Final Report on the Safety Assessment of PEG-7, -30, -40, -78, and -80 Glyceryl Cocoate[1]

PEGs Glyceryl Cocoate polymers are the polyethylene glycol ethers of glyceryl cocoate. They function as skin conditioning agents, emollients, surfactants, nonionic emulsifying agents, and solubilizing agents in cosmetic formulations. Only limited data on the safety of PEG-7 Glyceryl Cocoate were found, and no data were available on the higher molecular weight polymers in this group. Data from previous safety assessments of Polyethylene Glycol (PEG), and several fatty acids (Stearic Acid, Oleic Acid, Lauric Acid, Palmitic Acid, and Myristic Acid) were considered relevant and added to the review. PEG has low oral and dermal toxicity. The fatty acids have slight oral toxicity, but little or no dermal toxicity. Dermal application of PEG-7 Glyceryl Cocoate at a concentration of SO% did not produce irritation in mice and guinea pigs, but did produce slight irritation in rabbits. Intracutaneous injection of PEG-7 Glyceryl Cocoate at a concentration of 10% did not produce sensitization. This same concentration was not an ocular irritant in animal tests. PEG-7 Glyceryl Cocoate was not phototoxic at a concentration of SO%. Although monoalkyl ethers of ethylene glycol are reproductive and developmental toxins, given the methods of manufacture of PEG-7 Glyceryl Cocoate, there is no likelihood of such compounds being present as impurities. The structure of the PEGs Glyceryl Cocoate polymers is such that it is unlikely that they would cause reproductive or developmental effects. PEG did not produce reproductive toxicity in oral toxicity studies. Oleic Acid in feed at a concentration of 15% did impair reproductive capacity in female rats, but growth and general health were not affected. No data were available on genotoxicity or carcinogenicity of PEGs Glyceryl Cocoate. PEG was not genotoxic. The fatty acids were generally not genotoxic, but positive results were seen for Oleic Acid in one assay. Neither PEG nor the fatty acids were carcinogenic in animals tests. Of concern was the possible presence of 1,4-dioxane and ethylene oxide impurities. The importance of using the necessary purification procedures to remove these impurities was stressed. In clinical studies PEG-7 Glyceryl Cocoate was neither a dermal irritant nor a photosensitizer. The principal clinical finding related to PEGs is based on data in burn patients—PEGs were mild irritant/sensitizers and there was evidence of nephrotoxicity. No such effects were seen in animal studies on intact skin. Cosmetic manufacturers should adjust product formulations containing Polyethylene Glycol to minimize any untoward effects when products are used on damaged skin. In recognition that PEG-7 Glyceryl Cocoate can enhance the skin penetration of other chemicals, care should also be exercised in using these ingredients in products where the penetration of other ingredients is aconcern. Based on the limited data on PEGs Glyceryl Cocoate and on safety assessments of other related ingredients, it was concluded that PEG-7, -30, -40, -70, and -80 Glyceryl Cocoate are safe as used in rinse-off products and safe at concentrations up to 10% in leave-on products.

INTRODUCTION

The PEGs Glyceryl Cocoate polymers serve a variety of functions in cosmetic formulations. PEG-7 Glyceryl Cocoate serves as a skin-conditioning agent, emollient, surfactant, and nonionic emulsifying agent in cosmetic formulations. PEG-30, -40, -78, and -80 Glyceryl Cocoate function as surfactants-cleansing agents and solubilizing agents. Because there are limited data specifically on PEG-7 Glyceryl Cocoate, and no data are available on PEG-30-80 Glyceryl Cocoate, the data concerning the PEGs and the C 12-C 18 fatty acids have been summarized in this review as an additional basis for the assessment of safety of PEG-7 Glyceryl Cocoate. Note that the different chain length PEGs are formed by condensing ethylene oxide and water, with the average number of moles of ethylene oxide used corresponding to the number in the name.

Polyethylene Glycol, Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid have been reviewed previously by the Cosmetic Ingredient Review (CIR) Expert Panel and the Final Reports have been published. The following conclusions were made:

> 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 the Final Report. The Expert Panel recommends that cosmetic formulations containing these PEGs not be used on damaged skin (Andersen 1993).
>
> Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, and Stearic Acid are safe in present practices of use and concentration in cosmetics (Elder 1987).

CHEMISTRY

Definition and Structure

PEG-7 Glyceryl Cocoate (CAS Nos. 66105-29- 1; 6820 1-46-7 [generic]) is a polyethylene glycol ether of Glyceryl Cocoate (q. v.). It generally conforms to the formula shown in Figure 1. where RCO-represents the coconut oil–derived fatty acids and n has the average value of 7 (Wenninger and McEwen 1997). PEG-30, -40, -78, and -80 Glyceryl Cocoate (CAS No.68201-46-7; generic) conform to the same formula shown in Figure 1: again, n has an average value equal to the number in the name.

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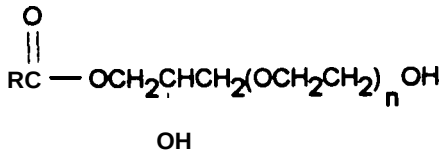

FIGURE 1
Chemical formula for PEGs Glyceryl Cocoate (Wenninger and McEwen 1997). RCO- represents the coconut oil-derived fatty acids and n has the average value corresponding to the PEG chain length.

Other names for PEG-7 Glyceryl Cocoate are Polyethylene Glycol (7) Glyceryl Monococoate Polyoxyethylene (7) Glyceryl Monococoate (Wenninger and McEwen 1997), Polyoxyethylated Glycerol Stearic Acid Ester (Provost, Herbots, and Kinget 1989), and Polyoxyethylene (7) Stearyl Partial Glyceride (Provost and Kinget 1988). This compound is also commonly known by the trade name Cetiol HE (Provost, Herbots, and Kinget 1988; Wenninger and McEwen 1997). Synonyms for PEGs Glyceryl Cocoate are Polyethylene Glycol (n) Glyceryl Monococoate, Polyethylene Glycol (n) Glyceryl Cocoate, and Polyoxyethylene (n) Glyceryl Cocoate. PEG-40 Glyceryl Cocoate is also known as Polyethylene Glycol 2000 Glyceryl Cocoate (Wenninger and McEwen 1997).

Physical and Chemical Properties

PEG-7 Glyceryl Cocoate is the partial ester of polyoxyethylated glycerol with stearic acid and has approximately seven ethylene oxide residues. It is a clear, pale yellow oil with a mild, fatty odor (Nikitakis and McEwen 1990). PEG-7 Glyceryl Cocoate has low viscosity (Henkel Corporation, 1996). PEG-7 Glyceryl Cocoate has a hydrophile-lipophile balance (HLB) value of 15 (Provost and Kinget 1988), indicating that the compound is water-dispersible or soluble (Balsam and Sagarin 1974). The HLB illustrates the simultaneous relative attraction of PEG-7 Glyceryl Cocoate for both water and oil. The compound forms spherical micelles in water when dispersed at concentrations at or above the critical micelle concentration. The micelles have a hydrophilic polar surface and lipophilic apolar center (Provost and Kinget 1988).

PEG-7 Glyceryl Cocoate is water and ethanol soluble, and is insoluble in mineral oil (Nikitakis and McEwen 1990). When PEG-7 Glyceryl Cocoate cools in water, hydrogen bonding between some of the water molecules and the ether oxygens of the oxyethylene groups occurs, resulting in hydration of PEG-7 Glyceryl Cocoate such that the bound water does not freeze (Provost 1989; Provost, Herbots, and Kinget 1990). The hydroxyl value for PEG-7 Glyceryl Cocoate is 172-187, and the saponification value 90-100. Iodine and acid values each have a maximum of 5.0 (Nikitakis and McEwen 1990). Table 1 is a summary of the compound's physical properties.

Analytical Methods

PEG-7 Glyceryl Cocoate can be determined by infrared spectroscopy (Nikitakis and McEwen 1990). When analyzed by differential scanning calorimetry, PEG-7 Glyceryl Cocoate undergoes a single, very broad, endothermal transition (Provost 1989; Provost, Herbots, and Kinget 1990) with an onset temperature of 0.7°C and a minimum temperature of −11.9°C (Provost, Herbots, and Kinget 1990).

Method of Manufacture

No information was available on the method of manufacture of PEGs Glyceryl Cocoate. PEGs are formed by condensing ethylene oxide and water, with the average number of moles of ethylene oxide polymerized indicated by the number in the name (Andersen 1993). Oleic, Stearic, Palmitic, Myristic, and Lauric Acids are generally produced by the hydrolysis of common animal and vegetable fats and oils, followed by fractionation of the resulting animal acids. Oleic Acid has been prepared from animal tallow and olive oil, and is a by product in the manufacture of Palmitic and Stearic Acids. Lauric Acid is commonly isolated from coconut oil. Palmitic Acid is produced by the hydrolysis and fractionation of palm oil, tallow oil, coconut oil, Japan Wax, Chinese vegetable tallow, and spermaceti. It is also a by-product in the manufacturing process for Stearic Acid. Myristic Acid is isolated from tall-oil fatty acids from 9-ketotetradecanoic acid,

TABLE 1
Physical properties of PEG-7 Glyceryl Cocoate

Property	Description	Reference
Physical	Clear; pale yellow oil; mild, fatty odor	Nikitakis and McEwen 1990
Solubility	Soluble in water and ethanol; insoluble in mineral oil	Nikitakis and McEwen 1990
Hydrophile-lipophile balance	15	Provost and Kinget 1988
Hydroxyl value	172-187	Nikitakis and McEwen 1990
Saponification value	90–100	Nikitakis and McEwen 1990
Acid value	Maximum of 5.0	Nikitakis and McEwen 1990
Iodine value	Maximum of 5.0	Nikitakis and McEwen 1990

by electrolysis of a methyl hydrogen adipate and decanoic acid mixture, by Maurer oxidation of myristanol or cetanol, or by the fractional distillation of hydrolyzed coconut oil, palm kernel oil, or coconut acids (Elder 1987).

Impurities

No information on the impurities that may be found in PEGs Glyceryl Cocoate is available. Silverstein et al. (1984) reported that PEG-6 may contain small amounts of monomer and dimers. The amounts were not quantified. Peroxides, formed as a result of autoxidation, are found in PEG-32 and PEG-75 (Hamburger, Azaz, and Donbrow 1975). The amount of peroxide in PEGs is dependent upon the molecular weight of the PEG and its age. The older the compound, the greater the concentration of peroxides. In a colorimetric assay used to determine the peroxide concentrations in several production lots of PEGs, PEG-6 and PEG-8 were each added to acidified potassium iodide solution, and the iodine liberated was titrated against a standard thiosulfate solution. PEG-6 had peroxide concentrations ranging from 1.4 to 9.3 μEq thiosulfate/ml glycol. PEG-8 had concentrations ranging from 3.24 to 5.7 μEq thiosulfate/ml glycol. The specific peroxides present in the PEGs were not determined, but they were thought to be organic peroxides rather than hydrogen peroxide (McGinity, Hill, and La Via 1975).

Ethoxylated surfactants may also contain 1,4-dioxane, a by-product of ethoxylation (Robinson and Ciurczak 1980). 1,4-Dioxane is a known animal carcinogen (Kociba et al. 1974; Hoch-Ligeti, Argus, and Arcos 1970; Argus, Arcos, and Hoch-Ligeti 1965). In the CIR safety assessment of the PEGs Stearate polymers, the cosmetic industry reported that it is aware that 1,4-dioxane may be an impurity in PEGs and, thus, uses additional purification steps to remove it from the ingredient before blending into cosmetic formulations (Elder 1983).

Fatty acids used in foods, drugs, and cosmetics normally exist as mixtures of several fatty acids, depending on the source and manufacturing process. The individual fatty acids predominate in the mixture, ranging from 74% (Oleic Acid) to 95% Myristic Acid. All contain varying amounts of unsaponifiable matter, and some grades contain glyceryl monoesters of fatty acids. Butylated hydroxytoluene may be added to all five fatty acid preparations as an antioxidant. In cosmetics containing unsaturated materials, the butylated hydroxytoluene concentration range is 0.01–0.1% (Elder 1987).

USE

Cosmetic

PEG-7 Glyceryl Cocoate serves as a skin-conditioning agent, emollient, surfactant. and emulsifying agent in cosmetic formulations. PEG-30 and -80 Glyceryl Cocoate function as surfactant-cleansing agents and solubilizing agents (Wenninger and McEwen 1997). In formulation data submitted to the Food and Drug Administration (FDA), PEG-7 Glyceryl Cocoate was listed as being in 173 cosmetic formulations (Table 2). PEG-30, -40, -78, and -80 Glyceryl Cocoate were used in 10, 5, 1, and 2 formulations, respectively (FDA 1996). Concentration of use data are no longer requested by FDA, but concentration of use data submitted by the cosmetic industry in 1984 stated that PEG-7 Glyceryl Cocoate was used at concentrations from 0.1 to 50% (FDA 1984). Recent data submitted by industry indicated that PEG-7 Glyceryl Cocoate was generally used in foam baths and shower baths to enhance moisturizing characteristics and that O.l-0.5% was typically used in cosmetic product formulations (Dewhirst Lorien Ltd. 1996). Two face cream formulations contained 0.03% PEG-7 Glyceryl Cocoate (Ivy Laboratories 1995), and one night cream contained 0.03% PEG-7 Glyceryl Cocoate (Cosmetic, Toiletry, and Fragrance Association [CTFA] 1996).

PEG-7 Glyceryl Cocoate serves as an emulsifier in transparent oil-water (TOW) gels (Provost and Kinget 1988; Provost 1989; Provost, Herbots, and Kinget 1990; De Vos, Vervoort, and Kinget 1993a) which function as vehicles for skin care preparations (Provost and Kinget 1988; Provost, Herbots, and Kinget 1990). Concentrations of up to 30% (w/w) PEG-7 Glyceryl Cocoate are used in the preparation of the gels (Provost and Kinget 1988), and the compound is essential for the incorporation of oil into the gel structure (Provost and Kinget 1988; Provost 1989). The presence of the emulsifier allows TOW gels to retain their transparency, even when containing a relatively large amount of oil (Provost 1989).

International

PEG-7 Glyceryl Cocoate is listed in the ***Comprehensive Licensing Standards*** of ***Cosmetics by Category*** (CLS) and must conform to the standards of the ***Japanese Cosmetic Ingredient Codex*** (JCIC) (Yakuji Nippo, Ltd. 1994). It can be used without restriction in all CLS categories except eyeliners, lipsticks and lip creams, and dentifrices.

Noncosmetic

TOW gels serve as vehicles for topical treatment of dermatological diseases using pharmaceutical preparations (Provost and Kinget 1988). TOW gels formed using PEG-7 Glyceryl Cocoate release both hydro- and lipophilic drugs at a relatively high rate and enable them to penetrate isolated human epidermis at rates similar to those from other dermatological vehicles (Provost 1989). TOW gels containing PEG-7 Glyceryl Cocoate adhere to mucosae, wet wounds, and other hydrophilic supports (Provost, Herbots, and Kinget 1988). Nonionic surfactants (such as PEG-7 Glyceryl Cocoate) act as penetration enhancers, conditioning the stratum comeum to enable and promote drug diffusion by reversibly inserting into the lipid structure, thereby disrupting lipid packing, and lowering the transition temperature of human stratum comeum (De Vos, Vervoort and Kinget 1993b).

BIOLOGICAL PROPERTIES

Absorption, Metabolism, and Distribution

Gastrointestinal absorption of PEGs is dependent on the molecular weight of the compound. In general, the greater the

TABLE 2
Product formulation data (FDA 1996)

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
PEG-7 Glyceryl Cocoate		
Baby shampoos	23	1
Other baby products	37	2
Bath oils, tablets, salts	147	5
Bubble baths	211	8
Other bath preparations	166	6
Eye makeup remover	95	1
Other eye makeup preparations	136	1
Hair conditioners (noncoloring)	715	1
Shampoos (noncoloring)	972	22
Tonics, dressings, and other hair grooming aids	604	1
Hair dyes and colors	1612	58
Bath soaps and detergents	372	6
Douches	19	1
Other personal cleanliness products	339	10
Aftershave lotion	268	3
Other shaving preparations products	63	2
Cleansing	820	13
Face and neck (excluding shaving)	300	4
Body and hand (excluding shaving)	1012	7
Moisturizing	942	2
Paste masks (mud packs)	300	3
Skin fresheners	244	2
Other skin care preparations	810	11
Suntan gels, creams, and liquids	196	2
Other suntan preparations	68	1
1996 total		**173**
PEG-30 Glyceryl Cocoate		
Other baby products	37	1
Other eye makeup preparations	136	1
Hair straighteners	50	1
Permanent waves	434	2
Shampoos (noncoloring)	972	4
Cleansing	820	1
1996 totals		**10**
PEG-40 Glyceryl Cocoate		
Bath oils, tablets, and salts	147	1
Bubble baths	211	1
Eye makeup remover	95	2
Cleansing	820	1
1996 total		**5**
PEG-78 Glyceryl Cocoate		
Cleansing	820	1
1996 total		**1**
PEG-SO Glyceryl Cocoate		
Shampoos (noncoloring)	972	2
1996 total		2

molecular weight of the PEG compound, the lesser the absorption that occurs. In both oral and intravenous studies, no metabolism was observed and the PEGs were rapidly eliminated unchanged in the urine and feces. In a study with human bum patients, monomeric ethylene glycol was isolated in the serum following topical exposure to a PEG-based antimicrobial cream, indicating that PEGs are readily absorbed through damaged skin (Andersen 1993).

Increasing fatty acid chain length slighly decreased the digestibility of fatty acids. Stearic Acid was the most poorly absorbed of the common fatty acids. Dietary fatty acids are absorbed in micellar aggregates and transported esterified to glycerol in chylomicrons and very low density lipoproteins. Oleic, Palmitic, Myristic, and Stearic Acids are primarily transported via the lymphatic system. Lauric Acid is transported by the lymphatic and (as a free fatty acid) portal systems. Fatty acids originating from the adipose tissue stores are either bound to serum albumin or remain unesterified in the blood. Oleic Acid has been reported to penetrate the skin of rats. Within 10 min of topical application, fluorescence from absorbed Oleic Acid was found in the epidermal cell layers of skin removed from treated rats. The path of penetration was suggested to be via the hair follicles. Minute amounts of Oleic Acid were visualized in the blood vessels. Skin permeability increased with the lipophilic nature of the compound. Radioactivity was present in the heart, liver, lungs, spleen, kidneys, muscles, intestine, adrenal glands, blood, lymph, and adipose, mucosal, and dental tissues after administration of radioactive Oleic, Palmitic, and Stearic acids. Uptake and transport of fatty acids into the brain have been observed. Free fatty acids readily cross the placental barrier in rabbits, guinea pigs, rats, and humans. Fatty acids taken up by tissues are either stored as triglycerides or oxidized for energy via #?-oxidation and tricarboxylic acid cycle pathways (Elder 1987).

ANIMAL TOXICOLOGY

Acute Toxicity

Rats were given PEG-7 Glyceryl Cocoate by gavage and 10 rats were tested. Administration of 19.9 mg/kg did not produce signs of toxicity (Henkel Corporation 1996).

Results of toxicity studies with rats, rabbits, and dogs indicate that PEGs have low oral and dermal toxicity. In general, the higher molecular weight PEGs appear to be less toxic than the lower molecular weight PEGs in oral studies. Acute oral LD50s for PEGs in rabbits were 17.3 g/kg (100% PEG-6) and 76 g/kg (100% PEG-75). In acute dermal toxicity studies, no deaths were reported in groups of rabbits dosed with undiluted PEG-6 (20 ml/kg) or 40% PEG-20M (20 ml/kg) (Andersen 1993).

Oleic, Lauric, Palmitic, Myristic, and Stearic Acids had slight acute oral toxicity in rats given 15-19 g/kg doses or cosmetic formulations containing the acids. In studies using albino rats, the acute oral LD50 of Oleic Acid was >2 1.5 ml/kg; the LD50 of both Palmitic Acid and Myristic Acid was > 10.0 g/kg. Little or no apparent toxicity was produced by topical application of Oleic, Palmitic, and Stearic Acid to the skin of rabbits, mice, or guinea pigs (Elder 1987).

Short-Term Toxicity

No evidence of toxicity was observed in a group of rabbits that received daily topical applications of PEG-20M (0.8 g/kg/day) for 30 days, with the exception of transient, mild erythema. The only evidence of systemic toxicity that resulted from dermal exposure was renal failure in rabbits that received repeated applications of an antimicrobial cream containing 63% PEG-6, 5% PEG-20, and 32% PEG-75 to excised skin sites for 7 days (Andersen 1993).

Chicks given 5% Oleic Acid or 50% Stearic Acid in feed for 4 weeks had no adverse effects. Rats given high-fat diets containing 5% Stearic Acid had decreased clotting time, moderate hyperlipemia, and severe phlebothrombosis following initiation by an intravenous injection of ***Salmonella*** *typhosa* lipopolysaccharide. Hyperlipemia was observed in rats fed diets containing 4.6 g/kg/day Palmitic Acid for 6 weeks. A microscopic "foreign body reaction" was observed in adipose tissue in rats given 50% Stearic Acid in feed for 8 weeks. In a 9-week study, rats given high-fat diets (6% Stearic Acid) had severe aortic atherosclerosis and thrombosis after induction by *S. typhosa* lipopolysaccharide; high mortality was observed. In short-term dermal studies using mice and rabbits, Oleic Acid, Lauric Acid, Palmitic Acid, and Myristic Acid (concentrations up to 30%) caused transient erythema, desquamation, follicular keratosis, follicular epidermal hyperplasia, or slight irritation. Stearic Acid at concentrations of 20–50% caused slight edema and desquamation (Elder 1987).

Subchronic Toxicity

In subchronic, 90-day oral toxicity studies using groups of albino rats, the largest (PEG-20M) and smallest (PEG-6) molecular weight PEGs tested neither induced toxicity nor death when administered daily at concentrations of 4% or less; PEG-20M was administered in the diet and PEG-6 in drinking water. In a dermal toxicity study, no evidence of toxicity was observed in a group of rabbits that received daily applications of PEG-6 5 days per week (2 ml/kg/day) for 18 weeks (Andersen 1993).

In a 24-week study using rats, a "foreign body reaction" was observed in the perigonadal fat and the reversible formation of lipogranulomas was observed following the administration of 50 g/kg/day of Stearic Acid in feed. Anorexia, severe pulmonary infection, and high mortality were observed in rats given diets containing 3000 ppm Stearic Acid for 30 weeks (Elder 1987).

Chronic Toxicity

Toxic effects also were not observed in groups of dogs that received PEG-8, PEG -32, and PEG-75 at concentrations of 2% in the diet for 1 year (Andersen 1993).

Dermal Irritation and Sensitization

Kastner (1977) compared the topical irritancy potential of fatty or fat-derived cosmetic ingredients, including 50% PEG-7

Glyceryl Cocoate (in Vaseline) on the skin of various animals (four per group) in 24-hour skin patch tests. Patches were applied to the shaved backs of adult male New Zealand White rabbits, male Pirbright White guinea pigs (average weight 300 g), and male and female adult mutant hairless mice. Porous leucoplastic fixed the patches to the guinea pigs and hairless mice. All test sites were observed at 24 hours (when the patches were removed) and 48 hours. Any reactions were then rated and placed into reaction classes 1–5, with 5 having the highest skin irritation potential. Rabbits had the greatest sensitivity to PEG-7 Glyceryl Cocoate, with a class 3 reaction (slight, with the resulting rash fading). Guinea pigs and hairless mice failed to react to PEG-7 Glyceryl Cocoate, and were classified in the lowest reaction group.

PEG-7 Glyceryl Cocoate was applied to the intact and abraded skin of three albino rabbits in a Draize primary irritation test. The test material caused moderate erythema and mild edema. The primary irritation index was 1.66, and PEG-7 Glyceryl Cocoate was classified as a mild dermal irritant. In a second study, PEG-7 Glyceryl Cocoate was applied to the clipped skin of two rabbits. The test sites were rinsed after 1 hour and scored at 24 hours and 48 hours. Directly after removal of PEG-7 Glyceryl Cocoate, the treated skin sites had slight reddening that could not be seen after 24 hours (Kastner 1977).

A 10% solution of PEG-7 Glyceryl Cocoate was given to five male Pirbright White W58 guinea pigs by 10 intracutaneous injections into the paravertebral depilated skin at intervals of two days. The test volume of each injection was 0.1 ml. A challenge injection (10% concentration, 0.1 ml test volume) was given 14 days after the last induction injection. Guinea pigs given PEG-7 Glyceryl Cocoate had sharply demarcated necrotic changes of the skin (about the size of a pea), but no general signs. These changes subsided during the 14-day interval. Body weight gain of the treated animals was comparable to controls. No other reactions were noted at the sites of the necrotic foci. No evidence of sensitization was observed (Henkel Corp. 1996).

The PEGs were not irritating to the skin of rabbits or guinea pigs, and PEG-75 was not a sensitizer. In skin irritation tests, undiluted PEG-6 was applied to the skin of rabbits for 4 hours and 50% PEG-75 was applied to guinea pigs for 4 days and to rabbits over a 13-week period. In the guinea pig skin sensitization test, PEG-75 was tested at a concentration of 0.1% (Andersen 1993).

Various concentrations of Oleic Acid, Stearic Acid, Palmitic Acid, Myristic Acid, and Lauric Acid produced minimal to mild erythema in primary skin irritation studies using rabbits, but were mainly nonirritating. Cosmetic formulations containing Stearic Acid and Oleic Acid were not sensitizing to female Hartley guinea pigs when tested at concentrations of 5.08% (Oleic Acid), and 3.5% and 1.0% (Stearic Acid) (Elder 1987).

Ocular Irritation

PEG-7 Glyceryl Cocoate at a concentration of 10% (aqueous) did not produce ocular irritation when instilled into the conjunctival sac of two rabbits (Henkel Corp. 1996).

PEGs-6 and -75 did not cause cornea1 injuries when instilled (undiluted, 0.5 ml) into the conjunctival sac of rabbits. PEG-8 (35% solution, 0.1 ml) and PEG-32 (melted in water bath, 0.1 ml) induced mild ocular irritation in rabbits (Andersen 1993).

Oleic Acid, Stearic Acid, Lauric Acid, Palmitic Acid, and Myristic Acid were nonirritating to the eyes of rabbits in ocular irritation studies using Draize procedures (Elder 1987).

Phototoxicity

PEG-7 Glyceryl Cocoate at a concentration of 50% was coated onto the dorsal skin of hairless mice (five per group). Treated skin sites were exposed to ultraviolet (UV) radiation in a single 30-minute session; the mice were kept 50 cm from the UV lamp during exposure. Control A received the vehicle (olive oil) and control B did not receive either the test material or the vehicle prior to UV exposure. The mice were examined at 6, 24, 30, 48, and 96 hours after exposure. No local or general signs of phototoxicity were observed during the study. Measurements of skin thickness indicated that all mice had swelling that peaked at 30 hours after exposure and subsided by 66 hours. No differences in swelling or skin thickness were observed in treated mice compared to controls (Henkel Corp. 1996).

Photosensitization

Cosmetic formulations containing 2.8% Stearic Acid were not photosensitizing when tested using male Hartley guinea pigs. The concentrations of the product formulations tested ranged from 25–100% (in water) (Elder 1987).

Comedogenicity

The comedogenicity of UVA-irradiated and nonirradiated Oleic Acid at a concentration of 99% was evaluated using Japanese and New Zealand White rabbits. After 18 hours of irradiation, a significant increase in lipid peroxide level of Oleic Acid was observed. A test volume of 2 ml of the irradiated Oleic Acid was applied topically to the ventral surface of one ear per rabbit each day for 2 weeks. An equal volume of nonirradiated Oleic Acid was applied to the other ear. Both Oleic Acid and its peroxides induced fairly large cornedones. The lipid peroxide concentration was positively correlated with the degree of comedone formation (Elder 1987).

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 (CIR 1996). In summary, it was concluded that the ethylene glycol monoalkyl ethers are not toxic.

but rather, that one or more alcohol or aldehyde dehydrogenase metabolites are toxic. From the available data, it was 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.).

The PEGs Glyceryl Cocoate polymers, however, are the partial esters of polyoxyethylated glycerol with stearic acid, and as such, are chemically different from the alkyl ethers. Thus, the Panel concluded no reproductive or developmental hazard is posed by these compounds.

Polyethylene Glycol

No adverse reproductive effects occurred during subchronic (90 days) and chronic (2 years) oral toxicity studies of PEG-6-32 and PEG-75. In the subchronic study, PEG-75 was tested at a dose of 0.23 g/kg/day. In the chronic study, PEG-75 was tested at doses up to 0.062 g/kg/day and, PEG-6-32, at doses up to 1.69 g/kg/day (Andersen 1993).

Fatty Acids

No adverse effects on growth or general health were observed in rats given 15% Oleic Acid in feed for 10–16 weeks; however, reproductive capacity of treated female rats was impaired (Elder 1987).

MUTAGENICITY

PEG-8 was negative in the Chinese hamster ovary cell mutation test and the sister chromatid exchange test; the maximum test concentration in both studies was 1%. In the unscheduled DNA synthesis assay, a statistically significant increase in radioactive thymidine incorporation into rat hepatocyte nuclei was noted only at the highest concentration tested (0.1% PEG-8). PEG-150 was not mutagenic in the mouse lymphoma forward mutation assay when tested at concentrations up to 150 g/l (Andersen 1993).

Oleic Acid (100–500 μg/ml), Lauric Acid (1 O-200 @g/ml), and Stearic Acid (up to 500 μg/ml) did not induce mitotic aneuploidy and crossing over of chromosomes in the D_6 strain of ***Saccharomyces cerevisiae.*** Stearic Acid was nonmutagenic in ***Salmonella typhimurium*** strains TA98, TA100, TA1535, TA1537, and TA1538, with or without metabolic activation. Concentrations of Oleic Acid from 2.5-10.0 μg/ml induced higher incidences of aneuploidy and tetraploidy in a genotoxicity assay using V79 Chinese hamster lung fibroblasts, compared to controls. The mean number of sister chromatid exchanges per metaphase was similar to controls. Oleic, Lauric, Stearic, and Palmitic Acids inhibited the mutagenicity of several compounds (e.g., N-nitrosodialkylamines) in modified Ames tests using ***Escherichia*** *coli* and ***S. typhimurium*** (Elder 1987).

CARCINOGENICITY

All of the carcinogenicity data available on the PEGs was specifically on PEG-8, which was used as a solvent control for a number of studies. PEG-8 was not carcinogenic when administered orally to mice (30 weeks of dosing), intraperitoneally to rats (6 months of dosing), subcutaneously (20 weeks of dosing to rats; 1 year of dosing to mice), or when injected into the gastric antrum of guinea pigs over a period of 6 months (Andersen 1993).

No malignant tumors were induced by repeated subcutaneous injections of l-16.5 mg Oleic Acid per injection using female BALB/c or Swiss-Webster mice. Repeated subcutaneous injections of Lauric Acid (25-50 mg/injection), Palmitic Acid (25-50 mg/injection), or Stearic Acid (up to 82 mg/injection) did not increase the incidence of carcinomas, sarcomas, and lymphomas in mice. In oral studies, mice fed a diet containing up to 200 mg of Oleic Acid had intestinal and gastric tumors, and feeding of up to 50 g/kg/day of Stearic Acid was noncarcinogenic (Elder 1987).

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation and Sensitization

Kastner (1977) applied patches containing 50% PEG-7 Glyceryl Cocoate to the upper arms of four volunteers for 24 hours. Test sites were evaluated at patch removal and at 24 hours later. Any reactions were rated and placed into reaction classes l-5, with 5 having the greatest skin irritation potential. The subjects failed to react to 50% PEG-7 Glyceryl Cocoate and were classified in the lowest reaction group.

No evidence of dermal irritation was observed after PEG-7 Glyceryl Cocoate was applied (concentration not given) with a test plaster to the forearms of five subjects for 1 hour. In another study, undiluted PEG-7 Glyceryl Cocoate was applied to 40 volunteers in a primary irritation patch test. No skin irritation was observed (Henkel Corp. 1996).

In clinical studies, PEG-6 and PEG-8 induced mild sensitization in 9% and 4% of 23 male subjects tested, respectively. However, later production lots of PEG-6, as well as PEG-75, did not cause reactions in any of the 100 male and 100 female subjects tested. A product formulation containing 3% PEG-8 induced minimal to mild irritation (induction phase) in over 75% of 90 volunteers participating in a skin irritation and sensitization study. Responses (not classified) were noted in 22 subjects at the 24 hours challenge reading. Cases of systemic toxicity and contact dermatitis in bum patients were attributed to PEG-based topical ointments. The ointment that induced systemic toxicity contained 63% PEG-6, 5% PEG-20, and 32% PEG-75 (Andersen 1993).

Oleic, Myristic, and Stearic Acids at concentrations of 100% or 40–50% in mineral oil were nonirritating in primary and cumulative dermal irritation studies. Mild to intense erythema was observed in single insult occlusive patch tests, soap chamber tests, and 21-day cumulative irritation studies that tested cosmetic formulations containing 2-93% Oleic, Palmitic, Myristic, or Stearic Acid. These results were generally not related to the fatty acid concentration in the formulations, however.

Formulations containing up to 13% Oleic, Lauric, Palmitic, or Stearic Acid were not sensitizing (Elder 1987).

Ocular Irritation

Mascara formulations containing 2-3% Oleic Acid did not produce ocular irritation in two 3-week exaggerated use studies (Elder 1987).

Photosensitization

The photosensitization of a SPF 15 facial cream containing 0.03% PEG-7 Glyceryl Cocoate was determined using 28 adult volunteers. The minimal erythema dose (MED) of each subject was determined by exposing one side of the midback (1 -cm-diameter circular exposure areas) to a series of exposures in 25% increments from a 150-watt xenon arc solar simulator. Each volunteer then underwent the induction phase of testing. The facial cream was applied as an 80 mg dose to a 2 x 2–cm skin site on the lower back. The sites were covered with 2 x 2–cm squares of nonabsorbing cotton cloth, which was fastened to the skin with overlapping strips of occlusive tape. The patches were removed after 24 hours. The test sites were exposed to three MEDs from the xenon arc solar simulator. The sites were left uncovered for 48 hours, and the patches were reapplied for 24 hours to the same sites under an occlusive dressing. The patches were removed and the skin sites were exposed to an additional three MEDs. This procedure was repeated twice weekly for 3 weeks. Ten to 14 days after the last induction exposure, the volunteers received a single challenge exposure. The facial cream was applied (80 mg) in duplicate to untreated 2 x 2–cm skin sites on the opposite side of the lower back. The sites were covered with an occlusive dressing for 24 hours. One set of patches was removed, and each site was irradiated with 4 J/cm^2 of UVA, obtained by filtering the exit beam from the solar simulator to eliminate UVB wavelengths. The duplicate set of patches was unirradiated and served as control unexposed treated sites. All test sites were examined for photosensitization reactions at 48 hours and 72 hours. Of the 28 volunteers, two were dropped from the study for reasons unrelated to the test procedure. The only reactions observed during induction included mild erythema, desquamation, and tanning; these reactions were attributed to the repeated exposures to three MEDs. No signs of photosensitization were observed following challenge in any of the 26 test subjects (Ivy Laboratories 1995).

A second facial cream (SPF 15) containing 0.3% PEG-7 Glyceryl Cocoate was tested using the same procedures. Thirty-one subjects participated in the study; six withdrew from the study during induction. Mild erythema, desquamation, and tanning occurred during induction, and no signs of photosensitization were observed during challenge (Ivy Laboratories 1996).

Formulations containing up to 13% Oleic, Lauric, Palmitic, or Stearic Acid were not photosensitizing (Elder 1987).

SUMMARY

PEG-7, -30, -40, -78, and -80 Glyceryl Cocoate are the polyethylene glycol (PEG) ethers of glyceryl cocoate. The PEGs Glyceryl Cocoate function as skin-conditioning agents, emollients, surfactants, nonionic emulsifying agents, and solubilizing agents in cosmetic formulations. In 1996, the PEGs Glyceryl Cocoate were reported to be used in 19 1 cosmetic products. PEG-7 Glyceryl Cocoate was reportedly used in cosmetic formulations at concentrations of 0.1–0.5%.

PEG-7 Glyceryl Cocoate is used as an emulsifier in TOW gels, which serve as vehicles for topical pharmaceutical preparations. TOW gels that contain PEG-7 Glyceryl Cocoate release hydro- and lipophilic drugs at a relatively high rate and enable them to penetrate isolated human epidermis at rates similar to those from other dermatological vehicles. The gels adhere to mucosae, wet wounds, and other hydrophilic supports. In general, nonionic surfactants act as penetration enhancers by conditioning the stratum comeum to enable and promote drug diffusion.

Limited data on the safety of PEG-7 Glyceryl Cocoate were found. No data on the other PEGs Glyceryl Cocoate were available. Most of the available safety test data are summaries from the previous safety assessments on PEG-6 through -20M, Stearic Acid, Oleic Acid, Lauric Acid, Palmitic Acid, and Myristic Acid.

No specific absorption, metabolism, or distribution data on the PEGs Glyceryl Cocoate were available. In oral and intravenous studies, no metabolism of PEG was observed and the administered PEGs were excreted unchanged in the urine and feces. PEGs are absorbed through damaged skin. In general, fatty acids (such as Stearic Acid) are readily absorbed and distributed in humans. Fatty acids can traverse the placental barrier.

Treatment of rats with 19.9 mg/kg PEG-7 Glyceryl Cocoate by gavage produced no signs of toxicity. PEGs have low oral and dermal toxicity. Oleic, Lauric, Palmitic, Myristic, and Stearic Acids have slight oral toxicity. Little or no apparent toxicity was produced by topical application of the fatty acids. In subchronic and chronic feeding studies, no adverse effects were reported following administration of the PEGs. High mortality, anorexia, and severe pulmonary infection were observed in rats given 3000 ppm Stearic Acid in feed for 30 weeks.

PEG-7 Glyceryl Cocoate at a concentration of 50% did not produce dermal irritation in a single-insult patch test using mice and guinea pigs; slight irritation was observed in rabbits. In a second primary irritation study, PEG-7 Glyceryl Cocoate was a mild dermal irritant in rabbits. Intracutaneous injections of 10% PEG-7 Glyceryl Cocoate in guinea pigs caused necrotic changes of the skin, but no signs of sensitization. The PEGs were not irritating to the skin of rabbits or guinea pigs, and PEG-75 was not a sensitizer. The fatty acids were mainly nonirritating, but various concentrations of Oleic, Stearic, Palmitic, Myristic, and Lauric Acids produced minimal to mild erythema in primary irritation studies. Cosmetic formulations containing 1–5.08% Stearic Acid and Oleic Acid were nonsensitizing. PEG-7 Glyceryl Cocoate was not an ocular irritant when tested at a

concentration of 10% using rabbits. Undiluted PEG-6 and PEG-75 were not irritating to the eyes of rabbits, and the fatty acids were not ocular irritants.

PEG-7 Glyceryl Cocoate was not phototoxic at a concentration of 50%, and Stearic Acid at a concentration of 2.8% in formulation was not photosensitizing. Oleic Acid and its UVA-induced peroxides induced the formation of fairly large comedones after topical application to sites on the ventral surface of rabbit ears.

Although monoalkyl ethers of ethylene glycol are reproductive toxins and teratogenic agents, PEG-7 Glyceryl Cocoate is the partial ester of polyoxyethylated glycerol with stearic acid. It was considered unlikely that the PEGs Glyceryl Cocoate would cause reproductive or developmental effects based on their structural characteristics. The PEGs did not produce reproductive or developmental toxicity in subchronic or chronic oral toxicity studies. Reproductive capacity was impaired in female rats given 15% Oleic Acid in feed for 10–16 weeks, but growth and general health were not affected adversely.

No specific genotoxicity or carcinogenicity data were available on the PEGs Glyceryl Cocoate. PEG-8 was negative in the Chinese hamster ovary cell mutation test and the sister chromatid exchange test. PEG- 150 was not mutagenic in the mouse lymphoma forward mutation assay. Oleic Acid, Lauric Acid, and Stearic Acid did not induce mitotic aneuploidy or crossing over of chromosomes in ***Saccharomyces cerevisiae.*** Stearic Acid was nonmutagenic in the Ames test. Oleic Acid induced aneuploidy and tetraploidy in Chinese hamster lung fibroblasts. Oleic, Lauric, Palmitic, and Stearic Acids inhibited the mutagenicity of N-nitrosodialkylamines in modified Ames tests. PEG-8 was noncarcinogenic in rats, guinea pigs, and mice after 30 weeks to 1 year of treatment by various routes. Daily subcutaneous injection of l-16.5 mg Oleic Acid produced no malignant tumors in mice. Intestinal and gastric tumors occurred in mice given 200 mg/day dietary Oleic Acid. Stearic Acid given at up to 50 g/kg/day in feed was not carcinogenic in mice.

In clinical studies, PEG-7 Glyceryl Cocoate was not a dermal irritant or photosensitizer. PEG-6 and PEG-8 produced mild sensitization. Bum patients receiving a PEG-based topical ointment had signs of systemic toxicity and contact dermatitis. SPF 15 facial creams containing 0.3% PEG-7 Glyceryl Cocoate did not produce signs of photocontact allergenicity during clinical trials. Oleic, Myristic, and Stearic Acids did not cause irritation in primary and cumulative dermal irritation studies. Cosmetic formulations containing the fatty acids were not sensitizers, photosensitizers, or ocular irritants.

DISCUSSION

The CIR Expert Panel has previously reviewed the safety of the PEGs in cosmetics, as well as the safety of Lauric, Stearic, Oleic, Palmitic, and Myristic Acids. Although little safety data were available on the PEGs Glyceryl Cocoate polymers, the Expert Panel concluded that the limited data provided on PEG-7 Glyceryl Cocoate and the data from the previous reports were adequate to support the safety of the PEGs Glyceryl Cocoate polymers in cosmetics. As discussed earlier in this report, the possibility of reproductive and developmental effects was determined not to be of concern. The PEGs Glyceryl Cocoate polymers were considered safe as used in rinse-off products and safe up to 10% in leave-on products. The concentration limit for leave-on products was based on the ocular and sensitization data provided in this report. Any party seeking to modify or remove the concentration limit should provide safety test data on the PEGs Glyceryl Cocoate polymers.

The CIR Expert Panel was concerned about the sensitization and toxicity potential of the PEGs Glyceryl Cocoate polymers when applied to damaged skin. This concern arose because of positive results in patch tests and incidences of nephrotoxicity in bum 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. The cosmetic industry should continue to use the necessary procedures to remove these impurities from the PEGs Glyceryl Cocoate ingredients before blending them into cosmetic formulations.

The Expert Panel recognized that PEG-7 Glyceryl Cocoate can enhance the skin penetration of other chemicals, and recommends that care should be exercised in using the PEGs Glyceryl Cocoate in cosmetic products where the penetration of other ingredients is a concern.

CONCLUSION

On the basis of the available animal and clinical data presented in this report and in other reports on related ingredients, the CIR Expert Panel concludes that PEG-7, -30, -40, -78, and -80 Glyceryl Cocoate are safe as used in rinse-off products and safe up to 10% in leave-on products.

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