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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

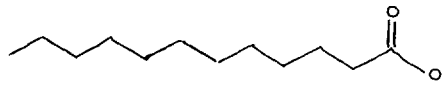
Lauric, Myristic, Palmitic, and Stearic Acids are saturated fatty acids of 12-, 14-, 16-, and 18-carbon lengths. Oleic Acid is an 18-carbon *cis*-mono unsaturated fatty acid. These fatty acids consist of long hydrocarbon chains with a terminal carboxyl group. Synonyms for the fatty acids (Table 1) were 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

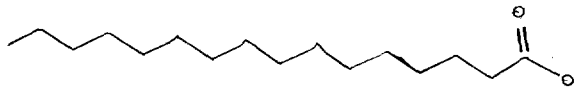
OLEIC ACID

$C_{18}H_{34}O_2$



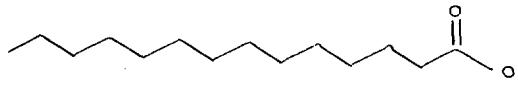
LAURIC ACID

$C_{12}H_{24}O_2$



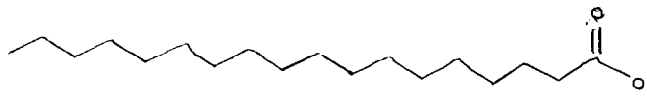
PALMITIC ACID

$C_{16}H_{32}O_2$



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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