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Final Report on the Safety Assessment of Sodium Laureth Sulfate and Ammonium Laureth Sulfate

Sodium Laureth Sulfate and Ammonium Laureth Sulfate are used in cosmetic products as cleansing agents, emulsifiers, stabilizers, and solubilizers. The ingredients have been shown to produce eye and/or skin irritation in experimental animals and in some human test subjects; irritation may occur in some users of cosmetic formulations containing the ingredients under consideration. The irritant effects are similar to those produced by other detergents, and the severity of the irritation appears to increase directly with concentration. However, Sodium and Ammonium Laureth Sulfate have not evoked adverse responses in any other toxicological testing. On the basis of available information, the Panel concludes that Sodium Laureth Sulfate and Ammonium Laureth Sulfate are safe as presently used in cosmetic products.

CHEMICAL AND PHYSICAL PROPERTIES

Sodium Laureth Sulfate and Ammonium Laureth Sulfate are salts of sulfated ethoxylated lauryl alcohol. The Laureths, the conventional name for the ethoxylated form of lauryl alcohol, are poly-ethoxyethers (polyethylene glycol ethers) of lauryl alcohol that have the general formula $CH_3(CH_2)_{10}CH_2-(OCH_2-CH_2)_nOH$, where "n" is the average number of ethylene oxide (EO) moieties.[1] The terminal OH groups can be sulfated and then neutralized with either NaOH or NH_4OH.[2,3] Laureths 1, 2, 3, and 4 are mixtures of EO adducts of higher or lower "n" values. Accordingly, Sodium (Ammonium) Laureth Sulfate 1 through 4 will be referred to as Sodium (Ammonium) Laureth Sulfate.

Production

Production of Sodium and Ammonium Laureth Sulfate involves three major steps:

1. Ethoxylation of lauryl alcohol with "n" moles of ethylene oxide,

$$C_{12}H_{25}OH + (CH_2CH_2O)\text{"n"} \xrightarrow[\text{Catalyst}]{KOH} C_{12}H_{25}O(CH_2CH_2O)\text{"n"}H$$

"n" = 1–12 depending on the molar ratio of ethylene oxide to lauryl alcohol in the particular ingredient.

2. Sulfation of the product with sulfur trioxide (SO_3) or chlorosulfonic acid ($ClSO_3H$),

$$C_{12}H_{25}O(CH_2CH_2O)_nH \xrightarrow{SO_3} C_{12}H_{25}O(CH_2CH_2)_nSO_3H$$

3. Neutralization to form either the sodium or the ammonium salt,

$$C_{12}H_{25}O(CH_2CH_2O)_nSO_3H \xrightarrow[\text{Cation}^+]{OH^-} C_{12}H_{25}O(CH_2CH_2O)_nSO_3Na$$

or SO_3NH_4.

The complete mechanism for producing this class of compounds has been described previously.[1]

Structure and Synonyms

The structure and other chemical names for each ingredient under review are as follows:[4]

1. Sodium Laureth Sulfate, CAS Number 1335-72-4

$C_{12}H_{25}O(CH_2CH_2O)_nSO_3Na$

where n has an average value between 1 and 4.
Other names:

Sodium Dodecyl Polyoxyethylene Sulfate
Sodium Lauryl Ether Sulfate
Sodium Lauryl Ethoxysulfate
Sodium Polyoxyethylene Lauryl Sulfate

2. Ammonium Laureth Sulfate, RD Number 977052-96-2

$C_{12}H_{25}O(CH_2CH_2O)_nSO_3NH_4$

where n has an average value between 1 and 4.
Other names:
Ammonium Lauryl Ether Sulfate

Properties

In general, Sodium and Ammonium Laureth Sulfate are free-flowing, clear liquids whose viscosity varies from a few hundred to several thousand centipoises.[5] Sodium Laureth Sulfate is a clear, yellow, viscous liquid with a

characteristic odor; it is soluble in water and alcohol. Ammonium Laureth Sulfate is a pale, clear, yellow liquid with a characteristic odor. It is soluble in water but generally insoluble in oils, fats, and waxes. The physical characteristics of the ingredients are given in Table 1.[6,7]

Micellar Properties

The critical micelle concentration (CMC) is that point at which a surfactant solute ceases to be in a dispersed state and instead has an equilibrium between molecules (or ions) and aggregates (micelles).[8] Surface tension and other properties of a surfactant may change abruptly at the CMC. When, as in Sodium and Ammonium Laureth Sulfate, a polar oxyethylene group (EO) is introduced into a straight chain ionic surfactant molecule, the material's solubility and detergency characteristics increase; however, as these same polar EO groups are introduced, the CMC decreases. The extent to which this occurs depends on the position and number of EO units introduced. Weil et al.[9] showed that CMC values decreased in Sodium-n-alkyl ether alcohol sulfates when the hydrophobic group chain length increased and the hydrophilic group chain length remained constant.

The "Effective Chain Length" concept was developed to describe the changes in surfactant properties caused by the addition of EO groups to a molecule. Effective chain length can be used to describe the relationship between CMC and hydrophile–lipophile balance (HLB). According to the HLB, a molecule of any surface active agent contains both hydrophobic and hydrophilic groups. Lin and Marszall[10] have characterized this relationship with their hydrophobicity index (HI), the ratio of the effective numbers of $-CH_2-$ groups in a chain to the actual number in it. On the basis of the effective chain length, together with the definition of HI, values of HI that are greater than one owing to the addition of EO groups indicate an increase in hydrophilic character of surfactants. This is the case up to the point at which the number of EO units, with their hydrophilic forces, balance the hydrophobic hydrocarbon chain forces. As the length of the EO chain increases, the HI value decreases.[10]

Analytical Methods

Reverse-phase thin-layer chromatography can be used to separate a homologous series of ethoxylated alkyl sulfate surfactants. The best separations were ob-

TABLE 1. Physical Characteristics.[a]

	Approx. M.W.	*Approx. melting point, °C*	*Approx. Krafft point 1% °C*[b]	*Approx. pH of 10% aqueous solution*	*Approx. cloud point*	*Approx. viscosity at 25°C*
Sodium Laureth Sulfate	420	126–136	<0	7.5–9.0	0°C max	2500 cps max
Ammonium Laureth Sulfate	400	–[c]	–	6.0–7.0	0–4°C	–

[a]Data from Refs. 6 and 7.
[b]Temperature at which 1% solution becomes clear on gradual heating.
[c]Not available.

tained with glass plates covered with a 250 μm layer of Alumina H, Alumina G, or Silica Gel G impregnated with a 3%–5% (v/v) solution of n-dodecanol in ethanol. The use of Pinacryptol yellow (0.05% w/v in water) with an ultraviolet viewing chamber was found to be a satisfactory spot detection procedure. Sodium Laureth Sulfate appears as a spot of blue color.[11]

Alkyl sulfates may be determined by cationic titration and by the p-Toluidine Hydrochloride method.[2,3]

The amount of unsulfated material from the alkyl sulfates may be determined by extraction with carbon tetrachloride from an alcohol–water solution; once this is accomplished, the carbon tetrachloride is evaporated and the residue weighed. Petroleum ether determination also detects unsulfated material.[2,3]

The inorganic sulfate in surfactant solutions can be determined with a potentiometric lead nitrate titration. During this process, the potential remains nearly constant as long as the ratio of ferri–ferro cyanide does not change. When the sulfate has been consumed, the excess titrant precipitates lead ferrocyanide, and the potential is changed to indicate the end point.[2,3]

Environmental levels of anionic alcohol ethoxy sulfates (AES) may be determined by the azure A colorimetric process and the two-phase titration method. The amount of sulfate ion formed during biodegradation of surface active organic sulfate can be measured either colorimetrically or turbidimetrically.[12]

Thin-layer, paper, and gas chromatography, as well as IR and UV spectroscopic methods, are used to conduct analyses for the anionic AES group.[12]

Impurities, Diluents, Additives

The impurities, diluents, and additives of Sodium and Ammonium Laureth Sulfate are listed in Table 2.[2,3] Data were not available on the possible presence of traces of ethylene glycol or 1,4-dioxane. Formaldehyde may be present as a preservative in both Sodium and Ammonium Laureth Sulfate. Formaldehyde, in concentrations of 2% and above, is a sensitizer according to the North American

TABLE 2. Impurities, Diluents, Additives.[a]

Compound	*Sodium Laureth Sulfate*	*Conc. (%) max.*	*Ammonium Laureth Sulfate*	*Conc. (%) max.*
Impurities	Sodium chloride	3	Ammonium chloride	2
	Sodium sulfate	2	Ammonium sulfate	2
	Unsulfated alcohol	3	Unsulfated alcohol	4
Diluents	Water	–[b]	Water	–
	Ethanol	14	Ethanol	–
Additives	Sodium bicarbonate	–	Ammonium citrate	–
	Sodium citrate	–	Formaldehyde	–
	Formaldehyde	–		

[a]Data from Refs. 2 and 3.
[b]Not available.

Contact Dermatitis Group.[13] A preliminary report of a long-term study stated that inhalation of formaldehyde at the 15 ppm level for 15 months induced squamous cell carcinomas of the rat nasal cavity.[14] Concentrations at this level would be extremely irritating to humans; occupational exposure concentrations shall not exceed 1.2 mg/m^3 air (1 ppm) for any 30-minute sampling period.[15]

USE

The U.S. International Trade Commission has reported that approximately 10 million pounds of ethoxylated sulfated salts of lauryl alcohol were produced in 1973.[16]

Noncosmetic Uses

The anionic AES groups are used in light-duty dishwashing detergents.[12]

Cosmetic Uses

The laureth sulfates are used as shampoo, bath, and skin cleansing ingredients, primarily because of both their high degree of foaming and detergency and their "softness" to the skin. They also function as emulsifiers, stabilizers, and perfume solubilizers and are compatible with nonionics, amides, amphoterics, and other anionic systems. Their surface-active characteristics allow the laureth sulfates to be especially useful ingredients in products that require hard water tolerance and lime soap dispersing power. These last characteristics increase with the degree of ethoxylation. The laureth sulfates also have a low cloud point.[5,12,17]

Scope and Extent of Use in Cosmetics

The August 31, 1976, Food and Drug Administration (FDA) voluntary submission of cosmetic formulation data lists Sodium and Ammonium Laureth Sulfates as having 298 and 63 uses, respectively.[18] (See Table 3.) The FDA reported in 1979 that these ingredients were used in 209 and 90 formulations, respectively.[19]

The laureth sulfates are used primarily in hair care and bath preparations, in concentrations ranging from $<1\%$ to $>50\%$.[18]

Surfaces, Frequency, and Duration of Application

Products containing Sodium and Ammonium Laureth Sulfates (Table 3) are used on all body surfaces and around all body orifices. Sodium and Ammonium Laureth Sulfates may be applied to the body as often as several times a day (in bath soaps and detergents) or as infrequently as once each month or two (in hair-coloring preparations). The duration of these applications may vary according to use, and occasional or daily use may extend over a period of years.

TABLE 3. Product Formulation Data.[a]

Product category[b]	Total no. containing ingredient	No. product formulations within each concentration range (%)[b]							
		Unreported concentration	>50	>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Sodium Laureth Sulfate									
Other baby products	2	–	–	–	–	2	–	–	–
Bath oils, tablets, and salts	11	–	9	2	–	–	–	–	–
Bubble baths	59	–	9	13	19	18	–	–	–
Other bath preparations	78	–	4	6	2	24	42	–	–
Eye makeup remover	1	–	–	–	–	–	1	–	–
Permanent waves	13	–	–	–	1	1	5	6	–
Hair rinses (noncoloring)	1	–	–	–	–	–	1	–	–
Hair shampoos (noncoloring)	89	–	8	16	33	19	13	–	–
Hair dyes and colors (all types requiring caution statement and patch test)	2	–	–	–	–	2	–	–	–
Hair bleaches	1	–	–	–	–	1	–	–	–
Bath soaps and detergents	4	–	–	–	4	–	–	–	–
Other personal cleanliness products	2	–	–	–	–	–	2	–	–
Skin cleansing preparations (cold creams, lotions liquids, and pads)	19	–	–	12	4	2	1	–	–
Depilatories	9	–	–	–	–	2	4	1	2
Skin fresheners	1	–	–	–	–	–	–	1	–
1976 TOTALS	298	–	30	49	69	71	69	8	2
1979 TOTALS[c]	209	–	25	35	46	63	28	11	1

Ammonium Laureth Sulfate									
Baby shampoos	1	–	–	–	–	1	–	–	–
Bubble baths	6	–	–	1	1	–	1	3	–
Hair rinses (noncoloring)	1	–	–	–	–	–	–	1	–
Hair shampoos (noncoloring)	23	–	1	1	1	5	14	1	–
Hair dyes and colors (all types requiring caution statement and patch test)	31	–	–	–	1	30	–	–	–
Bath soaps and detergents	1	–	–	–	1	–	–	–	–
1976 TOTALS	63	–	1	2	4	36	15	5	–
1979 TOTALS[c]	90	1	1	3	12	37	31	5	–

[a]Data from Ref. 18.
[b]Preset product categories and concentration ranges in accordance with federal filing regulations (21 CFR 720.4).
[c]Data from Ref. 19.

BIOLOGICAL PROPERTIES

Sodium Laureth Sulfate

Absorption, Metabolism, and Excretion

Sodium Laureth Sulfate and other detergents are thought to modify the physical configuration of proteins in the skin.[20] The protein chains unfold temporarily into a random, unpatterned coil rather than into the normal helix, β-sheet, or other regular conformation. In this state, the amide groups of the peptide chain form hydrogen bonds with surrounding water molecules rather than with each other. The characteristic physiochemical properties of the protein are lost, and changes occur in such parameters as sedimentation constant, viscosity, and light absorption.[21] There is no cleavage of the primary protein structure; this process may therefore be reversed by the removal of the modifying agent.[21]

When the increase in sulfhydryl groups (SH) is measured, it is possible to determine the amount of protein that unfolds. In one study, powdered human callus exposed to 1m*M* (approximately 4 g percent) and 10 m*M* (approximately 40 g percent) concentrations of Sodium Laureth Sulfate liberated more sulfhydryl groups than did water alone.[22] In similar studies with powdered human callus, concentrations ranging from 0.25% to 2% of Sodium Laureth Sulfate did not liberate SH groups. Smeenk did not specify the number of ethoxy groups in the test compound, referring to that compound simply as "Sodium salt of ethoxylate of broadcut lauryl alcohol, anionic."[23,24]

The ability of Sodium Laureth Sulfate to extract material from the stratum corneum was determined through the use of the Vermeer washing simulator and guinea pig dorsal skin. The test animal served as its own control. While the left flank was washed with 20 ml distilled water, the right one was washed with 20 ml of the 25 m*M* test solution. Following approximately five minutes of washing at 22°C, the wash fluid was analyzed for soluble proteins and amino acids. Sodium Laureth Sulfate was shown to elute the proteins, whereas water alone failed to produce such effects. Sodium Laureth Sulfate and water alone extracted the same amounts of amino acids.[23]

The effect of Sodium Laureth Sulfate on the permeability of human skin was studied using the method of Bettley.[25] Two opposing perspex chambers are filled with test solution and separated by isolated human epidermis. One chamber was filled with a 1% solution of Sodium Laureth Sulfate to which 10 mEq of KCl/l had been added; the other was filled with distilled water. The control was distilled water to which 10 mEq of KCl/l was added. The chambers were rotated in a special apparatus at 4 rpm for one week. The quantity of potassium ions that had diffused through the skin was used as the measure of the epidermis permeability; this amount was determined by flame photometry. Results showed that the skin is more permeable to K+ ion transfer when it has been bathed in Sodium Laureth Sulfate. This was consistently apparent, although the skin preparations from different persons showed considerable differences in epidermal permeability. There was good agreement in results obtained in duplicate experiments with pieces of the same skin.[23]

The percutaneous absorption of Sodium Laureth Sulfate labeled with ^{14}C at the α-Carbon position of the alkyl chain was studied using the dorsal skin of four

live guinea pigs. The material was applied cutaneously in 0.6 ml of water (3 μmol) to an area of 22.5 cm^2 on the flanks of guinea pigs. After ten minutes of rubbing, the treated areas were washed with water and then covered with nonocclusive patches for 24 hours. The fate of the label during the 24 hours following application is shown in Table 4. Most of the radioactivity was found in the skin rinsings, on the patches, or bound to the site of application. No attempt was made to determine if the activity was in the epidermis or dermis. The level of radioactivity in the blood was measured in samples obtained by cardiac puncture immediately before death. No discernible radioactivity was found.[22]

Separate animals received similar doses of labeled Sodium Laureth Sulfate by intraperitoneal (IP) injection. The proportion of the known IP dose excreted in a given time in urine, feces, and exhaled CO_2 was determined. To calculate the amount of absorption through the skin, investigators divided the amount that was excreted from the cutaneously treated animal by that excreted from the IP treated animal. It was concluded that 2.4% of the material applied cutaneously penetrated the guinea pig skin during the 24-hour exposure.[24]

Female Carworth Wistar rats were used to study the skin penetration of Sodium Laureth Sulfate. The animals were treated with samples of the radio labeled compound, Sodium [1-^{14}C] dodecyl triethoxy sulfate, in concentrations of 0.2% – 2.0% (w/v); solutions were kept at 37°C. Aliquots of 150 or 200 μl were dispensed from a microliter syringe onto a 10 cm^2 area of the skin, which was then covered. Expired CO_2, urine, and feces were collected each 24 hours for two days, after which time the animals were sacrificed. The treated areas of skin were excised and the carcass retained for measurement of radioactivity. Whereas large amounts of the applied surfactant were rinsed off the skin (92.1 ± 10.4%), the treated skin retained a low proportion of the sample (5.8 ± 0.9%), and little adhered to the patch (1.2 ± 0.2%). This evidence suggested that skin penetration was less than 1%. The actual amount of such penetration was determined from the quantity of radioactivity excreted in the urine during the two days (0.39 ± 0.12 μg/cm^2). The penetration of Sodium Laureth Sulfate is believed to be low because the ingredient's ethoxylation decreases its biological activity.[26]

Other groups of rats were given the surfactant by oral intubation or by intraperitoneal or subcutaneous injection. The rate of excretion during the two days, and the carcass residue were determined. When the rats were intubated or injected parenterally, the urine contained a high proportion of the administered sample. The feces and expired air contained small quantities of radioactivity. Two days after injection, the carcass retained less than 1% of the dose.[26]

TABLE 4. Distribution of Radioactivity During 24 Hours Following Application [^{14}C] Labeled Sodium Laureth Sulfate to the Skin of Guinea Pigs.[a]

Recovered radioactivity (%)[b]							
Exhaled CO_2	Urine	Feces	Kidney	Liver	Carcass	Skin at site	Patch
0.6	0.5	0.3	0.0	0.95	0.0	56.9	2.0

[a]Data from Ref. 24.
[b]Mean of four animal assays; remaining radioactivity was recovered from the rinsings.

The effect of Sodium Laureth Sulfate on histamine release was studied in using the mast cells of isolated rat peritoneum.[22] In the absence of Sodium Laureth Sulfate there was a low level of spontaneous histamine release from the mast cells on incubation (approx. 10% or less); however, up to 85% of total stored histamine was released when the mast cells came into contact with 0.05 m*M* concentrations of the test material. This concentration was below the material's CMC of 0.15–.02 m*M* in buffer at 22°C.[22,27]

Skin Swelling

When in concentrations near or above the CMC, some surfactants cause skin to swell. Putterman et al.[28] used Hartley guinea pig skin to study this effect. Squares of skin 20 × 20 mm were excised, epilated, and exposed to ammonia vapors. The separated epidermal sheets were air-dried, soaked in water for one hour, lifted out of the water, and measured. After these sheets were immersed in a 0.05 *M* solution of Sodium Laureth Sulfate (CMC = 4.8×10^{-3} *M*) for 16 hours, their dimensions were again determined. Swelling is expressed in this experiment as the percent increase in the area of a sheet, after it was exposed to the second solution, as compared to the amount of swelling caused by the water. The level of swelling produced by Sodium Laureth Sulfate, a hydrophilic surfactant, was low in comparison with that produced by a purely hydrophobic, more lipid soluble surfactant such as sodium lauryl sulfate. The hydrophobic chain favors epidermal swelling.[28]

Animal Toxicology

Acute

Oral: The acute oral toxicity of Sodium Laureth Sulfate was tested by intubating albino rats. The test methods used and the results are listed in Table 5. These studies indicate that Sodium Laureth Sulfate is moderately to slightly toxic. At high doses (16–64 g/kg), the toxic effects in the animals included: lethargy, diarrhea, rectal and nasal hemorrhage, and impaired locomotion. The animals autopsied revealed no gross or microscopic abnormalities attributable to the test compound. Table 5 outlines these studies.

Dermal: Sodium Laureth Sulfate was tested on the intact and abraded skin of rabbits for dermal irritation. The results are listed in Table 6. Albino rabbits were clipped free of hair on 10% of the toal body area; the posterior portion of the clipped area was abraded. One 0.5 ml sample of the various compound test solutions was placed over each scarified and unscarified area. These test patches were then sealed in place with surgical tape, and the animals were immobilized for 24 hours. After 24- and 48-hour contact periods, the skin was evaluated according to the Draize method.*

Applications of solutions of the compound produced no irritation at 5%–5.6%. Mild erythema and edema occurred at 6%–10%, and at 17.5% and

*Standard Indices of Toxicity according to Draize–Primary Skin Irritation (Draize, rabbits, 8.0 max.): 0.0–no irr. potential; 0.1–0.9–potential for slight irr.; 1.0–1.9–potential for mild irr.; 2.0–2.9–potential for mod. irr.; 3.0–4.9–potential for severe irr.; 5.0+ –primary skin irr.; C–corrosive.

TABLE 5. Acute Oral Toxicity of Sodium Laureth Sulfate.

No. and species of Rats	Test solution		Effects			Comments	Ref.
	Conc. (%)	Dose/Kg	No. dead / No. dosed	LD50 values/Kg: Test Solution	LD50 values/Kg: Ingredient		
10 albino	5.6	5 g	0/10	>5 g	>0.28 g	No changes observed.	32
10 Wistar albino	7.5	5 g	2/10	>5 g	>0.38 g	Nontoxic.	33
10 Wistar albino	7.5	5.0 g or 4.76 ml	0/10	>5 g	>0.38 g	–	34
10 Wistar albino	25	5 ml	3/10	>5 ml	>1.25 ml	Animals fasted 24 hours prior to treatment.	35
10 Wistar albino	25	–[a]	–	–	1.6 ± 0.27 g	Compound administered in a single dose. Food and water ad libitum 14 days of observation. 3 deaths on day one only.	36
35 albino in 7 groups of 5	26	2–64 ml	21/35	13.00 ml	3.38 ml	2–4.00 ml/kg–unkempt coats. 8.00 ml/kg–diarrhea, sluggishness, unkempt coats. 16.00–24.00 ml/kg–lethargy, diarrhea, nasal hemorrhage. 32.00–64.00 ml/kg–severe rectal hemorrhage, lethargy, diarrhea, impaired locomotion, nasal hemorrhage.	31
35 albino in 7 groups of 5	28	4–64 ml	20/35	11.3 ml	3.2 ml	4.0–8.0 ml/kg–lethargy, diarrhea. 10.0–12.5 ml/kg–lethargy, nasal hemorrhage, diarrhea. 16.00 ml/kg–rectal and nasal hemorrage, lethargy, diarrhea. 32.00–64.00 ml/kg–severe rectal hemorrhage, lethargy, almost comatose.	31
10	28	5 g	0/10	>5 g	>1.4 g	No changes observed.	32
5	30	5 g	–	>5 g	>1.5 g	Nontoxic.	37
10 Wistar albino	58	5 ml	2/10	>5 g	>2.9 g	–	38
Sprague–Dawley	58	–	–	–	1.82 g	–	39
Groups of 5M and 5F Cartworth Farm "E" strain	24	–	–	–	2.0 g	No abnormalities found. Food and water available ad libutum after intubation.	40

[a]No data available.

TABLE 6. Cutaneous Toxicity of Sodium Laureth Sulfate.

No. and species of animals	Route of admin.	Test solution		No. days on test	Type of irritation	Day of		Primary irritation Index (PII)	Comment No. irritated subjects / No. dosed	Refs.
		Conc. (%)	Dose (ml)			Onset	Clear			
3 albino rabbits	Clipped abraded and nonabraded skin of back	5.0	0.5	3	–	–	–	0.0	No irritation	41
6 albino rabbits	as above	5.6	0.5	3	–	–	–	0.0	No irritation	32
8 albino rabbits	2 in.^{2} patch on clipped skin of back	6	0.5	2	Erythema	1	–		Application no. 1–erythema in 5/8 Application no. 2–erythema in 7/8	42
6 albino rabbits	as above	7.5	0.5	3	Slight erythema	1	2	0.50	Mild transient; not a primary dermal irritant	33
6 albino rabbits	Abraded and nonabraded skin of back-occluded patch	7.5	0.5	3	Redness, edema	1	3	1.15	Mild transient redness and edema	34
albino rabbits	Skin of back	10		3	–	–	–	0.56	Minimal irritation	43
rabbits	as above	10	–	–	–	–	–	1.2	FHSLA–not an irritant	43
rabbits	Skin of back	10						0.6	Not an irritant	43
rabbits	Skin of back	15		3	Erythema	1			Application no. 1–severe erythema in 1/6; edema in 1/6 Application no. 2–severe erythema in 3/6; edema in 4/6 Application no. 3–severe erythema in 5/6; edema in 5/6	29
albino rabbits	as above	17.5		7		1	7	1.28	Mild irritant	30
6 albino rabbits	Abraded and nonabraded back-occluded patch	25	0.5	3	Edema, erythema	1		5.3	Primary dermal irritant; edema and erythema persisting to day 3	34
6 albino rabbits	as above	25	0.5	3	Erythema, edema	1		6.13	Erythema and edema were observed in intact and abraded skin of all 6 animals which persisted to 72 hours. Severe irritant	35

6 albino rabbits	Clipped abraded and nonabraded skin of back-occluded patch	26	0.5	3	Very slight erythema and edema	1	3	0.54 0.8	FHSLA–6/6 showed mild irritation in abraded skin which cleared within 72 hours in 3/6 DOT	31
6 albino rabbits	Clipped abraded and nonabraded skin of back	26	0.5	3				0.0 0.2	FHSLA–no irritation DOT–mild irritation	31
6 albino rabbits	as above	28	0.5	3				2.04	Potential for moderate irritation	32
3 albino rabbits	Skin of back	30		3	Edema, erythema				Application no. 1 produced severe edema in 3/6; edema in 2/6 Application no. 3 produced severe erythema in 5/6; edema and cracking and drying in 2/6	29
6 female albino rabbits	Topical occluded patch to clipped skin of back	30	0.5	3	Erythema, beet red reaction	1			Application no. 1 –erythema in 5/6 –severe erythema in 4/5 –beet red reaction in 1/5	44
rabbits	Skin of back	30		7	Moderate irritation	1		3.04	Potential for skin irritation	45
6 albino rabbits	as above	58	0.5	3				0.0	Not considered a primary irritant	46
rats	Abraded and non-abraded skin of back-occluded patch	(0.25M) 5–10	–	3	Erythema edema	3	–	–	Slight erythema and edema after 3 days application.	22

[a]No data available.

26%. In other tests, 15%, 25%, 28%, and 30% induced severe irritation. The 15% solution of Sodium Laureth Sulfate was also tested as described above, with one variation: three applications of the compound were made to the rabbits' backs on three consecutive days. After the first application, severe edema occurred in 3/6 and edema in 2/6; after the third, there was severe erythema in 5/6 and edema in 2/6 with cracking and drying.[29] Similar studies using a 17.5% solution of Sodium Laureth Sulfate found the compound to be a mild irritant having a Primary Irritation Index (PII) of 1.28.[30]

Studies conducted in like manner on two 26% solutions of Sodium Laureth Sulfate produced PIIs of 0.54 and 0.0 on the Federal Hazardous Substances Labeling Act (FHSLA) scale (ranging from 0 to 8), and 0.8 and 0.2 on the Department of Transportation (DOT) scale. The compound produced mild irritation in the abraded skin in 6/6 rabbits which cleared within 72 hours in 3/6.[31]

When concentration of 28% Sodium Laureth Sulfate was tested thus on six albino rabbits, it produced moderate irritation and a PII of 2.04.[32]

Three different studies on 30% solutions of Sodium Laureth Sulfate were conducted as described above. Three applications were made in the first of these: application number one produced edema in 5/6 animals, and 3/6 showed severe edema; while 5/6 exhibited severe erythema, and 2/6 experienced cracking and drying after the third application.[29] The second study produced severe erythema after the first application in 5/6 animals, and 1/5 showed a beet-red reaction.[44] The third study produced potential for severe irritation and a PII of 3.04.[45]

An additional study conducted as above on the ingredient Sodium Laureth Sulfate in 58% concentration produced a PII of 0.0 in the six rabbits tested and cannot be considered a primary irritant.[46]

Sodium Laureth Sulfate was applied directly to the shaved dorsal skin of weanling rats as a 0.25 *M* solution (representing between a 5% and 10% solution by weight). After the first and third days of application, the degree of irritation was assessed macroscopically in terms of erythema and edema, scaling and cracking of the stratum corneum, and superficial drying of the stratum corneum. Applications of water served as the experimental control. Sodium Laureth Sulfate produced no irritation after one day's application and only very slight erythema and edema after three days.[22] These studies are also outlined in Table 6.

Skin Sensitization: A 0.1% aqueous solution of Sodium Laureth Sulfate was applied topically to ten guinea pigs three times per week for three weeks. It caused no skin sensitization when topically challenged ten days after the final weekly application. Nevertheless, animals challenged by intradermal injections showed a "blistering effect" one hour after the challenge. At 24 hours, there was a "very strong positive reaction" in three animals and a positive reaction in the remaining seven. At 48 hours after the challenge, six animals continued to show a definite positive reaction, and four showed a slight reaction.[12]

Immersion Tests: The primary skin irritation potential of Sodium Laureth Sulfate was tested by immersion. Male or female guinea pigs with shaved bellies were immersed in the test solution for four hours on three successive days. Skin responses were graded daily for six days starting two days after the last treatment (or on the fifth day of the test). The scoring system ranged from ten (normal) to two (severe skin damage). A 0.07% solution of Sodium Laureth Sulfate produced slight irritation which persisted to the sixth observation day.[47] When three 0.5%

concentrations of 30% Sodium Laureth Sulfate (representing a 0.15% active concentration of the compound) were tested, they produced minimal to no irritation.[48,49] (See Table 7.)

Eye Irritation: Ocular toxicity of Sodium Laureth Sulfate was tested by the Standard Draize Method; 0.1 ml of the material was instilled, with or without rinse, into the conjuctival sacs of albino rabbits, and the eyelids were momentarily closed to ensure even distribution of the compound. The eyes were observed for one week and were graded according to Draize scores* for corneal, iridial, and conjunctival involvement. Any eye exhibiting corneal opacity on day 7 was considered to show a severe eye irritation. Potential corneal abnormalities were also checked with a 2% sodium fluoroscein dye solution.

Effects ranged from no irritation to severe eye damage and were independent of the concentration range of 1.3–58.0 of the compound in the test solution. Test methods used and results are compiled in Table 8.

Subcronic

Oral: Sodium Laureth Sulfate (24% w/w) was fed to two groups of six Carworth Farm "E" strain rats for 13 weeks. In each study, groups of 12 male and 12 female five-week-old rats were fed dietary levels of 40, 200, 1000, or 5000 ppm of the active material; control groups (18 males and 18 females) received a standard diet. Daily observations were made on the health of the animals; food intake and body weights were recorded weekly for each animal. Urine samples were collected from the 5000 ppm and control groups during week 12 and were examined for color, pH, protein, reducing substances, bile salts, and microscopic constituents. Terminal blood samples were taken by cardiac puncture. Erythrocyte and leukocyte counts and determinations of hematocrit and hemoglobin were made, along with measurements of total plasma protein and urea concentrations. At autopsy, pathological examinations were undertaken. Histological examinations were made of sections of a wide range of organs from animals of the 5000 ppm and control groups. Terminal body weights, food intakes, and organ weights were statistically analyzed. The health, behavior, body weights, food intake, hematological results, plasma proteins, urinary findings, and urea concentrations were within normal limits. Rats fed 5000 ppm had increased kidney weight in males and increased heart, liver, and kidney weights in females, but increases in relative organ weights were not statistically significant.

There was no evidence of pathological changes at necropsy. Spontaneous lesions, mainly hydronephrosis, were present in both the control and experimental groups of animals. The authors consider 1000 ppm as the "no-effect" dietary level for this test material.[40]

Dermal: Rubisz-Brzezinska et al.[50] conducted a study on the effect of anion-active detergent Sodium Laureth Sulfate on the skin and the hair cycles of rats. The experiments were conducted on 65 seven- to eight-week-old male Wistar rats weighing 60–70 g. The hair of the animals was in telogen when the experiment was begun. The animals were separated into five groups: Group I received the pure detergent (60%); group II, 30%; group III, 9%; group IV, 0.9%;

*Ocular Irritation (Draize, rabbits, 110 max.): 0.0–0.5–nonirr.; 0.5–2.5–practically nonirr.; 2.5–15–minimally irr.; 15–25–mildly irr.; 25–80–severely irr.; 80–110–extremely irr.

TABLE 7. Acute Immersion Tests.[a]

Compound Sodium Laureth Sulfate	*Species of animal*	*Route of administration*	*Ingred. conc. (%)*	*Dose*	*Irritation Score/Day* 1	2	3	4	5	6	7	*Comment*	*Ref.*
Raw material	Guinea pig	Shaved abdomens	0.07	4-hr	8	8	9	9	9	9	–[b]	Slight degree of irritation	47
	as above	abdomens	0.15	immersion	7	8	9	6	7	7	–	– – –	48
	as above	as above	0.15	for 3 days	10	8	9	6	10	–	–	– – –	49
	as above	as above	0.15	as above	8	10	10	9	10	10	–	Practically no irritation	

[a]Graded two days after last treatment: 10 = normal; 2 = severe skin damage.
[b]No data available.

TABLE 8. Eye Irritation of Sodium Laureth Sulfate–Draize Method.

No. and type rabbits	Wash Y/N	No. of Instillations	Test solution: Conc. (%)	Test solution: Dose (ml)	Average Score Per Day[a]: 1	2	3	4	5	6	7	10	14	Comment	Ref.
9 New Zealand albino	N	1	1.3	0.1	1.3	0	0	0			0			Mild, transient irritant	51
	Y 30 sec	1	1.3	0.1	0	0	0	0			0				
	Y 4 sec	1	1.3	0.1	0	0	0	0			0				
3 albino	N	1	1.5		21	9	1.3	0						High irritation at day 1; disappearing at day 4	52
albino	N	1	1.75		33	24	18	15			8			Moderate eye irritant	30
albino	N	1	3	0.1	25	12	10							Transient irritant	37
		1	3	0.1	22	15	5								
albino	Y	1	3	0.1	2	0	0							Less severe reaction that cleared earlier	
		1	3	0.1	2	1									
3 albino	N	1	5	0.1	2.7									Mild conjunctival irritation that cleared by day 2	51
3 albino	N	1	5	0.1	0									Mild conjunctival irritation that cleared by day 7	51
9 New Zealand albino	N	1	5	0.1	0									No irritation seen in washed eyes.	53
	Y 30 sec	1	5	0.1	0									Transient, barely perceptible conjunctivitis seen in one of three unwashed eyes.	54
	Y 4 sec	1	5	0.1	0										
3 albino	N	1	5	0.1										Mild irritation that cleared by day 2	32
6 albino	N	1	5.6		7.5	6.7	6.3	7.5			8.5			Minimally irritating	
6 albino (M and F)	N	1	6	0.1	0	0		0			0			Did not produce irritation	55
6 albino (M and F)	N	1	7.5	0.1	14.3	6.5	3.3	0						Mild ocular irritant	34
6 albino (M and F)	N	1	7.5	0.1	10.0	5.0	0.7	0						Transient, mild ocular irritant	33
3 albino	N	1	10		32	30	21	20			10				45
3 albino	N	1	10.5		25	25	15	10			7			Moderate eye irritant	56
albino	N	1	15	0.1	34	30	28	16			21				29
albino	N	1	15		34	30	24	25			13				

TABLE 8. (Continued.)

No. and type rabbits	Wash Y/N	No. of Instillations	Test solution: Conc. (%)	Test solution: Dose (ml)	Average Score Per Day[a]: 1	2	3	4	5	6	7	10	14	Comment	Ref.
albino	N	1	17.5		33	24	31	27			31			Moderate eye irritant	30
3 albino	N	1	20	0.1	33	32	37	32			40			Severe initial eye irritant including swelling, redness, iritis, corneal opacity, and possible permanent eye damage	57
3 albino	N	1	25	0.1										Each conjunctival showed intense chemosis discharge and vessel injections. Returned to normal by 7 days.	58
6 albino (M and F)	N	1	25	0.1	31.2	30.5	29.7	26.3			17.7			Moderate to severe ocular irritant	34
9 albino	N	1	26	0.1	8	13.3	22.7	28	27.3	20.3	9				31
	Y 2 sec	1	26	0.1	4	2.6	0.6								
	Y 4 sec	1	26	0.1	4.7	4	2								
3 albino	N	1	27	0.1										Cornea and irises normal. Conjunctivae showed vessel injection, discharge, and chemosis which cleared by day 7.	59
9 New Zealand albino	N	1	28	0.1	6.7	15.3	20.7	27.3	22.7	14.7	11.7				13
9 New Zealand albino	Y 30 sec	1	28	0.1	2	0.7	0								31
	Y 4 sec	1	28	0.1	4	2	0								
6 albino	N	1	28	0.1	14.7	12.0	9.3	8.3			7.5			Minimally irritating	32
albino	N	1	30	0.1	25	35	37	23			16				29
albino	N	1	30		31	33	36	24			15				
3 albino	N	1	30	0.1	24	22	20	20			13			Product at 30% induced corneal opacity and iritis persistent through day 7.	49
	Y	1	30	0.1	3	0									
	N	1	30	0.1	21	20	21	18			13				
	Y	1	30	0.1	6	3	3	0							
	N	1	30	0.1	36	35	33	27			28				
3 albino	N	1	58	0.1	1.33	0	0	0			0			Transient, mild ocular irritant	38

[a]Maximum possible score is 110.

group V, 0% (control). Tap water was used for dilution and control. The detergent was applied to a 3 cm^2 area on the depilated backs of the animals daily for 65 days. At seven-day intervals, the condition of the skin and hair growth, histopathological changes of the skin, and the progress of the induced and spontaneous hair cycles were also investigated during the 65 days of the experiment.

Daily local applications of the detergent affected the animals' skin only in groups I and II. On the 12th day of the experiment, animals in group I showed hyperkeratosis and parakeratosis, thinning of the epidermis, inflammatory reactions, and some of the follicles were in catagen. Seven animals in group I died between days 13 and 15, and the remainder gained weight when application of the detergent was discontinued for four days. On the 33rd day there was parakeratosis, epidermal hyperplasia, acanthosis, and disappearance of the granular layer. The inflammation of the skin persisted during the next two weeks of applications.

Animals in group II, on 30% Sodium Laureth Sulfate, had mild erythema after two weeks. After 30 days, the epidermis showed epidermal hypertrophy, and the upper part of the skin had an inflammatory reaction.

Rats in group III showed no changes of the skin owing to the application of the detergent, except for day 65 when a mild inflammatory reaction occurred. No changes occurred in group IV animals.

The animals in group I (60%) showed shortened anagen and premature synchronized telogen in both the induced and the spontaneous hair cycle. Although the induced cycle was normal in group II (30%) animals, the anagen phase was shortened and premature telogen occurred in the spontaneously growing follicles. Induced and spontaneous hair cycles were normal in rats in groups III and IV.

It was concluded that the histopathological changes were similar to those caused by certain organic solvents and that alterations of the hair cycle depended on the concentration of the detergent. The experiments show that sodium salt of the ethoxylated sulfate of lauryl alcohol applied to the skin of rats causes inflammatory changes, epidermal hyperplasia, epidermoid cyst formation, and diffuse hair loss. A 30% solution caused similar but less severe changes; when solutions of 9% or less were applied for two months, no changes occurred in skin or in the hair cycle.[50]

Chronic

Oral: Tusing et al.[39] fed a diet containing Sodium Laureth Sulfate at 0.1%, 0.5%, and 0% (control) to groups of 30 rats for 105 weeks. All three groups received water *ad libitum*. At 52 weeks, ten animals of each group were sacrificed for blood and urine studies and for gross and microscopic pathological evaluation. Body weights and food and water consumption of individual rats were recorded at weekly intervals, as were observations about general appearance, condition, and behavior. Rats surviving at 105 weeks were sacrificed and gross pathology recorded. At the completion of the study, there were no differences between experimental and control rats in appearance, behavior, organ weights, and organ to body weight ratios. Moreover, growth rates, food consumption, and survival of the treated and control rats did not differ markedly during the first 22 months. Male rats in the test groups had an unexplained loss of weight in the last

eight weeks. Clinical laboratory studies at 52 and 105 weeks revealed no significant alterations in the experimental animals as compared to the controls. Other observations, including gross and microscopic pathology and the occurrence of tumors, were similar in both the experimental and control groups.

Special Studies

Reproduction

Tusing et al.[39] mated ten male and ten female rats after being fed 0.1 and 0% Sodium Laureth Sulfate for 14 weeks. The first generation offspring (F_1) were maintained on the same diets as their parents. When approximately 100 days old, the F_1 rats were bred and the F_2 animals were kept on the same diet for five weeks after weaning. It was concluded that ingestion of 0.1% Sodium Laureth Sulfate had no adverse effect on fertility, litter size, lactation, or survival of offspring. The material induced no changes in blood picture or urinalysis in F_1 and F_2 generations, and there were no findings by gross or microscopic examination that could be attributed to the test compound.[39]

Skin Tumorigenicity

The tumorigenicity of Sodium Laureth Sulfate was tested in groups of 30 female Swiss mice.[39] Approximately 0.1 ml of a 5% aqueous solution was applied twice weekly to the skin of the interscapular area for 105 weeks. The total quantity of Sodium Laureth Sulfate applied to each mouse was about 1 g. Controls had only the solvent applied. No skin tumors appeared, and mortality did not differ substantially in the two groups.

Vaginal Mucosa

Sodium Laureth Sulfate (0.28% active) was applied to the vaginal mucosa of three dogs; no irritation had occurred 24 hours later. The undiluted material (28% active) produced a slight redness in two of three dogs and a diffuse tissue irritation in the third animal.[12]

Twenty milliliters of a bubble bath formulation containing 0.07% Sodium Laureth Sulfate were administered by intravaginal douche daily, five days a week to three healthy, adult purebred female beagle dogs weighing between 8.2 and 9.8 kg. Three other dogs received 20 ml saline as a control.

Both before and after application, daily observations were made for signs of systemic toxicity and vaginal irritation. Body weights were recorded weekly, and hematology and urinalysis were determined at weeks zero and three. At the end of the study, the dogs were sacrificed and necropsied.

The test material produced no grossly visible alterations attributable to treatment. Two test animals showed a reddening of the surface of the vaginal mucosa during the first and last weeks of treatment, but this finding was considered incidental since it was observed prior to the initiation of treatment in both animals.

Hematological results, urinalysis, and pathological evaluations of vagina, kidneys, and liver showed no changes attributable to the test material.[60]

Clinical Assessment of Safety

Acute

Dermal Irritation: A 24-hour occlusive patch test was used to evaluate the irritancy of a 60% aqueous solution of 30% Sodium Laureth Sulfate (18%). Three of the 20 subjects tested showed low level irritation. The remaining 17 had no reaction.[61]

A similar test on another 60% solution of 30% Sodium Laureth Sulfate (18% active) produced mild irritation in 11 of the 20 subjects. The remaining nine had no reaction.[62]

A repeat insult patch test of a dandruff shampoo containing Sodium Laureth Sulfate was tested on 196 subjects. This shampoo containing 0.5% Sodium Laureth Sulfate produced minimal primary irritation and no sensitization.[63]

The above-mentioned Human Clinical Data studies are compiled in Table 9.

Subchronic Dermal Irritation

A 21-day cumulative irritancy assay of the Maibach type repeated insult patch test of a shower gel formulation containing 1.25% active concentration Sodium Laureth Sulfate was tested on 13 subjects. The compound scored 697 out of a possible 819. It was clearly considered to be highly irritating, although specific details of the irritation produced by the ingredient were not presented.[64]

A 21-day cumulative patch test for the irritancy potential of a product containing 14.3% Sodium Laureth Sulfate was tested on 10 subjects. A 0.5% concentration of the test material (0.7% Sodium Laureth Sulfate) was applied daily to the backs of the panelists for 21 days or until a maximum irritation score was reached. If the latter occurred, the patch was removed and the area scored for residual irritation during the remaining scoring dates. Twenty-three hours after the last application, the patches were removed and the areas were washed. Six panelists withdrew from the study. The four panelists who completed the test showed a moderate potential for mild cumulative irritation.[60]

Contact Sensitization

A maximization test to determine the contact sensitization potential of a bubble bath formulation containing 14.3% Sodium Laureth Sulfate was conducted on 25 human subjects. The material* 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 hours with 2.5% aqueous sodium lauryl sulfate under occlusion. After a 10-day rest period, a challenge occluded patch of the material was applied to a different site for a 48-hour period. Prior to challenge, 5%–10% sodium lauryl sulfate was applied to the test site one hour before the test material was applied. Observations were made immediately after the removal of the challenge patch and 24 hours thereafter. There were no instances of contact sensitization from this material.[60]

*It was not stated whether or not the material was diluted. The test result reported only that the "material was applied under occlusion."

TABLE 9. Human Clinical Data.

Sodium Laureth Sulfate	*No. of human subjects*	*Route of admin.*	*Test solution (%) Active*	*No. of reactors* *Min*	*0*	*±*	*1*	*1+*	*2*	*2±*	*3*	*3±*	*8*	*(Max)*	*PII*	*Comment*	*Ref.*
60% of a 30% aq. solution	20	24-hr occlusive patch	18		17	1	2	–[a]	–	–	–	–	–		–	Low level of irritation	61
	20	24-hr occlusive patch	18		9	2	9	–	–	–	–	–	–		–	Low level of irritation	62
Shampoo	196		0.5													Minimal primary irritation No sensitization	63

[a]No data available.

Photosensitivity and Contact Irritation

A sample of a bubble bath formulation containing 0.07% Sodium Laureth Sulfate was tested in a repeated insult patch test with ultraviolet (UV) light for contact irritation, sensitization, and photosensitization. One-hundred and three subjects were used. After their upper back skin was thoroughly cleansed and dried, the product was applied under occlusion and results were read 48 hours later. An open patch was simultaneously applied to the volar aspect of the right wrist and read 48 hours later. Second open and closed insults were applied after 14 days and inspected 48 hours later.

The subjects' backs were exposed to an UV light source (Hanovia Tanette Mark I Lamp with a wavelength including 3600 Å) at a distance of 12 inches for one minute. The skin sites beneath the patches were exposed and irradiated after the second insult had been read. After 48 hours, 4 of the 103 subjects showed a weak "nonvesicular" reaction, and all the others were negative.[60]

In a similar repeated insult photosensitivity test, a total of ten open and closed insults of the test products were applied every Monday, Wednesday, and Friday for three-and-a-half weeks. After the subjects were rested for 14 days, additional open and closed insults were applied. After 48 hours, the test areas were inspected and then exposed for one minute to UV light (Hanovia Tanette Mark I Lamp) 12 inches away from the source. The skin sites under the patches were irradiated after the 1st, 4th, 7th, 10th, and 11th insults were read. The effect of UV exposure on the test sites were inspected 48 hours after irradiation. Two of the 56 subjects showed a mild reaction of unspecified type, but the other panelists were not affected.[60]

Ammonium Laureth Sulfate

Animal Toxicology

Acute

Oral: Ammonium Laureth Sulfate solutions were tested on groups of albino rats for acute oral toxicity. The test methods used and the results of these studies are compiled in Table 10. Concentrations of the test compound solution ranged from 7.5% to 27%. The LD50s of the test solutions were found to be >5 ml/kg. The LD50s of the ingredient in these solutions ranged from >0.38 ml/kg to >3.3 g/kg. One sample of a 12.5% concentration of Ammonium Laureth Sulfate caused seven deaths in a test population of ten rats. No other results were given. At the 27% concentration, 12 out of 50 animals died within 24 hours. The animals that died had reddened lungs, livers, stomachs, intestines, and kidneys at the 12.1–14.7 g/kg dosage level.[65]

A similar study on a 26% solution caused death in 5 out of 50 animals.[65] (See Table 10.)

Dermal: Acute dermal irritation of Ammonium Laureth Sulfate was tested on the clipped intact and abraded skin of albino rabbits. Concentrations of the compound in the test solutions ranged from 7.5% to 60%. Reactions ranged from the potential for slight irritation to severe primary irritation. Test methods used and results of these studies are compiled in Table 11.

TABLE 10. Acute Oral Toxicity of Ammonium Laureth Sulfate.

No. and type of rats	Test solution		Effects			Comment	Ref.
	Conc. (%)	Dose/Kg	No. dead/ No. dosed	LD50 Values/Kg Test soln.	LD50 Values/Kg Ingredient		
10 albino	7.5	5.0 ml	0/10	>5 ml	>0.38 ml	Not a toxic material	33
10 albino	7.5	5.0 ml	0/10	>5 ml	>0.38 ml	No gross pathology seen at autopsy	33
10 albino	7.5	5.0 ml	0/10	>5 ml	>0.38 ml	No gross pathology seen at autopsy	67
10 albino	12.5	5.0 ml	7/10	>5 ml	<0.63	Toxic at this dosage level	68
10 albino	25	5.0 ml	0/10	>5 ml	>1.25 ml	–[a]	33
10 albino	25	5.0 ml	0/10	>5 ml	>1.25 ml	No gross pathology seen at autopsy	69
50 Charles River; Sprague-Dawley	27	1–100 g	12/50	11.9 g,M 12.3 g,F	3.2 g,M 3.3 g,F	All deaths occurred within 24 hours	65
50 Charles River; Sprague-Dawley	26	1–100 g	5/50	6.8 g	1.7 g	In both 26 and 27% solutions, all animals that died showed reddened lungs, livers, stomachs, intestines, and kidneys at the 12.1–14.7 g/kg dosage level.	65

[a]No data available.

Acute Dermal LD50: A bubble bath formulation containing 22% Ammonium Laureth Sulfate was tested for acute dermal LD50 on four albino rabbits. The backs of the rabbits were clipped of hair, and a 1% solution (0.22% Ammonium Laureth Sulfate) was applied in 5 g/kg doses. It should be noted that the dose of the specific ingredient was only 0.01 g/kg. The sample was applied under rubber dental dam and held in place for 24 hours. The animals were observed for 14 days, after which they were sacrificed and examined for gross pathology. None of the animals died during the observation period, and none showed signs of intoxication. There were no gross pathological findings at necropsy.[66]

Acute Immersion: Ammonium Laureth Sulfate was evaluated for skin irritancy by immersing two groups of guinea pigs in 0.06% solutions for four hours per day for three days. The compound produced mild irritation;[76] solutions containing 0.07% and 0.14% produced no irritation.[70]

Ocular Irritation: The acute ocular irritation of Ammonium Laureth Sulfate was tested according to the Draize method on groups of albino rats. Concentrations of the test solutions ranged from 7.5% to 60% and were instilled into the eyes, with or without wash-out, in doses of 0.1 ml. Effects ranged from transient, mild ocular irritation to severe irritation. Test methods and results of the studies are compiled in Table 12. (See footnote on Draize eye irritation scores.)

Vaginal Irritation: Ammonium Laureth Sulfate in a bubble bath was tested for local vaginal irritation and systemic toxicity in beagles for three weeks. The sample, which contained 0.11% concentration of the compound, was applied by

TABLE 11. Acute Dermal Irritation of Ammonium Laureth Sulfate.

No. of albino rabbits	Route of admin.	Test solution		No. days on test	Type of irritation	Day of		PII	Comment (No. irritated subjects/No. dosed)	Ref.
		Conc. (%)	Dose			Onset	Clear			
6	Clipped abraded and nonabraded skin of back	7.5	1.5	3	Erythema	1		0.5	Potential for slight irritation; rarely irritating to people; slight erythema at day 1	33
6	as above	7.5	1.5	3	Erythema	1		0.9	Potential for slight irritation; erythema at day 1 in 6/6, persisting to day 3 on 4/6	67
6	as above	7.5	1.5	3	Erythema	1	3	0.7	Erythema seen at 24 hours, but disappearing after 72 hours	67
8	as above	12	1.5	3	Erythema	1			6/8 showed definite erythema after day 1; 8/8 after day 2	42
9	as above	15	1.5	3				2.00	Moderate skin irritant	70
9	as above	15	1.5	3				3.23	Moderate skin irritant	71
9	as above	15	1.5	3				3.22	Moderate skin irritant	72
6	as above	25	1.5	3	Erythema, edema	1		8.0	Severe primary irritant	73
6	as above	25	1.5	3	Erythema, edema	1		5.21	Severe irritant to the skin	69
6	as above	25	1.5	3	Erythema, edema	1		4.1	Potential for severe irritation	67
6	Clipped abraded and nonabraded skin of back	31	1.5	3				1.76	Mild irritation	74
6	as above	31	1.5	3				2.11	Moderate skin irritation (unspecified)	75
6	as above	31	1.5	3				1.17	Moderate skin irritation (unspecified)	75
6	as above	61	1.5	3	Severe erythema	1			At least moderate to severe irritation after application in 6/6	42

TABLE 12. Eye Irritation of Ammonium Laureth Sulfate–Draize Method.[a]

No. of albino rabbits	Wash Y/N	No. of Instillations	Test solution Conc. (%)	Test solution Dose (ml)	Average Score Per Day 1	2	3	4	5	6	7	10	14	Comment	Ref.
6	N	1	7.5	0.1	15.7	11.8	4.7	1.2			0			Transient mild ocular irritant	67
6	N	1	7.5	0.1	13.3	13.6	7.6	10			10.1			Mild ocular irritant	67
6	N	1	7.5	0.1	15.5	8.5	7.3	2.1			0			Mild ocular irritant	33
6	N	1	15	0.1	32	25	33	22			16				70
			15	0.1	36	15	16	11			8				77
3	N	1	20	0.1	32	26	21	12			4			Corneal opacity and iritis clearing by day 7	44
6	N	1	25	0.1	25.1	23.3	24.7				21.5			Severe irritant to rabbit eye when not followed by washout	69
6	N	1	25	0.1	16.1	16.3	13				4.7			Severe transient irritant when not followed by washout	73
3	N	1	25	0.1	17.6	17.6	21.5				22.6			Severe ocular irritant	67
3	N	1	26	0.1	16	14.3	13.7	13.7					4.6	Corneal damage, iritis, beefy redness, chemosis	65
3	Y 2 sec	1	26	0.1	2	1.3	1.3	0.6			0.3			Slight redness of conjunctivae	65
3	Y 4 sec	1	26	0.1	3.3	2	0.6	0.6			0				
3	N	1	27	0.1	10.7	12.3	17.3	17.3	3		3		0.66	Corneal damage, beefy redness, iritis, chemosis	65
3	Y 2 sec	1	27	0.1	0.3	2	1.3	1.3			0			Slight redness of conjunctivae	65
3	Y 4 sec	1	27	0.1	2	0	0.6	1.3							
3	N	1	30	0.1	31	25	21	21			21				74,75,76
6		1	30	0.1	35	26	24	21			11				74,75,76
6	N	1	30		45	34	25	23			8				74,75,76
	N	1	30		55	44	35	31			28				74,75,76
	N	1	30		30	26		18			15				74,75,76
	N	1	30		31	23	20	20			15				74,75,76
	N	1	30		31	25	21	21			21				74,75,76
3	N	1	60	0.1	38	29	27	20			14			Corneal effects and iritis	57

[a]See footnote on Draize eye irritation scores.

vaginal douche for five days a week. Three untreated dogs served as the control. Daily observations were made for systemic toxicity and vaginal irritation, body weights were recorded weekly, and hematology and urinalysis were determined at weeks 0 and 3.

During the study, all dogs maintained their normal appearances and behavior and gained weight. Hematology and urinalysis of treated and control dogs were comparable. Gross pathology showed slight redness in the distal portion of the vagina in one treated dog, and redness in proximal and distal portions of a second one; neither appeared to be compound-related. The product produced no gross or microscopic changes in the vaginal mucosa.[66]

Subchronic

Dermal: In a 28-day irritation study, unrestrained rabbits with abraded skin sites were treated with aqueous solutions of "Ammonium alcohol ethoxy sulfate" (the specific alcohol and degree of ethoxylation were not stated). The first topical application contained 200 mg/kg of active ingredient; all applications thereafter contained 50 mg/kg. Histological examinations revealed moderate to severe skin inflammation.[12]

Clinical Assessment of Safety

Dermal Contact Irritation/Sensitization

A bubble bath containing 23% Ammonium Laureth Sulfate was used in a standard Repeated Insult Human Patch test on 189 subjects. A 1.25% aqueous solution of the product (0.29% Ammonium Laureth Sulfate) was used for the induction phase; the challenge concentration was 0.63% (0.15% Ammonium Laureth Sulfate). During induction, one-third of the subjects had mild to moderate irritation. When the challenge concentration was lowered to 0.63% in order to minimize irritation responses, nine persons exhibited weak sensitization reactions; follow-up testing did not confirm reactivity in these individuals. It was concluded that this formulation possessed a minimal potential for inducing irritant contact dermatitis.[78] These same conclusions were reached when a 0.115% active solution of Ammonium Laureth Sulfate in a bubble bath was tested on 86 subjects.[79] When 94 subjects were tested with this bubble bath at a 1% aqueous solution at induction (0.23% Ammonium Laureth Sulfate) and 0.5% solution at challenge (0.115% Ammonium Laureth Sulfate) the results showed a minimal potential for irritant contact dermatitis.[80]

A bubble bath formulation containing 23% Ammonium Laureth Sulfate was tested for skin irritation on 20 human subjects. The 1.25% test concentration (0.28% ingredient concentration) was applied under occlusion in a single insult for 24 hours. The material produced no effect in 11 of the 20 subjects, faint uniform or spotty erythema in 4 of 20, mild, pink, uniform erythema covering most of the contact sight in 4 of 20, and marked bright red erythema with edema, petechiae and papules in 1 of the 20.[81]

A three-week repeated insult occluded patch test was conducted on 68 men and women with a 0.5% solution of a bubble bath containing 22% Ammonium Laureth Sulfate. (This is a 0.11% concentration of the compound in the sample.) Patch sites were scored prior to the patch applications at the second through the

tenth visit. Challenge sites were scored 48 and 96 hours after application. The bubble bath sample was essentially nonirritating following initial application. Repeated applications of the sample produced moderate irritation in about 16% of the panelists, but there was no indication of sensitization following the applications.[66]

Table 13 presents these results.

Phototoxicity

Twenty-five men and women were used to study the phototoxic properties of a bubble bath containing 0.11% Ammonium Laureth Sulfate. Occlusive patches of the test material at 0.5 ml per patch were applied to the arms of the panelists at 2:00 p.m. on each of five consecutive days, and removed at 1:00 p.m. the following day. The test sites were scored immediately after patch removal. On all except two consecutive days, about 0.1 ml of each test material was then swabbed into the respective test sites, and the panelists exposed the areas to direct sunlight for 30 minutes.

Moderate skin irritation was seen on six panelists following the application of the sample. The irritation was transitory and in several instances occurred even when not exposed to light. The 6 of the 22 panelists who showed irritation were believed not to have phototoxic reactions.[66]

TABLE 13. Human Clinical Data–Dermal Irritation/Sensitization of Ammonium Laureth Sulfate.

Cosmetic product type	*No. of human subjects*	*Route of admin.*	*Test solution (%) active*	*PII*	*Comment*	*Ref.*
Bubble bath	189	Single and repeat insult occlusive patches	0.29 at induction	–[a]	One-third of the panelists exhibited mild to moderate irritation.	78
			0.15 at challenge	–	Nine exhibited weak sensitization reactions; follow-up testing did not confirm reactivity in these individuals.	78
Bubble bath	86	as above	0.115	–	0/86 sensitized; mild to moderate irritation at induction; no follow-up sensitization	79
Bubble bath	94	as above	0.23 at induction	–	0/94 sensitized	80
			0.115 at challenge		This bubble bath formulation possesses no to minimal potential for inducing contact dermatitis.	
Bubble bath	20	as above	0.28	–	11/20–no reaction	81
				0.48	4/20–mild reaction	
				–	4/20–mild reaction; erythema over most of contact site	
					1/20 marked erythema, edema, papules	
Bubble bath	69	as above	0.11	–	16% of the panelists showed irritation after repeat applications. No indication of sensitization	66

[a]No data available.

Twenty-One-Day Cumulative Sensitivity Test

Two bubble bath preparations containing 0.11% Ammonium Laureth Sulfate were used to study sensitization potential.

Patches with test samples were applied to the back of each of 12 panelists. Daily applications of the samples were made to the same test sites for 21 consecutive days or until irritation scores of 3 or equivalent were observed. In the latter cases, application of the sample was discontinued.

The 20-mm^2 squares of cotton patches were affixed to adhesive patches. Five patches were applied to each side of the back for a total of ten per subject; these were removed 23 hours after each daily application, and panelists were instructed to bathe or shower immediately after removal and to keep the areas dry at other times. Reactions were scored 24 hours after the sample had been applied.

The material caused erythema and papules, and it was concluded that the two products showed evidence of having moderate potential for mild cumulative irritation under continued reapplication and occlusion.[66]

Ocular Irritation

Tests were performed on ammonium alcohol ethoxy sulfate (the length of alkyl chain and degree of ethoxylation was not specified) in 10 and 20% concentrations of a liquid formulation containing 9% active material. This substance was found to be nonirritating when instilled into the eyes of 20 human volunteers.[12]

Mucosal Irritation

When applied once daily for two weeks to male and female genitalia, a 25% solution of a product containing 9% "ammonium alcohol ethoxy sulfate" was found to be nonirritating.[12]

SUMMARY

Sodium Laureth Sulfate and Ammonium Laureth Sulfate are salts of sulfated ethoxylated lauryl alcohol, which conforms to the general formula: $CH_3(CH_2)_{10}CH_2-(OCH_2CH_2)_nOH$, where n is the average number of ethylene oxide moieties. The terminal-OH groups are sulfated and then neutralized with either NaOH or NH_4OH to form the sodium or ammonium salts. The Laureth Sulfates are clear liquids, soluble in water and alcohol. Used as shampoo, bath, and skin cleansing ingredients, these also function as emulsifiers, stabilizers, and solubilizers. The concentration of Sodium Laureth Sulfate in cosmetics ranges from less than or equal to 0.1% to greater than 50%, and that of Ammonium Laureth Sulfate ranges from greater than 0.1% to greater than 50%. Laureth Sulfates are reported to contain unspecified amounts of formaldehyde. Formaldehyde vapor has been shown to induce tumors in rats; according to the North American Contact Dermatitis Group, formaldehyde is a skin sensitizer.

Skin bathed in Sodium Laureth Sulfate is more permeable to potassium ion transfer but has a low-level of percutaneous absorption. Concentrations of 0.05 m*M* of Sodium Laureth Sulfate released up to 85% of the total stored histamine

from isolated rat peritoneal mast cells. Since it is an hydrophilic surfactant, this salt produced a low level of swelling when in contact with excised guinea pig stratum corneum.

Studies have shown that Sodium Laureth Sulfate in concentrations ranging from 5.6 to 58% is slightly toxic to rats according to the classification of Hodge and Sterner.[82]

When Sodium Laureth Sulfate in concentrations of 60% and 30% was applied to the skin of rats, it produced severe epidermal irritation and impairment of hair growth. Applications of the compound to the clipped abraded and nonabraded dorsal skin of albino rabbits produced no irritation at concentrations of 5%–5.6%, minimal irritation at 6%–10%, and severe irritation at 25%. Immersion of guinea pigs in a 0.1% solution of the compound caused no skin sensitization and mild irritation at concentrations of 0.07%–0.19%.

In a subchronic oral toxicity study in rats, 1000 ppm of this compound in the diet had no effect. In a chronic oral toxicity study in rats fed 1000 ppm and 5000 ppm Sodium Laureth Sulfate in the diet for 105 weeks, none of the animals showed gross or microscopic changes. Rats eating 0.1% of the compound in the diet showed no effects in the reproductive performances of the F_0, F_1, or F_2 generation.

The application of 5 mg of Sodium Laureth Sulfate to mice twice a week for 105 weeks produced no skin tumors.

Solutions of 0.28% Sodium Laureth Sulfate were nonirritating to the vaginal mucosa of beagles, and a 28% solution produced redness. A formulation containing a 0.07% concentration of the compound did not cause any irritation on the vaginal mucosa of beagles when applied for three weeks.

In clinical studies, an 18% solution of the compound tested under occlusion produced a low level of irritation in 3 of 20 subjects. Another 18% solution brought about mild irritation in 11 out of 20 subjects. No primary irritation or sensitization was produced by a 0.5% solution of the compound in formulation when it was tested on 196 volunteers. A subchronic dermal study found a 1.25% solution of the material to be highly irritating, while another study using a 0.07% solution in formulation indicated a "moderate potential for mild cumulative irritation" in the four tested panelists. A formulation containing 14.3% Sodium Laureth Sulfate caused no contact sensitization.

A formulation containing a 0.07% concentration of the compound, when tested for phototoxicity, caused a "weak, nonvesicular" reaction in four of 103 panelists. A similar test produced a mild reaction of unspecified type in 2 of 56 subjects.

No absorption, metabolism, and excretion studies were reported for Ammonium Laureth Sulfate.

Ammonium Laureth Sulfate in concentrations ranging from 7.5% to 27% was tested for acute oral toxicity in rats; the material was considered to be slightly toxic.

Ammonium Laureth Sulfate in concentrations ranging from 7.5% to 60% was tested for dermal toxicity. At concentrations of 15% and greater, severe irritation occurred and the calculated acute dermal LD50 was greater than 5.0 g/kg. Guinea pigs immersed for four hours per day for four days in 0.06%–0.14% Ammonium Laureth Sulfate had mild skin irritation. In ocular irritation studies, a

7.5% concentration produced mild irritation. Irritation increased as concentration increased.

The vaginal mucosa of the beagles exposed to 0.11% solution of Ammonium Laureth Sulfate five days a week for three weeks showed no irritation. In a subchronic dermal study on rabbits, 200 mg/kg of the compound were used in the first application and 50 mg/kg in subsequent applications; the ingredient gave rise to moderate to severe skin irritation.

When a formulation containing 23% Ammonium Laureth Sulfate was tested for its potential for causing allergic reactions, it was adjudged to possess a minimal potential for contact dermatitis. The same conclusions were reached when a 0.115% solution in a formulation was tested on 86 subjects and a 0.23% on 94 others. A 0.28% sample of the compound tested on 20 subjects showed that 11 were reaction-free; 8 had a mild reaction, and 1 a moderate reaction. A formulation containing 0.11% Ammonium Laureth Sulfate was used for a repeated insult patch test on 68 subjects. The initial application produced no irritation. Repeated application produced moderate irritation in 16%, but no sensitization occurred.

A photosensitization test of a sample containing 0.11% of the compound produced irritation in 6 of the 22 panelists. However, the reactions probably indicated primary irritation and not phototoxicity. A 21-day cumulative irritancy test with a sample containing 0.11% of the compound produced erythema and papules. Ten and 20% concentrations of a liquid containing 9% active material were found to be nonirritating following instillation into the eyes of 20 volunteers. A 2.25% concentration of the compound caused no irritation when applied to male and female genitalia once a day for two weeks.

DISCUSSION

Sodium Laureth Sulfate and Ammonium Laureth Sulfate are cosmetic detergents that exert emulsifying action, thereby removing oil and soil from the hair and skin. The Panel wishes to point out that these two ingredients produce eye and/or skin irritation in experimental animals and in some human test subjects; irritation may occur in some users of cosmetic formulations containing the ingredients under consideration. The irritant effects are similar to those produced by other detergents, and the severity of the irritation appears to increase directly with concentration. However, Sodium and Ammonium Laureth Sulfate have not evoked adverse responses in any other toxicological testing.

CONCLUSION

It is recognized that Sodium and Ammonium Laureth Sulfate may induce eye and skin irritation. However, on the basis of available information, the Panel concludes that Sodium Laureth Sulfate and Ammonium Laureth Sulfate are safe as presently used in cosmetic products.

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REFERENCES

1. COSMETIC INGREDIENT REVIEW (CIR). (1979). Technical Analysis Report on Laneth-10 Acetate, and Related Compounds. Washington, DC: Cosmetic Ingredient Review.
2. COSMETIC, TOILETRY AND FRAGRANCE ASSOCIATION (CTFA). (Aug. 28, 1979). Submission of data. CTFA Cosmetic Ingredient Chemical Description. Sodium Laureth Sulfate Group.*
3. CTFA. (Aug. 28, 1979). Submission of data. CTFA Cosmetic Ingredient Chemical Description. Ammonium Laureth Sulfate Group.*
4. ESTRIN, N.F. (ed.). (1977). *CTFA Cosmetic Ingredient Dictionary,* 2nd ed. Washington, DC: Cosmetic, Toiletry and Fragrance Association.*
5. CTFA. (Aug. 28, 1979). Submission of data. Summary of unpublished safety data: Sodium Laureth Sulfate Group.*
6. ESTRIN, N.F. (ed.). (1977). CTFA Standards: Cosmetic Ingredient Descriptions. Washington, DC: Cosmetic, Toiletry and Fragrance Association.*
7. WEIL, J.K., STIRTON, A.J., and WRIGLEY, A.N. (1968). Synthesis and surface active properties of long-chain ether alcohol sulfates $R(OCH_2CHR)OSO_3Na$. Chem. Phys. Appl. Prot. Ag. Surface C.R. Congr. Int. Deterg. **5,** 45–51.
8. SAAD, H.Y. and SHAY, E.G. (1972). Application of physical chemistry in product development. J. Soc. Cosmet. Chem. **23,** 899–911.
9. WEIL, J.K., BISLENE, R.G., JR., and STIRTON, A.J. (1958). The critical micelle concentration of ether alcohol sulfates $R(OC_2H_4SO_3Na$. J. Phys. Chem. **62,** 1083–5.
10. LIN, I.J. and MARSZALL, L. (1976). CMC, HLB, and effective chain-length of surface-active anionic and cationic substances containing oxyethylene groups. J. Colloid Interface. Sci. **57**(1), 85–93.
11. BREYER, A.C., FISCHL, M., and SELTZER, E.J. (1973). A systematic study of the variables involved in the reverse-phase thin-layer chromatography of oxyethylated alkyl sulfate surfactants. J. Chromatogr. **82**(1), 37–52.
12. ANON. (May 31, 1977). "Human Safety and Environmental Aspect of Major Surfactants." A report to the Soap and Detergent Association, Arthur D. Little, Inc.
13. NORTH AMERICAN CONTACT DERMATITIS GROUP (NACDG). (1977). 3208.
14. SWENBERG, J.A., KERNS, W.D., MITCHEL, R.I., GRALLA, E.J., and PAVKOV, K.L. (Sept. 1980). Induction of Squamous Cell Carcinomas of the Rat Nasal Cavity by Inhalation Exposure to Formaldehyde Vapor. Cancer Res. **40,** 3398–402.
15. NATIONAL INSTITUTE OF OCCUPATIONAL SAFETY AND HEALTH (NIOSH). (Dec. 1976). Criteria for a recommended standard . . . occupational exposure to Formaldehyde. Washington, DC: DHEW.
16. U.S. INTERNATIONAL TRADE COMMISSION. (Jan. 1975). "Synthetic organic chemicals – production and sales of surface active agents."
17. SAUTE, R.E. (1972). Bath Preparation, vol. 2, in: *Cosmetics: Science and Technology,* 2nd ed., 3 vols. M.S. Balsam and E. Sagarin (eds.). New York: Wiley-Interscience. pp. 503–19.
18. FOOD AND DRUG ADMINISTRATION (FDA). (Aug. 31, 1976). Cosmetic product formulation data. Washington, DC.
19. FDA. (June 20, 1979). Cosmetic product formulation data. Washington, DC.
20. MONTGOMERY, R., DRYER, R.L., CONWAY, T.W., and SPECTOR, A.A. (1977). *Biochemistry: A case-oriented approach.* 2nd ed. St. Louis, MO: C.V. Mosby.
21. METZLER, D.E. (1977). *Biochemistry. The Chemical Reactions of Living Cells.* New York, NY: Academic Press.
22. PROTTLEY, D. and FERGUSON, T.F.M. (1976). The effect of surfactants upon rat peritoneal mast cells *in vitro.* Food Cosmet. Toxicol. **14,** 425–30.

*Available upon request: Administrator, Cosmetic Ingredient Review, Suite 810, 1110 Vermont Ave., N.W., Washington, DC 20005.

23. SMEENK, G. (1969). The influence of detergents on the skin (A clinical and biochemical study). Arch. Klin. Exp. Dermatol. **235,** 180–91.
24. SMEENK, G. and POLANO, M.K. (1965). Methods for comparative estimation of the irritancy of various detergents on human skin. Trans. St. Johns' Hosp. Derm. Soc. (London) **51,** 90–102.
25. BETTLEY, F.R. (1961). The influence of soap on the permeability of the epidermis. Brit. J. Dermatol. **73,** 448–54.
26. BLACK, J.G. and HOWES, D. (May/June 1979). Skin penetration of chemically-related detergents. J. Soc. Cosmet. Chem. **30,** 157–65.
27. PROTTLEY, D. and FERGUSON, T. (1975). Factors which determine the skin irritation potential of soaps and detergents. J. Soc. Cosmet. Chem. **26**(1), 29–46.
28. PUTTERMAN, G.J., WOLEGSZA, N.F., WOLFROM, M.A., and LADEN, K. (Sept. 1977). The effect of detergents on swelling of stratum corneum. J. Soc. Cosmet. Chem. **28,** 521–32.
29. AVON. (June 19, 1972). Submission of data by CTFA. Unpublished safety data on Sodium Laureth Sulfate.*
30. AVON. (Oct. 13, 1978). Submission of data by CTFA. Unpublished safety data on Sodium Laureth Sulfate.*
31. BIO-TOXICOLOGY LABS. (Oct. 10, 1975). Submission of data by CTFA. Unpublished safety data on Sodium Laureth Sulfate.*
32. BIOMETRICS. (Aug. 29, 1979). Submission of data by CTFA. Unpublished safety data on Sodium Laureth Sulfate. A-1757.*
33. CONSUMER PRODUCT TESTING CO. (CPTC). (March 16, 1977). Submission of data by CTFA. Unpublished safety data on Sodium and Ammonium Laureth Sulfates.*
34. CPTC. (May 9, 1977). Submission of data by CTFA. Unpublished safety data on Sodium Laureth Sulfate.*
35. FOOD AND DRUG RESEARCH LABS (FDRL). (Feb. 4, 1976). Submission of data by CTFA. Acute oral and dermal toxicity test with rats: Sodium Laureth Sulfate.*
36. INDUSTRIAL BIO-TEST LABS (IBTL). (June 18, 1976). Submission of data by CTFA. Acute oral toxicity test with rats: Sodium Laureth Sulfate.*
37. AVON. (July 9, 1976). Submission of data by CTFA. Unpublished safety data on Sodium Laureth Sulfate.*
38. LEBERCO LABS. (July 13, 1976). Submission of data by CTFA. Acute oral toxicity with rats; Acute eye irritation with rabbits: Sodium Laureth Sulfate.*
39. TUSING, T.W., PAYNTER, O.E., OPDYKE, D.L., and SNYDER, F.H. (1962). Toxicologic studies on sodium lauryl glyceryl ether sulfonate and sodium lauryl trioxyethylene sulfate. Toxicol. Appl. Pharmacol. **4,** 402–9.
40. WALKER, A.I.T., BROWN, V.K.H., FERRIGAN, L.W., PICKERING, R.G., and WILLIAMS, D.A. (1967). Toxicity of sodium lauryl sulfate, sodium lauryl ethoxy sulfate and corresponding surfactants derived from synthetic alcohols. Food Cosmet. Toxicol. **5**(6), 763–9.
41. LEBERCO LABS. (Jan. 13, 1977). Submission of data by CTFA. Primary skin irritation with rabbits: Sodium Laureth Sulfate.*
42. AVON. (July 17, 1970). Submission of data by CTFA. Unpublished safety data on Sodium and Ammonium Laureth Sulfate.*
43. IBTL. (June 19, 1975). Submission of data by CTFA. Primary Skin Irritation: Sodium Laureth Sulfate.*
44. AVON. (July 14, 1970). Submission of data by CTFA. Unpublished safety data on Sodium and Ammonium Laureth Sulfate.*
45. AVON. (Dec. 11, 1975). Submission of data by CTFA. Unpublished safety data on Sodium Laureth Sulfate.*
46. LEBERCO LABS. (July 25, 1975). Submission of data by CTFA. Primary skin irritation with rabbits: Sodium Laureth Sulfate.*
47. AVON. (Oct. 31, 1977). Submission of data by CTFA. Unpublished safety data on Sodium Laureth Sulfate.*
48. AVON. (Sept. 30, 1976). Submission of data by CTFA. Unpublished safety data on Sodium Laureth Sulfate.*
49. AVON. (Nov. 26, 1976). Submission of data by CTFA. Unpublished safety data on Sodium Laureth Sulfate.*
50. RUBISZ-BREZEZENSKA, J., MUSENBOUREZ, Dr., SZCZUREH, Z., and LUDYGA, K. (1976). Badanie wplys ure detergentu anconowoczynnego na skore i cykl wlosowmy u szuzurow. (Study of the effect of an anionactive detergent on the skin and hair cycle in rats.) Prezegl. Dermatol. **63**(1), 25–31.
51. CPTC. (June 9, 1976). Submission of data by CTFA. Unpublished safety data on Sodium Laureth Sulfate.*
52. AVON. (July 8, 1971). Submission of data by CTFA. Unpublished safety data on Sodium Laureth Sulfate.*
53. LEBERCO LABS. (June 13, 1977). Submission of data by CTFA. Eye irritation with rabbits: Sodium Laureth Sulfate.*
54. LEBERCO LABS. (Jan. 17, 1977). Submission of data by CTFA. Eye irritation with rabbits: Sodium Laureth Sulfate.*
55. LEBERCO LABS. (July 23, 1975). Submission of data by CTFA. Eye irritation with rabbits: Sodium Laureth Sulfate.*

56. AVON. (Dec. 14, 1975). Submission of data by CTFA. Unpublished safety data on Sodium Laureth Sulfate.*
57. AVON. (July 22, 1970). Submission of data by CTFA. Unpublished safety data on Sodium Laureth Sulfate.*
58. LEBERCO LABS. (Date of Transmittal Letter Sept. 3, 1979). Submission of data by CTFA. Eye irritation: Sodium and Ammonium Laureth Sulfate: 23982.*
59. LEBERCO LABS. (April 23, 1962). Submission of data by CTFA. Eye irritation: Sodium Laureth Sulfate.*
60. CTFA. (Jan. 25, 1980). Submission of data. Unpublished safety data on Sodium Laureth Sulfate.*
61. AVON. (June 15, 1972). Submission of data by CTFA. Unpublished safety data on Sodium Laureth Sulfate.*
62. AVON. (April 16, 1972). Submission of data by CTFA. Unpublished safety data on Sodium Laureth Sulfate.*
63. HILL TOP RESEARCH (HTR). (July 23, 1973.) Submission of data by CTFA. Data on Cosmetic Products. Repeat Insult Test—Human: Sodium Laureth Sulfate.*
64. HTR. (July 23, 1973). Submission of data by CTFA. Data on Cosmetic Products. Human Subchronic Dermal Irritation: Sodium Laureth Sulfate.*
65. HAZELTON LABS. (Sept. 21, 1973). Submission of data by CTFA. Acute oral toxicity; Acute Eye Irritation: Ammonium Laureth Sulfate.*
66. CTFA. (Jan. 25, 1980). Submission of data. Unpublished safety data on Ammonium Laureth Sulfate.*
67. CPTC. (Sept. 7, 1976). Submission of data by CTFA. Unpublished safety data on Ammonium Laureth Sulfate.*
68. FDRL. (June 1, 1976). Submission of data by CTFA. Acute oral toxicity with rats: Ammonium Laureth Sulfate.*
69. FDRL. (Feb. 4, 1976). Submission of data by CTFA. Acute oral and dermal toxicity test with rats: Ammonium Laureth Sulfate.*
70. AVON. (Jan. 6, 1977). Submission of data by CTFA. Unpublished safety data on Ammonium Laureth Sulfate.*
71. AVON. (Jan. 10, 1977). Submission of data by CTFA. Unpublished safety data on Ammonium Laureth Sulfate.*
72. AVON. (March 15, 1977). Submission of data by CTFA. Unpublished safety data on Ammonium Laureth Sulfate.*
73. FDRL. (May 24, 1976). Submission of data by CTFA. Primary skin irritation study with rabbits; Acute eye irritation with rabbits: Ammonium Laureth Sulfate.*
74. AVON. (June 17, 1976). Submission of data by CTFA. Unpublished safety data on Ammonium Laureth Sulfate.*
75. AVON. (Dec. 13, 1976). Submission of data by CTFA. Unpublished safety data on Ammonium Laureth Sulfate.*
76. AVON. (Sept. 26, 1977). Submission of data by CTFA. Unpublished safety data on Ammonium Laureth Sulfate.*
77. AVON. (Jan. 15, 1977). Submission of data by CTFA. Unpublished safety data on Ammonium Laureth Sulfate.*
78. HTR. (April 21, 1977). Submission of data by CTFA: Data on Cosmetic Products. Human contact Irritation/Sensitization: Ammonium Laureth Sulfate.*
79. CTFA. (Aug. 25, 1977). Submission of data. Unpublished safety data on Cosmetic Products. Ammonium Laureth Sulfate.*
80. CTFA. (Dec. 16, 1977). Submission of data. Unpublished safety data on Cosmetic Products. Ammonium Laureth Sulfate.*
81. CTFA. (May 16, 1978). Submission of data. Unpublished safety data on Cosmetic Products. Ammonium Laureth Sulfate.*
82. HODGE, H.C. and STERNER, J.H. (1949). Tabulation of Toxicity Classes. Am. Ind. Hyg. A. Quart. **10,** 93–6.