Final Report on the Safety Assessment of PEG-2, -3, -4, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150, and -175 Distearate'

PEG Distearate compounds are the polyethylene glycol (PEG) diesters of Stearic Acid. They are manufactured by the esterification of Stearic Acid with a the number of moles of ethylene oxide corresponding to the average polyethylene glycol chain length desired. PEGs Distearate are used as emulsifying, cleansing, and solubilizing agents in a wide variety of cosmetic formulations. Not all of the polymer chain lengths covered in this assessment are currently reported to be used, but all are listed as cosmetic ingredients and may have been used in the past and could be used in the future. Very little toxicity data are available for the PEGs Distearate. Related compounds including PEGs, PEGs Stearate, Steareths, and Stearic Acid, have previously been reviewed. In general, PEGs have a low level of toxicity whether the exposure is oral or dermal. Minimal ocular irritation is seen with PEGs, PEGs Stearate, Steareths, and Stearic Acid. No evidence of mutagenicity, carcinogenicity, or reproductive and developmental toxicity of these related compounds was found. Based on clinical data in bum patients, PEGs were mild irritant/sensitizers and there was evidence of nephrotoxicity. Cosmetic manufacturers should continue to adjust product formulations to minimize any untoward effects when products are used on damaged skin. PEGs Stearate, Steareths, and Stearic Acid were not irritants, sensitizers, or phototoxins. Because of the possibility of residual ethylene oxide and/or 1,4-dioxane impurities in PEGs Distearate, cosmetic formulators are urged to continue efforts to remove these impurities before blending PEGs Distearate into cosmetic formulations. Although metabolites of ethylene glycol monoalkyl ethers are reproductive and developmental toxins, it was considered unlikely that the relevant metabolites would be found in or produced from the use of PEGs Distearate in cosmetic formulations. Based on the available data on related compounds, and current industry practices in the use and manufacture of PEGs Distearate, it was concluded that PEG-2, -3, -4, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150, and -175 Distearate are safe for use in cosmetic formulations under the present practices of use.

INTRODUCTION

PEG-2, -3, -4, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150, and -175 Distearate are surfactants used in cosmetics as emulsifying, cleansing, and solubilizing agents. Chemically, these ingredients are the polyethylene glycol (PEG) diesters of Stearic Acid. 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.

Related chemicals (PEG, Stearic Acid, the Steareths, and PEG Stearates) have been reviewed previously by the Cosmetic Ingredient Review (CIR) Expert Panel and Final Reports have been published. The following conclusions were made:

> 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 1983).
>
> 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).
>
> Stearic Acid is safe for use as a cosmetic ingredient (Elder 1987).
>
> Steareth-2, -4, -6, -7, -10, -1 I, -13, -15, and -20 are safe as cosmetic ingredients in the present practices of use and concentration (Elder 1988).

The relevant data from these previous Final Reports have been summarized in this review as a further basis for the assessment of safety of PEG-2- 175 Distearate.

CHEMISTRY

Definition and Structure

PEG-2, -3, -4, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150, and -175 (CAS No. 9005-08-7 [generic]) Distearate are the polyethylene glycol diesters of Stearic Acid. These ingredients conform to the formula shown in Figure 1, where n has the average value of the number in the name (Wenninger and McEwen 1997).

Chemical and Physical Properties

The PEG Distearate group of cosmetic ingredients has a broad range of properties depending on the degree of polymerization of the PEG segment. The physical forms of these ingredients range from liquids to solids or flakes. Solubility properties are also dependent on the length of the PEG component. Typically, these ingredients are soluble in oil and hydrocarbon solvents when less than eight ethylene oxide units are present. Solubility in water begins with compounds containing 12-15 ethylene oxide units. Specific gravity and viscosity increase with increasing ethylene oxide content (Budavari 1989).

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'Reviewed by the Cosmetic Ingredient Review Expert Panel. Rebecca S. Lanigan, former Scientific Analyst and Writer, prepared this report. Address correspondence to Dr. F. Alan Andersen, Director, CIR, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

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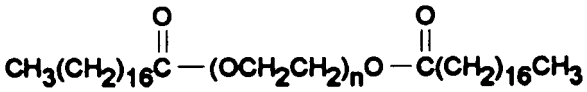

FIGURE 1
Chemical formula for the PEGs Distearate polymer (Wenninger and McEwen 1997). n is the average number corresponding to the number in the name.

Method of Manufacture

In general, the PEGs Distearate are manufactured by the esterification of Stearic Acid with ethylene oxide or with polyethylene glycol (Budavari 1989).

Impurities

Production lots of PEG-150 Distearate from different manufacturers had peroxide concentrations of 1.97 and 1.92 μEq thiosulfate/g glycol (McGinity, Hill, and La Via 1975).

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 byproduct 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 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 of the reactants, Stearic Acid, ethylene oxide, and the catalytic agents used, may remain in the finished product (Elder 1983).

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 1983).

USE

Cosmetic

The PEGs Distearate are surfactants used as emulsifying, cleansing, and solubilizing agents (Wenninger and McEwen 1997). The product formulation data submitted to the Food and Drug Administration (FDA) in 1996 indicated that PEG-2. -3, -4, -6, -8, -12, -50, and -150 Distearate were in use, and that they were collectively used in 283 cosmetic formulations (Table I) (FDA 1996). Concentration of use data were submitted by the Cosmetic, Toiletry, and Fragrance Association (CTFA) in 1995; 0.5% to >1–5% PEGs Distearate were used in cosmetic formulations (Table 2) (CTFA 1995).

International

The PEGs Distearate, with the exception of PEG-120 Distearate, are 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).

BIOLOGICAL PROPERTIES

Absorption, Metabolism, Distribution, and Excretion

PEG-40 Stearate is hydrolyzed in vitro by pancreatic lipase. When the same compound was hydrolyzed with alkali, a 5–1000 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 1983).

Gastrointestinal absorption of PEGs is dependent on the molecular weight of the compound. In general, the larger the molecular weight of the PEG compound, the lesser the absorption that occurs. In both oral and intravenous (i.v.) 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).

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. B-Oxidation of the fatty acids involves serial oxidation and reduction reactions yielding acetyl-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 (Elder 1987).

ANIMAL TOXICOLOGY

Acute Toxicity

Hopper, Hulpieu, and Cole (1949) reported the toxicological properties of several surface-active agents, including PEG-8 and PEG-20 Distearate. The LD50s for those two compounds were

TABLE 1
Product formulation data (FDA 1996)

Product category	Total no. formulations in category	Total no. formulations containing ingredient
PEG-2 Distearate		
Face and neck preparations (excluding shaving)	300	2
Moisturizing preparations	942	1
Night preparations	226	1
1996 total		**4**
PEG-3 Distearate		
Shampoos (noncoloring)	972	2
Cleansing preparations	820	4
Body and hand preparations (excluding shaving)	1012	2
1996 total		**8**
PEG-4 Distearate		
Hair conditioners (noncoloring)	715	4
Cleansing preparations	820	1
1996 total		**5**
PEG-6 Distearate		
Cleansing preparations	820	1
1996 total		**1**
PEG-8 Distearate		
Hair conditioners	715	9
Rinses (noncoloring)	60	2
Shampoos (noncoloring)	972	1
Tonics, dressings, and other hair grooming aids	60	1
Other hair preparations	395	1
Blushers (all types)	277	1
Face powders	313	1
Other makeup preparations	157	1
Deodorants (underarm)	303	6
Other personal cleanliness products	339	26
Aftershave lotion	268	6
Other shaving preparation products	63	3
Body and hand preparations (excluding shaving)	1012	3
Moisturizing preparations	942	1
Other skin care preparations	810	2
1996 total		**64**
PEG-12 Distearate		
Hair conditioners	715	6
Rinses (noncoloring)	60	5
Tonics, dressings, and other hair grooming aids	604	1
Makeup bases	154	1
1996 total		**13**
PEG-50 Distearate		
Cleansing preparations	820	1
1996 total		**1**

(Continued on next page)

TABLE 1
Product formulation data (FDA 1996) *(Continued)*

Product category	Total no. formulations in category	Total no. formulations containing ingredient
PEG-150 Distearate		
Baby shampoos	23	12
Other baby products	37	2
Bubble baths	211	15
Other bath preparations	166	12
Eye shadow	588	1
Eye lotion	22	1
Hair conditioners (non-coloring)	715	4
Hair straighteners	50	1
Permanent waves	434	1
Shampoos (non-coloring)	972	46
Tonics, dressings, and other hair grooming aids	604	2
Other hair preparations	395	3
Blushers (all types)	277	26
Face powders	313	2
Foundations	355	3
Makeup bases	154	1
Rouges	30	1
Nail creams and lotions	18	1
Bath soaps and detergents	372	14
Other personal cleanliness products	339	1
Aftershave lotion	268	1
Men's talcum	11	2
Shaving cream	158	7
Other shaving preparation products	63	3
Cleansing preparations	820	9
Body and hand preparations (excluding shaving)	1012	2
Moisturizing preparations	942	5
Night preparations	226	1
Paste masks (mud packs)	300	3
Other skin care preparations	810	3
Suntan gels, creams, and liquids	196	1
Indoor tanning preparations	67	1
1996 total		**187**

365 mg/kg and 220 mg/kg, respectively, when determined using rats.

The LD50s 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. The acute oral LD50 of a hair cream preparation containing 1.5% PEG-6 Stearate was > 34.6 g/kg in rats. The acute intraperitoneal (i.p.) LD50 of PEG-8 Stearate was >9 ml/kg in rats given 2 ml 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 injections. No signs of toxicity were observed in rats given i.p. 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 jejunem of a dog had no effect on blood pressure. That same day, an i.v. 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 LD50 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 1983).

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 studies, no

TABLE 2
Concentration of use (CTFA 1995)

Formulation	Concentration (%)
Unspecified PEG Distearate	
Hair conditioner	4
Antiperspirant	1
Cleanser	2
Penns	2
Shampoo	1.5
Nail cuticle cream	4
Moisturizer	1.5
PEG-150 Distearate	
Bubble bath, shower gel, liquid soap	up to 1.75
Moisturizing facial lotion, eye cream, moisturizing facial cream, moisturizing night cream	up to 0.5
Hair conditioner	1-5
Hair preparations	>1-5
Skin care preparations	>1-5

deaths were reported in groups of rabbits dosed with 20 ml/kg of either undiluted PEG-6 or 40% PEG-20M (Andersen 1993).

Acute oral toxicity was slight in animals of studies with Stearic Acid at concentrations as great as 10 g/kg, or with cosmetic formulations containing Stearic Acid at concentrations of 2.8-13% at a dose of 15-19 g/kg body weight. Intradermal injections of 10-100 mM Stearic Acid in olive oil produced mild erythema and slight induration of the skin of guinea pigs and rabbits (Elder 1987).

Two of 10 Wistar-derived albino rats died after being given a roll-on antiperspirant orally (containing 1.8% Steareth-2); upon necropsy, one had "fibrous tissue encasing the heart and lungs." The reported LD50 was > 10 g/kg. The acute oral LD50s in rats of Steareth-2 (40% in water), -10 (unspecified concentration), and -20 (25% in distilled water) were >25.1 g/kg, 2.91 g/kg, and 2.07 g/kg, respectively. The acute i.p. LD50 of 10% Steareth-2 in normal saline was 0.76 g/kg in rats; the i.p. LD50 of 1.5% Steareth-20 in a moisturizing formulation was 0.19 g/kg. The acute i.v. LD50 of 1% Steareth-2 in propylene glycol was 0.041 g/kg; that of 10% Steareth-20 in isotonic NaCl was 0.164 g/kg. A single oral dose of 25.1 g/kg Steareth-2 (40% in water) was given to groups of five male and five female Sprague-Dawley rats. The rats had been fasted for 16 hours prior to administration of the test chemical and the subsequent 14-day observation period. None of the rats died during the study (Elder 1988).

Short-Term Toxicity

Weanling hamsters fed a diet containing 5% or 15% PEG Monostearate for 2-10 weeks had pronounced changes 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 for periods ranging from 6 to 9 weeks. Rabbits exposed topically for 20 days to 0.5-2.0 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 1983).

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 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).

Feeding of 50% Stearic Acid to chicks for 4 weeks had no adverse effects. Rats fed high-fat diets containing 5% Stearic Acid had decreased clotting time, moderate hyperlipemia, and severe phlebothrombosis following initiation with an i.v. injection of lipopolysaccharide (LPS) from *Salmonella typhosa*. In a similar study, rats fed high-fat diets containing 6% Stearic Acid for 9 weeks developed severe aortic atherosclerosis and thrombosis following *S. ryphosa* LPS induction; high mortality was also observed. A diet containing 50% Stearic Acid fed to rats for 8 weeks resulted in a microscopic "foreign body-type reaction" in adipose tissue. Etythema, desquamation, and follicular keratosis were not observed in albino rabbits that received 3 ml daily topical applications (to the skin of the external ear canal) of 5% (*w/v*) Stearic Acid in alcohol 5 days per week for 6 weeks. Doses of 2 ml/kg 20% Stearic Acid in a product formulation applied to abraded and intact skin sites on the back daily for 4 weeks resulted in slight edema and desquamation, but no deaths, in rabbits. Daily topical applications of Stearic Acid (concentration not given) to the shaved skin of albino or Long-Evans rats had little effect after 2 weeks of treatment. Edema, slight desquamation, and slight scaling were observed in New Zealand white rabbits that received topical applications to the skin of the back of a product formulation containing 2% Stearic Acid daily for 4 weeks. Intact and abraded skin sites had similar reactions to the test product. All other physiological parameters were normal and no significant gross or microscopic alterations were observed (Elder 1987).

Subchronic Toxicity

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 74-260 days. Rabbits fed a diet containing 4% PEG-8 Stearate for 4 months or 5% PEG-8 Stearate for 19 weeks had no treatment-related effects (Elder 1983).

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).

A "foreign body-type reaction" in perigonadal fat and the reversible formation of lipogranulomas were observed in rats fed 50 g/kg/day Stearic Acid for 24 weeks. Stearic Acid at a concentration of 2% in two cosmetic product formulations did not cause dermal irritation in New Zealand white rabbits that received daily 2 ml/kg topical applications, 5 days per week, for 20 weeks to both abraded and intact skin sites on the back. Edema was observed in all test rabbits (6/6) and two had slight local desquamation of the skin that was of irregular duration. At necropsy, no significant microscopic lesions were noted. Product formulations containing 5.0% (4.0 ml/kg doses) and 2.4% (227 mg/kg) Stearic Acid were applied daily to the shaved dorsal skin of female albino and female Sprague-Dawley rats, respectively, in 13-week dermal toxicity studies. Minimal to moderate skin irritation was noted during each study. An unspecified number of rats that received 5.0% Stearic Acid had subclinical bronchitis and "focal interstitial mononuclear cell infiltration into the kidneys, liver, and heart." In the same group, five of 15 rats had grade 1 hyperkeratosis. Minimal hyperkeratosis of the epidermis was observed in an unspecified number of rats given 2.4% Stearic Acid (Elder 1987).

In two separate studies, no signs of systemic toxicity were observed in rabbits that received topical applications of cosmetic formulations containing 4% Steareth-20 daily for 3 months. Slight to moderate dermal irritation occurred in both studies (Elder 1988).

Chronic Toxicity

Hamsters fed 5–15% PEG Monostearate for 28-39 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 three successive generations (Elder 1983).

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

Anorexia, severe pulmonary infection, and high mortality were observed in rats fed 3000 ppm Stearic Acid for 30 weeks (Elder 1987).

Dermal Irritation

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 1983).

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).

In single insult occlusive patch tests for primary irritation, commercial grades of Stearic Acid, at doses of 35–65%, produced none to moderate erythema and slight, if any, edema in the skin of rabbits (Elder 1987).

In 24-hour patch tests, Steareth-2, -10, and -20 were either nonirritants or mild irritants when tested at concentrations up to 60% (Elder 1988).

Dermal Sensitization

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 1983).

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).

In maximization studies with two cosmetic product formulations containing 1 .O% Stearic Acid, slight reactions were observed to challenge patches. These formulations were considered weak, grade I, sensitizers. In another maximization study, after intradermal induction and booster injections of a formulation containing 3.5% Stearic Acid, reactions to topical challenge applications of the formulation were few and minimal in intensity. In guinea pig photosensitization studies, concentrations of up to 2.8% Stearic Acid in skin lotion formulations were not photoallergenic (Elder 1987).

Ocular Irritation

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

PEG-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).

Stearic Acid alone, as well as cosmetic product formulations containing 1–65% Stearic Acid, produced no irritation or minimal irritation after single and multiple instillations into the conjunctival sac of rabbits. Irritation was primarily manifested as mild conjunctival erythema (Elder 1987).

Concentrations of 0.6–60% Steareth-2 were nonirritating or mildly irritating to the eyes of rabbits tested using a modified Draize procedure. Steareth- 10 (1 0–60%) was minimally irritating. Mild to moderate irritation and/or slight conjunctivitis were seen in rabbits tested with 1.5–60% Steareth-20 (Elder 1988).

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 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.).

Because of the methods of manufacture of the PEGs Distearate, the likelihood of methoxyethanol, ethoxyethanol, and other similar compounds being present as an impurities is slight to nil. In addition, because the PEG Distearate compounds are diesters of polyethylene glycol, and as such, are chemically different from alkyl ethers, the Panel concluded no reproductive or developmental hazards are posed by these compounds.

In multigenerational studies, rats fed diets containing 10–20% 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 diets containing 20% PEG-8 and -40 Stearate. No reproductive effects were noted in rats fed 5% PEGs Stearate (Elder 1983).

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).

Stearic Acid was inactive in aneuploidy induction tests (concentrations up to 500 μg/ml) and in the Ames test (50 μg/ml) with or without metabolic activation in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 (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 evidence of carcinogenicity was observed in studies of rats fed 0.3% or 50 g/kg/day Stearic Acid. In subcutaneous studies, a low incidence of carcinomas, sarcomas, and lymphomas was observed in mice receiving repeated subcutaneous injections of up to 82 mg Stearic Acid (Elder 1987).

CLINICAL STUDIES

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 repeated-insult patch test (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-hours 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 1983).

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 bum 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).

Primary and cumulative irritation studies of up to 40% Stearic Acid in mineral oil were negative. Mild to intense erythema in single insult occlusive patch tests, soap chamber tests, and 2 1-day cumulative irritation studies were produced by cosmetic product formulations containing up to 13% Stearic Acid. These reactions were generally not related to the fatty acid concentrations in the formulations. In clinical repeated insult patch tests (open, occlusive, and semiocclusive), maximization tests, and prophetic patch tests with cosmetic product formulations containing up to 13% Stearic Acid, no primary or cumulative

irritation or sensitization was reported. A few subjects reacted to a few, isolated induction patches. Slight, if any, reactions were observed after challenge patching at original or adjacent sites on the upper backs or forearms of some subjects. Intensity of observed reactions to the formulations was not directly related to the concentrations of the fatty acid ingredients (Elder 1987).

Concentrations up to 60% Steareth-2, - 10, and -20 were nonirritating and nonsensitizing in human single insult and repeated insult patch tests. Steareth-20 (4%) was not a cumulative irritant and did not induce contact photoallergenicity, contact dermatitis, or sensitization. A suntan formulation containing 2.75% Steareth-2 and 2.25% Steareth-20 was not phototoxic or photosensitizing (Elder 1988).

SUMMARY

PEG-2, -3, -4, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150, and -175 Distearate are the polyethylene glycol diesters of Stearic Acid. These ingredients are surfactants that function as emulsifying, cleansing, and solubilizing agents in cosmetics. Product formulation data submitted to the Food and Drug Administration (FDA) indicate that PEG-2, -3, -4, -6,-8, - 12, -50, and - 150 Distearate were in use, and that they were used in 283 cosmetic formulations.

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

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

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

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

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

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

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

DISCUSSION

Safety test data on the PEGs Stearate polymers, the PEGs, Stearic Acid and the Steareths were all considered relevant and supportive of the safety of the PEGs Distearate polymers. The CIR Expert Panel was concerned about the sensitization and toxicity potential of the PEGs Distearate when applied to damaged skin. This concern arose because of positive 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 PEGs should not, therefore, be used on damaged skin.

Also of concern to the Expert Panel was the possible presence of 1,4-dioxane and ethylene oxide impurities. They stressed that the cosmetics industry should continue to use the necessary procedures to remove these impurities from the PEG Distearate ingredients before blending them into cosmetic formulations. Based on particle size and cosmetic use concentrations, it was not considered likely that these ingredients, in formulation, are respirable. Thus, the Expert Panel had no concerns regarding the absence of inhalation toxicity data, and the Panel considers the PEGs Distearate safe for use in aerosolized products.

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

CONCLUSION

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

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