Final Report on the Safety Assessment of Propylene Glycol (PG) Dicaprylate, PG Dicaprylate/Dicaprate, PG Dicocoate, PG Dipelargonate, PG Isostearate, PG Laurate, PG Myristate, PG Oleate, PG Oleate SE, PG Dioleate, PG Dicaprate, PG Diisostearate, and PG Dilaurate[1]

The Propylene Glycol Dicaprylate family of ingredients includes several esters and diesters of Propylene Glycol and fatty acids. These ingredients are used in cosmetic formulations as skin conditioning agents, viscosity increasing agents, and surfactants. Two skin irritation studies (minimal to no irritation) and a comedogenicity study (insignificant comedogen) on Propylene Glycol Dicaprylate/Dicaprate and a skin irritation study (slight) and an acute oral toxicity study (nontoxic) on Propylene Glycol Laurate were available. Available data were also found indicating that Propylene Glycol Dicaprylate/Dicaprate and Propylene Glycol Dipelargonate may enhance the skin penetration of other chemicals. Because of the ability of these Polyethylene Glycol esters and diesters to enhance penetration of other agents, it was recommended that care be taken in using these and other Polyethylene Glycol esters and diesters in cosmetic products. Previous Cosmetic Ingredient Review safety assessments of related ingredients, including Polyethylene Glycol, Polyethylene Glycol Stearate, Coconut Oils and Acids, Isostearic Acid, Lauric Acid, Myristic Acid, Oleic Acid, and Caprylic/Capric Triglyceride, were summarized. Included were mutagenicity, chronic toxicity, and skin irritation and sensitization data. Based in part on the limited data available on the ingredients included in the report, but more so on the previous reviews of chemically similar moieties, it was concluded that Propylene Glycol Dicaprylate, Propylene Glycol Dicaprylate/Dicaprate, Propylene Glycol Dicocoate, Propylene Glycol Dipelargonate, Propylene Glycol Isostearate, Propylene Glycol Laurate, Propylene Glycol Myristate, Propylene Glycol Oleate, Propylene Glycol Oleate SE, Propylene Glycol Dioleate, Propylene Glycol Dicaprate, Propylene Glycol Diisostearate, and Propylene Glycol Dilaurate are safe for use as cosmetic ingredients in the present practices of use.

The safety of the following Propylene Glycol esters and diesters in cosmetic products is reviewed: Propylene Glycol Dicaprylate; Propylene Glycol Dicaprylate/Dicaprate; Propylene Glycol Dicocoate; Propylene Glycol Dipelargonate; Propylene Glycol Isostearate; Propylene Glycol Laurate; Propylene Glycol Myristate; Propylene Glycol Oleate; Propylene Glycol Oleate SE (self-emulsifying); Propylene Glycol Dioleate; Propylene Glycol Dicaprate; Propylene Glycol Diisostearate; and Propylene Glycol Dilaurate.

With the exceptions of two skin irritation studies and a comedogenicity study on Propylene Glycol Dicaprylate/Dicaprate and a skin irritation study and acute oral toxicity study on Propylene Glycol Laurate, no other studies on the toxicity of the Propylene Glycol esters or diesters included in this review have been found.

However, the Cosmetic Ingredient Review (CIR) Expert Panel has issued Final Reports on the safety of Propylene Glycol, Propylene Glycol Stearate, Propylene Glycol Stearate SE, and other chemical moieties of the Propylene Glycol esters and diesters included in the present review, and determined that the data included in these Final Reports are sufficient for evaluating the safety of the thirteen Propylene Glycol esters and diesters that are mentioned above.

Therefore, data from the following CIR Final Reports were considered: Propylene Glycol (Andersen 1994); Propylene Glycol Stearate and Propylene Glycol Stearate SE (Elder 1983a); Caprylic/Capric Triglyceride (Elder 1980); Coconut Acid and Coconut Oil (Elder 1986); Isostearic Acid (Elder 1983b); and Lauric Acid, Myristic Acid, and Oleic Acid (Elder 1987). The results of studies from these safety assessments are included in the report summary.

CHEMISTRY

Chemical and Physical Properties

Properties of the following Propylene Glycol esters and diesters are summarized in Table 1: Propylene Glycol Dicaprylate; Propylene Glycol Dicaprate; Propylene Glycol Dicaprylate/Dicaprate; Propylene Glycol Dipelargonate; Propylene Glycol Laurate; Propylene Glycol Dilaurate; Propylene Glycol Oleate; and Propylene Glycol Dioleate. Properties of Propylene Glycol Dicaprylate/Dicaprate and Propylene Glycol Laurate, submitted to the Cosmetic Ingredient Review by a chemical supplier, are included in Table 2.

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TABLE 1
Properties of Propylene Glycol Esters and Diesters

Property	Value/description	Reference
	Propylene Glycol Dicaprylate	
Formula weight	328.49	STN International 1995
Boiling point @ 0.050 torr	108°C	STN International 1995
Density @ 60°C	0.891	Patwardhan, Thapar, and Subrahmanyam 1974
Molar volume @ 60°C	368	Patwardhan, Thapar, and Subrahmanyam 1974
Refractive index @ 60°C	1.422	Patwardhan, Thapar, and Subrahmanyam 1974
Molar refraction @ 60°C	93.26	Patwardhan, Thapar, and Subrahmanyam 1974
Viscosity (centipoises) @ 40°C	4.08	Patwardhan, Thapar, and Subrahmanyam 1974
Viscosity @ 50°C	3.69	Patwardhan, Thapar, and Subrahmanyam 1974
Viscosity @ 60°C	3.33	Patwardhan, Thapar, and Subrahmanyam 1974
	Propylene Glycol Dicaprylate/Dicaprate	
Form	Clear, odorless, oily liquid	Nikitakis and McEwen 1990
Identification	Positive: close match to a standard IR spectrum with no indication of foreign materials	Nikitakis and McEwen 1990
Specific Gravity @ 25°/25°C	0.912 to 0.922	Nikitakis and McEwen 1990
Solubility	Soluble in most organic solvents; insoluble in water	Nikitakis and McEwen 1990
Acid value	0.1 maximum	Nikitakis and McEwen 1990
Iodine value	1.0 maximum	Nikitakis and McEwen 1990
Saponification value	315 to 335	Nikitakis and McEwen 1990
Moisture	0.1% maximum	Nikitakis and McEwen 1990
	Propylene Glycol Diperlargonate	
Formula weight	356.54	STN International 1995
Form	Odorless, colorless liquid	Nikitakis and McEwen 1990
Identification	Positive: close match to a standard IR spectrum with no indication of foreign materials	Nikitakis and McEwen 1990
Specific gravity @ 25°/25°C	0.895 to 0.935	Nikitakis and McEwen 1990
Density @ 80°C	0.873 g/cm^3	Lewis and Subrahmanyam 1983
Dynamic viscosity @ 80°C	0.022 g/cm·s	STN International 1995
Refractive index @ 80°C	1.417 (λ = 589 nm)	Lewis and Subrahmanyam 1983
Solubility	Soluble in common organic solvents; insoluble in water	Nikitakis and McEwen 1990
Acid value	0.5 maximum	Nikitakis and McEwen 1990
Ester value	310 to 325	Nikitakis and McEwen 1990
Iodine value	1.0 maximum	Nikitakis and McEwen 1990
	Propylene Glycol Laurate	
Formula weight	258.40	STN International 1995
Form	Light, yellow liquid with mild, fatty odor	Nikitakis and McEwen 1990
Identification	Positive: close match to a standard IR spectrum with no indication of foreign materials	Nikitakis and McEwen 1990
Specific gravity @ 25°/25°C	0.905 to 0.915	Nikitakis and McEwen 1990
Refractive index @ 25°/25°C	1.440 to 1.446	Nikitakis and McEwen 1990

TABLE 1
Properties of Propylene Glycol Esters and Diesters *(Continued)*

Property	Value/description	Reference
Solubility	Soluble in organic solvents; insoluble in propylene glycol or water	Nikitakis and McEwen 1990
Boiling point @ 0.6 torr	138 to 141°C	STN International 1995
Acid value	3.0 to 5.0	Nikitakis and McEwen 1990
Saponification value	230 to 250	Nikitakis and McEwen 1990
Iodine value	2.0 maximum	Nikitakis and McEwen 1990
	Propylene Glycol Dilaurate	
Form	Liquid	STN International 1995
Formula weight	440.71	STN International 1995
Density @ 30°C	0.897	STN International 1995
Refractive index @ 30°C	1.444 (λ = 589 nm)	STN International 1995
Melting point	21.9°C	STN International 1995
	35.0°C (in acetone)	STN International 1995
Boiling point @ 0.04 torr	196°C	STN International 1995
	Propylene Glycol Oleate	
Form	Liquid	STN International 1995
Molecular weight	340	STN International 1995
	Propylene Glycol Dioleate	
Formula weight	605	STN International 1995
	Propylene Glycol Dicaprate	
Formula weight	384.60	STN International 1995
Melting point	24.2 to 25.2°C (in acetone)	STN International 1995
	24.2 to 25.2°C (in petroleum ether and ethyl acetate)	STN International 1995
Refractive index	1.4276 (70°C; λ = 589 nm)	STN International 1995

TABLE 2
Chemical and physical properties of Propylene Glycol Dicaprylate/Dicaprate, and Propylene Glycol Laurate (Stepan Company 1996)

Property	Propylene Glycol Dicaprylate/Dicaprate	Propylene Glycol Laurate
Form	Liquid at 75°F	Liquid
Appearance	Slightly yellow color; free of suspended matter	Off-white color
Odor	Bland	Typical, mild fatty
Type	—	Nonionic
Melting point	—	8 to 12°C (specification)
Flash point (closed cup)	—	370°F
Solubility	Soluble in alcohol containing up to 20% water	Insoluble in water; soluble in isopropyl alcohol, mineral oil, and vegetable oil (peanut)
Moisture	0.05%	—
Free fatty acid (as oleic)	0.03%	—
Acid value	—	3.0 max (specification)
Iodine value	0.1	1.0 max (specification)
Saponification value	326	231–241 (specification)
Hydroxyl value	1.0	—

Information on the chemical and physical properties of Propylene Glycol Dicocoate, Propylene Glycol Isostearate, Propylene Glycol Myristate, Propylene Glycol Oleate SE, and Propylene Glycol Diisostearate were not identified in the published literature.

Propylene Glycol Dicaprylate

Propylene Glycol Dicaprylate (CAS Nos. 7384-98-7 and 56519-70-1) is the diester of propylene glycol and caprylic acid that conforms generally to the formula shown in Figure 1 (Wenninger and McEwen 1997). Other names for this chemical

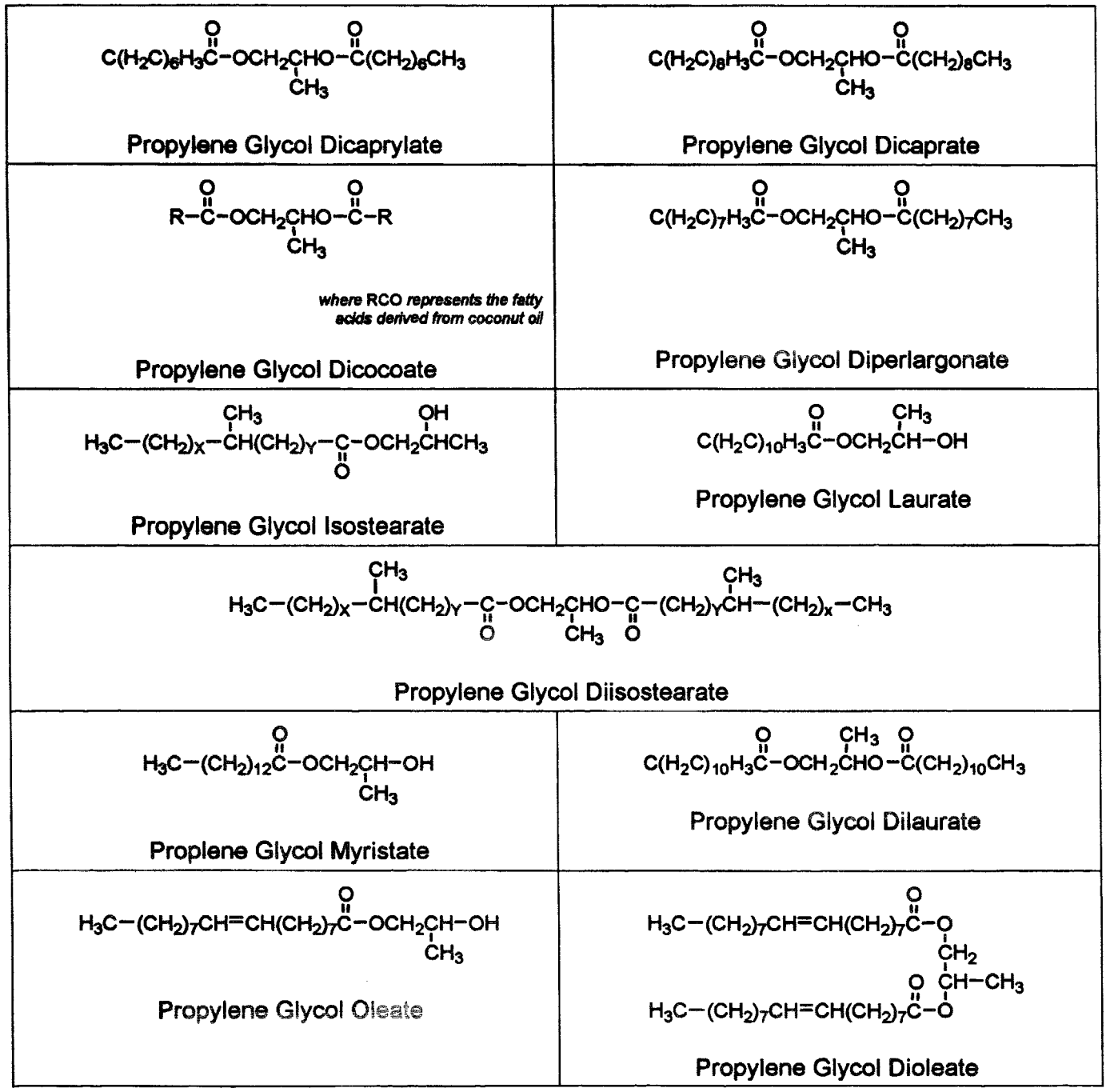

FIGURE 1
Chemical formulas for esters and diesters of Propylene Glycol and fatty acids.

are as follows: Octanoic Acid, 1-Methyl-1,2-Ethanediyl Ester; 1,2-Dicaprylin; 1-Methyl-1,2-Ethanediyl Octanoate; 1,2-Propanediol Dioctanoate; 1,2-Propyleneglycol Dioctanoate; and Propylene Di(Octanoate) (Wenninger and McEwen 1997; Chemline 1995; The Scientific and Technical Information Network [STN] International 1995).

Propylene Glycol Dicaprate

Propylene Glycol Dicaprate (CAS No. 56519-72-3) is the diester of propylene glycol and capric acid that conforms to the formula shown in Figure 1 (Wenninger and McEwen 1997). Other names for this chemical are as follows: Decanoic Acid, 1,3-Propanediyl Ester; n-Decanoic Acid, 1,3-Propanediyl Ester; Decanoic Acid, Trimethylene Ester (Wenninger and McEwen 1997; Chemline 1995); and 1,3-Bis-decanoyloxy-propane; 1,3-Bis-decanoyloxy-propan; and Decanoic Acid, 3-Decanoyloxy-propyl ester (STN International 1995).

Propylene Glycol Dicaprylate/Dicaprate

Propylene Glycol Dicaprylate/Dicaprate (CAS Nos. 58748-27-9; 9062-04-8; and 68988-72-7) is a mixture of the propylene glycol diesters of caprylic and capric acids (Wenninger and McEwen 1997). The structures of Propylene Glycol Dicaprylate and Propylene Glycol Dicaprate appear on the preceding page. Propylene Glycol Dicaprylate/Dicaprate is also defined as the propylene glycol diester of short chain, predominantly naturally derived C_8–C_{10} fatty acids (Nikitakis and McEwen 1990). It is soluble in alcohol containing up to 20% water and its viscosity is usually low (Stepan Company 1996). Other names for this mixture include: Decanoic Acid, 1-Methyl-1,2-Ethanediyl Ester mixed with 1-Methyl-1,2-Ethanediyl Dioctanoate; Decanoic Acid, Mixed Diesters with Octanoic Acid and Propylene Glycol; Caprylic, Capric Acid, Propylene Glycol Diester; Propylene Glycol Dicaprate-Caprate; and Propylene Glycol, Caprylate Caprate Diester (Wenninger and McEwen 1997; Chemline 1995). Propylene Glycol Dicaprylate/Dicaprate has also been defined as the propylene glycol diester of saturated vegetable acids (C_8–C_{10} chain length) that contains 65 to 80% caprylic acid and 15 to 30% capric acid (Mahjour et al. 1993).

Propylene Glycol Dicocoate

Propylene Glycol Dicocoate (CAS No. 68953-19-5) is the diester of propylene glycol and coconut acid that conforms generally to the formula shown in Figure 1 (Wenninger and McEwen 1997). The RCO group represents the fatty acids derived from coconut oil. Other names for this chemical are as follows: Coconut Fatty Acids, 1-Methyl-1,2-Ethanediyl Ester; Propylene Glycol Dicoconate; Propylene Glycol Diester Coconut Acids; and Fatty Acids, Coco, 1-Methyl-1,2-Ethanediyl Esters (Wenninger and McEwen 1997; Chemline 1995).

Propylene Glycol Dipelargonate

Propylene Glycol Dipelargonate (CAS No. 41395-83-9) is the diester of propylene glycol and pelargonic acid that conforms generally to the formula shown in Figure 1 (Wenninger and McEwen 1997). Other names for this chemical include Nonanoic Acid, 1-Methyl-1,2-Ethanediyl Ester; 1-Methyl-1,2-Ethanediyl Nonanoate; and Propylene Dinonanoate (Wenninger and McEwen 1997; Chemline 1995; STN International 1995).

Propylene Glycol Isostearate

Propylene Glycol Isostearate (CAS Nos. 32057-15-1 and 68171-38-0) is the ester of propylene glycol and isostearic acid (Wenninger and McEwen 1997) with the formula shown in Figure 1 (Sciarra, Iannacone, and Mores 1976). The sum of any combination of x and y values in the structure is 14 ($x + y = 14$). Other names for this chemical include Isooctadecanoic Acid, Monoester with 1,2-Propanediol and Propylene Glycol Monoisostearate (Wenninger and McEwen 1997).

Two commercially available forms of Propylene Glycol Isostearate were identified in the published literature. Propylene Glycol Monoisostearate consists of 52% monoester and 48% diester. Propylene Glycol Monoisostearate (90%) consists of 90% monoester and 10% diester (Sciarra, Iannacone, and Mores 1976).

Propylene Glycol Diisostearate

Propylene Glycol Diisostearate (CAS No. 68958-54-3) is the diester of propylene glycol that conforms generally to the formula shown in Figure 1 (Wenninger and McEwen 1997). Isooctadecanoic Acid, 1,3-Propanediyl Ester is another name for Propylene Glycol Diisostearate (Wenninger and McEwen 1997).

Propylene Glycol Laurate

Propylene Glycol Laurate (CAS No. 142-55-2) is the ester of propylene glycol and lauric acid that conforms generally to the formula shown in Figure 1 (Wenninger and McEwen 1997). It is a mixture of lauric acid esters of 1,2-propylene glycol in which the monoester predominates (Nikitakis and McEwen 1990). More recent information indicates the following composition of Propylene Glycol Laurate: free Propylene Glycol (0%), monoester (43.52%), and diester (56.48%) (Stepan Company 1996). Other names for Propylene Glycol Laurate are as follows: Dodecanoic Acid, 2-Hydroxypropyl Ester; Dodecanoic Acid, Monoester with 1,2-Propanediol; 2-Hydroxypropyl Dodecanoate; Propylene Glycol Monolaurate; Lauric Acid, 2-Hydroxypropyl Ester; and 2-Hydroxypropyl Laurate (Wenninger and McEwen 1997; Chemline 1995; STN International 1995).

Propylene Glycol Dilaurate

Propylene Glycol Dilaurate (CAS No. 22788-19-8) is the diester of propylene glycol and lauric acid that conforms generally to the formula shown in Figure 1 (Wenninger and McEwen 1997). Other names for this chemical include Dodecanoic Acid, 1-Methyl-1,2-Ethanediyl Ester; Lauric Acid, Propylene Ester; and 1,2-Bis-Lauroyloxy-Propane (Wenninger and McEwen 1997; Chemline 1995; STN International 1995).

Propylene Glycol Myristate

Propylene Glycol Myristate (CAS No. 29059-24-3) is the ester of propylene glycol and myristic acid that conforms generally to the formula shown in Figure 1 (Wenninger and McEwen 1997). Other names for this chemical are as follows: Propylene Glycol Monomyristate; Tetradecanoic Acid, Monoester with 1,2-Propanediol; and Myristic Acid, Monoester with 1,2-Propanediol (Wenninger and McEwen 1997; Chemline 1995).

Propylene Glycol Oleate

Propylene Glycol Oleate (CAS Nos. 27213-39-4 and 1330-80-9) is the ester of propylene glycol and oleic acid that conforms generally to the formula shown in Figure 1 (Wenninger and McEwen 1997). Other names for this chemical include 9-Octadecanoic Acid, Monoester with 1,2-Propanediol; Oleic Acid, Monoester with 1,2-Propanediol; and Propylene Glycol Monooleate (Wenninger and McEwen 1997; Chemline 1995; STN International 1995).

Propylene Glycol Oleate SE

Propylene Glycol Oleate SE (Self-Emulsifying) is a self-emulsifying grade of Propylene Glycol Oleate (q.v.) that contains some sodium and/or potassium oleate (Wenninger and McEwen 1997).

Propylene Glycol Dioleate

Propylene Glycol Dioleate (CAS No. 105-62-4) is the diester of propylene glycol and oleic acid that conforms to the formula shown in Figure 1 (Wenninger and McEwen 1993). Other names for Propylene Glycol Dioleate are as follows: 1-Methyl-1,2-Ethanediyl 9-Octadecenoate; 9-Octadecenoic Acid, 1-Methyl-1,2-Ethanediyl Ester; 9-Octadecenoic Acid, 1,3-Propanediyl Ester; and 9-Octadecenoic Acid (Z)-, 1-Methyl-1,2-Ethanediyl Ester (Wenninger and McEwen 1993; Chemline 1995), 1,2-Bis-Oleoyloxy-Propane; 1,2-Bis-Oleoyloxy-Propan; 1-Methyl-1,2-Ethanediyl Dioleate; and Octadec-9- Enoic Acid 1-Methyl-2-Octadec-9-Enoyloxy-Ethyl Ester (STN International 1995).

Methods of Production

Propylene Glycol Dicaprylate

Propylene Glycol Dicaprylate is a product of the reaction of propane-1,2-diol and octanoyl chloride with pyridine (% yield = 45% at 12 hours) (STN International 1995).

Propylene Glycol Dicaprylate/Dicaprate

Propylene Glycol Dicaprylate/Dicaprate is produced via the combination of Propylene Glycol with capric and caprylic acids. The mixture is heated to temperatures high enough to cause esterification. Water of reaction is removed to drive the reaction to completion and to obtain the low hydroxyl specification. The product is then fully refined and deodorized (Stepan Company 1996).

Propylene Glycol Dicaprate

Propylene Glycol Dicaprate is a product of the reaction of decanoic acid with propane-1,3-diol (temperature = 180°C) (STN International 1995).

Propylene Glycol Dipelargonate

Propylene Glycol Dipelargonate may be prepared by reacting nonanoyl chloride and $C_{12}H_{24}O_3$ with pyridine (solvent = $CHCl_3$) at 15°C or room temperature (STN International 1995).

Propylene Glycol Laurate

In the production of Propylene Glycol Laurate, Propylene Glycol and lauric acid are charged to the reactor, and a nitrogen sparge is initiated. The reactor is heated to approximately 225°C, and the water of reaction is removed. Vacuum is applied to remove unreacted propylene glycol when water evolution ceases. After specifications have been met, the finished product is cooled and drummed (Stepan Company 1996).

Propylene Glycol Dilaurate

Propylene Glycol Dilaurate may be prepared using either of the three methods: (1) reacting lauric acid and propylene oxide with the reagent, potassium hydroxide at 160°C; (2) reacting lauroyl chloride and propylene glycol with pyridine; and (3) reacting dodecanoic acid and propane-1,2-diol with the reagent, 0.2 M phosphate buffer (pH 7, solvent = water) at 45°C; % yield = 18.4% at 18 hours (STN International 1995).

Propylene Glycol Oleate

Propylene Glycol Oleate has been produced via the acylation of propylene glycol with oleic anhydride (*Pseudomonas* lipase catalyst; 160 to 180°C) (Shaw and Lo 1994).

Propylene Glycol Dioleate

Propylene Glycol Dioleate is a product of the reaction of propylene glycol with oleic acid chloride (STN International 1995).

The methods for production of the following esters and diesters were not identified in the published literature: Propylene Glycol Dicocoate; Propylene Glycol Myristate; Propylene Glycol Oleate SE; Propylene Glycol Isostearate; and Propylene Glycol Diisostearate.

Reactivity

Propylene Glycol Oleate

Propylene Glycol Oleate is stable under normal temperatures and pressures. It may burn, but does not ignite readily. Thermal decomposition products may include toxic oxides of carbon (STN International 1995). Propylene Glycol Oleate is incompatible with strong oxidizers (fire and explosion hazard). Under normal temperatures and pressures, hazardous polymerization has not been reported (STN International 1995).

Analytical Methods

Propylene Glycol Dicaprylate

Propylene Glycol Dicaprylate has been analyzed by infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy (STN International 1995) and mass spectrometry (Le Tellier and Nawar 1975).

Propylene Glycol Dipelargonate

Propylene Glycol Dipelargonate has also been analyzed by mass spectrometry (Le Tellier and Nawar 1975).

Propylene Glycol Oleate

Propylene Glycol Oleate has been analyzed by gas chromatography–flame ionization detection (Shaw and Lo 1994).

Information on analytical methods for the following Propylene Glycol esters and diesters were not identified in the published literature: Propylene Glycol Dicaprylate/Dicaprate; Propylene Glycol Dicaprate; Propylene Glycol Laurate; Propylene Glycol Dilaurate; Propylene Glycol Dioleate; Propylene Glycol Dicocoate; Propylene Glycol Myristate; Propylene Glycol Oleate SE; Propylene Glycol Isostearate; and Propylene Glycol Diisostearate.

Impurities

Information on the presence of impurities (e.g., potential pyridine residues) in the Propylene Glycol esters and diesters that are being reviewed was not identified in the published literature.

USE

Purpose in Cosmetics

Skin-conditioning agent–occlusive and viscosity increasing agent–nonaqueous are the intended cosmetic uses for the following propylene glycol diesters: Propylene Glycol Dicaprylate, Propylene Glycol Dicaprate, Propylene Glycol Dicocoate, Propylene Glycol Dipelargonate, Propylene Glycol Diisostearate, Propylene Glycol Dilaurate, and Propylene Glycol Dioleate. Propylene Glycol Dicaprylate/Dicaprate is intended for use as a skin-conditioning agent–occlusive. Propylene Glycol Oleate SE is used as a surfactant-emulsifying agent (Wenninger and McEwen 1997).

Other propylene glycol esters, listed as follows, are intended for use as skin-conditioning agent–emollients and surfactant-emulsifying agents: Propylene Glycol Isostearate, Propylene Glycol Laurate, Propylene Glycol Myristate, and Propylene Glycol Oleate (Wenninger and McEwen 1997).

Scope and Extent of Use in Cosmetics

The product formulation data submitted to the Food and Drug Administration in 1996 (FDA 1996) included the following use frequencies for Propylene Glycol esters and diesters: Propylene Glycol Dicaprylate (1 product); Propylene Glycol Dicaprylate/Dicaprate (202 products); Propylene Glycol Oleate (6 products); Propylene Glycol Myristate (11 products); Propylene Glycol Isostearate (22 products); Propylene Glycol Dipelargonate (82 products); and Propylene Glycol Laurate (87 products). Product formulation data on Propylene Glycol esters and diesters are summarized in Table 3 (FDA 1996).

The following Propylene Glycol ester/diesters reviewed in the present report were not reported to FDA as being used in cosmetic products: Propylene Glycol Dicocoate, Propylene Glycol Oleate SE, Propylene Glycol Dioleate, Propylene Glycol Dicaprate, Propylene Glycol Diisostearate, and Propylene Glycol Dilaurate.

Concentration of use values are no longer reported to FDA by the cosmetics industry (FDA 1992). Data on Propylene Glycol esters and diesters were received from industry (CTFA 1995) and are included in Table 4.

Cosmetic products containing Propylene Glycol esters and diesters are applied to the skin (eyelids and lips included), hair, and nails and may come in contact with the ocular, nasal, and oral mucosae. These products may be used on a daily basis, and have the potential for being applied frequently over a period of several years.

International Use

With the exceptions of Propylene Glycol Dilaurate, Propylene Glycol Myristate, and Propylene Glycol Oleate SE, the Propylene Glycol esters that are being reviewed in the present report are also listed in the *CTFA List of Japanese Cosmetic Ingredients*. Ingredients that are used in cosmetic products marketed in Japan appear on this list. The inclusion of any ingredient on the *CTFA List of Japanese Cosmetic Ingredients* does not guarantee either that the ingredient is safe for use as a cosmetic ingredient, or that the use of the substance as a cosmetic ingredient complies with the laws and regulations governing such use in Japan. Neither Propylene Glycol Dilaurate, Propylene Glycol Myristate, nor Propylene Glycol Oleate is prohibited from use in cosmetics manufactured in or imported into Japan (Rempe and Santucci 1992).

None of the Propylene Glycol esters or diesters reviewed in the present report is included among the substances listed as prohibited from use in cosmetic products that are marketed in the European Union (Dupuis 1994).

Noncosmetic Use

Propylene Glycol esters have been used as emulsifiers in foods and pharmaceuticals (Rosen 1978). FDA has determined that Propylene Glycol mono- and diesters of fats and fatty acids can be used safely in food, provided that (1) they are produced from edible fats and/or fatty acids in compliance with 21 CFR (Code of Federal Regulations) 172.860 and/or oleic acid derived from tall oil fatty acids in compliance with 21 CFR 172.862, and (2) they are used in food in amounts not in excess of that reasonably required to produce their intended effect (21 CFR 172.856). Propylene Glycol mono- and diesters of fats and fatty acids also

TABLE 3
Product formulation data on Propylene Glycol Dicaprylate and Propylene Glycol Dicaprylate/Dicaprate (FDA 1996)

Product category	Total no. of formulations in category	Total no. containing ingredient
Propylene Glycol Dicaprylate		
Moisturizing skin care preparations	942	1
1996 totals		**1**
Propylene Glycol Dicaprylate/Dicaprate		
Baby lotions, oils, powders, and creams	64	1
Eye shadows	588	4
Eye lotions	22	2
Eye makeup removers	95	5
Other eye makeup preparations	136	3
Other fragrance preparations	195	12
Blushers (all types)	277	6
Face powders	313	1
Foundations	355	27
Lipsticks	997	24
Makeup bases	154	2
Rouges	30	1
Other makeup preparations	157	1
Cuticle softeners	26	1
Nail polish and enamel removers	36	1
Other manicuring preparations	83	2
Aftershave lotions	268	2
Other shaving preparation products	63	1
Cleansing preparations (cold creams, cleansing lotions, liquids, and pads)	820	10
Face and neck skin care preparations (excluding shaving preparations)	300	5
Body and hand skin care preparations (excluding shaving preparations)	1012	15
Foot powders and sprays	33	1
Moisturizing skin care preparations	942	52
Night skin care preparations	226	3
Paste masks (mud packs)	300	2
Other skin care preparations	810	7
Suntan gels, creams, and liquids	196	6
Indoor tanning preparations	67	3
Other suntan preparations	68	2
1996 totals		**202**
Propylene Glycol Oleate		
Other eye makeup preparations	136	1
Foundations	355	1
Makeup bases	154	1
Body and hand (excluding shaving preparations)	1012	2
Foot powders and sprays	33	1
1996 totals		**6**

TABLE 3
Product formulation data on Propylene Glycol Dicaprylate and Propylene Glycol Dicaprylate/Dicaprate (FDA 1996) *(Continued)*

Product category	Total no. of formulations in category	Total no. containing ingredient
Propylene Glycol Myristate		
Lipstick	997	1
Other makeup preparations	157	1
Face and neck skin care preparations (excluding shaving preparations)	300	1
Body and hand skin care preparations (excluding shaving preparations)	1012	3
Other skin care preparations	810	3
Suntan gels, creams, and liquids	196	2
1996 totals		**11**
Propylene Glycol Isostearate		
Eye makeup remover	95	1
Foundations	355	2
Lipstick	997	1
Other makeup preparations	157	1
Shaving cream (aerosol, brushless, and lather)	158	6
Other shaving preparations products	63	7
Cleansing preparations (cold creams, cleansing lotions, liquids, and pads)	820	1
Moisturizing skin care preparations	942	1
Other skin care preparations	810	1
Suntan gels, creams, and liquids	196	1
1996 totals		**22**
Propylene Glycol Dipelargonate		
Baby lotions, oils, powders, and creams	64	1
Bath oils, tablets, and salts	147	1
Eye makeup remover	95	1
Other eye makeup preparations	136	1
Powders (dusting and talcum, excluding aftershave talc)	307	1
Other fragrance preparations	195	4
Blushers (all types)	277	4
Face powders	313	1
Foundations	355	26
Lipstick	997	8
Makeup bases	154	1
Other makeup preparations	157	2
Other personal cleanliness products	339	1
Aftershave lotion	268	1
Preshave lotions (all types)	20	1
Cleansing preparations (cold creams, cleansing lotions, liquids, and pads)	820	5
Body and hand skin care preparations (excluding shaving preparations)	1012	4
Moisturizing skin care preparations	942	9
Paste masks (mud packs)	300	1
Other skin care preparations	810	9
1996 totals		**82**

(Continued on next page)

TABLE 3
Product formulation data on Propylene Glycol Dicaprylate and Propylene Glycol Dicaprylate/Dicaprate (FDA 1996) *(Continued)*

Product category	Total no. of formulations in category	Total no. containing ingredient
Propylene Glycol Laurate		
Eye lotion	22	2
Mascara	218	2
Other eye makeup preparations	136	2
Cologne and toilet waters	834	6
Perfumes	286	3
Other fragrance preparations	195	2
Hair conditioners	715	1
Shampoos (noncoloring)	972	2
Tonics, dressings, and other hair grooming aids	604	3
Other hair preparations	395	1
Blushers (all types)	277	3
Foundations	355	9
Lipstick	997	7
Makeup bases	154	4
Makeup fixatives	11	3
Other makeup preparations	157	3
Cuticle softeners	26	1
Other personal cleanliness products	339	1
Aftershave lotion	268	1
Other shaving preparations products	63	2
Cleansing skin care preparations (cold creams, cleansing lotions, liquids, and pads)	820	6
Body and hand skin care preparations (excluding shaving preparations)	1012	9
Moisturizing skin care preparations	942	4
Paste masks (mud packs)	300	1
Other skin care preparations	810	4
Suntan gels, creams, and liquids	196	3
Indoor tanning preparations	67	1
Other suntan preparations	68	1
1996 totals		**87**

can be used as components of the food-contact surface of paper and paperboard, provided that the food-contact surface of the paper or paperboard complies with the prescribed limitations for extractives (21 CFR 176.170).

Defoaming agents containing Propylene Glycol mono- and diesters of fats and fatty acids can be used safely in processed foods in accordance with the provisions included in the preceding paragraph (21 CFR 173.340). Additionally, defoaming agents containing Propylene Glycol esters can be used safely in the manufacture of paper and paperboard intended for use in packaging, transporting, or holding food (21 CFR 176.210).

Reaction products resulting from the reaction of Propylene Glycol with certain fats, oils, fatty acids, and fatty alcohols are among the substances that are used in the production of, or are added to, textiles and textile fibers. Such textiles and textile fibers can be used safely as articles or components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food (21 CFR 177.2800). Similarly, esters resulting from the reaction of reconstituted oils (from triglycerides or fatty acids derived from certain oils) with Propylene Glycol are ingredients of resinous and polymeric coatings. Coatings of this composition may be used safely as the food-contact surface or articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food (21 CFR 175.300).

TABLE 4
Concentration of use data (CTFA 1995)

Ingredient	Product type	Use concentrations
Propylene Glycol Dicaprylate/Dicaprate	Blush	45%
	Makeup	24%
	Sun block stick	24%
	Moisturizer	16%
	Lip products	10%
	Eyeshadow	7%
	Eyeliner	19%
	Makeup remover	27%
	Antiperspirant	33%
	Aftershave balm	7%
Propylene Glycol Dipelargonate	Body oils	up to 8%
	Moisturizer	4%
	Aftershave balm	4%
	Other hair preparations	33.7960%
	Blushers (all types)	5%
	Foundations	9.30%
	Nail polish and enamel removers	5%
	Face and neck skin care	5%
	Moisturizing skin care	3%
	Night skin care	1%
Propylene Glycol Diester	Eye shadow	23.5%
	Blushers (all types)	51.730%
	Face powders	15%
	Foundations	30.640%
	Cuticle softeners	3.5%
	Nail creams and lotions	21.6%
	Other manicuring preparations	8%
	Face and skin care	1%
	Moisturizing skin care	2.5%
	Night skin care	1%
Propylene Glycol Isostearate	Shave gel	1.4%
Propylene Glycol Laurate	Hairdress	22%
	Tanning gel moisturizer	6%
	Shampoo	1.25%
	Lash gel	1%
	Eye shadow	1.3%
	Lipstick	9%

BIOLOGICAL PROPERTIES

Absorption, Distribution, Metabolism, and Excretion

Pharmacokinetic studies on the Propylene Glycol esters and diesters reviewed in the present report were not identified in the published literature.

Skin Penetration Enhancement

Propylene Glycol Dicaprylate/Dicaprate

Propylene Glycol Dicaprylate/Dicaprate reportedly enhanced the in vitro skin permeation rate of several transdermal drug candidates across human and hairless mouse skin, making it a

potential candidate for use in marketed transdermal products. The investigators suggested that these findings can indicate a nondiscriminative enhancement effect that resulted from a reduction in the stratum corneum diffusional resistance. This reduction could have been caused by an increase in the stratum corneum lipid fluidity or by extraction of the stratum corneum's lipids by Propylene Glycol Dicaprylate/Dicaprate (Mahjour et al. 1993).

Propylene Glycol Dipelargonate

Similarly, in another study, a saturated solution of Propylene Glycol Dipelargonate in propylene glycol promoted the percutaneous penetration of drugs across excised human skin in vitro. The investigators suggested that this property can be linked to the comparatively low polarity of Propylene Glycol Dipelargonate, enabling it to penetrate into the stratum corneum and interact with the lipid bilayers, thus, increasing their fluidity or forming fluid-like channels (Bonina et al. 1993). The results of an in vitro embryotoxicity study suggest that the skin penetration enhancement property of propylene glycol esters and diesters noted above can be due to the presence of propylene glycol. In this study, the exposure of $B_6D_2F_1$ mouse zygotes to $\geq$2.5 M propylene glycol for 2 to 7 minutes altered both intracellular pH and developmental potential. In that these effects were independent of volume changes noted in zygotes, and, therefore, intracellular propylene glycol concentrations, the researchers postulated that the toxicity of propylene glycol is mediated by direct alteration of the cell membrane (Damien, Luciano, and Peluso 1989).

TOXICOLOGY

Regarding all Propylene Glycol esters and diesters reviewed in this report, the following types of studies were not identified in the published literature: subchronic toxicity, mutagenicity, carcinogenicity, reproductive and developmental toxicity, and skin sensitization/photosensitization.

Acute Oral Toxicity

Propylene Glycol Laurate

In a study involving rats (number and strain not stated), the oral LD_{50} for Propylene Glycol Laurate was greater than 34.6 g/kg. The test substance was classified as practically nontoxic (Stepan Company 1996).

Antitumor Activity

Propylene Glycol Myristate

The antitumor activity of Propylene Glycol Myristate in vivo was evaluated using 20 ddY mice (5 weeks old; 18 to 22 g). Following the intraperitoneal implantation of one-million tumor cells, the test substance (in 0.86% NaCl solution or suspension) was administered once daily for 5 consecutive days. The final test concentrations administered were expressed as 0.5 mg/10^7 tumor cells (10 mice) and 2.5 mg/10^7 tumor cells (10 mice). After 7 days, tumor growth, body weight gain, and life span up to 30 days were evaluated. Ten control mice received injections of untreated tumor cells. Tumors were not observed in any of the 10 mice treated with the higher concentration (average survival time $>$ 30 days). At the lower concentration (10 mice), there were no cytotoxic effects on tumor cells. Tumors were observed in each mouse after 7 days, and the average survival time was 21.6 days. The average survival time for the 10 control mice (100% tumor incidence) was 18.8 days (Kato et al. 1971).

In a similar study, the antitumor activity of Propylene Glycol Myristate in vivo was evaluated using four 5-week-old ddY mice. Following the intraperitoneal injection of one million Ehrlich ascites tumor cells, the test substance (in saline solution or suspension) was administered (5 and 20 mg/mouse/day, 2 mice per dose) once daily for 5 consecutive days. Two untreated mice that were injected with tumor cells served as controls. Tumor growth and body weight gain were evaluated after 7 days. Compared to untreated controls, Propylene Glycol Myristate inhibited tumor growth and prolonged the life span of treated mice. No tumor growth was observed in mice dosed with 5 and 20 mg/day and the survival time for both groups was $>$30 days. The life span of control mice (marked tumor growth) was 16 days (Kato et al. 1969; 1970).

Propylene Glycol Oleate

Propylene Glycol Oleate had no antitumor activity in the preceding study by Kato et al. (1969; 1970). Tumor growth was marked at doses of 5 mg/mouse/day (2 mice) and 20 mg/mouse/day (2 mice), and the life span of treated mice (both doses) was 16 days (Kato et al. 1970).

Skin Irritation

Propylene Glycol Dicaprylate/Dicaprate

The skin irritation potential of Propylene Glycol Dicaprylate/Dicaprate was evaluated using six rabbits (strain not stated). Patches (type not stated) were applied for 24 hours. An average skin irritation score of 0.5 (maximum score possible = 8) was reported, and the test substance was classified as minimally irritating to the skin (Stepan Company 1996).

Propylene Glycol Laurate

The skin irritation potential of Propylene Glycol Laurate was also evaluated in a study involving rabbits (number and strain not stated). The experimental procedure was not included. An average skin irritation score of 0.8 (maximum score possible = 8) was reported, and the test substance was classified as slightly irritating to the skin (Stepan Company 1996).

Comedogenicity

Propylene Glycol Laurate

The comedogenicity of Propylene Glycol Laurate was evaluated in a 14-day study using three rabbits (strain not stated).

Details concerning the experimental protocol were not included. An average comedogenicity score of 0.7 (maximum score possible = 3) was reported, and the test substance was classified as an insignificant comedogen (Stepan Company 1996).

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation

Propylene Glycol Dicaprylate/Dicaprate

The skin irritation potential of a 95% ethanol:Propylene Glycol Dicaprylate/Dicaprate mixture (20:80) was evaluated using three volunteers (two females, one male). Four patches (2.5 cm^2 surface area), each containing 50 $\mu l/cm^2$ of the mixture, were applied for 24 hours to the lower dorsal left forearm of each female and to both arms of the male subject. At the end of the contact period and 24 hours later, test sites were examined grossly for signs of either erythema or edema. Skin irritation was not observed in either of the three subjects tested. Similar results were reported when a fourth subject (male) was tested with a 95% ethanol:Propylene Glycol Dicaprylate/Dicaprate mixture (40:60) according to the same procedure (Mahjour et al. 1993).

SUMMARY

Propylene Glycol Esters and Diesters

The limited information on chemical properties of Propylene Glycol esters and diesters indicates that, generally, these ingredients are soluble in most organic solvents. Methods of production that have been reported for some of the esters and diesters included in this review are as follows: Propylene Glycol Oleate is produced via the acylation of propylene glycol with oleic anhydride, and the dioleate is a product of the reaction of propylene glycol with oleic acid chloride. Propylene Glycol Dicaprate is a product of the reaction of decanoic acid with propane-1,3-diol. Similarly, Propylene Glycol Dicaprylate is produced by reacting propane-1,2-diol and octanoyl chloride with pyridine. Pyridine is also used in the production of Propylene Glycol Dipelargonate and Propylene Glycol Dilaurate. Propylene Glycol is a product of the reaction of nonanoyl chloride and $C_{12}H_{24}O_3$ with pyridine, and, Propylene Glycol Dilaurate, a product of the reaction of lauroyl chloride and propylene glycol with pyridine.

Cosmetic uses of Propylene Glycol esters and diesters include skin-conditioning agent–occlusive, viscosity increasing agent–nonaqueous, skin conditioning agent–emollients, and surfactant-emulsifying agents. These ingredients are used widely in a variety of rinse-off and leave-on cosmetics products. Data submitted to CIR by the cosmetics industry in 1995 indicated that Propylene Glycol diesters were used at concentrations up to 51.7%, and, Propylene Glycol esters, at concentrations up to 22%.

Propylene Glycol Dicaprylate/Dicaprate and Propylene Glycol Dipelargonate promoted the percutaneous penetration of drugs across excised human skin/hairless mouse skin in vitro.

Propylene Glycol Laurate was classified as practically nontoxic (LD_{50} > 34.6 g/kg) when administered orally to rats.

In two skin irritation studies involving rabbits, Propylene Glycol Dicaprylate/Dicaprate and Propylene Glycol Laurate were classified as minimally irritating and slightly irritating, respectively. Propylene Glycol Dicaprylate/Dicaprate was also classified as an insignificant comedogen in rabbits.

Antitumor activity (in vivo) in ddY mice was observed following the intraperitoneal injection of Propylene Glycol Myristate, but not Propylene Glycol Oleate. Skin irritation was not observed in either of the three subjects patch tested with a 95% ethanol:Propylene Glycol Dicaprylate/Dicaprate mixture (20:80). Patches were removed at 24 hours postapplication. Similar results were reported for a fourth subject patch tested with a 95% ethanol:Propylene Glycol Dicaprylate/Dicaprate mixture (40:60).

Propylene Glycol, Esters, and Fatty Acids

Propylene Glycol

Propylene Glycol (PG) was relatively harmless (LD_{50} = 21 g/kg) in acute oral toxicity studies involving rats.

Test substance–related lesions were not observed in rats that were fed diets containing 50,000 ppm PG (2.5 g/kg/day) for 15 weeks or in rats that were fed PG concentrations up to 50,000 ppm in the diet for 2 years. Similar results were reported in a study in which dogs were fed 2 or 5 g/kg PG in the diet for approximately 103 weeks. In another subchronic study, dogs received 5% PG in drinking water for 5 to 9 months. The results of tests for hepatic and renal impairment were negative.

PG did not induce corneal damage in the Draize test and was classified as a slight ocular irritant in another ocular irritation study.

In a 24-hour skin irritation test involving nude mice, no reactions to 10% PG were observed. Hypertrophy, dermal inflammation, and proliferation were observed at a concentration of 50% PG.

Draize test results indicated that PG was, at most, a mild skin irritant when applied for 24 hours to abraded and intact skin of rabbits. When PG was applied to the skin of guinea pigs and rabbits (guinea pigs and rabbits lack sweat glands) for 48 hours using open and closed patches, no reactions were observed. The results of 48-hour and 21-day open and closed patch tests involving Gottingen swine (no sweat glands) indicated no reactions to PG.

Results were negative for 100% PG in a mouse external ear swelling sensitization test. The results of a guinea pig maximization test, open epicutaneous test, and chamber (Finn chamber) test indicated no sensitization reactions to 70% PG. In another maximization test, PG was classified as a potentially weak sensitizer. The results of six other guinea pig sensitization tests indicated that PG was not an allergen.

PG was not teratogenic in female CD-1 mice when administered at a concentration of 10,000 ppm on days 8 to 12 of gestation. Malformations were observed in 5 of 226 living fetuses from female mice injected subcutaneously with PG (dose =

0.1 ml/g body weight on day 9, 10, or 11 of gestation). Three fetuses with malformations were noted among 1026 living fetuses from the untreated control group of pregnant mice.

In a continuous breeding reproduction study, no significant differences were observed between control and experimental groups of albino mice with respect to the following: mating index, fertility index, mean number of live pups per litter, proportion of pups born alive, and sex of pups born alive.

Embryonic development was reduced in cultures of mouse zygotes exposed to 3.0 M PG and inhibited completely in cultures exposed to 6.0 M PG for 20 min.

In the Ames test, PG was not mutagenic in strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100 of *Salmonella typhimurium* with and without metabolic activation. PG caused a dose-dependent increase in the frequency of sister chromatid exchanges (SCEs) in a Chinese hamster cell line, and was classified as a weak inducer of SCEs. In another study, PG was not mutagenic when tested in a sister chromatid exchange assay involving human cultured fibroblasts and a cultured Chinese hamster cell line both with and without metabolic activation. PG also was not mutagenic in additional in vitro tests: chromosomal aberrations, mitotic recombination, base pair substitution, micronucleus test, reverse mutation, and DNA damage.

PG disturbed the proliferation of urinary bladder epithelial cells from the rat, having reduced DNA production in tetraploid cells 1 and 2 months after the rats were injected subcutaneously. This effect was not observed at 3 months.

The results were negative when PG was tested in the hamster embryo cell transformation bioassay. In a 2-year feeding study involving CD strain rats, PG was not carcinogenic when concentrations up to 50,000 ppm were administered in the diet. In a life-time dermal carcinogenicity study, three groups of Swiss mice received dermal applications of 10, 50, and 100% PG, respectively. The tumor incidence in each of the three groups did not differ from that noted in the negative control group; skin tumors were not observed.

PG induced skin irritation and sensitization reactions in normal subjects and in patients. In these studies, test concentrations ranged from 2 to 100% PG. Reactions were observed at concentrations as low as 10% PG in predictive tests, and as low as 2% in provocative tests.

PG also increased the allergic responses in 43 patients patch tested with 50 μg of 1% nickel sulfate solution.

Propylene Glycol Stearate and Propylene Glycol Stearate SE

In rats, the acute oral toxicity of Propylene Glycol Stearate (PGS) was approximately 25.8 g/kg. The raw ingredient produced no significant dermal toxicity, skin irritation, or ocular irritation in acute tests with rabbits. Subchronic animal studies produced no evidence of oral or dermal toxicity. In a 6-month feeding study, no signs of toxicity were observed in dogs or rats fed a mixture containing 17% PGS; the mixture was incorporated into the diet at a concentration of 10%. PGS was negative in in vitro microbial assays for mutagenicity.

Although Propylene Glycol Stearate Self-Emulsifying (PGS-SE) has not been tested as extensively as PGS, it produced no apparent significantly different results in any of the animal tests. The acute oral LD_{50} in rats was estimated as greater than 32 g/kg. The ingredient produced no significant skin or ocular irritation in Draize rabbit irritation tests, and it was not a sensitizer in a guinea pig sensitization test. No other subchronic or chronic studies were available.

In clinical studies, PGS produced no significant skin irritation at concentrations up to 55% in 24 h single insult skin patch tests. A 28-day controlled use test on a product containing 2.5% PGS demonstrated no cumulative irritation with normal product use, but mild to moderate irritation with a challenge skin patch; the offending ingredient was not identified. Several skin sensitization tests on product formulations containing 1.5% to 2.5% PGS produced no evidence of sensitization reactions in a total subject population of 4084. Two photo-contact allergenicity tests on product formulations containing 1.5% PGS were negative.

No clinical data were available for PGS-SE. However, the chemical components of PGS-SE that distinguish it from PGS have been considered previously to be safe, and the information generally applicable to PGS is considered applicable to PGS-SE.

Caprylic/Capric Triglyceride

Caprylic/Capric Triglyceride has very low toxicity in humans and animals, as indicated by results of tests involving oral ingestion, intraperitoneal and intramuscular injection, skin and eye irritation tests, skin sensitization, percutaneous toxicity and, finally, by two-generation feeding studies.

The safety assessment of this ingredient rests on the information at hand and on the considerable usage at various concentrations in a variety of cosmetic and other consumer products. Additional biological assessments might reasonably be recommended to include studies on photosensitization.

Coconut Acid and Related Compounds

The results of oral toxicity studies indicate that Coconut Oil and Hydrogenated Coconut Oil are relatively nontoxic by ingestion. Administered as a single 5 g/kg dose to rats, neither compound caused deaths over a 7-day observation period. In a 90-day subchronic feeding study of diets containing 25% Coconut Oil, rats had slight fatty change of the liver but no other pathological changes. The results of a chronic study in which mice were fed, for a lifetime, diets supplemented with 15% Hydrogenated Coconut Oil indicated no effect on lifespans of the test animals.

Hydrogenated Coconut Oil was nontoxic when applied dermally. A single 3 g/kg dose applied to guinea pigs caused no deaths during a 7-day observation period. It was nonirritating to the skin in three single-insult occlusive patch tests. A primary irritation index of 0.11/8.0, indicating minimal irritation, was reported in a fourth study. Hydrogenated Coconut Oil was not a sensitizer in guinea pigs when applied to the skin in a modified Buehler test.

Coconut Oil did not cause skin irritation when applied to rabbit skin in a 24-hour single-insult occlusive patch test. It was nonsensitizing to the skin in a Magnusson-Kligman maximization test.

Coconut Acid caused minimal irritation in rabbits when assayed in a 24-hour single-insult occlusive patch test. Primary irritation indices of 0.13/4.0 and 0.17/4.0 were reported for 10% Coconut Acid in corn oil and undiluted Coconut Acid, respectively. These scores were indicative of minimal skin irritation.

Results of several studies suggest that the eye irritation potential of Coconut Oil and Hydrogenated Coconut Oil is low. Coconut Oil in Draize eye tests scored a maximum of 2/110, indicating minimum irritation. Hydrogenated Coconut Oil was assayed in ten Draize eye tests. In nine tests, ocular irritation ($\leq$2/110) was minimal, and in one test it was mild (6/110).

No mutagenicity data are available on any of the Coconut Oil ingredients. Coconut Oil was reported less effective than polyunsaturated fat as a tumor promoter for mammary tumors in rats induced by 7,12-dimethylbenz(a)anthracene.

Clinical assessment of cosmetic products containing Coconut Oil has used a variety of assays. Bar soaps containing 13% Coconut Oil, when tested using standard Draize procedures, produced very minimal skin reactions. In a 2-week normal use test, bar soaps caused no unusual irritation response. The results of soap chamber tests of bar soaps were minimal irritation in one study and mild irritation in another. No phototoxicity or photosensitivity was produced by these same bar soap formulations. A tanning butter containing 2.5% Coconut Oil did not cause erythematous reactions in a six-week repeat insult predictive patch test.

Lipstick containing 10% Hydrogenated Coconut Oil was tested using Schwartz-Peck prophetic patch test procedures. There was no evidence of primary irritation after a single patch application and no indication of sensitization in retests performed 14 days later.

Isostearic Acid

In rats, the acute oral LD_{50} for Isostearic Acid was estimated at greater than 32 ml/kg. The pure ingredient produced no significant skin or eye irritation in Draize rabbit eye irritation tests, whereas variable degrees of irritation were produced by product formulations containing Isostearic Acid. A product formulation both with and without 2.5% Isostearic Acid was tested in a rabbit ear comedogenicity assay. The formulation without Isostearic Acid was irritating but did not produce comedones; however, the formulation with Isostearic Acid was both irritating and comedogenic.

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

Lauric, Myristic, and Oleic Acids and Related Compounds

Little acute toxicity was observed when Oleic, Lauric, Palmitic, Myristic, or Stearic Acid, or cosmetic formulations containing these fatty acids at concentrations of 2.2 to 13% were given to rats orally at doses of 15 to 19 g/kg body weight.

In subchronic oral toxicity studies, Oleic, Palmitic, Myristic, and Stearic Acids were fed to rats at doses ranging from 5 to 50%. Thrombosis, aortic atherosclerosis, anorexia, and mortality were observed. In a subchronic study, no signs of toxicity were observed in chicks fed 5% dietary Stearic and Oleic Acids. Rats fed 15% Oleic Acid (in diet) in a chronic study had normal growth and general health, but reproductive capacity of female rats was impaired.

Results from topical application of Oleic Acid (at concentrations from 50% Oleic Acid to commercial grade Oleic Acid) to the skin of mice, rabbits, and guinea pigs ranged from no toxicity to signs of erythema, hyperkeratosis, and hyperplasia. Intradermal administration to guinea pigs of 25% Oleic Acid to commercial grade Oleic Acid resulted in local inflammation and necrosis. A formulation containing 2.2% Palmitic Acid was considered nontoxic to rabbits. A topically applied dose of 5 g/kg commercial grade Stearic Acid was not toxic to rabbits. Intradermal administration of 10 to 100 mM Stearic Acid was not toxic to rabbits. Intradermal administration of 10 to 100 mM Stearic Acid to guinea pigs and rabbits resulted in mild erythema and slight induration.

Eighteen mmol% concentrations of the fatty acids topically applied to the skin of the external ear canals of albino rabbits for 6 weeks produced a range of responses, varying from no irritation with Stearic Acid to slight irritation with Myristic and Palmitic Acids to erythema, desquamation, and persistent follicular keratosis with Oleic and Lauric Acids. Slight local edema and no deaths were observed among New Zealand white rabbits after 4 weeks of topical administration of product formulations containing 2.0% Stearic Acid.

In 13-week dermal toxicity studies, two cosmetic product formulations containing, at most, 5% Stearic Acid produced moderate skin irritation in rats receiving 4.0 ml/kg and 227 mg/kg doses. All other physiological parameters were normal.

In single-insult occlusive patch tests for primary irritation, commercial grades of all five fatty acids (Oleic, Stearic, Myristic, Lauric, and Palmitic), at doses of 35 to 65% in vehicles (Stearic Acid only) and at 1 to 13% in cosmetic product formulations (other fatty acids), produced none to moderate erythema and slight, if any, edema in the skin of rabbits. Slight increases in

irritation were observed in the short-term repeated insult patch tests (daily for 3 to 14 days) of Oleic and Myristic Acids.

In maximization studies with two cosmetic product formulations containing 5.08% Oleic Acid and 1.0% Stearic Acid, slight reactions to challenge patches were observed. These formulations were considered weak, grade 1, sensitizers. In another maximization study, after intradermal induction and booster injections of a formulation containing 3.5% Stearic Acid, reactions to topical challenge applications of the formulation were few and minimal in intensity.

Skin lotion formulations containing 2.8% Stearic Acid were not photosensitizing to the skin of Hartley guinea pigs.

Oleic Acid and its UVA-induced peroxides were associated with increased comedone formation on the treated ears of two species of rabbits.

In ocular irritation studies, the fatty acids alone and at concentrations ranging from 1 to 19.4% in cosmetic product formulations produced no to minimal irritation after single and multiple (daily, 14-day) instillations into the eyes of albino rabbits. Irritation was primarily in the form of very slight conjunctival erythema. A single instillation of Lauric Acid also produced corneal opacity and iritis.

Although Oleic and Lauric Acids induced mitotic aneuploidy in in vitro mutagenicity tests, both have been noted as inhibitors of mutagenicity produced by positive controls, such as *N*-nitrosopyrrolidine and sodium azide, in other tests. Stearic Acid was inactive in aneuploidy induction tests and in the Ames test, and it did not inhibit mutagenicity, as did Oleic and Lauric Acids. No increase in mitotic crossing-over events was induced by Oleic, Lauric, or Stearic Acids. Oleic Acid did not increase the number of sister chromatid exchanges over background.

In carcinogenicity studies, no malignant tumors were induced by repeated subcutaneous injections of 1 to 16.5 mg Oleic Acid in two species of mice. Intestinal and gastric tumors were found in mice receiving dietary Oleic Acid at daily concentrations up to 200 mg/mouse. Repeated subcutaneous injections of 25 and 50 mg Lauric Acid into mice were not carcinogenic. Low incidences of carcinomas, sarcomas, and lymphomas were observed in mice receiving single or repeated subcutaneous injections of 25 and 50 mg Palmitic and up to 82 mg Stearic Acid. Stearic Acid fed to mice in dietary doses of up to 50 g/kg/day was not carcinogenic.

In clinical primary and cumulative irritation studies, Oleic, Myristic, and Stearic Acids at concentrations of 100% or 40 to 50% in mineral oil were nonirritating. Mild to intense erythema in single-insult occlusive patch tests, soap chamber tests, and 21-day cumulative irritation studies were produced by cosmetic product formulations containing 2 to 93% Oleic, Palmitic, Myristic, or Stearic Acid and were generally not related to the fatty acid concentrations in the formulations.

In clinical repeated-insult patch tests (open, occlusive, and semiocclusive), maximization tests, and prophetic patch tests with cosmetic product formulations containing Oleic, Lauric, Palmitic, and Stearic Acids at concentrations ranging from <1 to 13%, no primary or cumulative irritation or sensitization was reported. A few subjects (<5% of approximately 4000 subjects tested) reacted to a few, isolated induction patches. Slight, if any, reactions were observed after challenge patching at original or adjacent sites on the upper backs or forearms of some subjects ($\lesssim$2%). Intensity of observed reactions to the formulations was not directly related to the concentrations of the fatty acid ingredients.

Cosmetic product formulations containing 1 to 13% Oleic, Palmitic, or Stearic Acid produced no photosensitization in human subjects. Slight reactions to a few induction patches were observed.

No treatment-related ocular irritation was observed in female subjects, some of whom wore contact lenses, involved in two 3-week exaggerated-use studies of mascara formulations containing 2 and 3% Oleic Acid. These formulations were used in combination with other eye area cosmetics.

DISCUSSION

With the exceptions of two skin irritation studies and a comedogenicity study on Propylene Glycol Dicaprylate/Dicaprate and a skin irritation study and acute oral toxicity study on Propylene Glycol Laurate, no other studies on the toxicity of the Propylene Glycol esters or diesters included in this review have been found. However, the CIR Expert Panel has issued Final Reports on the safety of Propylene Glycol, Propylene Glycol Stearate, and other chemical moieties of the Propylene Glycol esters and diesters included in the present review and, because of chemical similarities, determined that the data included in these Final Reports are sufficient for evaluating the safety of the following thirteen Propylene Glycol esters and diesters: Propylene Glycol Dicaprylate; Propylene Glycol Dicaprylate/Dicaprate; Propylene Glycol Dicocoate; Propylene Glycol Dipelargonate; Propylene Glycol Isostearate; Propylene Glycol Laurate; Propylene Glycol Myristate; Propylene Glycol Oleate; Propylene Glycol Oleate SE (self-emulsifying); Propylene Glycol Dioleate; Propylene Glycol Dicaprate; Propylene Glycol Diisostearate; and Propylene Glycol Dilaurate.

Accordingly, data from the following CIR Final Reports were considered in the present safety assessment: Propylene Glycol (Andersen 1994); Propylene Glycol Stearate and Propylene Glycol Stearate SE (Elder 1983a); Caprylic/Capric Triglyceride (Elder 1980); Coconut Acid (Elder 1986); Isostearic Acid (Elder 1983b); and Lauric Acid, Myristic Acid, and Oleic Acid (Elder 1987). The CIR Expert Panel concluded that Propylene Glycol is safe at concentrations up to 50%, and that the remaining ingredients are safe in the present practices of use. Except for Caprylic/Capric Triglyceride, most of these ingredients can be easily identified (by name) as components of one or more of the 13 Propylene Glycol esters and diesters reviewed in this report. The Caprylic/Capric moiety of Caprylic/Capric Triglyceride is also similar to the dipelargonate moiety of Propylene Glycol Dipelargonate. Propylene Glycol Dipelargonate is the

diester of propylene glycol and pelargonic acid ($C_9H_{18}O_2$), and pelargonic acid is similar to caprylic acid ($C_8H_{16}O_2$) and capric acid ($C_{10}H_{20}O_2$).

The more crucial studies that were used in arriving at the safe as used ingredient conclusions in the CIR Final Reports noted above are as follows: Propylene Glycol Stearate (mutagenicity, chronic toxicity, and skin sensitization); Caprylic/Capric Triglyceride (reproductive toxicity, chronic toxicity, and skin sensitization); Coconut Acid (chronic toxicity, tumor promotion, and skin sensitization, phototoxicity, and photosensitization); Isostearic Acid (skin sensitization, photosensitization, and phototoxicity); and Lauric Acid, Myristic Acid, and Oleic Acid (reproductive toxicity, carcinogenicity, and skin sensitization and photosensitization). The 50% concentration limit on Propylene Glycol is based on the CIR Expert Panel's assessment of the skin irritation potential of this cosmetic ingredient. In consideration of this limitation relative to the review of Propylene Glycol esters and diesters, the Panel noted that use concentrations of these ingredients should not be limited, even though certain Propylene Glycol diesters are used in cosmetics at concentrations as high as 51.7%. This decision is based on data from a chemical supplier indicating that Propylene Glycol Laurate does not contain any free Propylene Glycol, and the assumption that this is true of other Propylene Glycol esters and diesters.

The Expert Panel recognizes that, reportedly, Propylene Glycol Dicaprylate/Dicaprate and Propylene Glycol Dipelargonate can enhance the skin penetration of other chemicals, and recommends that care should be exercised in using these and other Propylene Glycol esters and diesters in cosmetic products.

CONCLUSION

Based on the available animal and clinical data included in this report and data from CIR Final Reports on chemically similar cosmetic ingredients/ingredient moieties (Propylene Glycol, Propylene Glycol Stearate, Propylene Glycol Stearate SE, Caprylic/Capric Triglyceride, Coconut Acid, Isostearic Acid, Lauric Acid, Myristic Acid, and Oleic Acid) that are referenced in the report discussion, the CIR Expert Panel concludes that Propylene Glycol Dicaprylate, Propylene Glycol Dicaprylate/Dicaprate, Propylene Glycol Dicocoate, Propylene Glycol Dipelargonate, Propylene Glycol Isostearate, Propylene Glycol Laurate, Propylene Glycol Myristate, Propylene Glycol Oleate, Propylene Glycol Oleate SE, Propylene Glycol Dioleate, Propylene Glycol Dicaprate, Propylene Glycol Diisostearate, and Propylene Glycol Dilaurate are safe as cosmetic ingredients in the present practices of use.

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