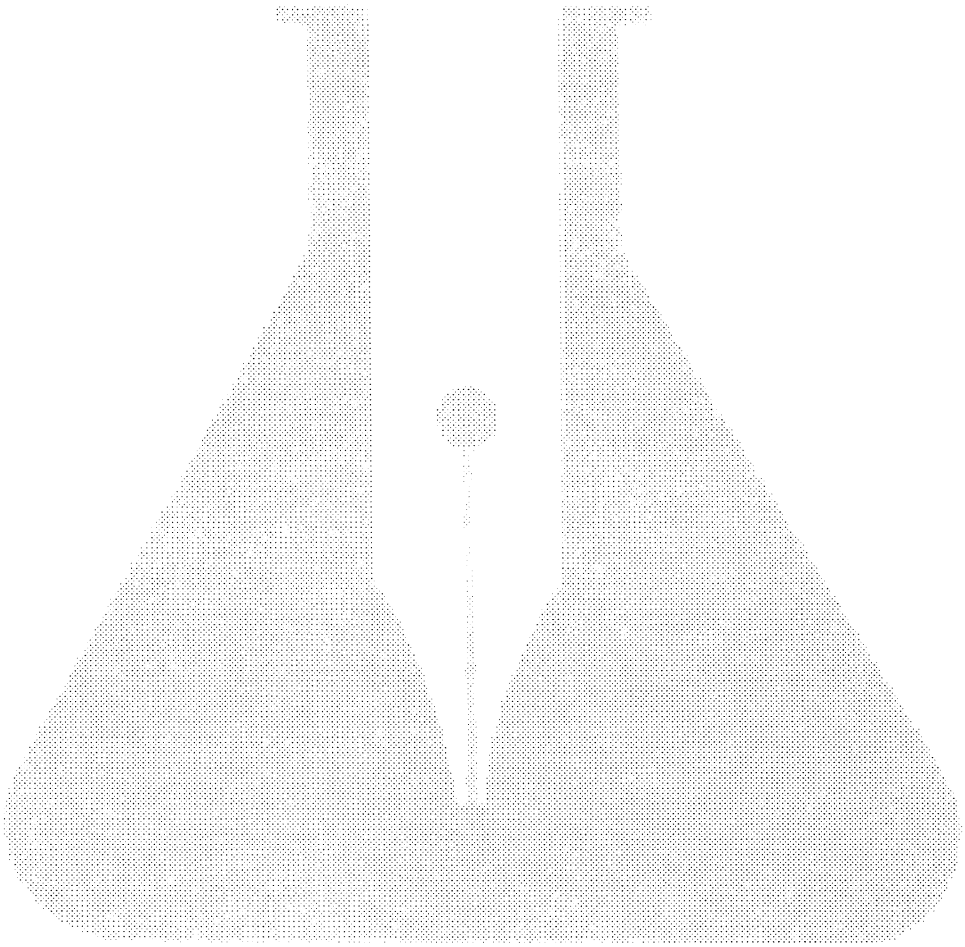
FINAL REPORT

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, 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

ABSTRACT

The safety of 43 glyceryl monoesters listed as cosmetic ingredients is reviewed in this report. Glyceryl monoesters are used mostly as skin conditioning agents - emollients and/or surfactant - emulsifying agents in cosmetics. Only 20 of these 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 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 RIPT studies, but the other glyceryl monoesters tested failed to produce any significant positive reactions. Glyceryl Rosinate did not produce sensitization in clinical tests at concentrations up to 4.0%. The safety of Arachidonic Acid was not documented and substantiated for cosmetic product use in an earlier safety assessment. Based on these data, the CIR Expert Panel found that these glyceryl monoesters are safe as currently used in cosmetic formulations, except that Glyceryl Rosinate and Hydrogenated Glyceryl Rosinate should not be used at concentrations above 4%, and that the available data are insufficient to support the safety of Glyceryl Arachidonate. Additional data needed to support the safety of this ingredient 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

The safety of glyceryl monoesters is reviewed in this report. Of the 43 ingredients reviewed in this safety assessment, toxicity data are available only on eight (Glyceryl Laurate, Glyceryl Caprate, Glyceryl Isostearate, Glyceryl Linoleate, Glyceryl Myristate, Glyceryl Oleate, Glyceryl Rosinate, and Glyceryl Citrate/Lactate/Linoleate-/Oleate). It is the expectation that the data on these eight ingredients may be extrapolated to other similar ingredients in the group.

Each of the glyceryl monoesters has glycerin as its basic building block. Glycerin is classified as a generally recognized as safe (GRAS) food ingredient based on a literature review published in 1973 (Informatics., Inc., 1973).

In an earlier safety assessment, the CIR Expert Panel concluded that the following glyceryl monoesters are safe in the present practices of use and concentration in cosmetics: Glyceryl Stearate and Glyceryl Stearate SE (Elder, 1982), and Glyceryl Oleate (Elder, 1986).

Also in an earlier safety assessment of Arachidonic Acid the CIR Expert Panel concluded that the available data are insufficient to support the safety of this ingredient in cosmetic formulations (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 mostly mixtures with mono-, di-, and tri-ester contents of approximately 4:4:2 (Unichema International, 1997b). According to more recent reference, the guaranteed purity of commercial and conventional Monoglyceride is a minimum of 90 % (Danisco Ingredients, 1999c,d).

Octanol/Water Partition Coefficient

The octanol/water partition coefficient (K_{ow}) is 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. In terms of $\log(K_{ow})$, the range is from -3 to 7. Experimental data on the octanol/water partition coefficient were not available, but calculations have been done as described below.

One method for calculating $\log(K_{ow})$ involves the use of fragment constants (Leo et al., 1971; Lyman et al., 1982). A measured value for a structurally related component is desirable, but not required. 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. Values received from one supplier (Danisco Ingredients, 1999a) are given in Table 1.

Table 1. Calculated Octanol/water Partition Coefficients of Glyceryl Monoesters (Danisco Ingredients, 1999a)

Ingredient	log (K o/w)
Glyceryl Laurate	4.22
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 Oleate	7.00
Glyceryl Elaidate	6.45
Glyceryl Palmitate	6.38
Glyceryl Stearate	7.69
Glyceryl Palmitoleate	5.37
Glyceryl Hydroxystearate	5.59

The physical properties of glyceryl monoesters are shown in Table 2.

Table 2. Physical Properties of Glyceryl Monoesters

Property	Description	Reference
Glyceryl Laurate		
Form	cream-colored paste	Lewis, 1993
	white crystalline	Huls 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	Huls America, Inc, no date
Calculated Octanol/water partition coefficient ($\log(K_{ow})$)	4.22	Danisco Ingredients, 1999a
Specific rotation	-	
Odor	faint	Lewis, 1993
	faint, fatty odor	Huls America, Inc, no date
Molecular weight	274.4	Kabara, 1984
Melting point	23-27°C	STN International, 1997b
	56-60°C	Huls America, Inc, no date; Henkel KgaA, 1996
Dropping point	56°C	
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)	Huls America, Inc, no date
Hydroxyl value	395	Danisco Ingredients, 1996
Iodine value	5-8	Lewis, 1993
	2% max. (based on I_2)	Huls America, Inc, no date; Henkel KgaA, 1996
	<1	Danisco Ingredients, 1996
Iodine color	3mg/100ml max. (based on I_2)	Huls America, Inc, no date
Saponification value	200-206	STN International, 1997b
Glyceryl Laurate		
	195-205mg KOH/g	Huls America, Inc, no date Henkel KgaA, 1996
	205	Danisco Ingredients, 1996
Acid value	3mg KOH/g max.	Huls America, Inc, no date
	3% max.	Henkel KgaA, 1996
UV absorption	λ_{max} at 238nm; λ_{min} at 295nm	Danisco Ingredients, 1999e

Table 2 (continued). Physical Properties of Glyceryl Monoesters

Property	Description	Reference
Glyceryl Behenate		
Calculated Octanol/water partition coefficient (log(K_{ow}))	9.62	Danisco Ingredients, 1999a
UV absorption	λ_{max} at 238nm; λ_{min} at 288nm and 290nm	Danisco Ingredients, 1999e
	Glyceryl Caprate	
Calculated Octanol/water partition coefficient (log(K_{ow}))	3.14	Danisco Ingredients, 1999a
UV absorption	λ_{max} at 238nm; λ_{min} at 287nm and 291nm	Danisco Ingredients, 1999e
Glyceryl Caprylate		
Form	white crystalline	Huls America, Inc, no date
Solubility	practically insoluble in water; hardly soluble to readily soluble in various water/ethanol mixtures; readily solubel in acetone, diethyl ether, and heptane	Huls America, Inc, no date
Calculated Octanol/water partition coefficient (log(K_{ow}))	2.06	Danisco Ingredients, 1999a
Iodine value	1g/100g max. (based on I_2)	Huls America, Inc, no date
Iodine color	3mg/100ml max. (based on I_2)	Huls America, Inc, no date
Saponification value	245-265 mg KOH/g	Huls America, Inc, no date
Acid value	3mg KOH/g max.	Huls America, Inc, no date
UV absorption	λ_{max} at 238nm; λ_{min} at 295nm	Danisco Ingredients, 1999e
Glyceryl Caprylate/Caprate		
UV absorption	λ_{max} at 238nm; λ_{min} at 295nm	Danisco Ingredients, 1999e
Glyceryl Citrate/Lactate/Linoleate/Oleate		
Form	viscous, yellowish liquid	Huls America, Inc, no date
Odor	odor likened to soya bean oil; neutral taste	Huls America, Inc, no date
pH	6-7 (10% in water)	Huls America, Inc, no date
Saponification value	230-250mg KOH/g	Huls America, Inc, no date
Acid value	15mg KOH/g max.	Huls America, Inc, no date
Glyceryl Cocoate		
Form	white to slightly yellowish liquid	Huls 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 heptane	Huls America, Inc, no date
Odor	odor likened to coconut oil	Huls America, Inc, no date
Melting point	31-37°C	Huls America, Inc, no date
Iodine value	3g/100g max. (based on I_2)	Huls America, Inc, no date
Iodine color	5mg/100ml max. (based on I_2)	Huls America, Inc, no date
Saponification value	200-300mg KOH/g	Huls America, Inc, no date
Acid value	2mg KOH/g max.	Huls America, Inc, no date
Glyceryl Elaidate		
Calculated Octanol/water partition coefficient (log(K_{ow}))	6.45	Danisco Ingredients, 1999a
Glyderyl Erucate		
Calculated Octanol/water partition coefficient (log(K_{ow}))	8.61	Danisco Ingredients, 1999a

Table 2 (continued). Physical Properties of Glyceryl Monoesters

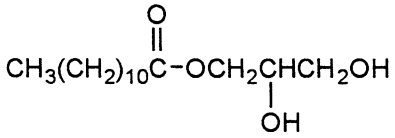
Property	Description	Reference
Glyceryl Hydrogenated Soyate		
UV absorption	λ_{max} at 238nm; λ_{min} at 287nm and 291nm	Danisco Ingredients, 1999e
Glyceryl Hydroxystearate		
Calculated Octanol/water partition coefficient (log(K_{ow}))	5.59	Danisco Ingredients, 1999a
Glyceryl Isostearate		
Form	crystals; 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.s	Gattefossé, 1998
Peroxide value	<6meq O_2/kg	Gattefossé, 1998
Hydroxyl value	180-280mg KOH/g	Gattefossé, 1998
Iodine value	<15g/100g (based on I_2)	Gattefossé, 1998
Saponification value	150-170mg	Gattefossé, 1998
Acid value	<4mg 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
Calculated Octanol/water partition coefficient (log(K_{ow}))	5.44	Danisco Ingredients, 1999a
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 238nm; λ_{min} at 270nm	Danisco Ingredients, 1999e
Glyceryl Myristate		
Calculated Octanol/water partition coefficient (log(K_{ow}))	5.3	Danisco Ingredients, 1999a
UV absorption	λ_{max} at 238nm; λ_{min} at 293nm	Danisco Ingredients, 1999e
	Glyceryl Oleate/Elaidate	
UV absorption	λ_{max} at 239nm; λ_{min} at 270nm	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 238nm; λ_{min} at 295nm	Danisco Ingredients, 1999e

Table 2 (continued). Physical Properties of Glyceryl Monoesters

Property	Description	Reference
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 239nm; λ_{min} at 287nm	Danisco Ingredients, 1999e
Glyceryl Palmitate/Stearate		
UV absorption	λ_{max} at 238nm; λ_{min} at 295nm	Danisco Ingredients, 1999e
Glyceryl Palmitoleate		
Calculated Octanol/water partition coefficient (log(K_{ow}))	5.37	Danisco Ingredients, 1999a
UV absorption	λ_{max} at 238nm; λ_{min} at 270nm and 280nm	Danisco Ingredients, 1999e
Glyceryl Sesquioleate		
UV absorption	λ_{max} at 239nm	Danisco Ingredients, 1999e
Glyceryl Stearate		
Calculated Octanol/water partition coefficient (log(K_{ow}))	7.69	Danisco Ingredients, 1999a
Glyceryl Stearate/Citrate		
Form	white ivory-colored powder	Huls 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	Huls America, Inc, no date
Odor	neutral, fatty odor	Huls America, Inc, no date
Melting point	59-63°C	Huls America, Inc, no date
pH	10-30 (10% in water 1:1)	Huls America, Inc, no date
Saponification value	230-260mg KOH/g	Huls America, Inc, no date
Acid value	15-25mg KOH/g max.	Huls America, Inc, no date

Glyceryl Laurate

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 (Wenninger et al., 2000):



According to a chemical supplier, two isomeric forms (α and β) exist; the structure included earlier in the report text is the alpha 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 (Wenninger et al., 2000); 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, 1997a).

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). More recent data from a chemical supplier confirms the 90% monoester content of Glyceryl Laurate and indicates that free glycerin is present at concentrations up to 2% (Henkel KgaA, 1996). Similar information on the compositon of Glyceryl Laurate from other chemical suppliers is included below.

Glyceryl Laurate contains free glycerol (1%), monoglycerides (95%), diglycerides (2%), and water (max 1%) (Hüls America, Inc., no date). According to another source, the composition of Glyceryl Laurate is as follows: monoester content (min. 90%), free glycerol (max. 1%), and free fatty acids (max. 1.5%) (Danisco Ingredients, 1996).

Glyceryl Laurate SE

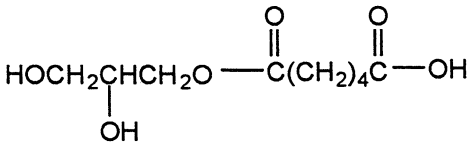
Glyceryl Laurate SE is a self-emulsifying grade of Glyceryl Laurate that contains some sodium and/or potassium laurate (Wenninger et al., 2000).

Glyceryl Laurate/Oleate

Glyceryl Laurate/Oleate is the monoester of glycerin and a blend of lauric and oleic acids (Wenninger et al., 2000).

Glyceryl Adipate

Glyceryl Adipate (CAS No. 26699-71-8) is the ester of glycerin and adipic acid that conforms to the following formula (Wenninger et al., 2000):



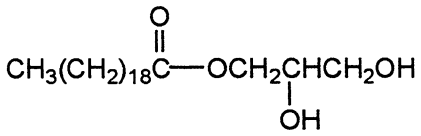
Hexanedioic Acid, Monoester with 1,2,3-Propanetriol is another name for this chemical (Wenninger et al., 2000).

Glyceryl Alginate

Glyceryl Alginate is the ester of glycerin and alginic acid. Alginic Acid, Glyceryl Ester is another name for this chemical (Wenninger et al., 2000).

Glyceryl Arachidate

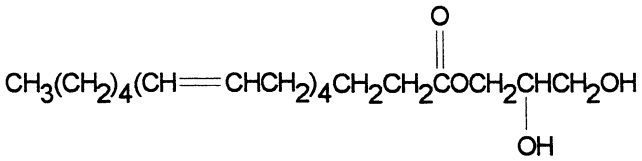
Glyceryl Arachidate (CAS Nos. 30208-87-8 and 50906-68-8) is the ester of glycerin and arachidic acid that conforms to the following formula (Wenninger et al., 2000):



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 (Wenninger et al., 2000).

Glyceryl Arachidonate

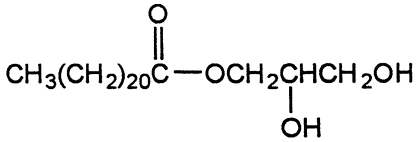
Glyceryl Arachidonate (CAS No. 35474-99-8) is the monoester of glycerin and arachidonic acid that conforms to the following formula (Wenninger et al., 2000):



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 (Wenninger et al., 2000).

Glyceryl Behenate

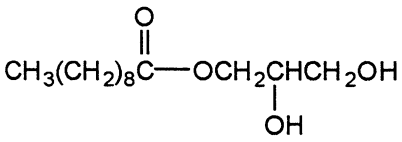
Glyceryl Behenate (CAS Nos. 6916-74-1 and 30233-64-8) is the monoester of glycerin and behenic acid that conforms to the following formula (Wenninger et al., 2000):



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 (Wenninger et al., 2000).

Glyceryl Caprate

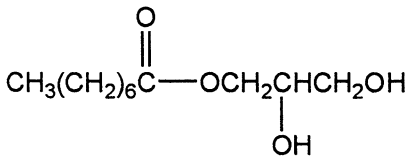
Glyceryl Caprate (CAS No. 26402-22-2) is the monoester of glycerin and capric acid that conforms to the following formula (Wenninger et al., 2000):



Other names for this chemical include Decanoic Acid, Monoester with 1,2,3-Propanetriol and Glyceryl Monocaprate (Wenninger et al., 2000).

Glyceryl Caprylate

Glyceryl Caprylate (CAS No. 26402-26-6) is the monoester of glycerin and caprylic acid that conforms to the following formula (Wenninger et al., 2000):



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 (Wenninger et al., 2000), 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 (max. = 1%) (Hüls America, Inc., no date).

Glyceryl Caprylate/Caprate

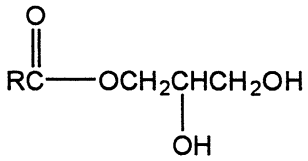
Glyceryl Caprylate/Caprate is a mixture of monoglycerides of caprylic and capric acids (Wenninger et al., 2000).

Glyceryl Citrate/Lactate/Linoleate/Oleate

Glyceryl Citrate/Lactate/Linoleate/Oleate is the ester of glycerin and a blend of citric, lactic, linoleic and oleic acids (Wenninger et al., 2000).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

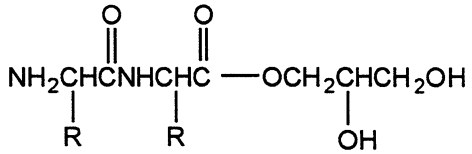
Glyceryl Cocoate (CAS No. 61789-05-7) is the monoester of glycerin and coconut fatty acids that conforms to the following formula, where RCO- represents the fatty acids derived from coconut oil (Wenninger et al., 2000):



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}-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 (Wenninger et al., 2000). The typical composition of Glyceryl Cocoate is described as follows: free glycerol (1%), monoglycerides (45%), diglycerides (35%), triglycerides (15%), and water (max. = 1%) (Hüls America, Inc., no date).

Glyceryl Collagenate

Glyceryl Collagenate is the ester of glycerin and collagen (q.v.) (Wenninger et al., 2000). It consists of ~25% solids (Brooks Industries, 1998). Its chemical structure is shown below:



where R is a side chain amino group typical of collagen.

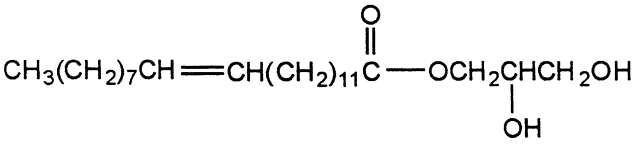
Properties of Glyceryl Collagenate are included in Table 3.

Table 3. Properties of Glyceryl Collagenate (Brooks Industries, Inc., 1998)

Property/Compositiion	Specification/Typical Vaues
Appearance/Odor	Clear to hazy amber liquid with proteinaceous odor
Solubility	At 5% is soluble in water, glycerine, 40% aqueous alcohol, sodium lauryl sulfate, and cocoamidopropyl betaine
Specific Gravity	1.2
Boiling Point	215°C
% Volatile by volume	80%

Glyceryl Erucate

Glyceryl Erucate (CAS No. 28063-42-5) is the monoester of glycerin and erucic acid that conforms generally to the following formula (Wenninger et al., 2000):



Other names for this chemical include Glyceryl Monoerucate and Erucic Acid, Monoester with 1,2,3-Propanetriol (Wenninger et al., 2000).

Glyceryl Hydrogenated Rosinate

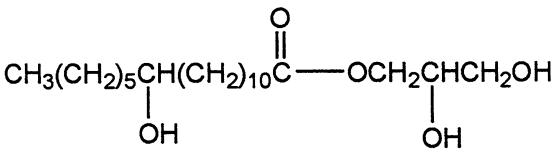
Glyceryl Hydrogenated Rosinate is the monoester of glycerin and hydrogenated mixed long chain acids derived from rosin (Wenninger et al., 2000).

Glyceryl Hydrogenated Soyate

Glyceryl Hydrogenated Soyate is the monoester of glycerin (q.v.) and hydrogenated mixed long chain acids derived from soy (Wenninger et al., 2000). According to a chemical supplier, it is a distilled monoglyceride made from edible, fully hydrogenated vegetable oil (Danisco Ingredients, 1999c).

Glyceryl Hydroxystearate

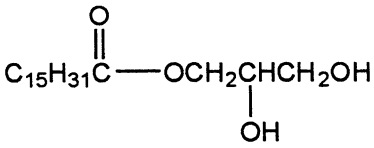
Glyceryl Hydroxystearate (1323-42-8) is the monoester of glycerin and hydroxystearic acid (q.v.) that conforms to the following formula (Wenninger et al., 2000):



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 (Wenninger et al., 2000).

Glyceryl Isopalmitate

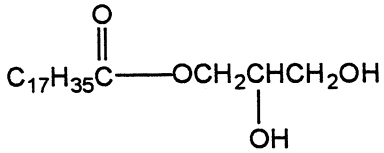
Glyceryl Isopalmitate is the monoester of glycerin and a branched chain 16- carbon aliphatic acid that conforms to the following formula (Wenninger et al., 2000):



Other names for this chemical include Isopalmitic Acid, 2,3-Dihydroxypropyl Ester and Isopalmitic Acid, Monoester with 1,2,3-Propanetriol (Wenninger et al., 2000).

Glyceryl Isostearate

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 (Wenninger et al., 2000):



Other names for this chemical include Glyceryl Isostearate (1), Glyceryl Monoisostearate, and Isooctadecanoic Acid, Monoester with 1,2,3-Propanetriol (Wenninger et al., 2000).

According to a chemical supplier, the composition of Glyceryl Isostearate is as follows: 1-monoglycerides content (> 30%), free glycerol content (< 7%), and water (< 0.50% (Gattefossé, 1998).

Glyceryl Isostearate/Myristate

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 (Wenninger et al., 2000).

Glyceryl Isostearates

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) (Wenninger et al., 2000).

Glyceryl Isotridecanote/Stearate/Adipate

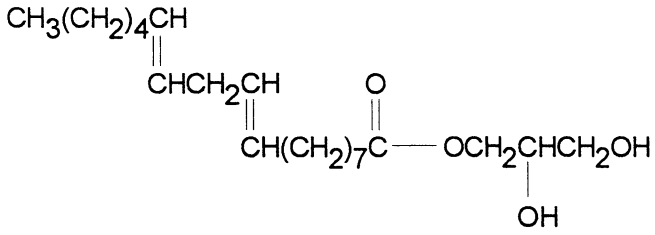
Glyceryl Isotridecanote/Stearate/Adipate is the ester of glycerin (q.v.) and a blend of isotridecanoic acid, stearic acid, and adipic acid (Wenninger et al., 2000).

Glyceryl Lanolate

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 (Wenninger et al., 2000).

Glyceryl Linoleate

Glyceryl Linoleate (CAS No. 2277-28-3) is the monoester of glycerin and linoleic acid that conforms to the following formula (Wenninger et al., 2000):

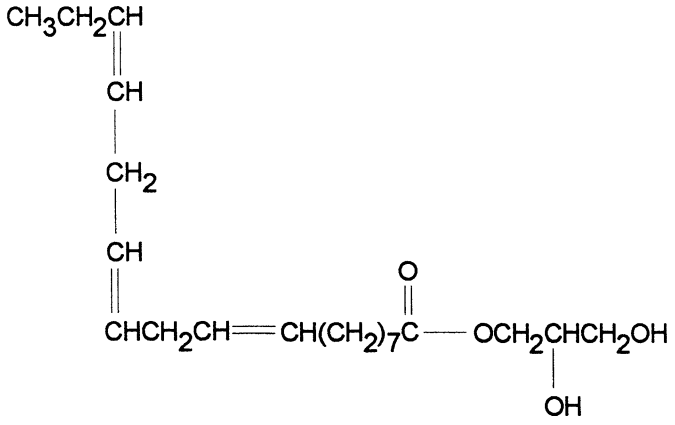


Other names for this chemical include: 2,3-Dihydroxypropyl 9,12-Octadecadienoate; Glyceryl Monolinoleate; Linoleic Acid, Monoester with 1,2,3-Propanetriol; Monolinolein; 9,12-Octadecadienoic Acid, 2,3-Dihydroxypropyl Ester; and 9,12-Octadecadienoic Acid, Monoester with 1,2,3-Propanetriol (Wenninger et al., 2000).

According to a chemical supplier, the composition of Glyceryl Linoleate is as follows: monoester content (min. 90%); free glycerol (max. 1%); free fatty acid (max. 1.5%); BHA, as antioxidant (max. 200 ppm); and citric acid, as antioxidant (max. 200 ppm) [Note: Citric acid is dissolved in propylene glycol] (Danisco Ingredients, 1996).

Glyceryl Linolenate

Glyceryl Linolenate (CAS No. 18465-99-1) is the monoester of glycerin and linolenic acid that conforms to the following formula (Wenninger et al., 2000):



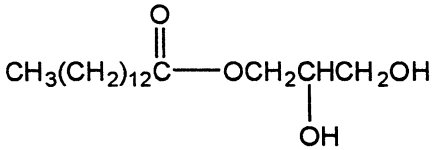
According to a chemical supplier, Glyceryl Linolenate is a distilled monoglyceride that is made from edible, refined sunflower oil (Danisco Ingredients, 1999c). Other names for Glyceryl Linolenate include: 2,3-Dihydroxypropyl 9,12,15-Octadecatrienoate; Glyceryl monolinolenate; Linolenic Acid, Monoester with 1,2,3-Propanetriol; and 9,12,15-Octadecatrienoic Acid, 2,3-Dihydroxypropyl Ester (Wenninger et al., 2000).

Glyceryl Montanate

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 (Wenninger et al., 2000).

Glyceryl Myristate

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 (Wenninger et al., 2000):



According to a chemical supplier, it is a distilled monoglyceride that is made from vegetable fatty acids (mainly myristic acid) (Danisco Ingredients, 1999c). Other names for this chemical include: Glyceryl Monomyristate; Monomyristin; and Tetradecanoic Acid, Monoester with 1,2,3-Propanetriol (Wenninger et al., 2000).

Glyceryl Oleate SE

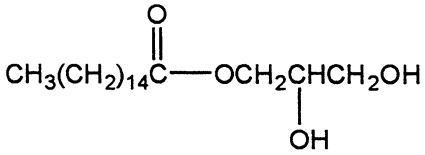
Glyceryl Oleate SE is a self-emulsifying grade of Glyceryl Oleate (q.v.) that contains some sodium and/or potassium oleate (Wenninger et al., 2000).

Glyceryl Oleate/Elaidate

Glyceryl Oleate/Elaidate is a mixture of monoglycerides of oleic and elaidic acids (Wenninger et al., 2000). According to a chemical supplier, It is a distilled monoglyceride made from edible, partially hydrogenated soya bean oil (Danisco Ingredients, 1999c).

Glyceryl Palmitate

Glyceryl Palmitate (CAS No. 26657-96-5) is the monoester of glycerin and palmitic acid that conforms to the following formula (Wenninger et al., 2000):

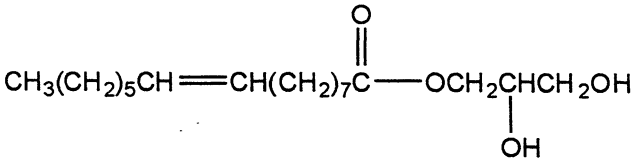


Other names for this chemical include: Glyceryl Monopalmitate; Hexadecanoic Acid, 2,3-Dihydroxypropyl Ester; and hexadecanoic Acid, Monoester with 1,2,3-Propanetriol (Wenninger et al., 1997).

Glyceryl Palmitate/Stearate

Glyceryl Palmitate/Stearate (CAS No. 68002-71-1) is the monoester of glycerin and a blend of palmitic and stearic acids (Wenninger et al., 2000). According to a chemical supplier, it is a distilled monoglyceride made from edible, fully hydrogenated lard or tallow (Danisco Ingredients, 1999c).

Glyceryl Palmitoleate

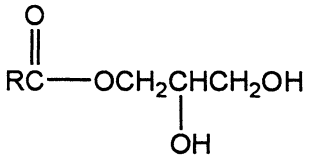


Glyceryl Palmitoleate is the monoester of glycerin and palmitoleic acid that conforms to the following formula (Wenninger et al., 2000):

According to a chemical supplier, it is a distilled monoglyceride that is made from edible, refined palm oil (Danisco Ingredients, 1999c). Other names for this chemical include: Glyceryl Monopalmitoleate; Palmitoleic Acid, 2,3-Dihydroxypropyl Ester; and Palmitoleic Acid, Monoester with 1,2,3-Propanetriol (Wenninger et al., 2000).

Glyceryl Pentadecanoate

Glyceryl Pentadecanoate is the monoester of glycerin and pentadecanoic acid that conforms to the following formula, where RCO- represents the pentadecanoyl radical (Wenninger et al., 2000):



2,3-Dihydroxypropanepentadecanoate is another name for this chemical (Wenninger et al., 2000).

Glyceryl Polyacrylate

Glyceryl Polyacrylate is the ester of glycerin (q.v.) and polyacrylic acid (q.v.) (Wenninger et al., 2000).

Glyceryl Rosinate

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 (Wenninger et al., 2000). Rosin is defined by The Dispensatory of the United States of America (1960 edition) 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*." 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 (FDA, 1988).

Glyceryl Sesquioleate

Glyceryl Sesquioleate is a mixture of mono- and di-esters of glycerin and oleic acid (Wenninger et al., 2000).

Glyceryl/Sorbitol Oleate/Hydroxystearate

Glyceryl/Sorbitol Oleate/Hydroxystearate is the mixed esterification product of glycerin and sorbitol with hydroxystearic and oleic acids (Wenninger et al., 2000).

Glyceryl Stearate/Acetate

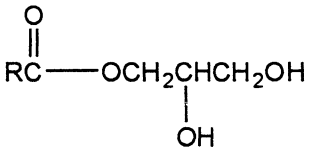
Glyceryl Stearate/Acetate is the monoester of glycerin and a blend of stearic and acetic acids. Glyceryl Monostearate Monoacetate is another name for this chemical (Wenninger et al., 2000).

Glyceryl Stearate/Maleate

Glyceryl Stearate/Maleate is the monoester of glycerin and a blend of stearic and maleic acids (Wenninger et al., 2000).

Glyceryl Tallowate

Glyceryl Tallowate is the monoester of glycerin and tallow fatty acids that conforms to the following formula (Wenninger et al., 2000):

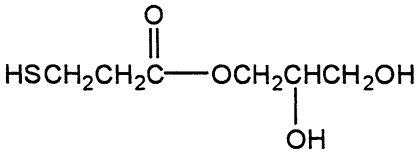


where RCO- represents the fatty acids derived from tallow.

Glyceryl Monotallowate is another name for this chemical (Wenninger et al., 2000).

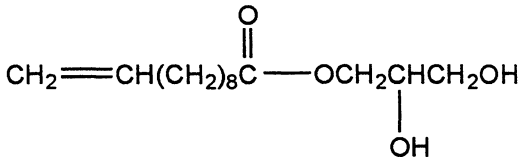
Glyceryl Thiopropionate

Glyceryl Thiopropionate is the organic compound that conforms to the following formula (Wenninger et al., 2000):



Glyceryl Undecylenate

Glyceryl Undecylenate is the ester of glycerin and undecylenic acid that conforms to the following formula (Wenninger et al., 2000):



Other names for this chemical are Glyceryl Monoundecylenate and Undecylenic Acid, Monoester with 1,2,3-Propanetriol (Wenninger et al., 2000).

Analytical Methods

Glyceryl Laurate

Glyceryl Laurate has been analyzed by thin-layer chromatography, gas-liquid chromatography (Kabara, 1984), reversed phase high performance liquid chromatography (Maruyama and Yonese, 1986; Takano and Kondoh, 1987), capillary supercritical fluid chromatography (Giron et al., 1992), and UV spectral analysis - results summarized in Table 2 (Danisco Ingredients, 1999e).

Methods of Production

Glyceryl Laurate

As noted earlier, Glyceryl Laurate has been described as a distilled monoglyceride. Reportedly, 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. 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 (Kabara, 1984).

Glyceryl Collagenate

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

Composition/Impurities

Data on the chemical characterization of Glyceryl

Table 4. Impurities Data on Glyceryl Monoesters (Danisco Ingredients, 1999c,d)

Ingredients	%GL*	%DIGL*	%FFA*	%DIGL-MONO*	1,2 DI Ratio*
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

*GL = glycerol; DIGL = diglycerol; FFA = free fatty acid; DIGL-MONO = diglycerol monoester; 1,2 DI ratio = ratio of 1,2-(mono)glycerol diester to total (mono)glycerol diester

Monoesters are summarized in this section. Impurities data included in Table 4 refer to the % composition of glycerol, diglycerol, free fatty acid, and diglycerol monoester in Glyceryl Monoesters that was provided by a chemical supplier, Danisco Ingredients (1999c).

The following statements, from Danisco Ingredients, can be used to interpret data included in Table 4: "In the manufacturing of Distilled Monoglyceride's a content of 3.5-4% total (mono)glycerol diester's are common, 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. Since 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 a approximate concentration of 1,2 (mono)glycerol diester of 1.2%." (Danisco Ingredients, 1999d)

Glyceryl Laurate

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

Glyceryl Caprylate

Glyceryl Caprylate also contains ash at a maximum concentration of 0.1% (Hüls America, Inc., no date).

Glyceryl Cocoate

Ash (max 0.1%) is one of the impurities that has been identified in Glyceryl Cocoate (Hüls America, Inc., no date).

Glyceryl Collagenate

Glyceryl Collagenate contains a low level of sodium chloride, byproduct of the production process (Brooks Industries, 1976). It also contains non-volatile matter (25 to 31%) and moisture (67 to 73%).

Glyceryl Hydrogenated Soyate

According to a chemical supplier, some of the specifications for Glyceryl Hydrogenated Soyate are as follows: monoester content (min. 90%), iodine value (max. 2), free glycerol (max. 1%),

free fatty acids (max. 1.5%), dropping point (≈72°C), and form (beads). Specifications for heavy metal impurities include: arsenic (As) [max. 3 mg/kg], lead (Pb) [max. 5 mg/kg], mercury (Hg) [max. 1 mg/kg], Cadmium (Cd) [max. 1 mg/kg], and heavy metals (as Pb) [max. 10 mg/kg] (Danisco Ingredients, 1999c).

Glyceryl Isostearate

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

Glyceryl Linoleate

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

Glyceryl Linolenate

According to a chemical supplier, specifications for Glyceryl Linolenate include: monoester content (min. 90%), iodine value (approx. 105), free glycerol (max. 1%), free fatty acids (max. 1.5%), temperature at which completely melted (≈ 45°C), and form (paste) (Danisco Ingredients, 1999c). Specifications for heavy metal impurities are as follows: arsenic (As) [max. 3 mg/kg], lead (Pb) [max. 5 mg/kg], mercury (Hg) [max. 1 mg/kg], cadmium (Cd) [max. 1 mg/kg], and heavy metals (as Pb) [max. 10 mg/kg] (Danisco Ingredients, 1999c). Glyceryl Linolenate also contains the antioxidants, BHA (max. 200 ppm) and citric acid dissolved in propylene glycol (max. 200 ppm) (Danisco Ingredients, 1999c).

Glyceryl Myristate

According to a chemical supplier, specifications for Glyceryl Myristate include: monoester content (min. 90%), free glycerol (max. 1%), and free fatty acids (max. 1.5%) (Danisco Ingredients, 1999c). The typical value for heavy metals (as Pb) in Glyceryl Myristate is < 10 mg/kg (Danisco Ingredients, 1999c).

Glyceryl Oleate/Elaidate

According to a chemical supplier of Glyceryl Monoesters (Danisco Ingredients), the specifications for heavy metal impurities in Glyceryl Oleate/Elaidate are as follows: arsenic (As) [max. 3 mg/kg], lead (Pb) [max. 5 mg/kg], mercury (Hg) [max. 1 mg/kg], cadmium (Cd) [max. 1 mg/kg], and heavy metals (as Pb) [max. 10 mg/kg]. It also contains the antioxidants, citric acid ester (max. 300 ppm), α-tocopherol (max. 200 ppm), and ascorbyl palmitate (max. 200 ppm) (Danisco Ingredients, 1999c).

Glyceryl Palmitate/Stearate

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

Glyceryl Palmitoleate

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

Stability/Reactivity

Glyceryl Laurate

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

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

Glyceryl Isostearate

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, 1999).

USE

Purpose in Cosmetics

Information on the functions of Glyceryl Monoesters in cosmetics is summarized in Table 5. These ingredients are used mostly as skin conditioning agents - emollients and/or surfactant - emulsifying agents (Wenninger et al., 2000).

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). While 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.

Table 5. Functions of Glyceryl Monoesters in Cosmetics (Wenninger et al., 2000)

INGREDIENT	FUNCTION(S)
Glyceryl Laurate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Laurate SE	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Laurate/Oleate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Adipate	skin conditioning agent - emollient surfactant - emulsifying agent
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 surfactant - emulsifying agent
Glyceryl Behenate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Caprate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Caprylate	skin conditioning agent - emollient surfactant - emulsifying agent

Table 5 (continued). Functions of Glyceryl Monoesters in Cosmetics (Wenninger et al., 2000)

INGREDIENT	FUNCTION(S)
Glyceryl Caprylate/Caprate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Citrate/Lactate/Linoleate/Oleate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Cocoate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Collagenate	hair conditioning agent skin-conditioning agent - emollient skin conditioning agent - miscellaneous
Glyceryl Erucate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Hydrogenated Rosinate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Hydrogenated Soyate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Hydroxystearate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Isopalmitate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Isostearate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Isostearate/Myristate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Isostearates	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Isotridecanoate/Stearate/Adipate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Lanolate	hair conditioning agent skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Linoleate	skin conditioning agent - emollient surfactant - emulsifying agent

Table 5 (continued). Functions of Glyceryl Monoesters in Cosmetics (Wenninger et al., 2000)

INGREDIENT	FUNCTION(S)
Glyceryl Linolenate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Montanate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Myristate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Oleate SE	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Oleate/Elaidate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Palmitate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Palmitate/Stearate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Palmitoleate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Pentadecanoate	skin conditioning agent - emollient surfactant - emulsifying agent
Glyceryl Polyacrylate	film former
Glyceryl Rosinate	film former
Glyceryl Sesquioleate	film former
Glyceryl/Sorbitol Oleate/Hydroxystearate	film former
Glyceryl Stearate/Acetate	film former
Glyceryl Stearate/Maleate	film former
Glyceryl Thiopropionate	hair waving/straightening agent; reducing agent
Glyceryl Undecylenate	skin conditioning agent - emollient surfactant - emulsifying agent

Table 6. Product Formulation Data on Glyceryl Monoesters (FDA, 1998)

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 makeup remover (84)	-	0.1%
Eye Shadow (506)	1	-
Eye Makeup Remover (84)	2	-
Permanent Waves (192)	9	-
Shampoos (noncoloring) (560)	-	0.3-2%
Tonics, dressings, and other hair grooming aids (549)	-	0.4%
Wave sets (55)	-	0.4%
Other hair preparations (noncoloring) (276)	-	0.4%
Bath Soaps and Detergents (385)	4	-
Deodorants (Underarm) (250)	3	-
Douches (5)	-	0.3%
Other Personal Cleanliness Products (291)	3	-
Skin cleansing (cold creams, cleansing lotions, liquids, and pads (653)	-	4%
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (796)	-	1%
Moisturizing Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (769)	5	-
Other skin care preparations	-	4%
1998 Total Uses for Glyceryl Laurate	***27***	
Glyceryl Alginate		
Moisturizing Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (769)	1	-
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (796)	-	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 (167)	-	2%
Suntan gels, creams, and liquids (136)	-	5%
1998 Totals for Glyceryl Behenate	-	
Glyceryl Caprylate		
Moisturizing Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (769)	1	-
1998 Totals for Glyceryl Caprylate	***1***	
Glyceryl Caprylate/Caprate		
Hair Sprays (Aerosol Fixatives) (261)	1	-
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (796)	-	2%
1998 Totals for Glyceryl Caprylate/Caprate	***1***	

Table 6 (continued). Product Formulation Data on Glyceryl Monoesters (FDA, 1998)

Product Category (Number of Formulations Reported to FDA) (FDA, 1998)	Number of Formulations Containing Ingredient (FDA, 1998)	Current Concentration of Use (CTFA, 1999)
Glyceryl Cocoate		
Cleansing Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (653)	1	1-5%
Bubble bath (200)	-	1%
Lipstick (790)	-	0.3% - 2%
Bath soaps and detergents (385)	-	4%
1998 Totals for Glyceryl Cocoate	***1***	
Glyceryl Erucate		
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (796)	-	0.5%
1998 Totals for Glyceryl Erucate	***-***	
Glyceryl Hydroxystearate		
Other eye makeup preparations (120)	-	2%
Lipstick (790)	1	-
Deodorants (250)	-	2%
Other Personal Cleanliness Products (291)	1	-
Shaving Cream (139)	1	-
Cleansing Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (653)	2	-
Face and Neck (Excluding Shaving) Skin Care Prep arations (Creams, Lotions, Powders, and Sprays) (263)	5	-
Body and Hand Skin Care (Excl. Shaving) Preparations (Creams, Lotions, Powders, and Sprays) (796)	2	2%
Foot Powders and Sprays (35)	1	-
Moisturizing Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (769)	5	0.8%
Night Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (188)	1	-
Paste Masks (Mud Packs) (255)	4	-
Other Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (692)	3	-
Suntan Gels, Creams, and Liquids (136)	1	-
1998 Totals for Glyceryl Hydroxystearate	***27***	
Glyceryl Isostearate		
Bath oils, tablets, and salts (124)	-	1%
Eye Shadow (506)	3	0.5 - 2%
Eye Lotion (18)	-	0.8%
Mascara (167)	1	-
Face Powders (250)	1	-
Foundations (287)	24	4 - 6%
Skin cleansing (cold creams, cleansing lotions, liquids, and pads (653)	-	3%
Face and Neck (Excluding Shaving) Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (263)	1	2%

Table 6 (continued). Product Formulation Data on Glyceryl Monoesters (FDA, 1998)

Product Category (Number of Formulations Reported to FDA) (FDA, 1998)	Number of Formulations Containing Ingredient (FDA, 1998)	Current Concentration of Use (CTFA, 1999)
Glyceryl Isostearate (continued)		
Moisturizing Skin Care Prep aarations (Creams, Lotions, Powders, and Sprays) (769)	2	3%
Night Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (188)	1	-
Paste masks (mud packs) (255)	-	0.3%
Other Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (692)	1	-
1998 Totals for Glyceryl Isostearate	***34***	
Glyceryl Lanolate		
Body and Hand Skin Care (Excl. Shaving) Preparations (Creams, Lotions, Powders, and Sprays)796	2	-
Moisturizing Skin Care Prep- arations (Creams, Lotions, Powders, and Sprays) (769)	1	-
1998 Totals for Glyceryl Lanolate	***3***	
Glyceryl Linoleate		
Eye Shadow (506)	1	-
Other Fragrance Preparations (148)	1	-
Face Powders (250)	1	-
Foundations (287)	2	0.7%
Lipstick (790)	-	0.7%
Other personal cleanliness products (291)	-	0.7%
Cleansing Skin Care Prepara tions (Creams, Lotions, Powders, and Sprays) (653)	2	1%
Face and Neck (Excluding Shaving) Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (263)	2	1%
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (796)	-	1%
Moisturizing Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (769)	2	-
Paste Masks (Mud Packs) (255)	1	-
Other Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (692)	1	-
1998 Totals for Glyceryl Linoleate	***13***	
Glyceryl Linolenate		
Eye Shadow (506)	1	-
Foundations (287)	-	0.7%
Lipstick (790)	-	0.7%
Other personal cleanliness products (291)	-	0.7%
Skin cleansing (cold creams, cleansing lotions, liquids, and pads) (653)	-	1%
Face and Neck (Excluding Shaving) Skin Care Preparations (Creams, Lotions Powders, and Sprays) (263)	2	1%
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (796)	-	1%
Moisturizing Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (769)	2	-
Other Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (692)	1	-
1998 Totals for Glyceryl Linolenate	***6***	

Table 6 (continued). Product Formulation Data on Glyceryl Monoesters (FDA, 1998)

Product Category (Number of Formulations Reported to FDA) (FDA, 1998)	Number of Formulations Containing Ingredient (FDA, 1998)	Current Concentration of Use (CTFA, 1999)
Glyceryl Myristate		
Other Fragrance Preparations 148	1	-
Makeup Bases (132)	1	-
Deodorants (Underarm) (250)	1	-
Glyceryl Myristate (continued)		
Face and Neck (Excluding Shaving) Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (263)	3	1 - 6%
Body and Hand Skin Care (Excl. Shaving) Preparations (Creams, Lotions, Powders, and Sprays) (796)	2	6%
Moisturizing Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (769)	4	-
Night Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (188)	1	-
Paste Masks (Mud Packs) (255)	1	-
Other Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (692)	1	6%
Suntan Gels, Creams, and Liquids (136)	1	-
Other Suntan Preparations (38)	1	-
1998 Totals for Glyceryl Myristate	***17***	
Glyceryl Oleate/Elaidate		
Foundations (287)	-	2%
Makeup bases (132)	-	0.3%
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (263)	-	2%
Moisturizing creams, lotions, powders, and sprays (769)	-	2%
1998 Totals for Glyceryl Oleate/Elaidate	***-***	
Glyceryl Palmitate		
Body and Hand Skin Care (Excl. Shaving) Preparations (Creams, Lotions, Powders, and Sprays) (796)	1	-
Moisturizing Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (769)	1	-
1998 Totals for Glyceryl Palmitate	***2***	
Glyceryl Polyacrylate		
Hair conditioners (636)	-	0.4%
Tonics, dressings, and other hair grooming aids (549)	-	0.2%
Face and Neck (Excluding Shaving) Skin Care Preparations (Creams, Lotions, Powders, and Sprays) (263)	1	2%
1998 Totals for Glyceryl Polyacrylate	***1***	
Glyceryl Rosinate		
Eyebrow pencil (91)	-	10%
Eye shadow (506)	-	2%
Mascara (167)	2	0.08 - 12%
Other hair coloring preparations (59)	-	3%
Blushers (all types) (238)	-	2%

Table 6 (continued). Product Formulation Data on Glyceryl Monoesters (FDA, 1998)

Product Category (Number of Formulations Reported to FDA) (FDA, 1998)	Number of Formulations Containing Ingredient (FDA, 1998)	Current Concentration of Use (CTFA, 1999)
Foundations (287)	1	0.06 - 4%
Lipstick (790)	-	0.4-6%
Depilatories (28)	1	-
1998 Totals for Glyceryl Rosinate	***4***	
Glyceryl Stearate/Acetate		
Tonics, dressings, and other hair grooming aids (549)	-	7%
Skin cleansing (cold creams, cleansing lotions, liquids, and pads) (653)	-	1%
Face and neck creams, lotions, powders, and sprays (excluding shaving preparations) (263)	-	2%
Body and hand creams, lotions, powders, and sprays (excluding shaving preparations) (796)	-	2%
Moisturizing creams, lotions, powders, and sprays (769)	-	3%
Suntan gels, creams, and liquids (136)	-	3%
Indoor tanning preparations (62)	-	2%
1998 Totals for Glyceryl Stearate/Acetate	*-*	
Glyceryl Undecylenate		
Moisturizing Skin Care Prep arations (Creams, Lotions, Powders, and Sprays) (769)	1	-
1998 Totals for Glyceryl Undecylenate	***1***	

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.

International Use

Fifteen of the 43 ingredients reviewed in this report are listed in the *Japanese Comprehensive Licensing Standards of Cosmetics by Category* (*CLS*) (Rempe and Santucci, 1997). The following three ingredients, which conform to the specifications of the Japanese Cosmetic Ingredients Codex, have precedent for use without restriction in all CLS categories: Glyceryl Erucate, Glyceryl Hydroxystearate, and Glyceryl Tallowate.

The following five ingredients have precedent for use without restrictions in all CLS categories except for the cosmetic categories designated as Eyeliner Preparations, Lip Preparations, Oral Preparations, and Bath Preparations: Glyceryl Behenate, Glyceryl Lanolate, Glyceryl Myristate, Glyceryl Stearate/Maleate, and Glyceryl Undecylenate.

Glyceryl Undecylenate has also been limited to concentrations up to 3% in the remaining seven CLS categories (Cleansing Preparations, Hair Care Preparations, Treatment Preparations, Make-Up Preparations, Fragrant Preparations, Suntan • Sunscreen Preparations, and Nail Makeup Preparations).

Glyceryl Stearate/Acetate has precedent for use without restrictions in all CLS categories except for the cosmetic categories designated as Eyeliner Preparations, Lip Preparations, and Oral Preparations.

Additionally, the following six ingredients have precedent for use without restrictions in all CLS categories except for Eyeliner Preparations: Glyceryl Cocoate, Glyceryl Isostearate, Glyceryl Isostearate Myristate, Glyceryl Linoleate, Glyceryl Laurate, and Glyceryl Sesquioleate.

None of the 43 ingredients reviewed in this safety

assessment are included among the substances listed as prohibited from use in cosmetic products marketed in the European Union (European Economic Community, 1995).

Noncosmetic Use

Glyceryl Laurate

Glyceryl Laurate has the following noncosmetic uses: emulsifying and dispersing agent for food products, oils, waxes, and solvents; antifoaming agent; and dry-cleaning soap base (Lewis, 1993). It has also been detected in pharmaceutical excipients (Giron et al., 1992).

Glyceryl Caprylate

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

Glyceryl Isostearate

Reportedly, 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).

Rosin

The following Information on rosin is included in this section because Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate are esters of glycerin and acids derived from 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 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 et al., 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

μg/cm^2/h (3 to 5 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 μg/cm^2/h) (Okumura et al., 1990).

Effect on Platelet Aggregation

Glyceryl Arachidonate

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

EffecTon 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).

The following sections on Signal Transduction and Cell Growth and Proliferation are included because 1,2-diacylglycerol has been dectected as an impurity in at least one of the Glyceryl Monoesters that is being reviewed.

Effect on Signal Transduction

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. 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) (Lee and Severson, 1994).

The results of a study on the role of diacylglycerols in the activation of PKC are summarized in the following two paragraphs. This study is followed by studies on cell growth and proliferation, effects that may be mediated by diacylglycerol (second messsenger)-induced PKC activation.

The lipid activation of PKC α was studied by comparing the activation capacity of different 1,2-diacylglycerols and 1,3-diacylglycerols incorporated into mixed micelles or vesicles. PKC isoenzymes are a large family of serine/threonine kinases that are involved in cellular signalling. [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 (Lévy et al., 1994).] 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. Study results are summarized below (Sánchez-Piñera et al., 1999).

Study results indicated that 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 higher 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. Given these results, it is important to note that sonicated phosphatidylserine vesicles were used in the earlier study, whereas, unsonicated preparations of multilamellar vesicles were used in the preceding study (Nomura et al., 1986).

Effect on Cell Growth and Proliferation

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 EGF/TGFα, PDGF, and 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 (Huckle and Earp, 1994).

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).

Lévy et al. (1994) report that various studies have indicated 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. PKC has been linked directly to the pathogenesis of several human cancers, including skin, colon, and breast cancer. 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 (Blobe et al., 1994). 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.

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).

More recent publications indicate that 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 et al., 1994). Further research has indicated 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 (Projan et al., 1994).

Other studies on the bactericidal activity of Glyceryl Laurate have been identified in the published literature (Chaibi et al., 1996a,b; Oh and Marshall, 1996; Petschow et al., 1996).

ANIMAL TOXICOLOGY

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 3-6% 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.

Relative to item 3 above, the Food Protection Committee noted that the most extensive study on the safety of glycerides of lauric acid appears to have been the study done by the Division of Pharmacology of the FDA (Fitzhugh et al., 1960). Short-term feeding studies (18-week duration, rats) of lauric acid and a long-term study (2-yr duration, rats) of a commercial mixture of lauric acid glycerides containing 40-45% Glyceryl Laurate, 45% Glyceryl Dilaurate, and 8% Glyceryl Trilaurate [Trilaurin] were conducted. Study results indicated that no lesions were attributable to lauric acid or lauric acid glycerides. Changes of questionable significance were observed in hepatic cells of rats fed lauric acid glycerides. No effects on weight gain or mortality were noted. [Additional details concerning the long-term study on the mixture are included in the section on Chronic Oral Toxicity later in the report text.]

Additional studies relating to the acute, short-term, subchronic, or chronic toxicity of Glyceryl Laurate and other Glyceryl Monoesters are included in the following text.

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 LD50 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 LD50 was > 20,000 mg/kg. (Henkel KgaA, 1994).

In another experiment, Glyceryl Laurate (dose = 2000 mg/kg) did not induce systemic toxicity in animals (number, species, and weights not stated) (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 Citrate/Lactate/Linoleate/Oleate

The acute oral 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 administered to each animal using a rigid gastric pharyngeal probe. Each rat received a single oral dose of 2,000 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. Macroscopically detectable organ changes were not noted at necropsy. The LD50 was > 2,000 mg/kg in male and female rats (Hüls AG, 1996a).

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 = 2,000 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 LD50 was > 2,000 mg/kg in male and female rats. Results on the skin irritation potential of Glyceryl Citrate/Lactate/Linoleate/Oleate are included in the section on Skin Irritation later in the report text (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 one-hour exposures during a three-week period. A no-effect-level of 280 mg/m^3 was reported. Details concerning the test protocol and study results were not included (Unichema International, 1997b).

Short-term Oral Toxicity

Glyceryl Laurate

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

Chronic Oral Toxicity

Glyceryl Laurate

Two groups of 24 albino rats of the Osborne-Mendel strain were fed a mixture consisting of Trilaurin (8%), Glyceryl Dilaurate (45%), and Glyceryl Laurate (40 to 45%) at a concentration of 25% in the diet for two years. Thus, 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 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 a small amount in 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 et al., 1960).

Hematotoxicity

Glyceryl Laurate

The hemolytic activity of Glyceryl Laurate was evaluated 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 seven-fold dilution of the starting concentration of Glyceryl Laurate. Glyceryl Laurate had strong hemolytic activity (Kato et al., 1971).

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 (avg. of 24, 48, and 72 h readings) for corneal reactions and erythema of the conjunctiva were 0.17 (max. score, corneal lesions = 80) and 1.33 (max. score, conjunctival lesions = 20), respectively. Reactions were not observed in the iris (Henkel KgaA, 1994).

The ocular irritation potential of a 20% Glyceryl Laurate emulsion was evaluated 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 (6 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

Glyceryl Isostearate was not classified as 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. Details concerning the test protocol were not provided (Unichema International, 1997a).

In another study, 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 (max. Score = 20). Glyceryl Isostearate was classified as a non-irritant (Institut Français de Recherches et Essais Biologiques [IFREB], 1977).

A mixture consisting of Glyceryl Isostearate and the following other components (concentrations not stated) was also evaluated in an ocular irritation test: glyceryl stearate, propylene glycol isostearate, propylene glycol stearate, ceteth-25, and oleth-25. 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 non-irritant based on the mean ocular irritation scores that were recorded (Centrede Recherche et d'Elevage des Oncins, 1975).

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

The skin irritation potential of a 20% Glyceryl Laurate emulsion was evaluated 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 [beet redness] to slight eschar formations [injuries in depth]) and 0 (no edema) to 4 (severe edema [raised more than 1 mm and extending beyond the area of exposure]). 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).

In another study, the skin irrritation potential of undiluted Glyceryl Laurate was evaluated 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 (Henkel KgaA, 1994).

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

Glyceryl Isostearate

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 aninmal. Patches were secured with hypoallergenic microporous adhesive tape and and then covered with elastic material that surrounded the animal's torso. After 4 h of contact, all patches were removed. A guaze 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 semi-occlusive bandage, reactions were scored according to the following scales: 0 (no erythema) to 4 (severe erythema [purplish red] with or without formation of scars [deep lesions] and presence of a lesion representing a significant reaction such as a burn or necrosis); 0 (no edema) to 4 (severe edema [thickness greater than 1 mm and area greater than area of application] representing a significant reaction such as a burn). 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 skin irritation potential of Glyceryl Isostearate was evaluated using six male New Zealand white rabbits (albino rabbits). A sterile absorbent gauzepad 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 non-irritant (PII = 0.21) (Institut Français de Recherches et Essais Biologiques [IFREB], 1977).

A mixture consisting of Glyceryl Isostearate and the following other components (concentrations not stated) was also evaluated in a skin irritation test: glyceryl stearate, propylene glycol isostearate, propylene glycol stearate, ceteth-25, and oleth-25. 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 non-allergenic, 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) (Centre de Recherche et d'Elevage des Oncins, 1975).

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 (5 males, 5 females). The test substance (dose = 2,000 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).

The skin irritation potential of undiluted Glyceryl Citrate/Lactate/Linoleate/Oleate was evaluated 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 (Hüls AG, 1996d).

Skin Sensitization

Glyceryl Laurate

The skin sensitization potential of Glyceryl Laurate was evaluated in the 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 at concentrations ranging from 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. The maximization study is summarized below (Anonymous, 1975).

Ten guinea pigs (6 males, 4 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 observeed in either of the ten animals tested. Glyceryl Laurate was classified as a non-sensitizer (Anonymous, 1975).

The skin sensitization potential of a 20% Glyceryl Laurate emulsion was evaluated in the guinea pig maximization test (Magnusson and Kligman, 1969). To induce sensitization, ten animals were treated by intradermal injection in the shoulder region. At seven 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 (Kabara, 1984).

In the preceding experiment, a second challenge was initiated seven 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 since positive reactions were observed in test and control groups (after 1st and 2nd challenge), it is likely that irritation, and not sensitization, was responsible for these observations (Kabara, 1984).

Glyceryl Isostearate

The skin sensitization potential of Glyceryl Isostearate was evaluated using the maximization test procedure by Magnusson and Kligman. 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 (Anonymous, 1985).

Glyceryl Citrate/Lactate/Linoleate/Oleate

The skin sensitization potential of Glyceryl Citrate/Lactate/Linoleate/Oleate was evaluated according to the Buehler method using 20 guinea pigs. Ten guinea pigs served as controls. The reference for the the Buehler test protocol used in this study was not included. 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, non-irritating concentration. Reportedly, Glyceryl Citrate/Lactate/Linoleate/Oleate did not induce systemic effects or any adverse effects on body weight gain. Details were not provided. At 30 h post application in induction phases I, II, and III, skin irritation was not observed in the 20 test animals or ten 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

A study was conducted to investigate whether the esterification of rosin with glycerol or other polyalcohols would, in effect, alter the allergenicity of rosin. Both guinea pigs and humans were tested in this investigation. The animal study is summarized as follows, and the clinical study is included in the section on Clinical Assessment of Safety (under Skin Sensitization subheading) later in the report text. 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 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 (Shao et al., 1993).

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 (2 reactions) was less than that of 20% gum rosin (9 reactions). The esterification of rosin with glycerol, in effect, reduced the allergenicity of rosin. GTA was non-allergenic and did not cross-react with allergens in unmodified gum rosin (Shao et al., 1993). The allergenicity of GTA and other esters of glycerol and abietic acid was evaluated in the study summarized below.

Products formed from the esterification of abietic acid (mentioned in the preceding study) with glycerol include: glycery triabetate (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, respectively. 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, $p < 0.05$), and 3.3% (6 of 14 , $p < 0.01$). 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 ($p < 0.01$) 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. Human patch test results from this study are included in the section on Clinical Assessment of Safety (under Skin Sensitization subheading) (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) - 2 groups, control (C), and normal (N), respectively. The mice in groups T and C were injected s.c. with 0.05 ml/mouse of SRBC (3×10^9 cells/ml). Injections were made into the right hind footpads. The mice in group T were then immediately injected 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 SRBC (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 at cyclosporin A (immunosuppressive drug) 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 et al., 1996).

GENOTOXICITY

Glyceryl Citrate/Lactate/Linoleate/Oleate

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/Linoleate/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. The positive controls were mutagenic (Huls America, Inc., 1996).

Resin Acids

The following information on the mutagenicity of resin acids is included in this section because 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

Saffioti and Shubik (1963) tested the tumor promoting activity of Glyceryl Stearate on the clipped dorsal skin of Swiss mice. One week after a single application of 9,10-dimethylbenz(a)anthracene (DMBA) (1-1.5% in mineral oil), 5% Glyceryl Stearate (in acetone) was applied to skin twice weekly. No tumors developed; slight epidermal hyperplasia at the site of application was noted.

Tumor Inhibition

Glyceryl Laurate

The *in vitro* antitumor activity of Glyceryl Laurate was evaluated using cell cultures of 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 IC50 was obtained by probit diagramming analysis. The IC50 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 (Kabara et al., 1985).

On the basis of the *in vitro* results in the preceding test, Glyceryl Laurate was evaluated in a survival test using five-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 (1st 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 lifespan 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, the *in vivo* antitumor activity of Glyceryl Laurate in five-week-old ddY mice (weights = 18 to 22 g) was evaluated using Ehrlich ascites tumor cells (Kato et al., 1969; Kato et al., 1971). 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 five 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 seven 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 the second study, approximately one-million tumor cells were implanted i.p. into twelve test mice (2 groups of 6) and six controls, and a solution or suspension of Glyceryl Laurate in 0.86% NaCl solution was administered i.p. daily for five 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 seven 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 (Kato et al., 1971). In an additional experiment (Kato et al., 1971), the *in vitro* action of Glyceryl Laurate on Ehrlich ascites tumor cells was evaluated. This experiment was conducted based on the assumption 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.

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.

Rosin

The following data on rosin are included in this section because Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate are esters of glycerin and acids derived from rosin: Following the administration of hexane extracts of *Pinus ponderosa* needles to mice by stomach tube, increased embryonic resorptions were observed. Recall that 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*. 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 (FDA, 1988).

CLINICAL ASSESSMENT OF SAFETY

Inhalation Toxicity

Jensen and O'Brien (1993) reviewed the effects of inhaled aerosols 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 ACGIH has defined three particle-size-selective threshold limit values (PSS TLVs): 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.

These three particulate mass fractions are quantitatively defined by ACGIH (1991) as follows:

1. Inhalable particulate mass (IPM) consists of those particulates that are captured according to the following collection efficiency regardless of sampler orientation with respect to wind direction:

$$SI(d_a) = 50\% \times (1 + \exp(-0.06 d_a)$$

$$\text{....for } 0 < d_a \leq 100\ \mu$$

where SI (d_a) is the collection efficiency in percent and d_a is the aerodynamic diameter in μ.

2. Thoracic particulate mass (TPM) consists of those particles that are captured according to the following collection efficiency:

$$ST(d_a) = SI(d_a) \times (1 - F(x)),$$

$$x = \frac{\ln(d_a/\Gamma)}{\ln(\Sigma)}$$

where $ST(d_a)$ is the collection efficiency in percent, the mass median aerodynamic dynamic diameter, Γ, is 11.64 μ, the geometric standard deviation, Σ, is 1.5, and F(x) is the cumulative probability function of a standard lognormal variable, x.

3. Respirable particulate mass (RPM) consists of those particles that are captured according to the following collection efficiency:

$$SR(d_a) = SI(d_a) \times (1 - F(x)),$$

$$x = \frac{\ln(d_a/\Gamma)}{\ln(\Sigma)}$$

where SR (d_a) is the collection efficiency in percent, the mass median aerodynamic diameter, Γ, is 4.25 μm, the geometric standard deviation, Σ, is 1.5, and F(x) is the cumulative probability function of a standardized lognormal variable, x.

The mean aerodynamic diameter of 4.25 ± 1.5 μ of respirable particles above may be compared with diameters of anhydrous hair sprays particles of 60 - 80 μ (typically, <1% are below 10 μ) and pump hair sprays with particle diameters of ≥80 μ (Bower, 1999).

Skin Irritation

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 three 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 Irritation and Sensitization

Glyceryl Laurate and Glyceryl Linoleate

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 ten "Finn-chambers" were fixed in pairs. The three glyceryl monoesters were tested at a concentration of 50% w/v in 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). Study results are summarized below.

Seventeen of the 91 subjects withdrew for reasons unrelated to treatment (16 subjects) and 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). The study immediately below was conducted by the same company to evaluate the sensitization potential of Glyceryl Laurate at a lower test concentration.

Glyceryl Laurate, Glyceryl Myristate and Glyceryl Oleate

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 repeated 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 one 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 ten 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 non-treatment period was initiated after reactions to the tenth 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

Eight dermatitis patients who had previously reacted to colophony (gum rosin) were patch tested (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 8 patients had positive reactions to 10% tall oil rosin (in petrolatum), whereas, 4 of 8 patients had positive reactions to 20% glycerol-esterified tall oil rosin (in petrolatum). Also, 7 of 8 patients had positive reactions to 5% Portuguese gum rosin (in petrolatum) and 3 of 8 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 6 of the 8 patients tested and that this incidence was lower than that reported for Portuguese gum rosin (7 of 8 patients). The results of this study indicated that esterification with glycerol reduced the allergenicity of rosin (Shao et al., 1993).

The allergenicity of the following compounds (in petrolatum) in patients with contact allergy to gum rosin was evaluated: 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 six 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 ten 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 sensitization potential of a foundation containing 4% Glyceryl Rosinate was evaluated using 28 healthy adult volunteers (13 males and 15 females; 18 to 46 years old). Twenty-five subjects completed the study; three subjects were removed for reasons that were unrelated to application of the test substance. The test procedure was referred to as a maximization assay. 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 semi-open 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. Patch removal was followed by re-application 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 pre-treatment was discontinued and replaced with a 24 h non-treatment period between applications of the test substance. Following a 10-day non-treatment period, the challenge phase was initiated. Pre-treatment 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 semi-open 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 vesiculo-bullous 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). Pre-treatment 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).

The skin irritation and sensitization potential of a lipstick containing 1% Glyceryl Rosinate, as supplied, was evaluated 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 two-week non-treatment 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).

Rosin/Rosin Acids

Information on the skin irritation/sensitization potential of rosin/rosin acids is included in this section because Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate are esters of glycerin and acids derived from rosin. The following statements represent a summary of the comments and conclusions included in toxicology reviews that were conducted as part of FDA's assessment of the safety of various rosins (as components of color additive lakes).

Although rosin has a history of use as a skin salve and as a soap, the Division of Toxicology could find no toxicological data, specifically dermal irritation studies, that would support the safe use of rosin when in contact with the skin, particularly mucous membranes (e.g. in the lip area). The gum and wood rosins that are listed 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 (from CTFA) 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 ten 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). The following information on the skin irritation potential of rosin at relatively high concentrations (up to 60%, no color additive lake) was also included in FDA's review.

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). Information on the skin sensitization potential of rosin from FDA's review is summarized below.

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).

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 of 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 (0-1 patient), 0.01% gum rosin (2-3 patients), 0.1% gum rosin (8 patients), 1% gum rosin (12 patients) and 10% gum rosin (10-12 patients). In the results for 10% gum rosin, all but two patients were tested with both preparations of gum rosin (Karlberg, 1988).

Based on the toxicology reviews on rosin mentioned above, a concluding statement on the skin irritation/sensitization potential of rosin by FDA's Office of Cosmetics and Colors (OCAC) is included below:

"OCAC review and evaluation of rosin at the concentrations used in lipsticks containing rosin lakes finds that there is little or no potential for dermal irritation reactions due to rosin. 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 is available regarding the skin absorption and subsequent skin sensitization potential of rosin contained in color additive lakes. Hence, OCAC recommends that skin sensitization data be required using unmodified rosin as the sensitizing (inducing) agent and subsequent challenge with rosin color additive lakes." (FDA, 1994a)

The preceding conclusion was amended as follows after human skin sensitization data (from CTFA) 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 from CTFA: "OCAC concludes 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, submitted by CTFA, included a photoallergy test using 312 subjects and a composite of repeat insult patch tests on a total of 2,381 subjects (FDA, 1994b). In light of

the preceding information, it is important to note that studies addressing the issue of which rosin components are associated with possible allergic reactions have been conducted. Reportedly, abietic acid* is not 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). [*Note: Abietic acid and dehydroabietic acid, resin acids, are main component of rosin.] However, oxidation products of abietic and dehydroabietic acid (which can be formed during storage) have been found to be allergenic. The most potent sensitizer (oxidation product) was identified as 15-hydroperoxyabietic acid, and it was also proposed that the methyl ester derivative was the active sensitizer. A reduction in the allergenic potency of these oxidized gum rosin acids was accomplished by hydrogenation of the respective rosin acid. It is important to note that human patch results have indicated cross sensitization between several oxidized rosin acids. Additionally, relative to oxidation products, it has been stated that the oxidation of rosin acids might be necessary in order to induce immunologic properties (FDA, 1994a).

It has also been proposed 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-oxo-dehydroabietic acid; 13, 14-epoxy abietic acid; and 8,12-peroxido-dihydroabietic 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

The phototoxicity of a lipstick containing 1.0% Glyceryl Rosinate, as supplied, was evaluated using ten 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 - 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 (290-320 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

The photoallergenicity of a lipstick containing 1% Glyceryl Rosinate, as supplied, was evaluated 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 three 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 MED's 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

Glyceryl Isotearate

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 et al., 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).

CIR SAFETY ASSESSMENT ON ARACHIDONIC ACID

The summary, discussion, and conclusion sections from the CIR Final Report on the safety of Arachidonic Acid (Andersen, 1993) in cosmetics are presented below:

Summary - 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. In 1992, it was reported to the FDA that Arachidonic Acid was used in 29 cosmetic formulations.

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 if TG' colonies, phagocyte-induced SCEs, chromosomal aberrations, thioether synthesis, MAL number, and the incorporation of [^{3}H]thymidine/mg cellular DNA.

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

Discussion

The CIR Expert Panel recognizes that dermal absorption data are lacking in this report and believes that such data are necessary before a determination of safety can be made. Based on the results of dermal absorption studies, there may be a need for additional data. The studies by Rheins and Nordlund (1986) and Rheins et al. (1987) indicate that Arachidonic Acid may be involved in UV light-induced cutaneous immune suppression. Therefore, 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.

Section 1, paragraph (p) of the CIR Procedures states that "A lack of information about an ingredient shall not be sufficient to justify a determination of safety." In accordance with Section 30(j)(2)(A) of the Procedures, the Expert Panel informed the public of its decision that the data on Arachidonic Acid are insufficient to determine whether the ingredient, under each relevant condition of use, is either safe or unsafe. The Panel released a "Notice of Insufficient Data Report" on February 12, 1992 outlining the data needed to assess the safety of Arachidonic Acid. The types of data required included:

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

No offer to supply the dermal absorption data was received. In accordance with Section 45 of the CIR Procedures, the Expert Panel will issue a Final Safety Evaluation Report - Insufficient Data. When the requested new data are available the Panel will reconsider the Final Report in accordance with Section 46 of the CIR Procedures, Amendment of a Final Report.

Conclusion

The safety of this ingredient has not been documented and substantiated for cosmetic product use. The CIR Expert Panel cannot conclude whether Arachidonic Acid is safe for use in cosmetic products until the appropriate safety data have been obtained and evaluated.

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, 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.

Glyceryl Monoesters are not pure monoesters, but are mostly mixtures with mono-, di-, and tri-esters 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.

In addition to the cosmetic uses of Glyceryl Monoesters, they have also been approved by FDA for use as direct or indirect food addtives. Furthermore, 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 LD50 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 2,000 mg/kg. Similar results were reported in an acute dermal toxicity study in which 2,000 mg/kg Glyceryl Citrate/Lactate/Linoleate/Oleate was administered to rats.

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 one-hour exposures during a 3 wk 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 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 a non-irritating to the skin of rabbits in a study in which single, semi-occlusive 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 non-irritating to the skin of rabbits in another study in which single occlusive patch applications were made to intact and abraded skin sites.

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 in rabbits 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 two of ten guinea pigs challenged with a 10% dilution of 20% Glyceryl Laurate emulsion. When a second challenge was initiated seven 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 photoallergeniciy 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 at cyclosporin A (immunosuppressive drug) 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 five 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 five 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) (1-1.5% 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 repeated 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, wheras 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.

The following information relates to the safety of Glyceryl Rosinate.

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).

Phototoxicity was not induced in a group of ten 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 repeated 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 (0-1 patient), 0.01% gum rosin (2-3 patients), 0.1% gum rosin (8 patients), 1% gum rosin (12 patients) and 10% gum rosin (10-12 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 8 patients had positive reactions to 10% tall oil rosin in petrolatum, whereas 4 of 8 patients had positive reactions to 20% glycerol-esterified tall oil rosin in petrolatum. Additionally, 7 of 8 patients had positive reactions to 5% Portuguese gum rosin in petrolatum and 3 of 8 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's Office of Cosmetics and Colors 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 the Cosmetics, Toiletry and Fragrance Association (CTFA), included a photoallergy test using 312 subjects and a composite of repeat insult patch tests on a total of 2,381 subjects.

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

The CIR Final Report on the safety of Arachidonic Acid concluded that the safety of Arachidonic Acid has not been documented and substantiated for cosmetic product use, and, therefore, the Panel cannot conclude whether Arachidonic Acid is safe for use in cosmetic products until the appropriate safety data have been obtained and evaluated. The types of data required 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

After reviewing impurities data on 14 Glyceryl Monoesters (90% pure) from a chemical supplier, 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%. 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%.

The calculated octanol-water partition coefficients for Glyceryl Caprylate had the $\log K_{ow}$ value of 2.06. This means that the anticipated rate of Glyceryl Caprylate percutaneous absorption would be considerably greater than, e.g., that of Glyceryl Behenate with a calculated value of 9.62, thereby increasing the likelihood of percutaneous absorption of the former. With this in mind, together with the fact that Glyceryl Laurate had a calculated $\log K_{ow}$ value of 4.22 and is known to enhance the skin penetration of other chemicals, the Panel agreed that the manufacturers should consider the skin penetration enhancement potential of 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 median aerodynamic diameter of 4.25 ± 1.5 μ for a respirable particulate mass was small compared to the particle sizes of anhydrous hair sprays (60 - 80 μ and pump hair sprays (>80 μ).

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.

Data on the tumor promotion activity of Glyceryl Monoesters also were not available. However, the Panel determined that any concern over the tumor promotion potential of Glyceryl Monoesters is not warranted, based on data (in CIR Final

Report on Glyceryl Stearate and Glyceryl Stearate SE) indicating that 5% Glyceryl Stearate in acetone was not a tumor promoter in Swiss mice, and the observation that maximum use concentrations of Glyceryl Monoesters associated with most (but not all) of the product type categories for cosmetics are ≤ 5%.

The Panel expressed specific concerns relating to the safety of Glyceryl Rosinate, Glyceryl Hydrogenated Rosinate, Glyceryl Collagenate, and Glyceryl Arachidonate in cosmetics. Each of these is discussed in turn.

Rosinate

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 there is 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.

In considering the issue of free rosin or rosin acids as impurities in cosmetics and their sensitization potential, 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. After reviewing human skin sensitization data on cosmetic products containing 1, 2, and 4% Glyceryl Rosinate that were received from the cosmetics industry, the Panel agreed that Glyceryl Rosinate does not pose a sensitization risk to the consumer at concentrations up to and including 4% in cosmetic products. The Panel also determined that this concentration limit is applicable to Glyceryl Hydrogenated Rosinate.

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.

Collagenate

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.

Arachidonate

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. The data needs are indicated below :

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

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 used in cosmetic products: 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 Collegenate, Glyceryl Erucate, 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 Sesquioleate, Glyceryl/Sorbitol Oleate/Hydroxystearate, Glyceryl Stearate/Acetate, Glyceryl Stearate/Maleate, Glyceryl Tallowate, Glyceryl Thiopropionate, and Glyceryl Undecylenate.

The Panel also concludes that Glyceryl Rosinate and Glyceryl Hydrogenated Rosinate are safe as used in cosmetic formulations at concentrations up to and including 4.0%, and that the available data are insufficient to support the safety of Glyceryl Arachidonate in cosmetic formulations.

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REFERENCES

American Conference of Governmental Industrial Hygienists (ACGIH). (1991) Threshold limit values for chemical substances and physical agents in the workroom environment with intended changes for 1990-1991. Cincinnati: American Conference of Governmental Industrial Hygienists.

Andersen FA. (1993) Final report on the safety assessment of arachidonic acid. *Journal of the American College of Toxicology*:481-559.

Anonymous. (1985) Skin sensitization study (test reference SSM85288). Glyceryl isostearate. Unpublished data submitted by CTFA, May 11, 1999.[1]

Anonymous. (1975) Guinea pig skin sensitization test no. 75.213. Laurinic monoglyceride. Unpublished data submitted by CTFA, May 11, 1999.[1]

Aungst BJ, Rogers NJ, Shefter E. (1986) Enhancement of naloxone penetration through human skin *in vitro* using fatty acids, fatty alcohols, surfactants, sulfoxides and amides. *Int J Pharm* 33:225-34.

Biogir S.A. Conseil Recherche. (1989) Assessment of cutaneous tolerance in the rabbit. Index of primary cutaneous irritatojn. Extol 2040 glycerol mono-isostearate No. 82350. (English translation). Report No. IC 88.1516. Unpublished data submitted by CTFA , May 11, 1999. (18 pages).[1]

Biosearch, Inc. (1992a) Irritation screening study. Pure Gloss 3402-35 (lipstick, as supplied) containing 1% glyceryl rosinate. Unpublished data submitted by CTFA (14 pages).[1]

Biosearch, Inc. (1992b) Modified Draize repeated insult patch test study in human subjects. Pure Gloss 3402-35 (lipstick, as supplied) containing 1% glyceryl rosinate. Unpublished data submitted by CTFA (11 pages).[1]

Biosearch, Inc. (1992c) Human phototoxicity test. Pure Gloss 3402-35 (lipstick, as supplied) containing 1% glyceryl rosinate. Unpublished data submitted by CTFA (8 pages).[1]

Blobe GC, Obeid LM, Hannun YA. (1994) Regulation of protein kinase C and role in cancer biology. *Cancer Metastasis Rev* 13:411-431.

Bower D. (1999) Unpublished information on hair spray particle sizes as provided at the September 9, 1999 meeting of the CIR Expert Panel.

Brooks Industries. (1998) Specification, material safety data sheet, and technical data on Glyceryl Collagenate. Unpublished data submitted by CTFA, May 21, 1999.[1]

Budavari S. (1989) *The Merck Index. An Encyclopedia of Chemicals, Drugs, and Biologicals.* Rahway:Merck & Co., Inc., 983-984, 1530-1531, 1534.

Centre de Recherche et d'Elevage des Oncins. (1975) Tests de tolerance chez le lapin: Indice d'irritation primaire. Irritation oculaire. Unpublished data submitted by CTFA, March 10, 1999 (10 pages).[1]

Chaibi A, Ababouch LH, Busta FF. (1996a) Inhibition of bacterial spores and vegetative cells by glycerides. *Journal of Food Protection* 59:716-22.

Chaibi A, Ababouch LH, Busta, FF. (1996b) Inhibition by monoglycerides of L-alanine-triggered *Bacillus cereus*. *Journal of Food Protection* 59:832-37.

Cosmetic, Toiletry, and Fragrance Association CTFA. (1999). Ingredient use survey - use concentration data. Unpublished data submitted by CTFA, July 26, 1999 (4 pages).[1]

Danisco Ingredients. (1996) A modified Draize repeat insult patch test in healthy volunteers to investigate the irritation and sensitization potential of nine cosmetic ingredients of edible quality and a control (liquid paraffin) following repeated cutaneous patch applications (Report No. DANF001). Unpublished data submitted by Danisco Ingredients. February, 1999 (70 pages).[1]

Danisco Ingredients. (1999a) Calculation of the octanol/water partition coefficients. Unpublished data submitted by CTFA, July 15, 1999 (3 pages).[1]

Danisco Ingredients. (1999b) Inhalation toxicity data. Unpublished data submitted by CTFA, July 15, 1999 (1 page).[1]

[1]Available for review from the Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC, 20036, U.S.A.

Danisco Ingredients. (1999c) Impurity analysis for glycerol monoesters. Unpublished data submitted by CTFA, August 25, 1999 (20 pages).[1]

Danisco Ingredients. (1999d) "Impurity analysis" for glycerol monoesters. Unpublished data submitted by CTFA, September 9, 1999 (2 pages).[1]

Danisco Ingredients. (1999e) UV-spectra for glycerol monoesters. Unpublished data submitted by CTFA, August 30, 1999 (18 pages).[1]

Danisco Ingredients. (1999f) A modified Draize repeat insult patch test in healthy volunteers to investigate the irritation and sensitization potential of nine cosmetic ingredients of edible quality and a control (liquid paraffin) following repeated cutaneous patch applications. Unpublished data submitted by CTFA, July 22, 1999 (108 pages).[1]

Eagle E, Poling CE. (1955) The oral toxicity and pathology of polyoxyethylene derivatives in rats and hamsters. *Food Research* 21:348-61.

Elder RL, ed. (1982) Final report on the safety assessment of glyceryl stearate and glyceryl stearate/SE. *J Am Coll Toxicol* 1:169-92.

Elder RL, ed. (1986) Final report on the safety assessment of glyceryl oleate. *J Am Coll Toxicol* 5:391-413.

European Economic Community (EEC). (1995) EEC Cosmetics Directive 76/768/EEC, as amended, Annexes I through VII. Brussels:EEC.

Fitzhugh OG, Schouboe PJ, Nelson AA. (1960) Oral toxicities of lauric acid and certain lauric acid derivatives. *Toxicol Appl Pharmacol* 2:59-67.

Food and Drug Administration (FDA). (1988) Memorandum dated June 27, 1998. Color additive petition no. 7T0130. Safety evaluation of substrata and precipitants used in the manufacture of color additive lakes. Washington:FDA.

FDA. (1992) Modification in voluntary filing of cosmetic product ingredient and cosmetic raw material composition statements. *Federal Register* 57:3128-30.

FDA. (1994a) Memorandum dated July 13, 1994. Safety evaluation of rosin in color additive lakes. Washington:FDA.

FDA. (1994b) Memorandum dated August 22, 1994. Safety evaluation of dermal sensitization and photosensitization of rosinated lakes of D&C Red No. 6, D & C Red No. 7, and D&C Red No. 34.. Washington:FDA.

FDA. (1998). Frequency of use of cosmetic ingredients. *FDA database*. Washington:FDA.

Fregert S. (1981) Manual of contact dermatitis. 2nd ed. Copenhagen:Munksgaard, 71-81.

äfvert E, Shao LP, Karlberg A-T, Nilsson U, Nilsson JLG. (1994) Allergenicity of rosin (colophony) esters. II. Glyceryl monoabietate identified as contact allergen. *Contact Dermatitis* 28:229-234.

Gattefossé s.a. (1998) Data sheet. Peceol isostearique (Glyceryl Isostearate). Unpublished data submitted by CTFA, March 10, 1999 (2 pages).[1]

Gattefossé s.a. (1999) Material safety data sheet according to 91/155 EC. Unpublished data submitted by CTFA, March 10, 1999 (4 pages).[1]

Gerrard JM, Graff G. (1980) 1-arachidonyl-monoglyceride causes platelet aggregation: indirect evidence for an acylglycerol acylhydrolase involvement in the release of arachidonic acid for prostaglandin synthesis. *Prostaglandins Med* 4:419-430.

Giron D, Link R, Bouissel S. (1992) Analysis of mono-, di- and triglycerides in pharmaceutical excipients by capillary supercritical fluid chromatography. *J Pharm Biomed Anal* 10:821-30.

Hayakawa R, Matsunaga K, Suzuki M, Arima Y, Ohkido Y. (1987) Lipstick dermatitis due to C18 aliphatic compounds. *Contact Dermatitis* 16:215-219.

Henkel KgaA. (1994) Monomuls®90-L12 (Glyceryl Laurate)Toxicological Evaluation. Unpublished data submitted by CTFA, January 27, 1999 (4 pages).[1]

Henkel KgaA. (1996) Monomuls®90-L12 (Glyceryl Laurate). Quality control and product descriptive data. Unpublished data submitted by CTFA, January 27, 1999 (2 pages).[1]

Holland KT, Taylor D, Farrell AM. (1994) The effect of glycerol monolaurate on growth of, and production of toxic shock syndrome toxin-1 and lipase by, *Staphylococcus aureus*. *J Antimicrob Chemother* 33:41-55.

Huckle WR, Earp HS. (1994) Regulation of cell proliferation and growth by angiotensin II. *Prog Growth Factor Res.* 5:177-194.

Hüls AG. (1996a) Prüfung der akuten oraien toxicität von Imwitor 375 an der ratte (Testing of the acute oral toxicity of Imwitor 375 [Glyceryl Citrate/Lactate/Linoleate/Oleate] on rats - English translation) (Final Report No. AO-96/0182). Unpublished data submitted by CTFA, May 5, 1999 (3 pages).[1]

Hüls AG. (1996b) Prüfung der akuten dermalen toxizität von Imwitor 375 an der ratte, (Testing of the acute dermal toxicity of Imwitor 375 on rats - English translation) (Final Report No. AD-96/0182). Unpublished data submitted by CTFA, May 5, 1999 (3 pages).[1]

Hüls AG. (1996c) Prüfung auf akute augen- und schleimhautreizung von Imwitor 375 am kaninchen (Testing for acute eye and mucous membrane irritation of Imwitor 375 on rabbits - English translation) (Final Report No. AA-96/0182). Unpublished data submitted by CTFA, May 5, 1999 (3 pages).[1]

Hüls AG. (1996d) Prüfung auf akute hautreizwirkung von Imwitor 375 am kaninchen (Testing of the acute skin irritation effect of Imwitor 375 on rabbits - English translation (Final Report No. AH-96/0182). Unpublished data submitted by CTFA, May 5, 1999 (3 pages).[1]

Hüls AG. (1996e) Prüfung auf akute augen- und schleimhautreizung von Imwitor 375 am kaninchen (Testing for sensitization of the skin of Imwitor 375 on guinea pigs [Buehler method]) (Final Report No. HS-96-0182). Unpublished data submitted by CTFA, May 5, 1999 (3 pages).[1]

Hüls America, Inc. (No date) Product information on glyceryl citrate/lactate/linoleate/oleate, glyceryl stearate citrate, glyceryl cocoate, and glyceryl caprylate. Unpublished data submitted by CTFA (15 pages)[1]

Informatics, Inc. (1973) *GRAS (Generally Recognized as Safe) Food Ingredients - Glycerine and Glycerides*. NTIS Report No. PB-221 227.

Institut Français de Recherches et Essais Biologiques [IFREB]. (1977) Indice d'irritation oculaire chez le lapin. Indice d'irritation primaire cutanée chez le lapin. Unpublished data submitted by CTFA, March 10, 1999 (22 pages).[1]

International Research Services, Inc. (1995) A study to assess the skin sensitization potential of four (4) test products when applied topically to the skin of healthy humans in a shared panel assay (IRSI 1241 1294PSL. Unpublished data submitted by CTFA (11 pages).[1]

Ivy Laboratories. (1990) The determination of the contact-sensitizing potential of four materials by means of the maximization test. Lip gloss 90033-01 containing 2.0% glyceryl rosinate RI9149. Unpublished data submitted by CTFA (12 pages).[1]

Ivy Laboratories. (1996) The determination of the contact-sensitizing potential of four materials by means of the maximization assay. Foundation 06636-11 containing 4.0% glyceryl rosinate (RI2326). Unpublished data submitted by CTFA (10 pages).[1]

Ivy Laboratories. (1997) The determination of the contact-sensitizing potential of one material by means of the maximization assay. Sample: Blush (07980-22) containing 2.0% glyceryl rosinate (RI 2326). Unpublished data submitted by CTFA (11 pages).[1]

Jensen PA, Obrien D. (1993) Industrial Hygiene. In: Willeke K, Baron PA eds. *Aerosol Measurement. Principles Techniques and Applications*. New York: John Wiley and Sons, Inc., 538-540.

Kabara JJ. (1984) *Cosmetic and Drug Preservation. Principles and Practice*. New York:Marcel Dekker, 305-322, 618, 740.

Kabara JJ, Ohkawa M, Ikekawa T, Katori T, Nishikawa N. (1985) Examinations on antitumor, immunological, and plant-growth inhibitory effects of monoglycerides of caprylic, capric, and lauric acids and related compounds. *Pharmacol Eff Lipids* 13:263-72.

Karlberg A. (1988) Contact allergy to colophony. (VII). Sensitizing studies with oxidation products of abietic and related acids. *Acta Dermato-Venereologica* Suppl 139:1-46.

Kato A, Ando K, Suzuki S, Tamura G, Arima K. (1969) Antitumor activity of monoglycerides and other esters of fatty acids. *J Antibiot* 22:83-4.

Kato A, Ando K, Tamura G, Arima K. (1971) Effects of some fatty acid esters on the viability and transplantability of Ehrlich ascites tumor cells. *Cancer Res* 31:501-4.

Lee MW, Severson DL. (1994) Signal transduction in vascular smooth muscle: diacylglycerol second messengers and PKC action. *Am J Physiol* 267:C659-678.

Leo A, Hansch C, Elkins D. (1971) Partition coefficients and their uses. *Chemical Reviews* 71:525-616.

Lévy L, Alvaro V, Dubray C, Joubert D. (1994) Ca(2+)-dependent protein kinase C isoforms in rat pituitary hyperplasia: effect of *in vivo* treatment with quinagolide. *Eur J Pharmacol* 16:327-334.

Lewis, RJ, ed. (1993) *Hawley's Condensed Chemical Dictionary*. 12th ed. New York:Van Nostrand Reinhold, 568,1088,1180.

Lide DR, Frederikse HPR, eds. (1993) *CRC Handbook of Chemistry and Physics. A Ready-Reference Book of Chemical and Physical Data*. 74th ed. Boca Raton:CRC Press, 3-260 to 3-261, 3-502 to 3-504.

Lyman WJ, Reehl WF, Rosenblatt DH. (1982) *Handbook of chemical property estimation methods*. New York:McGraw-Hill.

Maruyama K, Yonese C. (1986) Separation and quantitative determination of monoacylglyceryol mixtures by reversed phase HPLC. *J Am Oil Chem Soc* 63:902-5.

Mattson FH, Volpenhein RA. (1964) The digestion and absorption of triglycerides. *J Biol Chem* 239: 2772-2777.

National Academy of Sciences (NAS). (1960) The safety of mono- and diglycerides for use as intentional additives in food (NAS publication no. 251). Washington:NAS.

Niederpruem H, Schweikert H, Thueroff JW, Zaenker KS. (1995) Inhibition of steroid 5 alpha-reductase activity by aliphatic fatty acids. Candidates for chemoprevention of prostate cancer. *Ann NY Acad Sci* 768:227-30.

Nomura H, Katsuhiko A, Sekiguchi K, Kikkawa U, Nishizuka Y. (1986) *Biochem Biophys Res Commun* 140:1143-1151.

Oh D-H, Marshall DL. (1996) Monolaurin and acetic acid inactivation of *Listeria monocytogenes* attached to stainless steel. *Journal of Food Protection* 59:249-52.

Okumura M, Nakamori Y, Yoshida Y, Niwa H, Sugibayashi Y. (1990) Effect of monoglycerides on the percutaneous absorption of papaverine hydrochloride. *Drug Des Delivery* 6:137-48.

Petschow BW, Batema RP, Ford LL. (1996) Susceptibility of *Helicobacter pylori* to bactericidal properties of medium-chain monoglycerides and free fatty acids. *Antimicrob Agents Chemother* 40:302-6.

Procter & Gamble Company. (1950) The comparative nutritive value of certain mono-, di-, and triglycerides. (Submitted by FDA in response to an FOI request - 1998; 41 pages).[1]

Projan SJ, Brown-Skrobot S., Schlievert PM, Vandenesch G, Novick RP. (1994) Glycerol monolaurate inhibits the production of beta-lactamase, toxic shock toxin-1, and other staphylococcal exoproteins by interfering with signal transduction. *J Bacteriol* 176:204-9.

Rempe JM, Santucci LG, eds. (1997) *CTFA List of Japanese Cosmetic Ingredients*. 3rd ed. Washington:CTFA, 41-43.

Sánchez-Piñera P, Micol V, Corbalán-Garcia, Gómez-Fernández JC. (1999) A comparative study of the activation of protein kinase C α by different diacylglycerol isomers. *Biochem J* 337:387-395.

Saffiotti U, Shubik P. (1963) Studies on promoting action in skin carcinogenesis. *Natl Cancer Inst Monogr* 10:489-507.

Schlievert PM, Deringer JR, Kim MH, Projan SJ, Novick RP. (1992) Effect of glycerol monolaurate on bacterial growth and toxin production. *Antimicrob Agents Chemother* 36:626-31.

Scientific & Technical Information Network (STN) International. (1997) Properties of esters of glycerin and lauric acid. *Registry database file*. Columbus:STN International.

Shao LP, Gäfvert E, Karlberg A-T, Nilsson U, Nillson JLG. (1993) The allergenicity of glycerol esters and other esters of rosin (colophony). *Contact Dermatitis* 31:11-17.

Takano S, Kohdoh Y. (1987) Monoglyceride analysis with reversed phase HPLC. *J Am Oil Chem Soc* 64:1001-3.

Tanaka M, Shimizu S, Miyakawa S. (1993) Contact dermatitis from glyceryl di-isostearate. *Contact Dermatitis* 29:41-42.

Unichema International. (1997a) Isostearate esters of glycerol and polyglycerol : Safety evaluation. Unpublished data submitted by CTFA, May 4, 1998 (8 pages)[1]

Unichema International. (1997b) Glyceryl monoesters of fatty acids: Safety evaluation. Unpublished data submitted by CTFA, May 4, 1998 (12 pages).[1]

Wenninger JA, Canterbery RC, McEwen, GN Jr., eds. (2000) *International Cosmetic Ingredient Dictionary and Handbook*. 8th ed. Washington:CTFA.

Willeke K, Baron PA., eds. (1993) *Aerosol measurement. Principles, techniques and qpplications*. New York:Van Nostrand Reinhold.

Witcher KJ, Novick RP, Schlievert PM. (1996) Modulation of immune cell proliferation by glycerol monolaurate. *Clin Diagn Lab Immunol* 3:10-3.