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Article accepted on 10/04/2022

Surfactant irritations and allergies

Surfactants are long-chain compounds comprising a hydrophobic tail and a hydrophilic head, lending them the ability to act as a “bridge” between oil and water. Their detergent, foaming and other properties prove useful in a number of settings, including home and workplace sanitation, cosmetics (rinse and no-rinse cleansers) and medicine. When used on skin, surfactants reduce the superficial surface tension of proteins and lipids on the stratum corneum. This helps to eliminate skin debris such as sebum, oils and dirt, but also presents a risk of damage to the skin barrier. The irritation potential of surfactants has long been common knowledge, but with the development and deployment of novel compounds, notably to replace first-generation, mostly sodium-lauryl-sulphate-based products, their potential to cause allergic contact dermatitis has come to light. Knowledge about this allergic potential and the associated dermatitis must also become commonplace so that contact allergies are considered in the presence of surfactant exposure.

Key words: allergic contact dermatitis, contact allergen, cosmetics, irritant contact dermatitis, surfactant

Surface-active agents, or surfactants for short, are long-chain compounds comprising a hydrophobic tail and a hydrophilic head (*figure 1*). This amphiphilic nature allows them to act as “bridges” between water and oil, an aspect lending them great utility as cleaning agents. Indeed, surfactants trap (generally hydrophobic) dirt and grime and enable their removal by rinsing. Many surfactants are also able to reduce surface tension between water and air. They are thus able to stabilize bubbles, which makes them effective foaming agents. In the public mind, foaming properties are often inaccurately conflated with cleaning properties.

When used on skin, surfactants reduce the superficial surface tension of proteins and lipids on the stratum corneum. This helps to eliminate skin debris such as sebum, oils and dirt, but also presents a risk of damage to the skin barrier. This latter aspect explains, in part, why surfactants are able to provoke both irritant and allergic contact dermatitis. Surfactants are used in a wide variety of settings, including home and workplace sanitation, cosmetics (e.g., rinse and no-rinse cleansers) and even medicine [1]. Surfactants are classified as non-ionic, cationic, anionic, or zwitterionic (or amphoteric) as a function of the charge of the head group.

In general, surfactants irritate skin because they are able to solubilize membrane lipids, which increases skin permeability. They also bind to keratin and other tissue proteins, resulting in stratum corneum oedema and tissue destruction [2]. This is also the case for rinse surfactants.

There is a general consensus that zwitterionic surfactants are less irritating for the skin than their anionic or cationic counterparts. Moreover, non-ionic surfactants appear to be less irritating and better tolerated than all the others, but often less efficacious. And finally, although cationic surfactants are somewhat less irritating than anionic surfactants, they may be more cytotoxic [3] (*table 1*).

The intrinsic integrity of the skin barrier is also an important element to consider. For example, atopic skin is more prone to irritation when exposed to surfactants.

The primary prevention of surfactant-associated irritation comprises avoiding repeated exposure, protecting the skin and applying reparative emollients thereto. The current COVID-19 pandemic illustrates these issues: healthcare personnel are experiencing an increased rate of irritant contact dermatitis due to repetitive handwashing (as early as 10 washings per day). This risk appears to be lessened by the use of lukewarm water and emollients after each handwashing, or the use of hand sanitizer instead of soap whenever possible [4].

Surfactants and irritation

Most surfactants will provoke an inflammation when applied to the skin; they are thus classified as irritants, similar to acids, bases and solvents. This irritative nature has been known since the advent of soaps and as a result, certain surfactants have become model substances, deployed frequently for research on skin irritation.

Surfactants and allergy

Historically, because of its efficacy, sodium lauryl sulphate (SLS) has been the most widely used surfactant. However, one drawback is its strong irritation potential, and thus, as years pass, SLS is being progressively replaced by more tolerable compounds. These latter compounds include other

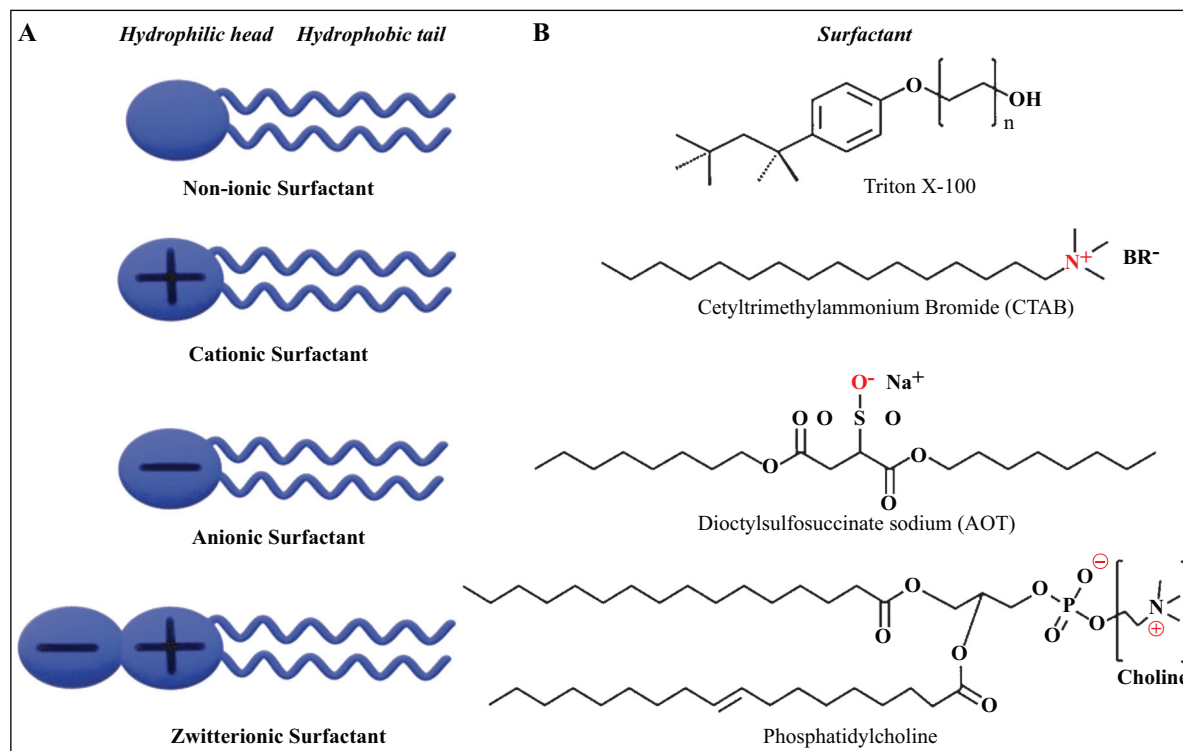


Figure 1. **A)** Schema of different types of surfactants and **(B)** chemical structures of several surfactants (adapted from Soleimani Zohr Shiri *et al* [3]).

anionic (e.g., glutamates, sulfonates, sulfosuccinates) as well as catatonic (betaines), zwitterionic (dialkyl ethanalamines) and non-ionic (glucosides) agents.

These replacements have indeed proved less aggressive for skin, but as data on them has gathered, some were found to have allergenic potential.

Although surfactant-associated eczema can occur anywhere on the skin, it tends to develop most frequently on the hands due to the use of cleansers, and on hairlines, ears and eyelids due to the use of shampoos. More generalized cases of allergic contact dermatitis are often due to soaps and cleansing gels.

Table 1. Classification and properties of the principal surfactants.

Class	Surfactants	Properties
Anionic (-)	SLS Sodium laureth sulphate	Very effective but irritating
Cationic (+)	Quaternium-15* BAC OAPD* AA* DMAPA*	Equally irritating but more cytotoxic than anionic surfactants
Amphoteric (- +)	CAPB*	Mild, well tolerated
Non-ionic	Alkyl glucoside including DG* Cocamide DEA*	Least irritating and better tolerated

AA: amiodamine; BAC: benzalkonium chloride; CAPB: cocamidopropyl betaine; cocamide DEA: cocamide diethanolamine; DMAPA: dimethylaminopropylamine; OAPD: oleamidopropyl dimethylamine; SLS: sodium lauryl sulphate. *Most allergenic surfactants.

Prevalence of surfactant use

The American Contact Dermatitis Society's Contact Allergen Management Program is built upon a database comprising the ingredients of close to 5,000 products available on the American market. A study performed in 2019 sought to determine how frequently 12 groups of surfactants and 12 individual surfactants were used in these products in this database [5].

The laureth/pareth sulphate group dominated (17.9% prevalence) across all product categories (e.g., shampoos and other hair care products, dishwashing liquids and laundry detergents) except household cleaning products or eye products. The betaine/sultaine group was the second most prevalent (13.5%; especially in mouth, skin and hair care products), and the most widely used member of this group was cocamidopropyl betaine (CAPB). Glucosides were the third most prevalent, at a rate of 10%, mostly in household cleaning and skincare products.

Concerning individual ingredients, CAPB, SLS, triethylamine (TEA), decyl glucoside (DG) and benzalkonium chloride (BAC) were the five most prevalent in this study.

Surfactant-associated allergic contact dermatitis

Although surfactants appear to be relatively rarely involved in allergic contact dermatitis, the increasing number of studies and case reports on them in that setting suggests that they should nonetheless not be neglected. The incidence and prevalence of surfactant-associated allergic contact dermatitis are not precisely known. However, using

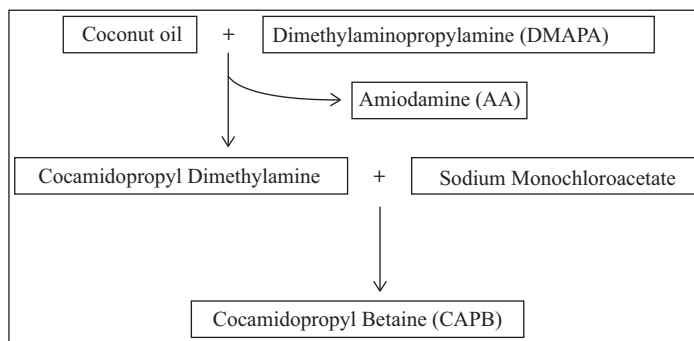


Figure 2. Synthesis of CAPB from DMAPA.

a standardized battery of 70 allergens comprising seven surfactants, the North American Contact Dermatitis Group (NACDG) reported that surfactants were second only to antiseptics for contact allergenicity, with rates ranging from 3.5% for oleamidopropyl dimethylamine (OAPD) to 0.9% for cocamide diethanolamine (cocamide DEA) [6]. The surfactants most frequently associated with allergic contact dermatitis are, in decreasing order: OAPD, quaternium-15, dimethylaminopropylamine (DMAPA), DG, CAPB, amiodamine (AA) and cocamide DEA (*table 1*). These surfactants are discussed in greater detail below.

Sodium lauryl sulphate and the laureth/pareth sulphate group

SLS is considered to be an irritant only; it is not allergenic. This compound is progressively being replaced by the less irritating sodium lauryl ether sulphate (also called sodium laureth sulphate [SLES]), which requires an extra ethoxylation step in its production.

The members of the laureth/pareth sulphate group are widely used in high-foaming products, such as shampoos and dish and laundry detergents, as they provide high lipophilic cleaning capacities at a low cost [7]. They are frequent irritants but not known to cause allergies.

Cocamidopropyl betaine and the betaine/sustained group

The zwitterionic betaine/sultana group was introduced to diminish surfactant-associated irritant reactions, but several of its members were found thereafter to act as contact allergens.

Among the betaines, CAPB is easily the most widely used compound. Sultanes are very similar to betaines, but used much less often in the setting of surfactants.

Cocamidopropyl betaine

CAPB provides better ocular tolerability than SLS. For that reason, its first widespread commercial use was as a surfactant in baby shampoos ("tear-free" formulations). CAPB is synthesized from fatty acids (coconut oil) and DMAPA in a process yielding cocamidopropyl dimethylamine and AA (*figure 2*).

Beyond shampoos and soaps, CAPB is also used in roll-on deodorants, contact lens solutions, toothpastes, bubble baths, liquid soaps, skincare products and antiseptics.

It was recognized as a contact allergen in the 1980s and, with an estimated prevalence falling between 3 and 7%, named Allergen of the Year in 2004 by the American Contact Dermatitis Society (ACDS) [1].

Although the clinical presentation of CAPB-associated dermatitis can be general in nature, it usually involves the eyelids, face, scalp and/or neck to a greater extent.

However, recent data appear to suggest that the veritable allergen may not be CAPB itself but rather a remaining impurity in the final formulation. Indeed, a number of studies have shown that highly purified CAPB rarely causes reactions in patients who test positive on CAPB patch tests, and highly impure CAPB causes the highest rates of sensitization. What the culprit is, however, remains unclear; North American studies suggest AA but European studies suggest DMAPA.

Finally, it is important to keep in mind that patch tests themselves can cause adverse reactions: a flair appearing at 48 hours post-test but disappearing thereafter should not be considered as a positive result.

Dimethylaminopropylamine and amiodamine

The potentially allergenic (but not irritant) surfactants, DMAPA and AA, are intermediates in the synthesis of CAPB (*figure 2*). They are thus more or less present in patch preparations and products containing CAPB. These residual impurities are not labelled. The possibility of residual DMAPA and/or AA in CAPB-containing products means that allergy testing for the latter should include investigation of all three compounds. If the patient is positive for any one of the three, all products that include ingredients with betaine or sultaine as part of their name should be avoided, as should those containing dimethylamine, for example OAPD or stearamidopropyl dimethylamine, also synthesized from DMAPA.

Oleamidopropyl dimethylamine

OAPD is a cationic emulsifier within the dimethylamine family. It is used in the cosmetics setting in moisturizing creams and lotions and in hair care products such as shampoos and conditioners. The first cases of contact allergy due to OAPD date back to 1984. As mentioned earlier, of

all the surfactants examined, OAPD was associated with the highest prevalence (3.5%) of allergic contact dermatitis in a recent North American patch test study [6].

Alkyl glucosides

Alkyl glucosides are synthesized via the condensation of fatty alcohols and glucose. They are non-ionic surfactants providing cleaning and emulsifying properties. Among the family's 19 members, DG is the most frequently used alkyl glucoside, followed by cetearyl glucoside, lauryl glucoside and coco glucoside. Because they cause little irritation and show an eco-friendly nature (produced from natural and renewable resources), alkyl glucosides started gaining popularity in the late 1990s. They are used today in both rinsed (e.g., shampoos, shower gels, hair dyes, rinsed anti-septics) and non-rinsed (creams, deodorants, sunscreens) products.

Since the 2000s, however, numerous cases of contact dermatitis due to alkyl glucosides have been reported, earning this family of compounds the 2017 Allergen of the Year title by the ACDS [1].

Moreover, DG has been shown to be a "hidden" allergen, responsible for contact dermatitis associated with the use of bisoctrizole (BASF, Duesseldorf, Germany), a sunscreen in which DG functions as a stabilizer, easing the dispersion of UV-filtering microparticles in water phase [8].

In 2014, the authors of a retrospective study on 11,842 patch-tested patients over a 19-year period reported 30 cases, mostly females, of allergic reactions to one or several alkyl glucosides [9]. Simultaneous reactions between different alkyl glucosides are frequent but not systematic, occurring most frequently between DG, lauryl glucoside, coco glucoside and cetearyl glucoside. Cross-reactivity is surely involved considering the structural similarities of the concerned compounds. Lauryl glucoside appears to be a good marker of sensitization for this family of compounds, but cases may nonetheless go undetected as it is not necessarily cross-reactive with all alkyl glucosides. Patients reacting to bisoctrizole (brand name: Tinosorb M) should be tested for DG.

Between 2005 and 2007, the GERDA group and REVIDAL GERDA systematically added a preparation of 2% DG in water to the European standard series. A 0.5% rate of DG allergy was observed in the tested patients. In 2008, the DG preparation was replaced by a preparation of 5% lauryl glucoside in petroleum jelly commercialized for skin tests. Since 2012, the lauryl glucoside positivity rate has remained greater than 1.5% (2%, 1.59% and 2.59% in 2012, 2013 and 2014, respectively). This observation led the GERDA members to maintain the 5% lauryl glucoside preparation as a systematic addition to the standard series [10].

Because their cross-reactivities have not been precisely determined and in the absence of all-inclusive testing, a patient allergic to one alkyl glucoside should avoid all of them.

Cocamide diethanolamine

Also known as coconut diethanolamine, cocamide DEA is a non-ionic surfactant used in household, industrial and cosmetic products for its foaming and stabilizing properties. Its irritation potential is low.

Allergic contact dermatitis due to cocamide DEA can be workplace-related, occurring particularly among hair-dressers, medical professionals and blue-collar workers. Among the latter, the problem is most frequently seen in the food, metal and cleaning industry, where exposure to such products as cutting fluids, hand cleansers, dishwashing detergents and protective creams is frequent. In the NACDG series, 0.9% of the 4,230 tested patients had positive reactions to this allergen [6].

Those allergic to cocamide DEA should avoid all products that include ingredients with DEA as part of their name. However, there is no data indicating a need to avoid other ethanolamines (mono, tri, etc.) or other coconut-derived products.

Quaternium-15

Quaternium-15 is largely known as a formaldehyde-releasing preservative, but it is also a surfactant used in numerous industrial and cosmetic products. It is a known potential allergen already included in the European standard series. In Europe, its concentration is limited to 0.2% when used in cosmetics. The prevalence of quaternium-15 allergic contact dermatitis in Europe is about 1.5%, although it appears to have diminished over the past 10 years

Conclusion

Potential irritation due to surfactants has long been common knowledge, but with the development and deployment of novel compounds, notably to replace first-generation, mostly SLS-based products, the potential of several among them to cause allergic contact dermatitis has come to light. Awareness of Knowledge about this allergic potential and the associated dermatitis must also become commonplace so that contact allergies are considered in cases with surfactant exposure. ■

Disclosures. Financial support: none. Conflicts of interest: none.

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