

Contact Dermatitis

Emerging Trends



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KEYWORDS

- Allergic contact dermatitis • Irritant contact dermatitis • Contact allergen • Patch testing
- Surfactants • Preservatives • Acrylates • Fragrances

KEY POINTS

- Contact dermatitis is a commonly encountered diagnosis in dermatology.
- Trends in allergic contact dermatitis are influenced by industrial practices and consumer behaviors.
- Successful diagnosis of contact dermatitis relies on awareness of existing trends and relevant allergens.
- There are many emerging contact allergens, including surfactants such as alkyl glucosides, the fragrances linalool and D-limonene, the preservative methylisothiazolinone, the metal cobalt, and propylene glycol.

INTRODUCTION

Contact dermatitis is a commonly encountered diagnosis in dermatology. Exposure to the natural and synthetic chemicals of everyday life, whether from consumer products, occupational settings, or personal diversions, can trigger a variety of irritant or allergic eruptions in susceptible hosts. Cutaneous manifestations of contact dermatitis depend on the chemical, the duration and nature of contact, and the susceptibility of the exposed individual. Awareness of emerging chemicals is essential to the successful diagnosis of allergic and irritant contact dermatoses, which are prevalent conditions that confer significant emotional, social, economic, and occupational burdens.

Trends in allergen exposure are constantly evolving and can vary by region. Although some allergens' clinical importance escalates over time, others become less relevant due to decreased usage. Certain allergens continue to dominate the list of most common offenders: nickel remains the most common allergen positive

on patch testing worldwide. Industrial settings and consumer goods frequently introduce new chemicals, such as methylisothiazolinone, resulting in shifts in allergen exposure and sensitization. Diligent observation of these trends allows dermatologists to identify new, relevant contact irritants and allergens.

The realm of contact dermatitis is complex. This article aims to distill the most recent and noteworthy trends within the field, organized by allergen category, with particular attention to newer and/or controversial allergens.

SURFACTANTS

Surfactants reduce the surface tension of proteins and lipids of the stratum corneum, aiding in removal of skin debris such as sebum, oil, and dirt. These properties of surfactants are used in a variety of leave-on and rinse-off cosmetics, including shower gels, shampoos, moisturizers, sunscreens, deodorants, mousses, fragrances, and baby wipes, among many other products.

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Although rinse-off products have transient contact with the skin, certain components can bind strongly to the stratum corneum and trigger irritation or allergy.

Increased attention to surfactants’ sensitizing potential was noted in 2004, when cocamidopropyl betaine (CAPB) was declared the American Contact Dermatitis Society (ACDS) allergen of the year (Table 1).¹ CAPB, well known for its use in many baby and gentle shampoos, is incorporated into many consumer products including body washes, toothpastes, makeup removers, and contact lens solutions. Cases of contact allergy from CAPB emerged as early as 1983; however, later studies suggested that the contaminants of CAPB, namely dimethylaminopropylamine and amidoamine, were largely to blame.²

More recently, alkyl glucosides, a botanic and biodegradable family of relatively gentle surfactants, have been “rediscovered,” becoming increasingly popular in ecofriendly consumer products.^{3,4} With this, increased rates of sensitization to surfactants have been observed. Alkyl glucoside became allergen of the year in 2017.⁵

Although alkyl glucoside has been available for more than 40 years, its use has burgeoned over the last 2 decades. Alkyl surfactants are derived from the condensation of renewable, biodegradable, and plant-based ingredients such as palm,

coconut, and rapeseed oil (which provide fatty alcohols) and corn, wheat starch, and potato (which provide glucose). They have been incorporated into numerous consumer products, which tout its natural appeal. Beyond their environmental allure, alkyl glucosides are also milder, more stable, and require lower concentrations for efficacy compared with other surfactants.

Although alkyl glucosides are generally considered to be of low irritancy and allergenicity, particularly when compared with the more irritating anionic surfactants sodium lauryl sulfate and sodium laureth sulfate, their increased use has sparked an increase in sensitization. Goossens and colleagues⁶ reported the first 2 cases of contact allergy to alkyl glucosides found in cosmetic and cleansing products in 2003.

Decyl glucoside is a “hidden” allergen in the sunscreen ingredient Tinosorb M (which is not yet approved for use in the United States by the Food and Drug Administration [FDA]). In 2011, the Voluntary Cosmetic Registration Program database reported that decyl glucoside was an ingredient in 492 cosmetics, mainly rinse-off products.⁷ As a result of increased reports of sensitivity to decyl glucoside, it was introduced to the North American Contact Dermatitis Group (NACDG) standard patch testing series in 2009, at a 5% concentration in petrolatum. The rate of positive patch test reactions to decyl glucoside has increased from 1.3% in 2014 to 2.2% in 2016.⁴ Patch testing for such surfactants can prove challenging, because they are tested at irritant concentrations. Strong positive reactions are thought to reflect actual sensitization.

ACRYLATES

Acrylates are a class of glues, adhesives, synthetic plastics, and resins that are used in innumerable products owing to their durable and inert properties. Plexiglass, a transparent safety glass made of polymethyl methacrylate, is a well-known example of an acrylate. Acrylates are found in medical devices (dental implants/prosthesis, contact lenses, bone cement, wound dressings, and surgical glues), aesthetics (eyelash and hair extensions, nail lacquers), and industrial products (plastics, glues, adhesives, paints, printing inks, and fiberglass).⁸

Acrylates are derived from acrylic or methacrylic acid monomers, which are potently volatile irritants and sensitizers. Once the unstable acrylate monomers polymerize (either spontaneously or on ultraviolet light exposure), they become more innocuous. Although acrylate hypersensitivity is relatively uncommon, it is an important cause of

Table 1 American Contact Dermatitis Society allergens of the year	
2018	Propylene glycol
2017	Alkyl glucosides
2016	Cobalt
2015	Formaldehyde
2014	Benzophenones
2013	Methylisothiazolinone
2012	Acrylate
2011	Dimethyl fumarate
2010	Neomycin
2009	Mixed dialkyl thiourea
2008	Nickel
2007	Fragrance
2006	p-Phenylenediamine
2005	Corticosteroids
2004	Cocamidopropyl betaine
2003	Bacitracin
2002	Thimerosal
2001	Gold
2000	Disperse blue dyes

Data from Refs.^{3,58,70}

contact dermatitis. The earliest case reports of contact dermatitis to acrylates first appeared in the 1940s, when Stevenson and Moody each reported a case of occupational contact dermatitis in a dental technician.^{9,10}

Historically, contact dermatitis from acrylates, particularly methyl methacrylate, was focused within occupational settings, including dentistry, orthopedic surgery, aeronautics, and printing industries.¹¹ However, the incorporation of acrylates in cosmetic products, particularly artificial nails, “shellac,” lacquers, and related items, has led to a shift in acrylate sensitization to beauticians and artificial nail consumers.^{12,13} A recent 2018 study by Gonçalves and colleagues¹⁴ demonstrated that 67.3% cases of positive patch test reactions to acrylates were attributable to nail aesthetics. Another group reported nails to be the culprit in 85.2% of positive tests among 54 patients.¹⁵

Nail technicians and consumers are at especially high risk for acrylate sensitization because they are directly exposed to (meth)acrylate in their unstable monomer form (before being stabilized by ultraviolet light exposure). Nail-related allergic contact dermatitis (ACD) from acrylates typically manifests as hand eczema, often with periungual involvement. Onycholysis, onychodystrophy, and fingertip paraesthesias can also be seen.¹³ Ectopic areas of involvement on the face and arms may result from airborne exposure to dust generated by nail sculpting, evaporation of acrylate monomers, or by transfer from contaminated surfaces or hands.¹¹

Patch testing for acrylates can be difficult, as the acrylate preparations are volatile and may evaporate from the chamber during storage, reducing patch test concentrations at the time of testing, which can lead to false-negative results.^{8,16,17} When patch tested, acrylate-allergic patients often display multiple positive tests, representing either cross-reactions or the presence of impurities not disclosed in material safety data sheets. The NACDG standard series includes methyl methacrylate, ethyl acrylate, and 2-hydroxyethyl methacrylate, which collectively seem to be sufficient for screening allergens in most cases.¹⁷ However, clinicians should remain vigilant for acrylate allergy even if initial screening is negative and consider an expanded panel of test chemicals, including ethyl acrylate, ethylene dimethacrylate, triethylene glycol diacrylate, and ethyl cyanoacrylate. Protective measures such as using gloves can be helpful; however, (meth)acrylates can permeate glove material even after brief exposure. Nitrile gloves confer better protection than latex.¹⁸ Of note, absorbent dressings and wound care products

have also been implicated as a newly emerging source of (meth)acrylate contact dermatitis.¹⁹

FRAGRANCES

Fragrances, a group of naturally derived and synthetic chemicals defined by their odor-enhancing or odor-blending properties, are incorporated into numerous food, industrial, clothing, cosmetic, and hygienic products.^{20,21} Although relatively innocuous chemicals overall, fragrances are the second most common cause of positive patch test results in the general population, after nickel.²² Within consumers of cosmetic products, fragrances represent the most common cause of ACD,²³ affecting 1% to 8% of the adult population, particularly middle-aged women.^{24–26}

A recent United Kingdom study from 1996 to 2015 found a 47-time higher incidence rate ratio of allergy to fragrance in beauticians, hairdressers, and those working in related occupations compared with all other reference occupations combined.²⁷ Perfumes can have upward of 100 different chemicals, many of which have sensitizing potential.²⁸ Notably, new fragrance allergens can be hidden ingredients on cosmetic and cleansing products, even those that describe themselves as “fragrance free.”

Fragrance mix I (FMI) was developed in 1977 by Larsen and was the most important screening marker for contact allergy to fragrances for decades.²⁸ FMI consists of 8 fragrance chemicals (amyl cinnamal, cinnamyl alcohol, cinnamal, eugenol, geraniol, hydroxycitronellal isoeugenol, and *Evernia prunastri* [oakmoss absolute]). Although these 8 chemicals continue to be relevant fragrance allergens to this day, a need for an expanded panel was recognized in the 1990s, when research suggested that 15% of relevant perfume allergies were not identified by FMI.²⁹ In 2005, fragrance mixed II was introduced—including the chemicals Lyrall, citral, citronellol, farnesol, coumarin, and hexyl-cinnamic aldehyde—which effectively identified additional patients with fragrance sensitivities missed by FMI.³⁰ However, as perfumery practices and exposure patterns continue to evolve, there is a new emerging cohort of fragrance-allergenic patients who are not being successfully identified by either fragrance mix panels.

Two emergent fragrance allergens are linalool and limonene, which are terpenes with a fresh, flowery or citrus odor and solvent properties. Although weakly allergenic in their pure forms, they can autooxidize into more potent hydroperoxide byproducts.³¹ On exposure to air, both linalool and limonene readily oxidize into their more

allergenic forms. This is relevant given their use in commercially available fragrances, which are delivered to the skin by aerosolization.³² Linalool can be detected in 88% of essential oils, including lavender, ylang-ylang, and rosemary oils.³³ α -Limonene can be found in upward of 97% of essential oils, including tea tree oil.

Unfortunately, available screening panels such as FMI, fragrance mix II, *Myroxylon pereirae* (balsam of Peru), and colophony fail to detect more than half of patients with linalool and α -limonene sensitivities.^{34,35} Recently, the ACDS added lavender absolute, which contains linalool, to its Core Allergen Series; however, lavender is not a perfect proxy because the linalool is not delivered in its oxidized (and more allergenic) form.³⁶ *Nonoxidized* linalool and α -limonene rarely demonstrate positive patch tests reactions.^{31,37} International studies have demonstrated that positive patch test findings for *oxidized* linalool and α -limonene, conversely, exceeds any other isolated fragrance allergens,^{34,35,38} leading experts to call for their inclusion as separate allergens on patch testing.^{31,39} This has fueled a growing consensus that the current screening fragrances are no longer sufficient to diagnose up-and-coming fragrance allergens.³⁸

PRESERVATIVES

Preservatives are biocidal chemicals that inhibit growth of microorganisms and prevent putrefaction of foods, cosmetics, and industrial products. Preservatives have been responsible for several “contact allergy epidemics,” dating back to the widespread use of formaldehyde in textiles and cosmetic products in the 1950s, methylchloroisothiazolinone/methylisothiazolinone (MCI/MI; trade names: Kathon G, Euxyl K 400) in the 1980s and, more recently, methyl dibromo glutaronitrile (MDBGN) in the 1990s. Each of these epidemics has spawned policy change, and even the banning of MDBGN in European cosmetic products.⁴⁰

Formaldehyde (or methanal) is a colorless, odorous gas created by incomplete combustion of wood, tobacco, coal, and gasoline. Formaldehyde has been incorporated into a wide range of products, including nail polish, personal hygiene products, wrinkle-free clothing, and Brazilian blowout treatments.

The use of formaldehyde has decreased over time owing to negative publicity of its carcinogenic and sensitizing effects. Formaldehyde-releasing preservatives (FRPs) were subsequently developed, with the idea that the amount of formaldehyde released would not be sufficient enough to cause a skin reaction. FRPs have essentially replaced formaldehyde in personal care products,

makeup, medications, and household cleaning products. According to the 2010 FDA Voluntary Cosmetic Registration Program database, FRPs could be found in approximately 20% of personal hygiene products and cosmetics (imidazolidinyl urea being the most common).⁴¹ FRPs are present in 24% of leave-on products registered with the FDA, including 20% of moisturizers commercially available in the United States. The most relevant formaldehyde-releasing preservatives (listed in order of most to least releasing) are quaternium 15, diazolidinyl urea, dimethyl-dimethyl hydantoin, imidazolidinyl urea, and 2-bromo-2-nitropropane-1,3-diol (bronopol).

The preservative pair MCI/MI was later introduced in 1980 in a 3:1 combination. MCI/MI offered lower rates of sensitization than formaldehyde or FRPs, with less concern for toxicity. Soon after their introduction, rates of contact allergy to MCI/MI increased as high as 8% in some populations, catalyzing a new contact allergy epidemic.⁴² Because MI was considered a weaker sensitizer than MCI, use of MI alone was approved for industrial and cosmetic products in 2000 and 2005, respectively.⁴³ With this, MI was increasingly incorporated into industrial and personal care products, with the number of MI-containing cosmetic products doubling between 2007 and 2010.⁴³ For example, MI was incorporated into moist toilet papers, instigating a wave of perianal dermatitis, and later into MI-containing makeup remover wipes, yielding many cases of eyelid dermatitis. The preservative methylisothiazolinone (MI) was thus named the ACDS contact allergen of the year in 2013.⁴³ MI alone is a less effective biocidal agent without MCI and therefore requires a higher (and more allergenic) concentration for effective use. Notably, a positive reaction to MI can be missed if a patient is patch tested only to the MCI/MI combination. The addition of MI alone, particularly at a concentration of 2000 ppm, greatly increases detection of MI sensitization.⁴⁴

Parabens, the family of preservatives derived from the esters of parahydroxybenzoic acid, are incorporated into foods and cosmetics for their antimicrobial effects. Like many of the aforementioned preservatives, they are favored ingredients because they are inexpensive, odorless, and colorless. Parabens are far less sensitizing than other preservatives; the NACDG reports rates of ACD between 0.6% and 1.4%.⁴⁵ Moreover, ACD to parabens seems to occur most frequently on application to areas of skin breakdown. In fact, patients sensitized to parabens are often able to tolerate paraben-containing products when applied to normal skin, a phenomenon that has been coined the “paraben paradox.”⁴⁶

Despite proving themselves as weak allergens with decades of supportive patch testing data, concerns related to parabens have escalated due to increased media coverage that called their safety into question. Because parabens demonstrate weak estrogenic activity *in vitro* and in animal models, a suggestion of their role as “endocrine disruptors” exploded in popular press, raising alarm that parabens cause breast cancer or reproductive abnormalities. However, follow-up studies have failed to validate their role in hormonal aberrations or infertility. Nonetheless, “paraben-free” is now emblazoned across many consumer products. Unfortunately, the preservatives tasked with replacing parabens, such as methylisothiazolinone, are actually more allergenic than parabens and are likely driving the recent increase in ACD, as just discussed.^{47,48}

METALS

Metals represent a common class of contact allergens in both occupational and nonoccupational settings. Gold was the first metal to be designated contact allergen of the year in 2001,⁴⁹ however, not without controversy. The clinical relevance of positive patch tests to gold sodium thiosulfate (as it is tested) and the interpretation of these results are disputed. Many patients with positive patch tests to gold do not necessarily react to direct contact with gold jewelry. Some have pointed to impurities in gold jewelry, such as cobalt, as being the true culprits. As such, ACDS has stated that patients with a positive patch test to gold but without dermatitis on environmental gold exposure can be considered to have an irrelevant sensitization.⁵⁰

Nickel was the next metal to be designated as allergen of the year in 2008. Nickel can be found in innumerable items including jewelry, clothing buckles and buttons, electronics (such as cell phones and tablets), doorknobs, multivitamins, food—the list continues. Rates of nickel sensitization remain unparalleled. Patch testing data collected by the NACDG between 1992 and 2004 show a steady increase in nickel sensitivity, from 14.5% in 1992 to 18.8% in 2004 ($P < .0001$).⁵¹ Among US children, rates of sensitization reached 28.1%, according to NACDG patch testing data from 2005 to 2012.⁵² Body piercings are a likely source of exposure. The number of positive tests to nickel seems to increase linearly with the number of piercings (14.3% for 1 piercing to 34.0% with ≥ 5 piercings).⁵³

In recent years, cobalt has surfaced as another metal with high sensitizing potential, earning the status of contact allergen of the year in 2016.⁵⁴

Cobalt is often alloyed with other metals to enhance hardness and strength and can be found in jewelry, vehicle engines, magnets, cosmetics, clothing snaps and buttons, construction materials, orthopedic implants, medical devices, ceramics, cements, and even in some plastics and leather products. Rates of contact sensitization to cobalt are estimated to be 5.23%, with female gender doubling the risk of sensitization.⁵⁵ Prior dogmas suggested that cobalt allergy co-occurs with nickel or chromate allergy; however recent data disprove this dogma. Unpublished data (Fowler, 2016) from the NACDG indicate that 40% of patients positive to cobalt were actually negative to nickel.⁵⁴ Of note, a unique feature seen in cobalt patch-testing is the false-positive “poral” reaction, in which inflammation specifically arises within the skin’s acrosyringium, giving a speckled irritant reaction.

PROPYLENE GLYCOL

Propylene glycol (PG) is a synthetic alcohol with emollient, solvent, antimicrobial, and emulsifying properties. PG is viscous, colorless, and has low toxicity with little smell or taste, making it a favorite ingredient in many cosmetics, personal hygiene products, medications (including topical corticosteroids), food products, and, more recently, electronic cigarettes.⁵⁶ Use of PG has expanded since its initial commercialization in the 1930s, and it is now present in more than 37% of the 4674 products logged in the ACDS’s 2016 CAMP database.⁵⁷ PG was anointed the contact allergen of the year in 2018.⁵⁸

Patch testing data suggest that PG sensitization rates range from 0.8% to 3.5%, depending on the testing concentration used (ie, 10% vs 30% in aqueous solution).^{56,59,60} Contact dermatitis to PG is most often observed on the face, and systemic reactions can also be seen. Patch testing for PG and its relevance as a contact allergen is controversial. PG is a relatively weak sensitizer but an important irritant. As a result, the optimal patch-test concentration and timing of final readings are debated, because it can be difficult to distinguish true allergic reactions from irritant reactions. Moreover, weak hypersensitivity reactions can be mistakenly interpreted as insignificant.

The NACDG initially tested PG at 10% in aqueous solution; however in 1996 it increased the potency to 30% in aqueous solution. Later, in 2013, the NACDG added 100% PG to their standard screening tray.⁶¹ Interpretation of results is multifaceted: reactions that are fast (<24 hours), with well-demarcated margins, or “decrescendo”

in nature (presenting weekly at 48 hours, then dissipating by 96 hours) are all thought to be irritant reactions. Crescendo reactions, in which a stronger reaction is seen days later, around 96 hours, is thought to be more suggestive of true contact allergy.⁶² Some experts suggest that any reaction to the 30% patch test concentration, whether allergic or irritant, has clinical relevance⁵⁷; however, most of the products with such high concentrations of PG are washed-off and have very limited contact with the skin.

PARA-PHENYLENEDIAMINE

Para-phenylenediamine (PPD), the 2006 contact allergen of the year, is an aromatic amine that is a highly potent sensitizer and common cause of ACD. Typically sensitized individuals include hair-dressers and consumers of hair dye, and henna tattoos, which can sensitize younger patients, compared with hair dye.⁶³ Hypersensitivity to PPD can manifest with an array of symptoms, ranging from pruritus, eczematous eruptions, and blisters to facial edema and even systemic reactions such as upper airway obstruction and myocarditis.⁶⁴ Prevalence of PPD sensitization is high, ranging from 1% to 6% of all patients with unspecified dermatitis, increasing from 38% to 97% in patients with suspected hair dye dermatitis.⁶⁵ Fortunately, new PPD-free hair dyes have emerged in the market and will hopefully reduce rates of ACD in this population.

DISCUSSION

The field of contact dermatitis is constantly evolving and expanding. Trends in ACD are shaped by the introduction of new chemicals, revival of older allergens, industrial practices, and consumer behaviors. A recent review by de Groot found that, on average, 17 newly described contact allergens causing ACD have been reported per year between 2008 and 2015, one-third of which are found in cosmetics.⁶⁶

A common theme in modern-day contact dermatitis is the growing use of “ecofriendly” allergens, likely owing to consumers’ increasing focus on nature-derived products. This popularity of hypoallergenic and natural products is shifting some of the burden of contact dermatitis from occupational workers to consumers. Similarly, new consumer fears of historically less allergenic ingredients, such as parabens, have catalyzed a shift toward use of “safer” chemicals, which are arguably no less toxic and in fact more potent sensitizers.

There is also increased attention on the co-occurrence of ACD among patients with atopic

dermatitis (AD). Some available research suggests that children with compromised skin barriers should practice preemptive avoidance of potent allergens to mitigate risk of developing ACD. Perhaps supporting this theory, many of the aforementioned contact allergens—including CAPB, D-limonene, fragrances, surfactants, cobalt, and more—demonstrate relatively higher rates of sensitization among patients with AD compared with the general population.^{55,67,68}

Another hot topic in contact dermatitis is how to assess for metal hypersensitivity in patients with implantable devices. Implantable devices include prosthetic joints, pacemakers, intrauterine devices, cardiovascular stents, and dental implants, among others. There are conflicting data and opinion on whether patients with known ACD to metals will tolerate implants and whether patients with implants and unexplained dermatitis warrant patch testing or, in extreme cases, device removal. The ACDS published its perspective in 2016, recommending presurgical patch testing only for patients with a clear self-reported metal sensitivity of severity significant enough to cause concern in the patient or health care provider. Although metal from an implanted device may cause sensitization, a positive patch test result does not prove symptom causality. When the history is uncertain and/or patch testing unavailable, the ACDS suggests use of titanium or oxinium-containing devices are preferable.⁶⁹

As history demonstrates, new innovations and ever-changing consumer practices influence the emergence (or reemergence) of sensitizing chemicals. Successful diagnosis and management of contact dermatitis relies on awareness of these existing trends and relevant allergens.

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