

Irritant and Sensitizing Potential of Eight Surfactants Commonly Used in Skin Cleansers: An Evaluation of 105 Patients

Monica Corazza, Maria Michela Lauriola, Anna Bianchi, Mario Zappaterra, and Annarosa Virgili

Background: Irritation from surfactants contained in detergents is a frequent adverse reaction to cosmetics. Sensitization to surfactants is also possible. In the literature, comparative studies about irritant and sensitizing potential of different surfactants are heterogeneous and inconclusive about the best molecules to use.

Objectives: We compared the irritant and sensitizing potential of some surfactants that are usual components in marketed synthetic detergents (syndets) to obtain practical information regarding commonly used detergents.

Methods: We patch-tested eight surfactants of the different types (anionic, cationic, amphoteric, and non-ionic) in 105 patients. Assessment of allergic reactions of tested surfactants was carried out in accordance with the recommendations of the International Contact Dermatitis Research Group; assessment of irritant power followed the amended Draize classification.

Results: None of the eight surfactants in our series gave positive allergic reactions. Only cocamidopropyl betaine from the Italian standard (Società Italiana di Dermatologia Allergologica, Professionale e Ambientale [SIDAPA]) series gave five positive reactions among 105 patients. None of the eight studied surfactants induced skin irritation. The most tolerated are two new mild anionics (sodium cocoyl glutamate and sodium lauroyl oat amino acids) and an amphoteric agent (disodium cocoamphodiacetate).

Conclusion: From this study, we deduce that cosmetic companies' efforts to search for and market new products with very mild surfactants have been generally successful.

SURFACTANTS (surface-active substances) are the key active agents in cleansers; they lower the surface tension on the skin and have an indispensable role in removing dirt, sebum, sweat, microorganisms, and exfoliated corneum cells from the skin in an emulsified form.^{1,2} Nevertheless, surfactants are known to damage the skin through protein denaturation, cutaneous lipid removal, and inflammatory processes with keratinocyte-derived cytokine release.³⁻⁵ Irritation from surfactants contained in detergents is considered to be among the most frequent and important adverse reactions to cosmetics. Sensitization to surfactants is rare but possible.⁶⁻⁸ Therefore, more-tolerable products are required on the market, and cosmetic companies continue to search for

new very mild surfactants for sensitive skin. Nevertheless, there is no international agreement in regard to the criteria for determining the mildness of cleansers, and better regulation is needed in this matter.^{5,9}

Physicians and even dermatologists often do not have sufficient cosmetologic knowledge to critically examine detergent ingredient listings and make proper recommendations to the patient.

In the literature, comparative studies on the irritant and sensitizing potential of different surfactants are heterogeneous and inconclusive as to the best molecules to use. In this study, we performed occlusive patch tests with some surfactants of synthetic detergents (syndets) presently on the market on 105 patients to compare the surfactants' irritant and sensitizing potential.

Methods

Patient Selection

We recruited 105 consecutive subjects (25 males and 80 females; mean age, 42.51 years; age range, 18–80 years) from patients who were referred to our section for various

From the Department of Clinical and Experimental Medicine, Section of Dermatology, and the Department of Pharmaceutical Science, University of Ferrara, Ferrara, Italy.

Address reprint requests to Maria Michela Lauriola, Department of Clinical and Experimental Medicine, Section of Dermatology, University of Ferrara, Via Savonarola 9, 44100 Ferrara, Italy. E-mail: michelalr@gmail.com

DOI 10.2310/6620.2010.10022

© 2010 American Contact Dermatitis Society. All Rights Reserved.

DECKER



diseases (28.6% of the patients had allergic contact dermatitis, 9.5% had irritant contact dermatitis, 1.9% had atopic dermatitis, and 60% had other nonallergic disorders).

Exclusion criteria were age less than 18 years; a personal history of systemic drug reactions; current therapies with antihistamines, corticosteroids, or immunosuppressive agents; pregnancy; and nursing.

Written informed consent was obtained from all patients, and the study was approved by the local ethical committee (University of Ferrara).

A detailed questionnaire about the patients' hygiene habits, the kind of detergents they purchased, and perceived adverse effects of the cleansers' use was given to the patients.

Patch Testing and Assessment

Single-application occlusive patch tests were performed with eight surfactants representing the different types (anionic, cationic, amphoteric, and non-ionic). The surfactants and their types are listed in Table 1. These surfactants are the usual components of marketed syndets; no new molecule was tested. The substances were tested at a 0.5% aqueous (aq) dilution.

All patients were tested with the Italian standard Società Italiana di Dermatologia Allergologica Professionale ed Ambientale (SIDAPA) series, which includes cocamidopropyl betaine 1% aq (amphoteric; Chemical Abstracts Service [CAS] number 61789-40-0). The patch tests were performed in occlusion with Haye's test chambers (Aj Alphen aan den Rijn, The Netherlands) on acrylic copolymer. The estimated amount of each surfactant applied to the skin was 40 μ L (0.04 mL). Exposure time was 48 hours, and readings were performed 15 minutes after the removal of the patch tests (day 2) and then after 24 hours (day 3). Late delayed readings were not

performed, and sodium lauryl sulfate (SLS) was not used as a positive control. One patch test with simple occlusion (without any substance) was performed on each patient as a negative patch-test control.

Allergic reactions to allergens were scored following the recommendations of the International Contact Dermatitis Research Group. Irritant reactions were estimated according to the arbitrary scale shown in Table 2. Erythema and edema scores were recorded for each patient at 15 minutes (day 2) and 24 hours (day 3) after removal of the patch tests. The average index of skin irritation (AII) for erythema and that for edema were calculated, and the total AII was obtained from the two averages. Assessment of the irritant power of tested surfactants was carried out in accordance with the amended Draize classification (Table 3).¹⁰

Results

Our research into consumer habits of detergent use showed how liquid cleanser use clearly exceeded soap bar use although some people declared that they used both (Fig 1). Females preferred liquid cleansers more than males did; in fact, 74% of subjects who claimed to use them were females. Moreover, most people said that they buy these products mainly at supermarkets (95%) rather than at chemist's (25%) or herbalist's shops (7%).

Atopic patients who gave their informed consent to participate were not excluded from our study; the percentage of these atopic patients was 14.3%.

Irritant potential evaluation according to the amended Draize classification was done only for eight surfactants at the 0.5% aqueous dilution in our integrative series, not for cocamidopropyl betaine in the SIDAPA series.

Table 1. Patch-Tested Surfactants

Surfactant*	Type	CAS No.
Sodium lauroyl sarcosinate	Mild anionic	137-16-6
Cocamide DEA	Non-ionic	68603-42-9
Sodium lauroyl oat amino acids	Mild anionic	222400-43-3
Disodium cocoamphodiacetate	Amphoteric	68650-39-5
Decyl glucoside	Non-ionic	54549-25-6
Sodium cocoyl glutamate	Mild anionic	68187-32-6
Lauryl glucoside	Non-ionic	59122-55-3
Cetrimonium chloride	Cationic	112-02-7

CAS = Chemical Abstracts Service; DEA = diethanolamine.

*By International Nomenclature of Cosmetic Ingredients (INCI) name.

Table 2. Irritant Reaction Rating Scale

Reaction	Score
Erythema	
None	0
Light (hardly visible)	1
Clearly visible	2
Moderate	3
Serious (dark red with possible formation of light eschars)	4
Edema	
None	0
Very light (hardly visible)	1
Light	2
Moderate (about 1 mm raised skin)	3
Strong (extended swelling even beyond application area)	4

Table 3. Definition of Average Index of Skin Irritation according to Amended Draize Classification

Index	Class
< 0.5	Nonirritating
0.5–2.0	Slightly irritating
2.1–5.0	Moderately irritating
5.1–8.0	Highly irritating

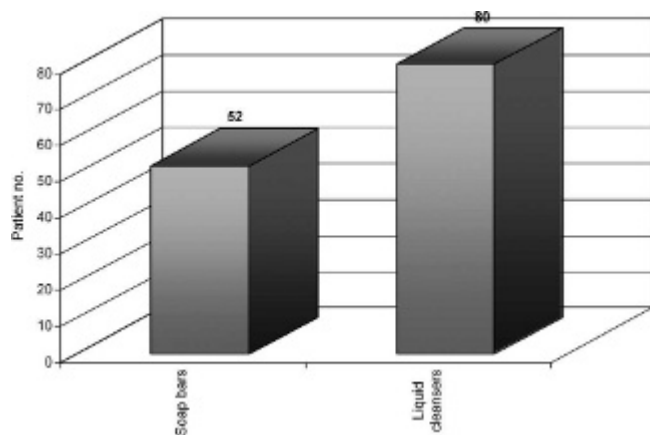
Table 4 and Figure 2 summarize the average index of skin irritation (AII) for erythema and for edema and data on the total AII for the eight examined surfactants. Substantially, considering the final values of the total AII (see Table 4), we concluded that none of the eight studied surfactants induced skin irritation.

Finally, none of these substances caused positive allergic reactions. We observed five positives (one in atopic patients and four in nonatopic patients, equal to 4.76% of the 105 patients tested) only to cocamidopropyl betaine 1% aq in the Italian standard SIDAPA series.

Discussion

Even if rinse-off cosmetic products are thought to have only a transient effect on the skin, some components can bind strongly to the stratum corneum.¹¹ Adverse cutaneous effects are possible not only with traditional soap bars, at an alkaline pH of 9.5 to 13, but also with the most recent syndets (moisturizing body washes and shower gels), at physiologic pH.

In the literature, studies on the irritant potential of surfactants are very heterogeneous owing to the large number of components and finished products, exposure methods, and visual and objective measurements to assess

**Figure 1.** Consumer habits of detergent use.**Table 4.** Average and Total Average Indexes of Skin Irritation for Eight Tested Surfactants

Surfactant*	Reactions at D2		Reactions at D3		Average Values between Reactions at D2 and D3		Total AII
	AII for Erythema	AII for Edema	AII for Erythema	AII for Edema	AII for Erythema	AII for Edema	
	Reactions at D2	Reactions at D2	Reactions at D3	Reactions at D3	Reactions at D2 and D3	Reactions at D2 and D3	
Sodium lauroyl sarcosinate (mild anionic)	0.143 ± 0.489	0.000	0.086 ± 0.281	0.000	0.115 ± 0.399	0.000	0.058 ± 0.287
Cocamide DEA (non-ionic)	0.152 ± 0.515	0.010 ± 0.097	0.086 ± 0.281	0.010 ± 0.097	0.119 ± 0.415	0.010 ± 0.097	0.065 ± 0.306
Sodium lauroyl oat amino acids (mild anionic)	0.076 ± 0.300	0.000	0.067 ± 0.250	0.000	0.072 ± 0.276	0.000	0.036 ± 0.198
Disodium cocoamphodiacetate (amphoteric)	0.076 ± 0.300	0.000	0.067 ± 0.250	0.000	0.072 ± 0.276	0.000	0.036 ± 0.198
Decyl glucoside (non-ionic)	0.086 ± 0.314	0.010 ± 0.097	0.076 ± 0.266	0.010 ± 0.097	0.081 ± 0.290	0.010 ± 0.097	0.046 ± 0.219
Sodium cocoyl glutamate (mild anionic)	0.067 ± 0.286	0.010 ± 0.097	0.057 ± 0.233	0.010 ± 0.097	0.062 ± 0.260	0.010 ± 0.097	0.036 ± 0.198
Lauryl glucoside (non-ionic)	0.095 ± 0.354	0.000	0.076 ± 0.266	0.000	0.086 ± 0.313	0.000	0.043 ± 0.225
Cetrimonium chloride (cationic)	0.286 ± 0.661	0.086 ± 0.281	0.190 ± 0.418	0.086 ± 0.281	0.238 ± 0.553	0.086 ± 0.281	0.162 ± 0.445

AII = average index of skin irritation; D2 = day 2; D3 = day 3; DEA = diethanolamine.

*By International Nomenclature of Cosmetic Ingredients (INCI) name.

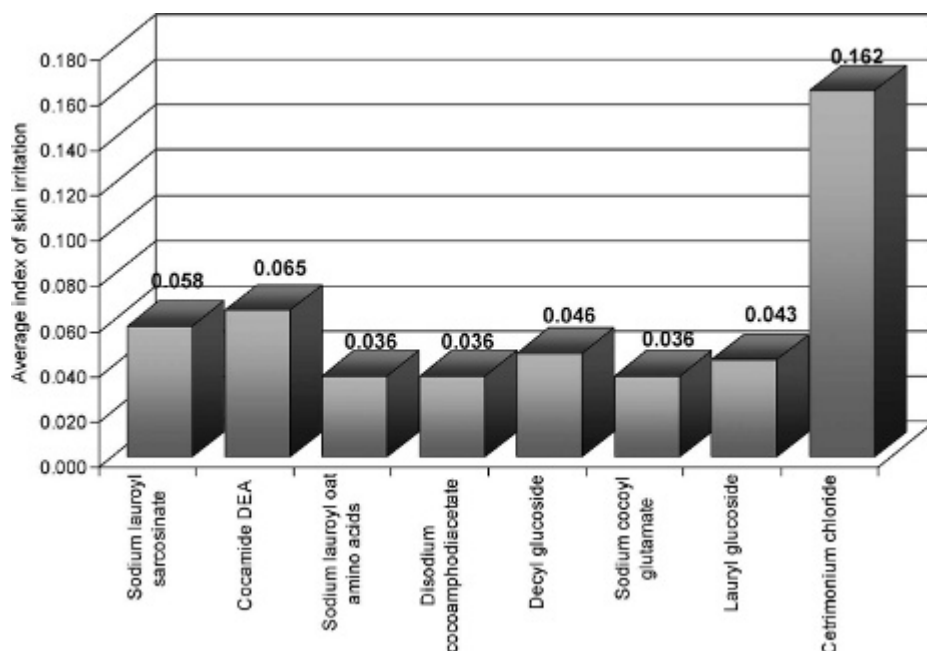


Figure 2. Average indexes of skin irritation for the tested surfactants, following the amended Draize classification. (DEA = diethanolamine.)

Sodium lauroyl sarcosinate (mild anionic; CAS 137-16-6)

Cocamide diethanolamine (DEA) (nonionic; CAS 68603-42-9)

Sodium lauroyl oat amino acids (mild anionic; CAS 222400-43-3)

Disodium cocoamphodiacetate (amphoteric; CAS 68650-39-5)

Decyl glucoside (nonionic; CAS 54549-25-6)

Sodium cocoyl glutamate (mild anionic; CAS 68187-32-6)

Lauryl glucoside (nonionic; CAS 59122-55-3)

Cetrimonium chloride (cationic; CAS 112-02-7)

reactions. Generally, these studies are complicated comparative analyses with numerous types of testing and different evaluating criteria. Therefore, single studies test but a few (often three or four) cleansing preparations, except for some recent studies⁵ regarding eight commercial liquid detergents.

On the other hand, although only cocamidopropyl betaine's sensitizing power is well known, sensitivity due to other synthetic surfactants is still discussed. Patch testing with surfactants is always problematic owing to the irritant activity of these substances, which may lead to false-positive reactions.

We conceived the present study to compare the irritant and sensitizing potential of some of the usual surfactants that are often found in marketed syndets and that are representative of the different classes of surfactants (anionic, cationic, amphoteric, and non-ionic).

Mild substances for sensitive skin were deliberately included in our surfactants series for their "critical" evaluation; agents such as benzalkonium chloride, SLS, and the corresponding ethoxylate (sodium laureth sulfate [SLES]) were excluded from this study because they are already well known for their irritant and cytotoxic effects.

SLES is the favorite primary surfactant in body washes, shower gels, and shampoos because of its good cleansing power and its low cost, even if its irritant potential is also demonstrated.¹²

As regards the dilution of rinse-off products for diagnostic patch tests, values ranging from 0.2 or 0.5% to 4% in water are reported in the literature.^{6,9,13} Considering that diagnostic patch testing for allergic potential should be done at the maximum nonirritant concentration, we preferred a surfactant dilution of 0.5% in water to avoid fast and excessive irritant reactions and to investigate possible sensitivity.

The most common tests used to evaluate rinse-off agents or their components are the repeated open application test and the use test. They permit the suitable evaluation of surfactant-containing products for frequent and repeated use (ie, for professional use). On the other hand, repeated occlusive patch testing as well as single-application occlusive or semioclusive patch testing can be adequate for estimating the cutaneous compatibility of a preparation.^{6,11}

When tests with detergents are performed, it necessary to recognize that the irritant cutaneous effect of a cleanser

can be expressed differently by various exposure methods. One-time occlusive tests can cause mainly erythema, whereas repeated tests promote scaling and roughness.⁸

In our study, because of the number of patients and tested surfactants, we opted for single-application occlusive patch tests, which are certainly simpler to perform than repeated application tests and allow an easy evaluation of more contemporaneously applied substances. Moreover, these tests do not have a long exposure time and are not too expensive. Single-application occlusive patch tests permit the assessment of both irritant and sensitizing reactions.

Unlike other studies, this study deliberately did not exclude atopic patients to evaluate the tolerability of the examined surfactants also on the very sensitive skin of this consumer group. Thus, deductions about the irritant and sensitizing power of the tested surfactants have been made with consideration of this not-negligible group (14.3%, 15 of 105 patients), an example being that the prevalence of atopic dermatitis in the general population is relevant (up to 15–20% of childhood atopic eczema in industrialized countries).^{14–16}

As regards allergic responses found in this study, none of the eight surfactants in our series gave positive results. Only rare cases of sensitizations due to new synthetic surfactants, such as allergic contact dermatitis by decyl glucoside,¹⁷ sodium lauroyl sarcosinate,¹⁸ disodium cocoamphodipropionate,¹⁹ aminoethylethanolamine,²⁰ cocamide diethanolamine (DEA) (coconut diethanolamide)^{21–23} are described in the literature as anecdotal reports.

On the other hand, the percentage of observed positive reactions to cocamidopropyl betaine was equal to 4.76% of all subjects in our study and accords with the 3.0 to 7.2% reported in the literature.^{24–26} Since 1980, this amphoteric agent has been responsible for increasing cases of allergic contact dermatitis (ACD) from shampoos and detergents. Nevertheless, according to recent studies, the real sensitizers for these patients seem to be impurities in the commercial product, such as the parent compound dimethylaminopropylamine.^{6,27,28}

Although irritant reactions to cocamidopropyl betaine are also possible,²⁴ we considered in our study only sensitization, neglecting the assessment of irritant potential following the amended Draize classification. This was our choice because cocamidopropyl betaine is a well-known hapten and is included in the Italian standard SIDAPA series at a 1% aqueous dilution, whereas the other eight surfactants are not routinely tested; we established their

aqueous dilution at 0.5%, according to other scientific research.¹³

From our study, it appears that none of the eight tested surfactants induced significant skin irritation even after prolonged exposure in occlusion (but with a substantial dilution at 0.5% in water). Because the selected molecules in our series are usual components of marketed syndets, we can deduce that the cosmetic companies' efforts to discover new very mild surfactants have been generally successful.

The total AII of cetyltrimethyl ammonium chloride (cetyltrimethyl ammonium chloride) was 0.162, the highest of all substances. This is a cationic agent belonging to quaternary ammonium salts such as cetrimide and benzalkonium chloride, and it is used as an antimicrobial preservative in ophthalmic products, as a disinfectant for medical instruments, and as a hair conditioning agent in shampoo.^{2,29} Cationic surfactants have lower detergent properties than anionic agents and have proved to be at least as irritating as anionics (although more cytotoxic).^{2,28,30} Occlusive patch tests with quaternary ammonium compounds can elicit irritant reactions even at a 0.1% aqueous dilution.²⁹

A typical chemical burn-like or xerosis-like contact dermatitis involving primarily the flexor sites or genital areas was recently described in Taiwan after improper self-application of antiseptic liquids, especially cetrimide. The wide use of these known irritants for personal hygiene has now become common to control the dermatosis due to Taiwan's hot and humid climate.³¹

The second-highest total AII (0.065) was that of cocamide DEA (coconut diethanolamide), manufactured from coconut oil. This is a common non-ionic agent with viscosity-enhancing and foam-stabilizing properties that is widely used in personal care products and as a corrosion inhibitor in metalworking fluids.^{21,22} Cocamide DEA is known as a possible mild irritant even for healthy skin, and it has sometimes caused ACD.²¹ This non-ionic agent has not been shown to be carcinogenic in animal studies, although it is possible that there is a contamination of nitrosamine due to the presence of impurities (diethanolamines) and preservatives (Bronopol) or other nitrosating system.^{32–34}

In our study, the total AII of sodium lauroyl sarcosinate (0.058) was lower than that of cocamide DEA. This mild anionic agent is widely used in at least 118 cleansing products, according to Food and Drug Administration data. The Cosmetic Ingredient Review Expert Panel defines this surfactant as nonirritating and nonsensitizing.^{18,35}

Following cetrimonium chloride, cocamide DEA, and sodium lauroyl sarcosinate in regard to total AII are two non-ionic agents derived from alkyl polyglucosides: decyl glucoside (total AII, 0.046) and lauryl glucoside (total AII, 0.043). Non-ionic surfactants are commonly considered to be the lowest skin irritants among the different types of surfactants.² Nevertheless, some authors have remarked that non-ionics alter the cutaneous lipid layer more than anionics do because they can solubilize fatty acids and cholesterol in skin.³

In our study, two new anionic surfactants were very well tolerated: sodium cocoyl glutamate (total AII, 0.036), which belongs to the acyl glutamates, and sodium lauroyl oat amino acids (total AII, 0.036), which is derived from oat amino acids. Disodium cocoamphodiacetate (total AII, 0.036), an amphoteric agent of amphotoacetates, also had very low irritant power. Sodium cocoyl glutamate, sodium lauroyl oat amino acids, and disodium cocoamphodiacetate showed better cutaneous compatibility than did tested non-ionics (cocamide DEA, decyl glucoside, and lauryl glucoside).

Patch-test data on the irritancy of surfactants are not sufficient for clinical relevance. Numerous use and wash tests (ie, hand immersion and repeated wash test), coupled with patch testing, could better define skin compatibility.

Although there is no ideal cleanser, it is very important to choose carefully to prevent possible cutaneous damage from chronic exposure. Thus, products with a simple formulation should be preferred, particularly those based on mild anionic surfactants (such as acyl glutamates), amphoteric agents with low irritant potential (amphodiacetates), or non-ionic agents (alkyl polyglucosides). Sophisticated syndets, containing mixtures of different surfactant classes (ie, anionics and amphoteric) and often including the known sensitizing betaines, should be avoided or limited. Skin care products should have a simple composition to reduce the risk of allergy.

In conclusion, if there are innovative mild surfactants today, finished products on the market are often too elaborated, and they can be more harmful than the single components, as well as more sensitizing.

Acknowledgments

Financial disclosures of author(s) and reviewer(s): None reported.

All of the authors have participated sufficiently to take public responsibility for appropriate portions of the work.

References

1. Kuehl BL, Fyfe KS, Shear NH. Cutaneous cleansers. *Skin Therapy Lett* 2003;8:1–4.
2. Effendy I, Maibach HI. Surfactants and experimental irritant contact dermatitis. *Contact Dermatitis* 1995;33:217–25.
3. Ananthapadmanabhan KP, Moore DJ, Subramanyan K, et al. Cleansing without compromise: the impact of cleansers on the skin barrier and the technology of mild cleansing. *Dermatol Ther* 2004;17:16–25.
4. Bárány E, Lindberg M, Lodén M. Biophysical characterization of skin damage and recovery after exposure to different surfactants. *Contact Dermatitis* 1999;40:98–103.
5. Lodén M, Buraczewska I, Edlund F. The irritation potential and reservoir effect of mild soaps. *Contact Dermatitis* 2003;49:91–6.
6. Foti C, Mastrandrea V, Conserva A, et al. Dermatite da contatto da detergenti. *Ann Ital Dermatol Allergol* 2003;57:1–8.
7. Lodén M, Buraczewska I, Edlund F. Irritation potential of bath and shower oils before and after use: a double-blind randomized study. *Br J Dermatol* 2004;150:1142–7.
8. Tupker RA, Bunte EE, Fidler V, et al. Irritancy ranking of anionic detergents using one-time occlusive, repeated occlusive and repeated open tests. *Contact Dermatitis* 1999;40:316–22.
9. Angelini G, Rigano L. Dermatite da contatto da cosmetici. In: Angelini G, Vena GA, editors. *Dermatologia professionale ed ambientale*. Brescia, Italy: ISED; 1997. p. 703–6.
10. Draize JH, Woodard G, Calvery HO. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J Pharmacol Exp Ther* 1944;82:377–90.
11. The European Cosmetics Association, COLIPA guidelines. Product test guidelines for the assessment of human skin compatibility. 1997. Available at: <http://www.colipa.eu/publications.html> (accessed March 2009).
12. Löffler H, Happle R. Profile of irritant patch testing with detergents: sodium lauryl sulphate, sodium laureth sulphate and alkyl polyglucoside. *Contact Dermatitis* 2003;48:26–32.
13. Wilhelm K-P, Freitag G, Wolff HH. Surfactant-induced skin irritation and skin repair. Evaluation of the acute human irritation model by noninvasive techniques. *J Am Acad Dermatol* 1994;30:944–9.
14. Williams HC. Atopic dermatitis. *N Engl J Med* 2005;352:2314–24.
15. Williams HC. Is the prevalence of atopic dermatitis increasing? *Clin Exp Dermatol* 1992;17:385–91.
16. Kay J, Gawkrödger DJ, Mortimer MJ, Jaron AG. The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol* 1994;30:35–9.
17. Horn HM, Murray C, Aldridge RD. Contact allergy to decyl glucoside. *Contact Dermatitis* 2005;52:227.
18. Zemtov A, Fett D. Occupational allergic contact dermatitis to sodium lauroyl sarcosinate in the liquid soap. *Contact Dermatitis* 2005;52:166–7.
19. De Groot AC, Weijland JW. Contact allergy to disodium cocoamphodipropionate. *Contact Dermatitis* 1996;35:248–9.
20. Foti C, Bonamonte D, Mascolo G, et al. Aminoethylethanolamine: a new allergen in cosmetics? *Contact Dermatitis* 2001;45:129–33.
21. Pinola A, Estlander T, Jolanki R, et al. Occupational allergic contact dermatitis due to coconut diethanolamide (cocamide DEA). *Contact Dermatitis* 1993;29:262–5.

22. Fowler JF. Allergy to cocamide DEA. *Am J Contact Dermatitis* 1998; 9:40–1.
23. De Groot A, De Wit FS, Bos JD, Weyland JW. Contact allergy to cocamide DEA and lauramide DEA in shampoos. *Contact Dermatitis* 1987;16:117–8.
24. Mowad CM. Cocamidopropyl betaine allergy. *Am J Contact Dermat* 2001;12:223–4.
25. De Groot AC, Van Der Walle HB, Weyland JW. Contact allergy to cocamidopropyl betaine. *Contact Dermatitis* 1995;33: 419–22.
26. Fowler JF, Fowler LM, Hunter JE. Allergy to cocamidopropyl betaine may be due to amidoamine: a patch test and product use test study. *Contact Dermatitis* 1997;37:276–81.
27. Angelini G, Foti C, Rigano L, Vena GA. 3-Dimethylamino-propylamine: a key substance in contact allergy to cocamidopropyl-betaine? *Contact Dermatitis* 1995;32:96–9.
28. Effendy I, Maibach HI. Detergent and skin irritation. *Clin Dermatol* 1996;14:15–21.
29. Rietschel RL, Fowler JF Jr, editors. *Fisher's contact dermatitis*. 4th ed. Baltimore: Williams & Wilkins; 1995. p. 198–9, 349–51.
30. Berardesca E. La deterzione. In: Caputo R, Monti M, editors. *Manuale di dermocosmetologia medica*. Milano: Raffaello Cortina Editore; 1995. p. 83–9.
31. Yu-Yun Lee J, Wang B Jr. Contact dermatitis caused by cetrimide in antiseptics. *Contact Dermatitis* 1995;33:168–71.
32. Final report on the safety assessment of cocamide DEA lauramide DEA linoleamide DEA oleamide DEA, *J Am Coll Toxicol* 1986;5: 415–54.
33. Harvery D, Hardy C. N-Nitrosamine in cosmetic products. *Cosm Toil* 1994;109:53–61.
34. "Cosmetics Directive" 76/768/EEC Annex III no. 60.
35. Lanigan RS. Final report on the safety assessment of cocoyl sarcosine, lauroyl sarcosine, myristoyl sarcosine, oleoyl sarcosine, stearoyl sarcosine, sodium cocoyl sarcosinate, sodium lauroyl sarcosinate, sodium myristoyl sarcosinate, ammonium cocoyl sarcosinate and ammonium lauroyl sarcosinate. *Int J Toxicol* 2001;20:1–14.