Final Report on the Safety Assessment of PEG-25 Propylene Glycol Stearate, PEG-75 Propylene Glycol Stearate, PEG-120 Propylene Glycol Stearate, PEG-10 Propylene Glycol, PEG-8 Propylene Glycol Cocoate, and PEG-55 Propylene Glycol Oleate[1]

The ingredients considered in this safety assessment are polyethylene glycol ethers of either propylene glycol itself, propylene glycol stearate, propylene glycol oleate, or propylene glycol cocoate. They function in cosmetic formulations as surfactant—cleansing agents; surfactant—solubilizing agents; surfactant—emulsifying agents; skin conditioning agents—humectant; skin-conditioning agents—emollient; and solvents. Those in current use are used in only a small number of cosmetic formulations. Some are not currently used. Polyethylene Glycol (PEG) Propylene Glycol Cocoates and PEG Propylene Glycol Oleates are produced by the esterification of polyoxyalkyl alcohols with lauric acid and oleic acid, respectively. Although there is no information available on the method of manufacture of the other polymers, information was available describing impurities, including ethylene oxide (maximum 1 ppm), 1,4-dioxane (maximum 5 ppm), polycyclic aromatic compounds (maximum 1 ppm), and heavy metals—lead, iron, cobalt, nickel, cadmium, and arsenic included (maximum 10 ppm combined). In an acute oral toxicity study, PEG-25 Propylene Glycol Stearate was not toxic. An antiperspirant product containing 2.0% PEG-25 Propylene Glycol Stearate was nonirritating to mildly irritating to the eyes of rabbits. This product was also practically nonirritating to the skin of rabbits in single-insult occlusive patch tests. In a guinea pig sensitization test, PEG-25 Propylene Glycol Stearate was classified as nonallergenic at challenge concentrations of 25% and 50% in petrolatum. PEG-25 Propylene Glycol Stearate and PEG-55 Propylene Glycol Oleate were negative in clinical patch tests. Based on the available data, it was concluded that these ingredients are safe as used (concentrations no greater than 10%) in cosmetic formulations. Based on evidence of sensitization and nephrotoxicity in burn patients treated with a PEG-based antimicrobial preparation, the ingredients included in this review should not be used on damaged skin.

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INTRODUCTION

The safety of PEG-25 Propylene Glycol Stearate, PEG-75 Propylene Glycol Stearate, PEG-120 Propylene Glycol Stearate, PEG-10 Propylene Glycol, PEG-8 Propylene Glycol Cocoate, and PEG-55 Propylene Glycol Oleate, as used in cosmetics, is reviewed in this report. Because there are limited data available with which to directly evaluate the safety of these ingredients, safety assessments on related ingredients/chemical moieties are included. Data from the following Cosmetic Ingredient Review (CIR) Final Reports are summarized in text: PEG-6 to -20M (Andersen 1993), Propylene Glycol and Polypropylene Glycol (Andersen 1994), Stearic Acid (Elder 1987), Coconut Oil and Related Ingredients (Elder 1986), PEGs-2 to -150 Stearate (Elder 1983), PEG-2 to -175 Distearates (Andersen 1999a), PEG-2 to -15 Cocamines (Andersen 1999b), Propylene Glycol Stearate and Stearate SE (Elder 1983), and Propylene Glycol Esters and Diesters, including Isostearate and Dicocoate (Andersen 1999c).

CHEMISTRY

Chemical and Physical Properties

PEG-25, -75, and -120 Propylene Glycol Stearates

PEG-25 Propylene Glycol Stearate, PEG-75 Propylene Glycol Stearate, and PEG-120 Propylene Glycol Stearate are polyethylene glycol (PEG) ethers of propylene glycol Stearate that conform generally to the formula (Wenninger, Canterbery, and McEwen 2000) shown in Figure 1.

For PEG-25, -75, and -120 Propylene Glycol Stearates, *n* in the preceding structure has an average value of 25, 75, and 120, respectively. Other names for PEG-25 Propylene Glycol Stearate include Polyethylene Glycol (25) Propylene Glycol Monostearate and Polyoxyethylene (25) Propylene Glycol Monostearate. This system of nomenclature is also applicable to PEG-75 and -120 Propylene Glycol Stearates (Wenninger, Canterbery, and McEwen 2000).

PEG-25 Propylene Glycol Stearate has been described as a cream-colored, unctuous paste (faint characteristic odor) that is soluble in water and ethanol. Specifications for this chemical

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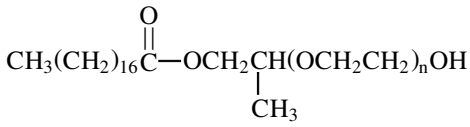

FIGURE 1
Formula for PEG-n Propylene Glycol Stearate.

include: hydroxyl value (35 to 55), acid value (2.0 maximum), saponification value (35 to 45), and moisture (3.0% maximum) (Nikitakis and McEwen 1990).

PEG-10 Propylene Glycol

PEG-10 Propylene Glycol is the PEG ether of propylene glycol that conforms generally to the formula shown in Figure 2 (Wenninger, Canterbery, and McEwen 2000).

In the formula shown in Figure 2, $x + y$ has an average value of 10. PEG-10 Propylene Glycol is also known as Polyethylene Glycol 500 Propylene Glycol and Polyoxyethylene (10) Propylene Glycol (Wenninger, Canterbery, and McEwen 2000).

PEG-8 Propylene Glycol Cocoate

PEG-8 Propylene Glycol Cocoate is the polyethylene glycol ether of propylene glycol cocoate that conforms generally to the formula shown in Figure 3 (Wenninger, Canterbery, and McEwen 2000).

In Figure 3, RCO– represents the coconut fatty moiety and n has an average value of 8. Other names for this chemical are Polyethylene Glycol 400 Propylene Glycol Cocoate and Polyoxyethylene (8) Propylene Glycol Cocoate (Wenninger, Canterbery, and McEwen 2000).

PEG-8 Propylene Glycol Cocoate has been described as a straw- to amber-colored, liquid (fatty odor) that is soluble in ethyl alcohol and fatty esters and dispersible in water. Specifications for this chemical include: specific gravity at 25°/25°C (1.025 to 1.035), acid value (5.0 maximum), and saponification value (87 to 97) (Nikitakis and McEwen 1990).

PEG-55 Propylene Glycol Oleate

PEG-55 Propylene Glycol Oleate is the polyethylene glycol ether of propylene glycol oleate. It conforms generally to the formula shown in Figure 4 (Wenninger, Canterbery, and McEwen 2000).

In the formula shown in Figure 4, n has an average value of 55. Other names for this chemical include Polyethylene Glycol (55) Propylene Glycol Oleate and Polyoxyethylene (55) Propylene Glycol Oleate (Wenninger, Canterbery, and McEwen 2000).

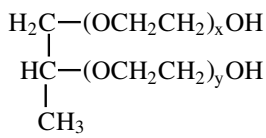

FIGURE 2
Formula for PEG-10 Propylene Glycol.

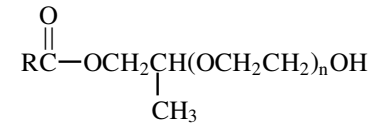

FIGURE 3
Formula for PEG-8 Propylene Glycol Cocoate.

Methods of Production

PEG-8 Propylene Glycol Cocoate

PEG-8 Propylene Glycol Cocoate is a specialty chemical that is prepared by esterification of polyoxyalkyl alcohols with lauric acid (Nikitakis and McEwen 1990).

PEG-55 Propylene Glycol Oleate

The method for the production of PEG-55 Propylene Glycol Oleate is described as a two-step process. In the first step, propylene glycol is ethoxylated with 55 moles of ethylene oxide, yielding a polyether. In the second step, the polyether is esterified with oleic acid. No solvents are involved in this process (Goldschmidt Chemical Corporation 1998).

Information on the methods of production of the following ingredients was not found in the published literature: PEG-25 Propylene Glycol Stearate, PEG-75 Propylene Glycol Stearate, PEG-120 Propylene Glycol Stearate, and PEG-10 Propylene Glycol.

Impurities

PEG-55 Propylene Glycol Oleate

Impurities data on PEG-55 Propylene Glycol Oleate are summarized as follows: oleic acid (maximum 5% *w/w*), ethylene oxide (maximum 1 ppm), dioxane (maximum 5 ppm), polycyclic aromatic compounds (maximum 1 ppm), and heavy metals—lead, iron, cobalt, nickel, cadmium, and arsenic included (maximum 10 ppm combined) (Goldschmidt Chemical Corporation 1998).

USE

Purpose in Cosmetics

PEG-25, -75, and -120 Propylene Glycol Stearates function as surfactant—cleansing agents and surfactant—solubilizing

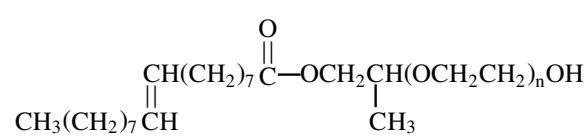

FIGURE 4
Formula for PEG-55 Propylene Glycol Oleate.

agents in cosmetics (Wenninger, Canterbery, and McEwen 2000).

PEG-10 Propylene Glycol functions as a skin-conditioning agent—humectant and solvent in cosmetic products (Wenninger, Canterbery, and McEwen 2000).

PEG-8 Propylene Glycol Cocoate functions as a skin-conditioning agent—emollient and as a surfactant—emulsifying agent in cosmetic products (Wenninger, Canterbery, and McEwen 2000).

PEG-55 Propylene Glycol Oleate functions as a surfactant—cleansing agent and a surfactant—solubilizing agent in cosmetics (Wenninger, Canterbery, and McEwen 2000).

Scope and Extent of Use in Cosmetics

Product formulation data submitted to the Food and Drug Administration (FDA) in 1998 indicated that PEG-25 Propylene Glycol Stearate was used in 10 cosmetic product formulations, and that PEG-8 Propylene Glycol Cocoate and PEG-55 Propylene Glycol Oleate were used in 1 and 18 formulations, respectively (Table 1). No uses were reported for PEG-75 Propylene Glycol Stearate, PEG-120 Propylene Glycol Stearate, or PEG-10 Propylene Glycol (FDA 1998).

Current concentration of use data for these ingredients used in the product categories listed in Table 1 were not available. However, other concentration of use data were available. One supplier indicated that PEG-55 Propylene Glycol Oleate is used in shampoos and body and bath cleanser products at concentrations ranging from 1% to 5%, and as a solubilizer in fragrances at concentrations ranging from 1% to 10% (Goldschmidt Chemical Corporation 1998). According to the results of a recent ingredient use survey, maximum use concentrations of PEG-8 Propylene Glycol Cocoate as a function of product category were as follows: eye shadow (0.6%), other eye makeup preparations (0.5%), and face powders (0.3%) (CTFA 1998).

For comparison purposes, historical product formulation data submitted to the FDA in 1984 indicated that the highest reported use concentration range for PEG-25 Propylene Glycol Stearate and PEG-8 Propylene Glycol Cocoate was 1% to 5% (FDA 1984). PEG-75 and -120 Propylene Glycol Stearates, PEG-10 Propylene Glycol, and PEG-55 Propylene Glycol Oleate were not included in the 1984 FDA database.

Cosmetic products containing PEG-25 Propylene Glycol Stearate, PEG-8 Propylene Glycol Cocoate, and PEG-55 Propylene Glycol Oleate are applied to most areas of the body, and could come in contact with ocular and nasal mucosae. These products could be used on a daily basis, and have the potential for being applied frequently over a period of several years.

International Use

None of the ingredients in this review is listed in the *Japanese Comprehensive Licensing Standards of Cosmetics by Category (CLS)* (Rempe and Santucci 1997). Additionally, the ingredients reviewed in this report are not included among the substances listed as prohibited from use in cosmetic products marketed in the European Union (European Economic Community 1995).

BIOLOGICAL PROPERTIES

Absorption, distribution, metabolism, and excretion data on the ingredients reviewed in this report were not found in the published literature.

TABLE 1
Product formulation data on PEG-25 Propylene Glycol Stearate, PEG-8 Propylene Glycol Cocoate, and PEG-55 Propylene Glycol Oleate (FDA 1998)

Product category	Total no. of formulations in category	Total no. containing ingredient
PEG-25 Propylene Glycol Stearate		
Tonics, dressings, and other hair-grooming aids	549	1
Other personal cleanliness products	291	6
Aftershave lotion	216	1
Other shaving preparation products	60	1
Body and hand (excluding shaving) skin care preparations	796	1
1998 totals for PEG-25 Propylene Glycol Stearate		**10**
PEG-8 Propylene Glycol Cocoate		
Tonics, dressings, and other hair-grooming aids	549	1
1998 totals for PEG-8 Propylene Glycol Cocoate		**1**
PEG-55 Propylene Glycol Oleate		
Shampoos (Noncoloring)	860	11
Personal cleanliness bath soaps and detergents	385	6
Other personal cleanliness products	291	1
1998 totals PEG-55 Propylene Glycol Oleate		**18**

ANIMAL TOXICOLOGY

Acute Oral Toxicity

PEG-25 Propylene Glycol Stearate

The acute oral toxicity of PEG-25 Propylene Glycol Stearate was evaluated using 10 male and 10 female fasted rats (strain and weights not stated). A single dose of the test substance (25.1 g/kg) was administered by gastric intubation. Depression, mucoid diarrhea, ruffed fur, pallor, and wet perineal area were noted during the observation period. Gross necropsy findings were as follows: hydronephrosis, congestion and slight edema of the lungs, gastrointestinal tract distended with gas and mucoid material, pale kidneys, and soft hearts. An LD_{50} of >25.1 g/kg (relatively harmless) was reported. The authors noted that because three female rats died within 24 hours, PEG-25 Propylene Glycol Stearate may be more toxic to female rats than to male rats (CTFA 1997).

Ocular Irritation

PEG-25 Propylene Glycol Stearate

The ocular irritation potential of undiluted PEG-25 Propylene Glycol Stearate was evaluated using nine rabbits. The test substance was instilled into the conjunctival sac of one eye of each rabbit; untreated eyes served as controls. Following instillation, the eyes of three and six rabbits were rinsed and not rinsed, respectively. Ocular reactions were scored at 1, 24, 48, 72, 96, and 168 hours post instillation according to the Draize scale (0 to 110). Throughout the study, no irritation was observed in rinsed or unrinsed eyes. Undiluted PEG-25 Propylene Glycol Stearate was classified as nonirritating to the eyes of rabbits (CTFA 1997).

In another study, an antiperspirant product containing 2.0% PEG-25 Propylene Glycol Stearate was instilled into the eyes of six rabbits (single instillation, no ocular rinsing). Ocular reactions were scored on days 1, 2, 3, 4, and 7, and the total ocular irritation score each day was determined according to the Draize scale (0 to 110). Total Draize scores of 3 and 0 were reported on days 1 and 7, respectively. The antiperspirant product was classified as mildly irritating to the eyes of rabbits (CTFA 1981a).

Skin Irritation

PEG-25 Propylene Glycol Stearate

The skin irritation potential of an antiperspirant product containing 2.0% PEG-25 Propylene Glycol Stearate was evaluated in a single-insult occlusive patch test involving nine rabbits. Reactions were scored at 2 and 24 hours post application, and the primary irritation index (PII, maximum = 8) was calculated. The product was practically nonirritating to the skin of rabbits (PII = 0.33) (CTFA 1980a). The same product was also practically nonirritating to the skin (nine rabbits tested; PII = 0.06) when evaluated according to the same procedure in another test (CTFA 1980b).

Skin Sensitization

PEG-25 Propylene Glycol Stearate

The skin sensitization potential of PEG-25 Propylene Glycol Stearate was evaluated using the Magnusson-Kligman maximization test procedure. Twenty female guinea pigs were used (10 test, 10 controls). During induction, each test animal received intradermal injections of each of the following (two different sites [left and right upper back, respectively] per substance injected): 50% aqueous Freund's complete adjuvant, 5% PEG-25 Propylene Glycol Stearate in propylene glycol, and 5% PEG-25 Propylene Glycol Stearate in 50% Freund's complete adjuvant. Each control animal received induction injections of 50% aqueous Freund's complete adjuvant, propylene glycol, and 1:1 propylene glycol in 50% aqueous Freund's complete adjuvant according to the same procedure. At 1 week post induction, 50% PEG-25 Propylene Glycol Stearate (topical booster) was applied to test animals and petrolatum (topical booster) was applied to controls. Two weeks after booster application, all animals were challenged with 50% and 25% PEG-25 Propylene Glycol Stearate in petrolatum at designated test sites. All of the guinea pigs were shaved 3 hours before reactions were scored according to the following grading scale: 0 (no evidence of any effect) to 4 (severe—deep red erythema with vesiculation or weeping with or without edema). PEG-25 Propylene Glycol Stearate was nonallergenic (Avon Products, Inc. 1981).

Short-term, subchronic, or chronic toxicity studies, including carcinogenicity and reproductive and developmental toxicity studies, were not found in the published literature. Phototoxicity, photosensitization, and mutagenicity studies also were not found.

The information on reproductive and developmental toxicity summarized below relates to the PEG moiety in the ingredients under review.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Ethylene Glycol and Its Ethers

It is generally recognized that the PEG monomer, ethylene glycol, and certain of its monoalkyl ethers (e.g., methoxyethanol, a.k.a. ethylene glycol monomethyl ether) are reproductive and developmental toxins. The CIR Expert Panel undertook a separate, limited scope review of these compounds in order to assess the possibility that PEG-derived cosmetic ingredients could present similar concerns (Andersen 1999d). In summary, this report concluded that the ethylene glycol monoalkyl ethers are not themselves toxic, but rather that one or more alcohol or aldehyde dehydrogenase metabolites are toxic. From the available data, the report also concluded that the toxicity of the monoalkyl ethers is inversely proportional to the length of the alkyl chain (methyl is more toxic than ethyl than propyl than butyl, etc.).

PEG Propylene Glycols and PEG Propylene Glycol Stearates, Cocoates, and Oleates

No data were available on the reproductive or developmental toxicity of these ingredients.

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation

PEG-25 Propylene Glycol Stearate

The skin irritation potential of 10% aqueous PEG-25 Propylene Glycol Stearate was evaluated using 1 to 20 patients (exact number or ages not stated) with, or suspected of having, contact allergy to cosmetic products. Patch test (procedure not stated) results were negative (de Groot 1994).

In another study, the skin irritation potential of an antiperspirant product containing 2.0% PEG-25 Propylene Glycol Stearate was evaluated in a single-insult occlusive patch test involving 20 human subjects. The duration of patch application was not stated. An additional group of 20 subjects tested with a different antiperspirant product served as controls. Skin irritation reactions were scored according to the following grading scale: 0 (no evidence of any effect) to 4 (severe—deep red erythema with vesiculation or weeping with or without edema). The primary irritation index (PII) was then calculated. It was concluded that there were no significant differences in irritancy between test (PII = 0.03) and control (PII = 0.05) groups (CTFA 1981b).

PEG-55 Propylene Glycol Oleate

Negative patch-test results (procedure not stated) for 10% aqueous PEG-55 Propylene Glycol Oleate were also reported in another study in which 1 to 20 patients (exact number and ages not stated) that had, or were suspected of having contact allergy to cosmetic products were evaluated. No evidence of skin irritation was reported (de Groot 1994).

Skin Sensitization

PEG-25 Propylene Glycol Stearate

The skin sensitization potential of PEG-25 Propylene Glycol Stearate was evaluated using 50 human volunteers. A piece of absorbent cotton twill covered with the test substance was sealed onto the skin of each subject using an elastic adhesive patch. The patches remained in place for 72 hours, after which any reactions were evaluated. At 7 days post removal of the first patch, the test substance was reapplied (same site) according to the same procedure. Again, any reactions that resulted were evaluated at 72 hours post application. In all subjects, reactions were not observed following removal of the first or second patch. PEG-25 Propylene Glycol Stearate was classified as nonsensitizing (CTFA 1997).

Clinical studies on the phototoxicity or photosensitization potential of the ingredients reviewed in this report were not found in the published literature.

SUMMARIES OF PRIOR SAFETY ASSESSMENTS

As noted in the introduction, the CIR Expert Panel considered the available data in safety assessments of related ingredients/chemical moieties. Summaries of these are provided below, with the original Expert Panel discussion and conclusion.

PEG-6, -8, -32, -75, -150, -14M, and -20M

(Andersen 1993)

PEG-6, -8, -32, -75, -150, -14M, and -20M are polymers of ethylene oxide used as humectants, solvents, binders, emulsion stabilizers, and viscosity increasing agents in cosmetics. The physical and biological properties of the individual PEGs are dependent on their molecular weight. In metabolism studies with rats, rabbits, dogs, and humans, the lower molecular weight PEGs were absorbed by the digestive tract and excreted in the urine and feces. The greater molecular weight PEGs were absorbed more slowly or not at all.

PEGs are used in the pharmaceutical industry as vehicles for drugs and as ointment bases. Studies presented in this report indicate that PEGs are not inert materials, but could have anticonvulsant and tumor inhibition properties.

In general, PEGs have low oral and dermal toxicity. The greater molecular weight PEGs appear to be less toxic than the lower PEGs in oral studies. The PEGs were not irritating to the skin of rabbits or guinea pigs. PEG-75 was not a sensitizer. PEGs cause mild, transient ocular irritation in rabbits. Inhalation of aerosolized PEG-75 (20% w:w in water) at concentrations up to 1008 mg/m^3 caused little or no toxicity in rats. No adverse reproductive effects occurred during subchronic and chronic oral toxicity, studies of PEG-6-32 and PEG-75. PEG-8 was negative in the Chinese hamster ovary cell mutation test, the sister-chromatid exchange (SCE) test, and the unscheduled DNA synthesis assay. PEG-150 was not mutagenic in the mouse $TK^{+}/^{-} \rightarrow TK^{-}/^{-}$ forward mutation assay. The mutation index ranged from 0.8 to 2.3. PEG-8 was not carcinogenic when administered orally, intraperitoneally, or subcutaneously to various test animals.

Cases of systemic toxicity and contact dermatitis in burn patients were attributed to a PEG-based topical ointment. In clinical testing, PEG-6 and PEG-8 caused mild cases of immediate hypersensitivity. However, in other clinical tests, PEG-8 was not a sensitizer, and PEG-6-32 and PEG-75 were not sensitizers.

The CIR Expert Panel discussed their concerns about the evidence of sensitization and nephrotoxicity in burn patients treated with a PEG-based antimicrobial cream. PEG was considered the causative agent in both animal and human studies. However, no evidence of systemic toxicity or sensitization occurred in studies with intact skin. Because of this, the Expert Panel qualified their conclusion on the safety of the PEGs to state that cosmetic formulations containing PEGs should not be applied to damaged skin.

The Expert Panel also expressed concern regarding the possible presence of 1,4-dioxane and ethylene oxide as impurities. They stressed that the cosmetics industry should continue to use the necessary purification procedures to remove these impurities from the ingredient before blending it into cosmetic formulations.

In general, the Panel noted that the PEGs have a low order of oral and dermal toxicity. Lower molecular weight PEGs are minimally absorbed and higher molecular weight PEGs (PEG-75 and greater) are not absorbed through intact skin. The PEGs were minimally irritating to human skin, but were not sensitizers in animal and human studies when applied to intact skin. The available data indicated that the PEGs are not mutagenic or carcinogenic.

On the basis of the data presented in this report, the CIR Expert Panel concluded that PEG-6, -8, -32, -75, -150, -14M, and -20M are safe for use at the concentrations reflected in the Cosmetic Use section and in the product formulation safety test data included in this report. The Expert Panel recommends that cosmetic formulations containing these PEGs not be used on damaged skin.

Propylene Glycol and Polypropylene Glycols

(Andersen 1994)

Propylene Glycol (PG) is an aliphatic alcohol and Polypropylene Glycol is a polymer of Propylene Glycol and water. In cosmetics, PG is used as a skin conditioning agent—humectant, solvent, viscosity decreasing agent, and humectant. Polypropylene Glycols (PPGs) are used as miscellaneous skin-conditioning agents. Information on PG supplied to the Cosmetic, Toiletry, and Fragrance Association (CTFA) indicate that concentrations of use range between 3% and 5% in products manufactured by one company, although the intention to use PG in cosmetics at concentrations as high as 80% was noted.

In mammals, the major route of PG metabolism is to lactaldehyde and then lactate via hepatic alcohol and aldehyde dehydrogenases. When PG was administered intravenously to human subjects (patients), elimination from the body occurred in a dose-related manner. The results of animal studies on PPGs 425, 1025, and 2025 indicate that they are readily absorbed from the gastrointestinal (GI) tract and are excreted in the urine and feces.

The cytotoxicity of human natural killer cells was decreased significantly in an assay in which target cells (cultured K562 erythroleukemia cells) were incubated with 1% PG.

PG was relatively harmless ($LD_{50} = 21$ g/kg) in acute oral toxicity studies involving rats. Acute oral toxicity studies on PPGs of various molecular weights (300 to 3900 Da) have indicated LD_{50} values (rats) ranging from 0.5 to >40 g/kg. In acute dermal toxicity studies involving groups of five albino rabbits, doses of PPG 1025 (20 ml/kg) and PPG 2025 (20 ml/kg) did not cause death. Two of five rabbits dosed with 20 ml/kg PPG 425 and one of five dosed with 10 ml/kg PPG 425 died. In subchronic oral toxicity studies, PPG 2000 induced, at most, slight decreases in growth and body weight effects in rats. PPG 750 caused slight increases in liver and kidney weights in rats. Following the subchronic oral administration of PPG 750 to dogs, slight increases in liver and kidney weights were noted. In a subchronic dermal toxicity study (rabbits) PPG 2000 did not cause any adverse effects at doses of 1 ml/kg. Slight depression of growth was observed after the administration of 5 and 10 ml/kg doses. 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 were given 5% PG in drinking water for 5 to 9 months. The results of tests for hepatic and renal impairment were negative. However, cats fed diets containing PG had erythrocyte destruction at concentrations as low as 6%.

PG did not induce corneal damage in rabbits in the Draize test and was classified as a slight ocular irritant in another ocular irritation study. PPGs 425, 1025, and 2025 were classified as harmless agents in rabbits in another ocular irritation study; PPG 1200 induced slight, transient ocular irritation in an albino rabbit. 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. Single and repeated applications of PPG 425, PPG 1025, and PPG 2025 did not cause skin irritation in the rabbit. Repeated applications of PPG 1200 to rabbits caused mild reactions at abraded skin sites and no reactions at intact sites.

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). However, three fetuses with malformations were also noted among 1026 living fetuses from the untreated control group. In a continuous breeding reproduction study, no significant differences were found 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 minutes.

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 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 SCE assay involving human cultured fibroblasts and a cultured Chinese hamster cell line both with and without metabolic activation. Chromosomal aberrations were induced in Chinese hamster fibroblasts in another assay. PG 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 concentration 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. Neither skin irritation nor sensitization reactions were observed in 300 subjects who received continuous and repeated dermal applications of undiluted PPG 2000.

Because of the results of human irritation and sensitization tests, the CIR Expert Panel considered that establishing a concentration limit for PG was necessary. Both provocative and predictive test data were considered in the process of making the final determination.

In provocative tests, allergic reactions were observed in 2 of 880 (0.2%) eczema patients patch-tested with 2% aqueous PG, in 13 of 330 (4%) patients patch-tested with 10% PG, and in 21 of 851 (2.5%) atopic patients patch-tested with 5% PG. Thirty-three (3.9%) of the 851 atopic patients also had irritant/follicular reactions. Furthermore, in a study by the North American Contact Dermatitis Group, 29 cutaneous reactions were observed in a population of 399 patients with cosmetic-related dermatitis who were patch-tested with 10% aqueous PG. Patients with diseased skin can be at risk with respect to developing irritation/sensitization reactions to PG, even at low concentrations.

Predictive tests are considered more appropriate in establishing concentration limits that are based on skin irritation or sensitization data. In these tests, normal subjects were patch-tested with PG concentrations ranging from 1% to 100%. In one of the studies, skin irritation was observed when 100% PG was tested under occlusive patches, but was not observed in open patch tests. When 50% and 100% PG were tested under occlusive patches using 16 subjects, 100% PG induced three 1+ reactions and no reactions to 50% PG were observed. In other studies, 24 normal subjects patch-tested (closed patches) with 1%, 3%, 10%, and 30% PG had skin irritation reactions only when exposed to concentrations of 10% and 30%, and neither skin irritation nor sensitization was observed in 204 subjects patch-tested with 12% PG (under occlusive patches) in a cream vehicle. These studies indicate that in normal subjects, PG can be a skin irritant when tested under occlusive patches, and that the skin irritation potential of this ingredient can be concentration dependent.

On the basis of the data included in this report, the CIR Expert Panel concluded that Propylene Glycol and Polypropylene Glycols are safe for use in cosmetic products at concentrations up to 50.0%.

Oleic, Lauric, Palmitic, Myristic, and Stearic Acids

(Elder 1987)

Oleic, Lauric, Palmitic, Myristic, and Stearic Acids are fatty acids with hydrocarbon chains ranging in length from 12 to 18 carbons with a terminal carboxyl group. The saturated fatty acids, Lauric (12C), Palmitic (16C), Myristic (14C), and Stearic (18C) are liquids at standard temperature and pressure.

The fatty acids are obtained by the hydrolysis of animal fats and vegetable oils. Cosmetic grade fatty acids occur as mixtures of several fatty acids, the content varying with method of manufacture and source. Fatty acid preparations could include up to 1.5% unsaponifiable matter, glyceryl monoesters of fatty acids, and butylated hydroxytoluene. Gas chromatography is the predominant analytical method for fatty acid identification.

The fatty acids are primarily used as intermediates of fatty acid salts. These salts are used as emulsifiers, emollients, and lubricants in cosmetic creams, cakes, soaps, lotions, and pastes that are slightly alkaline, ranging in pH from 7.5 to 9.5. In product formulation data voluntarily filed in 1981 with FDA by the cosmetics industry, 424 products contained Oleic Acid, 22 contained Lauric Acid, 29 contained Palmitic Acid, 36 contained Myristic Acid, and 2465 contained Stearic Acid at concentrations ranging from 0.1% to 25%.

Fatty acids are absorbed, digested, and transported in animals and humans. Radioactivity from labeled fatty acids administered orally, intravenously, intraperitoneally, and intraduodenally has been found in various tissues and in blood and lymph. β-Oxidation of the fatty acids involves serial oxidation are reduction reactions yielding acetyl–coenzyme A (CoA). Although placental transfer of fatty acids has been documented in several species and fetal lipid metabolism has been studied, no studies on

the teratogenicity of Oleic, Lauric, Palmitic, Myristic, or Stearic Acids were found. High intake of dietary saturated fatty acids has been associated with the incidence of atherosclerosis and thrombosis.

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, and Stearic Acids were fed, at concentrations ranging from 5% to 50%, to rats. 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. Feeding of 15% dietary Oleic Acid to rats in a chronic study resulted in 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 to guinea pigs and rabbits resulted in mild erythema and slight induration.

Eighteen millimole percent 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 defined 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, at doses of 35% to 65% in vehicles (Stearic Acid only) and at 1% to 13% in cosmetic product formulations (other fatty acids), produced no to moderate erythema and slight, if any, edema in the skin of rabbits. Slight increases in irritation were observed in the short-term repeated 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 were observed to challenge patches. 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 ultraviolet A (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 (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 indicated 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 SCEs 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. Treatment of mice with repeated subcutaneous injections of 25 and 50 mg Lauric Acid was 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. Feeding of up to 50 g/kg/day dietary Stearic Acid to mice 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 repeat-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 the approximate 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 ($\sim<2\%$). 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 were contact lens wearers, 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.

Although there were few data available for Myristic Acid, the Expert Panel included it in this safety assessment due to its structural similarity with the other fatty acids of this group.

Applications of Lauric and Oleic Acids to the skin of rabbits resulted in follicular keratosis and/or formation of comedones. These effects were considered by members of the Expert Panel in their safety assessment of the fatty acids reviewed in this report. Overall, on the basis of available data from studies using animals and humans, the Expert Panel concluded that these fatty acids are safe in the present practices of use and concentration in cosmetics.

On the basis of available data from studies using animals and humans, the Expert Panel concluded that Oleic, Lauric, Palmitic, Myristic, and Stearic Acids are safe in the present practices of use and concentration in cosmetics.

Coconut Oil and Related Ingredients (Elder 1986)

Coconut Oil is obtained by pressing the dried fruit of the coconut. Typically, it is 90% saturated triglycerides and low in nonglyceride impurities. Polycyclic aromatic hydrocarbons and aflatoxins have been found as contaminants of copra and crude Coconut Oil. These impurities are removed by conventional refining processes. In cosmetic products, Coconut Oil is used as a cleanser, foaming agent, or stabilizer. The highest reported concentrations in cosmetic products were 25% to 50%.

Results of dietary studies suggest 95% to 98% of ingested Coconut Oil is absorbed. No specific data were available indicating the extent of percutaneous absorption of Coconut Oil. Coconut Oil was used as a saturated fat control for metabolism studies and caused slight increases in serum cholesterol concentrations. The longevity of experimental animals in metabolism studies was not affected by diets containing Coconut Oil.

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. In a chronic study in which mice were fed for a lifetime diets supplemented with 15% Hydrogenated Coconut Oil, no effects on lifespans of test animals were observed.

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. 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 suggested that the eye irritation potential of Coconut Oil and Hydrogenated Coconut Oil was low. Coconut Oil in Draize eye tests scored a maximum of 2/110, indicating minimal irritation. Hydrogenated Coconut Oil was assayed in 10 Draize eye tests. In nine tests, eye 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 fats 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 6-week repeat-insult predictive patch test. Lipstick containing 10% Hydrogenated Coconut Oil was tested using Schwartz-Peck prophetic patch procedures. No evidence of primary irritation was observed after a single patch application, and the results of re-tests performed 14 days later were negative for sensitization.

On the basis of the available information presented in this report, the CIR Expert Panel concluded that Coconut Oil, Coconut Acid, Hydrogenated Coconut Oil, and Hydrogenated Coconut Acid are safe for use as cosmetic ingredients.

PEG Stearates (Elder 1983)

The PEG Stearates are the PEG esters of stearic acid. The identifying number of each PEG Stearate corresponds to the average number of ethylene oxide monomers in the polyether chain. These nonionic surfactants are used mainly in cosmetic products as surfactants and emollients at concentrations up to 25%.

The PEG Stearates, whose average number of ethylene oxide monomers range from 2 to 150, were nonlethal to test animals at doses up to 10 g/kg. They gave evidence of only low-level skin irritation and minimal eye irritation when tested at 100% concentrations in experimental test animals. PEG-8, -40, and -100 Stearates produced no significant changes in growth, mortality rates, histopathologic observations, or hematologic values in long-term feeding studies. Multiple generation studies of PEG-8 and -40 Stearates were negative for effects on reproduction; a carcinogenic effect was not reported in these long-term studies.

In clinical studies, PEG-2, -8, -40, -50, and -100 Stearates were neither irritants nor sensitizers at concentrations of ≥25%. No evidence of phototoxicity or photosensitization was observed with PEG-2 or -8 Stearate, or a formulation containing 1% to 3% PEG-100 Stearate.

Although the clinical data on certain PEG Stearates were marginal, the Panel concluded that the total available data on all PEG Stearates were sufficient for a decision regarding the safety of the entire group. This is particularly true in areas of phototoxicity and photosensitivity. With increasing ethoxylation, the fatty acid components of Stearic Acid moiety have less potential to produce phototoxicity and photosensitivity in humans and animals. Because no phototoxicity or photosensitivity reactions occurred in subjects tested with PEG-2 Stearate and PEG-8 Stearate, the Panel concluded that it was reasonable to extrapolate these data to the higher molecular weight species (e.g., PEG-20, -32, -40, -50, -100, and -150 Stearates). The converse of this latter statement, that is, the extrapolation of high molecular weight species to lower molecular weight species, may or may not be true.

On the basis of the available information presented in this report, the Panel concluded that PEG-2, -6, -8, -12, -32, -40, -50, -100, and -150 Stearates are safe as cosmetic ingredients in the present practices of concentration and use.

PEG Distearates (Andersen 1999a)

PEG-2, -3, -4, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150, and -175 Distearates are the PEG diesters of stearic acid. These ingredients are surfactants that function as emulsifying, cleansing, and solubilizing agents in cosmetics. Product formulation data submitted to the FDA indicate that PEG-2, -3, -4, -6, -8, -12, -50, and -150 Distearates were in use, and that they were used in 283 cosmetic formulations.

Because few data on the PEG Distearates regarding metabolism, toxicity, mutagenicity, carcinogenicity, and clinical safety were available, this review presented data on the PEGs, Stearic Acid, Steareths, and the PEG Stearates separately, as these data were considered applicable to the safety evaluation of the PEG Distearates.

PEG Distearate absorption and metabolism data were not available. PEG absorption is related to molecular weight. Lower molecular weight PEGs are readily absorbed through damaged skin. Oral and intravenous studies on PEGs indicate that these substances are excreted, unchanged, in the urine and feces. In general, fatty acids (such as Stearic Acid) are readily absorbed and distributed to the tissues in humans. Fatty acids can traverse the placental barrier.

Toxicity data for the PEG Distearates were not available. The PEG Stearates and Steareths had low oral toxicity in acute, short-term, subchronic, and chronic studies. PEGs in general have a low oral and dermal toxicity; the larger molecular weight PEGs appear to be less toxic than the smaller PEGs in oral studies. The acute toxicity of cosmetic formulations containing up to 13% Stearic Acid was low. In subchronic and chronic feeding studies using rats the effects were more severe.

PEG Stearates were slightly irritating at undiluted concentrations in test animals. PEGs were nonirritating to the skin of rabbits and guinea pigs, and PEG-75 was not a sensitizer. Stearic Acid irritation ranged from moderate to no reaction. Cosmetic product formulations containing 1.0% Stearic Acid were weak, grade 1 sensitizers. Primary irritation and sensitization studies involving Stearic Acid and the PEG Stearates were negative. Minimal ocular irritation occurred in tests with the PEGs, Stearic Acid, Steareths, and PEG Stearates.

Although monoalkyl ethers of ethylene glycol are reproductive toxins and teratogenic agents, it was considered unlikely that the PEG Distearates would cause reproductive or developmental effects based on their structural characteristics. In subchronic and chronic feed studies, PEG-6-32 and PEG-75 did not induce adverse reproductive effects in rats. In a multigenerational study lasting 2 years, feed containing 10% to 20% PEG-8 Stearate or PEG-40 Stearate was fed to rats; the rats fed the diet had decreased offspring survival time, reproductive performance, and lactation efficiency, as well as increased offspring mortality. Neither PEG-8 Stearate nor PEG-40 Stearate at a dietary concentration of 5% affected reproductive success.

In mutagenicity studies, PEG-8 was negative in the Chinese hamster ovary cell mutation test and the SCE test. At concentrations up to 150 g/l, PEG-150 was not mutagenic in the mouse lymphoma forward mutation assay. Stearic acid was not mutagenic in the Ames test. PEG-8 was not carcinogenic when administered orally, intraperitoneally, or subcutaneously to rodents. A low incidence of carcinomas, sarcomas, and lymphomas was evident in mice receiving multiple subcutaneous injections of Stearic Acid.

In clinical studies, PEG-8 was a mild sensitizer and irritant. Contact dermatitis and systemic toxicity in burn patients were attributed to a PEG-based topical ointment. The Steareths, PEG Stearates, and Stearic Acid were not irritants, sensitizers, or phototoxins. Formulations containing Stearic Acid were not photosensitizing.

The CIR Expert Panel was concerned about the sensitization and toxicity potential of the PEG Distearates when applied to damaged skin. This concern arose because of positive patch tests and incidences of nephrotoxicity in burn patients treated with an antimicrobial cream that contained PEG-6, PEG-20, and PEG-75. PEG was the causative agent in both animal and human studies; no evidence of systemic toxicity or sensitization was found in studies with intact skin. The Expert Panel concluded that cosmetic formulations containing PEG should not, therefore, be used on damaged skin. Also of concern to the Expert Panel was the possible presence of 1,4-dioxane and ethylene oxide impurities. They stressed that the cosmetic industry should continue to use the necessary procedures to remove these impurities from the PEG Distearate ingredients before blending them into cosmetic formulations.

Based on particle size and cosmetic use concentrations, it was not considered likely that these ingredients, in formulation, are respirable. Thus, the Expert Panel had no concerns regarding the absence of inhalation toxicity data, and the Panel considers the PEG Distearates safe for use in aerosolized products.

As discussed earlier in this report, the possibility of reproductive and developmental effects was determined not to be of concern.

The CIR Expert Panel concluded that PEG-2, -3, -4, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150, and -175 Distearates are safe for use in cosmetic formulations under the present practices of use.

PEG Cocamines (Andersen 1999b)

PEG-2, -3, -5, -10, -15, and -20 Cocamines are the PEG ethers of the primary aliphatic amine derived from coconut oil. These ingredients are surfactants that function as emulsifying and solubilizing agents in cosmetics. Product formulation data submitted to the FDA in 1996 indicate that only PEG-2, -3, -15, and -20 Cocamines are in use, and that they are used in 86 cosmetic formulations.

Little data on the PEG Cocamines regarding metabolism, toxicity, mutagenicity, carcinogenicity, or clinical safety were available. Therefore, this report presented data on the PEGs and Coconut Oil separately, with the view that these data were applicable to the PEG Cocamine compounds.

PEG Cocamine absorption and metabolism data were not available. PEG absorption is related to whether the substance is a liquid or a solid. PEGs were readily absorbed through damaged skin. Oral and intravenous studies on the PEGs indicated that these substances were excreted unchanged in the urine and feces. Ingested Coconut Oil was almost entirely absorbed with no mortality.

The oral LD_{50} value of PEG-15 Cocamine in rats was 1.2 g/kg, and for PEG-2 Cocamine, values ranged from 0.75 to 1.3 g/kg. No systemic toxic effects occurred in rats following a 6-week dermal application study using 10% PEG-15 Cocamine. PEGs have low oral and dermal toxicity; generally, the greater molecular weight PEGs appear to be less toxic than the lighter PEGs in oral studies. Coconut Oil and Hydrogenated Coconut Oil are relatively nontoxic by ingestion.

PEG-2 Cocamine was classified as a moderate cutaneous irritant, and PEG-15 Cocamine was considered a mild irritant. PEGs were nonirritating to the skin of rabbits and guinea pigs, and PEG-75 was not a sensitizer. Coconut Oil was neither a skin irritant nor a sensitizer. PEG-2 Cocamine was considered an ocular irritant, and PEG-15 Cocamine caused corneal irritation.

In mutagenicity studies, PEG-15 Cocamine was negative. PEG-8 was negative in the Chinese hamster ovary cell mutation test and the SCE test. At concentrations up to 150 g/l, PEG-150 was not mutagenic in the mouse lymphoma forward mutation assay. PEG-8 was not carcinogenic when administered orally, intraperitoneally, or subcutaneously.

Although monoalkyl ethers of ethylene glycol are reproductive toxins and teratogenic agents, it was considered unlikely that the PEG Cocamine compounds would cause reproductive or teratogenic effects based on their structural characteristics. In subchronic and chronic feed studies, PEG-6-32 and PEG-75 did not induce reproductive effects in rats.

In clinical studies, PEG-8 was a mild sensitizer and irritant. Contact dermatitis and systemic toxicity in burn patients were attributed to a PEG-based topical ointment. Bar soaps containing 13% Coconut Oil, when tested using Draize procedures, produced minimal skin reactions.

The CIR Expert Panel was concerned about the sensitization potential of the PEG Cocamines (PEG-2, -3, -5, -10, -15, and -20 Cocamines) when applied to damaged skin for the same reasons that are stated in the first paragraph of the preceding section on PEG Distearates.

After considering the basic chemical structure of PEGs and the negative phototoxicity and photosensitization data on bar soaps containing Coconut Oil, the CIR Expert Panel concluded that it is unlikely that the PEG Cocamines are either photosensitizers or phototoxic agents.

Additional data, however, were considered necessary. 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 PEG-2, -3, -5, -10, -15, and -20 Cocamines were not sufficient for determining whether the ingredients, under relevant conditions of use, were either safe or unsafe. The Panel released an Insufficient Data Announcement on May 23, 1995, outlining the data needed to assess the safety of the PEG Cocamine compounds. Concentration of use data were received in response to the announcement. No other comments were received during the 90-day public comment period. Additional data needed to make a safety assessment are: (1) physical and chemical impurities, especially nitrosamines; (2) genotoxicity in a mammalian system; (3) 28-day dermal toxicity using PEG-2 Cocamine; and (4) dermal sensitization data on PEG-2 Cocamine.

The CIR Expert Panel concluded that the available data are insufficient to support the safety of PEG-2, -3, 5, -10, -15, and -20 Cocamines for use in cosmetic products.

Propylene Glycol Stearate and Stearate SE (Elder 1983)

Propylene Glycol Stearate (PGS) is a mixture of the mono- and diesters of triple-pressed stearic acid and propylene glycol. Propylene Glycol Stearate SE (PGS-SE) is a self-emulsifying grade of PGS that contains an additional 5% to 6% potassium stearate and 7% to 10% free stearic acid. They are used in a wide variety of cosmetic products at concentrations of up to 25% for PGS and up to 10% for PGS-SE (1979 data). PGS is also approved for a variety of pharmaceutical uses and is considered Generally Recognized as Safe (GRAS) for food use.

Studies with ^{14}C-PGS indicate that it is readily metabolized following ingestion. In rats, the acute oral LD_{50} was approximately 25.8 g/kg. The raw ingredient produced no significant dermal toxicity, skin irritation, or eye irritation in acute tests with rabbits. Subchronic animal studies produced no evidence of oral or dermal toxicity. In a chronic 6-month feeding study, no signs of toxicity were observed when a mixture containing 17% propylene glycol monostearate was incorporated at 10% into the diets of rats and dogs. Propylene Glycol monostearate was negative in in vitro microbial assays for mutagenicity.

Although 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 greater than 32 g/kg. The ingredient per se produced no significant skin or eye 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-hour 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. In several skin sensitization tests on product formulations containing 1.5% to 2.5% PGS, no evidence of sensitization reactions was observed 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.

From the available information, the Panel concluded that PGS and PGS-SE are safe as cosmetic ingredients in the present practices of use.

Propylene Glycol Esters and Diesters (Andersen 1999c)

The limited information on chemical properties 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 Dipelargonate 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 cosmetic 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 using 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 post application. Similar results were reported for a fourth subject patch-tested with a 95% ethanol: Propylene Glycol Dicaprylate/Dicaprate mixture (40:60).

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 13 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 1983); Caprylic/Capric Triglyceride (Elder 1980); Coconut Acid (Elder 1986); Isostearic Acid (Elder

1983); 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 1 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.

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.

SUMMARY

The PEG Propylene Glycol Ethers are polyethylene glycol ethers of either propylene glycol itself, propylene glycol stearate, propylene glycol oleate, or propylene glycol cocoate. They function as surfactant—cleansing agents; surfactant—solubilizing agents; surfactant—emulsifying agents; skin conditioning agents—humectant; skin conditioning agents—emollient; and solvents. They are used in only a small number of cosmetic formulations, and current concentration of use data are available only on PEG-55 Propylene Glycol Oleate and PEG-8 Propylene Glycol Cocoate. PEG-55 Propylene Glycol Oleate is used in shampoos and body and bath cleanser products at concentrations ranging from 1% to 5%, and in fragrances at concentrations ranging from 1% to 10%. Similarly, historical data suggest use concentrations of PEG-25 Propylene Glycol Stearate and PEG-8 Propylene Glycol Cocoate in the 1% to 5% range. Current maximum use concentrations of PEG-8 Propylene Glycol Cocoate are as follows: eye shadow (0.6%), other eye makeup preparations (0.5%), and face powders (0.3%).

Although PEG Propylene Glycol Cocoates and PEG Propylene Glycol Oleates are produced by the esterification of polyoxyalkyl alcohols with lauric acid and oleic acid, respectively, there is no information available on the method of manufacture of the other polymers. Impurities data (provided only on PEG-55 Propylene Glycol) are summarized as follows: oleic acid (maximum 5% *w/w*), ethylene oxide (maximum 1 ppm), dioxane (maximum 5 ppm), polycyclic aromatic compounds (maximum 1 ppm), and heavy metals—lead, iron, cobalt, nickel, cadmium, and arsenic included (maximum 10 ppm combined).

In an acute oral toxicity study, PEG-25 Propylene Glycol Stearate was classified as relatively harmless in rats (LD_{50} >25.1 g/kg).

An antiperspirant product containing 2.0% PEG-25 Propylene Glycol Stearate was classified as nonirritating to mildly irritating to the eyes of rabbits. This product was also classified as practically nonirritating to the skin of rabbits in single-insult occlusive patch tests. In a guinea pig sensitization test, PEG-25 Propylene Glycol Stearate was classified as nonallergenic at challenge concentrations of 25% and 50% in petrolatum.

Clinical test data on 10% aqueous PEG-25 Propylene Glycol Stearate and 10% aqueous PEG-55 Propylene Glycol Oleate were negative in at least one patient suspected of having an allergy to cosmetic products. In another study, no significant differences in irritancy were observed between 20 normal subjects patch-tested with an antiperspirant containing 2.0% PEG-25 Propylene Glycol Stearate and 20 control subjects patch-tested with a different antiperspirant. Negative results were also reported in a sensitization study in which 50 volunteers were patch-tested with PEG-25 Propylene Glycol Stearate.

DISCUSSION

Although there are extensive data on the several ingredients that serve as the building blocks for the PEGs Propylene Glycol

Ethers, the CIR Expert Panel expressed concern over the lack of information on the manufacturing processes by which the ethers are formed, in particular, the possibility that impurities that may be present in the final product are not identified. In response to these concerns, a chemical supplier provided the Panel with current method of manufacture, impurities, and use concentration data on PEG-55 Propylene Glycol Oleate. According to these data, PEG-55 Propylene Glycol Oleate is used at concentrations ranging from 1% to 10% in fragrances and 1% to 5% in shampoos and body and bath cleanser products, and the following impurities have been detected: oleic acid (maximum 5% *w/w*), ethylene oxide (maximum 1 ppm), dioxane (maximum 5 ppm), polycyclic aromatic compounds (maximum 1 ppm), and heavy metals—lead, iron, cobalt, nickel, cadmium, and arsenic included (maximum 10 ppm combined). The Panel has considered the presence of some of these impurities (ethylene oxide, 1,4-dioxane, lead, and arsenic) in its assessments on cosmetic ingredient safety and, in some instances, established limitations. In this case, the Panel determined that, given the low level of each impurity reported for PEG-55 Propylene Glycol Oleate and the low to moderate use concentrations of this ingredient in cosmetics, there is little or no concern about the toxicity of impurities in cosmetics resulting from the presence of PEG-55 Propylene Glycol Oleate, PEG-10 Propylene Glycol, or other PEG Propylene Glycol Ethers.

The Panel also reiterated its concern over the evidence of sensitization and nephrotoxicity in burn patients treated with a PEG-based antimicrobial, initially addressed in the discussion section of the Final Report on PEG-6, -8, -32, -75, -150, -14M, and -20 M and, thus, concludes that cosmetic formulations containing either of the PEG Propylene Glycol ethers included in this review should not be used on damaged skin.

Of the ingredients included in this review, reportedly, PEG-75 Propylene Glycol Stearate, PEG-120 Propylene Glycol Stearate, and PEG-10 Propylene Glycol, are not being used in cosmetics. The Panel expects that these ingredients would not be used at concentrations higher than those that are currently used.

CONCLUSION

Based on the available animal and clinical data included in this report, the CIR Expert Panel concludes that PEG-25 Propylene Glycol Stearate, PEG-75 Propylene Glycol Stearate, PEG-120 Propylene Glycol Stearate, PEG-10 Propylene Glycol, PEG-8 Propylene Glycol Cocoate, and PEG-55 Propylene Glycol Oleate are safe as used in cosmetic products.

REFERENCES

Andersen, F. A., ed. 1993. Final report on the safety assessment of PEG-6, PEG-8, PEG-32, PEG-75, PEG-150, PEG-14M, and PEG-20M. *J. Am. Coll. Toxicol.* 12:429–457.

Andersen, F. A., ed. 1994. Final report on the safety assessment of Propylene Glycol and Polypropylene Glycols. *J. Am. Coll. Toxicol.* 13:437–491.

Andersen, F. A., ed. 1999a. Final report on the safety assessment of PEG-2, -3, -4, -6, -8, -9, -12, -20, -32, -75, -120, -150, and -175 Distearate. *IJT* 18:51–59.

Andersen, F. A., ed. 1999b. Final report on the safety assessment of PEG-2, -3, -5, -10, -15, and -20 Cocamine. *IJT* 18:43–50.

Andersen, F. A., ed. 1999c. 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. *IJT* 18:35–52.

Andersen, F. A., ed. 1999d. Special report on the reproductive and developmental toxicity of Ethylene Glycol and its ethers. *IJT* 18:53–67.

Avon Products, Inc. 1981. Guinea pig allergy—Magnusson-Kligman maximization procedure (Study No. GPA-11-81). Unpublished data submitted by CTFA (7 pages).[2]

Cosmetic, Toiletry, and Fragrance Association (CTFA). 1980a. Primary skin irritation test on an antiperspirant containing 2.0% PEG-25 propylene glycol stearate. Unpublished data submitted by CTFA (1 page).[2]

CTFA. 1980b. Primary skin irritation test on an antiperspirant containing 2.0% PEG-25 propylene glycol stearate. Unpublished data submitted by CTFA (1 page).[2]

CTFA. 1981a. Eye irritation test on an antiperspirant containing 2.0% PEG-25 propylene glycol stearate. Unpublished data submitted by CTFA (1 page).[2]

CTFA. 1981b. Clinical testing report. Human patch test on an antiperspirant containing 2.0% PEG-25 propylene glycol stearate. Unpublished data submitted by CTFA (1 page).[2]

CTFA. 1997. Oral toxicity, eye irritation, and dermal sensitization studies on PEG-25 propylene glycol stearate. Unpublished data submitted by CTFA (2 pages).[2]

CTFA. 1998. Current concentration of use information. Unpublished data submitted by CTFA (14 pages).[2]

de Groot, A. C., ed. 1994. *Patch testing. Test concentrations and vehicles for 3700 chemicals*, 2nd ed., 207. New York: Elsevier.

Elder, R. L., ed. 1980. Final report of the safety assessment for Caprylic/Capric Triglyceride. *JEPT* 4:105–120.

Elder, R. L., ed. 1983. Final report on the safety assessment of Propylene Glycol Stearate and Propylene Glycol Stearate Self-Emulsifying. *J. Am. Coll. Toxicol.* 2:101–124.

Elder, R. L., ed. 1986a. Final report on the safety assessment of Coconut Oil, Coconut Acid, Hydrogenated Coconut Acid, and Hydrogenated Coconut Oil. *J. Am. Coll. Toxicol.* 5:103–121.

Elder, R. L., ed. 1986b. Final report on the safety assessment of PEG-2, -6, -8, -12, -20, -32, -40, -50, -100, and -150 Stearates. *J. Am. Coll. Toxicol.* 2: 17–34.

Elder, R. L., ed. 1987. Final report on the safety assessment of Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid. *J. Am. Coll. Toxicol.* 6:321–401.

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

Food and Drug Administration (FDA). 1984. Frequency and concentration of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

FDA. 1998. Frequency of use of cosmetic ingredients. *FDA databases*. Washington, DC: FDA.

Goldschmidt Chemical Corporation. 1998. Method of manufacture, impurities, and use concentration data on PEG-55 Propylene Glycol Oleate. Unpublished data submitted by CTFA (2 pages).[2]

Nikitakis, J. M., and G. N. McEwen, Jr., eds. 1990. *CTFA compendium of cosmetic ingredient composition—Descriptions II*. Washington, DC: CTFA.

Rempe, J. M., and L. G. Santucci, eds. 1997. *CTFA list of Japanese cosmetic ingredients*, 3rd ed. Washington, DC: CTFA.

Wenninger, J. A., R. C. Canterbery, and G. N. McEwen, Jr., eds. 2000. *International cosmetic ingredient dictionary and handbook*, 8th ed. Washington, DC: and CTFA.

[2]Available for review: Director, Cosmetic Ingredient Review 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.