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Final Report on the Safety Assessment of Butyl Stearate, Cetyl Stearate, Isobutyl Stearate, Isocetyl Stearate, Isopropyl Stearate, Myristyl Stearate, and Octyl Stearate

The 7 Stearates described in this report are either oily liquids or waxy solids that are primarily used in cosmetics as skin emollients at concentrations up to 25 percent. The toxicology of the Stearates has been assessed in a number of animal studies. They have low acute oral toxicity and are essentially nonirritating to the rabbit eye when tested at and above use concentration. At cosmetic use concentrations the Stearates are, at most, minimally irritating to rabbit skin.

In clinical studies the Stearates and cosmetic products containing them were at most minimally to mildly irritating to the human skin, essentially nonsensitizing, nonphototoxic and nonphotosensitizing. Comedogenicity is a potential health effect that should be considered when the Stearate ingredients are used in cosmetic formulations.

On the basis of the information in this report, it is concluded that Butyl, Cetyl, Isobutyl, Isocetyl, Isopropyl, Myristyl, and Octyl Stearate are safe as cosmetic ingredients in the present practices of use.

CHEMISTRY

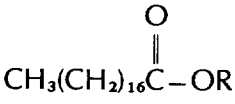
Definition and Structure

The seven cosmetic ingredients reviewed in this report are listed below in alphabetical order:

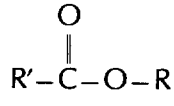
1. Butyl Stearate
2. Cetyl Stearate

3. Isobutyl Stearate
4. Isocetyl Stearate
5. Isopropyl Stearate
6. Myristyl Stearate
7. Octyl Stearate

The aforementioned Stearates are esters of stearic acid.[1] They conform to the general formula:



where R represents the alkyl moiety of butyl, cetyl, isobutyl, isocetyl, isopropyl, myristyl or octyl alcohol.[1-3] The safety of stearic acid as a fragrance raw material and as a food ingredient has been reviewed by the Research Institute for Fragrance Materials (RIFM)[4] and the Federation of American Societies for Experimental Biology (FASEB),[5] respectively. A review of the scientific literature from 1920 to 1973 on stearic acid has been published.[6] Because of the technical grade of the stearic acid and the alcohols used as starting materials, the commercially available Stearates are mixtures of esters conforming to the formula:

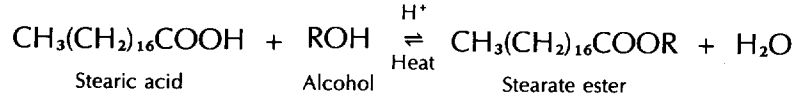


where R'–C  represents the acyl moiety present in commercial stearic acid and where R represents the alkyl moiety of 1 of the aforementioned alcohols.[1,2]

The chemical names and structural formulas of the 7 Stearates under review are presented in Table 1.

Methods of Manufacture

The Stearates are prepared by the esterification of stearic acid with the appropriate alcohol in the presence of an acid catalyst:



where R represents the alkyl moiety of butyl, cetyl, isobutyl, isocetyl, isopropyl, myristyl, or octyl alcohol.[1,2,9] The reaction products are refined either by catalyst neutralization, vacuum distillation, or various decolorization-deodorization techniques to remove residual traces of alcohol.[9,10]

The higher stearate esters (Isocetyl, Myristyl) can be made by heating with or without acidic catalysts. If an acidic catalyst is used, it is neutralized, and the product is filtered to remove the salts.[9]

Butyl Stearate can be prepared by the reaction of silver stearate with n-butyl iodide at 100°C[11,12] or by the transesterification of glyceryl tristearate (tristearin) with n-butyl alcohol.[12] This ester may also be prepared by the alcoholysis of glycerol stearate (stearin).[10]

Composition and Impurities

Butyl Stearate, as used in cosmetics, is a liquid mixture of butyl esters consisting of a minimum of 90 percent butyl palmitate and butyl stearate, with lesser amounts of butyl laurate, myristate, pentadecanoate, heptadecanoate, and oleate.[13,14] According to cosmetic ingredient specifications published by the Cosmetic, Toiletry and Fragrance Association,[13,14] the ester composition is:

> As specified by the buyer; provided that the sum of the specified mean levels equals 100.0 percent and that the individual mean levels and specification limits conform to the following:
>
> Butyl Stearate:
> Mean Level: Not less than 40.0 [percent]
> (Limits: ±5.0 [percent])
>
> Butyl Stearate plus Butyl Palmitate:
> Mean Level: Not less than 90.0 [percent]
> (Limits: ±5.0 [percent])
>
> Butyl Laurate, Myristate, Pentadecanoate, Heptadecanoate, and Oleate:
> Mean Level: Not more than 10.0 [percent]
> each (Limits: ±2.0 [percent])

Isocetyl Stearate, as used in cosmetics, is reported to contain a maximum of 1 percent free fatty acid.[1] There are no known diluents, solvents, or additives present in Butyl, Isobutyl, Isocetyl, Isopropyl, or Octyl Stearate.[1,2]

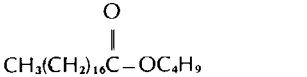
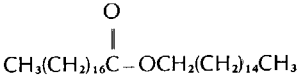
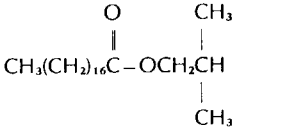
The composition and impurities of the various starting materials (stearic acid and butyl, cetyl, isocetyl, isopropyl, and myristyl alcohol) have been reported elsewhere.[13-17]

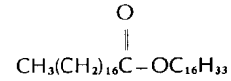
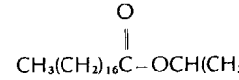
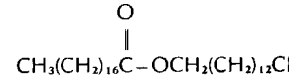
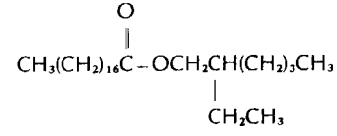
Properties

Butyl Stearate is a stable, colorless, oily liquid. It is resistant to oxidation and undergoes no appreciable degradation when exposed to a temperature of 205°C for 3 hours. At about 19°C, the ester solidifies. Butyl Stearate is slightly soluble to insoluble in water (0.2 percent) and is soluble in acetone, chloroform, ether, alcohol, ketones, ethyl acetate, aromatic and aliphatic hydrocarbons, fats, waxes, mineral oils, and many plasticizers.[10-14,18-21] The chemical and physical properties of this compound have been reviewed by Lower.[21] The infrared spectrum of Butyl Stearate is available in cosmetic specifications published by the Cosmetic, Toiletry and Fragrance Association.[14,22]

Isobutyl Stearate is a paraffinlike crystal substance at "low temperature;"[11] at room temperature, it is a liquid.[9] Isocetyl Stearate occurs as an oily, colorless or yellow liquid with practically no odor. It is soluble in ethanol, isopropanol, mineral oil, castor oil, acetone, and ethyl acetate and is insoluble in water, glycerin,

TABLE 1. Chemical Names and Structural Formulas[3,7,8]

Ingredient	*Chemical Names*	*CAS No.*	*Structural Formula*
Butyl Stearate	Butyl octadecanoate n-Butyl octadecanoate Butyl octadecylate n-Butyl stearate Octadecanoic acid, butyl ester Stearic acid, butyl ester	123-95-5	
Cetyl Stearate	Hexadecyl octadecanoate n-Hexadecyl stearate Octadecanoic acid, hexadecyl ester Stearic acid, hexadecyl ester	1190-63-2	
Isobutyl Stearate	Octadecanoic acid, 2-methylpropyl ester Stearic acid, 2-methylpropyl ester Stearic acid, isobutyl ester 2-Methylpropyl octadecanoate	646-13-9	

Isocetyl Stearate	Octadecanoic acid, isohexadecyl ester Stearic acid, isohexadecyl ester	25339-09-7	
Isopropyl Stearate	Octadecanoic acid, 1-methylethyl ester Stearic acid, isopropyl ester 1-Methyethyl octadecanoate	112-10-7	
Myristyl Stearate	Octadecanoic acid, tetradecyl ester Stearic acid, tetradecyl ester Tetradecyl octadecanoate Tetradecyl stearate	17661-50-6	
Octyl Stearate	2-Ethylhexyl stearate Octadecanoic acid, 2-ethylhexyl ester Stearic acid, 2-ethylhexyl ester 2-Ethylhexyl octadecanoate	22047-49-0	

and propylene glycol.[10,17,23] Isopropyl Stearate is a liquid at room temperature.[9] Myristyl Stearate is a waxy solid at room temperature.[9]

Chemical and physical data for the Stearate ingredients are presented in Table 2. No data were available for Cetyl Stearate.

TABLE 2. Chemical and Physical Data

Ingredient		*Reference*
Butyl Stearate		
Molecular formula	$C_{22}H_{44}O_2$	8, 11
Molecular weight	340.57	11, 19, 21, 25
Melting point	16°C	11
	18.5–20.5°C	21
	19.0–20°C	12
	19.5°C	18, 25
	19.5–20°C	10
	27.0°C	11
	27.5°C	8, 19
Boiling point	212–216°C (25 mm)	21
	220–225°C (25 mm)	18, 19
	343°C	11
	350°C	10
	351–360°C (760 mm)	21
Viscosity	8 centistokes (25°C)	21
Specific gravity	0.851–0.861 (20°/20°C)	20
	0.855–0.860 (25°/20°C)	10, 12
	0.855–0.875 (25°/25°C)	11, 19
	0.853–0.860 (25°C)	21
Vapor density	11.4	25
Refractive index	1.441 (25°C)	21
	1.4430 (20°C)	10, 12
	1.4328 (50°C)	8
Saponification value	146–177	20
	167–173	21
Acid value	1.0 maximum	2, 13, 14, 20
	1.2	21
Ester value (sap. val.) (acid val.)	168.0–175.0	2, 13, 14
Iodine value	1.0 maximum	2, 13, 14, 20
	2.4 (Wijs)	21
Moisture	0.8%	21
Ester content	99%	21
Unsaponifiable matter	0.5% maximum	21
Flash point:		
Closed cup	163.9°C	21
	160°C	10, 11, 25
Open cup	196°C	11
	188.9°C	21

TABLE 2. (Continued).

Ingredient		*Reference*
Autoignition temperature	355°C	25
Residue on ignition	0.1% maximum	20
Weight/gallon	7.14 lb (20°C)	10
Dipole moment	1.88 D in benzene (24°C)	21
Cubical expansion coefficient	0.00083/°C over 20–50°C	21
Vapor pressure	11 mm Hg (150°C)	21
Surface tension	31 dyne/cm (25°C)	21
Electrical conductivity	21 × 10^{-3} (30°C)	21
Dielectric constant	3.111 (30°C)	21
Heat of fusion	39/40 cal/g	21
Hydrolysis	0.16% (1 hr at 100°C)	21
Isobutyl Stearate		
Molecular formula	$C_{22}H_{44}O_2$	8, 11
Molecular weight	340.57	11
Melting point	20°C	11
Saponification value	170–180	2
Acid value	1.0 maximum	2
Iodine value	1.0 maximum	2
Isocetyl Stearate		
Molecular formula	$C_{34}H_{68}O_2$	8
Molecular weight	508	–
Specific gravity	0.852–0.858 (25°/25°C)	17, 23
Freezing point	0.10°C	17, 23
Viscosity	32.0 cp (25°C)	10
Refractive index	1.4510–1.4530 (25°C)	17, 23
Saponification value	110–118	1
	106–118	17
Acid value	2.0 maximum	1
	1.0 maximum	17
Iodine value	2.0 maximum	1
	1.0 maximum	17
Isopropyl Stearate		
Molecular formula	$C_{21}H_{42}O_2$	8
Molecular weight	326	–
Ester value	176–185	1
Acid value	1.0 maximum	1
Iodine value	1.0 maximum	1
Octyl Stearate		
Molecular formula	$C_{26}H_{52}O_2$	8
Molecular weight	396	–
Ester value	144–154	1
Acid value	1.0 maximum	1
Iodine value	1.0 maximum	1

Reactivity

The Stearates can be expected to undergo chemical reactions typical of esters.[24] Such reactions may include:

1. Conversion into stearic acid and the corresponding alcohol by chemical or enzymatic hydrolysis
2. Conversion into amides by ammonolysis
3. Conversion into different esters by alcoholysis or transesterification.

The purer grades of these saturated stearate compounds would not be expected to autoxidize readily.

Compatibility with Other Materials

Butyl Stearate is reported to be "compatible" with a number of materials, including butadiene/styrene rubber, butadiene/acrylonitrile rubber, benzyl cellulose, copal esters, cellulose nitrate, cellulose acetate butyrate, cellulose acetate propionate, chlorinated rubber, ester gums, ethyl cellulose, nitrocellulose, polystyrene, and phenolic resins.[21]

Analytical Methods

Among the analytical methods that have been used for the various Stearates are the following: gas chromatography,[26-34] thin-layer chromatography,[35-37] silver resin chromatography,[38,39] silver nitrate high performance liquid chromatography,[40] and photodensitometry.[42]

USES

Noncosmetic Uses

Butyl Stearate is used as a solvent for dyes in wax polishes, as a spreading and softening agent in plastics, textiles and rubber, as a plasticizer for inks, cellulose acetate butyrate, cellulose nitrate, ethyl cellulose, polystyrene, laminated fiber products, rubber hydrochloride, chlorinated rubber and cable lacquers, as a lubricant in textiles, molding, metals, and in the extrusion and molding of polyvinylchloride, as a waterproofing agent for concrete, as an emollient in pharmaceuticals, and as an ingredient of carbon paper, inks, and special lubricants and coatings.[8,10,11] The numerous and varied uses of Butyl Stearate have been extensively reviewed by Lower.[21]

A number of regulations pertaining to the use of Butyl Stearate as an indirect food additive, direct food additive, and synthetic flavoring agent have been issued by the Food and Drug Administration. As an indirect food additive, Butyl Stearate is permitted for use as a component of adhesives used in packaging or transporting food,[43] as a plasticizer of resinous and polymeric coatings,[44] as a plasticizer in resinous and polymeric coatings for polyolefin films,[45] as a component of defoaming agents used in coatings,[46] as a plasticizer in rubber articles

(not to exceed 30 percent by weight of rubber product),[47] as a surface lubricant used in the manufacture of metallic articles,[48] and as a plasticizer in the manufacture of various other food packaging materials.[49] As a direct additive, it is permitted as a defoaming agent component (no limitations) in the processing of beet sugar and yeast.[50] As a synthetic flavor, it may be safely incorporated into foods when used in accordance with good manufacturing practices and when used in the minimum quantity required to produce its intended effect.[51] Butyl Stearate is reported to be used in various beverages and foods in the following quantities:[12]

Nonalcoholic beverages	1.0 ppm
Alcohol beverages	5.0 ppm
Ice creams, ices, and so on	2.0 ppm
Candy	190 ppm
Chewing gum	330 ppm
Baked goods	340 ppm

Isobutyl Stearate is used as a component in waterproof coatings, polishes, ointments, dye solutions, inks, lubricants, and rubbers.[11] Isocetyl Stearate is used as a plasticizer, mold release agent, and textile softener. In pharmaceuticals, the isocetyl ester is used as a lubricant, fixative, and solvent.[10]

Cosmetic Use

The Stearate ingredients are used in cosmetics primarily as emollients for the skin.[9] In lipstick formulations, Butyl Stearate reduces the viscosity of the oil phase, thereby lessening the drag of the stick on the lips. Butyl Stearate may also function in lipsticks as a color-suspending agent. The low viscosity and oily nature of the compound allow it to wet and dissolve pigments more efficiently than oils of greater viscosity.[8,10,11,18,21,52] In nail varnishes, Butyl Stearate may be used as a water-repelling plasticizer. In hand creams and lotions, Butyl and Isopropyl Stearate function as spreading agents. When these 2 compounds are applied to the skin, a thin, oily film is deposited. The film is nongreasy and nontacky and is both continuous and hydrophobic in nature. Isopropyl Stearate also serves to increase the gelatin characteristics of hand product formulations.[18,21] Isocetyl Stearate is used in cosmetics as a lubricant, fixative, and solvent.[10]

Data submitted to the Food and Drug Administration (FDA) in 1981 by cosmetic firms participating in the voluntary cosmetic registration program indicated that Butyl, Cetyl, Isocetyl, Isopropyl, Myristyl, and Octyl Stearate were used in a total of 116, 4, 58, 16, 1, and 10 cosmetic formulations, respectively (Table 3). Product types in which the Stearate esters were most frequently used included eye makeup preparations, skin makeup preparations, lipstick, and skin care preparations. Concentrations of the Stearate esters in cosmetic products generally ranged from 1 to 25 percent, although there were a few reported instances of higher and lower concentrations.[53,54] No product formulation data were available for Isobutyl Stearate.

Voluntary filing of product formulation data with the FDA by cosmetic manufacturers and formulators conforms to the prescribed format of preset concentra-

TABLE 3. Product Formulation Data[53,54]

Product Category	Total No. of Formulations in Category	Total No. Containing Ingredient	No. of Product Formulations Within Each Concentration Range (%)			
			>10–25	>5–10	>1–5	>0.1–1
Butyl Stearate						
Eyeliner	396	4	–	–	4	–
Eye shadow	2582	3	–	–	2	1
Other eye makeup preparations	230	4	1	3	–	–
Hair conditioners	478	3	–	1	2	–
Makeup foundations	740	1	1	–	–	–
Lipstick	3319	78	69	1	8	–
Nail polish and enamel remover	41	2	–	–	1	1
Deodorants (underarm)	239	1	–	–	1	–
Feminine hygiene deodorants	21	1	–	–	–	1
Preshave lotions (all types)	29	3	–	2	1	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	1	–	–	1	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	8	–	–	6	2
Moisturizing skin care preparations	747	2	–	–	2	–
Wrinkle smoothers (removers)	38	1	–	1	–	–
Other skin care preparations	349	2	1	–	1	–
Suntan gels, creams, and liquids	164	2	2	–	–	–
1981 TOTALS		116	74	8	29	5
Cetyl Stearate						
Eye shadow	2582	3	–	3	–	–
Face powders	555	1	–	–	1	–
1981 TOTALS		4	–	3	1	–

Product Category	Total No. of Formulations in Category	Total No. Containing Ingredient	No. of Product Formulations Within Each Concentration Range (%)				
			>10–25	>5–10	>1–5	>0.1–1	≤0.1
Isocetyl Stearate							
Eye shadow	2582	1	–	1	–	–	–
Eye makeup remover	81	1	1	–	–	–	–
Blushers (all types)	819	2	–	1	1	–	–
Face powders	555	2	1	–	1	–	–
Makeup foundations	740	7	6	1	–	–	–
Lipstick	3319	1	–	–	1	–	–
Makeup bases	831	8	7	–	–	1	–
Rouges	211	1	1	–	–	–	–
Nail creams and lotions	25	1	–	–	1	–	–
Bath soaps and detergents	148	1	–	–	–	–	1
Other shaving preparation products	29	1	–	–	1	–	–

TABLE 3. (Continued)

Product Category	Total No. of Formulations in Category	Total No. Containing Ingredient	No. of Product Formulations Within Each Concentration Range (%)				
			>10–25	>5–10	>1–5	>0.1–1	≤0.1
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	5	–	–	2	–	3
Face, body, and hand skin care preparations (excluding shaving preparations)	832	11	–	–	10	1	–
Moisturizing skin care preparations	747	10	–	–	9	–	1
Night skin care preparations	219	2	–	1	–	1	–
Other skin care preparations	349	2	–	1	–	1	–
Suntan gels, creams, and liquids	164	1	1	–	–	–	–
Other suntan preparations	28	1	–	–	–	1	–
1981 TOTALS		58	17	5	26	5	5

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
Isopropyl Stearate							
Bath oils, tablets, and salts	237	1	–	–	1	–	–
Eye makeup preparations	230	1	–	1	–	–	–
Fragrance preparations	191	1	1	–	–	–	–
Personal cleanliness products	227	3	–	–	–	3	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	4	–	1	3	–	–
Moisturizing skin care preparations	747	4	–	2	2	–	–
Night skin care preparations	219	1	–	1	–	–	–
Skin lighteners	44	1	–	1	–	–	–
1981 TOTALS		16	1	6	6	3	–
Myristyl Stearate							
Makeup foundations	740	1	–	–	–	1	–
1981 TOTALS		1	–	–	–	1	–
Octyl Stearate							
Bath oils, tablets, and salts	237	3	–	–	–	2	1

TABLE 3. (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
Colognes and toilet waters	1120	4	–	–	–	–	4
Makeup foundations	740	1	–	–	–	–	1
Face, body, and hand skin care preparations (excluding shaving preparations)	832	1	–	–	–	–	1
Night skin care preparations	219	1	–	1	–	–	1
1981 TOTALS		10	–	1	–	2	7

tion ranges and product categories as described in Title 21 Part 720.4 of the Code of Federal Regulations.[55] Because data are only submitted within the framework of preset concentration ranges, opportunity exists 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.

Cosmetic products containing the Stearate compounds are applied to or have the potential to come in contact with eyes, hair (scalp), nails, vaginal mucosa, and skin. Small amounts of these esters could be ingested from lipstick.

Product formulations containing the Stearate ingredients may be used as infrequently as once a week to as frequently as several times per day. Many of these cosmetic products can be expected to remain in contact with body surfaces for as briefly as a few hours to as long as a few days. Each cosmetic product containing one of these esters can be repeatedly applied over the course of many years.

METABOLISM

Higher molecular weight aliphatic esters are readily hydrolyzed to the corresponding alcohol and acid and then generally oxidized to carbon dioxide and water.[19] In the case of the Stearate compounds, metabolism of stearic acid would be expected to occur in the same fashion as other fatty acids.

Isopropyl Stearate diluted in 9,10-$^{3}H_{2}$-labeled oleic acid was given by stomach tube to thoracic duct fistula rats. Measurement data of the specific radioactivity of the stearic chains in lymph triglycerides indicated that 85 to 95 percent of the chains were of "dietary origin." For every 100 radioactive stearic chains recovered in lymph lipids, less than 10 were in the form of isopropyl ester, which represented 2 to 3 percent of the total lymph lipids. It was calculated that less than 5 percent of the remaining radioactivity was in lymph phospholipids. Of the non-

phospholipid fraction (isopropyl esters being excluded), 95 percent or more of the radioactivity was detected in the triglycerides. It was concluded that ". . . a part of the isopropyl ester was hydrolyzed in the intestine, and that the acids thus liberated were reesterified and partitioned between lymph lipids."[56]

ANIMAL TOXICOLOGY

Comedogenicity

Butyl Stearate (50 percent in mineral oil) and mineral oil were each applied to 1 ear of 2 rabbits 5 days a week for 2 weeks. The treated sites were excised at 14 days, and comedogenicity was graded on a scale of 0 to 3. For 50 percent Butyl Stearate in mineral oil, scores were 2 and 3, indicating moderate and strong comedogenicity, respectively. Mineral oil produced reactions of grade 1 in both rabbits, indicating slight comedogenicity. These materials were only weakly comedogenic in relation to potent acnegens, such as tars and chlorinated oils. The authors discussed the possibility that daily use of Butyl Stearate for several years could produce low-grade comedonal reactions in susceptible women.[57]

The CIR Panel recognizes that currently available tests are inadequate to predict the potential for human comedogenicity of a cosmetic ingredient as used in a product formulation. However, comedogenicity is a potential health effect that should be considered when the stearate ingredients are used in cosmetic formulations.

Subcutaneous Toxicity

Undiluted Butyl Stearate was given by subcutaneous injection to 4 groups of male albino rats consisting of 6, 15, 6, and 15 animals at single doses of 4, 8, 16, and 32 g/kg, respectively. No deaths or gross lesions were observed in any of the animals.[58]

Intraperitoneal Toxicity

Four groups of male albino rats were administered undiluted Butyl Stearate by intraperitoneal injection. Single doses of 4, 8, 16, and 32 g/kg were administered to 6, 15, 6, and 15 animals, respectively. No gross lesions or deaths were noted.[58]

Acute Oral Toxicity

Results of studies conducted on rats and mice have indicated that Butyl, Isocetyl, Isopropyl, Myristyl, and Octyl Stearates have low acute oral toxicity. The individual acute oral studies are discussed below; results are summarized in Table 4.

Undiluted Butyl Stearate was administered in single oral doses of 4, 8, 16, and 32 g/kg to 4 groups of male albino rats consisting of 6, 15, 6, and 15 animals, respectively. No deaths or gross lesions were noted in any of the animals. The acute lethal oral dose was >32 g/kg.[58]

TABLE 4. Acute oral Toxicity

Ingredient	*Concentration (%)*	*Dose*	*No. and Kind of Animal*	*LD_{50}*	*Comments*	*Reference*
Butyl Stearate	100	4 to 32 g/kg	6, 15, 6, and 15 albino rats, respectively	>32 g/kg	No deaths or gross pathologic changes	58
Butyl Stearate (2 samples)	Each sample: 100	–	Rats	>5 g/kg	–	9, 59
Butyl Stearate	100	10 g/kg	10 rats	>10 g/kg	No deaths	9, 60
Butyl Stearate	100	8 ml/kg	5M and 5F albino rats	>8 ml/kg	No deaths; average body weight gain was 21.6% over 14-day observation period	9, 61
Butyl Stearate	100	2.0–64.0 ml/kg	6 groups of 5 albino rats	>64.0 ml/kg	No effect at 2.0 ml/kg. Rats given 4.0 and 8.0 ml/kg had unkempt coats. Rats given 16.0 and 32.0 ml/kg developed diarrhea and oily, unkempt coats. Rats given 64.0 ml/kg had diarrhea, alopecia, and oily, unkempt coats. Test material equally nontoxic to males and females	9, 62
Isocetyl Stearate	100	0.464–10.0 ml/kg	5 groups of 5M albino rats	>10.0 ml/kg	Rats given 0.464, 1.0, and 2.15 ml/kg exhibited normal appearance and behavior. Rats given 4.64 ml/kg had unkempt fur. At 10.0 ml/kg, depression and unkempt fur were noted. No deaths or gross pathological alterations observed at any dose level	9, 63
Isocetyl Stearate	100	5 g/kg	5M and 5F albino rats	>5.0 g/kg	One female rat died within 24 hours; gross necropsy revealed fibrous tissue encasing heart and lungs of 1 male	9, 64
Isocetyl Stearate	100	10 g/kg	10 rats	>10 g/kg	No deaths	9, 65
Isopropyl Stearate	100	8 ml/kg	5M and 5F albino rats	>8 ml/kg	1/10 rats died. Body weight gain averaged 21% over the 2-week observation period	9, 66
Myristyl Stearate	100 mg/ml of corn oil	5.0 or 10.0 g/kg	2 groups of 5 and 20 CFW mice, respectively	>10 g/kg (ingred. + corn oil); >1 g/kg (ingred. alone)	No deaths or visible "untoward effects"	9, 67
Octyl Stearate	100	8 ml/kg	5M and 5F rats	>8 ml/kg	No deaths; body weight gain averaged 25.7% during the 2-week observation period	9, 68

Two samples of 100 percent Butyl Stearate were tested for acute oral toxicity in an unspecified number of rats. The LD_{50} of each sample was >5 g/kg.[9,59]

A single 10 g/kg dose of undiluted Butyl Stearate was given orally to 10 rats. No deaths occurred during the 72-hour observation period. The investigators concluded that the LD_{50} was >10 g/kg.[9,60]

Five male and five female albino rats were administered 100 percent Butyl Stearate at an oral dose of 8 ml/kg. No rats died during the 14-day observation period. The LD_{50} was >8 ml/kg.[9,61]

Doses of 2.0 to 64.0 ml/kg of undiluted Butyl Stearate were given orally to 6 groups of albino rats (5 animals/group). Rats dosed at 2.0 ml/kg had no adverse effects. Unkempt coats were observed for 12 to 48 hours in animals receiving 4.0 and 8.0 ml/kg. Rats administered 16.0 and 32.0 ml/kg had slight diarrhea and wet, oily, unkempt coats; these animals returned to normal within 3 to 6 days. Slight to moderate diarrhea, alopecia, and wet, oily, unkempt coats were noted in rats dosed at 64.0 ml/kg. However, these animals appeared normal within 7 to 8 days. The test material was "equally nontoxic" to males and females. The LD_{50} of 100 percent Butyl Stearate was >64.0 ml/kg.[9,69]

Undiluted Isocetyl Stearate was given orally to 5 groups of 5 male Sprague Dawley rats at doses ranging from 0.464 to 10.0 ml/kg. All of the rats of the 0.464, 1.00, and 2.15 ml/kg groups showed normal appearance and behavior throughout the 14-day observation period. Rats administered 4.64 ml/kg had normal appearance and behavior during the day of dosage and from Days 4 through 14. However, on the first, second, and third day postdosing, unkempt fur was noted. At the 10.0 ml/kg dose, "depression" was observed on the day of dosing and unkempt fur observed on Days 1 through 3. From Day 4 through 14, all animals had normal appearance and behavior. Necropsy was performed on the rats of each dose group, and no gross alterations were observed. The average body weight gain for each group was normal for rats of the age, sex, and strain used in this study. No deaths occurred at any dose.[9,63]

Five male and five female albino rats received undiluted Isocetyl Stearate at an oral dose of 5.0 g/kg. One female rat died during the first 24 hours. Necropsy was conducted on each of the animals at the end of the 14-day observation period, and fibrous tissues encasing the heart and lungs were found in 1 male. The investigators considered the test material nontoxic under conditions of this test.[9,64]

A single 10 g/kg oral dose of undiluted Isocetyl Stearate was administered to 10 rats. No deaths occurred during the 72-hour observation period. The investigators considered the test material nontoxic.[9,65]

Five male and five female albino rats were dosed orally with 8 ml/kg of undiluted Isopropyl Stearate. On the eighth day of the 14-day observation period, 1 of the 10 rats died; necropsy findings were noncontributory as to the cause of death. The body weight gain of the test animals averaged 21 percent over the 2-week observation period. Under conditions of this test, the LD_{50} was >8 ml/kg.[9,66]

CFW mice of the Carworth strain were administered Myristyl Stearate in corn oil (100 mg/ml) at oral doses of 5.0 (5 mice) or 10.0 g/kg (20 mice). During the 5-day observation period, no deaths or visible "untoward effects" were observed.[9,67]

Undiluted Octyl Stearate was administered to 5 male and 5 female rats at oral doses of 8.0 ml/kg. No deaths occurred during the 14-day observation period. The body weight gain of test animals during the 2 weeks averaged 25.7 percent. The investigators considered the acute oral toxicity of this ester to be "very low."[9,68]

Eye Irritation

When instilled into the eyes of rabbits at concentrations of 100 percent, Isocetyl, Myristyl, and Octyl Stearates caused slight, transient irritation. No ocular irritation was observed in rabbits following instillation of 100 percent Butyl or Isopropyl Stearate. The various eye irritation studies are individually discussed below; results are summarized in Table 5.

Three groups of albino rabbits (3 animals/group) were treated with 100 percent Butyl Stearate for ocular irritation. The test material (0.1 ml) was instilled into the right eye of each animal; the untreated left eye served as control. The eyes of the first group of rabbits received no further treatment. In the second group, the treated eyes were washed with 20 ml of lukewarm water 2 seconds after instillation of the test material. In the third group, the treated eyes were rinsed in a similar fashion 4 seconds after instillation of the test substance. Both the treated and control eyes were examined every 24 hours for 4 days and then again on the seventh day. No eye irritation was observed in any of the animals.[9,62]

Two groups of rabbits (3 animals/group) were treated with 100 percent Isocetyl Stearate for ocular irritation. The eyes of the first 3 rabbits did not receive a water rinse after instillation of 0.1 ml of the test material. The eyes of the second group of rabbits were flushed with 20 ml of water 4 seconds after instillation of 0.1 ml Isocetyl Stearate. The average scores of the "no-wash" group were 7.33, 1.33, and 0.0 at the 1, 24, and 48-hour readings, respectively (maximum score, 110). The average scores of the rabbits receiving the 4-second "wash" were 10.67, 2.0, and 0.0 at the 1, 24, and 48-hour readings, respectively. According to the investigators, Isocetyl Stearate was slightly irritating.[9,70]

An eye irritation study was conducted with undiluted Isocetyl Stearate using 6 New Zealand rabbits. The test substance (0.1 ml) was instilled into the right eye of each animal; the untreated left eye of each rabbit served as a control. The treated eyes of all rabbits were not flushed with water. Numerical scores for ocular lesions were assigned according to the Draize[71] scoring system of 110 maximum points. At the 24-hour reading, 4 of the 6 animals had varying degrees of redness of the palpebral conjunctiva. Of the 4 rabbits with irritation, only 1 had chemosis. The 24-hour Draize scores for the 6 rabbits were 0, 0, 2, 2, 2, and 8, respectively. On the second day, all treated eyes were normal and remained so until the final observation on Day 3. The investigators concluded that the test material was a minimal ocular irritant to rabbit eyes under conditions of this test.[9,64]

Undiluted Isopropyl Stearate was instilled into the conjunctival sac of one eye of each of 6 New Zealand rabbits (3M, 3F). The treated eye received no further treatment. The single 0.1 ml exposure produced no corneal, conjunctival, or iridic irritation over a 3-day observation period.[72]

The eye irritation potential of undiluted Myristyl Stearate was determined in 3 albino rabbits. Each animal had 0.1 g of the test sample instilled into the right

TABLE 5. Eye Irritation

Ingredient	*Concentration (%)*	*No. of Rabbits*	*Wash (W)/ No Wash (NW)*	*Comments/Results*	*Reference*
Butyl Stearate	100	3	NW	No irritation observed on Days 1, 2, 3, 4, or 7	9, 62
		3	W after 2 seconds	No irritation observed on Days 1, 2, 3, 4, or 7	
		3	W after 4 seconds	No irritation observed on Days 1, 2, 3, 4, or 7	
Isocetyl Stearate	100	3	NW	The average scores were 7.33, 1.33, and 0.0 at the 1, 24, and 48 hour readings, respectively. (The max. score per observation interval = 110)	9, 70
		3	W after 4 seconds	The average scores were 10.67, 2.0, and 0.0 at the 1, 24, and 48 hour readings, respectively. (The max. score per observation interval = 110.) The investigators considered the material a slight irritant	
Isocetyl Stearate	100	6	NW	At 24-hour reading, 4/6 rabbits had redness of conjunctivae. The 24-hour Draize scores of the 6 rabbits were 0, 0, 2, 2, 2, and 8, respectively. (The max. score per rabbit observation = 110.) No irritation observed on Days 2 or 3. Investigators considered the material a minimal irritant	9, 64, 71
Isopropyl Stearate	100	6	NW	No corneal, conjunctival, or iridic irritation noted over a 3-day observation period	72
Myristyl Stearate	100	3	NW	At the 24-hour reading, all 3 rabbits had a "slight vessel injection involving only the conjunctivae." The 24-hour Draize scores for the 3 rabbits were 2, 4, and 6, respectively. (The max. score per rabbit per observation = 110.) No irritation was observed on Days 2, 3, 4, or 7	9, 73
Octyl Stearate	100	6	NW	Average ocular irritation indices at 1 hour and 1, 2, 3, 4, and 7 days were 4.67, 0, 0, 0, 0, and 0, respectively. (The max. score per observation period = 100.) Material did not provoke any significant eye injury	74, 75

eye with no further treatment. The left eye of each rabbit served as a control. Both treated and control eyes were examined every 24 hours for 4 days and then again on the seventh day. Eye irritation was evaluated according to the Draize scale of 110 maximum points per rabbit per observation. At the 24-hour reading, all 3 rabbits had a "slight vessel injection" involving only the conjunctiva. On the second day of observation, the treated eyes were normal and remained so until the final evaluation. The 24-hour Draize scores for the 3 rabbits were 2, 4, and 6, respectively.[9,73]

Undiluted Octyl Stearate was tested for eye irritation in 6 albino rabbits by methods outlined in the *Journal Officiel de la Republique Francaise.*[75] The test material (0.1 ml) was instilled into 1 eye of each animal; the other eye served as a control. The treated eyes of all animals received no water rinse. Ocular lesions were evaluated on the basis of a numerical scale ranging from 0 to 100. The average ocular irritation indices at 1 hour and at 1, 2, 3, 4, and 7 days were 4.67, 0, 0, 0, 0, and 0, respectively. According to the investigators, ". . . a compound does not provoke any significant injury to the eye mucous membrane when. . . the ocular index is less than 10."[74]

Skin Irritation

When tested at concentrations of up to 100 percent on rabbit skin, Butyl, Isobutyl, Isocetyl, Isopropyl, Myristyl, and Octyl Stearates caused at most mild to moderate irritation. Individual tests are discussed below; results are summarized in Table 6.

A skin irritation test was conducted with undiluted Butyl Stearate using 6 rabbits. The test material was applied to the abraded and intact skin under closed patches for 24 hours. All animals had slight to well-defined erythema at abraded and intact skin sites at the 24-hour evaluation. Two of the six rabbits had very slight edema at abraded sites at 24 hours. No skin irritation was observed in any of the animals at the 72-hour evaluation. The primary irritation index (PII) was 0.68, indicating mild irritation.[9,76]

Undiluted Butyl Stearate was tested for skin irritation in 6 rabbits. The ester was applied to the intact or abraded skin under closed patches for 24 hours. Very slight erythema was noted at both abraded and intact skin sites of 2 rabbits at the 24-hour reading. No irritation was observed in any of the animals at the 72-hour reading. The PII was 0.17, indicating mild irritation.[9,77]

The skin irritation potential of undiluted Butyl Stearate was determined in rabbits in 4 separate tests. In each test, the material was applied to the skin under closed patches for 24 hours. The PIIs were 0.33 and 0.39 in 2 of the tests, respectively, indicating minimal irritation.[9,78] The PIIs were 0.3 and 0.77 in the other 2 tests, indicating minimal to mild irritation.[9,59] Details of these tests were not reported.

Undiluted Butyl Stearate was tested for its skin irritating effects by means of the procedures described in the Department of Transportation Act.[79] The test material was applied to the intact and abraded skin of 6 albino rabbits under closed patches for 4 hours. Following an initial evaluation at 4 hours, all test sites were washed with an "appropriate" solvent to prevent further exposure. No irritation was noted in any of the animals at the 4-, 24-, or 48-hour readings; the PII was 0.0, indicating that the test material was "not a primary irritant."[9,69]

The Draize method[80] was used to evaluate the skin-irritating effects of undiluted Butyl Stearate. The test material (0.5 ml) was applied for 24 hours under closed patches to the abraded and intact skin of 6 albino rabbits. No irritation was noted in any of the animals at 24 or 72 hours; the PII was 0.0, indicating no observed skin irritation.[9,69]

Six rabbits were treated with 100 percent Butyl Stearate for evaluation of primary skin irritation. The test procedures employed were those as specified in the regulations under the Federal Hazardous Substances Act.[81] The test material was applied to both abraded and intact skin under occlusive patches for 24 hours. No irritation was noted in any of the rabbits at the 24- or 72-hour readings; the PII was 0.0.[9,82]

Undiluted Butyl Stearate was tested for skin irritation using 6 albino rabbits. The test material was applied under occlusive patches to the intact and abraded skin for 24 hours. At the 24-hour evaluation, all animals had well-defined to moderate erythema at both intact and abraded skin sites. Further, 2 of 6 rabbits had very slight edema of the intact skin and 1 of 6 rabbits had very slight edema of the abraded skin. By the 72-hour reading, all animals had well-defined to severe erythema but no edema. The PII was 2.75, indicating moderate irritation.[9,83]

A skin irritation test was conducted with undiluted Isobutyl Stearate on 6 rabbits. The test material was applied to the intact and abraded skin under occlusive patches for 24 hours. At the 24-hour evaluation, all 6 animals had very slight erythema of the intact skin, whereas 5 of the 6 rabbits had very slight erythema of the abraded skin. At the 72-hour evaluation, 2 of the 6 rabbits had very slight erythema at both abraded and intact skin sites. The PII was 0.62, indicating mild irritation.[9,84]

The skin irritation potential of undiluted Isocetyl Stearate was determined using 6 New Zealand rabbits. The test material was applied to the abraded and intact skin of both the back and abdomen under closed patches for 24 hours. The irritant effects following dorsal application were confined to very slight erythema at 1 of 6 intact and 2 of 6 abraded sites at the 24-hour evaluation; the PII was 0.13, indicating mild irritation. The irritant effects observed following ventral application included very slight erythema at 2 of 6 intact sites and 1 of 6 abraded sites at the 24-hour evaluation. At the 72-hour evaluation, very slight erythema was noted at 1 of 6 intact sites and 1 of 6 abraded sites. The PII of the test material was 0.21, indicating mild irritation.[9,63]

Two samples (A and B) of undiluted Isocetyl Stearate were tested for skin irritation on an unspecified number of rabbits. The test materials were applied to the skin daily for 3 days; "open patch contact time" was 24 hours. The PII scores for sample A were 0.17, 1.00, and 0.83, whereas sample B had PII scores of 0.00, 0.83, and 0.83. The investigators concluded that the 2 samples were "slight" skin irritants.[9,85]

An unspecified number of rabbits were used for skin irritation tests with 2 samples (A and B) of undiluted Isocetyl Stearate. The test materials were applied to the skin under closed patches for 24 hours. Sample A had a PII of 0.25, whereas sample B produced a PII of 0.12 (maximum score, 8.0). The investigators concluded that the 2 samples were "minimal" skin irritants.[9,85]

Six rabbits were treated with undiluted Isocetyl Stearate to determine its skin irritation potential. The test material was applied to the abraded and intact skin of the back under gauze pads for 24 hours. Within 24 hours, 3 of 6 animals had very slight erythema or edema of the intact and abraded skin sites. At 72 hours, 1 of the 6 rabbits had very slight erythema of the intact skin, and another had a similar reaction on abraded skin. The PII was 0.415, indicating mild irritation.[9,86]

TABLE 6. Skin Irritation

Ingredient	*Concentration (%)*	*No. of Rabbits*	*Method*	*Comments/Results*	*Reference*
Butyl Stearate	100	6	Material applied to intact and abraded skin for 24 hours; closed patches	PII,* 0.68; mild irritation	9, 76
Butyl Stearate	100	6	Material applied to intact and abraded skin for 24 hours; closed patches	PII, 0.17; mild irritation	9, 77
Butyl Stearate	100	Unspecified	In 4 separate tests, material was applied under closed patches for 24 hours	In 4 separate tests, the PIIs were 0.33, 0.39, 0.3, and 0.77, respectively, indicating minimal to mild irritation	9, 59, 78
Butyl Stearate	100	6	Dept. of Transportation.[79] Material applied to intact and abraded skin for 4 hours; closed patches	PII, 0.0; no irritation observed	9, 69
Butyl Stearate	100	6	Draize.[80] Material applied to intact and abraded skin for 24 hours; closed patches	PII, 0.0; no irritation observed	9, 69
Butyl Stearate	100	6	Federal Hazardous Substances Act.[81] Material applied to intact and abraded skin for 24 hours; closed patches	PII, 0.0; no irritation observed	9, 82
Butyl Stearate	100	6	Material applied to intact and abraded skin for 24 hours; closed patches	PII, 2.75; moderate irritation	9, 83
Isobutyl Stearate	100	6	Material applied to intact and abraded skin for 24 hours; closed patches	PII, 0.62; mild irritation	9, 84
Isocetyl Stearate	100	6	Material applied to intact and abraded skin of both the back and abdomen for 24 hours; closed patches	Back: PII, 0.13; mild irritation Abdomen: PII, 0.21; mild irritation	9, 63
Isocetyl Stearate Sample A	100	Unspecified	Each sample applied to skin daily for 3 days; "open patch contact time" was 24 hours	A: PIIs, 0.17, 1.00 and 0.83; slight irritation	9, 85

Sample B	100	Unspecified		B: PIIs, 0.00, 0.83, and 0.83; slight irritation	
Isocetyl Stearate					
Sample A	100	Unspecified	Each sample applied to skin for 24 hours; closed patches	A: PII, 0.25; minimal irritation	9, 85
Sample B	100	Unspecified		B: PII, 0.12; minimal irritation	
Isocetyl Stearate	100	6	Material applied to intact and abraded skin for 24 hours; closed patches	PII, 0.415; mild irritation	9, 86
Isocetyl Stearate	25 in corn oil	6	Draize et al.[71] Material applied to intact and abraded skin for 24 hours; closed patches	PII, 0.25; "potential for slight irritation"	9, 64
Isopropyl Stearate	100	6	A single 0.5 ml application of the test material to intact and abraded skin	PII, 2.35; moderate irritation	9, 83
Isopropyl Stearate	100	6	A single 0.5 ml application of the test material to intact and abraded skin	PII, 2.35; moderate irritation	87
Myristyl Stearate	100	3	Draize.[80] Material applied to intact and abraded skin for 24 hours; closed patches	PII, 0.0; no irritation observed	9, 88
Octyl Stearate	100	6	*Journal Officiel de la Republique Francaise.*[75] Material applied to skin for 24 hours; closed patches	PII, 0.0; no irritation observed	74
Octyl Stearate	10 in aqueous solution	6	*Journal Officiel de la Republique Francaise.*[75] Material applied to skin for 24 hours; closed patches	PII, 0.0; no irritation observed	74
Octyl Stearate	100	6	Federal Hazardous Substances Act.[81] Material applied to intact and abraded skin for 24 hours; closed patches	PII, 1.42; mild irritation	9, 89

*PII, primary irritation index.

The Draize method[71] was used to evaluate the skin irritation potential of 25 percent Isocetyl Stearate in corn oil. The test material was applied to the intact and abraded skin of 6 albino rabbits for 24 hours under occlusive wrapping. Very slight erythema was observed at both intact and abraded skin of 3 rabbits at the 24-hour evaluation; no signs of irritation were noted in any animals at the 72-hour evaluation. The PII was 0.25, indicating a potential for slight irritation.[9,64]

Albino rabbits were treated with undiluted Isopropyl Stearate for evaluation of primary skin irritation. The test material was applied under occlusive patches to the intact and abraded skin of each of 6 animals for 24 hours. Slight to moderate erythema was observed in all animals at both intact and abraded skin sites at the 24- and 72-hour evaluations. The PII was 2.35, indicating moderate irritation.[9,83]

Well-defined erythema was observed at the intact and abraded skin sites of 6 rabbits (3M, 3F) both 24 and 72 hours following a single 0.5 ml application of undiluted Isopropyl Stearate. The PII of the test material was 2.35, indicating moderate skin irritation.[87]

The Draize procedure[80] was employed to determine the skin irritation potential of undiluted Myristyl Stearate. The test material was applied for 24 hours under closed patches to the intact and abraded skin of 3 albino rabbits. No irritation was noted in any of the animals at the 24- or 72-hour readings. The PII was 0.0, indicating no irritation.[9,88]

The skin irritation potential of undiluted Octyl Stearate and an aqueous solution containing 10 percent Octyl Stearate was determined by procedures outlined in the *Journal Officiel de la Republique Francaise.*[75] Each test material (0.5 ml) was applied under occlusive patches for 24 hours to the clipped skin of 6 albino rabbits. Test sites were scored at 24, 48, and 72 hours. The primary irritation index of both test materials was 0.0, indicating no irritation.[74]

The skin-irritating effects of undiluted Octyl Stearate were determined according to the methods specified in the regulations under the Federal Hazardous Substances Act as cited in 16 CFR 1500.3 and 16 CFR 1500.41. The test material was applied under closed patches for 24 hours to the intact and abraded skin of 6 New Zealand rabbits. Well-defined erythema was noted at 24 hours in all rabbits on both intact and abraded sites; by 72 hours, the erythema had cleared on both sites in 5 of 6 animals. Very slight to slight edema was noted in 3 of 6 rabbits at 24 hours and 1 of 6 rabbits at 72 hours. The PII was 1.42, indicating mild irritation. However, the test material was not considered an irritant under the criteria outlined in Title 16 Part 1500.41 of the Code of Federal Regulations.[9,81,89]

Cumulative Skin Irritation

The cumulative skin irritation potential of 10 percent Octyl Stearate in aqueous solution and 100 percent Octyl Stearate was determined in albino rabbits by procedures outlined in the *Journal Officiel de la Republique Francaise.*[75] Each test material was applied to the shaved skin of 3 rabbits daily for 6 days. The rabbits were immobilized with a collar to prevent licking of the treated areas. The "mean maximum irritation index" of rabbits treated with undiluted Octyl Stearate was 0.67, indicating that it was "poorly tolerated." Gross examination of the treated skin in all 3 rabbits revealed vesicles and slight epidermal exfoliation. Mi-

croscopic changes included epidermal acanthosis and "congestive dermatitis." The "mean maximum irritation index" of rabbits administered 10 percent Octyl Stearate in aqueous solution was 0.33, indicating that the material was "relatively well tolerated." Grossly, vesicles were found in 2 rabbits, but no significant microscopic changes were observed.[74]

Skin Sensitization

The skin sensitization potential of 0.1 percent Butyl Stearate in physiological saline was determined in 2 white male guinea pigs. The test material was injected "intracutaneously" every other day or 3 times weekly until a total of 10 injections had been made. The first injection consisted of 0.05 ml of the test material, whereas the subsequent 9 injections consisted of 0.1 ml each. Two weeks following the tenth injection, a challenge injection was made using 0.05 ml of a freshly prepared test solution. Twenty-four hours after each injection, evaluations were made of the diameter, height, and color of skin reactions. No skin sensitization was observed in either animal.[9,90]

The skin sensitization potential of 0.1 percent Isocetyl Stearate in physiological saline was also determined in 2 white male guinea pigs. The test procedure employed was that as described above for Butyl Stearate. The saline solution containing 0.1 percent Isocetyl Stearate was nonsensitizing.[9,91]

Embryotoxicity and Effects on Reproduction

Groups of 20 male and 20 female rats were fed diets containing 6.25 percent Butyl Stearate for 10 weeks and then mated. No adverse effects were noted with respect to fertility, litter size, or survival of offspring. However, growth was significantly retarded during the preweaning and postweaning periods. No gross lesions were found among rats killed at the end of the 21-day postweaning period.[58]

Chronic Toxicity

In a 2-year feeding study, concentrations of either 0.0, 1.25, or 6.25 percent Butyl Stearate were provided in the diet to 3 groups of 16 male rats. Daily doses of the test material corresponded approximately to 0, 2500, and 6000 mg/kg, respectively. No significant differences were observed between treated and control groups with respect to growth, survival, and hematological values. As the treated and control groups increased in age, slight changes in the ratio of types of leukocytes were observed. Differential counts of bone marrow smears at 12, 23, and 24 months indicated that ingestion of Butyl Stearate did not affect either cellular distribution or the myeloid:erythroid ratio. Gross lesions included acute and chronic inflammatory pulmonary changes, nephrosis, and fatty degeneration of the liver. Other pathologic changes, such as tumors and infections, were found primarily in older rats but were not related to the Butyl Stearate administration.

Histopathological alterations observed in treated and control groups included chronic pneumonitis, diffuse fatty infiltration of the liver, focal necrosis of hepatic cells surrounding veins, and chronic nephrosis.[58]

Carcinogenicity

No data were available on the carcinogenicity of any of the Stearates under review. However, data were available on methyl stearate and stearic acid.

Female mice were injected subcutaneously with either 0.5 or 5.0 mg methyl stearate in 0.1 ml tricaprylin once a week for 26 weeks. Stearic acid was also tested in female mice at either 0.05 or 0.5 mg in 0.1 ml tricaprylin by subcutaneous injection once a week for a total of 26 injections. Mice receiving tricaprylin alone or no treatment served as controls. Results are presented in Table 7. In the 16 mice administered 5.0 mg methyl stearate, 2 subcutaneous and 2 pulmonary tumors were found. No tumors were observed in the stearic acid-treated mice. In the 16 vehicle control mice surviving at 6 months, a single breast carcinoma was observed. In the 171 untreated mice surviving 6 months, a total of 1 subcutaneous sarcoma, 10 pulmonary tumors, 14 mammary gland carcinomas, and 2 cutaneous carcinomas were recorded. The "background noise" of neoplasms in the mice used for the study was under 1 percent for subcutaneous sarcomas and under 10 percent for mammary and pulmonary tumors. Practically all tumors were found after 12 months of the study when the mice were 14 months old.[92] These data did not indicate carcinogenic activity for methyl stearate or stearic acid.

In a study involving 2 separate laboratories, female mice were injected subcutaneously with either 0.5 or 5.0 mg methyl stearate in 0.1 tricaprylin once a week for 26 weeks. Stearic acid was tested at 0.05 or 0.5 mg/0.1 ml of tricaprylin. Mice receiving tricaprylin alone or no treatment served as controls. The results of the 2 studies are summarized in Table 8. For methyl stearate, each laboratory observed 2 sarcomas at the site of injection after 21 months. According to the investigators, the findings with regard to methyl stearate were surprising, since the compound is relatively unreactive and its conversion in vivo to reactive species is difficult to envision. They considered the possibility that "solid-state" carcinogenesis was involved but noted that methyl stearate was lipid-soluble and gave clear solutions in the vehicle tricaprylin at the concentrations tested.[93]

No tumors developed in any of 10 rats fed stearic acid as 0.3 percent of their diet for 209 days.[5,94]

In a search for carrier materials for introducing potential carcinogens into mouse urinary bladders, stearic acid and other "inert vehicles" were tested for induction of bladder tumors. Pellets of stearic acid were implanted in the bladder of 62 mice and in those surviving 30 weeks. The bladder tumor incidence was 13 percent. The incidence of bladder tumors in mice implanted with either smooth (67 mice) or roughened (63 mice) glass beads was 4 and 29 percent, respectively.[95]

Experiments involving a possible action of the vehicle or a physical effect of the agent, such as in studies by subcutaneous injection or bladder implantation, are included in this evaluation of Stearate ingredients. However, the results of such tests require careful consideration, particularly if they are the only ones raising a suspicion of carcinogenicity.[96]

TABLE 7. Test Results for Carcinogenic Activity[92]

Compound	Dose/ Injection* (mg)	Schedule (Injection No./ Week/ Total Injections)	Total dose (mg Compound/ ml Tricaprylin)†	Mouse Strain‡	Mice Alive at Month						Tumor by Month of Appearance		
					0	6	9	12	15	18	Subcutaneous Sarcomas	Pulmonary Tumor	Other Tumors§
Tricaprylin	–	1/26	0/2.6	S	16	16	14	14	–	–	–	–	B(12)
None	–	–	–	S	24	23	23	22	17	13	–	24	–
None	–	–	–	S	100	80	66	56	51	21	14	14,17,17, 17,17	B(11,14, 15,17,17, 17,17,17, 18,18), C(14,15)
None	–	–	–	S	47	45	43	13	8	3	–	18	B(11,13, 16,18)
None	–	–	–	S	32	23	23	14	13	–	–	12,12,12	–
Stearic Acid	0.5	1/26	13/2.6	S	16	14	7	7	7	6	–	–	–
Stearic Acid	0.05	1/26	1.3/2.6	S	16	13	12	11	10	10	–	–	–
Methyl Stearate	5.0	1/26	130/2.6	S	16	16	16	16	14	11	15,15	15,15	–
Methyl Stearate	0.5	1/26	13/2.6	S	16	16	16	15	15	–	–	–	–

*Subcutaneous injection into inguinal area.
†Tricaprylin used was >99% pure.
‡S, Swiss Webster female mice.
§B, Breast carcinoma; C, cutaneous carcinoma.

TABLE 8. Induction of Sarcomas at Injection Site by SC Injection in Mice. Results at 21 Months[93]

Compound	*Laboratory*	*Dose (mg/0.1 ml Tricaprylin) Once Weekly**	*Total dose (mg)*	*No. of Mice at Start*	*No. of Mice Alive at 6 Months†*	*Sarcomas at Injection Site*	*Other Tumors*
Methyl Stearate	A‡	5.0	130	15	15	2	1
		0.5	13	15	15	0	3
	B§	5.0	130	16	16	2(15)‖	2
		0.5	13	16	16	0	0
Stearic Acid	A	0.5	13	15	14	0	1
		0.05	1.3	15	15	0	3
	B	0.5	13	16	14	0	0
		0.05	1.3	16	13	0	0
Tricaprylin	A	0.1 ml	–	15	15	0	0
	B	0.1 ml	–	16	16	0	1
No Treatment	A	–	–	15	15	0	0
	B	–	–	32**	23	0	3

*Injected SC, once weekly, for 26 weeks in inguinal area.
†From beginning of experiments. Median survival ranged from 15 to 21 months in test and control groups.
‡Laboratory A used ICR/Ha Swiss Millerton female mice.
§Laboratory B used CFW Swiss Webster female mice.
‖No. in parentheses indicates month when found.
**Some mice sacrificed for lung tumor observations to 6 months.

CLINICAL ASSESSMENT OF SAFETY

Ingestion

In assessing the potential hazards of ingesting Butyl Stearate when the compound was incorporated into food-wrapping film, Smith[58] calculated that a daily dose of 0.2 mg/kg would present little, if any, hazard to humans. Since rats chronically tolerated more than 14,000 times this amount without toxic effects (2500 and 6000 mg/kg daily for 2 years—see Chronic Toxicity section), the minimum safety factor to humans, according to the author, was in excess of 1400. Smith considered this value conservative.

Skin Irritation, Skin Sensitization, Phototoxicity, and Photosensitization

Results from a number of clinical studies indicate that the Stearates and cosmetic products containing the Stearates are essentially nonsensitizing, nonphototoxic, nonphotosensitizing, and at most minimal or mild skin irritants. These clinical tests are individually discussed below, and results have been summarized in Table 9.

Butyl, Cetyl, and Isocetyl Stearate were tested for skin irritation and sensitization using a panel of 111 Caucasian women. The concentration of each ingredient was 50 percent in mineral oil. The test materials were applied for 48 hours under semiocclusion to the intact skin of the back. A total of 10 consecutive induction patches were made. Following a 2-week nontreatment period, a 48-hour challenge patch was applied to the back. Butyl Stearate produced, at most, mild skin irritation in 10 subjects and sensitization in 2 subjects. Cetyl Stearate produced, at most, mild skin irritation in 10 subjects and sensitization in 1 subject. The Isocetyl ester caused mild irritation reactions in 10 subjects and no sensitization reactions. Many of the individuals with skin reactions had reactions to more than 1 Stearate. Reactions to the induction patches in any 1 individual were sporadic and did not occur throughout the entire patch series. In no instance were induction or challenge scores greater than 1 or 2 on a scale of 0 (no reaction) to 5. There were no reported areas of abnormal skin pigmentation.[97]

The procedures described by Jordan[98] and Jordan and King[99] were used to evaluate the skin irritating and sensitizing properties of both undiluted Isobutyl Stearate and undiluted Isocetyl Stearate. One hundred forty-nine men and women were selected for the study. Each cosmetic ingredient was applied under occlusive 48-hour patches to the skin of the back 3 times weekly for 3 weeks (9 induction applications). Fourteen days following the final induction application, 2 consecutive 48-hour challenge patches of the test material were applied to previously untreated sites of the back. Skin responses were evaluated on a scale of 0 (no reaction) to 4 (bullae or extensive erosions). For Isobutyl Stearate, the number of panelists having a 1+ reaction (macular, faint erythema involving at least 25 percent of the test area) was 2, 1, and 3 to induction application 3, 4, and 8, respectively. One individual had a 1+ reaction to the second challenge patch, and a second subject had a 2+ reaction (moderately intense erythema involving at least 25 percent of the test area) to the second challenge patch. No other skin

TABLE 9. Clinical Studies

Test	*Material Tested*	*Stearate Concentration (%)*	*No. of Subjects*	*Method*	*Comments/Results*	*Reference*
Skin Irritation/ Sensitization	Butyl, Cetyl, and Isocetyl Stearate each in mineral oil	Each at 50	111	Ten 48-hour induction patches followed by a 2-week nontreatment period, then a 48-hour challenge patch	Each Stearate was at most mildly irritating and essentially nonsensitizing to the skin. No abnormal skin pigmentation observed	97
Skin Irritation/ Sensitization	Isobutyl and Isocetyl Stearate	Each at 100	149	Repeat insult patch test as described by Jordon[98] and Jordan and King.[99] (Nine 48-hour induction patches, 14-day nontreatment period, two 48-hour challenge patches)	Isobutyl Stearate caused mild skin irritation and was nonsensitizing. Isocetyl Stearate was both nonirritating and nonsensitizing	100
Skin Irritation	Two samples of Isocetyl Stearate	Each sample at 100	40 (20/sample)	Single insult 24-hour occlusive patch	4/40 subjects developed minimal skin irritation	9, 101
Phototoxicity/ Photosensitization	Isobutyl and Isocetyl Stearate each in mineral oil	Each at 50	23	Repeat insult patch test procedure with UVA and/or UVB exposure (4400 $\mu W/cm^2$)	Both Stearates were nonphototoxic and nonphotosensitizing	102
Skin Irritation	Face cream	2.0 Butyl Stearate	Unspecified	24 and 48 hour closed patch test	The PII of the formulation was 0.03 and 0.11 at 24 and 48 hours, respectively	103
Skin Irritation/ Sensitization/ Photosensitization	Unspecified cosmetic product	10 Butyl Stearate	54 (RIPT) 10 (photosensitization)	Ten 48-hour occlusive patches followed by an 11-day nontreatment period, then a 48-hour challenge patch. UV treatments were made daily for 10 exposures	Product was nonirritating, and nonphotosensitizing	104, 105

Skin Irritation	Personal cleanliness product	1.0 Isopropyl Stearate	12	Applied to skin everyday for 21 days under Webril patches	Formulation was classified by the investigators as slightly irritating	106
Skin Sensitization	Two personal cleanliness products	Each product: 1.0 Isopropyl Stearate	105	Applied to skin for 24 hours every other day for 3 work weeks (that is, 10 applications)	No skin reactions observed. Investigators concluded that ". . . none of the test materials . . . possess any potential for skin sensitization under conditions of normal use"	106
Skin Irritation/ Sensitization	Personal cleanliness product	1.0 Isopropyl Stearate	40	"To use under normal conditions for 4 weeks"	No adverse reactions observed	106
Skin Irritation	Face cream	2.35 Myristyl Stearate	100	Prophetic patch test; 50 open and 50 closed patches	No skin reactions	107
Skin Irritation	Face cream	2.98 Myristyl Stearate	100	Prophetic patch test; 50 open and 50 closed patches	No skin reactions	107
Skin Irritation	Underarm cream	4.75 Myristyl Stearate	22	Applied to skin on 3 consecutive days	No skin reactions	107
Skin Irritation	Facial makeup stick	9.8 Myristyl Stearate	100	Prophetic patch test; 50 open and 50 closed patches	No skin reactions	107
Skin Irritation	Facial makeup stick	9.8 Myristyl Stearate	100	Prophetic patch test; all patches were closed	No skin reactions	107
Skin Irritation/ Sensitization	Suntan lotion and protective face cream	Each product: 7.6 Octyl Stearate	56	Applied to skin everyday under 24-hour closed patches for total of 10 induction applications; 24-hour challenge patch applied after 10–14-day nontreatment period	No skin reactions observed during induction or challenge phases. Investigators concluded that the 2 products were not capable of inducing significant irritation or sensitization in humans	108

TABLE 9. (Continued)

Test	*Material Tested*	*Stearate Concentration (%)*	*No. of Subjects*	*Method*	*Comments/Results*	*Reference*
Phototoxicity	Suntan lotion and protective face cream	Each product: 7.6 Octyl Stearate	10	Tape-stripped skin exposed to 0.2 g of each product for 24 hours under closed patch and to UV light (4400 $\mu W/cm^2$) for 15 minutes	No reactions noted at any time during the test. The investigators concluded that the 2 products were not capable of inducing significant phototoxic reactions in humans	108
Photosensitization	Suntan lotion and protective face cream	Each product: 7.6 Octyl Stearate	27	Skin exposed to 0.2 g of each product for 24 hours under closed patches and to UV light (4400 $\mu W/cm^2$) for 15 minutes; 24-hour challenge patches applied after 10–14-day nontreatment period, sites irradiated as before	"Slight reactions" observed in 4 subjects during the induction exposures; 1 of these 4 developed "erythema" at challenge. The protective face cream elicited reactions in 3 subjects during the induction phase; no reactions were observed at challenge. It was the investigator's opinion that the 2 products were not capable of inducing significant photoallergic reactions in humans	108

reactions to Isobutyl Stearate were observed. No reactions to Isocetyl Stearate were noted with the exception of 1 individual who developed a 1+ reaction to the initial challenge application. The investigator concluded that both Isobutyl and Isocetyl Stearate were nonsensitizing.[100]

A single insult, 24-hour occlusive patch test was performed with 2 samples (A and B) of undiluted Isocetyl Stearate on 40 subjects (20 subjects/sample). Of the 20 subjects tested with sample A, 2 had barely perceptible to mild skin erythema, and 18 had no skin irritation. Of the 20 subjects exposed to sample B, 2 had "barely perceptible" to mild skin erythema, whereas 18 had no skin irritation. The PII to each sample was 0.08 (maximum, 4.0), indicating minimal skin irritation.[9,101]

Twenty-three volunteers (17 women and 6 men) participated in a study designed to evaluate the phototoxicity and photosensitization of both Isobutyl and Isocetyl Stearate. Each cosmetic ingredient was prepared as a 50 percent concentration in mineral oil and subsequently tested in an identical manner. A 24-hour occlusive patch containing 0.1 ml of the test material was applied to the same site on the back of each subject on Monday, Wednesday, and Friday for 3 consecutive weeks (9 induction patches). Challenge patches were applied 2 weeks later to both the original site and to a previously untreated, adjacent site. Identical patches were also applied to the opposite side of the back to serve as nonirradiated controls. Of the 23 subjects tested, 9 received both UVA (320 to 400 nm) and UVB (280 to 320 nm) exposure, whereas 14 subjects received UVA only. The UVA exposure (50 percent transmission at 345 nm) was delivered by 4 BL fluorescent tubes at 10 cm from the skin at a dose of approximately 4400 $\mu W/cm^2$. Sites were irradiated for 5 minutes after patch removal on each Tuesday and Saturday during the induction phase. Additionally, a 150 W Xenon Arc Solar Simulator was used to deliver twice the individual minimal erythemal dose (MED) of UVB to those designated subjects after each UVA exposure. At challenge, test sites were exposed only to UVA irradiation. Skin responses were scored on a scale of 0 (no reaction) to 4 (erythema and papules) just prior to each new patch application and 72 hours after the last induction patch. Challenge sites were scored at 24, 48, 72, and 96 hours. For both Isobutyl and Isocetyl Stearate, the combination of UVA and UVB exposure produced erythematous reactions (score, 1) in all 9 subjects during the induction phase. According to the investigator, this was an expected result as the subjects were exposed to 2 times their MED. For Isobutyl Stearate, 2 of these 9 individuals (No. 4 and No. 20) had 3 reactions (erythema and edema) as a result of the first induction exposure. However, it was determined that the 2 subjects had received an excessive dose of UVB. The time of UVB exposure was subsequently reduced for these 2 individuals. Of the 2 subjects having a 3 reaction to the initial induction exposure, 1 had a second 3 reaction on the fourth induction exposure; all other scores during induction for this individual were no higher than 1. The second subject with an initial 3 induction score to Isobutyl Stearate had scores no higher than 1 throughout the remainder of the induction period. For Isocetyl Stearate, 3 subjects (No. 4, No. 13, No. 20) had 3 reactions to the first induction exposure due to an excessive dose of UVB irradiation. When the UBV exposure time was reduced for these 3 individuals, no induction reaction above 1 was noted. No other skin reactions were observed on irradiated or nonirradiated sites to either ingredient during induction or chal-

lenge phases. It was concluded that both Isobutyl and Isocetyl Stearate, each at 50 percent in mineral oil, were neither phototoxic nor photosensitizing agents in humans.[102]

A face cream containing 2.0 percent Butyl Stearate was tested for skin irritation on an unspecified number of subjects. The formulation was applied to the skin full strength under closed patches for either 24 or 48 hours. PII was 0.03 in subjects exposed for 24 hours and 0.11 in those exposed for 48 hours. No other details were reported.[103]

An unspecified type of cosmetic product containing 10 percent Butyl Stearate was found nonirritating and nonsensitizing to the skin in a repeat insult patch test (RIPT) with a panel of 54 women.[104] The same product was also nonphotosensitizing in a test involving UV exposure.[105] The induction phase of the RIPT procedure called for application of 10 consecutive 48-hour occlusive patches containing the product to the back of each of 10 women. Following an 11-day nontreatment period, a 48-hour challenge patch was applied to a previously unexposed site on the back. Application sites were graded following patch removal. In the photosensitization test, application of the product containing 10 percent Butyl Stearate "to the same areas with UV exposures was made daily for ten treatments." Additional details of the photosensitization test were lacking.

A personal cleanliness product containing 1 percent Isopropyl Stearate was tested for skin irritation on 12 subjects (1 male, 11 females). The formulation was applied under an occlusive patch once a day for 21 days to the skin of the back. The test material was reapplied to the same site throughout the study. Prior to application, the formulation was sprayed onto the patch and allowed to evaporate 10 minutes. Twenty-three hours after application, the patch was removed. The panelist was then instructed to bathe or shower immediately following removal of the patch. Reactions to the product were scored 1 hour after patch removal. Following the twenty-first treatment, a cumulative skin irritation score was calculated, and the test material was classified as one of the following: essentially nonirritating, slightly irritating, moderately irritating, or highly irritating. Under conditions of this test, the "personal cleanliness" product containing 1 percent Isopropyl Stearate was classified as slightly irritating.[106]

The skin-sensitizing potential of 2 personal cleanliness products each containing 1 percent Isopropyl Stearate was tested using 105 subjects. For the induction phase of the study, each product was applied to the skin of the back for 24 hours every other day for "three work weeks" (10 applications). The only exception to this procedure was that the third application of each week followed the second by only 10 hours; this was in contrast to the 24-hour interval between first and second applications. The test material was applied to the same site throughout the induction period. Fourteen days following the tenth induction patch, a 48-hour challenge patch was applied to the original site. A second 48-hour challenge patch was applied 8 days after the first. During the course of the study, no skin reactions were observed. The investigators concluded that ". . . none of the test materials. . . possess any potential for skin sensitization under conditions of normal use."[106]

Forty subjects were given a personal cleanliness product to use "under normal conditions" for 4 weeks. The formulation contained 1 percent Isopropyl Stearate. No adverse reactions were observed.[106]

Cosmetic products containing various concentrations of Myristyl Stearate were tested in 5 separate studies for skin irritation. A face cream containing 2.35 percent Myristyl Stearate and a second face cream containing 2.98 percent Myristyl Stearate were each applied to the skin of 100 subjects (200 total) in 2 prophetic patch tests. Fifty open and 50 closed patches were used in each study. No skin reactions were noted with either product. In another study, an underarm cream containing 4.75 percent Myristyl Stearate was applied to the skin of 22 subjects for 3 consecutive days. No skin irritation was observed. Two facial makeup sticks each formulated with 9.8 percent Myristyl Stearate were evaluated using groups of 100 subjects. The prophetic patch procedure called for 50 open and 50 closed patches in 1 study (100 subjects) and "all closed patches" in the other (100 subjects). No skin reactions were observed.[107]

A suntan lotion and a protective face cream each formulated with 7.6 percent Octyl Stearate were tested for skin irritation and/or sensitization. Approximately 0.2 g of each product was applied for 24 hours under closed patches to the inner aspect of the arm or skin of the back of 56 subjects. Patches were applied to the same site on Mondays, Wednesdays, and Fridays until a total of 10 induction applications had been made. Ten to fourteen days after the final induction patch, challenge patches were applied for 24 hours to both the original contact site and to a previously untreated adjacent site. Test sites were scored 24 and 48 hours after application. No skin reactions were observed during the induction or challenge phase to either of the product formulations. The investigator concluded that the 2 products did not produce significant irritation or sensitization in humans.[108]

To determine phototoxicity to a suntan lotion and protective face cream, 10 subjects were selected for study. Test sites on the inner aspect of the forearm were tape-stripped 6 to 10 times to remove several layers of cornified epithelium. Each product (0.2 g) was then applied under closed patches to control and test sites for 24 hours. At the end of this period, test sites were subjected to UV irradiation at a dose of 4400 $\mu W/cm^2$ for 15 minutes. The UV light source, held 10 to 12 cm from the skin, consisted of 4 GE F40 BL black light lamps. The wavelength of the light source was in the UVA range, with a peak at 360 nm. No reactions were noted to either product containing 7.6 percent Octyl Stearate. The investigator concluded that the 2 products did not produce significant phototoxic reactions in humans.[108]

Twenty-seven subjects were tested with a suntan lotion and protective face cream for photosensitization. Approximately 0.2 g of each product was applied to test sites under closed patches for 24 hours. Following removal of the patch, test sites were given nonerythrogenic UV irradiation at a dose of 4400 $\mu W/cm^2$ for 15 minutes. The UV light source consisted of a GE F40 BL black light with a peak wavelength of 360 nm. The control sites were covered with black tape to prevent UV exposure. Immediately following irradiation, all sites were evaluated. The patch sites were then covered with Webril or Dermicel to prevent inadvertent exposure to sunlight. This procedure was repeated each Monday, Wednesday, and Friday until "10 applications/irradiation" had been made. Following a 10 to 14-day nontreatment period, challenge patches were applied to the original contact site and to a previously untreated adjacent site. Twenty-four hours after application, the patches were removed, the sites examined for dermal response,

and the test areas irradiated again. Additional scorings were made 48 and 72 hours after application. The suntan lotion containing 7.6 percent Octyl Stearate produced "slight reactions" in 4 subjects. One subject developed "slight delayed reactions" to the sixth induction exposure at both control and irradiated test sites. However, no further reactions were observed at either site. A second and third subject had "slight reactions" to the ninth and tenth induction exposures, respectively. Neither of these 2 people reacted to the challenge patches. A fourth subject developed "erythema" as a result of the eighth induction exposure; this reaction dissipated after the site had been irradiated. This same subject also developed "erythema" at each of the 2 challenge sites. According to the investigators, the skin reactions of the fourth subject were "only slight and probably not significant." Three subjects reacted to the protective face cream containing 7.6 percent Octyl Stearate. Two subjects had erythema to the sixth and eighth induction exposures; 1 of these subjects "reacted" after the seventh induction patch at the nonirradiated control site. A third subject "reacted slightly" to the ninth induction exposure. No reactions were observed in any subjects at challenge. It was the investigator's opinion that the 2 product formulations containing 7.6 percent Octyl Stearate were not capable of inducing significant photoallergic reactions in humans.[108]

SUMMARY

The 7 Stearates described in this report are either oily liquids or waxy solids. They are prepared by esterification of stearic acid with the appropriate alcohol. Because of the technical grade of stearic acid and the alcohols used as starting materials, the commercially available stearates are often mixtures of various esters. These Stearates can be expected to undergo reactions typical of esters, such as conversion into stearic acid and the corresponding alcohol by chemical or enzymatic hydrolysis, conversion into amides by ammonolysis, and conversion into different esters by alcoholysis or transesterification.

Butyl, Isobutyl, and Isocetyl Stearate have a wide variety of noncosmetic applications. Some of these applications include use as a lubricant, solvent fixative, and/or emollient in pharmaceuticals, as a solvent for dyes, as a spreading and/or softening agent in textiles, plastics, and rubber, as a plasticizer, and as a waterproofing agent. Federal regulations permit the use of Butyl Stearate as a direct and indirect food additive and as a synthetic flavoring agent.

The Stearates are primarily used in cosmetics as skin emollients. Depending on the specific type of cosmetic product, these esters may also function as color-suspending agents, water-repelling plasticizers, spreading or "carrying" agents, stiffening agents, gelatin enhancers, lubricants, fixatives, solvents, or viscosity builders. When applied to the skin or lips, the low viscosity and oily nature of these ingredients provide a nongreasy, hydrophobic film.

Cosmetic firms participating in the voluntary cosmetic registration program reported to the FDA in 1981 that Butyl, Cetyl, Isocetyl, Isopropyl, Myristyl, and Octyl Stearates were used in a total of 116, 4, 58, 16, 1, and 10 cosmetic products, respectively. Stearate concentrations in these products generally ranged from 1 to 25 percent, although there were a few reported instances of higher and lower concentrations. The most frequent uses of the Stearates were in eye

makeup preparations, skin makeup preparations, lipstick, and skin care preparations. Cosmetics containing these esters are intentionally applied to or come in contact with eyes, skin, hair (and scalp), nails, and vaginal mucosa. Small amounts of these esters could be ingested from lipstick.

Aliphatic esters are hydrolyzed to the corresponding alcohol and acid and further metabolized. In the case of the Stearate ingredients, stearic acid would be metabolized in the same manner as other fatty acids.

The toxicology of the Stearates was assessed in a number of animal studies. Butyl Stearate (50 percent in mineral oil) was weakly comedogenic when applied to rabbit skin 5 days a week for 2 weeks. The subcutaneous and intraperitoneal LD_{50}s in rats of undiluted Butyl Stearate were both >32 mg/kg. Acute oral LD_{50} values varied according to ingredient and species tested. However, Butyl, Isocetyl, Isopropyl, Myristyl, and Octyl Stearates generally had low acute oral toxicity in rats and mice. Undiluted Butyl and Isopropyl Stearate was nonirritating to the rabbit eye, whereas undiluted Isocetyl, Myristyl, and Octyl Stearates caused slight transient ocular irritation in rabbits. Undiluted Butyl, Isobutyl, Isocetyl, Isopropyl, Myristyl, and Octyl Stearates produced at most minimal or moderate skin irritation in rabbits. Application of undiluted Octyl Stearate to the skin of rabbits daily for 60 days caused irritation (vesicles and slight epidermal exfoliation) and was generally "poorly tolerated." Microscopic changes in the treated skin included epidermal acanthosis and "congestive" dermatitis. Application of 10 percent Octyl Stearate in aqueous solution to rabbit skin daily for 60 days caused irritation (vesicles) but was "relatively well tolerated." No significant pathological reactions were observed upon microscopic examination of the treated skin. No skin sensitization was observed to either Butyl (0.1 percent in physiological saline) or Isocetyl Stearate (0.1 percent in physiological saline) when given intracutaneously to guinea pigs by means of 10 induction injections and 1 challenge injection. Fertility, litter size, and survival of offspring were normal in rats fed diets containing 6.25 percent Butyl Stearate for 10 weeks. However, growth was reduced in offspring during the preweaning and postweaning period. No gross lesions were noted among the offspring killed at the end of the 21-day postweaning period. Rats fed dietary concentrations of 1.25 or 6.25 percent Butyl Stearate (corresponding to 2500 and 6000 mg/kg, respectively) for 2 years had no significant differences from control animals with respect to growth, survival, blood counts, or other hematologic parameters.

In clinical studies, Butyl, Cetyl, Isobutyl, and Isocetyl Stearates (undiluted or 50 percent in mineral oil) and cosmetic products containing Butyl, Isopropyl, Myristyl, and Octyl Stearates (1.0, 2.0, 2.35, 2.98, 4.75, 7.6, and/or 9.8 percent) were at most minimally to mildly irritating to the human skin, essentially nonsensitizing, nonphototoxic, and nonphotosensitizing. It has been estimated by 1 investigator that daily ingestion of 0.2 mg/kg Butyl Stearate would present little, if any, hazard to humans. This estimation was based on the results of chronic feeding studies in rats.

DISCUSSION

Currently available tests are inadequate in predicting the ability of a cosmetic ingredient to cause comedones in humans. However, comedogenicity is a poten-

tial health effect that should be considered when the Stearate ingredients are used in cosmetic formulations.

CONCLUSION

On the basis of the information presented in this report, the CIR Expert Panel concludes that Butyl, Cetyl, Isobutyl, Isocetyl, Isopropyl, Myristyl, and Octyl Stearate are safe as cosmetic ingredients in the present practices of use.

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