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Sodium laurilsulfate used as an excipient

Report published in support of the 'Questions and answers on sodium laurilsulfate used as an excipient in medicinal products for human use' (EMA/CHMP/606830/2017)

* Deletion of the E number. Please see the corrected Annex for further details.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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Executive summary

This document and the related questions and answers [32] have been written in the context of the revision of the Annex of the European Commission Guideline on 'Excipients in the label and package leaflet of medicinal products for human use' [3, 20].

Sodium laurilsulfate (SLS) is an alkaline, anionic surfactant. In medicinal products, SLS has a number of functional uses as an emulsifying agent, modified-release agent, penetration enhancer, solubilising agent, tablet and capsule lubricant. SLS is not used in parenteral products.

There is currently no EU regulatory guideline or recommendations in place relating to the acceptable levels of SLS in medicinal products. The scope of this safety assessment is limited to medicinal products applied to the skin or the scalp, such as creams, ointments, gels and shampoos, which contain SLS.

Authorised medicinal products contain SLS at concentrations ranging from 0.2% $^{w}/_{w}$ (e.g. creams) to 25% $^{w}/_{v}$ (in medicated shampoos). The number of topical products using SLS as an emulsifier is expected to be low, e.g. only 2.4% of all products licensed in the UK contain SLS.

Reported adverse reactions to SLS in topical pharmaceutical formulations are skin irritation following prolonged application. The skin irritancy is thought to be due its surfactant properties, producing disruption of cell membranes and conformational changes of proteins. In addition, disruptions of the skin barrier by several mechanisms have been described including a direct action on corneocytes leading to their swelling in size, denaturation of keratin structures via direct binding, elevation of stratum corneum pH and alteration of lipid synthesis in this layer, possibly as a result of local pH changes.

There is a paucity of data in humans on the dermal absorption, metabolism, distribution and excretion of SLS, however, in vitro studies indicates limited penetration into the dermis. Some dermal studies have been conducted in rats but it should be noted that relative to humans, the rat skin is relatively more permeable and has a greater propensity to metabolise xenobiotics compared to other mammals. Overall, the amount penetrating into human skin and entering the systemic circulation is expected to be very low, and the fraction that reaches the systemic circulation is likely to be metabolised in a similar manner to fatty acids.

A large number of publications attest to the skin damaging properties of SLS applied on its own, however case studies on formulated products are rare. The skin effects are more pronounced in patients with eczematous conditions. When used in cleaning products designed to be washed off quickly, such as shampoos and soap, SLS rarely displays any adverse events.

Skin sensitivity to SLS varies according to the concentration of SLS, contact time, patient population and experimental approaches. Furthermore, attempts to elucidate the skin irritation threshold in humans is found to be dependent upon the site of the application, the vehicle in which SLS is dissolved, the method of application, duration and frequency of application, the duration of the study, the presence of other skin-irritating excipients and whether the application is under occlusion.

Recommending a threshold for SLS in topical products is difficult to establish given the range of confounding factors. However, it is known skin irritant and is used as a positive (irritant) control in the cosmetic industry.

This review recommends a threshold of zero for SLS be applied to topical products for all age groups.

Introduction

There is currently no EU regulatory guideline or recommendations in place relating to the acceptable levels of sodium laurilsulfate (SLS) in medicinal products.

The vast majority of SLS use is in oral products (tablets and capsules) where it rarely displays any adverse reactions. It is not recommended for the injectable or ophthalmic routes.

Reported adverse reactions to SLS in pharmaceutical formulations are skin irritation following topical application. The skin irritancy is thought to be due its surfactant properties, producing disruption of cell membranes and conformational changes of proteins.

SLS (also known as sodium dodecyl sulfate or sodium lauryl sulfate) is an organic compound with the formula $CH_3(CH_2)_{11}OSO_3Na$. In medicinal products, SLS has a number of functional uses in pharmaceutical preparations as an emulsifying agent, modified-release agent, penetration enhancer, solubilising agent, tablet and capsule lubricant. SLS is not used for parenteral preparations.

Being derived from inexpensive coconut and palm oils, SLS is a common component of many domestic cleaning products such as hand soaps, washing-up liquid etc. SLS is not a permitted food additive in the European Union.

The scope of this safety assessment is limited to topical products such as creams, ointments, gels and medicated shampoos applied to the skin or the scalp that contain SLS. This review will not cover its use as an excipient for other dosage forms or routes of administration (e.g. tablets and capsules, liquids for oral administration or toothpastes), or where SLS is used as active ingredient (e.g. laxative enema preparations).

Scientific discussion

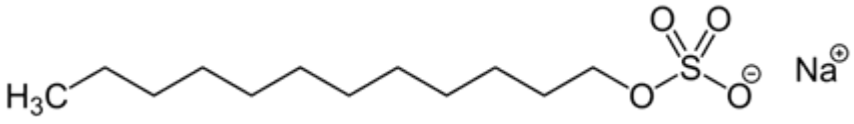
1. Characteristics

1.1 Category (function)

Anionic surfactant; emulsifying agent; modified-release agent; penetration enhancer; solubilising agent; tablet and capsule lubricant.

1.2 Properties

SLS is a mixture of sodium alkyl sulfates, which according to Ph. Eur 7.4 contains not less than 85% of sodium alkyl sulfates calculated as $C_{12}H_{25}NaO_4S$ i.e. sodium dodecyl sulfate (MW=288).



SLS is prepared by the sulfation of commercially available lauryl alcohol with either sulphur trioxide or chlorosulfonic acid. The product of this reaction is then neutralised with aqueous sodium hydroxide or sodium carbonate. Lauryl alcohol is in turn usually derived from either coconut oil or palm kernel oil by hydrolysis, which liberates their fatty acids, followed by hydrogenation. Due to the synthetic method, commercial samples of SLS are often a mixture with other alkyl sulfates, dodecyl sulfate as the main component.

SLS is available commercially in powder and pellet forms. The salt is a 12-carbon chain attached to a sulfate group giving the material the amphiphilic properties required of a detergent. Sodium coco-sulfate is essentially the same compound, but made from less purified coconut oil. A related surfactant, Sodium Laureth Sulfate (SLES) is more widely used as a detergent and surfactant in personal care products (soaps, shampoos, toothpaste etc.) and in some medicated shampoos. SLES is effective over a wide pH range, both in acidic and alkaline solution and in hard water (because of the solubility of the corresponding calcium and magnesium salts i.e. no common ion effect). It differs from SLS by virtue of presence of ethoxyl groups [$(OCH_2CH_2)_n$] in the backbone where n=3 or more, which is thought to give SLES extra foaming activity. Triethanolamine lauryl sulphate is also occasionally used in medicated shampoos.

SLS occurs as white or cream to pale yellow-coloured crystals, flakes, or powder having a smooth feel, a soapy, bitter taste, and a faint odour of fatty substances. The alkaline salt exhibits a pH = 7.0–9.5 (for a 1% $^{w}/_{v}$ aqueous solution); small amounts are sufficient to raise the pH of semi-solid preparations significantly enough to cause degradation of compounds, for example when diluents such as emulsifying ointment, which contains SLS, are used for compounding steroidal preparations. For this reason (and because of its skin irritancy properties discussed later), some manufacturers have removed SLS as a semi-solid emulsion stabiliser and replaced it with alternatives.

As a surfactant, SLS has bacteriostatic properties given its pore-forming ability in lipid membranes. It displays some action against Gram-positive bacteria, although it is ineffective against many Gram-negative microorganisms. It therefore is used in skin cleansing and medicated shampoo products, although SLES is more often used due to its better foaming properties. SLS potentiates the fungicidal activity of certain substances such as sulfanilamide and sulfathiazole, and has been demonstrated to exert microbicidal activity against Human Immunodeficiency Virus Type I.

1.3 Use in medicinal products

SLS has a number of functional uses in pharmaceutical preparations as an emulsifying agent, modified-release agent, penetration enhancer, solubilising agent, tablet and capsule lubricant. Table 1 lists the applications and concentrations typically used.

Table 1: Uses of SLS as an excipient (modified from The Handbook of Excipients [21])

Use	Concentration
Skin cleanser in topical applications	1% $^{w}/_{v}$
Tablet lubricant (for dispersible tablets)	0.5–2% $^{w}/_{w}$
Wetting agent in dentifrices (toothpastes)	1–2% $^{w}/_{w}$
Releasing agent in suppositories and pessaries	0.4–1% $^{w}/_{w}$
Dissolution / wetting agent in solid oral dosage forms	0.2–1.5% $^{w}/_{w}$
Foaming / lathering agent in shampoos	10–25% $^{w}/_{v}$

1.4 Regulatory status

SLS is a Generally Regarded as Safe (GRAS) excipient and is included in the FDA Inactive Ingredients Database (dental preparations; oral capsules, suspensions, and tablets; topical and vaginal preparations). In the EU, SLS is included in non-parenteral medicines.

2. Pharmaco-toxicological data

Given its long history of use, a wide range of non-clinical studies including acute and chronic toxicity studies, reproductive toxicity, mutagenicity studies and acute skin and ocular irritation studies have been conducted with SLS. The majority of these studies are not modern and were conducted before the introduction GLP according to the standards of the time but provide sufficient information to make a risk assessment. The non-clinical safety data for SLS has been reviewed in detail [11, 12, 36]. SLS is a moderately toxic material with acute toxic effects including irritation to the skin, eyes, mucous membranes, upper respiratory tract and stomach. The toxicity of SLS derives primarily from its surfactant properties, producing disruption of cell membranes and conformational changes of proteins.

2.1 Acute toxicity studies

SLS was moderately toxic in oral single dose studies in rats with LD_{50} values reported in the 0.8–3.1 g/kg range across a number of studies. The dermal acute dermal LD_{50} for SLS in rabbits was > 10 g/kg, with findings dermal irritation included severe erythema and oedema with sub-dermal haemorrhaging [11].

2.2 *Repeat-dose toxicity*

In a 13-week study in rats fed dietary levels of 0.004%, 0.02%, 0.1%, or 0.5% SLS the only significant finding was an increase in absolute organ weights in 0.5% group, and increased hepatic weights in females in the 0.5% group [35]. In weanling male rats fed for five months drinking water containing 0%, 0.05%, or 0.25% concentrations of SLS, at the highest concentration (0.25%), the weights of the lung and kidney were increased [19]. A chronic oral feeding study in rats of 0.25%, 0.5% or 1.0% SLS in the diet for two years produced no gross and microscopic abnormalities, nor did a similar two year study with 0.2% detergent in the diet [17]. A chronic oral one year toxicity study using beagle pups was conducted on 0%, 0.67%, 1.0%, or 2.0% SLS. Decreased weight gain occurred in the 2% group, but no other gross or microscopic abnormalities were noted [11].

2.3 *Genotoxicity*

SLS is reported to be negative in Salmonella mutagenicity tests [29] and in the mouse lymphoma forward mutagenicity test [26]. In vivo studies with rats fed 1.13% and 0.56% SLS in the diet for 90 days gave no indication of clastogenic effects [22].

2.4 *Carcinogenesis*

No conventional life-time rodent studies of carcinogenicity have been performed with SLS. However, there is no evidence from genotoxicity studies or chronic toxicity studies suggestive of carcinogenicity or from studies with related alkyl sulphates [30].

2.5 *Reproductive and developmental toxicity*

The developmental toxicity of SLS was evaluated in rats, rabbits and mice following oral dosing. Effects on litter parameters were restricted to doses causing significant maternal toxicity such as anorexia, weight loss, and death (doses between 300 and 500 mg/kg/day) and principal effects such as higher foetal loss and increased incidences of total litter losses. Apart from a higher incidence of delayed ossification or skeletal variation seen in mice at ≥ 500 mg/kg/day, which is indicative of delayed development, the incidences of malformations and visceral and skeletal anomalies were

unaffected [17]. The effect of dermal application of SLS on pregnant mice and their foetuses has been described. Daily applications of 1.5 ml/kg of 0.4%, 4.0%, and 6.0% aqueous SLS were made to a 3 x 3 cm^2 shaved areas of the backs of three groups of mice on Days 6–13 of pregnancy. There was a reduction in maternal weight and growth rate with application of the detergent, and the pregnancy rate was lowered for mice in the 6% treatment group. Delayed ossification and reduced foetal weight were observed in the 4% and 6% SLS-treated groups [33].

2.6 *Local tolerance*

A wide range of non-clinical acute skin irritation studies of SLS have been conducted which have largely been superseded by clinical data (see Section 4). These show that application of solutions containing 0.5–10% SLS cause slight to moderate irritation [11, 36). Applications of 10–30% SLS caused skin corrosion and severe irritation. In acute ocular tests, 10% SLS caused corneal damage to the rabbits' eyes if not irrigated, or if irrigation was delayed [11]. Upper respiratory tract irritation and inhibition of respiration in mice and rabbits was caused by SLS aerosols at 88 µg/l [7].

3. Pharmacokinetics (in humans)

3.1. ADME (absorption, distribution, metabolism, elimination)

There are no reports of either oral or dermal SLS pharmacokinetic studies in humans. Data for the topical route is the most relevant for this review although reference is made to oral studies for metabolism and excretion aspects. It is pertinent to note that the majority of medicinal products containing SLS were authorised several decades ago at a time where systemic exposure of excipients from topically applied products was not requested.

Absorption

In adult human skin, no measurable in vitro ^{14}C radiolabelled SLS penetration occurred until 24 h after application; however, the authors reported that penetration was rapid during the next 24 h [5]. Above the critical micelle concentration (0.24%), increased surfactant concentration did not appreciably alter the abundance of free surfactant molecules for dermal penetration; additional surfactant monomers simply formed more micelles, which could not readily penetrate because of their supra-molecular large size. However, after washing isolated human skin with 1% ^{35}S-radiolabelled SLS, it was observed that the amount of SLS penetrating was 50-100 times higher than that from a 0.1% solution but penetration form a 10% solution was only 10 times higher than from the 1% solution. In conclusion, SLS monomers did not appear to behave proportionally to the concentration applied on to the skin surface [25].

However, caution should be exercised with in vitro studies. A comparison of radiolabelled SLS penetration into living and excised guinea pig skin has shown that in vivo penetration occurs to a depth of 800 µm whereas in non-living skin absorption was limited to around 250 µm [6].

Distribution

There is confounding data of the extent of SLS entry into the systemic circulation following dermal application. Most studies distribution indicates confinement to the skin, specifically to the dermis. This property is made use of as a model skin irritant since it fulfils the important characteristics for experimental skin irritant: lack of systemic toxicity, not being a carcinogen or a sensitiser, chemically well-defined, lack of extreme pH value and tolerability to test subjects. However, one study in rats has shown that following a 10-minute application of 1% radiolabelled SLS to the skin, approximately 40%

of the radioactivity was found in the urine. Rats were kept in individual metabolic cages and the skin not protected with a patch. No such studies in primates are available in the published literature but it should be noted (as seen in the next section) that relative to humans, rat skin is relatively more permeable and the rat has a greater propensity to metabolise xenobiotics compared to other mammals [6].

Metabolism

Metabolic data is only available for the oral route. After administration of ^{35}S radiolabelled SLS in pigs for 8 days 90% of ^{35}S was recovered in the urine and 10% faeces. Traces of ^{35}S remained in the carcasses of pigs and some free ^{35}sulphate ions were detected in the urine. The distribution of ^{35}S in the body was similar to that found after administration of radiolabelled sodium sulphate. The authors concluded that SLS was extensively absorbed from the intestine and that only a small amount of the surfactant was degraded to the free sulfate. In rats, rapid intestinal absorption and appearance in urine was also seen, however, approximately 20% of the urinary ^{35}S was present as inorganic sulfate. The remainder was present as a single sulfate ester but not as the parent compound. The ^{35}S-labelled metabolite was more polar than the parent compound (potassium laurilsulfate) and was most likely butyric-acid-4-sulphate. This suggests that the rat is capable of metabolising n-alkyl sulfate such as SLS by ω-oxidation of the hydrophobic part followed by β-oxidation of the resulting carboxylic acid [6].

Excretion

ADME of ^{14}C-radiolabelled SLS across guinea pig skins has been studied in vivo. Radiolabelled SLS in water (16.3 µCi in 0.6 ml) was applied as a solution to the flanks of the animal by rubbing for 10 minutes and the covered by non-occlusive patches for 24 h. No radioactivity was found in faeces, liver, kidney or carcass; 0.1% was found in urine and a further 0.1% in exhaled CO_2. 50.2% was found on the skin at the site of the application, 47% in the skin rinsings and 2.3% was retained in the patch. No attempts were made by the authors to determine if the skin-associated SLS was located in the epidermis or dermis. Over a 24 h period, less than 0.4% of SLS had penetrated into the systemic circulation. The investigators concluded that the presence of the strongly anionic terminal group of SLS impaired its ability to penetrate through the skin [31].

Overall, from these reports it may be concluded that while dermal transfer of SLS through to the systemic circulation in humans is likely to be very low (< 1%), any that does escape to the blood is likely to be metabolised in the liver by cytochrome P450-dependent oxidation before being excreted via the urine. It appears unlikely that the majority of systemic SLS would be excreted unchanged. The radio-labelled studies do not give sufficient information about the metabolites, but the available data suggests that the parent compound is not found in urine. It is possible that in mammals alkyl sulphonates are probably metabolised via omega and beta oxidation of the alkyl chain akin to fatty acid metabolism. The major metabolite could therefore be a C_4 sulphonate.

3.2. Interactions

Interactions are mainly reports of SLS-mediated sensitisation to metals. Thus, while neither nickel nor SLS alone would cause an eczematous response, the combination did generate contact dermatitis in guinea pigs. Nickel particles were found deep in the skin tissue. The authors attributed the effect to an increase in the ‘water channel’ volume of the stratum corneum [6]. Kligman has described the SLS provocative patch test, a “method to reveal the threshold states of sensitisation” [23]. The procedure calls for pre-treatment of the test site to 10% SLS for 1 h before applying the test allergen. The test was developed as earlier studies had shown that SLS to enhance skin permeability and therefore to foster sensitisation. In this test, SLS can also be combined with the test allergen provided no

incompatibility exists between the surfactant and the test allergen [23]. As lower levels of SLS can start to alter skin permeability, clinically there is the potential that SLS can induce sensitisation to other, excipients or the active of the formulation.

4. Clinical safety data

4.1. Use: routes of administration, range of concentrations

At the time of compiling this report, examination of data from one member state listed 1646 licensed products containing SLS. The vast majority were for oral solid dosage forms (96%) of which the two largest groups were for coated and uncoated tablets and hard capsules. Products indicated for cutaneous route (creams, ointments, topical gels etc.) comprised only 2.4% or 38 products of which 26 were creams.

4.2. Adverse effects

Adverse reactions to SLS in cosmetics and pharmaceutical formulations mainly are reports of irritation to the skin following prolonged topical application particularly with emollients. Paradoxically, dermatitis is made worse with hydrocortisone cream containing SLS [16]. A recent UK safety review of a nationally authorised emollient product also reported such findings, particularly in the paediatric population [27].

As a mucosal irritant, this property is utilised in combination preparations used as enemas for the management of constipation. When used in products designed to be washed off quickly, such as shampoos, soap and toothpastes, SLS rarely displays any adverse events.

SLS is a moderately toxic material with acute toxic effects including irritation to the skin, eyes, mucous membranes, upper respiratory tract, and stomach. As such, it has become the standard reagent for experimental patch testing when investigating the effectiveness of topical anti-inflammatory drugs [15] or when comparing the irritancy potential of new cosmetic formulations. In skin tests, amounts varying from 0.25% to 10% are typically left on the skin for 24–48 h. Skin reaction is related to the purity of SLS. For example, Table 1 displays that SLS with a purity of 99% produced significantly stronger skin reactions compared to a laboratory reagent (Ph. Eur. 96.5%) grade as evaluated by four clinical tests [1].

Table 2: Median values (25/75% percentiles) for clinical grading, transepidermal water loss, blood flow and skin thickness for SLS patches using ultrapure (99%) and Ph. Eur. quality (96.5%) grades

	Ultrapure commercial grade (99%)	Ph. Eur grade (96.5%)	p-value
Clinical grading	2 (1–1.25)	1 (0.75–1)	P < 0.05
Transepidermal water loss	30.2 (22.3–40.6)	22.1 (15.7–28.4)	P < 0.05
Blood flow	82 (37–101)	37 (22–51)	P < 0.01
Oedema	1.5 (1.22–1.77)	1.25 (1.05–1.41)	P < 0.02

Dermatitis from SLS in hydrocortisone cream (1984)

Eubanks and Patterson [16] cited a patient who developed contact dermatitis to SLS (1%) found in the prescribed Hydrocortisone cream USP. Marked exacerbation of eczematous dermatitis responded

slowly over 3 weeks to cool water compress and fluocinonide 0.05% cream. Patch testing to individual components of the hydrocortisone cream (synthetic wax SX, beeswax, white petrolatum, light mineral oil, glycerine, methyl paraben and SLS) was negative for all excipients except SLS. Patch results were scored according to the North American Contact Dermatitis Group guidelines. Interestingly, the patient was sensitive to as little as 0.5% SLS in the closed patch test compared to the open test where concentration of 5% was required to elicit the same level of response.

Given that in clinical usage the patient applied the cream in the open form, this would suggest that the reaction to SLS was augmented by the other excipients in the formulation. However, the authors did not elucidate this combination.

Irritation by Hydrophilic Ointment under Occlusion (1973)

Bergstresser and Eaglstein [4] studied the effect of Hydrophilic Ointment USP, which contains 1% SLS, on the forearms of non-eczematous hospitalised patients and staff members. As a control, a vehicle similar to hydrophilic ointment was tested containing 2% polyoxyl 40 stearate as a substitute for SLS. Both applications were left on overnight under occlusion and the process repeated over 3–7 days. All subjects using the hydrophilic ointment developed dermatitis after 3 to 5 days occlusive treatment. In contrast, subjects using the ointment with 2% polyoxyl 40 stearate did not develop dermatitis after 7 days. To further elucidate if SLS was truly the causative agent, ordinary patch tests were applied to the skin of the back containing either a paraben mix in white petrolatum (methyl, ethyl, propyl, butyl and benzyl, 3% each), 1% propylene glycol in white petrolatum, 1% stearyl alcohol in white petrolatum or 1% SLS (the authors did not specify the vehicle but one assume it was white petrolatum). Variable results were produced in the 9 test subjects: after 48h, four had no reaction to SLS, three reacted but reactions were not typical of contact allergic dermatitis, one developed redness without vesiculation which disappeared after 24h and the remaining two developed persistent redness without vesiculation. No results were reported for the other excipient mixtures.

Again, it appears that the variability in adverse events to SLS may be dependent upon the presence of other excipients. It is possible that, as could be the case report of Eubanks and Patterson [16], adverse skin reactions to SLS may be augmented at concentration lower than 1%.

Adverse Event Reports from the UK

The Yellow Card Scheme is the UK system for collecting information on suspected Adverse Drug Reactions (ADRs) to medicines. Using this resource, 23 of the list of 38 topical products containing SLS were shown to induce a range of ADRs (Table 2).

Analysis of ADRs from the UK database shows, however, shows a lack of correlation between the SLS concentration and the absolute number of cutaneous ADRs reported via the Yellow Card Scheme. Cutaneous ADRs included the following terms (according to Medical Dictionary for Regulatory Activities classification): Pruritus, Rash, Rash generalised, Rash maculo-papular, Rash pustular, Rash Erythematous, Urticaria, Application site reaction, Skin exfoliation, Erythema, Rash popular, Blister, Dermatitis contact, Dermatitis exfoliative, Dermatitis allergic, Burning sensation, Skin irritation and Eczema. It must be remembered that under-reporting of ADRs is a well-known phenomenon, which is likely to be more pronounced for less severe reactions such as those observed with SLS. Patients simply stop using the product, particularly if it has been purchased over the counter, and through trial and error find one that is acceptable for their skin condition. This is the recommendation from various patient groups such as the National Eczema Society of Great Britain.

A lack of correlation can also be due other factors such as the number of patients using the product, frequency and duration of use and the application area size etc. For example, despite the very high levels of SLS in medicated shampoos, ADRs are virtually absent. This could be due to short contact

time of the shampoo with the scalp before being rinsed off as opposed to creams, which are rubbed into the skin. For example, an anti-viral cream displays that out of 1082 ADRs, 179 were of cutaneous origin but this may be confounded by the nature of the condition and/or other excipients.

Table 3: Total and cutaneous specific ADRs as a function of SLS content*

Name	SLS %	Total ADRs	Skin ADRs
Anti-infective cream	0.16%	0	0
Muscle rub	0.19%	0	0
Breast-feeding nipple cream	0.36%	12	8
Emollient lotion for dry skin	0.45%	0	0
Anti-itch cream	0.45%	52	28
Emollient cream	0.50%	0	0
Antiseptic cream	0.50%	1	1
Acne cream	0.50%	32	11
Emollient cream	0.52%	5	2
Anti-hyperpigmentation cream	0.60%	0	0
Antiseptic cream	0.75%	0	0
Anti-viral cold sore cream 1	0.75%	1082	179
Anti-viral cold sore cream 2	0.80%	0	0
Emollient cream	0.87%	34	23
Acne gel	0.87%	44	24
Muscle Rub	0.97%	0	0
Anti-psoriasis cream 1	1.00%	0	0
Anti-psoriasis cream 2	1.00%	19	10
Rozex Cream	1.25%	16	3
Anti-infective cream	1.50%	0	0
Anti-fungal vaginal cream	2.50%	604	47
Anti-psoriasis shampoo	17.80%	0	0
Anti-dandruff/fungal shampoo	25.00%	9	4

*Compiled 11th February 2013

Mechanism of SLS-mediated Adverse Events

Negatively-charged surfactants, such as SLS, comprise saturated or weakly unsaturated hydrocarbons chains to which a hydrophilic group, generally a strong acid such as a sulfate (-O-SO_3) or sulfonate (-SO_3), is linked. The irritancy of anionic surfactants is most likely due to their surface-active properties (i.e. disruption of cell membranes bilayers) but may also include their ability to denature proteins by binding to the positively-charged side groups, including enzymes resulting in inflammatory immune responses. Aqueous solutions of SLS produce a mild to moderate (but seldom severe) inflammatory reactions following prolonged contact, a property made use of in the cosmetics industry when designing new formulations. A sufficient inflammatory response can be produced, rendering the epidermis more permeable to express the sensitisation of a topical formulation.

Repeated, prolonged exposure to dilute solutions of SLS can cause drying and cracking of the skin ensuing to contact dermatitis, although regulatory compliant randomised controlled trials are lacking, and some experimental designs could be questioned in terms of an adequate comparator, or lack of controls [2]. However, basal transepidermal water loss, skin thickness, blood flow and skin colour have been examined before and after exposure of 28 patients with atopic dermatitis and 28 healthy controls to SLS [18]. Transepidermal water loss was measured with an evaporimeter, skin thickness by

ultrasound A-scanning, blood flow by laser Doppler flowmetry and skin colour by a chroma meter. Patients with atopic dermatitis were found to have higher basal transepidermal water loss than controls ($p < 0.0001$), and had an inclination towards an increased basal skin thickness ($p = 0.056$). No statistically significant differences were found with respect to basal blood flow or skin colour. The skin response to SLS was found to be statistically significantly increased in atopic patients compared with controls when evaluated by visual scoring and by increase in skin thickness, but not by increase in transepidermal water loss, blood flow or skin colour.

SLS is thought to disrupt the skin barrier by several mechanisms including a direct action on corneocytes leading to their swelling in size, denaturation of keratin structures via direct binding, elevation of stratum corneum (SC) pH and alteration of lipid synthesis in this layer, possibly as a result of local pH changes [9]. With respect to the effect of SLS on SC structure, the increase in transepithelial water loss (TEWL) has been correlated with intercellular lipid disorganisation and perturbation of lamellar bodies in the stratum compactum. The solubilisation and removal of SC lipids by SLS has also been deduced following the application of SLS at the similar concentration at which it is present in Aqueous Cream BP (~1%$^{w}/_{v}$). Not only does such an effect cause the TEWL to rise, it can permit a more facile penetration of irritant and sensitising xenobiotics from the environment. Further, it is important to note that the deleterious actions of SLS described have been seen upon treatment of normal skin with a competent barrier. Such adverse events are likely to be higher in patients with broken skin barrier such as that found in eczematous conditions as reviewed by Cork et al [9] who reported that environmental factors including the use of soap and detergents exacerbate epidermal barrier breakdown. This has been attributed to the elevation of stratum corneum pH; a sustained increase in pH enhances the activity of degradatory proteases and decreases the activity of the lipid synthesis enzymes. Measurements of lipid solubilisation by SLS indicate that, at concentrations ranging between 0.1 and 2%, the detergent initiates the removal free fatty acids, cholesterol, and esters. The most direct connection of the enhanced adverse reactions by SLS in disrupted skin barrier has been shown by Cowley and Farr [13] who reported a dose-response study of irritant reactions to SLS in patients with seborrhoeic dermatitis and atopic eczema.

4.3. Safety in special populations

In 2012 the MHRA undertook a review of Aqueous Cream (which contains 0.9% SLS) following reports of possible worsening of symptoms in paediatric patients with eczema [27]. This emanated from a series of publications in the period 2010–12 on adverse events associated with the use of Aqueous Cream BP. In addition Paediatric clinical guidelines from NICE and the National Eczema Society (UK) had previously reported similar findings when Aqueous Cream was used as a leave-on emollient but not when used as a wash product (as the product is rinsed off). Following this review, the MHRA issued the following advice:

- Aqueous Cream may cause local skin reactions, such as stinging, burning, itching, and redness, when it is used as a leave-on emollient, particularly in children with atopic eczema. The reactions, which are not generally serious, often occur within 20 minutes of application but can occur later. Reactions may be due to the presence of SLS or other ingredients.
- If a patient reports or shows signs of skin irritation with the use of aqueous cream, treatment should be discontinued and an alternative emollient that does not contain SLS should be tried.

Tsange and Guy [34] investigated the effects on the skin barrier function of skin health adult volunteers after application of Aqueous Cream BP. The left and right volar forearms of six human volunteers were each separated into treated and control sides. The treated sides of each forearm were subjected to twice daily applications of Aqueous Cream BP for four weeks at the end of which

concomitant tape-stripping and TEWL measurements were made. The untreated sides of the forearms were not exposed to any products containing SLS during the study period. Changes in stratum corneum (SC) thickness, baseline TEWL and rate of increase in TEWL during tape stripping were observed in skin treated with Aqueous Cream manufactured using the British Pharmacopoeia formula. The mean decrease in SC thickness was 1.1 µm (18%) ($P = 0.0016$) and the average increase in baseline TEWL was 2.5 g.m-2.h-1 (32%) ($P < 0.0001$). Reduced SC thickness and an increase in baseline TEWL, as well as a faster rate of increase in TEWL during tape stripping, were observed in 16 out of 27 treated skin sites. Mohammed et al [28] had earlier shown in human volunteers that the application of 2 ml of Aqueous Cream BP for 10 min to the treatment sites (approximately 40 cm^2) twice a day for 28 days led to decreased corneocyte maturity and size, increased protease activity (of the desquamatory kallikrein proteases, KLK5 and KLK7, and the inflammatory proteases tryptase and plasmin) and TEWL compared with untreated sites ($P < 0.05$). In addition, the amount of protein removed from deeper layers of treated sites was significantly lower than from untreated sites.

The authors noted that while the origin of the reaction could also have been due to the presence of either chlorocresol or phenoxyethanol, which have been reported as skin irritants, an equally likely suspect was SLS. It is pertinent to note that Aqueous Cream BP was initially designated as a wash product (soap substitute) rather than as a leave-on emollient, as it is now generally prescribed and used for skin moisturisation purposes in the UK. The authors concluded that the application of Aqueous Cream BP, containing 0.9% SLS reduced the SC thickness of healthy skin and increased its permeability to water loss. These observations called into question the continued use of this emollient on the compromised barrier of eczematous skin.

Aqueous Cream BP contains the preservatives phenoxyethanol, chlorocresol and/or parabens (two different compositions are listed in the British Pharmacopoeia). The latter two have been implicated in skin irritancy and are listed in the Guideline ‘Excipients in the label and package leaflet of medicinal products for human use (2003)’ [20] as agents that may cause allergic reactions. The study of Tsange and Guy [34] could have benefited from using a comparator cream that lacked SLS, for example, by formulating a compounded preparation with a non-ionic surfactant and using design of experiments.

The investigations of Tsange and Guy were prompted by an earlier study conducted in 2003 by Cork et al [8], which reported the results of a clinical audit in children, comparing the percentage of episodes of exposure to Aqueous Cream BP associated with immediate cutaneous reactions compared to all other emollients associated with these reactions. The notes of 100 children aged 1 to 16 with atopic eczema attending a paediatric dermatology clinic at Sheffield Children’s Hospital were assessed. 56% of the episodes of exposure to aqueous cream were associated with an immediate cutaneous reaction (defined as one or more of burning, stinging, itching and redness, developing within 20 min of application). 17.8% (111 out of 622) of episodes of exposure to other emollients (14 types available in the British National Formulary) were also associated with an immediate cutaneous reaction. The difference was reported to be statistically significant ($p < 0.001$). The authors concluded that the key to successful emollient therapy was education and tailoring the treatment to the individual child. The authors concluded that Aqueous Cream BP should only be used as a soap substitute and not as a leave-on emollient. The study did not report details of other emollients used. Furthermore, the paper appeared to infer that SLS was the causative agent.

Cork and Danby [10] re-investigated this aspect and reviewed a number of studies on the effects of aqueous cream in the skin of healthy volunteers and patients with atopic eczema. The authors concluded that the evidence suggested that aqueous cream, used as a leave-on emollient, was an important negative environmental factor contributing to skin barrier damage and the exacerbation of atopic dermatitis. This paper further highlighted the importance of not using emollients containing SLS, such as Aqueous Cream BP, because they exacerbated rather than reduced skin barrier damage.

Paediatric clinical guidelines and formularies in the UK had previously warned that aqueous cream could be associated with stinging when used as a leave-on emollient but could be used safely as a wash product. The difference in the irritation potential was related to the contact time with the skin as soap cleansers are largely removed in the washing process. It was widely recognised that patients with eczema were encouraged to try a range of emollient products in order to find the one most suitable for an individual given the heterogeneity of the eczematous conditions and the immune responses exhibited by individuals.

It is important to note that Aqueous cream, first appearing in the British Pharmacopoeia in 1959, was originally intended as a soap substitute and designed to be rinsed of quickly. Likewise, the FDA-supported Cosmetics Ingredient Review Panel [12] following its reassessment of SLS in cosmetic formulations, recommended that SLS appears “to be safe in formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin. In products intended for prolonged contact with skin, concentrations should not exceed 1%”.

5. Risk assessment and thresholds

This risk assessment is limited to topical products containing SLS as an excipient such as creams, ointments, gels and medicated shampoos applied to the skin or the scalp.

Given its long history of use, a range of non-clinical studies including acute and chronic toxicity studies, reproductive toxicity, mutagenicity studies and acute skin and ocular irritation studies have been conducted with SLS. SLS is a moderately toxic material with acute toxic effects including irritation to the skin, eyes, mucous membranes, upper respiratory tract and stomach. The toxicity of SLS derives primarily from its surfactant properties, producing disruption of cell membranes, cytokine release and conformational changes of proteins.

Sensitivity to SLS will vary according the type of formulation (and effects of other excipients), the concentration of SLS, the site of application, contact time, patient population and experimental methodologies. In the latter case, attempts to elucidate the skin irritation threshold in humans is found to be dependent upon the site of the application, the vehicle in which SLS is dissolved, the method of application (cream vs. filter paper), duration and frequency of application, the duration of the study (hours to weeks) and whether the application is under occlusion (patch or Finn chambers) or open. These factors have been summarised in a review by Lee and Maibach [24], who, in addition discuss biological and pathophysiological factors such as patient age and gender, skin sensitivity, hydration level, colour, thickness and disease. Such confounding experimental data does not lend itself well in attempting to derive a meaningful threshold for SLS in topical medicinal preparations for any age group. However, it has been known that sensitive patients such as those with chronic skin conditions are more prone to adverse skin reactions to SLS.

The irritant properties of SLS are well recognised. Skin irritation studies in mice, rats and rabbits using doses of SLS as low as 0.1% has demonstrated slight to moderate irritation under occluded patches [34]. Similar results have been obtained on human skin. SLS has become the standard reagent for experimental patch testing when investigating the effectiveness of topical anti-inflammatory drugs or when comparing the irritancy potential of new cosmetic formulations. In such skin tests, amounts varying from 0.25% to 10% are typically left on the skin for 24–48 h. The epidermal permeability barrier is mainly provided by the stratum corneum, a complex made up of intracellular lipids and corneocytes that form a highly ordered structure. Aqueous solutions of SLS have been shown to cause cutaneous irritation and elevate transepidermal water loss at concentrations of 1% and less. SLS is thought to disrupt the skin barrier by several mechanisms including a direct action

on corneocytes leading to their swelling in size, denaturation of keratin structures via direct binding, disruption of lipid bilayers layers and elevation of stratum corneum pH.

Skin irritation after exposure SLS is time and dose dependant. In the context of topical pharmaceutical formulations adverse reactions to SLS in cosmetics and pharmaceutical formulations are mainly reports of irritation to the skin following prolonged topical application. When used in products designed to be washed off quickly, such as shampoos and soap, SLS rarely displays any adverse events.

Skin irritation after exposure to SLS is known to vary considerably between individuals and may be related to differences in the integrity of the skin barrier. Patient populations with decreased skin barrier functions such as in atopic dermatitis have been shown to be more sensitive to the irritant properties of SLS. The thickness of the SC also varies considerably according to the body site and with age and is an important factor in the sensitivity to SLS.

In clinical practice, actual exposure of SLS, surfactant exposure via topical semi-solid preparations is usually of short duration, open application and cumulative. Thus, experimental studies using a single challenge of the skin to SLS is a transient reflection of skin susceptibility, which does not take into account the cumulative effect of long-term damage or repair mechanisms of the skin. Therefore, studies using methods that mimic the clinical situation, such as the repeated open application test and soak/wash test, may be more relevant. However, even in these studies, SLS is applied as an aqueous solution. Therefore, clinical case reports that cite adverse event reports to medicinal products (cream or ointment) containing SLS to derive a meaningful threshold are the most relevant sources. In this respect, a number of studies have been reviewed and summarised in the preceding section.

In concluding this review, reporting a threshold for SLS in topical products is difficult to establish given the range of confounding factors. However, it is known skin irritant and sees use as a standard irritating agent in the cosmetic industry. The benefit-risk balance has to be established individually for each medicinal product taking into account the duration of usage, the contact time with skin and augmentation of skin irritation in concert with other excipients in the formulation. The applicant or the market authorisation holder should provide a justification for the inclusion of SLS. It is proposed to have a threshold of zero for SLS in topical products.

6. Information for the package leaflet

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Sodium laurilsulfate	Cutaneous	Zero	This medicine contains x mg sodium laurilsulfate in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>. Sodium laurilsulfate may cause local skin reactions (such as stinging or burning sensation) or increase skin reactions caused by other products when applied on the same area.	The thickness of the skin varies considerably according to the body site and with age and can be an important factor in the sensitivity to sodium laurilsulfate (SLS). Sensitivity to SLS will also vary according the type of formulation (and effects of other excipients), the concentration of SLS, contact time and patient population (children, hydration level, skin color and disease). Patient populations with decreased skin barrier functions such as in atopic dermatitis are more sensitive to the irritant properties of SLS.

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