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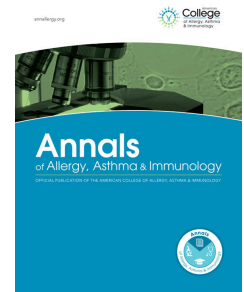
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Clinically Relevant Contact Allergens in the Modern Era

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Introduction

The field of contact dermatitis is constantly evolving, influenced by trends in industrial practices and consumer behaviors. The general population is exposed to hundreds of natural and synthetic chemicals each day. A single perfume, for example, may include up to 100 different chemicals. Many chemicals elicit irritant or allergic contact dermatoses (ACD) in susceptible hosts, which in turn may cause significant emotional, social, economic, and occupational impacts.

There are many clinically relevant contact allergens, however trends in their prevalence oscillate by region and over time as industrial, occupational, and consumer patterns of use shift. Certain allergens have remained highly prevalent causes of contact dermatitis for decades including nickel, the most common allergen positive on patch testing worldwide. Others have emerged as relatively newer sensitizers. Cobalt, for example, has surfaced as an increasingly important metal allergen, ranking within the top 20 allergens of 2018. This article aims to highlight noteworthy and clinically relevant allergens.

Preservatives

Preservatives protect against microbial growth in food, cosmetic, and industrial products. As a group, preservatives are highly allergenic, representing 5 of the top 20 allergens in North America (Table 1).¹ Preservatives have instigated several “contact allergy epidemics,” starting with formaldehyde’s introduction into textiles and cosmetic products in the 1950s. Formaldehyde lead to sensitization rates as high as 9% among patients undergoing patch testing, the gold standard for diagnosing ACD. Formaldehyde-releasing

preservatives (FRPs)—such as quaternium 15 and diazolidinyl urea—are relatively less carcinogenic and allergenic than formaldehyde, but widespread use has led to a parabolic rise and fall in sensitization rates over the past decades.

Among *non*-formaldehyde preservatives, rising sensitization rates have been observed for methylchloroisothiazolinone (MI), iodopropynyl butylcarbamate (IPBC), and methyldibromoglutaronitrile (MDGN). Notably, use of MI alone (without methylchloroisothiazolinone – Kathon) has increased substantially in personal care products.² Because MI alone is a less effective antimicrobial agent than MI/MCI in combination, industrial and cosmetic products incorporate it at higher (and more potentially sensitizing) concentrations. The number of MI-only-containing cosmetic products doubled between 2007 and 2010,² including MI-containing moist toilet papers and makeup remover wipes, leading to a wave of perianal and eyelid dermatitis, respectively. MI now dominates as the leading preservative contact allergen, and the second most prevalent positive patch test allergen in North America (after nickel).¹ Patch testing for MCI/MI as a pair leads to a high rate of false negatives; patch testing MI alone at its higher concentration (eg 0.2%) is necessary to detect an allergy.³

Parabens

Parabens represent another preservative family, favored for being inexpensive, odorless, and colorless. Parabens are the least sensitizing preservatives, with uncommon rates of ACD, ranging from 0.6% to 2.3% in over 25 years of NACDG patch testing data.⁴ Despite decades of safety data, many consumers have adopted a curious paraben fear prompted by negative media attention that parabens are dangerous “endocrine

disruptors.” While parabens have demonstrated weak estrogenic activity *in vitro* and in animal models, human and population studies have failed to demonstrate a convincing risk of endocrine disruption, infertility, or carcinogenesis to date, however intensive toxicology studies are still underway. Nonetheless, “paraben-free” products have become a consumer preference. Unfortunately, the preservative ingredients serving as parabens’ replacements, such as MI, are more potent sensitizers. This controversy led to parabens being named the American Contact Dermatitis Society’s “**non**-allergen” of the year in 2019.⁴

Fragrances

Fragrances are natural and synthetic chemicals with odor-enhancing or blending properties. Fragrance additives are commonplace in food, industrial, clothing, and personal care products. Owing to ubiquitous use, fragrances are a leading cause of positive patch tests in the North American general population, but the most common cause of ACD among cosmetic product consumers. Positive patch tests to fragrances can be noted in 4-5% of the general population, particularly middle-aged females. Sensitization rates are highest for consumers of leave on products such as antiperspirant, eye shadow, and face creams.⁵

Two increasingly relevant fragrance allergens are linalool and limonene, which offer a fresh, flowery, or citrus odor. Linalool is detectable in 88% of essential oils, including lavender, ylang-ylang, and rosemary oils.⁶ D-Limonene is a major constituent of citrus peel and tea tree oils. Both are weakly allergenic in their inert forms, but can oxidize into

potent, allergenic hydroperoxides upon exposure to air.⁷ This is a relevant concern given their use in cosmetic fragrances, which are dispensed to the skin via aerosolization.

Available patch testing screening panels such as fragrance mix I, fragrance mix II, *Myroxylon pereirae* (balsam of Peru), and colophony fail to detect more than half of patients with sensitivities to linalool and D-limonene. Recognizing this limitation, both linalool and D-limonene have been added to expanded patch test series, including an oxidized preparation.

Surfactants

Surfactants are a group of chemicals prevalent in leave-on and rinse-off cosmetics, aiding in removal of skin debris such as sebum, oil, and dirt. Cocamidopropyl betaine (CAPB) surfaced as a common contact allergen in the 1980s, particularly among hairdressers. Use of CAPB has waned in recent years, as has the rates of positive patch tests. In its place, the surfactant group alkyl glucosides have become increasingly popular. Made from condensation of glucose and alcohols, alkyl glucosides are a favored surfactant additive in ecofriendly, “natural” consumer products, owing to their botanic origins and biodegradable properties. Though alkyl glucosides are milder than other surfactants (such as sodium lauryl sulfate and sodium laureth sulfate), their revived use due to increasing consumer focus on nature-derived products has prompted a slight but steady raise in sensitization rates; they were named the ACDS Allergen of the Year in 2017.⁸

Acrylates

Acrylates are a class of synthetic plastics and resins found in medical devices (dental implants, contact lenses, bone cement, surgical glues), aesthetics (nail lacquers, eyelash and hair extensions), and industrial products (Plexiglass, fiberglass, plastics, glues, adhesives, paints). Acrylates' incorporation into artificial nails and nail lacquers, have lead to an increasing burden of acrylate contact allergy among nail technicians and consumers, manifesting as hand eczema, nail changes, and finger tip paresthesias.

Isobornyl acrylate (IBOA) is a newly emerging acrylate allergen,⁹ identified in adhesives of increasingly popular diabetes devices. Such wearable devices are adhered to diabetics' skin for prolonged periods of time; subcutaneous sensors allow for more accurate glucose monitoring and, in some cases, serve a dual function as insulin pumps. IBOA contact allergy from these devices is increasingly described in the literature. Sensitized patients are often precluded from using this otherwise advanced technology.

Propylene Glycol

Propylene glycol (PG) is a synthetic, colorless alcohol offering emollient, antimicrobial, solvent, and emulsifying properties. PG is incorporated into many cosmetic and personal hygiene products, medications, foods, and, more recently, electronic cigarettes. Increasing PG sensitization rates have paralleled its expanded use, with sensitization rates ranging from 0.8% to 3.5%, depending on the patch testing concentration (ie, 10% vs 30%).¹⁰ PG contact dermatitis most often occurs on the face, and systemic reactions have been reported.

Conclusion

Contact dermatitis trends are constantly in flux, mirroring the fluctuations in industrial, occupational, and consumer habits. Every year, many newly described contact allergens are reported and are often found in cosmetics and personal care products. Successful diagnosis and treatment of contact dermatitis relies on awareness of relevant emerging allergens, and including them on diagnostic patch tests.

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Allergen Rank	Allergen Name
1	Nickel 2.5%
2	Methylisothiazolinone 2000ppm [§]
3	Fragrance mix I*
4	Formaldehyde 2% [§]
5	Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI) [§]
6	Balsam of Peru*
7	Neomycin
8	Bacitracin
9	Formaldehyde 1% [§]
10	4-Phenylenediamine (PPD) 1%
11	Cobalt
12	Fragrance mix II*
13	Carba mix
14	Lanolin/Amerchol 50%
15	Propylene glycol 100%
16	Iodopropynyl butylcarbamate [§]
17	Cinnamic aldehyde*
18	Quaternium 15 [§]
19	Oleamidopropyl dimethylamine
20	Methyldibromoglutaronitrile (MDBGN)/phenoxyethanol [§]

Table 1. Top 20 positive patch test contact allergens from the North American Contact Dermatitis Group Patch Test Results: 2015-2016 (published December 2018)¹

*Fragrances

§Preservatives

Abbreviations: PPM, parts per million