2

Final Report on the Safety Assessment of Octyl Palmitate, Cetyl Palmitate and Isopropyl Palmitate

The Palmitates used in cosmetic products are esters of palmitic acid and octyl, cetyl, or isopropyl alcohol. The acute oral LD50 is estimated from studies with rats to be greater than 14.4 g/kg for Cetyl Palmitate and greater than 64.0 g/kg for Octyl and Isopropyl Palmitates. Acute studies with rabbits showed no evidence of dermal toxicity for any of the Palmitates. Isopropyl Palmitate was "well tolerated" and Octyl Palmitate was nontoxic in separate subchronic dermal studies.

Rabbit skin tests with the Palmitates showed that they are nonirritating and nonsensitizing. Also, Draize rabbit eye irritation tests on the Palmitates produced either no or only very slight ocular irritation.

One of three formulations containing Octyl Palmitate at concentrations between 40% and 50% produced mild irritation. Formulations containing Cetyl Palmitate at concentration of 2.7% were minimally irritating and produced no signs of sensitization, phototoxicity, or photo contact allergenicity. A formulation containing 45.6% Isopropyl Palmitate produced no signs of irritation, sensitization, phototoxicity, or photo contact allergenicity.

From the available information, it is concluded that Octyl Palmitate, Cetyl Palmitate, and Isopropyl Palmitate are safe as cosmetic ingredients in the present practices of use and concentration.

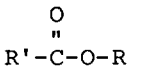
CHEMICAL AND PHYSICAL PROPERTIES

The Palmitates are esters of palmitic acid which conform to the general formula:

$$CH_3(CH_2)_{14}\overset{O}{\overset{\|}{C}}-O-R$$

where R represents the alkyl moiety of Octyl, Cetyl, or Isopropyl alcohol.

Because of the technical quality of the palmitic acid and of the alcohols used as industrial starting materials (see Impurities section), the commercially available Palmitates are mixtures of esters conforming to the formula:

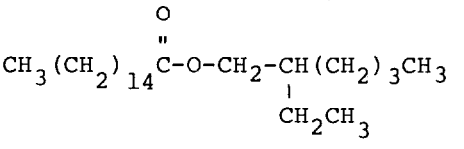


where R represents the alkyl moiety of one of the aforementioned alcohols, and R' represents the acyl moiety of palmitic acid.

Commercial production methods for most of the Palmitates are considered proprietary information. However, a description of the method of manufacturing a palmitate which is not included in this report[1] may also apply to those which are so included. According to this description, Palmitates may be prepared by esterifying the appropriate alcohol with palmitic acid in the presence of approximately 0.1% sulfuric acid. The reaction is performed under reduced pressure, so that the formed water is removed. When this process is completed, the catalyst is neutralized with sodium hydroxide and removed by several water washes.

Another ester-yielding reaction which is described in the literature and used in industry is transesterification.[2]

Octyl Palmitate: Octyl Palmitate is the ester of 2-ethylhexyl alcohol and palmitic acid. It conforms to the formula:[3]



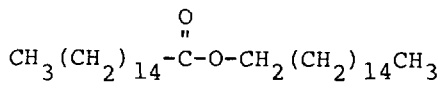
This ingredient is a clear, colorless, practically odorless liquid. It is soluble in acetone, castor oil, corn oil, chloroform, ethanol, and mineral oil and insoluble in water, glycerin, and propylene glycol.[4] The available chemical and physical parameters of Octyl Palmitate are listed in Table 1.

TABLE 1. Chemical and Physical Parameters of the Palmitates.[a]

Palmitate	*Mol. wt.*	*M.P.*	*Sp. Gr.*	*Refr. Ind.*	*Ester value*	*Acid value (max.)*	*Iodine value* (max.)
Octyl	388[b]	–[c]	0.850 to 0.865 @25°C	1.445 to 1.4465 @25°C	146 to 156	3.0	1.0
Cetyl	481[b]	46°C to 54°C	0.832[b] @25°C	1.4398[b] n_D70	106 to 120	4.0	1.0
Isopropyl	318[b]	11°C	0.850 to 0.855 @25°C	1.4355 to 1.4375 @25°C	182.0 to 191.0	1.0	1.0

[a]Data from Refs. 4, 5, and 21–27.
[b]Pure compound.
[c]No data.

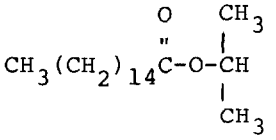
Cetyl Palmitate: Cetyl Palmitate is the ester of cetyl alcohol and palmitic acid. It conforms to the formula:[3]



Cetyl Palmitate is the chief constituent of commercial purified spermaceti.[5] It occurs naturally at a concentration of 0.25–0.5 percent in staghorn coral[6] and is biosynthesized by a particular paraffin-oxidizing strain of mycobacterium.[7]

It is a white, crystalline, wax-like substance which is soluble in alcohol and ether and insoluble in water.[5] Many reports are available concerning the physical chemistry of Cetyl Palmitate in crystalline and liquid states.[8-20] The available chemical and physical parameters of this ingredient are listed in Table 1.

Isopropyl Palmitate: Isopropyl Palmitate is the ester of isopropyl alcohol and palmitic acid. It conforms to the formula:[3]



As used in cosmetics, the product is a colorless, almost odorless, mobile liquid mixture of isopropyl esters consisting of a minimum of 60% Isopropyl Palmitate and lesser amounts of isopropyl laurate, myristate, pentadecanoate, heptadecanoate, and stearate. The ingredient is soluble in acetone, castor oil, chloroform, cottonseed oil, ethyl acetate, ethanol, and mineral oil; it is insoluble in water, glycerin, and propylene glycol.[21,22] One study has explored the crystalline structure of purified Isopropyl Palmitate.[20] The available chemical and physical parameters of Isopropyl Palmitate may be found in Table 1.

Reactivity

No specific information on the reactivity of these compounds was found. However, they can be expected to undergo chemical or enzymatic hydrolysis to palmitic acid and the corresponding alcohol.

Transesterification and other typical ester reactions may also occur. All of these esters are saturated compounds and would not be expected to autoxidize readily.

Analytical Methods

Octyl Palmitate: No specific methods for analysis of Octyl Palmitate were found. As is the case with other Palmitates, however, thin-layer and gas–liquid chromatographies and infrared spectrophotometry techniques would be applicable.

Cetyl Palmitate: Cetyl Palmitate was isolated as a component of spermaceti by high-temperature gas chromatography on a 10% silicone elastomer E301 column. The qualitative composition of spermaceti was determined by thin-layer chromatography. The alkyl ester content was determined by preparative-layer chromatography, and an isolated fraction was identified by infrared spectroscopy.[28]

Cetyl Palmitate was also qualitatively determined by thin-layer chromatography using silica plates which contained polyvinyl alcohol. Petroleum ether and 8:2:1 cyclohexane-Et_2O-AcOH were used successively as solvents. An intense violet color was developed by spraying the chromatogram successively with a saturated solution of iodine in petroleum ether and water.[29] Another chromatographic technique involves the use of a silicic acid-impregnated glass-fiber filter paper. Such a method was used to separate Cetyl Palmitate from marine-animal oils.[30]

Isopropyl Palmitate: Isopropyl Palmitate has been determined by gas–liquid chromatography. Triton X-450 on Fluoroport T and Carbowax 20M on Fluoroport T columns were used for separating the various ingredients of a lipstick that contained Isopropyl Palmitate. Interfering hydrocarbons were removed by column chromatography prior to the GLC analysis.[31]

Impurities

The Palmitates used as cosmetic ingredients are mixtures of fatty esters, since the palmitic acid which serves as a starting material is itself a mixture of acids and the alcohols used are mixtures of alcohols.

The CTFA Cosmetic Ingredient Chemical Description for palmitic acid lists the following as component acids:[32]

Palmitic Acid	80% min.
Stearic Acid	11% max.
Myristic Acid	7% max.
Heptadecanoic Acid	4.5% max.
Pentadecanoic Acid	1% max.

The CTFA Specification for palmitic acid also includes:[33]

Lauric Acid	1.3% max.
Oleic Acid	0.4% max.
Palmitoleic Acid	0.4% max.
Eicosanoic Acid	Trace (<0.05%)
Myristoleic Acid	Trace (<0.05%)

Palmitic acid may contain unsaponifiable material, mostly hydrocarbons, at a maximum concentration of 0.3%, and some grades may contain glyceryl monopalmitate at a maximum concentration of 0.07%. Butylated hydroxytoluene (BHT) may be present as an added antioxidant.[32]

Thus, the Palmitates used as cosmetic ingredients may be mixtures of compounds. For example, the CTFA Specification for Isopropyl Palmitate indicates that it consists of a minimum of 60% Isopropyl Palmitate and lesser amounts of isopropyl laurate, myristate, pentadecanoate, heptadecanoate, and stearate.[21]

Octyl Palmitate: Free fatty acids, mainly palmitic acid, are present at a maximum concentration of 1.4%. No known diluents, solvents, or additives are present.[26]

Cetyl Palmitate: Free fatty acids, mainly palmitic acid, are present at a maximum concentration of 1.8%. No known diluents, solvents, or additives are present.[23]

One manufacturer stated that the Cetyl Palmitate used in a particular skin

moisturizer formulation contains at least 90% Cetyl Palmitate, with the remaining material consisting predominantly of cetyl stearate.[23]

The CTFA Specification for cetyl alcohol includes the following impurities:[34]

Hydrocarbons	1.5% max.
Ash	0.05% max.
Lead (as Pb)	20 ppm max.
Arsenic (as As)	3 ppm max.

Isopropyl Palmitate: No known nonester impurities, diluents, solvents, or additives are present.[25]

The ester composition is varied according to the requirements of an ingredient's specific intended usage. However, such specifications must conform to the following limits.[21]

Isopropyl Palmitate:

Not less than 65.0%
(limits: ± 5.0%)

Isopropyl Stearate:

Not more than 35.0%
(limits: ± 5.0%)

Isopropyl Laurate, Myristate, Pentadecanoate, and Heptadecanoate:

None more than 35.0%
(limits: ± 2.0% each)

USE

Purpose in Cosmetics

The Palmitates have a wide spectrum of uses in cosmetic products. All are liquids except the cetyl derivative; they serve as emollients with such specific secondary functions as those of a solvent, plasticizing agent, and/or glossing agent.[2] The Palmitates are efficient opacifiers in cream and lotion shampoos.[35]

Octyl Palmitate: The only specific mention in the literature of the purpose of Octyl Palmitate in cosmetics is that it serves as an emollient.[36]

Cetyl Palmitate: Cetyl Palmitate not only functions as an emollient, but it also contributes a specific body and texture to the majority of cream and lotion products.[2] It functions as a base for ointments, cerates, and emulsions. It is also used in the manufacture of candles, soaps, etc.[5]

Isopropyl Palmitate: Isopropyl Palmitate functions as a physical stabilizer in antiperspirant sticks.[37] It also functions as an emollient, emulsifier, film former, spreader, and solvent in creams, lotions, and eye makeup.[5,36,38,39] It is suggested for use in alcohol hair lotions and aftershave preparations.[22] Three publications specifically discuss the use of Isopropyl Palmitate in cosmetics.[40-42]

Scope and Extent of Use in Cosmetics

Table 2 lists product types and the number of product formulations reported for each preset concentration range.[43] The cosmetic product formulation computer printout which is made available by the Food and Drug Administration (FDA) is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations (1979). Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the true, effective concentration found in the finished product; the effective concentration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration.

The concentrations that are used range to greater than 50% for Octyl and Isopropyl Palmitate, but to only 10% for Cetyl Palmitate. While these ingredients are most commonly used in the >1 to 5% concentration range, Isopropyl Palmitate is also frequently employed in the >25 to 50% range.

The Palmitates are employed in formulations applied to all those areas of the human integument that are in contact with or in close proximity to all body orifices. They are widely used in lipstick formulations and in products applied close to the eye.

Formulations containing the Palmitates may be applied several times a day and may remain in contact with the skin for variable periods of time following each application. Daily or occasional use may extend over many years.

TABLE 2. Product Formulation Data.[a]

Ingredient/ Cosmetic product type	*Concentration (%)*	*No. of product formulations*
Octyl Palmitate		
Bath oils, tablets, and salts	>5–10	1
	>1–5	6
Eyeshadow	>25–50	2
	>5–10	3
	>1–5	19
Eye makeup remover	>50	1
Other eye makeup preparations	>50	1
	>25–50	1
Perfumes	>50	1
	>1–5	2
Powders (dusting and talcum) (excluding aftershave talc)	>0.1–1	3
Other fragrance preparations	>1–5	1
Blushers (all types)	>50	2
	>25–50	1
	>10–25	2
	>5–10	6
	>1–5	3

TABLE 2. (Continued.)

Ingredient/ Cosmetic product type	*Concentration (%)*	*No. of product formulations*
Face powders	>5–10	5
	>1–5	9
Foundations	>1–5	8
	≤0.1	1
Lipstick	>5–10	11
	>1–5	40
Makeup bases	>1–5	8
Other makeup preparations	>1–5	1
Other personal cleanliness products	>1–5	2
	>0.1–1	1
Aftershave lotions	>1–5	1
Preshave lotions (all types)	>1–5	2
Cleansing (cold creams, cleansing lotions, liquids, and pads)	>1–5	1
Face, body, and hand (excluding shaving preparations)	>10–25	1
	>5–10	5
	>1–5	10
	≤0.1	5
Moisturizing	>10–25	3
	>5–10	1
	>1–5	13
	>0.1–1	3
	≤0.1	1
Night	>10–25	2
	>5–10	1
	>1–5	16
	>0.1–1	1
Skin fresheners	>1–5	4
Other skin care preparations	>10–25	1
	>1–5	6
Suntan gels, creams, and liquids	>5–10	5
	>1–5	3
Cetyl Palmitate		
Eyeshadow	>1–5	7
Sachets	>1–5	6
Tonics, dressings, and other hair grooming aids	>1–5	1
Blushers (all types)	>1–5	23
	>0.1–1	1
Foundations	>1–5	12
Lipstick	>5–10	1
	>1–5	289
Makeup bases	>1–5	15
Other makeup preparations	>1–5	4
Deodorants (underarm)	>1–5	1
Other personal cleanliness products	>1–5	2
Cleansing (cold creams, cleansing lotions, liquids, and pads)	>1–5	3
Face, body, and hand (excluding shaving preparations)	>1–5	1

TABLE 2. (Continued.)

Ingredient/ Cosmetic product type	*Concentration (%)*	*No. of product formulations*
Moisturizing	>1–5	4
	>0.1–1	1
Night	>1–5	1
	>0.1–1	1
Other skin care preparations	>1–5	1
Isopropyl Palmitate		
Lotions, oils, powders, and creams	>1–5	1
	>0.1–1	2
Bath oils, tablets, and salts	>50	8
	>25–50	13
	>10–25	14
	>5–10	1
	>1–5	1
	>0.1–1	5
Bath capsules	>25–50	3
Other bath preparations	>50	2
	>10–25	1
	>5–10	2
	>1–5	2
	≤0.1	1
Eyeshadow	>5–10	4
	>1–5	12
Eye makeup remover	>25–50	1
	>5–10	2
	≤0.1	1
Other eye makeup preparations	>10–25	5
	>5–10	1
Colognes and toilet waters	≤0.1	2
Perfumes	>50	2
	>25–50	46
	>10–25	8
	>5–10	1
	>1–5	1
Powders (dusting and talcum) (excluding aftershave talc)	>5–10	1
	>0.1–1	9
Sachets	>5–10	1
	>1–5	5
	>0.1–1	1
Other fragrance preparations	>25–50	37
	>10–25	8
	>5–10	2
	>1–5	1
	>0.1–1	2
	≤0.1	1
Hair conditioners	>1–5	1
Hair sprays (aerosol fixative)	>1–5	1
	>0.1–1	1
Permanent waves	>0.1–1	1
Rinses (noncoloring)	>10–25	2
Shampoos (noncoloring)	>0.1–1	1
Tonics, dressings, and other hair grooming aids	>1–5	1
Wave sets	>1–5	2
Other hair preparations	>1–5	1
Hair bleaches	>0.1–1	2

TABLE 2. (Continued.)

Ingredient/ Cosmetic product type	*Concentration (%)*	*No. of product formulations*
Blushers (all types)	>25–50	5
	>10–25	2
	>5–10	1
	>1–5	9
Face powders	>1–5	30
	>0.1–1	1
Foundations	>25–50	2
	>5–10	9
	>1–5	15
	>0.1–1	2
Lipstick	>10–25	18
	>5–10	67
	>1–5	135
Makeup bases	>10–25	1
	>5–10	2
	>1–5	1
Rouges	>25–50	1
Other makeup preparations	>10–25	1
	>5–10	1
	>1–5	3
	>0.1–1	1
Cuticle softeners	>1–5	1
Nail polish and enamel removers	>1–5	2
	>0.1–1	1
Deodorants (underarm)	>5–10	1
	>1–5	7
	>0.1–1	1
Feminine hygiene deodorants	>1–5	9
	>0.1–1	3
Other personal cleanliness products	>5–10	1
	>1–5	11
	>0.1–1	3
Aftershave lotions	>1–5	1
	>0.1–1	1
Preshave lotions (all types)	>10–25	1
Shaving cream (aerosol, brushless, and lather)	>0.1–1	1
Cleansing (cold creams, cleansing lotions, liquids, and pads)	>50	1
	>25–50	1
	>10–25	2
	>5–10	10
	>1–5	6
Face, body, and hand (excluding shaving preparations)	>50	1
	>10–25	4
	>5–10	6
	>1–5	34
	>0.1–1	16
Foot powders and sprays	>0.1–1	3
Hormone	>10–25	1
	>5–10	2
	>1–5	1
Moisturizing	>25–50	1
	>10–25	3
	>5–10	16
	>1–5	23
	>0.1–1	11
	≤0.1	1

TABLE 2. (Continued.)

Ingredient/ Cosmetic product type	*Concentration (%)*	*No. of product formulations*
Night	>10–25	2
	>5–10	9
	>1–5	5
	>0.1–1	1
Skin fresheners	>5–10	1
Wrinkle smoothing (removers)	>1– 5	2
Other skin care preparations	>50	2
Suntan gels, creams, and lotions	>25–50	1
	>10–25	4
	>5–10	2
	>0.1–1	1

[a]Data from Ref. 43.

BIOLOGICAL PROPERTIES

With respect to pharmacokinetics, pharmacodynamics, teratology, mutagenesis, and carcinogenesis, there was no reported information concerning any of the Palmitates.

Secondary Effects

When petroleum jelly was applied to human skin at 20 mg/cm^2, there was a nearly 100% decrease in skin respiration as measured by both oxygen uptake from and the CO_2 discharge to the surrounding air. In contrast, Octyl Palmitate added to petroleum jelly at 10% concentration allowed normal gas-exchange when similarly applied to the skin.[44]

Polar alcohols with low molecular weights penetrated cadaveric human abdominal skin (in a diffusion chamber) more rapidly from such nonpolar vehicles as Isopropyl Palmitate than they did from saline solutions.[45]

Absorption, Metabolism, Storage, and Excretion

Palmitic acid is a component of most animal fats, comprising up to 50% of them. The acid is normally metabolized by β-oxidation or stored in fat depots, as are most of the alcohol moieties after they are oxidized to fatty acids. The terminal groups of the iso-alcohols may yield acetone for excretion or for further metabolism.[46]

When fed at a dietary level of 20% to mature male rats, Cetyl Palmitate was quantitatively excreted in the feces.[47]

Animal Toxicology

Acute Studies

Oral toxicity

Octyl Palmitate: The acute oral toxicity of 100% Octyl Palmitate was evaluated in three separate studies.[48-50] In each study, young adult albino rats of both sexes were fasted for 24 hours and given a single administration of Octyl Palmitate by gavage. They were then allowed free access to food and water for

two weeks. In one study involving 10 rats, the maximum single dose administered was 8 ml/kg.[48] There were no deaths and no apparent signs of systemic toxicity. In another study, Octyl Palmitate was administered to groups of five rats each in doses of 2.5, 5.0, 10.0, 20.0, or 40.0 ml/kg.[49] No mortalities resulted, and no information regarding other signs of toxicity was reported. The third study used dosage levels of 2.0, 4.0, 8.0, 16.0, 32.0, and 64.0 ml/kg, with five rats at each dose.[50] The animals dosed at 16.0 ml/kg and below showed no apparent toxic symptoms. At 32.0 ml/kg, wet, unkempt coats and mild diarrhea were noted on the first day only. At 64.0 ml/kg, slight ocular hemorrhage and moderate diarrhea were observed. The coats on these animals appeared wet and unkempt for five days following the administration of Octyl Palmitate. No deaths were recorded during the 14-day observation period. No post-mortem or histopathology examinations were reported for any of the three studies.[49,50]

Acute oral toxicity studies similar to those described above were conducted on Octyl Palmitate and four formulations containing Octyl Palmitate, but no details of the procedure or results were reported.[51-55]

These studies allow one to estimate that for rats the acute oral LD50 of Octyl Palmitate is greater than 64.0 ml/kg.

Cetyl Palmitate: The acute oral toxicity of Cetyl Palmitate was evaluated in four separate studies.[56-59] In each, adult albino rats were given a single administration of diluted or undiluted Cetyl Palmitate via gavage and then allowed free access to food and water. All animals were fasted overnight prior to administration and observed for two weeks post-dosage. Gross necropsies were performed following the 14-day observation period, but no results were submitted. In one study, a 5% w/w dispersion in mineral oil was administered to 10 rats (4M, 6F).[56] The dosage level was 5 g of the dispersion per kg. One male died between Days 7 and 14. Another study[57] used undiluted Cetyl Palmitate which had been melted prior to being used. Ten rats (5M, 5F) received single doses of 5 ml/kg; one death occurred within 24 hours. In the third study, groups of five male rats each were given 0.464, 1.00, 2.15, 4.64, or 10.00 g of Cetyl Palmitate per kg, delivered as a 50% w/v suspension in corn oil.[58] There was no mortality. In the fourth study, doses of 5.00, 7.12, 10.14, and 14.43 g of Cetyl Palmitate per kg were administered as a 50% slurry in corn oil to 10 rats at each dosage level.[59] Diarrhea in one rat at each level was observed three hours following administration. No deaths were reported.

Two moisturizer formulations containing Octyl Palmitate were tested for acute oral toxicity.[1] In each test, each of 10 rats (5M, 5F) received a single oral dose of the preparation via gavage. The product containing 2.5% Cetyl Palmitate was given at 30 g/kg, while that containing the ingredient at 2.7% was given at 25 g/kg. No deaths or toxic signs were reported in either study.

From these data, it can be estimated that the acute oral LD50 of Cetyl Palmitate in rats is greater than 14.4 g/kg.

Isopropyl Palmitate: The acute oral toxicity of undiluted Isopropyl Palmitate was evaluated in five separate studies.[58,60-63] In each, young adult albino rats of both sexes were given single doses of Isopropyl Palmitate via gavage and then allowed free access to food and water. All animals fasted overnight prior to administration of the test material and were observed for two weeks post-dosage. Some studies included gross necropsy following the 14-day observation period. Doses of 5.0 ml/kg were administered to 10 rats in each of two studies.[58,60] Other than diarrhea and unkempt fur for 36–48 hours following intubation, no

symptoms of toxicity were evident. There were no deaths, and the rats appeared grossly normal for the remainder of the study. In another study, there was no mortality in a group of 10 rats given 8.0 ml/kg doses of Isopropyl Palmitate.[61] A different study also produced no mortality when 20.0 ml/kg doses were administered to 10 rats.[62] In this instance, two males and three females had diarrhea on Day 1, but on subsequent days all animals appeared normal. Gross necropsy revealed no remarkable results. A fifth study used 30 rats in groups of five at each of six dose levels from 2.0 to 64.0 ml/kg.[63] Except for slightly impaired locomotion during the first 24 hours, the animals exhibited no signs of toxicity. All animals were completely normal by the second day.

An acute oral toxicity study in rats was conducted on a bath oil formulation containing 45.6 percent Isopropyl Palmitate.[64] Ten rats (5M, 5F) were given single oral doses of 25 ml/kg via gavage. There was some evidence of decreased activity up to four hours after treatment, but all animals appeared normal by 24 hours.

From these data, it can be estimated that in rats the acute oral LD50 of Isopropyl Palmitate is greater than 64.0 ml/kg.

Dermal toxicity

Octyl Palmitate: An acute dermal toxicity study on Octyl Palmitate was conducted with eight rabbits.[48] The test material was applied to the intact and abraded clipped skin of the trunk and held in place with a plastic sleeve for 24 hours. The animals were divided into four groups:

Group I: 2 control rabbits received no test material
Group II: 2 rabbits received 3.9 ml/kg
Group III: 2 rabbits received 6.0 ml/kg
Group IV: 2 rabbits received 9.4 ml/kg

After the 24-hour exposure, the sleeves were removed and the skin reactions were scored for erythema and edema on a Draize scale of 0–4. The animals were further observed for two weeks. Initial gradings ranged up to a score of two, and it was concluded that the material produced only a mild irritation which disappeared in all dose levels by Day 10. There were no deaths, and Octyl Palmitate produced no toxic effects that might be evidenced by changes in urine, blood morphology, or gross appearance. There was no apparent dose response.

Cetyl Palmitate: In an acute dermal toxicity study on Cetyl Palmitate, a 50% slurry of the ingredient in distilled water was used.[59] After each of 10 rabbits was clipped free of abdominal hair and after five were given epidermal abrasions, a single dose of 2.0 g/kg of the slurry was applied to the exposed areas. These areas were then covered with gauze, and for 24 hours, the trunks were wrapped with an impervious material. At the end of the exposure period, dermal reactions were evaluated according to the Draize technique. The slurry caused only a slight dermal irritation with scores of one and two at 24 hours. No deaths occurred during a 14-day period, and it was concluded that the material is not dermally toxic under the conditions of the test.

Isopropyl Palmitate: An acute dermal toxicity study on Isopropyl Palmitate was conducted with six albino rabbits (3M, 3F).[60] The trunk skin was clipped free of hair, and in three animals the epidermis was abraded. The trunks were then enclosed in clear polyethylene sleeves, under which 2.0 ml/kg of Isopropyl Palmitate was deposited onto the skin. Following dosing, the rabbits were immobilized for 24 hours, after which time the sleeves and excess material were

removed. The skin was cleaned and examined for gross changes. No erythema, edema, or other outward signs of toxicity were noted for two weeks.

Primary skin irritation

Octyl Palmitate: The primary skin irritancy potential of Octyl Palmitate was tested in three studies by a Draize single insult patch test technique on the clipped intact and abraded skin of albino rabbits. One-half ml samples of Octyl Palmitate were applied and occluded for 24 hours, after which time the patch sites were evaluated for erythema and edema by the Draize technique. Grading was again performed at 72 hours. In one study with three rabbits, all scores were 0.0.[50] In the second study, six rabbits produced a Primary Irritation Index (PII) of 0.8.[65] In the third study, the resultant PII for six rabbits was 1.6.[48] It was concluded from the results of this last test that Octyl Palmitate is a mild irritant.

Cetyl Palmitate: Four separate studies used the Draize primary skin irritation technique to evaluate the irritancy potential of Cetyl Palmitate. In each, samples of diluted or undiluted Cetyl Palmitate were applied under occlusive patches on clipped areas of the intact and abraded skin of six albino rabbits and occluded for 24 hours. Dermal reactions were evaluated at 24 and 72 hours, and PIIs were calculated by averaging the means of the 24- and 72-hour readings. In one study, 0.5 ml of a 5% w/w dispersion of Cetyl Palmitate in mineral oil produced a PII of 0.38.[56] The mean score was 0.75 at 24 hours; all scores were 0.0 at 72 hours. In another study, 1.0 ml of a 50% dispersion in distilled water was used, giving an effective dosage of 0.5 g of Cetyl Palmitate.[59] All reaction scores were 0.0. In the third study, 0.5 g of Cetyl Palmitate moistened with saline produced a PII of 0.17.[58] In the fourth study, Cetyl Palmitate was melted and used as a liquid at 100% concentration.[57] A dose of 0.5 ml produced a PII of 0.4. The mean score at 24 hours was 0.8; all scores were 0.0 at 72 hours.

The Draize method for primary skin irritation was used to test two moisturizer formulations containing 2.5% and 2.7% Cetyl Palmitate, respectively.[1] On each of six rabbits, mild irritation was produced by a single 24-hour exposure under occlusion of 0.5 g of the test material at each patch site. The PIIs were 1.0 for the 2.5 percent formulation and 0.9 for the 2.7% formulation.

Isopropyl Palmitate: The Draize primary skin irritation technique was used to evaluate Isopropyl Palmitate in five separate studies.[58,60,65-67] In each, single doses of 0.5 g or 0.5 ml of the undiluted ingredient were applied under occlusive patches on clipped areas of intact and abraded skin of six albino rabbits. Cutaneous reactions were graded at 24 and 72 hours, and the PIIs were calculated by averaging the means of the 24- and 72-hour readings. The PIIs in the first four studies were determined to be 0.0,[60] 0.38,[66] 0.6,[58] and 0.92.[67] In the fifth study,[65] each of four samples of Isopropyl Palmitate was assayed twice, and the eight resultant PIIs ranged from 0.25 (nonirritating) to 1.25 (slightly irritating).

Eye irritation

Octyl Palmitate: The Draize rabbit eye irritation procedure was used to evaluate Octyl Palmitate in three separate studies.[48,50,65] In each, 0.1 ml of undiluted Octyl Palmitate was instilled into one eye of each rabbit, and there was no subsequent washing. The other eye remained untreated and served as a control. In one study, the six animals were evaluated for ocular reactions at 24, 48, and 72 hours after administration; the scoring scale differed from that prescribed

by Draize.[48] Slight conjunctival redness was observed in two animals at 24 hours, but no overall value was computed. If the data obtained at 24 hours are used to calculate according to the Draize technique, the resultant Ocular Irritation Index (OII) is 0.33 out of a possible total of 110. In the second study, three rabbits were used and the computed OII was 2.0;[50] the only reported reaction was conjunctival redness. In the third study, six animals were used and an OII of 4.17 was determined.[65] These values indicate that Octyl Palmitate is minimally irritating and does not cause any significant injury to the rabbit eye mucous membrane.

Cetyl Palmitate: In four separate studies, the Draize eye irritation technique was used to evaluate Cetyl Palmitate.[56-59] In each, 0.1 ml or 0.1 g of the test material was instilled into the conjunctival sac of one eye in each of six rabbits. All eyes remained unwashed, and the contralateral eyes served as controls. The treated eyes were examined and graded on the Draize eye irritation scale at 24, 48, and 72 hours. In one study, the Draize OII for a 5% w/w dispersion of Cetyl Palmitate in mineral oil was 0.0 for all days.[56] The Draize scores for 100% Cetyl Palmitate in another study were 0.3 on the first day and 0.0 thereafter.[57] In the third study, Cetyl Palmitate delivered as a white powder received scores of 2.3 on the first day, 0.7 on the second day, and 0.3 on the third day.[59] The OIIs for undiluted Cetyl Palmitate in the fourth study were 6.7 on the first day, 2.2 on the second day, and 0.0 on the third day.[58] It can be concluded from these data, that Cetyl Palmitate is minimally irritating to the rabbit eye.

Isopropyl Palmitate: The Draize rabbit eye irritation procedure was used to evaluate Isopropyl Palmitate in five separate studies.[58,60,66,68] In each, 0.1 ml of undiluted Isopropyl Palmitate was instilled into the conjunctival sacs of adult albino rabbits. One eye was treated in each animal, while the other remained untreated and served as a control. Irritative effects were scored at 24, 48, and 72 hours according to the method of Draize.

In one study, nine rabbits were divided into three groups of three animals each.[68] While the treated eyes of group one remained unwashed, those of the other two groups were washed with 20 ml of lukewarm water, one at two seconds and the other at four seconds after the test material had been instilled. There were no signs of irritation, and all scores were 0.0.

In another study, the eyes of six rabbits remained unwashed after treatment, and the Draize OII was 0.0.[60]

The six rabbits tested in the third study gave an OII of 0.3 out of a possible total of 110 at 24 hours.[58] At the 48- and 72-hour gradings, all scores were 0.0.

In the fourth study, six rabbits were used, and OIIs of 2.33, 0.67, and 0.33 were obtained at 24, 48, and 72 hours, respectively.[66]

The fifth study was conducted on four samples of Isopropyl Palmitate.[65] The resultant OIIs ranged from 3.33 to 6.50 at 48 hours. (An OII of less than 10 on the Draize scale indicates that the compound does not cause any significant injury to the rabbit eye mucous membrane.)

Inhalation

Isopropyl Palmitate: For one hour, ten adult male and female albino rats were exposed to an aerosol of Isopropyl Palmitate in an inhalation chamber.[60] The spray was directed away from the nasal and ocular areas and circulated throughout the chamber for the duration of the exposure. The maximum aerosolization of 200 mg/l achieved prior to the test was maintained throughout

the exposure period. The test animals did not exhibit any toxic symptoms during the 14-day post-exposure observation period; nor did gross autopsies produce any significant findings. The acute toxic dose by inhalation was shown to be greater than 200 mg/l of air.

Intraperitoneal injection

Isopropyl Palmitate: The lowest published lethal dose for intraperitoneal injection of Isopropyl Palmitate in the mouse is 100 mg/kg.[69]

Subchronic Studies

Oral toxicity

Cetyl Palmitate: Mature rats were fed diets containing 20% Cetyl Palmitate for nine days. The ingredient was quantitatively excreted in the feces, and no abnormalities were noted for the duration of the study.[46]

Skin sensitization

Octyl Palmitate: The Landsteiner and Jacobs guinea pig sensitization technique was used in two separate studies to determine the sensitization potential of Octyl Palmitate.[48,50] The only significant difference between the studies involved the vehicles that were used; in one, Octyl Palmitate was dissolved in Olive Oil USP[48] while in the other, Octyl Palmitate was suspended in sterile, pyrogen-free, physiological saline.[50] In each, 10 white male guinea pigs had their backs and flanks clipped free of hair. A 0.1% solution of Octyl Palmitate was injected intracutaneously three times weekly until a total of 10 injections had been made. While the first injection consisted of 0.05 ml, the remaining nine were 0.1 ml each. Two weeks after the tenth sensitization injection, a challenge injection of 0.05 ml of freshly prepared solution was made slightly below the sensitization area. The challenge site was evaluated 24 hours later, and readings from it were compared with ones taken after the earlier injections. In both studies, investigators concluded that Octyl Palmitate is not a sensitizer.

Cetyl Palmitate: In a guinea pig sensitization study, a 1% Cetyl Palmitate suspension in Mazola corn oil was applied topically to ten albino guinea pigs three times per week until a total of 10 sensitizing treatments were made.[59] While the first treatment consisted of topical application of 0.05 ml of the solution, the remaining nine were made with 0.1 ml volumes. A challenge dose of 0.05 ml was administered on the opposite side of the body two weeks after the tenth treatment. Skin reactions were evaluated 24 hours later and compared with earlier readings. The test solution of Cetyl Palmitate was minimally irritating to the skin when applied topically, but it did not appear to be a sensitizing agent in guinea pigs.

Dermal toxicity

Octyl Palmitate: Octyl Palmitate was applied daily in doses of 1.0 ml/kg by gentle inunction to the shaved skin of 10 male and 10 female albino rats.[51] Applications were made five days a week for a total of 27 applications in six weeks. Daily observations were made regarding general appearance, behavior, and toxicologic signs. Complete gross necropsy, histopathology, and blood test data were obtained at the termination of the study. The mean hematocrit and red blood cell values of male rats treated with Octyl Palmitate were significantly

lower than those of controls. However, "in the absence of any changes in normal relative ratios of formed elements in the bone marrow, the hematologic changes are of doubtful toxicologic significance."[51] All other data failed to show any adverse changes attributable to the test material, and it was concluded that Octyl Palmitate produced no systemic toxic effects.

A 60-day repeated insult dermal toxicity study was conducted on undiluted Octyl Palmitate.[65] The ingredient was applied daily to an 80 cm^2/kg area on the shaved back and flanks of each of three albino rabbits. A 5 cm^2 area remained untreated and served as control. The ingredient was "poorly tolerated" in two of the three rabbits, and histological examination showed congestive dermatitis in three of six biopsies (two from each animal).

Isopropyl Palmitate: A 60-day repeated insult dermal toxicity study was conducted on four samples of undiluted Isopropyl Palmitate.[65] The ingredient was applied daily to an 80 cm^2/kg area on the shaved back and flanks of each of three albino rabbits. A 5 cm^2 macroscopic evaluation showed that the ingredient was either "well tolerated" or "relatively well tolerated" with thickening of the skin and/or presence of vesicles in some rabbits. In some cases, histological evaluation revealed orthokeratosis and slight acanthosis.

Clinical Assessment of Safety

The available clinical data consist of various experiments involving cutaneous application of these ingredients or of product formulations containing them. Except for an undocumented history of safe cosmetic use, no other clinical safety information was available.

Octyl Palmitate

Primary irritation

A 48-hour occlusive human patch test was conducted on four cosmetic preparations containing Octyl Palmitate at various concentrations.[52-55] The preparations included an eye makeup product with 40–50% Octyl Palmitate, an eyeshadow with 1–5% Octyl Palmitate, and two moisturizing skin care preparations with 1–5% Octyl Palmitate. Each preparation was tested on 100 human subjects, and all results were reported as "negative."

An 18-day repeated insult patch test was conducted on three antiperspirant sticks, each containing either 45.72% or 46.52% Octyl Palmitate.[70] These products were tested along with others, in a multiple patch array on the backs of five male and 15 female predominantly white subjects. The test substance was applied to a 1-inch square of nonwoven cloth which was held to the skin of the back under an occlusive impermeable plastic tape. The patch remained in place for 24 hours and was reapplied each day at the same site. A 5-point rating scale (0–4) was used in grading the degree of irritation at each reapplication; there were no reactions, and all such graded scores were 0.0.

A 21-day repeated insult patch test similar to the test just described was conducted on the backs of 24 subjects.[71] The product tested was an antiperspirant stick containing 42.25% Octyl Palmitate; the formulation's other ingredients were not reported. The average cumulative score for the 21 days was 2.58 out of a maximum possible 84. A total of seven subjects exhibited signs of irritation after day eight and were given irritation ratings of at least one; 17 subjects did not react.

Cetyl Palmitate

A number of cutaneous studies have been conducted on a moisturizer preparation containing either 2.5 or 2.7 percent Cetyl Palmitate in alternate formulations.[1]

Primary irritation

The procedure described by Kligman and Wooding[72] was used to conduct a 10-day primary skin irritation study in which the moisturizer containing 2.7 percent Cetyl Palmitate was tested on 10 normal adult subjects. For 10 days, approximately 0.3 ml of the undiluted material was applied once daily to the same site under an occlusive patch. There was no evidence of primary irritation.[1]

Sensitization

The Kligman maximization procedure[73] was used on a total of 50 subjects to test a nonperfumed version of the moisturizer containing 2.5% Cetyl Palmitate. At challenge, most subjects had a slight erythema, which the investigator attributed to the application of sodium lauryl sulfate. There were six cases of definite erythema (score = +1) at the 48-hour reading, but only one reaction was still evident at 72 hours. According to the investigator, these reactions did not result from contact sensitization. On the basis of the maximization grading scale, he concluded instead that the material was a "weak potential sensitizer" that was "unlikely to present a risk of contact sensitization under conditions of normal intended use."[1]

The moisturizer containing 2.7% Cetyl Palmitate was used undiluted in 25 subjects according to Kligman's modified maximization procedure.[73,74] All patch sites were negative, and it was concluded that the material should be considered a "weak potential sensitizer of the lowest grade."[1]

Phototoxicity

A phototoxicity study with the moisturizer containing 2.7% Cetyl Palmitate was conducted on 10 normal adult subjects. The material was applied undiluted at 5 $\mu l/cm^2$ under occlusive patches. After six and 24 hours of contact, sites were irradiated with a 150-watt Xenon Solar Simulator that had been fitted with a Schott WG345 filter to eliminate burning rays (total UV-A irradiance = 25–30 mW/cm^2). No instances of phototoxicity were reported, and it was concluded that this formulation is "unlikely to present a risk of phototoxicity under conditions of normal intended use."[1]

Photo-contact allergenicity

A photo-contact allergenicity study with the moisturizer containing 2.7% Cetyl Palmitate was conducted on 25 normal adult subjects. Applications of 5 $\mu l/cm^2$ under an occlusive patch for 24 hours were followed by irradiation with a Xenon Solar Simulator (25–30 mW/cm^2); this procedure was repeated twice a week for a total of six exposures. A challenge was performed 10 days after the last induction exposure. No instances of photo-contact allergenicity were reported, and it was concluded that "the formulation appears to have a low potential for photo-contact allergenicity under conditions of normal intended use."[1]

Safety in-use studies

A safety-in-use study of the moisturizer containing 2.5% Cetyl Palmitate was conducted on 30 normal women of unreported age and race. Applications of the

undiluted product to the face and periorbital areas were made thrice daily for 28 days. Examinations for facial, periorbital, conjunctival, and mucous membrane irritations were performed at 14 and 28 days. Occlusive patches were applied pre- and post-treatment. There were no instances of irritation, and it was concluded that "the formulation appears to have a low potential for irritation or sensitization under conditions of normal intended use."[1]

A similar but longer study was conducted on the moisturizer containing 2.7% Cetyl Palmitate and on a nonperfumed version of this formula; 100 subjects and 50 subjects were used in the respective tests. Examinations for irritation were performed at 28 and 56 days. No instances of mucous membrane, periorbital, or conjunctival inflammation were reported. Although in the tests on the perfumed formulation, one subject did demonstrate a minimal facial erythema on Day 28, there were otherwise no instances of facial erythema. Reduction of the frequency of use to twice daily in this individual resulted in no signs of erythema at the 56-day examination. Of the 150 subjects, only two who used the nonperfumed formulation reacted to the post-treatment occlusive patches, one with minimal (+1) erythema at 28 and 48 hours and one with doubtful (±) erythema at 24 hours. It was concluded that "the formulation appears to have a low potential for irritation or acquired contact sensitization under conditions of normal intended use."[1]

Isopropyl Palmitate

Primary irritation

Three separate studies have been conducted to test the irritancy potential of Isopropyl Palmitate by a 24-hour occlusive patch test technique.[75-77] In each, an unspecified amount of the undiluted ingredient was used, and the skin reactions were scored on a scale of 0–4. One study employed 20 subjects for each of two different batches of Isopropyl Palmitate.[75] There were no signs of irritation, and all scores were 0.0. In another such study, two different batches of Isopropyl Palmitate produced one irritation score of 0.5 in a total of 40 subjects.[76] In the third primary irritation study, each of four batches of Isopropyl Palmitate was tested on 20 subjects.[77] Four of the 80 subjects involved in these three studies received irritation scores of 0.5; all other scores were 0.0. In the three studies overall, undiluted Isopropyl Palmitate was applied to 160 subjects, and it produced five irritation scores of 0.5.

To test a bath oil formulation containing 45.6 percent Isopropyl Palmitate,[64] a 10-day primary irritation study was conducted according to the technique described by Kligman and Wooding.[72] For a total of ten days, ten normal adult subjects received 0.3 ml of the undiluted material once daily at the same site under an occlusive patch. No instances of irritation were reported.

Sensitization

One hundred two men and women of unspecified race participated in a modified Draize-Shelanski repeated insult patch test which was used to ascertain the irritation and sensitization potential of Isopropyl Palmitate.[78] Approximately 0.1 ml of undiluted Isopropyl Palmitate was dispersed onto an absorbent nonwoven cotton swatch, 20 × 20 mm, which was then applied to the upper back under an adhesive bandage. The patches were applied three times a week for three weeks and were left in place for 24 hours at each application. Reactions

were scored on a 0–4 irritancy scale 24 hours after patch removal. Seventeen days after the last induction patch was removed, a 24-hour challenge application of the test material was made; 24 and 48 hours following the removal of these applications, the challenge reactions were graded. Barely perceptible erythema was noted in three subjects after the second induction insult. All other scores in the induction and challenge periods were 0.0, and it was concluded that Isopropyl Palmitate did not demonstrate a potential for inducing allergic sensitization.

Kligman's modified maximization procedure[73,74] was used on 25 subjects to test an undiluted sample of a bath oil formulation containing 45.6% Isopropyl Palmitate.[64] All patch tests were negative, and it was concluded that, "based on the maximization grading scale, the material would be considered the lowest grade, weak potential sensitizer and would be unlikely to present a risk of contact sensitization under conditions of normal intended use."

Phototoxicity

A phototoxicity study of a bath oil formulation containing 45.6% Isopropyl Palmitate was conducted on 10 normal adult subjects of unreported age, sex, and color.[64] Applications of 5 $\mu l/cm^2$ of the undiluted test material were made under occlusive patches, and the application sites were irradiated with a Xenon Solar Simulator (25–30 mW/cm^2) after six and 24 hours of contact. No instances of phototoxicity were reported, and it was concluded that this formulation is "unlikely to present a risk of phototoxicity under conditions of normal intended use."

Photo-contact allergenicity

Twenty-five adult subjects of unspecified age, sex, and race participated in a photo-contact allergenicity study of the same bath oil containing 45.6 percent Isopropyl Palmitate.[64] Applications of 5 $\mu l/cm^2$ of the undiluted test material were repeated twice a week for a total of six applications. The test site remained occluded for 24 hours after each application, and the area was irradiated with a Xenon Solar Simulator (25–30 mW/cm^2) following the removal of each patch. A challenge application with irradiation was made 10 days after the last induction exposure. No instances of photocontact allergenicity were reported, and it was concluded that this formulation is "unlikely to present a risk of photo-contact allergenicity under conditions of normal use."

SUMMARY

The Palmitates are esters of palmitic acid and octyl, cetyl, or isopropyl alcohol. They are used in a wide variety of cosmetic products and may be applied to all areas of the skin.

The Palmitates would be expected to be nontoxic in view of their hydrolysis to palmitic acid and to the corresponding alcohols. The acute oral LD50 is estimated from studies with rats to be greater than 14.4 g/kg for Cetyl Palmitate and greater than 64.0 g/kg for Octyl and Isopropyl Palmitate.

Acute studies with rabbits showed no evidence of dermal toxicity for any of the Palmitates.

In a subchronic dermal toxicity study with rabbits, Isopropyl Palmitate was

"well tolerated." Another subchronic dermal toxicity study concluded that Octyl Palmitate is nontoxic. There were no deaths in either of the studies.

Other rabbit skin tests with the Palmitates showed that they are nonirritating and nonsensitizing.

Draize rabbit eye irritation tests on the Palmitates produced either very slight ocular irritation or none at all.

The acute toxic dose in rats by inhalation of Isopropyl Palmitate was shown to be greater than 200 mg/l. The lowest published lethal dose for mouse intraperitoneal injection is 100 mg/kg.

A number of human skin tests with the Palmitates and with product formulations containing the Palmitates have been conducted. One of three formulations containing Octyl Palmitate at concentrations between 40% and 50% produced mild irritation. Moisturizer formulations containing Cetyl Palmitate at concentrations of 2.5% and 2.7% were minimally irritating and produced no signs of sensitization, phototoxicity, or photo-contact allergenicity. Undiluted Isopropyl Palmitate was minimally irritating and was reported to be a "weak potential sensitizer" of the "lowest grade." A bath oil formulation containing 45.6% Isopropyl Palmitate produced no signs of irritation, sensitization, phototoxicity, or photocontact allergenicity.

No human sensitization or photo-study data were available on Octyl Palmitate, nor was this ingredient tested at greater than 50% concentration for skin irritation. Clinical data on Cetyl Palmitate are limited to testing at a concentration of 2.7%.

CONCLUSION

On the basis of the available information, the Panel concludes that Octyl Palmitate, Cetyl Palmitate, and Isopropyl Palmitate are safe as cosmetic ingredients in the present practices of use and concentration.

ACKNOWLEDGMENT

Mr. Jeffrey Moore, Scientific Analyst and writer, prepared the literature review and technical analysis used by the Expert Panel in developing this chapter.

REFERENCES

1. COSMETIC, TOILETRY and FRAGRANCE ASSOC. (CTFA). (1977,1978). Submission of data by CTFA. Unpublished data on cetyl palmitate. Safety data on moisturizing formulation containing 2.5-2.7 percent cetyl palmitate.*
2. CTFA. (1978). Submission of data by CTFA. CTFA Cosmetic ingredient chemical description for isobutyl palmitate.*
3. ESTRIN, N.F. (ed.). (1977). *CTFA Cosmetic Ingredient Dictionary*, 2nd ed. Washington, D.C.: Cosmetic, Toiletry and Fragrance Association, Inc.

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

4. ESTRIN, N.F. (ed.). (1974). *CTFA Standards: Cosmetic Ingredient Specifications, 2-ethylhexyl Palmitate.* Washington, D.C.: Cosmetic, Toiletry and Fragrance Association.
5. HAWLEY, G.G. (ed.). (1971). *The Condensed Chemical Dictionary,* 8th ed. New York: Van Nostrand Reinhold Co.
6. LESTER, D. and BERGMANN, W. (1941). Marine products. VI. The occurrence of cetyl palmitate in corals. J. Org. Chem. **6,** 120–2.
7. KRASIL'NIKOV, N.A., KORONELLI, T.V. and BIS'KO, N.A. (1973). Biosynthesis of cetyl palmitate by a mycobacterium ceroformans culture. Mikrobiologiya **42**(6), 1028–31.
8. ALEBY, S., FISCHMEISTER, I. and IYENGAR, B.T.R. (1971). Infrared spectra and polymorphism of long chain esters. IV. Some esters from tetradecanol, hexadecanol, octadecanol, eicosanol, docosanol, and dodecanoic, tetradecanoic, hexadecanoic, octadecanoic, and eicosanic acid. Lipids **6**(6), 421–5.
9. ALEXANDER, A.E. and SCHULMAN, J.H. (1937). Orientation in films of long-chain esters. Proc. Roy. Soc. **A161,** 115–27.
10. ALEXANDER, A.E. and RIDEAL, E.K. (1937). Reaction kinetics in films. The hydrolysis of long-chain esters. Proc. Roy. Soc. **A163,** 70–89.
11. BRUMMAGE, K.G. (1947). An electron-diffraction study of the heating of straight-chain organic films and its application to lubrication. Proc. Roy. Soc. **191A,** 243–52.
12. DORSET, D.L. (1976). Dendritic forms of crystalline long-chain lipids. Naturwissenschaften **63**(9), 437–8.
13. DORSET, D.L. (1976). Electro-diffraction crystal structure analysis of cetyl palmitate. Bioorg. Khim. **2**(6), 781–8.
14. DRYDEN, J.S. and WELSH, H.K. (1969). Dielectric absorption and molecular motion in aliphatic compounds. Discuss. Faraday Soc. **48,** 174–80.
15. HUNTER, J. and EDDY, C.R. (1967). Dielectric properties of some long-chain esters in the solid state. J. Am. Oil Chem. Soc. **44**(6), 341–3.
16. KOHLHASS, R. (1938). X-ray investigation of definite single crystals of the cetyl ester of palmitic acid. Z. Krist. **98,** 418–38.
17. MACDOUGALL, G. and OCKRENT, C. (1942). Surface-energy relations in liquid/solid systems. I. The adhesion of liquids to solids and a new method of determining the surface tension of liquids. Proc. Roy. Soc. **A180,** 151–73.
18. TAMAMUSHI, B. (1934). The orientation of molecules on surfaces of water and aqeuous solutions. Bull. Chem. Soc. Japan **9,** 161–5.
19. THIESSEN, P.A. and SCHOON, Th. (1937). Electron diffraction on natural surfaces of organic single crystals. Z. Physik. Chem. **B36,** 216–31.
20. VORLANDER, D. and SELKE, W. (1927). The uniaxial structure of soft solid crystalline masses and of crystalline liquids. Z. Physik. Chem. **129,** 435–74.
21. ESTRIN, N.F. (ed.). (1974). *CTFA Standards: Cosmetic Ingredient Specifications, Isopropyl Palmitate.* Washington, D.C.: Cosmetic, Toiletry and Fragrance Association.
22. GREENBERG, L.A. and LESTER D. (1954). *Handbook of Cosmetic Materials.* New York: Interscience Publishers.
23. CTFA. Submission of data by CTFA. (1977,1978). Unpublished data on moisturizing formulation containing 2.5–2.7 percent cetyl palmitate.*
24. CTFA. (1978). Submission of data by CTFA. CTFA Cosmetic ingredient chemical description for cetearyl palmitate.*
25. CTFA. (1978). Submission of data by CTFA. CTFA Cosmetic ingredient chemical description for cetyl palmitate.*
26. CTFA. (1978). Submission of data by CTFA. CTFA Cosmetic ingredient chemical description for isopropyl palmitate.*
27. WINDHOLZ, M. (ed.). (1976). *The Merck Index,* 9th ed. Rahway, N.J.: Merck and Co.
28. HONOWAY, P.J. (1968). Chromatographic analysis of spermaceti. J. Pharm. Pharmacol. **20**(10), 775–9.
29. MARTINI, M.C. and CHAMBON, M. (1969). Color reactions characteristic of certain poly (vinyl alcohols). Their use in the detection of lipids in chromatography. Ann. Pharm. Fr. **27**(2), 143–6.
30. REISER, R., SORRELS, M.F., and BENDER, M. (1957). Chromatographic analysis of some constituents of marine-animal oils. Comm. Fisheries Rev. **19**(4a), 9–10.
31. GROSS, F.C. (1966). Gas–liquid chromatography of some fatty acid esters and alcohols in lipsticks. J. Assoc. Off. Anal. Chem. **49**(6), 1196–200.
32. CTFA. (1979). Submission of data by CTFA. CTFA Cosmetic ingredient chemical description for palmitic acid.*
33. ESTRIN, N.F. (Editor). (1974). CTFA Standards: Cosmetic Ingredient Specifications, palmitic acid 95 percent. Washington, D.C.: Cosmetic, Toiletry and Fragrance Association.
34. ESTRIN, N.F. (Editor). (1974). CTFA Standards: Cosmetic Ingredient Specifications, cetyl alcohol. Washington, D.C.: Cosmetic, Toiletry and Fragrance Association.

35. POWERS, D.H. (1972). Shampoos, in: *Cosmetics: Science and Technology*, 2nd ed. New York: Wiley-Interscience. v. 2. pp. 73–116.
36. RINZLER, C.A. (1977). *Cosmetics: What the Ads Don't Tell You.* New York: Thomas J. Crowell Co. pp. 142, 159.
37. PLECHNER, S. (1972). Antiperspirants and deodorants, in: *Cosmetics: Science and Technology*, 2nd ed. New York: Wiley-Interscience. v. 2. pp. 373–416.
38. BARNETT, G. (1972). Emollient Creams and Lotions, in: *Cosmetics: Science and Technology*, 2nd ed. New York: Wiley-Interscience. v. 1. pp. 27–104.
39. WETTERHAHN, J. (1972). Eye Makeup, in: *Cosmetics: Science and Technology*, 2nd ed. New York: Wiley-Interscience. v. 1. pp. 393–422.
40. BERGWEIN, K. (1954). Use of fatty acid esters of low molecular weight alcohols in cosmetics. Fette Seifen Anstrichm. **56,** 422–4.
41. HOLZNER, G. (1963). The use of isopropyl fatty esters in cosmetic formulations. Am. Perfum. Cosmet. **78**(10), 89–93.
42. TUAN, T.A. (1970). Use of isopropylic esters of some saturated fatty acids in cosmetology. Parfum. Cosmet. Savons **13**(6), 454–7.
43. FDA. (Aug. 31, 1976). Cosmetic product formulation data. Washington, D.C.: Food and Drug Administration.
44. JACOBI, O. (1970). Skin respiration and cosmetics. Am. Perfum. Cosmet. **85**(7), 25–30.
45. BLANK, I.H. (1964). Penetration of low-molecular-weight alcohols into skin. I. Effect of concentration of alcohol and type of vehicle. J. Invest. Dermatol. **43,** 415–20.
46. HILDITCH, T.P. (1940). The Chemical Constitution of Natural Fats. New York: John Wiley & Sons.
47. CALLOWAY, D.H., KURTZ, G.W., and POTTS, R.B. (1959). Some physiological characteristics of esters of cetyl alcohol. Can. J. Biochem. Physiol. **37**(1), 17–23.
48. KOLMAR RESEARCH CENTER. (Aug. 1967). Submission of data by CTFA. Unpublished data on octyl palmitate. The toxicological examination of alpha-ethyl-hexyl-palmitate (Wickenol 155).*
49. FOOD AND DRUG RESEARCH LABORATORIES. (April 6, 1976). Submission of data by CTFA. Unpublished data on octyl palmitate. Acute oral toxicity in rats.*
50. BIO-TOXICOLOGY LABORATORIES. (July 13, 1972). Submission of data by CTFA. Unpublished data on octyl palmitate. Toxicity studies, 2-ethylhexyl palmitate.*
51. CTFA. (May 21, 1975). Submission of data by CTFA. Unpublished data on octyl palmitate. Safety evaluation of selected raw ingredients.*
52. CTFA. (1975). Submission of data by CTFA. Unpublished data on octyl palmitate. CIR safety data submission: Eye makeup preparation, 40–50 percent octyl palmitate.*
53. CTFA. (1977). Submission of data by CTFA. Unpublished data on octyl palmitate. CIR safety data submission: Eyeshadow (waterproof type), 1–5 percent octyl palmitate.*
54. CTFA. (1977). Submission of data by CTFA. Unpublished data on octyl palmitate. CIR safety data submission: Moisturizing skin care lotion, 1–5 percent octyl palmitate.*
55. CTFA. (1978). Submission of data by CTFA. Unpublished data on octyl palmitate. CIR safety data submission: Moisturizing skin care cream, 1–5 percent octyl palmitate.*
56. BIOMETRIC. (1977). Submission of data by CTFA. Unpublished data on cetyl palmitate. Standamul 1616.*
57. CONSUMER PRODUCT TESTING. (1977). Submission of data by CTFA. Unpublished data on cetyl palmitate. Standamul 1616.*
58. ARMAK. (Oct. 25, 1972). Submission of data by CTFA. Unpublished data. Acute toxicity studies of Kessco esters. Bull. No. 73-1.*
59. MB RESEARCH LABORATORIES. (Oct. 25, 1974). Submission of data by CTFA. Unpublished data on isopropyl palmitate. Report on primary dermal irritation in rabbits.*
60. BIO-TOXICOLOGY LABORATORIES. (1975). Submission of data by CTFA. Unpublished data on isopropyl palmitate. Toxicity studies on isopropyl palmitate.*
61. KOLMAR RESEARCH CENTER. (June 20, 1972). Submission of data by CTFA. Unpublished data on isopropyl palmitate. The toxicological examination of Wickhen isopropyl palmitate (Wickenol 111).*
62. SPRINGBORN INSTITUTE FOR BIORESEARCH. (April 27, 1978). Submission of data by CTFA. Unpublished data on isopropyl palmitate. A study of the acute oral (LD50) toxicity: Starfol IPP.*
63. BIO-TOXICOLOGY LABORATORIES. (June 23, 1970). Submission of data by CTFA. Unpublished data on isopropyl palmitate. Toxicity study for Emery Industries.*
64. CTFA. (1978). Submission of data by CTFA. Unpublished data on isopropyl palmitate. Safety data on a bath oil formulation containing 45.6 percent isopropyl palmitate.*
65. GUILLOT, J.P., MARTINI, M.C., and GIAUFFRET, J.Y. (1977). Safety evaluation of cosmetic raw materials. J. Soc. Cosmet. Chem. **28**(7), 377–93.

66. HILL TOP RESEARCH. (July 3, 1968). Submission of data by CTFA. Unpublished data on isopropyl palmitate. Primary skin and acute eye irritation studies on a series of test materials.*
67. MB RESEARCH LABORATORIES. (1977). Submission of data by CTFA. Unpublished data. Waxenol 815.*
68. LEBERCO LABORATORIES. (Dec. 1, 1975). Submission of data by CTFA. Unpublished data on isopropyl palmitate. Eye irritation study: Emerest 2316.*
69. FAIRCHILD, E.J. (Ed.). (1977) Registry of Toxic Effects of Chemical Substances, vol. II. Cincinnati, Ohio: U.S. Dept. of H.E.W., Public Health Service, Center for Disease Control.
70. CTFA. (Sept. 16, 1977). Submission of data by CTFA. Unpublished data on octyl palmitate. Irritation study: 18-day repeat insult patch test.*
71. CTFA. (May 23, 1977). Submission of data by CTFA. Unpublished data on octyl palmitate. Irritation study: 21-day repeat insult patch test.*
72. KLIGMAN, A.M. and WOODING, W.M. (1967). A method for the measurement and evaluation of irritants on human skin. J. Invest. Dermatol. **49**(1), 78–94.
73. KLIGMAN, A.M. (1966). The identification of common contact allergens by human assay. III. The maximization test: a procedure for screening and grading contact sensitizers. J. Invest. Dermatol. **47**(5), 393–409.
74. KLIGMAN, A.M. and EPSTEIN, W. (1975). Updating the maximization test for identifying contact allergens. Contact Dermatitis **1**, 231–9.
75. CTFA. (April 5, 1972). Submission of data by CTFA. Unpublished data on isopropyl palmitate. Clinical evaluation report, profile No. 5007.*
76. CTFA. (Sept. 12, 1973). Submission of data by CTFA. Unpublished data on isopropyl palmitate. Clinical evaluation report, profile No. 42050.*
77. CTFA. (March 9, 1973). Submission of data by CTFA. Unpublished data on isopropyl palmitate. Clinical evaluation report, profile No. 40065.*
78. CTFA. (Sept. 20, 1976). Submission of data by CTFA. Unpublished data on isopropyl palmitate. Allergic contact sensitization test, No. 008–76.*