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SAGE

Final Report on the Safety Assessment of Sodium Cetearyl Sulfate and Related Alkyl Sulfates as Used in Cosmetics

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Abstract

Sodium cetearyl sulfate is the sodium salt of a mixture of cetyl and stearyl sulfate. The other ingredients in this safety assessment are also alkyl salts, including ammonium coco-sulfate, ammonium myristyl sulfate, magnesium coco-sulfate, sodium cetyl sulfate, sodium coco/hydrogenated tallow sulfate, sodium coco-sulfate, sodium decyl sulfate, sodium ethylhexyl sulfate, sodium myristyl sulfate, sodium oleyl sulfate, sodium stearyl sulfate, sodium tallow sulfate, sodium tridecyl sulfate, and zinc coco-sulfate. These ingredients are surfactants used at concentrations from 0.1% to 29%, primarily in soaps and shampoos. Many of these ingredients are not in current use. The Cosmetic Ingredient Review (CIR) Expert Panel previously completed a safety assessment of sodium and ammonium lauryl sulfate. The data available for sodium lauryl sulfate and ammonium lauryl sulfate provide sufficient basis for concluding that sodium cetearyl sulfate and related alkyl sulfates are safe in the practices of use and concentration described in the safety assessment.

Keywords

safety, cosmetics, sodium cetearyl sulfate

Introduction

Sodium cetearyl sulfate is a surfactant and/or cleansing agent found in a number of cosmetic products. In 1992, the Cosmetic Ingredient Review (CIR) Expert Panel concluded that sodium cetearyl sulfate was safe as a cosmetic ingredient in the (then) present practices of use and concentration.[1] This safety assessment was re-reviewed in 2007 to consider new data relevant to the safety of this ingredient. The Panel reaffirmed the original conclusion for sodium cetearyl sulfate and determined that the available data in the original safety assessment are sufficient to support the safety of an additional 14 cosmetic ingredients in the alkyl sulfate family:

- Ammonium coco-sulfate,
- Ammonium myristyl sulfate,
- Magnesium coco-sulfate,
- Sodium cetyl sulfate,
- Sodium coco/hydrogenated tallow sulfate,
- Sodium coco-sulfate,
- Sodium decyl sulfate,
- Sodium ethylhexyl sulfate,
- Sodium myristyl sulfate,
- Sodium oleyl sulfate,
- Sodium stearyl sulfate,
- Sodium tallow sulfate,
- Sodium tridecyl sulfate, and
- Zinc coco-sulfate.

These are considered as salts of sulfate esters or alkyl sulfates.

This safety assessment is a combination of the original safety assessment and the re-review document and includes the available data on the chemically similar ingredients.

The CIR Expert Panel previously published a safety assessment of sodium lauryl sulfate and ammonium lauryl sulfate, finding them safe in formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin. In products intended for prolonged contact with the skin, concentrations should not exceed 1%.[2] In a re-review that considered over 250 new studies, the Panel reaffirmed that conclusion.[3] Previously reviewed related ingredients, including fatty alcohols that are used to make this group of alkyl sulfates, are listed in Table 1.

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Table 1. Summary of Findings on Previously Reviewed Related Ingredients

Ingredient	Number of Products in Which Used	Use Concentrations	Conclusion	Reference
Sodium lauryl sulfate	1018	0.01%-50%	Safe in formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin. In products intended for prolonged contact with the skin, concentrations should not exceed 1%.	2, 3
Ammonium lauryl sulfate	306	3%-55%	Safe in formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin. In products intended for prolonged contact with the skin, concentrations should not exceed 1%.	2, 3
Myristyl alcohol		0.000001%-12%	Safe in the present practices of use	4, 5
Cetyl alcohol		0.000002%-15%	Safe in the present practices of use	4, 5
Oleyl alcohol	343	0.002%-18%	Safe as currently used in cosmetics	6, 7
Stearyl alcohol	1063	0.002%-56%	Safe as currently used in cosmetics	6, 7
Coconut alcohol	6	0.2%-0.9%	Safe in the present practices of use and concentration	8

Chemistry

Definition and Structure

As given in the *International Cosmetic Ingredient Dictionary and Handbook*,[9] the definitions, synonyms, formulas, and functions of ingredients included in this safety assessment are given in Table 2.

Sodium cetearyl sulfate is commercially available as a mixture of sodium salts of saturated fatty alcohol–sulfuric acid esters. Such a mixture consists of approximately equal parts of sodium cetyl sulfate and sodium stearyl sulfate.[10]

Chemical and Physical Properties

Sodium cetearyl sulfate is dispersible in most fatty substances and is also available as a 15% aqueous paste.[10] Chemical and physical properties of some of the ingredients in this report are given in Table 3.

Methods of Manufacture

Sodium alkyl sulfates can be synthesized from their corresponding alkyl alcohol by treating alcohol with a calculated amount of sulfuric acid, neutralizing the mixture with sodium hydroxide, and filtering rapidly.[18] The filtrate is evaporated and cooled, forming crystals.

According to the *International Cosmetic Ingredient Dictionary and Handbook*,[9] sodium cetearyl sulfate, sodium cetyl sulfate, sodium coco/hydrogenated tallow sulfate, and sodium oleyl sulfate have animal, plant, and synthetic sources. Ammonium coco-sulfate, ammonium myristyl sulfate, magnesium coco-sulfate, sodium coco-sulfate, sodium myristyl sulfate, and zinc coco-sulfate have plant and synthetic sources. Sodium stearyl sulfate and sodium tallow sulfate have animal and synthetic sources. Sodium decyl sulfate and sodium tridecyl sulfate have a synthetic source.

Sodium cetearyl sulfate. Sodium cetearyl sulfate may be produced via the sulfation of cetearyl alcohol with chlorosulfonic acid, sulfur trioxide, or sulfamic acid, followed by neutralization of the acid ester with sodium hydroxide.[19]

Sodium myristyl sulfate. Sodium myristyl sulfate can be produced by the sulfation of myristyl alcohol with chlorosulfonic acid.[15]

Analytical Methods

Sodium cetearyl sulfate. Sodium cetearyl sulfate has been identified via infrared spectroscopy.[10]

Sodium ethylhexyl sulfate. Sodium ethylhexyl sulfate has been identified via thin-layer chromatography, gas chromatography, and infrared, ultraviolet/visible, and nuclear magnetic resonance spectra.[13]

Sodium myristyl sulfate. Sodium myristyl sulfate has been identified by gas chromatography.[20]

Impurities

The following impurities are present in sodium cetearyl sulfate: inorganic chloride (2.2% maximum), unsulfated matter (4% maximum), and inorganic sulfate (5.5% maximum).[10]

Use

Cosmetic

Available use information for ingredients is given in Table 4.

There are no current reported uses for ammonium coco-sulfate, ammonium myristyl sulfate, magnesium coco-sulfate,

Table 2. Definitions, Synonyms, Formulas, and Functions of Currently Reviewed Ingredients as Given in the *International Cosmetic Ingredient Dictionary and Handbook*[4]

Ingredient (CAS No)	Synonyms	Definition	Formula	Function (as a Surfactant)
Sodium cetearyl sulfate (59186-41-3)	Sodium cetostearyl sulfate; sodium cetyl/stearyl sulfate	The sodium salt of a mixture of cetyl and stearyl sulfate	$CH_3(CH_2)_nCH_2OSO_3Na$; n, a value of 16 or 18	Cleansing agent
Ammonium coco-sulfate (90989-98-3)	Coconut oil, sulfate, ammonium salt; sulfuric acid, monococoyl ester, ammonium salt	An organic compound	$R\text{-}OSO_3NH_4$; R, alkyl groups derived from coconut alcohol	Cleansing agent; emulsifying agent
Ammonium myristyl sulfate (52304-21-9)	1-Tetradecanol, hydrogen sulfate, ammonium salt; tetradecyl ammonium sulfate	The ammonium salt of myristyl sulfate	$CH_3(CH_2)_{12}CH_2OSO_3NH_4$	Cleansing agent
Magnesium coco-sulfate (no CAS No)		The magnesium salt of coconut alcohol	$(R\text{-}OSO_3)_2Mg$; R, alkyl groups derived from coconut alcohol	Cleansing agent
Sodium cetyl sulfate (1120-01-0)	1-Hexadecanol, hydrogen sulfate, sodium salt; sodium hexadecyl sulfate; sodium palmityl sulfate	The sodium salt of cetyl sulfate	$CH_3(CH_2)_{15}OSO_3Na$	Cleansing agent
Sodium coco/hydrogenated tallow sulfate (no CAS No)		The sodium salt of the sulfate ester of the mixed fatty alcohols derived from coconut oil and hydrogenated tallow	$R\text{-}OSO_3Na$; R, alkyl groups derived from coconut oil and hydrogenated tallow	Cleansing agent; emulsifying agent
Sodium coco-sulfate (no CAS No)	Sulfuric acid, monococoyl ester, sodium salt	The sodium salt of the sulfate ester of coconut alcohol	$R\text{-}OSO_3Na$; R, alkyl groups derived from coconut oil	Cleansing agent; emulsifying agent
Sodium decyl sulfate (142-87-0)	Sulfuric acid, monodecyl ester, sodium salt	The sodium salt of decyl sulfate	$CH_3(CH_2)_9OSO_3Na$	Foam booster
Sodium ethylhexyl sulfate (126-92-1)	Sodium etasulfate; sodium 2-ethylhexyl sulfate; sodium octyl sulfate; sulfuric acid, mono (2-ethylhexyl) ester, sodium salt; sodium (2-ethylhexyl alcohol sulfate)	The sodium salt of 2-ethyl-hexyl sulfate	$CH_3(CH_2)_3CHCH_2OSO_3Na$; CH_3CH_2	Hydrotrope
Sodium myristyl sulfate (1191-50-0)	Sodium tetradecyl sulfate; sulfuric acid, monotetradecyl ester, sodium salt; 1-tetradecanol, hydrogen sulfate, sodium Salt	The sodium salt of myristyl sulfate	$CH_3(CH_2)_{13}OSO_3Na$	Cleansing agent
Sodium oleyl sulfate (1847-55-8; 16979-51-4)	9-octadecen-1-ol, hydrogen sulfate, sodium salt	The sodium salt of oleyl sulfate	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CH_2OSO_3Na$	Cleansing agent
Sodium stearyl sulfate (1120-04-3)	Sodium octadecyl sulfate; sulfuric acid, monooctadecyl ester, sodium salt	The sodium salt of stearyl sulfate	$CH_3(CH_2)_{17}OSO_3Na$	Cleaning agent; emulsifying agent
Sodium tallow sulfate (8052-50-4; 68140-10-3)	Sodium tallow alcohol sulfate; sulfuric acid, monotallow alkyl esters, sodium salts; tallow, sulfated, sodium Salt	A mixture of sodium alkyl sulfates	$R\text{-}OSO_3Na$; R, alkyl groups derived from tallow	Cleansing agent
Sodium tridecyl sulfate (3026-63-9)	1-Tetradecanol, hydrogen sulfate, sodium salt; 1-tridecanol, hydrogen sulfate, sodium salt	The sodium salt of tridecyl sulfate	$CH_3(CH_2)_{12}OSO_3Na$	Cleaning agent; emulsifying agent
Zinc coco-sulfate	Sulfuric acid, monodecyl ester, zinc salt (2:1)	The zinc salt of sulfated coconut alcohol	$(R\text{-}OSO_3)_2Zn$; R, alkyl groups derived from coconut alcohol	Cleansing agent; emulsifying agent

Table 3. Chemical and Physical Properties of Sodium Cetearyl Sulfate, Sodium Ethylhexyl Sulfate, Sodium Myristyl Sulfate, and Sodium Tridecyl Sulfate[a]

Property	Description	Reference
Sodium cetearyl sulfate		
Color	White to faintly yellow powder	10
Solubility	Soluble in water	10
pH of 0.25% aqueous solution	6.5	10
Assay	90% minimum	10
Identification	Positive: close match to a standard infrared spectrum with no indication of foreign materials	10
Sodium ethylhexyl sulfate		
Color (39.3% active)	Clear colorless liquid	11
Typical activity	40%	12
Molecular weight	232.24	12, 13
	233.31	14
Boiling point	96°-104° (F or C not specified; codistills alcohols and sulfates throughout the range; heavy gelatinous material toward the end of range)	13
Index of refraction (n^{20}_D)	1.3877 $\pm$ 0.0002	13
Sodium myristyl sulfate		
Color	White to pale yellow waxy flake with a faint characteristic odor	15[a]
pH (1%)	5.5-7.5	16[a]
Sodium tridecyl sulfate		
Color (24.7% active)	Clear yellow liquid	17

[a] Available for review: Director, Cosmetic Ingredient Review, 1101 17th St, NW, Suite 412, Washington, DC 20036.

sodium coco/hydrogenated tallow sulfate, sodium ethylhexyl sulfate, sodium oleyl sulfate, sodium tallow sulfate, sodium tridecyl sulfate, or zinc coco-sulfate.

According to the information supplied to the US Food and Drug Administration (FDA) by industry as a part of the Voluntary Cosmetic Registration Program (VCRP), sodium cetearyl sulfate was used in 111 cosmetic formulations[21] ranging from 0.1% to 10.0%.[22] Current VCRP data indicate that sodium cetyl sulfate is used in 11 cosmetic formulations[21] at concentrations of 0.3% to 2.0%.[22] Sodium coco-sulfate is used in 12 cosmetic formulations[21] at concentrations of 0.3% to 29.0%.[22]

Sodium decyl sulfate, sodium myristyl sulfate sodium, and stearyl sulfate were used in several cosmetic formulations,[21] but the concentration of use was not reported by industry.

Sodium cetearyl sulfate, sodium myristyl sulfate, and sodium oleyl sulfate are listed in the Japanese Cosmetic Ingredient Codex (JCIC), The Comprehensive Licensing Standards of Cosmetics by Category (JCLS), and Japanese Standards of Quasi-Drug Ingredients (JSQI).[9] Ammonium myristyl sulfate, sodium decyl sulfate, sodium ethylhexyl sulfate, and sodium tridecyl sulfate are listed in the JCLS. Sodium cetyl sulfate is listed in the JCLS and Japanese Standards of Cosmetic Ingredients (JSCI). Sodium stearyl sulfate is listed in the JCIC and JCLS.

Sodium cetearyl sulfate is not included in the list of substances that may not be used in cosmetic products marketed in countries of the European Union.[23]

Noncosmetic

Sodium cetyl sulfate, sodium decyl sulfate, sodium ethylhexyl sulfate, sodium myristyl sulfate, sodium oleyl sulfate, tallow fatty acids, sodium salts, tallow fatty acids, sulfated, and sodium tridecyl sulfate are indirect food additives.[24]

Sodium ethylhexyl sulfate. Sodium ethylhexyl sulfate is used in textile manufacturing and food processing.[25] It is a surfactant used as a wetting and dispersing agent in the textile industry.[12,13] It is used industrially, especially in textile technology, to obtain spreading and penetration of aqueous solutions. Sodium ethylhexyl sulfate has also been used at concentrations of $\geq$1% in alkaline solutions used to peel fruits and vegetables.

General Biology

Absorption, Distribution, Metabolism, Excretion

Sodium ethylhexyl sulfate. The dermal absorption of undiluted sodium ethylhexyl sulfate was determined by holding saturated cotton pads in contact with the skin of 30 guinea pigs for 4 days.[26] The authors stated that when the dose applied was equal to the oral LD_{50}, some of the animals died, indicating to the authors a slow but fairly complete penetration of intact skin; no other details were given. The authors did note that a definitive conclusion could not be made about penetration based on these data.

The metabolism and excretion of sodium ethylhexyl sulfate was investigated using groups of 6 male Carworth Farms-Elias rats.[27] The animals were dosed orally by gavage with a solution of 99 mg commercial sodium ethylhexyl sulfate and 1.0 mg of either [^{14}C] or [^{35}S]2-ethylhexyl sulfate (1.0 μc/mg specific activity). For the [^{14}C] studies, urine, feces, and respiratory carbon dioxide (CO_2) were collected for 4 days. For the [^{35}S] studies, urine and feces were collected for 3 days. At the end of the

Table 4. Extent of Use and Use Concentration Data as a Function of Product Category for Ingredients in Current Use

Product Category (Total Products in Category)	2007 Uses[11]	2007 Concentrations (%)[12]
Sodium cetearyl sulfate		
Bath products		
Soaps and detergents (1329)	—	—
Other (239)	1	—
Noncoloring hair care products		
Conditioners (1249)	1	10
Permanent waves (141)	—	2
Shampoos (1403)	3	0.8
Tonics, dressings, etc (1097)	1	0.5-2
Other (716)	2	—
Hair coloring products		
Dyes and colors (2481)	10	0.1-2
Bleaches (152)	2	1
Makeup		
Foundations (635)	—	0.3-0.9
Makeup bases (164)	1	—
Other (406)	1	0.3
Personal hygiene products		
Bath soaps and detergents (1329)	2	—
Shaving products		
Aftershave lotions (395)	1	0.9
Other (107)	1	0.2
Skin care products		
Cleansing creams, lotions, liquids, pads (1368)	14	0.4
Depilatories (62)	1	1
Face and neck creams, lotions, etc (1195)	1	0.3-2
Body and hand creams, lotions, etc (1513)	30	0.1-2
Foot powders and sprays (48)	1	—
Moisturizers (2039)	23	1
Night creams, lotions, powder, sprays (343)	3	1
Paste masks (mud packs) (418)	3	—
Other (1244)	5	—
Suntan products		
Suntan gels, creams, liquids, sprays (156)	3	0.3
Indoor tanning preparations (200)	1	0.1
Totals for sodium cetearyl sulfate	111	0.1-10
Sodium cetyl sulfate		
Noncoloring hair care products		
Tonics, dressings, etc (1097)	1	—
Personal hygiene products		
Douches (12)	1	—
Other (514)	2	—
Shaving products		
Shaving cream (162)	1	—
Other (107)	1	—
Skin care products		
Cleansing creams, lotions, liquids, pads (1368)	2	—
Moisturizers (2039)	—	0.3-1
Paste masks (mud packs) (418)	1	2
Fresheners (285)	2	
Total uses for sodium cetyl sulfate	11	0.3-2
Sodium coco-sulfate		
Bath products		
Bubble baths (262)	1	—
Noncoloring hair care products		
Shampoos (1403)	5	2
Personal hygiene products		
Bath soaps and detergents (1329)	4	6-29

(continued)

Table 4 (continued)

Product Category (Total Products in Category)	2007 Uses[11]	2007 Concentrations (%)[12]
Other (514)	—	11
Skin care products		
Cleansing creams, lotions, liquids, pads (1368)	—	1-11
Body and hand lotions (1513)	—	0.3
Other (1244)	2	5
Total for sodium coco-sulfate	12	0.3-29
Sodium decyl sulfate		
Noncoloring hair products		
Hair conditioners (1249)	1	—
Hair coloring products		
Hair dyes and colors (2481)	1	—
Total for sodium decyl sulfate	2	—
Sodium myristyl sulfate		
Bath products		
Bubble baths (262)	3	—
Personal hygiene products		
Douches (12)	1	—
Shaving products		
Other (107)	1	—
Skin care products		
Cleansing creams, lotions, liquids, pads (1368)	2	—
Fresheners (285)	2	—
Total for sodium myristyl sulfate	9	—
Sodium stearyl sulfate		
Personal hygiene products		
Douches (12)	1	—
Shaving products		
Other (107)	1	—
Skin care products		
Cleansing creams, lotions, liquids, pads (1368)	2	—
Fresheners (285)	2	—
Total for sodium stearyl sulfate	6	—

Dashes indicate data was not reported.

study, the animals were killed, and the carcasses of 2 animals from each group were analyzed for residual radioactivity.

Over the 4-day period following dosing with [^{14}C]sodium ethylhexyl sulfate, an average of 77.5%, 6.6%, and 7.1% of the dose was excreted in the urine, feces, and CO_2, respectively; total recovery was 91.2%. [^{14}C] was not detected in the carcasses of the animals that were examined. Identification of the urinary metabolites in the rats that were orally given [^{14}C]sodium ethylhexyl sulfate indicated that 60% of the radioactivity was present as 2-ethylhexyl sulfate, 30% as 2-ethyl-2,3-dihydroxyhexanoic acid, 5% as 2-ethylhexanoyl glucuronide, and 1% as 2-ethylhexanol. The authors stated that 2-ethyl-2-hydroxyhexyl sulfate was found in the urine of rats that were given 2-ethylhexyl sulfate intrahepatically.

Over the 3-day period following dosing with [^{35}S]sodium ethylhexyl sulfate, an average of 80.4% and 2.4% of the dose was excreted in the urine and feces, respectively. [^{35}S] was not detected in the carcasses of the animals that were examined. Evidence for the loss of inorganic sulfate[^{35}S] was obtained with [^{35}S]ethylhexyl sulfate.

Knaak et al performed a study in which 400 mg [^{14}C]sodium ethylhexyl sulfate (0.3 μc/mg) in 1.0 mL water was administered by intraperitoneal (IP) injection to 1 male albino rabbit.[27] The urine collected on day 1 contained 52% of the dose.

Dermal Effects

The ability of C_{10}-C_{16} alkyl sulfates to cause denaturation of keratin was examined by measuring the increase in the release of sulfhydryl (SH) groups from human callus.[28] All of these alkyl sulfates liberated more SH from keratin than water did. The C_{12} and C_{14} chain lengths had maximum activity.

The ability of sodium decyl sulfate, sodium myristyl sulfate, and sodium tridecyl sulfate to extract materials from the stratum corneum of guinea pig skin was also examined.[28] When compared with washing with water, sodium decyl sulfate, sodium myristyl sulfate, and sodium tridecyl sulfate increased extraction of soluble protein by 166.1%, 163.9%, and 198.5%, respectively, and of total amino acids by 84.2%, 110.3%, and 141.%, respectively.

Animal Toxicology

Acute Oral Toxicity

Sodium cetearyl sulfate. The acute oral toxicity of undiluted sodium cetearyl sulfate was evaluated using fasted, Wistar-derived albino rats (5 males, 5 females; weights = 200-250 g).[29] Each animal received a dose of 5.0 mL/kg of the test substance via gavage. The animals were observed for a period of 14 days. Necropsy was performed at the end of the observation period. None of the animals died, and gross lesions were not observed at necropsy. Similar results were obtained when Wistar albino rats (5 males, 5 females; weights 200-300 g) were tested with 10.0% aqueous sodium cetearyl sulfate according to the same procedure.[30]

In another study, the acute oral toxicity of sodium cetearyl sulfate (in olive oil) was evaluated using 10 male Wistar rats (average body weight 150 g). The test substance was administered via stomach tube at a dose of 10 g/kg, and the animals were observed for 8 days. The LD_{50} was not achieved at the administered dose.[31]

The acute oral toxicity of 20.0% aqueous sodium cetearyl sulfate was evaluated using 10 rats (5 males, 5 females; weights 200-300 g). The animals were fed a dose of 5 mL/kg of test material and observed for 14 days. None of the animals died.[32]

Sodium cetyl sulfate. The oral LD_{50} of sodium cetyl sulfate was determined using groups of 5 albino rats.[18] The oral LD_{50} of sodium cetyl sulfate was >3000 mg/kg.

The oral LD_{50} of sodium cetyl sulfate was reported to be >8000 mg/kg for mice, but no details were given.[33]

Sodium decyl sulfate. The oral LD_{50} of sodium decyl sulfate was determined using groups of 5 albino rats.[18] The oral LD_{50} of sodium cetyl sulfate was 1950 mg/kg. No further details were given.

The oral LD_{50} of sodium decyl sulfate was reported to be 2200 mg/kg for mice, but no details were given.[33]

Sodium ethylhexyl sulfate. Undiluted sodium ethylhexyl sulfate had an oral LD_{50} of 10.3 mL/kg for male albino Wistar rats and 3.8 mL/kg for male and female guinea pigs (groups of 32-48 animals of each species were used).[26]

The oral LD_{50} of sodium ethylhexyl sulfate was determined using groups of 5 albino rats.[18] The oral LD_{50} of sodium ethylhexyl sulfate was 3200 mg/kg. No further details were provided.

The acute oral toxicity of undiluted commercial sodium ethylhexyl sulfate was evaluated using groups of 5 albino rats over a period of 12 years.[34] The LD_{50} for male and female rats ranged from 5.61 to 10.4 mL/kg and 6.5 to 9.19 mL/kg, respectively. (More males than females were tested.) The researchers stated that the difference in the LD_{50}s did "not necessarily indicate changes in the toxicity of commercial production" but was "probably attributable to minor changes in technique." Shock from gastric irritation and hemolysis indicative of injury from oral dosing was observed.

The acute oral toxicity of sodium ethylhexyl sulfate was determined using groups of 5 female albino mice, male albino guinea pigs, and male New Zealand giant rabbits.[34] The oral LD_{50}s were 5.19, 1.30, and 3.58 mL/kg for the mice, guinea pigs, and rabbits, respectively. No further details were provided.

Sodium myristyl sulfate. The oral LD_{50} of sodium myristyl sulfate was determined using groups of 5 albino rats.[18] The oral LD_{50} of sodium myristyl sulfate was >3500 mg/kg. No further details were provided.

The oral LD_{50} of sodium myristyl sulfate was 3000 mg/kg for mice, but no details were given.[33]

Sodium stearyl sulfate. The oral LD_{50} of sodium stearyl sulfate was determined using groups of 5 albino rats.[18] The oral LD_{50} of sodium stearyl sulfate was >3000 mg/kg. No further details were provided.

The oral LD_{50} of sodium stearyl sulfate was >8000 mg/kg for mice, but no details were given.[33]

Acute Dermal Toxicity

Sodium ethylhexyl sulfate. The acute dermal toxicity of sodium ethylhexyl sulfate was determined using groups of 4 male albino rabbits.[34] The test article was applied to a clipped area of the trunk under a vinyl film that was left in place for 16 to 24 hours. On removal, the skin was wiped and examined. The animals were observed for 14 days. The dermal LD_{50} was 6.54 mL/kg for male rabbits.

Acute Parenteral Toxicity

Sodium cetyl sulfate. The IP LD_{50} of sodium cetyl sulfate was determined using groups of 10 mice, 5 per sex per group.[18] The IP LD_{50} for mice was 356 mg/kg. No further details were provided.

Sodium decyl sulfate. The IP LD_{50} of sodium decyl sulfate was determined using groups of 10 mice, 5 per sex per group.[18] The IP LD_{50} for mice was 285 mg/kg. No further details were provided.

Sodium ethylhexyl sulfate. The IP LD_{50} of sodium ethylhexyl sulfate was determined using groups of 10 mice, 5 per sex per group.[18] The IP LD_{50} for mice was 396 mg/kg. No further details were provided.

The acute subcutaneous and IP toxicity of sodium ethylhexyl sulfate was determined using groups of 5 albino rats.[34] The subcutaneous LD_{50} was 4.73 and 8.24 mL/kg for 2 groups of male rats and 5.62 and 6.16 mL/kg for 2 groups of female rats. The IP LD_{50} ranged from 0.32 to 0.54 mL/kg for 3 groups of male rats and was 0.71 mL/kg for 1 group of female rats. An intravenous (IV) LD_{50} was not determined. A 1% solution of sodium ethylhexyl sulfate in 0.75% sodium chloride was hemolytic, but none of the rats died as a result of a 5 mL/kg IV injection.

Sodium myristyl sulfate. The IP LD_{50} of sodium myristyl sulfate was determined using groups of 10 mice, 5 per sex per group.[18] The IP LD_{50} for mice was 342 mg/kg. No further details were provided.

The subcutaneous LD_{50} of sodium myristyl sulfate for Fischer 344 rats was 40 mg/kg, but no details were given.[35]

Sodium stearyl sulfate. The IP LD_{50} of sodium stearyl sulfate was determined using groups of 10 mice, 5 per sex per group.[18] The IP LD_{50} for mice was 477 mg/kg. No further details were provided.

Short-Term Oral Toxicity

Sodium ethylhexyl sulfate. A group of 10 albino rats were given 0.25% sodium ethylhexyl sulfate and groups of 5 albino rats were given 0.5% to 4.0% sodium ethylhexyl sulfate in drinking water for 30 days; the average daily dose was 0.23 to 1.51 g/kg.[26] None of the animals died during testing. Occasional casts, primarily hyaline, were observed in the urine. Albumin was detected in the urine of animals of the 2% and 4% dose groups. Microscopically, the kidneys of 2 rats (of 16 examined) had slight injury.

Short-Term Inhalation Toxicity

Sodium ethylhexyl sulfate. Using conventional aerosol chambers, Hall[36] exposed groups of 2 guinea pigs to 0.1%, 0.5%, or 1.0% sodium ethylhexyl sulfate for 8 h/d for 6 days. Controls were exposed to water only. All animals were killed at the termination of dosing. None of the animals died during dosing. The animals of the low-dose group showed no effects. The animals of the mid- and high-dose groups had dyspnea characterized as 1+ and 2+, respectively, and the high-dose animals were lethargic. The onset of dyspnea was rapid, occurring 1 to 3 hours after exposure. Only minimal microscopic changes were seen in the lungs.

The inhalation toxicity of sodium ethylhexyl sulfate was determined using groups of 6 male and 6 female albino rats.[34] A 0.1% aqueous solution was aerosolized to produce droplets approximately 2 μm in diameter. The animals were exposed for 7 h/d for 5 days. Eyes were stained with fluorescein after the first, third, and fifth exposures. Half of the animals were killed and examined on day 6 and the remainder on day 19. Corneal necrosis did not occur. Slight lung congestion was observed; this effect regressed during the 14 days following exposure.

Short-Term Parenteral Toxicity

Sodium myristyl sulfate. Groups of 5 male and 5 female Fischer F344 rats were given a daily subcutaneous dose of 0, 14, 28, 56, 84, 112, or 140 mg/kg sodium myristyl sulfate in water for 14 days.[35] Animals were examined at study termination for toxic effects. No toxic effects were observed with doses of $\leq$84 mg/kg. Some inflammation of the injection site was seen at doses of $\geq$28 mg/kg. The authors reported that some deaths occurred with doses of 112 and 140 mg/kg, although the number of deaths was not given.

These authors also gave groups of 2 adult Beagle dogs, 1 male and 1 female, a daily subcutaneous dose of 0, 10, or 40 mg/kg sodium myristyl sulfate in water for 14 days. Animals were examined at study termination for toxic effects. Inflammation was reported at the injection site of the 40 mg/kg group.[35]

Subchronic Oral Toxicity

Sodium ethylhexyl sulfate. Groups of 10 male and 10 female CFE rats, housed 5 per cage, were fed diets containing 0%, 0.01%, 0.05%, 0.25%, or 1.25% sodium ethylhexyl sulfate for 90 days.[34] Body weight gains were similar for test and control animals. None of the animals died during the study period. The liver weights of high-dose females were significantly decreased compared with the controls. Male and female high-dose animals had a significant increase in the incidence of swelling of the proximal convoluted tubules of the kidney and the central hepatic cord, with an increase in intrahepatic cell lipoid droplets, compared with controls.

Groups of 10 male and 10 female F344/N rats and $B6C3F_1$ mice were fed diets containing 0, 10 000, 20 000, or 40 000 ppm sodium ethylhexyl sulfate for 13 weeks. None of the animals died during the study period. No compound-related effects were observed on gross or microscopic examination. The mean body weights of females of all dose groups were decreased by >10% compared with the controls. Feed consumption was similar for all animals.

Chronic Oral Toxicity

Sodium ethylhexyl sulfate. Groups of CFE rats, 36 per sex, were fed a diet containing 0%, 0.01%, 0.04%, 0.16%, or 0.64% sodium ethylhexyl sulfate for 2 years.[34] Four to 8 animals/sex per dose were killed at 6, 9, and 12 months; 20 of each sex were kept until dying or study termination. Gross and microscopic examinations were performed in all animals. No significant differences between test and control animals were observed in erythrocyte counts, hematocrit values, weight, or any of the parameters measured or in any of the examinations.

These same authors also conducted a 2-year study in which 4 groups of 3 male and 3 female Beagle dogs were fed a diet containing 0%, 0.04%, 0.16%, or 0.64% sodium ethylhexyl sulfate 7 d/wk for 8 months and then 5 d/wk for the remaining 16 months. One female of the 0.16% dose group died at week 18; the death was not treatment related. No significant differences between test and control animals were observed in erythrocyte counts, hematocrit values, weight, or any of the parameters measured or in any of the examinations.

Ocular Irritation

Ocular irritation studies are summarized in Table 5. The total ocular irritation score is calculated by a formula that gives the greatest weight to corneal changes (total maximum scores = 80 for cornea, 10 for the iris, and 20 for the conjunctiva).

Table 5. Ocular Irritation Studies[a]

Animal/Test System	Concentration	Procedure	Results	Reference
Sodium cetearyl sulfate				
Albino New Zealand rabbits, M/F	Undiluted	0.1 mL instilled into the unrinsed right eye	Mean ocular irritation scores (day): 14.0 (1); 13.0 (2); 16.3 (3); 20.1 (4); 12.8 (7)—moderate ocular irritant	29
3 rabbits	20.0% aqueous	As above	No irritation observed	32
6 albino rabbits	10.0% aqueous	As above	Iridial effects, 4 animals; corneal effects, 6 animals; moderate transient irritant	30
Sodium cetyl sulfate				
18 rabbits	2.5%	Draize test	Average irritation score 21.4	37
24 Rabbits	86.5 mmol/L		Average irritation score 24	
Rabbits	0.01%-5% of a C_{16} alkyl sulfate	Draize test	No irritation after 24 or 48 hours at 0.01%, 0.05%, and 0.1% 0.5%-2% after 24 hours and 0% after 48 hours 1.0%-4% after 24 hours and 0% after 48 hours 5%-30% after 24 hours, 16% after 48 hours, 4% after 72 hours, 2% after 96 hours, and 0% after 112 hours	38
		Ogura method	0.01%—no irritation 0.05%—slight congestion 0.1%—considerable congestion 0.5% and 1%—edema and photophobia	
4 rabbits	1%	50 μL instilled into the eye and not rinsed	Scores of 12.5 at 2 hours; 10 at 6 hours; and 0 at 24-72 hours	39
Sodium decyl sulfate				
18 rabbits/group	2.5% 86.5 mmol/L	Draize test	Average irritation score—16.5 Average irritation score—14.7	37
Rabbits	0.01%-5% of a C_{10} alkyl sulfate	Draize test	No irritation after 24 or 48 hours at 0.01%, 0.05%, and 0.1% 0.5%-2% after 24 hours and 0% after 48 hours 1.0%-4% after 24 hours and 0% after 48 hours 5%-30% after 24 hours, 9% after 48 hours, 6% after 72 hours, 2% after 96 hours, and 0% after 112 hours	38
		Ogura method	0.01%—no irritation 0.05%—slight congestion 0.1%—considerable congestion 0.5% and 1%—edema and photophobia	
4 rabbits	1%	50 μL instilled into the eye and not rinsed	Scores of 32.5, 27.5, 7.5, and 0 at 2, 6, 24, and 48-72 hours	39
In vitro	10^{-2}	Opacity in bovine cornea	Produced 85% opacity	
Sodium ethylhexyl sulfate				
Rabbits			8%—lowest concentration to produce corneal injury	26

(continued)

Table 5 (continued)

Animal/Test System	Concentration	Procedure	Results	Reference
6 rabbits/group	0.1%-100%	Normal eyes: 2 drops, 1×/d for 7 days	0.1%—blepharospasm 0.25%—slight conjunctival hyperemia 0.5%, 1.0%—some conjunctival effects 100%—marked conjunctival effects and corneal effects	40
		Normal eyes: 2 drops, 4 ×/d for 7 days	0.1%, 0.25%—mild conjuctival irritation and considerable blepharospasm 1%—Corneal changes after 7 days	
	0.1% or 0.5%	Abraded corneas; 4 drops, 4×/d for 7 d	Delayed regeneration of corneal epithelium	
18 rabbits	2.5%; 86.5 mmol/L	Draize test	Average irritation score—5.9; Average irritation score—3.2	37
9 New Zealand albino rabbits	39.3% active	0.1 mL instilled into the eye; 3 eyes were rinsed	MTS at 24 hours was 52.0/110 for unrinsed eyes and 45.7/110 for rinsed eyes; considered severely irritating (unrinsed) and moderately irritating (rinsed)	11
4 rabbits	1%	50 μL instilled into the eye and not rinsed	Scores of 2.5, 5.0, 2.5, and 0 at 2, 6, 24, and 48-72 hours	39
Sodium myristyl sulfate				
18 rabbits	2.5%	Draize test	Average irritation score 23.1	37
24 rabbits	86.5%		Average irritation score 21.1	
Rabbits	0.01%-5% of a C_{16} alkyl sulfate	Draize test	No irritation after 24 or 48 hours at 0.01%, 0.05%, and 0.1% 0.5%-2% after 24 hours and 0% after 48 hours 1.0%-4% after 24 hours and 0% after 48 hours 5%-21% after 24 hours, 12% after 48 hours, 4% after 72 houors, 0% after 96 hours, and 0% after 112 hours	38
		Ogura method	0.01%—no irritation 0.05%—slight congestion 0.1%—considerable congestion 0.5 and 1%—edema and photophobia	
4 rabbits	1%	50 μL instilled into the eye and not rinsed	Scores of 27.5, 25, 5, and 0 at 2, 6, 24, and 48-72 hours	39
Sodium stearyl sulfate				
18 rabbits/group	2.5% 86.5%	Draize test	Average irritation score 21.4 Average irritation score 25.4	37
Rabbits	0.01%-5% of a C_{16} alkyl sulfate	Draize test	No irritation after 24 or 48 hours at 0.01%, 0.05%, and 0.1% 0.5%-2% after 24 hours and 0% after 48 hours 1.0%-4% after 24 hours and 0% after 48 hours 5%-30% after 24 hours, 16% after 48 hours, 4% after 72 hours, 2% after 96 hours, and 0% after 112 hours	38
		Ogura method	0.01%—no irritation 0.05%—slight congestion 0.1%—considerable congestion 0.5% and 1%—edema and photophobia	
4 rabbits	1%	50 μL instilled into the eye and not rinsed	Scores of 12.5, 7.5, and 0 at 2, 6, and 24-72 hours	39
Sodium tridecyl sulfate				
9 New Zealand albino rabbits	24.7% active	0.1 mL instilled into the eye; 3 eyes were rinsed	MTS at 24 hours was 39.3/110 for unrinsed eyes and 25.3/110 for rinsed eyes; considered moderately irritating	17

F, female; M, male; MTS, maximum total score.

Table 6. Irritant Testing of 0.0225 N Alkyl Sulfate Salts

Test Material	% Positive Reaction			
	Neat	NaCl	$NaSO_4$	$NaCO_4$
Sodium cetyl sulfate	5%	5%	5%	8%
Sodium decyl sulfate	5%	25%	25%	47%
Sodium ethylhexyl sulfate	5%	14%	14%	31%
Sodium myristyl sulfate	24%	72%	67%	39%
Sodium stearyl sulfate	—	—	—	8%

In Vivo Ocular Irritation

Sodium cetearyl sulfate. The ocular irritation potential of undiluted sodium cetearyl sulfate was evaluated using male and female albino New Zealand rabbits. Sodium cetearyl sulfate was classified as a moderate ocular irritant.[29]

In another study, the ocular irritation potential of 20.0% aqueous sodium cetearyl sulfate was evaluated using rabbits. Ocular irritation was not observed at any time during the study.[32]

The ocular irritation potential of 10.0% aqueous sodium cetearyl sulfate was evaluated using 6 albino rabbits. Sodium cetearyl sulfate (10.0% aqueous) is a moderate, transient irritant to the rabbit eye when instillation is not followed by ocular rinsing.[30]

Sodium cetyl sulfate. A Draize study was performed to compare the ocular irritation of 2.5% and 86.5 mmol/L sodium cetyl sulfate using 18 and 24 rabbits, respectively.[37] The average irritation scores for the conjunctiva were 21.4 and 24, respectively.

The ocular irritation of a C_{16} alkyl sulfate (sodium cetyl sulfate) was evaluated in rabbit eyes using both the Draize and Ogura methods.[38] Results are shown in Table 6.

In a Draize test, 50 µL of a 1% sodium cetyl sulfate solution was instilled into the eyes of 4 rabbits, and the eyes were not rinsed.[39]

Sodium cetyl sulfate is considered an ocular irritant.

Sodium decyl sulfate. A Draize study was performed to compare the ocular irritation of 2.5% and 86.5 mmol/L using 18 rabbits for each dose.[37] The average irritation scores for the conjunctiva were 16.5 and 14.7, respectively.

The ocular irritation of 0.01% to 5% of a C_{10} alkyl sulfate (sodium decyl sulfate) was evaluated in rabbits using the Draize method and 0.01-and Ogura methods.[38] Results are shown in Table 6.

The ocular irritation potential of 0.1 mol/L sodium decyl sulfate was determined by instilling 0.1 mL directly on the corneas of the right eyes of 6 white rabbits.[41] The eyes were scored 24 hours after instillation. A total irritation score of 7.37/20 was observed.

In a Draize test, 50 µL of a 1% sodium decyl sulfate solution was instilled into the eyes of 4 rabbits, and the eyes were not rinsed.[39] The conjunctiva was scored for irritation (in percentage of maximal possible reactions) at 2, 6, 24, 48, and 72 hours after instillation. The scores were 32.5, 27.5, 7.5, 0, and 0, respectively.

The ability of 10^{-2} sodium decyl sulfate to induce opacity in the bovine cornea was examined and measured using an opacitometer. Sodium decyl sulfate produced approximately 85% opacity. Muir reported that sodium decyl sulfate rapidly and potently caused opacity.[42]

Sodium decyl sulfate is considered an ocular irritant.

Sodium ethylhexyl sulfate. The minimal volume of sodium ethylhexyl sulfate that produced corneal necrosis in the eyes of rabbits was 0.005 mL.[26] The minimum concentration that will produce this injury on excessive application is 8%.

The ocular irritation of sodium ethylhexyl sulfate was determined using normal and abraded rabbit eyes.[40] Concentrations of 0.1% to 100% in isotonic saline, pH 7, were examined using normal rabbit eyes. The results are shown in Table 6.

A Draize study was performed to compare the ocular irritation of 2.5% and 86.5 mmol/L sodium ethylhexyl sulfate using 18 rabbits for both doses.[37] The average irritation scores for the conjunctiva were 5.9 and 3.2, respectively.

The ocular irritation potential of sodium ethylhexyl sulfate, 39.3% active, was evaluated in a modified eye irritation study using 9 New Zealand albino rabbits.[11] The maximum total score (MTS) at 24 hours was 52/110 (severely irritating) for unrinsed eyes and 54.7/110 (moderately irritating) for eyes that were rinsed.

In a Draize test, 50 µL of a 1% sodium ethylhexyl sulfate solution was instilled into the eyes of 4 rabbits, and the eyes were not rinsed.[39] The results are shown in Table 6.

Sodium ethylhexyl sulfate is considered an ocular irritant.

Sodium myristyl sulfate. A Draize study was performed to compare the ocular irritation of 2.5% and 86.5 mmol/L sodium myristyl sulfate using 18 and 24 rabbits, respectively.[37] The average irritation scores for the conjunctiva were 23.1 and 21.1, respectively.

The ocular irritation of 0.01% to 5% of a C_{14} alkyl sulfate was evaluated using both the Draize and Ogura methods.[38] The results are shown in Table 6.

In a Draize test, 50 µL of a 1% sodium myristyl sulfate solution was instilled into the eyes of 4 rabbits, and the eyes were not rinsed.[39] The conjunctiva was scored for irritation (in percentage of maximal possible reactions) at 2, 6, 24, 48, and 72 hours after instillation. The scores were 27.5, 25, 5, 0, and 0, respectively.

Sodium myristyl sulfate is considered an ocular irritant.

Sodium stearyl sulfate. A Draize study was performed to compare the ocular irritation of 2.5% and 86.5 mmol/L sodium stearyl sulfate using 18 rabbits for each dose.[37] The average irritation scores for the conjunctiva were 21.4 and 25.4, respectively.

The ocular irritation of 0.01% to 5% of a C_{18} alkyl sulfate (sodium stearyl sulfate) was evaluated using both the Draize and Ogura methods.[38] The results are shown in Table 6.

In a Draize test, 50 µL of a 1% sodium stearyl sulfate solution was instilled into the eyes of 4 rabbits, and the eyes were not rinsed.[39] The conjunctiva was scored for irritation (in percentage of maximal possible reactions) at 2, 6, 24, 48, and 72 hours after instillation. The scores were 12.5, 7.5, 0, 0, and 0, respectively.

Sodium stearyl sulfate is considered an ocular irritant.

Sodium tridecyl sulfate. The ocular irritation potential of sodium tridecyl sulfate, 24.7% active, was evaluated in a modified eye irritation study using 9 New Zealand albino rabbits.[17] The researchers stated that the sodium tridecyl sulfate, 24.7% active, could be classified as moderately irritating and that irritation increased with time after instillation.

In Vitro/In Vivo comparisons. An assay examining the cytotoxic effect of anionic detergents using the fluorescein diacetate/ethidium bromide (FDA/EB) test was performed to predict ocular irritation in vitro.[43] According to this assay, sodium cetyl sulfate was a statistically significantly more potent irritant than sodium myristyl sulfate, which was a statistically significantly more potent irritant than sodium decyl sulfate. However, in vivo testing indicated that the potency of irritation was sodium decyl sulfate > sodium myristyl sulfate > sodium cetyl sulfate.

Stern et al compared the EpiOcular assay and the Draize test to predict the ocular irritation potential of sodium cetearyl sulfate.[44] Sodium cetearyl sulfate was predicted to be a moderate ocular irritant in both.

Dermal Irritation

Sodium cetearyl sulfate. The skin irritation potential of undiluted sodium cetearyl sulfate was evaluated by the Draize method using 6 albino New Zealand rabbits (3 males, 3 females; 1.8-2.4 kg). Single applications of the test substance (0.5 mL) were made to abraded and intact skin sites that had been clipped free of hair under occlusive conditions. The mean irritation scores at 24 and 72 hours were averaged to calculate the primary irritation index (PII). The PII was 0.8, interpreted as slight irritation.[29]

In another study, the skin irritation potential of 20.0% aqueous sodium cetearyl sulfate was evaluated using 6 albino rabbits. The test substance (0.5 mL) was applied to intact and abraded skin sites (2 × 2 cm) that had been clipped free of hair. Each site was covered with a patch. After 24 and 48 hours, the sites were scored. Skin irritation was not observed at any time during the study.[32]

The skin irritation potential of 10.0% aqueous sodium cetearyl sulfate was evaluated using 6 adult albino rabbits. The test substance (0.5 mL or 0.5 g) was applied, under a patch made of surgical gauze, to shaved intact and abraded skin sites on the back of each animal. Erythema was observed on abraded and intact skin of all animals. In only 1 animal, erythema had cleared by 72 hours postapplication. The PII was 1.88, classifying the test substance as a mild irritant.[30]

Ammonium myristyl sulfate. In a review, Kästner[39] stated that guinea pigs used in an immersion test with 0.25% ammonium myristyl sulfate had irritation scores that ranged from 8.3 to 10 on a scale of 10 (*no reaction*) to 1 (*strongest reaction*). Details were not provided.

Sodium tridecyl sulfate. A skin corrosion study was performed on sodium tridecyl sulfate, 24.7% active, using 6 New Zealand White albino rabbits.[45] The test material, 0.10 mL, was applied to the shaved intact skin of each animal, and the trunk of each animal was wrapped with a rubberized elastic cloth. The wrap was removed after 4 hours, and the test site was washed. Corrosion readings were performed 4 and 48 hours after dosing. (Destruction or irreversible alteration of the tissue was considered corrosion.) Sodium tridecyl sulfate, 24.7%, was found to be a corrosive agent.

In Vitro Irritation Tests

A neutral red (NR) uptake assay using the human keratinocyte cell line HaCaT was used to predict the dermal irritation potential of sodium cetyl sulfate, sodium decyl sulfate, sodium ethylhexyl sulfate, and sodium myristyl sulfate.[46] The results were then compared with irritant responses as measured by transepidermal water loss (TEWL) and erythema. The decrease in NR uptake by HaCaT cells was dose dependent and varied based on the length of the hydrocarbon chain. The cytotoxicity first increased with increasing chain length up to C_{12} and then decreased. The concentrations that resulted in a 50% inhibition of NR uptake (IC_{50}) for sodium ethylhexyl sulfate, sodium decyl sulfate, sodium myristyl sulfate, and sodium cetyl sulfate were 1.2, 0.35, 0.175, and 0.5 mmol/L, respectively. The results of the in vivo testing were similar to the in vitro results. Both TEWL and erythema increased with increasing hydrocarbon chain length until a length of C_{12}, and then a decrease was seen.

Dermal Sensitization

Sodium cetearyl sulfate. The skin sensitization potential of sodium cetearyl sulfate was evaluated using 20 white female guinea pigs of the Pirbright breed (average body weight 463 g). The control group consisted of 10 guinea pigs. Small quantities of a 25.0% aqueous solution of the test substance were rubbed into the shaved skin of the hindquarters at 24 hours intervals for a total of 10 applications. After a 14-day nontreatment period, 2 applications (24-hour interval) of 1.0% aqueous sodium cetearyl sulfate were made. Reactions were not observed in experimental or control groups at any time during the study.[47]

Vaginal Irritation

Sodium myristyl sulfate. A vaginal irritation study was performed using groups of 5 female New Zealand White rabbits.[35] Hydrogenated vegetable oil suppositories containing 0, 10, 25, or 50 mg sodium myristyl sulfate were administered twice

daily for 7 days. The reproductive tract and urinary bladder were examined grossly and microscopically at study termination. No vaginal irritation was observed with twice daily application of the 0 and 10 mg suppositories. Slight-to-moderate irritation was observed with the 25 and 50 mg suppositories, and 2 of the rabbits of the 50-mg suppository group had mild cystitis.

Reproductive/Developmental Toxicity

No reproductive or developmental toxicity studies were found.

Genotoxicity

In Vitro

Sodium ethylhexyl sulfate. The mutagenic potential of 100 to 10 000 μg/plate sodium ethylhexyl sulfate (approximately 40% active) was determined using *Salmonella typhimurium* strains TA100, TA1535, TA1537, and TA98 in the presence and absence of metabolic activation.[13] Dimethyl sulfoxide (DMSO) was used as the solvent and negative control. Sodium ethylhexyl sulfate was not mutagenic with or without metabolic activation.

The ability of sodium ethylhexyl sulfate (39.6% purity) to induce chromosomal aberrations and sister chromatid exchanges (SCEs) was determined using Chinese hamster ovary cells in the presence and absence of metabolic activation.[48] Medium and solvent (distilled water) controls were used. The positive controls were mitomycin C and cyclophosphamide in the absence and presence of metabolic activation, respectively. Sodium ethylhexyl sulfate did not induce chromosomal aberrations at a dose range of 0 to 5010 μg/mL in the presence or absence of metabolic activation. It also did not induce SCEs at a dose range of 0 to 1480 or 0 to 4980 μg/mL without or with metabolic activation, respectively. The positive controls gave the expected results.

The mutagenic potential of sodium ethylhexyl sulfate was evaluated in the L5178y tk^+/tk^- mouse lymphoma cell forward mutation assay with and without metabolic activation.[49] The vehicle control was DMSO, and the positive control was either methyl methanesulfonate without metabolic activation or 3-methylcholanthrene with metabolic activation. Without metabolic activation, 2 trials with test concentrations of 200 to 4200 and 1000 to 5000 μg/mL were negative, 1 trial with test concentrations of 156.25 to 2500 μg/mL was inconclusive, and 1 trial with test concentrations of 1000 to 4200 μg/mL was positive at all concentrations tested. In the inconclusive trial, a dose of 1250 μg/mL had a statistically significant increase in the group average mutant fraction, while a nonsignificant response was seen at the high dose of 2500 μg/mL. With metabolic activation, 2 trials with test concentrations of 200 or 1000 to 4200 μg/mL were negative. Trials with test concentrations of either 1000 or 2600 to 4200 μg/mL were inconclusive. The authors stated that sodium ethylhexyl sulfate was not mutagenic, based on the weight of the evidence.

In Vivo

Sodium ethylhexyl sulfate. The ability of sodium ethylhexyl sulfate (approximately 40% active) to induce sex-linked recessive lethal mutations in *Drosophila* was determined using a feeding dose of 50 000 ppm and an injection dose of 5000 ppm.[13,14] A negative control was used; a positive control was not indicated. Statistically significant changes were not observed.

Carcinogenicity

Sodium Ethylhexyl Sulfate

Groups of 50 male and 50 female F344/N rats and 50 female $B6C3F_1$ mice were fed 10 000 or 20 000 ppm and groups of 50 male $B6C3F_1$ mice were fed 5000 or 10 000 ppm sodium ethylhexyl sulfate (approximately 40% active) in the diet for 2 years to evaluate its carcinogenic potential.[12,13,25] Negative controls were given untreated feed. All animals that died during the study and those killed at study termination were necropsied, and major tissues were examined microscopically. Weight gain was significantly decreased for the high-dose male rats and female mice. Survival of the treated male rats and male and female mice was not significantly different from that of the controls. However, from week 80 until study termination, the survival of treated female rats was significantly reduced compared with the controls.

In the rats, a statistically significant increased incidence of chronic focal inflammation (nephritis) was observed in high-dose males and was considered associated with dosing. Mild-to-moderate hyperplasia of the pelvic transitional epithelium was also observed. An increased incidence of focal calcification of the kidney was observed in high-dose male and female rats. A transitional-cell papilloma of the kidney was found in 1 male rat and 1 female rat of the high-dose group, and a tubular-cell adenoma was found in another high-dose female rat. The incidence of transitional-cell papilloma in the high-dose male rats was not statistically significantly different from the historical incidence of the test laboratory or the National Toxicology Program. The incidence of transitional-cell papillomas and tubular-cell adenomas in the high-dose female rats was not statistically significantly different from the historical incidence of the test laboratory, but it was significantly different from the incidence of these lesions in untreated female rats in the National Toxicology Program.

In mice, hepatocellular carcinomas occurred in females with a positive trend, and the incidence in the high-dose group was greater than that of controls using the incidental tumor test. Hepatocellular adenomas were increased numerically, but the increase was not statistically significant. In female mice, hepatocellular adenomas or carcinomas (combined) occurred with a statistically significant dose-related trend. In male mice, the incidence of hepatocellular neoplasms was comparable among test and control groups. An increased incidence of epithelial hyperplasia was found in the forestomach of treated male and female mice. The increased incidence of this lesion in female

mice was considered test article–related. In treated male mice, the incidence of this lesion may be test article–related, but the evidence was not convincing enough to establish a definite association.

The researchers concluded that there was no evidence of carcinogenicity in male or female F344/N rats or in male $B6C3F_1$ mice with sodium ethylhexyl sulfate. For female $B6C3F_1$ mice, there was equivocal evidence of carcinogenicity as indicated by the marginally increased incidence of hepatocellular neoplasms.

Clinical Assessment of Safety

Irritation/Sensitization

The dermal irritation of 0.1% and 0.25% aqueous solutions of sodium cetyl sulfate, sodium decyl sulfate, sodium ethylhexyl sulfate, sodium myristyl sulfate, and sodium stearyl sulfate was compared in a closed-cup test with a contact time of 22 to 24 hours.[50] Details, including the number of participants, were not provided. Sodium myristyl sulfate was reportedly the most irritating, followed by sodium decyl sulfate and sodium ethylhexyl sulfate. Sodium cetyl sulfate and sodium stearyl sulfate did not elicit any irritation reactions.

The dermal irritation potential of sodium cetyl sulfate, sodium decyl sulfate, sodium ethylhexyl sulfate, and sodium myristyl sulfate was evaluated by measurement of TEWL and erythema.[51] Both TEWL and erythema increased with increasing hydrocarbon chain length until a length of C_{12}, then the values decreased. The TEWL for both sodium ethylhexyl sulfate and sodium cetyl sulfate was approximately 6 g/m^2 per hour and for both sodium decyl sulfate and sodium myristyl sulfate was approximately 11 g/m^2 per hour. The control value for TEWL was approximately 4 g/m^2 per hour. The erythema score, as determined by skin color reflectance (SCR) measurements, for sodium ethylhexyl sulfate was approximately 8.5, for sodium decyl sulfate was approximately 10.2, for sodium myristyl sulfate was approximately 10.25, and for sodium cetyl sulfate was 9.0. The control score for erythema was approximately 7.9.

Sodium cetearyl sulfate. TKL Research, Inc, conducted a human repeat insult patch test with challenge, using a face care product containing 0.4% sodium cetearyl sulfate, on 59 participants (44 females, 15 males; ages 18-65 years old).[52] Fifty-six participants completed the study; 2 participants were lost to follow-up, and 1 voluntarily withdrew consent. During induction, patches of the product were applied 3 times a week for 3 weeks. The participants returned after 48 or 72 hours for patch removal, and the sites were evaluated after 15 to 30 minutes. After a 2-week rest period, patches were applied to the original sites and untreated sites and left in place for 48 hours. These sites were evaluated 30 minutes and 48 hours after removal. Some participants may have been rechallenged if a doubtful reaction occurred during the challenge phase. As soon as any reactions had resolved, these patches were applied to new sites on the back for 48 hours and then evaluated at 48, 72, and 96 hours after application. No adverse events were reported.

Institute d'Expertise Clinique[53] studied the cutaneous acceptability of a product containing 0.4% sodium cetearyl sulfate. Forty Chinese participants, 30 to 50 years old, used the product for 4 consecutive weeks, applying the liquid to the face and neck twice a day (morning and evening). There were no observed or reported adverse effects.

The irritant action of a number of 0.0225 N alkyl sulfate salts was assessed in 24 males and 14 females with and without the addition of 0.002 N sodium chloride, sodium sulfate, or sodium carbonate.[54] The results are presented in Table 6.

Effect on Skin Hydration

Sodium cetyl sulfate. The effect of sodium cetyl sulfate on stratum corneum (SC) hydration, TEWL, and erythema was evaluated using 10 Caucasian participants (sex not specified).[55] A volume of 0.2 mL of a sodium cetyl sulfate solution (20 mmol/L) was applied to the volar forearm using occlusive plastic chambers; the patches were fixed with nonocclusive tape. Evaluations were made 30 minutes after removal and then daily for 7 days. (Readings were not done on the weekends.) SC hydration was evaluated by capacitance measurements. TEWL was measured with an evaporimeter. Erythema was quantified with a tristimulus Chroma Meter.

Sodium cetyl sulfate caused an initial decrease in SC hydration 1 hour after removal of the test article; the capacitance was approximately 46 IU. (The control was approximately 60 IU throughout the study.) By day 2, the SC hydration level was approximately 60 IU and not significantly different from the controls. By day 7, the score was approximately 54 IU. Transepidermal water loss increased to approximately 15 g/m^2 per hour on day 1 and decreased to approximately 11 g/m^2 per hour by day 2; the value was approximately 7.5 g/m^2 per hour by day 7. (Control values were approximately 5 g/m^2 per hour throughout the study.) Erythema increased from approximately 8 on day 0 to approximately 13 on day 1 as measured by tristimulus SCR. It then decreased over time, reaching a score similar to the controls by day 7. The control values were approximately 8.0 to 8.5 during the study.

Sodium decyl sulfate. The effect of sodium decyl sulfate on skin hydration was determined following the methods described previously.[55] Sodium decyl sulfate also caused an initial decrease in SC hydration 1 hour after removal of the test article; the capacitance was approximately 50 IU. (The control was approximately 60 IU throughout the study.) By day 2, the SC hydration level had increased to approximately 65 IU and was not significantly different from the controls. By day 7, the score was approximately 43 IU. Transepidermal water loss was increased compared with the controls. The TEWL values were approximately 20 g/m^2 per hour on day 1, increased to approximately 24 g/m^2 per hour on day 2, and then decreased for the remainder of the study reaching a score of approximately

9 g/m^2 per hour by day 7. (Control values were approximately 5 g/m^2 per hour throughout the study.) Erythema increased from approximately 8 on day 0 to approximately 10.5 and 12 on days 1 and 2, respectively, as measured by SCR. It then decreased over time, reaching a score of approximately 9 by days 4 to 7. The control values were approximately 8.0 to 8.5 during the study.

Sodium myristyl sulfate. The effect of sodium myristyl sulfate on skin hydration was also determined following the methods described previously.[55] An initial decrease in SC hydration was again observed 1 hour after removal of the test article; the capacitance was approximately 50 IU. (The control was approximately 60 IU throughout the study.) By day 2, the SC hydration levels had increased to approximately 62 IU, which was very similar to the control value. By day 7, the score was approximately 46 IU. Transepidermal water loss was increased compared with the controls. The values were approximately 17.5 and 17.0 g/m^2 per hour on days 1 and 2, respectively; the values decreased after day 2, reaching a value of approximately 10 g/m^2 per hour by day 7. (Control values were approximately 5 g/m^2 per hour throughout the study.) Erythema increased from approximately 8 on day zero to approximately 12.5 on days 1 and 2 as measured by SCR, reaching a score of approximately 9.5 to 9.0 by days 4 to 7. It then decreased over time. The control values were approximately 8.0 to 8.5 during the study.

Case Reports

Sodium myristyl sulfate. In a varicose vein clinic, 2300 patients were treated by injection-compression sclerotherapy using 0.1% to 3.0% sodium myristyl sulfate.[56] Allergic reactions occurred in only 4 patients (0.17%). One patient developed periorbital swelling and 3 developed urticaria after their first treatment. For one of the patients, the reaction developed 8 hours after treatment. All allergic reactions were of the immunoglobulin E (IgE)-mediated type and easily treated with oral antihistamines.

Summary

Sodium cetearyl sulfate is the sodium salt of a mixture of cetyl and stearyl sulfate (alkyl sulfates) produced via the sulfation of the alcohol with chlorosulfonic acid, sulfur trioxide, or sulfamic acid, followed by neutralization of the ester with sodium hydroxide.

All of the ingredients included in this review are surfactants. Sodium cetearyl sulfate is used in 111 cosmetics at concentrations ranging from 0.1% to 10%. In addition, sodium cetyl sulfate is used in 11 formulations at 0.3% to 2%, sodium coco-sulfate is used in 12 formulations at 0.3% to 29%, sodium decyl sulfate is used in 2 formulations, sodium myristyl sulfate is used in 9 formulations, and sodium stearyl sulfate is used in 6 formulations. No current uses were reported for ammonium coco-sulfate, ammonium myristyl sulfate, magnesium coco-sulfate, sodium coco/hydrogenated tallow sulfate, sodium ethylhexyl sulfate, sodium oleyl sulfate, sodium tallow sulfate, sodium tridecyl sulfate, or zinc coco-sulfate.

A number of the alkyl sulfates included in this report are indirect food additives. Sodium ethylhexyl sulfate has been used in textile manufacturing and food processing. Sodium myristyl sulfate has been used in the treatment of varicose veins.

Sodium ethylhexyl sulfate penetrated intact guinea pig skin. In an oral study, 91.2% of a dose of [^{14}C]sodium ethylhexyl sulfate was recovered in the urine, feces, and expired CO_2. In the urine, 60% of the radioactivity was present as 2-ethylhexyl sulfate and 30% as 2-ethyl-2,3-dihydroxyhexanoic acid.

In acute toxicity tests, sodium cetearyl sulfate, sodium cetyl sulfate, sodium decyl sulfate, sodium ethylhexyl sulfate, sodium myristyl sulfate, and sodium stearyl sulfate were relatively nontoxic. All rats survived a 30-day study in which 0.25% to 4% sodium ethylhexyl sulfate was administered in the drinking water. In a 6-day inhalation study of 0.1% to 1.0% sodium ethylhexyl sulfate, dyspnea was observed in the mid- and high-dose groups; only minimal microscopic changes were seen in the lungs. In a 5-day study with 0.1% sodium ethylhexyl sulfate, slight lung congestion was observed.

In subchronic oral testing, all animals survived dosing with $\leq$1.25% or $\leq$40 000 ppm sodium ethylhexyl sulfate, and generally no effects due to dosing were observed. In chronic studies in which rats and dogs were fed $\leq$0.64%, no compound-related effects were observed.

In ocular irritation tests, in 1 study, 20.0% aqueous sodium cetearyl sulfate was not irritating to the eyes of rabbits, but 100% and undiluted solutions were moderate ocular irritants. Sodium cetyl sulfate, sodium decyl sulfate, sodium ethylhexyl sulfate, sodium myristyl sulfate, sodium stearyl sulfate, and sodium tridecyl sulfate were also ocular irritants.

In skin irritation tests, 20.0% aqueous sodium cetearyl sulfate was not irritating to the skin of rabbits, but 10% and undiluted solutions were mild irritants. In an immersion study using guinea pigs, 0.25% ammonium myristyl sulfate did not produce very strong reactions. In a study using an occlusive wrap, sodium tridecyl sulfate was a corrosive agent to rabbit skin. In a study using rabbits, sodium cetearyl sulfate (tested at concentrations of 25% and 1% during induction and challenge phases) was not a sensitizer. In a vaginal irritation study, suppositories containing 10-mg sodium myristyl sulfate were not a vaginal irritant, while those containing 25 and 50 mg produced slight-to-moderate irritation.

Sodium ethylhexyl sulfate was not mutagenic to *S typhimurium* and did not induce SCEs. In a mouse lymphoma cell assay, the researchers concluded that sodium ethylhexyl sulfate was not mutagenic but could not explain a positive response in 1 trial without metabolic activation. Sodium ethylhexyl sulfate did not induce sex-linked recessive lethal mutations in *Drosophila*.

In a 2-year feeding study, sodium ethylhexyl sulfate did not produce any evidence of carcinogenicity in male or female

F344/N rats or male $B6C3F_1$ mice. However, in female $B6C3F_1$ mice, there was equivocal evidence of carcinogenicity as indicated by the marginally increased evidence of hepatocellular neoplasms.

Clinical studies were performed on a number of the ingredients included in this review. In a comparative closed-cup test and a study looking at TEWL and erythema, sodium myristyl sulfate and sodium decyl sulfate were generally the most irritating in comparison with sodium cetyl sulfate, sodium ethylhexyl sulfate, and sodium stearyl sulfate. This finding indicated that irritation increased with increasing hydrocarbon chain length, until a length of C_{12}, and then a decrease was generally seen.

In clinical irritation studies, sodium cetearyl sulfate did not produce adverse effects. In irritation studies using 38 participants, sodium decyl sulfate and sodium ethylhexyl sulfate produced positive results in 5% of the participants, sodium myristyl sulfate produced positive reactions in 24% of the participants, and sodium stearyl sulfate did not produce any positive results. In tests evaluating the effects on skin hydration, sodium cetyl sulfate caused an initial decrease in hydration; values were similar to controls by day 2. Erythema increased until day 1 and then reached control values by day 7. The same effects were seen with sodium decyl sulfate and sodium myristyl sulfate. In a case report of patients at a varicose vein clinic, who were treated with sclerotherapy using 0.1% to 3.0% sodium myristyl sulfate, only 0.17% of the patients had an allergic reaction.

The CIR Expert Panel has previously completed a safety assessment of sodium and ammonium lauryl sulfate that included subchronic and chronic oral toxicity, reproductive and developmental toxicity, genotoxicity, carcinogenicity, and photosensitization studies. Sodium and ammonium lauryl sulfate were found safe in formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin. In products intended for prolonged contact with the skin, concentrations should not exceed 1%. In a re-review of the safety assessment of sodium and ammonium lauryl sulfate that considered over 250 new studies, the Panel reaffirmed the conclusion for the salts of sulfated lauryl alcohol.

Discussion

As discussed in the original safety assessment of sodium cetearyl sulfate, there are limited acute oral toxicity, ocular irritation, and dermal irritation and sensitization data. When these limited data are coupled with the available subchronic and chronic oral toxicity, reproductive and developmental toxicity, genotoxicity, carcinogenicity, and photosensitization data available for sodium lauryl sulfate and ammonium lauryl sulfate and when these data are extrapolated to sodium cetearyl sulfate, there is a sufficient basis for concluding that sodium cetearyl sulfate is safe in the practices of use and concentration described in the safety assessment, and that finding is reaffirmed in this report.

The Expert Panel recognizes that in a study examining the carcinogenic potential of sodium ethylhexyl sulfate, there was equivocal evidence of carcinogenicity, as indicated by an increased incidence of hepatocellular neoplasms, in female mice. However, in that the mice used were highly susceptible to carcinogenic findings and they were fed a high dose, the Expert Panel concluded that there was not a significant carcinogenic potential with regard to sodium ethylhexyl sulfate or any of the other ingredients in this report as used in cosmetics.

The CIR Expert Panel considers that there is little chemical or toxicological difference between members of this group of salts of sulfated fatty alcohols. The salts are expected to be dissociated in any product formulation independent of whether the salt is sodium, ammonium, magnesium, or zinc. Various fatty alcohol components for these ingredients are included in Table 1. It is the experience of the Panel in its review of fatty acids of varying carbon chain lengths that there is little difference in toxicity. Accordingly, the available data for sodium cetearyl sulfate are considered supportive of the safety of the entire group as used in cosmetics.

The Panel recognizes that use concentration data are not available for all ingredients in this group and that some ingredients in the group are not in current use. The Panel considers that the ingredients that are not currently in use are not likely to be used at concentrations different from the use concentrations for sodium cetearyl sulfate. Were those ingredients not in current use to be used in the future, the Panel expects that they would be used in products and at concentrations similar to those reported for sodium cetearyl sulfate. In the case of sodium myristyl sulfate, which was reported as used in douches while sodium cetearyl sulfate was not, the Panel referenced the information in sodium lauryl sulfate, which confirmed its safe use in douches.

The Panel recognizes that sodium lauryl sulfate is a dermal irritant. It may be used safely in cosmetics by limiting the use to rinse-off formulations or by limiting its use concentration in leave-on products. Sodium cetearyl sulfate and the related alkyl sulfates named in this report are not significant irritants in cosmetic products at the concentrations used, and no restrictions are needed.

Conclusion

Based on the available data, the CIR Expert Panel concluded that sodium cetearyl sulfate, ammonium coco-sulfate, ammonium myristyl sulfate, magnesium coco-sulfate, sodium cetyl sulfate, sodium coco/hydrogenated tallow sulfate, sodium coco-sulfate, sodium decyl sulfate, sodium ethylhexyl sulfate, sodium myristyl sulfate, sodium oleyl sulfate, sodium stearyl sulfate, sodium tallow sulfate, sodium tridecyl sulfate, and zinc coco-sulfate are safe for use as cosmetic ingredients in the practices of use and concentration described in this safety assessment. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group.

Authors' Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1101 17th Street, Suite 412, Washington, DC 20036, USA.

Declaration of Conflicting Interests

No potential conflict of interest relevant to this article was reported. Alan Andersen, PhD, and Monice Fiume are employed by the Cosmetic Ingredient Review.

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