Final Report of the Amended Safety Assessment of Glyceryl Laurate, Glyceryl Laurate SE, Glyceryl Laurate/Oleate, Glyceryl Adipate, Glyceryl Alginate, Glyceryl Arachidate, Glyceryl Arachidonate, Glyceryl Behenate, Glyceryl Caprate, Glyceryl Caprylate, Glyceryl Caprylate/Caprate, Glyceryl Citrate/Lactate/Linoleate/Oleate, Glyceryl Cocoate, Glyceryl Collagenate, Glyceryl Erucate, Glyceryl Hydrogenated Rosinate, Glyceryl Hydrogenated Soyate, Glyceryl Hydroxystearate, Glyceryl Isopalmitate, Glyceryl Isostearate, Glyceryl Isostearate/Myristate, Glyceryl Isostearates, Glyceryl Lanolate, Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Montanate, Glyceryl Myristate, Glyceryl Isotridecanoate/Stearate/Adipate, Glyceryl Oleate SE, Glyceryl Oleate/Elaidate, Glyceryl Palmitate, Glyceryl Palmitate/Stearate, Glyceryl Palmitoleate, Glyceryl Pentadecanoate, Glyceryl Polyacrylate, Glyceryl Rosinate, Glyceryl Sesquioleate, Glyceryl/Sorbitol Oleate/Hydroxystearate, Glyceryl Stearate/Acetate, Glyceryl Stearate/Maleate, Glyceryl Tallowate, Glyceryl Thiopropionate, and Glyceryl Undecylenate[1]

The safety of 43 glyceryl monoesters listed as cosmetic ingredients was reviewed in a safety assessment completed in 2000. Additional safety test data pertaining to Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate were received and served as the basis for this amended report. Glyceryl monoesters are used mostly as skin-conditioning agents—emollients and/or surfactant—emulsifying agents in cosmetics. The following 20 glyceryl monoesters are currently reported to be used in cosmetics: Glyceryl Laurate, Glyceryl Alginate, Glyceryl Arachidonate, Glyceryl Behenate, Glyceryl Caprylate, Glyceryl Caprylate/Caprate, Glyceryl Cocoate, Glyceryl Erucate, Glyceryl Hydroxystearate, Glyceryl Isostearate, Glyceryl Lanolate, Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Myristate, Glyceryl Oleate/Elaidate, Glyceryl Palmitate, Glyceryl Polyacrylate, Glyceryl Rosinate, Glyceryl Stearate/Acetate, and Glyceryl Undecylenate. Concentration of use data received from the cosmetics industry in 1999 indicate that Glyceryl Monoesters are used at concentrations up to 12% in cosmetic products. Glyceryl Monoesters are not pure monoesters, but are mostly mixtures with mono-, di-, and tri-esters. The purity of commercial and conventional Monoglyceride (Glyceryl Monoester) is a minimum of 90%. Glyceryl Monoesters (monoglycerides) are metabolized to

Received 12 February 2004; accepted 4 June 2004.

[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. This report was prepared by Wilbur Johnson, Jr., Senior Scientific Analyst and Writer.

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International Journal of Toxicology, 23(Suppl. 2):55–94, 2004

ISSN: 1091-5818 print / 1092-874X online
DOI: 10.1080/10915810490499064

free fatty acids and glycerol, both of which are available for the resynthesis of triglycerides. Glyceryl Laurate enhanced the penetration of drugs through cadaverous skin and hairless rat skin in vitro and has been described as having a wide spectrum of antimicrobial activity. A low-grade irritant response was observed following inhalation of an aerosol containing 10% Glyceryl Laurate by test animals. Glyceryl monoesters have little acute or short-term toxicity in animals, and no toxicity was noted following chronic administration of a mixture consisting mostly of glyceryl di- and mono- esters. Glyceryl Laurate did have strong hemolytic activity in an in vitro assay using sheep erythrocytes. Glyceryl Laurate, Glyceryl Isostearate, or Glyceryl Citrate/Lactate/Linoleate/Oleate were not classified as ocular irritants in rabbits. Undiluted glyceryl monoesters may produce minor skin irritation, especially in abraded skin, but in general these ingredients are not irritating at concentrations used in cosmetics. Glyceryl monoesters are not sensitizers, except that Glyceryl Rosinate and Hydrogenated Glyceryl Rosinate may contain residual rosin, which can cause allergic reactions. These ingredients are not photosensitizers. Glyceryl Citrate/Lactate/Linoleate/Oleate was not mutagenic in the Ames test system. Glyceryl Laurate exhibited antitumor activity and Glyceryl Stearate was negative in a tumor promotion assay. At concentrations higher than used in cosmetics, Glyceryl Laurate did cause moderate erythema in human repeat-insult patch test (RIPT) studies, but the other glyceryl monoesters tested failed to produce any significant positive reactions. Glyceryl Rosinate was irritating to animal skin at 50%, but did not produce sensitization in clinical tests at concentrations up to 10% and covered with semioccluded patches. There is reported use of Glyceryl Rosinate at 12% in mascara, which is somewhat higher than the concentration in the clinical testing. It was reasoned that the available data do support the safety of this use because there would be minimal contact with the skin and no occlusion. The safety of Arachidonic Acid was not documented and substantiated for cosmetic product use in an earlier safety assessment and those same safety questions apply to Glyceryl Arachidonate. Based on these data, the Cosmetic Ingredient Review (CIR) Expert Panel found that these glyceryl monoesters are safe as cosmetic ingredients in the present practices of use and concentration: except that the available data are insufficient to support the safety of Glyceryl Arachidonate. Additional data needed to support the safety of Glyceryl Arachidonate include (1) dermal absorption data; and, based on the results of the absorption studies, there may be a need for (2) immunomodulatory data; (3) carcinogenicity and photocarcinogenicity data; and (4) human irritation, sensitization, and photosensitization data.

INTRODUCTION

Glyceryl monoesters are a group of ingredients comprising esters of glycerin and assorted fatty acids or fatty acid derivatives. The 43 glyceryl monoesters listed in the *International Cosmetic Ingredient Dictionary and Handbook* (Pepe et al. 2002), which have uses in a wide variety of cosmetic products, mostly as conditioning agents, are included in this safety assessment. A final safety assessment of glyceryl monoesters was updated with additional safety test data for Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate and an amended conclusion was reached.

Only 16 of the 43 ingredients were reported to the U.S. Food and Drug Administration (FDA) by industry as being used in cosmetics, but data received directly from industry indicate that an additional 4 ingredients are being used in cosmetics. If ingredients that are currently not used were to be used in the future, the Cosmetic Ingredient Review (CIR) Expert Panel expects that the types of products and the concentrations used would be similar to those in current use.

Safety test data are available for only a limited number of ingredients. The CIR Expert Panel also considered safety assessments of related ingredients to be relevant. These include the earlier safety assessments of Glyceryl Stearate and Glyceryl Stearate SE (Elder 1982), Glyceryl Oleate (Elder 1986), and Arachidonic Acid (Andersen 1993).

CHEMISTRY

Chemical and Physical Properties

The glyceryl monoesters of fatty acids are primarily white to yellow oils or oily waxes with faint fatty odors. These substances are not pure monoesters, but are mixtures with mono-, di-, and tri-ester contents of approximately 4:4:2 (Unichema International 1997b). Danisco Ingredients (1999c, 1999d) guarantees that the purity of their commercial and conventional Monoglyceride is a minimum of 90%.

The octanol/water partition coefficient (K_{ow}) is normally a measured value defined as the ratio of a chemical's concentration in the octanol phase to its concentration in the aqueous phase of a two-phase octanol/water system. The partition coefficient is normally represented by its $\log_{10}$ value.

The octanol/water partition coefficient may be calculated. One method for calculating $\log(K_{ow})$ involves the use of fragment constants (Leo, Hansch, and Elkins 1971; Lyman, Reehl, and Rosenblatt 1982). The development of a method for calculation of $\log(K_{ow})$ for glycerol monoesters is based on the known values of glycerol monoacetate and glycerol monobutyrate. Knowing these values, the fragment-constant of the glycerol-ester part can be calculated. From this value, the $\log(K_{ow})$ of any glycerol monoester can be calculated using the chain-length and the number of double bonds (DB) of the acid part.

Physical properties of glyceryl monoesters are listed in Table 1.

These ingredients may be supplied as trade mixtures. The physical properties of one such trade mixture (50% Gylceryl Rosinate with 50% octyldecyl myristate) are shown in Table 2.

Further descriptions of the ingredients in this safety assessment follow.

Glyceryl Laurate (CAS nos. 142-18-7 and 27215-38-9) is the monoester of glycerin and lauric acid that conforms generally to the formula (Pepe, Wenninger, and McEwen 2002):

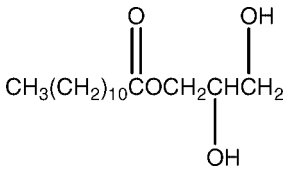


TABLE 1
Physical properties of Glyceryl Monoesters

Property	Description	Reference
	Glyceryl Laurate	
Form	Cream-colored paste	Lewis 1993
	White crystalline	Hüls America, Inc., no date
	White to cream-colored powder	Henkel KgaA 1996
	Off-white pellets	Danisco Ingredients 1996
Solubility	Dispersable in water; soluble in methanol, ethanol, toluene, naphtha, mineral oil, cottonseed oil, and ethyl acetate	Lewis 1993
	Practically insoluble in water; hardly soluble to readily soluble in acetone, diethyl ether, and heptane	Hüls America, Inc., no date
Odor	Faint	Lewis 1993
	Faint, fatty odor	Hüls America, Inc., no date
Molecular weight	274.4	Kabara 1984
Melting point	23–27°C	Scientific & Technical Information Network (STN) International 1997
	56–60°C	Hüls America, Inc., no date Henkel KgaA 1996
Dropping point	56°C	Hüls America, Inc., no date Henkel KgaA 1996
Density	0.98	Lewis 1993
pH	8.0–8.6 (25°C for 5% aqueous dispersion)	Lewis 1993
	4–5 (10% in methanol/water 1:1)	Hüls America, Inc., no date
Hydroxyl value	395	Danisco Ingredients 1996
Iodine value	5–8	Lewis 1993
	2% max. (based on I_2)	Hüls America, Inc., no date Henkel KgaA 1996
	<1	Danisco Ingredients 1996
Iodine color	3 mg/100 ml max. (based on I_2)	Hüls America, Inc., no date
Saponification value	200–206	STN International 1997
	195–205 mg KOH/g	Hüls America, Inc., no date Henkel KgaA 1996
	205	Danisco Ingredients 1996
Acid value	3 mg KOH/g max.	Hüls America, Inc., no date
	3% max.	Henkel KgaA 1996
UV absorption	λ_{max} at 238 nm; λ_{min} at 295 nm	Danisco Ingredients 1999e
	Glyceryl Behenate	
UV absorption	λ_{max} at 238 nm; λ_{min} at 288 nm and 290 nm	Danisco Ingredients 1999e
	Glyceryl Caprate	
UV absorption	λ_{max} at 238 nm; λ_{min} at 287 nm and 291 nm	Danisco Ingredients 1999e
	Glyceryl Caprylate	
Form	White crystalline	Hüls America, Inc., no date
Solubility	Practically insoluble in water; hardly soluble to readily soluble in various water/ethanol mixtures; readily soluble in acetone, diethyl ether, and heptane	Hüls America, Inc., no date
Iodine value	1 g/100 g max. (based on I_2)	Hüls America, Inc., no date
Iodine color	3 mg/100 ml max. (based on I_2)	Hüls America, Inc., no date
Saponification value	245–265 mg KOH/g	Hüls America, Inc., no date
Acid value	3 mg KOH/g max.	Hüls America, Inc., no date

(Continued on next page)

TABLE 1
Physical properties of Glyceryl Monoesters *(Continued)*

Property	Description	Reference
UV absorption	λ_{max} at 238 nm; λ_{min} at 295 nm	Danisco Ingredients 1999e
	Glyceryl Caprylate/Caprate	
UV absorption	λ_{max} at 238 nm; λ_{min} at 295 nm	Danisco Ingredients 1999e
	Glyceryl Citrate/Lactate/Linoleate/Oleate	
Form	Viscous, yellowish liquid	Hüls America, Inc., no date
Odor	Odor likened to soya bean oil; neutral taste	Hüls America, Inc., no date
pH	6–7 (10% in water)	Hüls America, Inc., no date
Saponification value	230–250 mg KOH/g	Hüls America, Inc., no date
Acid value	15 mg KOH/g max.	Hüls America, Inc., no date
	Glyceryl Cocoate	
Form	White to slightly yellowish liquid	Hüls America, Inc., no date
Solubility	Practically insoluble in water; hardly soluble to soluble in variouys water/ethanol mixtures; readily soluble in acetone, soluble in diethyl ether, and hardly soluble in heptane	Hüls America, Inc., no date
Odor	Odor likened to coconut oil	Hüls America, Inc., no date
Melting point	31–37°C	Hüls America, Inc., no date
Iodine value	3 g/100 g max. (based on I_2)	Hüls America, Inc., no date
Iodine color	5 mg/100 ml max. (based on I_2)	Hüls America, Inc., no date
Saponification value	200–300 mg KOH/g	Hüls America, Inc., no date
Acid value	2 mg KOH/g max.	Hüls America, Inc., no date
	Glyceryl Collagenate	
Appearance	Clear to hazy amber liquid	Brooks Industries 1998
Odor	Proteinaceous odor	Brooks Industries 1998
Solubility	At 5%, soluble in water, glycerine, 40% aqueous alcohol, sodium lauryl sulfate, and cocamidopropyl betaine	Brooks Industries 1998
Specific gravity at 20°C	1.2	Brooks Industries 1998
Boiling point	215°C	Brooks Industries 1998
% volatile by volume	80%	Brooks Industries 1998
	Glyceryl Erucate	
Calculated Octanol/water partition coefficient ($\log(K_{ow})$)	8.61	Danisco Ingredients 1999a
UV absorption	λ_{max} at 238 nm; λ_{min} at 287 nm and 291 nm	Danisco Ingredients 1999e
	Glyceryl Isostearate	
Form	Crystals; color <6 on Gardner scale	Gattefossé 1998
Odor	Faint	
Specific gravity at 20°C	0.930 to 0.970	Gattefossé 1998
Refractive index at 20°C	1.455 to 1.475	Gattefossé 1998
Viscosity at 20°C	0.7 to 1.2 Pa	Gattefossé 1998
Hydroxyl value	180–280 mg KOH/g	Gattefossé 1998
Iodine value	<15 g/100 g (based on I_2)	Gattefossé 1998
Saponification value	150–170 mg	Gattefossé 1998
Acid value	<4 mg KOH/g	Gattefossé 1998
	Glyceryl Linoleate	
Form	Crystals obtained from benzene as solvent	Lide and Frederikse 1993
	Soft plastic	Danisco Ingredients 1996
Solubility	Soluble in ether, benzene, and chloroform	Lide and Frederikse 1993

(Continued on next page)

TABLE 1
Physical properties of Glyceryl Monoesters *(Continued)*

Property	Description	Reference
Refractive index	1.4758 at 20°C	Lide and Frederikse 1993
Molecular weight	354.53	Lide and Frederikse 1993
Melting point	14.5°C	Lide and Frederikse 1993
	45°C (completely melted)	Danisco Ingredients 1996
Hydroxyl value	310	Danisco Ingredients 1996
Iodine value	105	Danisco Ingredients 1996
Saponification value	160	Danisco Ingredients 1996
UV absorption	λ_{max} at 238 nm; λ_{min} at 270 nm	Danisco Ingredients 1999e
	Glyceryl Myristate	
UV absorption	λ_{max} at 238 nm; λ_{min} at 293 nm	Danisco Ingredients 1999e
	Glyceryl Oleate/Elaidate	
UV absorption	λ_{max} at 239 nm; λ_{min} at 270 nm	Danisco Ingredients 1999e
	Glyceryl Palmitate	
Specific rotation	−4.37 (in pyrimidine)	Lide and Frederikse 1993
Calculated Octanol/water partition coefficient ($\log(K_{ow})$)	6.38	Danisco Ingredients 1999a
Molecular weight	330.51	Lide and Frederikse 1993
Melting point	71–72°C	Lide and Frederikse 1993
UV absorption	λ_{max} at 238 nm; λ_{min} at 295 nm	Danisco Ingredients 1999e
	Glyceryl Palmitate/Lactate	
Form	Off-white pellets	Danisco Ingredients 1996
Dropping point	50°C	Danisco Ingredients 1996
Hydroxyl value	160	Danisco Ingredients 1996
Iodine value	<2	Danisco Ingredients 1996
Saponification value	245–265	Danisco Ingredients 1996
Acid value	5 max.	Danisco Ingredients 1996
UV absorption	λ_{max} at 239 nm; λ_{min} at 287 nm	Danisco Ingredients 1999e
	Glyceryl Palmitate/Stearate	
UV absorption	λ_{max} at 238 nm; λ_{min} at 295 nm	Danisco Ingredients 1999e
	Glyceryl Palmitoleate	
UV absorption	λ_{max} at 238 nm; λ_{min} at 270 nm and 280 nm	Danisco Ingredients 1999e
	Glyceryl Sesquioleate	
UV absorption	λ_{max} at 239 nm	Danisco Ingredients 1999e
	Glyceryl Stearate/Citrate	
Form	White ivory-colored powder	Hüls America, Inc., no date
Solubility	Well soluble in acetone; insoluble in alcohols and ethers; sparingly soluble in ethanol; and turbid soluble in medium shain triglycerides and fatty oils	Hüls America, Inc., no date
Odor	Neutral, fatty odor	Hüls America, Inc., no date
Melting point	59–63°C	Hüls America, Inc., no date
pH	10–30 (10% in water 1:1)	Hüls America, Inc., no date
Saponification value	230–260 mg KOH/g	Hüls America, Inc., no date
Acid value	15–25 mg KOH/g max.	Hüls America, Inc., no date

TABLE 2
Physical properties of Purified Ester Gum-2-OctylDodecyl Myristate (Purified Ester Gum/M.O.D.), a trade mixture containing 50% Glyceryl Rosinate and 50% Octyldecyl Myristate

Property	Description	Reference
Appearance	Viscous transparent light-brown liquid with almost no odor	Shin-Ei Chemical Company Ltd. 1998
Description	Viscous liquid made up of purified ester gum dissolved in 2-octyl dodecyl myristate in a 50:50 ratio. Ester gum is a rosin ester whose main component is ester of abietic acid and glycerol	Cosmo Trends, no date
Specific Gravity (d_{25}^{25})	0.9625 to 0.9725	U.S. Cosmetics Corporation 1998
Refractive Index (n_D^{20})	1.4930 to 1.4980	U.S. Cosmetics Corporation 1998
Solubility	Soluble in olive oil, castor oil, petrolatum, and liquid paraffin. Insoluble in glycerin, water, and propylene glycol	Shin-Ei Chemical Company Ltd. 1998
Melting point	No data available	Shin-Ei Chemical Company Ltd. 1998
Flash point	272°C	U.S. Cosmetics Corporation 1998
Acid value	<12	U.S. Cosmetics Corporation 1998
Heavy metals (ppm)	<20	U.S. Cosmetics Corporation 1998
Arsenic (ppm)	<2	U.S. Cosmetics Corporation 1998
Moisture (%)	<0.1 g	U.S. Cosmetics Corporation 1998
Solid content (%)	50 ± 2	U.S. Cosmetics Corporation 1998
Percent volatile	Almost none	Shin-Ei Chemical Company Ltd. 1998
Volatile organic compounds	None identified	Shin-Ei Chemical Company Ltd. 1998
Oxidation	Little tendency to oxidize	Shin-Ei Chemical Company Ltd. 1998
Stability	Stable with almost no reactivity	Shin-Ei Chemical Company Ltd. 1998
Hazardous decomposition products	Almost none	Shin-Ei Chemical Company Ltd. 1998

According to Danisco Ingredients (1999c), two isomeric forms (α and β) exist; the structure above is the α form. Glyceryl Laurate also has been described as a distilled monoglyceride that is made from edible vegetable fatty acids (mainly lauric acid) (Danisco Ingredients 1999c) as well as a molecular distillated lauric acid monoglyceride (Henkel KgaA 1994). Other names for this chemical include Dodecanoic Acid, 2,3-Dihydroxypropyl Ester; Dodecanoic Acid, Monoester with 1,2,3-Propanetriol; Glyceryl Monolaurate; and Lauricidin (Pepe, Wenninger, and McEwen 2002); Laurin, 1-Mono; alpha-Monolaurin; 1-Glyceryl Laurate; 1-Monododecanoylglycerol; 1-Monolaurin; Dodecanoic Acid alpha-Monoglyceride; Glycerin 1-Monolaurate; Glycerol alpha-Monolaurate; Glycerol 1-Laurate; Glycerol 1-Monolaurate; Glyceryl Monododecanoate; Glyceryl Monolaurate; Lauric Acid alpha-Monoglyceride; and Lauric Acid 1-Monoglyceride (Scientific & Technical Information Network [STN] International 1997).

Commercial Glyceryl Laurate consists of 90% monoester, free glycerol (maximum 4%), and free fatty acid (maximum 1%). Its fatty acid profile is as follows: C_{10} (maximum 10%), C_{12} (maximum 90%), and C_{14} (maximum 8%) (Kabara 1984).

Henkel KgaA (1996) confirmed the 90% monoester content of Glyceryl Laurate and indicated that free glycerin is present at concentrations up to 2%.

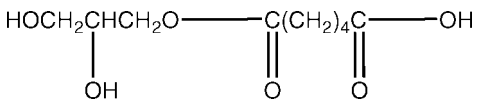
Hüls America, Inc. (no date) states that Glyceryl Laurate contains free glycerol (1%), monoglycerides (95%), diglycerides (2%), and water (maximum 1%).

Danisco Ingredients (1996) states that the composition of Glyceryl Laurate is as follows: monoester content (minimum 90%), free glycerol (maximum 1%), and free fatty acids (maximum 1.5%).

Glyceryl Laurate SE is a self-emulsifying grade of Glyceryl Laurate that contains some sodium and/or potassium laurate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Laurate/Oleate is the monoester of glycerin and a blend of lauric and oleic acids (Pepe, Wenninger, and McEwen 2002).

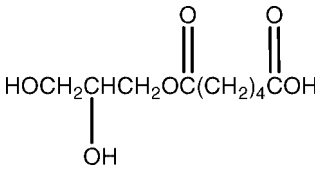
Glyceryl Adipate (CAS no. 26699-71-8) is the ester of glycerin and adipic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Hexanedioic Acid, Monoester with 1,2,3-Propanetriol is another name for this chemical (Pepe, Wenninger, and McEwen 2002).

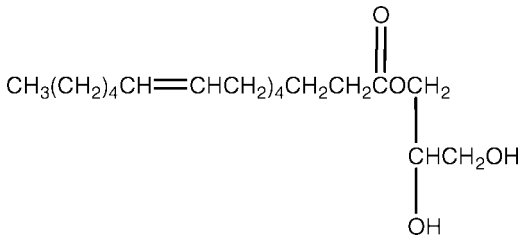
Glyceryl Alginate is the ester of glycerin and alginic acid. Alginic Acid, Glyceryl Ester is another name for this chemical (Pepe, Wenninger, and McEwen 2002).

Glyceryl Arachidate (CAS nos. 30208-87-8 and 50906-68-8) is the ester of glycerin and arachidic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



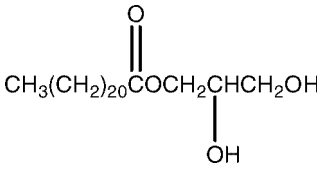
Other names for this chemical include 2,3-Dihydroxypropyl Eicosanoate; Eicosanoic Acid, 2,3-Dihydroxypropyl Ester; Eicosanoic Acid, Monoester with 1,2,3-Propanetriol; and Glyceryl Monoarachidate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Arachidonate (CAS no. 35474-99-8) is the monoester of glycerin and arachidonic acid that conforms to the following formula (Wenninger et al. 2000):



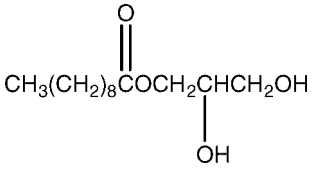
Other names for this chemical include: Arachidonic Acid, Monoester with 1,2,3-Propanetriol; 2,3-Dihydroxypropyl 5,8,11,14-Eicosatetraenoate; 5,8,11,14-Eicosatetraenoic Acid, 2,3-Dihydroxypropyl Ester-; and Glyceryl Monoarachidonate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Behenate (CAS nos. 6916-74-1 and 30233-64-8) is the monoester of glycerin and behenic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



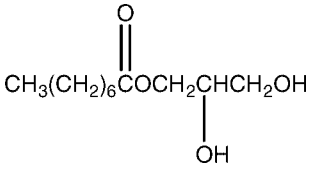
Other names for this chemical include 2,3-Dihydroxypropyl Docosanoate; Docosanoic Acid, 2,3-Dihydroxypropyl Ester; Docosanoic Acid, Monoester with 1,2,3-Propanetriol; and Glyceryl Monobehenate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Caprate (CAS no. 26402-22-2) is the monoester of glycerin and capric acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Other names for this chemical include Decanoic Acid, Monoester with 1,2,3-Propanetriol and Glyceryl Monocaprate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Caprylate (CAS no. 26402-26-6) is the monoester of glycerin and caprylic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):

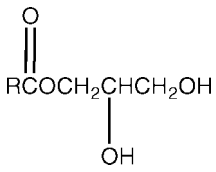


It has a molecular weight of 218.29 (Budavari 1989). Other names for this chemical include Glyceryl Monocaprylate and Octanoic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002), and Monooctanoin (Budavari, 1989). The typical composition of Glyceryl Caprylate is described as follows: free glycerol (1%), monoglycerides (90%), diglycerides (7%), triglycerides (1%), and water (maximum 1%) (Hüls America, Inc., no date).

Glyceryl Caprylate/Caprate is a mixture of monoglycerides of caprylic and capric acids (Pepe, Wenninger, and McEwen 2002).

Glyceryl Citrate/Lactate/Linoleate/Oleate is the ester of glycerin and a blend of citric, lactic, linoleic and oleic acids (Pepe, Wenninger, and McEwen 2002). More specifically, it is a partially neutralized ester of mono- and diglycerides of unsaturated edible fatty acids with citric acid and lactic acid (Hüls America, Inc., no date).

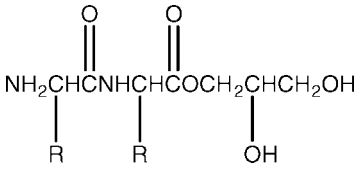
Glyceryl Cocoate (CAS no. 61789-05-7) is the monoester of glycerin and coconut fatty acids that conforms to the following formula, where R represents the fatty acids derived from coconut oil (Pepe, Wenninger, and McEwen 2002):



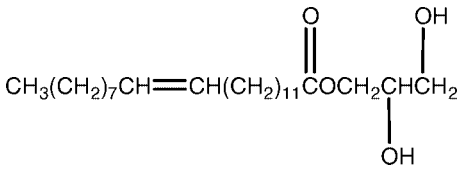
More specifically, it is composed of partial glycerides (mono/di/triglycerides) of the saturated fatty acids of coconut oil. The chain length is C_{10} to C_{18}; the main component is C_{12}, as in coconut oil (Hüls America, Inc., no date). Other names for this chemical include: Glycerides, Coconut Oil Mono-; Glycerol Mono Coconut Oil; Glyceryl Coconate; and Glyceryl Monococoate (Pepe, Wenninger, and McEwen 2002). The typical composition of Glyceryl Cocoate is described as follows: free glycerol (1%), monoglycerides (45%), diglycerides (35%), triglycerides (15%), and water (maximum 1%) (Hüls America, Inc., no date).

Glyceryl Collagenate is the ester of glycerin and collagen (q.v.) (Pepe, Wenninger, and McEwen 2002). It consists

of ~25% solids and its chemical structure, where R is an amino group typical of collagen, is included below (Brooks Industries 1998):



Glyceryl Erucate (CAS no. 28063-42-5) is the monoester of glycerin and erucic acid that conforms generally to the following formula (Pepe, Wenninger, and McEwen 2002):

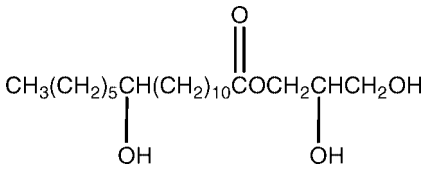


Other names for this chemical include Glyceryl Monoerucate and Erucic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Glyceryl Hydrogenated Rosinate is the monoester of glycerin and hydrogenated mixed long chain acids derived from rosin (Pepe, Wenninger, and McEwen 2002). It also exists as a mixture of 50% Glyceryl Hydrogenated Rosinate and 50% Octyldodecyl Myristate (McEwen 2000).

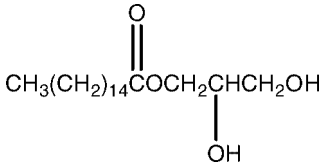
Glyceryl Hydrogenated Soyate is the monoester of glycerin (q.v.) and hydrogenated mixed long chain acids derived from soy (Pepe, Wenninger, and McEwen 2002). According to Danisco Ingredients (1999c), this ingredient is a distilled monoglyceride made from edible, fully hydrogenated vegetable oil.

Glyceryl Hydroxystearate (CAS no. 1323-42-8) is the monoester of glycerin and hydroxystearic acid (q.v.) that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



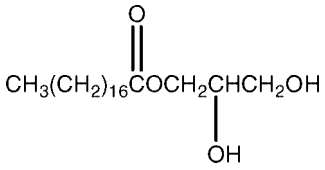
Other names for this chemical are as follows: Glyceryl Hydroxystearate (1); Glyceryl Hydroxystearate (2); Glyceryl Monohydroxystearate; Hydroxystearic Acid, Monoester with Glycerol; and Stearic Acid, Hydroxy-, Monoester with Glycerol (Pepe, Wenninger, and McEwen 2002).

Glyceryl Isopalmitate is the monoester of glycerin and a branched chain 16-carbon aliphatic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Other names for this chemical include Isopalmitic Acid, 2,3-Dihydroxypropyl Ester and Isopalmitic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Glyceryl Isostearate (CAS nos. 66085-00-5 and 61332-02-3) is the monoester of glycerin and isostearic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Other names for this chemical include Glyceryl Isostearate (1), Glyceryl Monoisostearate, and Isooctadecanoic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Gattefossé s.a. (1998) described the composition of Glyceryl Isostearate as containing 1-monoglycerides (>30%), free glycerol (<7%), and water (<0.50%).

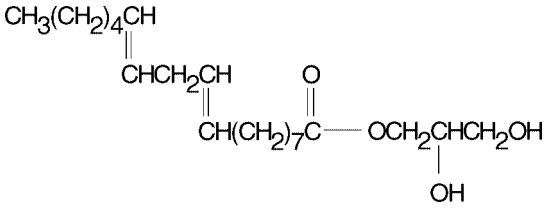
Glyceryl Isostearate/Myristate is the monoester of glycerin and a blend of isostearic and myristic acids. Glyceryl Monisostearate Monomyristate is another name for this chemical (Pepe, Wenninger, and McEwen 2002).

Glyceryl Isostearates is a mixture of the mono-, di-, and triesters of glycerin and isostearic acid. This chemical is also known as Glyceryl Isostearate (2) (Pepe, Wenninger, and McEwen 2002).

Glyceryl Isotridecanote/Stearate/Adipate is the ester of glycerin (q.v.) and a blend of isotridecanoic acid, stearic acid, and adipic acid (Pepe, Wenninger, and McEwen 2002).

Glyceryl Lanolate is the monoester of glycerin and lanolin acid (q.v.). Other names for this chemical include Glyceryl Monolanolate and Lanolin Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Glyceryl Linoleate (CAS no. 2277-28-3) is the monoester of glycerin and linoleic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002).

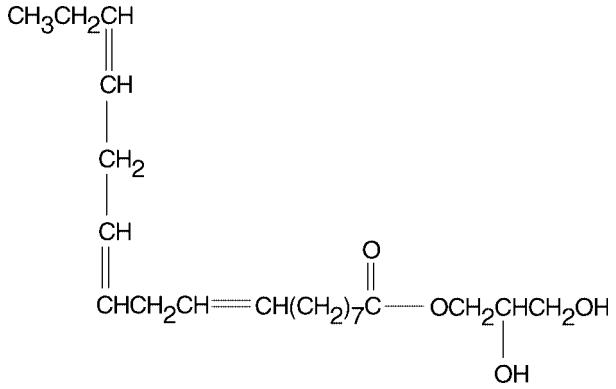


Other names for this chemical include 2,3-Dihydroxypropyl 9,12-Octadecadienoate; Glyceryl Monolinoleate; Linoleic Acid,

Monoester with 1,2,3-Propanetriol; Monolinolein; 9,12-Octadecadienoic Acid, 2,3-Dihydroxypropyl Ester; and 9,12-Octadecadienoic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Danisco Ingredients (1996) stated that the composition of Glyceryl Linoleate is as follows: monoester content (minimum 90%); free glycerol (maximum 1%); free fatty acid (maximum 1.5%); butyl hydroxy anisole (BHA), as antioxidant (maximum 200 ppm); and citric acid, as antioxidant (maximum 200 ppm) (*Note*: Citric acid is dissolved in propylene glycol.)

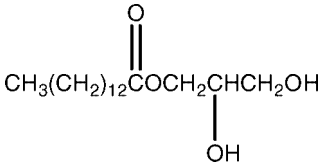
Glyceryl Linolenate (CAS no. 18465-99-1) is the monoester of glycerin and linolenic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



According to Danisco Ingredients (1999c), Glyceryl Linolenate is a distilled monoglyceride that is made from edible, refined sunflower oil. Other names for Glyceryl Linolenate include 2,3-Dihydroxypropyl 9,12,15-Octadecatrienoate; Glyceryl monolinolenate; Linolenic Acid, Monoester with 1,2,3-Propanetriol; and 9,12,15-Octadecatrienoic Acid, 2,3-Dihydroxypropyl Ester (Pepe, Wenninger, and McEwen 2002).

Glyceryl Montanate (CAS no. 68476-38-0) is the monoester of glycerin and montan acid wax. Other names for this chemical include 2,3-Dihydroxypropyl Octacosanoic Acid; Glycerides, Montan-Wax; Montan-Wax Fatty Acids, Glyceryl Esters; and Octacosanoic Acid, 2,3-Dihydroxypropyl Ester (Pepe, Wenninger, and McEwen 2002).

Glyceryl Myristate (CAS nos. 589-68-4 and 27214-38-6) is the monoester of glycerin and myristic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):

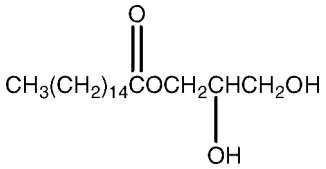


According to Danisco Ingredients (1999c), it is a distilled monoglyceride that is made from vegetable fatty acids (mainly myristic acid). Other names for this chemical include: Glyceryl Monomyristate; Monomyristin; and Tetradecanoic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Glyceryl Oleate SE is a self-emulsifying grade of Glyceryl Oleate (q.v.) that contains some sodium and/or potassium oleate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Oleate/Elaidate is a mixture of monoglycerides of oleic and elaidic acids (Pepe, Wenninger, and McEwen 2002). According to Danisco Ingredients (1999c), it is a distilled monoglyceride made from edible, partially hydrogenated soya bean oil.

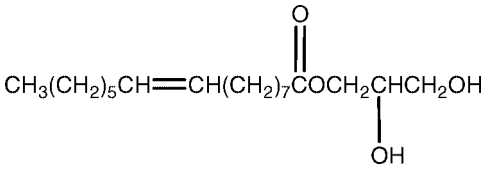
Glyceryl Palmitate (CAS no. 26657-96-5) is the monoester of glycerin and palmitic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Other names for this chemical include: Glyceryl Monopalmitate; Hexadecanoic Acid, 2,3-Dihydroxypropyl Ester; and Hexadecanoic Acid, Monoester with 1,2,3-Propanetriol; Hexadecanoic acid α-monoglyceride; Palmiric Acid Monoglyceride; Palmitin, mono-; and Palmitin, 1-mono- (Pepe, Wenninger, and McEwen 2002).

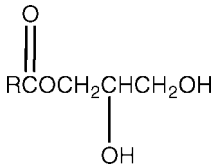
Glyceryl Palmitate/Stearate (CAS no. 68002-71-1) is the monoester of glycerin and a blend of palmitic and stearic acids (Pepe, Wenninger, and McEwen 2002). According to Danisco Ingredients (1999c), it is a distilled monoglyceride made from edible, fully hydrogenated lard or tallow.

Glyceryl Palmitoleate is the monoester of glycerin and palmitoleic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



According to Danisco Ingredients (1999c), it is a distilled monoglyceride that is made from edible, refined palm oil. Other names for this chemical include Glyceryl Monopalmitoleate; Palmitoleic Acid, 2,3-Dihydroxypropyl Ester; and Palmitoleic Acid, Monoester with 1,2,3-Propanetriol (Pepe, Wenninger, and McEwen 2002).

Glyceryl Pentadecanoate is the monoester of glycerin and pentadecanoic acid that conforms to the following formula, where RCO- represents the pentadecanoyl radical (Pepe, Wenninger, and McEwen 2002):



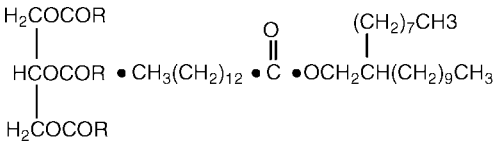
Another name for this chemical is 2,3-dihydroxypropane-pentadecanoate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Polyacrylate is the ester of glycerin (q.v.) and polyacrylic acid (q.v.) (Pepe, Wenninger, and McEwen 2002).

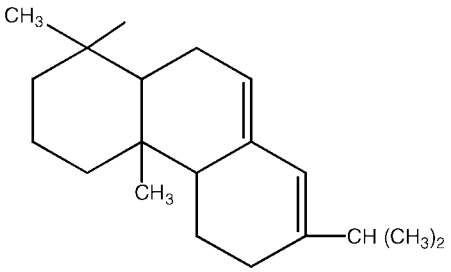
Glyceryl Rosinate (CAS no. 8050-31-5) is the monoester of glycerin and mixed long chain acids derived from rosin (q.v.). Glycerin monorosinate and resin acids and rosin acids, esters with glycerin are two other names for this chemical (Pepe, Wenninger, and McEwen 2002).

In an FDA review of safety (FDA 1988), rosin is the residue remaining when the volatile oil is distilled from turpentine or a product of the distillation, solvent extraction, or both, of the stumps or fallen trees of various species of *Pinus*. Abietic acid and dehydroabietic acid are the main components that have been identified. Rosin nomenclature is based on the source from which it is obtained. Thus, rosin obtained from offical (gum) turpentine is known as gum rosin. Wood rosin is rosin distilled or extracted out of the wood of stumps of fallen trees. These rosins differ in color, % resene, and in the softening point.

Glyceryl Rosinate is supplied as a trade mixture that is known as Purified Ester Gum-2-OctylDodecyl Myristate (Purified Ester Gum/M.O.D.) (US Cosmetics Corporation, no date). Purified Ester Gum-2-OctylDodecyl Myristate consists of 50% Glyceryl Rosinate and 50% octyldodecyl myristate (Shin-Ei Chemical Company Ltd. 1998), and properties of this trade mixture are presented in Table 2. The structural formula for Purified Ester Gum-2-Octyldodecyl Myristate is indicated below (US Cosmetics Corporation, no date):



Where R =



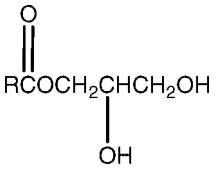
Glyceryl Sesquioleate is a mixture of mono- and di-esters of glycerin and oleic acid (Pepe, Wenninger, and McEwen 2002).

Glyceryl/Sorbitol Oleate/Hydroxystearate is the mixed esterification product of glycerin and sorbitol with hydroxystearic and oleic acids (Pepe, Wenninger, and McEwen 2002).

Glyceryl Stearate/Acetate is the monoester of glycerin and a blend of stearic and acetic acids. Glyceryl monostearate monoacetate is another name for this chemical (Pepe, Wenninger, and McEwen 2002).

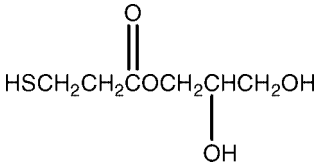
Glyceryl Stearate/Maleate is the monoester of glycerin and a blend of stearic and maleic acids (Pepe, Wenninger, and McEwen 2002).

Glyceryl Tallowate is the monoester of glycerin and tallow fatty acids that conforms to the following formula, where RCO- represents the fatty acids derived from tallow (Pepe, Wenninger, and McEwen 2002):

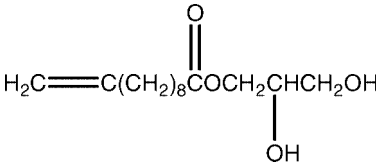


Another name for this chemical is glyceryl monotallowate (Pepe, Wenninger, and McEwen 2002).

Glyceryl Thiopropionate is the organic compound that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Glyceryl Undecylenate is the ester of glycerin and undecylenic acid that conforms to the following formula (Pepe, Wenninger, and McEwen 2002):



Other names for this chemical are glyceryl monoundecylenate and undecylenic acid, monoester with 1,2,3-propanetriol (Pepe, Wenninger, and McEwen 2002).

Octanol/Water Partition Coefficients

Measured octanol/water partition coefficients were not available. Calculated values received from one supplier are given in Table 3.

Analytical Methods

Glyceryl Laurate has been analyzed by thin-layer chromatography, gas-liquid chromatography (Kabara 1984), reverse-phase high performance liquid chromatography (HPLC) (Maruyama and Yonese 1986; Takano and Kondoh 1987), capillary supercritical fluid chromatography (Giron, Link, and Bouissel 1992), and ultraviolet (UV) spectral analysis—results are summarized in Table 1 (Danisco Ingredients 1999e).

TABLE 3
Calculated octanol/water partition coefficients of Glyceryl Monoesters (Danisco Ingredients 1999a)

Ingredient	log (*Ko*/w)
Glyceryl Laurate	4.22
Glyceryl Oleate	7.00
Glyceryl Behenate	9.62
Glyceryl Caprate	3.14
Glyceryl Caprylate	2.06
Glyceryl Erucate	8.61
Glyceryl Linoleate	5.44
Glyceryl Linolenate	4.60
Glyceryl Myristate	5.30
Glyceryl Elaidate	6.45
Glyceryl Palmitate	6.38
Glyceryl Stearate	7.69
Glyceryl Palmitoleate	5.37
Glyceryl Hydroxystearate	5.59

Methods of Production

According to Kabara (1984), industrial monoglycerides can be prepared by the direct esterification of glycerol with a fatty acid, yielding mixtures of mono-, di-, and tri- glycerides, depending on the molar ratio of the reactants. In the case of Glyceryl Laurate, the lauric acid that is used for esterification is generally derived from the oil of various species of palm, such as coconut and babassu. The glycerolysis of fats and oils, a transesterification reaction, is a common commercial method for the preparation of monoglycerides.

Glyceryl Collagenate is produced via the esterification of hydrolyzed collagen with United States Pharmacopeia (USP) glycerine 99% (Brooks Industries 1998).

Glyceryl Rosinate is contained in a trade mixture of purified ester gum-2-octyldodecyl myristate (containing 50% Glyceryl Rosinate and 50% octyldecyl myritstate), which is prepared by mixing (with heat) purified ester gum and 2-octyldodecyl myristate in a 1:1 ratio. The mixture is then subjected to purification processes such as decoloration, dehydration, deodorization and filtration (US Cosmetics Corporation, no date).

Composition/Impurities

Data on the chemical characterization of Glyceryl Monoesters are shown in Table 4.

Danisco Ingredients (1999d), indicated that a content of 3.5% to 4% total (mono)glycerol diester's are common in the manufacturing of distilled monoglyceride's. In the manufacturing of any less than 90% monoglyceride (commonly referred to as mono-diglycerides, albeit the INCI name does not differentiate), the content of (mono)glycerol diester's is higher. Because there is some diglycerol then there is also a "family" of diglycerol esters (mono- and di-esters). Consequently one can read from the tabulation of "impurities" for instance for a main product like DIMODAN PM [Glyceryl Palmitate/Stearate], that out of approximately 4% (mono)glycerol diester's, then approximately 29% of this is 1,2 (mono)glycerol diester. This would correspond to an approximate concentration of 1,2 (mono)glycerol diester of 1.2%.

Glyceryl Laurate contains ash (maximum 0.1%) (Hüls America, Inc., no date) and heavy metals, as Pb (<10 mg/kg) (Danisco Ingredients 1996).

TABLE 4
Impurities data on Glyceryl Monoesters (Danisco Ingredients 1999c, 1999d)

Ingredients	% glycerol	% diglycerol	% free fatty acid	% diglycerol monoester	Ratio of 1,2-(mono)glycerol diester to total (mono)glycerol diester
Glyceryl Laurate	0.07	0.24	0.16	—	24.8
Glyceryl Behenate	0.03	0.09	0.15	—	29.1
Glyceryl Caprate	1.03	0.43	0.06	—	21.0
Glyceryl Caprylate/Caprate	5.37	—	—	—	34.3
Glyceryl Linolenate	0.03	0.15	0.11	—	35.8
Glyceryl Myristate	0.30	0.57	0.14	—	27.8
Glyceryl Oleate/Elaidate	0.03	0.12	0.35	—	33.4
Glyceryl Palmitate	0.03	0.06	0.79	—	10.6
Glyceryl Palmitate/Lactate	0.04	—	0.82	—	30.6
Glyceryl Palmitate/Stearate	0.27	0.10	0.98	0.28	29.2
Glyceryl Palmitoleate	0.04	0.14	0.41	—	27.3
Glyceryl Sesquioleate	0.24	—	0.42	—	30.5
Glyceryl Hydrogenated Soyate	0.60	0.28	0.11	—	26.0

Glyceryl Caprylate and Glyceryl Cocoate contain ash at a maximum concentration of 0.1% (Hüls America, Inc., no date).

Glyceryl Collagenate contains a low level of sodium chloride, byproduct of the production process (Brooks Industries 1998). It also contains nonvolatile matter (25% to 31%) and moisture (67% to 73%).

Glyceryl Hydrogenated Soyate specifications, given by Danisco Ingredients (1999c), include: monoester content (minimum 90%), iodine value (maximum 2%), free glycerol (maximum 1%), free fatty acids (maximum 1.5%), dropping point (≈72°C), and form (beads). Specifications for heavy metal impurities include: arsenic (As) (maximum 3 mg/kg), lead (Pb) (maximum 5 mg/kg), mercury (Hg) (maximum 1 mg/kg), Cadmium (Cd) (maximum 1 mg/kg), and heavy metals (as Pb) (maximum 10 mg/kg).

Glyceryl Isostearate impurities are as follows: alkaline impurities (<80 ppm NaOH), sulfated ash content (<0.2%), and heavy metals (<10 ppm Pb) (Gattefossé s.a. 1998).

Glyceryl Linoleate contains heavy metals (as Pb) at <10 mg/kg (Danisco Ingredients 1996).

Glyceryl Linolenate specifications, given by Danisco Ingredients (1999c), include monoester content (minimum 90%), iodine value (approximately 10%), free glycerol (maximum 1%), free fatty acids (maximum 1.5%), temperature at which completely melted (≈45°C), and form (paste). Specifications for heavy metal impurities are as follows: arsenic (As) (maximum 3 mg/kg), lead (Pb) (maximum 5 mg/kg), mercury (Hg) (maximum 1 mg/kg), cadmium (Cd) (maximum 1 mg/kg), and heavy metals (as Pb) (maximum 10 mg/kg). Glyceryl Linolenate also contains the antioxidants, BHA (maximum 200 ppm) and citric acid dissolved in propylene glycol (maximum 200 ppm).

Glyceryl Myristate specifications, given by Danisco Ingredients (1999c), include monoester content (minimum 90%), free glycerol (maximum 1%), and free fatty acids (maximum 1.5%). The typical value for heavy metals (as Pb) in Glyceryl Myristate is <10 mg/kg.

Glyceryl Oleate/Elaidate specifications, given by Danisco Ingredients (1999c), include arsenic (As) (maximum 3 mg/kg), lead (Pb) (maximum 5 mg/kg), mercury (Hg) (maximum 1 mg/kg), cadmium (Cd) (maximum 1 mg/kg), and heavy metals (as Pb) (maximum 10 mg/kg). It also contains the antioxidants, citric acid ester (maximum 300 ppm), α-tocopherol (maximum 200 ppm), and ascorbyl palmitate (maximum 200 ppm).

Glyceryl Palmitate/Stearate specifications, given by Danisco Ingredients (1999c), include monoester content (minimum 90%), iodine value (maximum 2%), free glycerol (maximum 1%), free fatty acids (maximum 1.5%), dropping point (≈70°C), and form (beads). Specifications for heavy metal impurities are as follows: arsenic (As) (maximum 3 mg/kg), lead (Pb) (maximum 5 mg/kg), mercury (Hg) (maximum 1 mg/kg), cadmium (Cd) (maximum 1 mg/kg), and heavy metals (as Pb) (maximum 10 mg/kg).

Glyceryl Palmitoleate specifications, given by Danisco Ingredients (1999c), include monoester content (minimum 90%), iodine value (≈40), free glycerol (maximum 1%), free fatty acids (maximum 1.5%), dropping point (≈60°C), and form (plastic). Specifications for heavy metal impurities are as follows: arsenic (As) (maximum 3 mg/kg), lead (Pb) (maximum 5 mg/kg), mercury (Hg) (maximum 1 mg/kg), cadmium (Cd) (maximum 1 mg/kg), and heavy metals (as Pb) (maximum 10 mg/kg). Glyceryl Palmitoleate also contains the antioxidants, BHA (maximum 200 ppm) and citric acid dissolved in propylene glycol (maximum 200 ppm).

Stability/Reactivity

Glyceryl Laurate is classified as a combustible material (Lewis 1993). It is compatible with most emulsifiers, but is inactivated in the presence of sodium lauryl sarcosine and ethoxylated and propoxylated nonionics (e.g., Tween 80, a.k.a. Polysorbate 80) (Kabara 1984).

Glyceryl Cocoate is stable against oxidation and forms an emulsion with water when heated (Hüls America, Inc., no date).

Glyceryl Isostearate reacts with strong acids and oxidizing agents. Additionally, incomplete combustion of Glyceryl Isostearate leads to the release of monoxyd carbon and dioxyd carbon (Gattefossé s.a. 1999).

USE

Cosmetic Use

Glyceryl Monoesters are used mostly as skin conditioning agents—emollients and/or surfactant-emulsifying agents, but several other uses are reported (Pepe, Wenninger, and McEwen 2002). The current function in cosmetics for each ingredient in this safety assessment is summarized in Table 5.

Table 6 presents information on the types of products in which these ingredients are used (FDA 1998; CTFA 1999), the frequency with which they are used as reported by industry to FDA (FDA 1998), and the current concentration at which the ingredients are used as reported by industry (CTFA 1999). Although only 16 of the 43 ingredients in this safety assessment were reported to FDA as being used in cosmetics, the current concentration of use data received from the cosmetics industry indicates that four additional glyceryl monoesters are in use. Also, concentrations of use are reported in product groups for which no uses were reported in 1998.

Cosmetic products containing glyceryl monoesters are applied to most areas of the body, and could come in contact with the ocular and nasal mucosae. These products could be used on a daily basis, and could be applied frequently over a period of several years.

None of the 43 ingredients reviewed in this safety assessment is included among the substances listed as prohibited from use in cosmetic products marketed in the European Union (European Economic Community 2001).

Japan describes the following 11 categories of cosmetic preparations: 1. skin cleansing; 2. hair care; 3. treatment;

TABLE 5
Functions of Glyceryl Monoesters in Cosmetics (Pepe, Wenninger, and McEwen 2002)

Ingredients	Functions
Glyceryl Laurate	Skin-conditioning agent—emollient and/or surfactant—emulsifying agent
Glyceryl Laurate SE	As above
Glyceryl Laurate/Oleate	As above
Glyceryl Adipate	As above
Glyceryl Alginate	Skin-conditioning agent—emollient; viscosity-increasing agent—aqueous
Glyceryl Arachidate	Skin-conditioning agent—emollient; surfactant-emulsifying agent; viscosity-increasing agent—nonaqueous
Glyceryl Arachidonate	Skin-conditioning agent—emollient and/or surfactant—emulsifying agent
Glyceryl Behenate	Skin-conditioning agent—emollient and/or surfactant—emulsifying agent
Glyceryl Caprate	As above
Glyceryl Caprylate	As above
Glyceryl Caprylate/Caprate	As above
Glyceryl Citrate/Lactate/Linoleate/Oleate	As above
Glyceryl Cocoate	As above
Glyceryl Collagenate	Hair-conditioning agent; skin-conditioning agent—emollient; skin-conditioning agent—miscellaneous
Glyceryl Erucate	Skin-conditioning agent—emollient and/or surfactant—emulsifying agent
Glyceryl Hydrogenated Rosinate	As above
Glyceryl Hydrogenated Soyate	As above
Glyceryl Hydroxystearate	As above
Glyceryl Isopalmitate	As above
Glyceryl Isostearate	As above
Glyceryl Isostearate/Myristate	As above
Glyceryl Isostearates	As above
Glyceryl Isotridecanoate/Stearate/Adipate	As above
Glyceryl Lanolate	Hair-conditioning agent; Skin-conditioning agent—emollient; surfactant—emulsifying agent
Glyceryl Linoleate	Skin-conditioning agent—emollient and/or surfactant—emulsifying agent
Glyceryl Linolenate	As above
Glyceryl Montanate	As above
Glyceryl Myristate	As above
Glyceryl Oleate SE	Skin-conditioning agent—emollient and/or surfactant—emulsifying agent
Glyceryl Oleate/Elaidate	As above
Glyceryl Palmitate	As above
Glyceryl Palmitate/Stearate	As above
Glyceryl Palmitoleate	As above
Glyceryl Pentadecanoate	As above
Glyceryl Polyacrylate	Film former
Glyceryl Rosinate	As above
Glyceryl Sesquioleate	As above
Glyceryl/Sorbitol Oleate/Hydroxystearate	As above
Glyceryl Stearate/Acetate	As above
Glyceryl Stearate/Maleate	As above
Glyceryl Thiopropionate	Hair-waving/straightening agent; reducing agent
Glyceryl Undecylenate	Skin-conditioning agent—emollient; surfactant—emulsifying agent

4. makeup; 5. fragrance; 6. suntan/ sunscreen; 7. nail makeup; 8. eyeliner; 9. lip product; 10. oral product; and 11. bath product. Table 7 lists the ingredients in this safety assessment according to the *International Cosmetic Ingredient Dictionary and Handbook* name (INCI name), the categories for which there is precedent (or not) for use in Japan, and any limitations on use (Rempe and Santucci 1997).

TABLE 6
Product formulation data on Glyceryl Monoesters

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999) (%)
Glyceryl Laurate		
Eye shadow (551)	2	—
Eye makeup remover (99)	1	0.1
Other fragrance preparations (173)	1	—
Permanent waves (211)	9	—
Shampoos (noncoloring) (851)	—	0.3–2
Tonics, dressings, and other hair-grooming aids (577)	—	0.4
Wave sets (53)	—	0.4
Other hair preparations (noncoloring) (276)	—	0.4
Bath soaps and detergents (405)	4	—
Deodorants (underarm) (247)	4	—
Douches (5)	—	0.3
Other personal cleanliness products (307)	3	—
Skin cleansing (cold creams, cleansing lotions, liquids, and pads) (733)	—	4
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	1
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	5	—
Other skin care preparations (715)	—	4
1998 total uses for Glyceryl Laurate	29	
Glyceryl Alginate		
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	1	—
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	0.5
1998 totals for Glyceryl Alginate	1	
Glyceryl Arachidonate		
Suntan gels, creams, and liquids (136)	2	—
1998 totals for Glyceryl Arachidonate	2	
Glyceryl Behenate		
Mascara (187)	—	2
Suntan gels, creams, and liquids (131)	—	5
1998 totals for Glyceryl Behenate	—	
Glyceryl Caprylate/Caprate		
Hair sprays (aerosol fixatives) (267)	1	—
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	2
1998 totals for Glyceryl Caprylate/Caprate	1	
Glyceryl Cocoate		
Bubble bath (209)	—	1
Lipstick (942)	—	0.3–2
Bath soaps and detergents (405)	—	4
Cleansing skin care preparations (creams, lotions, powders, and sprays) (733)	1	1–5
1998 totals for Glyceryl Cocoate	1	
Glyceryl Erucate		
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	—	0.5
1998 totals for Glyceryl Erucate	—	

TABLE 6
Product formulation data on Glyceryl Monoesters *(Continued)*

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999) (%)
Glyceryl Hydroxystearate		
Other eye makeup preparations (151)	—	2
Lipstick (942)	1	—
Deodorants (247)	—	2
Other personal cleanliness products (307)	1	—
Shaving Cream (133)	1	—
Cleansing skin care preparations (creams, lotions, powders, and sprays) (733)	4	—
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	5	—
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	2	2
Foot powders and sprays (35)	1	—
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	8	0.8
Night skin care preparations (creams, lotions, powders, and sprays) (200)	1	—
Paste masks (mud packs) (269)	4	—
Other skin care preparations (creams, lotions, powders, and sprays) (715)	3	—
Suntan gels, creams, and liquids (131)	1	—
1998 totals for Glyceryl Hydroxystearate	32	
Glyceryl Isostearate		
Bath oils, tablets, and salts (140)	—	1
Eye shadow (551)	23	0.5–2
Eye lotion (23)	—	0.8
Face powders (301)	1	—
Foundations (319)	24	4–6
Skin cleansing (cold creams, cleansing lotions, liquids, and pads) (733)	—	3
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	1	2
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	2
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	2	3
Night skin care preparations (creams, lotions, powders, and sprays) (200)	1	—
Paste masks (mud packs) (269)	—	0.3
Other skin care preparations (creams, lotions, powders, and sprays) (715)	1	—
1998 totals for Glyceryl Isostearate	32	
Glyceryl Lanolate		
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	2	—
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	1	—
1998 totals for Glyceryl Lanolate	3	
Glyceryl Linoleate		
Eye shadow (551)	1	—
Other fragrance preparations (173)	1	—
Face powders (301)	1	—

(Continued on next page)

TABLE 6
Product formulation data on Glyceryl Monoesters *(Continued)*

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999) (%)
Foundations (319)	2	0.7
Lipstick (942)	3	0.7
Other personal cleanliness products (307)	—	0.7
Cleansing skin care preparations (creams, lotions, powders, and sprays) (733)	3	1
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	2	1
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	1
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	2	—
Paste masks (mud packs) (269)	1	—
Other skin care preparations (creams, lotions, powders, and sprays) (715)	1	—
1998 totals for Glyceryl Linoleate	17	
Glyceryl Linolenate		
Eye shadow (551)	1	—
Foundations (319)	—	0.7
Lipstick (942)	3	0.7
Other personal cleanliness products (307)	—	0.7
Cleansing skin care preparations (creams, lotions, powders, and sprays) (733)	1	1
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	2	1
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	1
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	2	—
Other skin care preparations (creams, lotions, powders, and sprays) (715)	1	—
1998 totals for Glyceryl Linolenate	10	
Glyceryl Myristate		
Other fragrance preparations (173)	1	—
Makeup bases (136)	1	—
Deodorants (underarm) (247)	1	—
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	3	1–6
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	2	6
Moisturizing skin care preparations (creams, lotions, powders, and sprays) (881)	4	—
Night skin care preparations (creams, lotions, powders, and sprays) (200)	1	—
Paste masks (mud packs) (269)	3	—
Other skin care preparations (creams, lotions, powders, and sprays) (715)	1	6
Suntan gels, creams, and liquids (131)	1	—
Other suntan preparations (37)	1	—
1998 totals for Glyceryl Myristate	19	
Glyceryl Oleate/Elaidate		
Foundations (319)	—	2
Makeup bases (136)	—	0.3

TABLE 6
Product formulation data on Glyceryl Monoesters *(Continued)*

Product category (number of formulations reported to FDA) (FDA 1998)	Number of formulations containing ingredient (FDA 1998)	Current concentration of use (CTFA 1999) (%)
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	—	2
Moisturizing creams, lotions, powders, and sprays (881)	—	2
1998 totals for Glyceryl Oleate/Elaidate	—	
Glyceryl Polyacrylate		
Hair conditioners (630)	—	0.4
Tonics, dressings, and other hair-grooming aids (577)	—	0.2
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	1	2
1998 totals for Glyceryl Polyacrylate	1	
Glyceryl Rosinate		
Eyebrow pencil (99)	—	10
Eye shadow (551)	—	2
Mascara (187)	2	0.08–12
Other hair coloring preparations (59)	—	3
Blushers (all types) (243)	—	2
Foundations (319)	1	0.06-4
Lipstick (942)	—	0.4–6
Depilatories (28)	1	—
1998 totals for Glyceryl Rosinate	4	
Glyceryl Stearate/Acetate		
Tonics, dressings, and other hair-grooming aids (577)	—	7
Skin cleansing (cold creams, cleansing lotions, liquids, and pads) (733)	—	1
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (304)	—	2
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (827)	—	2
Moisturizing creams, lotions, powders, and sprays (881)	—	3
Suntan gels, creams, and liquids (131)	—	3
Indoor tanning preparations (68)	—	2
1998 totals for Glyceryl Stearate/Acetate	—	
Glyceryl Undecylenate		
Moisturizing creams, lotions, powders, and sprays (881)	2	—
1998 totals for Glyceryl Undecylenate	2	

Noncosmetic Use

Glyceryl Laurate has noncosmetic uses as an emulsifying and dispersing agent for food products, oils, waxes, and solvents; an antifoaming agent; and a dry-cleaning soap base (Lewis 1993). It has also been detected in pharmaceutical excipients (Giron, Link, and Bouissel 1992).

Glyceryl Caprylate has been used to dissolve gallstones by direct biliary infusion (Budavari 1989).

Glyceryl Isostearate is used in textiles (Unichema International 1997b).

Glyceryl Behenate has been approved for use as a direct food additive (21 CFR 184.1328). Additionally, Glyceryl Monoesters have been approved for use as components of adhesives, coatings, paper and paperboard, and other materials that come in contact with food (i.e., indirect food additive uses) (21 CFR 175.105; 175.300; 176.170; 176.180; 176.200; 176.210; 177.1210; 177.2800; 178.3120; 178.3800; and 178.3870).

Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate both contain rosin. Rosin is regulated for use as a diluent in color additive ink mixtures for marking gum, confectionery, fruits, vegetables, and tablet forms of food supplements. Rosin (as colophony, a.k.a. Portuguese gum rosin) is listed for use as a flavoring agent in alcoholic beverages. Derivatized and some of the modified rosins are regulated as softeners for chewing gum

TABLE 7
Glyceryl Monoesters used in Japan (Rempe and Santucci 1997)

INCI name	Japanese name	Category with precedent for use*	Category with no precedent for use*
Glyceryl Laurate	Glyceryl Monoaurate	1, 2, 3, 4, 5, 6, 7, 9, 10, 11	8
Glyceryl Behenate	Glyceryl Behenate	1, 2, 3, 4, 5, 6, 7	8, 9, 10, 11
Glyceryl Cocoate	Glyceryl Cocoate	1, 2, 3, 4, 5, 6, 7, 9, 10, 11	8
Glyceryl Erucate	Glyceryl Monoerucate	All	—
Glyceryl Hydroxystearate	Glyceryl Hydroxystearate (1)	1, 2, 3, 4, 5, 6, 7	8, 9, 10, 11
	Glyceryl Hydroxystearate (2)	1, 2, 3, 4, 5, 6, 7	8, 9, 10, 11
	Glyceryl Monohydroxystearate	All	—
Glyceryl Isostearate	Glyceryl Isostearate (1)	1, 2, 3, 4, 5, 6, 7, 9, 10, 11	8
Glyceryl Isostearate/Myristate	Glyceryl Monoisostearate Monomyristate	1, 2, 3, 4, 5, 6, 7, 9, 10, 11	8
Glyceryl Lanolate	Glyceryl Monolanolate	1, 2, 3, 4, 5, 6, 7	8, 9, 10, 11
Glyceryl Linoleate	Glyceryl Linoleate	1, 2, 3, 4, 5, 6, 7, 9, 10, 11	8
Glyceryl Myristate	Glyceryl Monomyristate	1, 2, 3, 4, 5, 6, 7	8, 9, 10, 11
Glyceryl Sesquioleate	Glyceryl Sesquioleate	1, 2, 3, 4, 5, 6, 7, 9, 10, 11	8
Glyceryl Stearate/Acetate	Glyceryl Monostearate Monoacetate	1, 2, 3, 4, 5, 6, 7, 11	8, 9, 10
Glyceryl Stearate/Maleate	Glyceryl Stearate Maleate	1, 2, 3, 4, 5, 6, 7	8, 9, 10, 11

*See text for explanation of categories.

base. Wood rosin and certain derivatized modified forms of rosin are listed for use as coatings on fresh citrus fruits. Indirect uses of derivatized rosin as components of paper and paperboard in contact with dry food are permitted (FDA 1988).

BIOLOGICAL PROPERTIES

Absorption and Metabolism

The metabolic fate of monoglycerides (glyceryl monoesters) is summarized below. Because monoglycerides are products of triglyceride and diglyceride metabolism, these compounds are also mentioned.

Triglyceride digestion begins in the intestinal tract. Initially, the triglyceride is hydrolyzed to α,β-diglyceride, which is then hydrolyzed to β-monoglyceride. These hydrolytic reactions occur at an oil-water interface. Approximately 28% of the β-monoglyceride is isomerized to α-monoglyceride, and approximately 75% of the α-monoglyceride is further hydrolyzed to free glycerol. Free glycerol enters the intestinal wall independent of the lipids, and it has no further use in terms of lipid absorption. The free fatty acids and glycerol are available for the resynthesis of triglycerides. β-Monoglycerides are not hydrolyzed because of their transfer to a water-soluble phase and, also, because of enzyme specificity. However, they can be acylated directly to triglyceride (Mattson and Volpenhein 1964).

Skin Penetration Enhancement

Glyceryl Laurate

The effect of Glyceryl Laurate or Dilaurate on the penetration of naloxone-HCl across cadaver skin was evaluated using Franz diffusion cells. Naloxone is a potent opioid antagonist used for the reversal of narcosis. Naloxone concentrations in the reservoir were determined by HPLC using UV detection. Glyceryl Laurate was evaluated at a concentration of 10% in propylene glycol. The average flux through human cadaver skin (10 experiments) for naloxone alone was 1.6 ± 0.4 $\mu g/cm^2 \cdot h$. In the presence of Glyceryl Dilaurate (10% in propylene glycol), average Naloxone flux increased to 18.7 ± 1.8 $\mu g/cm^2 \cdot h$ (3 experiments), and increased even greater in the presence of Glyceryl Laurate (23.4 ± 3.6 $\mu g/cm^2 \cdot h$; 3 experiments). In the presence of urea (10% in propylene glycol), the average Naloxone flux was 0.4 ± 0.1 $\mu g/cm^2 \cdot h$ (3 experiments) (Aungst, Rogers, and Shefter 1986).

In another study, the effect of Glyceryl Laurate on penetration of the water-soluble drug, papaverine HCl through hairless rat skin (from abdominal area) was demonstrated using diffusion cells. The mean flux of papaverine HCl was 23.7 ± 5.2 $\mu g/cm^2/h$ (three to five experiments) in the presence of 10% Glyceryl Laurate. This value was compared with the mean value for papaverine HCl flux in the presence of the water control (1.1 ± 0.2 $\mu g/cm^2/h$) (Okumura et al. 1990).

Platelet Aggregation

Glyceryl Arachidonate

Phosphatidylcholine liposomes containing 1-Arachidonyl-Monoglyceride caused aggregation of human platelets in vitro (Gerrard and Graff 1980).

Enzyme Activity

Glyceryl Laurate

The effect of Glyceryl Laurate and various fatty acids and derivatives on 5α-reductase activity in vitro was evaluated

because of the established link between cancer of the prostate gland and high dietary fat intake. Prostate gland tissue specimens (human) were used. 5α-Reductase catalyzes the reduction of testosterone to dihydrotestosterone, which controls cellular division in the prostate gland. It has been suggested that the modulation/inhibition of this enzyme could prevent carcinogenesis in the prostate gland. Results indicated that the inhibitory effect of lauric acid on 5α-reductase activity was decreased by esterification to Glyceryl Laurate and was totally lost by esterification to Glyceryl Dilaurate and Trilaurin (Niederpruem et al. 1995).

Signal Transduction

This section is included because glyceryl diesters may be present in glyceryl monoester ingredients. Although most glyceryl diesters that are found would be expected to be 1,3-glyceryl diesters, some may be 1,2-diesters, which can have signal transduction effects.

Lee and Severson (1994), in a review signal transduction in smooth muscle, state that the generation of intracellular second messengers is a common mechanism of signal transduction for external stimuli such as hormones, neurotransmitters, growth factors, and drugs (agonists) that interact with plasma membrane receptors. They go on to say that the established role of phospholipid turnover in signal transduction mechanisms is based on the observations that agonist-induced hydrolysis of a minor phospholipid in the plasma membrane, phosphatidylinositol 4,5-bisphosphate (PIP_2), in a reaction catalyzed by a phosphoinositide-specific phospholipase C (PI-PLC) enzyme generated the following two intracellular second messengers: (1) inositol 1,4,5-triphosphate (IP_3), responsible for the mobilization of Ca^{2+} from intracellular stores, and (2) diacylglycerol, responsible for the activation of protein kinase C (PKC). Lévy et al. (1994) reported that PKC consists of a family of 10 isozymes that phosphorylate serine and threonine residues. Classical PKC isozymes (α, β_I, β_{II}, γ) are dependent on Ca^{2+} and phospholipids and are activated by diacylglycerol. These isozymes transduce mitotic signals induced by growth factors.

Sánchez-Piñera et al. (1999) studied the lipid activation of PKC α by comparing the activation capacity of different 1,2-diacylglycerols and 1,3-diacylglycerols incorporated into mixed micelles or vesicles. PKC α, as well as other isoenzymes in this family, are activated by Ca^{2+}, phosphatidylserine, and diacylglycerols. Diacylglycerols are considered to be hydrophobic anchors that may recruit PKC to the membrane, leading to an increase in the enzyme's membrane affinity and to the activation of PKC.

Unsaturated 1,2-diacylglycerols were more potent activators of protein kinase C α than saturated 1,2-diacylglycerols when 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoserine (POPS)/Triton X-100 mixed micelles and pure POPS vesicles were used. These differences were not observed when 1-palmitoyl -2-oleoyl-sn-glycero-3-phosphocholine (POPC)/POPS (4:1 molar ratio) vesicles were used. Additionally, 1,2-diacylglycerols had a considerably greater activating capacity than 1,3-diacylglycerols in POPS Triton X-100 mixed micelles and in POPC/POPS vesicles. However, the difference between 1,2- and 1,3-diacylglycerols was smaller when pure POPS vesicles were used. That is, both were able to activate PKC α practically to the same extent. Nevertheless, saturated diacylglycerols induced significant activation of PKC α in Triton X-100 micelles and in pure POPS vesicles in this study (Sánchez-Piñera et al. 1999).

Unlike the preceding study, a very low capacity for 1,3-diacylglycerol–induced activation was demonstrated in an earlier study (Nomura et al. 1986). In the Nomura et al. (1986) study, however, sonicated phosphatidylserine vesicles were used, whereas unsonicated preparations of multilamellar vesicles were used in the Sánchez-Piñera et al. (1999) study.

Cell Growth and Proliferation

This section is included because glyceryl diesters may be present in glyceryl monoester ingredients. Although most glyceryl diesters that are found would be expected to be 1,3-glyceryl diesters, some may be 1,2-diesters, which can have cell growth and proliferation effects.

Huckle and Earp (1994) report that activation of the type 1 angiotensin II receptor rapidly increases intracellular levels of inositol phosphates, notably inositol 1,4,5-triphosphate (IP_3), and 1,2-diacylglycerol (DAG) in adrenal cortical cells, hepatocytes, and vascular smooth muscle. The type 1 angiotensin II receptor is responsible for all known physiologic actions of angiotensin II. Angiotensin II, an octapeptide, is well known as an acute regulator of vasomotor tone and fluid homeostasis. It exhibits many characteristics of the 'classical' peptide growth factors such as epidermal growth factor/transforming growth factor alpha (EGF/TGFα), platelet-derived growth factor (PDGF), and insulin-like growth factor (IGF)-1. Characteristics of these growth factors include the regulation of growth in a self-contained autocrine/paracrine fashion, and the ability to stimulate tyrosine phosphorylation, to activate MAPKs (mitogen-activated protein kinases), and to increase expression of nuclear proto-oncogenes. Angiotensin II has trophic or mitogenic (increases rate of cell division) effects on a variety of target tissues, including adrenal cells and vascular smooth muscle cells.

In vascular smooth muscle, hydrolysis via the lipase pathway is the predominant metabolic fate of diacylglycerol. The activation of PKC in vascular smooth muscle modulates agonist-stimulated phospholipid turnover, produces an increase in contractile force, and regulates cell growth and proliferation (Lee and Severson 1994).

Blobe, Obeid, and Hannun (1994) reviewed various studies indicating that the sustained activation or inhibition of PKC (diacylglycerol-activated isoenzyme) activity in vivo may play a critical role in the regulation of long term cellular events such as proliferation, differentiation, and tumorigenesis. Many of the signals transduced by PKC are mitogenic signals that have been sent by growth factors (e.g., platelet-derived growth factor [PGDF] and epidermal growth factor [EGF]). For

example, PGDF binds to its high-affinity receptor (PDGFR) and activates this receptor's intrinsic tyrosine kinase activity to mediate the initiation of DNA synthesis and other cellular effects. It is important to note that PKC has been linked directly to the pathogenesis of human skin, colon, and breast cancers. In the epithelium, long-term changes in PKC activity, either through the action of phorbol esters or by specific changes in PKC isoenzyme levels, either leads to growth of melanocytes, the differentiation of keratinocytes, or to transformation. In colon cancer, PKC acts as a tumor suppressor. Thus, decreasing the levels of PKC activity can result in transformation. In breast cancer, an increase in PKC activity appears to correlate with enhanced oncogenicity.

Evidence of increased PKC activity in hyperplastic pituitary cells has also been reported. Furthermore, the increase in diacylglycerol content paralleled the increase in PKC activity (Lévy et al. 1994).

Antimicrobial Activity

Glyceryl Laurate

Lauricidin (registered trademark for Glyceryl Laurate) has been described as having a wide spectrum of antimicrobial activity against diverse microbial species (viruses, fungi, molds, yeasts, and bacteria included). However, it is generally inactive against gram-negative bacteria. When Lauricidin was tested in cell culture using 16 human RNA- and DNA-enveloped viruses, all viruses were reduced in infectivity by 99.9% at relatively low concentrations (1.0%) of Lauricidin. Antifungal activity (inhibition of mycelial growth) of Glyceryl Laurate has been demonstrated in 12 strains at a concentration of 0.5%, and in three additional strains at a concentration of 0.05% (Kabara 1984).

Glyceryl Laurate inhibited the production of staphylococcal toxic shock toxin-1, the toxin responsible for toxic shock syndrome, at assay concentrations of 20, 100, and 300 μg/ml (Schlievert et al. 1992) and 17 mg/L (Holland, Taylor, and Farrell 1994). Projan et al. (1994) reported that Glyceryl Laurate inhibited the synthesis of most staphylococcal toxins at the level of transcription. It blocked the induction but not the constitutive synthesis of β-lactamase, suggesting that transmembrane signal transduction was the target of Glyceryl Laurate action.

Other studies on the bactericidal activity of Glyceryl Laurate include inhibition of bacterial spores and vegetative cells (Chaibi, Ababouch, and Busta 1996a, 1996b); inhibition of *Listeria monocytogenes* (Oh and Marshall 1996); and susceptibility of *Heliobactor pylori* (Petschow, Batema, and Ford 1996).

ANIMAL TOXICOLOGY

General

The safety of mono- and diglycerides in food has been reviewed by the Food Protection Committee of the National Academy of Sciences National Research Council Food and Nutrition Board (National Academy of Sciences 1960). The Food Protection Committee concluded that there appears to be no reason to question the safety of mono-, di-, or triglycerides of lauric acid (i.e., Glyceryl Laurate, Glyceryl Dilaurate, or Glyceryl Trilaurate [Trilaurin]) as food additives. This conclusion was based on the following: (1) Lauric acid glycerides are used in important foods, such as human and cow's milk, at concentrations of 3% to 6% and large quantities are present in coconut oil. The use of these foods has not been accompanied by recognized toxic effects. (2) Lauric acid glycerides undergo the usual metabolic changes of the higher fatty acids. (3) When lauric acid glycerides are fed in diets containing a variety of glycerides, there is not evidence of a specific toxic or harmful effect.

Acute Inhalation Toxicity

Glyceryl Laurate

A low-grade irritant response was noted following inhalation of an aerosol containing 10% Glyceryl Laurate. The strain of animals tested and details concerning the test protocol and study results were not included (Unichema International 1997b).

Acute Oral Toxicity

Glyceryl Laurate

The acute oral toxicity of Glyceryl Laurate was evaluated using 31 male rats (strain not stated; weights = 150 to 220 g). The test substance was administered by stomach tube after 18 h of fasting. An LD_{50} of 53.4 ml/kg was reported (Eagle and Poling 1955).

Glyceryl Laurate (in olive oil) was administered orally to young Wistar rats (weights not stated). Doses of 10,000 and 20,000 mg/kg were administered to five male and five female rats, respectively. The LD_{50} was >20,000 mg/kg. (Henkel KgaA 1994).

Glyceryl Isostearate

A single oral dose (2 g/kg body weight) of Glyceryl Isostearate did not result in any harmful effects in rats. Details concerning the test protocol were not provided (Unichema International 1997a).

Glyceryl Rosinate

The acute oral toxicity of undiluted, Purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) was evaluated using fasted Wistar albino rats (five males, five females; weight range 220 to 292 g). A single oral dose of the test substance (5 g/kg) was administered to each animal. Dosing was followed by a 14-day observation period, and gross necropsy (results not included) was performed on all animals. None of the animals died, and it was concluded that the test substance was not toxic (LD_{50} > 5 g/kg) (Consumer Product Testing Company 1990a).

Glyceryl Citrate/Lactate/Linoleate/Oleate

Hüls AG (1996a) provided unpublished data on the acute oral toxicity of Glyceryl Citrate/Lactate/Linoleate/Oleate using five male and five female Wistar rats. The undiluted test substance (highly viscous) was liquefied by heating in a water bath and then administered to each animal using a rigid gastric pharyngeal probe. Each rat received a single oral dose of 2000 mg/kg (dose volume = 2.004 ml/kg body weight). The animals were observed over a period of 14 days after dosing. None of the animals died. Body weight gain was described as normal, and no signs of toxicity were noted. Grossly detectable organ changes were not noted at necropsy. The LD_{50} was >2000 mg/kg in male and female rats.

Acute Dermal Toxicity

Glyceryl Citrate/Lactate/Linoleate/Oleate

The acute dermal toxicity of Glyceryl Citrate/Lactate/Linoleate/Oleate was evaluated using five male and five female Wistar rats. The undiluted test substance (highly viscous) was liquefied by heating in a water bath and then applied dermally (dose = 2000 mg/kg; dose volume = 2.004 ml/kg) to each animal using a gauze patch. Each patch was secured with a semiocclusive dressing for 24 h. None of the animals died, and gross lesions were not observed. Particularly, no gross changes were observed in the subcutaneous tissue in the area of application. The acute dermal LD_{50} was >2000 mg/kg in male and female rats (Hüls AG 1996b).

Short-Term Inhalation Toxicity

Glyceryl Laurate

The short-term inhalation toxicity of Glyceryl Laurate was evaluated using rats. The animals were given a total of 14 1-hour exposures during a 3-week period. Although details concerning the test protocol and study results were not included, a no-effect level of 280 mg/m^3 was reported (Unichema International 1997b).

Short-Term Oral Toxicity

Glyceryl Laurate

The short-term oral toxicity of Glyceryl Laurate was evaluated using 10 weanling rats. The test substance was administered orally at a concentration of 25% in the diet for a period of 10 weeks. No gross or microscopic lesions were found that were attributable to administration of the test diet (Procter & Gamble Company 1950).

Chronic Oral Toxicity

Glyceryl Laurate

Fitzhugh, Schouboe, and Nelson (1960) fed two groups of 24 albino rats of the Osborne-Mendel strain a mixture consisting of Trilaurin (8%), Glyceryl Dilaurate (45%), and Glyceryl Laurate (40% to 45%) at a concentration of 25% in the diet for 2 years. The individual glyceryl esters were fed at effective dietary concentrations of ~2% (Trilaurin), ~11% (Glyceryl Dilaurate), and ~10% to 11% (Glyceryl Laurate). Of the two control groups, one was fed 25% hydrogenated cottonseed oil in the diet (concurrent control), and, the other, basal diet only.

After 26 or 52 weeks of dosing, no significant differences in weight gain between the test and concurrent control groups were noted. No significant differences in the total number of deaths were noted when the test group was compared with both control groups. At necropsy, no gross lesions were observed in test animals. At microscopic examination, a slight increase in hepatic cell fatty change was observed in test animals, compared to the control group fed the basal diet. However, this finding in test animals was no greater than that observed in the control group fed hydrogenated cottonseed oil. The same difference occurred to a lesser and questionably significant degree when the incidence of intrahepatic bile duct proliferation in test animals was compared to that noted in controls (Fitzhugh, Schouboe, and Nelson 1960).

Ocular Irritation

Glyceryl Laurate

The ocular irritation potential of undiluted Glyceryl Laurate was evaluated in the Draize test using three albino rabbits. The test substance (0.1 ml) was instilled into the conjunctival sac of one eye of each animal. Untreated eyes served as controls. Ocular reactions were scored every 24 h up to day 7 post instillation. Mean scores (average of 24-, 48-, and 72-h readings) for corneal reactions and erythema of the conjunctiva were 0.17 (maximum score, corneal lesions = 80) and 1.33 (maximum score, conjunctival lesions = 20), respectively. Reactions were not observed in the iris (Henkel KgaA 1994).

Kabara (1984) evaluated the ocular irritation potential of a 20% Glyceryl Laurate emulsion using six albino rabbits. The test substance (0.1 ml) was instilled into the conjunctival sac of the right eye of each animal. Untreated left eyes served as controls. Ocular reactions were scored at 24, 48, and 72 h post instillation according to the Draize scale: 0 to 110.

According to the test protocol, reactions would be classified as positive if the test substance induced any of the following: ulceration of the cornea (other than a slight dulling of the normal luster), inflammation of the iris (other than a slight circumcorneal injection of the blood vessels), or if the substance produced in the conjunctivae an obvious swelling with partial eversion of the lids or a diffuse crimson-red with individual vessels not easily discernible. Study results were positive only if four or more animals had positive reactions.

An average irritation score (six animals) of 0 was reported for both corneal opacity and inflammation of the iris. The average irritation score for conjunctival irritation was 3.7. Because only one rabbit had a positive reaction, the 20% Glyceryl Laurate emulsion was classified as a "negative ocular irritant" (Kabara 1984).

Glyceryl Isostearate

Although details concerning the test protocol were not provided, Unichema International (1997a) concluded that Glyceryl Isostearate was not an ocular irritant in rabbits. Reactions classified as minior ocular irritation had cleared by 48 h post instillation, reactions were not observed in the cornea or iris.

In a study by the Institut Français de Recherches et Essais Biologiques (1977), the ocular irritation potential of Glyceryl Isostearate was evaluated using six male New Zealand white rabbits. The test substance (undiluted, 0.1 ml) was instilled into the left conjunctival sac of each animal. Untreated right eyes served as controls. After instillation, the eyelids were held together for several seconds to avoid loss of the test substance. The animals were restrained for a period of 18 h. Ocular reactions were scored at 1, 2, 3, 4, and 7 days post instillation (maximum score = 20). Glyceryl Isostearate was classified as a nonirritant.

The Centre de Recherche et d'Elevage des Oncins (1975) evaluated a mixture consisting of Glyceryl Isostearate in an ocular irritation test. Other components of the mixture included glyceryl stearate, propylene glycol isostearate, propylene glycol stearate, ceteth-25, and oleth-25, but the concentration of each component was not provided. The mixture, 20% in sterile water, was instilled (0.1 ml) into the conjunctival sac of the left eye of each of six New Zealand rabbits. Contralateral eyes served as controls. Reactions were scored at 24, 48, and 72 h post instillation according to the Draize scale. Mean Draize ocular irriation scores were 3.0 (at 24 h), 2.67 (at 48 h), and 1.67 (at 72 h). Total Draize scores (Scale: 0 to 110) were 18, 16, and 10 at 24 h, 48 h, and 72 h, respectively. The mixture was classified as a nonirritant based on the mean ocular irritation scores that were recorded.

Glyceryl Rosinate

The ocular irritation potential of undiluted, Purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) was evaluated using six New Zealand white rabbits. The test substance was instilled (0.1 ml) into the conjunctival sac of one eye of each animal. Untreated eyes served as controls. Eyes were not rinsed for up to 24 h post instillation. Ocular reactions were scored at 24, 48, and 72 h post instillation according to the Draize scale (maximum total score = 110). Reactions were also scored at days 4 and 7 if irritation reactions persisted. Average Draize scores of 1.3 and 0.3 were reported at 24 and 48 h post instillation, respectively. At 72 h, an average score of 0 was reported. The test substance was not an ocular irritant (Consumer Product Testing Company 1990b).

Glyceryl Citrate/Lactate/Linoleate/Oleate

The ocular irritation potential of Glyceryl Citrate/Lactate/Linoleate/Oleate was evaluated using three female rabbits. The test substance (0.1 ml) was instilled into the conjunctival sac of one eye of each animal. At 24 h post instillation, the eyes were flushed with warm physiological saline solution. The conjunctivae, iris, and cornea were examined for any signs of ocular irritation at 24, 48, and 72 h post instillation. Ocular irritation was not observed in either of the three rabbits tested (Hüls AG 1996c).

Skin Irritation

Glyceryl Laurate

Kabara (1984) evaluated the skin irritation potential of a 20% Glyceryl Laurate emulsion using six albino rabbits. The test substance, 0.5 ml, was applied to both an abraded and intact skin site (clipped free of hair) on each animal, and each site was then covered with an occlusive patch. Patches were secured with adhesive tape, and the entire trunk of each animal was wrapped with an impervious material. The animals were immobilized during the 24-h contact period.

At 24 h and 72 h after patch removal, reactions at abraded and intact sites were scored according to the following scales: 0 (no erythema) to 4 (severe erythema to slight eschar formations); and 0 (no edema) to 4 (severe edema).

The primary irritation score for the group of six rabbits was 3.9, classifying the Glyceryl Laurate emulsion as a moderate skin irritant (Kabara 1984).

Henkel KgaA (1994) reported the results of a study to evaluate the skin irritation potential of undiluted Glyceryl Laurate using six rabbits. The test substance was applied (0.5 g under an occlusive patch) to dorsal skin of each animal. The test sites of three rabbits were shaved and those of the remaining three were scarified. Reactions were scored after 24 h and 72 h. Glyceryl Laurate induced minor erythema (mean score = 0.8) and edema (mean score = 0.9) in animals with intact skin. The scores for the three rabbits with scarified skin were not included.

Although details concerning the test protocol and study results were not included Unichema International (1997b) reported that Glyceryl Laurate was less irritating to the skin of rabbits, on an active for active basis, than sodium lauryl sulfate (SLS). Solutions of Glyceryl Laurate were equivalent in irritancy to SLS concentrations of approximately one fifth the strength.

Glyceryl Isostearate

Biogir S.A. Conseil Recherche (1989) conducted a study in which the skin irritation potential of Glyceryl Isostearate was evaluated using three New Zealand albino rabbits. The test substance (0.5 ml on hydrophilic gauze) was applied to skin, clipped free of hair, on the right side of each animal. Patches were secured with hypoallergenic microporous adhesive tape and then covered with elastic material that surrounded the animal's torso. After 4 h of contact, all patches were removed. A gauze square moistened with 0.5 ml of distilled water was applied to a control site on the left side of each animal according to the same procedure.

At 1, 24, 48, and 72 h post removal of the semiocclusive bandage, reactions were scored according to the following scales: 0 (no erythema) to 4 (severe erythema, with or without formation of scars and presence of a lesion representing a significant reaction such as a burn or necrosis); 0 (no edema) to 4 (severe

edema). Because slight irritation persisted beyond 72 h post removal, the animals were observed until all lesions had regressed completely.

Mild erythema was observed in two rabbits at 1, 24, and 48 h post removal. A more severe reaction (moderate irritation) was observed in the third rabbit; the reaction did not clear until day 5. Very mild edema was noted in two rabbits at 1 h post removal, and persisted to 48 h post removal in one rabbit. Slowly reversible, slight changes in the structure of the skin were also observed. It was concluded that Glyceryl Isostearate was not a skin irritant in albino rabbits (Biogir S.A. Conseil Recherche 1989).

The Institut Français de Recherches et Essais Biologiques (1977) evaluated the skin irritation potential of Glyceryl Isostearate using six male New Zealand albino white rabbits. A sterile absorbent gauze pad containing the test substance (0.5 ml) was applied to a scarified site on the right flank and an intact site on the left flank of each animal. Both sites had been clipped free of hair. Each gauze pad was secured with a non-allergenic, adhesive occlusive patch.

The patches remained in place for 23 h; reactions were scored at 24 and 72 h post application according to the following scales: 0 (no erythema) to 4 (severe erythema, crimson red, with slight eschar formation [injuries in depth]) and 0 (no edema) to 4 (severe edema, raised more than 1 mm and extending beyond area of application). The primary irritation index (PII) was calculated after all scores had been recorded. Glyceryl Isostearate was classified as a nonirritant (PII = 0.21) (Institut Français de Recherches et Essais Biologiques [IFREB] 1977).

The Centre de Recherche et d'Elevage des Oncins (1975) evaluated a mixture consisting of Glyceryl Isostearate and glyceryl stearate, propylene glycol isostearate, propylene glycol stearate, ceteth-25, and oleth-25 in a skin irritation test using rabbits. The concentrations of each component were not stated. The mixture (0.5 ml, 20% in sterile water) was applied to an intact site and an abraded site (each 2 cm^2 and clipped free of hair) on each of six male New Zealand rabbits. A nonallergenic, adhesive patch was placed over each test site, and the trunk of each animal was wrapped with an adhesive plaster. Patches were removed at 24 h post application and reactions scored (at 24 h and 72 h) according to the scales indicated in the preceding paragraph. The mixture was classified as a slight irritant (PII = 0.92).

Glyceryl Rosinate

The skin irritation potential of undiluted, Purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) was evaluated using six New Zealand white rabbits. The test substance (0.5 ml) was applied to abraded and intact skin (two sites per animal), and sites were covered with occlusive patches for 24 h. The patches were secured with hypoallergenic cloth tape and the entire trunk of each animal was encased in an impermeable plastic, occlusive wrapping. Reactions were scored at 24 and 72 h post application according to the following scales: 0 (very slight erythema, barely perceptible) to 4 (severe erythema [beet redness] to slight eschar formation [injuries in depth]) and 1 (very slight edema, barely perceptible) to 4 (severe edema, area raised approximately 1 mm and extending beyond area of exposure). The mean scores at 24 and 72 h were averaged and a PII calculated. A PII of 3.40 (potential for severe irritation—warning label may be considered) was reported (Consumer Product Testing Company 1990c).

Glyceryl Citrate/Lactate/Linoleate/Oleate

In an acute dermal toxicity study summarized earlier in the report text, undiluted Glyceryl Citrate/Lactate/Linoleate/Oleate (heated) was applied to the skin of Wistar rats (five males, five females). The test substance (dose = 2000 mg/kg; dose volume = 2.004 ml/kg) was applied to each animal using a gauze patch, and each patch was secured with a semiocclusive dressing for 24 h. Neither erythema nor edema was observed in any of the animals tested (Hüls AG 1996b).

Hüls AG (1996d) reported another study of the skin irritation potential of undiluted Glyceryl Citrate/Lactate/Linoleate/Oleate using three rabbits (strain not stated). The test substance was applied to shaved, intact skin for 4 h. At 24 h post application, clearly circumscribed erythema and very mild to clear edema were observed. Barely perceptible to clearly circumscribed erythema and very mild edema were observed at 48 and 72 h post application. After day 6 post application, erythema and swelling were barely detectable. In one animal, a brown stain was noted at the application site; the skin surface was described as dry and squamous. Very slight erythema, dryness, and scaling were noted in all animals on day 8. These reactions were accompanied by slight swelling in one of the three animals. All reactions classified as erythema or edema had cleared by day 10 post application. Scaling was observed in one animal (day 10), but had cleared by day 14. The average score for erythema and scabbing (24, 48, and 72 h readings included) was 1.67. The average score for edema formation (24-, 48-, and 72-h readings included) was 1.11.

Comedogenicity

The comedogenicity of undiluted, Purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) was evaluated using three male New Zealand white rabbits (3 months old). The test substance (0.1 ml) was applied to the internal base of the right ear of each rabbit 5 days per week for 3 weeks (15 applications per rabbit). Untreated left ears (internal base) served as controls. Test sites were evaluated for comedone formation and enlarged pores daily. Terminal biopsies of treated and control ears were performed. All specimens were graded for the extent of acanthosis, keratosis, and keratin ("plugging") according to the following scale: 0 (no different from untreated/treated control) to 3 (approximately 75% greater than untreated/treated control). At gross examination, erythema at the application site was noted in all three rabbits. At microscopic examination, all tissues were within normal histological limits. Follicular hyperkeratosis

(comedone formation) was not observed (Consumer Product Testing Company 1990d).

Skin Sensitization

Glyceryl Laurate

The Cosmetic, Toiletry, and Fragrance Association (CTFA) provided the results of a 1975 study of the skin sensitization potential of Glyceryl Laurate in a maximization test using guinea pigs.

Prior to study initiation, a preliminary irritation test (intradermal injection and topical application procedures) was performed using two groups of four males, respectively. In the intradermal injection test, the four animals were injected intradermally with Glyceryl Laurate (0.05% to 1% in 6% absolute alcohol/saline). Reactions described as faint, pink erythema predominated. In the topical application test, the other four males were tested with concentrations ranging from 5% to 25% in absolute alcohol. Scaling was observed in one guinea pig tested with 25% Glyceryl Laurate.

Ten guinea pigs (six males, four females) were tested in the maximization test. The animals were subjected to four sensitizing injections of 2% Glyceryl Laurate and then challenged with intradermal injections of 0.8% Glyceryl Laurate and topical applications of 25% Glyceryl Laurate. Four male guinea pigs served as controls. The grading scale for intradermal challenge reactions ranged from faint, pink erythema to deep, pink erythema. Topical challenge reactions were scored according to the following scale: ± (barely perceptible erythema) to ++++ (erythema–breakdown of surface–necrosis). Positive reactions were not observed in either of the ten animals tested. Glyceryl Laurate was classified as a nonsensitizer (CTFA 1975).

Kabara (1984) studied the skin sensitization potential of a 20% Glyceryl Laurate emulsion in a guinea pig maximization test. To induce sensitization, 10 animals were treated by intradermal injection in the shoulder region. At 7 days post injection, sensitization was boosted by placement of an occlusive patch over the injection site; an occlusive challenge patch was applied to the flank at 14 days post injection. Four additional guinea pigs were treated in a manner similar to that of the test group, except that the test substance was applied only during the challenge phase. Positive challenge reactions were observed in two test animals challenged with a 10% dilution of the test substance. No visible reactions were present in control animals challenged with a 10% dilution of the test substance or either test or control animals challenged with a 5% dilution.

A second challenge was initiated 7 days after the first. Positive reactions were observed in five test animals and two control animals challenged with a 10% dilution of the test substance. Positive reactions were also observed in four test animals challenged with a 5% dilution of the test substance; no reactions were present in the control group. It was concluded that because positive reactions were observed in test and control groups (after first and second challenge), it is likely that irritation, and not sensitization, was responsible for these observations (Kabara 1984).

Glyceryl Isostearate

CTFA reported the results of a 1985 study of the skin sensitization potential of Glyceryl Isostearate using a guinea pig maximization test procedure. Eighteen guinea pigs (10 test, 4 treated controls, and 4 untreated controls; strain not stated) were used. During induction, the animals were injected intradermally (0.1-ml injections) in the shoulder region with 2.5% Glyceryl Isostearate in a vehicle consisting of polyethylene glycol (PEG), microcrystalline cellulose (MCC), and Dobs/saline (dodecyl benzene sulfonate in physiological saline).

At 5 to 7 days after the last injection, an occlusive induction patch saturated with 100% Glyceryl Isostearate was maintained in contact with the injection site for 48 h. Intradermal injection reactions were scored according to the following scale: fp (faint pink erythema) to dp (deep pink erythema). The challenge phase was initiated 12 to 14 days after application of the induction patch. An occlusive challenge patch containing 50% Glyceryl Isostearate (in PEG and MCC) was applied to the skin for 24 h. Further challenges were made at weekly intervals, or longer, as required. Challenge reactions were scored according to the following scale at 24 and 48 h: 0 (no reaction) to 3 (marked erythema).

The four treated controls consisted of four guinea pigs that were tested according to the preceding study protocol, with the exception that Glyceryl Isostearate was omitted only from the intradermal and covered patch induction procedures. The untreated control group consisted of four previously untreated animals that were challenged with Glyceryl Isostearate according to the procedure described earlier.

The results of the first challenge yielded one positive reaction at 24 h and two positive reactions at 48 h. Following the second challenge, positive reactions were not noted at 24 or 48 h. The slight sensitization reactions noted following the first challenge were confirmed by results of the third challenge (CTFA 1985).

Glyceryl Citrate/Lactate/Linoleate/Oleate

Hüls AG (1996e) reported results of the skin sensitization potential of Glyceryl Citrate/Lactate/ Linoleate/Oleate using 20 guinea pigs. Ten guinea pigs served as controls. Any reactions, particularly those classified as erythema and edema, were assessed 30 and 54 h after the initiation of treatment. Undiluted Glyceryl Citrate/Lactate/Linoleate/Oleate was tested during induction phases I, II, and III (dermal application) because the undiluted material did not induce skin irritation in a preliminary test.

During the fourth week of testing, a "trigger concentration" was determined for initiation treatment on three guinea pigs that were the same ages as those in the main test. The undiluted test substance was administered (dermal application) as the highest, nonirritating concentration.

Glyceryl Citrate/Lactate/Linoleate/Oleate did not induce systemic effects or any adverse effects on body weight gain. At 30 h post application in induction phases I, II, and III, skin irritation was not observed in the 20 test animals or 10 vehicle-control animals. "Trigger" treatment with the undiluted test substance did not induce erythema or edema of the right rear flank at 30 or 54 h post application in test or control animals. Also, in patch tests, the vehicle did not cause skin reactions in animals of the test or control group. It was concluded that Glyceryl Citrate/Lactate/Linoleate/Oleate did not induce sensitization in guinea pigs (Hüls AG 1996e).

Glyceryl Rosinate

Shao et al. (1993) conducted a study to investigate whether the esterification of rosin with glycerol or other polyalcohols would alter the allergenicity of rosin. The allergenicity of Glyceryl Rosinate was evaluated using three groups of 15 female Dunkin-Hartley guinea pigs.

During induction, the first group (group I) received four closed epidermal applications of 8.3% glyceryl triabietate (GTA) in petrolatum (abietic acid, esterified to yield this compound, is the main component of rosin) on days 0, 2, 7, and 9 and two injections of Freund's complete adjuvant (FCA) on day 7. In the second group (group II), the induction procedure (same protocol) consisted of four closed epidermal applications of 20% gum rosin and two injections of FCA. The control group was sham treated.

All three groups were challenged with the following: 0.93%, 2.8%, and 8.3% GTA; 10% glycerol esterified tall oil rosin (TORG), 20% gum rosin; and petrolatum vehicle control. Challenge patches (Finn chambers) were removed after 24 h, and reactions scored at 48 and 72 h post application. Study results (challenge phase, 72-h reading) are summarized below.

In group I, results indicated one positive reaction to 0.93% GTA; 2.8% GTA; 20% gum rosin; and petrolatum. The incidence of positive reactions in group II was as follows: 1 (8.3% GTA); 2 (10% TORG); 3 (0.93% and 2.8% GTA); and 9 (20% gum rosin). One positive reaction to 0.93% GTA and two positive reactions to 8.3% GTA were observed in the control group. Scores at 48 and 72 h were not significantly different from one another. It is important to note that in group II, the incidence of positive reactions to 10% TORG (two reactions) was less than that of 20% gum rosin (nine reactions). The esterification of rosin with glycerol, in effect, reduced the allergenicity of rosin. GTA was nonallergenic and did not cross-react with allergens in unmodified gum rosin (Shao et al. 1993).

This same laboratory evaluated the allergenicity of GTA and other esters of glycerol and abietic acid (Gäfvert et al. 1994). Products formed from the esterification of abietic acid (mentioned in the preceding study) with glycerol include: glyceryl triabietate (GTA); glyceryl 1,2-diabietate ($GDA_{1,2}$); glyceryl 1,3-diabietate ($GDA_{1,3}$); and glyceryl 1-monoabietate (GMA).

The allergenicity of these compounds was evaluated according to the procedure in the preceding study using female Dunkin-Hartley guinea pigs. Group I (14 animals) and Group II (15 animals) animals were induced with 3.3% GMA in petrolatum and 20% gum rosin in petrolatum, respectively. Petrolatum was applied to animals of Group III (control). The animals were challenged with the following: GMA (0.37%, 1.1%, and 3.3%); 5.7% $GDA_{1,3}$; 5.7% $GDA_{1,2}$; 8.3% GTA, and 10% unmodified gum rosin. Challenge reactions at 72 h post application were reported. All statistically significant findings are accompanied by p values.

In group I, GMA induced sensitization at concentrations of 0.37% (1 of 14 animals), 1.1% (4 of 14, $p < .05$), and 3.3% (6 of 14, $p < .01$). The incidence of sensitization reactions to GMA in group II was as follows: 0.37% GMA (1 of 15 animals), 1.1% (3 of 15), and 3.3% (2 of 15). No significant responses were noted when $GDA_{1,3}$ and $GDA_{1,2}$ were tested on animals that were sensitive to GMA. Gum rosin induced sensitization in 8 of 15 animals ($p < .01$) in group II and in 1 of 14 animals in group I. No significant cross-reactivity with GMA was noted in animals that were sensitive to unmodified gum rosin. Neither GTA nor petrolatum induced sensitization in either of the three groups (Gäfvert et al. 1994).

Phototoxicity and Photoallergy

Glyceryl Isostearate

The phototoxicity and photoallergenicity potentials of Glyceryl Isostearate was evaluated using 20 albino guinea pigs. The back and sides of each animal were divided into the following six treatment areas: test material + UVA, test material + UVB, test material alone, positive control (8-methoxypsoralen) + UVA, UVB alone, and UVA alone. Doses of the test material and positive control (dose for each = 0.02 ml/cm^2) were applied 30 min prior to irradiation. UV irradiations were performed using Philips tubes (TL 20W/09 for UVA and TL 20W/12 UV for UVB). Cutaneous reactions were evaluated at 24 h post treatment. Glyceryl Isostearate did not induce significant cutaneous reactions with or without UV irradiation. The positive control (8-methoxypsoralen) induced severe reactions (Unichema International 1997a).

Immunologic Activity

Glyceryl Laurate

The effect of Glyceryl Laurate on delayed-type hypersensitivity to sheep erythrocytes was evaluated using mice. The four groups (10 mice per group) of female ICR mice used in the study were designated as treated (T; two groups), control (C), and normal (N). The mice in groups T and C were injected subcutaneously (s.c.) with 0.05 ml/mouse of sheep red blood cells (SRBCs) (3×10^9 cells/ml). Injections were made into the right hind footpads. The mice in group T were then immediately injected intraperitoneally (i.p.) with a saline suspension of Glyceryl Laurate, and group C mice were injected with saline alone. On day 4, mice of groups T, C, and N were injected (s.c.) in the left hind footpads with SRBCs (0.05 ml/mouse). Left footpad

thickness was measured with a caliper 24 h later. The i.p. administration of Glyceryl Laurate did not cause significant enhancement of the immunological response. Mean footpad thickness was 4.20 ± 0.44 mm, compared to 4.23 ± 0.36 mm and 3.55 ± 0.23 mm for untreated mice and saline controls, respectively (Kabara et al. 1985).

The modulation of immune cell proliferation in vitro by Glyceryl Laurate was evaluated using lymphocytes obtained from murine spleens. Lymphocyte proliferation was stimulated at Glyceryl Laurate concentrations between 10^{-5} and 5 μg/ml per 5×10^5 lymphocytes. At concentrations greater than 5 μg/ml, Glyceryl Laurate inhibited lymphocyte proliferation and blocked the proliferative effects of the lymphocyte mitogens, phorbol myristate acetate and concanavalin A, and the toxic shock syndrome toxin-1 (potent T-cell mitogen). Furthermore, the results of experiments using purified immune cell subsets indicated that Glyceryl Laurate (0.1 μg/ml) optimally induced T-cell proliferation, but did not affect B cells. Glyceryl Laurate–induced T-cell proliferation was blocked by cyclosporin A (immunosuppressive drug) at concentrations as low as 20 ng/ml, suggesting that Glyceryl Laurate could be exerting its effect along the calcium-dependent inositol phospholipid, signal transduction pathway (Witcher, Novick, and Schlievert 1996).

In Vitro Hemolytic Activity

Glyceryl Laurate

Kato et al. (1971) evaluated the hemolytic activity of Glyceryl Laurate using sheep erythrocytes. The erythrocytes were washed with 0.86% NaCl and suspended in NaCl solution. Glyceryl Laurate was dissolved or suspended in NaCl solution at several dilutions (starting with 1 mg/ml), and an equal volume of the red blood cell suspension in NaCl was added. Hemolytic activity, expressed by the highest dilution in which hemolysis was observed, was determined after incubation for 4 h at 37°C. The highest dilution in which hemolysis was observed was a sevenfold dilution of the starting concentration of Glyceryl Laurate. Glyceryl Laurate had strong hemolytic activity.

GENOTOXICITY

Glyceryl Citrate/Lactate/Linoleate/Oleate was evaluated for its potential to induce reverse mutations in the following *Salmonella typhimurium* strains: TA 98, TA 100, TA 1535, and TA 1537. The Ames test (plate incorporation and preincubation methods) was used in this evaluation. Five concentrations of Glyceryl Citrate/Lactate/Linole-ate/Oleate (50 to 5000 μg/plate) were tested in triplicate both with and without metabolic activation. Tetrahydrofurane served as the solvent control, and the three positive controls were as follows: 2-nitrofluorene, sodium azide, and 9-aminoacridine. Glyceryl Citrate/Lactate/Linoleate/Oleate was not mutagenic (all strains) in the plate incorporation test or the preincubation test either with or without metabolic activation (Hüls AG 1996f).

Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate are esters of glycerin and acids derived from rosin, which is composed of diterpene resin acids. In studies on the mutagenicity of resin acids, only neoabietic acid (component of rosin) was mutagenic in the Ames/*Salmonella* assay (FDA 1988).

CARCINOGENICITY

Glyceryl Stearate was tested for tumor promoting activity (Saffioti and Shubik 1963) on the clipped dorsal skin of 20 female Swiss mice. One week after a single application of 9,10-dimethylbenz(a)anthracene (DMBA) (1% to 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.

Tumor Inhibition

Glyceryl Laurate

Kabara et al. (1985) evaluated the in vitro antitumor activity of Glyceryl Laurate using two leukemia cell lines, L-5178Y and L-1210. Leukemia cells were cultured (1.0×10^5 cells/ml, 48 h at 37°C) with various concentrations of the test substance, suspended in physiological saline containing 5.0% DMSO. Untreated cultures served as controls. The growth inhibitory effect was determined as the ratio of cell numbers in treated and control cultures at the end of the incubation period. Based on this ratio, the IC_{50} was obtained by probit diagramming analysis. The IC_{50} values were 50 and 62 mg/ml in L-1210 and L-5178Y cell lines, respectively. Thus, marked antitumor activity was demonstrated against both cell lines.

On the basis of the above results, these authors evaluated Glyceryl Laurate in a survival test using 5-week-old, female BDF_1 mice implanted intraperitoneally with L-1210 leukemia cells (1.0×10^5 cells/mouse). A suspension of the test substance in saline was injected i.p. into each animal once daily for five consecutive days (first injection, 24 h after tumor transplantation). One group of mice received daily injections of 30 mg/kg, and the other, daily injections of 100 mg/kg. Control mice were injected with saline.

Study results indicated that Glyceryl Laurate was ineffective in prolonging the life span of tumor-bearing mice. Survival times for test mice were 9.83 days (30 mg/kg dose group) and 9.66 days (100 mg/kg dose group). The survival time for control mice was also 9.83 days. The investigators stated that the in vivo inactivity of Glyceryl Laurate could have been due to the inappropriateness of the experimental conditions adopted, and that further tests should be performed using different routes of administration, dosages, or vehicles (Kabara et al. 1985).

In two earlier studies (Kato et al. 1969, 1971), the in vivo antitumor activity of Glyceryl Laurate in 5-week-old ddY mice (weights = 18 to 22 g) was evaluated using Ehrlich ascites tumor cells. In one study, 2×10^6 tumor cells were implanted i.p. into each of eight mice. Glyceryl Laurate was then administered i.p. daily for 5 successive days at doses of 2.5 mg/mouse/day

(2 mice) and 10 mg/mouse/day (2 mice). The four control mice were injected with tumor cells only. After 7 days, tumor growth and body weight gain were noted. Tumor growth was not observed in mice given either of the two doses. Survival was 27 and 24 days for the two mice dosed with 2.5 mg/day and 28 and >30 days for the two mice dosed with 10 mg/day. Tumor growth in four control mice was marked and survival was 13 to 17 days. Glyceryl Laurate inhibited tumor growth completely and increased the survival time of mice injected with tumor cells (Kato et al. 1969).

In a study by Kato et al. (1971), approximately one million tumor cells were implanted i.p. into 12 test mice (two groups of six) and six controls, and a solution or suspension of Glyceryl Laurate in 0.86% NaCl solution was administered i.p. daily for 5 successive days. The two test groups received doses of 2.5 and 10 mg/mouse/day, respectively, and control mice were injected with 0.2 ml of NaCl solution. After 7 days, tumor growth and body weight gain were noted. Tumor growth was marked in control mice (survival time = 16 days). However, no tumor growth was observed in either group of test mice. Survival times for 2.5 mg/day and 10 mg/day test mice were 26 and >29 days, respectively.

In an additional experiment, these authors evaluated the in vitro action of Glyceryl Laurate on Ehrlich ascites tumor. The hypothesis was that Glyceryl Laurate might have a specific affinity for the tumor cells, and, if strong enough, attack the cells. In vitro attack of the cells was measured using the viability of treated tumor cells. In the assay for viability, the viability of treated tumor cells (mixture of Glyceryl Laurate in phosphate-buffered saline with the tumor cell suspension) was determined by staining the cells with safranin dye. Glyceryl Laurate was tested at concentrations of 5, 50, and 500 μg/ml. The percentage of dead cells in the mixture was determined by counting the number of cells microscopically. Cell death (100%) was noted at concentrations of 50 and 500 μg/ml (Kato et al. 1971).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Studies on the reproductive and developmental toxicity of the Glyceryl Monoesters reviewed in this report were not found in the published literature. Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate are derived from rosin. As stated earlier, rosin is defined as the residue remaining when the volatile oil is distilled from turpentine or a product of the distillation, solvent extraction, or both, of the stumps or fallen trees of various species of *Pinus*. FDA (1988) reported that, following the administration of hexane extracts of *Pinus ponderosa* needles to mice by stomach tube, increased embryonic resorptions were observed. Recall that it is important to note that the following active components of the extracts tested, diterpene resin acids, were identified: pimaric acid, isopamaric acid, sandaracopimaric acid, palustric/levopimaric acid, abietic acid, dehydroabietic acid, and neoabietic acid. Abietic acid and dehydroabietic acid have been identified as main components of rosin.

CLINICAL ASSESSMENT OF SAFETY

Inhalation Toxicity

Glyceryl Caprylate/Caprate is used in hair sprays. Jensen and O'Brien (1993) reviewed the potential adverse effects of inhaled aerosols, which depend on the specific chemical species, the concentration, the duration of the exposure, and the site of deposition within the respiratory system. Particle size is the most important factor affecting the location of deposition.

The determination of the health consequences of exposure to an aerosol requires an analysis of the inhalation and deposition of the aerosol within the human respiratory system. The toxic action of an aerosol may be related to the number of particles, their surface area, or the mass deposited. Many occupational diseases are associated with the deposition of particles within a certain region of the respiratory tract.

The aerosol properties associated with the location of deposition in the respiratory system are particle size and density. The parameter most closely associated with this regional deposition is the aerodynamic diameter, $\mathbf{d_a}$, defined as the diameter of a sphere of unit density possessing the same terminal setting velocity as the particle in question.

Many particles present in the air do not enter the respiratory tract because of the size-selective sampling of the nose and the mouth. Still others are removed in the upper respiratory tract. The concept of size-selective air sampling calls for measurement of particles in industrial aerosols of the size that are associated with a specific health effect. For chemical substances present in inhaled air as suspensions of solid particles or droplets, the potential hazard depends on the particle size as well as on mass concentration. The American Conference of Governmental Industrial Hygenists (ACGIH) has defined three particle-size-selective threshold limit values (PSS TLVs) (ACGIH 1991): inhalable particulate mass TLVs (IPM TLVs) for those materials that are hazardous when deposited anywhere in the respiratory tract; thoracic particulate mass TLVs (TPM TLVs) for those materials that are hazardous when deposited anywhere within the lung airways and the gas-exchange region; and respirable particulate mass TLVs (RPM TLVs) for those materials that are hazardous when deposited anywhere in the gas-exchange region (Jensen and O'Brien 1993).

The mean aerodynamic diameter of 4.25 $\pm$ 1.5 μm of respirable particles above may be compared with diameters of anhydrous hair spray particles of 60 to 80 μm (typically, <1% are below 10 μm) and pump hair sprays with particle diameters of $\geq$80 μm (Bower 1999).

Skin Irritation

Glyceryl Rosinate

The skin irritation potential of a lipstick containing 1.0% Glyceryl Rosinate, as supplied, was evaluated using 12 volunteers (21 to 45 years old). All subjects were in good heath and free of any visible skin disease or anomaly. The lipstick was crushed (to mix the inner and outer layers) and applied to an

occlusive patch. Patches (one per subject) covered with the lipstick were applied to the back and remained in place for 24 h. Reactions were scored 3 days later according to the following scale: 0 (no visible erythema) to 3 (severe erythema [very intense redness]). A new patch containing the test substance was reapplied to the same site on each subject and removed after 24 h. Reactions were scored after patch removal and 24 h later. The grading period was followed by a second new patch application (24 h), and reactions were scored at the same intervals. The lipstick containing 1.0% Glyceryl Rosinate did not elicit an irritation response (all scores = 0) in either of the 12 subjects tested (Biosearch, Inc. 1992a).

Skin Sensitization

General

Human studies have indicated that the incidence of contact sensitization is dose dependent and that the induction of skin sensitization is dependent on the dose of a chemical per unit area of skin (Kimber, Gerberick, and Basketter 1999).

Glyceryl Laurate and Glyceryl Linoleate

Danisco Ingredients (1996), reported a study in which the skin irritation and sensitization potential of Glyceryl Laurate and Glyceryl Linoleate was evaluated using 91 healthy volunteers (males and females, 18 to 65 years old) in a modified Draize repeat-insult patch test. The study was classified as single-blind. Patches consisted of a 5 cm wide strip of Scanpor tape to which 10 "Finn-chambers" were fixed in pairs. The three glyceryl monoesters were tested at a concentration of 50% w/v in liquid paraffin. Glyceryl Linoleate (0.02 ml) was dispensed directly into individual Finn chambers. Glyceryl Laurate was heated to 60°C and 0.02 g was placed directly into individual Finn chambers; 0.02 ml liquid paraffin was dispensed onto a filter disc in the chamber. Liquid paraffin served as the negative control.

The 91 volunteers were divided into two groups, group 1 (39 subjects) and group 2 (52 subjects), respectively. In group 1, the first set of induction patches was applied to the upper back for 23 h and subsequent patch applications were 47 h in duration. The patch test schedule for these subjects was as follows: days 1, 2, 4, 7, 9, 11, 14, 16 and 18. In group 2, 47-h induction patch applications were made according to the following schedule: days 1, 3, 5, 8, 10, 12, 15, 17, and 19. In both groups, induction patches were applied to the same site, unless a reaction stronger than mild erythema was observed. Reactions were scored after patch removal according to the following scale: 0 (no visible reaction) to 5 (bullous reaction).

During the challenge phase, initiated on day 35, patches were applied to new sites on the upper back for 47 h. Challenge reactions were scored at 1 and 49 h after patch removal. Classification of either test substance as irritating was based on 10% of the induction scores defined as >1 (mild erythema). Sensitization was defined as a rapid response to challenge patch application, characterized by severe erythema and edema (usually with papules and/or vesicles).

Seventeen of the 91 subjects withdrew for reasons either unrelated to treatment (16 subjects) or because the patch was painful (1 subject). Seventy-four subjects (64 women, 10 men) completed the study. Glyceryl Linoleate did not induce skin irritation or sensitization. However, Glyceryl Laurate induced mild, erythematous reactions during induction in most of the subjects and questionable reactions during the challenge phase in seven subjects. During induction and challenge (1 and 49 h post removal) phases, reactions to Glyceryl Laurate ranged from 1 (mild erythema) to 2 (moderate erythema) (Danisco Ingredients 1996).

Glyceryl Laurate, Glyceryl Myristate, and Glyceryl Oleate

Danisco Ingredients (1999f) reported results of a study in which the skin irritation and sensitization potential of Glyceryl Laurate, Glyceryl Myristate, and Glyceryl Oleate was evaluated in a single-blind study using 93 healthy volunteers (ages between 18 and 65 years). Ten of the original 107 subjects withdrew for reasons unrelated to the conduct of the study. The repeat-insult patch test procedure (similar to procedure in preceding study) was a modification of the Draize test. Glyceryl Laurate was tested at a concentration of 25% in liquid paraffin oil, whereas Glyceryl Myristate and Glyceryl Oleate were each tested at a concentration of 50% in liquid paraffin oil. Liquid paraffin oil served as the control. Induction patches (Finn chambers on Scanpor tape) containing either of the three test substances or the control were applied to the upper back of each subject. The subjects were instructed to remove and discard the patches at the end of the 47-h contact period. This procedure was repeated (same sites) for a total of nine induction applications.

Test sites were evaluated prior to application of the next patch and 1 hour after patch removal on the last day of the induction phase according to the following scale: 0 (no visible reaction) to 5 (bullous reaction). Challenge patches were applied to the upper back (distant from induction site) of each subject on day 36. The patches were removed and discarded at the end of the 47-h contact period. Reactions were evaluated at 1 and 49 h after challenge patch removal.

Glyceryl Laurate (25% in liquid paraffin oil) induced moderate erythema (score = 2) in eight subjects during induction and in one subject during the challenge phase. Glyceryl Myristate and Glyceryl Oleate did not induce irritation or sensitization at a concentration of 50% in liquid paraffin oil. The investigators concluded that the three test substances did not induce sensitization during induction or challenge phases (Danisco Ingredients 1999f).

Glyceryl Caprate

The skin sensitization potential of 15% Glyceryl Caprate in paraffinium perl. DAB 10 (pharmaceutical grade) was evaluated in a modified Draize assay using 63 subjects, 58 of whom completed the study. During induction, the test substance was applied (0.025 ml, occlusive patches–Finn chamber) to the scapular region of the back three times per week (on Mondays, Wednesdays, and Fridays) for a total of 10 applications. At the end of each

48-h period (72 h on weekend), patches were removed and sites rinsed with distilled water. Reactions were scored according to the following scale: 0 (no reaction) to 4 (erythema, edema, and bullae). A 12-day nontreatment period was initiated after reactions to the 10th induction patch were scored. At the end of the 12-day period, occlusive challenge patches were applied to new sites on the scapular back for 48 h. Challenge reactions were scored at 48 and 72 h post application. The test substance did not induce irritation or sensitization reactions in any of the subjects tested (International Research Services, Inc. 1995).

Glyceryl Rosinate

Shao et al. (1993) patch tested eight dermatitis patients who had previously reacted to colophony (gum rosin) using Finn chambers with various rosins and rosin esters. Ten healthy subjects served as controls. Results indicated that the number of reactions to the rosin esters was lower, compared to the results for rosin. Five of eight patients had positive reactions to 10% tall oil rosin (in petrolatum), whereas four of eight patients had positive reactions to 20% glycerol-esterified tall oil rosin (in petrolatum). Also, seven of eight patients had positive reactions to 5% Portuguese gum rosin (in petrolatum) and three of eight patients had positive reactions to 20% glycerol-esterified gum rosin (in petrolatum). Additionally, neither of the eight subjects had positive reactions to glyceryl triabietate or petrolatum.

Positive reactions to each test substance ranged from + (erythema and infiltration) to +++ (erythema, infiltration, and vesicles). Because abietic acid is a main component of rosin and is easily oxidized to form contact allergens, the concentrations of this acid in the following rosin esters and rosins that were tested are indicated as follows: Portuguese gum rosin (42% abietic acid); tall oil rosin (55%); glycerol-esterified gum rosin (0.3%); and glycerol-esterified tall oil rosin (3.7%). It is important to note that the methylated oxidation product of abietic acid, 15-hydroperoxyabietic acid methyl ester (contact allergen) induced positive reactions in six of the eight patients tested and that this incidence was lower than that reported for Portuguese gum rosin (seven of eight patients). The results of this study indicated that esterification with glycerol reduced the allergenicity of rosin (Shao et al. 1993).

Gäfvert et al. (1994) evaluated the allergenicity of the following compounds (in petrolatum) in patients with contact allergy to gum rosin, 5% Portuguese gum rosin (GR), 10% tall oil rosin (TOR), 20% glycerol-esterified gum rosin (GGR), 20% glycerol-esterified tall oil rosin (TORG), 5.4% glyceryl-monoabietate (GMA), 9.5% glyceryl-1,2-diabietate ($GDA_{1,2}$), and 9.5% glyceryl-1,3-diabietate ($GDA_{1,3}$). $GDA_{1,2}$, $GDA_{1,3}$, and GMA are products that result from the esterification of abietic acid with glycerol (mentioned in preceding study). Except for patch tests with $GDA_{1,2}$ and $GDA_{1,3}$ (6 patients), 12 patients were used in the evaluation of each compound. Patch tests (Finn chambers) involved the application of each compound to the skin for 48 h. Reactions were scored at 72 h post application. Ten control subjects were patch tested according to the same procedure.

Results for the rosins and rosin esters were similar to those in the preceding study. Over half of the patients had reactions (++ to +++) to these compounds. Five of the 12 patients had positive reactions to GMA (++ to +++), and neither of the 6 patients had positive reactions to $GDA_{1,2}$, or $GDA_{1,3}$. The patch testing of an additional patient with the latter two compounds also yielded negative results. No reactions were observed in the 10 healthy control subjects. This study confirmed the contact sensitization potential of rosin and rosin esters in patients with contact allergy to gum rosin and identified glyceryl-1-monoabietate as a contact allergen (Gäfvert et al. 1994).

The Consumer Product Testing Company (1997) patch tested 53 subjects (males and females, 18 to 69 years old) with a test material consisting of 20% Purified Ester Gum-2-Octyldodecyl Myristate and 80% white petrolatum (a.k.a. PEGMODWP-20). (Because Purified Ester Gum-2-Octyldodecyl Myristate is a trade mixture consisting of 50% Glyceryl Rosinate and 50% Octyldodecyl Myristate, the effective concentration of Glyceryl Rosinate in the test material is 10%.) Forty-nine of the original 53 subjects completed the study; 4 withdrew for reasons that were unrelated to testing.

Approximately 0.2 ml of the test material (contains 10% Glyceryl Rosinate) was applied to the upper back, between the scapulae, of each subject on Mondays, Wednesdays, and Fridays for a total of 10 induction applications. Sites were covered with a semiocclusive patch immediately after each application of the test material. Nontreatment periods of 24 h followed patch removals on Tuesdays and Thursdays. Saturday patch removals were followed by 48 h nontreatment periods. The induction phase was followed by a 2-week nontreatment period, after which a challenge patch was applied to the same site and a previously untreated site. Challenge reactions were scored at 24 and 48 h post application according to the following scale: 0 (no visible reaction) to 4+ (erythema and edema with vesiculation and ulceration). Induction reactions were also evaluated according to this grading scale.

One subject had a score of 2+ (well-defined erythema, possible presence of barely perceptible edema) during induction and at 24 and 48 h during the challenge phase (at new test site, but not at original site). At 72 h, the same subject also had a challenge reaction of 3+ (erythema and edema) at the new test site, but not at the original site. None of the remaining 48 subjects had induction or challenge reactions. It was concluded that the test material did not have the potential for inducing skin irritation and/or sensitization in this study (Consumer Product Testing Company 1997).

Ivy Laboratories (1996) evaluated the sensitization potential of a foundation containing 4% Glyceryl Rosinate using 28 healthy adult volunteers (13 males and 15 females; 18 to 46 years old). Twenty-five subjects completed the study; 3 subjects were removed for reasons that were unrelated to application of the test substance. Patches were applied to the upper outer arm,

volar forearm, or to the back of each subject. During induction, approximately 0.1 ml of 0.25% aqueous sodium lauryl sulfate (SLS) was applied under an occlusive patch (secured with occlusive tape) that was removed after 24 h. The foundation (0.1 ml on semiopen induction patch) was then applied to the test site for 48 h (or 72 h, i.e., over the weekend). If skin irritation was not observed at the time of patch removal, an occlusive patch containing 0.25% aqueous SLS was reapplied for 24 h. Patch removal was followed by reapplication of a fresh induction patch (semi-open) containing the foundation.

This sequence of SLS and test substance application was repeated for a total of five induction exposures. If irritation was observed at any time during induction, SLS pretreatment was discontinued and replaced with a 24 h nontreatment period between applications of the test substance. Following a 10-day nontreatment period, the challenge phase was initiated. Pretreatment with SLS was performed prior to challenge patch application. Approximately 0.1 ml of 5% aqueous SLS was applied, under an occlusive patch, to a fresh skin site for 1 h. After patch removal, a semiopen challenge patch containing 0.1 ml of the foundation was applied to the same site for 48 h. Challenge reactions were graded 1 h after patch removal and 24 h later according to the following scale: 0 (not sensitized) to 3 (strong sensitization, large vesiculobullous reaction).

Contact allergy was not observed in any of the subjects during either of the two grading periods (all scores = 0). It was concluded that the foundation containing 4% Glyceryl Rosinate did not possess a detectable contact-sensitizing potential and, hence, is not likely to cause contact sensitivity reactions under normal use conditions (Ivy Laboratories 1996).

The maximization assay described in the preceding study was also used to evaluate the sensitization potential of a blush containing 2% Glyceryl Rosinate. Twenty-seven healthy adult volunteers (11 males and 16 females;18 to 56 years old) were tested. Contact allergy was not observed in any of the subjects during either of the two grading periods (all scores = 0). It was concluded that the blush containing 2% Glyceryl Rosinate did not possess a detectable contact-sensitizing potential and, hence, is not likely to cause contact sensitivity reactions under normal use conditions (Ivy Laboratories 1997).

The sensitization potential of a lip gloss containing 2.0% Glyceryl Rosinate was evaluated using 27 healthy adult volunteers (7 males, 20 females; 18 to 60 years old). Basically, the same maximization assay procedure (indicated above), was used with the following modifications: Patches were applied to the upper outer arm of each subject. During induction, the application of 0.1 ml of 1% aqueous SLS (occlusive patch) was followed by the application of 0.1 g of the test material (site covered with occlusive tape, referred to as induction patch). Prior to initiation of the challenge phase, the challenge site (new site on opposite arm) was pre-treated with 0.1 ml of 10% aqueous SLS (under occlusive patch). Pretreatment was followed by application of the test substance (same site) under an occlusive challenge patch secured with occlusive tape. Contact allergy was not observed in any of the subjects during either of the two grading periods (all scores = 0), and there were no unusual or unexpected side effects. It was concluded that the lip gloss containing 2% Glyceryl Rosinate did not possess a detectable contact-sensitizing potential and, hence, is not likely to cause contact sensitivity reactions under normal use conditions (Ivy Laboratories 1990).

Biosearch, Inc. (1992b) evaluated the skin irritation and sensitization potential of a lipstick containing 1% Glyceryl Rosinate, as supplied, using 78 volunteers (16 to 55 years old). Eleven of the original 89 subjects withdrew from the study for personal reasons. All subjects selected for the study were in good health and free of any visible skin disease or anomaly in the area of skin designated for patch testing. Approximately 0.15 g of the test substance was placed on an occlusive patch that was applied to the back of each subject for 24 h. Reactions were scored at 48 h post application according to the following scale: 0 (no visible erythema) to 3 (severe erythema [very intense redness]).

At the end of the grading period, a second patch was reapplied (same site) to each subject according to the same procedure. The test procedure was repeated on alternate days (Monday, Wednesday, and Friday) for a total of nine applications. Patches applied on Friday were removed on Saturday, and reactions were scored at 72 h post application. After a 2-week nontreatment period, a challenge patch containing the test substance was applied for 24 h to a new test site (adjacent to initial site) on each subject. Challenge reactions were scored at 48 and 72 h post application. Neither irritation nor sensitization reactions were observed in any of the subjects tested. The lipstick containing 1.0% Glyceryl Rosinate did not elicit a sensitization response (Biosearch, Inc. 1992b).

Glyceryl Hydrogenated Rosinate

The Consumer Product Testing Company (2000) patch tested sixty subjects (males and females, 17 to 75 years old) with a test material consisting of 20% Hydrogenated Purified Ester Gum-2-Octyldodecyl Myristate and 80% white petrolatum (a.k.a. Hydrogenated PEGMOD [20]). (Because Hydrogenated Purified Ester Gum-2-Octyldodecyl Myristate is a trade mixture consisting of 50% Hydrogenated Glyceryl Rosinate and 50% Octyldodecyl Myristate, the effective concentration of Hydrogenated Glyceryl Rosinate in the test material is 10%.) Fifty-one of the original 60 subjects completed the study, because 9 withdrew for reasons that were unrelated to testing.

A semiocclusive patch containing approximately 0.2 ml of the test material (contains 10% Hydrogenated Glyceryl Rosinate) was applied to the upper back, between the scapulae, of each subject on Mondays, Wednesdays, and Fridays for a total of nine, 24-h induction applications. Nontreatment periods of 24 h followed patch removals on Tuesdays and Thursdays. Saturday patch removals were followed by 48 h nontreatment periods. The induction phase was followed by a 2-week nontreatment period, after which a challenge patch was applied to a new test site, but not to the original site. Challenge reactions were scored at

24 and 72 h post application according to the following scale: 0 (no visible skin reaction) to 4 (severe erythema, possible edema, vesiculation, bullae and/or ulceration). The same scale was also used to evaluate induction reactions.

Neither skin irritation nor sensitization was observed in any of the subjects tested. It was concluded that the test substance did not not have the potential for inducing dermal irritation or allergic contact sensitization in this study (Consumer Product Testing Company 2000).

Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate

These are esters of glycerin and acids derived from rosin. In its reviews of rosin in color additive lakes, the FDA assessed the safety of various rosins (FDA 1988, 1994a, 1994b). The agency's findings are summarized below.

Although rosin has a history of use as a skin salve and as a soap, there were no toxicological data (e.g., from dermal irritation studies) that would support the safe use of rosin in contact with the skin or mucous membranes (e.g., in the lip area). Gum and wood rosins may be safely ingested; however, there are no data that support the safe use of rosin(s) as a substratum in color additive lakes intended for external uses (FDA 1988). In a more recent toxicology review, after considering that the "worst case" estimate for rosin content in lipsticks is 7.7% and that a more realistic estimate for lipstick rosin content is 0.6%, it was determined that, based on human patch test results, there appears to be little risk of irritant reactions due to rosin contained in lipsticks (FDA 1994a).

Furthermore, data submitted to FDA in 1994 indicated that lipsticks, blush, lipliner pencil, and nail polish containing rosinated lakes did not induce skin irritation in human subjects. Specifically, no skin irritation was observed when 197 subjects were patch tested (48-h single application) with blush products containing rosinated color additive lakes (9.3%) or when 10 subjects were tested with a lipstick product containing 1.07% rosinated color additive lakes in a phototoxicity test. Thus, FDA concluded that rosinated color additive lakes in cosmetic products at concentrations up to 9.3% do not present a health hazard due to irritation (FDA 1994b).

Skin irritation reactions to rosin/colophony have been reported; however, the intensity of these reactions is dependent upon the test concentration as well as the particular rosin that is being tested. In a human study on 60% colophony (Portuguese gum rosin), patch test results indicated that skin irritation could have been observed. However, in other studies, no evidence of skin irritation was found in more than 2300 subjects tested with 60% rosin or in 1132 patients patch tested with 20% rosin. Additionally, a number of commercially available, structurally modified rosin acids have been reported to induce dermal irritation. Most have an irritation threshold at concentrations greater than 10% (FDA 1994a).

FDA concluded that rosin/colophony can be classified as a moderate sensitizer. Sensitization to gum rosin exhibits a dose-response relationship (0.001% to 20%), indicating that sensitization can be minimized by reducing the concentration (details from the original study referenced in FDA's review of rosin are included in the next paragraph). It is important to note that positive allergic responses to rosin have been confirmed in both animal and human studies. Because of the allergenicity of rosin in human subjects, this compound is included in the standard 23-compound allergic contact dermatitis screen that is used by dermatologists (FDA 1994a).

FDA also considered results of a study by Karlberg (1988) using the method of Fregert (1981) in which patients with suspected rosin-allergy were patch tested with serial dilutions of Portuguese gum rosin in petrolatum according to the internationally accepted method for diagnosis of contact allergy by Fregert (1981). Finn chambers and Scanpor surgical tape were used. Patches were removed after 48 h of contact and reactions were scored at 72 h post application.

Twelve patients were tested with Portuguese gum rosin at concentrations ranging from 0.001% to 20%. Another group of 12 patients who had +++ reactions to 20% gum rosin in an earlier study was retested with two different preparations of Portuguese gum rosin (one in petrolatum) at concentrations ranging from 0.001% to 10%.

A clear dose-response relationship (with a maximum response at doses of 10% to 20%) was observed in the serial dilution test with 0.001% to 20% gum rosin (w/w) in petrolatum. The author stated that these results imply that a concentration of 10% gum rosin is worth considering for routine testing. The incidence of positive reactions to two different preparations of gum rosin in the second group of 12 patients is summarized as follows: 0.001% gum rosin (0 to 1 patient), 0.01% gum rosin (2 to 3 patients), 0.1% gum rosin (8 patients), 1% gum rosin (12 patients), and 10% gum rosin (10 to 12 patients). In the results for 10% gum rosin, all but 2 patients were tested with both preparations of gum rosin (Karlberg 1988).

Overall, FDA concluded that there is little or no potential for dermal irritation reactions due to rosin at the concentrations used in lipsticks containing rosin lakes. Therefore rosin, at the concentrations that can be present in lipstick containing color additive rosin lakes, does not present a health hazard due to irritation. OCAC reports that unmodified rosin is a moderate sensitizer and can induce allergic reactions in sensitized individuals. At the concentration of rosin that can be present as a component of color additive lakes (up to 7%), rosin can cause sensitization in unsensitized individuals. It is possible that rosin is bound during the color laking process and is not available to induce sensitization. However, no information was available regarding the skin absorption and subsequent skin sensitization potential of rosin contained in color additive lakes. FDA recommended further studies be undertaken to address this issue (FDA 1994a).

FDA amended its conclusion after human skin sensitization data on various cosmetic products containing rosinated lakes of D&C Red No. 6, D&C Red No. 7, and D&C Red No. 34 at several different concentrations were received. FDA concluded that

the use of rosin as a substratum in color additive lakes is safe, up to rosinated color additive concentrations of 9.0% in cosmetics products. This conclusion was based on the observation that no skin sensitization or photoallergic reactions to cosmetic formulations containing rosinated color additives at concentrations up to 9.0% were noted in human subjects. The human data included a photoallergy test using 312 subjects and a composite of repeat insult patch tests on a total of 2,381 subjects (FDA 1994b).

FDA also included in its consideration the components of rosin. Abietic acid and dehydroabietic acid, resin acids, are the main component of rosin. Abietic acid was not considered a contact allergen and the risk of resin acids inducing contact sensitivity in workers exposed to tall oil-containing products was considered minimal (FDA 1988).

The later review noted that oxidation products of abietic and dehydroabietic acid (which can be formed during storage) have been found to be allergenic. Hydrogenation of rosin acid reduced the allergenic potency of these oxidized gum rosin. There may be cross sensitization between several oxidized rosin acids. The oxidation of rosin acids might be necessary in order to induce immunologic properties (FDA 1994a).

The FDA review also considered that peroxides and hydroperoxides of rosin acids can contribute to the sensitization potential of rosin. Specifically, the test results for nine synthesized oxidation products of abietic acid and other rosin acids indicated that 7-oxodehydroabietic acid; 13,14-epoxy abietic acid; and 8,12-peroxidodihydroabietic acid, (strongest sensitizer of the three) are moderate sensitizers. Furthermore, the sensitization potential of a mixture of oxidation products from the polar fraction was found to be as strong as that of the peroxido compound. Methyl ester, keto, hydroxy, and hydroxylated unsaturated ketone derivatives were weak to poor sensitizers (FDA 1994a).

Phototoxicity

Biosearch, Inc. (1992c) evaluated the phototoxicity of a lipstick containing 1.0% Glyceryl Rosinate, as supplied, using 10 volunteers (17 to 55 years old). All subjects were in good health and free of any visible skin disease or anomaly in the area of skin designated for patch testing. Subjects on medication (especially medications suspected of causing photobiological reactions or medications with the potential for modifying the inflammatory response) were excluded. The subjects were classified as Fitzpatrick skin types I, II, and III. The degree of skin pigmentation did not significantly influence responses to UV light or interfere with the scoring of skin reactions. The test substance was applied (approximately 20 mg/site) to two sites on the back of each subject and spread to cover the areas uniformly. One of the test sites was irradiated with 0.5 MED (minimal erythemal dose, in seconds) of UVA and UVB light (continuous spectrum in UVA and UVB regions, 290 to 400 nm) between 30 and 60 min after application of the test substance. The MED was defined as the shortest exposure time at which erythema was first observed 20 ± 4 h after exposure. Irradiation with UVA and UVB light was followed by exposure to a total of 14 Joules/cm^2 of UVA. A 2 mm thick WG-345 Schott filter was interposed to eliminate UVB (290 to 320 nm) radiation from the ultraviolet source.

Reactions were scored at 24, 48, and 72 h post irradiation according to the following scale: 0 (no visible erythema) to 3 (severe erythema [very intense redness]). The second site to which the test substance had been applied was not irradiated and served as an irritation control. A third site served as the untreated, irradiated control. Skin irritation was not observed (score = 0) at control or irradiated sites in either of the ten subjects tested. The lipstick containing 1.0% Glyceryl Rosinate did not elicit a phototoxicity response (Biosearch, Inc. 1992c).

Photoallergenicity

Biosearch, Inc. (1992d) evaluated the photoallergenicity of a lipstick containing 1% Glyceryl Rosinate, as supplied, using 26 volunteers (17 to 55 years old). Four of the original 30 subjects withdrew for personal reasons. All subjects were in good health and free of any visible skin disease or anomaly in the area of skin designated for patch testing. Subjects on medication (especially medications suspected of causing photobiological reactions or medications with the potential for modifying the inflammatory response) were excluded. Skin types were variable and the degree of skin pigmentation did not significantly influence responses to UV light or interfere with the scoring of skin reactions. During the induction phase, each of the subjects received six applications of the test substance over a period of 3 weeks. For each application, approximately 0.15 g of the test substance was placed on an occlusive patch that was applied to the back for 24 h. Patches were applied on Tuesdays and Thursdays. After patch removal, each site was exposed to 2.0 MEDs of UVB radiation and 4 Joules/cm^2 of UVA radiation. The subjects were instructed to keep the back covered throughout the study to avoid exposure to natural or artificial sunlight. The challenge phase was initiated 18 days after the last induction exposure. Challenge patches containing the test substance were applied to two new, adjacent test sites for 24 h. After patch removal, reactions were scored according to the scale indicated in the preceding study.

One of the test sites was then exposed to a combination of 0.5 MED of UVB and 4 Joules/cm^2 of UVA light. The other site was not exposed to UVA light and served as the irritation control. The UV light control site was defined as an additional site that was not exposed to the test substance but was irradiated with 0.5 MED of UVB and 4 Joules/cm^2 of UVA light. Challenge sites were scored at 24, 48, and 72 h post-irradiation. No reaction (score = 0) was observed at control or test sites on any of the 26 volunteers tested. The lipstick containing 1.0% Glyceryl Rosinate did not elicit a photoallergy response (Biosearch, Inc. 1992d).

Case Reports

A strong positive reaction was observed when a 35-year-old female patient with itchy, facial erythema was tested with 0.01% glyceryl monoisostearate. Reportedly, the itchy, facial erythema

resulted from the use of a foundation containing 1.77% glyceryl diisostearate. It is important to note that Glyceryl Monoisostearate was one of the impurities detected in glyceryl diisostearate (Tanaka, Shimizu, and Miyakawa 1993).

Glyceryl Monoisostearate (0.01% in petrolatum) induced ++ reactions (at 48 and 72 h) in an 18-year-old girl with a history of what was described as lip cream dermatitis (Hayakawa et al. 1987).

SAFETY INFORMATION ON ARACHIDONIC ACID

Information from the CIR Final Report on the safety of Arachidonic Acid in cosmetics (Andersen 1993) is summarized below.

Arachidonic Acid is an essential, polyunsaturated, fatty acid that is used as a surfactant-cleansing agent and a surfactant—emulsifying agent in cosmetic formulations. Arachidonic Acid is a liquid at room temperature, is soluble in alcohol, ether, and water, and absorbs in the ultraviolet B (UVB) range. Arachidonic Acid is well absorbed from the gastrointestinal tract and the circulatory system, it distributes rapidly into the lipid compartment of the body, and is rapidly converted to phospholipid by the liver. Arachidonic Acid can be metabolized by three different pathways: the cyclooxygenase, lipoxygenase, and cytochrome P450 systems.

Arachidonic Acid metabolites are involved in the inflammatory process. A chronic cellular imbalance of Arachidonic, γ-linolenic, and eicosapentaenoic acids, and of their respective eicosanoid derivatives, may have major health implications. Arachidonic Acid may alter the cutaneous immune response.

In a study in which Arachidonic Acid was applied to the pinnae of mice, an increase in pinnal thickness was observed. Microscopic effects were also observed throughout the study. Application of Arachidonic Acid to mouse skin produced edema and inflammation, with high doses possibly causing ulceration of the skin.

Arachidonic Acid did not produce teratogenic effects. Exogenous Arachidonic Acid appeared to help prevent the teratogenic effects caused by hyperglycemia and phenytoin. Subcutaneous administration to pregnant diabetic rats significantly reduced neural tube defects, cleft palate, and micrognathia. Arachidonic Acid has also dose-dependently reversed antimasculinization caused by a number of compounds. However, indomethacin has been found to stop the reversal of teratogenic effects by Arachidonic Acid.

Arachidonic Acid has mutagenic potential. Arachidonic Acid has increased the frequency of TG^r colonies, phagocyte-induced SCEs, chromosomal aberrations, thioether synthesis, MAL number, and the incorporation of [^{3}H]thymidine/mg cellular DNA.

In 24 h single insult patch tests, a formulation containing 0.04% Arachidonic Acid was not an irritant.

The CIR Expert Panel recognized that dermal absorption data were lacking and that such data were necessary before a determination of safety can be made. And based on the results of those studies, still further data may be needed. Because Arachidonic Acid may be involved in UV light-induced cutaneous immune suppression, immunomodulatory data may be requested (dependent on the results of the dermal absorption studies). In addition to immunomodulatory data, carcinogenicity, photocarcinogenicity, and human irritation, sensitization, and photosensitization data may also be requested.

Accordingly, the CIR Expert Panel found that the safety of this ingredient has not been documented and substantiated for cosmetic product use. The additional data needed were described as follows:

1. Dermal absorption data

Based on the results of the absorption studies, the Panel indicated there may be a need for the following data:

2. Immunomodulatory data
3. Carcinogenicity and photocarcinogenicity data
4. Human irritation, sensitization, and photosensitization data (Andersen 1993)

SUMMARY

The safety of the following 43 Glyceryl Monoesters in cosmetics is reviewed in this report: Glyceryl Laurate, Glyceryl Laurate SE, Glyceryl Laurate/Oleate, Glyceryl Adipate, Glyceryl Alginate, Glyceryl Arachidate, Glyceryl Arachidonate, Glyceryl Behenate, Glyceryl Caprate, Glyceryl Caprylate, Glyceryl Caprylate/Caprate, Glyceryl Citrate/Lactate/Linoleate/Oleate, Glyceryl Cocoate, Glyceryl Collagenate, Glyceryl Erucate, Glyceryl Hydrogenated Rosinate, Glyceryl Hydrogenated Soyate, Glyceryl Hydroxystearate, Glyceryl Isopalmitate, Glyceryl Isostearate, Glyceryl Isostearate/Myristate, Glyceryl Isostearates, Glyceryl Lanolate, Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Montanate, Glyceryl Myristate, Glyceryl Isotridecanoate/Stearate/Adipate, Glyceryl Oleate SE, Glyceryl Oleate/Elaidate, Glyceryl Palmitate, Glyceryl Palmitate/Stearate, Glyceryl Palmitoleate, Glyceryl Pentadecanoate, Glyceryl Polyacrylate, Glyceryl Rosinate, Glyceryl Sesquioleate, Glyceryl/Sorbitol Oleate/Hydroxystearate, Glyceryl Stearate/Acetate, Glyceryl Stearate/Maleate, Glyceryl Tallowate, Glyceryl Thiopropionate, and Glyceryl Undecylenate.

According to one source, Glyceryl Monoesters are not pure monoesters, but are mostly mixtures with mono-, di-, and triesters in a ratio of approximately 4:4:2, respectively. Another source indicates that the guaranteed purity of commercial and conventional Monoglyceride (Glyceryl Monoester) is a minimum of 90%, meaning that impurities account for a maximum of 10% of the composition. The results of impurities analyses of 14 Glyceryl Monoesters indicated that only one, Glyceryl Palmitate/Stearate, contained (mono)glycerol diester at a concentration of 1.2%.

UV spectral analyses of 14 Glyceryl Monoesters indicated maximum absorbance at 238 or 239 nm.

Glyceryl Monoesters are used mostly as skin conditioning agents—emollients and/or surfactant—emulsifying agents in cosmetics. Frequency of use data provided by FDA in 1998 indicate that of the 43 ingredients in this safety assessment, the following 16 are used in cosmetics: Glyceryl Laurate, Glyceryl Alginate, Glyceryl Arachidonate, Glyceryl Caprylate, Glyceryl Caprylate/Caprate, Glyceryl Cocoate, Glyceryl Hydroxystearate, Glyceryl Isostearate, Glyceryl Lanolate, Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Palmitate, Glyceryl Myristate, Glyceryl Polyacrylate, Glyceryl Rosinate, and Glyceryl Undecylenate.

Concentration of use data received from the cosmetics industry in 1999 indicate that Glyceryl Monoesters are used at concentrations up to 12% in cosmetic products.

Glyceryl Monoesters have also been approved by FDA for use as direct or indirect food addtives. The Food Protection Committee of the National Academy of Sciences National Research Council Food and Nutrition Board concluded that there appears to be no reason to question the safety of mono-, di-, or triglycerides of lauric acid (i.e., Glyceryl Laurate, Glyceryl Dilaurate, or Glyceryl Trilaurate [Trilaurin]) as food additives.

Glyceryl Monoesters (monoglycerides) are metabolized to free fatty acids and glycerol, both of which are available for the resynthesis of triglycerides.

Glyceryl Laurate enhanced the penetration of drugs through cadaverous skin and hairless rat skin in vitro.

Lauricin (registered trademark for Glyceryl Laurate) has been described as having a wide spectrum of antimicrobial activity against diverse microbial species (viruses, fungi, molds, yeasts, and bacteria included).

A low-grade irritant response was observed following inhalation of an aerosol containing 10% Glyceryl Laurate by test animals.

An LD_{50} of >20,000 mg/kg was reported for rats dosed orally with Glyceryl Laurate. In other studies, neither Glyceryl Isostearate nor Glyceryl Citrate/Lactate/Linoleate/Oleate induced toxicity in rats that received a single oral dose of 2000 mg/kg. Similar results were reported in an acute dermal toxicity study in which 2000 mg/kg Glyceryl Citrate/Lactate/Linoleate/Oleate was administered to rats.

Undiluted, Purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) was not toxic (LD_{50} > 5 g/kg) when administered orally to fasted Wistar albino rats (five males, five females; weight range 220 to 292 g). None of the animals died.

A no-effect level of 280 mg/m^3 was reported for Glyceryl Laurate in a short-term inhalation toxicity study involving rats. Rats were subjected to 14 1-hour exposures during a 3-week period. Neither gross nor microscopic lesions were noted in rats fed 25% Glyceryl Laurate in another short-term (10 weeks) study.

No test substance–related gross or microscopic changes were observed in albino rats fed a mixture of mono-, di-, and triglycerides containing 40% to 45% Glyceryl Laurate for two years.

Glyceryl Laurate had strong hemolytic activity in an in vitro assay using sheep erythrocytes.

Glyceryl Laurate, Glyceryl Isostearate, or Glyceryl Citrate/Lactate/Linoleate/Oleate were not classified as ocular irritants in rabbits. Undiluted, purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) also was not irritating to the eyes of rabbits.

Undiluted Glyceryl Laurate induced minor erythema and edema when applied (occlusive patches, single application) to intact skin of rabbits. In another study, single occlusive patch applications of 20% Glyceryl Laurate emulsion to abraded and intact skin caused moderate skin irritation in rabbits.

Overall, Glyceryl Isostearate was classified as nonirritating to the skin of rabbits in a study in which single, semiocclusive patch applications were made to intact skin. The most severe reaction (moderate irritation) did not clear until day 5 post removal. Glyceryl Isostearate was also classified as nonirritating to the skin of rabbits in another study in which single occlusive patch applications were made to intact and abraded skin sites.

A PII of 3.40 (potential for severe irritation—warning label may be considered) was reported in an occlusive patch test evaluating the skin irritation potential of undiluted, Purified Ester Gum-2-Octyldodecyl Myristate (contains 50% Glyceryl Rosinate and 50% octyldodecyl myristate) in rabbits. Follicular hyperkeratosis (comedone formation) was not observed in another study in which the same undiluted test substance was applied to the ears of rabbits.

Neither erythema nor edema was observed in rabbits after semiocclusive patches containing heated Glyceryl Citrate/Lactate/Linoleate/Oleate (single application) were applied to intact skin. In another study, Glyceryl Citrate/Lactate/Linoleate/Oleate (single applicatioin) induced clearly circumscribed erythema and very mild edema when applied to intact skin of rabbits. All reactions had cleared by day 10 post application.

The skin sensitization potential of Glyceryl Laurate was evaluated in the maximization test. Guinea pigs were subjected to four sensitizing injections of 2% Glyceryl Laurate and then challenged with intradermal injections of 0.8% Glyceryl Laurate and topical applications of 25% Glyceryl Laurate. No positive reactions were observed. In another maximization test, skin sensitization was induced in 2 of 10 guinea pigs challenged with a 10% dilution of 20% Glyceryl Laurate emulsion. When a second challenge was initiated 7 days after the first, positive reactions were observed in five animals. Positive reactions were also observed in four animals challenged with a 5% dilution of 20% Glyceryl Laurate emulsion. Because positive reactions were also noted in the control group after the first and second challenge, the results were attributed to skin irritation (but not sensitization) effects of the test substance.

Glyceryl Isostearate was also evaluated in the maximization test. After induction, ten guinea pigs were challenged with 50% Glyceryl Isostearate in polyethylene glycol (PEG) and microcrystalline cellulose (MCC). Two additional challenges were also conducted. The first challenge yielded one and two positive

reactions (all slight reactions) at 24 and 48 h, respectively. These results were confirmed by reactions observed after the third challenge.

The sensitization potential of Glyceryl Citrate/Lactate/Linoleate/Oleate in 20 guinea pigs was evualated using the Buehler method. Following the dermal application of undiluted test substance during induction and challenge phases, no evidence of irritation or sensitization was observed.

The reaction of rosin with glycerol to form two esterification products (glyceryl triabietate [GTA] and glycerol esterified tall oil rosin [TORG]), in effect, reduced the allergenicity of rosin. GTA results from the esterification of glycerol with abietic acid, the major component of rosin. The incidence of positive challenge reactions in 15 guinea pigs tested was as follows: 1 (8.3% GTA), 2 (10% TORG), 3 (0.93% and 2.8% GTA), and 9 (20% gum rosin). Glyceryl diabietate and glyceryl monoabietate induced either the same incidence or a higher incidence of sensitization in other experiments (similar test groups) in the same study.

No evidence of significant cutaneous reactions, with or without UV irradiation, was found when the photoxicity and photoallergenicity potential of Glyceryl Isostearate was evaluated using 20 guinea pigs.

In a study (using mice) investigating the effect of Glyceryl Laurate on delayed-type hypersensitivity to sheep erythrocytes, the test substance did not cause significant enhancement of the immunological response. In another study using lymphocytes from murine spleens, Glyceryl Laurate–induced T-cell proliferation was blocked by cyclosporin A (immunosuppressive drug) at concentrations as low as 20 ng/ml. These results suggest that Glyceryl Laurate could be exerting its effect along the calcium-dependent inositol phospholipid, signal transduction pathway.

In Ames plate incorporation and preincubation mutagenicity tests, Glyceryl Citrate/Lactate/Linoleate/Oleate was not mutagenic (with or without metabolic activation) to the following *Salmonella typhimurium* strains: TA 98, TA 100, TA 1535, and TA 1537. In studies on the mutagenicity of resin acids, only neoabietic acid (component of rosin) was mutagenic in the Ames/*Salmonella* assay. Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate are esters of glycerin and acids derived from rosin, which is composed of diterpene resin acids.

Marked antitumor activity against two leukemia cell lines in vitro was observed in the presence of Glyceryl Laurate. A follow-up study to the preceding assay indicated that Glyceryl Laurate (i.p. injection, saline suspension) was ineffective in prolonging the lifespan of tumor-bearing BDF_1 mice that had been implanted i.p. with L-1210 leukemia cells. Doses of 30 and 100 mg/kg were injected daily for 5 consecutive days. In other experiments, the antitumor activity of Glyceryl Laurate against Ehrlich ascites tumor cells was demonstrated both in vivo and in vitro. In the two in vivo studies, Glyceryl Laurate (in saline) was injected i.p. into ddY mice that had been implanted i.p. with Ehrlich ascites tumor cells. Doses of 2.5 and 10.0 mg/mouse were injected daily for 5 successive days. Test results (both studies) indicated no tumor growth and increased survival time (compared to controls) at both doses.

The tumor promoting activity of Glyceryl Stearate on the clipped dorsal skin of Swiss mice was evaluated. One week after a single application of 9,10-dimethylbenz(*a*)anthracene (DMBA) (1% to 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.

Following the administration of hexane extracts of *Pinus ponderosa* needles to mice by stomach tube, increased embryonic resorptions were observed. Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate are esters of glycerin and acids derived from rosin, and rosin is obtained from trees of various species of *Pinus*.

Glyceryl Laurate, Glyceryl Linoleate, and Glyceryl Palmitate were each tested at a concentration of 50% w/v, in liquid paraffin, in a repeat insult patch test (RIPT) (Finn chambers) involving 91 healthy human subjects. Glyceryl Linoleate did not induce skin irritation or sensitization in the 74 subjects who completed the study. Glyceryl Laurate induced mild, erythematous reactions during induction in most of the subjects and questionable reactions in seven subjects during the challenge phase. Reactions ranged from mild to moderate erythema (score = 2) during induction and challenge phases.

The skin irritation and sensitization potential of Glyceryl Laurate, Glyceryl Myristate, and Glyceryl Oleate was evaluated in a second RIPT (Finn chambers) using 107 healthy subjects, 93 of whom completed the study. Glyceryl Laurate was tested at a concentration of 25% in liquid paraffin oil, whereas Glyceryl Myristate and Glyceryl Oleate were tested at a concentration of 50% in paraffin oil. Glyceryl Laurate induced moderate erythema (score = 2) in eight subjects during induction and in one subject during the challenge phase. Glyceryl Myristate and Glyceryl Oleate did not induce irritation or sensitizatiion. Neither of the three test substances was considered a sensitizer. In another study, Glyceryl Caprylate (15%) did not induce skin irritation or sensitization in an RIPT involving 63 healthy subects, 58 of whom completed the study.

Two case reports indicated skin reactions to two cosmetic products containing Glyceryl Isostearate, as well as positive patch test reactions to this ingredient.

Skin irritation was not observed in 12 healthy volunteers patch tested (occlusive patches) with a lipstick containing 1.0% Glyceryl Rosinate. Neither skin irritation nor sensitization was observed in 78 healthy volunteers patch tested (occlusive patches) with the same product in a repeated insult patch test.

The contact sensitization potential of three product formulations containing Glyceryl Rosinate was evaluated in three maximization assays (healthy human subjects), respectively. Results were negative for the following three study groups: foundation containing 4.0% Glyceryl Rosinate (25 subjects), blush containing 2.0% Glyceryl Rosinate (27 subjects), and lip gloss containing 2.0% Glyceryl Rosinate (27 subjects).

Skin irritation and sensitization were observed in one of 49 subjects patch tested (RIPT, semiocclusive patches) with a material consisting of 20% Purified Ester Gum-2-Octyldodecyl Myristate and 80% white petrolatum (a.k.a. PEGMODWP-20). (Because Purified Ester Gum-2-Octyldodecyl Myristate is a trade mixture consisting of 50% Glyceryl Rosinate and 50% Octyldodecyl Myristate, the effective concentration of Glyceryl Rosinate in the test material is 10%.) The challenge reaction was observed at the original test site, but not at the new site. It was concluded that the positive reaction observed was unique to that individual.

Neither skin irritation nor sensitization was observed in any of the 51 subjects patch tested (semiocclusive patches) with a material consisting of 20% Hydrogenated Purified Ester Gum-2-Octyldodecyl Myristate and 80% white petrolatum (a.k.a. Hydrogenated PEGMOD [20]). (Because Hydrogenated Purified Ester Gum-2-Octyldodecyl Myristate is a trade mixture consisting of 50% Hydrogenated Glyceryl Rosinate and 50% Octyldodecyl Myristate, the effective concentration of Hydrogenated Glyceryl Rosinate in the test material is 10%.) The subjects were challenged at a new test site, but not at the original site.

Phototoxicity was not induced in a group of 10 healthy volunteers tested with a lipstick containing 1.0% Glyceryl Rosinate. Patches were not applied to test sites. Similarly, photoallergenicity was not induced in a group of 26 healthy volunteers patch tested (occlusive patches) with the same product in a repeat insult patch test.

Data on 12 patients suspected of having gum rosin allergy indicated that sensitization to Portuguese gum rosin exhibited a dose-response relationship (0.001% to 20%). In the same study, the incidence of positive reactions to Portuguese gum rosin in a second group of 12 patients with gum rosin allergy was summarized as follows: 0.001% gum rosin (0 to 1 patient), 0.01% gum rosin (2 to 3 patients), 0.1% gum rosin (8 patients), 1% gum rosin (12 patients), and 10% gum rosin (10 to 12 patients). These data were based on patch tests with serial dilutions of Portuguese gum rosin in petrolatum.

The esterification of rosin with glycerol, in effect, reduced the allergenicity of rosin in dermatitis patients. Five of eight patients had positive reactions to 10% tall oil rosin in petrolatum, whereas four of eight patients had positive reactions to 20% glycerol-esterified tall oil rosin in petrolatum. Additionally, seven of eight patients had positive reactions to 5% Portuguese gum rosin in petrolatum and three of eight patients had positive reactions to 20% glycerol-esterified gum rosin in petrolatum.

Glyceryl-1-monoabietate was identified as a contact allergen in another study evaluating the allergenicity of rosin and its esterification products. Abietic acid (esterified to form glyceryl-1-monoabietate) is a main component of rosin, and, furthermore, clinical data indicate that it is easily oxidized to form contact allergens (e.g., 15-hydroperoxyabietic acid and its methyl ester). It is also important to note that oxidation products of abietic acid and dehydroabietic acid (also a main component of rosin) that can be formed during storage have been found to be allergenic.

FDA concluded that the use of rosin as a substratum in color additive lakes is safe up to rosinated color additive concentrations of 9.0% in cosmetic products. This conclusion was based on the observation that no skin sensitization or photoallergic reactions to cosmetic formulations containing rosinated color additives at concentrations up to 9.0% were noted in human subjects. The human data, submitted by CTFA, included a photoallergy test using 312 subjects and a composite of repeat-insult patch tests on a total of 2381 subjects.

Information from the earlier safety assessment of Arachidonic Acid is considered relevant, in that the concerns raised therein also apply to the safety assessment of Glyceryl Arachidonate. The CIR Expert Panel had concluded that the safety of Arachidonic Acid had not been documented and substantiated for cosmetic product use. Additional safety data that are needed include

1. Dermal absorption data

Based on the results of the absorption studies, the Panel indicated that there may be a need for the following data:

2. Immunomodulatory data
3. Carcinogenicity and photocarcinogenicity data
4. Human irritation, sensitization, and photosensitization data.

DISCUSSION

A primary concern regarding the safety of Glyceryl Monoesters is the possible presence of Glyceryl Diesters, and, specifically, the 1,2 diesters, which are known to have adverse effects. After reviewing impurities data on 14 Glyceryl Monoesters (90% pure), the Panel concluded that the level of 1,2-diacylglycerols (1,2 (mono)glycerol diester) in Glyceryl Monoesters is not sufficient to warrant any concern about effects on signal transduction and resulting effects on cell growth and proliferation that are associated with 1,2-diacylglycerol–induced activation of protein kinase C (PKC). The results of the impurities analysis indicated that only one of the 14 Glyceryl Monoesters, Glyceryl Palmitate/Stearate, contained (mono)glycerol diester.

Of approximately 4% of the (mono)glycerol diester content of Glyceryl Palmitate/Stearate, 29% is actually the 1,2 (mono)glycerol diester. Thus, the concentration of 1,2 (mono)glycerol diester in Glyceryl Palmitate/Stearate is approximately 1.2%. In addition, the Panel noted the absence of tumor promotion activity in a study using Glyceryl Stearate. The Panel noted that if 1.2% represents the maximum concentration of this impurity in cosmetic grade Glyceryl Monoester, then the concentration of 1,2-diacylglycerol in cosmetics would be significantly less, considering that current use concentration data from the cosmetics industry indicate that product concentrations of Glyceryl Monoesters range from 0.1% to 12%.

Given that Glyceryl Laurate is known to enhance the skin penetration of other chemicals, but that data are not available on the

penetration enhancement activity of other Glyceryl Monoesters, the Panel agreed that the manufacturers should consider the skin penetration enhancement potential of all Glyceryl Monoesters when formulating cosmetic products to ensure safety.

The Expert Panel previously stated that the available inhalation toxicity data are insufficient for addressing the Panel's concern over the use of Glyceryl Monoesters in aerosolized products, which relates to the potential surfactant activity of these ingredients on the lungs. After further review of this issue, focusing primarily on the use of Glyceryl Caprylate/Caprate in hair sprays, the Panel determined that Glyceryl Caprylate/Caprate can be used safely in these products, because the ingredient particle size is not respirable. The Panel reasoned that the particle size of anhydrous hair sprays (60 to 80 μm) and pump hair sprays (>80 μm) was large compared to the median aerodynamic diameter of 4.25 $\pm$ 1.5 μm for a respirable particulate mass.

Though mammalian genotoxicity data on the Glyceryl Monoesters were not available, the Panel concluded that they are not likely genotoxic agents based on the chemical structures of these compounds and negative Ames test data. Limited carcinogenicity data were negative, and data on the Glyceryl Monoester, Glyceryl Stearate indicated that 5% Glyceryl Stearate in acetone was not a tumor promoter in Swiss mice. These data, combined with the observation that maximum use concentrations of Glyceryl Monoesters associated with most (but not all) of the product type categories for cosmetics are $\leq$5%, led the Panel to discount any carcinogenic risk.

The Panel expressed specific concerns relating to the safety of Glyceryl Rosinate, Glyceryl Hydrogenated Rosinate, Glyceryl Collagenate, and Glyceryl Arachidonate in cosmetics, based on the specific chemical with which glycerin is esterified.

Glyceryl Rosinate is defined as the monoester of glycerin and mixed long-chain acids derived from rosin, and Glyceryl Hydrogenated Rosinate is defined as the monoester of glycerin and hydrogenated mixed long-chain acids derived from rosin. The Panel recognizes the potential for contamination of cosmetic grade samples of Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate with rosin, a moderate sensitizer. The Panel also noted that abietic acid, the main component of rosin, is easily oxidized to form contact allergens such as 15-hydroperoxyabietic acid and its methyl ester; glyceryl-1-monoabietic acid. Moderating this concern are data indicating that the sensitization potential of rosin is reduced by esterification with glycerol.

The Panel determined that this concern could be adequately addressed by establishing a concentration limit for Glyceryl Rosinate in cosmetic products that is based on the highest test concentration in human skin sensitization studies that did not induce sensitization. Skin irritation and sensitization were observed in 1 of 49 subjects patch tested (semiocclusive patches) with a trade mixture containing 10% Glyceryl Rosinate. In the other human study, neither skin irritation nor sensitization was observed in any of the 51 subjects patch tested (semiocclusive patches) with a trade mixture containing 10% Glyceryl Hydrogenated Rosinate. After reviewing these negative data and considering that the highest reported use concentrations of Glyceryl Rosinate at 10% in an eyebrow pencil and up to 12% in a mascara (products applied to the eyebrows or eyelashes), the Panel agreed that Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate could be considered safe as used in cosmetic products. The Panel reasoned that any sensitization potential associated with Glyceryl Rosinate or Glyceryl Hydrogenated Rosinate at a concentration of 10% or 12% in a semiocclusive patch test would be significantly reduced in cosmetic products in which the mode of application results in minimal contact with the skin and does not involve any form of occlusion.

After reviewing the positive skin irritation study (rabbits, occlusive patches) on an undiluted trade mixture containing 50% Glyceryl Rosinate and 50% octyldodecyl myristate, the Panel agreed that the irritation potential of this material would be significantly reduced under the conditions of cosmetic use (i.e., dilution to current use concentrations of Glyceryl Rosinate and absence of occlusion).

The Panel noted that the photosensitization potential of Glyceryl Monoesters in cosmetics is not an issue, based on the negative UV absorption data on 14 ingredients and human photoallergenicity data on a cosmetic product containing 1% Glyceryl Rosinate that were provided.

Because protein found in cartilage and other connective tissues in animals is the source of collagen, the Expert Panel stipulates that Glyceryl Collagenate should be free of infectious agents.

The CIR Expert Panel has issued a Final Report with an insufficient data conclusion on Arachidonic Acid. Because it is likely that Glyceryl Arachidonate will be hydrolyzed to Arachidonic Acid, the Panel noted that the data needed for completion of the safety assessment on Arachidonic Acid are also applicable to Glyceryl Arachidonate. Dermal absorption data are needed. Based on the results of the absorption studies, the Panel indicated that there may be a need for the following data: immunomodulatory data; carcinogenicity and photocarcinogenicity data; and human irritation, sensitization, and photosensitization data.

CONCLUSIONS

Based on the available animal and clinical data included in this report, the CIR Expert Panel concludes that the following Glyceryl Monoesters are safe as cosmetic ingredients in the present practices of use and concentration: Glyceryl Laurate, Glyceryl Laurate SE, Glyceryl Laurate/Oleate, Glyceryl Adipate, Glyceryl Alginate, Glyceryl Arachidate, Glyceryl Behenate, Glyceryl Caprate, Glyceryl Caprylate, Glyceryl Caprylate/Caprate, Glyceryl Citrate/Lactate/Linoleate/Oleate, Glyceryl Cocoate, Glyceryl Collagenate, Glyceryl Erucate, Glyceryl Hydrogenated Rosinate, Glyceryl Hydrogenated Soyate, Glyceryl Hydroxystearate, Glyceryl Isopalmitate, Glyceryl Isostearate, Glyceryl Isostearate/Myristate, Glyceryl Isostearates, Glyceryl Lanolate, Glyceryl Linoleate, Glyceryl Linolenate, Glyceryl Montanate, Glyceryl Myristate, Glyceryl

Isotridecanoate/Stearate/Adipate, Glyceryl Oleate SE, Glyceryl Oleate/Elaidate, Glyceryl Palmitate, Glyceryl Palmitate/Stearate, Glyceryl Palmitoleate, Gyceryl Pentadecanoate, Glyceryl Polyacrylate, Glyceryl Rosinate, Glyceryl Sesquioleate, Glyceryl/Sorbitol Oleate/Hydroxystearate, Glyceryl Stearate/Acetate, Glyceryl Stearate/Maleate, Glyceryl Tallowate, Glyceryl Thiopropionate, and Glyceryl Undecylenate.

The Panel also concludes that the available data are insufficient to support the safety of Glyceryl Arachidonate in cosmetic formulations.

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