

Impact of trends in new and emerging contact allergens

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ABSTRACT

Allergic contact dermatitis represents a T cell-mediated, delayed-type hypersensitivity response to exogenous agents. While allergic contact dermatitis is one of the most common causes of skin disease encountered by dermatologists, emerging trends within the field are in constant flux, as influenced by ever-changing industry practices and evolving consumer behaviors. Although certain allergens continue to predominate, new chemicals are frequently being introduced, thus shifting the pattern of allergen exposure and sensitization. This review examines the impact of trends in new and emerging contact allergens, with particular attention to clinical contexts in which these agents may be encountered. In addition, we offer a working knowledge of these allergens' characteristics, sources, and relevance, while outlining recommendations to accurately evaluate, diagnose, and provide appropriate counseling for these diseases.

Keywords: ACD, allergic contact dermatitis, cosmetic products, patch test, skin of color

Introduction

Allergic contact dermatitis (ACD) represents a T cell-mediated, delayed-type hypersensitivity response to exogenous agents.¹ Cutaneous manifestations of ACD depend on the allergen, the duration and nature of contact, and the susceptibility of the exposed individual.² Emerging trends in ACD are influenced by ever-changing industry practices, as well as evolving consumer behaviors. Although certain allergens continue to predominate, new chemicals are frequently introduced, shifting the pattern of allergen exposure and sensitization. This article will review the impact of trends in new and emerging contact allergens, with particular attention to clinical contexts in which these agents may be encountered.

Methylisothiazolinone

Methylisothiazolinone (MI) is a widely used compound first introduced as a preservative in 1980, normally combined with methylchloroisothiazolinone (MCI).³ It was approved for use alone as a preservative in 2005, in concentrations of up to 200 parts per million.³ Because MI was used at a much higher concentration as a stand-alone preservative, a marked rise in the inclusion of MI, particularly in cosmetics, toiletries, skin care and hygiene products, hair dyes, soaps/cleansers/sanitizers, sunscreens, moisturizers, laundry detergents/softeners/additives, and surface disinfectants has been appreciated in recent years.⁴ MI was the most commonly identified

preservative in hair care and household products,⁵ with 53% of shampoos and 45% of conditioners containing MI.⁴ One study querying the American Contact Dermatitis Society's Contact Allergy Management Program database revealed that 12.9% of all personal care products (PCPs) contained MI.⁵ This is supported by the 2015–2016 North American Contact Dermatitis Group patch testing results, in which MI was found to be positive in 13.4% of tested patients and also had the highest significance-prevalence index number.⁶ A significant concern when assessing for ACD to MI is that a positive reaction to this allergen may be missed by testing with MCI/MI, 0.02% aq MI allergy can be missed in up to 60% of cases if patch testing to MCI/MI, 0.02% aq but not MI, 0.2% aq alone, likely due to the low concentration of MI in the MCI/MI patch test substance.³

The most common reaction patterns to MI described include dermatitis of the hands, perianal/perivulvar area, face (particularly the eyelids), and scalp, corresponding with the application of the most common MI-containing products described above.

The popular children's toy, homemade slime, has recently been implicated as a cause of hand dermatitis in children. It is a viscous gel that when made at home from a mixture of such MI-containing household products such as glue, laundry detergent, dish soap, and shaving cream. In 1 study, MI was implicated as the likely sensitizer in greater than 70% of cases of ACD to slime ("slime dermatitis").⁷ Problematically, MI is not always listed on household product labels, and patients with ACD to MI may not be aware of the extent of this exposure.

Alkyl glucosides

Alkyl glucosides (AGs) are biodegradable, plant-derived ingredients that function primarily as mild surfactants in cosmetics, skin and hair cleansers/conditioners,⁸ and are often marketed as "natural" and "eco-friendly" in these products. Decyl glucoside is currently the most used AG, with 1 study identifying it in 492 (mainly rinse-off) cosmetic formulations; cetearyl glucoside, lauryl glucoside, and coco glucoside are also frequently used.⁸

The first cases of ACD to AGs were described in 2003,^{9–11} and there has since been a steady rise in the frequency of sensitization as the cosmetic industry has increasingly incorporated these agents in rinse-off, but also in leave-on products (such as sunscreens, deodorants, and antiseptics).⁸ One retrospective

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International Journal of Women's Dermatology (2022) 8:e006

Received: 23 September 2021; Accepted 9 December 2021

Published online 25 March 2022

DOI: 10.1097/JW9.000000000000006

What is known about this subject in regard to women and their families?

- Emerging trends in allergic contact dermatitis (ACD) are influenced by ever-changing industry practices, evolving consumer behaviors, and shifting patterns of allergen exposure/sensitization; this can disproportionately impact female consumers targeted by certain market trends, for example, when discussing allergens of concern in personal care products.
- Families of patients with ACD can endure consequences related to the direct and indirect cost of taking time from work; these impacts upon families may be further complicated by occupational avoidance measures, such as complex strategies to reduce exposure to responsible chemicals and products.
- Very few publications have sought to review the impact of trends in new and emerging contact allergens, while bringing attention to the contexts in which these agents may be encountered.

What is new from this article as messages for women and their families?

- Workers at highest risk of ACD include health professionals, chemical industry workers, and beauticians/hairdressers, with women estimated to make up 76.8–90.8% of the latter group in the United States.
- ACD to cosmetic products is widely reported, with 65% of women in the United States using such a personal care product daily, compared with only 37% of men.
- ACD to hair care products is also a major concern, with studies showing that women, and in particular, those of African American and African Caribbean descent, use more hair products when compared with other demographics, suggesting that exposure to sensitizers in hair products and risk of developing ACD may be higher in this group.

review identified 30 cases of ACD to different AGs over 19 years¹²; since then, additional publications have described further cases of ACD, particularly in glucoside-containing wound dressings.^{13,14}

Several clinical scenarios should suggest allergy to AGs. One pattern commonly described is eczema on the face, and to a lesser degree, on the neck, arms, chest to sunscreen. In the case of some shampoos, dermatitis localized to the scalp, with accentuation on the anterior and posterior hairline to a greater extent than on the face and trunk can be seen.¹⁵ In cases of occupational exposure, eczematous plaques are observed predominantly on the hands, such as by medical staff applying antiseptic agents or hairdressers applying shampoo/hair care products.¹⁶

Cross-reactions between AGs occur frequently and are most commonly observed between decyl glucoside, cetearyl glucoside, lauryl glucoside, and coco glucoside, given their structural similarities. Additionally, AGs are commonly found in products marketed as hypoallergenic or as being safe for sensitive skin, which may be problematic as conditions such as atopic dermatitis and occupational irritation have been shown to enhance the penetration of AGs.^{8,9,17} Although the incidence of ACD to AGs at present remains low, it is important to remember that a positive patch test reaction to these allergens carries high degree of clinical importance^{18,19} with rate of global relevance as high as 88.3% in 1 study.²⁰ As the trend towards greater incorporation of ingredients considered “natural” and “eco-friendly” is increasing, we suspect AG allergy will become more prevalent.

Essential oils and their constituents

Essential oils are substances most commonly obtained by steam distillation of plant material to produce the characteristic fragrance of the source from which they are extracted. Essential oils have widespread applications in the flavor/food, fragrance, and cosmetic industries, with a particularly rapid growth in the world of aromatherapy. The oils are usually applied to the skin but can also be ingested orally giving rise to systemic contact dermatitis or disbursed via aerosolized/inhaled products. Given the rising popularity of these agents, providers are confronting a greater frequency of ACD to essential oils.

Lavender oil

Lavender oil (essential oil of lavender) is the essential oil obtained by distillation of lavender (*Lavandula angustifolia* Mill), a plant native to the Mediterranean region. Linalool, linalyl acetate, and caryophyllene are the principal allergens in patients allergic to lavender.²¹ Lavender oil is thought to have analgesic/sedative, acaricidal, antidepressant, anti-infective, and carminative properties.²² It has been demonstrated to improve sleep and reduce anxiety^{23–25} as well as have antispasmodic effects that have been used to relieve headaches and labor pain.²⁵ Its growing popularity as a common fragrance ingredient, leading to inclusion in PCPs such as soaps, cleansers, and moisturizers with scents, and in aromatherapy/massage oil has led to increasing reports of ACD.

Linalool and linalyl acetate produce hydroperoxide products upon air exposure, which increase their allergenicity.^{26–28} The rate of sensitivity to lavender oil was estimated to be 3.7% in 1 large Japanese study,²⁹ a figure that exceeded that of other fragrances tested, and which exhibited an increase to 13.9% by study's end. Studies in patients suspected of having ACD to lavender oil demonstrate prevalence rates of 0.2–1.2% positive patch test reactions, with definite and probable relevance of 30–69%.^{18,19}

The most common reaction pattern to lavender described involves dermatitis of the upper extremities (hands, fingers, forearms). Other common sites of involvement include the face, the genital area,³⁰ or in a disseminated fashion in cases of airborne ACD.³¹ Occupational ACD to lavender is a significant risk factor,³² with hairdressers, massage/aromatherapists, physiotherapists, naturopathic therapists, and reflexologists recognized as being particularly at risk.^{33–36}

Peppermint oil

Peppermint oil (essential oil of peppermint) is obtained from the peppermint (*Mentha × piperita* L), a plant widely used as a medicinal remedy for gastrointestinal symptoms. Peppermint oil has vasoconstrictive and cooling properties exploited in the pharmaceutical industry for external application in products aimed at relieving muscle spasms, pain (eg, headache, neuralgia, etc.), and pruritus. It is also commonly utilized for flavoring, fragrances, and cosmetic products. Menthol is the most common compound in peppermint oil and is purported to be the main allergen. The first 2 cases of ACD to peppermint were reported in 1940, in which 2 Floridian bartenders developed hand dermatitis exclusively during seasons when they prepared drinks containing peppermint leaves; complete resolution of the rash ensued following strict avoidance of the plant.³⁷ Numerous reports of ACD to oral products have now been described, leading to the development of stomatitis, oral/perioral swelling, burning mouth syndrome, recurrent oral ulcers, and lichenoid (mucosal) reactions from peppermint oil-containing lip balm. Depilatory cream, antiseptic spray, mouthwash, various skin care products and foods, and other products are sources of exposure to peppermint oil.²¹ Occupational ACD has also been observed in aromatherapists and food handlers.

Carvone

Carvone is a terpenoid secondary oxidation product of D-limonene (a major component of citrus-based volatile oils) and exists as 2 enantiomers, L- and D-carvone.³⁸ L-carvone is the majority constituent in spearmint oil and is also found in other volatile oils, such as peppermint, dill, and caraway seed. Because of its spearmint-like odor, carvone is widely included in oral health products (eg, toothpaste, mouthwash), shampoos, soap, foods, toiletries, and cosmetics.³⁹ A Swedish study demonstrated L-carvone is ubiquitous in toothpaste, identified in 97% of products tested.⁴⁰ It is difficult to identify this component in the product labels as labeling of individual flavor agents in oral hygiene products is not required to be declared in the United States and Europe.^{40,41}

The first 4 confirmed cases of ACD to carvone were reported in 1978 in Denmark—3 patients who experienced sore mouth, stomatitis, and/or dermatitis around the mouth and 1 dentist with hand eczema.⁴² The most commonly affected anatomic site is the face, with oral/perioral reactions predominating, including cheilitis, urticarial reactions,⁴³ and oral lichenoid reactions.⁴⁰ Additional commonly affected sites include the eyelids, eyes, nose, and hands.⁴⁴ Hand dermatitis was observed in as high as 86.7% of carvone-positive patients in 1 study.⁴⁴

Isobornyl acrylate

Isobornyl acrylate (IBOA) is a key photopolymerizable acrylate monomer used for the manufacture of acrylic resins, giving rise to materials with enhanced thermal stability. It is thus an ideal agent for the production of paints/coatings, sealants, glues/adhesives, inks, and as a plasticizer, where its inherent properties of hardness combined with flexibility/impact resistance make it an ideal substance in medical devices.

The first 2 cases of ACD to IBOA were reported in 1995 in the setting of a reaction to insulin pump infusion sets.⁴⁵ With the increasing popularity of continuous glucose monitors and concomitant expanding use of insulin pumps after 2014, IBOA has become an important consideration in dermatitis under these devices. One study of FreeStyle Libre (Abbott, Abbott Park, IL) glucose sensors indicated that more than two-thirds of users experienced skin reactions.⁴⁶ IBOA has been isolated as the culprit allergen in 80% of patients with severe ACD after use of Freestyle Libre,⁴⁷ with chemical investigations demonstrating the highest concentrations of IBOA in the plastic parts of the unit itself.^{48,49} It is suspected that sensitization to IBOA is facilitated by the long-wearing time of these devices on the skin, possibly exacerbated by preceding irritant contact dermatitis, sweating, and/or friction, with the majority of reactions occurring after approximately 6 months of use.

The most common reaction pattern to IBOA consists of intractable pruritus and occasional burning, followed by severe erythema, edema, blistering, and a yellowish exudate in those areas in direct contact with IBOA-containing medical devices. The reactions progressively worsen over time, and in some cases, distant spreading of the reaction occurs.⁵⁰ In severe instances, erosions and even ulcers that appear to patients as “burn wounds” have been reported. Some cases result in such robust suppuration that the device spontaneously detaches.⁵⁰ Such reaction have been described not only underlying the body of different glucose sensor sets,^{46,51} but also to areas in contact with other medical devices, such as blood pressure cuffs.⁵²

Ethnic hair products

ACD to cosmetic products is widely reported, with hair care products being a major concern. Sensitizers often found in them include fragrances (most common allergen in these products), preservatives, surfactants, and conditioners. Studies have shown

that African American and African Caribbean women use more hair products when compared with other groups, indicating that exposure to chemicals in hair products may differ by race and/or ethnicity.⁵³

Hair care regimens most commonly employed by skin of color patients emphasize reduction of hair dryness/fragility.^{54,55} Multiple products may be used with the goal of providing moisture to the hair, but this can increase the risk of sensitization and subsequent development of ACD.⁵⁶ In 1 study examining the top 100 best-selling shampoos, conditioners, and styling products for ethnic and nonethnic hair products from 3 major online retailers, numerous important observations were noted. The first was that, although there existed no significant difference in fragrance content between the ethnic and nonethnic hair care products, the number of fragrance-free ethnic hair care products was few, identifying only 1 fragrance-free shampoo, 1 conditioner, and 8 styling products.⁵⁷ Second, although many common hair allergens already tested in standard screening series (eg, fragrances, MCI/MI, MI, formaldehyde releasers, and tocopherol) were shared between ethnic and nonethnic hair products, decyl glucoside, sodium benzoate, and phenoxyethanol were 3 compounds more commonly found in ethnic hair products.⁵⁷ The allergen content of hair products marketed for individuals with ethnic hair is of particular importance as the market for targeting these consumers continues to increase.

Men's products

Like market trends in ethnic hair products, retailers/manufacturers are increasingly branding PCPs specifically for male consumers. US men are spending more than ever before on an increasingly varied selection of skin care/grooming products, \$6.9 billion in 2017 alone.⁵⁸ Of particular concern appear to be male moisturizers, as 1 study found that ≥50% of men with dermatitis related to a PCP had a positive patch test to an ingredient in their moisturizer.⁵⁹ In a study examining 65 men's PCPs from 7 major online retailers, numerous important observations were noted.⁶⁰ An average of 12 American Contact Dermatitis Society Core and 9 North American Contact Dermatitis Group allergens were identified per product.⁶⁰ The most frequently encountered allergens were fragrances (98.5% of products); propylene glycol/derivatives (32.3%); parabens (29.2%); and AGs (26.2%).⁶⁰

Aluminum

Aluminum is a metal found as a component of immunizations, allergen-specific immunotherapy injections, food, antiperspirants and other PCPs, tattoos, jewelry, cosmetics, electronics, and the manufacturing/construction industries. Aluminum exposure is ubiquitous, from inhalation in dust particles, to greater concentrations directly consumed in medications such as antacids,^{61,62} to cutaneous exposure via elemental metal or aluminum salts. Despite such pervasive daily contact with aluminum, aluminum allergy is comparatively uncommon.⁶³ The first case of ACD to aluminum was not reported until 1980, in a child who developed a pruritic erythematous eczematous reaction of the axilla to antiperspirants having previously undergone hyposensitization therapy (for allergic rhinitis to grass pollen).⁶⁴ In a study of 376 children participating in clinical trials of an aluminum hydroxide-adsorbed pertussis toxoid vaccine from the Statens Serum Institute in Copenhagen, Denmark, developed chronic, pruritic, subcutaneous nodules/granulomas within months of injection. Subsequent patch tests to both metallic aluminum (empty Finn Chambers; Bio-Diagnostics Upton-Upon-Severn, Worcestershire, UK) and an aluminum salt (aluminum chloride hexahydrate) were positive.⁶⁵ This reaction remains of importance, as in the United States, aluminum-based vaccines currently in use include diphtheria and tetanus toxoids and acellular pertussis vaccine,

pediatric formulation and tetanus & diphtheria vaccine, adult/adolescent formulation/tetanus, diphtheria & acellular pertussis vaccine, adult/adolescent formulation, hepatitis A and B, human papillomavirus, and some pneumococcus/meningococcus.^{66,67} The prevalence of aluminum allergy confirmed by patch testing was calculated in 1 meta-analysis reviewing 25 studies to be 5.61% for children and 0.36% for adults.⁶⁸

The 3 most classic reactions to aluminum described include subcutaneous nodules after injections, axillary eczematous eruptions, as well as ring reactions to aluminum Finn Chambers (Bio-Diagnostics Upton-Upon-Severn, Worcestershire, UK) during patch testing. In fact, sensitization is often incidentally identified during patch testing with these aluminum-based chambers. Other described presentations include "otitis externa" following the use of an aluminum-containing ear drops, hand dermatitis, and widespread eczematous eruptions owing to topical medicaments.⁶⁹

It is recommended that testing be performed with both empty aluminum Finn Chambers (Bio-Diagnostics Upton-Upon-Severn, Worcestershire, UK), as well as aluminum chloride hexahydrate 2% pet in children younger than 8 years and 10% for adults, to avoid false negatives that may occur in adults at lower concentration.⁷⁰

Acetophenone azine

Acetophenone azine (AA) is a suspected byproduct of ethylene and vinyl acetate synthesis, a copolymer commonly used in sports equipment cushioning foam, including shin guards and footwear.⁷¹ To date, 12 confirmed cases have been reported,⁷²⁻⁷⁶ all but 1 in males under the age of 17.⁷⁷ The reaction pattern to AA begins with localized eczema at areas in contact with foam padding. It may be followed by a severe diffuse eruption, in some cases spreading to involve the entire body.⁷² A higher amount of AA

Table 1.

The sources of exposure and clinical presentations of new and emerging contact allergens

Allergens/haptens	Uses/found in	Clinical presentation
AA	Sports equipment (shin guards, footwear)	Localized eczema at areas in contact with foam padding (initial) Diffuse eruption, occasionally involving the entire body (severe)
AGs	Cosmetics Skin care products (sunscreens) Hair care products (shampoos) Hygiene products (deodorants) Rinse-off products Antiseptic agents Wound dressings "Natural" and "eco-friendly" products	Eczema (scalp [anterior/posterior hairlines], head and neck, upper extremities [hands], chest)
Aluminum	Cosmetics Hygiene products (antiperspirants) Foods Medications Tattoos Jewelry Electronics Immunizations and allergen-specific immunotherapy injections Metallic aluminum and aluminum salts Manufacturing/construction industrial supplies	Subcutaneous nodules (after) injections Eczematous eruptions (hands, "otitis externa," axillary, widespread) Ring reactions to aluminum Finn Chambers (Bio-Diagnostics Upton-Upon-Severn, Worcestershire, UK) (patch testing)
IBOA	Household products (paints/coatings, sealants, glues/adhesives) Medical devices, such as insulin pump infusion sets and blood pressure cuffs Inks	Pruritus and burning (initial) Erythema, edema, blistering, and exudate Erosions and ulcers ("burn wounds," suppuration) (severe)
MI	Cosmetics Toiletries (sanitary wipes, shaving creams) Hygiene products (deodorants) Skin care products (sunscreens, moisturizers) Hair care products (shampoos, conditioners, hair dyes) Laundry products (detergents, softeners, additives) Household products (surface disinfectants, soaps [liquid/dish], cleansers, sanitizers, glues, paints) Homemade slime	Dermatitis (scalp, face [eyelids], hands, anogenital)
Essential oils and their constituents		
Lavender oil	Fragrances	Dermatitis (head and neck, upper extremities [hands, fingers, forearms], anogenital) Disseminated (airborne contact)
Peppermint oil	Soaps/cleansers Moisturizers Aromatherapy/massage oils Cosmetics (depilatory creams) Oral health products (mouthwash) Skin care products (lip balms) Foods (flavoring) Fragrances Antiseptic sprays Aromatherapy/massage oils	Dermatitis (hands) Stomatitis Oral/perioral swelling Burning mouth syndrome Recurrent oral ulcers Lichenoid (mucosal) reactions
Carvone	Cosmetic products	Oral/perioral reactions: cheilitis, urticarial reactions, oral lichenoid reactions, "sore mouth," stomatitis and perioral dermatitis
	Foods (flavoring) Oral health products (toothpaste, mouthwash) Toiletries	Dermatitis of the face, including eyelids and periorcular area, nose Hand eczema

AA, acetophenone azine; AG, alkyl glucoside; IBOA, isobornyl acrylate; MI, methylisothiazolinone.

Table 2.
The most common allergens in ethnic hair and men's products

	Most common allergens
Ethnic hair products	Fragrances Preservatives, including methylchloroisothiazolinone/MI, MI, formaldehyde releasers Tocopherol Decyl glucoside Sodium benzoate phenoxyethanol Surfactants (other) Conditioners (other)
Men's products	Fragrances Propylene glycol/derivatives parabens Alkyl glucosides

MI, methylisothiazolinone.

is found in shin guards relative to footwear,⁷⁷ and most subjects become sensitized from their shin pads, presumably because of a wider area of exposure and thinner skin compared with the soles.

Some authors have suggested patch testing with a concentration of 0.1% in acetone or petrolatum, but no commercially available product is currently available. Materials therefore require acquisition directly from chemical products distributors. Given AA's potency and areas commonly involved by its reaction, it would be prudent to consider ACD to AA in instances presumed to be irritant contact dermatitis or dyshidrosis, as 1 study revealed at least 14% of sampled footwear contained AA.⁷¹

Disinfectants

The recent emergence of severe acute respiratory syndrome coronavirus 2 has resulted in the widespread use of various consumer sanitation products to reduce the spread of infections. In a recent study of skin reactions to disinfectant use during the COVID-19 pandemic, surfactants composed a significant fraction of sensitizers in disinfectants, with commonly implicated contact allergens including dodecylbenzene sulfonic acid, benzalkonium chloride, dodecyl dimethyl ammonium chloride, and sodium lauryl sulfate.⁷⁸ These allergens differ in their ability to sensitize the skin but together carry a high risk of ACD as a result of the relative increase in the handling of disinfectants among the public during the COVID-19 pandemic. The poor handling, storage, and application of these disinfectants further compounds the risk of exposure and adverse reactions to these allergens. In general, alcohol-based hand disinfectants have been shown to have lower penetration and overall cause fewer ACD reactions.⁷⁸

Conclusion

Trends in allergen exposure are constantly evolving. Table 1 summarizes the sources of exposure and clinical presentations of those new and emerging contact allergens discussed in this review. Table 2 highlights the common allergens identified in ethnic hair and men's products. New agents are introduced into patients' environments via industrial, occupational, and PCPs seemingly every day. Clinicians must remain vigilant and foster an awareness of these shifting exposure patterns. Expanded patch testing beyond the T.R.U.E. TEST (SmartPractice Denmark ApS, Hillerød, Denmark) is crucial to the ability to fully evaluate patients suspected of ACD to these newer allergens.

Author contributions

All authors contributed equally to this work.

Conflicts of interest

None.

Funding

None.

Study approval

The author(s) confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

Patient consent

Informed, written consent was received from all patients and confirmed to the journal prepublication, stating that the patients gave consent for their photos and case history to be published.

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