# Final Report on the Safety Assessment of PEG (Polyethylene Glycol)-2, -4, -6, -8, -12, -20, -32, -75, and -150 Dilaurate; PEG-2, -4, -6, -8, -9, -10, -12, -14, -20, -32, -75, -150, and -200 Laurate; and PEG-2 Laurate SE[1]

**PEGs Dilaurate and PEGs Laurate are the diesters and monoesters, respectively, of polyethylene glycol and lauric acid used in a wide variety of cosmetic formulations as surfactants—emulsifying agents. PEG esters are produced by the ethoxylation of fatty acids. In general, ethoxylated fatty acids can contain 1,4-dioxane as a by-product of ethoxylation. Traces of the reactants (fatty acid, ethylene oxide, and any catalysts) may remain in the finished product. Current concentration of use data were not available; the highest previously reported concentration was 25%. The PEGs Dilaurate and PEGs Laurate are similar to the PEGs Stearate and PEGs Distearate, and to the components (Polyethylene Glycol and Lauric Acid); all of which have been addressed in previous safety assessments. PEGs were readily absorbed through damaged skin. Fatty acids such as Lauric Acid are absorbed, digested, and transported in animals and humans. The acute oral $LD_{50}$ of PEG-12 Laurate was >25 g/kg in mice. In short-term feeding studies, PEGs Laurate were irritating to the gastrointestinal tract, but not necrotizing. In chronic oral toxicity studies, there was some evidence of liver damage and hyperplasia in several tissues. It is generally recognized that the PEG monomer, ethylene glycol, and certain of its monoalkyl ethers are reproductive and developmental toxins. These esters and diesters are chemically different from PEG alkyl ethers and are not expected to cause adverse reproductive or developmental effects. In actual studies, PEGs Stearate, and PEGs Distearate did not cause reproductive or developmental toxicity, and were not carcinogenic. Likewise, PEGs were not carcinogenic. Although sensitization and nephrotoxicity were observed in burn patients treated with a PEG-based cream, no evidence of systemic toxicity or sensitization was found in studies with intact skin. Because of the possible presence of 1,4-dioxane reaction product and unreacted ethylene oxide residues, it was considered necessary to use appropriate procedures to remove these from PEGs Dilaurate and PEGs Laurate ingredients before blending them into cosmetic formulations. Based on the limited data on the PEGs Dilaurate and the PEGs Laurate, on the data available on the component ingredients, and on the data available on similar PEG fatty acid esters, it was concluded that PEG-2, -4, -6, -8, -12, -20, -32, -75, and -150 Dilaurate; PEG-2, -4, -8, -9, -10, -12, -14, -20, -32, -75, -150, and -200 Laurate; and PEG-2 Laurate SE are safe for use in cosmetics at concentrations up to 25%.**

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## INTRODUCTION

Polyethylene Glycol (PEG)-2, -4, -6, -8, -12, -20, -32, -75, and -150 Dilaurate and PEG-2, -4, -6, -8, -9, -10, -12, -14, -20, -32, -75, -150 and -200 Laurate are PEG diesters or esters of lauric acid that serve as surfactants—emulsifying agent or surfactants—cleaning agents in cosmetic product formulations. PEG-2 Laurate SE is a self-emulsifying grade of PEG-2 Laurate that contains some sodium and/or potassium laurate; PEG-2 Laurate SE is used as a surfactant—emulsifying agent in cosmetic product formulations.

The PEGs Dilaurate and PEGs Laurate are similar to the PEGs Stearate and PEGs Distearate, and to the components (Polyethylene Glycol and Lauric Acid), all of which have been addressed in previous safety assessments. The conclusions reached in those earlier assessments are described below.

PEG-2, -6, -8, -12, -20, -32, -40, -50, -100, and -150 Stearates are safe as cosmetic ingredients in the present practices of concentration and use (Elder 1983a).

PEG-2, -3, -4, -8, -9, -12, -20, -32, -50, -75, -120, -150, and -175 Distearate are safe for use in cosmetic formulations in the present practices of use (CIR 1996).

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).

Laureth-4 and -23 (polyethylene glycol ethers of lauryl alcohol) are safe as cosmetic ingredients in the present practices of use and concentration (Elder 1983b).

Lauric Acid is safe for use as a cosmetic ingredient (Elder 1987).

Because there are limited data available to address the safety of PEGs Dilaurate and PEGs Laurate, and because the PEGs Dilaurate and PEGs Laurate are similar to the PEGs Stearate and

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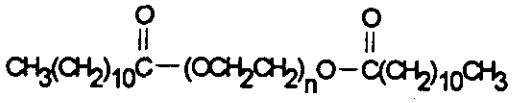

**FIGURE 1**
PEG-n Dilaurate.

PEGs Distearate, and to the components (Polyethylene Glycol and Lauric Acid), the relevant data from the previous safety assessments have been summarized in this review as a further basis for the assessment of safety of the PEGs Dilaurate and PEGs Laurate.

## CHEMISTRY

### Definition and Structure

The PEGs Dilaurate (generic CAS No. 9005-02-1) are polyethylene glycol diesters of lauric acid (coconut-derived) that conform generally to the formula in Figure 1, where *n* has an average value equal to the number in the name. PEG-n Dilaurate is also known as Polyoxyethylene (*n*) Dilaurate. Synonyms for PEG-2 Dilaurate are Polyethylene Glycol (100) Dilaurate; Dodecanoic Acid, Oxydi-2,1-Ethanediyl Ester; and Oxydi-2,1-Ethanediyl Dodecanoate. PEG-4 Dilaurate is known as Polyethylene Glycol 200 Dilaurate. PEG-6 Dilaurate is called Polyethylene Glycol 300 Dilaurate. Synonyms for PEGs-8 and -12 Dilaurate are Polyethylene Glycol 400 Dilaurate and Polyethylene Glycol 600 Dilaurate, respectively. Other names for the remaining PEGs Dilaurate are Polyethylene Glycol 1000 Dilaurate(-20), Polyethylene Glycol 1540 Dilaurate(-32), Polyethylene Glycol 4000 Dilaurate(-75), and Polyethylene Glycol 6000 Dilaurate(-150) (Wenninger, Canterbery, and McEwen 2000).

The PEGs Laurate (generic CAS No. 9004-81-3) conform generally to the structure in Figure 2, where *n* has an average value equal to the number in the name. A general synonym for the PEGs Laurate is Polyoxyethylene (*n*) Monolaurate. PEG-2 Laurate is also known as Diethylene Glycol Monolaurate; Diglycol Laurate; Diglycol Monolaurate; Dodecanoic Acid, 2-(2-Hydroxyethoxy)Ethyl Ester; and Polyethylene Glycol 100 Monolaurate. Synonyms for PEG-4 Laurate are Dodecanoic Acid, 2-[2-(2-Hydroxyethoxy)Ethoxy]Ethyl Ester; 2-[2-[-2(2-Hydroxyethoxy)Ethoxy]Ethoxy]Ethyl Dodecanoate; and Polyethylene Glycol 200 Monolaurate. Other names for PEG-6 Laurate are Dodecanoic Acid, 17-Hydroxy-3,6,9,12,15-Pentaoxaheptadec-1-yl Ester; 17-Hydroxy-3,6,9,12,15-Pentaoxaheptadec-1-yl Dodecanoate; and Polyethylene Glycol 300 Monolaurate. PEG-8 Laurate is also known as Dodecanoic Acid,

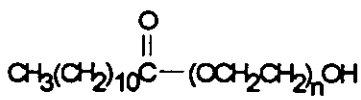

**FIGURE 2**
PEG-n Laurate.

23-Hydroxy-3,6,9,12,15,18,21-Heptaoxatricos-1-yl Ester; 23-Hydroxy-3,6,9,12,15,18,21-Heptaoxatricos-1-yl Dodecanoate; and Polyethylene Glycol 400 Monolaurate. PEG-9, -10, -12, -20, -32, -75, and -150 Laurate are also known as Polyethylene Glycol 450 Monolaurate; Polyethylene Glycol 500 Monolaurate; Polyethylene Glycol 600 Monolaurate; Polyethylene Glycol 1000 Monolaurate; Polyethylene Glycol 1540 Monolaurate; Polyethylene Glycol 4000 Monolaurate; Polyethylene Glycol 6000 Monolaurte, respectively. A synonym for PEG-14 Laurate is Polyethylene Glycol (14) Monolaurate (Wenninger, Canterbery, and McEwen 2000).

PEG-2 Laurate SE is a self-emulsifying grade of PEG-2 Laurate that contains sodium and/or potassium laurate. Other names for this compound are Polyethylene Glycol 100 Monolaurate Self-Emulsifying and Polyoxyethylene (2) Monolaurate Self-Emulsifying (Wenninger, Canterbery, and McEwen 2000).

### Chemical and Physical Properties

The chemical and physical properties of PEG-4, -8, and -150 Dilaurate are described in Table 1, and the properties of PEG-2, -4, -8, and -12 Laurate are described in Table 2.

### Impurities

PEG-n Laurate contains unspecified amounts of lauric acid diester of PEG and unreacted PEG (Yakuji Nippo 1979).

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 $\mu$Eq thiosulfate/ml glycol. PEG-8 had concentrations ranging from 3.24 to 5.7 $\mu$Eq 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 Cosmetic Ingredient Review (CIR) safety assessment of the PEG Stearates, 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. Traces

**TABLE 1**
Chemical and physical properties of PEGs Dilaurate

| Property | Description | Reference |
|---|---|---|
| PEG-4 Dilaurate | | |
| Appearance | Pale yellow, viscous (oily) liquid | Nikitakis and McEwen 1990a |
| Solubility | Soluble in mineral oil, triolein, methyl alcohol, acetone, ethyl alcohol, ethyl acetate, toluol, vegetable oil and isopropyl alcohol; dispersible in water, isopropyl myristate, and glycerin | Nikitakis and McEwen 1990a |
| | When hot, completely soluble in naphtha and mineral oil; when cold, miscible in certain proportions in naphtha and poorly soluble in mineral oil | Glyco Chemicals, Inc. No date |
| Acid value | 8.0 max. | Nikitakis and McEwen 1990a |
| Hydroxyl value | 20–40 | Nikitakis and McEwen 1990a |
| Saponification value | 180–190 | Nikitakis and McEwen 1990a |
| Iodine value | 3.0 max. | Nikitakis and McEwen 1990a |
| Specific gravity at 25°C | 0.96 | Glyco Chemicals, Inc. No date |
| Melting point or solidification point (°C) | <14 | Glyco Chemicals, Inc. No date |
| pH of 5% aqueous dispersion | 4.0–5.0 | Glyco Chemicals, Inc. No date |
| Moisture | 0.5% max. | Nikitakis and McEwen 1990a |
| PEG-6 Dilaurate | | |
| HLB value | 6.3 | Cosmetic Science & Technology On-line 1997 |
| PEG-8 Dilaurate | | |
| Appearance | Clear, pale yellow liquid with a slightly fatty odor | Nikitakis and McEwen 1990b |
| Solubility | Soluble in isopropyl alcohol, methyl alcohol, ethyl alcohol, acetone, ethyl acetate, toluol, naphtha, mineral oil, vegetable oil, and toluene | Glyco Chemicals, Inc. No date |
| | Soluble in isopropanol and toluene and dispersible in water | Nikitakis and McEwen 1990b |
| Specific gravity at 25/25°C | 0.985–0.995 | Nikitakis and McEwen 1990b |
| pH of 5% aqueous dispersion | 3.0–6.0 | Nikitakis and McEwen 1990b |
| Acid value | 10.0 max. | Nikitakis and McEwen 1990b |
| Saponification value | 125–137 | Nikitakis and McEwen 1990b |
| Iodine value | 10.0 max. | Nikitakis and McEwen 1990b |
| HLB value | 10.4 | Cosmetic Science & Technology On-line 1997 |
| Melting point or solidification point (°C) | <15 | Glyco Chemical Inc. No date |
| PEG-150 Dilaurate | | |
| Physical properties | Tan, waxy solid with a slightly fatty odor | Nikitakis and McEwen 1990b |
| Solubility | Soluble in isopropanol, toluene, and water | Nikitakis and McEwen 1990b |
| Melting range | 53–60°C | Nikitakis and McEwen 1990b |
| Acid value | 9.0 max. | Nikitakis and McEwen 1990b |
| Saponification value | 14–22 | Nikitakis and McEwen 1990b |
| Iodine value | 1.5 max. | Nikitakis and McEwen 1990b |

**TABLE 2**
Chemical and physical properties of PEGs Laurate

| Property | Description | Reference |
|---|---|---|
| PEG-2 Laurate | | |
| Appearance | Light yellow, oily liquid | Nikitakis and McEwen 1990b |
| Solubility | Soluble in alcohol and mineral oil; dispersible in water | Nikitakis and McEwen 1990b |
| Specific gravity at 25°/25°C | 0.97–0.99 | Nikitakis and McEwen 1990b |
| pH of 5% aqueous solution | 8.4–9.4 | Nikitakis and McEwen 1990b |
| Acid value | 6.0 max. | Nikitakis and McEwen 1990b |
| Saponification value | 165–175 | Nikitakis and McEwen 1990b |
| Iodine value | 10 max. | Nikitakis and McEwen 1990b |
| PEG-4 Laurate | | |
| Physical properties | Light yellow, oily liquid with a "typical odor" | Nikitakis and McEwen 1990b |
| Solubility | Soluble in ethanol; insoluble in mineral oil; dispersible in water | Nikitakis and McEwen 1990b |
| pH of 5% aqueous dispersion | 3.0–5.0 | Nikitakis and McEwen 1990b |
| Acid value | 5.0 max. | Nikitakis and McEwen 1990b |
| Saponification value | 130–135 | Nikitakis and McEwen 1990b |
| Hydroxyl value | 134–144 | Nikitakis and McEwen 1990b |
| Iodine value | 9.5 max. | Nikitakis and McEwen 1990b |
| PEG-8 Laurate | | |
| Appearance | Light yellow, oily liquid with a "characteristic odor" | Glyco Chemicals, Inc. No date |
| Solubility | Soluble in water and ethanol; insoluble in mineral oil | Nikitakis and McEwen 1990b |
| Specific gravity at 25°/25°C | 1.025–1.040 | Nikitakis and McEwen 1990b |
| pH of 10% aqueous solution | 3.0–6.5 | Nikitakis and McEwen 1990b |
| Acid value | 5.0 max. | Nikitakis and McEwen 1990b |
| HLB value | 13.1 | Cosmetic Science & Technology On-line 1997 |
| Saponification value | 86–105 | Nikitakis and McEwen 1990b |
| Iodine value | 5.0 max. (<8) | Nikitakis and McEwen 1990b |
| Melting point (°C) | <8 | Glyco Chemicals, Inc. No date |
| Moisture | 1.0% max. | Nikitakis and McEwen 1990b |
| PEG-12 Laurate | | |
| Appearance | Light yellow liquid at 25°C | Nikitakis and McEwen 1990b |
| Solubility | Soluble in water and ethanol; insoluble in mineral oil | Nikitakis and McEwen 1990b |
| pH of 3% aqueous solution | 4.2–4.8 | Nikitakis and McEwen 1990b |
| pH of 5% aqueous dispersion | 6.0–8.0 | Glyco Chemicals, Inc. No date |
| Specific gravity at 25°/25°C | 1.01 | Glyco Chemicals, Inc. No date |
| Melting point (°C) | 20–25 | Glyco Chemicals, Inc. No date |
| Acid value | 5.0 max. (<6) | Nikitakis and McEwen 1990b |
| Saponification value | 66–80 | Nikitakis and McEwen 1990b |
| Iodine value | 5.0 max. (<8) | Nikitakis and McEwen 1990b |
| Moisture | 1.0% max. | Nikitakis and McEwen 1990b |
| PEG-20 Laurate | | |
| HLB value | 16.5 | Cosmetic Science & Technology On-line 1997 |

of the reactants, stearic acid, ethylene oxide, and the catalytic agents used, may remain in the finished product (Elder 1983a, 1983b).

### Reactivity

PEGs Stearate are relatively stable compounds; however, the ether oxygens are potentially reactive and the ester bonds are potentially vulnerable to enzymatic cleavage (Elder 1983a).

### Method of Manufacture

In general, polyoxyethylene ester emulsifiers and surfactants are produced using the ethoxylation of fatty acids such as lauric acid and stearic acid. Two modes of reaction between alkylene oxides and fatty acids can occur: uncatalyzed and alkali catalyzed. The uncatalyzed addition is a slow reaction, which involves alkoxylation, esterification, and alkylene oxide hydrolysis. The alkali-catalyzed ethoxylation is more complex, and involves interesterification. No significant chain lengthening with ethylene oxide occurs until complete formation of the glycol monoester has been achieved (Swern 1979).

PEG-2 Laurate is produced by an interesterification reaction of coconut oil with diethylene glycol (Nikitakis and McEwen 1990b).

## USE

### Cosmetic

The PEGs Dilaurate function as surfactants—emulsifying agents in cosmetic formulations. PEG-75 Dilaurate and PEG-150 Dilaurate also serve as surfactants-solubilizing agents (Wenninger, Canterbery, and McEwen 2000). Data submitted to the Food and Drug Administration (FDA) in 1996 indicated that PEG-8 and -12 Dilaurate were used in 40 cosmetic formulations, and PEG-2, -4, -8, -10, -15, and -200 Laurate were used in 20 formulations (Table 3). PEG-2, -6, -12, -20, -32, -75, and -150 Dilaurate, PEG-2 Laurate SE, and PEG-6, -9, -12, -14, -20, -32, -75, and -150 Laurate had no reports of use (FDA 1996).

Current concentration of use data are not available from industry, but historical data are available (FDA 1984). In 1984, PEG-4 Dilaurate was used at concentrations of 1% to 25% (mostly 5%–10%), and PEG-8 Dilaurate was used at concentrations of 0.1% to 25%. PEG-2 Laurate was used at concentrations of 0.1% to 10% (mostly 0.1%–1%). PEG-2 Laurate SE and PEG-9 Laurate were used at unknown concentrations. PEG-4 Laurate was used at concentrations of 0.1% to 25% (mostly 0.1% to 1%). The concentrations of use of PEG-8 Laurate ranged from 0.1% to 10% (mostly 1%–5%). PEG-12 Laurate was used at 5% to 10%.

### Noncosmetic

The PEGs Dilaurate are indirect food additives that are used in resinous and polymeric coatings, paper and/or paperboard, and textiles and/or textile fibers as described in the Code of Federal Regulations (CFR) in 21CFR 175.105, 175.300, 176.170, 176.180, 176.200, 176.210, 177.1210, 177.2260, 177.2800, and 178.3520 (CFR 1992).

PEG-8 Dilaurate is used as a plasticizer for vinyls. PEG-12 Laurate is used as a liquid nonionic detergent for woolens, dishes, and other items. PEG-8 Laurate is used as an antistatic agent in weaving nylon and saran, as an ingredient in latex emulson paints, as an emulsifier for solvents and oils, as a dye assistant and penetrating agent for dyeing cotton and rayon, and as a nonionic wetting agent (Glyco Chemicals, Inc. No date).

## GENERAL BIOLOGY

### Absorption, Metabolism, Distribution, and Excretion

*PEGs Stearate*

PEG-40 Stearate is hydrolyzed in vitro by pancreatic lipase. When the same compound was hydrolyzed with alkali, a 5 to 1000 mg percent concentration range of the polyoxyethylene hydrolysate had no hemolytic effect on defibrinated human blood tested at 37°C for 18-hours: PEG-40 Stearate also produced no significant interference with oxygen uptake by kidney tissue preparations. PEG-20, -30, and -40 Stearate activated the cytochrome oxidase enzyme system in heart muscle preparations up to a concentration of 150 mg/ml (Elder 1983a).

*Polyethylene Glycol*

Gastrointestinal absorption of PEGs is dependent on the molecular weight of the compound. In general, the greater the molecular weight of the PEG compound, the lesser the absorption that occurs. In both oral and intravenous (IV) studies, no metabolism was observed and the PEGs were rapidly eliminated unchanged in the urine and feces. In a study with human burn 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).

*Lauric Acid*

In general, fatty acids such as stearic acid 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. $\beta$-Oxidation of the fatty acids involves serial oxidation and reduction reactions yielding acetyl coenzyme A (CoA). Placental transfer of fatty acids has been documented in several species and fetal lipid metabolism has been studied. High intake of dietary saturated fatty acids has been associated with increased incidence of atherosclerosis and thrombosis. Fatty acids are typically transported esterified to glycerol in chylomicrons and very low density lipoproteins. Lauric Acid is transported via the lymphatic and (as a free fatty acid) portal systems. Lauric Acid inhibited the growth of various microorganisms, including bacteria and fungi, and inactivated enveloped viruses such as herpes, influenza, Sendai, and Sindbis viruses. The minimal inhibitory concentrations (at 37°C)

**TABLE 3**
Frequency of use of PEGs Dilaurate and PEGs Laurate (FDA 1996)

| Product category (Number of Formulations Reported to FDA) | Number of formulations containing ingredient |
|---|---|
| PEG-4 Dilaurate | |
| Bath oils, tablets, and salts (147) | 9 |
| Other fragrance preparations (195) | 1 |
| Aftershave lotion (268) | 1 |
| Cleansing preparations (820) | 1 |
| Body and hand (excluding shaving) preparations (1012) | 1 |
| Moisturizing preparations (942) | 1 |
| Other skin care preparations (810) | 1 |
| **1996 Total for PEG-4 Dilaurate** | **15** |
| PEG-8 Dilaurate | |
| Bath oils, tablets, and salts (147) | 7 |
| Hair conditioners (715) | 5 |
| Shampoos (Noncoloring) (972) | 1 |
| Tonics, dressings, and other hair grooming aids (604) | 7 |
| Cuticle softeners (26) | 1 |
| Cleansing preparations (820) | 3 |
| Other skin care preparations (810) | 1 |
| **1996 Total for PEG-8 Dilaurate** | **25** |
| PEG-2 Laurate | |
| Body and hand (excluding shaving) (1012) | 1 |
| **1996 Total for PEG-2 Laurate** | **1** |
| PEG-4 Laurate | |
| Cuticle softeners (26) | 1 |
| Cleansing (820) | 3 |
| Face and neck (excluding shaving) (300) | 1 |
| **1996 Total for PEG-4 Laurate** | **5** |
| PEG-8 Laurate | |
| Permanent waves (434) | 1 |
| Tonics, dressings, and other hair grooming aids (604) | 1 |
| Other hair preparations (395) | 1 |
| Cleansing (820) | 1 |
| Body and hand (excluding shaving) (1012) | 1 |
| Other skin care preparations (810) | 1 |
| Suntan gels, creams, and liquids (196) | 1 |
| Indoor tanning preparations (67) | 1 |
| Other sutan preparations (68) | 1 |
| **1996 Total for PEG-8 Laurate** | **9** |
| PEG-10 Laurate | |
| Shampoos (Noncloring) (972) | 2 |
| **1996 Total for PEG-10 Laurate** | **2** |
| PEG-15 Laurate | |
| Indoor tanning preparations (67) | 2 |
| **1996 Total for PEG-15 Laurate** | **2** |
| PEG-200 Laurate | |
| Shaving cream (158) | 1 |
| **1996 Total for PEG-200 Laurate** | **1** |

of Lauric Acid ranged from 0.062 mM (*Streptococcus pneumoniae*) to 4 mM (*Candida utilis*) (Elder 1987).

### Miscellaneous Effects

The deposition of the germicide trichlorocarbanilide (TCC) on the skin was enhanced in the presence of both PEG-8 Laurate and sodium chloride (Elkhouly and Woodroffe 1970, 1973). The antibacterial activity of TCC/PEG-8 Laurate systems was also increased when 0.5% sodium chloride was added.

## ANIMAL TOXICOLOGY

### Acute Toxicity

*Laureths*

The acute oral $LD_{50}$ of Laureths was between 4.9 and 9.1 g/kg in rats and mice, between 5 and 10 g/kg in Swiss mice, and >25 g/kg in rats (Elder 1983b).

*PEGs Laurate*

The acute oral $LD_{50}$ of PEG-12 Laurate was >25 g/kg and the intravenous $LD_{50}$ was 500 mg/kg in Harlan albino mice (Hopper, Hulpieu, and Cole 1949).

*PEGs Distearate*

Hopper, Hulpieu, and Cole (1949) reported the toxicological properties of several surface-active agents, including PEG-8 and PEG-20 Distearate. The $LD_{50}$ values for those two compounds were 365 mg/kg and 220 mg/kg, respectively, when administered intravenously to albino Harlan mice weighing between 14 and 23 g.

*PEGs Stearate*

The acute oral $LD_{50}$ values of 50% PEG-2-150 Stearate (in corn oil unless specified) were each determined using rats. The $LD_{50}$ values were >10 g/kg for PEG-2 Stearate; >10 g/kg (in corn oil) and >31.6 g/kg (aqueous) for PEG-8 Stearate; >10 g/kg for PEG-12 Stearate; >10 g/kg and 19.9 g/kg for PEG-20

Stearate; >10 g/kg for PEG-32 Stearate; 32 g/kg for PEG-40 Stearate (vehicle not specified); >25 g/kg for aqueous solutions of both PEG-50 and -100 Stearate; and >10 g/kg for PEG-150 Stearate. The acute oral $LD_{50}$ of hair cream preparation containing 1.5% PEG-6 Stearate was >34.6 g/kg in rats. The acute intraperitoneal (IP) $LD_{50}$ of PEG-8 Stearate was >9 ml/kg in rats given 2-ml injections. No signs of toxicity were observed in rats given IP injections of 2.5 g/kg PEG-50 Stearate or PEG-100 Stearate. A concentration of 5% PEG-40 Stearate given as a 5-ml injection into the lumen of the jejunum of a dog had no effect on blood pressure. That same day, an IV injection produced a prolonged hypotensive response. It was stated that this response was a "characteristic reaction" of the dog to a variety of polyoxyethylene compounds. The acute dermal $LD_{50}$ of 15% PEG-8 Stearate was >10 ml/kg in rabbits; the only effect noted was moderate erythema at the application sites at 24 hours which cleared by day 3 (Elder 1983a).

*Polyethylene Glycol*

Acute oral $LD_{50}$ values for PEGs in rabbits were 17.3 g/kg (100% PEG-6) and 76 g/kg (100% PEG-75). In acute dermal studies, no deaths were reported in groups of rabbits dosed with 20 ml/kg of either undiluted PEG-6 or 40% PEG-20M (Andersen 1993).

*Lauric Acid*

Male albino rats (five per group) were given 0.464 to 10.0 g/kg Lauric Acid in order to determine the acute oral toxicity of the fatty acid. Rats treated with 4.64 g/kg and 10.0 g/kg Lauric Acid had transient signs of toxicity. Slight depression, depressed righting and placement reflexes, oily and unkempt fur, mucoid diarrhea, excessive salivation, and serosanguineous discharge from the nose and eyes were observed. One rat given 10.0 g/kg Lauric Acid died 1 day after treatment; this rat had congested lungs and kidneys, and advanced autolytic changes.

A product formulation containing 8.7% Lauric Acid was administered to five albino rats as a 5-g/kg oral dose. No signs of toxicity were observed (Elder 1987).

## Short-Term Toxicity

*PEGs Laurate*

Ringrose and Waller (1959) fed male New Hampshire cockerel chicks PEG-4, -8, and -20 Laurate for 10 weeks. In one study, 192 chicks (12 per group) were fed 0.1% or 1.0% PEG-20 Laurate. In the second study, 400 chicks (10 per group) were given 0.1%, 1.0%, or 2.0% PEG-4 or -8 Laurate. Chicks fed the PEGs Laurate were normal with respect to mortality, diarrhea, growth, gross findings, and flavor, as compared to chicks of the control group.

*PEGs Laurate and PEGs Stearate*

Male weanling Sprague-Dawley rats (13 per group) were fed a diet containing 25% PEG-20 Laurate or PEG-8 Stearate for 59 days (Harris et al. 1951). Rats of the control group ($n = 13$) were given feed containing hydrogenated oils (Crisco). The rats were weighed twice weekly and observed daily for changes in gross appearance and/or activity. For rats given PEG-20 Laurate, the mean weight gain/rat was 74 g, and the weight of feed consumed was 15.9 g/rat/day. For rats given PEG-8 Stearate, the mean weight gain/rat was 88 g, and the weight of feed consumed was 13.4 g/rat/day. In order to determine whether the compounds affected the rate of blood clotting, the blood-clotting time was measured on days 14 and 42 using several rats taken from random from each group. On day 59, the animals were decapitated and examined for gross lesions.

No changes in the rate of blood clotting were observed in rats of any treatment group. Rats of the control group had no signs of toxicity. All rats given PEG-20 Laurate had diarrhea, but inflammation of the anal region was not as severe as in rats given PEG-20 Sorbitan Laurate. In several instances, blood clots in the anorectal region were observed at necropsy. A few of the rats improved somewhat during the second half of the study. The rats gained weight continually after the third day, but their weight gain was somewhat less than that of rats given PEG-8 Stearate; this weight gain reduction suggested that the laurate compound was more harmful than the stearate. One rat died before scheduled necropsy, and three rats had bladder stones, which were tentatively identified as oxalate crystals.

Rats given PEG-8 Stearate had neither hemorrhage nor diarrhea, their fur was sleek and tidy, and they appeared normal throughout the study. The rats had an initial loss in weight, but gained weight consistently after day 3. The weight increase was lower in rats of this group than in rats of the control group.

The investigators also fed PEG-20 Laurate and PEG-8 Stearate to Sprague-Dawley rats (14 male and 16 female) for 70 days. The beginning test concentration of 5% was sequentially increased to 10%, 15%, and 25% during the first 10 days of the study; this procedure was used to reduce the shock from a sudden feeding of large amounts of the test substances. The rats were weighed and observed as above, and were killed by decapitation on day 70.

The rats fed PEG-20 Laurate had diarrhea within 2 weeks of feeding. The severity of the diarrhea increased until the anal region of most rats was highly inflamed. The mean weight gains per rat were 210 g (male) and 121 g (female). The mean weight of feed consumed was 12.7 g/rat/day. The mean weight gain of rats in this group was 62% of that of rats of the control group (hydrogenated oils); the mean weight gains per rat were 98 g (male) and 62 g (female). The mean weight of feed consumed by rats of the control group was 5.7 g/rat/day. Rats given PEG-8 Stearate had no gross signs of toxicity except that growth was 67% of that of the control rats.

Organ weights of rats fed either PEG-20 Laurate or PEG-8 Stearate did not differ from those of controls. All of the test substances were irritating to the gastrointestinal tract, but not necrotizing, as compared to the control substance. The cortical tubules of the kidneys had mild degeneration (probably reversible), and stains for fat were negative. Significant hepatic

changes were not observed. In the spleen of treated rats, giant cells were noted more frequently than in the spleen of control rats. These cells were presumably of monocyte/macrophage origin. Monocyte/macrophage hyperplasia was also observed. Males given the test substances had areas of incomplete maturation in the testes; findings in the ovaries of females were inconclusive. Rats of all groups had thickening of the alveolar wall by chronic inflammation cells (pneumonitis), but these changes were more frequent and prominent in rats given the test substances.

*PEGs Stearate*

Weanling hamsters fed a diet containing 5% or 15% PEG Monostearate for 2 to 10 weeks had severe lesions in the duodenum, ileum, liver, kidneys, and testes. Severe erosion of the ileal mucosa and necrosis of the liver were observed. Spermatogenic activity was decreased and tubular degeneration occurred in the kidneys. No signs of toxicity were observed in rats, monkeys, mice, and dogs fed diets containing up to 4% PEG-8, -40, -50, or -100 Stearate. Rabbits exposed topically for 20 days to 0.5 to 2.0 g/kg of 1.5% PEG-6 Stearate in a product formulation had erythema, dryness, wrinkling, desquamation, and hyperkeratosis at the application sites. No other signs of toxicity were noted (Elder 1983a).

*Polyethylene Glycol*

No toxicity was reported in rabbits that received daily topical applications of PEG-20M (0.8 g/kg/day) for 30 days. The only effect noted in the study was transient, mild erythema. The only evidence of systemic toxicity that resulted from dermal exposure was noted 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 seven days (Andersen 1993).

*Lauric Acid*

The follicular-keratogenic properties of Lauric Acid were studied after topical application to the skin of the external ear canal of four albino rabbits. Lauric Acid (~18 mmol % in alcohol) was applied daily, 5 days per week for 6 weeks, as a 3-ml test volume. Rabbits of the control groups received either no treatment or absolute alcohol. Rabbits given Lauric Acid had erythema on the second day of treatment. The intensity of the observed redness increased over the next few days, and desquamation developed. Distinct follicular keratosis was observed within 1 month. After discontinuation of the applications, the erythema and scaling gradually disappeared, but the keratosis persisted after the 6-week treatment period had ended (Elder 1987).

## Subchronic Toxicity

*Laureths*

Rabbits were treated topically with 0.4 ml/kg/day of Laureth-4 at 6% in a 52% ethanol/water solution for 21 days. Epidermal acanthosis in the animals was attributed to the alcohol (Elder 1983b).

*PEGs Stearate*

Six large calculi (4–6 mm in diameter; 50–95 mg in weight) were found in the urinary bladders of hamsters fed unspecified PEGs Stearate for 74 to 260 days. Rabbits fed a diet containing 4% PEG-8 Stearate for four months or 5% PEG-8 Stearate for 19 weeks had no treatment-related effects (Elder 1983a).

*Polyethylene Glycol*

In subchronic, 90-day toxicity studies involving groups of albino rats, the largest (PEG-20M) and smallest (PEG-6) molecular weight PEGs tested did not induce toxicity or death when administered daily in the diet or drinking water, respectively, at concentrations of 4% or less. No evidence of toxicity was observed in rabbits that received topical applications of 2 ml/kg/day of PEG-6 daily, 5 days/week, for 18 weeks (Andersen 1993).

## Chronic Toxicity

*Laureths*

Rabbits were treated topically with 0.4 ml/kg/day of Laureth-4 at 6% in a 52% ethanol/water solution daily for 3 months. Edema, erythema, and eschar formation, hyperkeratosis, acanthosis, and dermatitis in the animals was attributed to the alcohol (Elder 1983b).

*PEGs Dilaurate*

Nine Sprague-Dawley rats were fed 6% PEG-8 Dilaurate for 505 days to determine the compound's chronic toxicity (Krehl, Cogwell, and Whedon 1955). PEG-8 Dilaurate was added to the basal diet in lieu of lard, which was present in the feed given to 9 rats of the control group. Feed consumption was greater in rats given PEG-8 Dilaurate than in rats of the control group, but this was not considered significant. Four rats fed PEG-8 Dilaurate died, and four rats of the control group also died. The remaining rats were killed at the end of the experimental period, and the spleen, liver, lungs, testes, thyroid gland, adrenal glands, kidneys, intestines, urinary bladder, heart vessels, and heart muscle were removed, weighed, and prepared for gross and microscopic examinations. One rat had cystic spots on the liver, one rat had hemorrhagic lungs, and one had a large neoplasm (fibrosarcoma, weight = 128.6 g). At microscopic examination, focal parenchymal hepatitis was observed in three rats of the test group.

*PEGs Stearate*

Hamsters fed 5% to 15% PEG Monostearate for 28 to 39 weeks had high mortality, chronic diarrhea, atrophic testes, enlarged kidneys, thickened urinary bladder walls, striking hepatic, cecal, and splenic hemosiderosis, enlarged ceca, and obstructive nephropathy. Rats fed a diet containing 4% PEG-8 Stearate or 2% PEG-100 Stearate for 2 years had no treatment-related lesions over 3 successive generations (Elder 1983).

*PEG-20 Laurate and Lauric Acid*

The oral toxicities of PEG-20 Laurate and lauric acid were evaluated for up to 2 years using Osborne-Mendel albino rats

(Fitzhugh, Schouboe, and Nelson 1960). Five male rats were fed 10% lauric acid for 18 weeks, and five rats of the control group were fed a basal diet. Neither clinical signs of toxicity nor adverse effects on weight gain were observed. None of the rats of either the control group or test group died. No differences were noted in gross findings or organ weights between the control and test animals.

In another study by the same investigator, male and female rats (12 each per group) were fed 2%, 5%, 10%, or 25% PEG-20 Laurate for 2 years. The growth of rats given 2% to 10% PEG-20 Laurate did not differ from that of control rats. Male rats given 25% PEG-20 Laurate had significant reductions in growth after weeks 26 and 52. Mortality did not differ from that of controls. Behavior and appearance of rats of the test group were normal.

Hepatic cysts and cecal enlargement were observed at necropsy. Three rats of the high-dose group had slight gastric mucosal hyperplasia. The hepatic cysts were unilocular or multilocular, often multiple, and varied in size. The cysts were observed in five rats given 25%, four rats given 10% (smaller and fewer), and one rat each for the remaining groups. All hepatic cysts but one were in surviving animals. Cecal enlargement occurred in 17 rats fed 25%, 4 rats fed 10%, 3 rats fed 5%, 1 rat fed 2%, and 0 rats fed the control diet, respectively (male plus female rats). The most affected ceca had approximately three times the normal volume, and the enlargement appeared to be both a distention and increase in mass. The common bile duct was not enlarged.

When 61 rats were sectioned microscopically, the hepatic cysts were of bile duct origin, and were lined by columnar epthelium. No generalized intrahepatic bile duct dilatation was observed, but in several instances, the ducts adjacent to the cysts had slight proliferation or dilatation. Hepatic cells were not affected by treatment with PEG-20 Laurate. The ceca of the treated rats did not differ microscopically from the controls, with the exception of distention (evidenced by thinner wall and short glands) in parts of the sections. The stomachs of four rats given 25% and one rat given 10% had slight squamous epithelial hyperplasia, with "low-grade" inflammation within and under the hyperplastic epithelium (at the junction of the two main portions of the stomach). The heart, lungs, spleen, pancreas, small intestine, colon, kidneys, adrenal glands, testes, ovaries, uterus, thyroid gland, parathyroid glands, prostate, urinary bladder, leg bones and muscles, and bone marrow were not affected by treatment with PEG-20 Laurate.

*Polyethylene Glycol*

Toxic effects were not observed in groups of dogs fed 2% PEG-8, PEG-32, or PEG-75 for 1 year (Andersen 1993).

## Skin Irritation

*Laureths*

Undiluted Laureth-4 produced edema in intact and abraded rabbit skin at 72 hours after 24-hours patch testing. A bath oil product containing 1.8% Laureth-4 (undiluted or in 2% aqueous suspension), applied to the skin of six rabbits per group for 4 hours under occlusion, produced no irritation (Elder 1983b).

*PEGs Stearate*

Skin irritation was slight when PEG Stearate compounds were tested at 100% concentrations in experimental test animals. PEG-2, -6, -8, -12, -20, -32, -40, and -150 Stearate were nonirritating in primary irritation patch tests using rabbits (Elder 1983a).

*Polyethylene Glycol*

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

*Lauric Acid*

Six rabbits were used in a 24-hour, single-insult occlusive patch test to determine the skin irritancy potential of Lauric Acid. Commercially supplied Lauric Acid and a product formulation containing 8.7% Lauric Acid (as a 5% aqueous solution) were applied to intact and abraded skin sites at a dose volume of 0.5 ml. The primary irritation index (PII; maximum = 8.00) of the commercially supplied Lauric Acid was 1.12; signs of irritation included minimal erythema at 24 hours, and minimal edema at several abraded test sites at 72 hours. Rabbits treated with the product formulation had no signs of irritation (PII = 0) (Elder 1987).

## Skin Sensitization

*PEGs Stearate*

PEG-2 Stearate (as a 0.1% suspension) was evaluated for dermal sensitization potential using guinea pigs and the Landsteiner and Jacobs sensitization procedure. Under the test conditions, PEG-2 Stearate was nonsensitizing. Likewise, PEG-8 and -40 Stearate were nonsensitizers (Elder 1983a).

*Polyethylene Glycol*

PEG-75 was not a sensitizer. In the guinea pig skin sensitization test, PEG-75 was tested at a concentration of 0.1% (Andersen 1993).

## Ocular Irritation

*Laureths*

Undiluted Laureth-4 was moderately irritating, and 10% and 20% dilutions were minimally irritating to eyes of rabbits. An undiluted body shampoo containing 17% Laureth-4 produced irritation when instilled into the conjunctival sac of rabbits. An undiluted bath oil containing 1.8% Laureth-4 produced only transient mild conjunctivitis, which disappeared by 72 hours (Elder 1983b).

*PEGs Laurate*

PEG-12 Laurate (pH = 7.6) at a concentration of 1% did not cause ocular irritation in rabbits (Hopper et al. 1949).

*PEGs Stearate*

PEGs Stearate produced minimal ocular irritation when tested at concentrations up to 100% (Elder 1983a).

*Polyethylene Glycol*

PEG-6 and -75 did not cause corneal 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).

*Lauric Acid*

Lauric Acid (as commercially supplied) caused persistent corneal opacity, mild conjunctivitis, and iritis to the eyes of six albino rabbits. The mean ocular irritation scores were 35 after 24 hours, 39 after 48 hours, and 41 after 72 hours. Ocular irritation was not observed after a product formulation (8.7% Lauric Acid; 8.0% aqueous dilution) was instilled into the conjunctival sacs of six New Zealand white rabbits. A soap formulation containing 1.95% Lauric Acid (1% aqueous dilution) caused maximum mean scores of 0.3 for unrinsed eyes (three per group) and 0.7 for rinsed eyes (six per group). New Zealand white rabbits treated with the soap prior to rinsing had grade 1 conjunctival erythema. Treated, unrinsed eyes had no signs of ocular irritation (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, also known as ethylene glycol monomethyl ether) are reproductive and developmental toxins. The CIR Expert Panel undertook a separate, limited review of these compounds in order to assess the possibility that PEG-derived cosmetic ingredients could present similar concerns (CIR 1996). 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.). In particular, because the PEG Laurate and PEG Dilaurate compounds are diesters of polyethylene glycol, and as such, are chemically different from alkyl ethers, the Panel concluded no reproductive or developmental hazards are expected to be posed by these compounds.

*Laureths*

No abnormalities were found in teratogenicity, multiple generation, fertility, and peri- and postnatal development studies in rats exposed topically to 0.4 ml/kg/day of a 6% Laureth-4 solution (Elder 1983b).

### PEGs Stearate

In multigenerational studies, rats fed diets containing 10% to 20% PEG-8 and -40 Stearate had decreased newborn litter survival time due to maternal neglect. Impairment of lactation efficiency as evidenced by lower weanling weights, greater mortality of nurslings, and decreased reproductive performance in the F3 generation were observed in rats fed diet containing 20% PEG-8 and -40 Stearate. No reproductive effects were noted in rats fed 5% PEGs Stearate (Elder 1983a).

*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).

## 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-150 was not mutagenic in the mouse lymphoma forward mutation assay when tested at concentrations up to 150 g/l (Andersen 1993).

Lauric Acid at concentrations of 10 to 200 mg/ml increased the incidence of aneuploidy in the $D_6$ strain of *Saccharomyces cerevisiae*, but did not increase the frequency of mitotic crossing over events. The inhibitory action of Lauric Acid on the mutagenicity of several compounds has been demonstrated using two bacterial systems (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 for rats; 1 year of dosing for mice), or when injected into the gastric antrum of guinea pigs over a period of 6 months (Andersen 1993).

Lauric Acid was classified as a noncarcinogen after being administered to female BALB/c and CFW mice via subcutaneous injections during two studies. In one study, 16 mice were given 2 injections/week (25 total) of 1 mg Lauric Acid in 0.1 ml tricaprylin. Of the mice, five were alive at 18 months. The mice

had one subcutaneous sarcoma, one pulmonary tumor, and two leukemia-lymphomas at 4 and 5 months. In the second study, 15 mice were injected with 5.0 mg Lauric Acid in 0.1 ml tricaprylin (3 injections/week; 10 total). Eight mice were alive at 18 months, and they had one pulmonary tumor and one leukemia-lymphoma at 23 months.

Lauric Acid dissolved in chloroform (concentration not given) stimulated the formation of skin papillomas, but not the formation of malignant tumors during tumor promotion studies. Several fats and oils, including Lauric Acid, produced acanthosis of guinea pig skin. Upon continued topical application, the acanthosis gradually receded.

Lauric Acid (8 mg/day; in Polysorbate 80) was an inhibitor of Ehrlich ascites tumor in vivo after the tumor was implanted into Swiss albino mice of strain ddy. The survival time of treated mice versus mice of the control group more than doubled (Elder 1987).

## CLINICAL STUDIES

*Laureths*

Laureth-23 did not produce cutaneous irritation in 50 subjects treated with a 60% solution, although undiluted Laureth-23 did cause erythema in one subject. Repeated Insult Patch Test (RIPT) studies using 96 and 150 subjects found no evidence of sensitization for Laureth-23, nor was there evidence of phototoxicity or photoallergenicity (Elder 1983b).

*PEGs Stearate*

Clinical studies of the PEGs Stearate indicate that these ingredients are neither irritants nor sensitizers, and no evidence of phototoxicity or photosensitization was observed in studies of the ingredient alone or in formulation. PEG-2 Stearate (25% aqueous) did not induce skin irritation or sensitization in a RIPT involving 168 subjects. Neither photosensitization nor phototoxic reactions to PEG-2 Stearate were noted in a group of 28 subjects. Reactions also were not observed in 10 subjects patch tested (two 48-hour applications) with undiluted PEG-100 Stearate, and the same was true for 188 subjects patch tested (RIPT) with a skin conditioner containing 1% to 3% PEG-100 Stearate. A skin conditioner containing 1% to 3% PEG-100 Stearate also was not phototoxic to human subjects (Elder 1983a).

*Polyethylene Glycol*

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-hour challenge reading. Cases of systemic toxicity and contact dermatitis in burn patents 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).

*Lauric Acid*

No irritation or sensitization was observed after 46 to 48 subjects were treated with 1% Lauric Acid (1.95% in liquid soap formulation) during a repeated insult patch test (Elder 1987).

## SUMMARY

The PEGs Dilaurate, PEGs Laurate, and PEG-2 Laurate SE are PEG diesters or esters of lauric acid that function as surfactants in cosmetic formulations. In 1997, PEG-8 Dilaurate and PEG-12 Dilaurate were used in 40 cosmetic formulations, and PEG-2, -4, -8, -10, -15, and -200 Laurate were used in 20 formulations. The remaining ingredients from this family had no reports of use. In 1984, data submitted to the FDA indicated that the PEGs Dilaurate and PEGs Laurate were used at concentrations up to 25%.

The CIR Expert Panel has previously reviewed the safety in cosmetics of the PEGs Stearate, PEGs Distearate, PEGs, Laureths, and Lauric Acid. Based on the similarity in chemical structures, data from those evaluations have been used as a further basis for the safety assessment of the PEGs Dilaurate and PEGs Laurate in cosmetics.

These polyoxyethylene ester surfactants and emulsifiers are produced by the ethoxylation of fatty acids during uncatalyzed or alkali-catalyzed reactions. PEG-2 Laurate has been produced by the interesterification of coconut oil with diethylene glycol. PEG-n Laurate could contain unspecified amounts of the lauric acid diester of PEG and unreacted PEG. PEG-6 may contain small, unquantified amounts of monomer and dimers, and samples PEG-32 and PEG-75 contained peroxides as a result of autoxidation. In general, ethoxylated surfactants can contain 1,4-dioxane, a by-product of ethoxylation, which is then removed during purification of the finished products. Traces of the reactants, stearic acid, ethylene oxide, and the catalysts used could remain in the finished product.

Data on the absorption, metabolism, distribution, and excretion of the PEGs Dilaurate and PEGs Laurate were not available. PEG-40 Stearate was hydrolyzed in vitro by pancreatic lipase. 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 PEGs were readily absorbed through damaged skin.

Fatty acids such as Lauric Acid are absorbed, digested, and transported in animals and humans. During labeling studies, radioactivity was found in various tissues, blood, and lymph after oral, IV, IP, and intraduodenal administration of labelled fatty acids. The fatty acids can undergo $\beta$-oxidation to yield acetyl-CoA. Placental transfer of the fatty acids has been observed. Lauric Acid is transported via the lymph and portal systems; fatty acids are typically transported esterified to glycerol in chylomicrons and very-low-density lipoproteins.

The acute oral $LD_{50}$ of PEG-12 Laurate was >25 g/kg in Harlan mice. In the same study, the IV $LD_{50}$ was 500 mg/kg. During short-term feeding studies using chicks, concentrations of up to 2% PEG-4 or-8 Laurate did not cause adverse effects. Rats fed a diet containing 15.9 g/kg/day of 25% PEG-20 Laurate had diarrhea, inflammation of the anal region, and blood clots in the anorectal region after 59 days of treatment. In a 70-day study, rats given 5% to 25% PEG-20 Laurate had diarhhea and inflammation of the anal region. The ingredient was irritating to the gastrointestinal tract, but not necrotizing, and monocyte/macrophage hyperplasia and splenic giant cells were noted more frequently in rats of the treated group than rats of the control group. In a chronic oral toxicity study, nine rats were fed 6% PEG-8 Dilaurate for 505 days. Four of the rats in each of the treatment and control groups died. Of the rats given PEG-8 Dilaurate, one had cystic spots on the liver, one had hemorrhagic lungs, and one had a large fibrosarcoma. In microscopic examinations, three rats had focal parenchymal hepatitis. Of the rats of the control group, four had hemorrhagic and congested lungs, one had hypertrophied testes, one had a concretion in the urinary bladder, two had cystic kidneys, and two had hepatic parasites. In microscopic examinations, one control rat had adrenal cortical hyperplasia, two had chronic interstitial nephritis of the kidneys, two had splenic lymphoid hyperplasia, one had focal parenchymal hepatitis, and one had hepatic vacuolization. During another feeding study, rats fed up to 25% PEG-20 Laurate for 2 years had hepatic cysts, cecal enlargement, slight gastric mucosal hyperplasia, and slight squamous epithelial hyperplasia. PEG-12 Laurate at a concentration of 1% did not cause ocular irritation in rabbits.

The IV $LD_{50}$ values in Harlan mice for PEG-8 and -20 Distearate were 365 mg/kg and 220 mg/kg, respectively. The oral $LD_{50}$ values of PEG-2-150 Stearate ranged from >10 g/kg to 32 g/kg in rats. The IP $LD_{50}$ of PEG-8 Stearate in rats was >9 ml/kg. No signs of toxicity were observed when rats were given IP injections of 2.5 g/kg PEG-50 or -100 Stearate. A hair cream containing 1.5% PEG-6 Stearate had an oral $LD_{50}$ of >34.6 g/kg. The acute dermal $LD_{50}$ of 15% PEG-8 Stearate in rabbits was >10 ml/kg; the only effect noted was erythema at the application site at 24 hours. The PEGs Stearate caused only slight skin irritation and minimal ocular irritation when tested at concentrations of 100% in animals. PEG-8, -40, and -100 Stearate did not cause significant changes in growth mortality rates, microscopic observations, or hematological values during long-term feeding studies. In clinical studies, the PEGs Stearate were not irritating or sensitizing when tested at concentrations of 25%. In addition, they did not cause photosensitization. PEG-8 and -40 Stearate did not cause reproductive or developmental effects, and were noncarcinogenic.

In acute toxicity studies, the PEGs had low oral and dermal toxicity. The PEGs were not irritating to the skin of rabbits or guinea pigs, and minimally irritating to the skin of humans. They did not cause sensitization in animal or human studies using intact skin, but sensitization and nephrotoxicity were observed in burn patients that were treated with a PEG-based cream. PEG was determined to be the causative agent in both animal and human studies. In ocular irritation studies, the PEGs caused mild, transient ocular irritation in rabbits. Cosmetic product formulations containing up to 13% Lauric Acid did not cause primary or cumulative irritation and did not cause sensitization. The available data indicated that the PEGs were not mutagenic or carcinogenic.

A product formulation containing 5% Lauric Acid was nontoxic to rats during an oral toxicity study. Transient signs of toxicity (mucoid diarrhea, depression, unkempt fur, etc.) were observed when male rats were fed 0.46 to 10 g/kg Lauric Acid. In this study, one rat died; it had congested lungs and kidneys, and advanced autolytic changes. In a subchronic oral toxicity study, rats fed 10% Lauric Acid had no signs of toxicity. Lauric Acid was also noncarcinogenic in animal tests.

It is generally recognized that the PEG monomer, ethylene glycol, and certain of its monoalkyl ethers are reproductive and developmental toxins. The PEGs Dilaurate and PEGs Laurate are diesters and esters of PEG and, as such, are chemically different from PEG alkyl ethers. Hence, they are not expected to cause adverse reproductive or developmental effects.

## DISCUSSION

The CIR Expert Panel was concerned about the sensitization and toxicity potential of the PEGs Dilaurate and PEGs Laurate 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.

Also of concern to the Expert Panel was the possible presence of 1,4-dioxane and ethylene oxide impurities. The Panel stressed that the cosmetics industry should continue to use the necessary procedures to remove these impurities from the PEG Dilaurate and PEG Laurate ingredients before blending them into cosmetic formulations.

Although few data were available on the PEGs Dilaurate and PEGs Laurate, the Expert Panel concluded that the data on the structurally related ingredients (PEGs Distearate, PEGs Stearate, PEGs, and Lauric Acid) were sufficient. Although current concentration of use data were not available, the highest reported concentration of use in 1984 was 25%. The PEGs Dilaurate and PEGs Laurate were considered safe for use at concentrations up to 25% based upon the results of short-term and chronic oral toxicity studies.

## CONCLUSION

On the basis of the available data, the CIR Expert Panel concludes that PEG-2, -4, -6, -8, -12, -20, -32, -75, and -150 Dilaurate; PEG-2, -4, -6, -8, -9, -10, -12, -14, -20, -32, -75, -150, and -200 Laurate; and PEG-2 Laurate SE are safe for use in cosmetics at concentrations up to 25%.

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