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Final Report on the Safety Assessment of TEA-Lauryl Sulfate

TEA-Lauryl Sulfate is the triethanolamine salt of lauryl sulfuric acid. It is used in cosmetics as a detergent, a stabilizer and a solubilizer. The ingredient was moderately to slightly toxic in acute oral studies with rats; reported LD50s ranged from 0.27 to >1.95 g/kg. Animal studies showed that the surfactant is a significant skin and eye irritant. In clinical studies, shampoos containing 10.5% TEA-Lauryl Sulfate caused no irritation under semioccluded conditions. Diluted shampoos containing 0.15–7.5% of the surfactant caused human skin reactions ranging from no irritation to moderate irritation. This skin irritation phenomenon is observed with most detergents. Undiluted shampoos containing 10.5% TEA-Lauryl Sulfate showed low potential for eliciting human skin sensitization. No evidence of photosensitization was observed in subjects exposed to solutions containing up to 0.42% TEA-Lauryl Sulfate. On the basis of the available animal and human data, the Panel concludes that TEA-Lauryl Sulfate can be used without significant irritation at a final concentration not exceeding 10.5%. Greater concentrations may cause irritation, especially if allowed to contact the skin for significant periods of time.

CHEMICAL AND PHYSICAL PROPERTIES

Definition and Structure

TEA-LAURYL Sulfate is the triethanolamine salt of lauryl sulfuric acid and conforms to the formula:[1]

$$CH_3(CH_2)_{10}CH_2OSO_3 : HN(CH_2CH_2OH)_3$$

TEA-Lauryl Sulfate (CAS No.:139-96-8) is also known as Triethanolamine Lauryl Sulfate, Triethanolammonium Lauryl Sulfate and Triethanolamine-1-Dodecyl Sulfate.[1,2]

Properties

TEA-Lauryl Sulfate is a viscous, yellow liquid or vaseline-like substance having a faint characteristic odor.[3,4] It is completely miscible with water at all temperatures. At "low" temperatures it forms a gel.[4] Additional chemical and physical properties are presented in Table 1.

TEA-Lauryl Sulfate is an anionic "surface-active agent."[3] A surface-active agent may be defined as "any compound that reduces surface tension when dissolved in water or water solutions, or which reduces interfacial tension between two liquids or between a liquid and a solid."[5] The terms "detergent" or "surfactant" are also frequently used to indicate surface-active compounds.[5,6] Anionic surfactants such as TEA-Lauryl Sulfate are characterized by a structural balance between a negatively charged hydrophilic group and a lipophilic residue.[6]

Surfactants may lose their surface-active properties if the cosmetic products in which they are

TABLE 1. CHEMICAL AND PHYSICAL PROPERTIES OF TEA-LAURYL SULFATE.

Properties	*Reported value*	*Ref.*
Molecular formula	$C_{18}H_{41}NO_7S$	3
Molecular weight	415.59	3
Nitrogen content	3.5%	9
Sulfur content	7.65%	9
Melting point	139°–140°C	9
Clarification point	14°C	10
Cloud point	Approx. 0°C	10
Critical Micelle concentration (23°C)	4.0×10^{-3} *M*	11,12
Titratable Alkalinity of 40 percent in aqueous solution	0.2 meq/g max.	1
pH of 4% or 10% in aqueous solution (25°C)	7.0–7.5	1,13

found are contaminated with bacteria. In a study on bacteria/surface-active agent relationships, several bacterial species (*Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli, Aerobacter aerogenes, Salmonella enteritidis* and *Paracoloactrum aerogenoides*) were able to utilize TEA-Lauryl Sulfate as the sole source of organic carbon. As the bacteria decomposed TEA-Lauryl Sulfate, the surface tension of the compound's synthetic media rose. These results could be significant with respect to emulsions or cosmetic usage where compound and/or surface activity alteration may result in "undesired effects."[6]

TEA-Lauryl Sulfate provides detergent, foaming and wetting properties to cosmetic formulations. In comparison with ammonium or sodium lauryl sulfates, TEA-Lauryl Sulfate is less corrosive to metal packaging materials and "less sensitive to salt viscosity response."[7]

The infrared spectrum of 40% TEA-Lauryl Sulfate in aqueous solution has been published.[8]

Reactivity

In a study of the corrosive activity of detergents in pressure-propelled products, TEA-Lauryl Sulfate was less corrosive in pressurized metal containers than sodium lauryl sulfate, which in turn was less corrosive than ammonium lauryl sulfate. The detergents were tested under accelerated condtions of 55°–60°C and 67°–82°C for 40 days. Tests conducted at the latter temperature range more accurately predicted corrosion at room temperature than the tests conducted at 55°–60°C. Partial filling of the pressurized metal containers with detergent increased corrosion at room temperature.[14]

TEA-Lauryl Sulfate loses its foaming properties when combined with cationic detergents.[15,16]

Method of Manufacture and Impurities

TEA-Lauryl Sulfate is manufactured by neutralizing lauryl sulfuric acid with aqueous triethanolamine. Lauryl sulfuric acid is commercially produced either by sulfating a predominantly C_{12} linear alcohol with chlorosulfonic acid (CSA) or sulfur trioxide (SO_3). Since lauryl sulfuric acid is unstable (rapid hydrolysis), the acid is neutralized immediately with the triethanolamine to produce the desired stable salt. Differences in product purity will be observed, depending on the sulfating source (CSA or SO_3). CSA is supplied as an anhydrous product containing one mole of HCl per mole of H_2SO_4 (H_2SO_4° HCl). During the post-sulfating step (digestion), any unremoved HCl is neutralized by the amine forming an ammonium chloride which becomes an impurity in the finished product. The use of SO_3 as a sulfating agent eliminates the introduction of the chloride ion; thus, none is present in the completed product. Reported impurities are presented in Table 2. Data were not available on the possible presence of diethanolamine and

TABLE 2. IMPURITIES.[a]

Impurities	*Structure*	*Percent W/W*
Triethanolamine	$(CH_2CH_2OH)_3N$	3.0 max.
Triethanolamine Sulfate	$[(CH_2CH_2OH)_3NH]^+HSO_4^-$	2.0 max.
Unsulfated Alcohol	$CH_3(CH_2)_{10}CH_2OH$	1.0 to 2.0
Triethanolamine Chloride	$(CH_2CH_2OH)_3HN^+Cl^-$	1.0 max.
Formaldehyde (in some grades)	HCHO	0.02–0.04
Lead	Pb	20 ppm max.
Iron	Fe	5 ppm max.
Arsenic	As	3 ppm max.

[a]From Refs. 2,13.

N-nitroso-diethanolamine. TEA-Lauryl Sulfate is usually supplied as a 35–40% active ingredient in aqueous media.[7,13]

Analytical Methods

TEA-Lauryl Sulfate may be analytically determined by cationic titration using tetradecyl dimethyl benzyl ammonium chloride or benzethonium chloride. In this method, TEA-Lauryl Sulfate reacts with methylene blue to form a chloroform soluble salt. Upon shaking an acidified two-phase (chloroform-water) system containing methylene blue and TEA-Lauryl Sulfate, the blue color concentrates in the chloroform layer. The addition of the cationic surfactant causes the preferential formation of a complex with the anionic surfactant, which results in the displacement of the bound methylene blue into the water layer. The endpoint is arbitrarily taken when the color intensities of the water and chloroform layers are equal.[13,17]

A second reported analytical method for the determination of TEA-Lauryl Sulfate involves reacting the alkyl sulfate with p-toluidine hydrochloride to form the amine salt. The salt is then extracted with carbon tetrachloride and the amount of alkyl sulfate determined by titration with sodium hydroxide.[13]

USE

Purpose in Cosmetics

TEA-Lauryl Sulfate is used in cosmetics as a detergent, a stabilizer for dispersing systems, and a solubilizer for fragrances. It is also used as a wetting, foaming, dispersing, and emulsifying agent.[5,6,10,18-24]

The presence of the sulfate group in TEA-Lauryl Sulfate reduces lime soap formation in hard water, offering "manageability" to the hair and "gentleness" to the skin.[7] When the compound is used as an anionic detergent in shampoos, the lauryl sulfate portion degreases the hair and makes it "receptive" to materials that follow.[23]

Scope and Extent of Use in Cosmetics

Table 3 presents product formulation data voluntarily reported to the Food and Drug Administration (FDA) in 1976, and is broken down by cosmetic product type, number of product formulations and concentration range. Table 4 presents 1979 FDA product formulation data, and is broken down by concentration range and number of product formulations only; data on product types were unavailable. During 1976 and 1979, TEA-Lauryl Sulfate was reported to be an ingre-

TABLE 3. PRODUCT FORMULATION DATA FOR TEA-LAURYL SULFATE.[a]

Cosmetic Product Type	*Concentration[b] (Percent)*	*No. of Product Formulations*
Baby shampoos	>10–25	1
	>1–5	2
Bath oils, tablets, and salts	>25–50	5
	>10–25	4
	>5–10	1
Bubble baths	>50	6
	>25–50	14
	>10–25	16
	>5–10	10
	>1–5	5
	Not reported	3
Other bath preparations	>50	1
	>25–50	6
	>5–10	2
Perfumes	>0.1–1	2
Hair conditioners	>10–25	1
Hair straighteners	Not reported	2
Shampoos (noncoloring)	>50	9
	>25–50	76
	>10–25	127
	>5–10	52
	>1–5	30
	>0.1–1	6
Wave sets	≤0.1	1
Other hair preparations	>10–25	2
Hair dyes and colors (all types requiring caution statement and patch test)	>1–5	31
Hair shampoos (coloring)	>10–25	1
Blushers (all types)	>1–5	1
Foundations	>0.1–1	1
Leg and body paints	>0.1–1	1
Makeup bases	>1–5	1
	>0.1–1	1
	≤0.1	2
Cuticle softeners	>10–25	2
Bath soaps and detergents	>25–50	3
	>10–25	3
	>5–10	1
	>1–5	1
Other personal cleanliness products	>5–10	2
	>1–5	6
	>0.1–1	5
Shaving cream (aerosol, brushless, and lather)	>1–5	13
	>0.1–1	8
Shaving soap (cakes, sticks, etc.)	Not reported	1
Face, body, and hand (excluding shaving preparations)	>10–25	1
	>0.1–1	3
	≤0.1	4
Cleansing (cold creams, cleansing lotions, liquids, and pads)	>25–50	11
	>10–25	6
	>5–10	4
	>1–5	2
	>0.1–1	4

TABLE 3. (Continued).

Cosmetic Product Type	*Concentration[b] (Percent)*	*No. of Product Formulations*
Moisturizing	>50	1
	>0.1-1	2
Paste masks (mud packs)	>0.1-1	5
	≤0.1	1
Skin fresheners	>0.1-1	3
Other suntan preparations	>5-10	1
Suntan gels, creams, and liquids	>0.1-1	1
	Total	517

[a]From Ref. 25.
[b]Preset concentration ranges in accordance with Federal filing regulations [21 CFR 720.4 (d)(1)].

dient in 517 and 339 cosmetic formulations, respectively, at concentrations ranging from ≤0.1->50%.[25-27]

Potential Interactions with other Ingredients

There were no reports of potential chemical interactions of TEA-Lauryl Sulfate with other cosmetic ingredients. It is suspected that in the presence of nitrite or other nitrosating agents, cosmetic preparations containing TEA-Lauryl Sulfate may give rise to N-nitrosodiethanolamine.

Surfaces to which Commonly Applied

Cosmetic products containing TEA-Lauryl Sulfate are applied to or have the potential to come in contact with skin, eyes, hair, nails and mucous membranes.

Frequency and Duration of Application

Product formulations containing TEA-Lauryl Sulfate may be used from once a week up to several times a day. Many of the products may be expected to remain in contact with body surfaces for as briefly as a few minutes to as long as a few days. Each product has the potential for being applied hundreds of times over the course of several years.

TABLE 4. PRODUCT FORMULATION DATA FOR TEA-LAURYL SULFATE.[a]

Cosmetic Product Type	*Concentration[b] (Percent)*	*No. of Product Formulations*
Not reported	>50	16
	>25-50	65
	>10-25	83
	>5-10	46
	>1-5	50
	>0.1-1	28
	≤0.1	10
	Not reported	41
	Total	339

[a]From Refs. 26, 27.
[b]Preset concentration ranges in accordance with Federal filing regulations. [21 CFR 720.4 (d)(1)].

Non-cosmetic Use

TEA-Lauryl Sulfate has been tested as a component for pharmaceutical and dermatological vehicles.[9,28] Hydrophilic ointment bases prepared with 3.0% TEA-Lauryl Sulfate were rated superior according to several criteria.[9] Increasing concentrations of the surfactant, however, retarded the release of medicaments.[29]

BIOLOGICAL PROPERTIES

General Effects

TEA-Lauryl Sulfate was tested for its ability to produce "in-plane swelling" (increase in surface area) of guinea pig skin. Excised stratum corneum squares immersed in 0.5 *M* TEA-Lauryl Sulfate for 16 h showed an average swelling of 12.2% with a standard deviation of ±2.3%. Swelling was caused by a "reversible conformation change" in the stratum corneum protein "resulting from cooperative binding of the detergent." According to the authors, amphiphilic substances combine with native proteins by binding to specific sites on the protein. The binding occurs with detergent monomers rather than micelles. (Micelle formation, in fact, is in competition with protein binding.) This study was carried out above the critical micelle concentration of 4.0×10^{-3} *M* to ensure maximum concentration of detergent monomer. The investigators suggested that "stratum corneum swelling could be of value for studying detergent-skin interactions and for predicting detergent penetration of skin and possible subsequent skin irritancy."[11]

When shampoo formulations containing 6.0 percent TEA-Lauryl Sulfate were applied to the skin of guinea pigs, no inflammatory skin reactions occurred; however, an increase in cutaneous capillary permeability was observed in some animals. Histomorphological tests of the treated skin proved normal.[30]

Animal Toxicology

General Studies

Acute

The acute toxicity studies conducted with TEA-Lauryl Sulfate on animals include acute oral toxicity, skin irritation, eye irritation, and inhalation.

Acute oral toxicity

Acute oral studies demonstrate that TEA-Lauryl Sulfate is moderately toxic when given to rats. These studies are discussed below and the results summarized in Table 5.

Aqueous solutions or emulsions of 10% TEA-Lauryl Sulfate were administered to female albino rats by oral intubation. Groups of five rats each were given doses ranging from 0.252 to 7.95 g/kg. The LD50 of the solution, calculated by the Weil Modification of the Method of Thompson, was 2.7 g/kg.[31]

An aqueous solution containing 10.0 percent TEA-Lauryl Sulfate was administered by gavage to five groups of six albino rats each. Single doses of 10.0, 15.0, 20.0, 23.0 , and 25.0 ml/kg resulted in 1/6, 3/6, 3/6, 5/6, and 5/6 deaths, respectively. The LD50 of the solution was 16.5 ml/kg.[32]

A single 5.0 g/kg dose of 12% TEA-Lauryl Sulfate in aqueous solution was administered orally to each of 10 rats (5M, 5F). One death occurred on the seventh day of the 14-day observation period. The LD50 of the solution was >5.0 g/kg.[33]

A 39% TEA-Lauryl Sulfate solution was similarly administered to each of 10 rats (5M, 5F). Two deaths occurred on the first day of the 14-day observation period. The LD50 of the solution was >5.0 g/kg.[34]

Doses of 2.0 to 64.0 ml/kg of 40 percent TEA-Lauryl Sulfate were administered orally to 9 groups of albino rats (5 animals/group). All animals dosed at ≥6.4 ml/kg died. Unkempt coats were noted for 8–12 h following administration at the 2.0 and 3.2 ml/kg dosage levels. Diarrhea, nasal hemor-

TABLE 5. ACUTE ORAL TOXICITY OF TEA-LAURYL SULFATE.

Concentration of ingredient (Percent)	*No. of rats/Dose*	*Dose*	*No. of deaths/ Dosed*	*LD50 of Aq. Soln. or Formulation*	*LD50 of ingredient*	*Comments*	*Ref.*
10 in aq. soln. or emulsion	5	0.252–7.95 g/kg	Not Reported	2.7 g/kg	0.27 g/kg	–	31
10 in aq. soln.	5	10–25 ml/kg	17/30	16.5 ml/kg	1.65 ml/kg	Solution was practically nontoxic. Equally toxic to males and females.	32
12 in aq. soln.	10	5 g/kg	1/10	>5.0 g/kg	>0.6 g/kg	Only death on 7th day.	33
39 in aq. soln.	10	5 g/kg	2/10	>5.0 g/kg	>1.95 g/kg	2 deaths first day.	34
40 in aq. soln.	5	2–64 ml/kg	30/45	4.5 ml/kg	1.8 ml/kg	No deaths, 3.2 ml/kg dose. All deaths at 6.4 ml/kg and above. Equally toxic to males and females.	35
22 in shampoo formulation	10	10–20 ml/kg	19/40	14.5 ml/kg	–	–	36

rhage, lethargy, and unkempt coats were noted at levels ranging from 4.0 to 6.4 ml/kg; survivors returned to normal by the fifth day of the 14-day observation period. Lethargy was accompanied by severe diarrhea and nasal hemorrhage at 8.0 and 16.0 ml/kg. At 32.0 and 64.0 ml/kg, severe rectal hemorrhage began within 10–15 min after dosing; loss of motor control, lethargy, diarrhea and comas preceded death. All animals succumbed within 1 h at 64.0 ml/kg. The test material was equally toxic to males and females. The LD50 of the solution was 4.5 ml/kg.[35]

A shampoo formulation containing 22% TEA-Lauryl Sulfate was administered by oral intubation to four groups of 10 albino rats each in single doses of 10.0, 12.6, 15.9, and 20.0 ml/kg. The LD50 of the formulation was 14.5 ml/kg.[36]

Skin irritation

In studies with rabbits and guinea pigs, aqueous solutions containing 0.2–46% TEA-Lauryl Sulfate produced skin reactions ranging from no irritation to moderate irritation. Skin irritation tests conducted on guinea pigs with 0.5% of the surfactant in aqueous solution indicated that this compound may be absorbed in toxic amounts. These studies are discussed below and the results summarized in Table 6.

The Draize procedure was used to test three albino rabbits with 5% TEA-Lauryl Sulfate in aqueous solution for primary skin irritation.[46] The test material (0.5 ml) was applied to intact and abraded skin under an occlusive patch for 24 h. Scores for erythema, eschar formation, and edema were all 0 at 24 and 72 h. The Primary Irritation Index (PII) was 0.0 indicating no irritation.[37]

Aqueous solutions of 1.0%, 10%, 25% TEA-Lauryl Sulfate were each tested for skin irritation in three albino rabbits using the Draize method.[45] The test materials (0.5 ml) were applied under an occlusive patch to both intact and abraded skin for a 24-hour period. The 1.0% solution caused no reaction in 10 of the 12 treated areas and only a barely perceptible erythema at the other two test sites. The 10% solution caused a very slight to well-defined erythema and edema in most areas by 24 h; these reactions persisted after 72 h at a few sites but had regressed at others. The 25% solution produced a well-defined erythema and slight edema by 24 h; in most areas, these reactions became more marked by 48 and 72 h and consisted of bright red raised scabs and roughened, cracked epidermis. The PIIs of the 1.0%, 10%, and 25% solutions were 0.1 (mild irritation), 1.6 (mild irritation), and 2.9 (moderate irritation), respectively.[39]

The skin irritation potentials of 12% and 39% TEA-Lauryl Sulfate in aqueous solutions were tested in albino rabbits by means of the Draize procedure.[45] Each test material (0.5 ml) was applied to the intact and abraded skin of six rabbits under an occlusive patch for 24 h. The PIIs for 12% and 39% aqueous solutions were 0.33 (slight irritation) and 2.9 (moderate irritation), respectively.[33,34]

Aqueous solutions of 10%, 40%, and 40% TEA-Lauryl Sulfate were each tested for primary skin irritation in six albino rabbits using the methods of Draize,[45] Federal Hazardous Substances Labeling Act (FHSLA) (16 CFR 1500.41), and Department of Transportation (DOT) (49 CFR 173.240), respectively. In each case, the test material (0.5 ml) was applied to abraded and intact skin under an occlusive patch and the sites scored thereafter at various intervals. The results of the three tests were as follows:

1. At 10% concentration (Draize procedure), very mild erythema was observed in two of six animals; no irritation was seen in the remaining four rabbits. The PII was 0.30 indicating slight irritation.[40]
2. At 40% concentration (FHSLA procedure), two rabbits exhibited erythema of intact skin and all six rabbits exhibited erythema on abraded skin at 24 h. By 72 h, the erythema on all rabbits had cleared. The PII was 0.38 indicating mild irritation.[35]
3. Again at 40% concentration (DOT procedure), all six rabbits showed slight erythema on abraded skin, whereas one of six rabbits showed slight erythema of intact skin by 4 h. At 24 h, two rabbits showed slight erythema on abraded skin only. By 48 h, all six rabbits showed no signs of irritation. The PII was 0.30 indicating mild irritation.[35]

A skin irritation test was conducted on nine rabbits with 1%, 5%, and 25% TEA-Lauryl Sulfate in aqueous solution; three animals were exposed to one of the aforementioned concentrations. Each

TABLE 6. SKIN IRRITATION OF TEA-LAURYL SULFATE.

Concentration (Percent in aq. soln.)	*No. and type of animal*	*Method*	*PII (Max. score = 8)*	*Conclusion/Comments*	*Ref.*
5	3 albino rabbits	46	0	No irritation	38
1	3 albino rabbits	45	0.1	Mild irritation	39
10	3 albino rabbits		1.6	Mild irritation	
25	3 albino rabbits		2.9	Moderate irritation	
12	6 albino rabbits	45	0.33	Slight irritation	33
39	6 albino rabbits		2.91	Moderate irritation	34
10	6 albino rabbits	45	0.30	Slight irritation	40
40	6 albino rabbits	FHSLA (16 CFR 1500.41)	0.38	Mild irritation	35
40	6 albino rabbits	DOT (49 CFR 173.340)	0.30	Mild irritation	35
1	3 albino rabbits	Applied under occlusive patch to intact and abraded skin of abdomen: intact skin contact, 14 days; abraded skin contact, 3 days.	–	Very slight to slight erythema	31
5	3 albino rabbits			Slight erythema to a moderate burn	
25	3 albino rabbits			Moderate burn	
1	3 albino rabbits	Applied to uncovered intact skin of ear for 14 days	–	Very slight to slight erythema	31
5	3 albino rabbits			Very slight to slight erythema	
25	3 albino rabbits			Moderate burn	
46	rabbits	FHSLA (16 CFR 1500.41)	–	8 labs rated as irritant and 8 as a nonirritant	41,42
46	8 rabbits tested in each of 22 labs	FHSLA (16 CFR 1500.41)	–	Median scores for erythema, edema, necrosis and primary irritation calculated from 22 labs (see text).	41,42
0.2	9 guinea pigs	Immersion	–	Caused cracking, fissuring and scurfing of skin	43
0.5	36 guinea pigs			28 of 36 animals died before grading	44

test material was applied to one-inch square cotton pads and held in contact to both abraded and intact abdominal skin areas. Ten applications of 5 ml each were made to the intact areas over a 14-day period, and three similar applications were made to abraded areas. This method resulted in continuous contact of the test material to intact skin for 14 days, and to abraded skin for three days. In no instances were applications carried on beyond the production of a substantial burn or eschar formation. Skin reactions were evaluated after each application and at subsequent intervals up to three weeks from the start of the study. Reactions were scored on a scale from 1 ("essentially no irritation") to 6 ("burn from one 24-hour application"). At 1% concentration, scores ranged from 1.0 to 3.5 indicating very slight to slight erythema. At 5% concentration, scores ranged from 3.5 to 5.4 indicating slight erythema to a moderate burn; at 25% concentration scores ranged from 5.0 to 5.4 indicating a moderate burn.[31]

Aqueous solutions of 1%, 5%, and 25% TEA-Lauryl Sulfate were each tested for skin irritation in three albino rabbits. The test materials (5 ml) were applied daily for 14 days to the intact skin of the ear; the treated areas were left uncovered. Skin reactions were evaluated after each application and at subsequent intervals up to three weeks from the start of the study. Reactions were scored on the same scale as in the previous test. The "average reaction" of three rabbits to repeated applications of 25% TEA-Lauryl Sulfate in water was a moderate burn; scores ranged from approximately 4.0 to 4.5. At 1% and 5% in water, a very slight to slight erythema occurred; scores ranged from approximately 1.0 to 1.7, and from 1.7 to 4.0, respectively.[31]

In an investigative study of intra- and interlaboratory variability in test scores,[41,42] eight labs rated 46% TEA-Lauryl Sulfate in aqueous solution as a skin irritant to rabbits, and eight labs rated it as a nonirritant. The procedures used in each lab were similar to those specified in the FHSLA (16 CRF 1500.41).

In the same study, median scores for erythema, edema, necrosis, and primary irritation were calculated from 22 labs testing eight rabbits each with 46% TEA-Lauryl Sulfate in aqueous solution. The procedures used in each lab were similar to those specified in the FHSLA (16 CFR 1500.41). The following results were reported:[41,42]

1. *Erythema:* The median score of 22 labs for erythema was 16.5 after 24 h and 20.0 after 72 h (max. possible score for erythema = 32).
2. *Edema:* The median score of 22 labs for edema was 14.5 after 24 h and 16.5 after 72 h (max. possible score for edema = 32).
3. *Necrosis:* Fourteen labs reported skin necrosis while eight labs reported none. Median scores of the 14 labs reporting necrosis was 22.0 after 24 h and 75.0 after 72 h (max. possible score for necrosis = 120). Scores for the eight labs reporting no necrosis were 0 at 24 and 72 h.
4. *Primary Irritation:* The median primary irritation score of the 14 labs reporting necrosis was 10.8; the median primary irritation score of the eight labs reporting no necrosis was 4.0 (max. possible score for primary irritation = 23).

Guinea pig immersion tests were conducted with aqueous solutions of 0.2% and 0.5% TEA-Lauryl Sulfate in nine and 36 guinea pigs, respectively. The abdomens of all pigs were shaved, then they were immersed up to their axillae in the test solution for four hours on three successive days. Skin responses were graded two days after the last treatment. The grading system used ranged from 2.0 (extreme skin damage) to 10 (normal); scores greater than 7.0 were considered "acceptable." Scores for the nine guinea pigs tested with 0.2% concentration averaged 5; the skin showed cracking, fissuring, and severe scurfing. Of the 36 guinea pigs tested with 9.5% concentration, 28 died before grading; the eight surviving animals were scored an average of 5.[43,44]

Eye irritation

In studies with rabbits, aqueous solutions containing 1–46% TEA-Lauryl Sulfate produced a range of eye reactions varying from no irritation to severe irritation. These studies are discussed below and the results summarized in Table 7.

The Draize procedure was used on nine albino rabbits to test the eye irritation potential of 2% TEA-Lauryl Sulfate in aqueous solution.[46] The test procedure called for a 0.1 ml single dose of the

TABLE 7. EYE IRRITATION OF TEA-LAURYL SULFATE.

Concentration (Percent in aq. soln.)	*No. and type of rabbits*	*Method*	*W/NW*[a]	*Draize Score (max. = 110) Days* 1	2	3	4	7	*Conclusion/Comments*	*Ref.*
2	3 albino	46	NW	0	0	0	0	0	No irritation observed.	47
2	3 albino		W after 4 sec	0	0	0	0	0		
2	3 albino		W after 30 sec	0	0	0	0	0		
5	3 albino	46	NW	0	0	0	0	0	No irritation observed.	37
10	3 albino	46	NW	7	5	3	0	0	Mildly irritating.	49
10	3 albino		W after 2 sec	3	0	0	0	0		
10	3 albino		W after 4 sec	4	1.3	0	0	0		
1.25	3 albino	48	See text	–	–	–	–	–	Concentrations of 2.5 to 10 percent caused significant eye irritation; 20 percent concentration caused serious impairment to eye mucosa. See Table 8 for scores.	50
2.5	3 albino			–	–	–	–	–		
5	3 albino			–	–	–	–	–		
10	3 albino			–	–	–	–	–		
20	3 albino			–	–	–	–	–		
1	3 albino	See text	NW and W after 30 sec	–	–	–	–	–	At 25 percent concentration in unwashed eye, slight conjunctivitis to moderate corneal injury observed. Very slight to slight conjunctivitis observed in unwashed eye at 1 and 5 percent. See text for effects of washing.	31
5	3 albino		NW and W after 30 sec	–	–	–	–	–		
25	3 albino		NW and W after 30 sec	–	–	–	–	–		

TABLE 7. (Continued).

Concentration (Percent in aq. soln.)	*No. and type of rabbits*	*Method*	*W/NW*[a]	*Draize Score (max. = 110) Days*					*Conclusion/Comments*	*Ref.*
				1	*2*	*3*	*4*	*7*		
1	3 albino	45	W after 4 sec	2	2	0.7	–	–	At 1 and 10 percent,	39
10	3 albino		W after 4 sec	7.7	4.7	0.7	–	–	reddening, swelling of	
25	3 albino		W after 4 sec	20.7	2	0	–	–	eyelids, and discharge observed. At 25 percent, cloudiness of cornea observed after 24 hrs. None of the 3 solutions left any residual effects.	
12	6 albino	45	NW	9.5	12	17.7	17.7	16.2	Severely irritating.	33
39	6 albino		NW	12.5	12.7	12.5	12.5	6.2	Moderately irritating.	34
40	3 albino	46	NW	6	11	23	24	19	Severely irritating based on	35
40	3 albino		W after 2 sec	0	0	0	0	0	results of the no wash	
40	3 albino		W after 4 sec	0	0	0	0	0	group.	
46	–	FHSLA	–	–	–	–	–	–	23 labs rated solution as irritant and 1 lab rated solution as nonirritant.	41,42
46	132 rabbits/ 22 labs	FHSLA	–	31	–	26	–	10	Scores presented to the left represent median scores calculated from 22 labs.	41,42

[a]W = wash/NW = no wash.

test material followed by either no wash (3 rabbits), a wash after a four-second exposure (3 rabbits), or a wash after a 30 sec exposure (3 rabbits). No irritation was observed in any of the unwashed or washed eyes. Scores on Days 1, 2, 3, 4, and 7 were all 0.0.[47]

Five percent TEA-Lauryl Sulfate in aqueous solution was tested by the Draize method for its eye irritancy potential in three albino rabbits.[46] The test sample (0.1 ml) was instilled into the right eye of each animal; the untreated left eye of each rabbit served as control. Scores were 0.0 on Days 1, 2, 3, 4, and 7 indicating no irritation.[37]

Nine albino rabbits were tested by means of the Draize procedure to determine the potential of 10% TEA-Lauryl Sulfate in aqueous solution to produce eye irritation.[46] The test procedure called for a 0.1 ml single dose of the test material followed by either no wash (3 rabbits), a wash after a 2 sec exposure (3 rabbits), or a wash after a 4 sec exposure (3 rabbits). The average scores for the no-wash group were 7, 5, 3, 0, and 0 on Days 1, 2, 3, 4, and 7, respectively. For the group of three rabbits receiving a wash after a 2 sec exposure, the average score was 3 on Day 1 and 0.0 thereafter. For the group receiving a wash after a 4 sec exposure, the average scores were 4 and 1.3 on Days 1 and 2, respectively; scores thereafter were 0.0. Under conditions of this test, the material should be considered mildly irritating.[49]

Aqueous solutions containing 1.25%, 2.5%, 5%, 10%, and 20% TEA-Lauryl Sulfate were tested for eye irritation in albino rabbits according to the method of Draize and Kelley.[48] At each concentration, three eyes were tested: one eye was not rinsed, one eye was rinsed after 2 sec with 20 ml distilled water at 37°C, and one eye was similarly rinsed after four seconds. A reference test (negative control) was also conducted to determine the effect of rinsing with 37°C distilled water. In addition, a known anionic eye irritant, sodium dioctyl sulfosuccinate (positive control), was utilized to create typical ocular damage. The irritation reactions were read at 1 h and 1, 2, 3, 4, and 7 days after instillation. Total scores for cornea + iris + conjunctiva (max. score/animal/observation interval = 110) are shown in Table 8. Concentrations of 2.5–10% TEA-Lauryl Sulfate caused significant eye irritation, whereas concentrations of 20% caused serious impairment to eye mucosa.[50]

An eye irritation test was conducted on nine rabbits to determine the irritation potential of aqueous emulsions or solutions containing 1, 5, or 25% percent TEA-Lauryl Sulfate; three rabbits were tested at each concentration. (The eyes of all rabbits tested were determined to be free of corneal injury; those selected showed no reaction to an aqueous solution of 5% fluorescein disodium salt 24 h prior to use.) Two drops of the test material were applied to each eye. Within 30 sec, one eye was washed with flowing tap water for 2 min; the other eye remained unwashed. Both eyes were examined for conjunctival or corneal injury, and for iritis and lenticular damage immediately following application, and again after 1 h, 24 h, 48 h, and one week. Fluorescein was utilized in all cases as an aid in assessing corneal injury. The type and intensity of reaction was evaluated according to a scale ranging from one ("no effect") to six ("very severe effect . . . with total loss of vision due to serious injury to the cornea or internal structure of the eye"). At 25% concentration in the unwashed eye, scores ranged from approximately 2.0–4.4 indicating slight conjunctivitis to moderate corneal injury with no permanent effects. At 1% and 5% concentration in the unwashed eye, scores were 3.4 or less indicating very slight to slight conjunctivitis. At 5% concentration in the washed eye, scores were ≤ 1.5 indicating a very slight conjunctivitis. At 1.0% concentration in the washed eye, the range of scores was not reported.[31]

Aqueous solutions of 1%, 10%, and 25% TEA-Lauryl Sulfate were each tested using the Draize method for eye irritation in three albino rabbits.[45] When placed in the eye, all three concentrations caused immediate reaction as evidenced by closing of the eyelids and watering of the eye. None of the three solutions tested left any residual effects. Eye reactions at each concentration were as follows:[39]

1. At 1% concentration, a minimal reaction in the form of a slight reddened lining of the eyelid was observed. In addition, there was slight swelling of the nictitating membrane and slight discharge about the eye. The average scores were 2.0, 2.0, and 0.7 on Days 1, 2, and 3, respectively.
2. At 10% concentration, there was reddening and swelling of the eyelids and a copious

TABLE 8. EYE IRRITATION.[a]

Test material (0.1 ml)	*Concentration (Percent in aq. soln.)*	*1 h*			*1 day*			*2 days*			*3 days*			*4 days*			*7 days*		
		1	*2*	*3*	*1*	*2*	*3*	*1*	*2*	*3*	*1*	*2*	*3*	*1*	*2*	*3*	*1*	*2*	*3*
TEA-Lauryl Sulfate	1.25	25	11	16	2	0	0	0	0	0	–	–	–	–	–	–	–	–	–
	2.5	21	11	7	49	0	0	39	0	0	22	0	0	7	0	0	0	0	0
	5	18	15	18	61	47	2	33	7	2	2	0	2	2	0	0	2	0	0
	10	44	18	20	77	0	2	77	0	0	16	0	0	7	0	0	0	0	0
	20	35	35	37	53	26	47	39	19	16	27	0	0	12	0	0	0	0	0
Sodium Dioctyl-sulfosuccinate	2.5	28	16	16	59	0	0	57	0	0	55	0	0	58	0	0	19	0	0
	5	22	15	20	11	0	23	33	0	21	39	0	0	39	0	0	20	0	0
	10	30	30	30	46	16	35	49	6	39	43	0	28	17	0	29	0	0	23
	20	57	20	39	79	2	43	73	0	53	39	0	58	19	0	43	2	0	2
Distilled Water	–	2	2	2	0	2	0	0	0	–	–	–	–	–	–	–	–	–	–

[a]From Refs. 48, 50.

Total Score (max. = 110) for Cornea + Iris + Conjunctiva.

1 = No rinsing.

2 = Rinsing after 2 sec.

3 = Rinsing after 4 sec.

discharge. These reactions were still present after 24 h. The average scores were 7.7, 4.7, and 0.7 on Days 1, 2, and 3, respectively.

3. At 25% concentration, there was marked eye reaction consisting of matting of the eyelids and exudate at 24 h. Faint cloudiness of the cornea was present at 24 h. All eye reactions had regressed considerably at 48 and 72 h. The average scores for three rabbits were 20.7, 2, and 0 on Days 1, 2, and 3, respectively.

The potential of 12% and 39% TEA-Lauryl Sulfate in aqueous solution to produce eye irritation was determined in albino rabbits by means of the Draize method.[45] Each test material (0.1 ml) was instilled by a single application into the right eye of each of six animals; the left eye served as control. The treated eyes of each animal remained unwashed after instillation. At 12% concentration, the average scores for all six rabbits on Days 1, 2, 3, 4, and 7, were 9.5, 12.0, 17.7, 17.7, and 16.2, respectively. At 39% concentration, the average scores for the six rabbits tested were 12.5, 12.7, 12.5, 12.5, and 6.2 on Days 1, 2, 3, 4, and 7, respectively. According to the scoring procedure used, 12% and 39% TEA-Lauryl Sulfate in aqueous solution must be considered severe and moderate eye irritants in rabbits, respectively.[33,34]

An aqueous solution containing 40% TEA-Lauryl Sulfate was tested for eye irritation in nine albino rabbits according to the Draize method.[46] The test procedure utilized a 0.1 ml single dose of the test material followed by either no wash (3 rabbits), a wash after a 2 sec exposure (3 rabbits), or a wash after a 4 sec exposure (3 rabbits). The average scores for the no-wash group were 6, 11, 23, 24, and 19 on Days 1, 2, 3, 4, and 7, respectively. According to the scoring procedure used, "A preparation which has elicited corneal and iris lesions which have not cleared by the seventh day is considered a severe irritant." The scores for the remaining two groups (wash after 2 sec and 4 sec exposure) were 0.0. On the basis of the results obtained from the no-wash group, the test material should be considered severely irritating to the rabbit eye.[49]

In a study designed to investigate intra- and interlaboratory variability in test scores, 23 labs rated 46% TEA-Lauryl Sulfate in aqueous solution as an eye irritant to rabbits and one lab rated it a nonirritant. All labs used procedures identical to those specified for Federal Hazardous Substances testing; the irritation tests were modifications of the Draize procedures. The median Draize scores calculated from 22 labs, each testing six rabbits with 46% TEA-Lauryl Sulfate in aqueous solution, were 31, 26, and 10 on Days 1, 3, and 7, respectively. Thus, 22 labs reported a healing trend over this time period.[41,42]

Inhalation

Mice and rabbits were exposed to aerosolized 15% and 25% aqueous solutions of TEA-Lauryl Sulfate for two to five minutes by a "head exposure method." Four to eight animals were tested at each exposure level; chamber concentrations were 130, 175, or 73 μg/l air. All particles were determined to be < 12.5 μm in diameter. At all exposure levels, rabbits exhibited a 50–60% inhibition of respiration. Exposure of mice to TEA-Lauryl Sulfate concentrations of 130, 170, and 73 μg/l resulted in a 2–35%, 55–65%, and 20% inhibition of respiration, respectively. The reflex inhibition of respiration was mediated through stimulation of receptors in membranes of the respiratory tract.[51]

Subchronic

A 28-day dermal toxicity study was conducted with two groups of 10 (5M, 5F) rabbits. One group served as untreated control and the other received 2.0 ml/kg of a water-diluted shampoo formulation containing 1.5% TEA-Lauryl Sulfate. The test material was applied five days a week for four weeks to the shaved, unoccluded skin. In each group, two males and two females had abraded skin. No significant adverse effects were observed with respect to hematology, blood chemistry, or urine analyses. Gross skin changes were characterized by erythema, mild edema, wrinkling, and severe desquamation. Microscopic examination revealed focal to diffuse acanthosis and hyperkeratosis among most of the treated rabbits. Chronic inflammation of the subadjacent dermis and eschar formation involving the surface of the test skin were noted in a few animals. Losses in body weight were noted in two rabbits of the control group and in seven rabbits of the treated group. Four rabbits of the treated group died "due to naturally occurring respiratory disease."[52]

A thirteen-week dermal toxicity study was conducted on two groups of 14 rabbits. One group served as untreated control and the other received 0.5 ml/kg of a water-diluted shampoo formulation containing 2.4% TEA-Lauryl Sulfate. The test material was applied to the skin by gentle inunction five days a week for a total of 65 applications. Each day the diluted formulation was left in contact with the skin for one-hour and then rinsed off; collars prevented ingestion of the test material. No significant adverse effects were observed with respect to appearance, behavior, survival, body weight, blood chemistry, hematology, gross necropsy, or histopathology. Dermal effects were limited to mild erythema and dryness which are expected with products of this type under these test conditions.[53]

Clinical Assessment of Safety

Shampoo formulations containing TEA-Lauryl Sulfate were tested for their human skin irritation, sensitization and photosensitization potential. Undiluted shampoos containing 10.5% active TEA-Lauryl Sulfate elicited no skin irritation under semioccluded conditions or under "use" testing. Water-diluted shampoos containing 0.15%, 0.2%, 0.25%, 0.3%, 0.42%, 1.5%, 4.4%, or 7.5% TEA-Lauryl Sulfate caused skin reactions ranging from no irritation to moderate irritation. A diluted shampoo containing 4.4% of the surfactant was highly irritating to the human skin when tested by means of a 21-day cumulative, closed patch test; however, the irritancy potential of this material would be expected to be high under such a closed patch test system.

No skin sensitization was observed in subjects tested with undiluted shampoos containing 10.5% TEA-Lauryl Sulfate, or diluted formulations containing 0.15%, 0.2%, 1.5%, 4.4%, or 7.5% of the ingredient. One diluted shampoo containing 0.42% active TEA-Lauryl Sulfate did induce weak, nonvesicular to strong, edematous/vesicular reactions when applied in a challenge patch to the human skin; however, these reactions were considered to be indicative of low grade irritation rather than allergic sensitization. Subjects exposed to both aqueous solutions containing 0.3% or 0.42% TEA-Lauryl Sulfate and UV radiation showed no signs of being photosensitized. Details of studies are discussed below; results are summarized in Table 9.

Primary Skin Irritation

Three dermatologic vehicles were prepared from triethanolammonium salts of various alkylsulfuric acids, the corresponding alcohols and propylene glycol. The ointment bases contained either 19%, 24%, or 42% (by weight) TEA-Lauryl Sulfate. Twenty-four hour "patch tests" were then performed on the glabrous skin of the forearm of 30 subjects. No evidence of skin irritation was detected.[9] This report gives a limited information base; thus, the Panel could not evaluate the data. The results of this study were not included in Table 9.

A 21-day cumulative closed patch test was conducted on 12 subjects using a water-diluted shampoo formulation containing 4.4% TEA-Lauryl Sulfate. The method employed was a modification of that described by Phillips et al.[72] The "Composite Total Score" for all panelists was 694/756 indicating that the aqueous shampoo solution was highly irritating. According to the investigator, however, the diluted shampoo ". . . should create no problem because its contact with the skin is brief . . . ".[54]

Four water-diluted shampoo formulations containing 0.3% TEA-Lauryl Sulfate were each tested on 19 subjects for skin irritation potential. A single insult (24-hour) occlusive patch procedure was used. The four aqueous shampoo solutions elicited PIIs of 0.34, 0.60, 0.68, and 1.26, respectively, indicating minimal to mild skin irritation.[55-58]

Nineteen subjects were tested for skin irritation using a water-diluted shampoo formulation containing 0.25% TEA-Lauryl Sulfate. A single insult (24-hour) occlusive patch procedure was employed. The aqueous shampoo solution elicited a PII of 0.76 indicating minimal to mild irritation.[59]

The skin irritation potential of a water-diluted shampoo containing 0.25% TEA-Lauryl Sulfate was determined in 20 subjects by means of a single insult (24-hour) occlusive patch procedure. The aqueous shampoo solution elicited a PII of 1.15 indicating mild to moderate irritation.[60]

TABLE 9. CLINICAL STUDIES CONDUCTED WITH TEA-LAURYL SULFATE.

Test	*Material tested*	*Concentration (Percent)*	*Method*	*No. of subjects*	*Conclusion/ Comments*	*Ref.*
Skin Irritation	aq. shampoo soln.	4.4	21-day cumulative closed patch test—mod. of Phillips et al. 1972	12	Highly irritating to skin	54
Skin Irritation	4 aq. shampoo solns.	0.3	Single insult (24 h); occlusive patch	76 (4×19)	PIIs = 0.34, 0.60, 0.68, and 1.26; minimal to mild skin irritation	55–58
Skin Irritation	aq. shampoo soln.	0.25	Single insult (24 h); occlusive patch	19	PII = 0.76; minimal to mild skin irritation	59
Skin Irritation	aq. shampoo soln.	0.25	Single insult (24 h); occlusive patch	20	PII = 1.15; mild to moderate skin irritation	60
Skin Irritation	aq. shampoo soln.	0.2	Single insult (24 h); occlusive patch	17	PII = 1.0; mild skin irritation	61
Skin Irritation	aq. shampoo soln.	0.2	Single insult (24 h); occlusive patch	20	PII = 0.48; minimal skin irritation	62
Skin Irritation and Sensitization	7 shampoos	10.5	Each material applied under semioccluded patches everyday, 4 days/wk, for 2 wks; after 2-wk rest, 24 h challenge patch applied.	350 shampoo (7×50)	No skin reactions observed in any of the 350 panelists tested.	63
Skin Irritation and Sensitization	shampoo	10.5	Shampooing 5 days/wk for 9 consecutive wks (45 days)	51	No skin reaction observed in the 48 subjects completing the study (3 individuals dropped).	64
Skin Irritation and Sensitization	aq. shampoo soln.	7.5	Material applied under semioccluded patch for 48 h; after a 2-wk rest, a 48 h challenge patch applied.	100	No skin reactions observed during induction or challenge phases.	65

TABLE 9. (Continued).

Test	*Material tested*	*Concentration (Percent)*	*Method*	*No. of subjects*	*Conclusion/ Comments*	*Ref.*
Skin Irritation and Sensitization	aq. shampoo soln.	1.5	Material applied under occlusive patch 3 times a wk for a total of 10 applications; after a 2-wk rest, challenge patch applied.	53	No primary skin irritation or sensitization observed.	66
Skin Irritation and Sensitization	aq. shampoo soln.	0.42	Material applied under 48 h occlusive patch 3 times/wk for a total of 10 applications; after a 2-wk rest, a 48 h challenge patch applied. Positive reactors to initial challenge were rechallenged following a 2nd 2-wk rest. Positive reactors to 2nd challenge patch then open patched daily for 5 days.	204	82/204 subjects showed "Weak" nonvesicular and "Strong" edematous/vesicular skin reactions as a result of the 10 induction patches and the initial challenge patch. One out of 14 subjects demonstrated a "Weak" nonvesicular reaction when tested with a 2nd challenge patch; results were negative when this individual was open patched daily for 5 days.	67

Skin Irritation and Sensitization	aq. shampoo soln.	0.15	Draize (1959); repeated insult patch test	196	Minimal skin irritation; no evidence of sensitization.	68
Skin Irritation and Sensitization	aq. shampoo soln.	0.2	Draize (1959); repeated insult patch test	101	Slight skin irritant to 14 subjects, moderate irritant to 16 subjects, and essentially nonirritating to rest; no reactions indicative of sensitization.	69
Sensitization	aq. shampoo soln.	4.4	Maximization Test (see text)	25	No instances of contact sensitization.	70
Photosensitization	aq. shampoo soln.	0.42	Material applied under 48 h occlusive patch 3 times a wk for a total of 10 applications; after a 2-wk rest, a 48 h challenge patch applied. Following 1st, 4th, 7th, 10th and challenge insults, test sites exposed to UV light.	49	No signs of photosensitization noted.	67

A skin irritation test was conducted with a water-diluted shampoo formulation containing 0.2% TEA-Lauryl Sulfate. A single insult (24-hour) occlusive patch procedure was used. The aqueous shampoo solution elicited a PII of 1.0 indicating mild irritation.[61]

Twenty subjects were tested for skin irritation using a water-diluted shampoo formulation containing 0.2% TEA-Lauryl Sulfate. A single insult (24-hour) occlusive patch procedure was employed. The aqueous shampoo solution elicited a PII of 0.48 indicating minimal irritation.[62]

Seven shampoo formulations each containing 10.5% active TEA-Lauryl Sulfate were tested on each of 50 subjects for skin irritation and sensitization potential. The undiluted test material was applied every day four days a week for two weeks under semioccluded patches to the outer aspects of the upper arm. Test sites were graded every 24 h following each of the eight induction exposures. After a 2-week rest period, a challenge patch was applied to the skin under semioccluded conditions. The challenge patch was removed after 24 h of contact and the test sites graded immediately and at intervals at 24, 48, and 72 h. No skin reactions ". . . which could be considered compatible with a diagnosis of primary irritation, fatiguing or sensitization" were observed in any of the 350 panelists tested.[63]

An undiluted shampoo containing 10.5% active TEA-Lauryl Sulfate was evaluated in a "use study" for its ability to produce irritation and sensitization on the skin of 51 individuals. The test group consisted of Caucasian males between the ages of seventeen and forty. "Monitored" shampooing with the product was carried out every day, five days a week for nine consecutive weeks. Skin reactions were evaluated at the beginning of the study, and at the end of one, three, six, and nine weeks. *Pretest* examinations of the scalp, neck and facial areas of the test subjects revealed inflammatory-type skin disorders; however, none of these disorders appeared to be aggravated by shampooing with the product. No skin reactions attributable to the shampoo were observed in the 48 subjects completing the study (three individuals withdrew).[64]

A panel of 100 individuals was subjected to a patch test to determine the skin irritation and sensitization potential of a water-diluted shampoo containing 7.5 percent active TEA-Lauryl Sulfate. The test material was applied under a semioccluded patch to the cleansed skin of each subject. Forty-eight hours following application, the patches were removed and the test sites graded. A final examination for delayed reactions was made 72 h after application of the test patch. Following a two-week rest, a 48-hour challenge patch was applied. No skin reactions were observed in any subjects during the induction or challenge phases.[65]

A repeated insult patch test was conducted on 53 subjects to determine the skin irritation and sensitization potential of a water-diluted shampoo containing 1.5% active TEA-Lauryl Sulfate. Panelists ranged in age from 18 to 81 years. Approximately 0.15 ml of the test material was applied to the skin of the upper back of each subject under an occlusive dressing. The patch was then removed after 24 h of contact with the skin. This procedure was repeated three times a week for 3.5 weeks for a total of 10 applications. At the conclusion of a 14-day rest period following the 10th application, a challenge patch was applied to the original site and to a virgin site on the volar forearm. Each test site was evaluated 24 and 48 h after the challenge application. No primary irritation or sensitization was observed in any of the subjects.[66]

The Draize–Shelanski Repeat Insult procedure was used to test the skin irritation and sensitization potential of a water-diluted shampoo containing 0.42% TEA-Lauryl Sulfate. The test material was applied to the upper back of each of 204 subjects under an occlusive patch. After 48 h of contact, the patches were removed and the test sites graded. Patches were applied three times a week for 3.5 weeks for a total of 10 induction applications. Any subject who showed a skin reaction on the first or second insult was not repatched. At the conclusion of a two-week rest period following the 10th application, a 48-hour challenge patch was applied. Over the series of 11 patches (10 induction and one challenge), there were a total of 82 reactors out of the 204 subjects tested. A total of 129 "Weak," nonvesicular skin reactions and seven "Strong," edematous or vesicular skin reactions occurred during the induction phase; 13 "Weak" reactions and one "Strong" reaction were observed during the challenge phase. The investigator stated that the positive reactions observed, including those at challenge, were ". . . indicative of low grade irritation. . . ." All subjects who had reacted

to the challenge insult were rechallenged with a 48-hour patch following a 13-day rest. Of the 14 subjects rechallenged, one showed a "Weak," nonvesicular reaction. This individual was then *open* patched with the test material daily for five days; results were negative.[67] Under conditions of this test, it appears TEA-Lauryl Sulfate is an irritant in the closed patch system, but not an irritant in the open system.

The skin irritation and sensitization potential of a water-diluted shampoo formulation containing 0.15% TEA-Lauryl Sulfate was determined in 196 subjects by means of the repeated insult patch test procedure of Draize.[46] The aqueous shampoo solution elicited "minimum primary irritation and no evidence of sensitization."[68]

The Draize repeated insult patch test method was conducted on 101 subjects to determine the skin irritation and sensitization potential of a water-diluted shampoo formulation containing 0.2% TEA-Lauryl Sulfate.[46] The aqueous shampoo solution produced slight skin irritation on 14 panelists and moderate irritation on 16 panelists. The remaining subjects were "essentially free of irritation" throughout the study. The "few slight moderate reactions" observed at challenge were similar to those observed during serial applications and were "probably due to primary irritation." There were no reactions to challenge applications which were indicative of sensitization.[69]

A maximization test for sensitization was conducted on 25 healthy adults using a water-diluted shampoo formulation containing 4.4% TEA-Lauryl Sulfate. The diluted formulation was applied under occlusion to the same site on the volar forearm or back of all subjects for five alternate-day 48-hour periods. The patch site was pretreated for 24 h with 2.5% aqueous sodium lauryl sulfate under occlusion. Following a 10-day rest period, a challenge patch of the aqueous shampoo solution was applied to a different site for a 48-hour period under occlusion. Prior to challenge, 5–10% sodium lauryl sulfate was applied to the test site for 1 h before application of test material. Observations were made immediately after removal of the challenge patch and 24 h thereafter. There were no instances of contact sensitization from the aqueous shampoo solution containing 4.4% TEA-Lauryl Sulfate.[70]

Photosensitization

An aqueous shampoo solution containing 0.42% TEA-Lauryl Sulfate was tested for its ability to produce photosensitization. The test material was applied under an occlusive 48-hour patch to the upper back of each of 49 subjects. Patches were applied three times a week for 3.5 weeks for a total of ten applications. Following a two-week rest period, a single 48-hour challenge patch containing the test material was applied. Any subject who showed a skin reaction on the first or second insult was not repatched. Test sites where each of the closed patches had been applied were exposed to UV light after the first, fourth, seventh and tenth challenge insults. The UV light source had a wave length including 3600 Å and was held at a distance of 12 in from the treated skin for 1 min. Skin reactions were graded 48 h following UV exposure. No signs of photosensitization were noted in any of the subjects.[67]

Formaldehyde and Triethanolamine Sensitization

The North American Contact Dermatitis Group (NACDG) reported that the incidence of skin sensitization among 2103 patients exposed to 2% formaldehyde in aqueous solution was 7%. The incidence of skin sensitization among 479 subjects exposed to 5 percent triethanolamine in aqueous solution was 2%.[71] As noted earlier, both formaldehyde and triethanolamine can occur as impurities in TEA-Lauryl Sulfate (See Table 2).[2,13]

SUMMARY AND DISCUSSION

TEA-Lauryl Sulfate, a viscous, yellow liquid or vaseline-like substance, is the triethanolamine salt of lauryl sulfuric acid. As an anionic surface-active agent (anionic surfactant), TEA-Lauryl Sulfate is characterized by a structural balance between a negatively charged hydrophilic group and a lipophilic residue. It is manufactured by sulfating lauryl alcohol with sulfur trioxide or chlorosulfonic acid followed by neutralization with aqueous triethanolamine. The surfactant is usually supplied at a concentration of 35–40% in aqueous solution. Reported impurities include

triethanolamine, triethanolamine sulfate, unsulfated alcohol, triethanolamine chloride, formaldehyde (in some grades), lead, iron, and arsenic.

TEA-Lauryl Sulfate is used in cosmetics as a detergent, as a stabilizer for dispersing systems, and as a solubilizer for fragrances; it is also used as a wetting, foaming, dispersing, and emulsifying agent. The surfactant is used in a variety of cosmetics including shampoos, bath products, hair dyes, and colors, shaving creams, and cleansing preparations. During 1976 and 1979, TEA-Lauryl Sulfate was reported to be used in 517 and 339 cosmetic formulations, respectively, at concentrations ranging from $\leq 0.1\%$ to $> 50\%$. Of those products reported to be formulated with TEA-Lauryl Sulfate in 1976, 57% (296/517) contained the surfactant at concentrations $> 10\%$. In 1979, this number had dropped to 48% (164/339). The concentrations voluntarily reported by industry to FDA may reflect the percentage of the material of commerce as supplied to formulators (35–40%), or the final concentration in the formulation. Products containing the surfactant can be applied to or come in contact with eyes, skin, hair, and mucous membranes. It is suspected that in the presence of nitrite or other nitrosating agents, cosmetic preparations containing TEA-Lauryl Sulfate may give rise to N-nitrosodiethanolamine. Data were not available on the degradation of TEA-Lauryl Sulfate on skin, nor on its metabolism in skin. Such data would contribute to our understanding of the skin irritating ability of this compound.

In studies with excised guinea pig skin, 0.5 *M* TEA-Lauryl Sulfate produced stratum corneum swelling. Shampoo formulations containing 6 percent of the surfactant increased cutaneous capillary permeability in guinea pigs.

TEA-Lauryl Sulfate was moderately to slightly toxic in acute oral studies with rats; reported LD50s ranged from 0.27 to > 1.95 g/kg. Studies conducted with aqueous solutions containing up to 46% TEA-Lauryl Sulfate generally showed that the surfactant is a significant skin and eye irritant to rabbits. Skin irritation tests conducted in guinea pigs with 0.5% TEA-Lauryl Sulfate in aqueous solution suggested that this compound may be absorbed in toxic amounts. Rabbits and mice showed a reflex inhibition of respiration when exposed in an inhalation study to aerosolized, aqueous solutions containing 15% and 25% TEA-Lauryl Sulfate.

In a 28-day dermal toxicity study, rabbits treated with a diluted shampoo containing 1.5% TEA-Lauryl Sulfate exhibited erythema, edema, wrinkling, eschar formation, and severe desquamation of the skin. Microscopic examination revealed acanthosis and hyperkeratosis. Losses in body weight were also observed. In a 13-week dermal toxicity study, rabbits exposed to a diluted shampoo containing 2.4% TEA-Lauryl Sulfate showed no effects except for a mild erythema and dryness of the skin.

In clinical studies, shampoos containing 10.5% TEA-Lauryl Sulfate caused no irritation under semioccluded conditions or under "use" testing. Diluted shampoos containing 0.15–7.5% of the surfactant caused skin reactions ranging from no irritation to moderate irritation. A diluted shampoo containing 4.4% of the surfactant was highly irritating to the human skin when tested in a 21-day cumulative, closed patch test; however, the irritancy potential of this material would be expected to be high under such a closed patch test system. This skin irritation phenomenon is observed with most detergents. Undiluted shampoos containing 10.5% TEA-Lauryl Sulfate and formulations containing 0.15–7.5% of the ingredient tested as dilutions also showed low potential for eliciting human skin sensitization. No evidence of photosensitization was observed in subjects exposed to both aqueous shampoo solutions containing 0.3–0.42% TEA-Lauryl Sulfate and UV radiation.

CONCLUSION

On the basis of the available animal and human data, the Panel concludes that TEA-Lauryl Sulfate can be used without significant irritation at a final concentration thereof not exceeding 10.5%. Greater concentrations may cause irritation, especially if allowed to remain in contact with the skin for significant periods of time.

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