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.

INTRODUCTION

- 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**.

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

SURFACTANTS

- 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

SURFACTANTS

- 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.

SURFACTANTS

- **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**.

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

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 **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

ACRYLATES

- 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 lead to a shift in **acrylate sensitization** to **beauticians and artificial nail consumers**.12,13
- A recent 2018 study by Gonc¸alo 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

ACRYLATES

- 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 **ultraviolent 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

ACRYLATES

- **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**.

ACRYLATES

- 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

FRAGRANCES

- 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**."

FRAGRANCES

- **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 **Lyral, 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.

FRAGRANCES

- 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
- **D-limonene** can be found in upward of **97%** of **essential oils**, including **tea tree oil**.

FRAGRANCES

- 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 D-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 D-limonene rarely** demonstrate **positive patch tests** reactions.31,37
- International studies have demonstrated that **positive patch test** findings for **oxidized linalool and D-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, **methyldibromo 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**.

PRESERVATIVES

- 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)**.

PRESERVATIVES

- 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

PRESERVATIVES

- 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

PRESERVATIVES

- **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

PRESERVATIVES

- 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, "**parabenfree**" 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 non-occupational 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

METALS

- **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

METALS

- 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

PROPYLENE GLYCOL

- 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.

PROPYLENE GLYCOL

- 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 relevance**57; 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 **hairdressers 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**.

DISCUSSION

- 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

DISCUSSION

- 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

DISCUSSION

- 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.