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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 ± 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 ≥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%	Draize test	Average irritation score 21.4	37
	86.5%		Average irritation score 25.4	
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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Final Report of the Amended Safety Assessment of Sodium Laureth Sulfate and Related Salts of Sulfated Ethoxylated Alcohols

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Abstract

Sodium laureth sulfate is a member of a group of salts of sulfated ethoxylated alcohols, the safety of which was evaluated by the Cosmetic Ingredient Review (CIR) Expert Panel for use in cosmetics. Sodium and ammonium laureth sulfate have not evoked adverse responses in any toxicological testing. Sodium laureth sulfate was demonstrated to be a dermal and ocular irritant but not a sensitizer. The Expert Panel recognized that there are data gaps regarding use and concentration of these ingredients. However, the overall information available on the types of products in which these ingredients are used and at what concentrations indicates a pattern of use. The potential to produce irritation exists with these salts of sulfated ethoxylated alcohols, but in practice they are not regularly seen to be irritating because of the formulations in which they are used. These ingredients should be used only when they can be formulated to be nonirritating.

Keywords

cosmetics, safety, sodium laureth sulfate, salts of sulfated ethoxylated alcohols

The Cosmetic Ingredient Review (CIR) Expert Panel previously evaluated the safety of sodium myreth sulfate, with the conclusion, based on data for sodium myreth sulfate and sodium laureth sulfate, that sodium myreth sulfate is safe as a cosmetic ingredient in the present practices of use and concentration.[1, p157]

> Sodium myreth sulfate is the sodium salt of sulfated, ethoxylated myristyl alcohol which is used as a surfactant and cleansing agent in cosmetics at concentrations ranging from >1.0%-5.0% to >50.0%. A formulation containing 7.0% sodium myreth sulfate was shown to be an ocular irritant in experimental animals and in some human test subjects. These irritant effects were similar to those previously reported for the chemically similar compound sodium laureth sulfate, which was shown to be safe for use in cosmetics. The report summarizes the safety test data on sodium laureth sulfate. Based upon the combined data cited in the report on both cosmetic ingredients, it is concluded that sodium myreth sulfate is safe as a cosmetic ingredient in the present practices of use and concentration.

The reference to data for sodium laureth sulfate acknowledges an earlier safety assessment completed for ammonium laureth sulfate and sodium laureth sulfate, in which the Expert Panel acknowledged that although these ingredients can be eye and skin irritants, they can be used safely in the practices of use and concentration reported.[2,p1]

> 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

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information, the panel concludes that sodium laureth sulfate and ammonium laureth sulfate are safe as presently used in cosmetic products.

In 2002, the CIR Expert Panel considered all available new data on ammonium laureth sulfate and sodium laureth sulfate and reaffirmed that these ingredients are safe in the practices of use and concentration given.[3]

The CIR Expert Panel has further considered these related ingredients and determined that the data available for sodium myreth sulfate and for both ammonium laureth sulfate and sodium laureth sulfate support the safety of a larger group of chemically similar salts of sulfated ethoxylated alcohols.

Accordingly, the CIR Expert Panel is amending both original safety assessments to include other ingredients.[1,2] This report addresses the safety of the following ingredients:

- Sodium myreth sulfate
- Ammonium capryleth sulfate
- Ammonium C12-15 pareth sulfate
- Ammonium laureth sulfate
- Ammonium myreth sulfate
- Magnesium coceth sulfate
- Magnesium laureth sulfate
- Magnesium myreth sulfate
- Magnesium oleth sulfate
- Sodium C10-15 pareth sulfate
- Sodium C12-13 pareth sulfate
- Sodium C12-15 pareth sulfate
- Sodium coceth sulfate
- Sodium deceth sulfate
- Sodium laneth sulfate
- Sodium laureth sulfate
- Sodium oleth sulfate
- Sodium trideceth sulfate
- Zinc coceth sulfate

Chemistry

Definition and Structure

Table 1 presents synonyms, technical names, and trade names; chemical classes; definitions; and structures for each of the ingredients in this report as given in the *International Cosmetic Ingredient Dictionary and Handbook*.[4]

Use

Cosmetic

Table 2 presents the available product use information provided by manufacturers to the US Food and Drug Administration (FDA) under the Voluntary Cosmetic Reporting Program (VCRP) for sodium myreth sulfate, ammonium laureth sulfate, magnesium laureth sulfate, magnesium oleth sulfate, sodium coceth sulfate, sodium C12-15 pareth sulfate, sodium laureth sulfate, sodium oleth sulfate, and sodium trideceth sulfate.[5]

No uses were reported under the VCRP for ammonium capryleth sulfate, ammonium myreth sulfate, ammonium C12-15 pareth sulfate, magnesium coceth sulfate, magnesium myreth sulfate, sodium C10-15 pareth sulfate, sodium C12-13 pareth sulfate, sodium laneth sulfate, sodium deceth sulfate, or zinc coceth sulfate.

The reported use concentrations from a survey conducted by the Personal Care Products Council are shown in Table 2.[6] No use concentrations were reported for ammonium myreth sulfate and magnesium myreth sulfate.

In some cases, ingredient uses were not reported to FDA in the VCRP; however, concentrations were provided to the Personal Care Products Council. It should be presumed that there is at least 1 use in a product category if a use concentration is reported in the industry survey. In other cases, the uses were reported but no concentration was provided. In that case, it may be presumed that the use concentrations are similar to other use concentrations of related ingredients in that product category.

As reported in the safety assessment of ammonium and sodium laureth sulfate, the laureth sulfate salts 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.[2] 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.

Noncosmetic

The anionic surfactants included in this report are generally recognized for their thickening effect and ability to create lather; therefore, they have applications in industrial products including engine degreasers, floor cleaners, and car wash soaps.

New Safety Data

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.[7]

Mucosal Irritation

When applied once daily for 2 weeks to male and female genitalia, a 25% solution of a product containing 9% ammonium alcohol ethoxy sulfate was found to be nonirritating.[7]

Table 1. Synonyms, Technical Names, and Trade Names, Chemical Classes, Definitions, and Structures[4]

Ingredient (CAS No.)	Synonyms/Technical Names/Trade Names	Definition	Formula/Structure
Ammonium capryleth sulfate (no CAS No.)	Ammonium polyethylene glycol (1-4) caprylyl ether sulfate Ammonium polyoxyethylene (1-4) myristyl ether sulfate Polyethylene glycol (1-4) caprylyl ether, ammonium salt Polyoxyethylene (1-4) myristyl ether sulfate, ammonium salt	Ammonium salt of ethoxylated caprylyl sulfate that conforms generally to the formula where n has an average value between 1 and 4.	$CH_3(CH_2)_6CH_2(OCH_2CH_2)_nOSO_3NH_4$
Ammonium C12-15 pareth sulfate (no CAS No.)	Ammonium pareth-25 sulfate	Ammonium salt of a sulfated polyethylene glycol ether of a mixture of synthetic C12-15 fatty alcohols. It conforms generally to the formula where R represents the C12-15 alcohols and n has a value between 1 and 4.	$R(OCH_2CH_2)_nOSO_3NH_4$
Ammonium laureth sulfate (CAS Nos. 32612-48-9, generic; 67762-19-0, generic)	Ammonium lauryl ether sulfate Ammonium polyoxyethylene alkyl ether sulfate (3E.O.) solution Ammonium polyoxyethylene lauryl ether sulfate solution PEG (1-4) lauryl ether sulfate, ammonium salt Polyethylene glycol (1-4) lauryl ether sulfate, ammonium salt Poly(oxy-1,2-ethanediyl), α-sulfo-ω-(dodecyloxy)-, ammonium salt Polyoxyethylene (1-4) lauryl ether sulfate ammonium salt	Ammonium salt of ethoxylated lauryl sulfate that conforms generally to the formula (see structure) where n has a value between 1 and 4.	$CH_3(CH_2)_{10}CH_2(OCH_2CH_2)_nOSO_3NH_4$
Ammonium myreth sulfate (CAS No. 27731-61-9)	Ammonium myristyl ether sulfate Polyethylene oxide monotetradecyl ether sulfate ammonium salt ammonium (tetradecyloxy)-poly(oxy-1,2-ethanediyl) sulfate, ammonium salt Desulf AMES-603 Standapol EA-40 Sulfochem AM-60 Unipol EA-40	Ammonium salt of ethoxylated myristyl sulfate that conforms generally to the formula where n has a value between 1 and 4.	$CH_3(CH_2)_{12}CH_2(OCH_2CH_2)_nOSO_3NH_4$
Magnesium coceth sulfate (no CAS No.)	Zetesol MG/C	Magnesium salt of sulfated, ethoxylated coconut alcohol. It conforms generally to the formula (see structure) where R represents the alkyl groups derived from coconut oil and n has an average value of 3.	$[R(OCH_2CH_2)_nOSO_3^-]_2\ Mg^{+2}$

(continued)

Table 1 (continued)

Ingredient (CAS No.)	Synonyms/Technical Names/Trade Names	Definition	Formula/Structure
Magnesium laureth sulfate (CAS No. 62755-21-9)	Magnesium lauryl ether sulfate AEC magnesium laureth sulphate Empicol EGB Empicol EGC Empicol EGC 70 Zoharpon MGES	Magnesium salt of ethoxylated lauryl sulfate that conforms generally to the formula where n has a value between 1 and 4.	$[CH_3(CH_2)_{11}(OCH_2CH_2)_nOSO_3^-]_2\ Mg^{+2}$
Magnesium myreth sulfate (no CAS No.)	Magnesium polyethylene glycol (1-4) myristyl ether sulfate Magnesium polyoxyethylene (1-4) myristyl ether sulfate	Magnesium salt of the sulfated ethoxylated myristyl alcohol that conforms generally to the formula where n has an average value of 1 to 4.	$[CH_3(CH_2)_{13}(OCH_2CH_2)_nOSO_3^-]_2\ Mg^{+2}$
Magnesium oleth sulfate (CAS No. 87569-97-9)	Magnesium polyethylene glycol (1-4) oleyl ether sulfate Magnesium polyoxyethylene (1-4) oleyl ether sulfate	Magnesium salt of sulfated, ethoxylated oleyl alcohol that conforms generally to the formula where n has an average value between 1 and 4.	
Sodium C10-15 pareth sulfate (no CAS No.)	None	Sodium salt of a sulfated polyethylene glycol ether of a mixture of synthetic C10-15 alcohols. It conforms generally to the formula where R represents the C10-15 alkyl group and n has an average value between 1 and 4.	$R(OCH_2CH_2)_nOSO_3Na$
Sodium C12-13 pareth sulfate (no CAS No.)	Sodium pareth-23 sulfate Sodium polyoxyethylene alkyl (12-13) ether sulfate (3E.O.) Alscoap DA-3S Alscoap DA-330S Empimin KESH 70 Empimin KSL 68 Empimin KSN27/LA Empimin KSN70/LA Genapol 23-2S	Sodium salt of a sulfated polyethylene glycol ether of a mixture of synthetic C12-13 fatty alcohols. It conforms generally to the formula where R represents the C12-13 alkyl group and n has an average value between 1 and 4.	$R(OCH_2CH_2)_nOSO_3Na$
Sodium C12-15 pareth sulfate (CAS No. 91648-56-5)	Sodium pareth-25 sulfate Sodium polyoxyethylene alkyl (12-15) ether sulfate (3E.O.) Sulfuric acid, mono[2-[2-[2-(C12-15 alkyloxy)ethoxy]ethoxy]ethyl] esters, sodium salts Empicol ESB 3/X; ESB70/X Empimin KSN70/L Nikkol NES-203-27 Rhodasurf L-790, Rhodasurf LA Series Zetesol AO 328 Zoharpon ETA 270, ETA 603, ETA 700	Sodium salt of a sulfated polyethylene glycol ether of a mixture of synthetic C12-15 fatty alcohols. It conforms generally to the formula where R represents the C12-15 alkyl group and n has an average value between 1 and 4.	$R(OCH_2CH_2)_nOSO_3Na$

(continued)

Table 1 (continued)

Ingredient (CAS No.)	Synonyms/Technical Names/Trade Names	Definition	Formula/Structure
Sodium coceth sulfate (no CAS No.)	Sodium polyethylene glycol (1-4) coconut ether sulfate Sodium polyoxyethylene (1-4) coconut ether sulfate Zetosol 270/C, LES 2/C	Sodium salt of the sulfate ester of the polyethylene glycol ether of coconut alcohol that conforms generally to the formula where R represents the alkyl groups derived from coconut oil and n has an average value of 1 to 4.	$R(OCH_2CH_2)_nOSO_3Na$
Sodium deceth sulfate (no CAS No.)	Sodium decyl ether sulfate	Sodium salt of sulfated ethoxylated decyl alcohol that conforms generally to the formula where n has an average value between 1 and 4.	$CH_3(CH_2)_9(OCH_2CH_2)_nOSO_3Na$
Sodium laneth sulfate (CAS No. 68919-23-3, generic)	Sodium polyoxyethylene lanolin ether sulfate	Sodium salt of sulfated ethoxylated lanolin alcohol that conforms generally to the formula where R represents the lanolin alcohol radical and n has a value between 1 and 4.	$R(OCH_2CH_2)_nOSO_3Na$
Sodium laureth sulfate (CAS Nos. 1335-72-4; 3088-31-1; 9004-82-4, generic; 68585-34-2, generic; 68891-38-3, generic; 91648-56-5)	Dodecyl sodium sulfate PEG-(1-4) lauryl ether sulfate, sodium salt Polyethylene glycol (1-4) lauryl ether sulfate, sodium salt Poly(oxy-1,2-ethanediyl), α-sulfo-ω-(dodecyloxy)-, sodium salt Polyoxyethylene (1-4) lauryl ether sulfate, sodium salt Sodium PEG lauryl ether sulfate Sodium polyoxyethylene lauryl ether sulfate Sodium polyoxyethylene lauryl sulfate Sodium laureth sulfate is offered under 120 trade names and is included in 111 trade name mixtures.	Sodium laureth sulfate is the sodium salt of sulfated ethoxylated lauryl alcohol that conforms generally to the formula (see structure) where n averages between 1 and 4.	$CH_3(CH_2)_{11}(OCH_2CH_2)_nOSO_3Na$
Sodium myreth sulfate (CAS No. 25446-80-4)	PEG-(1-4) myristyl ether sulfate, sodium salt Polyethylene glycol (1-4) myristyl ether sulfate, sodium salt Sodium myristyl ether sulfate Sodium polyoxyethylene myristyl ether sulfate (3E.O.) Sodium polyoxyethylene myristyl ether sulfate solution DeSulf SMES-603 Standapol ES-40 Sulfochem ME-60 Texapon K 14 S, Texapon K 14 S Spez 70% Unipol ES-40 Zetesol 470	Sodium salt of sulfated ethoxylated myristyl alcohol that conforms generally to the formula where n has a value between 1 and 4.	$CH_3(CH_2)_{13}(OCH_2CH_2)_nOSO_3Na$

(continued)

Table 1 (continued)

Ingredient (CAS No.)	Synonyms/Technical Names/Trade Names	Definition	Formula/Structure
Sodium oleth sulfate (CAS No. 27233-34-7)	Sodium polyethylene glycol (1-4) oleyl ether sulfate Sodium polyoxyethylene (1-4) oleyl ether sulfate	Sodium salt of the sulfate ester of the polyethylene glycol ether of oleyl alcohol that conforms generally to the formula where n has an average value between 1 and 4.	
Sodium trideceth sulfate (CAS No. 25446-78-0)	Sodium polyoxyethylene tridecyl sulfate Sodium tridecyl ether sulfate Cedepal TD-407; TD-484; TD-403 DeSulf STDES-30 Genapol XRO Rhodapex EST-30 Sulfochem TD-3	Sodium salt of sulfated ethoxylated tridecyl alcohol (qv) that conforms generally to the formula where n has a value between 1 and 4.	$CH_3(CH_2)_{12}(OCH_2CH_2)_nOSO_3Na$
Zinc coceth sulfate (no CAS No.)	Zetesol ZN	Zinc salt of sulfated, ethoxylated coconut alcohol that conforms generally to the formula where R represents the alkyl groups derived from coconut alcohol and n has an average value of 3.	$[R(OCH_2CH_2)_nOSO_3^-]_2\ Zn^{+2}$

Table 2. Reported Uses and Use Concentrations as a Function of Product Category in Cosmetics

Product Category	2007 Uses[5]	2008 Use Concentrations[6]
Sodium myreth sulfate		
Makeup		
Eye shadow (1061)	—[a]	0.008%
Noncoloring hair preparations		
Shampoos (1022)	14	0.6%-20.0%
Hair tonics, dressings, etc (623)	—	0.01%
Hair coloring products		
Hair dyes and colors (1600)	1	
Shaving preparations		
Shaving cream (135)	1	
Bath preparations		
Bath soaps and detergents (594)	1	7%
Bath oils, tablets, and salts (207)	1	
Bubble baths (256)	5	
Other bath preparations (276)	2	
Personal hygiene products		
Douches (8)	—	10%
Skin care preparations		
Cleansers (1009)	1	20%
Total uses/ranges for sodium myreth sulfate	26	0.008%-20%
Ammonium laureth sulfate		
Baby products		
Shampoos (38)	1	—
Other baby products (64)	1	—
Bath preparations		
Oils, tablets, and salts (207)	1	10%
Bubble baths (256)	45	—
Other bath preparations (276)	3	—
Fragrance preparations		
Other fragrance preparations (187)	1	—
Noncoloring hair preparations		
Conditioners (715)	1	—
Permanent waves (169)	1	—
Rinses (46)	3	—
Shampoos (1022)	149	7%-36%
Hair tonics, dressings, etc (623)	2	—
Other noncoloring hair preparations (464)	1	—
Hair coloring products		
Hair dyes and colors (1600)	—	5%
Makeup		
Makeup bases (273)	2	—
Personal hygiene products		
Bath soaps and detergents (594)	21	1%-20%
Other personal hygiene products (390)	5	—
Skin care preparations		
Cleansers (1009)	14	1%-30%
Face and neck creams, lotions, etc (546)	1	—
Body and hand creams, lotions, etc (992)	2	8%
Paste masks (312)	1	—
Total uses/ranges for ammonium laureth sulfate	255	1%-36%
Magnesium laureth sulfate		
Baby products		
Shampoos (38)	3	0.4%
Baby lotions, oils, powders, and creams (67)	—	0.2%
Other baby products (64)	1	0.4%[b]
Eye makeup products		
Eye makeup remover (114)	10	0.02%-0.04%

(continued)

Table 2 (continued)

Product Category	2007 Uses[5]	2008 Use Concentrations[6]
Noncoloring hair preparations		
Shampoos (1022)	23	0.05%-4%
Bath preparations		
Bath soaps and detergents (594)	3	0.05%-3%
Personal cleanliness products		
Other personal cleanliness products (390)	—	7%[c]
Skin care preparations		
Cleansers (1009)	11	0.7%
Paste masks (mud packs) (312)	—	2%
Other skin care preparations (915)	1	—
Total uses/ranges for magnesium laureth sulfate	52	0.02%-7%
Magnesium oleth sulfate		
Baby products		
Shampoos (38)	2	0.1%
Baby lotions, oils, powders, and creams (67)	—	0.04%
Other baby products (64)	1	0.1%
Eye makeup products		
Eye makeup remover (114)	12	0.01%-0.02%
Noncoloring hair preparations		
Shampoos (1022)	20	0.2%
Other noncoloring hair preparations (464)	1	—
Personal cleanliness products		
Bath soaps and detergents (594)	3	0.2%
Other personal cleanliness products (390)	1	0.1%[d]
Skin care preparations		
Cleansers (1009)	8	0.2%
Paste masks (mud packs) (312)	—	
Other skin care preparations (915)	1	—
Total uses/ranges for magnesium oleth sulfate	49	0.01%-0.2%
Sodium coceth sulfate		
Bath preparations		
Bubble baths (256)	1	—
Other bath preparations (276)	1	—
Eye makeup preparations		
Eye makeup remover (114)	1	—
Fragrance preparations		
Other fragrance preparations (187)	1	—
Noncoloring hair preparations		
Shampoos (noncoloring) (1022)	—	0.8%
Body and hand creams, lotions, and powders (992)	—	0.2%
Personal cleanliness products		
Bath soaps and detergents (594)	2	—
Other personal cleanliness products (390)	2	—
Sodium coceth sulfate		
Skin care preparations		
Cleansers (1009)	5	—
Total uses/ranges for sodium coceth sulfate	13	0.2%-0.8%
Sodium C12-15 pareth sulfate		
Personal hygiene products		
Douches (8)	—	0.2%
Skin care preparations		
Cleansing (1009)	1	—
Total uses/ranges for sodium C12-15 pareth sulfate	1	0.2%
Sodium laureth sulfate		
Baby products		
Shampoos (38)	15	10%
Other baby products (64)	22	5%-25%

(continued)

Table 2 (continued)

Product Category	2007 Uses[5]	2008 Use Concentrations[6]
Bath products		
Bath oils, tablets, salts (207)	7	14%
Bubble baths (256)	117	6%-24%
Bath capsules (5)	1	—
Other bath products (276)	114	6%-19%
Eye makeup products		
Eyeliner (639)	1	—
Lotion (32)	1	—
Eye makeup remover (114)	16	0.1%
Mascara (308)	18	0.1%-0.3%
Fragrance preparations		
Other fragrance preparations (187)	6	18%
Noncoloring hair preparations		
Conditioners (715)	2	0.7%
Permanent waves (169)	—	0.6%
Rinses (46)	1	—
Shampoos (1022)	745	11%-50%
Tonics, dressings, etc (623)	8	—
Other noncoloring hair preparations (464)	13	—
Hair coloring products		
Hair dyes and colors (1600)	134	3%-10%
Coloring shampoos (27)	26	—
Bleaches (103)	1	—
Other hair coloring products (73)	4	14%
Makeup		
Foundations (530)	4	—
Bases (273)	1	—
Other makeup (304)	1	15%
Oral hygiene products		
Dentifrices (8)	1	—
Personal hygiene products		
Bath soaps and detergents (594)	512	2%-47%
Douches (8)	3	—
Feminine deodorants (7)	2	7%
Other personal hygiene products (390)	106	13%-16%
Shaving preparations		
Aftershaves (260)	2	—
Shaving cream (135)	11	1%-5%
Shaving soap (2)	2	—
Other shaving preparations (64)	4	—
Skin care products		
Cleansers (1009)	206	0.6%-25%
Face and neck creams, lotions, etc (546)	19	—
Body and hand creams, lotions, etc (992)	19	11%-17%
Foot powders and sprays (43)	1	11%
Moisturizers (1200)	6	0.5%
Paste masks (312)	6	—
Other skin care products (915)	20	—
Suntan products		
Suntan gels, creams, lotions (138)	1	
Other suntan products (41)	1	—
Total uses/ranges for sodium laureth sulfate	2180	0.1%-50%
Sodium oleth sulfate		
Baby products		
Shampoos (38)	2	0.4%
Baby lotions, oils, powders, and creams (67)	—	0.1%
Other baby products (64)	1	0.4%

(continued)

Table 2 (continued)

Product Category	2007 Uses[5]	2008 Use Concentrations[6]
Eye makeup preparations		
Eye makeup remover (114)	11	0.01%-0.02%
Noncoloring hair preparations		
Shampoos (1022)	19	0.5%
Other noncoloring hair preparations (464)	1	
Personal cleanliness products		
Bath soaps and detergents (594)	3	0.4%-2%
Other personal cleanliness products (390)	1	0.4%[e]
Skin care preparations		
Cleansing (1009)	8	0.2%
Other skin care preparations (915)	1	—
Total uses/ranges for sodium oleth sulfate	47	0.01%-2%
Sodium trideceth sulfate		
Baby products		
Shampoos (38)	25	3%
Baby lotions, oils, powders, and creams 67)	—	3%
Other baby products (64)	20	2%-3%
Bath preparations		
Other bath preparations (276)	1	—
Eye makeup		
Eye makeup removers (114)	7	—
Noncoloring hair preparations		
Shampoos (1022)	13	2%-17%
Hair coloring products		
Coloring shampoos (27)	1	—
Personal hygiene products		
Bath soaps and detergents (594)	29	2%-10%
Other personal cleanliness products (390)	1	3%-19%
Feminine hygiene deodorants (7)	—	3%
Skin care preparations		
Cleansing (1009)	35	0.6%-18%
Total uses/ranges for sodium trideceth sulfate	132	0.6%-19%

[a] Dash indicates not reported. In some cases, ingredient uses were not reported to FDA in the voluntary industry product survey program; however, concentrations were provided. In other cases, the uses were reported but no concentration was provided.
[b] 0.4% in a baby wash.
[c] 7% in a shower gel.
[d] 0.1% in a shower gel.
[e] 0.4% in a shower gel.

Summary

An earlier safety assessment by the Cosmetic Ingredient Review Expert Panel considered sodium laureth sulfate and ammonium laureth sulfate and another had considered sodium myreth sulfate. This amended safety assessment combined and extended the previous assessments to include all salts of sulfated ethoxylated alcohols. Sodium laureth sulfate was the most studied of this group of cosmetic ingredients, all of which are salts of sulfated, ethoxylated alcohols, used primarily as surfactant emulsifiers and cleansing agents in soaps and shampoos, over a wide range of concentrations from 0.008% to 50.0%.

Data on additional ingredients were limited and did not raise any safety concerns.

Discussion

The CIR Expert Panel recognized that most of the acute oral toxicity, dermal irritation and sensitization, subchronic and chronic oral toxicity, reproductive and developmental toxicity, carcinogenicity, and photosensitization studies have been conducted on ammonium laureth sulfate and sodium laureth sulfate. There are limited safety test data on most of the other ingredients included in this safety assessment. Sodium and ammonium laureth sulfate have not evoked adverse responses in any toxicological testing, including acute oral toxicity, subchronic and chronic oral toxicity, reproductive and developmental toxicity, carcinogenicity, and photosensitization studies. These data, however, are considered a sufficient basis

for concluding that the other ingredients are safe in the practices of use and concentration described in the safety assessment because of the fundamental chemical similarities between them and because they all are chemically similar salts (salts are expected to be dissociated in any product formulation independent of whether the salt is sodium, ammonium, magnesium, or zinc) of sulfated ethoxylated alcohols, and they all function as surfactants in cosmetic formulations. Based on these considerations, safety test data on 1 ingredient may be extrapolated to all of them.

The CIR Expert Panel also recognized that there are data gaps regarding use and concentration of these ingredients. However, the overall information available on the types of products in which these ingredients are used and at what concentrations indicates a pattern of use that was considered by the Expert Panel in assessing safety. (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 with others in the group.)

The panel noted that sodium laureth sulfate and ammonium laureth sulfate can 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 these ingredients. The irritant effects, however, are similar to those produced by other detergents, and the severity of the irritation appears to increase directly with concentration.

Conclusion

The CIR Expert Panel concludes that sodium myreth sulfate, ammonium capryleth sulfate, ammonium myreth sulfate, ammonium laureth sulfate, ammonium C12-15 pareth sulfate, magnesium coceth sulfate, magnesium laureth sulfate, magnesium myreth sulfate, magnesium oleth sulfate, sodium coceth sulfate, sodium C10-15 pareth sulfate, sodium C12-13 pareth sulfate, sodium C12-15 pareth sulfate, sodium laneth sulfate, sodium laureth sulfate, sodium oleth sulfate, sodium deceth sulfate, sodium trideceth sulfate, and zinc coceth sulfate are safe as cosmetic ingredients in the present practices of use and concentration when formulated to be nonirritating.[1]

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. F. Alan Andersen, PhD, and Valerie C. Robinson are employed by Cosmetic Ingredient Review.

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Final Report of the Amended Safety Assessment of Sodium Laureth Sulfate and Related Salts of Sulfated Ethoxylated Alcohols

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Abstract

Sodium laureth sulfate is a member of a group of salts of sulfated ethoxylated alcohols, the safety of which was evaluated by the Cosmetic Ingredient Review (CIR) Expert Panel for use in cosmetics. Sodium and ammonium laureth sulfate have not evoked adverse responses in any toxicological testing. Sodium laureth sulfate was demonstrated to be a dermal and ocular irritant but not a sensitizer. The Expert Panel recognized that there are data gaps regarding use and concentration of these ingredients. However, the overall information available on the types of products in which these ingredients are used and at what concentrations indicates a pattern of use. The potential to produce irritation exists with these salts of sulfated ethoxylated alcohols, but in practice they are not regularly seen to be irritating because of the formulations in which they are used. These ingredients should be used only when they can be formulated to be nonirritating.

Keywords

cosmetics, safety, sodium laureth sulfate, salts of sulfated ethoxylated alcohols

The Cosmetic Ingredient Review (CIR) Expert Panel previously evaluated the safety of sodium myreth sulfate, with the conclusion, based on data for sodium myreth sulfate and sodium laureth sulfate, that sodium myreth sulfate is safe as a cosmetic ingredient in the present practices of use and concentration.[1, p157]

> Sodium myreth sulfate is the sodium salt of sulfated, ethoxylated myristyl alcohol which is used as a surfactant and cleansing agent in cosmetics at concentrations ranging from >1.0%-5.0% to >50.0%. A formulation containing 7.0% sodium myreth sulfate was shown to be an ocular irritant in experimental animals and in some human test subjects. These irritant effects were similar to those previously reported for the chemically similar compound sodium laureth sulfate, which was shown to be safe for use in cosmetics. The report summarizes the safety test data on sodium laureth sulfate. Based upon the combined data cited in the report on both cosmetic ingredients, it is concluded that sodium myreth sulfate is safe as a cosmetic ingredient in the present practices of use and concentration.

The reference to data for sodium laureth sulfate acknowledges an earlier safety assessment completed for ammonium laureth sulfate and sodium laureth sulfate, in which the Expert Panel acknowledged that although these ingredients can be eye and skin irritants, they can be used safely in the practices of use and concentration reported.[2,p1]

> 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

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information, the panel concludes that sodium laureth sulfate and ammonium laureth sulfate are safe as presently used in cosmetic products.

In 2002, the CIR Expert Panel considered all available new data on ammonium laureth sulfate and sodium laureth sulfate and reaffirmed that these ingredients are safe in the practices of use and concentration given.[3]

The CIR Expert Panel has further considered these related ingredients and determined that the data available for sodium myreth sulfate and for both ammonium laureth sulfate and sodium laureth sulfate support the safety of a larger group of chemically similar salts of sulfated ethoxylated alcohols.

Accordingly, the CIR Expert Panel is amending both original safety assessments to include other ingredients.[1,2] This report addresses the safety of the following ingredients:

- Sodium myreth sulfate
- Ammonium capryleth sulfate
- Ammonium C12-15 pareth sulfate
- Ammonium laureth sulfate
- Ammonium myreth sulfate
- Magnesium coceth sulfate
- Magnesium laureth sulfate
- Magnesium myreth sulfate
- Magnesium oleth sulfate
- Sodium C10-15 pareth sulfate
- Sodium C12-13 pareth sulfate
- Sodium C12-15 pareth sulfate
- Sodium coceth sulfate
- Sodium deceth sulfate
- Sodium laneth sulfate
- Sodium laureth sulfate
- Sodium oleth sulfate
- Sodium trideceth sulfate
- Zinc coceth sulfate

Chemistry

Definition and Structure

Table 1 presents synonyms, technical names, and trade names; chemical classes; definitions; and structures for each of the ingredients in this report as given in the *International Cosmetic Ingredient Dictionary and Handbook*.[4]

Use

Cosmetic

Table 2 presents the available product use information provided by manufacturers to the US Food and Drug Administration (FDA) under the Voluntary Cosmetic Reporting Program (VCRP) for sodium myreth sulfate, ammonium laureth sulfate, magnesium laureth sulfate, magnesium oleth sulfate, sodium coceth sulfate, sodium C12-15 pareth sulfate, sodium laureth sulfate, sodium oleth sulfate, and sodium trideceth sulfate.[5]

No uses were reported under the VCRP for ammonium capryleth sulfate, ammonium myreth sulfate, ammonium C12-15 pareth sulfate, magnesium coceth sulfate, magnesium myreth sulfate, sodium C10-15 pareth sulfate, sodium C12-13 pareth sulfate, sodium laneth sulfate, sodium deceth sulfate, or zinc coceth sulfate.

The reported use concentrations from a survey conducted by the Personal Care Products Council are shown in Table 2.[6] No use concentrations were reported for ammonium myreth sulfate and magnesium myreth sulfate.

In some cases, ingredient uses were not reported to FDA in the VCRP; however, concentrations were provided to the Personal Care Products Council. It should be presumed that there is at least 1 use in a product category if a use concentration is reported in the industry survey. In other cases, the uses were reported but no concentration was provided. In that case, it may be presumed that the use concentrations are similar to other use concentrations of related ingredients in that product category.

As reported in the safety assessment of ammonium and sodium laureth sulfate, the laureth sulfate salts 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.[2] 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.

Noncosmetic

The anionic surfactants included in this report are generally recognized for their thickening effect and ability to create lather; therefore, they have applications in industrial products including engine degreasers, floor cleaners, and car wash soaps.

New Safety Data

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.[7]

Mucosal Irritation

When applied once daily for 2 weeks to male and female genitalia, a 25% solution of a product containing 9% ammonium alcohol ethoxy sulfate was found to be nonirritating.[7]

Table 1. Synonyms, Technical Names, and Trade Names, Chemical Classes, Definitions, and Structures[4]

Ingredient (CAS No.)	Synonyms/Technical Names/Trade Names	Definition	Formula/Structure
Ammonium capryleth sulfate (no CAS No.)	Ammonium polyethylene glycol (1-4) caprylyl ether sulfate Ammonium polyoxyethylene (1-4) myristyl ether sulfate Polyethylene glycol (1-4) caprylyl ether, ammonium salt Polyoxyethylene (1-4) myristyl ether sulfate, ammonium salt	Ammonium salt of ethoxylated caprylyl sulfate that conforms generally to the formula where n has an average value between 1 and 4.	$CH_3(CH_2)_6CH_2(OCH_2CH_2)_nOSO_3NH_4$
Ammonium C12-15 pareth sulfate (no CAS No.)	Ammonium pareth-25 sulfate	Ammonium salt of a sulfated polyethylene glycol ether of a mixture of synthetic C12-15 fatty alcohols. It conforms generally to the formula where R represents the C12-15 alcohols and n has a value between 1 and 4.	$R(OCH_2CH_2)_nOSO_3NH_4$
Ammonium laureth sulfate (CAS Nos. 32612-48-9, generic; 67762-19-0, generic)	Ammonium lauryl ether sulfate Ammonium polyoxyethylene alkyl ether sulfate (3E.O.) solution Ammonium polyoxyethylene lauryl ether sulfate solution PEG (1-4) lauryl ether sulfate, ammonium salt Polyethylene glycol (1-4) lauryl ether sulfate, ammonium salt Poly(oxy-1,2-ethanediyl), α-sulfo-ω-(dodecyloxy)-, ammonium salt Polyoxyethylene (1-4) lauryl ether sulfate ammonium salt	Ammonium salt of ethoxylated lauryl sulfate that conforms generally to the formula (see structure) where n has a value between 1 and 4.	$CH_3(CH_2)_{10}CH_2(OCH_2CH_2)_nOSO_3NH_4$
Ammonium myreth sulfate (CAS No. 27731-61-9)	Ammonium myristyl ether sulfate Polyethylene oxide monotetradecyl ether sulfate ammonium salt ammonium (tetradecyloxy)-poly(oxy-1,2-ethanediyl) sulfate, ammonium salt Desulf AMES-603 Standapol EA-40 Sulfochem AM-60 Unipol EA-40	Ammonium salt of ethoxylated myristyl sulfate that conforms generally to the formula where n has a value between 1 and 4.	$CH_3(CH_2)_{12}CH_2(OCH_2CH_2)_nOSO_3NH_4$
Magnesium coceth sulfate (no CAS No.)	Zetesol MG/C	Magnesium salt of sulfated, ethoxylated coconut alcohol. It conforms generally to the formula (see structure) where R represents the alkyl groups derived from coconut oil and n has an average value of 3.	$[R(OCH_2CH_2)_nOSO_3^-]_2\ Mg^{+2}$

(continued)

Table 1 (continued)

Ingredient (CAS No.)	Synonyms/Technical Names/Trade Names	Definition	Formula/Structure
Magnesium laureth sulfate (CAS No. 62755-21-9)	Magnesium lauryl ether sulfate AEC magnesium laureth sulphate Empicol EGB Empicol EGC Empicol EGC 70 Zoharpon MGES	Magnesium salt of ethoxylated lauryl sulfate that conforms generally to the formula where n has a value between 1 and 4.	$[CH_3(CH_2)_{11}(OCH_2CH_2)_nOSO_3^-]_2\ Mg^{+2}$
Magnesium myreth sulfate (no CAS No.)	Magnesium polyethylene glycol (1-4) myristyl ether sulfate Magnesium polyoxyethylene (1-4) myristyl ether sulfate	Magnesium salt of the sulfated ethoxylated myristyl alcohol that conforms generally to the formula where n has an average value of 1 to 4.	$[CH_3(CH_2)_{13}(OCH_2CH_2)_nOSO_3^-]_2\ Mg^{+2}$
Magnesium oleth sulfate (CAS No. 87569-97-9)	Magnesium polyethylene glycol (1-4) oleyl ether sulfate Magnesium polyoxyethylene (1-4) oleyl ether sulfate	Magnesium salt of sulfated, ethoxylated oleyl alcohol that conforms generally to the formula where n has an average value between 1 and 4.	
Sodium C10-15 pareth sulfate (no CAS No.)	None	Sodium salt of a sulfated polyethylene glycol ether of a mixture of synthetic C10-15 alcohols. It conforms generally to the formula where R represents the C10-15 alkyl group and n has an average value between 1 and 4.	$R(OCH_2CH_2)_nOSO_3Na$
Sodium C12-13 pareth sulfate (no CAS No.)	Sodium pareth-23 sulfate Sodium polyoxyethylene alkyl (12-13) ether sulfate (3E.O.) Alscoap DA-3S Alscoap DA-330S Empimin KESH 70 Empimin KSL 68 Empimin KSN27/LA Empimin KSN70/LA Genapol 23-2S	Sodium salt of a sulfated polyethylene glycol ether of a mixture of synthetic C12-13 fatty alcohols. It conforms generally to the formula where R represents the C12-13 alkyl group and n has an average value between 1 and 4.	$R(OCH_2CH_2)_nOSO_3Na$
Sodium C12-15 pareth sulfate (CAS No. 91648-56-5)	Sodium pareth-25 sulfate Sodium polyoxyethylene alkyl (12-15) ether sulfate (3E.O.) Sulfuric acid, mono[2-[2-[2-(C12-15 alkyloxy)ethoxy]ethoxy]ethyl] esters, sodium salts Empicol ESB 3/X; ESB70/X Empimin KSN70/L Nikkol NES-203-27 Rhodasurf L-790, Rhodasurf LA Series Zetesol AO 328 Zoharpon ETA 270, ETA 603, ETA 700	Sodium salt of a sulfated polyethylene glycol ether of a mixture of synthetic C12-15 fatty alcohols. It conforms generally to the formula where R represents the C12-15 alkyl group and n has an average value between 1 and 4.	$R(OCH_2CH_2)_nOSO_3Na$

(continued)

Table 1 (continued)

Ingredient (CAS No.)	Synonyms/Technical Names/Trade Names	Definition	Formula/Structure
Sodium coceth sulfate (no CAS No.)	Sodium polyethylene glycol (1-4) coconut ether sulfate Sodium polyoxyethylene (1-4) coconut ether sulfate Zetosol 270/C, LES 2/C	Sodium salt of the sulfate ester of the polyethylene glycol ether of coconut alcohol that conforms generally to the formula where R represents the alkyl groups derived from coconut oil and n has an average value of 1 to 4.	$R(OCH_2CH_2)_nOSO_3Na$
Sodium deceth sulfate (no CAS No.)	Sodium decyl ether sulfate	Sodium salt of sulfated ethoxylated decyl alcohol that conforms generally to the formula where n has an average value between 1 and 4.	$CH_3(CH_2)_9(OCH_2CH_2)_nOSO_3Na$
Sodium laneth sulfate (CAS No. 68919-23-3, generic)	Sodium polyoxyethylene lanolin ether sulfate	Sodium salt of sulfated ethoxylated lanolin alcohol that conforms generally to the formula where R represents the lanolin alcohol radical and n has a value between 1 and 4.	$R(OCH_2CH_2)_nOSO_3Na$
Sodium laureth sulfate (CAS Nos. 1335-72-4; 3088-31-1; 9004-82-4, generic; 68585-34-2, generic; 68891-38-3, generic; 91648-56-5)	Dodecyl sodium sulfate PEG-(1-4) lauryl ether sulfate, sodium salt Polyethylene glycol (1-4) lauryl ether sulfate, sodium salt Poly(oxy-1,2-ethanediyl), α-sulfo-ω-(dodecyloxy)-, sodium salt Polyoxyethylene (1-4) lauryl ether sulfate, sodium salt Sodium PEG lauryl ether sulfate Sodium polyoxyethylene lauryl ether sulfate Sodium polyoxyethylene lauryl sulfate Sodium laureth sulfate is offered under 120 trade names and is included in 111 trade name mixtures.	Sodium laureth sulfate is the sodium salt of sulfated ethoxylated lauryl alcohol that conforms generally to the formula (see structure) where n averages between 1 and 4.	$CH_3(CH_2)_{11}(OCH_2CH_2)_nOSO_3Na$
Sodium myreth sulfate (CAS No. 25446-80-4)	PEG-(1-4) myristyl ether sulfate, sodium salt Polyethylene glycol (1-4) myristyl ether sulfate, sodium salt Sodium myristyl ether sulfate Sodium polyoxyethylene myristyl ether sulfate (3E.O.) Sodium polyoxyethylene myristyl ether sulfate solution DeSulf SMES-603 Standapol ES-40 Sulfochem ME-60 Texapon K 14 S, Texapon K 14 S Spez 70% Unipol ES-40 Zetesol 470	Sodium salt of sulfated ethoxylated myristyl alcohol that conforms generally to the formula where n has a value between 1 and 4.	$CH_3(CH_2)_{13}(OCH_2CH_2)_nOSO_3Na$

(continued)

Table 1 (continued)

Ingredient (CAS No.)	Synonyms/Technical Names/Trade Names	Definition	Formula/Structure
Sodium oleth sulfate (CAS No. 27233-34-7)	Sodium polyethylene glycol (1-4) oleyl ether sulfate Sodium polyoxyethylene (1-4) oleyl ether sulfate	Sodium salt of the sulfate ester of the polyethylene glycol ether of oleyl alcohol that conforms generally to the formula where n has an average value between 1 and 4.	
Sodium trideceth sulfate (CAS No. 25446-78-0)	Sodium polyoxyethylene tridecyl sulfate Sodium tridecyl ether sulfate Cedepal TD-407; TD-484; TD-403 DeSulf STDES-30 Genapol XRO Rhodapex EST-30 Sulfochem TD-3	Sodium salt of sulfated ethoxylated tridecyl alcohol (qv) that conforms generally to the formula where n has a value between 1 and 4.	$CH_3(CH_2)_{12}(OCH_2CH_2)_nOSO_3Na$
Zinc coceth sulfate (no CAS No.)	Zetesol ZN	Zinc salt of sulfated, ethoxylated coconut alcohol that conforms generally to the formula where R represents the alkyl groups derived from coconut alcohol and n has an average value of 3.	$[R(OCH_2CH_2)_nOSO_3^-]_2\ Zn^{+2}$

Table 2. Reported Uses and Use Concentrations as a Function of Product Category in Cosmetics

Product Category	2007 Uses[5]	2008 Use Concentrations[6]
Sodium myreth sulfate		
Makeup		
Eye shadow (1061)	—[a]	0.008%
Noncoloring hair preparations		
Shampoos (1022)	14	0.6%-20.0%
Hair tonics, dressings, etc (623)	—	0.01%
Hair coloring products		
Hair dyes and colors (1600)	1	
Shaving preparations		
Shaving cream (135)	1	
Bath preparations		
Bath soaps and detergents (594)	1	7%
Bath oils, tablets, and salts (207)	1	
Bubble baths (256)	5	
Other bath preparations (276)	2	
Personal hygiene products		
Douches (8)	—	10%
Skin care preparations		
Cleansers (1009)	1	20%
Total uses/ranges for sodium myreth sulfate	26	0.008%-20%
Ammonium laureth sulfate		
Baby products		
Shampoos (38)	1	—
Other baby products (64)	1	—
Bath preparations		
Oils, tablets, and salts (207)	1	10%
Bubble baths (256)	45	—
Other bath preparations (276)	3	—
Fragrance preparations		
Other fragrance preparations (187)	1	—
Noncoloring hair preparations		
Conditioners (715)	1	—
Permanent waves (169)	1	—
Rinses (46)	3	—
Shampoos (1022)	149	7%-36%
Hair tonics, dressings, etc (623)	2	—
Other noncoloring hair preparations (464)	1	—
Hair coloring products		
Hair dyes and colors (1600)	—	5%
Makeup		
Makeup bases (273)	2	—
Personal hygiene products		
Bath soaps and detergents (594)	21	1%-20%
Other personal hygiene products (390)	5	—
Skin care preparations		
Cleansers (1009)	14	1%-30%
Face and neck creams, lotions, etc (546)	1	—
Body and hand creams, lotions, etc (992)	2	8%
Paste masks (312)	1	—
Total uses/ranges for ammonium laureth sulfate	255	1%-36%
Magnesium laureth sulfate		
Baby products		
Shampoos (38)	3	0.4%
Baby lotions, oils, powders, and creams (67)	—	0.2%
Other baby products (64)	1	0.4%[b]
Eye makeup products		
Eye makeup remover (114)	10	0.02%-0.04%

(continued)

Table 2 (continued)

Product Category	2007 Uses[5]	2008 Use Concentrations[6]
Noncoloring hair preparations		
Shampoos (1022)	23	0.05%-4%
Bath preparations		
Bath soaps and detergents (594)	3	0.05%-3%
Personal cleanliness products		
Other personal cleanliness products (390)	—	7%[c]
Skin care preparations		
Cleansers (1009)	11	0.7%
Paste masks (mud packs) (312)	—	2%
Other skin care preparations (915)	1	—
Total uses/ranges for magnesium laureth sulfate	52	0.02%-7%
Magnesium oleth sulfate		
Baby products		
Shampoos (38)	2	0.1%
Baby lotions, oils, powders, and creams (67)	—	0.04%
Other baby products (64)	1	0.1%
Eye makeup products		
Eye makeup remover (114)	12	0.01%-0.02%
Noncoloring hair preparations		
Shampoos (1022)	20	0.2%
Other noncoloring hair preparations (464)	1	—
Personal cleanliness products		
Bath soaps and detergents (594)	3	0.2%
Other personal cleanliness products (390)	1	0.1%[d]
Skin care preparations		
Cleansers (1009)	8	0.2%
Paste masks (mud packs) (312)	—	
Other skin care preparations (915)	1	—
Total uses/ranges for magnesium oleth sulfate	49	0.01%-0.2%
Sodium coceth sulfate		
Bath preparations		
Bubble baths (256)	1	—
Other bath preparations (276)	1	—
Eye makeup preparations		
Eye makeup remover (114)	1	—
Fragrance preparations		
Other fragrance preparations (187)	1	—
Noncoloring hair preparations		
Shampoos (noncoloring) (1022)	—	0.8%
Body and hand creams, lotions, and powders (992)	—	0.2%
Personal cleanliness products		
Bath soaps and detergents (594)	2	—
Other personal cleanliness products (390)	2	—
Sodium coceth sulfate		
Skin care preparations		
Cleansers (1009)	5	—
Total uses/ranges for sodium coceth sulfate	13	0.2%-0.8%
Sodium C12-15 pareth sulfate		
Personal hygiene products		
Douches (8)	—	0.2%
Skin care preparations		
Cleansing (1009)	1	—
Total uses/ranges for sodium C12-15 pareth sulfate	1	0.2%
Sodium laureth sulfate		
Baby products		
Shampoos (38)	15	10%
Other baby products (64)	22	5%-25%

(continued)

Table 2 (continued)

Product Category	2007 Uses[5]	2008 Use Concentrations[6]
Bath products		
Bath oils, tablets, salts (207)	7	14%
Bubble baths (256)	117	6%-24%
Bath capsules (5)	1	—
Other bath products (276)	114	6%-19%
Eye makeup products		
Eyeliner (639)	1	—
Lotion (32)	1	—
Eye makeup remover (114)	16	0.1%
Mascara (308)	18	0.1%-0.3%
Fragrance preparations		
Other fragrance preparations (187)	6	18%
Noncoloring hair preparations		
Conditioners (715)	2	0.7%
Permanent waves (169)	—	0.6%
Rinses (46)	1	—
Shampoos (1022)	745	11%-50%
Tonics, dressings, etc (623)	8	—
Other noncoloring hair preparations (464)	13	—
Hair coloring products		
Hair dyes and colors (1600)	134	3%-10%
Coloring shampoos (27)	26	—
Bleaches (103)	1	—
Other hair coloring products (73)	4	14%
Makeup		
Foundations (530)	4	—
Bases (273)	1	—
Other makeup (304)	1	15%
Oral hygiene products		
Dentifrices (8)	1	—
Personal hygiene products		
Bath soaps and detergents (594)	512	2%-47%
Douches (8)	3	—
Feminine deodorants (7)	2	7%
Other personal hygiene products (390)	106	13%-16%
Shaving preparations		
Aftershaves (260)	2	—
Shaving cream (135)	11	1%-5%
Shaving soap (2)	2	—
Other shaving preparations (64)	4	—
Skin care products		
Cleansers (1009)	206	0.6%-25%
Face and neck creams, lotions, etc (546)	19	—
Body and hand creams, lotions, etc (992)	19	11%-17%
Foot powders and sprays (43)	1	11%
Moisturizers (1200)	6	0.5%
Paste masks (312)	6	—
Other skin care products (915)	20	—
Suntan products		
Suntan gels, creams, lotions (138)	1	
Other suntan products (41)	1	—
Total uses/ranges for sodium laureth sulfate	2180	0.1%-50%
Sodium oleth sulfate		
Baby products		
Shampoos (38)	2	0.4%
Baby lotions, oils, powders, and creams (67)	—	0.1%
Other baby products (64)	1	0.4%

(continued)

Table 2 (continued)

Product Category	2007 Uses[5]	2008 Use Concentrations[6]
Eye makeup preparations		
Eye makeup remover (114)	11	0.01%-0.02%
Noncoloring hair preparations		
Shampoos (1022)	19	0.5%
Other noncoloring hair preparations (464)	1	
Personal cleanliness products		
Bath soaps and detergents (594)	3	0.4%-2%
Other personal cleanliness products (390)	1	0.4%[e]
Skin care preparations		
Cleansing (1009)	8	0.2%
Other skin care preparations (915)	1	—
Total uses/ranges for sodium oleth sulfate	47	0.01%-2%
Sodium trideceth sulfate		
Baby products		
Shampoos (38)	25	3%
Baby lotions, oils, powders, and creams 67)	—	3%
Other baby products (64)	20	2%-3%
Bath preparations		
Other bath preparations (276)	1	—
Eye makeup		
Eye makeup removers (114)	7	—
Noncoloring hair preparations		
Shampoos (1022)	13	2%-17%
Hair coloring products		
Coloring shampoos (27)	1	—
Personal hygiene products		
Bath soaps and detergents (594)	29	2%-10%
Other personal cleanliness products (390)	1	3%-19%
Feminine hygiene deodorants (7)	—	3%
Skin care preparations		
Cleansing (1009)	35	0.6%-18%
Total uses/ranges for sodium trideceth sulfate	132	0.6%-19%

[a] Dash indicates not reported. In some cases, ingredient uses were not reported to FDA in the voluntary industry product survey program; however, concentrations were provided. In other cases, the uses were reported but no concentration was provided.
[b] 0.4% in a baby wash.
[c] 7% in a shower gel.
[d] 0.1% in a shower gel.
[e] 0.4% in a shower gel.

Summary

An earlier safety assessment by the Cosmetic Ingredient Review Expert Panel considered sodium laureth sulfate and ammonium laureth sulfate and another had considered sodium myreth sulfate. This amended safety assessment combined and extended the previous assessments to include all salts of sulfated ethoxylated alcohols. Sodium laureth sulfate was the most studied of this group of cosmetic ingredients, all of which are salts of sulfated, ethoxylated alcohols, used primarily as surfactant emulsifiers and cleansing agents in soaps and shampoos, over a wide range of concentrations from 0.008% to 50.0%.

Data on additional ingredients were limited and did not raise any safety concerns.

Discussion

The CIR Expert Panel recognized that most of the acute oral toxicity, dermal irritation and sensitization, subchronic and chronic oral toxicity, reproductive and developmental toxicity, carcinogenicity, and photosensitization studies have been conducted on ammonium laureth sulfate and sodium laureth sulfate. There are limited safety test data on most of the other ingredients included in this safety assessment. Sodium and ammonium laureth sulfate have not evoked adverse responses in any toxicological testing, including acute oral toxicity, subchronic and chronic oral toxicity, reproductive and developmental toxicity, carcinogenicity, and photosensitization studies. These data, however, are considered a sufficient basis

for concluding that the other ingredients are safe in the practices of use and concentration described in the safety assessment because of the fundamental chemical similarities between them and because they all are chemically similar salts (salts are expected to be dissociated in any product formulation independent of whether the salt is sodium, ammonium, magnesium, or zinc) of sulfated ethoxylated alcohols, and they all function as surfactants in cosmetic formulations. Based on these considerations, safety test data on 1 ingredient may be extrapolated to all of them.

The CIR Expert Panel also recognized that there are data gaps regarding use and concentration of these ingredients. However, the overall information available on the types of products in which these ingredients are used and at what concentrations indicates a pattern of use that was considered by the Expert Panel in assessing safety. (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 with others in the group.)

The panel noted that sodium laureth sulfate and ammonium laureth sulfate can 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 these ingredients. The irritant effects, however, are similar to those produced by other detergents, and the severity of the irritation appears to increase directly with concentration.

Conclusion

The CIR Expert Panel concludes that sodium myreth sulfate, ammonium capryleth sulfate, ammonium myreth sulfate, ammonium laureth sulfate, ammonium C12-15 pareth sulfate, magnesium coceth sulfate, magnesium laureth sulfate, magnesium myreth sulfate, magnesium oleth sulfate, sodium coceth sulfate, sodium C10-15 pareth sulfate, sodium C12-13 pareth sulfate, sodium C12-15 pareth sulfate, sodium laneth sulfate, sodium laureth sulfate, sodium oleth sulfate, sodium deceth sulfate, sodium trideceth sulfate, and zinc coceth sulfate are safe as cosmetic ingredients in the present practices of use and concentration when formulated to be nonirritating.[1]

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. F. Alan Andersen, PhD, and Valerie C. Robinson are employed by Cosmetic Ingredient Review.

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1

Final Report on the Safety Assessment of Cocoamphoacetate, Cocoamphopropionate, Cocoamphodiacetate, and Cocoamphodipropionate

Cocoamphoacetate (CAA), Cocoamphopropionate (CAP), Cocoamphodiacetate (CADA), and Cocoamphodipropionate (CADP) are imidazoline-derived amphoteric organic compounds. These amphoteric compounds are used in cosmetics as surfactants, mild foaming and cleansing agents, detoxifying agents, and conditioners at concentrations ranging from $\leq$ 0.1 to 50 percent.

In acute oral toxicity studies, CADA and CAA were nontoxic in rats and mice, CADP was nontoxic in rats, and CAP was nontoxic in mice. An oral LD_{50} of 7.8 ml/kg was reported for mice dosed with 70% CADP.

The results of ocular irritation studies of these compounds, as commercially supplied, varied widely. CADA was moderately to severely irritating when eyes were not rinsed and practically nonirritating to mildly irritating when rinsed. CADP was practically nonirritating under unrinsed conditions. CAA was minimally to severely irritating and CAP was practically nonirritating to minimally irritating under unrinsed conditions. In a clinical ocular study, 1, 3, and 10% dilutions of a shampoo containing 28.1% CADA were nonirritating to the human eye.

CAP, CADA, and CADP were nonmutagenic in the Ames assay, both with and without metabolic activation.

CAA and CAP, at a concentration of 10%, were neither irritants nor sensitizers in a repeated insult patch test on 141 subjects.

Based upon the available data, it is concluded that CAA, CAP, CADA, and CADP are safe for use as cosmetic ingredients.

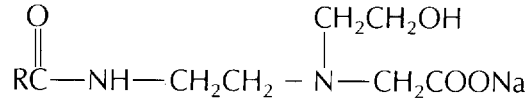
INTRODUCTION

The following report encompasses the four ingredients represented by the old nomenclature of Amphoterics-1 and -2: Cocoamphoacetate, Cocoamphopropion-

ate, Cocoamphodiacetate, and Cocoamphodipropionate.* Amphoteric-6, a complex of Amphoteric-2 and sodium lauryl sulfate, is currently regarded as a simple mixture and has been withdrawn from the third edition of the *CTFA Cosmetic Ingredient Dictionary*.[1]

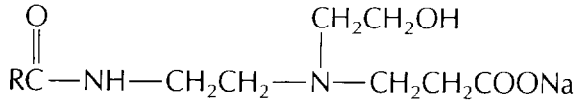
CHEMICAL AND PHYSICAL PROPERTIES

Cocoamphoacetate (CAA), Cocoamphopropionate (CAP), Cocoamphodiacetate (CADA), and Cocoamphodipropionate (CADP) are amphoteric organic compounds generally conforming to the following structural formulas:[2]



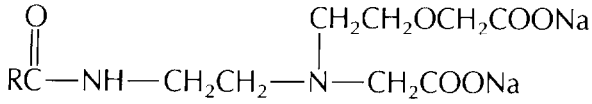
Cocoamphoacetate

I

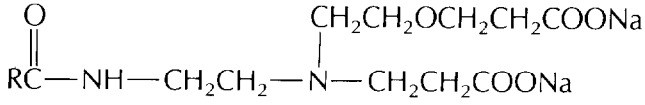


Cocoamphopropionate

II



Cocoamphodiacetate



Cocoamphodipropionate

where RCO– represents the mixed coconut acid moieties. The alkyl imidazolines were previously thought to be ring structured; however, they now are known to have a linear structure.[2–4] Cosmetic suppliers do not agree on the representation of the structures for CADA and CADP. In the opinion of some chemists, the second carboxylate group may be unattached to the amphoteric structure.[1]

These products are prepared by reacting coconut acid with aminoethylethanolamine and appear to form an imidazoline as an intermediate. The cocoimidazoline is

*New designations in supplement to the 3rd edition of the *CTFA Cosmetic Ingredient Dictionary*: Cocoamphoacetate formerly Cocoamphoglycinate (CAG), Cocoamphodiacetate formerly Cocoamphocarboxyglycinate (CACG); Cocoamphodiapropionate formerly Cocoamphocarboxypropionate (CACP). These substances are used as sodium salts in cosmetics.

then reacted with monochloracetic acid or monochloropropionic acid in the presence of sodium hydroxide to form the sodium salts either of a mono- (CAA and CAP) or dicarboxylated (CADA and CADP) product.[1,5,6]

These compounds are supplied as amber liquids, usually containing 40 to 50 percent solids, with a faintly fruity odor. Their viscosity can be controlled by the addition of sodium chloride (the more sodium chloride added, the more viscous the solution becomes). All of these products are soluble in water and insoluble in nonpolar organic solvents. CAP and CADP, containing only traces of sodium chloride ($\leq 0.02\%$), are also soluble in alcohol.[1,2] The pH range for solutions of these ingredients has been reported to be from 8.1 to 10.2 (Table 1).[2]

CAA, CAP, CADA, and CADP can be positively identified by close match to standard infrared spectra.[2] Another analytical method is based on the ionization curves formed by plotting pH changes upon addition of acids and alkalis to the amphoteric solution. Each ionization curve is unique and allows for immediate identification as well as giving information about the purity and degree of carboxylation of the compound.[7]

IMPURITIES

No information is available on impurities.

USE

Cosmetic

CAA, CAP, CADA, and CADP are used in cosmetics as surfactants, mild foaming and cleansing agents, detoxifying agents, and conditioners.[1,5,8–10]

Blends of cosmetic amphoterics and anionics act synergistically to reduce irritation potential, improve viscosity, and enhance foam volume and longevity.[11,12] Ampho-

TABLE 1. Physicochemical Properties

Property	*Cocoamphoacetate*	*Cocoamphopropionate*	*Cocoamphodiacetate*	*Cocoamphodipropionate*
Description (in aqueous solution)	Clear, viscous, light amber solution[1,2]	Clear, light amber solution[1,2]	Viscous, light tan solution[1,2]	Clear, light amber solution[1,2]
Odor	Faintly fruity[2]	Faintly fruity[2]	Faintly fruity[2]	Faintly fruity[2]
pH at 30°C	9.0–9.5[2]	9.8–10.2[2]	8.1–8.3[2] (of 20% aqueous soln)	9.4–9.8[2]
Solubility				
Water	S[1,2,5]	S[1,2,5]	S[2,5]	S[2,5]
Alcohol	I[2]	S[2]	I[2]	S[2]
Nonpolar organic solvents	I[2]	I[2]	I[2]	I[2]
Chloride (as NaCl)	7.0–7.7%[2]	0.02% maximum[2]	11.2–11.8%[2]	0.02% maximum[2]
Nitrogen	2.4–2.6%[2]	2.7–2.9%[2]	2.3–2.5%[2]	2.4% minimum[2]
Non-volatiles	43% minimum[2]	36–38%[2]	49% minimum[2]	38% minimum[2]

terics have less severe defatting effects compared with anionics and promote hair and skin substantivity at acid pH when they become cationic in character.[11] Goddard et al.[13] studied the effect of CAP on the adsorption of Polymer JR-400 on bleached and unbleached hair. CAP increased adsorption with each successive shampooing; CAP-Polymer JR-400 was one of the surfactant-polymer systems with the highest deposition on the hair.

The FDA product formulation data for CAA, CAP, CADA, and CADP are summarized in Table 2.[14] The cosmetic product formulation data, made available by the FDA, are compiled through voluntary filing in accordance with Title 21 part 720.4 (d)(1) of the Code of Federal Regulations.[15] Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100 percent concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration. CAA and CADA are used in cosmetic products at concentrations of $\geq$ 1.0 to 10.0% and $\leq$ 0.1 to 50.0%, respectively, and, CADP, at concentrations of $>$ 1.0 to 25.0%. There are no reported cosmetic uses of CAP.[14]

TABLE 2. Product Formulation Data

Product Category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*						
			>25-50	*>10-25*	*>5-10*	*≥5*	*>1-5*	*>0.1-1*	*≤0.1*
Cocoamphoacetate									
Hair shampoos (noncoloring)	859	5	—	—	2	—	3	—	—
1989 Totals		5	—	—	2	—	3	—	—
Cocoamphopropionate									
1989 Totals	—	0	—	—	—	—	—	—	—
Cocoamphodiacetate									
Hair shampoo	878	13	1	7	4	—	1	—	—
Skin cleansing preparations	1298	10	—	1	—	—	7	1	1
Miscellaneous other cosmetics	2134	7	—	—	2	—	—	4	1
1989 Totals		30	1	8	6	—	8	5	2
Cocoamphodipropionate									
Hair shampoo	859	8	—	1	6	—	1	—	—
Other hair products	772	7	—	1	—	—	6	—	—
Skin cleansing preparations	751	2	—	—	1	—	1	—	—
1989 Totals		17	—	2	7	—	8	—	—

Source: From Ref. 14.

The formulation data presented in Table 2 indicate that cosmetic products containing these amphoterics may contact all external body surfaces and hair, conjunctivae, and other mucous membranes. These products may be used daily or occasionally over a period of up to several years. The frequency and duration of application could result in continuous exposure.

Noncosmetic

CAA, CAP, CADA, and CADP are widely used in heavy-duty liquid, steam, pressure, metal, and all-purpose cleaners.[5,16] They are used in the caustic lye peeling of fruit and potatoes and are commonly found in household products such as oven cleaners, wash and wax floor polishes, dishwashing machine compounds, copper and silver cleaners, and hard-surface cleaners.[5]

Other uses of these amphoterics include pharmaceutical formulations for the treatment of glaucoma (CADA, 0.2%) and hemorrhoids (CADP, 0.25%), contact lens disinfecting solution (CADP, 0.0035–0.04%), and in material for bandages (CADA).[17–20]

GENERAL BIOLOGY

Hirai et al.[21] studied the effects of surfactants on the nasal absorption of insulin in rats. The addition of 1% CADA to the solution administered nasally to rats significantly enhanced insulin absorption as measured by a 56.9% decrement in plasma glucose concentration from 0 to 4 h. The absolute bioavailability of insulin was increased from 5 to 30% by the addition of a surfactant such as CADA. The surfactants appeared to promote nasal absorption either by increasing the permeability of the nasal mucosa or by reducing the activities of proteolytic enzymes.

A blend containing CADA, sodium lauryl sulfate, and hexylene glycol was tested for antimicrobial activity and inhibition of the formation of *in vitro* plaque by oral bacteria. The blend had antimicrobial activity against *Actinomyces viscosus, A. naeslundii,* and *Streptococcus mutans.* However, it was significantly less effective than other detergents tested and had an ID_{50} (dose resulting in 50% inhibition of bacterial growth) of 2.0 to 5.0 $\times 10^{-5}$ M. The blend was not active against *A. viscosus* in the plaque assay and had very limited activity against *A. naeslundii* and *S. mutans* with ID_{50}s of 10^{-1}M or greater.[22]

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

CADA, CADP, CAA, and CAP, as commercially supplied, have all been evaluated for acute oral toxicity using rats or mice. LD_{50} values ranged from >5.0 to 16.60 g/kg for CADA, >5.0 to 16.30 g/kg for CADP, 15.9 to 28.0 ml/kg for CAA, and a value of 20.0 ml/kg was reported for CAP in two studies. Results of these and other acute oral toxicity tests are reported in Table 3.

Additionally, CADA and CADP were each fed to albino rats (number unspecified) at concentrations of 0.25 and 0.50% in the diet for 10 days. Control groups were

TABLE 3. Acute Oral Toxicity

Ingredient	*Animal*	*LD_{50} Value*	*Comments*	*Reference*
CADA: As commercially supplied	Rats: 5 females	>5.0 g/kg	No toxic effects	23
CADA: As commercially supplied	Rats: 10	>5.0 ml/kg	—	26
CADA: As commercially supplied	Mice: 3 groups of 10	>15 ml/kg	—	27
CADA: As commercially supplied	Rats: groups of 10	16.60 g/kg	Nontoxic	24
CADA:				24
0.50% in the diet	Rats: unspecified no.	—	Rats fed daily for 10 days; nontoxic	
0.25% in the diet	Rats: unspecified no.	—	Rats fed daily for 10 days; nontoxic	24
CADP: As commercially supplied	Rats: groups of 10	16.30 g/kg	Nontoxic	25
CADP: As commercially supplied	Rats: 5 males 5 females	>5.0 ml/kg	—	28
CADP: 70% active (as commercially supplied)	Mice: 3 groups of 10	7.8 ml/kg	—	29
CADP:				25
0.50% in the diet	Rats: unspecified no.	—	Rats fed for 10 days; nontoxic	
0.25% in the diet	Rats: unspecified no.	—	Rats fed for 10 days; nontoxic	25
CAA: As commercially supplied	Mice: 3 groups of 5 males and 5 females each	28.0 ml/kg	—	30
CAA: As commercially supplied	Mice: 4 groups of 10	15.9 ml/kg	—	30
CAA: 25% (of supplied) in water	Rats: 10	>5.0 ml/kg	Nontoxic	31
CAP: As commercially supplied	Mice: 10	20.0 ml/kg	—	32
CAP: As commercially supplied	Mice: 4 groups of 10	20.0 ml/kg	—	33
CADA with sodium lauryl sulfate and hexylene glycol: 30%	Rats: groups of 10	10.25 g/kg	Nontoxic	34
CADA: 4% in a shampoo cream	Rats: 5 males 5 females	>5.0 ml/kg	No signs of systemic toxicity; no gross pathological effects	35
CADA: 4% in a shampoo cream	Rats: 5 males 5 females	>5.0 ml/kg	No signs of systemic toxicity; no gross pathological effects	35

maintained on a standard diet. At the end of the 10-day period, the rats were weighed and observed for changes in behavior, general appearance and activity. The rats on the test diets did not differ from the controls in any of the above parameters. CADA and CADP were considered nontoxic when fed to rats daily for ten days at concentrations of 0.25 and 0.50%.[24,25]

Dermal

Two shampoo creams, each containing 4.0% CADA, were evaluated for acute dermal toxicity in rabbits. Each test group consisted of two male and two female New Zealand albino rabbits. A single application of each undiluted shampoo was applied to the clipped, intact skin of the back of each rabbit at a dose of 10.0 ml/kg. Test sites were covered for 24 h with an impervious plastic binder and tape. Upon removal of the binders, excess test material was removed. Animals were observed for signs of systemic toxicity and dermal irritation for 14 days. No deaths occurred, although clinical signs of systemic toxicity included depression, labored respiration, phonation upon handling, tremors, and weight loss (in one animal only). At necropsy, six rabbits had no gross lesions and two had changes unrelated to treatment. Gross dermal lesions included moderate to marked erythema and edema accompanied by blanched areas (in two animals) and most of the lesions had cleared by day 8. Moderate to marked atonia and marked desquamation developed during the first week in all animals. Coriaceous areas and fissures were also observed. Sloughing of the damaged skin with eschar formation occurred in two rabbits. Slight to moderate desquamation was noted at termination in all animals and two animals had moderate atonia.[36]

Irritation

Ocular

CADA, CADP, CAA, and CAP, as commercially supplied, have been evaluated for ocular irritation primarily by Draize or modified Draize tests. In all tests, a 0.1 ml sample of the substance was instilled into the conjunctival sac of each rabbit; the other eye served as the untreated control. The eyes of those rabbits designated for testing with a rinse-out procedure were rinsed either 4 seconds after instillation with 20 or 60 ml of water or 10 seconds after instillation with 300 ml of water. Ocular irritation responses were scored according to Draize (max = 110) on days 1, 2, 3, 4, and 7. CADA, at concentrations of 10 to 12% active as well as solutions of unstated activity, was moderately to severely irritating when not rinsed from the eye and practically nonirritating to mildly irritating when tested using rinse-out procedures. CADP, at a concentration of 7.5% active, was practically nonirritating under unrinsed conditions. CAA, at concentrations of 16 to 50% active as well as solutions of unstated activity, was minimally to severely irritating under unrinsed conditions. CAP, at concentrations of 5 and 16% active, was practically nonirritating to minimally irritating under unrinsed conditions. Cosmetic products containing CADA (as supplied) at concentrations of 1.5 to 28.1% and CADP (as supplied) at concentrations of 25 to 36% also have been evaluated by the Draize test. All ocular irritation test results are given in Table 4.

North-Root et al.[37] also investigated the cellular toxicity of cationic, anionic, nonionic, and amphoteric surfactants *in vitro* using an established line of rabbit corneal cells and compared the results with those from an *in vivo* ocular irritation test in New Zealand albino rabbits. CADP had an LC_{50} of 35.5 ppm for the SIRC rabbit corneal cells (other surfactant LC_{50}s ranged from 2.2 to 36000 ppm); the CADP concentration predicted to cause a Draize score of 20 was approximately 90.0%. A 0.01 ml sample of CADP (at a concentration not exceeding 30%) was administered to the cornea of each of three male and three female rabbits. Corneal, iridial, and conjunctival responses were scored according to Draize 24, 48, and 72 hours after application. Individual

TABLE 4. Ocular Irritation

Ingredient	*Test method*	*No. of rabbits*	*Results*	*Reference*
CADA: As commercially supplied	Draize[a]	6: Unrinsed	HAIS[b] of 32 on day 1, 3 on day 7; moderately irritating	39
CADA: As commercially supplied	Draize	6: Unrinsed	HAIS of 30 on day 1, 3 on day 7; moderately irritating	40
CADA: As commercially supplied	Draize	6: Unrinsed	HAIS of 32 on day 1, 18 on day 7; moderately to severely irritating	41
CADA: As commercially supplied	Draize	3: Rinsed 4 s after instillation w/20 ml water	HAIS of 8 on day 1, eyes normal by day 4; minimally irritating	42
CADA: As commercially supplied	Draize	3: Rinsed 4 s after instillation w/20 ml water	HAIS of 1 on day 1, eyes normal by day 2; practically nonirritating	43
CADA: As commercially supplied	Draize	6: Unrinsed 3: Rinsed 4 s after instillation w/20 ml water	Unrinsed: HAIS of 37.17 on day 1, corneal and iridial irritation at day 7; severely irritating Rinsed: HAIS of 12.00 on day 1, some conjunctival irritation at day 7; mildly irritating	44
CADA: As commercially supplied	Draize (max = 104, discharge category omitted from scoring system)	3: Rinsed 10 s after instillation w/150 ml water/min for 2 min	HAIS of 5.33 for days 1–3, eyes normal by day 5; mildly irritating	45
CADA: 21% aqueous dilution of CADA (as supplied)	Draize	6: Unrinsed 3: Rinsed 4 s after instillation w/20 ml water	Unrinsed: HAIS of 3.67 at day 1, minimal conjunctival irritation at day 7; minimally irritating Rinsed: all scores of 0; nonirritating	46
CADA: 25% dilution of CADA (as supplied)	Draize	3: Unrinsed	HAIS of 5.33 on day 1, eyes normal by day 4; minimally irritating	47
CADA: 12% active (as commercially supplied)	Draize	3: Unrinsed	All scores: 0; nonirritating	48
CADA: 10% active (as commercially supplied)	Draize	3: Unrinsed	HAIS of 4.0 on day 1, eyes normal by day 3; minimally irritating	49
CADA: 5% (as commercially supplied) in water	—	6	Irritation cleared by 24 h	50
CADA: 5% (supplied w/1% $NaBH_4$) in water	—	6	Irritation cleared by 24 h	51
CADA: at 2, 10, and 20% in water	Draize	Groups of 5, unrinsed	Dose response observed; CADA was the second least irritating surfactant tested; 2%, score of 10 at 1 h, 0 at 24 h; 10%, score of 35 at 1 h, 5 at 7 days; 20%, score of 55 at 1 h, 5 at 7 days	52
CADP: 25% dilution of CACP (as commercially supplied) pH adjusted to 8	Draize	6: Unrinsed	HAIS of 1 on day 1, eyes normal by day 2; nonirritating	53

TABLE 4. *Continued*

Ingredient	*Test method*	*No. of rabbits*	*Results*	*Reference*
CADP: 7.5% active (as commercially supplied)	Draize	3: Unrinsed	HAIS of 1.33 on day 2, eyes normal by day 3; practically nonirritating	54
CADP	*In vitro* rabbit corneal cell toxicity test	—	LC_{50} = 35.5 ppm; least irritating amphoteric tested	37
CADP: concentration not > 30%	Draize	6: Unrinsed	CADP was the least irritating amphoteric; order of toxicity was cationic > anionic = amphoteric > nonionic; individual scores not given	37
CAA: As commercially supplied	Draize	6: Unrinsed	HAIS of 5.33 on day 1, eyes normal by day 7; minimally irritating	55
CAA: 50% active (as commercially supplied)	—	6	Draize scoring over 24 h, HAIS of 5.67 at 2 and 8 h, 1.0 at 24 h; minimally irritating	56
CAA: 50% active (as commercially supplied)	Modified Draize	6	HAIS of 29.4 on day 1, corneal and iridial irritation at day 7 in 2 rabbits; severely irritating	57
CAA: 16% active (as commercially supplied) pH adjusted to 7.0	Draize	3: Unrinsed	HAIS of 8.7 on day 1, minimal conjunctival irritation on day 7; minimally irritating	58
CAA: 25% aqueous dilution (of supplied)	Draize	6: Unrinsed	HAIS of 1.7 on day 1, eyes normal by day 2; nonirritating	31
CAA: 20% aqueous solution of 50% active CAG	Draize	6	HAIS of 5.67 on day 1, minimal conjunctival irritation on day 7; minimally irritating	59
CAA: 5% aqueous solution of 50% active CAG	Draize	6	HAIS of 1.0 on day 1, eyes normal by day 3; nonirritating	60
CAP: 16% active (as commercially supplied) pH adjusted to 7.0	Draize	3: Unrinsed	HAIS of 5.33 on day 1, eyes normal by day 4; minimally irritating	61
CAP: 5% active (as commercially supplied)	Draize	3: Unrinsed	HAIS of 1.33 on day 1, eyes normal by day 2; practically nonirritating	62
CADA: 28.1% in a shampoo (32% active)	Draize	6: Unrinsed	HAIS of 2.33 on day 1, eyes normal by day 3; practically nonirritating	63
CADA: 4% in a shampoo cream	Draize	5: Rinsed 4 s after instillation w/60 ml water	HAIS of 10.4 at 1 h, 4.8 by day 1, eyes normal by day 3; minimally irritating	64
CADA: 4% in a shampoo cream	Draize	5: Rinsed 4 s after instillation w/60 ml water	HAIS of 16.4 at 1 h, 5.2 by day 1, eyes normal by day 4; mildly irritating	64
CADA: 4% in an eye cream	Draize	5: Unrinsed	HAIS of 3 at 1 h, 1 by day 1, eyes normal by day 2; minimally irritating	65

TABLE 4. *Continued*

Ingredient	*Test method*	*No. of rabbits*	*Results*	*Reference*
CADA: 1.5% in a facial scrub	Draize	5: Unrinsed 5: Rinsed 4 s after instillation w/60 ml water	Unrinsed: HAIS of 27.4 on day 1, corneal and iridial irritation cleared by day 4, minimal conjunctival irritation at day 7; moderately irritating Rinsed: HAIS of 7.2 at 1 h, 0.4 by day 1, eyes normal by day 3; minimally irritating	66
CADA: at 0.14% with a formulation containing menthol	Draize	Unspecified	Totally eliminated the ocular irritation effects of menthol in the formulation— Draize score reduced to 0 (max = 110)	38
CADA: at 0.14% with a cologne	Draize	Unspecified	Reduced corneal irritation score of the cologne to 0; also reduced total score to 6 and 29 at 72 h and 7 days, respectively	38
CADA: 0.3% blend of CADA with sodium lauryl sulfate and a cologne	Draize	Unspecified	Equivocal reduction of ocular irritation; Draize scores of 7 and 27 for the cornea, 17 and 92 total scores, for 72 h and 7 days, respectively	38
CADP: 36.842% in a shampoo (38% active)	Draize	6: Unrinsed	HAIS of 8 at 1 h, 0 by day 1; not an ocular irritant	67
CADP: 25% in a shampoo (38% active) tested as 10 percent aqueous dilution	Draize	6: Unrinsed	HAIS of 1 on day 1, 0 thereafter; practically nonirritating	68

[a]Maximum score = 110.
[b]HAIS = Highest average irritation score (ocular).

results for CADP were not given. The order of ocular irritancy and cytotoxicity was cationic > anionic = amphoteric > nonionic. A significant correlation existed between relative toxicity in the rabbit corneal cells *in vitro* and relative ocular irritation when tested *in vivo*. CADP was the least irritating amphoteric surfactant; only the three nonionic surfactants were less irritating.

Additionally, Goldemberg[38] found that CADA had anti-irritant activity. CADA eliminated the ocular irritation effects of menthol in a Draize ocular irritation test using a pre-electric shave formulation consisting of 20% butyl stearate in ethanol as the "control." Groups of three rabbits received instillations of the control solution, the control solution with 0.7% menthol, and the control solution with 0.7% menthol and 0.14% CADA. The control formulation had baseline scores of 10, 6.2, and 5.0 at 24, 48, and 72 hours, respectively. The addition of menthol increased the scores to 14.7, 12.4, and 6.5 at 24, 48, and 72 hours, respectively. With addition of CADA, all scores were 0. The determination of the amount of CADA necessary to neutralize the effects of menthol was likened to titration by the investigator. At concentrations of CADA lower than 0.14% some ocular irritation was observed; higher concentrations were not more efficient. The efficiency ratio was 0.14/0.7 indicating that, in this case, 20% CADA neutralized the ocular irritation effects of menthol.

Goldemberg[38] conducted similar studies using a cologne formulation as the "control." Groups of three rabbits received instillations of the cologne alone, the

cologne with 0.14% CADA, and the cologne with 0.3% of a blend containing CADA and sodium lauryl sulfate. The addition of CADA alone was more effective in reducing ocular irritation than the blend. The cologne (96% SDA 39C ethanol) contained approximately 1% diethyl phthalate, which also may have had anti-irritant activity. The effective anti-irritant/irritant ratio for CADA/triethanolamine lauryl sulfate was 1:3.[38]

Dermal

CADA, CADP, CAA, and CAP, as commercially supplied, have been evaluated for dermal irritation primarily by single insult patch test (SIPT) procedures. In each test, an occlusive patch was applied for 24 hours to the clipped skin of the back of the rabbit. Intact or intact and abraded sites were used. In those tests using intact sites only, scores were taken 2 and 24 hours after patch removal on a maximum scale of 4. In those tests using the Draize procedure, with intact and abraded sites, scores were taken at 24 and 72 hours on a maximum scale of 8. CADA, at a concentration of 10 to 12% active, as well as solutions of unstated activity, was nonirritating to severely irritating to rabbit skin. CADP, at concentrations of 7.5 and 70% active, was nonirritating. CAA, at a concentration of 16% active as well as solutions of unstated activity, was nonirritating to severely irritating. CAP, at concentrations of 15 and 16% active, was slightly irritating. Cosmetic products containing CADA (as supplied) at concentrations of 1.5 to 4% and CADP (as supplied) at concentrations of 25 to 36.8% also have been evaluated for dermal irritation by the Draize procedure. Dermal irritation test results are given in Table 5.

These four ingredients also have been evaluated for dermal irritation in rabbits by use of a single intradermal injection. Each injection consisted of 0.5 ml of a 5% solution of CADA, CADP, or CAP (supplied as 20% active solutions—giving actual test concentrations of 1%); CAA was evaluated as a 0.1% solution. In each case, a second group of rabbits received injections of an olive oil castile shampoo as the control. The rabbits were observed for signs of irritation at the injection site 24 hours later and scored on a maximum scale of 4. CADA had a score of 0 and was considered nonirritating.[69] CADP, CAA, and CAP had scores of 1 and were considered less irritating than the control shampoos, which had scores of 2.[70–72]

Sensitization

The Magnusson-Kligman maximization test was used to evaluate the sensitization potential of CAA in 15 guinea pigs. CAA was tested at concentrations of 25, 50, and 100%. Negative (15 guinea pigs) and positive (15 guinea pigs) control groups were tested with distilled water and methylmethacrylate (25, 50, and 100%), respectively. CAA did not induce sensitization in any of the animals tested. Sensitization reactions were observed in the positive control group.[94]

MUTAGENICITY

The mutagenic potentials of CAP, CADA, and CADP were evaluated in the Ames *Salmonella*/microsome assay, using *Salmonella typhimurium* strains: TA-1535, TA-1537, TA-1538, TA-98, and TA-100.[95] CAP, CADA, and CADP (each diluted with deionized water) were tested at concentrations ranging from 0.005 to 1.00 μl per plate. Each test substance was incubated with each bacterial strain (three plates per dose, 37 ± 2°C) for 48 to 72 h in both the presence and absence of metabolic activation. The number of his+ revertant colonies was determined using an automated colony counter.

TABLE 5. Dermal Irritation

Ingredient	*Test method*	*No. of rabbits*	*Results*	*Reference*
CADA: As commercially supplied	SIPT[a]	9	AII[b] = 1.8; mildly irritating	73
CADA: As commercially supplied	SIPT	9	AII = 1.89; mildly irritating	74
CADA: As commercially supplied	SIPT	5	AII = 4.0; severely irritating	75
CADA: As commercially supplied	Draize[c]	6	PII[d] = 4.49; severely irritating	76
CADA: As commercially supplied	Draize	6	PII = 1.5; mildly irritating	48
CADA: 21% aqueous solution of CADA (as commercially supplied)	Draize	6	PII = 0.96; mildly irritating	77
CADA: 12% active (as commercially supplied)	Draize	3	PII = 0; nonirritating	78
CADA: 10% active (as commercially supplied)	Draize	3	PII = 0.85; slightly irritating	49
CADA: 10% in water	Draize	6	PII = 0; nonirritating	79
CADA: 10% in mineral oil	SIPT	9	AII = 0.11; minimally irritating	80
CADA: 2, 10, 20% aqueous solutions	Draize	6	PIIs = 2.25, 2.5, and 3.0 for the 2, 10, and 20% aqueous solutions; 2 and 10% solutions considered moderately irritating; 20% solution considered severely irritating	52
CADA: Actual concentration of 1% (5% of 20% active solution)	SIDI[e]	Unspecified	All scores = 0 (max = 4); nonirritating	69
CADP: 70% active (as commercially supplied)	Draize	3	PII = 0; nonirritating	81
CADP: 25% dilution of the CADP supplied	Draize	6	PII = 0; nonirritating	82
CADP: 7.5% active (as commercially supplied)	Draize	3	PII = 0; nonirritating	83
CADP: actual concentration of 1% (5% of 20% active solution)	SIDI	Unspecified	Score = 1 (max = 4); considered less irritating than control shampoo	72
CAA: As commercially supplied (pH adjusted to 7.0)	Draize	6	PII = 0; nonirritating	84
CAA: 25% (of supplied) in water	Draize	6	PII = 0.08; nonirritating	31
CAA: 16% active (as commercially supplied; pH adjusted to 7.0)	Draize	3	PII = 3.83; severely irritating	85
CAA: 0.1%	SIDI	Unspecified	Score = 1 (max = 4); considered less irritating than control shampoo	70
CAP: 16% active (as commercially supplied—pH adjusted to 7)	Draize	3	PII = 0.5; slightly irritating	86
CAP: 15% active (as commercially supplied)	Draize	6	PII = 0.5; slightly irritating	87
CAP: actual concentration of 1% (5% of 20% active solution)	SIDI	Unspecified	Score = 1 (max = 4); considered less irritating than control shampoo	71

TABLE 5. *Continued*

Ingredient	*Test method*	*No. of rabbits*	*Results*	*Reference*
CADA: 4% in an eye cream	Draize	4	PII = 3.13; severely irritating	88
CADA: 4% in a shampoo cream tested at 2.5% in water	Draize	4	PII = 1.56; mildly irritating	89
CADA: 4% in a shampoo cream tested at:	Draize			89
2.5% in water		4	PII = 2.94; moderately irritating	
1.25% in water		4	PII = 1.63; mildly irritating	
CADA: 1.5% in each of three facial scrubs; tested at	Draize	4	PII = 0.81; slightly irritating	90
		4	PII = 1.06; mildly irritating	
1.25% in water		4	PII = 2.00; moderately irritating	
CADA: with sodium lauryl sulfate and hexylene glycol; unspecified concentration	Draize	3	PII = 0.5; slightly irritating	91
CADP: 36.842% in a shampoo (38% active)	Draize	6	PII = 0.12; slightly irritating	92
CADP: 25% in a shampoo (38% active); tested as 10% aqueous dilution	Draize	6	PII = 0.21; slightly irritating	93

[a]SIPT = Single insult patch test = 24 h occlusive on intact site. Scores taken at 26 and 48 h.
[b]AII = Average irritation index (max = 4).
[c]Draize = Single 24 h occlusive patch on intact and abraded sites. Scores taken at 24 and 72 h.
[d]PII = Primary irritation index (max = 8).
[e]SIDI = Single intradermal injection.

Solvent controls were incubated with 50.0 μl of deionized water. Positive control cultures (all strains, metabolic activation) were incubated with 2-anthramine (2.5 μg/plate). Other positive control cultures (no metabolic activation) were incubated with: sodium azide in water (10.0 μg/plate, TA-1535 and TA-100), 2-nitrofluorene in dimethyl sulfoxide (DMSO) (10.0 μg/plate, TA-1538 and TA-98), and quinacrine mustard in DMSO (5.0 μg/plate, TA-1537). CAP, CADA, and CADP were not mutagenic to any of the strains tested in either the presence or absence of metabolic activation. The positive controls (with and without metabolic activation) induced large increases in the numbers of revertants in all of the strains tested.[96–98]

CLINICAL ASSESSMENT OF SAFETY

Ocular Irritation

A children's shampoo containing 28.1% CADA (32% active) was evaluated for ocular irritation using 30 adult subjects. Three dilutions of the shampoo were tested: 1, 3, and 10%. Each dilution was instilled into the conjunctival sac of one eye of each of 10 subjects; the other eye was treated with sterile distilled water. Positive reactions were noted only at the 30-s posttreatment evaluation. These consisted primarily of mild irritation scores for the bulbar and palpebral conjunctivae for all groups (including water treated); one subject each in the 3 and 10% groups as well as one treated with distilled water had a moderate score for irritation of the bulbar conjunctiva. Stinging

was noted in 1, 3, 4, and 2 subjects in the 1, 3, and 10% groups and water-treated eyes, respectively. When weighted for the number of eyes exposed, no significance was found in the positive responses. In all but seven of the positive reactions to the shampoo dilutions, distilled water elicited a positive reaction in the other eye. This was attributed to the eye sensitivity of individual subjects. None of the shampoo dilutions were considered more irritating than sterile distilled water.[99]

Dermal Irritation and Sensitization

The skin sensitization potential of CAA and CAP was evaluated using 32 male (18–65+ years) and 109 female (18–65 years) subjects. The chemicals were diluted to a concentration of 10% w/v in distilled water prior to testing. During induction, each chemical was applied to the back three times per week for three successive weeks. Sites were covered for 24 h with nonocclusive patches secured with surgical tape. Repeated applications of both chemicals were made to the same test sites. Reactions were scored 48 or 72 h after each induction application according to the Draize[100] scale: 0 (no erythema and eschar formation, no edema) to 4 (severe erythema to slight eschar formation, severe edema). The challenge phase was initiated 10 to 15 days after application of the final induction patch. Challenge patches (nonocclusive) were applied for 24 h to new sites on the back; reactions were scored 48 and 96 h later. CAA and CAP did not induce skin irritation or sensitization in any of the subjects tested.[101] Results of all irritation and sensitization tests are reported in Table 6.

A children's shampoo containing 28.1% CADA (32% active) was evaluated for irritation and sensitization by a Repeated Insult Patch Test (RIPT) using 105 subjects. Occlusive patches containing a 5.0% dilution of the shampoo were applied to the backs of the subjects on Mondays, Wednesdays, and Fridays for the first five inductions; however, due to the large number of irritant reactions, semiocclusive patches were used on a new site for the remaining four inductions. Sites were scored upon patch removal (and prior to next patch application) on a scale of 0–3+. After a two-week nontreatment period, a challenge patch was applied for 48 h to the same site and the site was scored after 48 and 72 h. Under semiocclusive conditions, the shampoo elicited, at most, two ? (barely perceptible erythema) reactions and one 1+ (definite erythema) reaction during induction. Three and one ? reactions were observed 48 and 72 h after the challenge, respectively. The shampoo was nonirritating and nonsensitizing under semiocclusive patch test conditions.[102]

A shampoo cream and a facial scrub containing 4 and 0.61% CADA, respectively, were evaluated for irritation and sensitization by RIPT at a concentration of 1% in water. In each test, a series of eight induction patches was applied to the upper portion of the arm of each subject on four consecutive days per week for two weeks. These patches were semiocclusive and contained 0.3 or 0.2 ml of the shampoo or scrub test solutions, respectively. Patches were removed after 24 h and sites scored on a scale of 0 to 5. After a 2-week nontreatment period, semiocclusive challenge patches were applied to adjacent sites for 24 h. Reactions were scored at 24, 48, and 72 h for both test solutions, and additionally at 96 h for the facial scrub. In both tests, slight erythema (score of 1) was noted during induction, whereas no reactions were observed at challenge. The shampoo and facial scrub were nonirritating and nonsensitizing in the 45 and 53 subjects, respectively, who completed the studies.[103,104]

TABLE 6. Clinical Irritation and Sensitization

Ingredient	*Test method*	*No. of subjects*	*Results*	*References*
CAA: 10% in distilled water	RIPT[a] (nonocclusive)	141	Nonirritating and nonsensitizing	101
CAP: 10% in distilled water	RIPT (nonocclusive)	141	Nonirritating and nonsensitizing	101
CADA: 28.1% in a shampoo (32% active); tested as 5% dilution in water	RIPT (occlusive switched to semiocclusive)	105	Large number of irritant reactions—to induction patches 1-5 under occlusive conditions; switched to semiocclusive patches; nonirritating and nonsensitizing	102
CADA: 4.0% in a shampoo cream and tested at 1% in water	RIPT (semiocclusive)	45	Nonirritating and nonsensitizing	103
CADA: 1.1% in an eye makeup remover (70% active)	RIPT (occlusive)	102	Nonirritating and nonsensitizing	105
CADA: 1.1% in an eye makeup remover (70% active)	RIPT (occlusive)	103	Produced some irritation; nonsensitizing	112
CADA: 0.61% in a facial scrub; tested at 1% in water	RIPT (semiocclusive)	53	Nonirritating and nonsensitizing	104
CADA: 25% in a facial cleanser (45.6% active)	Controlled use; twice daily for one month	54	No adverse reactions	106
CADP: 10% in a hair product (diluted to 1% in water)	Kligman maximization	25	No adverse reactions; nonsensitizing	107
CADP: 5% in a cleansing cream	RIPT (occlusive)	204	Nonirritating and nonsensitizing	108
CADP: 5% in a cleansing cream	21-Day cumulative irritation (occlusive)	12	Total score = 109 (max = 1008); very mildly irritating	109
CADP: 5% in a cleansing cream	Controlled use; daily for one month	53	Nonirritating	110
CADP: 5% in a cleansing cream	Controlled use; once or twice daily for two weeks	24	No adverse reactions	111

[a]RIPT = Repeated Insult Patch Test

An eye makeup remover containing 1.1% of 70% active CADA (actual concentration of 0.77%) was evaluated for irritation and sensitization by a modified Draize RIPT. Occlusive patches containing 0.3 ml of the test material were applied for 24 h to the upper portions of the arms of 102 volunteers on alternate days for a total of 10 applications. After a two to three week nontreatment period, an occlusive challenge patch was applied for 24 h to the same test site on each volunteer. Reactions were scored upon patch removal and at 24 h. All scores were 0 (max = 4); the eye makeup remover was considered neither a primary skin irritant, sensitizer, nor fatiguing agent.[105]

Another eye makeup remover also containing 1.1% of 70% active CADA (actual concentration of 0.77%) was evaluated for irritation and sensitization by an RIPT. Occlusive patches were applied for 48 h to the same site on the back of 113 panelists on

alternate days for a total of 10 applications. Patches applied on Friday remained in place until Monday. Sites were scored 15 minutes after patch removal. After a nontreatment period, an occlusive challenge patch was applied for 48 h to a fresh site on the back. Reactions were then scored at 15 min and 24 h after patch removal. Of the 103 panelists who completed the study, only one reaction (score of 2, max = 4) was noted at challenge. However, positive irritant reactions to the product were observed during the induction phase in 28 of 113 panelists. Except for one subject, none of the irritation scores exceeded 2, even with continued application of the product. This particular subject had a score of 4+ after six applications; however, no irritation was seen when the product was reapplied under nonocclusive conditions. The irritancy level of this product would not be considered significant when applied for a short duration to normal skin although the proximity of its use to the eye should be taken into consideration. The eye makeup remover produced no evidence of sensitization but did produce some irritation.[112]

A facial cleanser containing 25% CADA (45% active) was evaluated in a controlled use study with 54 subjects. The subjects were instructed to use the cleanser twice daily for one month; 29 of the subjects used the cleanser alone and 25 used the cleanser with an antiseptic lotion. The cleanser produced no adverse reactions.[106]

A Kligman maximization test was conducted to evaluate the skin sensitization potential of a hair product containing 10% CADP. Another formulation not containing CADP was simultaneously tested. Twenty-five subjects participated in the study. The study was conducted without sodium lauryl sulfate (SLS) pretreatment, as it was determined that both test materials were mildly irritating by pretest with test solutions and SLS. The hair product was diluted with distilled water to a concentration of 1% and applied (0.3 ml) to each patch. The occlusive induction patches remained in place for 48 h, after which there was a 24-h nontreatment period. These procedures were repeated for a total of five inductions. The induction sites were scored only in the event of exacerbation or a flare. Ten days after removal of the last induction patch, occlusive challenge patches were applied to previously untreated sites for 48 h. None of the subjects had reactions to induction or challenge patches that contained samples of the hair product with 10% CADP. The investigators concluded there was no evidence of contact sensitization elicited by this product.[107]

Cleansing creams containing 5% CADP were evaluated for irritation and sensitization by an RIPT, a 21-day cumulative irritation test, and two controlled use studies. In the modified Draize-Shelanski-Jordan RIPT, a series of 10 occlusive induction patches were applied on alternate days to 204 subjects (147 males, 57 females). These patches were left in place for 24 h and results were scored (max = 4) upon removal. After a 13-day nontreatment period, challenge patches were applied for 48 h to new sites on the back. Seven days later, a second challenge patch was applied for 48 h. Challenge site reactions were scored at 48 and 72 h. Mild erythema (score of 1) was noted in 16 subjects during induction and challenge; these reactions were considered isolated and clinically insignificant. Intense erythema (score of 2) was noted in a subject after the eighth induction patch. Open patches were used thereafter and no further reactions were observed. This was considered to be an example of nonspecific irritation typical of cleansing creams. The cleansing cream was nonirritating and nonsensitizing.[108]

In the 21-day cumulative irritation test using 12 subjects, occlusive patches containing the cream were applied daily for 21 consecutive days (patches applied on Saturday remained in place until Monday). Patches were applied to the back, removed

after 24 h, and reactions were scored immediately (max = 4). Solutions of 0.5 and 2% sodium lauryl sulfate were used as markers, and had total scores of 67 and 298 (max = 1008), respectively. The cream had a total score of 109 and was considered very mildly irritating.[109]

In the first controlled use study, the cream was used by 53 subjects on a daily basis for four weeks. One subject noted a feeling of "irritation" after a few days, although no specific erythema or dermatitis was evident. This subject discontinued use. No rash, itching, burning, or irritation was noted by the other subjects.[110]

In the second controlled use study, 24 subjects used the cream once or twice daily for two weeks. No adverse reactions were noted.[111]

Photoallergenicity

The photoallergenicity of CAA, CAP, and CADA was evaluated using 5 male and 25 female subjects (18–55 years). Distilled water served as the control. Each chemical was diluted to a concentration of 10% w/v in distilled water prior to testing. During induction, a total of nine duplicate applications of each chemical were made to the back three times per week for three weeks. Each site was covered for 24 h with a gauze pad secured with surgical tape. Within 10 min after each patch removal, sites were irradiated with UVA light (4.0 J/cm^2, 22–25 s). The application sites of 13 subjects were irradiated with twice the minimal erythemal dose of UVB light (2–5 min, 2–5 mJ/cm^2) immediately after UVA irradiation. UVA (320–400 nm) and UVB (290–320 nm) radiation was emitted from a 1000 W xenon arc solar simulator with appropriate filters. Reactions were scored 48 h after applications 1, 2, 4, 5, and 8, and 72 h after applications 3, 6, and 9 according to the scale: 0 (no evidence of any reaction) to 5 (vesicular/bullous eruption). The challenge phase was initiated two weeks after the conclusion of induction. Duplicate 24-h challenge applications of each test substance were made to new sites on the back. At the conclusion of exposure, half of the challenge patches applied (one per chemical) were removed and sites were irradiated with UVA light (4.0 J/cm^2, 22–23 s). Challenge patches were then removed from the remaining nonirradiated sites. Reactions were scored at approximately 24, 48, and 72 h after patch removal. Mild to moderate erythema, at either experimental or control induction sites, was observed in a total of 11 subjects. The 11 subjects were among the 13 exposed to UVA and UVB light. The authors stated that such reactions generally result from sunburn derived from UVB exposure. CAA, CAP, and CADA did not induce photoallergic reactions or delayed contact hypersensitivity in any of the subjects tested.[101]

SUMMARY

Cocoamphoacetate (CAA), Cocoamphopropionate (CAP), Cocoamphodiacetate (CADA), and Cocoamphodipropionate (CADP) are imidazoline-derived amphoteric organic compounds. These products are prepared by reacting coconut acid with aminoethylethanolamine to produce an imidazoline, which is then reacted with monochloracetic acid or monochloropropionic acid in the presence of sodium hydroxide to form the mono- (CAA and CAP) or dicarboxylated (CADA and CADP) products.

These amphoteric compounds are supplied as amber liquids containing 40 to 50% solids. The viscosity may be increased by the addition of sodium chloride. All are soluble in water and insoluble in nonpolar organic solvents; CAP and CADP are also soluble in alcohol. The pH range for commercially available solutions of CAA, CAP, CADA, and CADP has been reported to be from 8.1 to 10.2.

CAA, CAP, CADA, and CADP can be assayed by close match to standard infrared spectra and ionization curves.

The amphoteric compounds are used in cosmetics as surfactants, mild foaming and cleansing agents, detoxifying agents, and conditioners. These ingredients are present in cosmetics at concentrations ranging from ≤ 0.1 to 50%. Product use may lead to contact of all external body surfaces, hair, eyes, and mucous membranes; frequency and duration of application could result in continuous exposure.

The amphoteric compounds are used widely in industrial and household cleaning products.

In acute oral toxicity studies, CADA and CAA were nontoxic in rats and mice, CADP was nontoxic in rats, and CAP was nontoxic in mice. CADA and CADP were also nontoxic when fed to rats for 10 days at concentrations of 0.25 and 0.50% of the diet. An oral LD_{50} of 7.8 ml/kg was reported for mice dosed with 70% CADP (as commercially supplied).

In acute dermal toxicity studies, two shampoo creams containing 4.0% CADA had LD_{50}s >10.0 ml/kg. Primary signs of systemic toxicity included depression, labored respiration, and phonation upon handling. Moderate dermal irritation also was noted.

Results of Draize ocular irritation studies in rabbits were that these ingredients, as commercially supplied, varied widely in their ocular irritancy. CADA was moderately to severely irritating when eyes were not rinsed and practically nonirritating to mildly irritating when rinsed from the eye. CADP was practically nonirritating under unrinsed conditions. CAA was minimally to severely irritating and CAP was practically nonirritating to minimally irritating under unrinsed conditions. CADA also has distinct anti-irritant activity when used in formulations.

Single insult patch tests of these ingredients in rabbits with intact or intact and abraded skin have produced varying results. As commercially supplied, CADA and CAA were nonirritating to severely irritating, CADP was nonirritating, and CAP was slightly irritating. When intradermally injected into rabbits, CADA (1%) was nonirritating while CAA (0.1%), CADP (1%), and CAP (1%) were less irritating than the control shampoo.

CAA, at a concentration of 50% active, was nonsensitizing in guinea pigs when evaluated by the Magnusson-Kligman maximization test.

The mutagenic potential of CAP, CADA, and CADP was evaluated in the standard Ames assay with and without a metabolic activation system and with positive and negative controls. The three test compounds were not mutagenic.

In a clinical ocular study, 1, 3, and 10% dilutions of a shampoo containing 28.1% CADA (32% active) were no more irritating to the human eye than sterile distilled water. CAA and CAP (concentrations = 10% in distilled water) were nonirritating and nonsensitizing in a repeated insult patch test (RIPT) involving 141 subjects; nonocclusive patches were applied. In other RIPTs, products containing CADA at concentrations of 0.61 to 28.1% were essentially nonirritating and nonsensitizing under semiocclusive conditions. These products did produce some irritation under occlusive patch conditions. A facial cleanser containing 25% CADA (45.6% active) produced no adverse

reactions in 54 subjects using the product twice daily for one month. Cleansing creams containing 5% CADP were nonirritating and nonsensitizing in 204 subjects evaluated by RIPT (occlusive), very mildly irritating in 12 subjects evaluated by a 21-day cumulative irritation test (occlusive), and nonirritating in 53 and 24 subjects using the products daily for one month or once or twice daily for two weeks, respectively. In the maximization test, a hair product (diluted to 0.1% CADP) did not induce sensitization in any of the 25 subjects tested. CAA, CAP, and CADA (concentrations = 10% in distilled water) did not induce photoallergic reactions or delayed contact hypersensitivity in a study involving 30 subjects.

DISCUSSION

The Expert Panel recognizes that Cocoamphoacetate, Cocoamphopropionate, Cocoamphodiacetate, and Cocoamphodipropionte, as commercially supplied, induced mild to severe ocular irritation in the Draize test and, also, that cosmetic products containing these ingredients are buffered.

Mutagenicity data on Cocoamphoacetate were not available. However, the Expert Panel concluded that this ingredient was not mutagenic, based on negative Ames test results for Cocoamphodiacetate.

CONCLUSION

Based upon the available data included in this report, the Expert Panel concludes that CAA, CAP, CADA, and CADP are safe as cosmetic ingredients in the present practices of use.

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Final Report of the Cosmetic Ingredient Review Expert Panel

Amended Safety Assessment of Dodecylbenzenesulfonate, Decylbenzenesulfonate, and Tridecylbenzenesulfonate Salts as Used In Cosmetics

March 24, 2009

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Amended Safety Assessment of Dodecylbenzenesulfonate, Decylbenzenesulfonate, and Tridecylbenzenesulfonate Salts as Used In Cosmetics

Abstract: Sodium Dodecylbenzenesulfonate is one of a group of salts of alkylbenzene sulfonates used in cosmetics as surfactant-cleansing agents. Sodium Dodecylbenzenesulfonate is soluble in water and partially soluble in alcohol, with dermal absorption dependent on pH. Docedylbenzenesulfonate salts are not toxic in single-dose oral and dermal animal tests, and no systemic toxicities were observed in repeat-dose dermal animal studies. For example, in dermal animal studies, no evidence of reproductive or developmental toxicity was reported. At high concentrations, Dodecylbenzenesulfonate salts were severely irritating to the skin of animals and humans, but they were not skin sensitizers in animal or clinical tests.The CIR Expert Panel concluded that the irritant properties of these ingredients are similar to those of other detergents, with severity dependent on concentration and pH. Products containing these ingredients should be formulated to ensure that the irritancy potential is minimized.

INTRODUCTION

The Cosmetic Ingredient Review (CIR) Expert Panel reviewed the safety of Sodium Dodecylbenzenesulfonate, TEA-Dodecylbenzenesulfonate, Sodium Decylbenzenesulfonate as used in cosmetics in an earlier report, with the conclusion that these ingredients were safe as cosmetic ingredients in the [then] present practices of use (Elder 1993).

In a routine re-review of this earlier safety assessment, the CIR Expert Panel determined that the available data were sufficient to support the safety of the entire group of salts of sulfonated alkylbenzenes used in cosmetics. Accordingly, this safety assessment has been expanded to include:

- Ammonium Dodecylbenzenesulfonate,
- Calcium Dodecylbenzenesulfonate,
- DEA-Dodecylbenzenesulfonate,
- Isopropylamine Dodecylbenzenesulfonate,
- Magnesium Isododecylbenzenesulfonate,
- MIPA-Dodecylbenzenesulfonate,
- Potassium Dodecylbenzenesulfonate,
- Sodium Decylbenzenesulfonate,
- Sodium Dodecylbenzenesulfonate,
- Sodium Tridecylbenzenesulfonate,
- TEA-Dodecylbenzenesulfonate (TEA-DDBS), and
- TEA-Tridecylbenzenesulfonate.

Sodium Dodecylbenzenesulfonate is a linear alkylbenzene sulfonate. As described in the original safety assessment (Elder 1993), linear alkylbenzene sulfonate (LAS) is not a specific chemical name but the name has been used to describe the material studied in several publications. LAS can be considered to have an average molecular weight close to that of Sodium Dodecylbenzenesulfonate, but could contain some of alkyl groups of similar size. Also, the point of attachment of the benzene ring to the alkyl chain would be distributed along the chain, with attachment at the number 2 carbon being prominent; several isomers would be present. Data from 3 manufacturers reported in the original safety assessment, for example, demonstrated that a 12-carbon chain length moiety comprises 18.1% to 35% and a 10-carbon chain length moiety comprises 0.5% to 20.6% of commercial LAS products.

The CIR Expert Panel also has reviewed the safety of several ingredients that form a portion of the ingredient structures addressed in this safety assessment. These include DEA (diethanolamine), TEA (triethanolamine), and MIPA (monoisopropanolamine). **Table 1** list these and related ingredients and the conclusion regarding safety reached by CIR.

CHEMISTRY

Definition and Structure

The definitions and technical/other names of the cosmetic ingredients included in this assessment as given in the *International Cosmetic Ingredient Dictionary and Handbook* (Gottschalck and Bailey 2008) are listed in **Table 2**. All of these ingredients are in the chemical class alkyl aryl (benzene) sulfonates and function as surfactant - cleansing agents.

Figure 1 shows the structures of the cosmetic ingredients addressed in this safety assessment.

Sodium Decylbenzenesulfonate is also known as Decyl Benzene Sodium Sulfonate and Sodium Decylbenzenesulfonamide (Sweet 1987).

Sodium Dodecylbenzenesulfonate is also known as Dodecyl Benzene Sodium Sulfonate; Dodecylbenzenesulphonate, Sodium Salt; Sodium Laurylbenzenesulfonate (Sweet 1987); and Dodecylbenzene Sodium Sulfonate (Windholz et al. 1983).

TEA-Dodecylbenzenesulfonate is also known as Linear Alkylbenzene Sulfonate and Triethanolamine Salt (Hunting 1983).

Photodegradation

Murakami et al. (1992) reported that Sodium Dodecylbenzenesulfonate exposed to a combination of ultraviolet radiation (UVR) and ozone for 4 h breaks down into formaldehyde and glyoxal. When exposed to UVR and ozone for up to 10 h, linear dodecylsulfonates decreased in a linear manner up to 5 h while the concentrations of formaldehyde and glyoxal increased until ~5 h then decreased. When exposed to ozone alone, linear dodecylsulfonates decreased in a linear manner for up to 15 h and formaldehyde and glyoxal increased and leveled off at ~7 h. The concentrations for formaldehyde and glyoxal were lower when just exposed to ozone and not UVR.

Table 1. Cosmetic ingredients with DEA, MIPA, or TEA reviewed by CIR.

Ingredient	Conclusion	Reference
	DEA and TEA	
TEA and DEA	Safe in rinse off products; safe at less than 5% in leave on products; should not be used where N-nitroso compounds could be formed	Elder 1983b
	DEA containing ingredients	
Cocamide DEA	Safe in rinse off products; safe at less than 10% in leave on products; should not be used where N-nitroso compounds could be formed	Elder 1986
	Safe in rinse off products; safe at less than 10% in leave on products; should not be used where N-nitroso compounds could be formed	Andersen 1996
Isostearamide DEA	Safe in rinse off products; safe at less than 40% in leave on products (which would limit ethanolamines to 5%); should not be used where N-nitroso compounds could be formed	CIR 1995
Lauramide DEA	Safe in rinse off products; safe at less than 10% in leave on products; should not be used where N-nitroso compounds could be formed	Andersen 1996
Linoleamide DEA	Safe in rinse off products; safe at less than 10% in leave on products; should not be used where N-nitroso compounds could be formed	Andersen 1996
Myristamide DEA	Safe in rinse off products; safe at less than 40% in leave on products (which would limit ethanolamines to 5%); should not be used where N-nitroso compounds could be formed	CIR 1995
Stearamide DEA	Safe in rinse off products; safe at less than 40% in leave on products (which would limit ethanolamines to 5%); should not be used where N-nitroso compounds could be formed	CIR 1995
	TEA containing ingredients	
TEA-Cocoyl Hydrolyzed Collagen	Safe as a cosmetic ingredient	Elder 1983a
	Confirmed	Andersen 2005
TEA-EDTA	Safe as a cosmetic ingredient	Andersen 2002
TEA-Lauryl Sulfate	Safe up to 10.5%, formulate to not cause irritation	Elder 1982
	MIPA	
MIPA[a] Monisopropanolamine,	Safe as cosmetic ingredients	Elder 1987
	Confirmed	Andersen 1996

[a] Included Diisopropanolamine, Triisopanolamine, and Mixed Isopropanolamines

Table 2. The definition of and technical/other names listed in the *International Cosmetic Ingredient Dictionary and Handbook* for the ingredients that are included in this safety assessment (Gottschalck and Bailey 2008).

Ingredient (CAS No.)	Definition	Technical/other names
Ammonium Dodecylbenzenesulfonate (CAS No. 1331-61-9)	substituted aromatic compound with structure shown in Figure 1	• Ammonium Lauryl Benzene Sulfonate and • Benzenesulfonic Acid, Dodecyl-, Ammonium Salt
Calcium Dodecylbenzenesulfonate (CAS No. 26264-06-2)	substituted aromatic compound with structure shown in Figure 1	• Benzenesulfonic Acid, Dodecyl-, Calcium Salt and • Dodecylbenzenesulfonic Acid, Calcium Salt
DEA-Dodecylbenzenesulfonate (CAS No. 26545-53-9)	diethanolamine salt of dodecylbenzene sulfonic acid (q.v.) with the structure shown in Figure 1	• Benzenesulfonic Acid, Dodecyl-, Compd. with 2,2'-Iminobis[Ethanol](1:1) and • Diethanolamine Dodecylbenzene Sulfonate
Isopropylamine Dodecylbenzenesulfonate (CAS No 26264-05-1)	salt of isopropylamine and dodecylbenzene sulfonic acid (q.v.) with the structure shown in Figure 1	• Benzenesulfonic Acid, Dodecyl-, Compd. with 2-Propanamine (1:1); • Dodecylbenzenesulfonic Acid, Comp. with 2-Propanamine (1:1); and • Isopropylammonium Dodecylbenzenesulfonate
Magnesium Isododecylbenzenesulfonate (CAS No. 27479-45-4)	organic compound with structure shown in Figure 1	• None listed
MIPA-Dodecylbenzenesulfonate (CAS No. 42504-46-1, 54590-52-2)	monoisopropanolamine salt of a substituted aromatic compound with structure shown in Figure 1	• Benzenesulfonic Acid, Dodecyl-, Compd with 1-Amino-2-Propanol (1:1) and • Monoisopropanolamine Dodecylbenzenesulfonate
Potassium Dodecylbenzensulfonate (CAS No. 27177-77-1)	substituted aromatic compound with structure shown in Figure 1	• Benzenesulfonic Acid, Dodecyl-, Potassium Salt and • Dodecylbenzenesulfonic Acid, Potassium Salt
Sodium Decylbenzenesulfonate (CAS No. 1322-98-1)	substituted aromatic compound with structure shown in Figure 1	• Benzenesulfonic Acid, Decyl-, Sodium Salt and • Decylbenzenesulfonic Acid, Sodium Salt
Sodium Dodecylbenzenesulfonate (CAS No 25155-30-0)	substituted aromatic compound with structure shown in Figure 1	• Sodium Lauryl Benzene Sulfonate; • Benzenesulfonic Acid, Dodecyl-, Sodium Salt; • Dodecylbenzenesulfonic Acid, Sodium Salt; and • Sodium Lauryl Phenyl Sulfonate
Sodium Tridecylbenzenesulfonate (CAS No. 26248-24-8)	substituted aromatic compound with structure shown in Figure 1	• Benzenesulfonic Acid, Tridecyl-, Sodium Salt and • Tridecylbenzenesulfonic Acid, Sodium Salt
TEA-Dodecylbenensulfonate (CAS No. 27323-41-7)	substituted aromatic compound with structure shown in Figure 1	• Benzenesulfonic Acid; Dodecyl-, Compd with 2,2'2"-Nitrilotris [ethanol] (1 :1); • Dodecylbenzenesulfonic Acid, Compd with 2,2',2"-Nitrilotris[Ethanol] (1 :1); and • Triethanolamine Dodecylbenzenesulfonate
TEA-Tridecylbenzenesulfonate (CAS No. 59599-58-5, 61886-59-7)	substituted aromatic compound with structure shown in Figure 1	• Benzenesulfonic Acid, Tridecyl-, Compd. with 2,2',2"-Nitrilotris[Ethanol](1:1); • Tridecylbenzenesulfonic Acid, Compd. with 2,2',2"-Nitrolotris [Ethanol](1:1); and • Triethanolamine Tridecylbenzenesulfonate

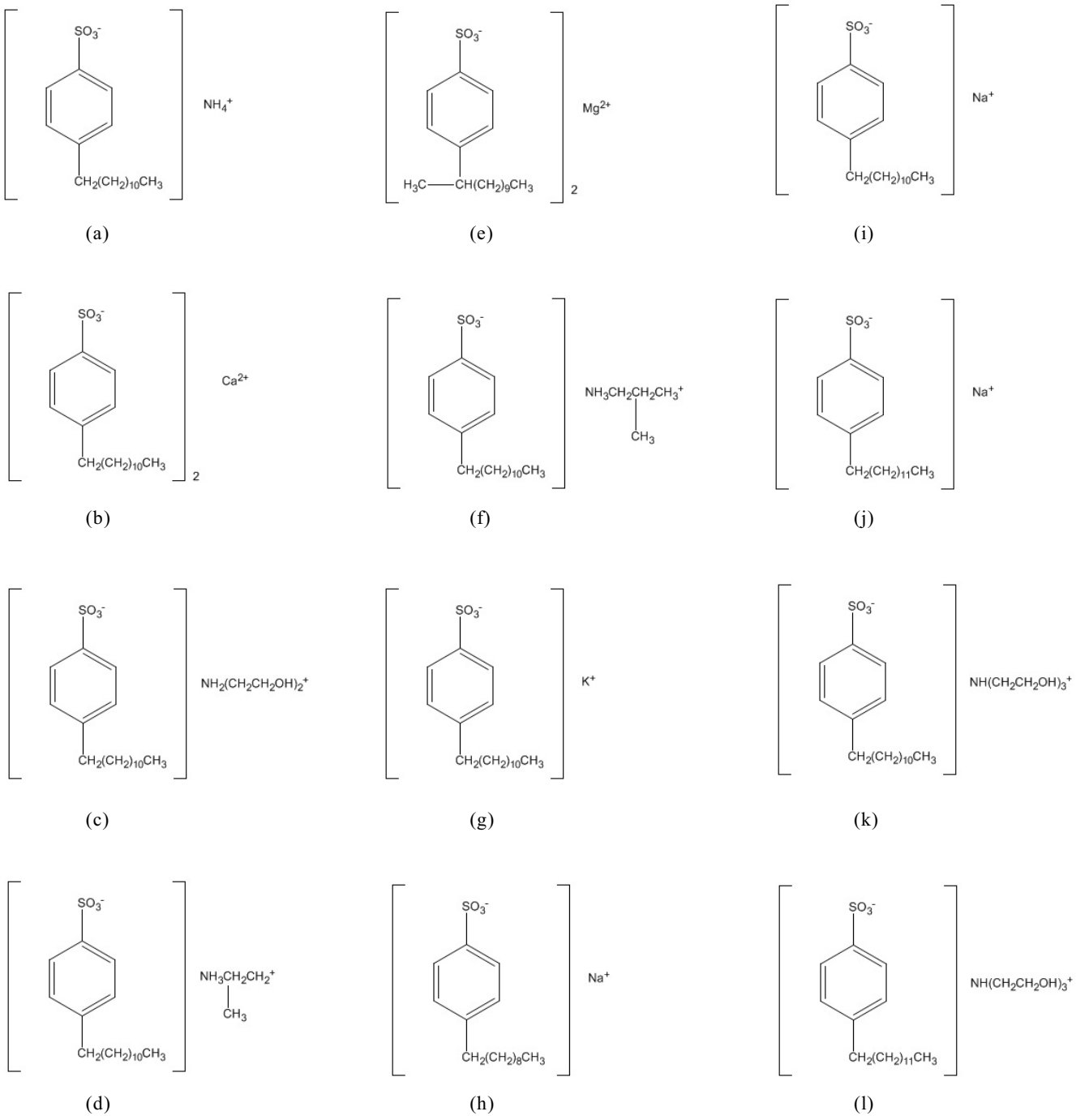

Figure 1. Chemical structures for salts of alkylbenzene sulfonates: (a) Ammonium Dodecylbenzenesulfonate, (b) Calcium Dodecylbenzenesulfonate,(c) DEA-Dodecylbenzenesulfonate, (d) Isopropylamine Dodecylbenzenesulfonate, (e) Magnesium Isododecylbenzenesulfonate, (f) MIPA-Dodecylbenzenesulfonate, (g) Potassium Dodecylbenzenesulfonate, (h) Sodium Decylbenzenesulfonate, (i) Sodium Dodecylbenzenesulfonate (j) Sodium Tridecylbenzenesulfonate, (k) TEA-Dodecylbenzenesulfonate, (l) TEA-Tridecylbenzenesulfonate.

Murakami et al. (1996) reported that Sodium Dodecylbenzenesulfonate (3,490 µg/ml) exposed to UVR and ozone for 4 h decreased to 16 µg/ml and formaldehyde was present at 63.0 µg/ml and glyoxal at 38.3 µg/ml.

Xia et al. (2002) reported that the photocatalytic degradation rates of Sodium Dodecylbenzenesulfonate with titanium oxide (TiO_2) was affected by added anions. Cl-, SO_4^{2-}, NO^{3-}, and HCO^{3-} as NaCl, $NaSO_4$, $NaNO_3$, and $NaHCO_3$ (12 or 36 mmol/l) retarded the rates of linear dodecylsulfonates degradation at different degrees. PO_4^{-3} increased the degradation rate at the lower concentration but not the higher. The authors concluded that the mechanisms for this effect were: anions compete for the radicals, anions are absorbed on the surface of the catalyst and lock the active site of the catalyst, and anions added to the solution change the pH value and influence the formation of ·OH radicals and the adsorption of linear dodecylsulfonates on the catalyst.

Chemical and Physical Properties

Sodium Dodecylbenzensulfonate is commercially available as a yellow colored slurry or off-white dry product (CTFA 1991a). The slurry is usually 30% to 50% active (percentage activity defined as solids minus salts (Nikitakis 1990). Slurries with activity >50% contain a hydrotrope, usually sodium xylene sulfonate, for easier handling (CTFA 1991a). The dry product, which can be in the form of a powder, flake, or bead, is usually 40% to 90% active. The chemical and physical properties of SDDBS are summarized in **Table 3**.

TEA-Dodecylbenzenesulfonate is a clear yellow liquid that is commercially available as 40% to 60% aqueous solutions (CTFA 1991b). Properties of TEA-DDBS are also summarized in Table 3.

Sodium Decylbenzenesulfonate has a molecular weight of 320.46 (Sweet 1987).

Chemical and physical properties were not available for the other ingredients in this safety assessment.

Manufacture and Production

Sodium Dodecylbenzenesulfonate is made by reacting dodecylbenzene with sulfuric acid (Oleum process) or air/SO_2, to produce dodecylbenzene sulfonic acid (CTFA 1991a). The dodecylbenzenesulfonic acid is then neutralized with sodium hydroxide. SDDBS is then sold as a slurry. It can be dried by a drum drier to form flakes and powders or dried by a spray drier to form beads.

TEA-Dodecylbenzesulfonate is made by reacting dodecylbenzenesulfonate with sulfuric acid (Oleum process) and air/SO_2, to produce dodecylbenzene sulfonic acid (CTFA 1991 b). The dodecylbenzene sulfonic acid is then neutralized with triethanolamine.

Linear Alkylbenzene Sulfonate is made by the sulfonation of straight-chain alkylbenzenes prepared from petroleum distillates (Buehler et al. 1971).

In 1987, approximately 2.15 billion pounds of linear alkylbenzene sulfonate were used in North America, Western Europe, and Japan, with Dodecylbenzene Sulfonate being the most widely used (Greek and Layman 1989).

Analytical Methods

Sodium Dodecylbenzenesulfonate was analyzed by high-pressure liquid chromatography (HPLC) and Karl Fisher titration (Coy et al. 1990).

Two-phase titration can be used for the determination of total cationic or anionic surfactants in mixtures (Mohammed and Cantwell 1980; Tsubouchi and Mallory 1983).

Linear Alkylbenzene Sulfonate was determined by HPLC (Yoshikawa et al. 1984); by spectroscopic methods, particularly HPLC with UV detection; by chromatographic techniques; by spectrophotometric methods, especially the assay for methylene blue active substances (MBAS); by volumetric methods; by potentiometric methods; and by physicochemical methods (Arthur D. Little, Inc. 1991). MBAS and spectrophotometric methods are considered to be inadequate for trace surfactant measurements requiring identification of specific surfactants and isomers.

Impurities

Sodium Dodecylbenzenesulfonate contains impurities that include neutral oil (unsulfonated materials), arsenic (As), iron (Fe), and lead (Pb) (Estrin et al. 1982).

TEA-Dodecylbenzenesulfonate contains sulfates (as TEA hydrosulfate) at a maximum of 4.0% (Elder 1983b).

Linear Alkylbenzenesulfonates are produced by the alkylation of benzene, which results in a number of side reactions (Arthur D. Little, Inc. 1991). Some of the dialkylbenzenes that result from the side reactions could not be separated from the primary product with ease and, following sulfonation, remained in commercial Linear Alkylbenzenesulfonates. Other dialkylbenzenes and the diphenylalkanes that form as products of the side reactions boil at temperatures sufficiently above the linear monoalkylbenzene, facilitating their removal.

Six samples of commercial *Linear Alkylbenzenesulfonates* were analyzed for dialkyltetralins and dialkylnaphthalenes (Vista Chemical Co. 1992a). These compounds were detected as impurities in concentrations ranging from 0% to 15% and 0% to 0.25%, respectively. Gas chromatography and mass spectral analysis also revealed the presence of dialkylindanes in these Linear Alkylbenzenesulfonates samples; however, the concentration of these impurities amounted to only about 1/10 of that of alkyltetralins.

Ultraviolet Absorbtion

Three commercial samples of Linear Alkylbenzene Sulfonate, dissolved in water at concentrations up to 1.0 g/l, did not absorb in the UVB region of the spectrum. All absorption maxima were in the UVC region; λmax 218-224, λmax 254-255, and λshoulder 260-261 (Vista Chemical Company 1992b).

USE

Cosmetic

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Ingredient Reporting Program (VCRP) in the original report, Sodium Dodecylbenzenesulfonate was used in a total of 45 cosmetic products in 1992. Use concentrations were not reported (Elder 1993).

Table 3. Physical and chemical properties of Sodium Dodecylbenzensulfonate, Sodium Decylbenzenesulfonate, TEA-Dodecylbenzenesulfonate, and Linear Alkylbenzene Sulfonates.

Property	Value	Reference
	Sodium Dodecylbenzenesulfonate	
Physical appearance	Yellow colored slurry or off-white dry product (powder, flakes, or beads)	CTFA 1991a
	Pale yellow paste or slurry, spray-dried powder, or as a flake	Hunting 1983
Odor	Bland	Estrin et al. 1982
% Active Slurry	30 - 50%	CTFA 1991a
	Usually 30% - 60%	Hunting 1983
Dried product	40% - 90%	CTFA 1991a
	~90%	Hunting 1983
Molecular weight	349	CTFA 1991a
	348.52	Sweet 1987
	348.49	Windholz et al. 1983
Solubility	Water dispersible, soluble at low concentrations	Hunting 1983
	Soluble in water; partially soluble in alcohol	Estrin et al. 1982
Stability	Stable in the presence of a strong acid and base; generally non-reactive and does not polymerize	CTFA 199a
Specific gravity (at 25°C)	Slurry: 1.02 - 1.05; dry product: 0.45 - 0.65	CTFA 1991a
pH		
10%	Slurry: 7 - 8; dry product: 7 - 9	CTFA 1991a
1% aqueous solution	7.0 - 9.0	Estrin et al. 1982
Impurities		
Neutral oil	1% maximum	
Arsenic (as As)	3 ppm maximum	
Iron (as Fe)	10 ppm maximum	
Lead (as Pb)	20 ppm maximum	
Moisture	3.5% maximum	Estrin et al. 1982
Ionic type	Anionic	Hunting 1983
	Sodium Decylbenzenesulfonate	
Molecular weight	320.46.	Sweet 1987

Table 3. Physical and chemical properties of Sodium Dodecylbenzensulfonate, Sodium Decylbenzenesulfonate, TEA-Dodecylbenzenesulfonate, and Linear Alkylbenzene Sulfonates.

Property	Value	Reference
	TEA-Dodecylbenzenesulfonate	
Physical appearance	Clear yellow liquid	CTFA 1991b
	Clear yellow or amber liquid	Hunting 1983
	Clear, pale yellow viscous liquid	Estrin et al. 1982
Odor	Mild, slightly oily	Estrin et al. 1982
% Activity	40% - 60%	CTFA 1991a
	50% - 60%	Hunting 1983
Aqueous solution	60%	Estrin et al. 1982
Molecular weight	475	CTFA 1991b
	476.77	Sweet 1987
Solubility	Soluble in water	Hunting 1983
	Soluble in water and alcohol	Estrin et al. 1982
Stability	Stable under normal cosmetic use conditions	CTFA 1991b
Specific gravity (at 25°/25°C)	1.08	Estrin et al. 1982
pH		
10%	5.5 - 7.5	CTFA 1991b
At 25°C	6.8 - 7.5	Estrin et al. 1982
Viscosity (at 25°C)	6.8 - 7.5	Estrin et al. 1982
Assay (average molecular weight 462)	54% - 60%	Estrin et al. 1982
Impurities		
Sulfates (as TEA hydrosulfate)	4.0% maximum	Estrin et al. 1982
Water	3% - 42%	Estrin et al. 1982
	Linear Alkylbenzene Sulfonates	
Impurities	Dialkyltetralin, dialkylnaphthalene, and to a lesser extent dialkylindane may be present in the final product	Vista Chemical Co. 1992a

Currently, VCRP data indicated that Sodium Dodecylbenzenesulfonate is used in 12 cosmetic products (FDA 2007). A survey of current use concentrations conducted by the Personal Care Products Council (Council) reported a range from 2% to 3% (Council 2008).

Based on VCRP data, TEA-Dodecylbenzenesulfonate was used in a total of 54 cosmetic products at the time of the first safety assessment (Elder 1993). Currently, VCRP indicated that it is used in 39 products (FDA 2007) at concentrations ranging from 0.002% to 3% (Council 2008).

Sodium Decylbenzenesulfonate is reported to be use at a concentration of 0.02% (Council 2008).

Available use and use concentration data are listed in **Table 4**.

There were no reported uses or use concentrations for Ammonium Dodecylbenzenesulfonate, Calcium Dodecylbenzenesulfonate, DEA-Dodecylbenzenesulfonate, Isopropylamine Dodecylbenzenesulfonate, Magnesium Isodecylbenzenesulfonate, MIPA-Dodecylbenzenesulfonate, Potassium Dodecylbenzenesulfonate, Sodium, and TEA-Tridecylbenzenesulfonate.

Straight-chain sodium alkylbenzenesulfonate is on the list of quasi-drugs in Japan (Ministry of Health, Labor and Welfare [MHLW] 2001).

Non-Cosmetic

Sodium Dodecylbenzensulfonate is used as a detergent in hospitals (Tsubouchi and Mallory 1983) and as an industrial neutral cleansing agent (Itokawa et al. 1973). Large quantities of Dodecylbenzene Sulfonates are used in household detergent and dishwashing products (Hunting 1983). Almost 80% of the total U.S. production of LAS is used in household products (Arthur D. Little 1991).

Table 4. Historical and current cosmetic product uses and concentrations[a] for Ingredient Sodium Dodecylbenzenesulfonate, TEA-Dodecylbenzenesulfonate, and Sodium Decylbenzenesulfonate.

Product Category (FDA 2008)	1992 uses (Elder 1993)	2007 uses (FDA 2007)	2008 concentrations (The Council 2008) (%)
	Sodium Dodecylbenzensulfonate		
Baby products			
Other	-	-	3
Bath products			
Oils, tablets, and salts	-	1	-
Soaps and detergents	6	9	3
Bubble baths	33	1	-
Other personal cleanliness products	3	-	-
Eye makeup			
Eyeliners	3	-	2
Other	-	1	-
Total uses/ranges for Sodium Dodecylbenzenesuflonate	**45**	**12**	**2-3**
	TEA-Dodecylbenzenesulfonate		
Baby products			
Shampoos	-	-	0.02
Noncoloring hair care products			
Conditioners	-	-	0.01-0.02
Shampoos	18	6	0.002-5
Tonics, dressings, etc.	-	-	0.003
Hair coloring products			
Dyes and colors	36	31	-
Skin care products			-
Skin cleansing creams, lotions, liquids, and pads	-	1	0.9
Moisturizers	-	1	-
Total uses/ranges for TEA-Dodecylbenzenesuflonate	**54**	**39**	**0.002-5**
	Sodium Decylbenzenesulfonate		
Skin care products			
Moisturizers	n/a	-	0.02
Total uses/ranges for Sodium Decylbenzenesuflonate	**n/a**	**-**	**0.02**

[a] Concentration of use was not recorded at the time of the first assessment.

Sodium Dodecylbenzenesulfonate was used in a microemulsion system with butanol and decane to partition cytochrome *c* between an aqueous phase in equilibrium (Jolivalt et al. 1993).

Tsukatani et al. (2006) suggested that Dodecylbenzenesulfonate anions have a possible use as a chelate extraction solvent.

Sodium *n*-Dodecylbenzenesulfonate is used in the removal of heavy metals (Tokuyama and Iwama 2007).

As given in the Code of Federal Regulations (CFR), FDA has approved Sodium Dodecylbenzenesulfonate and Linear Alkylbenzene Sulfonate as chemicals used in washing or to assist in the peeling of fruits and vegetables at levels not to exceed 0.2 percent in wash water. May be used in washing or to assist in the lye peeling of fruits and vegetables (21CFR Sec. 173.315).

GENERAL **BIOLOGY**

Absorption, Distribution, Metabolism and Excretion

Sodium Dodecylbenzenesulfonate

Six female Colworth-Wistar rats were dosed with either 0.1 or 0.5 ml ^{14}C-Sodium Dodecylbenzenesulfonate; 3 animals were dosed by i.p. injection and 3 animals by s.c. injection (Howes 1975).

The animals were killed 24 h after being dosed. Both the i.p. and s.c. administrations had the same rate and route of excretion. After 24 h, 78 ± 4% of the dose was recovered in the urine, 1.5 ± 0.6% was recovered in the feces, and <0.1% was recovered in expired CO_2. In the carcass, 22 ± 5% was recovered after 24 h.

^{14}C-Sodium Dodecylbenzenesulfonate was used to determine the distribution and elimination of Sodium Dodecylbenzenesulfonate in rats; the location of the ^{14}C in the molecule was not stated (Lay et al. 1983). Twelve male Wistar rats were fed ^{14}C-Sodium Dodecylbenzenesulfonate in the diet, ad libitum, at a concentration of 1.4 mg/kg for 35 days. Every 24 h, feed consumption was measured and urine and feces were collected. On day 35, 6 of the rats were killed and a determination of radioactive residues was made. The remaining 6 rats were kept for 1 wk to determine clearance.

During the test period, the rats consumed approximately 34.66 µg ^{14}C-Sodium Dodecylbenzenesulfonate daily; the ^{14}C was excreted rapidly. A total of 81.8% of the ^{14}C was excreted; 52.4% in the feces and 29.4% in the urine. During the clearance period, 6.55% of the remaining ^{14}C was excreted in the feces and 1.27% was excreted in the urine, for a total of 7.82%. The fecal and urinary ^{14}C-Sodium Dodecylbenzenesulfonate-derived activity consisted of highly polar metabolites. Approximately 90% of the ^{14}C in the feces and 65% in the urine was recovered, and unchanged Sodium Dodecylbenzenesulfonate was not detected.

All the tissues examined after 35 days of treatment had small but significant amounts of ^{14}C residue. The relatively high concentrations in the colon and small intestine suggested the excretion of ^{14}C in the bile.

In another experiment, 8 male Wistar rats received a single intraperitoneal (i.p.) injection of 384.7 µg ^{14}C-Sodium Dodecylbenzenesulfonate in a 0.6% NaCl solution. Feces and urine were monitored for 10 days for ^{14}C excretion. On day 1, 84.7% of the dose was excreted, 35.0 ± 4.6% in the feces and 49.7 ± 5.7% in the urine. During days 2 through 10, ^{14}C was primarily excreted in the feces. By day 10, 94.5% of the dose was excreted. The fecal and urinary ^{14}C-Sodium Dodecylbenzenesulfonate-derived activity consisted of highly polar metabolites (Lay et al. 1983).

Linear Alkylbenzenesulfonate

Michael (1968) orally administered ^{35}S-labeled LAS (0.6, 1.2, 8.0, or 40.0 mg; 1.0 ml) to male albino Charles River rats (n = 3 or 5) after fasting. The animals were housed individually and urine and feces were collected daily for 3 days. The rats were then killed, radioassayed and necropsied. After 3 days, radioactivity from the test substance was detected in the urine at 40.2%, 57.7%, 40.2%, and 41.7% for 0.6, 1.2, 8.0, or 40.0 mg, respectively and in the feces at 56.1%, 38.9%, 41.1% and 43.5%, respectively. After 3 days, no ^{35}S residue (< 0.1% of the dose) could be detected in the carcasses that received the 40 mg dose.

The route of absorption was investigated by the oral administration of ^{35}S-Linear Alkylbenzene Sulfonate(40 mg) to thoracic duct-cannulated rats (n = 3). Lymph was collected in a single 42-h fraction. ^{35}S was detected in the lymph collected (1.6% of total). The author concluded that absorption was from the gastrointestinal tract and transported by some route other than the lymphatic system.

The ability of the rats to absorb Linear Alkylbenzene Sulfonate (1.2 mg) administered orally was determined in bile-duct ligated rats. The urine and feces were collected for 90 h. The test substance (83% recovered) was excreted mostly in the urine (89% of ^{35}S recovered) and not the feces (11%). The author stated that this indicates absorption from the gastrointestinal tract.

In bile duct-canulated rats (n =2) fed ^{35}S-Linear Alkylbenzene Sulfonate (1.2 mg), 46% of the recovered test substance was detected in the urine, 29% in the feces, and 25% in the bile. Recovery was 90%.

In another experiment, the proximal end of the bile duct was cannulated on rat 1 which then fed into the distal end of the bile duct of rat 2. Rat 1 was then administed Linear Alkylbenzene Sulfonate (1.2 mg) by stomach tube. Bile was collected from an additional cannula in rat 2. Urine and feces were collected from both rats for 90 h. The ^{35}S-containing compounds that were excreted in the bile of rat 1 and transferred to rat 2 were completely absorbed from the gastrointestinal tract of rat 2; nearly 2/3 of this activity was excreted in the bile of rat 2. The author concluded that 89 to 90% of an oral dose of Linear Alkylbenzene Sulfonate was readily adsorbed from the gastrointestinal tract (Michael 1968).

Four adult rhesus monkeys, 2 males and 2 females, were administered 30 mg/kg ^{14}C-Linear Alkylbenzene Sulfonate in aqueous solution, approximately 25 µCi, by oral intubation to study the excretion of ^{14}C-Linear Alkylbenzene Sulfonate (Cresswell et al. 1978). Urine was collected 0-8 and 8-24 h after dosing, and then at 24 h intervals for 4 days; feces were collected at 24 h intervals for 5 days. Blood samples were taken 30, 48, 72, and 96 h after dosing. To determine plasma radioactivity concentrations, blood samples were drawn prior to dosing, at various times within the initial 24 h period following dosing, and then at 24 h intervals until radioactivity concentrations were below the limit of detection.

The majority of the radiolabel was excreted within 24 h of administration. In the first 24 h, male monkeys eliminated 66.5% and female monkeys eliminated 72.1% of the radioactivity in urine. Over 5 days, the total amount excreted in the urine by male and female monkeys was 68.3% and 74.0%, respectively. The male monkeys excreted 14.9% and the female monkeys 12.7% of the ^{14}C-Linear Alkylbenzene Sulfonate in the feces in the first 24 h; over the 5 day period, these values were 25.9% and 20.3%, respectively.

Approximately 5% of the dose was recovered in cage washing and debris. The mean overall recovery of radioactivity was 100.3%. After 30 h, the mean plasma radioactivity concentration was 1.5 µg/ml; this value decreased to 0.2 µg/ml after 96 h.

The same animals were used to study plasma concentrations (CresswelI et al. 1978). The animals were administered single oral doses of 150 mg/kg or 300 mg/kg ^{14}C-Linear Alkylbenzene Sulfonate, both ~ 26 µCi, at intervals of 2 to 3 weeks. Approximately 2 to 3 weeks after the last single dose, each animal received 7 consecutive daily oral doses of ^{14}C-Linear

Alkylbenzene Sulfonate at a dose of 30 mg/kg, approximately 28 µCi/day, in water.

To determine plasma concentrations, blood samples were taken prior to the first of these doses and at various intervals for the first 7.5 h afterwards. Blood samples were also taken immediately before administration of the remaining doses. After the last dose, samples were taken at various times until the animals were killed. The animals were killed 2, 4, 24, or 48 h after the last dose.

After a single oral dose of 150 mg/kg ^{14}C-Linear Alkylbenzene Sulfonate, plasma radioactivity concentrations reached a maximum mean plasma concentration of 0.0056% dose/ml (41.2 µg/mI) at 4 h. The concentrations decreased during the 6 to 24 h period and were below the limit of detection, <0.0001% dose/ml or <1.0 µg/ml, at 48 h. The mean half-life was ~6.5 h.

After the single 300 mg/kg dose, mean plasma concentrations of radioactivity reached a maximum of 0.0024% dose/ml, 36.3 µg/ml, at 4 h. Plasma concentrations decreased during 6 to 24 h and the mean concentrations were below the limits of detection at 48 h. The mean half-life was approximately 5.5 h.

After the first daily 30 mg/kg dose, a maximum mean plasma concentration of 33.6 µg/ml was reached at 4 h; this value decreased to 1.8 µg/ml at 24 h. The mean elimination half-life was ~ 5 h. The predose concentration on the following 5 days did not increase. The mean concentration 24 h after the sixth dose was 2.2 µg/ml. After the seventh dose, the maximum mean plasma concentration was 43.5 µg/ml at 4 h; this value decreased until 24 h. The mean half-life was ~6 h.

Plasma concentrations in the male and female monkeys killed 24 and 48 h after the last dose were 2.4 and 1.0 µg/ml, respectively. In the monkey killed 2 h after the last of the 7 consecutive doses, there were high concentrations of radioactivity in the stomach, liver, kidneys, lungs, pancreas, adrenal glands, and pituitary gland. After 4 h, the concentrations were decreased in all of these tissues except for the pituitary gland, in which the concentration had increased; the concentrations also were increased in the heart, brain, gonads, eyes, spleen, thyroid gland, and subcutaneous (s.c.) fat. After 24 h, the concentration of ^{14}C was less than 2 µg/g in all tissues except for the intestinal tract, 255.4 µg/g, and the liver, 10.5 µg/g. After 48 h, concentrations in all tissues were generally less. The concentration of ^{14}C was lower in most tissues than in the plasma, indicating no specific accumulation or localization of either Linear Alkylbenzene Sulfonate or its metabolites in the tissues.

Four adult rhesus monkeys, 2 males and 2 females, were used to study the excretion of a single s.c. dose of ^{14}C-Linear Alkylbenzene Sulfonate (Cresswell et al. 1978). An injection of 1 mg/kg ^{14}C-Linear Alkylbenzene Sulfonate, 16 to 40 µCi, in water was administered into the s.c. tissue of the scapular region. Urine, blood, and feces were collected as described earlier. The washings from the cages and cage debris were collected every 24 h.

The majority of the dose was excreted in the first 48 h. In the first 24 h, male monkeys eliminated 55.1% and female monkeys eliminated 50.3% of the dose in urine; over 5 days, the total amount of the dose excreted in the urine by male and female monkeys was 63.8% and 64.3%, respectively. The male monkeys excreted 4.9% and the female monkeys excreted 1.6% of the ^{14}C-label in the feces in the first 24 h; over the 5 day period, these values were 12.5% and 9.2%, respectively. The mean overall recovery of radioactivity was 94.6%. The plasma concentrations of radioactivity determined from the blood samples were less than 0.5 µg/ml for all samples; mean concentrations declined from 0.3 µg/ml at 30 h to 0.1 µg/ml at 96 h.

The same animals were used to study plasma concentrations after receiving s.c. injections of 0.5 mg/kg (8 to 22 µCi) and 0.1 mg/kg (2 to 5 µCi) ^{14}C-Linear Alkylbenzene Sulfonate at intervals of 2 to 3 weeks. Approximately 2 to 3 weeks after the last single dose, each animal received daily s.c. injections of 1 mg/kg ^{14}C-Linear Alkylbenzene Sulfonate, approximately 24 pCi/day, in water for 7 days. Blood samples were taken as described previously. The animals were killed 2, 4, 24, or 48 h after the last dose.

After a single s.c. dose of 0.1 mg/kg ^{14}C-Linear Alkylbenzene Sulfonate, mean plasma radioactivity concentrations reached a maximum of 0.16 µg/ml after 2h. This concentration decreased rapidly during the 7.5 to 24 h period; the mean concentration was 0.03 µg/ml at 24 h and 0.01 µg/ml at 72 h. The mean half-life was approximately 8 h.

After the single 0.50 mg/kg dose, mean plasma radioactivity concentrations reached a maximum of 0.72 µg/ml at 4 h. This concentration decreased rapidly during the 7.5 to 24 h period; the mean concentration was 0.15 µg/ml at 24 h and 0.03 µg/ml at 120 h. The mean half-life was approximately 8.5 h.

After the first daily 1 mg/kg dose, a mean maximum concentration of 1.13 µg/ml was reached at 2 h. The mean half-life was approximately 10 h. The mean predose concentration on the following 6 days increased gradually to 0.71 µg/ml prior to the seventh dose. After the seventh dose, the maximum mean plasma concentration was 1.1 µg/mI at 4 h; this value decreased until 24 h. The mean half-life was ~13 h.

Plasma radioactivity concentrations in male and female monkeys killed 24 and 48 h after the last dose were 0.49 and 0.47 µg/ml, respectively.

In the monkey killed 2 h after the seventh daily dose, the greatest concentrations of radioactivity were in the intestine, kidneys, lungs, spleen, thyroid gland, and pituitary gland. After 4 h, the concentrations were decreased in all of these tissues except the liver and kidneys. The relatively high concentrations of radioactivity in the gastrointestinal tract indicated the probable presence of material eliminated in the bile. After 24 h, the concentrations had decreased in most tissues. After 24 and 48 h, the concentrations were greatest in the tissues of the liver, kidneys, lungs, and adrenal glands. However, the tissue concentrations were less than the plasma concentration after 24 h. With the exception of the gastrointestinal tract, the concentration of ^{14}C was similar to or less than that in the plasma in most tissues after 48 h; this indicated that there was no specific accumulation or localization of Linear Alkylbenzene Sulfonate or its metabolites in the tissue (Cresswell et al. 1978).

Dermal Absorption

Campeau (1960) tested the dermal adsorption of Dodecylbenzenesulfonate in the form of triethanolamine salt of alkyl (kerosene) benzenesulfonic acid (alkyl benzenesulfonate [52%], triethanolamine sulfate [8%], and water [40%]) in rabbits and guinea pigs (n not provided). The test substance was used as a scrub for 2 min. The substance was extracted from the skin using acid methanol in a test tube with a known area of the mouth by inverting the test tube over the skin 30 times. The absorption was determined by the amount of recovered Dodecylbenzenesulfonate. On the flanks of depilated or shaved albino rabbits, the amount of Dodecylbenzenesulfonate recovered was 78 and 0 $\mu g/cm^2$ skin. On the shaved flanks of shaved albino guinea pigs, 20 $\mu g/cm^2$ skin was recovered.

Two-tenths ml of a 3 mM aqueous suspension of Sodium *p*-1-[1-^{14}C] Dodecylbenzenesulfonate (8.5 µCi/mg) was applied to the dorsal skin of 6 lightly anesthetized female Colworth-Wistar rats (Howes 1975). The test solution was applied to a 7.5 cm^2 area of skin on the back that was clipped free of hair. The solution was lathered over the test area for 1 min. After 15 min, the skin was rinsed thoroughly and dried. Restraining collars were used to prevent grooming. After 24 h the animals were killed and the treated skin was removed.

No ^{14}C was detected in expired CO_2 urine, feces, and carcasses. The treated skin was examined by autoradiography for ^{14}C; heavy deposition of SDDBS was found on the skin surface and in the upper regions of the hair follicles. Penetration, based on the amount of ^{14}C excreted in the urine, feces, and expired CO_2 during the 24 h after application plus the amount in the carcass at 24 h, was determined to be <0.1 $\mu g/cm^2$ (Howes 1975).

In Vitro Dermal Penetration

Human abdominal skin samples were obtained from females at autopsy and prepared epidermal samples were mounted in penetration cells (Howes 1975). One-tenth ml of a 6 mM Sodium *p*-1-[1-^{14}C] Dodecylbenzenesulfonate (8.5 µCi/mg) solution was placed on the corneum and 8.0 ml of saline was kept in the sampling compartment. At various times, 1.0 ml samples were removed and replaced with an equal volume of fresh saline to monitor ^{14}C. After 48 h, the corneum was washed with distilled water and monitored for ^{14}C by solubilizing.

No measurable penetration of SDDBS was observed until 24 h after application; the rate of penetration then increased rapidly. After 48 h, 87.2 ± 24.1 $\mu g/cm^2$ had penetrated. After rinsing, 30% to 50% of the applied ^{14}C remained in the epidermis.

In another experiment, the dorsal skin of female Colworth-Wistar rats was clipped 24 h prior to killing the animals, after which the skin was excised and mounted in penetration cells. A 6 mM Sodium *p*-1-[1-^{14}C] Dodecylbenzenesulfonate (8.5 µCi/mg; 0.25 ml) solution was placed on the epidermal surface of the skin and 10.0 ml of saline added to the sampling compartment against the dermis. Hourly, 1.0 ml of saline was removed and replaced with an equal volume of fresh saline to monitor ^{14}C. After 24 h, the epidermal surface was washed with distilled water and monitored for ^{14}C by solubilizing.

No measurable penetration was found up to 24 h after application. The ^{14}C-SDDBS was not easily removed from the skin; after washing with distilled water, 30% of the ^{14}C was recovered in the rinse water and 70% remained in contact with the skin (Howes 1975).

Miscellaneous Studies

Organ Effects

An increase in the release of alkaline phosphatase was observed when the jejunum was perfused with Ringer's bicarbonate solution that contained 0.5% Sodium Dodecylbenzenesulfonate (Kimura et al. 1982; Kimura and Yoshida 1982).

Gupta et al. (1986) orally administered Linear Alkylbenzenesulfonate (50, 100, 250 mg/kg) to developing male albino rats for 10 weeks. At the end of treatment, the rats were killed, the liver and kidneys removed and enzyme activity measured. For the livers, adenosine triphosphatase activity was decreased in all treatment groups ($p < .01$ and .001). Acid phosphatase activity was increased ($p < .001$) and glutamic pyruvic transaminase activity was reduced ($p < .01$) in the high-dose group. Alkaline phosphatase and glutamic oxaloacetic transaminase activity were unaffected.

In the kidneys, adenosine triphosphatase activity was decreased in the high-dose group ($p < .01$). Alkaline phophatase activity was decreased in the mid- ($p < .01$) and high-dose ($p < .001$) groups. Acid phosphatase, glutamic oxaloacetic transaminase activity, and glutamic pyruvic transaminiase were unaffected. The authors concluded that ingestion of Linear Alkylbenzenesulfonate can affect enzymatic activity in the liver and kidneys, possibly due to cellular injury (Gupta et al. 1986).

Antimicrobial Effects

Sodium Dodecylbenzenesulfonate may act bacteriostatically on micro-organisms (Yamada 1979). In some strains of *Escherichia coli,* a longer lag phase due to the presence of SDDBS has been observed (Pollack and Anderson 1970).

Bautista-Toledo et al. (2008) exposed the bioluminescent marine bacteria *Vibrio fisheri* NRRL-B-11177 to Sodium Dodecylbenzenesulfonate for 15 min and used the luminescence as a measure of inhibition. There was no inhibition below 5 mg/l. Inhibition started at 10 mg/l and increased to ~45% at 50 mg/l.

Versteeg et al. (1997) reported the effective concentration to inhibit growth by 20% (EC_{20}) of Sodium Alkylbenzenesulfonate on *Brachionus calyciflorus*, a rotifer, to be 1.4 (confidence interval 0.882 to 2.27) mg/l and the EC_{50} to be 2.0 (1.70 to 2.33) mg/l.

Emzyme Effects

Freeman et al. (1945) reported that a mixture of Sodium Alkylbenzenesulfonates inhibited activity of amylase, lipase, trypsin, pepsin, and phosphatase enzymes collected from a dog and a human.

A decrease in sucrase and alkaline phosphatase activities was observed when Wistar rats were fed diet containing 2.5% Sodium Dodecylbenzenesulfonate , with and without the addition of fiber (Kimura and Yoshida 1982; Kimuraet al. 1980).

In an in vitro study using an enzyme preparation from the small intestine, 0.1% Sodium Dodecylbenzenesulfonate inhibited

sucrase, maltase, and leucine aminopeptidase activity; alkaline phosphatase activity was not affected. Albino rats were fed 0.25 g/kg body wt Sodium Dodecylbenzenesulfonate in feed for 3 months and then administered a single dose of either Sodium Dodecylbenzenesulfonate or water; the blood glucose concentration of rats given a single dose of 0.094 g/ml/100 g body wt of Sodium Dodecylbenzenesulfonate was increased compared to rats given a single dose of distilled water (Antal 1972).

Immunosuppressive Potential

Coy et al. (1990) used a human mixed lymphocyte reaction to evaluate the immunosuppressive potential of Sodium Dodecylbenzenesulfonate. The ingredient was nontoxic and non inhibitory, suggesting no immunosuppressive potential.

ANIMAL TOXICOLOGY

Acute Oral Toxicity

Sodium Dodecylbenzenesulfonate

The oral median lethal dose (LD_{50}) of Sodium Dodecylbenzenesulfonate was 2.0 g/kg for mice and 1.26 g/kg for rats (Sweet 1987).

The oral LD_{50} of a detergent solution containing 15% Sodium Dodecylbenzenesulfonate was 7.5 ml/kg for rats and 12.6 ml/kg for mice (Arthur D. Little 1991). A lethal dosage for dogs was 400 ml/kg; 100 ml/kg had no effect.

TEA-Dodecylbenzenesulfonate

Five groups of Sprague-Dawley rats (5 males and 5 females per group) were dosed orally by gavage with 0.464, 1.00, 2.15, 4.64, or 10.00 ml/kg of a 1:128 aqueous dilution (195.3 mg/kg body wt) of TEA-Dodecylbenzenesulfonate (Hilltop Research 1977). The animals were observed for 14 days, after which they were killed and necropsied. No deaths occurred. Diarrhea was the only clinical sign. No significant observations were made at necropsy. The oral LD_{50} of a 1:128 aqueous dilution in rats was >10 ml/kg.

Linear Alkylbenzene Sulfonate

The oral LD_{50} of 10% and 40% solutions of Linear Alkylbenzene Sulfonate in distilled water administered intragastrically to male and female FDRL strain (Wistar derived) rats was determined (Oser and Morgareidge 1965). Linear Alkylbenzene Sulfonate had a nominal chain length of 12 carbon atoms (range, C9-C12), an average molecular weight of 346, and was 39.5% active. For male and female rats, the LD_{50} (expressed on an active ingredient basis) was 0.65 ± 0.063 g/kg, with a slope factor of 0.173.

The oral LD_{50} of LAS for mice was 2.30 g/kg (Tiba 1972).

Alkyl Aryl Sulfonate

Hine et al. (1953) orally administered a product containing Alkyl Aryl Sulfonate (alkyl aryl sulfonate ≥40%, moisture ~2%, unsulfonated oil ~1%; 1.4, 1.8, 2.1, 2.4, or 2.5 g/kg) to Fisher albino mice (n = 10) and observed them for 6 days. There exhibited gelatinous diarrhea containing traces of blood in 90% of the mice. There was a decrease in motor activity immediately after administration. Necropsy revealed bloody feces, and slight hemorrhage in the pyloric mucosa. Mortality was 0, 2, 6, 8, and 10 for 1.4, 1.8, 2.1, 2.4, and 2.5 g/kg, respectively. All but 1 death in the high-dose group occurred within 12 h.

The above experiment was repeated with Golden Syrian hamsters. The hamsters had diarrhea and decreased motor activity. Mortality was 0 of 10, 1 of 10, 8 of 11, and 8 of 8 for 0.7, 1.0, 1.2, and 1.5 g/kg. The average time to death was 14 h.

The same experiment on young Long Evans rats resulted in severe diarrhea and sluggishness. Mortality was 0 of 12, 5 of 14, and 15 of 20 for 2.0, 2.6, and 3.5 g/kg, respectively. Deaths occurred between 16 h and day 1 except for 1 on day 6.

The same experiment on adult albino Fisher rabbits resulted in diarrhea and sluggishness. Mortality was 0 of 4, 2 of 4, and 3 of 4 for 0.5, 1.5, and 2.2 g/kg, respectively. Deaths occurred between days 1 and 3 (Hine et al. 1953).

Acute Dermal Toxicity

TEA-Dodecylbenzenesulfonate

A dose of 21.5 ml/kg of a 1:128 aqueous dilution of TEA-Dodecylbenzenesulfonate was applied under an occlusive patch for 24 h to clipped skin on the backs of New Zealand white rabbits (4 males, 4 females); the skin of 4 of the rabbits was abraded (Hilltop Research, 1977). Following patch removal, residual test material was removed and the animals were observed for 14 days, after which they were killed and necropsied. No deaths occurred. Diarrhea and emaciation in 2 rabbits and erythema were the only physical observations. No significant observations were made at necropsy. The dermal LD_{50} of a 1:128 aqueous dilution of TEA-Dodecylbenzenesulfonate in rabbits was >21.5 ml/kg.

Linear Alkylbenzene Sulfonate

Two mg/kg of 5%, 10%, and 25% w/v aqueous Linear Alkylbenzene Sulfonate solution was applied to the skin (site unspecified) of rabbits (number, species, and sex unspecified) under occlusive patches for 24 h (Arthur D. Little, Inc. 1991). No evidence of systemic toxicity or mortality was observed.

The minimum lethal dosage of a 20% solution the test formulations applied to intact skin of rabbits was in the range of 200 to 1,260 mg/kg (Arthur D. Little, Inc. 1991). The dermal LD_{50} for Linear Alkylbenzene Sulfonate solution for rabbits was determined to be >500 mg/kg (Arthur D. Little, Inc. 1991).

Acute Intravenous Toxicity

Sodium Dodecylbenzenesulfonate

The intravenous (i.v.) LD_{50} of SDDBS for mice was 105 mg/kg (Sweet 1987).

Short-term Oral Toxicity

Sodium Dodecylbenzenesulfonate

Hazleton Laboratories (1956) incorporated Sodium Dodecylbenzenesulfonate (200, 2000, 10,000, or 20,000 ppm; 0.02%, 0.2%, 1.0% 2.0%, respectively) in the feed of male albino rats (strain not specified; n = 5) for 33 days. No controls were used. At the end of the treatment period, the rats were killed and necropsied.

There were no deaths during the treatment period. There were incidences of wheezing, nasal discharge, rough fur, a blood-like

discharge around the eyes or nose, excitability, and unthriftiness. These observations were greater in the 10,000 and 20,000 ppm groups. At necropsy, all doses had occasional pale and/or granular livers or kidneys. At 20,000 ppm, the urinary bladder of 1 rat was slightly distended with urine and another rat had marked reduction in body fat stores (Hazleton Laboratories 1956).

Reagent-grade Sodium Dodecylbenzenesulfonate was dissolved in tap water and administered to 8 groups of 8 male Wistar rats with either normal or polychlorinated biphenyl (PCB)-supplemented feed (Itokawa et al. 1975). The control group received normal diet and tap water, groups 2 to 4 were fed PCB-supplemented diet at concentrations ranging from 10 to 500 ppm and tap water, group 5 was fed normal diet and water containing 1000 ppm Sodium Dodecylbenzenesulfonate, group 6 was fed PCB-supplemented diet at 10 ppm and water containing 1000 ppm Sodium Dodecylbenzenesulfonate, group 7 received PCB-supplemented diet at 100 ppm and water containing 1000 ppm Sodium Dodecylbenzenesulfonate, and group 8 was fed PCB-supplemented diet at 500 ppm and water containing 1000 ppm Sodium Dodecylbenzenesulfonate. Both feed and water were provided ad libitum; consumption of both was measured every 2 days. The rats were killed after 1 month.

No significant differences in feed or water consumption were observed between treated and control groups. In group 5, Sodium Dodecylbenzenesulfonate only, the relative liver weight and serum urea and iron levels were similar to controls as were serum, total, and free cholesterol in the liver. Aniline hydroxylase, sodium-potassium-magnesium-dependent ATPase, and magnesium-dependent ATPase activities in the liver were similar to controls.

In the 2 groups that were given 500 ppm PCB, body weight gains were decreased. Liver weights increased with increased PCB concentrations; a synergistic effect of Sodium Dodecylbenzenesulfonate upon PCB was observed in the groups given 500 ppm PCB. Also, serum urea concentrations increased in the groups given 500 ppm PCB. Iron concentrations increased in groups 7 and 8; which the authors suggested was probably due to the hemolytic action of Sodium Dodecylbenzene-sulfonate. In group 8, serum cholesterol and liver free cholesterol concentrations were increased. In the groups given 100 and 500 ppm PCB, total liver cholesterol concentrations increased. Cholesterol concentrations were more marked in the groups in which PCB and Sodium Dodecylbenzenesulfonate were combined. Aniline hydroxylase activity increased and Na-K-Mg-dependent ATPase decreased, both changing in proportion with the PCB concentration. In the 500 ppm PCB-treated groups, Mg-dependent ATPase was slightly decreased. No changes in serum and liver triglyceride and nonesterified fatty acid concentrations were observed in any group (Itokawa et al 1975).

Alkylbenzenesulfonate

Hine et al. (1953) incorporated a product containing Alkylbenzesulfonate (alkyl aryl sulfonate ≥40%, moisture ~2%, unsulfonated oil ~1%; 10, 25, or 50%) into the feed of young Long-Evans rats (n = 10) for 45 days. The rats were then killed and necropsied. All rats survived the treatment period. Feed consumption and weight gains were similar between groups. Pathological examinations were unremarkable. The authors concluded that Alkylbenzensulfonate was not classified as a toxic compound.

The authors applied the product (5% aqueous) to the backs of rats and rabbits 6 days/week for 30 days. There were no clinical signs. One rabbit showed a +1 erythema at day 11 which was clear by day 12 (Hine et al. 1953).

Sodium Alkybenzenesulfonate Mixture

Freeman et al. (1945) orally administered a Sodium Alkylbenzenesulfonate (2.0, 3.0, or 4.0 g/d) mixture to dogs (25 to 30 lbs; breed not specified; n = 2) in capsules just before feeding for 1 month. The dogs were then killed and necropsied. The dogs in the high-dose group had decreased feed consumption after 1 week. One dog in the high-dose group died at 3 weeks. The other dog in the high-dose group and one in the mid-dose group were killed due to poor condition. One dog in the low-dose group developed anorexia that worsened over time. One dog in the mid-dose group vomited the first few days then developed anorexia and stopped eating in week 3. Both dogs in the high-dose group stopped eating by week 3. Necropsy revealed an excess of mucous and bile in the small intestine and liquid stools in the colons of 5 dogs. There was some accentuation of the lobular markings of the liver in the dogs that died at 3 weeks. Histological examination revealed only a few discrete foci of leucocyte infiltration in the cortex of the kidneys of 1 mid-dose dog.

In another experiment, the Sodium Alkylbenzenesulfonate mixture (0.5g/100 g feed) was incorporated into the feed of rats (strain not specified; 21 days old; n = 21) for 65 days. Control rats received the basal diet. The rats were then killed and necropsied. The treated rats had slight weight loss for the first 3 days of treatment then weights were similar to controls. Hemoglobin determinations at 35 and 65 days were similar. Macroscopic and microscopic examinations revealed no abnormalities (Freeman et al. 1945).

Short-term Oral and Subcutaneous Toxicity

Linear Alkylbenzenesulfonate

Heywood et al. (1978) simultaneously administered Linear Alkylbenzenesulfonate to Rhesus monkeys (*Macaca mulatta*; n = 6; 3 males, 3 females) orally (0, 30, 150, 300 mg/kg/d in distilled water) and subcutaneously (0.1, 0.5, 1.0 mg/kg/d in saline) for 28 days. All the monkeys in the high-dose group vomited frequently, usually within 3 h of dosing. There was also salivation and/or retching. In the mid- and high-dose group, there was an increase in frequency of passage of loose or liquid stool. Body weights and feed and water consumption were similar among groups. There was an increase in the occurrence of chronic inflammatory cell infiltration (mainly fibroblasts) at the s.c. injection sites in a dose-dependent manner. There were injection-associated pseudocysts, hemorrhage, and necrosis. There were no treatment related findings with regards to ophthalmological, laboratory, and other pathological tests.

Short-term Dermal Toxicity

Linear Alkylbenzenesulfonate

Rabbits (number, gender, and strain unspecified) were dosed with

≤30% Linear Alkylbenzenesulfonate for several weeks (Sadai and Mizuno 1972). No systemic toxicity was observed at concentrations of ≤20%. Weight loss was observed after 15 days of dosing with 30% LAS.

Subchronic Oral Toxicity

Sodium Dodecylbenzenesulfonate

Industrial Bio-Test Laboratories, Inc. (1961a) incorporated Sodium Dodecylbenzenesulfonate (0.020%, 0.10%, or 0.50%) into the feed of weanling Sprague-Dawley rats (n = 20; 10 males, 10 females) for 90 days. After the test period, the rats were killed and necropsied. Two sets of controls (n = 20; 10 males, 10 females) were fed either the basal diet or the basal diet incorporated with sodium sulfate (0.125%). All rats were fed ad libitum. After the test period, the rats were killed and necropsied.

There were no mortalities or clinical signs observed during the test period. Body weights and weight gains were similar between groups; the high-dose male group had decreased growth but did not reach significance. The authors concluded that the decreased weight was due to palatability issues. There were no differences in the hematological studies and urinalysis among groups. There were no gross pathological findings attributable to Sodium Dodecylbenzenesulfonate ingestion. Gross and microscopic histopathological studies were unremarkable (Industrial Bio-Test Laboratories, Inc. 1961a).

Industrial Bio-Test Laboratories, Inc. (1961b) incorporated Sodium Dodecylbenzenesulfonate (0, 0.020%, 0.10%, or 0.50%) into the feed of Beagle dogs (n = 6; 3 males, 3 females) for 90 days. After the test period, the dogs were killed and necropsied. There were no mortalities during the test period. There were no differences between the controls and treatment groups with regards to weight, hematologic studies, urinalysis, or gross and microscopic pathology. There was no evidence of organ dysfunction. Feed consumption of the treatment groups was below that of the control group for the first few weeks of the experiment. It then increased but remained below that of the controls. The authors suggested that it was due to palatability and differences in the initial body weights between groups.

Industrial Bio-Test Laboratories, Inc. (1961c) incorporated Sodium Dodecylbenzenesulfonate (0.020%, 0.10%, or 0.50%) into the feed of weanling Sprague-Dawley rats (n = 20; 10 males, 10 females) for 90 days. After the test period, the rats were killed and necropsied. Two sets of controls (n = 20; 10 males, 10 females) were fed either the basal diet or the basal diet incorporated with sodium sulfate (0.125%). All rats were fed ad libitum. After the test period, the rats were killed and necropsied.

There were no mortalities or clinical signs observed during the test period. Body weights and weight gains were similar between the controls and the low- and mid-dose groups; the high-dose males and female group had decreased growth rates that only reached significance in the females. The authors concluded that the depressed weight was likely due to palatability issues. There were no differences in the hematological studies and urinalysis among groups. There were no gross pathological findings attributable to Sodium Dodecylbenzenesulfonate ingestion. Gross and microscopic histopathological studies were unremarkable (Industrial Bio-Test Laboratories, Inc. 1961c).

Industrial Bio-Test Laboratories, Inc. (1961d) incorporated Sodium Dodecylbenzenesulfonate (0.020%, 0.10%, or 0.50%) into the feed of Beagle dogs (n = 6; 3 males, 3 females) for 90 days. The control group was fed the basal diet incorporated with sodium sulfate (0.125%). After the test period, the dogs were killed and necropsied. There were no mortalities nor clinical signs during the test period. Body weight and weight gains were similar among groups. All dogs in the test groups consumed less feed the first week of the test period, then increased consumption similar to the control group. Hematological studies and urinalysis were unremarkable. There was no evidence of kidney or liver dysfunction. Gross and microscopic pathology were unremarkable (Industrial Bio-Test Laboratories, Inc. 1961d).

Industrial Bio-Test Laboratories, Inc. (1961e) incorporated Sodium Dodecylbenzenesulfonate (0.020%, 0.10%, or 0.50%) into the feed of weanling Sprague-Dawley rats (n = 20; 10 males, 10 females) for 90 days. After the test period, the rats were killed and necropsied. Two sets of controls (n = 20; 10 males, 10 females) were fed either the basal diet or the basal diet incorporated with sodium sulfate (0.125%). All rats were fed ad libitum. After the test period, the rats were killed and necropsied.

There were no mortalities or clinical signs observed during the test period. Body weights and weight gains were similar between the controls and all treatment groups. There were no differences in the hematological studies and urinalysis among groups. There were no gross pathological findings attributable to Sodium Dodecylbenzenesulfonate ingestion. Gross and microscopic histopathological studies were unremarkable (Industrial Bio-Test Laboratories, Inc. 1961e).

Industrial Bio-Test Laboratories, Inc. (1962a) incorporated Sodium Dodecylbenzenesulfonate (0.020%, 0.10%, or 0.50%) into the feed of Beagle dogs (n = 6; 3 males, 3 females) for 90 days. The control group was fed the basal diet incorporated with sodium sulfate (0.125%). After the test period, the dogs were killed and necropsied.

There were no mortalities during the test period. The dogs in the high-dose group had generalized, comparative weakness and lack of activity. Body weights and weight gains were similar among the controls and the low- and mid-dose groups. The high-dose group had decreased body weights and weight gains, especially in the males. The dogs in the high-dose group had decreased feed consumption; the males in the mid-dose group has a slightly decreased feed consumption. There were lower values for hemoglobin, hematocrit, and erythrocyte counts in the high-dose group. There was microscopic evidence of hepatotoxic effects in the high-dose group; the livers of 4 dogs had mild degenerative changes in the form of slight hepatocellular edema without evidence of hepatic cell loss. A fifth dog, that was killed early due to poor condition, had extensive hepatocellular degeneration associated with mononuclear infiltrates. Absolute organ weights were similar to controls. Organ/body ratios were increased among dogs in the high-dose group. The authors suggested that this was due to weight loss of this group (Industrial Bio-Test Laboratories, Inc. 1962a).

Rats (number, gender, and strain unspecified) recieved a

formulation containing 15% SDDBS and 13% ammonium fatty alcohol polyglycolether sulfate in drinking water (Arthur D. Little 1991). A slight decrease in growth rate was observed for male rats given 2.5 ml/kg/d for 9 weeks followed by 3.75 ml/kg/d for an additional 9 weeks. Rapid weight loss was observed when the dosage was increased to 5.0 ml/kg/d at 18 weeks. The animals were given untreated water after 22 weeks; an increase in body weight gain was observed and control values were attained by week 26. Mild necrosis of intestinal mucosa with hemosiderosis of the spleen, liver, and kidneys were observed at microscopic examination. These lesions were not observed for animals in the group given 0.5 ml/kg/d.

In a second experiment, dogs (number, gender, and strain unspecified) were fed 10, 100, or 1,000 mg/kg/d of a formulation containing 15% SDDBS in the diet for 6 months. The only observation was a slight decrease in body weight gain for females of the 1,000 mg/kg/d group compared to controls. There was no difference between treated and control groups in hematologic or urine chemistry values. At microscopic examination, hemorrhagic necrosis of the intestine and infiltration of chronic inflammatory cells were observed in dogs given 10 mg/kg and hemosiderosis of the liver and spleen was observed in dogs administered 100 and 1,000 mg/kg (Arthur D. Little, Inc. 1991).

Sodium Alkylbenzenesulfonate

Freeman et al. (1945) reported a no observed effects level (NOEL) of 1 g/d for 6 months for dogs orally administered Sodium Alkylbenzenesulfonate.

Woodard and Calvery (1945) reported a NOEL of 0.2% Sodium Alkylbenzenesulfonate administered in drinking water for 6 months for guinea pigs.

Fitzhugh and Nelson (1948) reported a NOEL of 1.0% Sodium Alkylbenzenesulfonate administered in feed for 16 weeks for rats. Rats fed 4% Sodium Alkylbenzenesulfonate grew very little and died within the first week of the experiment. This dose group had severe bloating and diarrhea.

Linear Alkylbenzene Sulfonates

Three groups of Sprague-Dawley rats (10 males, 10 females per group) were fed diet containing 0.02%, 0.1%, or 0.5% Linear Alkylbenzene Sulfonates for 90 days (Kay et al. 1965). A control group of 20 rats was fed untreated diet for the same time period. Body weights and feed consumption were measured weekly. Hematologic studies and urinalysis were performed on samples taken from 5 males and 5 females from each group prior to dose initiation and after 30, 60, and 90 days of testing. At study termination, all animals were killed and necropsied. The tissues of some animals were examined microscopically. No differences were observed in body weight, feed consumption, survival, hematologic values, urinalysis, organ weights, or organ-to-body weight ratios between animals of the treated and control groups, and there were no gross or microscopic lesions in examined tissues.

Wistar rats (number, gender, and strain unspecified) were fed Linear Alkylbenzene Sulfonates in the diet for 6 months (Yoneyama et al. 1973). A concentration of 0.07% Linear Alkylbenzene Sulfonates in the diet (~40 mg/kg/d) did not produce adverse effects. Minor histologic changes were observed in the kidneys of rats given a concentration of 0.2% Linear Alkylbenzene Sulfonates; the severity of the lesions increased at concentrations of 0.6% and 1.8% Linear Alkylbenzene Sulfonates. At the highest dosage (concentration not specified), a decrease in body weight gain, tissue damage in the cecum and liver, and increased severity of renal lesions, specifically glomerular atrophy and necrosis of renal tubules, were observed.

Rats (number, gender, and strain unspecified) were fed ~5000 ppm (0.5%) Linear Alkylbenzene Sulfonates for up to 12 weeks (Oser and Morgareidge 1965). No significant changes were observed.

Two groups of FDRL rats (15 males, 15 females per group) were fed a diet containing 0.05 or 0.25 g/kg/d Linear Alkylbenzene Sulfonates (expressed as active ingredient) for 12 weeks. Linear Alkylbenzene Sulfonates had a nominal chain length of 12 carbon atoms (range C_9 to C_{12}), an average molecular weight of 346, and was 39.5% active. A control group was fed untreated diet. The rats were observed daily for signs of toxicity. Body weights and feed consumption of approximately 50% of the rats (males and females) were measured weekly. Hematology tests and urinalysis were performed on samples obtained from the remaining rats during weeks 6 and 12. At study termination, all animals were killed for necropsy. The tissues of some animals were examined microscopically. There was no difference in behavior between animals of the test and control groups. No differences were observed in either body weight, feed consumption, survival, hematological values, or urinalysis. Liver-to-body weight ratios were increased for male and female rats of the 0.25 g/kg/d group compared to rats of the control group. No microscopic lesions were observed that were attributed to test article administration (Oser and Morgareidge 1965).

Rats (number, gender, and strain unspecified) were dosed orally with ≤0.6% Linear Alkylbenzene Sulfonates for 6 months (Arthur D. Little, Inc. 1977). Slight renal damage was observed at a dose of 0.2%; this damage was increased at 0.6%.

Alkylbenzenesulfonate

Hine et al. (1953) incorporated a product containing Alkylbenzenesulfonate (alkyl aryl sulfonate ≥40%, moisture ~2%, unsulfonated oil ~1%; 1, 10, or 2 ppm) into the feed of Long-Evans rats for 6 months. At the end of the treatment period, the rats were killed and necropsied. There were no clinical signs during the treatment period. One rat in the low-dose group died in week 3 due to non-treatment causes. Feed consumption and body weights were similar among groups. Hematological tests and urinalysis were unremarkable. Females in the high-dose group had increased kidney weights compared to controls; there was no evidence of kidney damage. There were no morphologic lesions caused by Alkylbenzenesulfonate.

Sodium Alkybenzenesulfonate Mixture

Freeman et al. (1945) orally administered a Sodium Alkylbenzenesulfonate mixture (1.0 g/d) to dogs (25 to 30 lbs; breed not specified; n = 5) in capsules just before feeding for 6 months. The dogs were then killed and necropsied. Four of the dogs gained weight (2.5 to 8.5 lbs) and 1 lost weight (1.0 lb). A

liver function test at ~6 weeks showed no adverse effects. Gross and microscopic examination revealed 1 dog with bilateral cortical retention cysts or abscesses, one on the cortex of each kidney. Another dog had some pitting of the outer surface of the kidneys. There were few foci of leukocytic infiltration into the cortex in 3 dogs with occasional hyaline casts. The authors concluded that the kidney abnormalities were not related to treatment.

Subchronic Dermal Toxicity

TEA-Dodecylbenzenesulfonate

Burnett et al. (1976) applied a semipermanent hair dye formulation containing 0.5% TEA-Dodecylbenzenesulfonate dermally, twice weekly for 13 weeks, to a group of New Zealand white rabbits (6 males and 6 females). The test material was applied to shaved areas on the dorsolateral aspects of the thoracic-lumbar area, one on each side of the midline at a dose of 1 ml/kg; application sites were alternated to minimize irritation. Test sites of 3 males and 3 females were abraded on the first treatment day of each week. The test sites were rinsed 1 h after dosing. Three negative control groups of 12 rabbits per group were treated in the same manner as the test group, but no dye was applied.

All rabbits were weighed weekly; clinical chemistry and hematologic and renal function parameters were examined at the beginning of the study and at 3, 7, and 13 weeks. At the end of 13 weeks, all animals were killed and necropsied. Organ-to-body weight ratios were determined and selected tissues were examined microscopically.

No clinical signs of toxicity due to test substance administration were observed. Body weight gains of the test animals were at least equal to those of the controls. Relative organ-to-body weights may have been statistically different than the combined value of the three control groups, but no difference was observed when test group weights were compared with values from individual control groups; the differences were not accompanied by histologic evidence of toxicity.

The blood urea nitrogen values for all test rabbits and the leukocyte count for male rabbits were increased and the methemoglobin value for female rabbits was decreased compared to the control values. These differences were not considered toxicologically significant. Neither gross nor microscopic lesions due to test substance administration were observed. A semipermanent hair dye formulation containing 0.5% TEA-DDBS did not produce systemic toxicity (Burnett et al. 1976).

Linear Alkylbenzenesulfonate

Rabbits (number, gender, and strain unspecified) were given 2 ml applications of ≤ 10% Linear Alkylbenzenesulfonate (2 mg/kg) to abraded skin daily for 28 days and to intact skin for 91 days. No systemic toxicity was observed (Arthur D. Little, Inc. 1991).

Chronic Oral Toxicity

Sodium Dodecylbenzenesulfonate

Hazleton Laboratories (1956) incorporated Sodium Dodecylbenzenesulfonate (0 [n = 20 males, 20 females], 200 [n = 20 males], 1000 [n = 20 males, 20 females], or 2,000 ppm [n = 20 males]; 0, 0.02%, 0.1%, or 0.2%, respectively) in the feed of male and female albino rats (Carworth Farms strain) for 104 weeks. At the end of the treatment period, the rats were killed and necropsied. All rats that died during treatment were necropsied.

There were no behavioral or clinical signs in any of the treatment groups. Several rats in all treatment groups had unthrifty appearance, rough coats, alopecia, bloody noses and eyes, dyspnea, and sores on the head or body. Hematological test at baseline, 13, 52, 78, and 104 weeks showed no differences between control and treatment groups. Treated males in all groups had lower growth rates. The body weights and feed consumption for both treated males and females were not different from controls. Mortality was comparable between the control, 1000, and 2000 ppm groups. Mortality was higher in the 200 ppm group; this was probably not related to treatment. Pneumonitis was the cause of death for most of the rats that died before the end of treatment. Gross necropsy results were comparable between controls and treatment groups. There were no characteristic findings through histopathology. Organ/body weight ratios were comparable between controls and treatment groups (Hazleton Laboratories 1956).

Industrial Bio-Test Laboratories, Inc. (1962b) incorporated Sodium Dodecylbenzenesulfonate (0.02%, 0.10%, or 0.50%) into the feed of Beagle dogs (n = 6; 3 males, 3 females) for 104 weeks. Due to poor palatability, the high dose was adjusted to 0.10% in the feed and the remaining dose was administered by capsule. The control group was fed the basal diet containing 0.050% sodium sulfate. At the end of the test period, the dogs were killed and necropsied.

The high-dose group was observed to have comparative weakness and lack of activity. There were no differences in body weights in the low- and mid-dose groups; there was reduced weight gain in the high-dose group. Feed consumption was decreased in the high-dose group throughout the test period. The male dogs in the mid-dose group also had decreased feed consumption, but to a lesser extent. Hematologic studies revealed lower values for hemoglobin, hematocrit, and erythrocyte counts in the high-dose group. The high-dose group was anemic. The urinalysis revealed no differences among groups. There were no differences noted in gross pathologic examination.

Microscopic examination revealed that the livers of 4 of the dogs in the high-dose group had mild degenerative changes in the form of slight hepatocellular edema without evidence of hepatocyte loss. A fifth dog had extensive hepatocellular degeneration associated with a mononuclear infiltrate (this dog was killed shortly before the conclusion of the test period due to poor condition). Some organ/body ratios were increased in the high-dose group. The authors suggested that this was due to decreased body weights since there were no differences in absolute organ weights (Industrial Bio-Test Laboratories, Inc. 1962b).

Itokawa et al. (1975), studied 4 groups of 12 male Wistar rats. The first group served as the control group and received normal diet and tap water, the second group received normal diet and tap water that contained 1000 ppm Sodium Dodecyl-

benzenesulfonate, the third group received diet that was PCB-supplemented at 500 ppm and tap water, and the fourth group received PCB-supplemented diet at 500 ppm and tap water containing 1000 ppm Sodium Dodecylbenzenesulfonate. Both diet and water were available ad libitum. Feed and water consumption were measured every 2 days. After 1, 3, or 7 months, 4 rats from each group were weighed and killed.

There were no differences in feed or water consumption between any of the treated groups and the control group. There was no differences between controls and the Sodium Dodecylbenzenesulfonate only group.

In the groups receiving PCB alone or PCB plus Sodium Dodecylbenzenesulfonate, body weights were significantly decreased and liver weights significantly increased when compared to the controls. Swelling of individual hepatic cells, pyknotic nuclei, cytoplasmic vacuolation, and other degenerative changes were prominent in scattered areas of the liver. Also, the hepatic DNA concentration was decreased, but no significant change occurred in the total DNA content. Total RNA and protein content per liver increased proportionally with increased liver weight; no significant change was observed in RNA or protein concentration compared to controls.

After 7 months, the testicular weights had decreased in male rats that received both PCB and Sodium Dodecylbenzenesulfonate; the testicle-to-body weight ratio was 0.26 ± 0.03% for these rats compared to 0.44 ± 0.02% for male control rats. Upon microscopic examination, degeneration was considerable in the testes of these rats. Necrosis of the seminiferous tubules, lost of spermatogenic cells, hypertrophy of the interstitium between the tubules, and, in some cases, the appearance of bizarre spermatogenic cells were observed. No other significant microscopic changes were observed in any other tissues.

After 1, 3, and 7 months, serum cholesterol concentrations increased in rats that received PCB only or PCB plus Sodium Dodecylbenzenesulfonate. Total cholesterol concentrations increased markedly in the liver of rats in the PCB only group and particularly in the rats that received both PCB and Sodium Dodecylbenzenesulfonate after 3 and 7 months. After 7 months, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) activities were increased. Total hepatic cholesterol concentrations increased with test article administration.

In rats of the PCB only group, hepatic aniline hydroxylase activity was significantly increased; this increase in enzymatic activity was even greater when PCB and Sodium Dodecylbenzenesulfonate were combined. No changes were observed in either serum alkaline phosphatase or choline esterase activities.

In rats that received PCB only or PCB plus Sodium Dodecylbenzenesulfonate, hepatic Na-K-Mg-dependent ATPase activity decreased; this decrease was greater in rats that received both substances. No significant difference in Mg-dependent ATPase activity was observed (ltokawa et al. 1975).

Sodium Alkylbenzenesulfonate

Tusing et al. (1960) incorporated Sodium Alkylbenzenesulfonate (0, 0.5%, or 0.1%) into the feed of albino rats (Carworth Farms; n = 80; 40 female, 40 male) for 104 weeks. Ten of the rats of each sex of each group were killed and necropsied at 26 and 52 weeks. Any rats that died during treatment were necropsied. At the end of the treatment period the remaining rats were killed and necropsied.

The authors conducted a parallel study to compare consumption from drinking water. The rats (n = 40, 20 females, 20 males) were fed the basal diet above. Their drinking water contained 0.1% Sodium Alkylbenzenesulfonate. However, the daily intake was not comparable to the 0.1% feed group. The amount in the drinking water was adjusted to 0.04% to 0.06% after 4 weeks.

In the feed study, there were no differences between control and treatment groups with regard to mortality, body weights, feed consumption, hematological tests, or biochemical tests. There were no lesions observed in the test groups. There were no pathological differences between control and test groups. There were no differences in organ weights that could be attributed to the test substance except for cecums in males at 104 weeks which were heavier.

The results in the drinking water study were similar to the feed study. There was an increase in consumption in the test groups with no other signs of stress. The liver/body weight ratio in males and the empty cecum/body weight ratio in females were increased compared to controls. However, there was no evidence in the blood chemistry of stress to the organs. The authors concluded that there was no evidence of toxicity by Sodium Alkylbenzenesulfonate at these levels (Tusing et al. 1960).

Linear Alkylbenzenesulfonates

Four groups of Charles River rats, 50 males and 50 females per group, were fed diets containing 0.02%, 0.1%, or 0.5% LAS for 2 years; one group of rats, 50 males and 50 females, was fed a normal diet and used as a control group (Buehler et al. 1971). Feed and water were available ad libitum. Body weights and feed consumption were measured weekly for 12 weeks, after which they were measured monthly. Five males and 5 females from each group were killed after 8 and 15 months. An interim necropsy was performed and various hematologic parameters were evaluated. After 2 years, all surviving animals were killed for necropsy and hematologic parameters were evaluated.

During months 4, 11, 15, and 21, blood was obtained from the tails of 5 males and 5 females from each group for analysis. The same animals were used throughout the study; if any of these animals died during the study, they were replaced. At the interim sacrifice, no difference was observed in the body weights of animals in the test groups and controls. Organ to body weight ratios for rats of the high-dosage group were not different at these times compared to the controls. After 8 months, the rats of the 0.02% and 0.1% LAS groups had decreased liver-to-body weight ratios compared to controls. At study termination, no differences in body weights or organ-to-body weight ratios were observed for any of the test groups compared to the controls. Hematologic values that were different from the controls were not considered test substance-related. No test compound-related gross or microscopic lesions were observed. Test compound-related effects were not observed during microscopic examination of

tissues from animals that died on study (Buehler et al. 1971).

Ocular Irritation

TEA-Dodecylbenzenesulfonate

A volume of 0.1 ml of a 1:128 aqueous solution of TEA-Dodecylbenzenesulfonate was instilled in the conjunctival sac of the right eye of 9 New Zealand White rabbits (Hilltop Research 1977). The eyes of 3 rabbits were rinsed after 30 sec; the eyes of the other 6 rabbits were not rinsed. After 24 h, the eyes were scored for irritation; observations were made through day 7. No irritation was observed.

Sodium Decylbenzenesulfonate

Three drops of a 1% Sodium Decylbenzenesulfonate solution were instilled into the conjunctival sac of the eye of a rabbit (Feldman et al. 1948). Observations were made every 30 min for 3 h and then on the following day. On day 2, the rabbit was dosed twice; the second dose was administered 3 h after the first. Sodium Decylbenzenesulfonate produced severe irritation.

Sodium Alkylbenzenesulfonate

Maurer and Parker (1996) conducted a modified Draize test where the test substance is applied directly to the cornea. Sodium Alkylbenzenesulfonate (35.07% active; 10 µl) was instilled in the right eye of adult New Zealand albino rabbits (n = 6) and adult male Sprague-Dawley rats (n = 6). The eyelids were not held shut and the eyes were not washed. The eyes were observed after 3 h. Half of each group was then killed and the eyes and eyelids removed and examined. The remaining animals were observed on days 1, 2, 3, 4, 7, 14, 21, 28, and 35 then killed and the eyes removed and examined.

At 3 h, the overall mean score was 26.0 out of 110 for rabbits and 24.2/110 for rats. There was mild damage to the cornea (10.0/80 and 15.0/80 for rabbits and rats, respectively), conjuctiva (11.0/20 and 5.0/20, respectively), and the iris (5.0/10 and 4.2/10, respectively). The days to recovery for the rabbits was 4 to 7 days, and 3 to 7 days for the rats. Microscopic examination of the rabbit and rat corneas after 3 h showed erosion and denudation of the epithelium and neutrophils in the substantia propria. Examination of the conjunctiva showed erosion and denudation of the epithelium as well as edema and neutrophils in the substantia propria. At 35 days, microscopic examination of the rabbit conjunctiva showed a decreased prominence of goblet cells in the rabbits. The authors concluded that Sodium Alkylbenzenesulfonate was a mild irritant (Maurer and Parker 1996).

Maurer et al. (1998) performed the test describe above test on rats (n = 40). Sodium Alkylbenzenesulfonate (35.07% active, 10 µl) was instilled directly on the cornea. The eyelids were not held shut and the eyes were not washed. The eyes were examined at 3 h, and 1, 2, 3, 4, 7, 14, and 35 days. At each examination time, 5 rats were killed, the eyes removed, and examined.

At 3 h, the irritant score was 34.3 out of 110. The score for the cornea was 21.6 out of 80, 9.1 out of 20 for the conjunctiva, and 3.6 out of 10 for the iris. The conjunctiva had erosion/attenuation and denudation which was no longer evident on days 3 or 7. Regeneration was observed beginning on day 1 and no longer evident on day 14. Edema of the substantia propria occurred at 3 h and was no longer evident on days 4 or 7. Inflammation, principally neutrophilic associated with substantia propria, was noted at 3 h and no longer evident on day 14. The cornea had epithelial cell loss at 3 h with erosion/attenuation and denudation.

Regeneration in the form of conjunctivalization was observed beginning day 1. In the stroma, keratinocyte loss was evident at 3 h but not on day 7. Edema and inflammation, principally neutrophils, were present beginning at 3 h. Edema was no longer evident on days 4 or 7; inflammation was no longer evident on day 4. Neovascularization associated with the anterior stroma was observed beginning on day 2. Inflammation associated with the iris/ciliary body occurred in one rat at day 1. At day 35, 2 rats still had not fully recovered (Maurer et al. 1998).

Linear Alkylbenzenesulfonate

Concentrations of ≥1% Linear Alkylbenzenesulfonate produced irritation in the eyes of rabbits (Arthur D. Little, Inc. 1977).

Instillation of ≥5% LAS into the conjunctival sac of rabbits produced irritation. Congestion and edema have been observed at concentrations of 0.5 to 1.0%. Concentrations of ≤0.1% Linear Alkylbenzenesulfonate produced mild to no irritation (Arthur D. Little, Inc. 1991).

Alkylbenzensulfonate

Hine et al. (1953) instilled a product containing Alkylbenzenesulfonate (alkyl aryl sulfonate ≥40%, moisture ~2%, unsulfonated oil ~1%; 0.1 ml, 5%) into the eyes of rabbits and observed them at 1, 24, and 96 h. There was a moderate response that disappeared by the final reading. There was no loss of corneal substance.

Dermal Irritation

Sodium Dodecylbenzenesulfonate

Fujise and Aoyama (1984) evaluated the irritation potential of SDDBS by applying an olive oil dissolvent containing 10% SDDBS to a shaved dorsal area on the head and neck of male Wistar rats for 4 days. Three rats treated in the same manner, with the exception that olive oil or water only was applied, served as the negative control group. On day 5, the rats were killed and skin samples from the application site were prepared by two methods to determine proline hydroxylase activity. Erythema was visible on day 3; on day 5 erythema was evident on 3 rats. Erythema was not observed in the control group. Proline hydroxylase activity was increased three-fold for both methods of preparation compared to control values.

Schoenberg (1985) used 3 male albino rabbits to determine the irritation potential of Sodium Dodecylbenzenesulfonate. The test material was adjusted to a total of 15.0% active material at a pH of 7.0. The abdomens of the rabbits were shaved. Two application sites were abraded and 2 were left intact. The solution, 0.5 ml, was applied to the skin under gauze that was held in place for 24 h. After 24 h, the patches were removed and the skin was examined for irritation. The sites were re-examined after 72 h. SDDBS was severely irritating to the skin of rabbits, with a primary irritation score of 5.3/8.0.

In a study by Naruse et al. (1991), male ddY mice, 3 per group, were given a 0.1 ml i.v. injection of 1% Evan's blue in

physiological saline immediately followed by a s.c. injection of 0.2 ml of 0.02, 0.10, 0.20, 0.30, 0.40, or 0.50 mg/mI Sodium Dodecylbenzenesulfonate in physiological saline into the dorsal area. Mice of the control group were given an s.c. injection of physiological saline. The mice were killed 3 h after dosing and the s.c. reaction was evaluated. The strength of the reaction in terms of skin irritation was determined by multiplying the relative concentration of extravasated dye by the dye diameter. A score of 1 corresponded to a weak reaction, 2 to an intermediate reaction, and 3 to a strong reaction.

The mice dosed with physiological saline or 0.02 mg/mI Sodium Dodecylbenzenesulfonate had an average reactivity score of 0. The other test groups had the following average scores: 0.10 mg/ml was 0.1; 0.20 mg/ml was 0.8; 0.30 mg/ml was 1.6; 0.40 mg/ml was 2.0; and 0.50 mg/ml was 2.9 (Naruse et al. 1991).

TEA-Dodecylbenzenesulfonate

Six New Zealand white rabbits (gender not specified) were dosed with 0.5 ml of a 1:128 aqueous dilution of TEA-DDBS (Hilltop Research 1977). The solution was applied to a shaved intact and abraded area on the back of each rabbit under an occlusive patch for 24 h. After patch removal, any residual test material was removed. After 24 and 72 h, the primary irritation values were both 0 out of 8. Readings were not taken on 2 intact and 2 abraded sites.

Linear Alkylbenzenesulfonate

In the short-term dermal toxicity study reported by Arthur D. Little, Inc. (1991) described earlier, in which 2 mg/kg of 5%, 10%, or 25% w/v aqueous Linear Alkylbenzenesulfonate solution was applied to the skin (site unspecified) of rabbits (number, strain, and sex unspecified) under occlusive patches for 24 h, moderate skin irritation was observed at the 2 greatest concentrations.

In another short-term dermal toxicity study, in the same report, described earlier, in which rabbits (number, sex, and strain unspecified) were administered 2 ml applications of ≤ 10% Linear Alkylbenzenesulfonate (2 mg/kg) on abraded skin daily for 28 days and on intact skin for 91 days, severe dermal irritation was observed at the application site. This report also indicated that rabbits were either treated for 28 days using an abraded test site or for 91 days using an intact test site with a 10% solution of a formulation containing 19% Linear Alkylbenzene-sulfonate and 19% tallow alkyl ethoxylate sulfate. Moderate dermal irritation was observed.

Three 6-h applications of a 1% (w/v) aqueous solution of Linear Alkylbenzenesulfonate produced primary skin irritation using rabbits (number, strain, and gender not given) (Arthur D. Little, Inc. 1991). No effect was observed after the first application. Moderate to severe erythema and moderate edema, which were still evident after 7 days, were observed by the third application. Upon microscopic examination after 7 days, a moderate degree of hyperkeratosis and epidermal acanthosis with crusting focally was observed.

Rats (number, gender, and strain unspecified) were treated with an aqueous solution of ≤ 30% Linear Alkylbenzenesulfonate for 15 days; the application site was clipped (Sadai and Mizuno 1972). No severe dermal damage was observed with a dose of 20%, while 30% Linear Alkylbenzenesulfonate produced what the authors described as fairly pronounced dermal damage.

A 10% Linear Alkylbenzenesulfonate solution was an acute dermal irritant in rabbits; a 1% solution did not produce any dermal irritation (Arthur D. Little, Inc. 1977).

Imokawa examined dermal irritation as a function of different Linear Alkylbenzenesulfonate structures. The dermal irritation of a 2 g/100 ml aqueous solution of C_{12} Linear Alkylbenzene-sulfonate (97.88% purity) was evaluated using albino guinea pigs (gender not specified). A 1.5 cm^2 occlusive patch was used to apply 0.1 ml of the test material to the shaved backs of at least 6 guinea pigs for 24 h. The test sites were scored 2 and 24 h after patch removal by rating erythema and edema on a scale of 0 to 2 and then combining the scores for a maximum total score of 4. Moderate to severe dermal irritation resulted, with an irritation score of 3.0/4.0 at both readings. Using the same test procedure, a mixed Linear Alkylbenzenesulfonate solution (99.8% purity) containing 33.7% C_{12}, and 7.0% C_{10}, produced a dermal irritation score of 2.75/4.0 at both readings.

In a cumulative open patch test, a 2.0 g/100 ml aqueous solution of C_{12} Linear Alkylbenzenesulfonate (97.88% purity) in 10 mm diameter tubes was applied to the same site on the shaved backs of guinea pigs (number and gender unspecified) twice daily for a total of 9 treatments. The test sites were scored prior to each patch application as stated above. The dermal irritation score for the cumulative open patch test was 1.42/4.0. Following the same test procedure, a mixed Linear Alkylbenzenesulfonate solution (99.8% purity) containing 33.7% C_{12} and 7.0% C_{10} resulted in a dermal irritation score of 0.58/4 (Imokawa 1979).

Alkylbenzenesulfonate

Hine et al. (1953) performed a Draize test on intact and abraded skin using shaved rabbits. A product containing Alkylbenzenesulfonate (alkyl aryl sulfonate ≥40%, moisture ~2%, unsulfonated oil ~1%; 1, 10, or 20 ppm) was applied to occluded skin for 24 h. The skin was washed and evaluated immediately and at 48 and 96 h. There were no deaths and no evidence of absorption of the product. There was moderate edema, erythema, and scabbing of the abraded skin that returned to normal. There were no effects to the intact skin.

The authors applied the product (0.5 g) to 4 shaved areas (intact and abraded) on the backs of albino rabbits and the areas were occluded for 24 h. The covering was removed and the areas read immediately and at 72 h. There were no readings taken for the intact skin (no explanation given). Abraded skin had slight persistent edema and erythema (Hine et al. 1953).

Dermal Sensitization

Linear Alkylbenzenesulfonate

Guinea pigs (number unspecified) were injected intradermally with a 1% w/v aqueous solution of Linear Alkylbenzenesulfonate and challenged topically (Arthur D. Little, Inc. 1991). A sensitization reaction was not observed.

Robinson et al. (1989) observed positive sensitization results in up to 76% of the guinea pigs treated in a maximization test, with an induction injection of 0.6% to 5%, induction patch application

of 0.1% to 1%, and challenge patch application of 1%,. No dose-response pattern was evident. A repeat insult patch test (RIPT) conducted concurrently using 1.2% to 2.5% Linear Alkylbenzenesulfonate at induction and 0.5 to 1% at challenge produced only weakly positive responses.

This same author reported another RIPT, in which Linear Alkylbenzenesulfonate (with >90% of the alkyl chain lengths for the mixture in the range of C_{10} to C_{14}) ws tested at induction concentrations of 2% to 100% followed by challenge applications of 1% or 2% produced weak to moderate sensitization reactions using guinea pigs.

Alkylbenzenesulfonate

Hine et al. (1953) injected a product containing Alkylbenzenesulfonate (alkyl aryl sulfonate ≥40%, moisture ~2%, unsulfonated oil ~1%; 0.1% in 0.9% saline) intradermally into the backs of albino guinea pigs (n = 3) on alternate days for 10 injections. The first injection was 0.05 ml, all others were 0.01 ml. Readings were taken 24 h after each injection. Two weeks after the last injection a test injection (0.05 ml) was made into the flank. There was no erythema or wheal formation 24 h after the challenge injection. The authors concluded that Alkylbenzenesulfonate is non-irritating.

REPRODUCTIVE and DEVELOPMENTAL TOXICITY

Oral

Sodium Alkylbenzenesulfonate

Tusing et al. (1960) used 10 males and 10 females from each group in the Sodium Alkylbenzenesulfonate feeding study described earlier for a reproductive and developmental toxicity study. After 14 weeks on the treated feed (0, 0.05%, or 0.1% Sodium Alkylbenzensulfonate), the rats were paired and mated while continuing on the test diet. After 3 days, the males were returned to their original cages; the females were allowed to deliver and nurse for 21 days. They were then returned to their original cages and the pups were fed the parental diet. At ~ 130 day, the F_1 pups were paired and mated. The F_2 pups were continued on the parental diet for 8 weeks. Sodium Alkylbenzenesulfonate had no observed effects on fertility, litter size, lactation, or survival of offspring. There were no remarkable findings in the hematologic studies, urinalysis, or blood urea nitrogen tests. Gross and microscopic examinations of the offspring were also unremarkable.

Alkylbenzenesulfonate

Omori et al. (1968) incorporated Alkylbenzenesulfonate (0, 0.25%, 0.1%, 0.5%, 1.0%, or 2.0%) into the diets of pregnant rats (n = 15 [0, 0.25%, and 0.5%], 16 [0.1%], 14 [1.0%], 5 [2.0%]; strain not specified). Dams in the 1.0% and 2.0% groups had diarrhea. No clinical signs were noted in the other groups. Feed intake was decreased in the high-dose group. At necropsy, placenta weights were decreased compared to controls in the high-dose group (0.26 ± 0.01 vs. 0.36 ± 0.01). The number of pups per litter was reduced in the high-dose group (3.6 ± 2.4 vs 10.4 ± 0.7). The number of dead litters and dead pups were increased and the number of resorptions were reduced in the high-dose group. In the high-dose group, body weight, body length, and tail length of the pups were reduced. There were no differences in organ weights of the pups.

Mice (n = 22 to 24; strain not specified) were orally administered Alkybenzenesulfonate (0, 24, or 240 mg/kg) on days 7 and 13 of pregnancy. There was a slight decrease in maternal weight gain (80.6, 62.9, 56.3 g, respectively). There were no effects observed on the fetuses from dams in the low-dose group. The number of dead pups increased in the high-dose group. There were no congenital malformations observed in either treatment group (Omori et al. 1968).

Linear Alkylbenzenesulfonate

Charles River rats that were being used in a chronic toxicity study were concurrently used in a 3-generation reproductive study (Buehler et al. 1971). Twenty male and 20 female rats from each group were fed a diet containing 0, 0.5%, 0.1%, or 0.02% LAS then were mated after being on study for 84 days. There were no effects observed associated with Linear Alkylbenzenesulfonate administration.

Palmer et al. (1975a) tested for teratogenic effects of LAS in CD rats (n = 20), CD-1 mice (n = 20), and New Zealand white rabbits (n = 13). Linear Alkylbenzenesulfonate (0, 0.2, 2.0, 300, or 600 mg/kg/d in water) was orally administered from day 6 to day 15 in rats and mice and to day 18 in rabbits. The rats, mice, and rabbits were killed and necropsied on days 20, 17, and 29, respectively.

For the mice, 7 dams died in the 300 mg/kg/d group and 18 died in the 600 mg/kg/d group; all others survived. For the rats, only 1 died in the 600 mg/kg/d group. For the rabbits, 1, 11, and 13 died in the 2, 300, and 600 mg/kg/d groups, respectively. The mice in the 300 mg/kg/d group had retarded weight gains and weight loss was observed in the 600 mg/kg/d group. There was retarded weight gains for the rats in the 600 mg/kg/d group. There was weight loss for rabbits in the 300 and 600 mg/kg/d groups. In all species toxic effects of the gastrointestinal tract were observed, especially in the rabbits (diarrhea, anorexia, weight loss, and cachexia prior to death. Total litter loss (abortion and/or total resorption) tended to occur as a secondary consequence. The authors concluded that 300 and 600 mg/kg/d caused marked maternal toxicity or undue interference with maternal economy. At maternally toxic dosages there was increased fetal loss and reduced litter size in rabbits and mice, mostly due to total litter loss. At nontoxic and slight to moderately toxic dosages, values for litter size and fetal loss were unaffected (mice and rabbits, 0.2 and 2.0 mg/kg/d; rat, all dosages). Examination of the fetuses revealed no increase in abnormalities (Palmer et al. 1975a).

Pregnant ICR-SLC mice were dosed with 10, 100, or 300 mg/kg Linear Alkylbenzenesulfonate by stomach tube on days 6-15 of gestation (Shiobara and Imahori, 1976). The mice were killed on day 17 and their fetuses examined. Marked maternal and embryonic toxic effects, including maternal death, premature delivery, total litter loss, and high fetal death rate, were observed for mice of the 300 mg/kg dosage group. Maternal body weight gains and fetal body weights were significantly decreased in each of the dose groups. External malformations, such as cleft palate and exencephaly, were observed sporadically for fetuses of the control and dose groups.

Sodium Alkylbenzenesulfonate Mixture

As described earlier, Freeman et al. (1945) conducted a subchronic toxicity study in which the fertility of the treated rats also was determined. A Sodium Alkylbenzenesulfonate mixture (0.5g/100 g feed) was incorporated into the feed of rats (strain not specified; 21 days old; n = 21) for 65 days. Control rats received the basal diet. According to these authors, the Sodium Alkylbenzenesulfonate mixture had no effect on fertility in rats.

Dermal

TEA-Dodecylbenzenesulfonate

A semipermanent hair dye formulation containing 0.5% TEA-Dodecylbenzenesulfonate was applied dermally to a shaved dorsoscapular area of 20 pregnant Charles River CD rats (Burnett et al. 1976). A dose of 2 ml/kg was applied on days 1, 4, 7, 10, 13, 16, and 19 of gestation. Three negative control groups were shaved but not treated. The rats were killed on day 20 of gestation and the fetuses were examined. No signs of toxicity and no dermal irritation were observed in the treatment groups, other than discoloration of the skin and hair at the test site. There were no differences in body weight gains or feed consumption between the treated and negative control groups. The authors concluded that the test material did not produce embryotoxic or teratogenic effects.

Burnett et al. (1981) reported a study in which 25 male Sprague-Dawley CD rats were dosed dermally with 0.5 ml of a semipermanent hair dye formulation that contained 0.2% to 0.3% TEA-Dodecylbenzenesulfonate twice weekly for 10 weeks . The formulation was applied to a shaved 1 in^2 area on the back of each rat. A second group of 25 male Sprague-Dawley CD rats was untreated and served as a control group. After 10 weeks of dosing, each of the 25 treated male rats was mated with 3 10-week-old female Sprague-Dawley CD rats (1/week for 3 weeks) for a total of 75 mated females per group. The gravid females were allowed to deliver and the number and gender of live and dead pups were recorded. After 4 days, each litter was culled to a maximum of 6 males.

Two healthy 21-day-old males were selected from each litter as the F_1 males and kept until maturity. After 12 weeks, 100 F_1 males per group were mated with 3 sexually mature females (1/week for 3 weeks). The females were killed on days 14 to 16 of gestation and their uteri and fetuses were examined. There were no differences in body weight gains between the treated and control groups. The level of fertility was high for the initial test males as well as the controls, and the results of the matings of the F_1 males were similar for both groups.

There were no differences in the number of total and average live pups between the treated and control group. The authors concluded that the test material did not produce any adverse effects on reproduction in male Sprague-Dawley CD rats.

Linear Alkylbenzenesulfonate

Pregnant ICR-JCL mice were administered dermal applications of 0.5 ml of 0.85%, 1.7%, 2.55%, or 3.4% Linear Alkylbenzenesulfonate solutions on days 1 to 13 of gestation (Masuda et al. 1974). Controls were dosed with distilled water. The number of gravid dams was 20, 21, 16, 17, and 10 for the control, 0.88%, 1.7%, 2.55%, and 3.4% groups, respectively.

The final mean body weight of the 10 dams of the 3.4% Linear Alkylbenzenesulfonate group was increased compared to the final mean body weight of 10 dams of the control group. The absolute liver, kidney, and spleen weights were also increased for this group. There was no difference in body weight gain between test and control dams and no visceral defects were observed. Pregnancy rate was decreased in the 3.4% dose group, with a rate of 33.3% as compared to 69.0% for the controls; considerable dermal irritation was observed at the application site. Live fetus growth was decreased in all test groups except for the 1.7% group when compared to the controls. There was no difference in external or internal fetal anomalies. However, the frequency of retarded ossification of sternebrae was 25% and 27% for the 2.55% and 3.4% dose groups, respectively, as compared to 11% for the control group. The authors concluded that there was no conclusive evidence of teratogenic effects.

Pregnant ddY mice were administered dermal applications of 0.017%, 0.17%, or 1.7% Linear Alkylbenzenesulfonate solutions on days 2 to 14 of gestation. Two control groups were dosed with distilled water or were untreated. The number of gravid dams was 10, 7, 4, 10, and 5 for the untreated control, 0, 0.017%, 0.17%, and 1.7% groups, respectively. No adverse effects were observed for the test fetuses as compared to the controls. The authors concluded that there was no conclusive evidence of teratogenic effects (Masuda et al. 1974).

Palmer et al. (1975b) applied Linear Alkylbenzenesulfonate (0, 0.03%, 0.3%, or 3.0% in distilled water; 0.5 or 10 ml) to the shaved backs of CD-1 mice (n = 20), CD rats (n = 20), and New Zealand white rabbits (n = 13) to test for teraterogenic effects. The mice were treated days 2 to 13 of pregnancy, rats were treated days 2 to 15, and rabbits were treated days 1 to 16. The applications were not occluded or washed. One mouse died in the low-dose group, no rats died during treatment, and 1 rabbit in the mid-dose group died. The mouse and rabbit dams had dermal reactions consisting of erythema and edema with peak response at day 6 to 7. The mice also had dead skin and accumulated test material formed a scabrous layer; the rabbits had cracking and bleeding of the skin. There were minor dermal reactions in the rats. Recovery was evident in rats and rabbits after the peak response was attained. All animals had increasing irritability, with peak hypersensitivity at the same time as the local reactions. There was weight loss or marked weight retardation for mice and rabbits in the high-dose group. There was a decrease in number of litters containing viable young in the high-dose groups. The authors concluded that for the dams, marked toxicity was evident in the high-dose groups of mice and rabbits. Mild toxicity was observed in the mid-dose groups for mice and rabbits and the high-dose group for rats. Litter and mean pup weights were not affected by any dose in any of these species. There were no abnormalities associated with treatment at the low- and mid-dose levels. The high-dose level did not have enough litters for assessment.

Daly et al. (1980) tested the reproductive and developmental effects of dermally applied Linear Alkylbenzenesulfonate to clipped pregnant Wistar rats (n = 20 or 21). The test material was

Linear Alkylbenzenesulfonate (20.5%), alkylbenzene (0.2%), ash (0.6%), and water (77.7%). The 3 control groups were untreated and unclipped, clipped, or clipped and treated with water. The test groups were treated with the test material (1%, 5%, or 20% in water; 20, 100, or 400 mg/kg/d, respectively) by applying the test material, rubbing it in for 3 min, leaving it on for 30 min, and then rinsing off with water. The other test groups were treated with test material (0.05%, 0.1%, or 0.5%; 1, 2, or 10 mg/kg/d) which was not removed after application. The dams were treated daily from day 0 to 20 of gestation then killed and necropsied. The fetuses were examined for deformities.

There were no mortalities during the test period. The mean body weights of the high-dose wash off group were decreased compared to controls for gestation day 12 to 21. Feed consumption was comparable in all groups. There were no cutaneous manifestations in the 0.05%, 0.1%, or 0.5% leave-on groups. There was a light brown skin discoloration in 3 dams on days 3 to 6 of the 1.0% wash-off group, and 14 of 20 dams in the 5.0% wash-off group had slight erythema and dry skin on days 3 to 6 and slight skin thickening in 7 of 20 animals. After day 6, erythema and fissuring were no longer observed. Brown discoloration continued in 1 or 2 animals throughout treatment. The high-dose wash-off group had slight erythema on most dams on days 2 to 4. After day 6, this reaction was no longer observed. There was slight skin thickening at the application site on 2 dams on day 2 and on all dams by day 5. Moderate skin thickening was noted in 6 dams the first half of gestation. Slight fissuring was noted in 18 dams from day 4. Clear exudate and brown skin discoloration were occasionally noted.

There were no differences between groups with regards to number of corpora lutea, implantations, viable fetuses, or resorptions. No abnormalities were observed at necropsy. There were no differences among groups of offspring for viability or deformities. The authors concluded that Linear Alkylbenzenesulfonate applied to the skin of pregnant rats (either left on or washed off) elicits skin reactions and decreases maternal body weight but does not have any teratogenic or embryopathic effects (Daly et al. 1980).

A 20% Linear Alkylbenzenesulfonate solution (Nomura et al. 1980; Nomura et al. 1987) or a detergent containing a mixture of Linear Alkylbenzenesulfonate (27%) and alcohol sulfate was applied twice daily to the dorsal skin of pregnant JCL:ICR mice during the preimplantation period (days 0-2 of gestation). There was an increase in the number of embryos collected on day 3 that were severely deformed or remained at the morula stage. Most of the abnormal embryos were fragmented or remained at the 1- to 8-cell stages and were either dead or dying. The number of embryos in the oviducts was greater for the mice dosed with Linear Alkylbenzenesulfonate as compared to the control mice used in that study (which were dosed with water). No pathological changes were detected in the major organs of the dams.

GENOTOXICITY

Sodium Dodecylbenzenesulfonate

Kawachi et al. (1980) performed a variety of mutagenicity assays using Sodium Dodecylbenzenesulfonate. An Ames test using *Salmonella typhimurium* strains TA98 and TA100, a rec assay using *Bacillus subtilis* without metabolic activation, and a chromosomal aberration test using hamster lung fibroblast cells without metabolic activation all had negative results.

In another test, these authors used Sodium Dodecylbenzenesulfonate in a mutation test involving silk worms. The results were negative (Kawachi et al. 1980).

Linear Alkylbenzenesulphonate

In an in vitro transformation assay of Linear Alkylbenzenesulfonate, cryopreserved hamster embryo cells (n = 9) were used as the source of target and feeder cells. No transformations were produced at concentrations up to 50 µg/ml, but Linear Alkylbenzenesulfonate was cytotoxic at this concentration (Inoue et al. 1980).

Linear Dodecylbenzenesulfonates/Ozone/UV

Murakami et al (1992) exposed Linear Dodecylbenzenesulfonates to ozone and UV for 4 and 8.5 h or ozone alone for 16 h (with an antifoaming agent). A mutation frequency assay was performed using the resulting degradation products (0 to 100 µl/plate) and *S. typhimurium* (TA98, TA100, and TA104) with and without metabolic activation. The LDS decomposition products were lethal at 10^{-4} M. The degradation products from the 4-h treatment were mutagenic in a concentration dependent manner for all 3 strains, with and without metabolic activation. The products of the 8.5 h and ozone alone treatments were mildly mutagenic. The experiment was repeated with formaldehyde and glyoxal at the same concentrations as that resulting from the 4-h ozone/UV experiment and various concentrations of Linear Dodecylbenzenesulfonates and antifoaming agent. There were no interactions or effects observed. The same assay was repeated with just formaldehyde or glyoxal. Formaldehyde was mutagenic for TA104 with and without activation and TA100 with activation. Glyoxal was mutagenic for TA104 and TA100 with and without activation. The authors suggest that the mutagenic activity of decomposed Linear Dodecylbenzenesulfonates was in part due to formaldehyde and glyoxal, but not entirely.

Murakami et al. (1996) exposed Sodium Linear Dodecylbenzenesulfonates to UV and ozone for 4 h. The resulting degradation products (0.1 ml) or Linear Dodecylbenzenesulfonates (0.1 ml) were used in a mutation assay using *S. typhimurium* (TA100 and TA104) with and without metabolic activation. Sodium LDS was not mutagenic.

The decomposition products were mutagenic for both strains with and without activation. Linear Dodecylbenzenesulfonates with activation was not lethal to TA104 up to ~10^{-2} mol/l or without activation up to ~10^{-4} mol/l, but was above these concentrations. Linear Dodecylbenzenesulfonates with activation was not lethal to TA100 up to ~10^{-3} mol/l or without activation up to ~10^{-4} mol/l, but was above these concentrations. The authors calculated the total amount of formaldehyde and glyoxal in the decomposed Linear Dodecylbenzenesulfonates solution accounted for 44.9% of the total mutagenicity of the decomposed Linear Dodecylbenzenesulfonates solution without metabolic activation and 68.4% with activation for TA104. Formaldehyde and glyoxal accounted for 31.75% and 88.0% of the total

mutagenicity for TA100, respectively. However, when Linear Dodecylbenzenesulfonates, formaldehyde, and glyoxal were assayed in different combinations, the authors concluded that the mixture does not increase the mutagenicity by interaction between formadehyde and glyoxal.

CARCINOGENICITY

Oral

Sodium Dodecylbenzenesulfonate

Rats (number, gender, and strain unspecified) were given 100 ppm (0.01%) Sodium Dodecylbenzenesulfonate in drinking water for 100 weeks (Bornmann et al. 1961). Lesion occurrence, including incidences of neoplasms, was not changed. Body weight gain was not affected.

Linear Alkylbenzenesulfonate

Rats (gender and strain unspecified), 23 per group, were administered 0.01%, 0.05%, or 0.1% LAS in drinking water for 2 years (Tiba 1972). A control group of 21 rats was administered untreated water. No increase in neoplasm incidence was observed. Body weight was not affected.

Dermal

TEA-Dodecylbenzenesulfonate

A skin painting study was performed to determine the carcinogenic potential of a semipermanent hair dye formulation containing 0.5% TEA-Dodecylbenzenesulfonate (Burnett et al. 1980). The hair dye formulation, 0.05 ml, was applied to a shaved 1 cm^2 area of the intrascapular region of 100 Swiss Webster mice (50 males and 50 females) once a week for 23 months. Three negative control groups were shaved but not dosed for 23 (1 group) or 21 months (2 groups). Animals were observed daily for mortality, changes in behavior, and physical appearance, evidence of lesions was recorded weekly, and body weights were recorded monthly. After 9 months of dosing, 10 males and 10 females from each group were killed for necropsy; liver and kidney weights were recorded and organ to body weight ratios were determined. Gross and microscopic examinations were performed. There were no differences observed in mean or absolute liver or kidney weights or in organ to body weight ratios among the mice killed after 9 months. There was no difference in survival rate between the test and control groups. The incidence of neoplasms in test and control groups was also similar. The authors concluded that the test material did not produce carcinogenic effects.

Linear Alkylbenzenesulfonate

Percutaneous application of a formulation containing 15.6% Linear Alkylbenzenesulfonate to Swiss ICR mice (number, gender, and strain unspecified) at concentrations of 0.1%, 1.0%, or 10.0% 3 times per week for 18 months produced neither a dermal nor a systemic carcinogenic response (Arthur D. Little, Inc. 1991). In the 10% test group (50 animals), acanthosis and/or hyperkeratosis of the treated skin and one squamous papilloma were observed.

Physicochemical Screening Test

Sodium Dodecylbenzenesulfonate

A physicochemical screening test, the k_e test, was used to screen for the carcinogenic potential (Bakale and McCreary 1987); Sodium Dodecylbenzenesulfonate was determined not to be potentially carcinogenic.

CLINICAL ASSESSMENT of SAFETY

Oral Absorption

Linear Alkylbenzene Sulfonate

In a human oral absorption study (144 h after dermal administration of ^{35}S-Linear Alkylbenzene Sulfonate in another study) 90% of the radioactivity was excreted in the urine and feces. Approximately 50% of the dose was absorbed and excreted in the urine within 24 h (Arthur D. Little, Inc. 1991).

Dermal Absorption

Dodecylbenzenesulfonate

Campeau (1960) tested the dermal absorption of Dodecylbenzenesulfonate in the form of triethanolamine salt of alkyl (kerosene) benzenesulfonic acid (alkyl benzenesulfonate [52%], triethanolamine sulfate [8%], and water [40%]). The test substance was used as a scrub for 2 min. The substance was extracted from the skin using acid methanol in a test tube with a known area of the mouth by inverting the test tube over the skin 30 times. The absorption was used to determine the amount of recovered Dodecylbenzenesulfonate (n not provided). On the human palm, 570 $\mu g/cm^2$ was recovered. On the fingertips and the forearm, 360 and 94 $\mu g/cm^2$ Dodecylbezenssulfonate was recovered, respectively. When pH was adjusted, the amount of Dodecylbenzenesulfonate recovered increased as pH decreased. At a low pH of 3, adsorption continues even after prolonged scrub periods, but at pH 7, the rate of adsorption does not increase after 8 min. Dodecylbenzenesulfonate is completely removed from the skin with soap. The authors concluded that Dodecylbenzenesulfonate adsorbs readily to the skin.

Linear Alkylbenzene Sulfonate

A human dermal absorption study determined that 144 h after dermal application of ^{35}S-Linear Alkylbenzene Sulfonate, 99% of the radioactivity was removed from the application site and < 0.01% of the radioactivity was recovered in the urine and feces (Arthur D. Little, Inc. 1991).

Although penetration of Linear Alkylbenzene Sulfonate into human skin did not occur readily, adsorption was pH-dependent (Iimori 1971). With a pH range of 7.0 to 11 .0, absorption of Linear Alkylbenzene Sulfonate decreased as the alkalinity of a post dose rinse increased.

Oral Toxicity

Sodium Alkylbenzenesulfonate

Freeman et al. (1945) orally administered a Sodium Alkylbenzenesulfonate mixture (100 mg/d) in capsule form to male adults (n = 6) with meals (33.3 mg/meal) for 4 months. Red and white blood cell counts and hemoglobin content were not affected. There was no change in kidney function. There was transient flatulence and loss of appetite in 2 subjects. One subject

did not take the capsules with meal and suffered epigastric pain after ingestion which ceased after following instructions.

In another experiment, feces were collected from male subjects (n = 6) in 2 5-day periods, one with a consistent diet and the other with the consistent diet plus 33.3 mg Sodium Alkylbezenesulfonate mixture in capsules at each of 3 meals/d. In 5 of the subjects, there were no effects on the fat and nitrogen content of the feces. The sixth subject had an increase in fecal fat and nitrogen. The authors concluded that the Sodium Alkylbenzensulfonate mixture has a low order of toxicity when ingested with food or when taken just before a meal (Freeman et al. 1945).

Dermal Irritation

Sodium Dodecylbenzenesulfonate

An aqueous solution of 12.5 mmol Sodium Dodecylbenzenesulfonate (pH 6.4)/l (with a correction being made for percentage of active mass) was applied to an area on the forearm of 18 subjects, 8 males and 10 females (Tupker et al. 1989). Irritation was determined by measuring transepidermal water loss (TEWL) and by visual observation. The subjects were treated with 0.3 ml of the solution and treated twice daily each working day for 3 weeks (for a total of 28 applications). The solution was applied to a disc of absorbent Whatman paper that was taped to the volar side of the forearm, near the elbow, for 45 min. The mean interval between applications was 3 h and the test site was rinsed and dried after removal of the paper

Sodium Dodecylbenzenesulfonate application resulted in an increase in TEWL over the 3 weeks, with a mean TEWL of 10.1 g/m^2h on day 19; the mean baseline TEWL was 4.9 g/m^2h. Using mean TEWL values as the standard for comparison, Sodium Dodecylbenzenesulfonate was less irritating than sodium lauryl sulfate. After 3 weeks of dosing, the TEWL value increased to ≥ 5 g/m^2h and the visual score was 1 + for almost 70% of the subjects (Tupker et al. 1989).

Linear Alkylbenzenesulfonates

The soap chamber test was used to evaluate the irritation potential of 1.0% and 0.1% solutions of Linear Alkylbenzenesulfonates (Froebe et al. 1990). Occlusive patches were used to apply 0.2 ml of the aqueous solutions to the volar forearm of 8 female subjects for 24 h. After patch removal, the application site was rinsed and scored for erythema. On the following 4 days, patches were applied for 6 h to the same site. Erythema was scored at the test site prior to patch application and 72 h after removal of the final patch.

A 1% Linear Alkylbenzenesulfonates solution produced moderate/intense erythema in all subjects within 48 h; therefore, testing at this concentration was discontinued. The 0.1% Linear Alkylbenzenesulfonates solution produced negligible or mild erythema. The mean erythema score 72 h after removal of the final patch was 1.2/3 and 0/3 for the 2 groups tested with 0.1% Linear Alkylbenzenesulfonates solutions.

Cumulative irritation patch testing using 0.05% and 0.2% aqueous Linear Alkylbenzenesulfonates on 71 and 81 subjects, respectively, produced mild to moderate irritation (Arthur D. Little, Inc. 1991).

In Vitro

A study was performed correlating in vitro epidermis curling and in vivo dermal irritation (Tavss et al. 1985). Application of a 2.4% solution of LAS (pH 5.3) to epidermal strips caused the strips to twist and curl, resulting in a curling ratio of 0.25 ± 0.011. Application of a 10% solution of LAS (neutral pH) for 5 days to the forearms of 2 to 3 subjects using Duhring chambers produced severe irritation within the first day.

The relative intensity of skin roughness produced by LAS formulations of varying alkyl chain length was evaluated (Imokawa et al. 1975). LAS formulations with alkyl chain length of 12 carbons produced more skin roughening than LAS formulations with alkyl chain lengths of 8, 14, or 16 carbons.

Dermal Sensitization

Linear Alkylbenzenesulfonate

The sensitization potential of 0.05 and 0.2% aqueous concentrations of Linear Alkylbenzenesulfonate was evaluated using 71 and 81 subjects, respectively (Arthur D. Little, Inc. 1991). Sensitization reactions were not observed at either concentration.

The sensitizing potentials of a 0.1% aqueous Linear Alkylbenzenesulfonate solution and a 0.1% LAS solution in 50% ethanol/water were evaluated on 86 subjects (Arthur D. Little, Inc. 1991). The 0.1% aqueous solution of LAS did not produce a sensitization reaction in any subject. The 0.1% solution in 50% ethanol/water produced a sensitization response in 6 subjects. Subsequent testing of the 50% ethanol/water solution alone determined that the positive response was due to ethanol.

Human repeated insult patch testing of 0.01% to 0.113% Linear Alkylbenzenesulfonate alone using 2,294 subjects and 0.001% to 0.09% Linear Alkylbenzenesulfonate in formulation using 17,887 subjects did not produce a sensitization reaction in any of the subjects (Robinson et al. 1989). Extended product use testing reported no evidence of sensitization or any other skin reactions due to Linear Alkylbenzenesulfonate; patch testing of 79 consumers with skin problems due to products containing Linear Alkylbenzenesulfonate did not result in positive reactions to Linear Alkylbenzenesulfonate.

SUMMARY

An earlier safety assessment of Sodium Dodecylbenzenesulfonate, TEA-Dodecylbenzenesulfonate, and Sodium Decylbenzenesulfonate was expanded to include Ammonium Dodecylbenzenesulfonate, Calcium Dodecylbenzenesulfonate, DEA-Dodecylbenzenesulfonate, Isopropylamine Dodecylbenzenesulfonate, Magnesium Isodecylbenzenesulfonate, MIPA-Dodecylbenzenesulfonate, Potassium Dodecylbenzensulfonate, Sodium Tridecylbenzenesulfonate, and TEA-Tridecylbenzenesulfonate.

Sodium Dodecylbenezenesulfonate is a linear alkylbenzene sulfonate. The breakdown products of Sodium Dodecylbenzenesulfonate exposed to a combination of ultraviolet irradiation and ozone includes formaldehyde and glyoxal. Sodium Dodecylbenzenesulfonate is soluble in water; partially soluble in alcohol. Impurities can include organic fillers, sodium

sulfonate, sodium chloride, neutral oil, arsenic, iron, and lead. Linear Alkylbenzenesulfonates impurities include dialkyltetralin, dialkylnaphthalenes, and to a lesser extent, dialkylbenzene.

In data provided to the FDA under the VCRP, Sodium Dodecylbenzenesulfonate is currently used in 12 products at 2% to 3%. TEA-Dodecylbenzenesulfonae is currently used in 39 products at 0.002% to 5%. Sodium Decylbenzenesulfonate has no uses currently reported to FDA, but a use concentration of 0.02% has been reported by industry. There are no reports of uses or concentrations of use for Ammonium Dodecylbenzenesulfonate, Calcium Dodecylbenzenesulfonate, DEA-Dodecylbenzenesulfonate, Isopropylamine Dodecylbenzenesulfonate, Magnesium Isodecylbenzenesulfonate, MIPA-Dodecylbenzenesulfonate, Postassium Dodecylbenzensulfonate, Sodium Tridecylbenzenesulfonate, or TEA-Tridecylbenzenesulfonate. All of these ingredients function as surfactant-cleansing agents.

Rats fed Sodium Dodecylbenzenesulfonate excreted most of it in the feces and urine. All tissues had some residues with the highest concentrations in the colon and small intestine. Sodium Dodecylbenzenesulfonate injected i.p. or s.c. into rats was excreted primarily in the feces and urine. Rats orally administered Linear Alkylbenzene Sulfonates excreted almost all of it in the feces and urine. Orally administered Linear Alkylbenzene Sulfonates to rhesus monkeys was excreted mostly in the urine in first 24 h.

Dermal absorption was pH dependent. Dermally applied Sodium Dodecylbenzensulfonate was found on the skin surface and in the upper regions of the hair follicles. There was no measurable penetration of Sodium Dodecylbenzenesulfonate in human abdominal skin observed until 24 h after application; the rate of penetration then increased rapidly. There was no measurable penetration found up to 24 h after application of ^{14}C-Sodium Dodecylbenzenesulfonate.

Orally administered Linear Alkylbenzenesulfonates to developing rats for 10 weeks affected enzymatic activity in the liver and kidneys.

A mixture of Sodium Alkylbenzenesulfonates had inhibitory effects on amylase, lipase, trypsin, pepsin, phosphatase and various enzymes collected from a dog and a human. An increase in the release of alkaline phosphatase was observed when the jejunum was perfused with Ringer's bicarbonate solution containing 0.5% Sodium Dodecylbenzenesulfonate. A decrease in sucrase and alkaline phosphatase activities was observed when rats were fed a diet containing 2.5% Sodium Dodecylbenzenesulfonate. In an enzyme preparation from the small intestine, 0.1% Sodium Dodecylbenzenesulfonate inhibited sucrase, maltase, and leucine aminopeptidase activity; alkaline phosphatase activity was not affected.

Sodium Dodecylbenzenesulfonate was nontoxic and non inhibitory up to 5.7 x 10^{-6} M for the human mixed lymphocyte reaction.

The oral LD_{50} of Sodium Dodecylbenzenesulfonate was 2.0 g/kg for mice and 1.26 g/kg for rats. The oral LD_{50} of a detergent solution containing 15% Sodium Dodecylbenzenesulfonate was 7.5 ml/kg for rats and 12.6 ml/kg for mice. A lethal dosage for dogs was 400 ml/kg; 100 ml/kg had no effect. The oral LD_{50} of a 1:128 aqueous diIution of (195.3 mg/kg body wt) TEA-Dodecylbenzenesulfonate in rats was >10 ml/kg. For male and female rats, the LD_{50} of Linear Alkylbenzene Sulfonate was 0.65 ± 0.063 g/kg. The oral LD_{50} of Linear Alkylbenzene Sulfonate for mice was 2.30 g/kg. Alkylbenzene Sulfonate administered orally to mice caused death in all 8 mice administered 1.5 g/kg. At 3.5 g/kg, 15 of 20 rats died. At 2.2 g/kg, 3 of 4 rabbits died.

The dermal LD_{50} of a 1:128 aqueous dilution of TEA-Dodecylbenzenesulfonate in rabbits was >21.5 ml/kg. The dermal LD_{50} for Linear Alkylbenzene Sulfonate for rabbits was >500 mg/kg. The i.v. LD_{50} of Sodium Dodecylbenzenesulfonate for mice was 105 mg/kg.

In a short term study, there were incidences of wheezing, nasal discharge, rough fur, a blood-like discharge around the eyes or nose, excitability, and unthriftiness in rats fed Sodium Dodecylbenzenesulfonate up to 20,000 ppm. There were no effects observed in rats and dogs fed Sodium Dodecylbenzenesulfonate up to 0.50% for 90 days in several studies. In one other study, dogs administered 0.50% had generalized, comparative weakness and lack of activity, decreased body weights and weight gains, decreased feed consumption, lower values for hemoglobin, hematocrit, and erythrocyte counts. Microscopic examination showed mild degenerative changes of the liver. Sodium Dodecylbenzenesulfonate had synergistic hepatic effects when combined with polychlorinated biphenyl.

No significant changes were observed in rats fed Linear Alkylbenzene Sulfonate at ~ 5000 ppm or up to 0.25 g/kg/d for 12 weeks. Alkylbenzensulfonate was not classified as a toxic compound in rats at concentrations up to 50% for 45 days. Dogs orally administered a Sodium Alkylbenzenesulfonate up to 4.0 g/d showed anorexia.

There was increased chronic inflammatory cell infiltration at the subcutaneous injection sites and injection-associated pseudocysts, hemorrhage, and necrosis in rhesus monkeys injected s.c. with Linear Alkylbenzene Sulfonate after oral administration of Linear Alkylbenzene Sulfonate. There were no treatment related findings with regards to ophthalmological, laboratory, and other pathological tests.

No systemic toxicity was observed at concentrations of up to 10% Linear Alkylbenzene Sulfonate applied to intact and abraded skin of rabbits except for weight loss at the highest dose. A semipermanent hair dye formulation containing 0.5% TEA-DDBS was applied dermally, twice weekly for 13 weeks, to rabbits did not produce systemic toxicity.

In a subchronic study, Sodium Dodecylbenzenesulfonate at 2.5 ml/kg/d in drinking water growth rates were decreased in rats which became rapid weight loss at 5.0 ml/kg/d. Weight increased with discontinuation of treatment. Mild necrosis of intestinal mucosa with hemosiderosis of the spleen, liver, and kidneys were observed at necropsy.

Sodium Alkylbenzenesulfonate had an oral NOEL of 1 g/d over 6 months for dogs, 0.2% in the drinking water of guinea pigs for 6 months, and 1.0% for 16 weeks for rats. No effects were

observed in rats fed a diet containing up to 0.5% Linear Alkylbenzene Sulfonate for 84 days. Renal damage was observed in rats administered Linear Alkylbenzene Sulfonate at 0.2 or 0.6%.

No effects were observed for rats administered feed with ≥40% alkylbenzene sulfonate at 2 ppm except that females had increased kidney weights compared to controls; there was no evidence of kidney damage.

A Sodium Alkylbenzenesulfonate mixture (1.0 g/d) administered to dogs in capsules for 6 months had no adverse effects. Rats fed 0.5 g/100 g feed also had no adverse effects after 65 days.

Sodium Dodecylbenzenesulfonate in the feed of rats at 2,000 ppm over 104 weeks caused no behavioral or clinical signs. Several rats had unthrifty appearance, rough coats, alopecia, bloody noses and eyes, dyspnea, and sores on the head or body and had lower growth rates. Beagles fed Sodium Dodecylbenzenesulfonate at 0.5% for 104 weeks had weakness, lack of activity, decreased feed consumption, and anemia. Livers had slight degenerative changes. At microscopic examination, dogs given 100 and 1,000 mg/kg. Sodium Dodecylbenzenesulfonate in the diet had hemorrhagic necrosis of the intestine and infiltration of chronic inflammatory cells.

There was no evidence of toxicity by Sodium Alkylbenzenesulfonate at 0.1% in feed or drinking water to rats for 104 weeks. There were no adverse effect to rats administered feed with 0.5% Linear Alkylbenzene Sulfonate for 2 years. A decrease in body weight gain, tissue damage in the cecum and liver, and increased severity of renal lesions, specifically glomerular atrophy and necrosis of urinary tubules were observed in rats fed high doses (not specified) of Linear Alkylbenzene Sulfonate.

Sodium Alkylbenzenesulfonate at 1% was a mild ocular irritant in rabbits. Sodium Alkylbenzenesulfonate at 35% caused erosion/attenuation and denudation of the conjunctiva, edema of the substantia propria, and inflammation, principally neutrophilic associated with substantia propria. The cornea had epithelial cell loss at 3 h with erosion/attenuation and denudation. At day 35, 2/40 rats still had not fully recovered. Concentrations of ≤0.1% Linear Alkylbenzene Sulfonate produced mild to no irritation in rabbits. TEA-Dodecylbenzenesulfonate at a 1:128 dilution was not an ocular irritant in rabbits. Sodium Decylbenzenesulfonate produced severe ocular irritation in rabbits. There was a moderate response that disappeared by 96 h in the eyes of rabbits treated with Alkylbenzenesulfonate at 40%.

Sodium Dodecylbenzenesulfonate at 15.0% was severely irritating to the skin of rabbits, with a primary irritation score of 5.3/8.0. Erythema was evident on 3 rats dermally treated with Sodium Dodecylbenzenesulfonate at 10% after 5 days. A 0.5 ml of a 1:128 aqueous dilution of TEA-Dodecylbenzenesulfonate was not irritating to rabbit skin.

Moderate skin irritation was observed when a 10% and 25% w/v aqueous Linear Alkylbenzene Sulfonate solution was applied to rabbits. When rabbits were administered 2 ml applications of ≤10% Linear Alkylbenzene Sulfonate on abraded skin daily for 28 days and on intact skin for 91 days, severe dermal irritation was observed at the application site. Rabbits administered 3 6-h applications of 5% to 25% Linear Alkylbenzene Sulfonate resulted in moderate to severe erythema and moderate edema. Administration of 30% Linear Alkylbenzene Sulfonate produced dermal damage in rats. A 1% Linear Alkylbenzene Sulfonate solution did not produce any dermal irritation in rabbits. In guinea pigs, a 2g/100ml aqueous solution of C_{12} Linear Alkylbenzene Sulfonate (97.88% purity) produced moderate to severe dermal irritation, with irritation scores of 3.0/4.0 and 1.42/4.0 and a mixed Linear Alkylbenzene Sulfonate solution (99.8% purity) containing 33.7% C_{12}, and 7.0% C_{10}, produced dermal irritation scores of 2.75/4.0 and 0.58/4.

Alkylbenzenesulfonate applied to the abraded skin of shaved rabbits caused slight persistent edema and erythema.

None to moderate sensitization to Linear Alkylbenzene Sulfonate was observed in guinea pigs. Alkylbenzensulfonate was nonsensitizing.

There were no teratogenic effects of 0.5% TEA-DDBS in rats. Application of a hair dye formulation containing 0.3% TEA-DDBS did not produce any adverse effects on reproduction in male rats. Dermal application of Linear Alkylbenzene Sulfonate at 3.0% produced marked toxicity that was evident in mice and rabbit dams whereas there were no effects to the pups. Linear Alkylbenzene Sulfonate, up to 10 mg/kg/d, applied to the skin of pregnant rats elicited skin reactions and decreased maternal body weight but did not have any teratogenic or embryopathic effects.

Orally administered Sodium Alkylbenzenesulfonate at 1% had no observed effects on fertility, litter size, lactation, or survival of offspring in rats. Orally administered Alkylbenzenesulfonate at 1% and 2% caused diarrhea in pregnant rats. The weight of the placenta was reduced, the number of pups per litter was reduced, the number of dead litters and dead pups were increased, and the number of resorptions were reduced in the high-dose group. In the high-dose group, body weight, body length, and tail length of the pups were reduced. Pregnant mice orally administered Alkybenzenesulfonate had decreased maternal weight gain. There were no effects observed on the fetuses from dams at 24 mg/kg/d. The number of dead pups increased at 240 mg/kg/d. There were no congenital malformations observed in either treatment group.

There were no developmental effects observed associated with Linear Alkylbenzene Sulfonate, up to 0.02%, in the feed of pregnant rats. Linear Alkylbenzene Sulfonate was toxic to pregnant mice at 300 mg/kg/d, rabbits at 300 mg/kg/d, and rats at 600 mg/kg/d; at nontoxic and slight to moderately toxic dosages, values for litter size and fetal loss were unaffected. Maternal body weight gains and fetal body weights of mice were decreased at 10 mg/kg/d. A 20% Linear Alkylbenzene Sulfonate solution or a detergent containing a mixture of Linear Alkylbenzene Sulfonate (27%) dermally applied to pregnant mice resulted in an increase in the number of embryos that were severely deformed or remained at the morula stage on day 3.

Sodium Dodecylbenzenesulfonate was not mutagenic in an Ames test and a silkworm test. Linear Alkylbenzene Sulfonate was not mutagenic but was cytotoxic at 50 µg/ml. Linear Alkylbenzene

Sulfonate, treated with ozone and UV, was mutagenic to *S. typhimurium*.

Sodium Dodecylbenzenesulfonate at 0.01%, and Linear Alkylbenzene Sulfonate, at 0.1%, were not carcinogenic to rats when administered in drinking water for up to 2 years.

The dermal application of a hair dye formulation containing 0.5% TEA-Dodecylbenzenesulfonate did not produce carcinogenic effects in mice. At 10%, Linear Alkylbenzene Sulfonate caused acanthosis and/or hyperkeratosis of the treated skin of mice with one squamous cell papilloma observed. Sodium Dodecylbenzenesulfonate was predicted to be not carcinogenic using the electron attachment rate constant (k_e) test.

A Sodium Alkylbenzenesulfonate mixture has a low order of toxicity when humans ingested it with food or when taken just before a meal. In a human oral absorption study conducted 144 h after dermal administration of ^{35}S-Linear Alkylbenzene Sulfonate, 90% of the radioactivity was excreted in the urine and feces. Dodecylbenzenesulfonate adsorbs readily to human skin. After dermal application of Linear Alkylbenzene Sulfonate to human skin for 2 min, 99% was removed from the application site and < 0.01% was recovered in the urine and feces.

An aqueous solution of 12.5 mmol Sodium Dodecylbenzenesulfonate applied to human skin resulted in a minimal redness for almost 70% of the subjects. A 1% Linear Alkylbenzene Sulfonate solution produced moderate/intense erythema in all subjects within 48 h; 0.1% Linear Alkylbenzene Sulfonate solutions produced negligible or mild erythema. Repeated patch testing using 0.05% and 0.2% aqueous Linear Alkylbenzene Sulfonate produced mild to moderate irritation. Application of a 10% solution of Linear Alkylbenzene Sulfonate (neutral pH) for 5 days to subjects produced severe irritation within the first day.

Sensitization reactions were not observed at 0.05 and 0.2% Linear Alkylbenzene Sulfonate. Extended product use testing of 0.01% to 0.113% Linear Alkylbenzene Sulfonate and 0.001% to 0.09% Linear Alkylbenzene Sulfonate in formulation resulted in no evidence of sensitization or any other skin reactions. Patch testing of consumers with skin problems due to products containing Linear Alkylbenzene Sulfonate did not result in positive reactions to Linear Alkylbenzene Sulfonate.

DISCUSSION

The irritant properties of Sodium Dodecylbenzenesulfonate are similar to those of other detergents, with the severity of irritation dependent on the concentration and pH of the ingredient. While ocular irritation by Sodium Dodecylbenzenesulfonate may be dependent on the test setting, the CIR Expert Panel recognized that Sodium Dodecylbenzene-sulfonate, at pH 9, may be an ocular irritant. In preparations containing Sodium Dodecyl-benzenesulfonate designed to remain in contact with the skin, the product should be formulated to ensure that the irritancy potential is minimized.

The Expert Panel further noted that DEA, TEA, and MIPA had been evaluated previously and were found to be safe as used. Dialkylnaphthalenes and dialkyltetralin are impurities in alkylbenzylsulfonates. While the the concentrations are low, they may absorb through the skin. No evidence of carcinogenic activity was reported in oral studies of Sodium Dodecylbenzenesulfonate or Linear Alkylbenzene Sulfonate, or in dermal studies of TEA-Dodecylbenzenesulfonate or Linear Alkylbenzene Sulfonate, suggesting that the low level of such impurities were not carcinogenic. Because of concern about the carcinogenicity of N-nitroso compounds, however, these salts of alkylbenzene sulfonates should not be used in products where N-nitroso compounds may be formed.

The CIR Expert Panel recognized that there are data gaps regarding use and concentration of this ingredient. However, the overall information available on the types of products in which this ingredient is used and at what concentration indicated a pattern of use, which was considered by the Expert Panel in assessing safety.

Although there were minimal toxicity data available on the other ingredients in this report, the Expert Panel determined that the chemical structures of Sodium Dodecylbenzenesulfonate, Ammonium Dodecylbenzenesulfonate, Calcium Dodecyl-benzenesulfonate, DEA-Dodecylbenzenesulfonate, Isopropylamine Dodecylbenzenesulfonate, Magnesium Isodecyl-benzenesulfonate, MIPA-Dodecylbenzenesulfonate, Potassium Dodecylbenzenesulfonate, Sodium Decylbenzenesulfonate, Sodium Dodecylbenzenesulfonate, Sodium Tridecyl-benzenesulfonate, TEA-Dodecylbenzenesulfonate, and TEA-Tridecylbenzenesulfonate were all sufficiently similar, such that the safety test data available in this report could be extended to support the safety of all of the salts of alkylbenzene sulfonates.

AMENDED CONCLUSION

Salts of alkylbenzene sulfonates, including Ammonium Dodecyl-benzenesulfonate, Calcium Dodecyl-benzenesulfonate, DEA-Dodecylbenzenesulfonate, Isopropylamine Dodecylbenzenesulfonate, Magnesium Isodecylbenzenesulfonate, MIPA-Dodecylbenzenesulfonate, Potassium Dodecylbenzenesulfonate, Sodium Decylbenzenesulfonate, Sodium Dodecylbenzenesulfonate, Sodium Tridecylbenzene-sulfonate,TEA-Dodecylbenzenesulfonate, and TEA-Tridecyl-benzenesulfonate, are safe as cosmetic ingredients in the practices of use given in this safety assessment when formulated to be non-irritating.[1]

[1] 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, and also would be formulated to be non-irritating.

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4

Final Report on the Safety Assessment of Isostearic Acid

Isostearic Acid is a mixture of fatty esters consisting mainly of methyl branched isomers of octadecanoic acid and is used at concentrations up to 10% in a wide variety of cosmetic products. In rats, the acute oral LD50 is estimated to be greater than 32 ml/kg. The raw ingredient produced no significant skin or eye irritation in Draize rabbit irritation tests.

In clinical studies, 100 subjects showed no signs of irritation after a 24 h single insult skin patch with undiluted Isostearic Acid. Thirty-four percent Isostearic Acid was neither an irritant nor a sensitizer in 168 subjects, and gave no indication of phototoxicity in a subset of this population.

It is concluded that Isostearic Acid is safe as a cosmetic ingredient in the present practices of use. Consideration for the compound's potential for production of human comedogenicity is noted.

CHEMISTRY

Composition

Isostearic Acid is the Cosmetic, Toiletry and Fragrance Association (CTFA) adopted name for a complex blend of branched-chain saturated isomers of octadecanoic acid. The chemical literature sometimes uses the term Isostearic Acid to refer specifically to the isomer 16-methylheptadecanoic acid (CAS Number 2724-58-5). However, the ingredient which is used in cosmetics is a mixture of the 18 carbon isomers generally branching with the methyl group.[1,2] According to CTFA Specifications, Isostearic Acid consists of approximately 80% branched chain C_{16} and C_{18} acids and 20% straight-chain C_{14}, C_{16}, and C_{18} acids.[3] Approximate values for the distribution of the different types of fatty acids present in Isostearic Acid are listed in Table 1.

Isostearic Acid is prepared by dimerizing the fatty acids of Tall Oil, Soybean Oil, or Tallow in the presence of a catalyst. The reaction mixture is then separated into monomer and dimer fractions by distillation. The monomer fraction which is rearranged during the reaction is further refined by hydrogenation, solvent separation, and an additional distillation.[4,5]

Methods for the laboratory synthesis of 16-methylheptadecanoic acid have also been described.[6-10]

TABLE 1. Fatty Acid Components of Isostearic Acid.

Component	*Level (%)*
Methyl-branched isomers of octadecanoic acid	approx. 80
C14 linear saturated fatty acid (Myristic)	1–10
C18 linear saturated fatty acid (Stearic)	1–10
C16 linear saturated fatty acid (Palmitic)	4–8
C18 Oleic acid	0–2

Data from Ref. 4.

Physical Properties

Isostearic Acid is a clear, oily liquid with little odor. It is insoluble in water but easily soluble in such organic solvents as ethanol, acetone, ethyl ether, carbon tetrachloride, and others. Its alkaline salts are readily soluble in water.[2]

The different isomers are mutually soluble and show virtually identical properties. Since it is a mixture, the melting point of Isostearic Acid is much lower than one would expect for a saturated fatty acid of similar molecular weight.[2] Whereas the melting point of 16-methylheptadecanoic acid has been reported as 69.5°–69.7°C,[7] Isostearic Acid is a liquid at room temperature.

Table 2 presents CTFA specifications for Isostearic Acid[3] as well as measured values for the chemical and physical properties of Isostearic Acid obtained from three different commercial sources.[2]

Studies on the molecular and crystalline structures of 16-methylheptadecanoic acid have been conducted,[11,12] and infrared data are available.[13] The surface chemistry of Isostearic Acid as a cosmetic ingredient has also been studied.[14]

Reactivity

Isostearic Acid should participate in chemical reactions common to long chain, saturated fatty acids.

TABLE 2. Chemical and Physical Properties of Isostearic Acid.

Mol. wt.	*Solid pt.*	*Viscosity*	*Sp. gr.*	*Iodine value*	*Acid value*	*Sapon. value*
284	10 °C max.	50 cps 25 °C	0.89 25 °C	3.0 max.[a]	191.0–201.0[a]	197.0–204.0[a]
			0.906 25 °C	3.0	191.0–201.0	197.0–204.0
				8[b]	180–200	185–205
				8	177	189

[a]CTFA Specification.
[b]Resulting from chain branching, not from double bonds.
Data from Refs. 2,3.

Analytical Methods

Gas chromatography,[15,16] mass spectrometry,[17] infrared spectrometry,[13] and x-ray crystallography[11] have been used in the study of Isostearic Acid or its component isomers.

Impurities

Isostearic Acid typically contains unsaponifiable matter and moisture at levels of 3.0% and 1.0%, respectively.[4] Analysis of one sample of Isostearic Acid revealed unsaponifiables at 4% and moisture at 0.01%.[2]

USE

Purpose in Cosmetics

Isostearic Acid is an emollient[18] which shows some of the same chemical properties as stearic acid and has physical properties similar to those of oleic acid. It is used as a replacement for stearic acid when "smoother and more easily spreading" products are desired without the use of oleic acid. Emulsions using Isostearic Acid have desirable organoleptic properties and resist degradation of color and odor. This ingredient is also employed in synthesizing a wide variety of esters that are used in cosmetic formulations.[2]

Scope and Extent of Use in Cosmetics

Table 3 lists product types and the number of product formulations containing Isostearic Acid as reported by the Food and Drug Administration (FDA) in 1981. It is contained in a wide variety of cosmetic products at concentrations generally less than 5%; one fragrance preparation and one suntan product were reported to contain Isostearic Acid in the 5%–10% range.[19] Unpublished safety data (reviewed elsewhere in this report) on a skin cleansing product containing 35% Isostearic Acid suggest possible use at higher concentrations.[20,21]

The cosmetic product formulation computer printout which is made available by the FDA is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations. Ingredients are listed in prescribed concentration ranges under specific product type categories. Certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration. The value reported by the cosmetic formulator in such a case may not necessarily reflect the actual concentration found in the finished product; the actual concentration would be a fraction of that reported to the FDA. The fact that data are submitted only within the framework of preset concentration ranges also provides the opportunity for a two- to 10-fold overestimation of the actual concentration of an ingredient in a particular product.

Potential Interactions with Other Ingredients

Chemical interactions of Isostearic Acid with the other ingredients in cosmetic formulations have not been reported.

TABLE 3. Product Formulation Data on Isostearic Acid.

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)			
			>5-10	>1-5	>0.1-1	≤0.1
Isostearic Acid						
Eyeliner	396	2	–	1	1	–
Eye shadow	2582	17	–	2	14	1
Mascara	397	9	–	9	–	–
Blushers (all types)	819	20	–	10	9	1
Face powders	555	13	–	1	2	10
Makeup foundations	740	12	–	11	1	–
Lipstick	3319	8	1	–	6	–
Makeup bases	831	17	–	11	6	–
Rouges	211	1	–	1	–	–
Bath soaps and detergents	148	3	–	3	–	–
Other personal cleanliness products	227	2	–	–	2	–
Shaving cream (aerosol brushless, and lather)	114	2	–	2	–	–
Other shaving preparation products	29	1	–	–	1	–
Skin cleansing preparations (cold creams, lotions liquids and pads)	680	5	–	3	2	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	6	–	3	3	–
Moisturizing skin care preparations	747	19	–	8	11	–
Night skin care preparations	219	2	–	1	1	–
Skin lighteners	44	1	–	1	–	–
Suntan gels, creams, and liquids	164	1	1	–	–	–
Other suntan preparations	28	1	–	1	–	–
1981 TOTALS		142	2	68	59	12

Data from Ref. 19.

Surfaces to which Commonly Applied

Products containing Isostearic Acid are applied to all areas of the skin, hair, nails, and mucous membranes (Table 3). They may be applied as many as several times a day and remain in contact with the skin for various periods of time following each application. Daily or occasional use may extend over many years.

BIOLOGICAL PROPERTIES

Although branched chain fatty acids are not usually found in animal tissues,[22] the 16-methylheptadecanoic acid component of Isostearic Acid has been isolated from a number of animal sources. Hydrogenated mutton fat,[23]

wool,[7] and milk fat[15,16,24] have been found to contain trace amounts of 16-methylheptadecanoic acid. Likewise, it appeared in relatively small amounts in the mitochondrial and microsomal fractions of rat pituitary homogenate.[22] It was also detected in bovine muscle, where its relative concentration was significantly correlated with subjective evaluations of tenderness and flavor.[25]

Isostearate and other branched chain fatty acids supported the growth of a sterol requiring Mycoplasma (strain Y) which was unable to synthesize or alter the chain length of either saturated or unsaturated fatty acids.[26]

The incorporation of free fatty acids into myxoviruses was shown through the use of branched chain fatty acids as molecular markers. Gas–liquid chromatography revealed the presence of incorporated 16-methylheptadecanoic acid.[27]

Metabolism

Acyl coenzyme A synthetase of rat liver homogenate was found to activate Isostearic Acid.[28] Iso-fatty acids are metabolized in a way similar to that of straight-chain fatty acids by the mitochondrial and microsomal fractions of rat liver homogenate. In contrast, however, with the straight-chain fatty acids which are successively oxidized at the β carbon to yield two carbon fractions, the iso-fatty acids are also oxidized to a large extent at the ω carbon to ultimately form three carbon dicarboxylic acids. The enzymes catalyzing the ω-hydroxylation are present in the mitochondrial and microsomal fractions of liver homogenate, whereas the enzymes catalyzing the further oxidation into carboxylic acids have been demonstrated in the soluble fraction.[17]

Animal Toxicology

Acute Studies

Oral toxicity

The acute oral toxicity of Isostearic Acid was evaluated in three studies on the undiluted ingredient[29-31] and two studies on product formulations containing the ingredient.[32,33] In each study, young adult albino rats were fasted overnight and administered a single dose of the undiluted ingredient or product formulation by gastric intubation. They were then allowed free access to food and water for two weeks. The results and other details of these studies are summarized in Table 4. From these data, the acute oral LD50 of Isostearic Acid in rats is between 32 and 64 ml/kg.

Primary skin irritation and phototoxicity

The potentials for primary skin irritation caused by undiluted Isostearic Acid,[34] 15% Isostearic Acid in corn oil[30] and three product formulations containing Isostearic Acid[20,32,35] were evaluated using the Draize rabbit skin patch test technique. In each study, 0.5 ml samples were applied and occluded for 24 h, after which time the patch sites were graded for erythema and edema on the Draize scale. The results and other details of these studies are summarized in Table 5. The undiluted ingredient produced minimal irritation of the rabbit skin, whereas no irritation was noted when it was diluted to 15% in corn oil. Product

TABLE 4. Acute Oral Toxicity Tests on Isostearic Acid.

Concentration (%)	*Dose*	*Dose of Isostearic Acid (adjusted for dilution)*	*Animals*	*Results*	*Comments*	*Ref.*
100	2.0–64.0 ml/kg	2.0–64.0 ml/kg	5 rats at each of 6 dose levels	no deaths at doses up to 32 ml/kg; 3 died at 64.0 ml/kg	Slight nasal hemorrhage at 32.0 ml/kg; moderate to severe nasal hemorrhage at 64.0 ml/kg with erratic locomotion prior to death. Two survivors at 64.0 ml/kg were severely debilitated. LD50 between 32.0 and 64.0 ml/kg	29
100	5 g/kg	5 g/kg	10	no deaths		31
100	15.9 g/kg	15.9 g/kg	5 rats	no deaths		30
4.0 (in product formulation)	15.0 g/kg	0.6 g/kg	5 rats	no deaths		32
2.0 (in product formulation)	15.9 g/kg	0.32 g/kg	5 rats	no deaths		33

TABLE 5. Draize Primary Skin Irritation Tests on Isostearic Acid.

Concentration (%)	*Number of rabbits*	*Primary irritation index (max = 8)*	*Comments*	*Refs.*
100	6	0.63	Minimal irritation	34
100	6	0.3	Minimal transient irritation	37
15 (in corn oil)	6	0.0	No signs of irritation	30
35 (in product formulation)	9	1.89	Moderate irritation by product formulation	20
4 (in product formulation)	9	0.39	Minimal irritation by product formulation	32
4 (in product formulation)	9	0.06	Minimal irritation by product formulation	35
1.25 (aqueous solution of product formulation)	9	0.00	No signs of irritation by aqueous solution of product formulation	20

formulations containing Isostearic Acid produced minimal to moderate skin irritation, most probably by virtue of the other ingredients present in the formulations.

In a primary skin irritation and phototoxicity test, 200 mg of 100% Isostearic Acid was applied to the dorsal surface of New Zealand rabbits. The test material was applied for 2 h under gauze patches to 1-in^2 skin areas on both the left- and right-hand sides. The patch on the right-hand side was removed and exposed to 5×10^7 ergs/cm^2 black light (320–450 nm). The nonirradiated areas were shielded with aluminum foil during the light exposure. A positive Oxsoralen control was treated in a similar manner. The investigators concluded that the test material was mildly irritating without light exposure and only moderately irritating following light exposure. The investigator reported that a statistically significant difference was not detected between the nonirradiated and radiated sites.[36]

Eye irritation

The Draize rabbit eye irritation procedure or a modification of the test was used to evaluate undiluted Isostearic Acid[30,37] and four product formulations containing Isostearic Acid.[20,32,33,35] In each study, a 0.1 ml sample was instilled into the conjunctival sac of one eye of each rabbit with no washing; the untreated eye served as a control. Treated eyes were examined and graded on the Draize eye irritation scale at 1, 2, 3, 4, and 7 days. The results and other details of these studies are summarized in Table 6. The undiluted ingredient produced only minimal eye irritation which cleared by 24 h. Some of the product formulations produced moderate eye irritation, which is greater than that produced by the ingredient alone.

Comedogenicity

Comedogenicity* studies were conducted on two sunscreen formulations, one containing 2.5% Isostearic Acid and the other without Isostearic Acid.[38-40]

*Comedones are also known as blackheads.

TABLE 6. Draize Eye Irritation Tests on Isostearic Acid.

Type of product formulation	*Isostearic Acid concentration (%)*	*Number of rabbits*	*Ocular irritation index (max = 110)*					*Comments*	*Ref.*
			24 h	*48 h*	*72 h*	*4 days*	*7 days*		
None	100	3	0	0	0	0	0	Transient conjunctival irritation at 1 h; all eyes normal by 24 h.	30
None	100	6	0.3	0	0	0	0	Eyes unwashed; minimal transient irritation.	37
		3	0	0	0	0	0	Eyes washed with tepid water; no irritation.	
Skin cleanser	35 (in product formulation)	6	34	14	6	4	0	Moderate reversible eye irritation which gradually cleared; all eyes normal by Day 7.	20
Face color	4 (in product formulation)	6	1	0	0	0	0	Transient conjunctival irritation at 24 h; all eyes normal by 48 h.	32
Mascara	4 (in product formulation)	6	8	6	4	1	0	Minimal eye irritation which gradually cleared; all eyes normal by Day 7	35
		retest of same animals	2	1	0	0	0	after initial application and by 72 h after repeat application.	
Face makeup foundation	2 (in product formulation)	3	–	0	0	0	0	Transient conjunctival irritation at 24 h; all eyes normal by 48 h.	33

– No data.

The formulation containing Isostearic Acid was tested in two separate assays;[38,39] 1 ml of the product was applied to the glabrous inner portion of the right ear of each of nine rabbits. The left ear was untreated and served as a control. The test material was applied five days per week for a total of 20 applications. Observations of grossly appearing enlarged pores and hyperkeratosis were made daily, and terminal biopsies were made with histologic comparison of treated and control skin. The product containing Isostearic Acid was significantly comedogenic and irritating to rabbit ears under the conditions of this test. An identical assay on the product without Isostearic Acid[40] showed the formulation to be irritating but not comedogenic to the ears of six rabbits.

Clinical Assessment of Safety

Primary Skin Irritation

A 24 h occlusive patch test procedure was used to evaluate the primary skin irritation caused by undiluted Isostearic Acid[30] and by four product formulations containing Isostearic Acid.[21,33,41,42] The results and other details of these studies are summarized in Table 7. The undiluted ingredient tested "negative" in the single insult patch test; product formulations containing Isostearic Acid produced up to minimal irritation, most probably by virtue of the other ingredients present in the formulations.

A sunscreen formulation containing 2.5% Isostearic Acid was applied to the backs of 10 subjects. Approximately 50–200 mg of the test formulation containing 1.2–5.0 mg Isostearic Acid was used in the test. The test sites were occluded for 48 h before removal. No irritation was reported.[43]

In another study,[44] 19 women participated in a controlled-use test on the skin cleanser formulation containing 35% Isostearic Acid. The product was ap-

TABLE 7. Clinical 24-Hour Single Insult Patch Tests with Isostearic Acid.

Product type	*Isostearic Acid concentration (%)*	*Number of subjects*	*Results*	*Ref.*
None	100	100	"negative"	30
Face color	4 (in product formulation)	19	No signs of irritation	41
Mascara	4 (in product formulation)	18	No signs of irritation	42
Skin cleanser	0.44 (1.25% aqueous solution of product formulation containing 35% Isostearic Acid)	80 (20 each for four versions of the product formulation)	PIIs = 0.13 to 0.18; (max = 4.0) minimal irritation	21
Face makeup foundation	0.2 (10% in peach kernel oil of product formulation containing 2% Isostearic Acid)	104	"negative"	33

plied once on one cheek the first day and twice on the same cheek on Days 2–4 of the study. The other cheek, cleansed with soap, served as a control. None of the 19 participants noted discomfort. Although three reported mild to moderate dryness on the area treated with the cleanser, the product compared favorably to the control soap.

A sunscreen containing 2.5% Isostearic Acid was tested in a 21-day repeated insult patch test on 19 subjects. The test material, 0.2 g of formulation, was placed on nonwoven fabric patches and semioccluded on the backs of the subjects for 24 h. A total of 15 applications of the material were applied over a 21-day test period. A Cumulative Irritation Index (CII) of 0.87 out of a maximum score of 84 was reported. The investigator did not consider this value of CII to be clinically significant.[45]

Irritation/Sensitization

One hundred three subjects completed a repeated insult patch test of 10% Isostearic Acid dissolved in mineral oil. Each subject received a patch to the intact skin of the upper back under semiocclusion. The patches remained in place for 48 h (72 h on weekends) at which time they were removed, the sites were examined for irritation and new patches were applied. These procedures were repeated 10 times, followed by a two-week nontreatment period and rechallenge. The test ingredient had a mean cumulative irritation score of 0.243 ± 0.068. Mineral oil was included in the study as a nonirritating control and had a mean cumulative irritation score of 0.177 ± 0.042. Propylene glycol, a positive control as a known mild irritant, had a mean cumulative score of 0.388 ± 0.071. The investigators reported there were no skin reactions consistent with ingredient-induced sensitization.[46]

A repeated insult patch test was performed on 168 subjects (115F, 53M) using 0.1 ml of a 35% mineral oil solution of Isostearic Acid. The test material was applied at 48 h intervals, three times per week for three weeks on the back of the subjects. The test area was occluded for 24 h before removal, and washed with distilled water. The test sites were read at 48 h, after which fresh test material and the occlusive patch were reapplied. After a three-week nontreatment period, the test area, as well as a previously untreated site, were challenged using the same procedure as previously noted. The sites were scored for sensitization at 24, 48, and 72 h. The investigator noted that only transient reactions were observed during the test and that Isostearic Acid was neither an irritant nor a sensitizer.[47]

A sunscreen containing 2.5% Isostearic Acid was tested in a 21-day repeated insult patch test. Approximately 200 mg of the test formulation, which is equivalent to 5 mg of Isostearic Acid, was applied at 48 h intervals for 10 applications to the backs of 235 Caucasian females. Following a two-week nontreatment period, the subjects were re-exposed for 48 h. There were no reactions during the induction phase of the study, and the investigator concluded that the formulation's potential for sensitization was extremely low, or nonexistent.[48]

A mascara formulation containing 2.85% Isostearic Acid was tested in a repeated insult patch test on 98 subjects.[49] The induction phase of the procedure consisted of 10 consecutive occlusive patch applications to the same site over a period of two weeks. A single occlusive challenge patch was applied to

TABLE 8. Clinical Repeated Insult Patch Tests with Isostearic Acid.

Product Type	*Concentration (%)*	*Number of subjects*	*Results*	*Ref.*
None	35 (mineral oil dil.)	168	No irritation; no sensitization	47
None	10 (mineral oil dil.)	103	None to mild irritation; no sensitization	46
Mascara	2.85	98	1/98 show some irritation; no sensitization	49
Sunscreen	2.5	235	No irritation potential; as sensitizer, extremely low or nonexistent	48

the original contact site and/or a virgin site after a 10- to 14-day nontreatment period. During the induction phase of the experiment, one subject exhibited some skin irritation. There were no reactions at challenge and thus no indications of skin sensitization. The results of all repeated insult patch tests are summarized in Table 8.

Phototoxicity and Photosensitization

Twenty-eight of the 168 subjects tested for irritation and sensitization discussed above were randomly selected to test the ability of 35% Isostearic Acid in mineral oil to induce a phototoxic or photosensitive reaction following ultraviolet exposure. The test protocols were the same except that the forearm was used as a test site. The 28 subjects were divided into two groups; 19 received only UVA and 9 received both UVA and UVB. The UVA (320–400 nm) light was applied for 15 min to the 19 subjects (4.4 $\mu W/cm^2$ at the skin surface measured at a 360 nm wavelength peak). The UVB was applied at two times Mean Erythema Dose (MED) to nine subjects from a 150 watt Xenon Arc Solar Simulator emitting at 280–320 nm. The subjects receiving the UVB exposure were also exposed for 5 min to UVA as previously described. The investigator noted that only transient reactions were observed, and that Isostearic Acid was not a photosensitizer.[47]

SUMMARY

Isostearic Acid is a mixture of fatty esters consisting mainly of methyl branched isomers of octadecanoic acid. It is reported by the FDA to be used at concentrations up to 10% in a wide variety of cosmetic products which may be applied to all areas of the body; data have also been received on a product containing 35% Isostearic Acid.

Studies with rat liver homogenate suggest Isostearic Acid is readily metabolized following ingestion. In rats, the acute oral LD50 is estimated to be greater than 32 ml/kg. The raw ingredient produced no significant skin or eye irritation in Draize rabbit irritation tests, whereas variable degrees of irritation were produced by product formulations containing Isostearic Acid. A product for-

mulation both with and without 2.5% Isostearic Acid was tested in a rabbit ear comedogenicity assay. The formulation without Isostearic Acid was irritating but did not produce comedones; however, the formulation with Isostearic Acid was both irritating and comedogenic.

In clinical studies, 100 subjects showed no signs of irritation after a 24 h single insult skin patch with undiluted Isostearic Acid, and product formulations containing up to 4% Isostearic Acid produced, at most, minimal irritation when similarly tested on a total of 221 subjects. In another study, 35% Isostearic Acid in mineral oil was neither an irritant nor a sensitizer in 168 subjects. A subset population of 25 individuals from this study group, when tested in a similar manner but exposed to UVA + UVB, gave no indication that Isostearic Acid is a photosensitizer. Isostearic Acid at 10% in mineral oil was similarly not irritating nor sensitizing to 103 subjects. Product formulations containing 2.5%–2.85% Isostearic Acid produced no evidence of contact sensitization when tested in repeated insult patch tests on a total of 333 subjects.

DISCUSSION

The Panel expresses concern regarding the production of comedones in the rabbit ear assay by a product formulation containing commercially available Isostearic Acid. The Panel recognizes that currently available tests are inadequate to predict the potential for human comedogenicity of an ingredient as used in a product formulation. However, it is a potential health effect that should be considered when Isostearic Acid is used in cosmetic formulations.

CONCLUSION

On the basis of the available information presented in this report, the Panel concludes that Isostearic Acid is safe as a cosmetic ingredient in the present practices of use.

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Final Report of the Amended Safety Assessment of Myristic Acid and Its Salts and Esters as Used in Cosmetics

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Abstract

This report addresses the safety of the inorganic salts and esters of various fatty alcohols of myristic acid. Most of the esters are used as skin conditioning agents in many types of cosmetics in a range of concentrations. Myristate esters are readily hydrolyzed to the corresponding alcohols and acids, which are then further metabolized. Myristate salts readily dissociate in any likely cosmetic formulation. The Cosmetic Ingredient Review (CIR) Panel recognized that much of the data supporting the ingredients in this group were previously reviewed in safety assessments for related ingredients. Where specific data did not exist, the Panel considered structure–activity relationships in determining the safety of these ingredients as used in cosmetics. The Panel determined that myristic acid and its salts and esters are safe as cosmetic ingredients in the current practices of use and concentration.

Keywords

safety, cosmetics, myristic acid, salts, esters

Introduction

In 1990, the Cosmetic Ingredient Review (CIR) Expert Panel concluded that butyl myristate is a safe cosmetic ingredient.[1] This safety assessment was re-reviewed in 2006 to consider new safety data and the Expert Panel reaffirmed that myristic acid ester is safe as used in cosmetics. The Expert Panel re-opened this safety assessment to include other esters that are chemically similar to butyl myristate, along with the salts of myristic acid. The Panel determined that the available data in the original safety assessment are sufficient to support the safety of these additional salts and ester of myristic acid.

The Expert Panel also combined this expanded report with other myristates that have already been reviewed. These and other related ingredients that were previously reviewed by the CIR Expert Panel are listed in Table 1.

This amended safety assessment, therefore includes:

- aluminum dimyristate,
- aluminum isostearates/myristates,
- aluminum myristate,
- aluminum myristates/palmitates,
- calcium myristate,
- cetyl myristate,
- decyl myristate,
- ethylhexyl myristate,
- ethyl myristate,
- glyceryl dimyristate,
- glyceryl isostearate/myristate,
- glyceryl myristate,
- isobutyl myristate,
- isocetyl myristate,
- isodecyl myristate,
- isopropyl myristate,
- isostearyl myristate,
- isotridecyl myristate,
- lauryl myristate,
- magnesium myristate,
- methyl myristate,

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- myristic acid,
- myristyl myristate,
- octyldodecyl myristate,
- oleyl myristate,
- potassium myristate,
- propylene glycol myristate,
- sodium myristate,
- tetradecyloctadecyl myristate,
- tridecyl myristate, and
- zinc myristate.

Data from previous safety assessments on butyl myristate, glycerol myristate, myristic acid, isopropyl myristate and myristyl myristate were reviewed and considered during this assessment. For these ingredients, the previous conclusions CIR Panel (as applicable to the ingredients noted) are summarized in the following sections.

Butyl Myristate, JACT, *9(2) 1990*

Butyl myristate is the ester of butyl alcohol and myristic acid. It is a colorless, oily liquid, which is used in cosmetic formulations at concentrations up to 50%. Aliphatic esters such as butyl myristate may be readily hydrolyzed in vivo to the corresponding alcohol and acid, which are then further metabolized. The median lethal dose (LD_{50}) of butyl myristate was greater than 8 g/kg in rats. In animal tests, undiluted butyl myristate was moderately irritating but was not a skin sensitizer. No evidence of eye irritation was noted. On the basis of the available data presented in this report on butyl myristate, as well as other related myristate compounds, the CIR Expert Panel found butyl myristate safe for cosmetic formulation usage.

Glyceryl Myristate, IJT, *23(suppl 2:55-94)2004*

The safety of 43 glyceryl monoesters listed as cosmetic ingredients was reviewed in a safety assessment completed in 2000. Glyceryl myristate was included in this group. Glyceryl monoesters have little, acute or short-term toxicity in animals, and no toxicity was noted following chronic administration of a mixture consisting mostly of glyceryl di- and monoesters. Undiluted glyceryl monoesters may produce minor skin irritation, especially in abraded skin, but in general these ingredients are not irritating at concentrations used in cosmetics. These ingredients are not photosensitizers. Glyceryl monoesters tested failed to produce any significant positive reactions at concentrations used in cosmetics. Based on these data, the CIR Expert Panel found glyceryl myristic safe as a cosmetic ingredient in the current practices of its use and concentration.

Myristic Acid, JACT, *6(3) 1987*

Oleic, lauric, palmitic, myristic, and stearic acids were reviewed as part of a group. These fatty acids are absorbed, digested, and transported in animals and humans. Little acute toxicity was observed when oleic, lauric, palmitic, myristic, or stearic acid or cosmetic formulations containing these fatty acids were given to rats orally at doses of 15 to –19 g/kg body weight. Most of the data in this assessment was oleic, lauric, palmitic, and stearic acids; myristic acid was included in the safety assessment due to its structural similarity. In primary and cumulative irritation clinical studies, oleic, myristic, and stearic acids at high concentrations were nonirritating. Cosmetic product formulations containing oleic, lauric, palmitic, and stearic acids at concentrations ranging up to 13% were not primary or cumulative irritants, nor sensitizers. On the basis of available data from studies using animals and humans, it is concluded that oleic, lauric, palmitic, myristic, and stearic acids are safe in current practices of their use and concentration in cosmetics.

Myristyl Myristate and Isopropyl Myristate, JACT, *1(4) 1982*

Acute oral and dermal toxicity tests indicated that myristyl myristate is nontoxic to rats. This cosmetic ingredient produced minimal-to-mild skin irritation, minimal eye irritation in rabbits, and no sensitization in guinea pigs. Studies with rabbits indicated that undiluted isopropyl myristate was a mild irritant after 24 hours and moderate to severe when applied for3 consecutive days. Isopropyl myristate was minimally irritating to the rabbits' eyes and was not a skin sensitizer in studies with guinea pigs. In limited studies, isopropyl myristate was not carcinogenic on the skin of mice, but a mixture of isopropyl myristate and isopropyl alcohol significantly accelerated the carcinogenic activity of benzo(a)pyrene on the skin.

Human studies with isopropyl myristate indicated that it was not a human skin irritant or sensitizer when applied in a product formulation containing 15% to 58% of the ingredient. A product containing 43% of isopropyl myristate produced no phototoxicity and no photocontact allergenicity in human studies.

From the available information, it is concluded that myristyl myristate and isopropyl myristate are safe as cosmetic ingredients in the current practices of their use.

Summaries of the data from these reports are provided *in italics* where applicable throughout the report.

Chemistry

Definition and Structure

The definitions, structures, and function in cosmetics of myristic acid and the related salt and esters are given in Table 2.

Also, included in Table 2 are the formulas/structures and functions in cosmetics as given in the *International Cosmetic Ingredient Dictionary and Handbook.*[15] The myristates are esters and salts of myristic acid that have the general formula shown in Figure 1.[8]

According to the *International Cosmetic Ingredient Dictionary and Handbook,*[15] myristic acid (CAS No 544-63-8) is an organic acid also known as tetradecanoic acid.

Table 1. Related Ingredients Previously Reviewed by the CIR Expert Panel

Ingredient	Uses	Use Concentrations	Conclusion	Reference
n-Butyl alcohol	112; 29 (addendum)	≤0.1%-10%; 0.000007%-15%	Safe in nail preparations in the current practices of use.	2,3
Cetyl alcohol	2694; 2931 (re-review)	>0.1%-50%; 0.000002%-15%	Safe as cosmetic ingredients in the current practices of use.	4,5
Glyceryl dimyristate	None reported	None reported	Safe as cosmetic ingredients in the practices of use and concentration as described in this safety assessment.	6
Glyceryl isostearate/ myristate	None reported	None reported	Safe as cosmetic ingredients in the current practices of use and concentration.	7
Glyceryl myristate	19	1%-6%	Safe as cosmetic ingredients in the current practices of use and concentration.	7
Isopropyl myristate	2198; 881 (re-review)	≤0.1%->50%; 0.00008%-78%	Safe as cosmetic ingredients in the current practices of use.	6,8
Isostearyl alcohol	41; 16 (re-review)	>0.1%-50%; 0.001%-50%	Safe as cosmetic ingredients in the current practices of use.	5,9
Methyl alcohol	4	0.1%-5%	Safe as used to denature alcohol used in cosmetic products.	10
Myristic acid	36; 73 (re-review)	>0.1%-50%; 0.00001%-38%	Safe in the current practices of use and concentration in cosmetics.	2,11
Myristyl myristate	160; 244 (re-review)	0.1%-25%; 0.01%-20%	Safe as cosmetic ingredients in the current practices of use.	6,8
Oleyl alcohol	1018; 343 (re-review)	≤0.1%->50%; 0.002%-18%	Safe as currently used in cosmetics.	6,12
Propylene glycol myristate	11	None reported	Safe as cosmetic ingredients in the current practices of use.	13

Abbreviation: CIR, Cosmetic Ingredient Review.

Aluminum dimyristate (CAS No 56639-51-1) is also known as aluminum hydroxybis (tetradecanoate) and tetradecanoic acid, aluminum complex.

Aluminum Isostearates/Myristates (no CAS No) is also known as aluminum triisostearate/trimyristate.

Aluminum myristate (CAS No 4040-50-0) is also known as aluminum monomyristate; myristic acid, aluminum salt; and tetradecanoic acid, aluminum salt.

Aluminum myristates/palmitates (no CAS No) is also known as aluminum trimyristate/tripalmitate.

Butyl myristate (CAS No 110-36-1) is also known as butyl n-tetradecanoate; myristic acid, butyl ester, and tetradecanoic acid, butyl ester.

Calcium myristate (CAS No 15284-51-2) is also known as calcium tetradecanoate; myristic acid, calcium salt; and tetradecanoic acid, calcium salt.

Cetyl myristate (CAS No 2599-01-1) is also known as hexadecyl myristate; hexadecyl tetradecanoate: myristic acid, cetyl ester; myristic acid, hexadecyl ester; and palmityl myristate, and tetradecanoic acid, hexadecyl ester.

Decyl myristate (CAS No 41927-71-3) is also known as decyl tetradecanoate; myristic acid, decyl ester; and tetradecanoic acid, decyl ester.

Ethyl myristate (CAS No 124-06-1) is also known as ethyl tetradecanoate and tetradecanoic acid, ethyl ester.

Ethylhexyl myristate (CAS No 29806-75-5) is also known as 2-ethylhexyl myristate; octyl myristate; and tetradecanoic acid, 2-ethylhexyl ester.

Glyceryl dimyristate (CAS No 53563-63-6) is also known as dimyristin; glycerol dimyristate; and tetradecanoic acid, diester with 1,2,3-propanetriol.

Glyceryl isostearate/myristate (no CAS No) is also known as glyceryl monoisostearate monomyristate.

Glyceryl myristate (CAS Nos 589-68-4 and 27214-38-6) is also known as glycerin monomyristate; glycerol monomyristate; glyceryl monomyristate, monomyristin; myristic acid monoglyceride; and tetradecanoic acid, monoester with 1,2,3-propanetriol.

Isobutyl myristate (CAS No 25263-97-2) is also known as 2-methylpropyl tetradecanoate; myristic acid, isobutyl ester; and tetradecanoic acid, 2-methylpropyl ester.

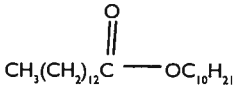
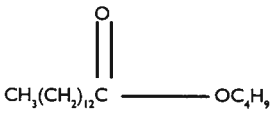
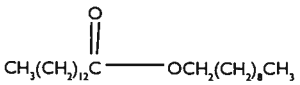
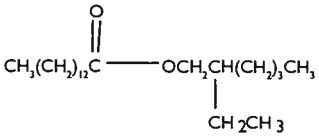
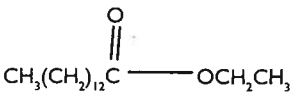
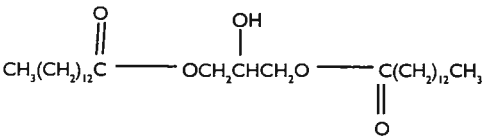
Isocetyl myristate (CAS No 83708-66-1) is also known as myristic acid, isocetyl ester; tetradecanoic acid, isocetyl ester; and tetradecanoic acid, isohexadecyl ester.

Isodecyl myristate (CAS Nos 17670-91-6 and 51473-24-6) is also known as 3,7-dimethyloctyl myristate; isodecyl tetradecanoate; myristic acid, isodecyl ester; tetradecanoic acid, 3,7-dimethyloctyl ester; tetradecanoic acid, isodecyl ester; and tetrahydrogeranyl myristate.

Isopropyl myristate (CAS No 110-27-0) is also known as IPM; isoproylis myristas; isopropyl tetradeconoate; 1-methylethyl tetradecanoate; myristic acid, isopropyl ester; and tetradecanoic acid, 1-methylethyl ester.

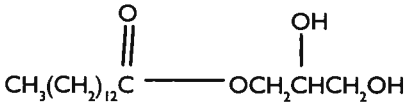
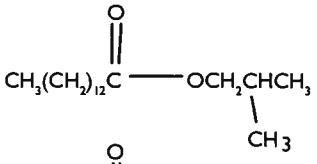
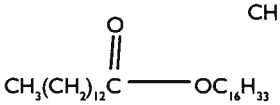
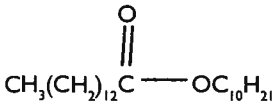
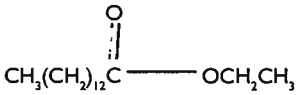
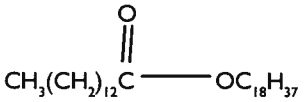
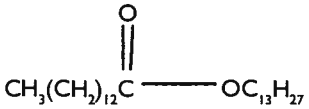
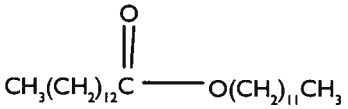
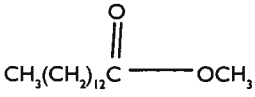
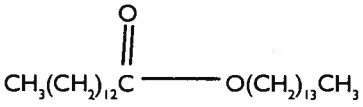
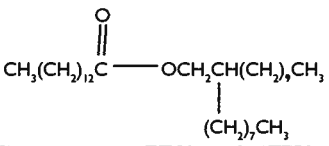
Isostearyl myristate (CAS No 72576-81-9) is also known as tetradecanoic acid, isooctadecyl ester.

Table 2. Definition, Structure, and Function of Myristic Acid and Its Salts and Esters Included in This Report as Given in the International Cosmetic Ingredient Dictionary and Handbook[14]

Ingredient	Definition	Formula/Structure	Function
Myristic acid	Organic acid that conforms generally to the formula:	$CH_3(CH_2)_{12}COOH$	Fragrance ingredient, opacifying agent, surfactant—cleansing agent
Salts			
Aluminum dimyristate	Aluminum salt of myristic acid	$[CH_3(CH_2)_{12}COO]_2AlOH$	Anticaking agent; emulsion stabilizer; viscosity increasing agent—nonaqueous
Aluminum isostearates/ myristates	Aluminum salt of a mixture of isostearic acid and myristic acid	None provided	Anticaking agent; emulsion stabilizer; viscosity increasing agent—nonaqueous
Aluminum myristate	Aluminum salt of myristic acid	$[CH_3(CH_2)_{12}COO]_3Al$	Anticaking agent; emulsion stabilizer; viscosity increasing agent—nonaqueous
Aluminum myristates/ palmitates	Aluminum salt of a mixture of palmitic acid and myristic acid	None provided.	Anticaking agent; emulsion stabilizer; viscosity increasing agent—nonaqueous
Calcium myristate	Calcium salt of myristic acid	$C_{14}H_{28}O_2 \cdot \frac{1}{2}Ca$	anticaking agent; emulsion stabilizer; viscosity increasing agent—nonaqueous
Magnesium myristate	Magnesium salt of myristic acid	$[CH_3(CH_2)_{12}COO^-]_2\ Mg^{+2}$	Anticaking agent; slip modifier; viscosity increasing agent—nonaqueous
Potassium myristate	Potassium salt of myristic acid	$C_3(C_2)_{12}\ COOK$	Surfactant—cleansing agent: surfactant—emulsifying agent
Sodium myristate	Sodium salt of myristic acid	$CH_3(CH_2)_{12}COONa$	Surfactant—cleansing agent; surfactant—emulsifying agent
Zinc myristate	Zinc salt of myristic acid	$[CH_3(CH_2)_{12}COO^-]_2\ Zn^{2+}$	Anticaking agent; slip modifier; viscosity increasing agent—nonaqueous
Esters			
Butyl myristate	Ester of butyl alcohol and myristic acid		skin-conditioning agent—emollient
Cetyl myristate	Ester of cetyl alcohol and myristic acid		Skin-conditioning agent—occlusive
Decyl myristate	Ester of decyl alcohol and myristic acid.		Skin-conditioning agent—occlusive
Ethylhexyl myristate	Ester of 2-ethylhexyl alcohol and myristic acid		Skin-conditioning agent—emollient
Ethyl myristate	Ester of ethyl alcohol and myristic acid		Fragrance ingredient; hair conditioning agent; skin-conditioning agent—emollient
Glyceryl dimyristate	Diester of glycerin and myristic acid		Skin-conditioning agent—emollient

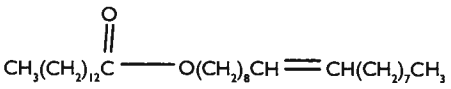
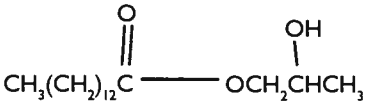
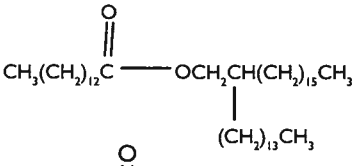
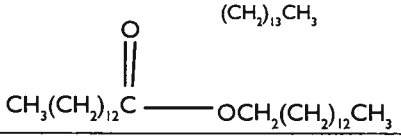
(continued)

Table 2 (continued)

Ingredient	Definition	Formula/Structure	Function
Myristic acid	Organic acid that conforms generally to the formula:	$CH_3(CH_2)_{12}COOH$	Fragrance ingredient, opacifying agent, surfactant—cleansing agent
Glyceryl isostearate/ myristate	Monoester of glyceryn esterfied with a blend of isostearic and myristic acids	None provided.	Skin-conditioning Agent—emollient; surfactant—emulsifying agent
Glyceryl myristate	Monoester of glycerin and myristic acid		Skin-conditioning agent—emollient; surfactant—emulsifying agent
isobutyl myristate	Ester of isobutyl alcohol and myristic acid		Skin-conditioning agent—emollient
Isocetyl myristate	Ester of isocetyl alcohol and myristic acid		Skin-conditioning agent—occlusive
Isodecyl myristate	Ester of branched chain decyl alcohols and myristic acid		Skin-conditioning agent—emollient
Isopropyl myristate	Ester of isopropyl alcohol and myristic acid		Binder; fragrance ingredient; skin-conditioning agent—emollient
Isostearyl mryistate	Ester of Isostearyl Alcohol and myristic acid		Binder; Skin-Conditioning Agent - Emollient
Isotridecyl myristate	Ester of myristic acid and isotridecyl alcohol		Hair conditioning agent; skin-conditioning agent—occlusive
Lauryl myristate	Ester of lauryl alcohol and myristic acid		Hair conditioning agent; skin-conditioning agent—occlusive
Methyl mryistate	Ester of methyl alcohol and myristic acid		Frangrance ingredient; skin-conditioning agent—emollient
Myristyl myristate	Ester of myristyl alcohol and myristic acid		Skin-conditioning agent—occlusive
Octyldodecyl Myristate	Ester of octyldodecanol and myristic acid.		Skin-conditioning agent—occlusive

(continued)

Table 2 (continued)

Ingredient	Definition	Formula/Structure	Function
Myristic acid	Organic acid that conforms generally to the formula:	$CH_3(CH_2)_{12}COOH$	Fragrance ingredient, opacifying agent, surfactant—cleansing agent
Oleyl myristate	Ester of oleyl alcohol and myristic acid		Hair conditioning agent; skin-conditioning agent—occlusive
Propylene glycol myristate	Ester of propylene glycol and myrisitic acid		Skin-conditioning agent—emollient; surfactant—emulsifying agent
Tetradecyloctadecyl myristate	Ester of tetradecyloctadecanol and myristic acid		Binder; emulsion stabilizer; film former; opacifying agent; skin-conditioning agent—occlusive
Tridecyl myristate	Ester of tridecyl alcohol and myristic acid		skin-conditioning agent—occlusive

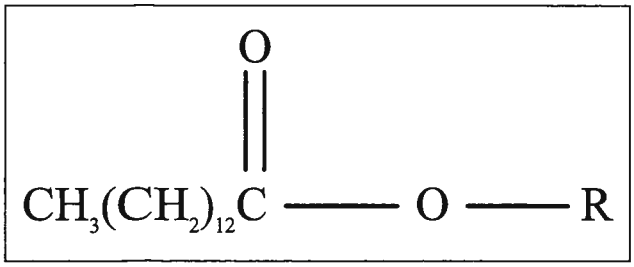


Figure 1. General myristate formula,[1] in which R may be as small as a methyl group for methyl myristate or a potassium ion for potassium myristate.

Isotridecyl myristate (CAS No 96518-24-0) is also known as tetradecanoic acid, isotridecyl ester.

Lauryl myristate (CAS No 2040-64-4) is also known as dodecyl tetradecanoate; myristic acid, dodecyl ester, and tetradecanoic acid, dodecyl ester.

Magnesium myristate (CAS No 4086-70-8) is also known as tetradecanoic acid, magnesium salt.

Methyl myristate (CAS No 124-10-7) is also known as methyl tetradecanoate; myristic acid, methyl ester; and tetradecanoic acid, methyl ester.

Myristyl myristate (CAS No 3234-85-3) is also known as tetradecanoic acid, tetradecyl ester, and tetradecyl tetradecanoate.

Octyldodecyl myristate (CAS Nos 22766-83-2 and 83826-43-1) is also known as myristic acid, 2-octyldodecyl ester; 2-octyldodecyl myristate; tetradecanoic acid, octyldodecyl ester; and tetradecanoic acid, 2-octyldodecyl ester.

Oleyl myristate (CAS No 22393-93-7) is also known as 9-octadecenyl tetradecanoate and tetradecanoic acid, 9-octadecenyl ester.

Potassium myristate (CAS No 13429-27-1) is also known as potassium tetradecanoate and tetradecanoic acid, potassium salt.

Propylene glycol myristate (CAS No 29059-24-3) is also known as propylene glycol monomyristate; propylene glycol monotetradecanoate; and tetradecanoic acid, monoester with 1,2-propanediol.

Sodium myristate (CAS No 822-12-8) is also known as sodium tetradecanoate and tetradecanoic acid, sodium salt.

Tetradecyloctadecyl myristate (no CAS No) is also known as myristic acid, tetradecyloctadecyl ester.

Tridecyl myristate (CAS No 36617-27-3) is also known as tetradecanoic acid, tridecyl ester.

Zinc myristate (CAS No 16260-27-8) is also known as tetradecanoic acid, zinc salt.

Physical and Chemical Properties

Myristic acid. Myristic acid occurs as a hard, white, or faintly yellow, glossy crystalline solid, as a white or yellow-white powder,[16] or as colorless leaflets.[17] Table 3 presents the physical and chemical properties of of myristic acid and octyldodecyl myristate.

Myristic acid is made of tetradecanoic acid (95% minimum), hexadecanoic acid (4% maximum), and dodecanoic acid (3% maximum) Cosmetic, Toiletries and Fragrance Association ([CTFA] Table 4).[25]

Table 3. Physical Properties of Myristic Acid and Octyldodecyl Myristate

Physical Property	Value	Reference
Myristic acid		
Molecular weight	228.36	18
	228.38	19
Density (g/mL) at 70°C	0.8528	18
Melting point (°C)	58.5	18
	58	19
	54.4	20
Boiling point (°C)	250.5	18
Solubility		
Water	Insoluble	16,18,19
Ethanol	Soluble	
Methanol	Very soluble	
Chloroform	Soluble	
Benzene	Very soluble	
Ether	Very soluble	
Viscosity (cp, at 75 (°C)	5.06	20
Acid value	245.7	20
Octyldodecyl Myristate		
Appearance	Oily liquid	21
Test at +8°C	Limpid	21
Odor	Faint	21
Color (Gardner Scale)	<1.5	21
Specific gravity at 20°C	1.435-1.457	21
Viscosity at 20°C	15-45 m.Pa.s	21
Acid value	< 7.00 mg KOH/g	21
Saponification value	90-110 mg KOH/g	21
Iodine value	<7.0 g I_2/100 g	21
Peroxide value	<6.0 meq O_2/kg	21
Alkaline impurities	<30 ppm NaOH	21
Water content	<0.50%	21
Sulphated ashes content	<0.1%	21
Heavy metals content	<10 ppm	21

Table 4. Comparison of Specifications[a]: Cosmetic and Food Grades of Myristic Acid[22]

Myristic acid	Cosmetics[22,23]	Foods[16]
Iodine value	0.5 maximum	1.0 maximum
Acid value	243-249	242-249
Saponification value	243-249	242-251
Unsaponifiable matter	0.2% maximum	1% maximum
Arsenic		3 ppm maximum
Heavy metals (eg, lead)		10 ppm maximum
Residue on ignition		0.1%
Titer (solidification point)	52-54°C	48-55°C
Water content		0.2%

[a] Cosmetic-grade myristic acid specifications for fatty acid composition is as follows: 12:0, 3% maximum; 14:0, 95% minimum; and 16:0, 4% maximum.[25]

Butyl myristate. Butyl myristate is a light, colorless, oily liquid. It is soluble in acetone, castor oil, chloroform, methanol, mineral oil, and toluene and insoluble in water. Other properties of butyl myristate include a freezing point range of 1°C to 7°C, a boiling point range of 167°C to 197°C (at 5 mm Hg), and a specific gravity between 0.850 and 0.858 at 25°C.[26]

Isocetyl myristate. Isocetyl myristate is an oily liquid with practically no odor. It has a density of 0.862, a freezing point of −39°C, and viscosity of 29.0 at 25°C. It is insoluble in water and soluble in most organic solvents. It is combustible.[27]

Nikko Chemicals Co, Ltd, reported that isocetyl myristate is a colorless liquid with a faint characteristic odor.[28] It has a

Table 5. Frequency of Use and Concentration of Myristic Acid and Its Salts and Esters in Cosmetics

Product Category (Total Number of Products in Each Category (FDA 2008))[69]	Frequency of Use[68]	Concentration of Use (%)[70,71]
Myristic Acid		
Bath products		
Soaps and detergents (1329)	9	0.1-19
Other (138)	–	2
Eye makeup		
Eye shadow (1196)	1	0.5
Mascara (463)	2	–
Noncoloring hair care products		
Conditioners (1249)	9	0.00003-0.0002
Shampoos (1403)	10	0.00002-5
Tonics, dressings, etc (1097)	6	0.00002-1
Other (716)	4	–
Hair-coloring products		
Color sprays/aerosol (8)	–	0.00002
Makeup		
Blushers (539)	–	0.3
Face powders (613)	1	0.5
Foundations (635)	15	0.04-0.8
Leg and body paints (29)	2	–
Lipsticks (1912)	5	–
Personal hygiene products		
Underarm deodorants (540)	1	2
Douches (12)	–	4
Other (514)	2	6-9[a]
Shaving products		
Aftershave lotions (395)	3	0.5
Shaving cream (162)	13	0.5-14
Other (107)	2	–
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1368)	101	0.08-15
Depilatories (62)	–	12
Face and neck creams, lotions, powder and sprays (1195)	1	39497
Body and hand creams, lotions, powder and sprays (1513)	13	0.8-10
Moisturizers (2039)	5	0.8
Night creams, lotions, powder and sprays (343)	–	0.005
Paste masks/mud packs (418)	–	4
Other (1244)	2	8
Suntan products		
Suntan gels, creams, liquids and sprays (156)	–	0.3
Indoor tanning preparations (200)	–	2
Total uses/ranges for myristic acid	207	0.00002-20
Aluminum dimyristate		
Eye makeup		
Eyeliners (684)	1	–
Eye shadow (1196)	133	0.2-3
Eye lotions (177)	–	0.09
Other (288)	1	0.3-2[b]
Makeup		
Blushers (539)	6	0.5-2
Face powders (613)	12	0.5-2
Foundations (635)	1	0.01-2
Makeup bases (164)	1	–
Rouges (99)	13	0.4
Other (406)	4	–

(continued)

Table 5 (continued)

Product Category (Total Number of Products in Each Category (FDA 2008))[69]	Frequency of Use[68]	Concentration of Use (%)[70,71]
Suntan products		
Other (62)	2	–
Total uses/ranges for aluminum dimyristate	174	0.01-3
Aluminum myristate		
Eye makeup		
Eye shadow (1196)	6	0.01-1
Makeup		
Blushers (539)	14	–
Face powders (613)	3	–
Total uses/ranges for aluminum myristate	23	0.01-1
Aluminum myistates/palmitates		
Makeup		
Face powders (613)	2	6
Total uses/ranges for aluminum myristates/palmitates	2	6
Butyl myristate		
Makeup		
Lipsticks (1912)	16	–
Makeup bases (164)	6	–
Rouges (99)	1	–
Other (406)	2	–
Skin care products		
Moisturizers (2039)	1	–
Total uses/ranges for butyl myristate	26	–
Cetyl myristate		
Eye makeup		
Eye shadow (1196)	1	–
Skin care products		–
Face and neck creams, lotions, powder and sprays (1195)	2	–
Body and hand creams, lotions, powder and sprays (1513)	1	6
Moisturizers (2039)	1	–
Other (1244)	2	–
Total uses/ranges for cetyl myristate	7	6
Glyceryl myristate		
Fragrance products		
Other (399)	1	–
Makeup		
Makeup bases (164)	1	–
Personal hygiene products		
Underarm deodorants (540)	1	–
Skin care products		
Face and neck creams, lotions, powder and sprays (1195)	3	–
Body and hand creams, lotions, powder and sprays (1513)	5	–
Moisturizers (2039)	5	–
Night creams, lotions, powder and sprays (343)	2	–
Paste masks/mud packs (418)	3	–
Other (1244)	2	–
Suntan products		
Suntan gels, creams, liquids and sprays (156)	1	–
Other (62)	1	–
Total uses/ranges for glyceryl myristate	25	–
Isobutyl Myristate		
Skin care products		

(continued)

Table 5 (continued)

Product Category (Total Number of Products in Each Category (FDA 2008))[69]	Frequency of Use[68]	Concentration of Use (%)[70,71]
Body and hand creams, lotions, powder and sprays (1513)	–	30
Paste masks/mud packs (418)	–	10
Suntan products		
Suntan gels, creams, liquids and sprays (156)	–	3
Total uses/ranges for isobutyl myristate	–	3-30
Isocetyl myristate		
Makeup		
Foundations (635)	5	–
Skin care products		
Other (1244)	1	–
Total uses/ranges for isocetyl myristate	6	–
Isodecyl myristate		
Makeup		
Foundations (635)	1	–
Total uses/ranges for isodecyl myristate	1	–
Isopropyl myristate		
Baby products		
Lotions, oils, powders, and creams (132)	4	3
Bath products		
Oils, tablets, and salts (257)	21	39494
Soaps and detergents (1329)	1	0.006-1
Other (239)	2	23
Eye makeup		
Eyebrow pencils (147)	12	0.04-20
Eyeliners (684)	49	39495
Eye shadow (1196)	31	39450
Eye lotions (177)	4	–
Eye makeup remover (131)	3	–
Other (288)	4	–
Fragrance products		
Colognes and toilet waters (1288)	9	39461
Perfumes (569)	3	11
Powders (278)	3	–
Sachets (28)	10	–
Other (399)	39	58
Noncoloring hair care products		
Conditioners (1249)	45	0.5-48
Sprays/aerosol fixatives (371)	1	0.02-10
Straighteners (144)	4	–
Permanent waves (141)	1	–
Shampoos (1403)	4	0.4-1
Tonics, dressings, etc (1097)	39	0.4-23
Other (716)	13	1-10[c]
Hair-coloring products		
Dyes and colors (2481)	1	30[d]
Shampoos (48)	1	–
Color sprays (8)	1	–
Bleaches (152)	2	22
Makeup		
Blushers (539)	36	0.07-2
Face powders (613)	16	0.3-4
Foundations (635)	39	0.001-14
Leg and body paints (29)	1	–
Lipsticks (1912)	49	39472
Makeup bases (164)	8	–
Makeup fixatives (38)	1	–

(continued)

Table 5 (continued)

Product Category (Total Number of Products in Each Category (FDA 2008))[69]	Frequency of Use[68]	Concentration of Use (%)[70,71]
Other (406)	14	2-3[f]
Nail care products		
Basecoats and undercoats (62)	1	–
Cuticle softeners (18)	2	39537
Creams and lotions (17)	1	38
Nail polish and enamel removers (41)	1	–
Other (124)	2	–
Personal hygiene products		
Underarm deodorants (540)	10	0.08-51
Feminine deodorants (21)	5	39579
Other (514)	13	3-60[g]
Shaving products		
Aftershave lotions (395)	11	–
Preshave lotions (27)	8	17
Shaving cream (162)	5	1
Other (107)	6	–
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1368)	52	39468
Depilatories (62)	2	–
Face and neck creams, lotions, powder and sprays (1195)	48	0.4-5
Body and hand creams, lotions, powder and sprays (1513)	157	2-39
Foot powders and sprays (48)	2	–
Moisturizers (2039)	129	0.2-17
Night creams, lotions, powder and sprays (343)	26	0.1-5
Paste masks/mud packs (418)	10	39521
Skin fresheners (285)	–	3
Other (1244)	61	3-82[h]
Suntan products		
Suntan gels, creams, liquids and sprays (156)	22	39486
Indoor tanning preparations (200)	6	–
Other (62)	6	1-3[i]
Total uses/ranges for isopropyl myristate	1057	0.001-82
Lauryl myristate		
Noncoloring hair care products		
Shampoos (1403)	3	–
Total uses/ranges for lauryl myristate	3	–
Magnesium myristate		
Eye makeup		
Eyeliners (684)	–	0.5
Eye shadow (1196)	76	0.6-7
Eye lotions (177)	1	–
Mascara (463)	1	–
Other (288)	1	6[k]
Fragrance products		
Powders (278)	2	5
Other (399)	1	–
Makeup		
Blushers (539)	6	0.2-5
Face powders (613)	80	0.3-10
Foundations (635)	9	0.05-0.09
Lipsticks (1912)	–	3
Makeup bases (164)	–	0.0001
Rouges (99)	1	–
Makeup fixatives (38)	2	–

(continued)

Table 5 (continued)

Product Category (Total Number of Products in Each Category (FDA 2008))[69]	Frequency of Use[68]	Concentration of Use (%)[70,71]
Other (406)	9	–
Nail care products		
Nail polishes and enamels (17)	1	–
Skin care products		
Body and hand creams, lotions, powder and sprays (1513)	–	5
Other (1244)	1	–
Suntan products		
Indoor tanning preparations (200)	1	–
Other (62)	2	–
Total uses/ranges for magnesium myristate	194	0.0001-10
Myristyl myristate		
Baby products		
Lotions, oils, powders, and creams (132)	14	39448
Other (138)	1	–
Bath products		
Oils, tablets, and salts (257)	5	–
Eye makeup		
Eyebrow pencils (147)	6	6
Eyeliners (684)	8	39611
Eye shadow (1196)	8	39575
Eye lotions (177)	5	0.4-4
Other (288)	7	4-6[j]
Fragrance products		
Perfumes (569)	–	39494
Other (399)	6	–
Noncoloring hair care products		
Conditioners (1249)	8	–
Rinses (47)	1	–
Shampoos (1403)	3	–
Tonics, dressings, etc (1097)	1	–
Other (716)	–	2[l]
Makeup		
Blushers (539)	1	1
Face powders (613)	–	0.5
Foundations (635)	7	0.8-5
Leg and body paints (29)	2	39605
Lipsticks (1912)	18	39607
Makeup bases (164)	3	–
Other (406)	5	3-7[m]
Nail care products		
Cuticle softeners (18)	1	3
Creams and lotions (17)	1	2
Other (124)	2	–
Personal hygiene products		
Underarm deodorants (540)	6	2
Other (514)	–	3
Shaving products		
Aftershave lotions (395)	9	2
Shaving cream (162)	7	0.3
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1368)	4	2
Face and neck creams, lotions, powder and sprays (1195)	26	0.5-8
Body and hand creams, lotions, powder and sprays (1513)	51	39449
Foot powders and sprays (48)	1	–

(continued)

Table 5 (continued)

Product Category (Total Number of Products in Each Category (FDA 2008))[69]	Frequency of Use[68]	Concentration of Use (%)[70,71]
Moisturizers (2039)	63	0.5-3
Night creams, lotions, powder and sprays (343)	10	2
Paste masks/mud packs (418)	5	0.5
Skin fresheners (285)	1	–
Other (1244)	6	39449
Suntan products		
Suntan gels, creams, liquids and sprays (156)	–	7
Indoor tanning preparations (200)	2	2
Total uses/ranges for myristyl myristate	??	0.3-17
Octyldodecyl Myristate		
Baby products		
Lotions, oils, powders, and creams (132)	2	–
Eye makeup		
Eyebrow pencils (147)	–	0.3
Eyeliners (684)	1	2
Eye shadow (1196)	3	0.3
Eye lotions (177)	1	2
Mascara (463)	1	–
Other (288)	1	–
Fragrance products		
Other (399)	2	–
Noncoloring hair care products		
Tonics, dressings, etc (1097)	1	–
Makeup		
Blushers (539)	2	0.007
Face powders (613)	2	–
Foundations (635)	8	39518
Lipsticks (1912)	10	0.07-21
Shaving products		
Aftershave lotions (395)	4	1
Preshave lotions (27)	2	–
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1368)	2	–
Face and neck creams, lotions, powder and sprays (1195)	9	39510
Body and hand creams, lotions, powder and sprays (1513)	8	0.9-4
Moisturizers (2039)	16	0.5-2
Paste masks/mud packs (418)	3	–
Skin fresheners (285)	–	0.3
Other (1244)	10	1
Suntan products		
Indoor tanning preparations (200)	7	–
Other (62)	–	1
Total uses/ranges for octyldodecyl myristate	95	0.007-21
Potassium Myristate		
Bath products		
Soaps and detergents (1329)	5	–
Eye makeup		–
Eyeliners (684)	1	–
Other (288)	1	–
Makeup		
Foundations (635)	1	–
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1368)	18	39574

(continued)

Table 5 (continued)

Product Category (Total Number of Products in Each Category (FDA 2008))[69]	Frequency of Use[68]	Concentration of Use (%)[70,71]
Other (1244)	1	–
Total uses/ranges for potassium myristate	27	5-7
Propylene glycol myristate		
Eye makeup		
Other (288)	1	–
Makeup		
Lipsticks (1912)	2	5
Other (406)	1	–
Skin care products		
Face and neck creams, lotions, powder and sprays (1195)	1	4
Body and hand creams, lotions, powder and sprays (1513)	3	–
Moisturizers (2039)	1	–
Other (1244)	4	–
Suntan products		
Suntan gels, creams, liquids and sprays (156)	2	6
Total uses/ranges for propylene glycol myristate	15	4-6
Sodium myristate		
Bath products		
Soaps and detergents (1329)	3	0.5-6
Noncoloring hair care products		
Conditioners (1249)	1	–
Shampoos (1403)	3	–
Personal hygiene products		
Underarm deodorants (540)	1	0.2
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1368)	6	–
Face and neck creams, lotions, powder and sprays (1195)	1	–
Total uses/ranges for sodium myristate	15	0.2-6
Zinc myristate		
Eye makeup		
Eyebrow pencils (147)	–	4
Eyeliners (684)	1	5
Eye shadow (1196)	50	0.5-6
Eye lotions (177)	–	0.05
Other (288)	9	–
Fragrance products		
Powders (278)	–	5
Makeup		
Blushers (539)	33	0.3-3
Face powders (613)	18	39526
Foundations (635)	5	0.001-6
Lipsticks (1912)	–	5
Makeup bases (164)	–	5
Other (406)	1	–
Nail care products		
Basecoats and undercoats (62)	–	0.00005
Nail polishes and enamels (419)	5	–
Skin care products		
Face and neck creams, lotions, powder and sprays (1195)	–	5
Suntan products		

(continued)

Table 5 (continued)

Product Category (Total Number of Products in Each Category (FDA 2008))[69]	Frequency of Use[68]	Concentration of Use (%)[70,71]
Suntan gels, creams, liquids and sprays (156)	–	0.1
Total uses/ranges for zinc myristate	122	0.00005-20

[a] 6% in a shower gel; 9% in a body scrub.
[b] 0.3% in a lash powder; 2% in a brow powder wax.
[c] 1% in an aerosol hair shine; 10% in a hair oil treatment.
[d] 5% after dilution.
[e] 11% after dilution.
[f] 4% in a lip liner pencil.
[g] 4% in a body scrub.
[h] 4% in a foot lotion; 82% in a massage oil.
[i] 1% and 3% in tanning oils.
[j] 6% in a lash powder.
[k] 4% in an eye pencil.
[l] 2% in a hairdressing créme conditioner.
[m] 7% in a concealer.
[n] 0.7% in a moisturizing sprays.

maximum acid value of 1 and a saponification value range of 120 to 130.

Isopropyl myristate. Isopropyl myristate is a colorless, almost odorless, mobile liquid with a bland taste. It is soluble in acetone, castor oil, chloroform, cottonseed oil, ethanol, ethyl acetate, mineral oil, and toluene and insoluble in water, glycerol, sorbitan, and propylene glycol. It is miscible with liquid hydrocarbons and fixed oils, and it dissolves lanolin, cholesterol, and many waxes.[29-31]

Octyldodecyl myristate. 2-Octyldodecyl myristate is a colorless, odorless liquid with a maximum acid value of 0.5, saponification value range from 105 to 111, and a maximum hydroxyl value of 5.0. On ignition, the residue has a maximum of 0.5%.[32]

Gattefossé[22] stated that octyldodecyl myristate was slightly soluble in ethanol at 96°C, soluble in chloroform and methylene chloride, insoluble in water, and freely soluble in mineral oils.

Potassium myristate. Potassium myristate is a white-to-pale yellow solid with a faint characteristic odor.[33]

Ultraviolet Absorption

Glyceryl myristate. Glyceryl myristate has UV absorption λ_{max} of 238 nm and λ_{min} of 270 nm.[34]

Reactivity

The myristate esters can be expected to undergo chemical or enzymatic hydrolysis to myristic acid and the corresponding alcohol. Transesterification and other typical ester reactions may also occur. Butyl myristate, if synthesized from a pure, saturated fatty acid, would not significantly autoxidize, discolor, or develop an odor.[35]

Methods of Manufacture

Aluminum dimyristate, aluminum myristate, butyl myristate, calcium myristate, decyl myristate, ethylhexyl myristate, ethyl myristate, glyceryl dimyristate, glyceryl myristate, isobutyl myristate, isocetyl myristate, isodecyl myristate, isopropyl myristate, isotridecyl myristate, lauryl myristate, magnesium myristate, methyl myristate, myristyl myristate, octyldodecyl myristate, potassium myristate, propylene glycol myristate, sodium myristate, tetradecyloctadecyl myristate, tridecyl myristate, and zinc myristate have plant and synthetic sources. Aluminum isostearates/myristates, aluminum myristates/palmitates, cetyl myristate, glyceryl isostearate/myristate, isostearyl myristate, and oleyl myristate have plant, animal, and synthetic sources.[15]

Myristic acid. According to the CTFA (now the Personal Care Products Council [the Council]), myristic acid is produced commercially by the saponification and fractionation of animal or vegetable fats and oils. The isolated acid fraction is hydrogenated to produce the saturated fatty acid.[35]

Myristic acid is a solid organic acid usually obtained from coconut oil, nutmeg butter *(Myristica fragrans* Houtt), palm seed oils, and milk fats.[18,20] Seed oils of the plant family, Myristaceae, contain the largest amounts of myristic acid (up to 80%), but small amounts have been measured in most animal fats and vegetable oils.

The following methods have been used in the preparation of myristic acid: isolation from tail-oil fatty acids, from 9-ketotetradecanoic acid; by electrolysis of a mixture of methyl hydrogen adipate and decanoic acid, by Maurer oxidation of myristanol; and from cetanol.[18] The most common means of preparation is by fractional distillation of hydrolyzed coconut oil, palm kernel oil,[36] or coconut acids.[17]

Butyl myristate. Butyl myristate is derived from the esterification of myristic acid and butyl alcohol in the presence of an

acid catalyst. The product is stripped to remove excess alcohol and alkali refined to neutralize the catalyst. Butyl myristate is obtained through fractional distillation.[35]

Isocetyl myristate. Nikko Chemicals Co, Ltd, reported that isocetyl myristate is produced by the esterification of isocetyl alcohol and myristic acid.[37]

Isopropyl myristate. Isopropyl myristate is commercially produced by distillation, which is preceded by the esterification of myristic acid and isopropanol, in the presence of an acid catalyst. The product is stripped to remove excess isopropanol, alkali refined to neutralize the catalyst, and then the product is distilled to obtain isopropyl myristate.[38]

Methyl myristate. Methyl myristate is derived by the esterification of myristic acid with methanol or alcoholysis of coconut oil with methanol.[27] It is purified by vacuum fractional distillation.

Myristyl myristate. Myristyl myristate is produced by the esterification of myristic acid and myristyl alcohol in the presence of an acid catalyst. The product is stripped to remove excess myristyl alcohol; alkali is used to neutralize the catalyst, and then purified to separate myristyl myristate.[39]

Octyldodecyl myristate. Octyldodecyl myristate is produced by the esterification of myristic acid with 2-octyl dodecanol, manufactured from vegetable sources.[22,40,41]

Potassium myristate. Potassium myristate is produced by the reaction of potassium hydroxide and myristic acid.[42]

Reacting lauric acid, myristic acid, and palmitic acid with water, glycerin, potassium hydroxide, and tetrasodium EDTA produces a product containing potassium myristate (15%) as well as potassium cocoate (23%), EDTA-4Na (0.2%), and water (61.8%).[43]

Analytical Methods

The myristates can be analyzed by thin-layer chromatography (TLC),[44] gas-liquid chromatography,[45] and x-ray powder diffraction.[46]

Two basic methods for the analysis of the fatty acids have been reported by the cosmetic industry. Primarily, gas chromatography (GC) of fatty acid methyl esters, prepared by the boron trifluoride–methanol method, is used for the separation and relative identification of fatty acids in a mixture.[47,48] Infrared spectra of the fatty acids are used for fingerprinting, functional group identification, and impurity screening.[23,49-53] Determination of physicochemical properties also aids in positive identification of a specific fatty acid.[20,47]

Flame ionization detection (FID) is usually coupled with the GC of fatty acid methyl esters. Mass spectrometry (MS) has also been used with GC for compound identification.[54]

Thin-layer chromatography and high-performance liquid chromatography (HPLC) are also used in fatty acid identification and quantitation.[54-57] Methods of detection include UV, fluorescence spectroscopic, and refractive index detection.

Mass spectrometry with temperature profiling of the chemical ionization source has been reported as a method for initial compound separation. Its coupling with a second MS allows direct analysis of complex lipid sources.[58] Other separation methods include centrifugal liquid and adsorption chromatography.[59] Identification procedures range from methods such as gravimetry[47] and histochemical staining[60] to ultraviolet, infrared, and nuclear magnetic resonance spectroscopy.[20,61,62]

Cotte et al[63] used Fourier-transform infrared (FT-IR) microscopy to locate myristic acid in dermal layers.

Impurities

Myristic acid. The myristates used as cosmetic ingredients are mixtures of fatty esters, as the myristic acid and alcohols used in the preparation of these ingredients are themselves mixtures of acids and alcohols, respectively. The CTFA Cosmetic Ingredient Chemical Description[51] for myristic acid lists the following as component acids:

- n-tetradecanoic acid, $CH_3(CH_2)_{12}COOH$ (95% minimum),
- n-hexadecanoic acid, $CH_3(CH_2)_{14}COOH$ (4% maximum),
- and n-dodecanoic acid, $CH_3(CH_2)_{10}COOH$ (3% maximum).

Myristic acid may contain unsaponifiable material, mostly hydrocarbons, at a maximum concentration of 0.2%, and some grades may contain glyceryl monomyristate at a maximum concentration of 0.07%. Butylated hydroxytoluene (BHT) may be present as an added antioxidant.[51]

Butyl myristate. Minor impurities, which may be present, are fatty acids (such as myristic acid) at a maximum of 0.2%.[35]

Glyceryl myristate. Impurities in glyceryl myristate include glycerol (0.3%), diglycerol (0.57%), and free fatty acid (0.14%).[64,65] The ratio of 1,2-(mono)glycerol diester to total (mono)glycerol diester is 27.8. Specifications include monoester content (minimum 90%), free glycerol (maximum 1%), and free fatty acids (maximum 1.5%). The typical value for heavy metals (as lead) in glyceryl myristate is <10 mg/kg.

Isocetyl myristate. Isocetyl myristate is 95% pure with a maximum of heavy metals of 20 ppm and arsenic of 2 ppm.[28]

Isopropyl myristate. Isopropyl myristate may have myristic acid, other free fatty acids are present at a maximum concentration of 1.0%, and unsaponifiable material is present at a maximum concentration of 0.2%. There are no known diluents, solvents, or additives present.[38]

The ester composition is varied according to the specific usage requirement, provided that the specification limits conform to the following: isopropyl myristate, not less than

90.0% (limits, ±5.0%); isopropyl palmitate, not more than 10.0% (limits, ±3.0%); and isopropyl laurate, tridecanoate, pentadecanoate, heptadecanoate, and stearate, none more than 10.0% (limits, 2.0% each).[66]

Methyl myristate. Technical grade methyl myristate is 93% pure and can be purified to >99.8%.[27] Spectrum Chemicals and Laboratory Products[67] stated that a sample of methyl myristate was 99.4% pure. Impurities were not listed.

Myristyl myristate. Myristyl myristate may have free fatty acids, mainly myristic acid, at a maximum concentration of 1.5%. There are no known diluents, solvents, or additives present.[39]

Octyldodecyl myristate. Nikko Chemicals Co, Ltd[32] stated that 2-octyldodecyl myristate has a maximum of 20 ppm heavy metals and 2 ppm arsenic.

Potassium myristate. Nikko Chemicals Co, Ltd[34] stated that potassium myristate has a maximum of 40 ppm heavy metals and 2 ppm arsenic.

Use

Cosmetic

Use information is supplied to the US Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Ingredient Reporting Program (VCRP).[68] Use concentration information is gathered by the Personal Care Products Council (Council) unless noted otherwise. Table 5 presents the use and concentration of myristic acid and its salts and esters in cosmetics.

There were no uses or use concentrations reported for the following:

- aluminum isostearates/myristates,
- calcium myristate,
- decyl myristate,
- ethyl myristate,
- ethylhexyl myristate,
- glyceryl dimyristate,
- glyceryl isostearate/myristate,
- glyceryl myristate,
- isostearyl myristate,
- isotridecyl myristate,
- oleyl myristate,
- tetradecyloctadecyl myristate, or
- tridecyl myristate.

Butyl myristate. Butyl myristate was used in 26 cosmetic products in 2007. Concentration of use data were not reported, although in 1990, concentrations ranged from 1% to 50%.[1]

Glyceryl myristate. Glyceryl myristate was used in 25 cosmetic products in 2007; no use concentrations were reported, although in 1998, its concentrations ranged from 1% to 6%.

Cosmetic Aerosols

Cetyl myristate is used in 2 face and neck creams, lotions, powders, and sprays.

The potential adverse effects of inhaled aerosols depend on the specific chemical species, the concentration, the duration of the exposure, and the site of deposition within the respiratory system.[72] In general the smaller the particle, the farther into the respiratory tree the particle will deposit and the greater the impact on the respiratory system.[73]

Anhydrous hair spray particle diameters of 60 to 80 μm have been reported, and pump hair sprays have particle diameters of ≥80 μm.[74] The mean particle diameter is around 38 μm in a typical aerosol spray.[75] In practice, aerosols should have at least 99% of particle diameters in the 10 to 110 μm range. This means that most aerosol particles are deposited in the nasopharyngeal region and are not respirable.

Noncosmetic

Myristic acid is used in foods as a plasticizing, lubricating, binding, and defoaming agent and as a reagent in the manufacture of other food-grade additives.[16,36,76] Myristic acid is used as a flavoring agent in foods.[17]

Straight-chain monobasic carboxylic acids from fats and oils derived from edible sources, such as the fatty acid myristic acid, are accepted as safe for use in food and in the manufacture of food-grade additives, provided they meet particular conditions and specifications. The unsaponifiable matter in the fatty acid or fatty acid-derived food additive must not exceed 2%, the food additive must be free of chick-edema factor, and it must be produced and labeled in accordance with good manufacturing practice.[77]

Butyl myristate is also used as a plasticizer, as a lubricant for textiles, and in paper stencils.[78]

Both ethyl and methyl myristate are generally recognized as safe food additives by the FDA.[79]

General Biology

Metabolism and Absorption

Myristic acid. Like other higher molecular weight aliphatic esters, the myristates are readily hydrolyzed to the corresponding alcohols and acids, which are then further metabolized.[76] Myristic acid is a digestible constituent of most vegetable and animal fats and is nontoxic when ingested.[80]

Rioux et al[81] incubated cultured Sprague-Dawley rat hepatocytes in radiolabeled myristic acid for 3, 6, 12, and 2 hours. Electrophoresis of the products revealed that myristic acid (4 nmol/L) was metabolized into 18 well-resolved proteins in the 10 to 20 kd range.

Cotte et al[63] used FT-IR to measure the penetration of pre-deuterated myristic acid in pig ear skin using Franz diffusion cells. After 1 day, myristic acid penetrated to the epidermis. For comparison, palmitic acid was detected in the stratum corneum and did not penetrate any further.

Ethyl myristate. Savary and Constantin[82] orally administered ethyl myristate mixed with olive oil in the feed (90% boiled rice, 10% lipid by wet weight) of rats with thoracic-duct fistula. Lymph was collected for 24 to 100 hours. The ester was recovered in small quantities in the thoracic-duct lymph. In the hydrolysis of lymph triglycerides, fatty acid yields from total dietary lipids were 55 mg/h coming from total dietary lipids and 22 mg/h coming from dietary monoalcohol fatty ester.

Ethyl and methyl myristate. Hydrolysis of ethyl myristate (emulsified in buffer) by rat pancreatic juice or pure porcine pancreatic lipase was at a lower relative rate (25% and 31%, respectively) than tetradecyl butyrate (100% and 110%), hexadecyl formate (55% and 80%), hexadecyl propionate (37% and 46%), hexadecyl butyrate (100% and 100%), and *n*-hexyl laurate (110% and 150%). The relative rates of hydrolysis for methyl myristate were 61% and 90%, respectively.[83]

Isopropyl myristate. Four monkeys were exposed for 5 seconds to the spray of an aerosol antiperspirant containing ^{14}C-labeled isopropyl myristate.[84] Two animals were killed immediately after exposure, and the other 2 were killed 24 hours later. The distribution of ^{14}C in the exhaled air and in several tissues indicated that only 0.25% of the dose sprayed at the animals was absorbed; about 10% of this reached the lower respiratory tract. Some 85% of the absorbed isopropyl myristate was eliminated in 24 hours, mainly as exhaled carbon dioxide; very little labeled material reached any tissues other than the lungs.

Suzuki et al[85] reported that ^{14}C-labeled isopropyl myristate penetrated into sebaceous glands, stratum spinosum, hair infundibula, and follicles.

Brinkmann and Müller-Goymann[86] used differential scanning calorimetry, wide-angle x-ray diffraction, and small-angle x-ray diffraction to examine human abdominal and breast skin soaked in isopropyl myristate. The authors reported a slight increase in the short distance of orthorhombically arranged lipids, while that of hexagonally packed lipids decreased. The long distance of the lamellar structure was unaffected. Isopropyl myristate insertion caused a more densely packed lipid order. The authors suggest that isopropyl myristate does a lateral insertion into lipophilic areas of the stratum corneum microstructure with an anchoring of the isopropyl group in the polar region of the layer.

Dermal Penetration Enhancement

Myristic acid has been tested for its ability to enhance the dermal penetration of a number of chemicals. In most cases, skin treated with myristic acid increased dermal penetration.[87-90] Enhanced penetration was also observed by butyl myristate. Testing of isopropyl myristate showed mixed results regarding dermal penetration enhancement.[90-96]

Other Effects

Dermal

Isopropyl myristate. Suzuki et al[85] reported that isopropyl myristate induced acanthosis, edematous degeneration of collagen fibers, and changes in blood vessels when applied to Angora rabbits.

Enzyme

Methyl myristate. Osama et al[97] reported that the half maximal inhibitory concentration (IC_{50}) of methyl myristate for the inhibition of rat brain prostaglandin D synthase and swine brain prostaglandin D_2 dehydrogenase was >200 μmol/L in both cases.

Cytotoxicity

Methyl myristate. Takeara et al[98] used the 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) test to evaluate the cytotoxicity of methyl myristate on 4 strains of leukemia cells. For acute promyeloblasic leukemia (HL-60) cells, the IC_{50} was 4.68 (1.52-14.44 confidence interval [CI]) μg/mL, >6.25 μg/mL for chronic myelogenic leukemia (K-526) cells, >6.25 μg/mL for lymphoblastic leukemia (CEM) cells, and 4.31 (3.66-5.09 DI) μg/mL for T-cell leukemia (Molt-4) cells.

Animal Toxicology

Acute Oral Toxicity

Data from a previous assessment of myristic acid showed that little acute toxicity was observed at oral doses of 15 to 19 g/kg body weight of 2.2% to 13% myristic acid in rats.[2] In an acute oral toxicity study of butyl myristate in rats, the LD_{50} was >8g/kg. The acute oral LD_{50} for undiluted isopropyl myristate is >16 mL/kg in rats and 49.7 mL/kg in mice.[1]

Butyl myristate. An acute oral toxicity study of butyl myristate was conducted using 10 rats (strain/sex not provided). Daily observations were made over a period of 14 days. The LD_{50} was >8 g/kg. No data on weights of animals tested, ranges of chemical concentration tested, or responses of individual rats were available.[35]

Laboratoire de Recherche et d'Experimentation[99] orally administered butyl myristate (2000 mg/kg) to male NMRI EOPS mice (n = 5). The mice were observed for 6 days. There was no mortality, and no clinical or behavioral signs were observed. Weight gain was satisfactory.

Ethyl myristate. Food and Drug Research Laboratories, Inc,[100] orally treated 10 rats (strain/sex not provided) with 5 g/kg ethyl myristate. Over a 14-day observation period, none of these animals died.

Acute Dermal Toxicity

Butyl myristate (2g/kg) was nontoxic and nonirritating when applied to the skin of rabbits.[101]

Ethyl myristate. Food and Drug Research Laboratories, Inc,[100] dermally treated 10 rabbits with 5 g/kg ethyl myristate. Over a 7-day observation period, 2 of 10 animals died.

Isopropyl myristate. The acute dermal toxicity of undiluted isopropyl myristate and 3 product formulations containing isopropyl myristate were evaluated. Isopropyl myristate was considered nontoxic to the animals tested (rabbits and guinea pigs).

Acute Parenteral Toxicity

Previous safety assessments noted that the intraperitoneal and subcutaneous LD_{20} for isopropyl myristate exceeded 79.5 mL/kg in rats and the intraperitoneal LD_{50} exceeded 50.2 mL/kg in mice.[1]

Sub-Chronic Dermal Toxicity

Previous safety assessments noted that myristic acid produced slight irritation after topical application to the skin of the external ear canal of 4 albino rabbits. No adverse effects were produced from subchronic topical application of myristic acid to rabbit skin.[2]

Subchronic dermal toxicity studies with product formulations containing 16% to 47% isopropyl myristate showed no toxicity over 4 weeks.[1] Butyl myristate and isopropyl myristate were nontoxic when applied to the skin of rabbits. Isopropyl myristate was moderately-to-severely irritiating when applied for 3 consecutive days to the clipped skin of rabbits. Butyl myristate was considered moderately irritating in rabbits in one study and nonirritating in another.

Inhalation Toxicity

Previous safety assessments cited acute inhalation toxicity studies in rats showing no adverse effects from 2 product formulations containing 16% to 20% isopropyl myristate.[1] No toxic effects were observed in subchronic inhalation toxicity studies in guinea pigs and in cynomolgus monkeys.

Chronic Toxicity

No chronic toxicity data were found.

Ocular Irritation

Previous safety assessments cited Draize testing of myristyl myristate and isopropyl myristate at concentrations up to 100% that produced minimum eye irritation in rabbits.[1] Butyl myristate (no concentration provided) was considered nonirritating to the rabbit eye. Undiluted isopropyl myristate produced only minimal eye irritation in rabbits. Myristic acid (1.5%) was minimally irritiating to the eyes of rabbits.[2]

Dermal Sensitization

Previous safety assessments cited data showing that butyl myristate was a moderate skin irritant when intradermaly administered to guinea pigs but was not a sensitizer.[1] Isopropyl myristate did not produce sensitization in guinea pigs. Myristyl myristate produced minimal skin irritation but no sensitization in guinea pigs administered myristyl myristate topically or intracutaneously.

Comedogenicity

Isopropyl and myristyl myristate. Treatment with isopropyl myristate resulted in comedogenic activity in the rabbit ear assay.[102-104]

Nguyen et al[105] applied myristyl myristate (50% in petrolatum; 0.5 g) and isopropyl myristate (50% in various mediums; 0.5 g) to the glabrous inner portion of both ears of New Zealand white rabbits (n = 6; male and female; 6 weeks old) for 5 days per week (Monday to Friday) for 4 consecutive weeks. The ears were then biopsied and scored for comedones through clinical examination and slide biopsy. The control substance was crude coal tar (10%). Isopropyl myristate was found to be comedogenic in all media; myristyl myristate was less comedogenic.

Genotoxicity

Isopropyl myristate. Blevins and Taylor[106] reported that isopropyl myristate tested negative in the *Salmonella*/microsome test in strains TA1538, TA1537, TA1535, TA100, and TA98, with and without activation.

Carcinogenicity

Previous safety assessments noted that isopropyl myristate was not carcinogenic on the skin of mice, but a mixture of isopropyl myristate and isopropyl alcohol significantly accelerated the carcinogenic activity of benzo(a)pyrene on the skin.[1]

Clinical Assessment of Safety

Previous safety assessments on the following ingredients are summarized below:

Isopropyl myristate. [1] Human primary skin irritation studies showed no reactions to isopropyl myristate alone and a mild irritation from product formulations containing 15% to 58% isopropyl myristate. Repeated application of undiluted isopropyl myristate for 21 days produced only slight irritation. Isopropyl myristate was not a human skin sensitizer when in petrolatur or in product formulations at 15% to 58%, although a case report of sensitization was found. A product containing 43% isopropyl myristate produced no phototoxicity and no photocontact allergenicity in human studies.

Myristic acid. [2] In clinical primary and cumulative irritation studies, myristic acid at concentrations of 100% or 40% to 50% in mineral oil were nonirritating. Mild-to-intense erythema in single insult occlusive patch tests, soap chamber tests, and 21-day cumulative irritation studies were produced by cosmetic product formulations containing 2% to 93% myristic acid, and were generally not related to the fatty acid concentrations in the formulations. The Expert Panel also considered data from other fatty acids (oleic, lauric, pamitic, and stearic) due to the structural similarities among these ingredients.

Dermal Sensitization

Ethyl myristate. Kligman[107] applied ethyl myristate for 5 alternate-day 48-hour periods on the volar side of the arm of 25 participants after pretreatment for 24 hours with 2.5% aqueous sodium lauryl sulfate under occlusion. Sodium lauryl sulfate (5%-15%) was applied to the test site for 1 hour before the application of the challenge. There were no signs of sensitization for either the 48- or 72-hour challenge. It was not stated in the text, but according to the Research Institute for Fragrance Materials (RIFM),[108] ethyl myristate was tested at 12%.

Provocative Skin Testing

Isopropyl myristate. Uter et al[109] performed a retroactive study of dermatitis patients patch tested for sensitization to isopropyl myristate. Isopropyl myristate was tested in 20% petrolatum using 8117 patients and 10% petrolatum using 4554 patients between January 1992 and December 2001. The higher concentration had 43 doubtful reactions, 5 irritant reactions, 6 + reactions, and 2 ++/+++ reactions. The lower concentration had 9 doubtful reactions, 2 irritant reactions, 7 + reactions, and 1 ++/+++ reaction. The authors concluded that isopropyl myristate does not need to be tested for during routine patch tests.

Case Reports

Isopropyl myristate. Bharati and King[110] reported a 64-year-old woman who presented with an eczematous rash from a commercial sunscreen. Patch testing of the European standard series gave positive results for formaldehyde, quaternium-15, imidazolidinyl urea, and diazolidinyl urea. A further patch test of the ingredients in the sunscreen resulted in positive reactions for isohexadacane 10% alcohol and isopropyl myristate 10% alcohol.

Summary

This report addressed the safety of the following inorganic salts and esters of various fatty alcohols of myristic acid, including:

- aluminum dimyristate,
- aluminum isostearates/myristates,
- aluminum myristate,
- aluminum myristates/palmitates,
- butyl myristate,
- calcium myristate,
- cetyl myristate,
- decyl myristate,
- ethylhexyl myristate,
- ethyl myristate,
- glyceryl dimyristate,
- glyceryl isostearate/myristate,
- glyceryl myristate,
- isobutyl myristate,
- isocetyl myristate,
- isodecyl myristate,
- isopropyl myristate,
- isostearyl myristate,
- isotridecyl myristate,
- lauryl myristate,
- magnesium myristate,
- methyl myristate,
- myristyl myristate,
- octyldodecyl myristate,
- oleyl myristate,
- potassium myristate,
- propylene glycol myristate,
- sodium myristate,
- tetradecyloctadecyl myristate,
- tridecyl myristate, and
- zinc myristate.

Most of the esters are used as skin conditioning agents in cosmetics, but other functions include the following: anticaking agents, emulsion stabilizers, viscosity increasing agents, surfactants—cleansing agents, surfactants—emulsifying agents, slip modifiers, fragrance ingredients, hair conditioning agents, binders, film formers, and opacifying agents.

Myristic acid is produced by the saponification and fractionation of animal or vegetable fats and oils followed by isolation of the acid fraction that is then hydrogenated.

Analytical methods include TLC, gas-liquid chromatography, x-ray powder diffraction, GC, infrared spectrometry, HPLC, MS, gravimetry, and histochemical staining.

Component fatty acids of myristic acid include *n*-tetradecanoic acid, *n*-hexadecanoic acid, and *n*-dodecanoic acid. Myristic acid and other myristates may contain unsaponifiable material, and some grades may contain glyceryl monomyristate. Impurities in glyceryl myristate include glycerol, diglycerol, and free fatty acid. Other impurities include heavy metals and arsenic.

Isopropyl myristate is the most commonly used ingredient in this assessment and is used in over 1000 products at concentrations of 0.001% to 82%.

Myristic acid, aluminum myristate, aluminum myristates/palmitates, butyl myristate, cetyl myristate, glyceryl myristate, isobutyl myristate, isocetyl myristate, isodecyl myristate, isodecyl myristate, isopropyl myristate, lauryl myristate, magnesium myristate, myristyl myristate, octyldodecyl myristate, potassium myristate, propylene glycol myristate, sodium

myristate, and zinc myristate are also reported as used and/or have reported concentration of use.

No uses or use concentrations were reported for aluminum isostearates/myristate, calcium myristate, decyl myristate, ethyl myristate, ethylhexyl myristate, glyceryl dimyristate, glyceryl isostearate/myristate, isobutyl myristate, isostearyl myristate, isotridecyl myristate, methyl myristate, oleyl myristate, tetradecyloctadecyl myristate, and tridecyl myristate.

Myristic acid is approved as a food reagent and additive. Butyl myristate is also used as a plasticizer, as a lubricant for textiles, and in paper stencils.

The myristates are readily hydrolyzed to the corresponding alcohols and acids, which are then further metabolized. Butyl myristate may be readily hydrolyzed in vivo to its corresponding acid and alcohol, which are then further metabolized.

When isopropyl myristate was aerosolized, 85% of the absorbed isopropyl myristate was eliminated in 24 hours, mainly as exhaled carbon dioxide; very little labeled material reached any tissues other than the lungs in monkeys.

Myristic acid, butyl myristate, and isopropyl myristate enhanced the dermal penetration of several drugs.

The IC_{50} of methyl myristate for the inhibition of rat brain prostaglandin D synthase and swine brain prostaglandin D_2 dehydrogenase was >200 μmol/L.

The acute oral LD_{50} of butyl myristate was >8 g/kg for rats. The acute oral LD_{50} for isopropyl myristate was >16 mL/kg in rats and 49.7 mL/kg in mice.

Acute dermal application of butyl myristate (2 g/kg) was nontoxic and nonirritating to rabbits. When 10 rabbits were treated with a single dermal dose of ethyl myristate (5 g/kg) resulted in the death of 2 over 7 days. The intraperitoneal and subcutaneous LD_{50} for isopropyl myristate exceeded 79.5 mL/kg in rats and the intraperitoneal LD_{50} was >50.2 mL/kg in mice.

No death occurred, and no evidence of systemic toxicity was found at necropsy when the rats were exposed to aerosolized isopropyl myristate.

Myristic acid, isopropyl myristate, and myristyl myristate were minimally irritating to the eyes of rabbits. Butyl myristate was nonirritating to the rabbit eye.

Myristic acid was nonirritating in a single insult occlusive patch test and slightly irritating in a repeat open patch test on rabbits. Butyl myristate was a moderate skin irritant in rabbits and guinea pigs. Isopropyl myristate and myristyl myristate were minimally irritating in several formulations in rabbits and mice.

Isopropyl myristate was nonirritating when injected parenterally in albino rabbits.

Butyl myristate and myristyl myristate were nonsensitizing to guinea pigs.

Isopropyl myristate and myristyl myristate were comedogenic to rabbit ears.

Isopropyl myristate tested negative in the Salmonella/Microsome test in strains TA1538, TA1537, TA1535, TA100, and TA98, with and without activation.

In clinical primary and cumulative irritation studies, myristic acid was nonirritating. Isopropyl myristate can produce slight irritation but is not a human sensitizer at 15% to 50%.

Isopropyl myristate up to 100% was nonirritating, nonirritating in cumulative skin irritation tests, nonphototoxic, and nonphotoallergenic in humans.

Discussion

The data on butyl myristate and the related salts and esters, coupled with the data on the related chemicals (myristic acid, myristyl myristate, and isopropyl myristate), are a sufficient basis for a safety assessment. The CIR Expert Panel believes that there is little toxicological and chemical difference between myristic acid and any of its inorganic salts included in this report. The salts are expected to dissociate in any product formulation, independent of whether the salt is aluminum, calcium, magnesium, potassium, sodium, or zinc. For the various esters of fatty alcohols and myristic acid, the CIR Expert Panel considers that these fatty acid esters are subject to hydrolysis to from myristic acid and the component fatty alcohols. It is the experience of the Panel in its review of fatty alcohols of varying length of carbon chains that there is little difference in toxicity. Accordingly, the available data were considered supportive of the safety of the entire group as used in cosmetics.

The Expert Panel recognized 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 Expert Panel considered that the use concentrations for the ingredients that are in use are not likely to be different from the use concentrations for other myristates. 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.

The Expert Panel recognized that these ingredients can enhance the penetration of other ingredients through the skin. The Panel cautioned that care should be taken in formulating cosmetic products that may contain these ingredients in combination with any ingredients whose safety was based on their lack of dermal absorption data, or when dermal absorption was a concern.

A number of the ingredients in this report—cetyl myristate, octyldodecyl myristate, and sodium myristate—have uses that include sprays. There are no data available on inhalation toxicity for these ingredients or the other ingredients in this assessment. The Expert Panel determined that there is sufficient inhalation toxicity data on isopropyl myristate in its assessment demonstrating no inhalation toxicity. In addition to the inhalation toxicity data, the Panel determined that butyl myristate and the salts and esters can be used safely in hair sprays, because the ingredient particle size is not respirable. The Panel reasoned that the particle size of aerosol hair sprays ($\sim$38 μm) and pump hair sprays (>80 μm) is large compared with respirable particulate sizes ($\geq$10 μm).

There are no data on the reproductive or developmental toxicity of myristic acid or its component parts for the derivatives. Based on structure–activity relationships, the Expert Panel considered that these chemicals had little potential for such toxicity when used as cosmetic ingredients.

Isopropyl myristate was not genotoxic in the Ames assay. The Expert Panel determined this to be sufficient carcinogenicity data for the related ingredients in this safety assessment.

Conclusion

The CIR Expert Panel finds that myristic acid, aluminum dimyristate, aluminum isostearates/myristates, aluminum myristate, aluminum myristates/palmitates, butyl myristate, calcium myristate, cetyl myristate, decyl myristate, ethyl myristate, ethylhexyl myristate, glyceryl dimyristate, glyceryl isostearate/myristate, glyceryl myristate, isobutyl myristate, isocetyl myristate, isodecyl myristate, isopropyl myristate, isostearyl myristate, isotridecyl myristate, lauryl myristate, magnesium myristate, methyl myristate, myristyl myristate, octyldodecyl myristate, oleyl myristate, potassium myristate, propylene glycol myristate, sodium myristate, tetradecyloctadecyl myristate, tridecyl myristate, and zinc myristate are safe as cosmetic ingredients in the current practices of use and concentration. 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 Interest

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

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3

Final Report on the Safety Assessment of Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid

Oleic, Lauric, Palmitic, Myristic, and Stearic Acids are fatty acids with hydrocarbon chains ranging in length from 12 to 18 carbons with a terminal carboxyl group. These fatty acids are absorbed, digested, and transported in animals and humans. Little acute toxicity was observed when Oleic, Lauric, Palmitic, Myristic, or Stearic Acid or cosmetic formulations containing these fatty acids were given to rats orally at doses of 15–19 g/kg body weight. Feeding of 15% dietary Oleic Acid to rats in a chronic study resulted in normal growth and health, but reproductive capacity of female rats was impaired. Results from topical application of Oleic, Palmitic, and Stearic Acid to the skin of mice, rabbits, and guinea pigs produced little or no apparent toxicity. Studies using product formulations containing Oleic and Stearic acids indicate that neither is a sensitizer or photosensitizing agent. Animal studies also indicate that these fatty acids are not eye irritants. Lauric, Stearic, and Oleic Acids were noncarcinogenic in separate animal tests. In primary and cumulative irritation clinical studies, Oleic, Myristic, and Stearic Acids at high concentrations were nonirritating. Cosmetic product formulations containing Oleic, Lauric, Palmitic, and Stearic Acids at concentrations ranging up to 13% were not primary or cumulative irritants, nor sensitizers. On the basis of available data from studies using animals and humans, it is concluded that Oleic, Lauric, Palmitic, Myristic, and Stearic Acids are safe in present practices of use and concentration in cosmetics.

INTRODUCTION

Oleic, Lauric, Palmitic, Myristic, and Stearic Acids are long hydrocarbon chain carboxylic acids, known as fatty acids. They are usually produced by hydrolysis of common animal and vegetable fats and oils. Fatty acids are generally used as intermediates in the manufacture of their alkali salts, which

are in turn used as emulsifiers, emollients, and lubricants in a variety of cosmetic creams, cakes, soaps, and pastes.

CHEMISTRY

Structure and Nomenclature

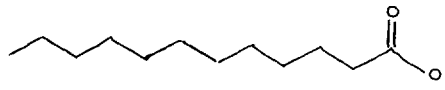
Lauric, Myristic, Palmitic, and Stearic Acids are saturated fatty acids of 12-, 14-, 16-, and 18-carbon lengths. Oleic Acid is an 18-carbon *cis*-mono unsaturated fatty acid. These fatty acids consist of long hydrocarbon chains with a terminal carboxyl group. Synonyms for the fatty acids (Table 1) were obtained from the following sources: Windholz et al.,[1] Estrin et al.,[2] Morrison and Boyd,[3] Lehninger,[4] and Osol.[5] Structural formulae are presented in Figure 1. A summary of some physicochemical properties appears in Table 2. Since the saturated fatty acids bear the carboxyl functional group and basically

TABLE 1. Synonyms for the Fatty Acids

Fatty acid	*Synonyms*
Oleic Acid	*cis*-9-Octadecenoic acid *cis*-Δ^9-Octadecenoic acid 9-Octadecenoic acid Oleinic acid Elaic acid Red oil 18:1Δ^9
Lauric Acid	n-Dodecanoic acid Dodecanoic acid Laurostearic acid Dodecoic acid 12:0
Palmitic Acid	n-Hexadecanoic acid Hexadecanoic acid Hexadecoic acid Hexadecylic acid Cetylic acid 16:0
Myristic Acid	n-Tetradecanoic acid Tetradecanoic acid Tetradecoic acid 14:0
Stearic Acid	n-Octadecanoic acid Octadecanoic acid Cetylacetic acid Stearophanic acid 18:0

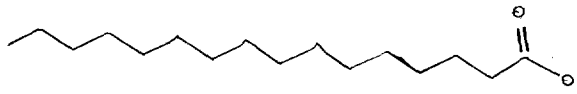
OLEIC ACID

$C_{18}H_{34}O_2$



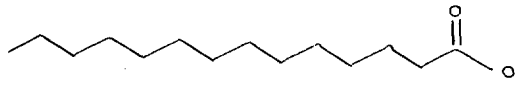
LAURIC ACID

$C_{12}H_{24}O_2$



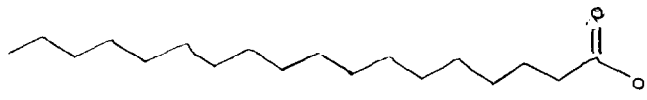
PALMITIC ACID

$C_{16}H_{32}O_2$



MYRISTIC ACID

$C_{14}H_{28}O_2$



STEARIC ACID

$C_{18}H_{36}O_2$

FIG. 1. Structural formulae of fatty acids.

differ from each other by 2–6 methylene groups, their properties are similar. The *cis* double bond of Oleic Acid alters several physical properties relative to those of Stearic Acid.[4]

Description and Source

Fatty acids have been found in marine and freshwater organisms,[6] bacteria,[4] and vegetable oils and animal fats.[3] Although mammalian tissues

TABLE 2. Physicochemical Properties of the Fatty Acids

Property	*Lauric Acid*	*Myristic Acid*	*Palmitic Acid*	*Stearic Acid*	*Oleic Acid*
CAS Registry No.	143-07-7	544-63-8	57-10-3	57-11-4	112-80-1
Empirical formula[a]	$C_{12}H_{24}O_2$	$C_{14}H_{28}O_2$	$C_{16}H_{32}O_2$	$C_{18}H_{36}O_2$	$C_{18}H_{34}O_2$
Molecular weight	200.31[a], 200.33[b]	228.36[a], 228.38[b]	256.42[a], 256.43[b]	284.47[a], 284.50[b]	282.45[a], 282.47[b]
Density (g/ml, °C)	0.8679_4^{50b}	0.8528_4^{70a}	0.8527_4^{62b}	0.847^{70a}	0.895_{25}^{25a}
Melting point (°C)	44, 48[a]	58.5[a], 58[b], 54.4[c]	63–64[a]	69–70[a, c], 71.2[b]	16.3[b]
Boiling point (°C, P in atm)[a]	225_{100}	250.5_{100}	215_{15}	383_1 (decomposes at 360_1)	286_{100}
Solubility[a, b, d]					
Water	Insol.	Insol.	Insol.	Insol.	Insol.
Alcohol	v. sol.—ethanol propanol—1 g/ml	sol.—abs. ethanol v. sol.—methanol	v. sol.—ethanol + heat v. sol.—propanol	sl. sol.—1 g/21 ml ethanol	v. sol.—ethanol
Chloroform	sol.	sol.	v. sol.	sol.—1 g/2 ml	v. sol.
Benzene	v. sol.	v. sol.	sol.	sl. sol.—1 g/5 ml	v. sol.
Ether	v. sol.	sl. sol.	v. sol.	v. sol.	v. sol.
Viscosity (cp, °C)[c]	7.3^{50}	5.06^{75}	7.1^{75}	9.04^{75}	23.01^{30}
Iodine number[a]	—	—	—	—	89.9
Acid value	280.1[c]	245.7[c]	218.0[c]	197.2[c]	198.6[a]

[a]Ref. 1.
[b]Ref. 7.
[c]Ref. 6.
[d]Ref. 8.
Insol., insoluble; sl. sol., slightly soluble; sol., soluble; v. sol., very or freely soluble.

normally contain trace amounts of free fatty acids, conjugated forms can be found in several tissues.[4] Free fatty acids have been found in human sebum and epidermal tissue.[9,10]

Oleic Acid, in esterified form, is found in many vegetable oils and animal fats, frequently constituting greater than 50% of the total fatty acid concentration. Oils rich in Oleic Acid include olive (80%), peanut (60%), teaseed (85%), and pecan (85%) oils; very few fats contain less than 10% Oleic Acid.[6]

Pure Oleic Acid is a colorless to pale yellow, oily liquid at temperatures above 5–7°C. At 4°C, it solidifies to a crystalline mass. Upon exposure to oxygen, it darkens gradually, and it decomposes when heated to 80–100°C at atmospheric pressure.[1,8,11] Oleic Acid has a characteristic lardlike odor and taste.[1,8]

Lauric Acid is one of the three most widely distributed naturally occurring saturated fatty acids; the others are Palmitic and Stearic Acids. Its common name is derived from the laurel family, Lauraceae. The fatty acid content of the seeds is greater than 90% Lauric Acid. Sources of Lauric Acid include coconut and palm kernel oils, babassu butter (approximately 40%) and other vegetable oils, and milk fats (2–8%). Camphor seed oil has a high Lauric Acid content.[1,6,8]

Lauric Acid occurs as a white or slightly yellow, somewhat glossy crystalline solid or powder[1,8] or as a colorless solid[11] with a slight odor of bay oil.[1]

The glyceryl ester of Palmitic Acid is widely distributed, being found in practically all vegetable oils and animal (including marine animal) fats at concentrations of at least 5%. Palmitic Acid is the major component of lard and tallow (25–30%), palm oil (30–50%), cocoa butter (25%), and other vegetable butters. Chinese vegetable tallow is reported to contain 60–70% Palmitic Acid.[1,6]

Palmitic Acid occurs as a mixture of solid organic acids obtained from fats that are primarily composed of Palmitic Acid with varying quantities of Stearic Acid. Its appearance ranges from a hard, white or faintly yellow, slightly glossy crystalline solid to a white or yellow-white powder,[8] white crystalline scales,[1] or colorless crystals.[11]

Myristic Acid is a solid organic acid usually obtained from coconut oil, nutmeg butter (*Myristica fragrans* Houtt), palm seed oils, and milk fats.[1,6] Seed oils of the plant family, Myristaceae, contain the largest amounts of Myristic Acid (up to 80%), but small amounts have been measured in most animal fats and vegetable oils.

Myristic Acid occurs as a hard, white or faintly yellow, glossy crystalline solid, as a white or yellow-white powder,[8] or as colorless leaflets.[11]

Stearic Acid is found primarily as a glyceride in animal fats and oils; lard and tallow contain approximately 10 and 20% Stearic Acid, respectively.[1,6] Most vegetable oils contain 1–5% Stearic Acid; cocoa butter contains about 35%.

Stearic Acid occurs as hard, white or faintly yellow, somewhat glossy crystals or leaflets or as an amorphous white or yellow-white powder.[1,5,8,12] It has a slight odor and taste resembling tallow.[1,8]

Method of Manufacture and Impurities

The fatty acids are usually produced by the hydrolysis of common animal and vegetable fats and oils followed by fractionation of the resulting fatty acids. Fatty acids that are used in foods, drugs, and cosmetics normally exist as mixtures of several fatty acids depending on the source and manufacturing process.

Processing operations in the manufacture of fatty acids from fats are known to alter their chemical compositions. The processes (e.g., distillation, high temperature and pressure hydrolysis, and bleaching) may result in *cis-trans* isomerization, conjugation of polyunsaturates, polymerization, and dehydration.[6]

Cosmetic-grade Oleic, Lauric, Palmitic, Myristic, and Stearic Acids occur as mixtures of fatty acids depending on their method of manufacture and source. The individual fatty acids predominate in the mixture ranging from 74% (Oleic Acid) to 95% (Myristic Acid). All contain varying amounts of unsaponifiable matter, and some grades also contain glyceryl monoesters of fatty acids. Butylated hydroxytoluene may be added to all five fatty acid preparations as an antioxidant.[13–17] In cosmetics containing unsaturated materials, the concentration range for butylated hydroxytoluene should be 0.01 to 0.1%.[18] Butylated hydroxytoluene has been used in some lanolin products containing unsaturated fatty acids, alcohols, esters, sterols, and terpenols, at concentrations ranging from 200 to 500 ppm.[19] Data on the components, impurities, and additives of these cosmetic grade fatty acids are presented in Table 3. Comparisons of specifications for cosmetic, food, and drug grade fatty acids are presented in Tables 4, 5, 6, 7, and 8. Cosmetic grade specifications for fatty acid composition are presented in Table 9.

Fourteen FAPC (Fatty Acid Producers Council of the Soap and Detergent Association) categories of fatty acids are contrasted by titer and iodine value. Typical fatty acid compositions are reported.[6] FDA files contain some composition data on Oleic and Stearic Acids, which were submitted with Food Additive Petitions (Notes from the composition data in CIR files).

Oleic Acid is produced by the hydrolysis and fractionation (e.g., saponification and distillation) of animal or vegetable fats and oils.[1,5,11,16] Preparation of Oleic Acid from animal tallow and olive has been reported.[1,5] It is also obtained as a byproduct in the manufacture of solid Stearic and Palmitic Acids. Crude (unpurified, unbleached) Oleic Acid of commerce, or red oil, contains Stearic and Palmitic Acids in varying quantities.[5,20]

Several commercial grades of Oleic Acid are available, distinguished by varying proportions of saturated fatty acids. The commercial grade contains 7–12% saturated acids and some unsaturated acids and is usually derived from edible sources (internally administered Oleic Acid must be derived from edible sources[5]). Oleic Acid derived from tallow contains varying amounts of linolenic and Stearic Acids and small but significant quantities of elaidic (*trans*-9-octadecenoic) acid, some of which is generated from certain processing operations (e.g., distillation and high-temperature bleaching with clays).[1,5,6]

Hawley[20] reported several technical grades of Oleic Acid: chick edema factor-free grade, U.S. Pharmacopeia (USP) grade, Food Chemicals Codex (FCC) grade, and purified technical grade Oleic Acid. The latter technical

TABLE 3. Components, Impurities, Additives in Cosmetic-Grade Fatty Acids[13–17]

Cosmetic-grade fatty acid	*Components in Mixture (%)*	*Minor Impurities (%)*	*Additives*
Oleic Acid	9-Octadecenoic acid (68–74)[a] 9,12-Octadecadienoic acid (4–12) 9-Hexadecenoic acid (7–11) Hexadecanoic acid (4) Tetradecanoic acid (3) 9-Tetradecenoic acid (1–3) Heptadecanoic acid (1–2) Pentadecanoic acid (0.5–2) Octadecanoic acid (1) Octadecatrienoic acid (1) Decanoic acid Dodecanoic acid	Unsaponifiable material (1.5 max)	Butylated hydroxytoluene[b] (BHT)
Lauric Acid	Dodecanoic acid (90 min) Tetradecanoic acid (6 max) Decanoic acid (5 max) Hexadecanoic acid (2 max)	Unsaponifiable material (0.3 max) (mostly hydrocarbon) Glyceryl monolaurate[b] (0.07 max)	BHT[b]
Palmitic Acid	Hexadecanoic acid (80 min) Octadecanoic acid (11 max) Tetradecanoic acid (7 max) Heptadecanoic acid (4.5 max) Pentadecanoic acid (1 max)	Unsaponifiable material (0.3 max) (mostly hydrocarbon) Glyceryl monopalmitate[b] (0.07 max)	BHT[b]
Myristic Acid	Tetradecanoic acid (95 min) Hexadecanoic acid (4 max) Dodecanoic acid (3 max)	Unsaponifiable material (0.2 max) (mostly hydrocarbon) Glyceryl monomyristate[b] (0.07 max)	BHT[b]
Stearic Acid	Octadecanoic acid (39–95)[a] Hexadecanoic acid (5–50) Tetradecanoic acid (0–3) 9-Octadecenoic acid (0–5) Heptadecanoic acid (0–2.5) Eicosanoic acid (0–2) Pentadecanoic acid (0–1)	9-Hexadecenoic acid 9,12-Octadecadienoic acid Unsaponifiable material (0.3 max) Glyceryl monostearate (0.07 max)	BHT[b]

[a] These are concentration ranges of a typical analysis.
[b] Present in some grades.

grade Oleic Acid contains ≥ 90% Oleic Acid and has a 4% maximum linoleic acid content and a 6% maximum saturated fatty acid content.

Lauric Acid is produced by the hydrolysis, usually via saponification, of animal or vegetable fats and oils followed by fractional distillation.[11,22] Lauric Acid is commonly isolated from coconut oil,[1,11] and several patents describe its chemical synthesis.[1]

Palmitic Acid is produced by the hydrolysis and fractionation of palm oil, tallow oil, coconut oil, Japan Wax, Chinese vegetable tallow, and spermaceti. Fractionation is usually by distillation or crystallization.[1,11,20] Palmitic Acid can also be obtained in the manufacturing process for Stearic Acid.

TABLE 4. Comparison of Specifications: Cosmetic and Food Grades

Oleic Acid	*Cosmetics*[21]	*Foods*[8]
Iodine value	83.0–99.0	83–103
Acid value	190.0–207.0	196–204
Saponification value	198.0–207.0	196–206
Unsaponifiable matter	1.0% max	2% max
Arsenic		3 ppm max
Heavy metals (e.g., Pb)		10 ppm max
Residue on ignition		0.01% max
Titer (solidification point)	2–6°C	< 10°C
Water content		0.4% max

TABLE 5. Comparison of Specifications: Cosmetic and Food Grades

Lauric Acid	*Cosmetics*[13, 14]	*Foods*[8]
Iodine value	0.5 max	3.0 max
Acid value	273–283	252–287
Saponification value	276–284	253–287
Unsaponifiable matter	0.3% max	0.3% max
Arsenic		3 ppm max
Heavy metals (e.g., Pb)		10 ppm max
Residue on ignition		0.1%
Titer (solidification point)	38–44°C	26–44°C
Water content		0.2% max

TABLE 6. Comparison of Specifications: Cosmetic and Food Grades

Palmitic Acid	*Cosmetics*[21]	*Foods*[8]
Iodine value	1.0 max	2.0 max
Acid value	213–221	204–220
Ester value	3.0 max	
Saponification value	216.5–220.5	205–221
Unsaponifiable matter	0.25% max	1.5% max
Arsenic		3 ppm max
Heavy metals (e.g., Pb)		10 ppm max
Residue on ignition		0.1%
Titer (solidification point)	59.4–60.4°C	53.3–62°C
Water content		0.2% max

The following methods have been used in the preparation of Myristic Acid: isolation from tall-oil fatty acids from 9-ketotetradecanoic acid, by electrolysis of a mixture of methyl hydrogen adipate and decanoic acid, by Maurer oxidation of myristanol, and from cetanol.[1] The most common means of preparation is by fractional distillation of hydrolyzed coconut oil, palm kernel oil,[20] or coconut acids.[11]

Commercial Stearic Acid has several crystalline forms and contains varying relative concentrations of other fatty acids depending on the sources and processing methods used.[9] Commercial Stearic Acid is primarily a mixture of

TABLE 7. Comparison of Specifications: Cosmetic and Food Grades

Myristic Acid	*Cosmetics*[13,14]	*Foods*[8]
Iodine value	0.5 max	1.0 max
Acid value	243–249	242–249
Saponification value	243–249	242–251
Unsaponifiable matter	0.2% max	1% max
Arsenic		3 ppm max
Heavy metals (e.g., Pb)		10 ppm max
Residue on ignition		0.1% max
Titer (solidification point)	52–54°C	48–55.5°C
Water content		0.2% max

TABLE 8. Comparison of Specifications: Cosmetic and Food Grades

Stearic Acid	*Cosmetics "95.0%"*[21]	*Foods*[8]
Iodine value	1.0 max	7 max
Acid value		196–211
Ester value	3.0 max	
Saponification value	196.4–200.4	197–212
Unsaponifiable matter	0.25% max	1.5% max
Arsenic		3 ppm max
Heavy metals (e.g., Pb)		10 ppm max
Residue on ignition		0.1% max
Titer (solidification point)	67.2–68.2°C	54.5–69°C
Water content		0.2% max

varying amounts of Stearic and Palmitic Acids. Palmitic Acid/Stearic Acid ratios in commercial preparations depend on several factors, such as source, geographical and climatic influences, genetic uniformity, and fat location site (in animals).[6]

Methods of processing for Stearic Acid include hydrolysis of tallow or hydrogenation of unsaturated fatty acids (e.g., Oleic Acid) in cottonseed and other vegetable oils, followed by methods of isolation, such as fractional distillation or crystallization.[1,5,6,9,11,17] A successive series of pressing operations has been used to separate the liquid unsaturated fatty acids from the solid saturated fatty acids.[6] The Palmitic Acid/Stearic Acid ratio obtained from tallow hydrolysis and triple-pressing or solvent crystallization is 55%/45%. Concentrations of Stearic Acid as high as 95–99%[6,9] have been reported from the hydrogenation of unsaturated fatty acids.

Both double-pressed (two successive pressings to expel unsaturated fatty acids) and triple-pressed Stearic Acid are used by the cosmetic industry.[6,9] Triple-pressed Stearic Acid is a product containing 1.5% 14C (14-carbon), 0.5% 15C, 50% 16C, 1% 17C, and 47% 18C fatty acids, with less than 0.2% Oleic Acid. Double-pressed Stearic Acid typically contains about 2.5% 14C, 50% 16C, 1% 17C, 40% 18C fatty acids, and 6% Oleic Acid.[6]

TABLE 9. Cosmetic-grade Specifications for Fatty Acid Composition (Reported as maximal or minimal acceptable percentage in composition)[21]

Fatty acid chain length[a]	*Oleic Acid*	*Lauric Acid*	*Palmitic Acid*	*Myristic Acid*	*Stearic Acid 37.5%*	*Stearic Acid 42.5%*	*Stearic Acid 95.0%*
8:0–12:0	1.0 max						
10:0		5 max					
12:0		90 min	1.3 max	3 max	0.1 max	0.1 max	Trace (< 0.05)
14:0	5.0 max	6 max	2.5 max	95 min	4.3 max	4.1 max	1.6 max
14:1			Trace (< 0.05)		0.1 max	0.1 max	Trace (< 0.05)
15:0	2.5 max		0.6 max		0.6 max	0.7 max	0.8 max
16:0	7.5 max	2 max	92.5–97.5	4 max	49.0–54.0	49.0–54.0	5.0 max
16:1	4.5–7.5		0.4 max		0.3 max	0.1 max	Trace (< 0.05)
17:0	1.5 max		2.3 max		2.5 max	2.7 max	2.0 max
18:0	3.5 max		5.0 max		35.0–40.0	40.0–45.0	92.5–97.5
18:1	70.0 min		0.4 max		5.5 max	0.6 max	0.6 max
18:2	2.0–12.0 max						
18:3	2.2 max						
16:0 + 18:0					89.0 min	94.0 min	97.5 min
16:0 + 18:0 + 14:0			97.5 min				
20:0			Trace (< 0.05)		0.1 max	0.1 max	Trace (< 0.05)

[a]A form of shorthand notation was used to denote the length of the fatty acid carbon chain and the number of double bonds in the chain (e.g., Myristic Acid—14:0; Oleic Acid—18:1). Information on the position and configuration of double bonds in unsaturated fatty acids was not included (e.g., elaidic acid, the *trans* isomer of Oleic Acid, would also be denoted as 18:1).

Three types of Stearic Acid distinguished by average Stearic Acid concentration, their specifications, and infrared spectra are included in *CTFA's Compendium of Cosmetic Ingredient Composition*.[21] These Stearic Acids, 37.5%, 42.5%, and 95.0%, have minimum Stearic plus Palmitic Acid concentrations of 89.0%, 94.0%, and 97.5%, respectively. Regular pharmaceutical grade Stearic Acid specifies a 40.0% minimum of either Stearic or Palmitic Acid and a 90.0% minimum for their sum.[23] Purified pharmaceutical grade Stearic Acid specifies a 90.0% minimum Stearic Acid content and a 96.0% minimum for the sum.[73] A comparison of these Stearic Acids is presented in Table 9.

Reactivity and Stability

Chemical reactions of the fatty acids are typical of reactions of carboxylic acids and alkanes (or alkenes, in the case of Oleic Acid). Typical reactions of carboxylic acids include reduction to form aldehydes and alcohols, esterification, formation of metal salts, high-pressure hydrogenation, formation of amides and acid halides, alkoxylation, and pyrolysis. Reactions of alkanes and alkenes are dehydrogenation and hydrogenation, halogenation and hydration.[3,6] Halogenation across carbon–carbon double bonds is a useful method for the quantitative titration for relative unsaturation.[4]

Insoluble stearates and oleates are formed in reactions of Stearic Acid and Oleic Acid with heavy metals and calcium. Oxidizing agents, such as nitric acid and potassium permanganate, added to Oleic Acid are known to produce various derivatives of this acid.[5] Other oxidation routes for fatty acids include oxidation via bacterial action, enzyme-catalyzed hydrolysis and oxidation, and autooxidation from atmospheric oxygen.[6]

A significant increase in lipid peroxide concentration has been observed after 18-h UVA-irradiation of Oleic Acid.[24]

Analytical Methods

Two basic methods for the analysis of the fatty acids have been reported by the cosmetic industry. Primarily, gas chromatography (GC) of fatty acid methyl esters, prepared by the boron trifluoride-methanol method, is used for the separation and relative identification of fatty acids in a mixture.[21,25] Infrared spectra of the fatty acids are used for fingerprinting, functional group identification, and impurity screening.[6,13–17,26] Determination of physicochemical properties also aids in positive identification of a specific fatty acid.[6,25]

Basic analysis of the fatty acids by GC[4,25] has evolved by technical advances in methylation procedures[23,27] and development of new derivatization reactants and techniques that allow easier detection of smaller quantities of fatty acids.[28] A method for the GC of nonmethylated fatty acids has been reported.[29]

Flame ionization detection (FID) is usually coupled with the GC of fatty acid methyl esters. Mass spectrometry (MS) has also been used with GC for compound identification.[30]

Thin-layer chromatography[30,31] and high-performance liquid chromatography (HPLC) are also used in fatty acid identification and quantitation. Precolumn chemical derivatization (e.g., forming benzyl, dansyl, phenacyl, and naphthacyl derivatives) of fatty acids is followed by reversed-phase HPLC. Methods of detection include ultraviolet and fluorescence spectroscopic and refractive index detection. The analysis of fatty acids by HPLC has been reviewed.[32,33]

Mass spectrometry with temperature profiling of the chemical ionization source has been reported as a method for initial compound separation. Its coupling with a second MS allows direct analysis of complex lipid sources.[34]

Other separation methods include centrifugal liquid and adsorption chromatography.[35] Identification procedures range from methods, such as gravimetry[25] and histochemical staining,[36] to ultraviolet, infrared, and nuclear magnetic resonance spectroscopy.[6,37,38]

USE

Cosmetic Use

The fatty acids, Oleic, Lauric, Palmitic, Myristic, and Stearic Acids, are primarily used as intermediates in the manufacture of corresponding alkali salts, which are, in turn, used as emulsifiers, emollients, and lubricants in a variety of cosmetic creams, cakes, soaps, and pastes.[5,9,39-41] They may also be used as base components (of the oil phase) of many cosmetic formulations.[38]

Emollient creams containing fatty acids are slightly alkaline, ranging in pH from 7.5 to 9.5. Other ingredients in these creams include sodium, potassium, and ammonium hydroxide, diethanolamine, triethanolamine, isopropanolamines, amino glycol, and borax.[9]

Stearic Acid is contained in 2465 cosmetic products listed by the Food and Drug Administration (FDA) in the 1981 product formulation data table.[41] Oleic Acid is contained in 424, Myristic Acid in 36, Palmitic Acid in 29, and Lauric Acid in 22 cosmetic formulations in several product categories[41] (Table 10).

The reported concentrations of the fatty acids in cosmetic products primarily range from 0.1 to 25%. Stearic Acid is found in cosmetics in all product categories of the FDA table; most products appear in skin care, makeup, and shaving preparation categories. Oleic Acid is found primarily in hair coloring and eye makeup preparation product categories. Lauric, Palmitic, and Myristic Acids are contained in skin care, shaving, and noncoloring hair preparations and personal cleanliness products.

Voluntary filing of product formulation data with FDA by cosmetic manufacturers and formulators conforms to the tabular format listing preset ingredient concentration ranges and product categories in accordance with Title 21 section 720.4 of the Code of Federal Regulations.[42]

Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration would be a fraction of that reported to the FDA. Data

TABLE 10. Product Formulation Data[41]

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)					
			> 25–50	> 10–25	> 5–10	> 1–5	> 0.1–1	≤ 0.1
Oleic Acid								
Baby shampoos	35	1	—	1	—	—	—	—
Baby lotions, oils, powders, and creams	56	1	—	—	—	1	—	—
Other baby products	15	2	—	1	—	1	—	—
Bath oils, tablets, and salts	237	1	—	—	1	—	—	—
Eyeliner	396	16	—	1	—	7	8	—
Eye shadow	2582	5	—	—	—	2	3	—
Eye makeup remover	81	2	—	—	—	2	—	—
Mascara	397	41	—	—	23	11	7	—
Other eye makeup preparations	230	1	—	—		1	—	—
Sachets	119	4	—	—	—	—	4	—
Other fragrance preparations	191	8	—	—	—	2	6	—
Hair conditioners	478	1	1	—	—	—	—	—
Permanent waves	474	1	—	—	—	—	—	1
Hair shampoos (noncoloring)	909	9	—	2	—	7	—	—
Tonics, dressings, and other hair grooming aids	290	1	—	—	—	—	1	—
Hair dyes and colors (all types requiring caution statement and patch test)	811	205	—	150	—	49	5	1
Hair tints	15	14	—	13	—	1	—	—
Hair shampoos (coloring)	16	7	—	—	—	6	1	—
Hair lighteners with color	2	1	—	—	—	1	—	—
Hair bleaches	111	8	3	3	1	1	—	—
Blushers (all types)	819	10	—	—	—	10	—	—
Face powders	555	1	—	—	—	—	1	—
Makeup foundations	740	20	—	—	—	15	5	—
Lipstick	3319	1	—	—	1	—	—	—
Makeup bases	831	5	—	—	—	2	2	1
Other makeup preparations (not eye)	530	4	—	3	—	—	1	—

TABLE 10. (Continued)

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*					
			> 25–50	*> 10–25*	*> 5–10*	*> 1–5*	*> 0.1–1*	*≤ 0.1*
Nail basecoats and undercoats	44	1	—	1	—	—	—	—
Bath soaps and detergents	148	5	—	—	—	4	1	—
Other personal cleanliness products	227	3	—	—	1	2	—	—
Aftershave lotions	282	3	—	—	—	—	2	1
Shaving cream (aerosol, brushless, and lather)	114	2	—	—	—	2	—	—
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	10	—	—	—	5	5	—
Face, body, and hand skin care preparations (excluding shaving preparations)	832	11	—	1	1	2	7	—
Hormone skin care preparations	10	1	—	—	—	1	—	—
Moisturizing skin care preparations	747	14	—	—	—	4	10	—
Other skin care preparations	349	2	—	—	—	1	1	—
Suntan gels, creams, and liquids	164	2	—	—	—	2	—	—
1981 TOTALS		424	4	176	28	142	70	4
Lauric Acid								
Hair shampoos (noncoloring)	909	3		1		2	—	—
Tonics, dressings, and other hair grooming aids	290	3	—	—	—	—	3	—
Deodorants (underarm)	239	5	—	—	—	—	4	1
Other personal cleanliness products	227	4	—	—	1	—	2	1
Shaving cream (aerosol, brushless, and lather)	114	3	—	—	1	2	—	—

Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	3	—	—	—	3	—	—
Moisturizing skin care preparations	747	1	—	—	—	—	1	—
1981 TOTALS		22	—	1	2	7	10	2
Palmitic Acid								
Eye shadow	2582	1	—	—	1	—	—	—
Hair shampoos (noncoloring)	909	2	—	—	—	2	—	—
Makeup foundations	740	2	—	—	—	1	1	—
Bath soaps and detergents	148	1	—	—	1	—	—	—
Shaving cream (aerosol, brushless, and lather)	114	4	—	—	3	—	1	—
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	8	—	1	1	6	—	—
Face, body, and hand skin care preparations (excluding shaving preparations)	832	3	—	—	—	1	2	—
Moisturizing skin care preparations	747	3	—	—	—	1	2	—
Night skin care preparations	219	3	—	2	—	1	—	—
Other skin care preparations	349	1	—	—	—	1	—	—
Suntan gels, creams, and liquids	164	1	—	1	—	—	—	—
1981 TOTALS		29	—	4	6	13	6	—

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*						
			> 50	*> 25–50*	*> 10–25*	*> 5–10*	*> 1–5*	*> 0.1–1*	*≤ 0.1*
Myristic Acid									
Mascara	397	2	—	—	—	—	—	2	—
Hair shampoos (noncoloring)	909	2	—	—	—	—	2	—	—
Bath soaps and detergents	148	3	—	—	1	2	—	—	—
Other personal cleanliness products	227	2	—	—	2	—	—	—	—

TABLE 10. (Continued)

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*						
			> 50	*> 25–50*	*> 10–25*	*> 5–10*	*> 1–5*	*> 0.1–1*	*≤ 0.1*
Beard softeners	4	2	—	2	—	—	—	—	—
Shaving cream (aerosol, brushless, and lather)	114	16	—	—	—	1	15	—	—
Other shaving preparation products	29	1	—	—	—	—	—	1	—
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	5	—	—	1	3	1	—	—
Face, body, and hand skin care preparations (excluding shaving preparations)	832	2	—	—	—	—	1	1	—
Moisturizing skin care preparations	747	1	—	—	—	—	—	1	—
1981 TOTALS		36	—	2	4	6	19	5	—
Stearic Acid									
Baby lotions, oils, powders, and creams	56	9	—	—	—	2	5	2	—
Other baby products	15	1	—	—	1	—	—	—	—
Other bath preparations	132	3	—	—	—	—	2	1	—
Eyebrow pencil	145	9	—	—	4	5	—	—	—
Eyeliner	396	55	—	5	6	4	29	11	—
Eye shadow	2582	128	—	—	—	—	111	17	—
Eye lotion	13	1	—	—	—	—	1	—	—
Eye makeup remover	81	1	—	—	—	—	—	1	—
Mascara	397	139	—	5	5	20	83	26	—
Other eye makeup preparations	230	26	—	—	—	2	20	4	—
Colognes and toilet waters	1120	3	—	—	—	—	3	—	—
Perfumes	657	3	—	—	—	—	3	—	—
Sachets	119	32	—	—	—	8	23	1	—
Other fragrance preparations	191	34	—	—	—	3	27	4	—

Hair conditioners	478	18	—	—	—	—	9	7	2
Hair sprays (aerosol fixatives)	265	1	—	—	—	—	1	—	—
Hair straighteners	64	6	—	—	—	2	—	4	—
Hair shampoos (noncoloring)	909	17	—	—	1	9	4	3	—
Tonics, dressings, and other hair grooming aids	290	18	1	—	1	4	7	4	1
Hair dyes and colors (all types requiring caution statement and patch test)	811	76	—	—	—	—	76	—	—
Hair bleaches	111	4	—	—	—	—	1	3	—
Other hair coloring preparations	49	8	—	—	8	—	—	—	—
Blushers (all types)	819	47	—	—	—	2	44	1	—
Face powders	555	2	—	—	—	—	—	2	—
Makeup foundations	740	190	—	—	2	3	179	6	—
Lipstick	3319	27	—	—	6	—	14	7	—
Makeup bases	831	263	—	—	1	1	256	5	—
Rouges	211	9	—	—	—	1	7	1	—
Makeup fixatives	22	1	—	—	—	—	1	—	—
Other makeup preparations (not eye)	530	20	—	—	1	—	18	1	—
Cuticle softeners	32	10	—	—	1	1	5	3	—
Nail creams and lotions	25	6	—	—	—	—	6	—	—
Other manicuring preparations	50	2	—	—	—	1	1	—	—
Bath soaps and detergents	148	13	—	—	9	1	3	—	—
Deodorants (underarm)	239	8	—	—	1	1	6	—	—
Other personal cleanliness products	227	8	—	—	1	—	7	—	—
Aftershave lotions	282	5	—	—	—	—	3	2	—
Shaving cream (aerosol, brushless, and lather)	114	100	—	7	11	63	16	3	—
Shaving soap (cakes, sticks, etc.)	7	1	—	1	—	—	—	—	—
Other shaving preparation products	29	6	—	—	2	—	4	—	—
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	173	—	—	18	12	118	24	1

TABLE 10. (Continued)

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*						
			> 50	*> 25–50*	*> 10–25*	*> 5–10*	*> 1–5*	*> 0.1–1*	*≤ 0.1*
Face, body, and hand skin care preparations (excluding shaving preparations)	832	432	—	2	32	39	325	34	—
Hormone skin care preparations	10	3	—	—	1	1	1	—	—
Moisturizing skin care preparations	747	327	—	2	11	21	259	33	1
Night skin care preparations	219	67	—	—	3	9	48	6	1
Paste masks (mud packs)	171	15	—	—	1	5	9	—	—
Skin lighteners	44	11	—	—	3	—	8	—	—
Skin fresheners	260	4	—	—	4	—	—	—	—
Wrinkle smoothers (removers)	38	4	—	—	—	—	4	—	—
Other skin care preparations	349	55	—	—	13	8	31	3	—
Suntan gels, creams, and liquids	164	48	—	—	1	3	36	8	—
Indoor tanning preparations	15	3	—	—	—	—	—	3	—
Other suntan preparations	28	13	—	—	—	—	12	1	—
1981 TOTALS		2465	1	22	148	231	1826	231	6

submitted within the framework of preset concentration ranges provide the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a 2- to 10-fold error in the assumed ingredient concentration.

Products containing these fatty acid ingredients may contact the skin, hair, and eyes. Use of Oleic and Stearic Acids in lipstick and manicuring preparations may lead to ingestion of small quantities of these ingredients. Frequency of application of the fatty acids may range from once per week to several times per day, from less than 1 h to several hours, due to the variety of cosmetic products in which they are contained.

Noncosmetic Use

Oleic, Lauric, Palmitic, Myristic, and Stearic Acids are used in foods as plasticizing, lubricating, binding, and defoaming agents and as reagents in the manufacture of other food-grade additives.[8,20,43] Myristic Acid is used as a flavoring agent in foods.[11]

Straight-chain monobasic carboxylic acids from fats and oils derived from edible sources, such as the fatty acids, Oleic, Lauric, Palmitic, Myristic, and Stearic Acids, are accepted as safe for use in food and in the manufacture of food-grade additives providing they meet particular conditions and specifications.[42] The unsaponifiable matter in the fatty acid or fatty acid-derived food additive must not exceed 2%, the food additive must be free of chick-edema factor, and it must be produced and labeled in accordance with good manufacturing practice.[42]

The fatty acids as a group are permitted as direct food additives.[42] Oleic Acid derived from tall oil and Oleic Acid meeting the specifications in Section 172.860 are permitted as direct food additives.[42] Oleic Acid is also allowed as a food additive in preparations of Polysorbate 80 for which it was used as a reagent.[42] Stearic Acid is permitted as a direct food additive in chewing gum base.[42]

Particular salts of fatty acids are allowed as direct food additives.[42] These salts are not reviewed in this report.

There are no limitations other than the observance of current good manufacturing practice[42] on the use of Oleic and Stearic Acids as indirect food additives.[42] These two fatty acids are also listed as substances that are GRAS.[42]

Regulation of Oleic and Stearic Acids as GRAS substances is based on reviews and evaluation by the Select Committee on GRAS Substances (SCOGS).[44,45] Monographs prepared for these evaluations also are available.[46,47] Several additional reports on fatty acid salts and various ester derivatives have been developed by SCOGS.[48]

FDA files contain both published and unpublished data on the Oleic Acid Group fatty acids (and some of their salts) in the form of Flavor and Extract Manufacturers' Association Monographs, Food Additive Safety Profiles, GRAS Monographs, GRAS Petitions, Food Additive Petitions, and Color Additive

Petitions.* The agency's food safety evaluation of these fatty acids and their salts as direct and indirect food additives and as GRAS substances was based on reviews of these data (document dates range from 1928 to 1977).

Unpublished data from industry submissions to FDA include a two-generation feeding and reproduction study in the rat using Oleic Acid derived from tall oil,[49] a 90-day subchronic oral toxicity study of food-grade Oleic Acid in rats,[50] a 52-day subchronic feeding study of rats using Stearic Acid mixed with lactate salts,[51] a 1-month feeding study of control rats using Stearic Acid as a diet supplement,[52] and a 209-day chronic oral toxicity study of control rats fed a diet supplement of Stearic Acid.[53]

Fatty acids have pharmaceutical uses as lubricants in tablet formulations, in the manufacture of their salts for ointment base emulsifiers,[5] and as calorie sources in parenteral and enteral nutrition therapy.[54] Stearic Acid is widely used in the pharmaceutical coating of enteric pills and bitter remedies and in the preparation of suppositories and ointments.[1,5]

None of the five Oleic Acid Group fatty acids are currently on the Over-The-Counter (OTC) Ingredient list of substances currently being reviewed by OTC scientific panels.[55] Several OTC advisory review panels have determined the level of efficacy of Stearic Acid in the (1) miscellaneous external drug product, (2) topical analgesic including antirheumatic, otic, burn, sunburn treatment, and prevention products, (3) antimicrobial II, and (4) contraceptive and other vaginal drug products categories. However, no determination of its safety was made.[56] Sodium Oleate is under review as a stimulant laxative by the OTC Panel for review of laxatives.[55] The ingredients, "fatty acid," "Oleic Acid," and "Stearic Acid" are listed as "inactive ingredients for approved prescription drug products" that are not required in labeling of these products.[57] The "Inactive Ingredient" list also contains common sources for the fatty acids, such as olive, peanut, cottonseed, nutmeg, tall, and coconut oils.

Fatty acids are used in the manufacture of soaps, detergents, metal salts, driers, and rubber; they are used as solvents for water-insoluble compounds, in polishing compounds, lubricating oils, waterproofing, in candles, phonograph records, insulators, modeling compounds, and as intermediates in chemical synthesis.[1,11,20,43]

Recent clinical uses for fatty acids are their conjugation with antibodies to aid incorporation of the proteins into membranes[58] and their conjugation with antigens for immune potentiation.[59] A derivative of Stearic Acid is commonly used as a paramagnetic probe in the measurement of membrane fluidity by electron spin resonance spectroscopy,[60] and radioactive Palmitic Acid is a diagnostic radiotracer in positron emission tomography.[61]

BIOLOGY

Absorption, Distribution, Metabolism, Excretion

The digestion of dietary fatty acids, their absorption in micellar aggregates, and their transport esterified to glycerol in chylomicrons and very low density

*A listing of these documents was obtained through the Freedom of Information Act. Copies of and notes taken from originals have been placed in Cosmetic Ingredient Review (CIR) files.

lipoproteins has been reviewed.[62-65] Oleic, Palmitic, Myristic, and Stearic Acids are primarily transported via the lymphatic system, and Lauric Acid is transported by the lymphatic and (as a free fatty acid) portal systems.[64] Fatty acids originating from adipose tissue stores are either bound to serum albumin or remain unesterified in the blood.[66,67]

Absorption and distribution studies of some fatty acids were reported in GRAS evaluations and scientific literature reviews of Stearic[45,46] and Oleic Acids[44,47] and the sodium salts of oleate and palmitate.[68] Metabolizable energy values and digestibility coefficients were calculated for Oleic and Stearic Acids in rats, pigs, and chickens. Distribution of radioactivity into various lipid classes in lymph from the thoracic duct of rats was followed for Oleic and Palmitic Acids.

Another monograph on Stearic Acid reviewed its digestion, absorption, and metabolism.[69] It was noted that several investigators found that increasing fatty acid chain length slightly decreased their digestibility; Stearic Acid was the most poorly absorbed of the common fatty acids.[70,71]

Oleic Acid has been reported to penetrate the skin of rats.[72] On histological examination, fluorescence from absorbed Oleic Acid was found in epidermal cell layers of skin removed from treated rats within 10 min of its application. The path of penetration was suggested to be via the hair follicles.[73] Only minute amounts of Oleic Acid were visualized in the blood vessels throughout the experiment. Skin permeability was shown to increase with the lipophilic nature of a compound.[74]

Radioactivity has been traced to the heart, liver, lung, spleen, kidney, muscle, intestine, adrenal, blood, and lymph, and adipose, mucosal, and dental tissues after administration of radioactive Oleic, Palmitic, and Stearic Acids.[69,75,76] The sites of the radioactive atoms (^{3}H, ^{14}C, ^{131}I) were not stated in these studies. Radioactive fatty acids were administered orally, intravenously, intraperitoneally, and intraduodenally into rats, dogs, sheep, chicks, frogs, and humans in various physiological states. Uptake and transport of fatty acids into the brain have been observed.[77]

Proposed mechanisms for fatty acid uptake by different tissues range from passive diffusion to facilitated diffusion or a combination of both.[78,79] Fatty acids taken up by the tissues can either be stored in the form of triglycerides (98% of which occurs in adipose tissue depots) or they can be oxidized for energy via the β-oxidation and tricarboxylic acid cycle pathways of catabolism.[80]

The β-oxidation of fatty acids occurs in most vertebrae tissues (except the brain) using an enzyme complex for the series of oxidation and hydration reactions resulting in the cleavage of acetate groups as acetyl-CoA (coenzyme A). An additional isomerization reaction is required for the complete catabolism of Oleic Acid.[63] Alternate oxidation pathways can be found in the liver (ω-oxidation) and in the brain (α-oxidation).[81-83]

Fatty acid biosynthesis from acetyl-CoA takes place primarily in the liver, adipose tissue, and mammary glands of higher animals. Successive reduction and dehydration reactions yield saturated fatty acids up to a 16-carbon chain length. Stearic Acid is synthesized by the condensation of palmitoyl-CoA and acetyl-CoA in the mitochondria, and Oleic Acid is formed via a monooxygenase system in the endoplasmic reticulum.[4,82]

Fatty acid metabolism has been extensively studied under various physiological conditions,[84-86] in mammalian development,[87,88] in various organisms,[89] as affected by xenobiotics, such as ethanol[90,91] and drugs.[92] The regulation of fatty acid metabolism has been reviewed.[93-96]

Simultaneous ingestion of trace amounts of ^{14}C-triolein (10 μCi) and ^{3}H-Oleic Acid (20 μCi) in 42 g of carrier fat by patients with normal fecal fat excretion resulted in estimated fecal excretion of less than 10% of both substances.[97] Gastrointestinal transit times for ^{14}C-triolein, ^{3}H-Oleic Acid, and a nonabsorbable marker, $^{51}CrCl_3$, did not differ significantly.

Fatty acid metabolism has been studied in several tissues. Interest in the correlation between fatty acids, cholesterol, and coronary heart disease has spurred extensive research on myocardial fatty acid metabolism.[98-101] Fatty acid metabolism has also been studied in the liver,[102-104] the intestine and intestinal microflora,[105,106] the lungs,[107] the kidneys,[108-110] skeletal muscle,[111] bone and cartilage,[112] and oral mucosal epithelium.[113]

Maternal–Fetal Transfer

Free fatty acids readily cross the placental barrier in rabbits, guinea pigs, rats, and humans.[114-118] A bolus of 1-^{14}C-Palmitic Acid was injected over 10 sec into the carotid artery of 4 pregnant guinea pigs ranging in gestational age from 48 to 65 days.[119] The fetal side of the placenta was perfused in situ. A rapid decline in maternal plasma radioactivity and a rapid appearance of radioactivity in the perfusate were observed. The disappearance profile of fetal radioactivity essentially paralleled that of maternal radioactivity after a lag time of 1.6 min. Other studies of maternal–fetal transfer of fatty acids were performed primarily with albumin-bound or lipoprotein-emulsified 1-^{14}C-Palmitic Acid.[119,120]

Dietary Fat and Coronary Heart Disease

The Select Committee on GRAS Substances stated its "concern over the role of saturated versus polyunsaturated fatty acids in the etiology of arteriosclerosis and associated vascular diseases" in their review of Stearic Acid.[45] The Committee noted a joint statement by the Food and Nutrition Board of the National Research Council and the Council on Foods and Nutrition of the American Medical Association that acknowledged the importance of reducing the intake of saturated fatty acids and cholesterol.[121] Cholesterol has been reviewed by Cosmetic Ingredient Review.[122]

Current studies and reviews confirm the correlation between dietary saturated fatty acid intake and the incidence of atherosclerosis and thrombosis found in earlier studies and reports.[123,124] Research is now focused on the mechanism(s) of induction and the elucidation of the multifactorial influence of diet on coronary heart disease.[100,101]

TABLE 11. Antimicrobial Activity of Fatty Acids[125, 126]

Organism	*Oleic Acid*	*Lauric Acid*	*Palmitic Acid*	*Myristic Acid*	*Stearic Acid*
	Minimal Inhibitory Concentration (mM)				
Aspergillus niger	—	> 4	—	—	—
Bacillus cereus	—	> 2	—	—	—
Bacillus subtilis	—	> 2, 0.5[b]	—	—	—
Candida albicans	NI[a]	2.49	NI	4.37	NI
Candida utilis	—	4, 1[b]	—	—	—
Micrococcus lysodeikticus	—	> 2	—	—	—
Penicillium citrinum	—	4	—	—	—
Pseudomonas aeruginosa	NI	NI	—	—	—
Streptococcus pneumoniae	NI	0.062	0.48	0.218	NI
Saccharomyces cerevisiae	—	> 4	—	—	—
Staphylococcus aureus	NI	2.49	NI	4.37	NI
Streptococcus Group A	1.77	0.124	3.9	0.547	NI
Streptococcus β-hemolytic type	—	0.249	3.9	2.18	NI

[a]NI, not inhibitory at concentrations tested (1.0 mg/ml or 3–6.0 m*M*).
[b]1st value obtained by agar dilution method, 2nd value obtained by broth dilution method.

Antimicrobial Activity

The antibacterial activities of Oleic, Lauric, Palmitic, Myristic, and Stearic Acids were studied by placing them in liquid broths containing different microorganisms.[125] Minimal inhibitory concentrations at 37°C were determined. Results of this study and of other studies on bacteria and fungi[126] are presented in Table 11.

The effects of Oleic, Lauric, Palmitic, Myristic, and Stearic Acids on aflatoxin B_1 production and growth of the fungus *Aspergillus parasiticus* were studied.[127] Concentrations of 5 m*M* fatty acid were added to liquid medium containing "three drops of the emulsifier, Tween-80." Myristic, Palmitic, and Stearic Acids stimulated and Oleic Acid inhibited toxin synthesis. Lauric Acid inhibited fungal growth.

The antiviral activity of Oleic Acid and other unsaturated fatty acids was studied.[128] These fatty acids inactivated enveloped viruses, such as herpes, influenza, Sendai, and Sindbis viruses at concentrations from 5 to 50 μg/ml. "Naked" viruses, such as polio, SV40, and encephalomyocarditis viruses, were not affected, indicating a direct memebrane effect. Stearic Acid did not inactivate any of the viruses at the concentrations tested.

TOXICOLOGY

Reviews of the literature from 1933 to 1976 were prepared for the safety evaluations of Oleic and Stearic Acids as GRAS substances by FDA[44–47] and of Stearic Acid as a fragrance raw material by Research Institute for Fragrance

Materials (RIFM).[69] RIFM Reviews of Oleic and Myristic Acids have been prepared and are pending publication. A subchronic oral toxicity study of Palmitic Acid was presented in a GRAS monograph on sodium oleate and sodium palmitate.[68]

Oral Toxicity Studies

Acute Oral Toxicity

Oleic, Lauric, Palmitic, Myristic, and Stearic Acids were tested for acute oral toxicity to rats (Table 12).

Administration of doses up to 21.5 ml/kg of Oleic Acid and up to 10.0 g/kg of Palmitic and Myristic Acids (commercial grades) by gavage to albino rats resulted in no deaths and no significant gross lesions at necropsy.[129,130] Doses of 10.0 g/kg of commercial grade Lauric Acid and of 25% (w/v) Stearic Acid in corn oil produced the deaths of 1 rat in each group. At necropsy of these rats, congested lungs and kidneys and advanced autolytic changes were observed. No significant gross lesions were found at necropsy of 2 rats of the 0.464 and 4.64 g/kg triple-pressed Stearic Acid dose groups. Transient signs of toxicity were observed in rats of the higher dose groups of 10.0 and 21.5 ml/kg Oleic Acid, 10.0 g/kg 25% Stearic Acid in corn oil, and the 4.64 and 10.0 g/kg Lauric, Palmitic, Myristic, and triple-pressed Stearic Acids. Signs of toxicity included slight depression, depressed righting and placement reflexes, oily and unkempt fur, mucoid diarrhea, excessive salivation, and sero-sanguineous discharge from the muzzle and eyes.

A cream formulation containing 5% Oleic Acid administered to rats at a dose of 5 ml/kg produced no mortalities. Signs of toxicity included transient weakness in the legs and colored urine and feces.[131]

Oral administration of a 5.0 g/kg dose of a product formulation containing 8.7% Lauric Acid to rats produced slight toxicity and no deaths.[132]

A shave cream formulation containing 2.2% Palmitic Acid administered to rats at a dose of 5 g/kg produced no deaths and was classified as "non-toxic."[133]

White rats were fed a diet containing 50% Stearic Acid.[144] Treated male rats died after an average of 8.2 days and female rats died after 10.2 days. Spasms and paralysis of the extremities of some rats and cardiac irregularities were observed immediately preceding death. With a lower concentration of 15% Stearic Acid in the diet, the rats lived for a much longer period.

In three studies, groups of 5 male albino rats received oral doses of 0.464–10.0 g/kg "eutectic, triple-pressed" Stearic Acid and 25% (w/v) Stearic Acid in corn oil,[130] or approximately 16% Stearic Acid in ethylene oxide and water (65% solution in ethylene oxide diluted 1:3 in water).[134] There were 2 deaths in the 4.64 g/kg dose group of the first study and 1 death in the 10.0 g/kg dose groups of the second and third studies.

A dose of 5 g/kg of a face cream formulation containing 13% Stearic Acid produced no deaths when administered to albino rats by gavage.[135] Skin lotion formulations containing 2.8% Stearic Acid administered at doses of 15 g/kg by gavage to groups of 10 albino rats resulted in 1 death in 1 group.[136,137]

At necropsy of the rat that died, fibrous tissue around the heart and reddish fluid throughout the thoracic cavity were observed. Normal behavior and appearance were observed, and there were no gross alterations in surviving rats. Slight dehydration and depression were observed in 1 rat.

In other studies, testing for acute oral toxicity of skin lotion formulations containing 2.8% Stearic Acid by administration of 5 ml/kg[140-143] and 5 g/kg[138,139] doses of the formulations resulted in few, if any, deaths. At necropsy of the rats that died, fibrous tissue encasing the heart and lungs was observed.

Subchronic and Chronic Oral Toxicity

Feeding of 5% Oleic Acid or 50% Stearic Acid diets to chicks for 4 weeks had no adverse effects (Table 13).[145,146] Decreased clotting time, moderate hyperlipemia, and severe phlebothrombosis following initiation with an intravenous injection of lipopolysaccharide from *Salmonella typhosa* were observed in rats fed high-fat diets containing 5% Stearic Acid.[147,148] Rats fed diets containing 4.6 g/kg/day Palmitic Acid for 6 weeks developed hyperlipemia.[148] A diet containing 50% Stearic Acid fed to rats for 8 weeks resulted in a microscopic "foreign body-type reaction" in adipose tissue.[149] Rats fed high-fat diets containing 6% Stearic Acid for 9 weeks developed severe aortic atherosclerosis and thrombosis induced by *S. typhosa* lipopolysaccharide; high mortality was also observed.[147]

Feeding 15% Oleic Acid diets to rats for 10–16 weeks had no adverse effects on growth or general health.[150] Of 4 female weanling rats fed the diet for 16 weeks, "all 4 were able to become pregnant; however 2 died at parturition, a litter was eaten at birth, and the remaining litter died within 3 days of birth." Mating of 7 adult female rats fed the diet for 16 weeks resulted in production of 52 young, 44 of which survived 1 week and 11 of which survived 3 weeks. Mammary development was retarded, and a few rats had ovarian cysts. No lesions were found in other organs.

A "foreign body-type reaction" in perigonadal fat and the reversible formation of lipogranulomas were observed in rats fed 50 g/kg/day Stearic Acid for 24 weeks.[151] Anorexia, severe pulmonary infection, and high mortality were observed in rats fed diets containing 3000 ppm Stearic Acid for 30 weeks.[152]

Dermal Toxicity Studies

Acute Dermal Toxicity

Oleic, Palmitic, and Stearic Acids were tested for acute dermal toxicity after topical application and intradermal administration to the skin of guinea pigs, rabbits, and mice (Table 14).

In one study, application of commercial grade Oleic Acid to the skin of guinea pigs produced no deaths and no signs of toxicity. The number of applications was not stated.[153] Marked irritation characterized by crusting, ulceration, and thickening of the skin was observed following topical application of commercial grade Oleic Acid to the skin of rabbits, guinea pigs, and

TABLE 12. Acute Oral Toxicity Studies

Fatty acid tested	*Dose*	*Species (No. per group)*	*Results*	*Reference*
Oleic Acid[a]	5.0 g/kg	5 albino rats (bodyweight 193–217 g)	Range of BW after 7 days—235–273 g. No deaths. Signs of toxicity not reported. Oleic Acid classified "slightly toxic by ingestion"	129
Oleic Acid[b]	0.464, 1.00, 2.15, 4.64, 10.0, 21.5 ml/kg	5 male albino rats (BW 214–220 g)	LD_{50} > 21.5 ml/kg. Range in avg. BW gains 65–99. No deaths in any group	130
Oleic Acid—5.0% in cream formulation	5 ml/kg of cream	10 Fischer 344 rats (BW 135–175 g)	No deaths. Transient leg weakness, colored urine and feces	131
Lauric Acid[a]	0.464, 1.00, 2.15, 4.64, 10.0 g/kg	5 male albino rats (BW 221–247 g)	Range, avg. BW gain—73–99 g. One death in group given 10.0 g/kg dose on 1st postdosage day	130
Lauric Acid—8.7% in product formulation	5.0 g/kg of product	5 albino rats (BW 155–160 g)	BW range after 7 days—209–230 g. No deaths. Signs of toxicity not reported. Lauric Acid classified "slightly toxic by ingestion"	132
Palmitic Acid[a]	0.464, 1.00, 2.15, 4.64, 10.0 g/kg	5 male albino rats (BW 209–254 g)	Range, avg. BW gain—65–92 g. No deaths	130
Palmitic Acid—2.2% in shave cream formulation	5 g/kg of cream	≥ 10 albino rats (BW 200–300 g)	Formulation classified "non-toxic." No data or procedures (other than administration by gavage) reported; reference for test method - 16 CFR 1500.3(b)(6)(i)(A)	133
Myristic Acid[a]	0.464, 1.00, 2.15, 4.64, 10.0 g/kg	5 male albino rats (BW 208–211 g)	Range, avg. BW gain—75–95 g. No deaths	130
Stearic Acid (eutectic)[a]	0.464, 1.00, 2.15, 4.64, 10.0 g/kg	5 male albino rats (BW 213–223 g)	Range, avg. BW gain—71–101 g. One death in 4.64 g/kg dose group on day of dosage; one death in 4.64 g/kg dose group on final day of study	130

Stearic Acid—25% (w/v) in corn oil	0.464, 1.00, 2.15, 4.64, 10.0 g/kg	5 male albino rats (BW 216–225 g)	Range, avg. BW gain—90–104 g at lower doses, 77 g at 10.0 g/kg dose. One death in 10.0 g/kg on Day 7 of study	130
Stearic Acid—65% in ethylene oxide, diluted 1 : 3 in water	5 and 10 g/kg	10 male young adult ARS/Sprague-Dawley albino rats (BW 215–239 g)	Final avg. BW 5 g/kg group—317 g; 10 g/kg group—258 g. One death in 10 g/kg dose group on Day 5 following dosage. No pharmacotoxical signs noted. No remarkable alterations at necropsy	134
Stearic Acid—13% in face cream formulation	5 g/kg face cream	≥ 10 albino rats (BW 200–300 g)	Formulation classified "non-toxic." No procedures (other than administration by gavage) or data reported. Reference for test method - 21 CFR 1500.3(b)(6)(i)(A)	135
Stearic Acid—2.8% in skin lotion formulation	15 g/kg skin lotion	10(5M, 5F)albino rats (BW 206–258 g)	Final BW range—228–378 g. One death on Day 2	136
Stearic Acid—2.8% in skin lotion formulation	15 g/kg skin lotion	10(5M, 5F)albino rats (BW 218–254 g)	Final BW range—198–414 g. No deaths	137
Stearic Acid—2.8% in skin lotion formulation	5 g/kg skin lotion	10(5M, 5F)albino rats (BW 184–238 g)	Final BW range—174–386 g. Two deaths on Days 9 and 10	138
Stearic Acid—2.8% in skin lotion formulation	5 g/kg skin lotion	10(5M, 5F)albino rats (BW 202–264 g)	Final BW range—210–430 g. One female rat died on Day 7 postdosage. All rats appeared normal throughout study. At necropsy, fibrous tissue was observed encasing heart and lungs of rat that died and no gross changes were observed in other rats	139
Stearic Acid—2.8% in skin lotion formulation	5.0 ml/kg skin lotion	10 Sprague-Dawley rats (BW 200–254 g)	Range in BW gain—75–127 g. No deaths. All rats appeared normal throughout study. At necropsy, thoracic and abdominal organs appeared normal.	140
Stearic Acid—2.8% in skin lotion formulation	5.0 ml/kg skin lotion	10 Sprague-Dawley rats (BW 174–200 g)	Range in BW gain—85–118 g. No deaths. All rats appeared normal throughout study. At necropsy, thoracic and abdominal organs appeared normal	141
Stearic Acid—2.8% in skin lotion formulation	5.0 ml/kg skin lotion	10 Sprague-Dawley rats (BW 175–189 g)	Range in BW gain—42–118 g. No deaths. All rats appeared normal throughout study. At necropsy, thoracic and abdominal organs appeared normal	142
Stearic Acid—2.8% in skin lotion formulation	5.0 ml/kg skin lotion	6 Sprague-Dawley rats (BW 205–214 g)	Range in BW gain—102–129 g. No deaths. All rats appeared normal throughout study. At necropsy, thoracic and abdominal organs appeared normal	143
Stearic Acid	5 g/kg	rat	No deaths	45

[a]Fatty acid commercially supplied.

[b]These studies were cited in reviews for the safety assessment of particular fatty acids as they are used in foods[44–47, 68] and in fragrances.[69]

TABLE 13. Subchronic and Chronic Oral Toxicity Studies[a]

Study type	*Fatty acid tested*	*Species*	*Results*	*Reference*
Subchronic feeding study (4 weeks)	Stearic Acid—50% in diet	Chick	No adverse effects	145, 146
Subchronic feeding study (4 weeks)	Oleic Acid—5% in diet	Chick	No adverse effects	145
Subchronic feeding study (6 weeks)	Stearic Acid—5% in high-fat diet	Rat	Decreased clotting time, moderate hyperlipemia, severe phlebothrombosis after initiation with *S. typhosa* lipopolysaccharide (LPS)	147, 148
Subchronic feeding study (6 weeks)	Palmitic Acid—4.6 g/kg/day in diet	Rat	Most hyperlipemic of all fatty acids tested (versus Lauric, Myristic, and Stearic Acids). Second to Stearic Acid in thrombogenic effect	148
Subchronic feeding study (8 weeks)	Stearic Acid—50% in diet	Rat	Microscopic foreign body type reaction in excised fat. No reaction in controls	149
Subchronic feeding study (9 weeks)	Stearic Acid—6% in high-fat diet	Rat	Severe aortic atherosclerosis, high mortality, severe thrombosis after *S. typhosa* LPS initiation	147
Subchronic feeding study (10 weeks)	Oleic Acid—15% in diet	Rat	Normal appearance. Mammary gland underdeveloped; few rats with ovarian cysts. No lesions in non-reproductive organs. Production of 52 young by 7 adult females—11/52 survived by 3rd week	150
Chronic feeding study (16 weeks)	Oleic Acid 15% in diet	Rat	No impairment of males' fertility. 4/4 females became pregnant; 2/4 deaths at parturition; 1 litter died within 3 days of birth	150
Chronic feeding study (20 weeks)	Oleic Acid—15% in diet	Rat	Normal growth observed	150
Chronic feeding study (24 weeks)	Stearic Acid—50 g/kg/day in diet	Rat	4/5 rats had foreign body type reaction in perigonadal fat. Lipogranulomas observed. Reversible effects	151
Chronic feeding study (30 weeks)	Stearic Acid—3000 ppm in diet	Rat	Anorexia, severe pulmonary infection, high mortality. No significant pathological lesions	152

[a] These studies were cited in reviews for the safety assessment of particular fatty acids as they are used in foods[44–47, 68] and in fragrances.[69]

TABLE 14. Acute Dermal Toxicity Studies[a]

Fatty acid tested	*Dose*	*Species (No. per group)*	*Results*	*Reference*
Oleic Acid[c]	3.0 g/kg	6 guinea pigs	No deaths. Oleic Acid classified "non-toxic"	153
Oleic Acid[c]	1–2 ml	5 rabbits	Potent depilatory agent. Marked irritation. Microscopic hyperkeratosis, acanthosis. (Observations in all 3 species)	154[b]
	1 ml	2 guinea pigs		
	0.3 ml	12 mice		
Oleic Acid—50% in mineral oil	1 ml	16 HRS/J mice	Epidermal hyperplasia and hyperkeratosis	155
Oleic Acid—25, 50, 75% in peanut oil	0.1 ml (intradermal)	2 guinea pigs	Local inflammation and necrosis. No alterations in controls given peanut oil	156[b]
Palmitic Acid—2.2% in shave cream formulation	2 g/kg	≥ 10 rabbits	No deaths. Formulation considered "non-toxic"	133
Stearic Acid—10–100 m*M* in olive oil	10–100 m*M* (intradermal)	guinea pigs rabbits	Mild erythema and slight induration of skin	157[b]

[a]Methods of most studies involved topical application of fatty acids. Intradermal administration noted parenthetically.

[b]Data from these studies were obtained from reviews for the safety assessment of particular fatty acids in foods[46, 47, 68] and fragrances.[69]

[c]Fatty acid as commercially supplied.

mice.[154] Microscopically, hyperkeratosis, pronounced acanthosis, follicular keratotic plugs, hyperplasia of sebaceous glands, and loss of hair shafts from follicles were observed. Treated skin returned to normal when treatment was discontinued.

Local skin inflammation and necrosis were observed at sites on the backs of guinea pigs receiving 0.1 ml intradermal injections of 25, 50, and 75% Oleic Acid in peanut oil and Oleic Acid as commercially supplied. No alterations were observed at sites injected with peanut oil alone.[156]

Epidermal hyperplasia and hyperkeratosis were observed in the skin of mice after topical application of 50% Oleic Acid in mineral oil.[155]

Application of a 2 g/kg dose of a shave cream formulation containing 2.2% Palmitic Acid was considered nontoxic to rabbits.[133,158]

Concentrations from 10 to 100 m*M* Stearic Acid in olive oil applied to the skin of guinea pigs and rabbits produced mild erythema and slight induration.[157]

Short-Term Dermal Toxicity

Follicular–keratogenic properties of Oleic, Lauric, Palmitic, Myristic, and Stearic Acids were studied after topical application to the skin of the external ear canal of 4 albino rabbits[159] (Table 15). A 5% (w/v) alcohol solution of Stearic Acid and alcohol solutions of the other fatty acids equimolar with the Stearic Acid solution were prepared [5% (w/v) Stearic Acid ~ 18 mmol% Stearic Acid]. A dose of 3 ml of each of the fatty acid solutions was applied once daily, 5 days per week, for 6 weeks. Controls in one group received similar treatment with absolute alcohol and those in another group received no treatment. Myristic and Palmitic Acids produced transient slight erythema and desquamation in the first 2 weeks of application. No clear alterations were observed after Stearic Acid treatment. One day after treatment with Oleic and Lauric Acids, erythema was observed. The intensity of the redness increased over the following few days and desquamation developed. Distinct follicular keratosis was observed within 1 month. After discontinuation of the applications, the erythema and scaling gradually disappeared, but the keratosis was discernible after 6 weeks.

Follicular epidermal hyperplasia was produced after topical application of undiluted commercial grade Oleic Acid (unspecified dose) to the backs of white mice 6 times per week for 1 month.[160]

In a recent study, no adverse effects were produced from subchronic topical application of Myristic Acid to rabbit skin.[161] One-half milliliter of a 30% preparation of Myristic Acid in ether and propylene glycol (solvents at a 1:1 ratio in concentration) was massaged into the depilated skin of the flanks of 5 rabbits daily for 30 days. The opposite flank of the rabbits was depilated and treated with solvent only. No significant macroscopic changes were observed. Microscopic lesions included thinning of collagen fibers in the superficial layers of the dermis after 10 days and a loose dermal infiltrate of lymphomononuclear cells and histiocytes after 20 and 30 days.

Stearic Acid application had little effect on the epidermis of rats.[72] Hair on the dorsa of albino or Long-Evans rats had been closely clipped before an unspecified dose of Stearic Acid was swabbed on the treatment sites once daily for 5 days to 2 weeks.

TABLE 15. Short-term Dermal Toxicity Studies

Fatty acid tested	*Dose*	*Species*	*Method Notes*[a]	*Results*	*Reference*
Oleic Acid—~ 18 mmol% in alcohol	3 ml	4 rabbits	External ear canal, 6 weeks	Erythema, desquamation, follicular keratosis	159[b]
Oleic Acid		Mice	Dorsa for 1 month	Epidermal hyperplasia	160[b]
Lauric Acid—~ 18 mmol% in alcohol	3 ml	4 rabbits	External ear canal, 6 weeks	Results similar to those after Oleic Acid application. Follicular keratosis persisted after treatment	159[b]
Palmitic Acid—~ 18 mmol% in alcohol	3 ml	4 rabbits	External ear canal, 6 weeks	Slight irritation for first 2 weeks	159[b]
Myristic Acid—~ 18 mmol% in alcohol	3 ml	4 rabbits	External ear canal, 6 weeks	Slight irritation for first 2 weeks	159[b]
Myristic Acid—30% in ether : propylene-glycol	0.5 ml	5 rabbits	Flank, 30 days	Microscopic thinning of dermal collagen. Cellular infiltration	161
Stearic Acid—50% (w/v) in alcohol	3 ml	4 rabbits	External ear canal, 6 weeks	No alterations	159[b]
Stearic Acid—20% in product formulation	2 ml/kg of product	6 rabbits	Abraded/intact sites on back, 4 weeks	No deaths. Slight edema, desquamation	162
Stearic Acid—20% in product formulation	2 ml/kg of product	6 rabbits	Abraded/intact sites on back, 4 weeks	No deaths. Slight edema, desquamation	163

[a]All methods involved repeated topical application to noted sites.
[b]Data from these studies were obtained from reviews for safety assessment of particular fatty acids in foods[46, 47, 68] and fragrances.[69]

Stearic Acid, at a concentration of 2.0% in 2 cosmetic product formulations was tested for subchronic dermal toxicity using groups of 6 New Zealand strain albino rabbits.[162,163] Hair was clipped from the backs of the rabbits, and the skin was either abraded or left intact. Doses of 2 ml/kg of the product formulations were applied to the sites daily, 5 days per week, for a total of 20 applications. The rabbits in the untreated control group had no signs of skin irritation. No mortalities were observed in the 2 groups of rabbits receiving applications of either formulation.

In the first group, the mean percentage gain in body weight was 33%, and the skin of all 6 rabbits was slightly edematous; edema was observed in 3/6 rabbits after the first week, 1/6 rabbits during the third week, and 2/6 rabbits during the fourth week. The skin of 5 of the 6 rabbits remained edematous for the duration of the study. Two of the rabbits had slight local desquamation of the skin that was of irregular duration. The brown color of the product obscured scoring of treatment sites for erythema. Both abraded and intact skin had similar reactions to treatment with the product. Individual fluctuations in hematological values were noted in animals of all groups including controls. Slight differences in serum glutamic-pyruvic transaminase values were observed that were considered unrelated to treatment. At necropsy, organ weights of the treated group were comparable to those of controls, and the pulmonary hemorrhages observed in 1 male were considered unrelated to treatment and common in New Zealand strain rabbits. Discharge from the left eye of 1 male rabbit was noted. No significant microscopic lesions considered to be treatment-related were noted.

In the second group of 6 NZW rabbits that received applications of a product formulation containing 2.0% Stearic Acid for 4 weeks, the mean body weight gain was 18%. The skin of all 6 rabbits was slightly edematous; edema was observed in 1/6 rabbits during the first week, 1/6 rabbits during the second week, and 4/6 rabbits during the fourth week. The edema observed in the skin of the first 2 rabbits disappeared after a few days, recurring in 1 during the fourth week. One rabbit had slight atonia during the second week only. Four rabbits during the second week and 2 rabbits during the third week developed slight desquamation of the skin at treatment sites, which returned to normal. Slight scaling of the skin was observed for the duration of the study. The brown-colored product obscured scoring of treatment sites for erythema. Clinical signs of toxicity included nasal discharge in 2 male rabbits (on days 18–28 and on days 10 and 11) and scabs on the back of a female rabbit (on days 7–28). Both intact and abraded sites had similar reactions to the treatment. No distinct treatment-related effects were noted in hematological, biochemical, or organ weight values. There were no significant gross or microscopic alterations.

A facial skin care product formulation containing 5.0% Stearic Acid was applied to the shaved dorsal skin of 15 female rats of the Crl:COBS CD(SD)BR strain in a 13-week dermal toxicity study.[164] Daily doses of 4.0 ml/kg of the product were applied 5 days per week for a total of 65 applications. The treatment was estimated to provide a dose 100-fold greater than the daily exposure to humans. Controls received no treatment. There were no deaths in the treatment group and one death in the control group. No major changes in

appearance or behavior were observed that were treatment-related, although minimal to moderate skin irritation was observed in all rabbits throughout the study. Statistically significant ($p < 0.05$) changes included decreased glucose and increased serum glutamic-pyruvic transaminase concentrations during the 7th week, and decreased hemoglobin, hematocrit, mean corpuscular volume, and total erythrocyte count during the 13th week. Urinalysis values were within normal limits. At necropsy, increases in absolute weights of the liver, heart, kidneys, and adrenals and in liver/body weight ratios were statistically significant ($p < 0.05$). The apparent statistical significance between hematological, biochemical, and organ weight values of treated and control groups was within normal limits. Subclinical bronchitis and "focal interstitial mononuclear cell infiltration into the kidneys, liver and heart" were noted in an unspecified number of rats. Grade 1 hyperkeratosis was observed in 5 of 15 treated rats.

A concealing cream product formulation containing 2.4% Stearic Acid was applied to the shaved dorsal skin of 15 female Sprague-Dawley rats in a 13-week dermal toxicity study.[165] Daily doses of 227 mg/kg of the product were applied 5 days a week for a total of 65 applications. As in the preceding study,[164] the treatment was estimated to provide a dose 100 times greater than the typical human exposure. Controls received no treatment. There were no deaths or significant differences in growth rates. Sporadic and transient skin irritation was observed in the treatment group throughout the study. Statistically significant ($p < 0.05$) differences between treatment and control groups in mean hematology values (decreased hemoglobin during weeks 7 and 13, decreased hematocrit during week 7, increased mean corpuscular volume during week 13, and decreased total erythrocyte count during weeks 7 and 13) and mean serum chemistry values (decreased serum alkaline phosphatase during week 13) were within normal limits. Urinalysis values were considered normal. At necropsy, changes in mean absolute organ weight (brain) and mean relative organ weights (liver/body, spleen/body) were considered toxicologically insignificant. Minimal hyperkeratosis of the epidermis was observed in some rats.

Administration of subcutaneous Oleic Acid injections at volumes increasing from 0.25 to 0.5 ml for 400 days had no adverse effects in the growth of albino mice. The life duration of mice of both sexes was lower than that expected for normal mice.[166]

Primary Skin Irritation

The fatty acids, Oleic, Lauric, Palmitic, Myristic, and Stearic Acid, were tested for primary skin irritation from topical application to the skin of rabbits (Table 16).

In a single insult occlusive patch test (SIOPT) with 6 albino rabbits, administration of a 0.5 ml dose of Oleic Acid, as commercially supplied, resulted in a primary irritation index (PII) of 0.5 (max PII = 8.0) and mild erythema 24 h after treatment.[130] In a Repeat Open Patch study with 6 rabbits (specific procedure not reported), application of commercial grade Oleic Acid produced mild to moderate erythema after 24 h, mild to marked erythema after 48 h, and moderate to marked erythema after 72 h. Slight to moderate

TABLE 16. Primary Skin Irritation Studies

Fatty acid tested	*Dose*	*No. of Rabbits*	*Method*	*Results*	*Reference*
Oleic Acid, as commercially supplied	0.5 ml	6	SIOPT,[a] I/A[b]	PII[c] 0.50. Minimal erythema at 24 h	130
Oleic Acid, as commercially supplied	~ 0.5 ml	6	Repeat Open Patch, 24, 48, 72 h patches	Cumulative irritation increasing from mild erythema and no edema at 24 h to marked erythema and moderate edema in some rabbits at 72 h	167
Oleic Acid—5.08% in product formulation	0.5 g of product	6	Modified Draize, 3 open patches	Minimal erythema after 72 h	169
Oleic Acid—5.08% in product formulation	0.5 g of product	6	See preceding entry	Minimal erythema in 3 rabbits after 72 h	170
Oleic Acid 5 % in product formulation	0.5 ml of product	6	Daily, 14 d	PII 2.3. Slight irritation after 4–7 days	131
Lauric Acid, as commercially supplied	0.5 ml	6	SIOPT, I/A	PII 1.12. Minimal erythema after 24 h. Minimal edema at few A sites after 72 h	130
Lauric Acid—8.7% in product formulation	0.5% of product in water	6	SIOPT, I/A	PII 0. No irritation	171
Palmitic Acid, as commercially supplied	0.5 ml	6	SIOPT, I/A	PII 0. No irritation	130
Palmitic Acid—74% "plus other fatty acids"	0.5 g	6	SIOPT, I/A 4-h exposure	PII 0.2. Very slight erythema at few I and at all A sites after 4 h	172
Palmitic Acid—4.4% in product formulation	0.5 ml of product	9	SIOPT	PII 1.00. Mild erythema after 2 h. Minimal to mild erythema after 24 h	173
Palmitic Acid—4.4% in product formulation	~ 0.5 ml of product	9	SIOPT	PII 1.00. See preceding entry	174
Palmitic Acid—2.2% in product formulation	0.5 g of product	≥ 6	SIOPT, I/A	"Non-irritating." No other data or specific procedures reported	133
Myristic Acid, as commercially supplied	0.5 ml	6	SIOPT, I/A	PII 0. No irritation	130
Myristic Acid, as commercially supplied	~ 0.5 g	6	Repeat Open Patch	Cumulative irritation increasing from no to mild/moderate erythema from 24 to 72 h	175

Stearic Acid, as commercially supplied	0.5 ml	6	SIOPT, I/A	PII 0. No irritation	130
Stearic Acid (eutectic), as commercially supplied	0.5 ml	6	SIOPT, I/A	PII 0. No irritation	130
Stearic Acid, as commercially supplied	~ 0.5 ml	9	SIOPT, 2-h exposure	PII 0.33. Few rabbits with barely perceptible erythema after 24 h	176
Stearic Acid—65% in ethylene oxide	0.5 g	6	SIOPT, I/A	PII 3.00. Defined erythema and slight edema after 24 and 72 h	134
Stearic Acid—59% "plus other fatty acids"	0.5 g	6	SIOPT, I/A, 4-h exposure	PII 0. No irritation	172
Stearic Acid—45% "plus other fatty acids"	0.5 g	6	SIOPT, I/A, 4-h exposure	PII 0. No irritation	172
Stearic Acid—50% in petrolatum	~ 0.5 ml	9	SIOPT, 2-h exposure	PII 0.56. Few with mild erythema after 2 h; decreased to barely perceptible erythema after 24 h	177
Stearic Acid—35% in water	~ 0.5 ml	9	SIOPT, 2-h exposure	PII 0.33. Few with barely perceptible erythema after 2 h	178
Stearic Acid—13% in product formulation	0.5 g of product	≥ 6	SIOPT, I/A	"Non-irritating." No other data or procedures reported	179
Stearic Acid—2.8% in product formulation	0.5 ml of product	6	SIOPT, I/A	PII 1.00. Transient minimal erythema after 24 h	138
Stearic Acid—2.8% in product formulation	0.5 ml of product	6	SIOPT, I/A	PII 1.05. Transient irritation after 24 h	139
Stearic Acid—2.8% in product formulation	0.5 g of product	6	SIOPT, I/A	PII 0.92. Very slight erythema after 24 and 72 h, persisting at most A sites. Transient minimal edema	140
Stearic Acid—2.8% in product formulation	0.5 ml of product	6	SIOPT, I/A	PII 1.45. Transient minimal to defined erythema and edema after 24 h. Dry skin noted	136
Stearic Acid—2.8% in product formulation	0.5 g of product	4	SIOPT, I/A	PII 0.63. Transient very slight erythema after 24 h	143
Stearic Acid—1.0% in product formulation	0.5 ml of product	6	SIOPT, I/A	PII 2.2. Transient defined erythema and edema after 24 h	180
Stearic Acid—1.0% in product formulation	0.5 ml of product	6	SIOPT, I/A	PII 2.0. Barely perceptible erythema, transient edema after 24 h	180

[a]SIOPT, single insult occlusive patch test, usually 24 h exposure period.
[b]I/A, patches applied to intact and abraded skin sites.
[c]PII, primary irritation index (max = 8.00).

edema was observed after 72 h.[167] In Modified Draize tests,[168] 3 repeated open patch topical applications of cream blush formulations containing 5.08% Oleic Acid produced mild erythema in 6 female NZW rabbits after 72 h. The formulations were not primary skin irritants.[169,170] In a 14-day study with 6 NZW rabbits, the daily topical applications of a red cream formulation containing 5% Oleic Acid produced slight to well-defined erythema and slight

In an SIOPT, commercial grade Lauric Acid applied to intact and abraded sites of the skin of 6 albino rabbits produced slight erythema at both sites after 24 h, which subsided by 72 h, minimal edema after 72 h, and a PII of 1.12. Blanching and some coriaceous tissue were noted at a few abraded sites.[130] In an SIOPT, a 5% aqueous preparation of a product formulation containing 8.7% Lauric Acid applied to intact and abraded skin of 6 albino rabbits resulted in a PII of 0.[171]

A dose of 0.5 ml of commercial grade Palmitic Acid applied to intact and abraded sites on the skin of 6 albino rabbits in an SIOPT resulted in a PII of 0.[130] Administration of product formulations containing 2.2–74% Palmitic Acid produced minimal erythema and no edema 2–24 h after application to the skin of albino rabbits.[133,172–174]

In an SIOPT, commercial grade Myristic Acid was applied to intact and abraded sites on the skin of 6 albino rabbits, and the PII was 0.[130] In a Repeat Open Patch test using commercial grade Myristic Acid, all 6 treated albino rabbits developed mild to moderate erythema from 24 to 72 h. One rabbit developed very slight edema after the 72-h scoring.[175]

No irritation was observed at intact or abraded sites of the skin of albino rabbits in two SIOPT studies involving a commercial grade Stearic Acid.[130] In an SIOPT of commercial grade Stearic Acid, transient minimal erythema and no edema were noted in 9 albino rabbits after a 2-h exposure period.[176]

A preparation of 65% Stearic Acid in ethylene oxide produced erythema and minimal edema 24 and 72 h after application to intact and abraded sites on the skin of 6 NZW rabbits. The PII for this SIOPT was 3.00.[134] No irritation was observed in SIOPT studies involving 4-h exposures of intact and abraded skin of 6 albino rabbits to 45 and 59% Stearic Acid in combination with "other fatty acids."[172] Two-hour exposures of the skin of 9 albino rabbits to 35.0% Stearic Acid in water and 50% Stearic Acid in petrolatum resulted in respective PIIs of 0.33 and 0.56. Transient mild erythema and no edema were observed in both SIOPT studies.[177,178]

SIOPT studies with lotion and cream formulations containing 1.0–13% Stearic Acid resulted in PIIs, ranging from 0.63 to 2.2, that were not directly related to Stearic Acid concentration. A face cream formulation containing 13% Stearic Acid was determined "non-irritating" in a 24-h SIOPT of the fatty acid applied to intact and abraded sites on the skin of at least 6 albino rabbits. The use of a standard procedure was reported,[158] and no additional data were recorded.[179]

In a 24-h SIOPT of a skin lotion formulation containing 2.8% Stearic Acid, the PII was 1.00, and barely perceptible erythema and edema were observed at most intact and abraded sites of 6 NZW rabbits after 24 h. Irritation had subsided after 72 h.[138]

Transient irritation was also observed in a 24-h SIOPT to intact and abraded sites of the skin of 6 NZW rabbits treated with a skin lotion formulation containing 2.8% Stearic Acid. Very slight to well-defined erythema was observed at both sites, and very slight edema was observed at some intact and all abraded sites after 24 h.[139]

A skin lotion formulation containing 2.8% Stearic Acid produced very slight erythema at both intact and abraded treatment sites and transient minimal edema at a few sites 1 day after a 24-h SIOPT.[140]

A skin lotion formulation containing 2.8% Stearic Acid produced minimal to well-defined erythema and edema at both intact and abraded sites of 6 NZW rabbits 24 h after treatment. Very slight erythema was observed at some of the sites after 72 h.[136] Dry skin was noted in all rabbits.

A skin lotion formulation containing 2.8% Stearic Acid produced very slight to well-defined erythema and edema at intact and abraded sites of 6 NZW rabbits 24 h after treatment. Very slight erythema was observed at a few sites, and there was no edema 48 h later.[137] Dry skin was noted at treatment sites of all rabbits.

Intact and abraded sites on the skin of 4 male albino rabbits were treated with a skin lotion formulation containing 2.8% Stearic Acid in a 24-h SIOPT study. Transient minimal erythema was observed after 24 h. One abraded site had very slight edema after 24 h.[143]

Intact and abraded sites on the skin of 6 NZW rabbits were treated with lotion formulations containing 1.0% Stearic Acid in two 24-h SIOPT studies.[180] Treatment with one formulation produced defined erythema and edema at both sites after 24 h, which had subsided by 72 h posttreatment.

Skin Sensitization

A cream blush formulation containing 5.08% Oleic Acid was tested for sensitization using a group of 24 female Hartley guinea pigs weighing 300–500 g.[181] In a maximization test,[182] single intradermal injections of 0.1 ml of 5% Freund complete adjuvant in water, of a 5% solution of the formulation in water, and of a 5% solution of the formulation, water, and Freund adjuvant were administered in rows along the dorsal midline of the guinea pigs. Seven days after the injections, a 10% preparation of sodium lauryl sulfate in petrolatum was topically applied to the clipped dorsal area. Twenty-four hours later, 1 g of the undiluted formulation was applied to the treatment sites under an occlusive patch. The challenge patch, 1 g of the undiluted formulation in a Duhring chamber (aluminum disk with diameter of 18 mm and 2 mm elevated flange), was topically applied under an occlusive wrapping 14 days after topical induction (22 days after the intradermal injection). After a 24-h exposure, the challenge patch was removed. Sites were scored at patch removal and 48 h later. None of the guinea pigs had reactions to the challenge patches. Although no other data were reported, the formulation was considered a weak, grade I, sensitizer.

A suntan lotion formulation containing 1.0% Stearic Acid was tested for sensitization on 22 young adult female Hartley guinea pigs[183] using the same

procedure as in the preceding study.[181] There was one sensitization reaction to the occlusive challenge patch of 1 g of the formulation in a Duhring chamber among the 22 treated guinea pigs. The formulation was considered a weak, grade I, sensitizer.

In a maximization study,[182] a cosmetic product formulation containing 3.5% Stearic Acid was tested for allergic contact sensitization using a group of 10 female guinea pigs.[184] Intradermal injections of 50% aqueous Freund complete adjuvant, 50% formulation in propylene glycol, and 50% formulation in 50% aqueous Freund adjuvant at each of three sites along the upper backs of the guinea pigs were followed 1 week later by a topical booster of a slightly irritating concentration of the formulation in petrolatum. A topical application of 10% sodium lauryl sulfate in petrolatum was made 24 h before the topical booster if the formulation was not sufficiently irritating. Guinea pigs in the control group received induction injections of 50% aqueous Freund complete adjuvant, propylene glycol, and a 1:1 preparation of propylene glycol and 50% aqueous Freund adjuvant along the upper back and topical booster applications of petrolatum. Two weeks after the topical booster application, occlusive challenge patches containing 50 or 100% of the formulation were applied to control and treated guinea pigs. Sites were scored 48 and 72 h later. Five of 10 treatment sites had minimal faint erythema, and 1 of 10 sites had mild erythema 48 h after challenge with the 100% concentration. There were 3 sites with minimal faint erythema after 72 h, 2 of which had signs of desquamation. Other treatment sites had no signs of sensitization. Challenge of the treatment sites with the 50% formulation preparation resulted in minimal faint erythema at 1 of 10 sites after 48 h, which was visible after 72 h. All other treatment sites challenged with the 50% concentration had no signs of sensitization. Two control guinea pigs died, and 4 of the remaining 8 sites challenged with the 100% formulation patch had minimal faint erythema after 48 h. Two of 8 sites challenged with the 50% concentration had minimal faint erythema, and desquamation was observed at another site after 72 h.

Photosensitization

Two skin lotion formulations containing 2.8% Stearic Acid were tested for phototoxicity.[185,186] Aqueous preparations of the formulations, 100, 75, 50, and 25%, were applied to four different sites on the backs of 10 male Hartley albino guinea pigs weighing 324–486 g[185] and 284–452 g.[186] These sites were exposed to UVA radiation. Ten control guinea pigs weighing 268–434 g[185] and 344–464 g[186] received the same topical applications but no UVA irradiation. Sites were evaluated 1 and 24 h after treatment. Neither formulation was considered phototoxic to the guinea pigs under these conditions because the control group had signs of irritation that were comparable to the irradiated test group. One guinea pig in the control group of one study died.[185] The test groups' reactions ranged from questionable to moderate erythema at 6 (50% preparation) to all 10 sites (75%, 100% preparations). The 25% preparations produced no signs of phototoxicity in either study. The control groups in both studies had questionable to moderate (50–100% sites,[185] 50–75% sites[186]) or considerable erythema (100% site[186]). No irritation was observed at control sites treated with the 25% preparations.

Two skin lotion formulations containing 2.8% Stearic Acid were tested for photoallergy using 12 male Hartley albino guinea pigs weighing 378–516 g[186] and 330–404 g.[185] Each guinea pig received 10 topical induction applications of the undiluted formulations. Two weeks after the last application, challenge applications of 10, 20, and 100% (w/v) preparations were made to two separate sites, one of which was irradiated. Control groups of 12 male guinea pigs (360–440 g,[185] 358–492 g[186]) received no induction applications and were treated as test animals in the challenge phase. Induction sites were evaluated daily and challenge sites were evaluated 24 and 48 h after treatment. In one study, 1 test animal died during the induction phase and 2 animals died during the challenge phase.[185] Neither formulation was considered photoallergenic to the guinea pigs under these conditions because the control group had signs of irritation comparable to the test group. Questionable to moderate erythema was observed at up to 11 of 12 sites by the second application of the induction phase. During the challenge phase, no irritation was observed at either irradiated or nonirradiated sites of guinea pigs in control and test groups at the 10 and 20% concentrations. Questionable to minimal erythema was observed at one or two nonirradiated sites and at five irradiated sites of the test group challenged with the undiluted formulation. In the control group, four to seven nonirradiated sites and five to six irradiated sites had questionable to minimal erythema after challenge with the undiluted formulation.

Comedogenicity

The comedogenicity of UVA-irradiated and nonirradiated Oleic Acid was evaluated.[24] A significant increase in lipid peroxide level of Oleic Acid was observed after 18 h of UVA irradiation. Daily applications of the nonirradiated Oleic Acid (approximately 2 ml of 99% Oleic Acid) for 2 weeks were made on the ventral surface of one ear of Japanese and New Zealand White rabbits. An equal volume of irradiated Oleic Acid was applied to the other ear. Both Oleic Acid and its peroxides induced fairly large comedones in both species of rabbit. The lipid peroxide concentration was positively correlated with the degree of comedo formation.

Ocular Irritation Studies

Oleic, Lauric, Palmitic, Myristic, and Stearic Acids were tested for ocular irritation (Table 17).

No or minimal conjunctival irritation was produced in eyes of 6 albino rabbits treated with 0.1 ml of Oleic Acid as commercially supplied. Using the Draize Method,[168] the single instillation was not rinsed from the eyes. Untreated eyes served as controls.[130,187,188] In other Draize studies, 0.1 ml of mascara and cream product formulations containing 2–5% Oleic Acid produced no or slight conjunctival irritation in the eyes of rabbits within 2 days of treatment.[131,191–192] No irritation was observed in eyes that had been irrigated 20 sec after treatment with 20 ml lukewarm water.[190] No irritation was observed in rinsed and unrinsed eyes of rhesus monkeys treated with a mascara formulation containing 6% Oleic Acid.[189]

TABLE 17. Ocular Irritation Studies

Fatty acid tested	*Species (no. per group)*	*Methods*[a]	*Results*	*Reference*
Oleic Acid, as commercially supplied	6 albino rabbits	Draize	Mean score 2 after 24 h; 1 after 48 and 72 h (max = 110). Mild conjunctivitis	130
Oleic Acid, as commercially supplied	3 albino rabbits	Draize	No irritation	187
Oleic Acid, as commercially supplied	3 albino rabbits	Draize	Total mean score 1 after 1 and 2 days; 0 after 3 days. Grade 2 conjunctival irritation	188
Oleic Acid—6% in mascara formulation	3 rhesus monkeys	Draize, ±rinse	No irritation in either group	189
Oleic Acid—5% in cream formulation	6 NZW rabbits	14 daily instillations, no rinse	Intermittent slight conjunctivitis during 1st week	131
Oleic Acid—3% in mascara formulation	3 albino rabbits	Draize, ±rinse	Grade 1 conjunctival erythema in unrinsed treated eyes clearing by 2nd day	190
Oleic Acid—2% in mascara formulation	3 albino rabbits	Draize, ±rinse	No irritation	191
Oleic Acid—2% in mascara formulation	6 albino rabbits	Draize	Mean score 0.66 after 24 h; 0.33 after 48 h. Grade 1 conjunctival erythema in 1 rabbit only	192
Lauric Acid, as commercially supplied	6 albino rabbits	Draize	Mean score 35 after 24 h; 39 after 48 h; 41 after 72 h. Persistent corneal opacity, mild conjunctivitis, iritis	130
Lauric Acid—8.7% in product formulation, 8.0% aqueous dilution tested	6 albino rabbits	Draize	No irritation	193
Lauric Acid—1.95% in soap formulation, 1% aqueous dilution tested	6 NZW rabbits (rinse group) 3 NZW rabbits (no rinse group)	Draize, ±rinse	Max. mean score 0.3 for unrinsed eyes; 0.7 for rinsed eyes. Grade 1 conjunctival erythema	194
Palmitic Acid, as commercially supplied	6 albino rabbits	Draize	No irritation	130
Palmitic Acid—19.4% in product formulation	6 albino rabbits	3 instillations, no rinse	Total mean score 3 after 1 and 2 days. No irritation after 3 days. Primarily conjunctival irritation	195

Palmitic Acid—19.4% in product formulation, 75% solution in corn oil	6 albino rabbits	Draize	Total mean score 1 after 1 day; 6 after 2 days; 1 after 3 days. No irritation after 4 days. Mild irritation of cornea, iris, and conjunctivae	196
Palmitic Acid—4.4% in product formulation	6 albino rabbits	Draize	No irritation	197
Palmitic Acid—4.4% in product formulation	6 albino rabbits	Draize	No irritation	198
Palmitic Acid—2.2% in product formulation	6 albino rabbits	Draize	No irritation	133
Myristic Acid, as commercially supplied	6 albino rabbits	Draize	Grade 1 conjunctival erythema in 3 rabbits after 24 h	130
Myristic Acid—50% in petrolatum	3 albino rabbits	Draize	Total mean score 2 after 1 day; 1 after 2 and 3 days; 0 after 4 days. Grade 2–4 conjunctival irritation	199
Myristic Acid—1.5% in product formulation	6 NZW rabbits (no rinse) 3 NZW rabbits (rinse)	Draize, ± rinse	Max. mean score 1.3 for unrinsed; 0.7 for rinsed treated eyes. Conjunctival erythema up to 72 h later	200
Myristic Acid—1.5% in product formulation	See preceding entry	Draize, ± rinse	Max. mean score 0.7 for unrinsed; 1.3 for rinsed treated eyes. Conjunctival erythema 24–48 h later	201
Stearic Acid, as commercially supplied	6 albino rabbits	Draize	No irritation	130
Stearic Acid (eutectic), as commercially supplied	6 albino rabbits	Draize	Mild conjunctival erythema in 2 rabbits, subsiding by 72 h	130
Stearic Acid—65% in ethylene oxide	6 NZW rabbits	Draize	No irritation	134
Stearic Acid—50% in petrolatum	6 albino rabbits	Draize	Total mean score 4 after 1 day. Conjunctival irritation subsided after 2 days	202
Stearic Acid—35% in corn oil	6 albino rabbits	Draize	Total mean score 1. Mild conjunctival irritation subsided after 2 days	203
Stearic Acid—13% in product formulation	6 albino rabbits	Draize	Iritis in 1 rabbit	179

TABLE 17. (Continued)

Fatty acid tested	*Species (no. per group)*	*Methods*[a]	*Results*	*Reference*
Stearic Acid—2.8% in product formulation	6 NZW rabbits (no rinse) 3 NZW rabbits (rinse)	Draize, ±rinse	Mean total score 0.7 for unrinsed treated eyes after 1 day; conjunctival erythema subsided after 2 days. No irritation in rinsed treated eyes	138
Stearic Acid—2.8% in product formulation	6 NZW rabbits	Draize	No irritation	139
Stearic Acid—2.8% in product formulation	3 NZW rabbits	Draize	Max. mean score 3.3; conjunctival irritation after 1 and 24 h, subsiding after 48 h	140
Stearic Acid—2.8% in product formulation	6 NZW rabbits (no rinse) 3 NZW rabbits (rinse)	Draize, ±rinse	Mean total score 0.7 after 48 h, 0.3 after 72 h and 4 days for unrinsed eyes. Similar scores for rinsed eyes. Slight conjunctival erythema	136
Stearic Acid—2.8% in product formulation	See preceding entry	Draize, ±rinse	Mean total score 0.7 after 24 h in both groups. Slight conjunctival erythema	137
Stearic Acid—2.8% in product formulation	3 NZW rabbits	Draize	Max. mean score 6.0 after 1 h. Conjunctival irritation in all rabbits, subsiding after 24 h	141
Stearic Acid—2.8% in product formulation	3 NZW rabbits	Draize	Max. mean score 6.0 after 1 h. Conjunctival irritation persisting up to 24 h	142
Stearic Acid—2.8% in product formulation	3 NZW rabbits	Draize	Max. mean score 4.0 after 1 h. Slight conjunctival erythema persisting up to 24 h	143
Stearic Acid—1% in product formulation	4 albino rabbits	Draize	Max. mean score 6.0 after 1 h. Slight conjunctival irritation, 2 rabbits had corneal irritation. Subsided by 24 h	204
Stearic Acid—1% in product formulation	6 albino rabbits	Draize	Max. mean score 2.83 after 1 h. Slight conjunctival irritation and iritis in 1–3 rabbits	153

[a]Draize Method[168] used in most studies: usually single instillation of 0.1 ml volume into 1 eye (untreated eye = control). Variant methods (e.g., "rinse" denoting rinsing of treated eyes or "±rinse" denoting that treated eyes of animals in 1 group were rinsed, while those of animals in other group left unrinsed) are noted.

Instillation of commercial grade Lauric Acid into the eyes of 6 albino rabbits produced corneal opacity, mild conjunctivitis, and iritis throughout the 72-h observation period.[130] An aqueous dilution of a product formulation containing 8.7% Lauric Acid produced no ocular irritation in 6 albino rabbits.[193] A 1% aqueous preparation of a soap formulation containing 1.95% Lauric Acid was not irritating to treated unrinsed eyes of rabbits. The preparation was minimally irritating to treated eyes that had been rinsed 30 sec after instillation with 20 ml deionized water at room temperature.[194]

Administration of commercial grade Palmitic Acid to the eyes of 6 albino rabbits produced no irritation.[130] Mild to moderate ocular irritation was produced in rabbits by product formulations containing 19.4% Palmitic Acid. One of these formulations had been diluted to 75% with corn oil.[195,196] Cosmetic product formulations containing 2.2 and 4.4% Palmitic Acid produced no ocular irritation in 6 albino rabbits.[133,197,198]

Slight conjunctival irritation was produced in the eyes of albino rabbits 1 day after instillation of commercial grade Myristic Acid[130] and 50% Myristic Acid in petrolatum.[199] Lotion formulations containing 1.5% Myristic Acid were minimally irritating to rinsed (20 ml ionized water at room temperature, 30 sec after instillation) and unrinsed treated eyes of rabbits.[200,201]

No ocular irritation was produced in 6 albino rabbits by commercial grade Stearic Acid, whereas mild conjunctival erythema was produced in 3 of 6 albino rabbits by commercial grade eutectic (triple-pressed) Stearic Acid.[130] Treatment with 65% Stearic Acid in ethylene oxide resulted in no ocular irritation.[134] Treatment with 35% Stearic Acid in corn oil and 50% Stearic Acid in petrolatum was "practically non-irritating," primarily producing mild conjunctival erythema, which had subsided within 2 days.[202,203]

Iritis was observed in 1 of 6 albino rabbits treated with a face cream formulation containing 13% Stearic Acid.[179] No irritation[139] or mild conjunctival irritation after 1 and 24 h[136–138,141–143,153,204] was observed in the unrinsed eyes of albino rabbits treated with lotion formulations containing 1 and 2.8% Stearic Acid. Mild iritis was also observed in one study.[153] Eyes of rabbits that had been irrigated with water after treatment with a skin lotion formulation containing 2.8% Stearic Acid had no signs of irritation[138] or slight conjunctival erythema after 24 and 48 h.[136,137]

MUTAGENICITY

Oleic, Lauric, and Stearic Acids were assayed for their abilities to induce mitotic aneuploidy and crossing-over of chromosomes in the D_6 strain of *Saccharomyces cerevisiae.(205)* Concentrations of Oleic Acid from 100 to 500 μg/ml and of Lauric Acid from 10 to 200 μg/ml increased aneuploidy, whereas Stearic Acid at concentrations up to 500 μg/ml was inactive. None of the fatty acids tested increased the frequency of mitotic crossing-over events; concentrations of Oleic and Lauric Acids up to 50 μg/ml and of Stearic Acid up to 500 μg/ml were used.

Stearic Acid was tested for mutagenicity using the Ames test[206] with *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538.[207]

Spot tests were performed using 50 mg/ml Stearic Acid suspensions in distilled water (50 μg/plate) with and without microsomal activation from hepatic S9 fractions from rats induced with Aroclor 1254 (50 μg/plate). Positive controls were 2-aminoanthracene and 4-nitro-o-phenylenediamine in dimethyl sulfoxide, 9-aminoacridine in ethanol, and sodium azide in distilled water. Stearic Acid had no mutagenic activity over background in the strains tested with and without metabolic activation.

The genotoxicity of Oleic Acid was studied using V79 Chinese hamster lung fibroblasts.[208] The three tested concentrations of Oleic Acid, 2.5, 5.0, and 10.0 μg/ml, produced a mean number of sister chromatid exchanges per metaphase that was similar to controls. Higher incidences of aneuploidy were observed in cultures at all three concentrations. The 2.5 μg/ml Oleic Acid-treated culture had a higher incidence of tetraploidy when compared to controls.

Isomers of Oleic Acid, *cis*-12- and *cis*-13-octadecenoic acids, produced a greater increase in mitochondrial DNA mutation in *S. cerevisiae* than did Oleic Acid.[209]

Inhibition of Mutagenesis

Oleic, Lauric, Stearic, and Palmitic Acids were tested for their inhibitory action on the mutagenicity of several compounds using two bacterial systems, *Escherichia coli* and *Salmonella typhimurium*. These studies and their results are summarized in Table 18.

In the *S. typhimurium* system, a modified Ames test[206] was used involving preincubation of a mixture containing the mutagen, dimethylsulfoxide (DMSO), fatty acid, S9, and bacteria before plating. A phosphate buffer at pH 6 was used for the preincubation mixture in the *E. coli* system. A significant decrease in the number of revertants compared to negative controls in both tests was interpreted as inhibition by the fatty acid. Positive controls with mutagen alone were done to determine maximum numbers of revertants.

Oleic Acid was toxic to *S. typhimurium* TA 100,[211] and Lauric Acid was toxic to *E. coli* WP2 uvrA/pKM101 in the absence of S9. In the presence of S9, Lauric Acid had a strong inhibitory effect on all N-nitrosodialkylamines tested.[212]

Mechanisms for Oleic and Lauric Acid-inhibition of potent mutagens have been discussed, and results of several bacterial tests for fatty acid inhibition of mutagenesis have been reported.[214]

CARCINOGENICITY

Oleic, Lauric, Palmitic, and Stearic Acids have been tested for carcinogenic activity. The studies were reviewed in the safety assessment of particular fatty acids (and their salts) as they are used in foods[44-47,68] and in fragrances.[69] Data and results from these and additional studies are summarized in Table 19.

TABLE 18. Inhibition of Mutagenicity by Fatty Acids

Fatty acid tested	*Bacterial system used*	*Metabolic activation*	*Results*	*Reference*
Oleic Acid isolated from fecal extract	*Salmonella typhimurium* TA98	S9 from livers of rats induced with poly-chlorinated biphenyl (PCB)	Inhibition of mutagenicity of: 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole; 2-amino-6-methyl-dipyrido[1,2-a:3′,2′-d]imidazole; 2-amino-9H-pyrido[2,3-b]indole; 2-amino-3-methyl-imidazo[4,5-d]-quinoline; benzo[a]pyrene (amino acid pyrolysis products) and aflatoxin B_1 Degree of inhibition increased with decreasing pH. I_{50}, 0.02–0.08 mg; I_{95}, 0.05–0.38 mg	210
Oleic Acid	*Escherichia coli* WP2 try, hcr	S9-phenobarbital-induced rat liver	Inhibition: 140 μmol N-nitrosodimethylamine (NDMA); 14 μmol N-nitrosodiethylamine (NDEA); 4 μmol N-nitrosodibutylamine (NDBA); 35 μmol N-nitrosopyrrolidine (NPYR); 35 μmol N-nitroso morpholine (NMOR). Dose-related inhibition observed No inhibition: 2 μmol N-methyl-N′-nitro-N-nitrosoguanidine (NMMG)	211
Oleic Acid	*E. coli* WP2 uvrA/pkM 101	S9-phenobarbital-induced hamster liver	Inhibition: NDMA	212
Lauric Acid	*S. typhimurium* TA100	None reported	Inhibition: sodium azide, 4-nitro-o-phenylene-diamine, N-amino-morpholine, ethylmethane-sulfonate	213
Lauric Acid	*E. coli* WP2 uvrA/pKM 101	S9-phenobarbital-induced hamster liver	Inhibition: NDMA, NDEA, NDBA, N-nitroso-piperidine, NMOR. Cytotoxic in N-methylnitroso-urea cultures	212
		S9-PCB-induced rat liver	Inhibition: benzo[a]pyrene No inhibition: 2-aminoanthracene	
Palmitic Acid	*S. typhimurium* TA98	S9-PCB-induced rat liver	No inhibition: amino acid pyrolysis products, aflatoxin B_1	210
Stearic Acid isolated from fecal extract	*S. typhimurium* TA98	S9-PCB-induced rat liver	No inhibition: amino acid pyrolysis products, aflatoxin B_1	210
Stearic Acid	*E. coli* WP2 try, hcr	S9-phenobarbital-induced rat liver	No inhibition: NDMA	211

I_n, amount of fatty acid needed to produce a percent inhibition.

TABLE 19. Carcinogenicity Studies on Fatty Acids

Fatty acid tested	*Dose*	*Animal*	*Method*	*Results and conclusions*	*Reference*
Oleic Acid in tricaprylin	1–16.5 mg	Mouse (BALB/c, CFW)	Repeated subcutaneous injections. Two experiments: (1) 0.1 mg Oleic Acid in 0.1 ml tricaprylin 3 injections/week, total of 10 injections (2) 0.5 mg Oleic Acid in 0.1 ml tricaprylin 2 injections/week, total of 33 injections	Not carcinogenic (1) 1/15 mice alive at 18 months. No subcutaneous sarcomas (2) 4/16 mice alive at 18 months. No subcutaneous sarcomas, 1 breast carcinoma at 9 months	215[a]
Oleic Acid with linoleic acid in corn oil in diet	150–200 mg/mouse/day of 1.5% fatty acids in in refined corn oil	Mouse (T.M. strain)	Feeding study—dietary supplement. Several groups: (1) Control—chow only ($n = 623$) (2) Refined corn oil supplement ($n = 375$) (3) Refined corn oil + 1.5% free fatty acid supplement (oleic and linoleic acids) ($n = 329$)	(1) Controls— < 20% total tumor incidence mainly lung tumors (2) Incidence of lung and brain nerve cell tumors, lymphosarcomas similar to Group 3. Incidence gastric tumors lower than Group 3. 1 heart tumor found (3) High incidence of lung (48.5%), stomach (27.4% forestomach papillomas, 12.5% pyloric tumors), and brain nerve cell (11%) tumors. Low incidence of mammary carcinomas, myomas, lymphosarcomas. 1 heart tumor found	216
Oleic Acid with linoleic acid in corn oil in diet	200 mg/mouse/day of 1.5% fatty acids in refined corn oil	Mouse	Feeding study—dietary supplement. Several groups (1) Control—chow only ($n = 195$) (2) Refined corn oil supplement ($n = 209$) (3) Crude corn oil supplement ($n = 196$)	Number of tumors Groups: (1) (2) (3) (4) Forestomach papillomas 2 6 49 87 Squamous cell carcinomas 1 1 6 10 Pyloric tumors 0 2 9 41 No intestinal polyps or adenocarcinomas	217

			(4) Refined corn oil + free fatty acid supplement (oleic and linoleic acids) ($n = 328$)		
Oleic Acid in corn oil diet	10 g of 1.5% (w/w) in corn oil in chow	Mouse (C57BL/1 strain)	Feeding study—dietary supplement. 2 groups (1) Control—chow only ($n = 36$) (2) Corn oil + Oleic Acid ($n = 55$)	(1) Incidence of tumorigenesis not reported for controls (2) Metastatic colon adenocarcinomas in 8% of mice. Polycystic kidney in 1 mouse No corn oil in chow group (i.e., treated control) C57BL/1 strain reported to be generally resistant to tumor formation	218
Oleic Acid	Unspecified	Mouse	Unspecified method—biweekly applications for 40 weeks. Series of experiments	No malignant tumors. In 3 experiments: 0/100 mice with tumors 1/200 mice with benign tumor at week 35 1/100 mice with benign tumor at week 15 No change to malignancy	219[a]
Lauric Acid in tricaprylin	25 and 50 mg	Mouse (BALB/c; CFW)	Repeated subcutaneous injections. Two experiments: (1) 1.0 mg Lauric Acid in 0.1 ml tricaprylin. 2 injections/week, total 25 injections (2) 5.0 mg Lauric Acid in 0.1 ml tricaprylin. 3 injections/week, total 10 injections	Not carcinogenic (1) 5/16 mice alive at 18 months. 1 subcutaneous sarcoma, 1 pulmonary tumor, 2 leukemia–lymphomas (4, 5 months) (2) 8/15 mice alive at 18 months. No subcutaneous sarcomas; 1 pulmonary tumor; 1 leukemia-lymphoma (23 months)	215[a]
Palmitic Acid in tricaprylin	25 and 50 mg	Mouse (BALB/c; CFW)	Repeated subcutaneous injections. Two experiments: (1) 1.0 mg Palmitic Acid in 0.1 ml tricaprylin. 2 injections/week, total of 25 injections (2) 5.0 mg Palmitic Acid in 0.1 ml tricaprylin. 3 injections, total of 10 injections	(1) 5/16 mice alive at 18 months. 1 subcutaneous sarcoma (8 months); 2 breast carcinomas (18 months); 1 leukemia -lymphoma (12 months) (2) 6/16 mice alive at 18 months. 1 subcutaneous sarcoma (19 months); 2 pulmonary tumors (19, 22 months); 1 breast carcinoma (22 months)	216[a]
Palmitic Acid in diet	50 g/kg/day	Rat (Holtzman)	Feeding study—dietary supplement	Lipogranulomas observed in fat associated with testis or ovary—reversible upon diet substitution Conclusion: effect due to dietary imbalance	151[a]

TABLE 19. (Continued)

Fatty acid tested	*Dose*	*Animal*	*Method*	*Results and conclusions*	*Reference*
Stearic Acid in olive oil	Unspecified	Mouse	Single subcutaneous injection	No sarcomas observed. Used as a control in study on cholesterol carcinogenicity	220[a]
Stearic Acid in tricaprylin	1.3–82 mg	Mouse (BALB/c and CFW Swiss Webster)	Repeated subcutaneous injections. Series of expts. using 0.05–1.0 mg Stearic Acid in 0.1 ml tricaprylin. 1–3 injections per week, total of 10–114 injections per study	7–90% of mice were alive at 18 months ($n = 10–16$). Only 1 group (0.05 mg, 2x/week, 114 injections) had subcutaneous sarcomas (4 in 4 survivors). 1 adrenal carcinoma, 1 leukemia–lymphoma, 3 pulmonary tumors in total of 92 mice (in entire series)	215[a]
Stearic Acid in tricaprylin	1.3–13 mg	Mouse (ICR/Ha Swiss Millerton and CFW Swiss Webster)	Repeated subcutaneous injections. Series of expts. using 0.05 or 0.5 mg Stearic Acid in 0.1 ml tricaprylin 1 injection per week, 26 weeks	1–3 deaths within 6 months ($n = 15–16$). No sarcomas at injection site. No carcinogenic activity	221[a]
Stearic Acid in diet	0.3%	Rat	Feeding study. Dietary supplement for 209 days	No carcinogenic activity	152[a]
Stearic Acid in diet	50 g/kg/day	Rat (Holtzman)	Feeding study–dietary supplement	Lipogranulomas observed in fat associated with testis or ovary—reversible upon diet substitution. Concluded that effect due to dietary imbalance rather than Stearic Acid-related	151[a]

[a] These studies appeared in reviews for the safety assessment of particular fatty acids as they are used in food[44–47] and in fragrance.[69]

The carcinogenicity of Oleic, Lauric, Palmitic, and Stearic Acids was studied from 1964 to 1967 in a series of experiments with female BALB/c or Swiss-Webster mice.[215] Subcutaneous injections were administered in the inguinal area 3 times per week for 4 weeks. Materials that were administered daily or for longer than 4 weeks were given in inguinal and axillary areas to prevent their accumulation into deposits of unabsorbed oil. The vehicle for the injections was tricaprylin, and the volume per injection was 0.1 ml. One group of control mice was administered tricaprylin alone; the other control group received no treatment. Mice were observed twice weekly for the appearance of subcutaneous neoplasms. Animals with neoplasms or those in poor condition were killed and necropsied.

Oleic Acid was administered to 15 Swiss-Webster mice at a dose of 0.1 mg 3 times per week for a total of 10 injections.[215] The total dose administered in the study was 1.0 mg Oleic Acid per 1 ml tricaprylin. Nine mice were alive after 12 months, and 1 was alive after 18 months. No neoplasms were observed after this treatment. Another group of 16 Swiss-Webster mice received 2 injections of 0.5 mg Oleic Acid per week for a total of 33 injections. The total dose administered was 11.5 mg per 2.3 ml tricaprylin. Eight mice were alive after 12 months, and 4 were alive after 18 months. One mammary gland carcinoma was found after 9 months.

Lauric Acid was administered to 15 Swiss-Webster mice at a dose of 1.0 mg 3 times per week for a total of 12 injections (total dose, 12 mg Lauric Acid/1.2 ml tricaprylin).[215] Thirteen mice were alive after 12 months, and 8 mice were alive after 18 months. One pulmonary neoplasm and 1 "leukemia–lymphoma" were found after 23 months. Another group of 16 Swiss-Webster mice received 2 injections of 5.0 mg weekly for a total of 25 injections (total dose, 125 mg Lauric Acid/2.5 ml tricaprylin). After 12 months, 8 mice were alive, and after 18 months, 5 were alive. One subcutaneous sarcoma and 1 pulmonary neoplasm were found after 18 months. Two "leukemia–lymphomas" were found after the fourth and fifth months.

Palmitic Acid was administered to 16 Swiss-Webster mice at a dose of 1.0 mg 3 times per week for a total of 10 injections (total dose, 10 mg Palmitic Acid/1 ml tricaprylin).[215] Eight mice were alive after 12 months, and 6 were alive after 18 months. One subcutaneous sarcoma was found after 19 months, 2 pulmonary neoplasms were found after 19 and 22 months, and 1 breast carcinoma was found after 22 months. Another group of 16 Swiss-Webster mice received two injections of 5.0 mg weekly for a total of 25 injections (total dose, 125 mg Palmitic Acid/2.5 ml tricaprylin). Eight mice were alive after 12 months, and 5 were alive after 18 months. A subcutaneous sarcoma was found after 8 months, 2 breast carcinomas were found after 18 months, and 1 "leukemia–lymphoma" was found after 12 months.

Stearic Acid was administered to groups of 16 Swiss-Webster mice at doses of 0.05 mg and 0.5 mg weekly for a total of 26 injections.[215] After 18 months, 10 mice were alive in the group given the lower dose, and 6 mice were alive in the group given the higher dose. A third group of 15 Swiss-Webster mice was given injections of 1.0 mg Stearic Acid 3 times per week for a total of 10 injections. Eight mice were alive after 12 months, and 1 was alive after 18 months. A fourth group of 10 BALB/c mice was given injections of 1.0 mg

Stearic Acid twice weekly for a total of 82 injections. Seven mice were alive after 18 months. No neoplasms were found in these four groups.

Neoplasms were found in three other groups of BALB/c mice administered Stearic Acid.[215] The first group of 15 mice was injected with 0.05 mg Stearic Acid twice weekly for a total of 104 injections. Thirteen mice were alive after 18 months, and 1 pulmonary neoplasm was found after 19 months. The second group of 10 mice received injections of 0.05 mg Stearic Acid twice weekly for a total of 114 injections. Four mice were alive after 18 months. Four subcutaneous sarcomas (1 after 6 months, 2 after 10 months, and 1 after 12 months), 1 pulmonary neoplasm (after 19 months), and 1 "leukemia–lymphoma" (after 19 months) were found. The 10 mice in the third group received 0.5 mg Stearic Acid per injection twice weekly for a total of 114 injections. Nine mice were alive after 18 months. After 21 months, 1 pulmonary neoplasm and 1 adrenal carcinoma were found.

In a study modeled after the Swern et al.[215] study, Van Duuren et al.[221] found Stearic Acid to be noncarcinogenic, confirming the previous study's conclusion (see Table 14 for details of study). Investigators in both studies indicated that a compound's carcinogenic activity was assessed by its ability to induce sarcomas at the injection site.

Statistical techniques were used to determine possible associations between dietary fatty acids in triglycerides and the incidence of spontaneous mammary tumors in C3H mice.[222] Eleven natural fats and oils and their mixtures were used to obtain 20 substances with varying concentrations of different fatty acids that were fed to mice. The saturated fatty acids, Lauric, Myristic, and Palmitic Acids, had little effect on tumor incidence or the time needed for a tumor to appear. The concentration of Stearic Acid was calculated to be inversely related to tumor incidence and directly related to the time for tumor appearance. Oleic Acid produced no significant effect on tumor incidence.

The effects of free fatty acids fed as dietary supplement to mice of the T.M. strain were studied.[216] Refined corn oil (free fatty acid content, approximately 1.5%, removed during refining process) fed to the mice at a rate of 150–200 mg/mouse/day contained 1.5% free fatty acids, Oleic and linoleic Acids. Feeding of the refined corn oil plus free fatty acid diet resulted in a high incidence of lung (48.5%), stomach (27.4% forestomach papillomas, 12.5% pyloric tumors), and brain nerve cell (11%) tumors and a low incidence of mammary carcinomas, myomas, and lymphosarcomas. Feeding of the refined corn oil diet resulted in a high incidence of lung and brain nerve cell tumors, lymphosarcomas, and a lower incidence of gastric tumors. One heart tumor was found in each treated group ($n = 329$ in refined corn oil plus free fatty acids group, $n = 375$ in refined corn oil group). Controls fed the standard diet ($n = 623$) had a total tumor incidence of less than 20%; tumors were mainly located in the lung.

A later study was done to determine the types of gastrointestinal tumors induced in the T.M. strain mice fed a standard diet supplemented with refined corn oil, crude corn oil (contains 1.5% free fatty acids), or refined corn oil plus the fatty acids, Oleic Acid and linoleic acid, at concentrations up to 1.5%.[217] These corn oil supplements were given to the mice in daily amounts of 200

mg/mouse. Controls were fed the standard diet. Mice were killed when they began to lose weight rapidly. The average age of the control mice was 645 days, and that of the treated mice was 454–540 days. In the group fed the refined corn oil plus fatty acid diet, 138 gastric tumors were found in 328 treated mice. In the refined corn oil diet group, 9 gastric tumors were found in 209 treated mice. The crude corn oil diet group had 63 gastric tumors in 196 treated mice. Three gastric tumors were observed in the 195 control mice. No intestinal polyps or adenocarcinomas were observed in control or treated mice. The types of induced gastric tumors included papillomas and squamous cell carcinomas.

The carcinogenic activity of a feed supplement of Oleic Acid in corn oil was studied using C57BL/1 black strain mice that were "generally resistant to tumor formation."[218] Control animals from a different supplier were fed chow alone, and the 55 treated mice were fed a diet consisting of 10 g of a mixture of 1.5 g Oleic Acid/100 g corn oil dispersed in 100 g of laboratory chow to which water was added. Throughout the study, randomly selected mice were killed and examined after 6, 12, 18, 21, and 24 months. Colon adenocarcinomas, which metastasized to the lung and muscle, were found in 8% (3/36) of the treated mice. Lipid profiles of the livers and pituitary glands of the mice were obtained. Results for the 2 groups of mice were compared and discussed.

Tumor-Promoting and Cocarcinogenic Activity

In 1932, Twort and Bottomley reported that the induction of nonmalignant skin tumors by chrysene was increased in mice when Oleic Acid was used as the solvent compared to liquid paraffin or benzene. In a later study comparing the induction of skin tumors in mice by carcinogenic hydrocarbons dissolved in various solvents, chrysene induced more tumors when dissolved in Oleic Acid than in chloroform, but benzo(a)pyrene and fractions of synthetic tar induced fewer tumors when dissolved in Oleic Acid.[223] Also, in that study, induction of benign tumors, but not malignant tumors, increased when 1,2,5,6-dibenzanthracene was dissolved in Oleic Acid, compared to liquid paraffin. Use of chloroform as the solvent increased the incidence of malignant tumors.

Shubik[224] tested Oleic Acid as a tumor promoter for 9,10-dimethyl-1,2-benzanthracene-initiated mouse skin. Oleic Acid was administered twice weekly for 20 weeks but did not promote tumors. Gwynn and Salaman[225] also reported negative results for the promotion of 9,10-dimethyl-1,2-benzanthracene-initiated mouse skin tumors when Oleic Acid was administered twice weekly for 12 weeks or weekly for 15 weeks. Holsti[226] demonstrated that more frequent administration of Oleic Acid could promote 9,10-dimethyl-1,2-benzanthracene-initiated skin papillomas in mice; 2 of 40 mice developed papillomas when undiluted Oleic Acid was administered twice weekly, but 27 of 44 mice developed such tumors when Oleic Acid was administered daily for 6 days a week. Oleic Acid or Lauric Acid, but neither Palmitic Acid nor Stearic Acid, dissolved in chloroform also stimulated the

formation of skin papillomas. No malignant tumors were seen in any of the mice treated with any of the fatty acids.

Van Duuren and Goldschmidt[227] tested Oleic Acid and Stearic Acid as cocarcinogens in groups of 50 mice each. Benzo(a)pyrene, administered in acetone, induced 26 papillomas in 16 mice and squamous cell carcinomas in 12 mice. Mice that received the benzo(a)pyrene and 25 mg of Oleic Acid in acetone 3 times a week for 440 days developed no skin tumors, benign or malignant. Benzo(a)pyrene and 4 mg of Stearic Acid, administered 3 times a week for 440 days, resulted in 38 papillomas in 25 mice, but only 7 mice had squamous cell carcinomas, fewer than the controls. The results were considered inconclusive for Stearic Acid but supportive of the possibility that Oleic Acid is not a cocarcinogen.

Hogan and Shamsuddin[228] studied the tumor-promoting properties of *cis*- and *trans*-Oleic Acid on the induction of intestinal cancer by azoxymethane. *cis*-Oleic Acid had no promoting effect; *trans*-Oleic Acid (elaidic acid) had a small promoting effect. Both *cis*- and *trans*-Oleic Acids increased the incidence of nephroblastomas and squamous ear duct tumors from 3/30 to 6/30 rats. No tumors were seen in rats fed a diet containing 25% *cis*-Oleic Acid without azoxymethane for 20 weeks.

Promotion of mammary gland carcinomas has been observed in mice and rats fed diets containing unsaturated fats, particularly polyunsaturated fats.[229]

Several fats, oils, and fatty acids, including Lauric and Oleic Acids, produced acanthosis in guinea pig skin.[230] The acanthosis gradually receded with continued topical application. Oleic Acid has been found to enhance proliferation of both normal and cancer cells in vitro.[231–233] Myristic, Palmitic, and Stearic Acids had an inhibitory effect on normal smooth muscle cell proliferation; ability to inhibit proliferation was observed to increase with increasing chain length.[234] Traul et al.[235] reported that Oleic Acid and Lauric Acid can enhance the transforming ability of 3-methylcholanthrene in Rauscher murine leukemia virus-infected rat embryo cells.

Numerous mechanisms for the role of fatty acids in tumorigenesis have been studied and reviewed. Hypotheses include indirect effects on gene expression, the endocrine system, and the immune system and direct effects on tumor cells, such as alterations in cellular metabolism, membrane fatty acid composition, and intercellular cooperation.[236,237]

Antitumorigenicity

The antitumor activity of Oleic, Lauric, Myristic, Palmitic, and Stearic Acids was studied in vivo using Ehrlich ascites and solid carcinomas implanted into Swiss albino mice of strain ddY.[238] Suspensions of the fatty acids in Tween 80 and distilled water were administered 24 h after tumor implantation and were continued daily for 5 consecutive days. Commercial fatty acid preparations used in the study were not purified, and no analysis of components was performed. Treated mice were killed 30 days after implantation and examined for tumors. Doses of 8 mg/mouse/day of Lauric and Myristic Acids were effective inhibitors against Ehrlich ascites tumor, more than doubling the survival time of treated versus control mice. Similar doses of Palmitic, Stearic,

and Oleic Acids were relatively ineffective against Erhlich ascites tumor. The mode of administration for these fatty acids was not stated.

Several modes of administration were tested using a 1:1 mixture of Oleic and linoleic Acids in the same dosage regimen.[238] Linoleic acid alone was an effective ascites tumor inhibitor. Intraperitoneal administration of the mixture was the most effective against the ascites tumor, and subcutaneous administration inhibited as much as 60% of the weight gain of the solid tumor.

Oleic Acid, at a concentration of 10 μM, inhibited the growth of rat neuroblastoma cells (cell line B104) in serum-free supplemented media.[239] At least a 50% decrease in cell number relative to controls was observed.

The antitumor activity of palmitoleic (*cis*-9-hexadecanoic) acid was compared to that of Oleic Acid using Erhlich ascites tumors in female ICR strain mice.[240] The fatty acids were dissolved in a 0.15 M sodium chloride (NaCl) solution containing 0.2% Tween 80 and, 24 h after tumor inoculation, were injected intraperitoneally once daily for 10 consecutive days. The experiment was terminated on day 60 after tumor inoculation. Control mice received the same volume of the NaCl plus Tween 80 solution. Significant inhibition of tumor growth was observed in Oleic Acid-treated mice at doses ranging from 37.5 to 300 mg/kg/day when compared to control mice. Palmitoleic Acid was more effective than Oleic Acid, inducing complete regression of the tumor in 5 of 10 treated mice at a dose of 75 mg/kg/day.

A diet supplement of Oleic Acid, at a daily dose of 1 mg per rat, failed to protect Sprague-Dawley rats from colon carcinoma caused by 1,2-dimethyl hydrazine (DMH).[241] All rats (22 rats per group) were killed 22 weeks after the first subcutaneous DMH injection and were examined for colon tumors. Control rats fed chow alone and injected with 15 mg/kg DMH weekly for 16 weeks developed 77 colon tumors, whereas those fed chow plus Oleic Acid before and during the DMH injections developed 90 colon tumors.

TERATOGENICITY

Food and fragrance safety evaluation reports on Oleic and Stearic Acids contained no data on their teratogenicity.[44,45,69] Reviews of the scientific literature from 1920 to 1973 were used for the final food safety assessments.[46,47]

Although placental transfer of fatty acids has been documented in several species and fetal lipid metabolism has been studied,[87,242] no studies on the teratogenicity of fatty acids were found.

CLINICAL ASSESSMENT OF SAFETY

A health hazard evaluation report was prepared by the National Institute for Occupational Safety and Health (NIOSH) after environmental and medical observations and examinations of 7 employees exposed to Lauric Acid.[243] Investigators found no significant decreases in pulmonary function, but interviews with workers indicated that Lauric Acid exposure caused local

irritation of moist body surfaces (eye, nose, throat, sweaty skin). Severe irritation was reported by 1 worker after exposure of moist occluded skin areas to Lauric Acid. The suggested reason for the observed irritation was the acidity of Lauric Acid.

Skin Irritation Studies

In a single insult occlusive patch test (SIOPT), commercial grade Oleic Acid produced no irritation in 18 and minimal erythema in 2 of the 20 panelists. The primary irritation index (PII) was 0.05 and Oleic Acid was considered "practically nonirritating"[244] (Table 20).

A 30% preparation of Oleic Acid in water produced barely perceptible erythema in 2, mild erythema in 1, and moderate erythema in 1 of 21 panelists in an SIOPT. There were no signs of irritation in 17 panelists. The PII was 0.19 and Oleic Acid was considered "practically nonirritating."[245]

In a soap chamber test,[251] 0.2 ml of a 50% solution of Oleic Acid in mineral oil was applied to the ventral skin of the forearm of 16 human subjects once daily for 5 days using the Duhring chamber, an aluminum cup with a 12 mm diameter, fitted with nonocclusive tape. The first exposure was usually 24 h long. Successive exposures to the same sites were for 6 h. The erythema score was 0.22 on a scale of 0 to 5. Oleic Acid was considered "non-irritating under conditions of this test."[246]

Several bar soap formulations with concentrations of Oleic Acid ranging from 2.53 to 92.7% were tested for skin irritation using 16 human subjects. A 0.2 ml volume of 8% aqueous preparations was applied to the ventral skin of the forearm under occlusive patches once daily for 5 days using the Frosch and Kligman soap chamber test.[251] The formulations were considered "slightly" to "moderately irritating." The erythema scores ranged from 1.41 to 3.21 on a scale of 0 to 5 and were not directly related to Oleic Acid concentrations in the formulations.[247–249,271]

In a cumulative irritation study, approximately 9.3 ml of each of 2 mascara formulations, a black cream and a brown cream, containing 6% Oleic Acid were applied to the backs of 14 female and 1 male panelist using closed patches.[250] The panelists removed the patches after 23 h and bathed. Reactions were scored 24 h after sample application. The samples were reapplied daily to the same test sites for 21 consecutive days or until irritation scores of 3, corresponding to erythema and papules, were observed.[252] Up to 7 panelists had minimum scores of 1 or slight erythema by the 5th application, and 3 to 4 panelists had maximal scores of 3 and 4 for erythema, papules, or edema by the 14th application. The total irritation scores for the formulations, a summation of the scores over the number of applications and panelists, were 212 and 204 compared with a maximal score of 945. Mean scores were 14.1 and 13.6 compared with a maximal score of 63. The positive control, an aerosol deodorant concentrate, had a total score of 828 and mean score of 55.2. The negative control, a clear liquid baby oil formulation, had a total score of 18 and a mean score of 1.2. The formulations were considered "slightly irritating."

A red paste cosmetic product formulation containing 5% Oleic Acid was tested for cumulative irritation on the skin of 10 human subjects.[255] Each of

TABLE 20. Clinical Skin Irritation Studies

Fatty acid tested	*Concentration*	*No. of subjects*	*Methods*	*Results*	*Reference*
Oleic Acid	As commercially supplied	20	SIOPT[a]	PII[b] 0.05. "Practically non-irritating"	244
	30%	21	SIOPT	PII 0.19. "Practically non-irritating"	245
	0.2 ml of 50% in mineral oil	16	Soap chamber test,[c] 5 daily occlusive patches	Erythema score 0.22. "Non-irritating"	246
	8% (92.7%)[c] in bar soap formulation	16	See preceding entry	Erythema score 2.13. "Moderately irritating"	247
	8% (2.53–41%) in 13 bar soap formulations	16	See preceding entry	Erythema scores ranged from 1.41 to 3.21 (slight to intense erythema). Scores not correlated with Oleic Acid concentration	248, 249
	6% in 2 mascara formulations	15	21-day cumulative irritation test[d]	CIS[e] 204 and 212 (max. 945). Mean irritation score 14 (max. 63). "Irritating"	250
	5% in product formulation	10	See preceding entry	CIS 95 (max. 630). "Probably mild..."	255
	2% in 3 mascara formulations	13	See preceding entry	One faint erythemal reaction to 4th patch of 1 formulation	256
Palmitic Acid	2.2% in shave cream formulation	101	Single patches, open and occlusive	No irritation	257
	2.2% in shave cream formulation	60	4-week controlled use[f]	"Non-irritating"	258
Myristic Acid	As commercially supplied	20	SIOPT	PII 0.2. "Practically non-irritating"	259
	50% in mineral oil	16	Soap chamber test[c]	Erythema score 0.48. "Non-irritating"	260
	8% (10–91%) in 3 bar soap formulations	16	Soap chamber test[c]	Erythema scores ranged from 1.41 to 1.95 (slight to moderate erythema)	261–263
	5% in cleanser lotion formulation	12	21-day cumulative irritation[d]	CIS 609 (max. 756). "Highly irritating"	264

TABLE 20. (Continued)

Fatty acid tested	*Concentration*	*No. of subjects*	*Methods*	*Results*	*Reference*
Stearic Acid	40% in mineral oil	21	SIOPT	No irritation	265
	13% in face cream formulation	101	Single patches, open and occlusive	Mild erythema to occlusive patch in 4 subjects. "Non-irritating"	266
	13% in face cream formulation	105	4-week controlled use[f]	"Non-irritating"	267
	8% in shave cream formulation	100	Single 48-h occlusive patch and 2–4 week daily home use	No reactions to patch. Complaints of minor pruritus from 2 subjects during home use unsubstantiated	268
	2.8% in liquid eyeliner formulation	13	21-day cumulative irritation[d]	CIS 216 (max. 675). "Moderately irritating"	269
	2.6% in 2 moisturizer formulations	12	See preceding entry	CIS 28 and 56. "Basically non-irritating"	270

[a]SIOPT, single insult occlusive patch test.

[b]PII, primary irritation index; maximum possible value 8.00.

[c]In Soap Chamber Test[251] volume of 0.2 ml usually applied; 8% aqueous preparations of bar soap formulations were tested and noted in Concentration column. Erythema scores reported—scale from 0–5.

[d]Ref. 252. Daily 23-h patches to same site. Some studies modified by Ref. 253.

[e]CIS, cumulative irritation scores; maximum possible score noted in parenthesis following CIS.

[f]Ref. 254.

the 21 consecutive closed-patch applications remained in contact with the skin for 23 h. Scoring for irritation and reapplication to the same test site was done 24 h after the preceding application.[252,253] The total irritation score for all subjects for all 21 applications of the formulation was 95 of a maximal possible score of 630. The total scores for the negative and positive controls were 7 and 554, respectively. The formulation was considered "probably mild in normal use."

Three mascara formulations containing 2% Oleic Acid were tested for cumulative irritation on the skin of 13 human subjects.[256] The closed patches were applied for 21 days, but no applications were made on weekends.[253] One of the 13 subjects had a single equivocal erythema reaction (scored ±) after the fourth application of one of the formulations. No other reactions were observed.

Shave cream formulations containing 2.2% Palmitic Acid were considered "non-irritating" to the skin of 101 panelists treated with closed and open patch applications[257] and to facial skin of 60 panelists in a 4-week controlled-use study.[254,258] Although the former skin irritation study was part of a prophetic patch test[272] in which patches usually remain in place for 24 h, no specific procedure was outlined.

In an SIOPT, commercial grade Myristic Acid produced no irritation in 17, mild erythema in 2, and moderate erythema in 1 of 20 panelists. The primary irritation index was 0.2, and Myristic Acid was considered "practically non-irritating."[259]

In a soap chamber test,[251] 0.2 ml of a 50% solution of Myristic Acid in mineral oil was applied to the ventral skin of the forearm of 16 human subjects once daily for 5 days.[260] The erythema score was 0.48 on a scale of 0 to 5. Myristic Acid was considered "non-irritating under conditions of this test."

Several bar soap formulations with concentrations of Myristic Acid of 10,[261] 22.1,[263] and 91%[262] were tested for skin irritation using 16 human subjects. A 0.2 ml volume of an 8% aqueous preparation was applied to the ventral skin of the forearm under occlusive patches once daily for 5 days using the Frosch-Kligman soap chamber test.[251] The formulations were considered "slightly"[261] to "moderately irritating,"[262] and erythema scores were 1.41, 1.73, and 1.95 on a scale of 0 to 5 for the formulations containing 10, 22.1, and 91% Myristic Acid, respectively.

A white cleanser lotion formulation containing 5% Myristic Acid was tested for cumulative irritation on the skin of 12 human subjects using a 21-day consecutive closed-patch test.[252,253] The total irritation score for all subjects for all 21 applications of the formulation was 609 of a maximal possible score of 756. The formulation was considered "highly irritating."[264]

In an SIOPT, 40% Stearic Acid in mineral oil produced no irritation in 21 panelists.[265]

A face cream formulation containing 13% Stearic Acid was considered "non-irritating" to the skin of 101 panelists treated with single 24-h closed and open patch applications. Four of the 101 panelists had mild erythemal reactions to the closed patch application; no other reactions were observed.[266]

A face cream formulation containing 13% Stearic Acid was tested for irritation of the facial skin of 105 panelists in a 4-week controlled-use study.[254] Under these conditions, the formulation was considered "non-irritating."[267]

As part of a Modified Schwartz/Peck prophetic patch study,[272] a shave foam formulation containing 8% Stearic Acid was tested for irritation of the dorsal skin of 100 male subjects.[268] The formulation was applied to subjects' backs for 48 h, then washed from the area. Subjects then used the formulation to shave at least once daily for 2–4 weeks. No irritation was observed after the 48-h occlusive patch, and the complaints of minor pruritus by 2 subjects during the home-use part of the study were not recorded because no clinical signs of erythema or other evidence of itching were noted.

A gray liquid eyeliner formulation containing 2.8% Stearic Acid was tested for cumulative irritation on the skin of 13 human subjects using a 21-day consecutive closed-patch test.[252,253] The total irritation score for all subjects for all 21 applications of the formulation was 216 of a maximal possible score of 675. The formulation was considered "moderately irritating."[269]

Two moisturizer product formulations containing 2.6% Stearic Acid were tested for cumulative irritation on the skin of 12 human subjects.[270] Occlusive patches were applied for 24 h to the skin of the scapular or interscapular area daily for 21 days. Scoring on a scale of 0 to 4 for erythema and edema was done after each patch was removed and before the next application. Markers of results after treatment with 0.5% and 2% sodium lauryl sulfate were used for comparison with sample treatment. Total irritation scores for the formulations from all 12 subjects for all 21 applications were 28 and 56, lower than the score of 67 obtained after treatment with 0.5% sodium lauryl sulfate. The 2% sodium lauryl sulfate score was 298. Both formulations were considered "basically non-irritating."

Skin Sensitization Studies

The maximization test[182] was used to test a black cream mascara formulation containing 6% Oleic Acid for contact sensitization (Table 21).[273] Induction sites on the volar aspect of the 14 subjects' forearms were pretreated with single 24-h occlusive patches of 5% aqueous sodium lauryl sulfate (SLS). Five alternate-day 48-h occlusive induction patches were followed by a 10–14-day nontreatment period. After pretreatment of new sites with single 30-min occlusive patches of 2% aqueous SLS, single 48-h occlusive challenge patches were applied. Results for the sites treated with the formulation were similar to those for control sites treated with petrolatum alone and petrolatum plus SLS, respectively. There was "no significant irritation or evidence of contact sensitization."

In a repeated insult patch test (RIPT), 200 human volunteers were tested for contact sensitization of a purple wax cosmetic formulation containing 5.0% Oleic Acid.[274] Nine 24-h closed induction patches containing 0.3 ml of the formulation were applied to sites on the volar forearm on Mondays, Wednesdays, and Fridays of 3 consecutive weeks during the induction phase of the study. Signs of irritation were scored 48 or 72 h after the application. After a 10–14 day nontreatment period, a single 48-h challenge patch was

made to a separate site, and the site was scored 48-h and 72-h to 96-h after application. Of the 200 subjects, 153 completed the study. Slight irritation was observed in 1 to 3 subjects during the induction phase, and 1 subject reacted slightly to the challenge patch after 48 h. "No contact sensitization" was produced by the formulation under the conditions of this study.

A mascara formulation containing 3.0% Oleic Acid was tested for irritation and sensitization using an RIPT and 222 human subjects, 200 of whom completed the study.[275] Ten occlusive induction patches were applied for 24 h to sites on the upper back on Mondays, Wednesdays, and Fridays. Sites were scored before application of the next induction patch. After a 2-week nontreatment period, 2 48-h challenge patches were applied 1 week apart. Challenge sites were scored after patch removal. Mild erythemal reactions to single induction patches were observed and considered toxicologically insignificant due to their transient nature. Three subjects reacted with mild erythema to the 2nd challenge patch after 48 h. Two different subjects with mild erythemal reactions 72 h after the 2nd challenge patch was applied were challenged again. One of the 2 had a mild reaction to this 3rd challenge patch. The formulation was considered "not irritating or allergenic."

A mascara formulation containing 2.0% Oleic Acid was tested for irritation and sensitization using an RIPT and 222 human subjects, 205 of whom completed the study.[276] The 10 semiocclusive induction patches, applied for 24 h, and the 2-week nontreatment phases were followed by 2 48-h challenge patches applied to a new site, 1 week apart. No irritation or sensitization was observed.

In a modified Draize RIPT[10] with 14 human subjects, there was "no evidence of allergic contact sensitization" produced by a mascara formulation containing 2.0% Oleic Acid.[277] The formulation had been applied to the skin of the upper arms or backs (unspecified) of subjects during the 9 occlusive patch induction phase (3 times weekly for 3 weeks) and after a 2-week nontreatment period during the single patch challenge phase. Induction and challenge patches remained in contact with the skin for 48 h or 72 h. One equivocal reaction to the challenge was observed. There was "no evidence of allergic contact sensitization."

In a modified Shelanski RIPT of a 1% aqueous dilution of a liquid soap formulation containing 1.95% Lauric Acid on intact and abraded skin of the backs of 52 human subjects, no primary or cumulative skin irritation and no sensitization were observed.[278] Approximately 0.2 ml of the preparation was applied to occlusive induction and challenge patches. A total of 12 24-h induction patches were were administered for 3 weeks, 4 times per week from Monday through Thursday. Sites were scored before application of the next patch. No patches were applied from Friday to Sunday of each week. A total of 4 24-h challenge patches were applied to a new site on the 4th week, after a 72-h nontreatment period, from Monday through Thursday. Of the 52 subjects who began the study, 46 subjects were present for the completion of the study.

In a prophetic patch test,[272] a shave cream formulation containing 2.2% Palmitic Acid was tested for irritation and sensitization of the skin of 101 human subjects.[257] Two 24-h closed and open patches are usually applied to

TABLE 21. Clinical Skin Sensitization Studies (Product Formulation Data Only)

Fatty acid tested	*Concentration*	*No. of subjects*	*Methods*	*Results*	*Reference*
Oleic Acid	6% in mascara formulation	23	Maximization	Similar results for treated and control sites. "No significant irritation or evidence of contact sensitization"	273
	5% in product formulation	153	RIPT[a]	Faint reactions to induction in 1–3 subjects. Slight reaction to challenge in 1 subject	274
	3% in mascara formulation	200	RIPT	Isolated irritation reactions. Mild reactions to 2nd challenge patch	275
	2% in mascara formulation	205	RIPT	No irritation or sensitization	276
	2% in mascara formulation	14	RIPT	Equivocal reaction to challenge in 1 subject	277
Lauric Acid	1% (1.95%)[b] in liquid soap formulation	46–48	RIPT, I/A[c]	No irritation or sensitization	278
Palmitic Acid	2.2% in shave cream formulation	101	Prophetic Patch, O/C[d]	Erythema to closed challenge patch in 3 subjects. No other reactions	257
	2.2% in shave cream formulation	52	RIPT, O/C	No irritation or sensitization	257
Stearic Acid	13% in face cream formulation	101	Prophetic Patch, O/C	Mild reactions to closed induction and challenge patch(es) in few subjects	266
	13% in face cream formulation	52	RIPT, O/C	Mild reactions to closed induction patches in few subjects. No reactions to challenge	266
	10% in product formulation	116	RIPT	Mild to moderate erythema to 2 induction patches in 1 subject. No reactions to challenge	279
	10% in mascara formulation	206	RIPT	Reactions to induction and 48–72 h after challenge. Cumulative irritation in 3 subjects	280
	8% in shave foam formulation	101	Prophetic Patch and In-Use Testing	Several reactions 48 h after induction and challenge, fewer 72 h later. No reactions during In-Use phase	22
	8% in shave foam formulation	100	See preceding entry	No reactions to induction or challenge. Complaints of minor pruritis from 2 subjects during In-Use phase	268

7.7% in mascara formulation	101	RIPT	1 subject had reaction to 8th induction patch. No reactions to challenge	281
5% in mascara formulation	205	RIPT, semiocclusive patches	No irritation or sensitization	282
4% in product formulation	48	RIPT	No irritation or sensitization	283
2.8% in hand lotion formulation	51	RIPT	Transient slight induction reactions in 2 subjects. No reactions to challenge at original or untreated site	284
2.8% in 2 skin lotion formulations	57	RIPT, 48-h patches	Reactions to induction in 1–5 subjects. Slight reactions 72 h after challenge	285
2.66% in eyeliner formulation	200	RIPT	Definite erythema to isolated induction patches in few subjects. No reactions to challenge	286
2.6% in moisturizer formulation	204	RIPT	Mild to intense reactions to induction and challenge. "Mild irritant under occlusion patch"	287
2.6% in moisturizer formulation	203	RIPT	Isolated, mild erythema to induction. Few intense reactions to challenge but none to repatching	288
2.6% in sun lotion formulations	208	RIPT, semiocclusive patches	No irritation or sensitization	289
2.6% in sun lotion formulations	208	RIPT, semiocclusive patches	Few subjects with isolated reactions to induction and challenge	290
2.6% in sun block formulations	208	RIPT, semiocclusive patches	Few subjects with isolated reactions to induction. No reactions to challenge	291
1.0% in hand lotion formulation	76	RIPT	Minimal to definite erythema in few subjects to induction and challenge at same site. No reactions to challenge at untreated site	292
1.0% in hand lotion formulation	76	RIPT	Minimal to moderate irritation to induction in few subjects. No reactions to challenge	292
1.0% in suntan lotion formulation	184	RIPT	No reactions to induction or challenge	293
1% (23%)[b] in bar soap formulation	25	Maximization	No contact sensitization	294
0.5% (25%) in product formulation	99	RIPT	Equivocal induction reaction in 1 subject	295

[a]RIPT, repeat insult patch test.
[b]0.5 or 1.0% aqueous dilutions of formulation containing percentage of fatty acid (percentage in parentheses).
[c]I/A, patches applied at intact and abraded sites.
[d]O/C, 2 series of patches, open and closed, applied at separate sites.

the skin 10–14 days apart in the standard Schwartz-Peck procedure. There were 3 reactions of mild to intense erythema to the closed challenge patch and the formulation was considered "nonirritating and nonsensitizing."

A modified Shelanski RIPT[296] in 52 human subjects involved 10 alternate-day 24-h induction patches, a 2- to 3-week nontreatment phase and a single 48-h challenge patch.[257] Closed and open patches with the same shave cream formulation containing 2.2% Palmitic Acid were applied. No irritation or sensitization was observed.

A face cream formulation containing 13% Stearic Acid was tested for photosensitization using a prophetic patch test[272] in 101 subjects and a modified RIPT in 52 subjects.[266] There were mild reactions in a few subjects to closed induction and challenge patches. The formulation was considered "nonirritating and nonsensitizing."

Approximately 0.1 ml of a cosmetic product formulation containing 10% Stearic Acid was tested for irritation and sensitization of sites on the upper back of 116 human subjects with an RIPT involving 9 alternate-day 24-h occlusive induction patches, a 3-week nontreatment period, and a single 24-h challenge patch at a new site.[279] Moderate erythema was observed in 1 subject after the 5th and 6th induction patches and the 7th induction patch at an adjacent site; the remaining 2 induction patches were eliminated. There were no other reactions to induction and no reactions to challenge.

In a modified Draize-Shelanski RIPT,[168,296] approximately 0.1 g of a mascara formulation containing 10% Stearic Acid produced mild to moderate irritation in a few subjects during induction.[280] Signs of erythema, edema, and induration or vesiculation were observed in 1 to 4 subjects 48 and 72 h after challenge application. The 206 subjects had received 10 alternate day 24-h occlusive induction patches and single 48-h occlusive challenge patches following a 2-week nontreatment period.

In a prophetic patch and in-use testing study, application of single 48-h occlusive induction patches was followed by a 4-week period of daily home use and single 48-h occlusive challenge patches of a shave foam formulation containing 8% Stearic Acid.[268] There were no reactions to induction or challenge patches, and 2 of the 100 subjects complained of minor pruritus during the in-use part of the study. However, there was no erythema or itching.

Several 1 + and a few 2 + reactions were observed 48 h after application of induction and challenge patches in another prophetic patch and in-use testing study.[22] Fewer reactions were noted after 72 h. No significant product-related reactions were reported during the in-use phase of the study.

In a modified Draize RIPT,[168] a mascara formulation containing 7.7% Stearic Acid was tested for irritation and sensitization in 101 human subjects.[281] Approximately 0.2 g was applied to upper arm sites with 24-h occlusive patches on Mondays, Wednesdays, and Fridays for 3 weeks during the induction phase and with single 48-h patches during the challenge phase, following a 2-week nontreatment period. One subject had minimal erythema after the 8th induction patch. There were no other reactions to induction and no reactions to challenge patches.

No irritation and no sensitization were noted in RIPTs of cosmetic product formulations containing 4%[283] and 5%[282] Stearic Acid. The 4% formulation

was tested using the 10 alternate-day 24-h occlusive induction patches followed by a single 24-h occlusive challenge patch to a separate site. The 5% formulation involved 10 alternate-day 24-h semiocclusive induction patches and 2 48-h semiocclusive challenge patches 1 week apart. Both studies had a 2-week nontreatment period between induction and challenge phases.

Although slight transient reactions were observed, a hand lotion formulation containing 2.8% Stearic Acid was considered nonirritating and nonsensitizing.[284] In an RIPT, 0.2 ml of the formulation was applied to the skin of 57 human subjects via 10 alternate-day 24-h occlusive induction patches and single 24-h challenge patches to the same site and to a new site following a 10–14-day nontreatment period.

In RIPTs of two skin lotion formulations containing 2.8% Stearic Acid, 9 consecutive 48-h induction patches, followed by a single 48-h challenge patch after a 13-day nontreatment period, were applied to the skin of 57 human subjects.[285] One to five reactions of barely perceptible to mild erythema were observed throughout the induction phase. Application of one lotion produced erythema and minimal edema to the induction patch and 1 reaction to the challenge patch 72 h after its application in 1 subject.

Several cosmetic product formulations containing 0.13% (0.5% aqueous dilution of formulation containing 25%[295]) to 2.66%[286] Stearic Acid were tested for irritation and sensitization in 76 to 208 human subjects. RIPTs involving 9 to 10 alternate-day 24-h occlusive (semiocclusive patches used in 1 study[289]) induction patches, a 13-day to 2-week nontreatment period, and single 48-h challenge patches[286,292,294,295] or 2 48-h challenge patches administered 1 week apart[287–291,293,296] resulted in isolated 1 + irritation reactions in few subjects during the induction phase. These occasional reactions were considered nonspecific; no cumulative irritation was produced. There were no or very few reactions to challenge patches, and the formulations were considered nonsensitizing.

No contact sensitization was produced in 25 human subjects tested with a 1% aqueous dilution of a bar soap formulation containing 23% Stearic Acid in a maximization study.[182] Five 48-h occlusive induction patches applied to volar forearm sites were followed by a single 48-h occlusive challenge patch. Sodium Lauryl Sulfate was used at concentrations of 2% for pretreatment of induction sites and 10% for the 1-h pretreatment of challenge sites.

Photosensitization Studies

Two makeup formulations containing 5.08%[298] and 1.5%[299] Oleic Acid were tested for photosensitization using the skin of the backs of 25 human subjects. A Xenon Arc Solar Simulator (150 W), which was filtered to produce a continuous emission spectrum in the ultraviolet region ranging from 290 to 400 nm (UVA and UVB), was used. Individual minimal erythemal dose (MED) values were determined.[300] Six alternate-day induction patches were applied, each left in place for 24 h, scored, irradiated with 3 MED using the full source spectrum, and scored again 48 h after the application. After a 10-day nontreatment period, single 24-h occlusive challenge patches were applied to new sites. Sites were scored, irradiated for 3 min, using a Schott WG345 filter over the light source, then scored again 15 min and 24, 48, and 72 h after

irradiation. There were no "reactions" to either formulation recorded. The liquid makeup formulation was considered nonphotosensitizing[299] and the blusher formulation nonphotoallergenic.[298] No data were presented to distinguish between "phototoxic reactions" and "photoallergic reactions."

The phototoxicity of a shave cream formulation containing 2.2% Palmitic Acid was tested in 101 human subjects using single 24-h closed and open patches.[257] Sites were UV-irradiated (wavelength and dosage unspecified) after patch removal. Irritation was observed at 1 site tested with a closed patch.

In a photosensitization study with 52 human subjects, sites under 4 induction patches and 1 challenge patch containing the shave cream formulation with 2.2% Palmitic Acid were UV-irradiated (wavelength and dosage unspecified) after patch removal.[257] Both closed and open patches were used. There were no reactions during induction or challenge phases, and the formulation was considered "non-photosensitizing."

No phototoxicity was observed in 101 human subjects exposed to UVA irradiation and single closed or open patches with a face cream formulation containing 13% Stearic Acid.[266]

Minimal to mild erythema was observed at a few sites after treatment with a lotion formulation containing 2.8% Stearic Acid or a 1% aqueous dilution of a bar soap formulation containing 23% Stearic Acid followed by UVA irradiation.[301,302] The lotion formulation was applied via 24-h occlusive patches to the forearm, and treatment sites were irradiated with UVA light for 15 min at a distance of approximately 10 cm, receiving a dose of 4400 $\mu W/cm^2$. The bar soap formulation was applied via 24-h occlusive patches to the infrascapular region of the back, and treatment sites were irradiated with UVA light from Xenon Arc Solar Simulator (150 W) with a Schott WG345 filter for 12 min. Similar results were observed at control sites that had received UVA irradiation alone.

A face cream formulation containing 13% Stearic Acid was tested for photosensitization using 52 human subjects and 4 induction patches and 1 challenge patch.[266] Closed and open 24-h patches were applied, and treated sites were irradiated with the full Xenon UV light spectrum at 3 times the individuals' predetermined MED after removal of each patch and 48 h later. After the 24-h challenge patch, treated sites were irradiated with UVA light (Xenon source plus Schott WG345 filter) for 3 min. There were no reactions observed at sites under closed or open patches at either induction or challenge sites.

No reactions were observed in 100 human subjects of a photosensitization study testing an eyeliner formulation containing 2.66% Stearic Acid.[286] In a 10 induction, 1 challenge occlusive patch RIPT, treated sites were irradiated with UV light from a Hanovia Tanette Mark 1 light source for 1 min at a distance of 1 foot after removal of the 1st, 4th, 7th, and 10th induction patches and after the challenge patch. Approximately 50% of the subjects were designated as "sensitive subjects" because of past experiences of rash or irritation from the use of facial products or because of reaction to a previous patch test with a facial product.

Most of the 30 human subjects tested with 2 lotion formulations had no photosensitization reactions.[303,304] Subjects had been treated with 10 24-h

occlusive induction patches, each patch followed by UVA irradiation of the site for 15 min at a distance of 10 cm from the source for a dosage of 4400 $\mu W/cm^2$. The single 24-h challenge patch was also UVA irradiated. Nonirradiated controls had isolated reactions of minimal erythema.

No reactions were observed in similar photosensitization studies testing suntan lotion,[305,308] moisturizing lotion,[306] and facial lotion[307] formulations containing 1% Stearic Acid in 20–27 human subjects. No other data were included in these studies.

Table 22 summarizes clinical photosensitization studies.

Ocular Irritation Studies

To evaluate ocular irritation produced by eye area cosmetics in contact lens and noncontact lens wearers, female volunteers participated in a 3-week exaggerated-use study. After a brief medical history with emphasis on ocular details (e.g., history of eye diseases, use of contact lenses and eye area cosmetics) and an eye examination, each subject was instructed to use assigned kits of test cosmetics twice daily (morning and early evening) for 3 weeks. The wearers of contact lenses were to handle, wear, and disinfect their contact lenses normally and to apply cosmetics after lens insertion into the eye. Examinations were performed on the 7th, 14th, and 21st days of the study. Eye area cosmetics in the test kits included mascaras containing 2–3% Oleic Acid and eye shadows.[309,310]

There were no product-related findings of irritation in any of the 23 subjects after daily use of a mascara formulation containing 2% Oleic Acid.[309] Investigators considered the "risk of any significant eye area irritation and/or ocular damage minimal, if existent at all."

Similar results were obtained in another 3-week exaggerated use study, with 35 female subjects testing mascara formulations containing 2% and 3% Oleic Acid in combination with eye shadow formulations.[310]

Other Studies

Graded intraduodenal administration of 5–40 ml of Oleic Acid in humans inhibited pentagastrin-stimulated gastric acid secretion.[311,312] Intracolonic infusion of Oleic Acid (117 cal., pH 7.4) into human subjects decreased pancreatic enzyme concentrations and bicarbonate ion output and inhibited biliary secretion.[313]

SUMMARY

Oleic, Lauric, Palmitic, Myristic, and Stearic Acids are fatty acids with hydrocarbon chains ranging in length from 12 to 18 carbons with a terminal carboxyl group. The saturated fatty acids, Lauric(12C), Palmitic(16C), Myristic(14C), and Stearic(18C) Acids, are solids and the *cis*-9,10 monounsaturated Oleic Acid(18C) is a liquid at standard temperature and pressure.

The fatty acids are obtained by the hydrolysis of animal fats and vegetable oils. Cosmetic grade fatty acids occur as mixtures of several fatty acids, the

TABLE 22. Clinical Photosensitization Studies

Fatty acid tested	*Concentration*	*No. of subjects*	*Study type*	*Results*	*Reference*
Oleic Acid	5.08% in blusher formulation	25	Photosensitization	No photoallergic reactions	298
	1.5% in liquid makeup formulation	25	Photosensitization	No indication of photosensitization	299
Palmitic Acid	2.2% in shave cream formulation	101	Phototoxicity	Phototoxic reaction to single closed patch in 1 subject	257
	2.2% in shave cream formulation	52	Photosensitization	No photosensitization reactions to closed or open patches	257
Stearic Acid	13% in face cream formulation	101	Phototoxicity	No phototoxic reactions to closed or open patches	266
	2.8% in lotion formulation	10	Phototoxicity	Minimal erythema after 48 h in 2 subjects similar to control group. No irritation after 1 week	301
	1.0% (23%)[a] in bar soap formulation	10	Phototoxicity	Mild erythema at all irradiated sites—both treated and control	302
	13% in face cream formulation	52	Photosensitization	No photosensitization reactions to closed or open patches	266
	2.66% in eyeliner formulation	200	Photosensitization	No reactions	286
	2.8% in lotion formulation	30	Photoallergy	No photoallergic reactions in most subjects. Non-irradiated control sites had isolated minimal erythema reactions	303
	2.8% in skin lotion formulation	30	Photoallergy	Minimal erythema at irradiated and nonirradiated control sites in 1–2 subjects	304
	1.0% in suntan lotion formulation	25	Photosensitization	No reactions. No other data included	305
	1.0% in moisturizing lotion formulation	27	Photosensitization	No reactions. No other data included	306
	1.0% in facial lotion formulation	27	Photosensitization	No reactions. No other data included	307
	1.0% in suntan lotion formulation	20	Photosensitization	No reactions. No other data included	308

[a] 1.0% aqueous dilution of bar soap formulation containing 23% Stearic Acid tested.

content varying with method of manufacture and source. Fatty acid preparations may include up to 1.5% unsaponifiable matter, glyceryl monoesters of fatty acids, and butylated hydroxytoluene. Gas chromatography is the predominant analytical method for fatty acid identification.

The fatty acids are primarily used as intermediates of fatty acid salts. These salts are used as emulsifiers, emollients, and lubricants in cosmetic creams, cakes, soaps, lotions, and pastes that are slightly alkaline, ranging in pH from 7.5 to 9.5. In product formulation data voluntarily filed in 1981 with FDA by the cosmetic industry, 424 products contained Oleic Acid, 22 contained Lauric Acid, 29 contained Palmitic Acid, 36 contained Myristic Acid, and 2465 contained Stearic Acid at concentrations ranging from 0.1 to 25%.

Fatty acids are absorbed, digested, and transported in animals and humans. Radioactivity from labeled fatty acids administered orally, intravenously, intraperitoneally, and intraduodenally has been found in various tissues and in blood and lymph. β-Oxidation of the fatty acids involves serial oxidation and reduction reactions yielding acetyl-CoA. Although placental transfer of fatty acids has been documented in several species and fetal lipid metabolism has been studied, no studies on the teratogenicity of Oleic, Lauric, Palmitic, Myristic, or Stearic Acids were found. High intake of dietary saturated fatty acids has been associated with the incidence of atherosclerosis and thrombosis.

Little acute toxicity was observed when Oleic, Lauric, Palmitic, Myristic, or Stearic Acid, or cosmetic formulations containing these fatty acids at concentrations of 2.2–13% were given to rats orally at doses of 15–19 g/kg body weight.

In subchronic oral toxicity studies, Oleic, Palmitic, and Stearic Acids were fed to rats in diets at doses ranging from 5 to 50%. Thrombosis, aortic atherosclerosis, anorexia, and mortality were observed. In a subchronic study, no signs of toxicity were observed in chicks fed 5% dietary Stearic and Oleic Acids. Feeding of 15% dietary Oleic Acid to rats in a chronic study resulted in normal growth and general health, but reproductive capacity of female rats was impaired.

Results from topical application of Oleic Acid (at concentrations from 50% Oleic Acid to commercial grade Oleic Acid) to the skin of mice, rabbits, and guinea pigs ranged from no toxicity to signs of erythema, hyperkeratosis, and hyperplasia. Intradermal administration to guinea pigs of 25% Oleic Acid to commercial grade Oleic Acid resulted in local inflammation and necrosis. A formulation containing 2.2% Palmitic Acid was considered nontoxic to rabbits. A topically applied dose of 5 g/kg commercial grade Stearic Acid was not toxic to rabbits. Intradermal administration of 10–100 m*M* Stearic Acid to guinea pigs and rabbits resulted in mild erythema and slight induration.

Eighteen mmol% concentrations of the fatty acids topically applied to the skin of the external ear canals of albino rabbits for 6 weeks produced a range of responses, varying from no irritation with Stearic Acid to slight irritation with Myristic and Palmitic Acids to defined erythema, desquamation, and persistent follicular keratosis with Oleic and Lauric Acids. Slight local edema and no deaths were observed among NZW rabbits after 4 weeks of topical administration of product formulations containing 2.0% Stearic Acid.

In 13-week dermal toxicity studies, 2 cosmetic product formulations containing, at most, 5% Stearic Acid produced moderate skin irritation in rats receiving 4.0 ml/kg and 227 mg/kg doses. All other physiological parameters were normal.

In single insult occlusive patch tests for primary irritation, commercial grades of all 5 fatty acids, at doses of 35–65% in vehicles (Stearic Acid only) and at 1–13% in cosmetic product formulations (other fatty acids), produced no to moderate erythema and slight, if any, edema in the skin of rabbits. Slight increases in irritation were observed in the short-term repeated patch tests (daily for 3–14 days) of Oleic and Myristic Acids.

In maximization studies with 2 cosmetic product formulations containing 5.08% Oleic Acid and 1.0% Stearic Acid, slight reactions were observed to challenge patches. These formulations were considered weak, grade I, sensitizers. In another maximization study, after intradermal induction and booster injections of a formulation containing 3.5% Stearic Acid, reactions to topical challenge applications of the formulation were few and minimal in intensity.

Skin lotion formulations containing 2.8% Stearic Acid were not photosensitizing to the skin of Hartley guinea pigs.

Oleic Acid and its UVA-induced peroxides were associated with increased comedo formation on the treated ears of two species of rabbits.

In ocular irritation studies, the fatty acids alone and at concentrations ranging from 1 to 19.4% in cosmetic product formulations produced no to minimal irritation after single and multiple (daily, 14-day) instillations into the eyes of albino rabbits. Irritation was primarily in the form of very slight conjunctival erythema. A single instillation of Lauric Acid also produced corneal opacity and iritis.

Although Oleic and Lauric Acids induced mitotic aneuploidy in in vitro mutagenicity tests, both have been indicated as inhibitors of mutagenicity produced by positive controls, such as N-nitrosopyrrolidine and sodium azide, in other tests. Stearic Acid was inactive in aneuploidy induction tests and in the Ames test, and it did not inhibit mutagenicity, as did Oleic and Lauric Acids. No increase of mitotic crossing-over events was induced by Oleic, Lauric, or Stearic Acids. Oleic Acid did not increase the number of sister chromatid exchanges over background.

In carcinogenicity studies, no malignant tumors were induced by repeated subcutaneous injections of 1–16.5 mg Oleic Acid in two species of mice. Intestinal and gastric tumors were found in mice receiving dietary Oleic Acid at daily concentrations up to 200 mg/mouse. Treatment of mice with repeated subcutaneous injections of 25 and 50 mg Lauric Acid was not carcinogenic. Low incidences of carcinomas, sarcomas, and lymphomas were observed in mice receiving single or repeated subcutaneous injections of 25 and 50 mg Palmitic and up to 82 mg Stearic Acid. Feeding of up to 50 g/kg/day dietary Stearic Acid to mice was not carcinogenic.

In clinical primary and cumulative irritation studies, Oleic, Myristic, and Stearic Acids at concentrations of 100% or 40–50% in mineral oil were nonirritating. Mild to intense erythema in single insult occlusive patch tests, soap chamber tests, and 21-day cumulative irritation studies were produced by

cosmetic product formulations containing 2–93% Oleic, Palmitic, Myristic, or Stearic Acid and were generally not related to the fatty acid concentrations in the formulations.

In clinical repeated insult patch tests (open, occlusive, and semiocclusive), maximization tests, and prophetic patch tests with cosmetic product formulations containing Oleic, Lauric, Palmitic, and Stearic Acids at concentrations ranging from <1 to 13%, no primary or cumulative irritation or sensitization was reported. A few subjects ($<5\%$ of the approximate 4000 subjects tested) reacted to a few, isolated induction patches. Slight, if any, reactions were observed after challenge patching at original or adjacent sites on the upper backs or forearms of some subjects ($\sim <2\%$). Intensity of observed reactions to the formulations was not directly related to the concentrations of the fatty acid ingredients.

Cosmetic product formulations containing 1–13% Oleic, Palmitic, or Stearic Acid produced no photosensitization in human subjects. There were slight reactions to a few induction patches.

There was no treatment-related ocular irritation in female subjects, some of whom were contact lens wearers, involved in two 3-week exaggerated-use studies of mascara formulations containing 2 and 3% Oleic Acid. These formulations were used in combination with other eye area cosmetics.

DISCUSSION

Although insufficient data were available for Myristic Acid, the Expert Panel included it in this safety assessment due to its structural similarity with the other fatty acids of this group.

Applications of Lauric and Oleic Acids to the skin of rabbits resulted in follicular keratosis and/or formation of comedones. These effects were considered by members of the Expert Panel in their safety assessment of the fatty acids reviewed in this report.

CONCLUSION

On the basis of available data from studies using animals and humans, the Expert Panel concludes that Oleic, Lauric, Palmitic, Myristic, and Stearic Acids are safe in present practices of use and concentration in cosmetics.

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8

Final Report on the Safety Assessment of Triethanolamine, Diethanolamine, and Monoethanolamine

Triethanolamine (TEA), Diethanolamine (DEA), and Monoethanolamine (MEA) are amino alcohols used in cosmetic formulations as emulsifiers, thickeners, wetting agents, detergents, and alkalizing agents. The nitrosation of the ethanolamines may result in the formation of N-nitrosodiethanolamine (NDELA) which is carcinogenic in laboratory animals.

In single-dose oral toxicity for rats, TEA was practically nontoxic to slightly toxic, and DEA and MEA were slightly toxic. Long-term oral ingestion of the ethanolamines by rats and guinea pigs produced lesions limited mainly to the liver and kidney. Long-term cutaneous applications to animals of the ethanolamines also produced evidence of hepatic and renal damage. TEA and DEA showed little potential for rabbit skin irritation in acute and subchronic skin irritation tests. MEA was corrosive to rabbit skin at a 30% concentration in a single semioccluded patch application and at a >10% concentration in 10 open applications over a period of 14 days.

The ethanolamines were nonmutagenic in the Ames test and TEA is also nonmutagenic to *Bacillus subtilis*. TEA did not cause DNA-damage inducible repair in an unscheduled DNA synthesis test. TEA had no carcinogenic or cocarcinogenic activity when dermally applied to mice for 18 months.

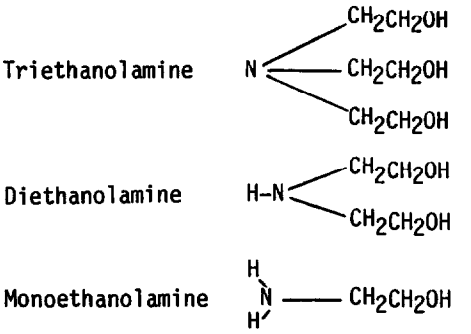
Clinical skin testing of TEA and cosmetic products containing TEA and DEA showed mild skin irritation in concentrations above 5%. There was very little skin sensitization. There was no phototoxicity or photosensitization reactions with products containing up to 20.04% TEA. A formulation containing 11.47% MEA and a formulation containing 1.6% DEA and 5.9% MEA were irritating to human skin in patch tests.

The Panel concludes that TEA, DEA, and MEA are safe for use in cosmetic 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, the concentration of ethanolamines should not exceed 5%. MEA should be used only in rinse-off products. TEA and DEA should not be used in products containing N-nitrosating agents.

CHEMICAL AND PHYSICAL PROPERTIES

Structure

Triethanolamine (CAS No. 102-71-6) (TEA), Diethanolamine (CAS No. 111-42-2) (DEA), and Monoethanolamine (CAS No. 141-43-5) (MEA) are amino alcohols. They are produced by aminating ethylene oxide with ammonia. The replacement with ethanol groups of three, two, or one hydrogen of ammonia results in TEA, DEA, or MEA, respectively. The chemical formulas of the ethanolamines are as follows:



Properties

TEA, DEA, and MEA are clear, colorless, viscous liquids with ammoniacal odors. They are hygroscopic and are strong bases. The ethanolamines are soluble in water, alcohol, and chloroform, and are insoluble in benzene, ether, and petroleum distillates.[1-6] Chemical and physical properties of TEA, DEA, and MEA are presented in Table 1. A sampling of the variety of values available in the literature is given for several chemical and physical properties. This variation may reflect the use of different grades of chemicals.

Reactivity

TEA, DEA, and MEA are reactive and are bifunctional, combining the properties of alcohols and amines. The ethanolamines will react at room temperature with fatty acids to form ethanolamine soaps, and DEA and MEA will react at temperatures between 140° and 160°C with fatty acids to form ethanolamides. The reaction of ethanolamine and sulfuric acid produces sulfates, and DEA and MEA may react, under anhydrous conditions, with carbon dioxide to form carbamates.[1-3]

The ethanolamines can act as antioxidants in the autoxidation of fats of both animal and vegetable origin. TEA and DEA have stronger antioxidant effects than MEA.[7] TEA is an antioxidant as measured by the *Tetrahymena* photodynamic assay.[8]

TEA and DEA can react with nitrite or oxides of nitrogen to form N-nitrosodiethanolamine (NDELA). As yet, MEA has not been found to form a stable nitrosamine.[9,10] MEA can react with an aldehyde to form DEA, and then can be

TABLE 1. Chemical and Physical Properties.

Property	*TEA*	*DEA*	*MEA*	*Ref.*
Molecular weight	149.19	105.14	61.08	6
Specific gravity				
20/4 °C	1.1242			
20/20 °C			1.0179	3,5
25/4 °C			1.0117	6
30/4 °C		1.0881		6
30/20 °C		1.0919		2
30/20 °C		1.092		5
40/4 °C			0.9998	6
60/4 °C	1.0985	1.0693	0.9844	6
not specified	1.1255			1
not specified	1.124			4
not specified	1.126			5
Viscosity (cps)				
20 °C	1013			1
25 °C	590.5		18.95	6
30 °C		380		2
30 °C		351.9		6
60 °C	65.7	53.85	5.03	6
not specified			24	3
Boiling Point (°C)				
760 mm Hg	360	decomposes	171	1–3
760 mm Hg	335.4	268.8	170.8	6
not specified	277–279	268.0	172.2	4
not specified	335, decomposes		170.5	5
Melting Point (°C)	17.9	28.0	10.3	1–3
	20–21.2	28.0	10.5	4
	21.2	28.0	10.5	5
	21.57	28.0	10.3	6
Heat of Vaporization (joules/g)				
760 mm Hg	534	660	825	1–3
Vapor Pressure (mm Hg)				
20 °C	<0.01		0.48	5
not specified	0.01	0.01	0.4	1–3
Refractive Index				
20 °C			1.4544	3
20 °C	1.4852		1.4539	6
30 °C		1.4747		2
30 °C		1.4753		6
pH of a 0.1 N aqueous solution	10.5	11.0	12.05	6

nitrosated to form NDELA.[9] The optimum pH for nitrosamine formation is variously reported to be between 1 and 6, and the reaction rate decreases as the pH increases.[9-12] Neutral solutions require 100,000 times as much nitrite as strong acid solutions in order to form the same amount of nitrosamine.[10,12] However, in the presence of catalysts such as chloral or an aldehyde, nitrosation reactions may occur up to a pH of 11.[9] The rate of NDELA formation in the pH range 4–9 is four to six times greater in the presence of formaldehyde than in its absence.[13] Higher temperatures and longer reactions times increase the yield of

nitrosamine.[11] Nitrosation reactions and salt formation reactions compete in aqueous solutions.[10] The nitrosation by nitrites of DEA in an oil-in-water emulsion to NDELA can be inhibited by ascorbic acid or sodium bisulfite or much less effectively inhibited by potassium sorbate incorporated into the aqueous phase or can be inhibited by ascorbyl palmitate incorporated into the oil phase.[14]

Methods of Manufacture and Impurities

The ethanolamines are commercially produced by aminating ethylene oxide with ammonia. The reaction temperature can be adjusted to produce mostly TEA or MEA.[1-3,15] The product is purified by distillation. A "low freeze grade" product can be prepared by adding up to 15% water.[1-3]

TEA contains small amounts of DEA and MEA, and DEA contains small amounts of TEA and MEA. MEA contains a small amount of DEA.[1-3,16] TEA used in cosmetics may contain a maximum of 0.5% water, 0.05% sulfated ash, and 15 ppm iron.[17]

Analytical Methods

Qualitative and quantitative determinations of the ethanolamines are made by colorimetric procedures,[16,18-21] titrimetric methods,[16,20,22-28] thin-layer chromatography,[29-32] gas chromatography,[23-25,33-39] gravimetric analysis,[39] thermogravimetric analysis,[40] the Kjeldahl method,[18] and the Van Slyke procedure.[41] Positive identification of the ethanolamines can be made by comparison with published infrared spectra.[39,42,43] UV absorbance spectra are available for TEA and MEA.[44]

Jones et al.[33] used gas chromatography to determine the amount of TEA in a simulated vanishing cream and shampoo. They did a preliminary separation into classes of compounds and were then able to recover between 96% and 101% of the TEA added to the cosmetic formulations.

USE

Purpose in Cosmetics

Ethanolamine soaps, formed from the reaction at room temperature of TEA, DEA, or MEA and fatty acids, and ethanolamides, formed from the reaction at elevated temperatures of DEA and MEA and fatty acids, are used in cosmetic formulations as emulsifiers, thickeners, wetting agents, detergents, and alkalizing agents.[1-3,45]

Scope and Extent of Use in Cosmetics

Product types and the number of product formulations containing TEA, DEA, or MEA reported voluntarily to the Food and Drug Administration (FDA) in 1981 are presented in Table 2. Table 2 does not include products containing TEA-lauryl sulfate or TEA-coco-hydrolyzed animal protein. These two ingredients have been reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel in

TABLE 2. Product Formulation Data.

Product category	Total no. of formulations in category	Total no. containing ingredient	No. product formulations within each concentration range (%)							
			Unreported concentration	>50	>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Triethanolamine										
Baby shampoos	35	1	–	–	–	–	–	–	1	–
Baby lotions, oils, powders, and creams	56	4	–	–	–	–	–	2	2	–
Other baby products	15	1	–	–	1	–	–	–	–	–
Bath oils, tablets, and salts	237	1	–	–	–	–	1	–	–	–
Bubble baths	475	5	–	–	–	–	–	–	2	3
Other bath preparations	132	5	–	–	–	–	–	–	5	–
Eyebrow pencil	145	6	–	–	–	–	–	1	5	–
Eyeliner	396	60	–	–	–	4	2	17	34	3
Eye shadow	2582	157	–	–	–	–	–	73	81	3
Eye lotion	13	1	–	–	–	–	–	–	–	1
Eye makeup remover	81	3	–	–	–	–	–	2	–	1
Mascara	397	141	–	–	–	5	10	94	32	–
Other eye makeup preparations	230	36	–	–	–	–	–	14	22	–
Colognes and toilet waters	1120	12	–	–	–	–	–	–	5	7
Perfumes	657	5	–	–	–	–	–	1	4	–
Sachets	119	40	–	–	–	–	–	17	23	–
Other fragrance preparations	191	40	–	–	–	–	–	14	26	–
Hair conditioners	478	10	–	–	–	1	–	2	6	1
Hair sprays (aerosol fixatives)	265	3	–	–	–	–	–	1	2	–
Permanent waves	474	3	–	–	–	–	–	3	–	–
Hair rinses (noncoloring)	158	1	–	–	–	–	–	–	–	1
Hair shampoos (noncoloring)	909	36	–	–	1	1	5	16	13	–
Tonics, dressings, and other hair grooming aids	290	24	–	–	–	–	1	9	10	4
Wave sets	180	44	–	–	–	–	–	3	41	–
Other hair preparations (noncoloring)	177	8	–	–	–	–	–	2	6	–

TABLE 2. (Continued.)

Product category	Total no. of formulations in category	Total no. containing ingredient	No. product formulations within each concentration range (%)							
			Unreported concentration	>50	>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Triethanolamine (Cont'd.)										
Hair dyes and colors (all types requiring caution statement and patch test)	811	40	–	–	–	–	–	–	40	–
Hair rinses (coloring)	76	1	–	–	–	–	–	–	1	–
Other hair coloring preparations	49	8	–	–	–	8	–	–	–	–
Blushers (all types)	819	65	–	–	–	–	–	32	28	5
Face powders	555	14	–	–	–	–	–	–	3	11
Makeup foundations	740	211	–	–	–	–	–	71	139	1
Lipstick	3319	17	–	–	–	–	–	–	14	3
Makeup bases	831	273	–	1	–	–	–	90	181	1
Rouges	211	11	–	–	–	–	–	4	6	1
Makeup fixatives	22	2	–	–	–	–	–	–	2	–
Other makeup preparations (not eye)	530	20	–	–	–	–	–	4	15	1
Cuticle softeners	32	9	–	–	–	–	2	–	6	1
Nail creams and lotions	25	6	–	–	–	–	–	3	3	–
Nail polish and enamel remover	41	1	–	–	–	–	–	–	1	–
Other manicuring preparations	50	2	–	–	–	–	1	–	1	–
Bath soaps and detergents	148	8	–	–	4	–	4	–	–	–
Deodorants (underarm)	239	2	–	–	–	–	–	–	2	–
Other personal cleanliness products	227	7	–	–	1	1	1	2	2	–

Aftershave lotions	282	22	–	–	–	–	–	1	18	3
Beard softeners	4	2	–	–	–	–	2	–	–	–
Shaving cream (aerosol, brushless, and lather)	114	64	–	–	–	–	3	56	5	–
Other shaving preparation products	29	11	–	–	–	–	–	3	6	2
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	214	–	–	–	–	1	69	131	13
Depilatories	32	1	–	–	–	–	–	1	–	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	403	2	–	–	–	4	105	276	16
Foot powders and sprays	17	1	–	–	–	–	–	–	1	–
Hormone skin care preparations	10	3	–	–	–	–	–	1	2	–
Moisturizing skin-care preparations	747	388	–	1	–	–	–	115	248	24
Night skin care preparations	219	88	–	–	–	–	–	34	48	6
Paste masks (mud packs)	171	19	–	–	–	–	–	1	16	2
Skin lighteners	44	5	–	–	–	–	–	2	3	–
Skin fresheners	260	19	–	–	–	–	1	–	11	7
Wrinkle smoothers (removers)	38	7	–	–	–	–	–	1	6	–
Other skin care preparations	349	69	–	–	1	–	1	21	40	6
Suntan gels, creams, and liquids	164	47	–	–	–	–	1	15	31	–
Indoor tanning preparations	15	3	–	–	–	–	–	–	3	–
Other suntan preparations	28	10	–	–	–	–	–	6	41	–
1981 TOTALS		2757	2	2	8	20	40	908	1650	127

TABLE 2. (Continued.)

Product category	Total no. of formulations in category	Total no. containing ingredient	No. product formulations within each concentration range (%)							
			Unreported concentration	>50	>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Diethanolamine										
Bubble baths	475	4	–	–	–	–	–	–	–	4
Permanent waves	474	1	–	–	–	–	–	1	–	–
Hair dyes and colors (all types requiring caution statement and patch test)	811	12	–	–	–	–	–	12	–	–
Nail basecoats and undercoats	44	1	–	–	–	–	–	1	–	–
1981 TOTALS		18	–	–	–	–	–	14	–	4
Monoethanolamine										
Mascara	397	1	–	–	–	–	–	–	1	–
Hair conditioners	478	2	–	–	–	–	–	–	2	–
Hair straighteners	64	2	–	–	–	–	–	2	–	–
Permanent waves	474	13	–	–	–	–	2	9	2	–
Hair dyes and colors (all types requiring caution statement and patch test)	811	25	–	–	–	–	9	7	9	–
Hair shampoos (coloring)	16	1	–	–	–	–	–	–	1	–
Hair bleaches	111	2	–	–	–	–	–	2	–	–
Other personal cleanliness products	227	3	–	–	–	–	–	2	–	1
Shaving cream (aerosol, brushless, and lather)	114	1	–	–	–	–	–	–	1	–
Moisturizing skin care preparations	747	1	–	–	–	–	–	–	1	–
1981 TOTALS		51	–	–	–	–	11	22	17	1

Data from Ref. 48.

other documents.[46,47] Voluntary filing of product formulation data by cosmetic manufacturers, packagers, and distributors conforms to the prescribed format of preset concentration ranges and product types as described in the Code of Federal Regulations (21 CFR, Part 720.4). Some cosmetic ingredients are supplied by the manufacturer at less than 100% concentration and, therefore, the value reported by the cosmetic formulator or manufacturer may not necessarily reflect the actual concentration of the finished product; the concentration in such a case would be a fraction of that reported to the FDA. The fact that data are submitted only within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to 10-fold error in the assumed ingredient concentration.

In 1981, TEA, DEA, and MEA were reported to be ingredients of 2757, 18, and 51 cosmetic products, respectively. The majority of these products contained TEA, DEA, or MEA in a concentration of less than or equal to 5%.[48]

Surfaces to Which Commonly Applied

Cosmetic products containing ethanolamines may be applied to or come in contact with skin, eyes, hair, nails, mucous membranes, and respiratory epithelium. Small amounts may be ingested from lipstick (Table 2).[48]

Frequency and Duration of Application

Product formulations containing ethanolamines may be applied as many as several times a day and may remain in contact with the skin for variable periods of time following each application. Daily or occasional use may extend over many years (Table 2).[48]

Potential Interactions with Other Cosmetic Ingredients

N-nitrosating agents, present as intentional ingredients or as contaminants of cosmetics, may react with the ethanolamines to form N-nitrosodiethanolamine (NDELA). NDELA has been found in cosmetic raw materials. Ninety-nine samples of 17 materials were evaluated and NDELA was detected in concentrations of greater than 1000 ppb, 501–1000 ppb, 101–500 ppb, and 50–100 ppb in 6, 3, 6, and 6 samples, respectively. NDELA was found in trace levels in nine samples and was not detected in 69 samples.[13,49] NDELA has also been detected in a variety of cosmetic products.[50-60] An on-going study by the FDA has provided NDELA analysis for 335 off-the-shelf cosmetic formulations. The FDA data are presented in Table 3. NDELA was detected in 110 of a total of 252 products containing TEA and in 25 of a total of 64 products not containing TEA. However, products with no TEA may have contained DEA or MEA. These findings suggest the possibility that TEA may lead to the formation of NDELA in some cosmetics.

Bronaugh et al.[61,62] investigated the percutaneous absorption of NDELA through excised human skin. NDELA was dissolved in water, propylene glycol, and isopropyl myristate, and the permeability constants were 5.5×10^{-6}, 3.2×10^{-6}, and 1.1×10^{-3} cm/h, respectively. The permeability of NDELA through ex-

TABLE 3. Association of NDELA with TEA in Cosmetics Analyzed by the FDA.

Cosmetic product samples reported to contain	*NDELA detected*	*No NDELA detected*
TEA	110	142
No TEA	25	39
Incomplete or no Ingredient information	5	14
	(Total) 140	(Total) 195

Data from Refs. 51–55.

cised human skin was greatly increased when applied from sufficiently lipoidal formulations. The major route of elimination after oral and topical administration of NDELA to rats was the urine.[63] NDELA was applied to the skin of monkeys and pigs and, afterwards, was detected in their urine.[64] NDELA was detected in rat urine following epicutaneous and intratracheal administration of NDELA and following percutaneous administration of DEA and oral administration of nitrite in drinking water.[65] After application of an NDELA-contaminated cosmetic. NDELA was detected in human urine.[66]

NDELA, in concentrations of 5–15 mg/plate, was mutagenic to *Salmonella typhimurium* strains TA1535 and TA100 in the presence of hamster liver S-9 but not in the presence of rat liver S-9.[67] NDELA is carcinogenic to rats after oral administration[68-70] and to hamsters after subcutaneous injections, skin painting, and oral cavity swabbing.[71,72] Although no epidemiological data were available, the International Agency for Research on Cancer[73] has suggested that "NDELA should be regarded for all practical purposes as if it were carcinogenic to humans."

Nitrites have been found in cosmetic raw materials.[13,49,74] TEA and DEA can be nitrosated to NDELA with 2-bromo-2-nitropropane-1,3-diol (BNPD), an antimicrobial agent used in cosmetics.[75-77] A report on the safety assessment of BNPD recommended against its usage in cosmetics where its actions with amines or amides could result in the formation of nitrosamines or nitrosamides.[75] Ong et al.[78] discovered that NDELA could be formed from the peroxidation and subsequent nitrosation of DEA. They found that peroxides could result from the autoxidation of compounds such as polysorbate 20 and that the addition of antioxidants prevented this. Under the same experimental conditions, TEA and MEA did not yield NDELA.

Noncosmetic Uses

The ethanolamines are used in the manufacture of emulsifiers and dispersing agents for textile specialties, agricultural chemicals, waxes, mineral and vegetable oils, paraffin, polishes, cutting oils, petroleum demulsifiers, and cement additives. They are intermediates for resins, plasticizers, and rubber chemicals. They are used as lubricants in the textile industry, as humectants and

softening agents for hides, as alkalizing agents and surfactants in pharmaceuticals, as absorbents for acid gases, and in organic syntheses.[5,6]

TEA, at a concentration not exceeding 2 ppm, and MEA, at a concentration not exceeding 0.3 ppm, may be used in flume water for washing sugar beets prior to slicing (21 CFR 173.315). TEA, DEA, and MEA, at no specific concentration limits, may be components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food[79] except that TEA and DEA may not exceed 5% by weight of rubber articles intended for repeated use.[80] TEA and DEA may be used as adjuvants for pesticide chemicals and are exempt from the requirement of tolerances[81] except that DEA maleic hydrazide may not be sold in the United States.[82]

GENERAL BIOLOGY

Antimicrobial Effects

TEA, DEA, and MEA inhibit the growth of a wide variety of microorganisms. The concentration of ethanolamine required to inhibit growth varies with genus and species.[8,83-87] DEA and MEA have some antimycotic activity when applied on the skin of guinea pigs.[88-90]

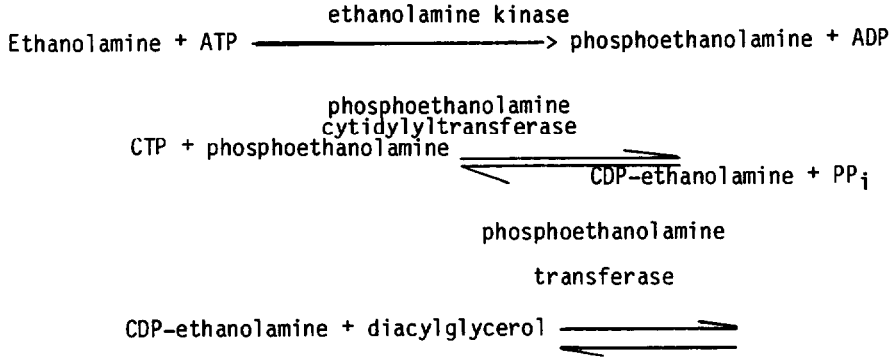
Effects on Chick Embryo

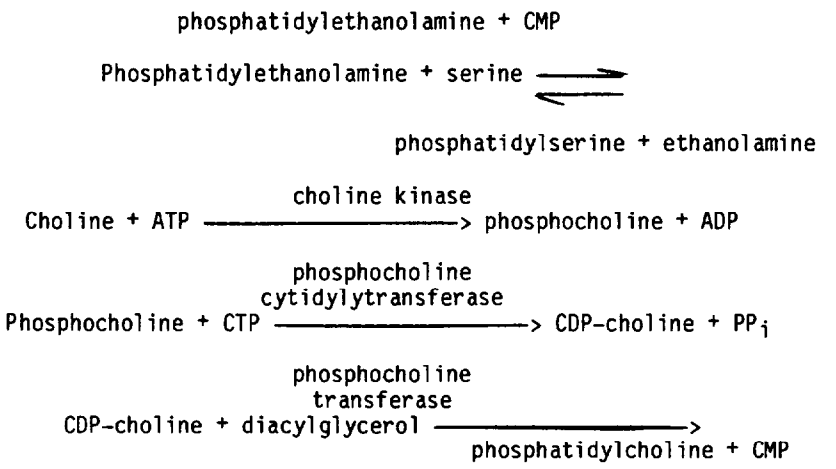
The incubation of chicken eggs with 0.03% MEA for 18 h increases the number of eggs with visible blastodisks, increases the synthesis of proteins, fats, and carbohydrates, and increases the number of hatching chicks.[91]

Effects on Enzymatic Activity

Effects on Enzymes Involved in Lipid Biosynthesis

TEA, DEA, and MEA affect the biosynthesis of lipids. Reactions of particular interest in mammals are those involved in the synthesis of the phosphoglycerides, phosphatidylethanolamine (PE), phosphatidylcholine (lecithin) (PC), and phosphatidylserine (PS):[92]





The administration of MEA at a dose of 60 mg/kg/day for 30 consecutive days to albino rats with experimentally-induced coarction of the aorta resulted in elevated levels of PE, PS, and PC in the rat myocardium. Metabolic changes produced by MEA action may have inhibited the development of cardiac insufficiency in these animals.[93] Hale et al.[94] grew chicken embryo fibroblasts in standard media with 40 mg/ml of choline in delipidated media without choline, and in delipidated media without choline and with 40 mg/ml of MEA. The PE content of the cells was increased in both delipidated media and hexose transport was slowed in the MEA supplemented medium. The authors suggested that some property of MEA other than its accompanying increase in PE must be responsible for the drop in hexose transport in these cells. Upreti[95] injected intraperitoneally approximately 168 mg/kg of MEA into male albino mice every day for four days. Mice were sacrificed at 6, 12, 24, 48, and 96 h. At all times from 12 to 96 h, the liver ethanol kinase levels of the treated mice were significantly higher than control mouse liver levels.

Barbee and Hartung[96] investigated the effect of the administration of DEA on the in vivo incorporation of MEA and choline into rat liver and kidney. They found that the administration of 250 mg/kg of labeled DEA in a single injection to male albino rats did not change the amount of injected labelled MEA and choline incorporated into liver or kidney. However, when labelled DEA was administered to male albino rats at a dose of 320 mg/kg/day in drinking water for up to three weeks, the results were different. Rats were sacrificed at 0, 1, 2, and 3 weeks, and the amounts of injected labeled MEA and choline incorporated in the liver and in the kidney were lower at 1, 2, and 3 weeks than at time 0. MEA and choline phospholipid derivatives were synthesized faster and in greater amounts, and were catabolized faster than DEA phospholipid derivatives. This may favor accumulation of DEA-containing phospholipids during chronic exposure. These researchers also investigated the effects of DEA on mitochondrial function in the male albino rat.[97] Administration of neutralized DEA at doses of 490 mg/kg/day for three days or of 160 mg/kg/day for one week in drinking water produced alterations of hepatic mitochondrial function. Barbee and Hartung hypothesize

that DEA phospholipids are formed and incorporated into mitochondrial membranes with subsequent disruption of mitochondrial metabolism.

The activity of glucosyltransferase, isolated from *Streptococcus mutans* culture supernatant solutions, was stimulated by TEA at a concentration of 50 m*M* and a pH of 6.5.[98] Glucosyltransferase catalyzes the formation of glucocerebroside, a sphingolipid, from ceramide and UDP-D-glucose.[92]

Effects on Other Enzymes

MEA inhibits the action of purified acetylcholinesterase from bovine erythrocytes.[99] Acetylcholinesterase catalyzes the reaction of acetylcholine and water to acetic acid and choline. This enzyme functions in the activity of the nervous system.[92]

DEA administered intraperitoneally or orally may affect directly or indirectly the serum enzyme levels, isozyme patterns, and concentrations of some amino acids and urea in the male rat liver and kidney. These changes were observed concomitant with or just after organ damage was histologically detectable.[100,101] Subchronic DEA administration in drinking water increased male rat hepatic mitochondrial ATPase and altered mitrochondrial structure and function.[97]

MEA stimulates the activity of purified aspartate transaminase from porcine heart[102] and intraperitioneal or intravenous administration of MEA decreases aspartate transaminase activity in rabbit kidney and heart.[103] The reversible reaction of L-aspartate and α-ketoglutarate to oxaloacetate and L-glutamate is catalyzed by aspartate transaminase.[92] Kotogyan et al.[104] found that the intravenous administration of MEA to rabbits for seven days increased the level of aspartate and glutamate in the kidneys and decreased the levels in the brain.

The intraperitoneal or intravenous administration of MEA to rabbits decreased the activity of alanine transaminase in the kidney and the heart.[103] Alanine transaminase is the enzyme involved in the reversible reaction that converts L-alanine and α-ketoglutarate to pyruvate and L-glutamate.[92]

Intraperitoneal administration of MEA to rats inhibited alcohol dehydrogenase. Ostroviskii and Bankovskii[105] suggested that this was the reason for the hepatic accumulation of endogenous ethanol and taurine.

Peroxidase activity and number of organic peroxide molecules in the blood, liver, and homogenate of chick embryos were decreased when chicken eggs were incubated with MEA.[91] Peroxidase acts in reactions in which hydrogen peroxide is an electron acceptor.

MEA can inactivate and partially dissociate β-galactosidase from *Escherichia coli*.[106] Beta-galactosidase catalyzes the formation of D-glucose and D-galactose from lactose and water.[92]

Effects on Hormones

MEA can affect the metabolism of catechol amines. The conversion of interest is as follows:

L-tyrosine → dihydroxyphenylalanine (DOPA) → dopamine → norepinephrine → epinephrine

Epinephrine and norepinephrine are hormones secreted by the adrenal medulla. They act in the regulation of heart rate and blood pressure. Epinephrine also activates glycogen breakdown to glucose in the liver and in muscle through its stimulation of adenylate cyclase.[92] Intraperitoneal injection of MEA into rats at 10 mg/kg increased norepinephrine and decreased epinephrine in the heart. A 25 mg/kg injection of MEA had the opposite effect. At the higher MEA dose, after three days the heart norepinephrine concentration remained altered and the DOPA concentration increased.[107] A 25 mg/kg intraperitoneal injection of MEA increased mouse heart muscle content of epinephrine and DOPA and decreased the content of norepinephrine.[108] Goncharenko et al.[109] found increased dopamine concentrations in rats following injection of MEA. DOPA decreased or remained unchanged.

Okano[110] reported that the in vitro conversion of proparathyroid hormone formed in the parathyroid gland to parathyroid hormone was strongly inhibited by the action of MEA. Parathyroid hormone is involved in the metabolism of calcium and phosphorus by the body.

Effects on Protein, Nucleic Acids, and Other Cellular Substances

Subchronic oral administration of MEA to castrated rams increased serum albumin concentrations and total protein concentrations.[111]

The administration of MEA to rabbits, either intraperitoneally or intravenously, increased RNA concentrations in the kidney, heart, and brain, decreased DNA concentrations in the heart and brain, and had no effect on total nitrogen or protein in any of the three tissues.[103]

Intraperitoneal administration of MEA to rats increased glycogen, ATP, and ascorbic acid concentrations in the liver, kidney, brain, and heart.[112]

Effects on Liver Structure

Grice et al.[100] assessed morphological damage to rat liver and kidney four and 24 h after intraperitoneal injection of DEA at 100 and 500 mg/kg. At both times, after both doses and in both organs, cytoplasmic vacuolization was observed. In addition, mitochondria of the hepatocytes were swollen and less dense than in the control animals, and after 24 h, liver nuclei were more deeply basophilic than normal. At both times at the high dose of DEA, there was some renal tubular degeneration and some cells were necrotic. Barbee and Hartung[97] found that the mitochondria from rats treated with 3 mg/kg/day of DEA for two weeks in their drinking water were consistently spherical and also appeared larger than mitochondria from control animals. Korsud et al.[101] administered 100 to 6400 mg/kg of DEA orally to rats. They discovered that liver and kidney weights and damage to the liver and kidney increased as dose increased. They confirmed the observations of Grice et al.[100] except that they found no morphological differences in mitochondria from control and treated rats.

Effects on the Heart

MEA, administered to rats with experimentally-induced coarction of the aorta, at doses from 5 to 50 mg/kg enhanced myocardial contractility. Thirty-day

administration of MEA in a dose of 10 mg/kg stimulated and 60 mg/kg of MEA inhibited the development of myocardial hypertrophy.[93] Increasing doses of MEA from 9.6×10^{-7} *M* to 1.2×10^{-5} *M* increased the atrial rate and force of contraction in the isolated rabbit atria.[113]

Effects on the Bovine Rhodopsin Chromophore

MEA bleached the visual pigment, rhodopsin, from water-washed bovine retinal rod chromophores, which are responsible for vision in dim light.[114]

ABSORPTION, METABOLISM, STORAGE, AND EXCRETION

MEA is the only naturally occurring ethanolamine in mammals and is excreted in the urine.[10] Much of the available scientific literature on the metabolism of the ethanolamines is concerned with the effect on phospholipid biosynthesis of the intraperitoneal and intracerebral or in vitro administration of MEA to intact mammals or mammalian tissue, respectively. Ansell and Spanner[115] have performed a respresentative experiment. Labeled MEA was administered intraperitoneally to adult female rats, the rats were sacrificed, and incorporation of MEA into phospholipids was traced in the liver, the blood, and the brain. They discovered that MEA was converted to phosphatidylethanolamine (PE) in all the tissues. However, the step-wise methylation of PE that converts it to phosphatidylcholine (PC), which occurs rapidly in the liver and less rapidly in extrahepatic tissues, did not occur at all in the brain. Morin[116] found that labelled MEA was incorporated into PE and also into PC in isolated human peripheral arteries. This suggests that the enzyme system for transmethylation of PE to PC may be active in human arteries. Researchers have found labeled respiratory carbon dioxide after intraperitoneal administration of labeled MEA to rats.[117] Further sources are available that corroborate these findings on the effect of MEA on lipid biosynthesis in mammals.[105,118-140]

In vitro administration of MEA had no effect on the incorporation of labeled phosphate into phospholipids in swine coronary and pulmonary arteries[141] or in rabbit or human endometria.[142] However, in both cases TEA did inhibit the incorporation of labeled phosphate into phospholipids.

Babior[143] labeled purified MEA from an unspecified source and demonstrated a coenzyme-B_{12}-dependent ethanolamine deaminase mediated conversion of MEA to acetaldehyde and ammonia. Ostrovskii and Bankovskii[105] administered MEA intraperitoneally to rats and observed an increase in blood urea and brain glutamine. They suggested that ethanolamine was an ammonia source. Sprinson and Weliky[144] labeled MEA and administered it in feed to rats. They detected labeled acetate in the urine of the rats. They suggested that MEA is phosphorylated by ATP in vivo, converted to acetaldehyde, ammonia, and inorganic phosphate and then the acetaldehyde is oxidized to acetate. These researchers hypothesize that the removal of phosphorylated MEA by its conversion to acetate may exert a regulatory effect on PE biosynthesis.

Labeled MEA was administered to dogs. The route of administration was unspecified. After 24 h, the total blood radioactivity as a percentage of dose was

1.69%. There was a persistence of low levels of radioactivity in dog whole blood samples; the half-life was 19 days. Excretion in urine of radioactivity as a percentage of dose was 11%.[145]

ANIMAL TOXICOLOGY

Oral Studies

Acute Toxicity

The acute oral toxicity of TEA, DEA, MEA, and a hair preparation containing DEA and MEA has been studied in guinea pigs[146-149] and in rats.[149-159] The animals were administered the material by gavage, and then were observed for 14 days. Table 4 presents data from the experiments. The LD50 values for rats of TEA, DEA, and MEA ranged from 4.19 g/kg to 11.26 g/kg, 0.71 ml/kg to 2.83 g/kg, and 1.72 g/kg to 2.74 g/kg, respectively. The LD50 values for DEA and MEA are quite similar and are lower than the LD50 values for TEA. In the Hodge and Sterner[160] classification of single-dose oral toxicity for rats, TEA, DEA, and MEA would be classified as practically nontoxic to slightly toxic, slightly toxic, and slightly toxic, respectively.

Oral Corrosivity

A study was conducted on rabbits to determine the oral tissue corrosivity potential of a hair preparation containing 1.6% DEA, 5.9% MEA, and 3.2% sodium borate.[161] The undiluted test material at a dose of 0.229 g/kg (0.210 ml/kg) was placed on the posterior tongue surface of four rabbits and they were allowed to swallow. Two rabbits were sacrificed at 24 h and two at 96 h. Gross and microscopic examinations of the tongue, adjacent pharyngeal structures, larynx, esophagus extending to the cardiac incisure, and stomach revealed no observable abnormalities. The hair preparation was not an irritant and was not corrosive in these tests.

Subchronic and Chronic Toxicity

Long-term oral toxicity of TEA, DEA, MEA or a composite of hair dyes and bases has been studied in guinea pigs,[149] in rats[149,155,156,162-165] and in dogs.[166] Table 5 presents data from the experiments. Considerably less data are available for DEA and MEA than for TEA. However, it does appear that DEA is the most toxic ethanolamine. Workers at the Mellon Institute[154] have suggested that this may be because MEA has a normal function in the lipid metabolism of the body and DEA is structurally similar enough to MEA to act in competition with it and interfere in lipid metabolism. TEA may be so sufficiently unlike MEA that it does not act in competition and therefore is less toxic than DEA.

Dermal Studies

Acute Toxicity

Undiluted TEAs, 91.8% and 88.1% active and both containing slightly more than 6% of DEA, were each applied to the intact skin of three rabbits and to the

TABLE 4. Acute Oral Toxicity.

Material tested	*Conc. of material tested (%) and vehicle*	*Dose of ethanolamine*[a]	*No. and species of animal*	*LD50*	*Comments*	*Ref.*
TEA, 99+ Percent	20 in water; 100	4.0; 5.0, 6.3 g/kg	2 rats at each dose level		0/2, 1/2, 2/2 deaths, moderate liver and kidney damage at all dose levels.	150
TEA, 99+ Percent	In gum arabic solution	0.6–7.0 g/kg	2–3 (unspecified) guinea pigs at each dose level		All survived 0.6 and 1.4 g/kg; None survived 7.0 g/kg.	146
TEA, 78.6% (DEA, 8.6%; MEA, 1.7%)	25 in water	2.6–7.4 ml/kg TEA	10 rats at each of 4 dose levels	4.03 ml/kg (4.19 g/kg)	No unusual observations.	151
TEA, 91.8% (DEA, 6.5%)	100	3.64–14.00 ml/kg	10 rats at each of 5 dose levels	7.11 ml/kg	Slight to moderate degrees of hemorrhagic rhinitis in rats dosed at ≥7.14 ml/kg.	152
TEA, 88.1% (DEA, 6.1%)	100	3.64–10.00 ml/kg	10 rats at each of 4 dose levels	5.39 ml/kg	Slight to moderate degrees of hemorrhagic rhinitis in rats dosed at ≥7.14 ml/kg.	152
TEA, Commercial or high purity grade	100	1.0–26.0 g/kg	10 guinea pigs at LD50 and at 1 g < LD50 estimated from single feedings	8 g/kg	Gross pathology confined to intestinal tract. Before death, diarrhea and prostration observed in most animals. Some were paralyzed in their hind quarters.	149
TEA, Commercial grade	100	1.0–12.0 g/kg	10 rats at LD50 and at 1 g < LD50 estimated from single feedings	8 g/kg	Gross pathology confined to intestinal tract. Before death, diarrhea and prostration observed in most animals.	149

TABLE 4. (Continued.)

Material tested	*Conc. of material tested (%) and vehicle*	*Dose of ethanolamine*[a]	*No. and species of animal*	*LD50*	*Comments*	*Ref.*
TEA, high purity grade	100	1.0–12.0 g/kg	10 rats at LD50 and at 1 g < LD50 estimated from single feedings	9 g/kg	Gross pathology confined to intestinal tract. Before death, diarrhea and prostration observed in most animals.	149
TEA	in water		6 male rats at each dose level	9.11 g/kg		156
TEA, produced from 1939–1960	20 in water/100		rats	8.54–9.85 ml/kg or 7.3–11.26 g/kg		154,155
DEA, 99+ Percent	in gum arabic solution	0.6–5.0 g/kg	2–3 (unspecified) guinea pigs at each dose level		All survived 6.0 and 1.0 g/kg; None survived 3.0 g/kg.	147
DEA	in water		6 male rats at each dose level	1.82 g/kg		156
DEA	100		5 female rats at each dose level	0.80 ml/kg		157
DEA	100		5 female rats at each dose level	0.71 ml/kg		158
DEA, produced from 1939–1949	20 in water		90–120 (unspecified) rats	1.41–2.83 g/kg		154

MEA, 99+ Percent	in gum arabic solution	0.64–1.4 g/kg	2.3 (unspecified) guinea pigs at each dose level		All survived 0.6 g/kg; None survived 7.0 g/kg.	148
MEA	in water		6 male rats at each dose level	2.74 g/kg		156
MEA			male rats	1.97 g/kg		159
MEA			female rats	1.72 g/kg		159
MEA, produced from 1939–1949	20 in water		90–120 (unspecified) rats	2.14–2.74 g/kg		154
Hair preparation (DEA, 1.6%; MEA, 5.9%; sodium borate, 3.2%)	100	8.72–17.4 g/kg (8.00–16.0 ml/kg) of undiluted preparation	10 rats at each of 4 dose levels	14.1 g/kg (12.9 ml/kg) for undiluted preparation	Animals receiving ≥ 13.8 g/kg of product had signs of melanuria, diarrhea, polyuria, and discoloration of stomach, intestinal mucosa, and gastrointestinal contents.	167

[a]Adjusted for concentration tested and material activity, when known.

TABLE 5. Subchronic and Chronic Toxicity.

Material tested	*Dose and vehicle*	*Length of study*	*No. and species of animals*	*Results*	*Ref.*
TEA	0–2.61 g/kg/day in food	90 days	10 rats at each dose level	No effects observed at ≤0.08 g/kg/day. Decreased weight gain at 1.27 g/kg/day. Heavy livers and kidneys produced when dose was ≥0.17 g/kg/day. Major pathology of small intestine, kidney, liver, or lung rare at ≤0.73 g/kg/day. Most major pathology observed was fatty degeneration of the liver. Some deaths at ≥0.73 g/kg/day.	154,156
TEA, 88.5% (DEA, 6%)	0–1.0 g/kg/day in food	91 days	20 rats of each sex at each of 4 dose levels	Increased weight gain in female rats receiving 0.25 g/kg/day. Increased feed consumption in female rats receiving 0.5 g/kg/day. No significant differences noted in organ to body weight ratios. No gross or histopathologic indications of a treatment related effect. No significant hematologic effects.	163
TEA, commercial or high purity grade	0.2–1.8 g/kg/day in food	60, 120 days	8 rats of each dose level for each time	Peripheral optic nerves showed scattered degeneration in the myelin of individual fibers at all doses for both 60 and 120 days. Liver changes were observed at ≥0.4 g/kg/day for 60 or 120 days. Kidney changes were observed at 0.2 to 0.225 g/kg/day for 120 days and at 0.4–0.45 g/kg/day for 60 or 120 days. Kidney damage was observed at ≥0.8 g/kg/day for 60 or 120 days. No kidney damage was severe enough to interfere with organ function.	149

TEA, commercial or high purity grade	0.2–1.8 g/kg/day in food	120 days and then, ~3 months without TEA	8 rats at each dose level	Kidney regeneration was observed after organ damage.	149
TEA, commercial or high purity grade	0.2–1.6 g/kg/day by pipette 5 days/week	60, 120 doses	8 guinea pigs at each dose level for each number of doses	Peripheral optic nerves showed scattered degeneration in the myelin of individual fibers at all doses for both 60 and 120 days. Liver and kidney damage was observed at ≥0.8 g/kg/day. No kidney or liver damage was severe enough to interfere with organ function.	149
TEA, commercial or high purity grade	0.2–1.6 g/kg/day by pipette 5 days/week	120 doses and then, ~3 months without TEA	8 guinea pigs at each dose level	Liver and kidney regeneration was observed after organ damage.	149
TEA, 99%	1.4 mg/l in drinking water; TEA in drinking water and 6.5% TEA solution applied to skin caudally for 1 h 5 days/week; TEA in drinking water and 13% TEA solution applied to skin caudally for 1 h	6 months	10 rats in each group	No toxic effect observed from 6.5 percent topical TEA and 1.4 mg/l TEA in drinking water. Changes observed after 1 month in the functions of the liver and central nervous system in animals receiving 13% topical TEA and 1.4 mg/l TEA in drinking water. Increase seen in number of segmented neutrophils after 3 months and increase seen in number of lymphocytes after 4 months.	165

TABLE 5. (Continued.)

Material tested	*Dose and vehicle*	*Length of study*	*No. and species of animals*	*Results*	*Ref.*
	5 days/week.				
DEA, neutralized salt (labeled)	1.0, 2.0, 3.0 m*M*/kg/day orally	11 days (5th–15th day after birth)	Neonatal rats	No changes observed in heart or brain. Moderate cloudy swelling seen in kidney proximal tubule. Periportal cloudy swelling and vacuolization seen in liver. Swollen hepatic mitochondria observed.	162
DEA, neutralized	4 mg/ml in drinking water	7 weeks	Male rats	Many deaths observed. There was liver and kidney damage and a pronounced normocytic anemia without bone marrow depletion or obvious increase in number or reticulocytes.	164
DEA	0–0.68 g/kg/day in food	90 days	10 rats at each dose level	No effects observed at ≤0.020 g/kg/day. Heavy livers and kidneys produced at ≥0.090 g/kg/day. Major pathology of small intestine, kidney, liver, or lung observed at ≥0.17 g/kg/day. Major pathology included cloudy swelling and degeneration of kidney tubules and liver fatty degeneration. Some animals died at 0.17 and 0.35 g/kg/day and all died at levels greater than that.	154,156
MEA	0–2.67 g/kg/day in food	90 days	10 rats at each dose level	No effects observed at ≤0.32 g/kg/day. Heavy livers and kidneys produced at ≥0.64 g/kg/day. Some deaths and major pathology at ≥1.28 g/kg/day.	154,156
Composite hair dyes and bases (MEA, 22 percent)	0–0.0975 g/kg/day of composite in food	2 years	12 beagle dogs at each of 3 dose levels.	No toxic effects observed.	166

abraded skin of three rabbits. The test was a 24 h closed patch test and the TEAs were applied to yield a rabbit exposure of 2 g/kg of actual TEA. The 88.1% TEA elicited mild erythema and no edema at 24 h and the skin returned to normal by Day 6. The 91.8% TEA produced moderate erythema and no edema at 24 h and the treated sites were normal by Day 10. The animals were observed for 14 days. All rabbits gained weight and none died.[168]

Subchronic and Chronic Toxicity

Kindsvatter[149] applied commercial and high purity grades of TEA each to the shaved skin of 10 guinea pigs. The test was a closed patch continuous exposure test in which 8 g/kg was applied daily for five days a week to guinea pigs. Deaths occurred at from 2 to 17 applications. No guinea pigs survived 17 applications. Adrenal, pulmonary, hepatic, and renal damage was observed.

Kostrodymova et al.[165] applied TEA caudally to rats for 1 h, five days per week, for six months. No toxic effects were observed with a 6.5% solution of TEA. A 13% solution of TEA did effect changes in the liver and central nervous system function. The toxic effect of TEA was not increased when rats were given 1.4 mg/l of TEA in their drinking water in addition to the dermal application of the 13% solution of TEA.

The percutaneous application of MEA to rats at a dose of 4 mg/kg/day resulted in nonspecific histological changes in the heart and lung. Hepatoxic manifestations included fatty degeneration of the liver parenchyma and subsequent focal necrosis.[169]

Groups of 16 rabbits had a cosmetic formulation containing 14% TEA stearate and 1% methycellulose, applied to one of two clipped sites on their backs that were alternated weekly, at doses of 1 and 3 ml/kg five times per week for 13 weeks. Mild to moderate skin irritation which cleared within 72 h was observed and this was followed by moderate to heavy skin scaling. No toxic effects were seen in any rabbits. The control rabbits received 3 mg/ml of 1% methylcellulose in water. The low dose group had significantly lower kidney weights and the high dose group gained less weight and had significantly greater kidney weights than the control rabbits.[153]

Burnett et al.[170] applied three hair dyes containing 0.10%–0.15% TEA, 1.500% TEA, or 2.0% DEA to the backs of groups of 12 rabbits for 13 weeks. The doses were 1 mg/kg twice weekly and two clipped sites were alternated. The skin of half the rabbits was abraded. The dye was placed on the skin, the rabbits were restrained for 1 h, then shampooed, rinsed and dried. Control rabbits were treated identically except that no dye was applied to their skin. No systemic toxicity was observed and there was no histomorphologic evidence of toxicity in the treated rabbits after 13 weeks.

Primary Skin Irritation

Rabbits were used in primary skin irritation studies for TEA,[171,172] DEA,[173,174] and MEA.[175-177] Data from these experiments are presented in Table 6. These data suggest that MEA is irritating to rabbit skin, and that TEA and DEA are much less irritating to rabbit skin than MEA.

TABLE 6. Primary Skin Irritation.

Material tested	*Concentration (%)*	*Method*	*Number of rabbits*	*Results*	*Ref.*
TEA, 99+ percent	100	10 0.1 ml open applications to the ear over 14 days. 10 24-hour semioccluded patch applications to the intact shaved abdomen.	Unspecified	Slight hyperemia after 7 applications. "Slight to moderately irritating, prolonged or repeated exposure may be irritating."	171
TEA, 99+ percent	100	3 24-hour semioccluded patch applications to the abraded shaved abdomen.	Unspecified	Moderate hyperemia, edema, and necrosis. "Slight to moderately irritating, prolonged or repeated exposure may be irritating."	171
TEA	100	1 24-hour occluded patch application to clipped back. Erythema (0 to 4), edema (0 to 4), and necrosis (0 to 15) evaluations are made at 24 and 72 hours and are added and divided by 2 to yield a primary irritation score (scale = 0 to 24). Total possible score for 22 laboratories was 400.	8 male/each laboratory	Primary irritation scores ranged from 0 to 5.5 for 22 laboratories. Total score for all 22 laboratories was 27.3.	172

DEA, 99+ percent	100	10 0.1 ml open applications to the ear over 14 days. 10 24-hour semioccluded patch applications to the shaved abdomen.	Unspecified	Some denaturation on ear after 10 doses and on belly after 3 doses. "Moderately irritating."	173
DEA, 99+ percent	10 in water		Unspecified	No irritation observed.	173
DEA, 99+ percent	50	Semioccluded patch applications to intact and abraded shaved skin. Erythema and edema reactions are evaluated at 24 and 72 h and values are averaged to yield a primary irritation score (scale = 0 to 8).	6	Essentially no irritation of the skin. Primary irritation score = 0.17. "Not a primary irritant."	174
DEA, 99+ percent	30		6	Essentially no irritation of the skin. Primary irritation score = 0.29. "Noncorrosive to skin."	174
MEA, 99+ percent	85, 100	Semioccluded patch applications to intact and abraded shaved skin. Reaction evaluated at 4 h.	1	Visible destructive alteration of the tissue at the site of application. "Corrosive."	176
MEA, 99+ percent	30	Semioccluded patch applications to intact and abraded shaved skin. Reaction evaluated at 4 and at 24 h.	6	Visible destructive alteration of the tissue at the site of application at 4 h. Necrosis observed at 24 h. "Corrosive to skin."	177
MEA, 99+ percent	1–100	10 0.1 ml open applications to the ear over 14 days. 10 24-hour semioccluded patch applications to the shaved abdomen.	Unspecified	10 percent or higher was corrosive to the skin, >1% was extremely irritating to the skin and 1% was irritating to the skin. "Extremely corrosive to skin."	175

Phototoxicity

The phototoxicity of a suntan lotion containing 1% TEA was evaluated by applying the lotion to the stripped ears of six guinea pigs. A known photosensitizer was used as a positive control in four other guinea pigs. Each animal was then exposed to ultraviolet (UVA) from two GE F8T5-BL lamps at a distance of 4–6 cm for 2 h. No erythema or edema was observed in any of the guinea pigs treated with suntan lotion. Results of the positive controls are unavailable.[178]

Skin Sensitization

Pairs of guinea pigs were treated dermally with 5%–100% TEA in water for 6 h with occlusion, and the treated sites were scored for erythema at 24 and 48 h. Since use of undiluted TEA resulted in only one erythemic reaction at 24 h, 100% TEA was used in both induction and challenge procedures in the subsequent sensitization test. Twenty guinea pigs received dermal applications of undiluted TEA once per week for three weeks. A challenge patch was applied after 14 days and again seven days later. One erythemic reaction occured in each of three animals during the induction procedure, in two other animals during the first challenge, and in one other animal during the second challenge. All the guinea pigs remained healthy and made normal weight gains during the test. There was no evidence of any skin sensitizing activity of undiluted TEA for guinea pigs.[179]

TEA from four different suppliers was evaluated in guinea pig skin sensitization tests.[180-183] The tests were conducted with 10 control and 20 treated guinea pigs. The induction patches were applied once a week for up to six hours for three weeks. Two weeks later challenge patches were applied to both control and treated guinea pigs. One test was conducted with undiluted TEA at induction and 90% TEA at challenge[181] and all the other tests were conducted with 50% TEA at induction and 90% TEA at challenge.[180,182,183] None of the animals showed clinical symptoms during or after the treatment period and no guinea pigs showed signs of primary irritation of the skin. Challenge reactions were measured with a reflectometer and average readings between control and experimental animals were compared. TEA was not a guinea pig skin sensitizer in these studies.

Patches containing a 25% active TEA solution and 10% and 5% TEA in aqueous solution were applied to the backs of four clipped guinea pigs. No irritation was observed in this preliminary study. Induction patches containing the 25% TEA solution were applied to the backs of 20 clipped guinea pigs for 6 h once per week for three weeks. One week later, a challenge patch containing 25% TEA was applied for 6 h to the clipped backs of the 20 treated and 10 control guinea pigs. Challenge reactions were read at 24 h and at 48 h. No irritation was observed. No positive primary irritation or sensitization responses were observed under the test conditions with the 25 percent active TEA solution.[184]

Eye Irritation

The eye irritation potential of TEA, DEA, MEA, or cosmetic products containing the ethanolamines has been studied in rabbits[171,172,174,177,185-187] and in rhesus monkeys.[188] Data from these experiments are presented in Table 7. In high concentrations and with long contact time, TEA, and DEA may be irritating to the rabbit eye and MEA is irritating to the rabbit eye.

TABLE 7. Eye Irritation.

Material tested	*Concentration (%)*	*Method*	*No. and species of animals*	*Results*	*Ref.*
TEA, 99+ percent	100	0.1 ml of test material instilled into conjunctival sac of both rabbit eyes. Left eye unwashed. After 30 sec. exposure, right eye washed for 2 min with tap water.	Rabbits	Moderate pain and swelling in unwashed eye. Slight conjunctival irritation which subsided in 48 h. No irritation observed in the washed eye. "Slight to moderately irritating, no corneal damage likely."	171
TEA, 99+ percent	10 in water		Rabbits	Essentially no irritation observed in washed or unwashed eyes.	171
TEA	100	0.005, 0.02 ml of test material applied to corneal center while eyelids are retracted. Lids released after 1 min. Eye injury scored on a scale of 0 to 20 points after 18–24 h.	Rabbits	0.005 ml yielded a score of ≤ 5.0, 0.02 ml yielded a score of >5.0. 5.0 is the level representative of severe injury; necrosis visible after staining and covering ~75% of the surface of the cornea.	185
TEA, 98 percent	100	0.01, 0.03, 0.10 ml of test material applied directly to cornea and eyelids released immediately. Eyes scored at days 1, 3, 7, 14 and 21 by the method of Draize, et al.[193] (scale = 0 to 110).	6 rabbits at each dose level	0.01 ml gave a 0 score on all days eyes were examined. 0.03 ml gave a score of 1 on Day 1 and 0 thereafter. 0.10 ml yielded a score of 4 on Day 1, 2 on Days 3 and 7, and 0 on Days 14 and 21. The median number of days for eyes to return to normal was 1 for 0.01 and 0.03 ml and 3 for 0.10 ml.	187
TEA	100	0.1 ml of test material was placed inside the lower eyelid. Lids were held together for a few seconds. Eyes were examined at 1, 24, and 72 hours and 7 days after application. Scoring was according to the scale of Draize et al.[193] (scale = 0 to 110).	6 male rabbits	Eye irritation scores ranged from 0–10 for 24 laboratories.	172

TABLE 7. (Continued.)

Material tested	*Concentration (%)*	*Method*	*No. and species of animals*	*Results*	*Ref.*
DEA, 99+ percent	30 in water	~0.2 ml of test material was placed into the conjunctival sac of the rabbit eye and allowed to remain for 15 sec. The eye was rinsed.	6 rabbits	The material was essentially nonirritating to the eye. "Noncorrosive to eye".	174
DEA, 99+ percent	50 in water		6 rabbits	Moderate to severe conjunctival irritation and corneal injury with slight reddening of the iris was observed. The eye essentially healed in 7 days. "Severe irritant".	174
DEA	100	0.005, 0.02 ml of test material applied to corneal center while eyelids are retracted. Lids released after 1 min. Eye injury scored on a scale of 0 to 20 points after 18 to 24 hours.	Rabbits	0.005 ml yielded a score of ≤5.0, 0.02 yielded a score of >5.0. 5.0 is the level representative of severe injury; necrosis visible after staining and covering ~75 percent of the surface of the cornea.	185
MEA, 99+ percent	30 in water	~0.2 ml of test material was placed into the conjunctival sac of the rabbit eye and allowed to remain for 15 sec. The eye was rinsed.	6 rabbits	Slight discomfort, slight conjunctival irritation, and slight corneal clouding which healed in 48 hours was observed. "Moderately irritating."	177
MEA	1,5,100	0.005 ml of undiluted or diluted test material applied to corneal center while lids are retracted. Lids released after 1 min. Eye injury scored on a scale of 0 to 20 points after 18 to 24 h.	Rabbits	1% solution yielded a score ≤5.0; 5 and 100% solutions yielded scores >5.0. 5.0 is the level representative of severe injury; necrosis visible after staining and covering ~75 percent of the surface of the cornea.	185

Shampoo (TEA, 12.6%)	100 of the shampoo	0.1 ml of the shampoo was instilled into the conjunctival sac of the left eye. Held closed for 1 sec. After 15 sec, rinsed with 50 ml tap water. Eyes were examined at 24, 48, and 72 hours and at 4 and 7 days post-instillation.	6 rhesus monkeys	Slit lamp examinations at 24 h revealed edematous cornea and slight sloughing of the corneal epithelium in the treated eyes of 2 animals. At 72 h, a slight positive fluorescein staining was observed in the eye of one monkey and at Day 7, a faint, diffuse positive staining was noted in one monkey.	188
Hair preparation (DEA, 1.6%; MEA, 5.9%; sodium borate, 3.2%)	100 of the hair preparation	0.1 ml of the hair preparation was placed into the conjunctival sac of one eye. The lids were held together for 1 sec. After 30 sec, the eyes of 3 animals were washed with 20 ml of deionized water. The eyes were examined at 24, 48, and 72 hours and at 4 and 7 days and were scored according to the method of Draize et al.[193] (scale = 0 to 110).	9 rabbits	Maximum average irritation scores for both washed and unwashed eyes was 0.7.	194

Vaginal Mucosa Irritation

A spermicidal preparation containing 1.92% TEA was tested for vaginal mucosa irritation using six female rats in the same stage of estrus. A 0.5 ml volume of the ointment was placed inside the vaginas of the rats at a depth of 0.6–0.8 cm daily for three days. On the fourth day, the vaginas were exposed and examined for erythema, exudate, and edema. The researchers classified the spermicidal preparation as a nonirritant to rat vaginal mucosa.[189]

Inhalation Studies

Respiratory difficulties and some deaths in male rats resulted from the short-term inhalation of 200 ppm DEA vapor or 1400 ppm DEA aerosols. Inhalation of 25 ppm DEA for 216 continuous hours resulted in increased liver and kidney weights. A workday schedule inhalation of 6 ppm DEA for 13 weeks resulted in growth rate depression, increased lung and kidney weights, and some deaths in male rats.[164]

Weeks et al.[190] reported that the dominant effects of continuous exposure of dogs, guinea pigs, and rats to 5–6 ppm MEA vapor were skin irritation and lethargy. The inhalation of MEA vapor at concentrations of 12–26 ppm for 90 days did not result in any mortality in dogs or rodents. Some deaths did occur after 25 days in dogs exposed to 102 ppm MEA vapor, and after 24–28 days in rodents exposed to 66–75 ppm MEA vapor. Exposure to 66–102 ppm MEA vapor caused behavioral changes and produced pulmonary and hepatic inflammation, hepatic and renal damage, and hematologic changes in dogs and rodents.

Parenteral Studies

The mouse acute intraperitoneal LD50s of TEA and MEA have been reported to be 1.450 and 1.050 g/kg, respectively.[191] Blum et al.[192] determined that the mouse acute intraperitoneal LD50 of DEA was 2.3 g/kg. This level of DEA produced hepatic steatosis, cellular degeneration and swollen hepatic mitochondria in the 24 h following the injection. After 24 h, survivors were apparently normal. The livers of mice that survived over 48 h appeared to have returned to normal. Other information can be found in the literature on the intraperitoneal administration of the ethanolamines to mice and rats.[164,195,196]

SPECIAL STUDIES

Mutagenesis

The Ames assay has been used to investigate the mutagenic potential of the ethanolamines.[197] TEA, 99+ percent, with or without metabolic activation, was not mutagenic at concentrations of 0.001 to 100 mg/plate to *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538.[198] The National Toxicology Program (NTP) tested 0–3.333 mg/plate of TEA and DEA in their preincubated *Salmonella* mutagenicity assay in strains TA98, TA100, TA1535, and TA1537 with and without metabolic activation and reported both

chemicals to be negative.[199] Hedenstedt[200] tested DEA and MEA with and without metabolic activation by liver preparations from rats induced with a polychlorinated biphenyl mixture in *S. typhimurium* strains TA100 and TA1535. There was no observed increase in the number of mutants per plate with either DEA or MEA.

The mutagenicity of TEA, sodium nitrite, and a mixture of the two, with and without metabolic activation by liver S-9, was tested with *Bacillus subtilis*. Only the mixture of TEA and sodium nitrite was mutagenic to the bacteria. N-nitrosodiethanolamine (NDELA) was found in this mixture, but NDELA does not induce mutations in *B. subtilis* without metabolic activation. Some other reaction mixture product must be mutagenic and this product loses its mutagenic activity in the presence of liver enzymes.[201]

Fresh primary rat hepatocyte cultures were treated simultaneously with TEA and ^{3}H-thymidine in an unscheduled DNA synthesis test. DNA repair was quantitated by microautoradiographic evaluation of the incorporation of ^{3}H-thymidine into nuclear DNA. The concentrations of TEA tested ranged from 10^{-8}–10^{-1} *M* and three cultures were tested per concentration. The authors reported that TEA did not appear to cause DNA-damage inducible repair.[202]

Carcinogenesis

Kostrodymova et al.[165] used a total of 560 male mice, strain CBA × $C_{57}Bl_6$, in a series of three experiments to study the possible carcinogenic and cocarcinogenic effects of pure TEA, 99+ percent, and industrial TEA, 80+ percent, and the combined effect of TEA and syntanol DC-10, applied cutaneously. The experiments ran for 14–18 months, and they found no evidence of TEA carcinogenicity or cocarcinogenicity.

Hoshino and Tanooka[201] fed a diet containg 0.01%, 0.03%, or 0.3% TEA to groups of 40 ICR-JCL male and 40 ICR-JCL female mice throughout the life-span of the animals. The malignant tumor incidence in females was 2.8%, 27%, and 36%, and in males was 2.9%, 9.1%, and 3.6% for the mice fed diets containing 0.0%, 0.03%, and 0.3% TEA, respectively. Treated females showed a much higher incidence of thymic and nonthymic tumors in lymphoid tissues than treated males. The mice fed TEA in their diet survived as long as the control mice.

DEA is currently being tested in an NTP carcinogenesis bioassay program. It is being administered in drinking water to rats and mice.[199]

Teratogenesis and Reproduction Studies

Hair dyes containing 0.10%–0.15% TEA, 1.5% TEA, or 2.0% DEA were topically applied to the shaved skin of groups of 20 pregnant rats on Days 1, 4, 7, 10, 13, 16, and 19 of gestation. On Day 20, the rats were sacrificed and comparisons were made with control rats. No significant soft tissue or skeletal changes were noted in the fetuses. The mean number of corpora lutea, implantation sites, live fetuses, resorptions per pregnancy, and number of litters with resorptions were not significantly different in the dye-treated and control rats.[170]

A composite hair dye and base containing 22% MEA was given to 60 female rats at concentrations of 0 to 7800 ppm in the diet from Day 6 to 15 of gestation.

The rats were sacrificed at Day 19 and there was no evidence of any adverse effects on the rats or their pups. No differences were observed in the average number of implantation sites, live pups, early or late resorptions per litter, or females with one or more resorption sites. Thirty male rats were fed diets containing 0–7800 ppm composite for eight weeks prior to mating and during mating to 60 female rats on a basal diet. Sixty female rats were fed 0–7800 composite-containing diets eight weeks prior to mating through Day 21 of lactation. They were mated with 30 male rats on the basal diet. In both experimental designs, there were no dose-related significant differences in male and female fertility, length of gestation, number of females with resorption sites, live pups per litter, pup body weights, and pup survival. The composite hair dye and base was also administered at a dose of 0–19.5 mg/kg/day by gavage to 48 artificially inseminated female rabbits from Day 6 to 18 of gestation. The rabbits were sacrificed at Day 30. There was no evidence of any teratologic effects. Fetal survival was not adversely affected and no grossly abnormal fetuses or soft tissue defects were seen.[166]

CLINICAL ASSESSMENT OF SAFETY

Dermal Studies

Patch tests can be used to measure skin irritation and sensitization by a chemical substance in human subjects. However, caution should be exercised in the interpretation of patch tests. Patches will elicit positive reactions in cases where the test material is a primary irritant or when the human subject has been sensitized by previous contact with the chemical, either in a past patch or in the course of his daily life.[203] In addition, patch tests may elicit positive responses because the threshold irritating concentration of a chemical has decreased after repeated exposure of the skin to irritants; this would be a fatigue response. The population from which the subjects are drawn is also important. Certain skin types may be predisposed to react more intensely to chemical insult.[204]

Triethanolamine is the only ethanolamine for which human skin irritation and sensitization data are presented. The results of six patch test experiments with triethanolamine and details of those experiments are presented in Table 8. TEA produced minimal irritation in 1143 "normal" subjects and was more irritating to subjects chosen because they were "hyper reactors" to skin irritants or because they were suffering from eczema.

The cosmetic industry has conducted studies on the skin irritation, sensitization, and photosensitization of a variety of products containing the ethanolamines. Data from these unpublished experiments are presented in Table 9. There was some evidence of irritation by some products.

Inhalation Studies

MEA inhalation by humans has been reported to cause immediate allergic responses of dyspnea and asthma[205] and clinical symptoms of acute liver damage and chronic hepatitis.[169]

TABLE 8. Skin Irritation and Sensitization by Triethanolamine.

Material tested	*Concentration and dose*	*Method*	*Number of subjects*	*Results*	*Ref.*
TEA, 88.6% (DEA, 6%)	0.5 ml of 1% active TEA	24 h semiocclusive induction patches were applied on the dorsal surface of the upper arm 3 times per week for 3 weeks. 14 days later, challenge patches were applied to the same site and the other arm and these were graded at 48 and 96 h on a scale of 0–6.	64	No irritation (0) in 451 inductions. Mild irritation (1) in 420 and moderate irritation (2) in 3 inductions (includes residual reactions). 188 and 68 scores of 0 and 1 at challenge, respectively. "No sensitization."[a]	214
TEA	5%	Patch test, 1979–1980	479	9 (2%) positive reactions for contact dermatitis observed. (Sensitizing)	215
TEA	2% in water	Patch tests, 1974–1976, Marseille, France	500	23 (4.6%) positive reactions for contact dermatitis observed. (Sensitizing)	216
TEA	5% in petrolatum	Patch tests	100	2 positive reactions for allergic contact dermatitis were observed. (Sensitizing)	217
TEA	100%; 10 and 5% in ethanol	Test material applied in an aluminum chamber containing a cotton disk once daily for 3 days, after light scarification of the forearm site with a needle. Readings on a scale of 0–4 at 72 h 30 min after chamber removal.	5–10 (unspecified) caucasian "hyper reactors" (gave brisk inflammatory reaction to 24 h forearm exposure of 5% aqueous sodium lauryl sulfate in an aluminum chamber.)	100% TEA was required to produce an irritant reaction on nonscarified skin. 10% TEA was a marked irritant (2.5–4.0) and pustules were observed and 5% TEA was a slight irritant (0.5–1.4) on scarified skin.	218
TEA	5%, 1% in eucerin with water	24 h patch tests. Readings after 24 and 48 h.	22 subjects suffering from different types of eczemas	4 and 3 positive reactions to 5% and 1% TEA, respectively. (Irritating)	219

[a]Conclusions of the researchers are in quotations. Interpretations of the Expert Panel are in parentheses.

TABLE 9. Skin Irritation, Sensitization, Phototoxicity, and Photosensitization by Products Containing the Ethanolamines.

Material tested	*Concentration and dose*	*Method*	*Number of subjects*	*Results*	*Ref.*
Shaving preparation (TEA, 4.2%)	100%	2 24-hour patches applied 10 to 14 days apart on the same site.[203] Simultaneous closed patch on back and open patch on arm. Scoring scale was + to + + +.[220] Additionally, there was UV exposure of the second patch.	508	46 weak (nonvesicular) (+) reactions to the first closed patch, 42 + and 7 strong (edematous or vesicular) (+ +) reactions to the second closed patch. 67 + reactions after UV (Hanovia Tanette Mark 1 lamp, 360 nm at 12 in for 1 min) exposure of the second patch. "Nonirritating." (Irritating. Either mildly phototoxic or UV enhancement of an irritation response).[a]	222
Shaving preparation (TEA, 4.2%)	100%	10 24-hour induction patches with 24-hour recuperative periods in between. After 2 to 3 weeks rest, a 48-hour challenge patch (modification of Ref. 221). Simultaneous closed patch on back and open patch on arm. Scoring scale was + to + + +.[220] Additionally, there was UV exposure of induction patches 1,4,7, and 10, and the challenge patch.	260	Between 31 and 64 + reactions were observed to closed induction patches 1 through 10. 1,3,3,4, and 4 strong + + reactions to closed induction 60 + and 2 + + reactions to the closed challenge patch. Following UV (Hanovia Tanette Mark 1 lamp, 360 nm at 12 inches for 1 min.) exposure, 7,6,1,4, and 8 + reactions were observed at induction patches 1,4,7, and 10, and the challenge patch, respectively. "Nonsensitizing and nonphotosensitizing." (Irritating)	222
Shaving preparation (TEA, 4.2%)	Normal use	Used on the face for 4 weeks and scored each week.	52 male	No reactions were observed. "Nonirritating."	223
Sun cream (TEA, 3.75%)	100%, ~0.1 ml	24-hour occlusive induction patches applied to the upper back 3 times a week for 3 weeks. After 2 weeks rest, a 24-hour occlusive challenge patch was applied to a previously unpatched site. Reactions were scored 24 and 48 hours after patch removal on a scale of 0 to 4.	48	1 barely perceptible (±) reaction; minimal faint (light pink) uniform or spotty erythema at induction patch 2. "No potential for inducing allergic sensitization."	186

Shaving cream (TEA, 3.3%)	100%	12-hour occlusive induction patches applied to the medial surface of the upper arm 4 times a week for 2 weeks and scored at patch removal on a scale of 0 to 4. After 2 weeks rest, a 24-hour occlusive challenge patch was applied. Reactions were scored at 24, 48, and 72 hours.	54	5, 16, and 14 very slight erythema (±), slight erythema (1), and well defined erythema (2) reactions, respectively, were observed to the 8 induction patches. Number of positive reactions increased with each induction. No reactions to the challenge patch. (Irritating)	224
Shaving cream (TEA, 3.3%)	100%		57	104, 36, 5, and 2 slight erythema (1), moderate erythema (2), severe erythema (3), and edema with or without erythema (4) reactions, respectively, were observed to the 8 induction patches. Number of positive reactions generally increased with each induction. 6 1+ and 1 2+ reactions were observed on challenge at 24 hours. At 48 hours, 4 1+ and 1 2+ reactions were observed, and at 72 hours, 2 1+ reactions were observed. (Irritating)	225
Shaving cream (TEA, 2.6%)	100%		51	27 slight erythema (1) and 1 moderate erythema (2) reactions were observed to the 8 induction patches. 1 1+ reaction was observed on challenge at 24 hours. (Mildly Irritating)	226
Mascara formulation (TEA, 2.1%)	100%, 0.2 ml	23-hour patches applied to the back every day for 21 days. Reactions were scored daily on a scale of 0 to 4.	15	7, 42, 2, and 3 questionable erythema (±), erythema (1), erythema and papules (2), and erythema, papules, vesicles, and possibly edema (3) reactions, respectively, to the 21 patches. (Irritating)	227
Mascara formulation (TEA, 2.1%)	100%, 0.2 ml		15	5, 54, and 6 ±, 1, and 2 reactions, respectively, to the 21 patches. (Irritating)	227
Mascara formulation (TEA, 2.1%)	100%	1 48-hour occluded patch was applied to the arm or back; 24-hour aqueous sodium lauryl sulfate occluded patch on arm or back, then 5 alternate day 48-hour occluded patches of the test material. After a 10-day rest, 5-10 percent sodium lauryl sulfate was applied to another test site for 1 hour and followed by a 48-hour occluded patch of the test material. Reactions were observed at patch removal and 24 hours later.	25	No reactions observed to challenge. "No sensitization."	228
Mascara formulation (TEA, 2.1%)	100%		25	No reactions observed to challenge. "No sensitization."	229

TABLE 9. (Continued.)

Material tested	*Concentration and dose*	*Method*	*Number of subjects*	*Results*	*Ref.*
Suntan lotion (TEA, 1.0%)	100%	48-hour occlusive induction patches were applied 3 times a week for a total of 10 times. Patches 1,5,6, and 7 were on the left shoulder, the others on the right. The sites were scored 24 to 48 hours after patch removal. After 8 days rest, a challenge patch was applied to a virgin back site and scored 24 hours after patch removal. The skin sites where patches 1,4,7, and 10 and the challenge patch had been were exposed to UV light (Hanovia Tanette Mark I Lamp) at a distance of 12 inches for 1 min and scored 48 hours later.	26 female	No reactions observed. "Not a photo-toxicant."	230
Mascara (TEA, 20.04%)	100%, ~0.1 ml/cm²	2 times/week for 3 weeks, duplicate 24-hour occlusive induction patches applied to the back. Then, one site and a control site (no test product) irradiated with 3 times the individual's "minimal erythema dose" (MED) using a Xenon arc solar simulator (290–400 nm). 48 hours later, both sites were read. There was a 10-day rest and then, duplicate challenge patches were applied at fresh sites. 24 hours later one site and a control site exposed to 3 min. of irradiation from the solar simulator (Schott W345 filter). Sites graded at 15, 24, 48, and 72 hours after light exposure.	26 female	2 slight reactions upon challenge to test product alone. One doubtful and one erythema reaction before irradiation. "No sensitization." (Irritation)	231
Mascara (TEA, 2.8%)	100%, ~0.1 ml/cm²		23	No reactions observed. "Not phototoxic or photoallergenic."	232

Skin lotion (TEA, 0.83%)	100%, ~0.2 ml	Sites on both forearms were tape-stripped several times. Duplicate 24-hour occlusive patches applied to each forearm. Then, one site irradiated with UV light for 15 min. at a distance of ~10 cm (~4,400 μW/cm^2 UVA). Sites scored after patch removal, after irradiation, and 24 and 48 hours after irradiation. Examined for tanning after 1 week. Scored on a scale of 0–4.	10	One subject had minimal erythema (±) at both sites at all readings except for the irradiated site at the 24-hour before and after irradiation readings. Another subject had minimal erythema (±) at the irradiated site at the 72-hour reading. No tanning was observed. "Not phototoxic." (Irritating)	233
Skin lotion (TEA, 0.83%)	100%, ~0.2 ml		10	One subject had minimal erythema (±) at both sites at all readings. Another subject had minimal erythema (±) at the irradiated site at the 48- and 72-hour readings. No tanning was observed. "Not phototoxic." (Irritating)	234
Skin lotion (TEA, 0.83%)	100%, ~0.2 ml	24-hour occlusive induction patches were applied 3 times a week to both forearms for a total of 10 times. At the end of 24 hours the sites were scored and 1 site was irradiated with nonerythrogenic UV radiation for 15 min. at a distance of 10 cm (~4,400 μW/cm^2 UVA) and then scored again. After 10 to 14 days rest, challenge patches were applied to virgin adjacent sites. 24 hours later, the sites were scored, 1 site was irradiated and scored. The challenge sites were also read 48 and 72 hours later. Scored on a scale of 0–4.	30	Among 300 induction readings for the nonirradiated sites, there were 13 minimal erythema (±) and 2 erythema (1) readings. There was 1 minimal erythema (±) challenge reading at 48 hours. Among 600 induction readings for the irradiated sites, there were 8 and 9 minimal erythema (±) readings before and after irradiation, respectively, and 4 erythema (1) readings after irradiation. There was 1 minimal erythema (±) reading after irradiation at 24 hours. "Does not induce photoallergy or contact allergy." (Irritating)	235
Skin lotion (TEA, 0.83%)	100%, ~0.2 ml		30	Among 300 induction readings for the nonirradiated sites, there were 15 minimal erythema (±) and 3 erythema (1) readings. There were 2 minimal erythema (±) challenge readings, one at 24 and one at 48 hours. Among 600 inductions for the irradiated sites, there were 7 and 10 minimal erythema (±) readings before and after irradiation, respectively, and 5 erythema (1) readings after irradiation. There was one erythema reading (1) after irradiation at 24 hours. "Does not induce photoallergy or contact allergy." (Irritating)	236

TABLE 9. (Continued.)

Material tested	*Concentration and dose*	*Method*	*Number of subjects*	*Results*	*Ref.*
Shaving cream (TEA, 2.1%)	100%	10 48- to 72-hour occlusive induction patch applications to the same site, readings before the application of the succeeding patch, followed by a rest period of about 3 weeks and then a final challenge patch on a fresh site. Modified Draize test.[193]	104	Among 1040 induction readings, there were 172 ± readings, 11 (1) readings and one (3) reading. There were 16 (?) challenge readings. (Irritating)	237
Shaving cream (TEA, 2.4%)	100%	9 8-hour "semi-open" induction applications, scored 48 to 72 hours later just before application of the next patch, a 2-week rest followed by challenge patches scored at 48 and 96 hours after application. Challenge patches were applied to the original and to virgin sites. Reactions were scored on a scale of 0–6.	76	Among 684 induction readings there were 231, 83, and 1 reaction of (1) (slight erythema), (2) (marked erythema) and (3) (erythema and papules), respectively. There were 28 (1), 4 (2), and 3 (E) (erythema and possibly also edema) reactions upon challenge at the original site and 23 (1) reactions at the virgin site among 304 challenge readings. "Moderately irritating following initial and repeated application. Very little cumulative irritation. No evidence of sensitization." (Sensitizing)	238
Shaving cream (TEA, 2.1%)	100%		76	Among 684 induction readings there were 222 and 101 reactions of (1) and (2), respectively. Among 304 challenge readings there were 33, 13, and 2 reactions of (1), (2), and (E), respectively, at the original site and 20, 2, and 1 reactions of (1), (2) and (E), respectively, at the virgin site. "Moderately irritating following initial and repeated application. Very little cumulative irritation. No evidence of sensitization." (Sensitizing)	238

Shaving cream (TEA, 2.1%)	100% 0.5 ml	9 24-hour "semi-open" patch induction applications scored 48 to 72 hours later just before application of the next patch a 2-week rest followed by challenge patches scored at 48 and 96 hours after application. Challenge patches were applied to original and virgin sites. Reactions were scored on a scale of 0–6.	63	Among 567 induction readings, there were 106, 4, 2, and 4 reactions of 1, 2, 3 and 4 (erythema, edema, and papules), respectively. Among 252 challenge readings there were 28, 6, 1, 9, and 1 reactions of 1, 2, 3, 4, and 6 (strong reaction spreading beyond test site), respectively, at the original site and 9, 4, and 2 reactions of 1, 2, and 3, respectively, at the virgin site. Slight irritation resulted from initial application and increases in irritation were observed following repeated application. Several moderately strong reactions were observed when challenge sites were scored at 48 hours but in all cases, there was marked remission of reaction severity when scored at 96 hour. "Proably skin fatigue."	239
Shaving cream (TEA, 2.1%)	100%, 0.5 ml		63	Among 567 induction readings, there were 144, 20, 8, and 12 reactions of 1, 2, 3, and 4, respectively. Among 252 challenge readings, there were 42, 8, 5, 19, and 1 reactions of 1, 2, 3, 4, and 6, respectively, at the original site and 19, 8, and 2 reactions of 1, 2, and 4, respectively, at the virgin site. Slight irritation resulted from initial application and increases in irritation were observed following repeated application. Several moderately strong reactions were observed when challenge sites were scored at 48 hours but in all cases, there was marked remission of reaction severity when scored at 96 hours. "Probably skin fatigue."	239

TABLE 9. (Continued.)

Material tested	Concentration and dose	Method	Number of subjects	Results	Ref.
Shaving cream (TEA, 2.1%)	100%, 0.5 ml		63	Among 567 induction readings, there were 131, 23, 2, and 14 reactions of 1, 2, 3, and 4, respectively. Among 252 challenge readings, there were 34, 16, 6, 18, and 1 reactions of 1, 2, 3, 4, and 6 respectively, and 19, 5, 1, and 1 reactions of 1, 2, 3, and 4, respectively, at the virgin site. Slight irritation resulted from initial application and increases in irritation were observed following repeated application. Several moderately strong reactions were observed when challenge sites were scored at 48 hours but in all cases, there was marked remission of reaction severity when scored at 96 hours. "Probably skin fatigue."	239
Shaving cream (TEA, 2.1%)	100%	Every other day for a total of 20 days (10 open-patch applications) a 1 in. square of gauze was dipped in sample and applied to the subjects' arm (the same site was used each time). 24 hours after application the sites were scored. A 10-day rest was followed by a challenge open patch which was observed 24 and 48 hours later. Reactions were scored on a scale of +1 to +4.	60	Among 600 induction and 120 challenge readings, there were no reactions. "Short-lived acute irritation, no sensitization."	240
Shaving cream (TEA, 2.6%)	100%		60	Among 600 induction readings there were 5 (1+) (mild erythema) reactions. There were no challenge reactions. "Short-lived acute irritation, no sensitization."	240
Shaving cream (TEA, 2.1%)	100%		60	Among 600 induction readings there were 5 (1+) reactions. There were no challenge reactions. "Short-lived acute irritation, no sensitization."	240
Shaving cream (TEA, 2.1%)	100%		60	Among 600 induction readings, there were 3 (1+) reactions. There were no challenge reactions. "Short-lived acute irritation, no sensitization."	240
Shaving cream (TEA, 1.9%)	100%		60	Among 600 induction readings, there was 1 (1+) reaction. There were no challenge reactions. "Short-lived acute irritation, no sensitization."	240

Shaving cream (TEA, 2.3%)	100%		60	Among 600 induction readings there were 2 (1+) reactions. There were no challenge reactions. "Short-lived acute irritation, no sensitization."	240
Sunscreen product (TEA, 0.45%)	100%, ~0.2 g	10 24-hour occlusive patch applications with 24- to 48-hour rest periods in between. Sites scored just prior to next patch application. An 11- to 15-day rest followed by a 24-hour challenge patch on a virgin site. Sites scored at 24 and 48 hours after application. Scored on a scale of 0–4.	52	Among 520 induction readings, there were 7 ± (minimal erythema) scores. Among 104 challenge readings, there were 2 ± scores. "No irritation or sensitization."	241
Sunscreen product (TEA, 0.45%)	100%, ~0.2 g	Forearms were tape-stripped to remove cornified epithelium. 24-hour occlusive patch applications to both arms, patches removed, sites scored, and one site subjected to 15 minutes of UV light (~4,400 $\mu W/cm^2$ UVA) at a distance of 10 cm and rescored. Additional readings were made 48 and 96 hours after application. Scored on a scale of 0–4.	10	There was 1 ± reaction at 24 hours and 1 ± reaction at another site after irradiation at 24 hours. "No phototoxic response."	241
Sunscreen product (TEA, 0.45%)	100%, ~0.2 g	10 24-hour occlusive patch applications to both arms with 24- to 48-hour rest periods in between. Sites scored at patch removal and then irradiated for 15 min at a distance of 10 cm (~4,400 $\mu W/cm^2$ UVA) and re-scored. An 11- to 15-day rest period, 24-hour challenges to virgin sites, patches removed and sites scored, irradiated, scored again and scored 24 and 48 hours later. Scored on a scale of 0–4.	26	Among 260 induction readings of the non-irradiated site, there were 5 ± scores. Among 78 challenge readings, there were 3 ± scores. Among 520 induction readings of the irradiated site there were 5 ± scores before and 5 ± scores after irradiation. Among 104 challenge readings, there were 2 ± scores. "No photoallergic response."	241
Shaving cream (TEA, 2.4%)	100%, ~0.1 ml/cm^2	10 48- to 72-hour nonocclusive induction patch applications. Sites scored at patch removal. 10th patch also scored 24 hours later, 11-day rest period, followed by a 48-hour challenge patch to a virgin site. Challenge site scored at patch removal and 24 hours later.	100	Among 1100 induction readings, there were 2 (doubtful reaction, very mild erythema, barely exceeding that of the untreated skin) reactions. There were no challenge reactions. "No irritation or sensitization."	242
Shaving cream (TEA, 2.1%)	100%, ~0.1 ml/cm^2		100	Among 1100 induction and 200 challenge readings, there were no reactions. "No irritation or sensitization."	242

TABLE 9. (Continued.)

Material tested	*Concentration and dose*	*Method*	*Number of subjects*	*Results*	*Ref.*
Dyeless Base Formulation (DEA, 2%), non-commercial product	0.3 ml, 10% in distilled water	24-hour semioccclusive patches applied to upper arm 3 times a week for 3 weeks. Scored 24 to 48 hours after patch removal. Challenge patches on the same site and a virgin site after 15 to 17 days. Challenges scored at 24 and 72 hours after patch removal on a scale of 0 to 5.	165	No reactions observed. "No contact sensitization."	243
Shave gel (DEA, 2.7%)	100%, ~0.1 ml/cm^2	10 48- to 72-hour nonocclusive induction patch applications. Sites scored at patch removal. 10th patch also scored 24 hours later, 11-day rest period, followed by a 48-hour challenge patch to a virgin site. Challenge site scored at patch removal and 24 hours later.	100	Among 1100 induction readings, there were 2 (doubtful reaction, very mild erythema, barely exceeding that of the untreated skin) reactions. There were no challenge reactions. "No irritation or sensitization."	242
Dyeless Base Formulation (MEA, 11.47%), non-commercial product	0.3 ml, 5% in 25% alcohol	24-hour semiocclusive patches applied to upper arm 3 times a week for 3 weeks. Scored 24 to 48 hours after patch removal. Challenge patches on the same site and a virgin site after 15 to 17 days. Challenges scored at 24 and 72 hours after patch removal on a scale of 0 to 5.	165	19, 1, 1, and 1 scores of mild erythema (1), definite papular response (2), definite edema (3), and definite edema and papules (4), respectively, during induction. No reactions observed at challenge. "No contact sensitization." (Irritating)	243
Hair preparation (DEA, 1.6%; MEA, 5.9%; sodium borate, 3.2%)	~0.2 ml, 100%	23-hour patches applied to the back every day for 21 days. Reactions were scored daily on a scale of 0 to 7.	12 female	4,3, and 225 scores of minimal erythema, barely perceptible (1), definite erythema, readily visible (2), erythema and papules (3). "Experimental cumulative irritant."	244
Hair preparation (DEA, 1.6%; MEA, 5.9%; sodium borate, 3.2%)	0.3 ml, 100%	48-hour occluded patch on the forearm; 5 48-hour occluded induction patches, a 10-day rest, then a 48-hour occluded challenge patch. Reactions scored at patch removal and 24 hours later on a scale of 0 to 3.	25	Test material was irritating during a pre-test. No reactions observed during the induction and challenge procedures. "No contact sensitization."	245

[a]Conclusions of the researchers are in quotations. Interpretations of the Expert Panel are in parentheses.

An eight-year-old female developed a nasal allergic reaction to a detergent containing TEA. The prick test was positive for 10^{-7}–10^{-4} *M* TEA and not for any of the other ingredients in the product. Sneezing was relieved after removal of the detergent from the clothes by extensive washing and recurred upon re-exposure.[206]

Potential hazards from inhalation of TEA and DEA are probably minimized by their low vapor pressures.[10]

Occupational Exposure

Information on vascular, neurologic, and hepatic disorders and respiratory and skin allergies of people who come in contact with the ethanolamines in their work environment can be found in the literature.[207-213]

SUMMARY

TEA, DEA, and MEA are amino alcohols and as such, are chemically bifunctional, combining the properties of alcohols and amines. The pHs of 0.1 N aqueous solutions of TEA, DEA, and MEA are 10.5, 11.0, and 12.05, respectively. Ethanolamine soaps and ethanolamides are used in cosmetic formulations as emulsifiers, thickeners, wetting agents, detergents, and alkalizing agents. In 1981, TEA, DEA, and MEA were reported to be ingredients of 2757, 18, and 51 cosmetic products, respectively. Most products contained TEA, DEA, and MEA in concentrations less than or equal to 5%. The nitrosation of the ethanolamines may result in the formation of N-nitrosodiethanolamine (NDELA) which is carcinogenic in laboratory animals. Traces of NDELA (below 5 ppm) have been found in a variety of cosmetic products.

The LD50 values for rats of TEA, DEA, and MEA ranged from 4.19 g/kg to 11.26 g/kg, 0.71 ml/kg to 2.83 g/kg, and 1.72 g/kg to 2.74 g/kg, respectively. In single-dose oral toxicity for rats, TEA is practically nontoxic to slightly toxic, and DEA and MEA are slightly toxic. Long-term oral ingestion of the ethanolamines by rats and guinea pigs produced lesions limited mainly to the liver and kidney. Long-term cutaneous applications to animals of the ethanolamines also produced evidence of hepatic and renal damage. TEA and DEA showed little potential for rabbit skin irritation in acute and subchronic skin irritation tests. MEA was corrosive to rabbit skin at a 30% concentration in a single semioccluded patch application and at a greater than 10% concentration in 10 open applications over a period of 14 days. A lotion containing 1% TEA was not phototoxic to guinea pigs, and TEA was not a guinea pig skin sensitizer. With long contact time TEA, DEA, and MEA are irritating to the rabbit eye at concentrations of 100%, 50%, and 5%, respectively.

The ethanolamines have been shown to be nonmutagenic in the Ames test and TEA is also nonmutagenic to *Bacillus subtilis*. TEA did not cause DNA-damage inducible repair in an unscheduled DNA synthesis test.

TEA had no carcinogenic or cocarcinogenic activity when dermally applied to mice for 18 months. There was a higher incidence of malignant lymphoid tumors in female mice fed diets containing TEA for their whole lifespan than in male mice on the same diet or in control mice.

Clinical skin testing of TEA and cosmetic products containing TEA and DEA showed mild skin irritation in concentrations above 5%. There was very little skin sensitization. There was no phototoxicity and photosensitization reactions with products containing up to 20.04% TEA. A dyeless base formulation containing 11.47% MEA and a hair preparation containing 1.6% DEA and 5.9% MEA were irritating to human skin in patch tests.

COMMENTS

In the presence of N-nitrosating agents, TEA and DEA may give rise to N-nitrosodiethanolamine, a known animal carcinogen.

TEA and DEA are mild skin and eye irritants and irritation increases with increasing ingredient concentration.

Animal studies with MEA indicate that it is both a skin and eye irritant and clinical studies with formulations containing MEA indicate that it is a human skin irritant. The longer MEA stays in contact with the skin the greater the likelihood of irritation. MEA is primarily used in rinse-off hair products.

CONCLUSION

The Panel concludes that TEA, DEA, and MEA are safe for use in cosmetic 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, the concentration of ethanolamines should not exceed 5%. MEA should be used only in rinse-off products. TEA and DEA should not be used in products containing N-nitrosating agents.

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