30 Sodium Lauryl Sulfate

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30.1 Sodium Lauryl Sulfate

Sodium lauryl sulfate (SLS) is an anionic surface active agent used as an emulsifier in many pharmaceutical vehicles, cosmetics, foaming dentifrices, and even foods and it is the sodium salt of lauryl sulfate that conforms to the formula: $CH_3(CH_2)10CH_2OSO_3Na$ [1]. The action of SLS on surface tension is putatively the cause of its irritancy, and its great capacity for altering the stratum corneum makes it useful to enhance penetration of other substances in patch tests and in animal assays.

Some important characteristics for experimentally used irritants have been proposed: lack of systemic toxicity, not carcinogenic, not a sensitizer, chemically well defined, no extreme pH value, and causing no cosmetic inconveniences to exposed subjects [2]. Kligman [3] found no sensitization to SLS was seen in 100 volunteers in which SLS was employed in provocative or prophetic patch test procedures. There are isolated reports of contact sensitization to SLS [4–6] that appear to fit our current scientific criteria as a model irritant in the study of experimental irritant contact dermatitis.

Sodium lauryl sulfate (SLS) has been used extensively as a model irritant in the study of cutaneous irritation. Tupker et al. [7] divide the studies on SLS into two categories with respect to aims. The first category, provocative testing, concerns studies in which SLS is used to induce a definite skin reaction in all individuals. The second category, susceptibility evaluation, concerns studies aimed to predict the irritant susceptibility of individuals, and investigate individual and environmental factors determining this susceptibility.

Recently, we have been impressed by the biologic complexity of irritant contact dermatitis. The sheer morphologic diversity, combined with animal studies of mechanism, suggest that not all chemical irritants may be acting in the same manner. We have examined the literatures on the irritant most comprehensively studied, SLS, in the hope of utilizing this rich data source as a basis for further investigative study.

30.2 Application Methods

Many studies concerned with cutaneous irritation utilize a 24-h patch application. Recently, a 7-h patch [8] and 4-h patch [9] have been developed when a high concentration of SLS is used. In real life surfactant exposure is usually of short duration, open application, and cumulative. A single challenge of the skin with an irritant insult is a momentary reflection of the skin susceptibility, which does not take into account the cumulative effect of irritation or the repair mechanisms of the skin. A correlation coefficient of 0.63 between single and 4-day repetitive exposure to patch testing with SLS was found [10]. Utilizing repeated open application of SLS for 5 days as well as a single 24-h patch test with SLS using small (8 mm) patch test chambers, only the degree of skin damage caused by the repeated open test was found to be associated with prior skin complaints [11].

In recent years, assay methods similar to real usage situations such as repeated short duration chamber test [12–14], repeated open application test [15–18], plastic occlusion stress test (POST) [19, 20], and soak or wash test [21, 22] were developed.

There are some variations in skin responses to identical patch tests and standardization of patch test procedure is necessary to minimize the variations in patch test responses.

30.2.1 Purity and Carbon Length of Sodium Lauryl Sulfate

There were significant differences in the irritant potential in vivo for different qualities of SLS and, in some SLS, part of the C12 chains had been substituted by longer and less irritating carbon chains [23]. C12 chains of SLS is known to elicit a maximum irritant reaction [24–26]. Agner et al. [23] suggested that only SLS qualities of high purity (>99%) should be used for irritant patch testing and that the quality and the purity of SLS should be stated.

30.2.2 Type of Vehicles

Pure SLS is water soluble (1 g/10 ml) and somewhat soluble in ethanol. Concentrations of SLS in the test material have varied from 0.1% to 10% [7]. Most of the patch tests with SLS have been performed using aqueous solution, although petrolatum was also used as a vehicle [27, 28]. No study has directly compared aqueous solution with petrolatum vehicle [7]. Agner et al. [29] demonstrated that approximately 70% of the SLS in aqueous solution was released from the system while the release from gels was significantly less. Tupker et al. [7] recommended high purity (99%).

30.2.3 Quantity and Concentration of Test Solution

Quantity of test solution is important and larger quantities of test solution give more intense skin reactions, though concentration of the irritant is kept the same [30, 31], and Agner [32] suggested that the Duhring chamber, the 12-mm Finn chamber, or even large chambers having larger test areas are more effective to elicit an irritant response. Mikulowska and Andersson [33] observed that the effect of 8-mm chambers could result in increased, unchanged, or decreased Langerhans cells (LC) numbers, while 12-mm chambers always produced a decrease in LC numbers. Lee et al. [34] also compared the effect of chamber size on SLS irritation on volar forearm using 3 different sizes (8-mm, 12-mm, 18-mm) of Finn chambers. The increase in skin response (visual score and TEWL) with large (12-mm) Finn chamber was larger than that with the small (8-mm) Finn chamber. However, there were no significant differences between large and extra-large (18-mm) Finn chambers. Recently Brasch et al. [35] have analyzed the synchronous reproducibility of patch tests with 0.0625%, 0.125%, 0.25%, 0.5%, and 1.0% SLS aqueous solution using large Finn chambers, and they suggested that 1% SLS aqueous solution is appropriate for an irritant patch test as a positive control.

30.2.4 Evaporation and Temperature of Test Solution

Berardesca et al. [36] reported significantly different skin responses to the temperature of test solution (4°C, 20°C, and 40°C). Skin damage was higher in sites treated with warmer temperatures and there was a highly significant correlation between irritation and temperature of test solution. The evaporation rate of aqueous solutions from Finn chambers was reported as 1 mg/3 min [37]. It has been demonstrated that evaporation from the patch before application inhibits the inflammatory response, even though the relative concentration of the irritant is increased by the process [38]. This inhibition of skin irritation could be caused by decreased amount or lowered temperature due to evaporation of test solution. Sugar et al.

Table 1. ESCD guidelines on SLS exposure tests with TEWL measurement [7]
*1 week is 5 application days. [b]Water temperature 35°C. [a]In temperature zones, it is not possible to elicit an irritation response in all subjects using 10% SLS for 60 min twice daily, and longer exposure times are not feasible.

	Susceptibility evaluation		Provocative testing	
	Acute	Cumulative	Acute	Cumulative
One-time occlusion test				
Application time	24 h	Not applicable	24 h	Not applicable
Mode of application	chamber 12 mm		Chamber 12 mm	
SLS w/v%	0.5%		2%	
Repeated occlusion test				
Application time	Not Applicable	2 h 1 × daily	Not applicable	2 h 1 × daily
Application period		3 weeks*		3 weeks*
Mode of application		Chamber 18 mm		Chamber 18 mm
SLS w/v%		0.25%		1%
Open test				
Application time	60 min 2 × daily	10 min 1 × daily	Not possible[a]	10 min 1 × daily
Application period	1 day	3 weeks*		3 weeks*
Mode of application	20 mm guard ring	20 mm guard ring		20 mm guard ring
SLS w/v%	10%	1%		1%
Immersion test[b]				
Immersion time	30 min 2 × daily	10 min 2 × daily	30 min 2 × daily	10 min 1 × daily
Application period	1 day	3 weeks	1 day	3 weeks*
Mode of application	Forearm immersion	Forearm immersion	Forearm immersion	Forearm immersion
SLS w/v%	0.5%	0.5%	2%	2%

[39] studied the influence of 4 different parameters (concentration, duration, temperature, material of the storage vials) on the stability of aqueous SLS solutions under the nonsterile conditions at 5 different concentrations (0.001%, 0.01%, 0.1%, 0.5%, 1%). After 4 weeks at 6°C and 23°C, the SLS concentration was found to be decreased for the 2 lowest concentrations (0.001% and 0.01%). In parallel to the loss of SLS, contamination with bacteria was found in the solutions at the 2 lowest concentrations. They suggested that the storage of SLS solutions of very low concentrations should be at low temperature and preferably in sterile vials.

30.2.5 Time of Evaluation

When noninvasive measurements of the skin response are made, the interval between removal of the patch and the measurements should allow for a period of increased evaporation following occlusion. For measurements of transepidermal water loss (TEWL), in most papers, the interval was reported to be 30 min [40–42]. The time course of TEWL after SLS patch testing demonstrated still significant reduction in TEWL values from 30 to 60 min after removal of patch, but not from 60 to 180 min [43]. Equalization of water diffusion between the stratum corneum and the ambient air is settled after 20 min of patch removal [44], and Agner and Serup [43] suggested that evaluation of irritant patch test reactions by measurement of TEWL can naturally be made at any time after removal of the patches, as long as the time period is precisely accounted for. Others have argued that a minimum waiting period of 2–3 h should be used to allow for evaporation of excessive water due to occlusion [10, 45].

30.2.6 Guidelines on Sodium Lauryl Sulfate Exposure Methods [7]

High purity (99%) SLS must be used in any study, dissolved water in occlusive and open testing, while tap

water may be acceptable in immersion testing. Standard-sized occlusion chambers with filter paper discs corresponding to large (12-mm, 60-ìl) and extra large (18-mm, 200-ìl) Finn chambers are recommended. The extra large Finn chambers are recommended for repeated applications. For open exposures, a 20-mm diameter plastic ring is advised. The volume of the solutions must be such that the total exposure area is covered (about 800 ìl). Chambers should be applied to the skin immediately, i.e., within 1 min after preparation with the test solution. TEWL measurement should be performed a minimum of 1 h after removal of test chambers. ESCD proposed new guidelines in terms of purposes and methods of SLS exposure tests (Table 1).

30.3 Biologic Endpoints

30.3.1 Clinical Appearance of Sodium Lauryl Sulfate Reaction

Erythema, infiltration, and superficial erosion can be seen during acute reaction to SLS. With higher concentrations, vesicular and pustular reactions may be seen. During healing of acute reactions, scaling and fissuring will take over. The same appearance of erythema, scaling, and fissuring is seen during repeated application of SLS. The soap effect consisting of fine wrinkled surface and/or chapping is not commonly seen in SLS patch test reaction [7]. Most recently, reported literatures have used the modified visual scoring system of Frosch and Kligman [12] to evaluate clinical skin reaction to SLS. Tupker et al. [7] developed the guideline concerning the visual scoring schemes for the acute and cumulative reactions to SLS (Tables 2, 3). They also proposed a new scoring system for subjective irritation (Table 4).

30.3.2 Histopathologic Findings of Sodium Lauryl Sulfate Reaction

The histopathologic changes induced by SLS depend on concentration, mode of application, time of evaluation, etc. In epidermis, SLS application can induce hyperkeratosis, parakeratosis, spongiosis, intracellular vacuolation, hydropic degeneration of basal cells, and necrosis [46–50]. In dermis, there were variable degrees of inflammatory cell infiltration, edema, and collagen degeneration. T lymphocytes are the predominant infiltrating cells and CD4(+) cells outnumbered the CD8(+) cells [51–55].

30.3.3 Mechanisms of Sodium Lauryl Sulfate Reaction

Many surfactants including SLS disrupt the skin barrier function resulting in increased TEWL [56, 57], and increased blood flow, clinically visible as erythema [58]. A number of hypotheses on the mechanism of SLS-induced skin irritation has been suggested. Leveque et al. [59] suggested that an increase in TEWL did not necessarily imply the alteration of stratum corneum and SLS-induced dry skin could hardly be interpreted in terms of lipid removal [60]. Wilhelm et al. [26] found an increase of both hydration and TEWL after 24-h patch irritation of SLS, and they suggested that the stratum corneum hydration resulted from a continuous disruption of the secondary and tertiary structure of keratin proteins exposing new water-binding sites, and the most likely explanation of SLS-induced increase in TEWL lay in the hyperhydration of stratum corneum and a possible disorganization of lipid bilayers. Forslind [61] proposed a domain mosaic model of skin barrier. Stratum corneum lipids are not randomly distributed, but are organized in domains. Lipids with very long chain lengths are segregated in gel, impermeable to water, and separated by grain borders populated by lipids with short chain lengths which are in fluid phase, permeable to water. Surfactants including SLS infiltrate the fluid phase permeable to water increasing the width of grain borders, and increase TEWL.

30.3.4 Noninvasive Bioengineering Techniques Assessing Sodium Lauryl Sulfate Reaction

Several noninvasive bioengineering methods to quantify and to obtain information which is not detectable clinically have been developed in recent decades (Table 5) [62]. Measurement of TEWL as a technique to evaluate skin barrier function is widely used [63, 64] and a positive dose-response relationship for skin response to SLS as measured by TEWL has been demonstrated [65]. When attempting to quantify irritant patch test reactions by electrical conductance measurement, the intraindividual variation in the results was so high that the method was found unhelpful for this purpose [66]. A positive relationship was found between dose of SLS and blood flow values recorded by laser Doppler flowmetry [65, 67]. However, wide fluctuations in laser Doppler blood flow values in response to SLS patches were found due to spotty erythema [41]. The skin color is expressed in a 3-D

Table 2. ESCL guideline on clinical scoring of acute SLS irritant reactions, simple scoring system [7]
Reading 25–96 h after one-time exposure.

Score	Qualification	Description
0	Negative	No reaction
1/2	Doubtful	Very weak erythema or minute scaling
1	Weak	Weak erythema, slight edema, slight scaling, and/or slight roughness
2	Moderate	Moderate degree of: erythema, edema, scaling, roughness, erosions, vesicles, bullae, crusting, and/or fissuring
3	Strong	Marked degree of: erythema, edema, scaling, roughness, erosions, vesicles, bullae, crusting, and/or fissuring
4	Very strong/caustic	As 3, with necrotic areas

Table 3. ESCD guideline on clinical scoring of subacute/cumulative SLS irritant reactions, simple scoring system [7]
*The ESCD simple scoring system may be used when no subdivision into the different qualities of irritation (erythema, scaling, roughness, edema, fissure) is necessary.
#The term "shiny surface" is used for those minimal reactions that can only be discerned when evaluated in skimming light as a "shiny area."
[a]The term "roughness" is used for reactions that can be felt as rough or dry, sometimes preceded or followed by visible changes of the surface contour, in contrast to "scaling," which is accompanied by visible small flakes.

Score	Qualification	Description
0	Negative	No reaction
1/2	Doubtful	Very weak erythema and/or shiny surface[#]
1	Weak	Weak erythema, diffuse or spotty, slight scaling, and/or slight roughness[a]
2	Moderate	Moderate degree of: erythema, scaling, roughness, and/or weak edema and/or fine fissures
3	Strong	Marked degree of: erythema, scaling, roughness, edema, fissures and/or presence of papules and/or erosions, and/or vesicles
4	Very strong/caustic	As 3, with necrotic areas

Table 4. ESCD guideline on subjective scoring of the SLS irritant reactions during or after exposure [7]

Qualification	Score	Description
Negative	0	No burning/stinging sensation
Weak	1	Weak burning/stinging
Moderate	2	Moderate burning/stinging
Strong	3	Strong burning/stinging

Table 5. Noninvasive bioengineering techniques used in the evaluation of cutaneous irritation

Technique	Measured skin function	Information obtained
Evaporimeter	Transepidermal water loss	Positive dose-response relationship for skin response to SLS. Most sensitive method for SLS-induced irritation
Laser-Doppler flowmeter	Blood flow	Positive relationship between applied dose of SLS and blood flows. Wide fluctuations in response to SLS due to spotty erythema
Ultrasound	Skin thickness	No preconditioning is necessary. Good relation to SLS concentrations, but minimal correlation with erythema or epidermal damage
Impedance, conductance, capacitance	Skin hydration	Correlation with epidermal damage, but intraindividual variation is so high, this method is unhelpful
Colorimeter	Skin colors	Positive correlation between changes in the a* color coordinates and doses of SLS, but not with epidermal damage

coordinate system: a*(from green to red), b*(from blue to yellow), and L* (from black to white) values [68]. Color (a*) coordinates have been demonstrated to correlate well with visual scoring of erythema in inflammatory reactions caused by soap or SLS [64, 69, 70]. Ultrasound examination has the advantage that no preconditioning of the subjects is necessary before measurement. Ultrasound A-scan has been found suitable for quantification of patch test reactions [27, 71] and also a promising method for quantification of SLS-induced inflammatory response, being consistently more sensitive than measurement of skin color [65], and Seidenari and di Nardo [72] demonstrated that B-scanning evaluation showed a good correlation with TEWL values in assessing superficial skin damage induced by SLS.

Comparing evaporimetry, laser Doppler flowmetry, ultrasound A-scan, and measurement of skin color, evaporimetry was found to be the best-suited method for evaluation of SLS-induced skin damage [64, 66]. Lee et al. [73] observed that measurement of erythema index using the Dermaspectrometer was less sensitive than TEWL measurement when comparing the cutaneous irritation to two types (8-mm and 12-mm) of Finn chambers. Wilhelm et al. [64] suggested that although TEWL measurements may be an accurate and sensitive method in evaluating skin irritation, color reflectance measurements may be a helpful complimentary tool for the clinician, because of its convenience to operate. Serup [74] suggested that transepidermal water loss is very sensitive and useful in the study of corrosive irritants, such as SLS, especially in the induction phase of irritant reaction, but has not a direct clinical relevance and the results need be backed up with some other measure of relevance.

Tupker et al. [75] found that the time course of TEWL after a 24-h SLS patch varied between different subjects. They could divide 35 subjects into four subgroup according to the day of maximum TEWL values after the single exposure; the number of subjects showing peak TEWL was 14 on the day of removal of the patch (day 2), 16 at day 3, 4 at day 4, 1 at day 5. Using SLS in varying concentrations, Serup and Staberg [27] found a delayed response only for reactions clinically scored as 1+, but not for more intense reactions, indicating that the kinetics of the response may depend on the severity of the reaction [76]. Wilhelm et al. [77] studied the skin function during healing phase after single 24-h patch application of 0.5% SLS solution. Erythema was most increased directly after patch removal with a slow gradual decrease thereafter. Erythema was not completely resolved even 18 days after treatment. The repair of the SC barrier function as indicated by TEWL measurements was completed 14 days after exposure. SC hydration evaluated by capacitance measurements did not return to baseline values before 17 days after surfactant exposure. Shin et al. [78] reported the recovery of skin function after single 24-h patch application of 1% SLS solution: the recovery rate of TEWL values at 6 days of patch removal (D6) was 89.51% and 58.5% in erythema index measured by Dermaspectrometer at D6.

30.4 Host-Related Factors

There are many host-related factors in cutaneous irritation: those that are to be considered skin disease, and those that represent variations from normal skin predisposing to irritation (Table 6).

Table 6. Host-related factors in cutaneous irritation

Age
Sex
Anatomic region
Race and skin color
Skin hydration
Sensitive skin
Hyperirritable skin
Skin disease (atopic dermatitis, hand eczema, seborrheic dermatitis)

30.4.1 Age

Increased susceptibility to SLS in young compared to elderly females, when assessed by visual scoring and TEWL, was reported and the increase in TEWL values was found to be more persistent in the older group [79, 80]. These findings imply less reaction to an irritant stimulus but a prolonged healing period in older people. There is no significant influence on skin susceptibility between 18 and 50 years of age [81].

30.4.2 Sex

Hand eczema is well-known to occur more frequently among women than men. However, many investigators have found no sex-relation in skin susceptibility [42, 82–84]. Reactivity to SLS at day 1 increased in the

menstrual cycle compared to days 9–11, when tested on opposite arms in healthy women [85]. Since no cyclical variation was found in baseline TEWL, the increased reactivity of the skin at day 1 in the menstrual cycle probably reflects an increased inflammatory reactivity, rather than changes in the barrier function.

30.4.3 Anatomic Region

Variation in skin responses within the same individual to identical irritant patch tests has been claimed to be considerable. Van der Valk and Maibach [86] have studied the differences in sensitivity of volar surface of the forearm to SLS and demonstrated that the potential for irritation increases from the wrist to the cubital fossa, and Panisset et al. [87] showed that TEWL values next to the wrist were found greater than on the other sites of volar forearm. Cua et al. [79] reported that the thigh had the highest reactivity and the palm the lowest. Dahl et al. [88] found that, for simultaneous Al-patch testing with SLS, the corresponding sites on the right and the left side were scored identically in only 53% of cases. Using large Finn chambers (12-mm), 84% of SLS patches showed identical visual score when tested simultaneously on right and left arms [66]. Rogiers [89] suggested that measurement of TEWL should be carried out on identical anatomic sites for all subjects involved, and the volar forearm is a good measurement site and corresponding places on the right and left forearms exhibit the same TEWL.

30.4.4 Skin Color

Bjornberg et al. [90] reported that fair skin and blue eyes showed the high intensity of the inflammatory response to a mechanical irritant. By determination of MED in Caucasians, the cutaneous sensitivity to UV light and to 7 different chemical irritants was found to correlate positively, while skin phototype based on complexion and history of sunburn proved less reliable [91]. In contrast to these reports, an inclination to increased susceptibility to SLS in black and Hispanic skin as compared to white skin was found when evaluated by measurement of TEWL [40, 92]. Assessing skin color by a tri-stimulus colorimeter, an association between light reflection (L*) from the skin surface and susceptibility to SLS was found [81]. Tanning may influence the susceptibility to irritants. A diminished reaction to SLS after UVB exposure was reported [93].

30.4.5 Skin Hydration

In repetitive exposure to SLS, higher susceptibility was reported in dry skin than in clinically normal skin in eczematous subjects and controls [75]. Comparing winter and summer skin, decreased skin hydration was found in winter, when a higher reactivity to SLS was also found [94]. Low outdoor temperature and low relative humidity in the winter lead to decreased ability of the stratum corneum to retain water [95]. Thus, these studies indicate that a decreased hydration state of the skin may be associated with impaired barrier function and increased skin susceptibility. In contrast, Lammintausta et al. [11] found no relationship between clinically dry skin and the response to repeated SLS exposure.

30.4.6 Sensitive Skin

Frosch and Kligman [96] reported a significant correlation between the skin response to particular irritants in healthy volunteers and patients with skin diseases. A 24-h forearm chamber exposure to 5% SLS was used for preselection of hyperreactors [12]. Murahata et al. [97] suggested a relationship between skin susceptibility to detergents and high baseline TEWL, and a highly significant correlation between baseline TEWL and TEWL after a single or repeated exposure to SLS was reported [10, 84, 85]. However, other studies reported an absent or poor correlation between baseline TEWL and TEWL after SLS exposure [40, 41, 92, 98].

30.4.7 Hyperirritable Skin (Excited Skin Syndrome)

Mitchell [99] introduced the term "angry back," describing the phenomenon of a single strong positive patch test reaction creating a back which is hyperreactive to other patch test applications. The "excited skin syndrome" was illustrated experimentally in guinea pigs, and increased susceptibility to an ointment containing 1% SLS was observed in animals stressed by inflammatory reactions in the neck area [100]. An increased susceptibility to SLS in patients with acute hand eczema, as compared to patients with

chronic or healed eczema, was reported [101]. Bruynzeel et al. [102] attempted to use SLS patches as markers of hyperirritability, and Agner [101] found the use of SLS to be useful as a marker of hyperirritable skin. Shahidullah et al. [103] reported increased TEWL values in the clinically normal skin of patients with eczema. But there was no significant difference in baseline TEWL values between patients with eczema and controls [101, 104].

30.4.8 Atopic Dermatitis

Several studies demonstrated a high risk for atopic persons to develop irritant contact dermatitis. Agner [105] reported that the increase in TEWL was not higher in atopics than in controls, but TEWL values before and after SLS were increased in atopics. Patients with atopic dermatitis in a quiescent phase were found to react more severely to SLS than controls as assessed by measurement of TEWL [75, 104], and there was an enhanced skin reactivity to SLS in patients with current atopic dermatitis compared to controls, when measured by visual scoring, increase in skin thickness [105], and laser Doppler flowmetry [106].

30.4.9 Hand Eczema

Baseline TEWL values in patients with localized, inactive, or healed eczema were not significantly higher than in controls [101, 104]. Agner [101] observed no increased skin reactivity to SLS in patients with chronic or healed eczema compared to controls, while hand eczema patients with acute eczema showed an increased skin reactivity to SLS compared to controls.

30.4.10 Seborrheic Dermatitis

There were several reports that patients with seborrheic dermatitis could be easily irritated to some chemicals including SLS [106, 107]. Tollesson and Frithz [108] observed increased TEWL values and abnormality in essential fatty acids in infantile seborrheic dermatitis, and they normalized TEWL values by applying the borage oil containing γ-linoleic acid.

30.5 Conclusion

It is clear that SLS data does not provide a unanimous opinion on all points. Yet, the preponderance of the observations suggest that we are beginning to understand some of the parameters, such as purity, dose, patch, anatomic site, single versus multiple application, and occluded versus open application, that influence diverse response of the skin irritation.

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