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Final Report on the Safety Assessment of Glyceryl Stearate and Glyceryl Stearate/SE

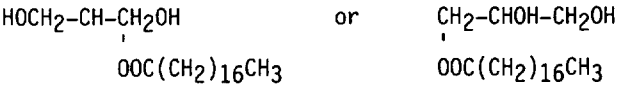
Glyceryl Stearate and Glyceryl Stearate/SE are the esterification products of glycerine and stearic acid, and are used in cosmetic formulations as emollients, emulsifiers, and stabilizers. In acute oral toxicity studies in rats, both ingredients were slightly toxic. Glyceryl Stearate in the diet of rats for three consecutive generations had no adverse effects. Five percent Glyceryl Stearate did not promote the carcinogenicity of DMBA in mouse skin. In subchronic and chronic dermal toxicity tests, Glyceryl Stearate was nontoxic to rabbits but did cause moderate irritation. Primary eye irritation studies, at concentrations up to 100%, were mildly irritating or nonirritating to rabbits. Single and Repeated Insult Patch Tests showed both ingredients to be nonsensitizing and nonirritating. Products containing 2% Glyceryl Stearate were nonphototoxic and nonphotoallergenic. On the basis of the available data, it is concluded that Glyceryl Stearate and Glyceryl Stearate/SE are safe for topical application to humans in the present practices of use and concentration.

CHEMISTRY

Description and Preparation

Glyceryl Stearate

GLYCERYL Stearate is the esterification product of glycerol and stearic acid. The monoglyceride can conform to either of the following structures:[1,2]



Glyceryl Stearate is prepared commercially by high temperature esterification of stearic acid and glycerol or by transesterification of an appropriate triglyceride with glycerine.[3] Verkade and Van der Lee[4] mixed anhydrous glycerol with the methyl ester of stearic acid in a solution of 1% sulfuric acid and sodium sulfate and added magnesium oxide to form the Glyceryl Stearate product. Bertoni et al.[5] reported a similar preparation, although he used a sodium methoxide catalyst and a pyridine solvent. Veikhertz[6] reacted stearic acid with anhydrous glycerol for 40 h at 200°C and extracted the Glyceryl Stearate in cold water. Cressey[2] reported a method in which stearic acid triglyceride is hydrolyzed in the presence of an alkaline catalyst. Lichnerova[7] prepared the 1-monoester by first reacting glycerol with acetone to form isopropylidene glycerol. With the hydroxy groups protected in the 2nd and 3rd positions, the one free primary alcohol group was esterified with the chloride salt of stearic acid. The resulting stearic ester was then partially hydrolyzed, resulting in the desired 1-glyceryl stearate.

In addition to these methods, Glyceryl Stearate can be extracted commercially from sea buckthorn, whale oil, and shark liver oil.[8-10]

Glyceryl Stearate/Self-Emulsifying

Glyceryl Stearate/Self-Emulsifying is the esterification product of glycerol and an excess of stearic acid; the excess stearic acid is reacted with potassium hydroxide to produce an emulsifying soap. Glyceryl Stearate/SE is prepared by the controlled high-temperature esterification of glycerol and excess stearic acid or by partial saponification of a triglyceride. The excess stearic acid is neutralized with potassium hydroxide to yield a product which contains potassium stearate.[3]

Properties

Glyceryl Stearate is a white or cream-colored wax-like solid with a faint odor and an agreeable fatty taste. It is soluble in alcohol, petroleum ether, benzene, acetone, and mineral oil but insoluble in water. Glyceryl Stearate is characterized by "plastic" flow at temperatures between 20° and 50°C.[3,7,11,12] The chemical and physical properties of Glyceryl Stearate are summarized in Table 1.

Glyceryl Stearate has a polymorphic crystalline structure with three modifications: a low melting α form and two higher melting forms, β and β'. The α form is the first to separate when molten glyceryl stearate is cooled. The α form changes rapidly into the more stable β form, which in turn slowly changes into the most stable β' form.[13,14] Lichnerova[7] reported a fourth, sub-α form which lacks a defined melting point and readily passes into the α form. The transformation of the sub-α form to the α form was reversible; this is an exception to the rule of irreversible crystalline transformation.

Glyceryl Stearate/SE is a white to cream-colored wax-like solid.[3] Its physical and chemical properties are summarized in Table 2.

Reactivity

Glyceryl Stearate undergoes reactions typical of fatty acid esters including glycerolysis, hydrolysis, transesterification, and enzymatic cleavage.[2,15,16] Under favorable conditions, Glyceryl Stearate can also autoxidize.[17] Glyceryl Stearate undergoes hydrolysis in aqueous media.[18]

Analytical Methods

Glyceryl Stearate is frequently determined by chromatographic analyses. These include gas chromatography, reversed-phase partition chromatography, thin-layer chromatography, high-performance liquid chromatography, and absorption chromatography.[19-27] Glyceryl Stearate can be analyzed directly or converted, prior to gas chromatographic analysis, to a trimethyl silyl ether derivative.[27] Glyceryl Stearate can also be added to acetyl nitrate in silicic acid and the nitrate derivative then separated by chromatographic methods.

Other analytical methods include x-ray diffraction, differential thermal analysis, periodimetry, periodic oxidation, electron spin resonance, and infrared spectroscopy.[2,13,14,33-36] Forman and Grady[37] identified Glyceryl Stearate from other compounds in pharmaceutical creams by a method of channel-type inclusion in urea.

Impurities

Both Glyceryl Stearate and Glyceryl Stearate/SE contain such reaction impurities as glycerol, stearic acid, and water.[3] Commercial Glyceryl Stearate and Glyceryl Stearate/SE may contain glyceryl distearate (42–44%), glyceryl tristearate (20–23%), free glycerol (3–5%) and small quantities of soap (if an alkaline catalyst is used in its preparation).[2] Certain preparations of Glyceryl Stearate and Glyceryl Stearate/SE also contain mono-, di-, and triesters of palmitic, oleic, and myristic acids, as well as unreacted fatty acids. The amount of these ester impurities is varied by the manufacturer to modify product stability and emulsification. Molecularly distilled Glyceryl Stearate contains over 90% of the monoester.[38]

TABLE 1. PHYSICAL AND CHEMICAL PROPERTIES OF GLYCERYL STEARATE.[a]

Property	*Value*
Molecular weight	358.57
Melting point	
α-form	74 °C
β-form	81 °C
β′-form	79 °C
Commercial	56 °–58 °C
Boiling point	238 °–240 °C
Density (g/cm³)	0.9841
Specific gravity (25°C)	0.97
Refractive index	1.400
pH (3%)	9.309
Acid value[b]	1.5–3.0
Iodine value	0.5–4.0
Saponification value	160–177
Fatty free acids	<5%
Monoglycerides	40–50%
Glycerol	1.0–8.0%
Water	1.0% (max.)

[a]Data from Refs. 3, 6, 12, 28–30.

[b]The acid value of Glyceryl Stearate increases as the compound ages.[31]

Additives

Both Glyceryl Stearate and Glyceryl Stearate/SE may contain 200 ppm butylated hydroxytoluene (BHT), which is added by the manufacturer as a preservative.[3] BHT is a Generally Recognized as Safe (GRAS) substance for which regulations have been issued under the Food, Drug and Cosmetic Act.[39] Its use in food as a GRAS food additive is limited to 0.02%.

TABLE 2. PHYSICAL AND CHEMICAL PROPERTIES OF GLYCERYL STEARATE/SE.[a]

Property	*Value*
Melting range	50 °–78 °C
Acid value	10–22 (max.)
Saponification value	138–170
Combustion residue	0.1% (max.)
Free glycerine	6–10%
Iodine value	3–6% (max.)
Isobutane soluble material	85.7%
Free fatty acids	76.0%
Combined glycerol	12.7%
Monoglycerides	30–45%
Potassium Stearate	5–12%
Water	1% (max.)
Ionic character	Nonionic/Anionic

[a]Data from Refs. 3, 32.

USE

Cosmetic Use

Purpose of Use

Glyceryl Stearate and Glyceryl Stearate/SE are widely used in cosmetics. When applied to skin, they produce a waxy, occlusive, water-soluble film, which makes it useful for hand lotions and creams. The viscosity of any emulsion that contains Glyceryl Stearate is directly proportional to the amount of Glyceryl Stearate present; Glyceryl Stearate is used to regulate the thixotropic index and viscosity of a cosmetic. Products that contain up to 3% Glyceryl Stearate are lotions, whereas those containing 10% Glyceryl Stearate are creams. Excessive skin defatting caused by the sulfates and sulfonates in detergent cleansing creams can be avoided by the presence of Glyceryl Stearate. Glyceryl Stearate base is used to stabilize a product, decrease water evaporation, make the product freeze-resistant, and keep it from forming surface crusts. Glyceryl Stearate also reduces the greasiness of oils used in certain cosmetic preparations. Glyceryl Stearate is used in cosmetic products as an opacifier, auxiliary oil/water emulsifier, acid stabilizer, and nonionic surfactant.[11,31,38,40-50]

Glyceryl Stearate/SE is used as an emulsifier and viscosity regulator. It needs no other auxiliary emulsifier to form a stable emulsion unlike Glyceryl Stearate, which requires such surfactants as soap to yield a stable preparation.[31]

Scope and Extent of Use in Cosmetics

According to the industry's voluntary submissions to the Food and Drug Administration (FDA) in 1976, Glyceryl Stearate and Glyceryl Stearate/SE are used in over 1200 and over 200 cosmetic formulations, respectively, in concentrations of ≥0.1–50%. Table 3 summarizes the product formulation data for the two ingredients.[51]

TABLE 3. PRODUCT FORMULATION DATA.[a]

Ingredient/Cosmetic Product Type	*Concentration (percent)*	*No. of product formulations*
Glyceryl Stearate		
Lotions, oils, powders, and creams	>0.1–5	11
Other bath preparations	>0.1–1	1
Eyeliner	>0.1–5	32
Eyeshadow	>0.1–10	28
Eye makeup remover	>1–5	2
Mascara	>25–50	1
	>10–25	7
	>5–10	12
	>1–5	24
	>0.1–1	2
Other eye makeup preparations	>1–10	7
Perfumes	>1–25	4
	≤0.1	1
Powders	>0.1–25	129
Sachets	>0.1–10	16
Hair conditioners	>0.1–25	65
Permanent waves	>1–5	1
	>0.1–1	1
Rinses	>1–5	9
	>0.1–1	4
Shampoos	>5–10	3
	>1–5	4
	>0.1–1	1

TABLE 3. (Continued).

Ingredient/Cosmetic Product Type	*Concentration (percent)*	*No. of product formulations*
Tonics and dressings	>1–5	6
	>1–10	3
Hair dyes	>5–10	2
Rinses	≤0.1	24
Bleaches	>1–5	1
Shampoos (coloring)	>1–5	1
	≤0.1	1
Blushers	>1–5	7
	>0.1–1	5
	≤0.1	3
Face powders	>0.1–1	2
	≤0.1	6
Foundations	>1–5	89
	>0.1–1	13
	≤0.1	5
Leg and body paints	>1–5	15
Makeup bases	>5–10	1
	>1–5	36
	>0.1–1	8
Rouges	>1–5	2
	>0.1–1	1
Skin care preparations (cleansing)	>10–25	7
	>5–10	6
	>1–5	64
	>0.1–1	27
	≤0.1	2
Depilatories	>1–5	2
Face, body, and hand	>10–25	4
	>5–10	15
	>1–5	151
	>0.1–1	42
Hormone	>1–5	2
	>0.1–1	1
Moisturizing	>10–25	2
	>5–10	16
	>1–5	183
	>0.1–1	49
Night	>10–25	1
	>5–10	6
	>1–5	35
	>0.1–1	3
Mud packs	>10–25	2
	>5–10	9
	>1–5	5
Skin lighteners	>10–25	4
	>5–10	1
	>1–5	2
Skin fresheners	>1–5	1
	>0.1–1	1
Fixatives	>1–5	1
	>0.1–1	1
Other makeup preparations (not eye)	>1–5	4
	>0.1–1	6

TABLE 3. (Continued).

Ingredient/Cosmetic Product Type	*Concentration (percent)*	*No. of product formulations*
Cuticle softeners	>10–25	1
	>5–10	2
	>1–5	5
Nail creams and lotions	>25–50	1
	>10–25	1
	>1–5	5
Bath soaps and detergents	>1–5	2
	≤0.1	1
Douches	>10–25	3
	>5–10	6
	>1–5	7
	>0.1–1	1
Other personal cleanliness products	>10–25	2
	>5–10	6
	>1–5	5
	>0.1–1	2
Aftershave lotions	>0.1–1	2
Shaving cream	>1–5	3
	>0.1–1	2
Other shaving preparations	>1–5	1
Wrinkle removers	>1–5	2
Other skin care preparations	>10–25	2
	>5–10	1
	>1–5	16
	>0.1–1	4
Suntan and sunscreen products (gels, creams, and liquids)	>5–10	9
	>1–5	23
	>0.1–1	4
Indoor tanning	>1–5	2
Glyceryl Stearate/SE		
Eyeliners	>0.1–1	32
Eyeshadows	>1–5	2
Eye lotion	>1–5	1
Mascara	>1–5	1
Other eye makeup preparations	>0.1–1	4
Sachets	>1–5	14
	>0.1–1	1
Other fragrance preparations	>1–5	1
Hair conditioners	>10–25	1
	>5–10	1
	>1–5	1
Hair straighteners	>5–10	4
Blushers	≤0.1	1
Foundations	>1–5	13
	>0.1–1	1
Makeup bases	>1–5	1
	>0.1–1	54
Other personal cleanliness products	>10–25	2
Aftershave lotions	>5–10	1
Skin care preparations (face, body, and hand)	>10–25	3
	>5–10	5
	>1–5	15
	≤0.1	1

TABLE 3. (Continued).

Ingredient/Cosmetic Product Type	*Concentration (percent)*	*No. of product formulations*
Hormone	>5-10	1
Moisturizing	≤0.1-25	32
Night	>1-5	2
	>0.1-1	1
Skin lighteners	>1-5	3
Skin fresheners	>0.1-5	1
Other skin care preparations	>10-25	1
	>1-5	2
	>0.1-1	1
	≤0.1	1
Cleansing creams	>5-10	2
	>1-5	4
	>0.1-1	3
	≤0.1	3

[a]From Ref. 51.

Non-Cosmetic Use

Glyceryl Stearate is used in food as a surfactant, emulsifier, flavor dispersant, antistalant, antisticking, and thickening agent. It is most widely used in bread for its emulsifying and surfactant properties; in baking products it serves as an antistalant and dough conditioner.[2,11,52-63]

Glyceryl Stearate is a GRAS substance regulated by the Food, Drug and Cosmetic Act.[39] Its concentration in food ranges from 0.01 to 2.0%; the possible average daily intake, based on the types of food consumed, is about 15 mg/kg for persons aged two or older and 150 mg/kg for infants. These estimates are considered to be maximum possible intakes; more realistically, a person is likely to ingest approximately 63 mg (or approximately 1 mg/kg) of Glyceryl Stearate daily.[64]

Glyceryl Stearate is also approved as a specific indirect food additive, under regulation of the Food, Drug and Cosmetic Act. There are no specific limitations on the use in food of Glyceryl Stearate as a surface lubricant and as a defoamer in coatings intended for use in food production, packaging, treating, transporting, or holding (21 CFR 176.200, 21 CFR 175.300).

Glyceryl Stearate is used in pharmaceutical preparations as a solidifier and controled release agent. It is used in suppositories as a lipophile and as an agent to prevent sedimentation of dispersed solids.[65-73] Glyceryl Stearate is used as a base in over-the-counter (OTC) topical analgesics (44 CFR 69771). Table 4 lists the non-cosmetic uses of Glyceryl Stearate.

BIOLOGICAL PROPERTIES

Bactericidal Properties

Glyceryl Stearate (1.50 μg/ml) did not inhibit growth of gram-positive bacteria.[74] Weddeburn[75] observed that in cosmetic preparations containing a preservative, and Glyceryl Stearate as a surfactant, the preservative's efficiency was reduced as the surfactant preservative ratio increased. He suggested that such nonionic surfactants as Glyceryl Stearate allow microorganisms to become resistant to preservatives.

Absorption, Metabolism, and Excretion

When ingested, monoglycerides are readily absorbed through the duodenal mucosa and converted to triglycerides. However, ingestion of 25 g of Glyceryl Stearate by human subjects caused no ap-

TABLE 4. NON-COSMETIC USE OF GLYCERYL MONOSTEARATE AS DRUG-RELEASE AGENT, SURFACTANT, AND EMULSIFIER.

Drug Released/In	*Surfactant in*	*Emulsifier in*
Aminophenazone/Suppositories[67,79-81]	Tablets[82]	Salves[83]
Azophen/Suppositories[84,85]	Macaroni[86-90]	Liquid milk replacers[52,91,92]
Salicylate/Suppositories[93-96]	Bread[97,98]	Ice cream[99,100]
Salicylate/Ointments[38,101]	Cakes[102]	Ointments[103,104]
Oxytetracyclene/Ointments[105]	Dehydrated potatoes[106]	Dental lotions[107]
Sulfathiazole + Ephedrine/ Ointments[108]	Coconut oil[109]	Cakes[110,111]
Sulfanilmide/Tablets[112]	Frying oils[113]	Bread[114]
Sulfosalicylate/PVC Tablets Matrix[115,116]	White petroleum[117]	Pasta[118,119]
Bromophenylamine Maleax/ —[120]	—	Margarine[121]
Ethyl Aminobenzoate/Dental Lotions[122]	—	Starch paste[123]
Phenindion/Capsules[124]	—	Peanut butter[125]
Isoprenaline/Tablets[126]	—	Food (general)[127,128]
Morphine-Naltrexone/Tablets[129]	—	—
Acetylsalicylic Acid/Tablets[130,131]	—	—

parent change in serum triglyceride concentrations. Only a slight increase occurred after ingestion of 50 g. Since stearic acid is a solid fat at body temperature, it may not be readily absorbed in the intestine.[76]

The effects of Glyceryl Stearate on kidney tissue and splenic enzymes have been studied. Gall[77] reported that a solution of 0.5 mg/ml Glyceryl Stearate had no deleterious effect on monkey kidney tissue cultures. Blonder et al.[78] observed that Glyceryl Stearate did not inhibit glucocerebrosidase activity in vitro.

Animal Toxicology

Oral Toxicity

Acute

Various high doses of Glyceryl Stearate and Glyceryl Stearate/SE at concentrations greater than those used in cosmetics, were practically nontoxic when administered to rats by gavage (Table 5).

Chronic

When incorporated in the diet of rats at concentrations of 15–25% for three consecutive generations, Glyceryl Stearate had no adverse effects on body weight, growth, and reproduction. In a simultaneous study, rats which consumed a diet containing 25% Glyceryl Stearate daily for two years developed renal calcifications and their liver weight increased.[10]

Dermal Toxicity

Primary irritation

The Draize method (or a modification of it), the Federal Hazardous Substances Labeling Act (FHSLA) method, and the Department of Transportation (DOT) method were used to evaluate the potential skin irritancy of Glyceryl Stearate and Glyceryl Stearate/SE. These two substances were reported to be nonirritating or mildly irritating even when they were tested at 100 percent concentrations. The highest reported Primary Irritation Index (PII) was 1.80 out of a possible 4.00 (Table 6).

Subchronic toxicity

Glyceryl Stearate (4–5%) was applied at 2 ml/kg/day five days a week for four weeks to the clipped abraded dorsal skin of six white rabbits. Comparison of mean body weights, clinical signs, hematological results, and gross pathology results showed no significant differences between

TABLE 5. ACUTE ORAL TOXICITY.

Compound	*Conc. (Percent)*	*No. of animals/Species*	*Dose*	*LD50*	*Comments*[c]	*Ref.*
GS[a]	33.3 in PGDD[d]	10 rats	10 g/kg	>10 g/kg	40% fatalities at 10 g/kg–mildly toxic/ practically nontoxic	132
GS	33.3 in PGDD	10 rats	10 g/kg	>10 g/kg	Practically nontoxic	133
GS	33.3 in PGDD	10 rats	10 g/kg	>10 g/kg	Practically nontoxic	134
GS	33.3 in corn oil	30 rats	1.0–32.0 g/kg	>32.0 g/kg	Relatively harmless	135
GS	20.0 in corn oil	30 rats	2–64 ml/kg	>64 ml/kg	Relatively harmless	135
GS (protective cream)	2 (active ingredient)	10 mice	15 ml/kg	>15 ml/kg	Relatively harmless	136
GS	100	5 rats (per grp)	–	>5.0 g/kg	Practically nontoxic	137
GS	100	5 rats (per grp)	–	>5.0 g/kg	Practically nontoxic	137
GS/SE[b]	33.3 in corn oil	30 rats	1.0–32.0 g/kg	>32 g/kg	Relatively harmless	138
GS/SE	33.3 in PGDD	10 rats	10 g/kg	>10 g/kg	40% fatalities at 10 g/kg–mildly toxic/ practically nontoxic	139
GS/SE	25 in corn oil	15 rats	7.5 and 10 g/kg	>10 g/kg	40% fatalities at 10 g/kg–mildly toxic/ practically nontoxic	140
GS/SE	25 in PGDD	10 rats	10 g/kg	>10 g/kg	Practically nontoxic	141
GS/SE	100	5 rats (per grp)	–	>5 g/kg	Practically nontoxic	137

[a]Glyceryl Stearate.
[b]Glyceryl Stearate/SE.
[c]According to Hodge and Sterner.
[d]Propylene glycol dicaprylate-dicaprate.

TABLE 6. PRIMARY SKIN IRRITATION.

Compound	*Protocol*	*No. of rabbits*	*Conc. (Percent)*	*PII*	*Comments*	*Ref.*
GS[a]	FHSLA	6	50 in corn oil	0	Nonirritating	138
GS	FHSLA	6	100	0	Nonirritating	144
GS	DOT	6	100	0	Nonirritating	144
GS	Draize	6	100	0.208	Erythema only—mostly at 24 h—mildly irritating	134
GS	Draize	6	100	0.208	One rabbit only—erythema and edema (1+) at 24 and 72 h—mildly irritating	133
GS	Draize (Mod)	2	100	0.625	Erythema and edema at 24 and 72 h—mildly irritating	132
GS	A[c]	9	100	0.039[d]	Minimally irritating	145
GS	A	9	20 in corn oil	0.039[d]	Minimally irritating	145
GS	Draize	3	3.0 in mineral oil	0.5	Erythema at 24 h only—mildly irritating	146
GS	A	9	50 in corn oil	0.72[d]	Mildly irritating	145
GS	A	9	50 in corn oil	0.11	Mildly irritating	137
GS	A	9	100	1.8	Mildly irritating	148
GS	A	9	100	1.6	Mildly irritating	148
GS	A	9	100	1.6	Mildly irritating	148
GS	A	9	100	1.4	Mildly irritating	148
GS	A	9	100	1.2	Mildly irritating	148
GS	A	9	100	1.5	Mildly irritating	148
GS	A	9	100	1.4	Mildly irritating	148
GS	A	9	100	1.33	Mildly irritating	148
GS	A	9	100	0.33	Minimally irritating	148
GS	A	9	50 in corn oil	0.06	Minimally irritating	148
GS (Protective cream)	Draize	3	2.0 (active ingredient)	0.5	Erythema at 24 h only—mildly irritating	136

GS (First aid cream)	A	3	5.0 (active ingredient)	0.89	Mildly irritating	149
GS (Blemish stick)	A	9	13.8 (active ingredient)	0.89	Mildly irritating	150
GS (Suntan lotion)	A	9	2.0 (active ingredient)	0.5	Mildly irritating	136
GS/SE[b]	Draize	6	100	0	Nonirritating	141
GS/SE	Draize	6	100	0	Nonirritating	140
GS/SE	Draize	6	100	0.25	Mildly irritating	139
GS/SE	FHSLA	6	50 in corn oil	0	Nonirritating	144
GS/SE	FHSLA	6	50 in corn oil	0	Nonirritating	135
GS/SE	DOT	6	50 in corn oil	0	Nonirritating	135
GS/SE	Draize (Mod)	3	5.0 in water	0	Nonirritating	146
GS/SE	A	9	50 in corn oil	0.22[d]	Mildly irritating	145
GS/SE	A	9	50 in corn oil	0.50	Mildly irritating	137
GS/SE	A	9	50 in corn oil	0.63	Mildly irritating	137
GS/SE	A	9	50 in corn oil	0.66	Mildly irritating	137
GS/SE	A	9	50 in corn oil	0.38	Mildly irritating	137
GS/SE	A	9	50 in corn oil	0	Nonirritating	137
GS/SE	A	9	50 in corn oil	0.17	Minimally irritating	137

[a]Glyceryl Stearate.

[b]Glyceryl Stearate/SE.

[c]0.5 ml applied to clipped intact back of each animal under occlusive patch. Patch removed at 24 h. Site scored at 24 and 72 h.[147]

[d]Maximum score (PII) = 4.

Glyceryl Stearate-treated rabbits and untreated controls. Animals treated with the Glyceryl Stearate solution developed such moderate irritation as slight to moderate desquamation and slight to well-defined erythema in all animals and many cases of atonia and fissuring.[142]

Chronic toxicity

A 4–5% solution of Glyceryl Stearate was applied at 2 ml/kg/day five days a week for 13 weeks to the clipped abraded dorsal skin of six white rabbits. Slight to moderate erythema, edema, atonia, and occasional fissuring occurred in all test animals. Dermatopathologic findings consisted of dermal inflammatory cell infiltrates, hyperkeratosis, and acanthosis. There were no changes in body weight, no gross toxic effects, no gross skin lesions, and no changes in organ weight attributable to the test material. It was concluded that the Glyceryl Stearate-solution was a moderate skin irritant.[143]

Sensitization

The Landsteiner/Jacobs Method and the Kligman Maximization Procedure were used to determine the sensitizing potential of Glyceryl Stearate and Glyceryl Stearate/SE in guinea pigs. Glyceryl Stearate and Glyceryl Stearate/SE proved to be nonsensitizing (Table 7).

Eye Irritation

The Draize procedure or a modification of it was used to evaluate the potential eye irritancy of Glyceryl Stearate and Glyceryl Stearate/SE. The ingredient was instilled into one eye of each test rabbit. In four tests, some eyes were rinsed after the introduction of the test substance. Eye irritation was scored for a specified number of days after the ingredient was instilled. These studies indicate that Glyceryl Stearate and Glyceryl Stearate/SE are nonirritating to mildly irritating to the eye at concentrations up to 100%. The highest reported mean irritation score at any time was 7 (maximum score = 110) (Table 8).

Carcinogenicity

Glyceryl Stearate was fed to 53 mice at doses of 50–100 mg daily until the animals died. Three mice (5.6%) developed brain tumors on the upper surface of the frontal lobe, consisting mainly of differentiated nerve cells. Glyceryl Stearate (50–100 mg/day) plus cholesterol (4–5 mg/day) in the diet induced brain tumors in ten of 72 mice (13.8%). Of 80 mice fed 4–5 mg/day cholesterol alone, 20 developed brain tumors (25%) but none of the 188 control mice did.[152]

A diet containing 1.5% Glyceryl Stearate was fed to mice daily until they died to determine if the ingredient induced gastric tumors. Two or 1.7% of the 115 mice developed forestomach papillomas. Two of the 195 control mice (1.0%) developed forestomach papillomas.[153]

Saffiotti and Shubik[154] tested the tumor promoting activity of Glyceryl Stearate on the clipped dorsal skin of Swiss mice. One week after a single application of 9,10-dimethylbenz(a)anthracene (DMBA) (1–1.5% in mineral oil), 5% Glyceryl Stearate (in acetone) was applied to skin twice weekly. No tumors developed; slight epidermal hyperplasia at the site of application was noted.

Glyceryl Stearate, administered orally in doses of 2.5 or 10 mg/day for five days, was not an effective antitumor agent in mice implanted with one-day-old Erlich ascites carcinomas.[155]

Clinical Assessment of Safety

Single Insult Patch Test (SIPT)

Seven lots of Glyceryl Stearate were tested for irritation on panels of 20 subjects each. A single occlusive patch containing the undiluted test material was applied to each subject's skin and left in place for 24 h. Patches were then removed and the skin sites scored for irritation. Of the 140 patches applied, only six resulted in irritation (no score was greater than 2 in a maximum of 4). The results indicated that undiluted Glyceryl Stearate is, at worst, a mild irritant.[148]

A blemish stick and a first aid cream containing 13.8% and 5.0% Glyceryl Stearate, respectively, were tested for potential skin irritancy using a SIPT. Each formulation was applied under occlusion to 20 subjects. The PIIs for the blemish stick and first aid cream were 0.03 and 0.3, respectively (maximum score = 4.0), indicating mild irritation.[150,159]

A modified Maibach Cumulative Irritancy Test was used to study a hair product containing

TABLE 7. SENSITIZATION.

Compound	*Dose/ Conc. (percent)*	*Method*	*No. of Guinea pigs*	*No. of Induction Phases/ Route/Time*	*Rest period*	*Challenge (site)*	*Comments*	*Ref.*
GS[a]	0.1 ml/0.1	Lansteiner/Jacobs	2	10 injections; every other day	2 weeks	0.05 ml (virgin)	Nonsensitizing	132
GS	0.1 ml/0.1	Lansteiner/Jacobs	2	10 injections; every other day	2 weeks	0.05 ml (virgin)	Nonsensitizing	133
GS	0.1 ml/0.1	Lansteiner/Jacobs	2	10 injections; every other day	2 weeks	0.05 ml (virgin)	Nonsensitizing	134
GS	5[c]	Kligman Max.	10	6 applied to abraded skin; every other day	2 weeks	0.5 ml	Nonsensitizing	151
GS/SE[b]	0.1 ml/0.1	Lansteiner/Jacobs	2	10 injections; every other day	2 weeks	0.05 ml (virgin)	Nonsensitizing	141
GS/SE	0.1 ml/0.1	Lansteiner/Jacobs	2	10 injections; every other day	2 weeks	0.05 ml (virgin)	Nonsensitizing	140
GS/SE	0.1 ml/0.1	Lansteiner/Jacobs	2	10 injections; every other day	2 weeks	0.05 ml (virgin)	Nonsensitizing	139

[a]Glyceryl Stearate
[b]Glyceryl Stearate/SE
[c]Booster of 75% GS in petrolatum (0.05 ml) applied occlusively for 48 h one week after last induction application.

TABLE 8. DRAIZE PRIMARY EYE IRRITATION.

Compound	No. of rabbits	Conc. (Percent)	Eye wash Y/N	Scores (Max = 110) Day						Comments	Ref.
				1 h	1	2	3	4	5		
GS[a]	9	100	Y	0	0	0	0	0	0	Nonirritating	156
GS	9	100	Y	0	0	0	0	0	0	Nonirritating	144
GS	6	100	N	–	0	0	0	–	–	Nonirritating	138
GS	3	3.0 in mineral oil	N	0	0	0	0	0	0	Nonirritating	157
GS	6	20 in corn oil	N	–	1	1	1	0	0	Minimally irritating	145
GS	6	100	N	–	2	1	0	0	0	Minimally irritating	148
GS	6	50 in corn oil	N	–	6	3	1	0	0	Mildly irritating	137
GS (Suntan lotion)	3	2.0 (active ingredient)	N	–	0	0	0	0	0	Nonirritating	136
GS (Blemish stick)	3	13.8 (active ingredient)	N	–	4	0	–	–	–	Minimally irritating	150
GS (First aid cream)	2	5.0 (active ingredient)	N	–	1	1	0	–	–	Minimally irritating	149
GS (Protective cream)	3	2.0 (active ingredient)	N	0	0	0	0	0	0	Nonirritating	136

GS/SE[b]	6	100	N	–	0	0	0	–	–	Nonirritating	158
GS/SE	9	50	Y	67	0	0	0	0	0	Minimally irritating	135
GS/SE	3	5.0 in water	N	0	0	0	0	0	0	Nonirritating	146
GS/SE	6	50 in corn oil	Y	–	1	1	0	0	0	Minimally irritating	137
GS/SE	6	50 in corn oil	N	–	1	1	0	0	0	Minimally irritating	137
GS/SE	6	50 in corn oil	N	–	1	1	0	0	0	Minimally irritating	137
GS	6	100	N	–	0	–	–	–	–	Nonirritating	137
GS	6	100	N	–	6	2	1	1	0	Slightly irritating	137
GS	6	100	N	–	5	2	1	0	–	Minimally irritating	137
GS	6	100	N	–	7	2	0	–	–	Slightly irritating	137
GS	6	100	N	–	4	2	1	–	0	Mildly irritating	137
GS	6	100	N	–	1	0	–	–	–	Nonirritating	137
GS	6	100	N	–	3	2	0	–	–	Mildly irritating	137
GS	6	100	N	–	2	2	0	–	–	Mildly irritating	148
GS	6	100	N	–	1	1	0	–	–	Minimally irritating	148
GS	6	100	N	–	2	1	0	–	–	Minimally irritating	148
GS	6	100	N	–	1	1	0	–	–	Minimally irritating	137
GS	6	50 in corn oil	N	–	2	0	–	–	–	Minimally irritating	137

[a]Glyceryl Stearate
[b]Glyceryl Stearate/SE
Y = Yes
N = No

12.5% Glyceryl Stearate on seven males and females. The test material was applied under occlusion to the back of each subject for 24 h; upon patch removal, sites were scored and a fresh patch applied. This procedure was repeated daily for 21 days. Although it produced minimal or definite erythema in five subjects, the product containing 12.5% Glyceryl Stearate was considered to be "essentially nonirritating," when compared to positive and negative control values.[160]

Repeated Insult Patch Test (RIPT)

A RIPT was used on 61 subjects to evaluate the potential irritancy and sensitizing effect of 20% Glyceryl Stearate in a 10% mineral oil/10 percent petrolatum vehicle. Ten to fifteen 24-hour occlusive patches were applied for two to three weeks. After a 10- to 14-day rest, a challenge patch was applied to either the original or a virgin site; the sites were scored on patch removal. Twenty percent Glyceryl Stearate did not induce sensitization.[137]

Patches containing 20% Glyceryl Stearate in petrolatum were applied daily for three days to the arms of 1206 subjects; the Chamber method was used. None of the subjects developed allergic reactions.[161]

A suntan lotion and a face cream, each containing 2.0% Glyceryl Stearate, were tested with a RIPT. Ten occlusive 24-hour patches containing the test substance were applied to one arm of each of 19 subjects for two weeks. Patch sites were scored 24 hours after each patch was removed, before a fresh patch was reapplied. Ten to 14 days after the removal of the tenth induction patch, 24-hour challenge patches were applied to each original site as well as to a virgin site. Sites were scored 24 and 48 h later. There were no reactions to either induction or challenge patches and it was concluded that the suntan lotion and the face cream are incapable of inducing significant irritation or sensitization.[162]

A similar RIPT was used to evaluate a first aid cream containing 5.0% Glyceryl Stearate. Occlusive patches with the test product were applied for 24 h to subject's skin once daily for two to three weeks. After a 10- to 14-day rest, a single occlusive 24-hour challenge patch was applied. Thirty-one of the 52 subjects tested experienced minimal irritation to the induction patches but none had a sensitization reaction to the challenge patch.[147,149]

The same first aid cream was tested for cumulative irritancy in a Maibach 21-day Cumulative Irritancy Test. Occlusive patches containing the test product were applied to the backs of nine subjects. The patches were removed 24 h later, the sites scored, and fresh patches reapplied to the site. This procedure was repeated until 21 patches had been applied. The cumulative irritation index for this formulation was calculated to be 48 (maximum score = 756).[149]

Photoallergy and Phototoxicity

A suntan lotion and a face cream, each containing 2% Glyceryl Stearate, were tested for potential phototoxicity and photoallergenicity. For the phototoxicity test, 0.2 ml of the lotion was tested under occlusive patches to a tape-stripped area of each arm of the subject. The patches were removed 24 h later and the sites scored for irritation. The contact site of the left arm was designated as the nonirradiated control and that of the right arm was exposed to four FYBL black lights (maximum output = 360 nm) at a dose of 4400 $\mu W/cm^2$ for 15 min at a distance of 10–12 cm. Immediately after irradiation and after 24, 48, and 168 h, none of the ten subjects showed reactions, either at control or irradiated sites. It was concluded that the two formulations are nonphototoxic.[162]

For the photoallergy test, the protocol was similar to that used above except that patches were applied and the sites irradiated every other day until ten patches had been applied. After a two-week rest, 24-hour challenge patches were applied to the original and to virgin sites. The treated sites were scored upon patch removal and then they were irradiated. Treated sites were again scored at 24, 48, and 72 h after irradiation. Occasional irritation occurred at various sites but both products were considered to be "incapable of producing significant photoallergy" in humans.[162]

Other Clinical Experience

Rudzki et al.[163] added various emulsifiers to a base containing a known irritant to determine if the emulsifiers enhanced percutaneous absorption. Patches containing various concentrations of potassium dichromate in a white paraffin base were applied to the arms of 66 men and women. When 10% Glyceryl Stearate was added to each patch, subjects reacted to lower dichromate concen-

trations. An in vitro study showed that 10% Glyceryl Stearate enhanced release of Cr(VI) from the white paraffin base.

Worker Experience

A chemical manufacturing company which has been producing Glyceryl Stearate and Glyceryl Stearate/SE for 14 years has no complaints of adverse reaction from any employee directly involved with the handling of these ingredients.[164]

SUMMARY

Glyceryl Stearate and Glyceryl Stearate/SE are the esterification products of glycerine and stearic acid. Glyceryl Stearate/SE contains excess stearic acid reacted with potassium hydroxide to produce a self-emulsifying product. Both Glyceryl Stearate and Glyceryl Stearate/SE are white to cream-colored wax-like solids. Either ingredient may contain mono-, di-, and triglyceride impurities and fatty acid impurities.

Glyceryl Stearate and Glyceryl Stearate/SE are widely used in cosmetic formulations as emollients, auxiliary emulsifiers, viscosifiers, stabilizers, bases, and surfactants. Glyceryl Stearate is used in more than 1200 cosmetic formulations at concentrations of ≥0.1–50%; Glyceryl Stearate/SE is used in over 200 cosmetic products at concentrations of ≥0.1–50%.

Glyceryl Stearate is also widely used in foods as a surfactant, emulsifier, and thickener. Glyceryl Stearate is an antistalant and dough conditioner in breads and is also used in pharmaceutical bases. Glyceryl Stearate has been granted regulatory status as GRAS ingredient, an indirect food additive, a direct food additive, and as an OTC substance.

In acute oral toxicity studies in rats, Glyceryl Stearate and Glyceryl Stearate/SE were nontoxic or mildly toxic. In chronic studies, 15–25% Glyceryl Stearate in the diet of rats for three consecutive generations had no adverse effects. Rats fed a diet containing 25% Glyceryl Stearate for two years developed renal calcifications.

Glyceryl Stearate and Glyceryl Stearate/SE at concentrations of up to 100% were reported to be mildly irritating or nonirritating to the skin of rabbits. In subchronic and chronic dermal toxicity tests, 4–5% Glyceryl Stearate was nontoxic to rabbits but did cause moderate irritation (slight to moderate erythema, edema, atonia, desquamation, and/or fissuring). In seven guinea pig sensitization studies, it was concluded that neither Glyceryl Stearate nor Glyceryl Stearate/SE was capable of inducing sensitization.

In primary eye irritation studies, Glyceryl Stearate and Glyceryl Stearate/SE at concentrations up to 100% were mildly irritating or nonirritating when instilled in the eyes of rabbits.

Glyceryl Stearate, fed to mice in doses of 50–100 mg/day or 1.5% in the diet until they died, did not induce significant brain or gastric tumor formation, respectively. Five percent Glyceryl Stearate did not promote the carcinogenicity of DMBA in mouse skin.

Single and Repeated Insult Patch Tests used to evaluate human skin irritation and sensitization potential of Glyceryl Stearate and Glyceryl Stearate/SE showed both ingredients to be nonsensitizing and nonirritating. Products containing 2% Glyceryl Stearate were nonphototoxic and nonphotoallergic. Worker experience shows that Glyceryl Stearate and Glyceryl Stearate/SE are nonirritating to human skin.

DISCUSSION

Glyceryl Stearates are used in 1,400 cosmetic formulations to regulate their thixotropic indices and viscosity. The viscosity of the emulsions containing these compounds is directly proportional to the amount of Glyceryl Stearates present. Thus, products that contain up to 3% are lotions and those containing 10% are creams.

In food products, Glyceryl Stearates are used as antistalants, surfactants, emulsifiers, flavor dispersants, antisticking, and thickening agents. They are GRAS ingredients and have been approved as direct food additives by the Food, Drug and Cosmetic Act. The compounds have also

been used in pharmaceutical preparations for about 40 years. In pharmaceuticals they are largely used as solidifiers and controlled release agents. They are also used in suppositories. It is not surprising, therefore, to find extensive literature on the preparation, usefulness, and safety of these ingredients. There are, in addition, numerous unpublished data on animal tests applicable to the assessment of the safety of these ingredients.

Glyceryl Stearates have been subjected to a number of chronic toxicity tests that show no adverse effects on reproduction in rats fed high levels in the diet through three generations,[10] no tumor initiation[152,153] and no tumor promotion in mice.[154]

Clinical safety data are limited, but long clinical experience and abundant animal studies prove these compounds to be nonsensitizing, nonphototoxic and nonphotosensitizing. Human phototesting, single and repeated patch testing has been carried out on too few subjects, but none of the available data provides suspicion of risk associated with the use of Glyceryl Stearate and Glyceryl Stearate/SE as cosmetic ingredients. Furthermore, chemical manufacturing worker experience for 14 years has produced no adverse employee reactions.

CONCLUSION

On the basis of the available animal data and clinical experience presented in this report, the Panel concludes that Glyceryl Stearate and Glyceryl Stearate/SE are safe for topical application to humans in the present practices of use and concentration.

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