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Final Report on the Safety Assessment of Isostearic Acid

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

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

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

CHEMISTRY

Composition

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

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

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

TABLE 1. Fatty Acid Components of Isostearic Acid.

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

Data from Ref. 4.

Physical Properties

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

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

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

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

Reactivity

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

TABLE 2. Chemical and Physical Properties of Isostearic Acid.

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

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

Analytical Methods

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

Impurities

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

USE

Purpose in Cosmetics

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

Scope and Extent of Use in Cosmetics

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

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

Potential Interactions with Other Ingredients

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

TABLE 3. Product Formulation Data on Isostearic Acid.

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

Data from Ref. 19.

Surfaces to which Commonly Applied

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

BIOLOGICAL PROPERTIES

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

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

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

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

Metabolism

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

Animal Toxicology

Acute Studies

Oral toxicity

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

Primary skin irritation and phototoxicity

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

TABLE 4. Acute Oral Toxicity Tests on Isostearic Acid.

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

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

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

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

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

Eye irritation

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

Comedogenicity

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

*Comedones are also known as blackheads.

TABLE 6. Draize Eye Irritation Tests on Isostearic Acid.

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

– No data.

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

Clinical Assessment of Safety

Primary Skin Irritation

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

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

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

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

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

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

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

Irritation/Sensitization

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

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

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

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

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

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

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

Phototoxicity and Photosensitization

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

SUMMARY

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

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

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

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

DISCUSSION

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

CONCLUSION

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

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