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## Final Report on the Safety Assessment of PEG-2, -6, -8, -12, -20, -32, -40, -50, -100, and -150 Stearates

The PEG Stearates are the polyethylene glycol esters of stearic acid. These nonionic surfactants are used mainly in cosmetic products as surfactants and emollients at concentrations up to 25%. The PEG Stearates, whose average number of ethylene oxide monomers range from 2 to 150, were nonlethal to test animals up to 10 g/kg. They gave evidence of only low-level skin irritation and minimal eye irritation when tested at 100% concentrations in test animals. PEG-8, -40, and -100 Stearates produced no significant changes in growth mortality rates, histopathologic observations or hematologic values in long-term feeding studies. Multiple generation studies of PEG-8 and -40 Stearates were negative for effects on reproduction; the presence or absence of a carcinogenic effect was not reported.

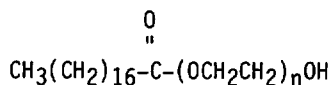
Clinical studies on the PEG Stearates indicated that these ingredients are neither irritants nor sensitizers at concentrations of  $\geq 25\%$ . There was no evidence of phototoxicity or photosensitization of PEG-2 or -8 Stearates.

It is concluded that 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.

### CHEMICAL AND PHYSICAL PROPERTIES

#### Structure

The PEG Stearates are the polyethylene glycol esters of stearic acid that conform to the following formula:



The *n* value corresponds to the average number of ethylene oxide monomers in the polyether chain and is expressed as the identifier for the various PEG Stearates used in cosmetic products. Because the *n* value is the average value of ethylene oxide monomers, any given PEG Stearate will not have a single chain length, but will contain shorter and longer chain lengths whose average is expressed as the chemical identifier.<sup>(1,2)</sup>

### Method of Manufacture

The PEG Stearates may be prepared in one of three ways:<sup>(2)</sup>

1. PEG-*n* Stearate is made by esterification of stearic acid and PEG-*n* under acid catalysis. The catalyst is neutralized following esterification.
2. Stearic acid can undergo direct ethoxylation under alkaline catalysis. The base is neutralized following ethoxylation.
3. Methyl stearate can be catalytically transesterified to polyethylene glycol. After preparation, the product is refined by vacuum stripping and/or filtration.

### Properties

The PEG Stearates are soft to waxy solids, white to tan in color, and most have a faint odor. In general, the monoesters are soluble in water and alcohol but not in mineral oil; the diesters are soluble in isopropyl alcohol and toluene, and dispersible or soluble in hot water.

The PEG Stearates are nonionic surfactants.<sup>(3,4)</sup> The monostearates are highly amphiphatic compounds. The long, 18-carbon stearate chain is lipophilic; the polyether chain is hydrophilic. Each ether oxygen atom carries a partial negative charge which attracts polar water molecules, thus potentiating water solubility of the monostearate. The longer the polyether chain (greater *n* value), the greater is the hydrophilicity of the ingredient. The hydrophile-lipophile balance (HLB) value is used to describe the PEG Stearates and facilitate the selection of an ingredient for a particular use. Typical HLB values are 4.3 for PEG-2 Stearate and 18.8 for PEG-150 Stearate.<sup>(2)</sup> As any surfactant interacting at an oil-water interface, PEG Stearates align themselves with the hydrophilic polyether part of the molecule dissolved in the aqueous phase and the lipophilic stearate part of the molecule dissolved in the oil phase. The amphoteric nature of these compounds affords them many of their physical properties and, thus, many of their uses in cosmetic and noncosmetic formulations.<sup>(4,5)</sup>

### Reactivity

PEG Stearates are relatively stable compounds.<sup>(6)</sup> Nevertheless, the ether oxygens are potentially reactive and the ester bonds are potentially vulnerable to enzymatic cleavage.

### Impurities

Traces of the reactants, stearic acid and ethylene oxide, and of the catalytic agents used, may remain in the finished product. The addition of antioxidants or other additives has not been reported.<sup>(2)</sup> A reaction product of ethoxylation,

1,4-dioxane, may also be present in trace amounts; industry is aware of this possible impurity and thus uses additional purification steps to remove it from the ingredient before blending into cosmetic formulations.<sup>(7)</sup>

## USE

### Noncosmetic Uses

#### Drugs

There are numerous references for the use of the PEG Stearates in drugs as emulsifiers, carriers and stabilizers. They are used to solubilize salicylic acid and barbitol and for dissolution of other poorly soluble pharmaceuticals.<sup>(5,8)</sup>

PEG Stearates make excellent emulsifying agents because of their dual solubility in both water and oil. A variety of emulsions and ointments containing these ingredients has been described as, for example, a benzoic acid emulsion and a zinc sulfadiazine topical burn ointment.<sup>(9-13)</sup> PEG Stearates provide ointment bases with stability to heat and cold.<sup>(12)</sup> One PEG Stearate emulsion has been found to be stable for over two years.<sup>(13)</sup>

#### Foods

The Food and Drug Administration (FDA) has approved without limits the use of PEG-40 Stearate as a defoaming agent used in coating food packaging materials.<sup>(14)</sup>

PEG Stearates are used in the bakery industry as bread softeners and antistaling agents.<sup>(15-19)</sup>

### Purpose and Frequency of Use in Cosmetics

PEG Stearates are used as surfactants in skin creams, emollients and conditioners, shampoos, body cleansers, and soapless detergents.<sup>(10-12,20)</sup>

PEG Stearate-containing formulations may be applied to the face (creams, emollients, cleansers), axillae (antiperspirants), hair and scalp (shampoos), skin in general (body cleansers, detergents) and the oral and gingival mucosae (toothpastes, dentifrices).

The frequency of application of PEG Stearate products may vary from daily (toothpastes, antiperspirants, skin creams) to occasional use (emollients, shampoos, skin conditioners). Duration of application can range from seconds (shampoos, toothpastes, body cleansers) to all day (skin conditioners and emollients, antiperspirants). This occasional or daily use may extend over a period of years.

PEG Stearates are used in over 500 cosmetic formulations. Most are used at concentrations from less than 0.1% to 10%.<sup>(20)</sup> Two products list concentrations in the >10%–25% range (Table 1).<sup>(21)</sup> The cosmetic product formulation computer printout which is made available by the FDA is a database compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations.<sup>(14)</sup> Ingredients are listed in prescribed concentra-

**TABLE 1. Product Formulation Data.**

Product category	Total no. containing ingredient	No. of product formulations within each concentration range (%)			
		> 10-25	> 5-10	> 1-5	> 0.1-1
<i>PEG-2 Stearate</i>					
Bath preparations	1	—	—	—	1
Fragrance preparations	11	—	9	2	—
Hair preparations (noncoloring)	4	—	1	2	1
Hair coloring preparations	1	—	—	—	1
Makeup preparations (not eye)	16	—	1	5	10
Manicuring preparations	1	—	—	1	—
Personal cleanliness products	1	—	—	—	1
Shaving preparations	6	—	—	—	6
Skin care preparations	20	—	5	13	2
Suntan and sunscreen preparations	1	—	—	1	—
1976 TOTALS	62	—	16	24	22
1979 TOTALS	103	2	8	2	91
<i>PEG-6 Stearate</i>					
Hair preparations (noncoloring)	1	—	—	1	—
Skin care preparations	3	—	—	3	—
1976 TOTALS	4	—	—	4	—
1979 TOTALS	3	—	—	3	—
<i>PEG-8 Stearate</i>					
Eye makeup preparations	1	—	—	—	1
Fragrance preparations	3	—	—	3	—
Hair preparations (noncoloring)	13	—	2	10	1
Makeup preparations (not eye)	5	—	—	4	1
Shaving preparations	1	—	—	1	—
Skin care preparations	3	—	—	1	2
Suntan and sunscreen preparations	1	—	—	1	—
1976 TOTALS	27	—	2	20	5
1979 TOTALS	37	—	7	25	5
<i>PEG-12 Stearate</i>					
Eye makeup preparations	1	—	—	—	1
1976 TOTALS	1	—	—	—	1
1979 TOTALS	2	—	—	1	1
<i>PEG-20 Stearate</i>					
Eye makeup preparations	4	—	1	2	1
Fragrance preparations	4	—	—	4	—
Hair preparations (noncoloring)	8	1	1	3	3
Hair coloring preparations	1	—	—	1	—
Makeup preparations (not eye)	3	—	—	—	3
Personal cleanliness products	3	—	—	1	2
Shaving preparations	2	—	—	2	—
Skin care preparations	10	—	—	4	6
1976 TOTALS	35	1	2	17	15
1979 TOTALS	23	1	2	11	9

TABLE 1. (Continued.)

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Product category	Total no. containing ingredient	No. of product formulations within each concentration range (%)			
		>10-25	>5-10	>1-5	>0.1-1
<i>PEG-32 Stearate</i>					
Eye makeup preparations	3	—	3	—	—
Personal cleanliness products	1	—	1	—	—
Shaving preparations	1	—	—	1	—
Skin care preparations	4	—	3	1	—
1976 TOTALS	9	—	7	2	—
1979 TOTALS	8	—	7	1	—
<i>PEG-40 Stearate</i>					
Bath preparations	1	—	1	—	—
Eye makeup preparations	4	—	2	2	—
Fragrance preparations	9	—	5	4	—
Hair preparations (noncoloring)	5	—	5	—	—
Makeup preparations (not eye)	42	—	39	3	—
Manicuring preparations	2	—	2	—	—
Personal cleanliness products	11	—	11	—	—
Shaving preparations	2	—	1	1	—
Skin care preparations	19	—	12	7	—
Suntan and sunscreen preparations	5	—	5	—	—
1976 TOTALS	100	—	83	17	—
1979 TOTALS	179	2	110	67	—
<i>PEG-50 Stearate</i>					
Eye makeup preparations	13	—	13	—	—
Hair preparations (noncoloring)	1	—	—	1	—
Skin care preparations	3	—	3	—	—
1976 TOTALS	17	—	16	1	—
1979 TOTALS	15	—	12	1	2
<i>PEG-100 Stearate</i>					
Hair preparations (noncoloring)	7	—	3	4	—
Personal cleanliness products	2	1	1	—	—
1976 TOTALS	9	1	4	4	—
1979 TOTALS	—	2	7	16	5
<i>PEG-150 Stearate</i>					
Hair preparations (noncoloring)	1	—	—	—	1
Skin care preparations	2	—	2	—	—
1976 TOTALS	3	—	2	—	1
1979 TOTALS	4	—	3	—	1

Data from Refs. 20, 21.

tion ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the concentration in such a case would be a fraction of that reported to the FDA. The fact that data are submitted only within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to 10-fold error in the assumed ingredient concentration.<sup>(20)</sup>

## BIOLOGICAL PROPERTIES

### General Effects

PEG-40 Stearate produced no significant interference with oxygen uptake by kidney tissue preparations.<sup>(22)</sup> PEG-20, -30, and -40 Stearates were reported to activate the cytochrome oxidase enzyme system in heart muscle preparations up to a concentration of 150 mg/ml.<sup>(23)</sup>

PEG-40 Stearate is hydrolyzed in vitro by pancreatic lipase.<sup>(24,25)</sup>

Krantz et al.<sup>(22)</sup> hydrolyzed PEG-40 Stearate with alkali and examined the polyoxyethylene hydrolysate. In a concentration range of 5–1000 mg percent, the hydrolysate was found to have no hemolytic effect on defibrinated human blood when tested at 37 °C for 18 h. The hydrolysate was injected intravenously (5 ml, 5% solution) into dogs; there were no resultant changes in blood pressure.

Weanling hamsters were fed a diet containing 5% or 15% PEG Monostearate or lard for 2–10 weeks. The animals were sacrificed, and a variety of tissues were examined microscopically. Pronounced changes were found in the duodenum, ileum, liver, kidney, and testes. Severe erosion of the ileal mucosa was observed along with necrosis of the liver. There was decreased spermatogenic activity and tubular degeneration of the kidney.<sup>(26)</sup>

Hamsters were fed 5%, 10%, or 15% dietary levels of PEG Monostearate for 28–39 weeks. For all concentrations used, the observations included a very high mortality rate, chronic diarrhea, atrophic testes, enlarged kidneys, thickened bladder walls, striking hepatic, cecal and splenic hemosiderosis, enlarged ceca, and obstructive nephropathy. Six large calculi (4–6 mm in diameter, 50–95 mg in weight) were found in the urinary bladders of hamsters fed PEG Stearates for periods ranging from 74 to 260 days.<sup>(27)</sup>

### PEG-2 Stearate

#### Animal Toxicology

##### *Acute oral*

A 50% w/v suspension of PEG-2 Stearate in corn oil was given orally to five groups of five rats each in a dosage range of 0.464–10.0 g/kg. There were no

deaths during the two week observation period. Body weight gains were normal; no abnormal gross lesions.<sup>(28)</sup>

Groups of 10 rats each were administered varying doses of PEG-2 Stearate orally. The 72-h LD50 was reported as > 10 g/kg.<sup>(29)</sup>

#### *Primary skin irritation*

PEG-2 Stearate (0.5 ml) was applied to intact and abraded skin sites on the back of each of six rabbits. Following 24 h of exposure, the sites were scored and again at 72 h according to the Federal Hazardous Substances Labeling Act (FHSLA) scale. The primary irritation index (PII) was found to be 0.08/8.00 indicating that the ingredient has a potential for slight irritation.<sup>(29)</sup> The same protocol and scoring procedure were used in another experiment. The resulting PII was 0.17/8.00 indicating the same low level of skin irritation potential for PEG-2 Stearate.<sup>(28)</sup>

#### *Eye irritation*

One hundred mg of PEG-2 Stearate were instilled into one eye of each of six rabbits according to the Draize procedure. The 24, 48, and 72 h ocular irritation scores were 6.3, 1.5, and 0.0/110, respectively. PEG-2 Stearate is a minimal eye irritant.<sup>(29)</sup>

#### *Skin sensitization*

The Landsteiner and Jacobs sensitization procedure was used on two guinea pigs to evaluate the effects of a 0.1% suspension of PEG-2 Stearate. Intracutaneous injections were made thrice weekly for a total of 10 exposures. The first induction injection was 0.05 ml while the remaining nine were 0.1 ml each. After two weeks, a challenge injection of 0.05 ml was made. The exposure sites were scored 24 h after each injection. The average score for the 10 sensitizing injections was compared with the score for the challenge. PEG-2 Stearate was considered to be a nonsensitizer.<sup>(29)</sup>

### **Clinical Studies**

#### *Irritation and sensitization*

A repeated insult patch test was performed on 168 subjects (115F, 53M) using 0.1 ml of a 25% water solution of PEG-2 Stearate. The test material was applied at 48 h intervals, three times per week for three weeks on the backs of the subjects. The test area was occluded for 24 h before removal, and washed with distilled water. The test sites were read at 48 h, after which fresh test material and the occlusive patch were reapplied. After a three-week rest period, the test area, as well as an untreated site, were challenged using the same procedure as previously noted. The sites were scored for sensitization at 24, 48, and 72 h. The investigator noted that only transient reactions were observed during the test and that PEG-2 Stearate was neither an irritant nor a sensitizer.<sup>(30)</sup>

#### *Phototoxicity and photosensitization*

Twenty-eight of the 168 subjects tested for irritation and sensitization discussed above were randomly selected to test the ability of PEG-2 Stearate to in-

duce a phototoxic or photosensitive reaction following ultraviolet exposure. The test protocols were the same except that the forearm was used as a test site. The 28 subjects were divided into two groups; 19 received only UVA and nine received both UVA and UVB. The UVA (320–400 nm) light was applied for 15 min to the 19 subjects ( $4.4 \mu\text{W}/\text{cm}^2$  at the skin surface measured at a 360 nm wave length peak). The UVB was applied at two times Mean Erythema Dose (MED) to nine subjects from a 150 watt Xenon Arc Solar Simulator emitting at 280–320 nm. The subjects receiving the UVB exposure were also exposed for 5 min to UVA as previously described. The investigator noted that only transient reactions were observed, and that PEG-2 Stearate was not a photosensitizer.<sup>(30)</sup>

### **PEG-6 Stearate**

#### **Animal Toxicology**

##### *Acute oral*

A hair cream preparation containing 1.5% PEG-6 Stearate was tested for acute oral toxicity on four groups of four rats each at 10.2, 15.4, 23.1, or 34.6 g/kg. There were no deaths or gross pathologic alterations. The LD50 was reported to be  $> 34.6 \text{ g/kg}$ .<sup>(31)</sup>

##### *Primary skin irritation*

The 1.5% PEG Stearate hair cream formulation was tested for primary skin irritancy on abraded and intact skin sites on each of four rabbits. The sites were exposed under occlusion for 24 h and then scored according to the Draize system. The PII was reported as 0.4/8.0.<sup>(31)</sup>

##### *Eye irritation*

The 1.5% PEG-6 Stearate hair cream formulation was tested for potential eye irritancy on two groups of five rabbits each. In the nonirrigated group, the Draize scores were 19.2, 9.8, and 2.6 at 1, 24, and 48 hours, respectively, postinstillation, and zero thereafter. In the group with eyes irrigated for 4 sec after instillation, the scores were 13.0 and 3.8 at 1 and 24 hours, respectively, and zero thereafter.<sup>(31)</sup>

##### *Subchronic dermal toxicity*

Three groups of 10 rabbits each were exposed topically for 20 days to 0.5, 1.0, or 2.0 g/kg of the 1.5% PEG-6 Stearate hair cream product. No significant adverse findings were noted; mortality, body weights, hematologic parameters, blood studies, urinalyses, and gross and micropathologic studies were negative. Erythema, dryness, wrinkling, desquamation and hyperkeratosis were found at the application sites of both experimental and control groups.<sup>(31)</sup>

#### **Clinical Studies**

The 1.5% PEG-6 Stearate hair cream was tested on 48 subjects for potential skin irritancy/sensitization. Four occlusive patches per week for two weeks were applied for 18–24 h each after which the patch was removed and the sites scored

on a scale of 0 to 8. Two weeks after the last induction patch, a challenge patch was applied to an adjacent area of the arm. These sites were scored 24 and 48 h later. All irritation scores were zero following the first five exposures. For insults 6, 7, and 8 there were 1, 4, and 7 reactors, respectively. All challenge scores were zero.<sup>(31)</sup>

## PEG-8 Stearate

### Animal Toxicology

#### General studies

*Acute Oral:* In two different tests, a 50% suspension of PEG-8 Stearate in corn oil was administered orally to five groups of five rats each in a dosage range of 0.464–10.0 g/kg. The LD50s were reported to be > 10 g/kg. There were no gross abnormalities.<sup>(28,32)</sup>

Ten ml/kg of a hair cream product containing 15% PEG-8 Stearate was given by gastric intubation to 10 rats. There were no deaths or gross lesions. The LD50 was reported as > 10 ml/kg.<sup>(31)</sup>

Groups of 10 rats each were orally administered varying doses of PEG-8 Stearate up to 10 g/kg. There were no deaths. The LD50 was estimated to be in excess of 10 g/kg.<sup>(29)</sup>

PEG-8 Stearate was given orally to nine rats; all animals survived. The LD50 was > 11.1 ml/kg.<sup>(33)</sup> The ingredient as a 50% w/v aqueous suspension was administered per os to groups of 10 rats. The LD50 was reported as > 31.6 g/kg. The compound was designated as "relatively harmless."<sup>(33)</sup>

*Subchronic and Chronic Oral:* Several PEG-8 Stearate feeding studies were conducted in rats, dogs, mice, rabbits, and monkeys (Table 2).<sup>(33)</sup>

*Acute Intraperitoneal:* Ten rats were injected intraperitoneally with 2 ml of PEG-8 Stearate. The IP LD50 was estimated to be > 9.0 ml/kg.<sup>(33)</sup>

*Acute Dermal:* Ten ml/kg of an undiluted hair cream product containing 15% PEG-8 Stearate was applied topically for 24 h to four rabbits. The acute dermal LD50 was reported to be > 10 ml/kg. There was moderate erythema at the exposure sites at 24 h which cleared by Day 3.<sup>(31)</sup>

*Primary Skin Irritation:* The PII was determined in rabbits in four studies on undiluted PEG-8 Stearate according to the protocol described for PEG-2 Stearate. The resulting indices were 3.29, 0.293, 3.42, and 0.5 out of 8 maximum. The irritation was primarily the result of erythema. The variability of test results between studies was most likely caused by the variation in abrading skin techniques, and not the ingredient used.<sup>(28,29,32,33)</sup>

An undiluted hair product containing 15% PEG-8 Stearate was tested for skin irritation potential in four rabbits according to the Draize protocol. The resulting PII was 0.81/8.00.<sup>(31)</sup>

*Skin Sensitization:* PEG-8 Stearate was tested for skin sensitization in the guinea pig according to the procedure described for PEG-2 Stearate. The ingredient was considered to be a nonsensitizer with all scores being 0.0.<sup>(29)</sup>

*Eye Irritation:* The Draize ocular irritation test was used to evaluate two samples of undiluted PEG-8 Stearate in rabbits. The maximum average scores at 24 h were 2.0 and 0.0/110, and zero thereafter.<sup>(28,32)</sup>

**TABLE 2.** PEG-8 Stearate Feeding Studies.

<i>Duration</i>	<i>Species</i>	<i>Number</i>	<i>Normal weight gain</i>	<i>Tissue changes</i>	<i>Hematology</i>	<i>Diet (%)</i>
9 Weeks	Rat	15	Yes	Normal	Normal	4
8 Weeks	Rat	15	Yes	Normal	Normal	2
2 Years	Rat	15	Yes	Normal	Normal	4
8 Weeks	Monkey	1	—	Normal	Normal	1 g/day
6 Weeks	Mouse	10	Yes	Normal	Normal	4
9 Weeks	Dog	2	—	Normal	Normal	2 g/day
19 Weeks	Rabbit	2	—	Normal	Normal	5
4 Months	Rabbit	11	Yes	Normal	Normal	4

Data from Ref. 33.

An undiluted hair cream formulation containing 15% PEG-8 Stearate was tested for ocular irritancy in 10 rabbits according to the Draize method. For nonirrigated eyes, the scores were 11, 7, 2, and 0.8/110 at 1, 24, 48, and 72 h, respectively, and zero thereafter. For irrigated eyes, the scores were 7 and 0.4/110 at 1 and 24 h, respectively, and zero thereafter.<sup>(31)</sup>

#### *Special studies*

*Multiple Generation:* Feeding of 4% PEG-8 Stearate in the diet of young rats for three successive generations did not affect growth or fecundity. No micropathological changes were observed in the livers or kidneys of first generation rats after 11 weeks on the diet, after 16 weeks in the second generation, and after 16 months in the third generation. The ratios of liver/body weight and kidneys/body weight were comparable for third generation and control animals.<sup>(33)</sup>

Another three-generation study was carried out on rats fed diets containing 5%, 10%, or 20% PEG-8 Stearate. In both control and experimental groups, seven of ten matings were successful. The reproduction and lactation responses for the 5% group were not different from control responses. At the 10% and 20% levels, newborn litter survival times were diminished probably as a result of maternal neglect. In the 20% group, there was some impairment of lactation efficiency as evidenced by lower weanling weights. In the 20% group, there was also a greater mortality rate of the nurslings. In the F<sub>2</sub> and F<sub>3</sub> generations, similar responses were reported. The overall level of reproductive performance was lower in the F<sub>3</sub> generation for the animals fed the 20% PEG-8 Stearate diet.<sup>(34)</sup>

### **Clinical Studies**

#### *Oral toxicity*

PEG Stearates have been used in the bakery industry as antistaling and bread softening agents suggesting that these ingredients are probably not toxic in those concentrations used.<sup>(17-19,35)</sup> More specifically, the Food Protection Committee of the National Research Council has reported that there is no consistent indication of toxic action of PEG-8 Stearate at animal dietary levels of less than 5%.

They have also stated that PEG-8 Stearate, at levels no greater than 0.05% in the human diet, would be considered safe.<sup>(36)</sup>

PEG-8 Stearate was fed to two children at a rate of 4 g/day for 14 or 16 days. No deleterious effects were reported with respect to behavior, general health, appetite, frequency or consistency of stools, or weight gain.<sup>(37)</sup>

#### *Skin irritation/sensitization*

An undiluted hair cream preparation containing 15% PEG-8 Stearate was applied topically to the upper arm of each of 48 males subjects. The patches containing 0.5 ml of sample were applied on the same sites on Days 1–4 and 6–9. The reactions were scored on Days 2–5 and 7–10. Following a two-week nontreatment period, challenge patches were applied and reactions read at 24, 72, and 96 h. All induction and challenge scores were zero for all subjects tested.<sup>(31)</sup>

A repeated insult patch test was performed on 168 subjects (115F, 53M) using 0.1 ml of a 25% water solution of PEG-8 Stearate. The test material was applied at 48 h intervals, three times per week for three weeks on the backs of the subjects. The test area was occluded for 24 h before removal, and washed with distilled water. The test sites were read at 48 h, after which fresh test material and the occlusive patch were reapplied. After a three-week nontreatment period, the test area, as well as an untreated site, were challenged using the same procedure as previously noted. The sites were scored for sensitization at 24, 48 and 72 h. The investigator noted that only transient reactions were observed during the test and that PEG-8 Stearate was neither an irritant nor a sensitizer.<sup>(30)</sup>

#### *Phototoxicity and photosensitization*

Twenty-eight of the 168 subjects tested for irritation and sensitization discussed above were randomly selected to test the ability of PEG-8 Stearate to induce a phototoxic or photosensitive reaction following ultraviolet exposure. The test protocols were the same except that the forearm was used as a test site. The 28 subjects were divided into two groups, 19 received only UVA and 9 received both UVA and UVB. The UVA (320–400 nm) light was applied for 15 min to the 19 subjects (4.4  $\mu\text{W}/\text{cm}^2$  at the skin surface measured at a 360 nm wave length peak). The UVB was applied at two times Mean Erythema Dose (MED) to nine subjects from a 150 watt Xenon Arc Solar Simulator emitting at 280–320 nm. The subjects receiving the UVB exposure were also exposed for 5 min to UVA as previously described. The investigator noted that only transient reactions were observed, and that PEG-8 Stearate was not a photosensitizer.<sup>(30)</sup>

### **PEG-12 Stearate**

#### **Animal Toxicology**

##### *Acute oral*

Five groups of five rats each were dosed by gavage with 0.464, 1.00, 2.15, 4.64, or 10.0 g/kg of PEG-12 Stearate. There were no deaths.<sup>(28)</sup>

##### *Primary skin irritation*

The PII in rabbits for undiluted PEG-12 Stearate was obtained according to

the procedure described for PEG-2 Stearate. The index was reported to be 2.42/8.00. Most of the irritancy score was the result of erythema.<sup>(28)</sup>

*Eye irritation*

The Draize eye irritation test was used to evaluate the effects of undiluted PEG-12 Stearate in rabbits. All scores were zero. The ingredient was considered to be nonirritating to the eye.<sup>(28)</sup>

## **PEG-20 Stearate**

### **Animal Toxicology**

*Acute oral*

A 50% w/v suspension of PEG-20 Stearate in corn oil was given orally to five groups of five rats each in two studies. The ingredient was equally toxic to males and females and caused no significant gross lesions. The LD50s were reported as 19.85 and > 10 g/kg.<sup>(38)</sup>

*Primary skin irritation*

Undiluted PEG-20 Stearate was tested for potential skin irritancy in rabbits in three tests according to the protocols of FHSLA and DOT as well as that stated previously for PEG-2 Stearate. The PII scores were reported as 0.00, 0.00, and 0.04/8.00, respectively. All scoring was according to the Draize standards.<sup>(28,39)</sup>

*Eye irritation*

The Draize rabbit eye irritation procedure was used to evaluate the ocular irritancy of undiluted PEG-20 Stearate in two studies. The maximum average scores were 2.0, 0.0, and 0.0/110 for unrinsed eyes, eyes rinsed 2 sec, and eyes rinsed 4 sec, respectively, with no corneal involvement.<sup>(39)</sup> In the second study, all scores were zero.<sup>(28)</sup>

## **PEG-32 Stearate**

### **Animal Toxicology**

*Acute oral*

A 50% w/v suspension of PEG-32 Stearate in corn oil was administered orally to five groups of five rats each up to a maximum dose of 10 g/kg. There were no deaths during the 14-day observation period. Normal body-weight gains and no gross lesions were reported.<sup>(28)</sup>

*Primary skin irritation*

The PII was determined for PEG-32 Stearate using the procedure described previously for PEG-2 Stearate. The PII in rabbits was calculated to be 0.32/8.00.<sup>(28)</sup>

*Eye irritation*

The Draize eye irritation procedure was used to evaluate undiluted PEG-32 Stearate in rabbits. The maximum average score was 2.0/110 with no corneal involvement.<sup>(28)</sup>

**PEG-40 Stearate****Animal Toxicology***General studies*

*Acute Oral:* A 50% w/v suspension of PEG-40 Stearate was given orally to six groups of five rats each. The LD50 was estimated to be 32 g/kg.<sup>(39)</sup>

Twenty rats were given 34.8 g/kg of undiluted PEG-40 Stearate by gastric intubation. The LD50 was reported as > 34.8 g/kg.<sup>(33)</sup>

*Subchronic and Chronic Oral:* Several PEG-40 Stearate feeding studies were conducted in rats and monkeys (Table 3).<sup>(33)</sup>

*Acute Injection Studies:* Five ml of 5% PEG-40 Stearate was injected into the lumen of the jejunum of a dog. There was no effect on blood pressure. In the same day, an intravenous injection produced a prolonged hypotensive response. It was stated that this response is a "characteristic reaction" of the dog to a variety of polyoxyethylene compounds.<sup>(33)</sup>

*Primary Skin Irritation:* PILs in the rabbit were determined for PEG-40 Stearate according to the protocol used for PEG-2 Stearate. In two tests, the scores were reported as 0.09 and 0.0/8.0.<sup>(33,39)</sup>

In skin tests on the guinea pig, PEG-40 Stearate was applied to intact, shaven sites on the back. The PIL scores ranged from 0.0 to 1.39/8.00 for the various batches tested.<sup>(40)</sup>

*Skin Sensitization:* Guinea pigs (unspecified number) received induction and challenge intradermal injections of 0.1 ml of a 0.1% PEG-40 Stearate solution in saline. No evidence of sensitization was reported.<sup>(33)</sup>

*Eye Irritation:* The Draize procedure was used to evaluate the ocular irritancy in the rabbit of undiluted PEG-40 Stearate. In two studies, the maximum average scores for eyes not rinsed following instillation were 2.7 and 1.33/110.

**TABLE 3.** PEG-40 Stearate Feeding Studies.

<i>Duration</i>	<i>Species</i>	<i>Diet (%)</i>	<i>Results</i>
24 h	Rat	Entire diet for one day (2.4 g/rat)	No toxic signs
9 Weeks	Rat	2	No effect on growth, no lesions
9 Weeks	Rat	4	No effect on growth, no lesions
8 Weeks	Monkey	1 g/day	No effect on growth, no lesions
2 Years	Rat	2	No effect on growth or mortality rate, no lesions and hematologic value normal

Data from Ref. 33.

For eyes rinsed at 2 or 4 sec after instillation, all scores were 0.0/110 in both tests.<sup>(33,38)</sup>

In another series of tests, 0.1 ml of the ingredient was instilled in rabbit eyes without subsequent washout. The maximum average scores ranged from 0.0 to 2.0/110 for the various batches tested.<sup>(40)</sup>

#### *Special studies*

**Multiple Generation:** Rats were fed diets containing 5%, 10%, or 20% PEG-40 Stearate in a three-generation study. For all groups including control, an average of seven out of 10 matings were successful. The lactation and reproduction responses for the 5% group were the same as for the control group. Survival of the newborn was slightly diminished for the 20% group. In the same group, there was an impairment of lactation. Similar lactation and survival responses were found for the two succeeding generations.<sup>(34)</sup>

### **Clinical Studies**

#### *Skin irritation/sensitization*

Schwartz prophetic patch tests on 60% and 30% PEG-40 Stearate were conducted on 50 and 10 volunteers, respectively. The test consisted of a 72 h occluded patch, scoring of skin site, seven-day nontreatment period, a second 72 h patch at the same site, and scoring the site again. There were no reactors following either exposure for both concentrations used. It was concluded that PEG-40 Stearate is "neither a primary irritant to human skin nor a skin sensitizer."<sup>(33)</sup>

Undiluted PEG-40 Stearate was evaluated in 147 subjects in a single insult, 24 h occlusive patch test. There were 4, 2, and 2 reactions graded as 1/2, 1, and 2, respectively. All other scores were zero.<sup>(40)</sup> When 10% PEG-40 Stearate in 5% glycine/95% water vehicle was similarly tested on 60 subjects, all skin irritation scores were zero.<sup>(40)</sup>

### **PEG-50 Stearate**

#### **Animal toxicology**

##### *Acute oral*

A 50% w/v aqueous solution of PEG-50 Stearate was given orally to 20 rats. There were no deaths at doses up to 25 g/kg.<sup>(41)</sup>

##### *Subchronic oral*

A diet containing 4% PEG-50 Stearate was fed to 10 rats for nine weeks. No deleterious effects were reported.<sup>(41)</sup>

##### *Acute intraperitoneal*

Ten rats were injected intraperitoneally with 2.5 g/kg of PEG-50 Stearate. No signs of toxicity were noted throughout the five-day observation period.<sup>(41)</sup>

##### *Eye irritation*

The Draize procedure was used to evaluate the ocular irritancy of a 50% w/v aqueous solution of PEG-50 Stearate. The maximum average scores were 0.67

and 0.33/110 at 1 and 24 h, respectively, and zero thereafter for eyes unrinsed. All scores were zero for eyes washed two seconds after exposure.<sup>(41)</sup>

## Clinical Studies

### *Skin irritation/sensitization*

The Schwartz patch test on 50% PEG-50 Stearate was conducted on 50 individuals. There was no irritation or sensitization. A 30% solution was similarly tested but with 48 h patches on 10 subjects resulting in identical findings.<sup>(42)</sup>

## PEG-100 Stearate

## Animal Toxicology

### *Acute oral*

A 50% w/v aqueous suspension of PEG-100 Stearate was given orally to 20 rats. The LD50 was reported to be in excess of 25.1 g/kg.<sup>(42)</sup>

Dosages of 2.5 g/kg of a 25% aqueous dispersion of PEG-100 Stearate or 10.0 g/kg of a 50% aqueous dispersion of the ingredient were given to two groups of 10 rats each. There were no deaths or signs of intoxication.<sup>(42)</sup>

### *Subchronic and chronic oral*

Two groups of 10 rats each were fed diets containing either 2% or 5% PEG-100 Stearate for eight weeks. There were no differences from control with respect to mortality, growth, hematologic values and histopathologic observations.<sup>(42)</sup>

Thirty rats were fed diets containing 2% PEG-100 Stearate for over two years. There were no differences from control with respect to growth, mortality, histopathologic observations, and hematologic values.<sup>(42)</sup>

### *Acute intraperitoneal*

Ten rats were injected intraperitoneally with 2.5 g of PEG-100 Stearate. No signs of toxicity were observed during the subsequent 5-day period.<sup>(42)</sup>

### *Subchronic and chronic dermal*

A 28-day abraded skin study and a 91-day intact skin percutaneous toxicity study were conducted on a skin conditioner containing 1%–3% PEG-100 Stearate. A dose of 2 ml/kg/day of undiluted product was applied topically to the shaven backs of rabbits. In both studies, mild to moderate skin erythema developed. Necropsy and histopathologic observations were unremarkable.<sup>(2)</sup>

## Clinical Studies

### *Skin irritation/sensitization*

Undiluted PEG-100 Stearate was patch-tested on 10 individuals. Two 48 h patches were applied with one week between applications. There were no reactions following either exposure.<sup>(2)</sup>

A repeated insult patch test on a skin conditioner containing 1%–3% PEG-100 Stearate (without fragrance) was conducted on 188 individuals. The in-

duction phase was followed by a 24 h challenge patch. There were 0/188 reactors to the challenge.<sup>(2)</sup>

#### *Phototoxicity*

A skin conditioner containing 1%–3% PEG-100 Stearate was phototested on humans. Exposure sites were irradiated with UV light with no adverse effects.<sup>(2)</sup>

### **PEG-150 Stearate**

#### **Animal Toxicology**

##### *Acute oral*

A 50% w/v suspension of PEG-150 Stearate in corn oil was given orally to five groups of five rats each. The LD50 was reported to be >10 g/kg. Body weight gains were normal and necropsy findings were negative.<sup>(28)</sup>

##### *Skin irritation*

The PII was determined for PEG-150 Stearate using the protocol described for PEG-2 Stearate. The value reported was 0.34/8.0.<sup>(28)</sup>

##### *Eye irritation*

The Draize procedure was used to evaluate the ocular irritancy in rabbits of undiluted PEG-150 Stearate. A maximum average score of 2.0/110 was reported for eyes that were unrinsed following instillation of sample.<sup>(28)</sup>

### **SUMMARY**

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

The PEG Stearates, whose average number of ethylene oxide monomers range from 2 to 150, were nonlethal to test animals up to 10 g/kg. They gave evidence of only low-level skin irritation and minimal eye irritation when tested at 100% concentrations in experimental test animals.

PEG-8, -40, and -100 Stearates produced no significant changes in growth, mortality rates, histopathologic observations, or hematologic values in long-term feeding studies. Multiple generation studies of PEG-8 and -40 Stearates were negative for effects on reproduction; the presence or absence of a carcinogenic effect was not reported in these long-term studies.

Clinical studies on PEG-2, -8, -40, -50, and -100 Stearates indicated that these ingredients are neither irritants nor sensitizers at concentrations of  $\geq 25$  percent. There was no evidence of phototoxicity or photosensitization of PEG-2 or -8 Stearate, nor in a formulation containing 1%–3% PEG-100 Stearate.

## DISCUSSION

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

## CONCLUSION

On the basis of the available information presented in this report, the Panel concludes that 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.

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