensitizing potential need to be considered.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 455).

- 1 Paulsen E, Christensen LP, Andersen KE. Miconidin and miconidin methyl ether from *Primula obconica*: new allergens in an old sensitizer. *Contact Dermatitis* 2006; 55:203–209.
- 2 Paulsen E, Christensen LP, Andersen KE. Compositae dermatitis from airborne parthenolide. *Br J Dermatol* 2007; 156:510–515.
- 3 Shaffer KK, Jaimes JP, Hordinsky MK, *et al.* Allergenicity and cross-reactivity of coconut oil derivatives: a double-blind randomized controlled pilot study. *Dermatitis* 2006; 17:71–76.
- 4 Quartier S, Garmyn M, Besacrt S, Goossens A. Allergic contact dermatitis to copolymers in cosmetics: case report and review of the literature. *Contact Dermatitis* 2006; 55:257–267.
- 5 Laurière M, Pecquet C, Bouchez-Mahiou I, *et al.* Hydrolysed wheat proteins present in cosmetics can induce immediate hypersensitivities. *Contact Dermatitis* 2006; 54:283–289.
- 6 De Castro Martinez FJ, Ruiz FJ, Tornero P, *et al.* Systemic contact dermatitis due to fusidic acid. *Contact Dermatitis* 2006; 54:169.
- 7 Campbell L, Zirwas MJ. Triclosan. *Dermatitis* 2006; 17:204–207.
- 8 Saïtta P, Brancaccio R. Allergic contact dermatitis to pimecrolimus. *Contact Dermatitis* 2007; 56:43–44.
- 9 Shaw DW, Maibach HI, Eichenfield LF. Allergic contact dermatitis from pimecrolimus in a patient with tacrolimus allergy. *J Am Acad Dermatol* 2007; 56:342–345.
- 10 Hughes TM, Stone NM. Benzophenone 4: an emerging allergen in cosmetics and toiletries? *Contact Dermatitis* 2007; 56:153–156.
- 11 DeLeo VA. P-Phenylenediamine. *Dermatitis* 2006; 17:53–55.
- 12 Patel S, Basketter DA, Jefferies D, *et al.* Patch test frequency to p-phenylenediamine: follow up over the last 6 years. *Contact Dermatitis* 2007; 56:35–37. This paper nicely demonstrates the increasing importance of paraphenylenediamine.
- 13 Sosted H, Hesse U, Menné T, *et al.* Contact dermatitis to hair dyes in a Danish adult population: an interview-based study. *Br J Dermatol* 2005; 153:132–135.
- 14 Teixeira M, de Wachter L, Ronsyn E, Goossens A. Contact allergy to paraphenylenediamine in a permanent eyelash dye. *Contact Dermatitis* 2006; 55:92–94.
- 15 Laing ME, Powell FC, O'Sullivan D, *et al.* The influence of contact dermatitis on career change in hairdressers. *Contact Dermatitis* 2006; 54:218–219.
- 16 Basketter DA, Jefferies D, Safford BJ, *et al.* The impact of exposure variables on the induction of skin sensitization. *Contact Dermatitis* 2006; 55:178–185. This study gives alarming evidence of the sensitization to paraphenylenediamine by use of paraphenylenediamine-containing hair dyes.
- 17 White JML, Basketter DA, Pease CK, *et al.* Intermittent exposure to low-concentration paraphenylenediamine can be equivalent to single, higher-dose exposure. *Contact Dermatitis* 2007; 56:262–265.
- 18 Jung P, Seszak-Greinhecker G, Wantke F, *et al.* A painful experience: black henna tattoo causing severe, bullous contact dermatitis. *Contact Dermatitis* 2006; 54:219–220.
- 19 Sosted H, Johansen JD, Andersen KE, Menné T. Severe allergic hair dye reactions in 8 children. *Contact Dermatitis* 2006; 54:87–91.
- 20 Birnie AJ, English JS. Immediate hypersensitivity to paraphenylenediamine. *Contact Dermatitis* 2007; 56:240.
- 21 White IR. Second cite: contact allergy to hair dyes is a well recognized problem. *Clin Exp Dermatol* 2006; 31:724–726.
- 22 Sosted H, Menné T, Johansen JD. Patch test dose–response study of p-phenylenediamine: thresholds and anatomical regional differences. *Contact Dermatitis* 2006; 54:145–149.
- 23 Hillen U, Grabbe S, Uter W. Patch test results in patients with scalp dermatitis: analysis of data of the Information Network of Departments of Dermatology. *Contact Dermatitis* 2007; 56:87–93.
- 24 Sosted H. Hair dye epidemiology in general population and diagnostics. *Contact Dermatitis* 2006; 55 (Suppl 1):24.
- 25 Jowsey IR, Basketter DA, McFadden JP, *et al.* Elicitation response characteristics to permanent hair dye in paraphenylenediamine-allergic volunteers. *Contact Dermatitis* 2006; 55:330–334.
- 26 Rastogi SC, Sosted H, Johansen JD, *et al.* Unconsumed precursors and couplers after formation of oxidative hair dyes. *Contact Dermatitis* 2006; 55:95–100.
- 27 Aalto-Korte K, Alanko K, Kuuliala O, Jolanki R. Late reactions in patch tests: a 4-year review from a clinic of occupational dermatology. *Contact Dermatitis* 2007; 56:81–86.
- 28 Hillen U, Jappe U, Frosch PJ, *et al.* Late reactions to patch-test preparations • para-phenylenediamine and epoxy resin: a prospective multicentre investigation of the German Contact Dermatitis Group. *Br J Dermatol* 2006; 154:665–670. A prospective study that highlights the possibility of sensitization to paraphenylenediamine by patch testing.
- 29 Gawkrödger DJ, English JSC. How safe is patch testing to PPD? *Br J Dermatol* 2006; 154:1025–1027.
- 30 Becker D, Mahler V, Szliska C, *et al.* The concentration of paraphenylenediamine (PPD) for routine patch testing in a standard series needs to be redefined. *Contact Dermatitis* 2005; 53:186–187.
- 31 Ryberg K, Isaksson M, Gruvbrger B, *et al.* Contact allergy to textile dyes in southern Sweden. *Contact Dermatitis* 2006; 54:313–321.
- 32 Hausen BM. The red lady. *Akt Dermatol* 2006; 32:527–533.
- 33 Green CM, Holden CR, Gawkrödger DJ. Contact allergy to topical medicaments becomes more common with advancing age: an age-stratified study. • *Contact Dermatitis* 2007; 56:229–231. This study shows that topical medicaments become more and more important as sensitizers in older patients.
- 34 Cox P, Chrisochoidis M. Directive 2003/15/EC of the European Parliament and the Council of 27 February 2003. *Official J European Union* 2003; L66:26–35.
- 35 Rastogi SC, Johansen JD, Bossi R. Selected important fragrance sensitizers in perfumes: current exposures. *Contact Dermatitis* 2007; 56:201–204. This analysis of fragrances proves that important fragrance sensitizers can occur in higher concentrations than approved by legislation.
- 36 Frosch PJ, Pirker C, Rastogi SC, *et al.* Patch testing with a new fragrance mix detects additional patients sensitive to perfumes and missed by current fragrance mix. *Contact Dermatitis* 2005; 52:207–215.
- 37 Frosch PJ, Rastogi SC, Pirker C, *et al.* Patch testing with a new fragrance mix: reactivity to the individual constituents and chemical detection in relevant cosmetic products. *Contact Dermatitis* 2005; 52:216–225.
- 38 Uter W, Geier J, Schnuch A, Frosch P. Patch test results with patient's own • perfumes, deodorants and shaving lotions: results of the IVDK 1998–2002. *J Eur Acad Dermatol Venereol* 2007; 21:374–379. This paper highlights that patch testing with patients' materials is needed to detect individual sensitization.
- 39 Belsito DV, Fowler JF, Sasseville D, *et al.* Delayed-type hypersensitivity to fragrance materials in a select North American population. *Dermatitis* 2006; 17:23–28.
- 40 Matura M, Sköld M, Börje A, *et al.* Not only oxidized R-(+)- but also S-(–)-limonene is a common cause of contact allergy in dermatitis patients in Europe. *Contact Dermatitis* 2006; 55:274–279.

- 41** Pereira TM, Flour M, Goossens A. Allergic contact dermatitis from modified colophonium in wound dressings. *Contact Dermatitis* 2007; 56: 5–9.
- 42** Schubert H. Skin disease in workers at a perfume factory. *Contact Dermatitis* 2006; 55:81–83.
- 43** Api AM. Only Peru Balsam extracts or distillates are used in perfumery. *Contact Dermatitis* 2006; 54:179.
- 44** Sheu M, Simpson EL, Law SV, Storrs FJ. Allergic contact dermatitis from a natural deodorant: a report of 4 cases associated with lichen acid mix allergy. *J Am Acad Dermatol* 2006; 55:332–337.