JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY
Volume 12, Number 5, 1993
Mary Ann Liebert, Inc., Publishers

Final Report on the Safety Assessment of Polyethylene Glycols (PEGs) -6, -8, -32, -75, -150, -14M, -20M

PEGs -6, -8, -32, -75, -150, -14M, and 20M are polymers of ethylene oxide used as humectants, solvents, binders, emulsion stabilizers, and viscosity-increasing agents in cosmetics. In metabolism studies with rats, rabbits, dogs, and humans, the lower molecular weight PEGs were absorbed by the digestive track and excreted in the urine and feces.

PEGs have low oral and dermal toxicity, and are not irritating to the skin of rabbits or guinea pigs; PEG-75 was not a sensitizer. PEGs caused mild, transient ocular irritation in rabbits. PEG-8 was negative in the Chinese hamster ovary cell mutation test, the sister chromatid exchange test, and the unscheduled DNA synthesis assay. PEG-150 was not mutagenic in the mouse $TK^{+}/^{-} \rightarrow TK^{-}/^{-}$ forward mutation assay.

PEG-8 was not carcinogenic when administered orally, intraperitoneally, or subcutaneously to various test animals. No adverse reproductive effects occurred during subchronic and chronic oral toxicity studies of PEG-6-32 and PEG-75. In clinical studies, PEG-8, PEG-6-32, and PEG-75 were not sensitizers.

On the basis of the individual and combined data on PEGs -6, -8, -32, -75, -150, -14M, and -20M, it is concluded that these ingredients are safe for use at the concentrations reflected in the Cosmetic Use section and in the product formulation safety test data included in this report. However, cosmetic formulations containing these PEGs should not be used on damaged skin.

INTRODUCTION

POLYETHYLENE GLYCOLS (PEGs) ARE CONDENSATION POLYMERS of ethylene oxide used for various purposes in cosmetics depending on molecular weight. Some of the more extensively used PEGs are reviewed in this report.

CHEMISTRY

Definition and Structure

PEGs -6, -8, -32, -75, -150, -14M, and -20M (CAS No. 25322-68-3) are polymers of ethylene oxide that conform generally to the formula:

$$H(OCH_2CH_2)_nOH$$

where n has an average value of -6, -8, -32, -75, -150, -14,000, and -20,000,

respectively. Other respective names for these polymers are: PEG-300, -400, -1,540, -4,000, -6,000, -600,000, and -20,000; and Polyoxyethylene-6, -8, -32, -75, -150, -14,000, and -20,000. Trade names for PEGs-6, -8, -32, -75, and -150 are "Carbowax" 300, "Carbowax" 400, "Carbowax" 1540, "Carbowax" 3350 or 4000, and "Carbowax" 6000 or 8000 (Estrin et al., 1982; Shaffer et al., 1948).

Properties

PEGs are condensation polymers of ethylene oxide whose properties vary with molecular weight. The number in the names indicates the average number of moles of ethylene oxide polymerized (Hunting, 1983; Hawley, 1971). PEG-14M (M stands for thousand) refers to a range of materials with different molecular weights and different molecular weight distributions, whose properties vary accordingly (Hunting, 1983).

PEGs with a molecular weight below 700 are clear to slightly hazy, colorless liquids that are slightly hygroscopic. PEGs between 700 and 900 are semisolids, and PEGs over 1000 are white waxy solids, flakes, or free-flowing powders (FAO, 1983). The properties of the individual PEGs are listed in Table 1.

"Carbowax" 1500 is a solid blend of equal weights of PEG-6 and PEG-32 (Smyth et al., 1950). It is discussed in this report when data are not available on the individual components.

Methods of Manufacture

PEG-6, -8, -32, -75, -150, -14M, and -20M are formed by condensing ethylene oxide and water. The average number of moles of ethylene oxide that are polymerized are indicated by the number in the name (Hunting, 1983).

Analytical Methods

PEG-8 can be extracted from biological fluids and analyzed by liquid chromatography (Delahunty and Hollander, 1986) and gas–liquid chromatography (Chadwick et al., 1977).

Solid PEGs can be quantitatively determined in biological materials using gravimetric and colorimetric methods based upon the reaction of the PEGs with heteropoly acids (silicotungstic acid and phosphomolybdic acid) (Shaffer and Critchfield, 1947a).

Impurities

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 autoxidatation, are found in PEG-32 and PEG-75 (Hamburger et al., 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

Table 1. Chemical and Physical Properties of PEGs-6, -8, -32, -75, -150, -14M, and -20M

Property	*PEG-6*	*PEG-8*	*PEG-32*	*PEG-75*	*PEG-150*	*PEG-14M*	*PEG-20M*
Physical description	Colorless, odorless, hygroscopic liquid	Viscous, slightly hygroscopic liquid with a slight odor	Odorless solid	White, free-flowing powder, or creamy white flakes	White, waxy solid, powder, or creamy, white flakes	White powder	Solid
Solubility	Water	Water			Water	Water	
Molecular weight range	260–315	285–420	1,300–1,600	3,000–4,800	6,000–9,000	600,000	
Melting point					58–62°C	65°C	
Flash point	385–415°F	435–460°F; 471°F	510°F	515–520°F	515–520°F		
Freezing range	−15 to −6°C	4–10°C	43–46°C	53–58°C	56–63°C		
Viscosity (210°F), centistokes		7.3		76–110	470–900		

Source: Adapted from Silverstein et al. (1984), FAO (1983), Hunting (1983), Windholz (1983), Sax (1979), and Patty (1963).

specific peroxides present in the PEGs were not determined, but they were thought to be organic peroxides rather than hydrogen peroxide (McGinity et al., 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 et al., 1970; Argus et al., 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 (Elder, 1983).

USE

Cosmetic

United States

PEGs -6, -8, -32, -75, and -150 are used as humectants and solvents in cosmetic products. PEG-75 and PEG-150 are also used as binders. PEGs -14M and -20M function as binders, emulsion stabilizers, and viscosity increasing agents (Nikitakis, 1988).

The product formulation data submitted to the Food and Drug Administration (FDA) in 1992 reported the number of formulations each of the PEGs were used in (Tables 2–7). Concentration of use values are no longer reported to the FDA by the cosmetic industry (Federal Register, 1992). However, the product formulation data submitted to the FDA in 1984 stated that PEG-8 was used at concentrations up to 50%, and that PEGs -6, -32, -75, -150 and -14M were used at concentrations up to 10% (FDA, 1984). PEG-20M was not reported as being used in 1984 or 1992, but was identified as being of interest to the cosmetic industry for future formulations.

International

PEG -6, -8, -32, -75, -150, -14M and -20M are approved for use in cosmetics in Japan (CTFA, 1983a).

Noncosmetic

PEGs are used in pharmaceuticals as vehicles for water soluble drugs (Bartoli Klugmann et al., 1986), as ointment bases, and in suppositories (Silverstein et al.,

Table 2. Cosmetic Product Formulation Data for PEG-6[a]

Product category	*Total no. of formulations in category (FDA, 1992)*	*Total no. of formulations containing ingredient (FDA, 1992)*	*Maximum concentration of use (FDA, 1984)*
Moisturizing skin care preparations	933	3	Category not reported in 1984
Suntan gels, creams, and liquids	290	7	Category not reported in 1984
No. uses under trade name (FDA, 1991)		7	
Total		17	

[a]CIR requests that the cosmetic industry provide current formulation data on each product category.

TABLE 3. COSMETIC PRODUCT FORMULATION DATA FOR PEG-8[a]

Product category	*Total no. of formulations in category (FDA, 1992)*	*Total no. of formulations containing ingredient (FDA, 1992)*	*Maximum concentration of use (FDA, 1984)*
Eye makeup remover	105	5	5%
Hair straighteners	78	3	Category not reported in 1984
Tonics, dressings, and other hair grooming aids	548	4	25%
Makeup foundations	398	15	Category not reported in 1984
Lipstick	937	4	Category not reported in 1984
Makeup bases	119	8	25%
Bath soaps and detergents	324	4	Category not reported in 1984
Deodorants (underarm)	290	12	10%
Other personal cleanliness products	323	3	50%
Aftershave lotions	252	5	5%
Shaving cream (aerosol, brushless, and lather)	157	3	1%
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	854	13	10%
Face and neck skin care preparations (excluding shaving preparations)	148	3	10%
Body and hand skin care preparations (excluding shaving preparations)	1229	23	10%
Moisturizing skin care preparations	933	15	10%
Night skin care preparations	263	6	25%
Paste masks (mud packs)	293	8	5%
Skin fresheners	246	5	5%
Other skin care preparations	848	18	10%
No. uses under tradename (FDA, 1991)		2	
Total		136	

[a]CIR requests that the cosmetic industry provide current formulation data on each product category.

1984). They also are used in metal and rubber processing, as additives to food and animal feed, and as laboratory reagents (Hawley, 1971). PEG-150 is used in water paints, paper coatings, polishes, and in the ceramics industry (Windholz, 1983).

PEGs have been used as laboratory tools to induce chemically the cell fusion of plant protoplasts, bacterial protoplasts, plant protoplasts with animal cells, and animal cells in culture (Blow et al., 1978).

BIOLOGICAL PROPERTIES

Absorption, Metabolism, and Excretion

Shaffer et al. (1950) used the method of Cori (1925) to study the intestinal absorption of PEG-8 in the rat. A known amount of PEG-8 was administered by stomach

TABLE 4. COSMETIC PRODUCT FORMULATION DATA FOR PEG-32[a]

Product category	*Total no. of formulations in category (FDA, 1992)*	*Total no. of formulations containing ingredient (FDA, 1992)*	*Maximum concentration of use (FDA, 1984)*
Mascara	247	3	Category not reported in 1984
Sachets	44	9	Category not reported in 1984
Dentifrices (aerosol, liquid, pastes, and powders)	59	7	10%
Moisturizing skin care preparations	933	9	5%
No. uses under tradename (FDA, 1991)		4	
Total		32	

[a]CIR requests that the cosmetic industry provide current formulation data on each product category.

tube. After a specified amount of time, the rats were killed and the amount of PEG-8 in the intestines was determined. The amount absorbed was calculated as the difference between the administered dose and the amount recovered. When albino rats were dosed with a 25% solution of PEG-8, approximately 62% of the dose was absorbed in 5 h.

Krugliak et al. (1989) later demonstrated that PEG-8 was absorbed by rat intestinal epithelium by both passive diffusion and solvent drag.

The extent of gastrointestinal absorption of solid PEGs was studied in the rat. Groups of 30 rats were given 25% solutions of PEGs -32, -75, and -150, and were killed at hourly intervals up to 5 h after dosing. Gravimetric methods were used to determine the amount of PEG absorbed. Less than 2% of PEG-32 was absorbed in 5 h. There was

TABLE 5. COSMETIC PRODUCT FORMULATION DATA FOR PEG-75[a]

Product category	*Total no. of formulations in category (FDA, 1992)*	*Total no. of formulations containing ingredient (FDA, 1992)*	*Maximum concentration of use (FDA, 1984)*
Hair conditioners	666	7	5%
Permanent waves	505	3	1%
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	854	3	5%
Moisturizing skin care preparations	933	3	5%
Night skin care preparations	263	4	5%
Other skin care preparations	848	5	Unknown
No. uses under tradename (FDA, 1991)		1	
Total		26	

[a]CIR requests that the cosmetic industry provide current formulation data on each product category.

Table 6. Cosmetic Product Formulation Data for PEG-150[a]

Product category	Total no. of formulations in category (FDA, 1992)	Total no. of formulations containing ingredient (FDA, 1992)	Maximum concentration of use (FDA, 1984)
Bath oils, tablets and salts	182	4	Category not reported in 1984
No. uses under tradename (FDA, 1991)		1	
Total		5	

[a]CIR requests that the cosmetic industry provide current formulation data on each product category.

no evidence that PEG-75 or PEG-150 was absorbed, since the initial dose was recovered from the gastrointestinal tract at each time interval (Shaffer and Critchfield, 1947b.

Shaffer and Critchfield (1947b) also reported that PEG-150 was not absorbed from the gastrointestinal tract of humans. Six men ingested 10 g PEG-150 dissolved in 150 ml water, and urine samples were taken at hourly intervals for 4 h after ingestion, and then at longer intervals up to 24 h. The presence of PEG-150 was not detected in the urine at any time.

Metabolic destruction of PEG-8 in the dog was demonstrated by Shaffer et al. (1950). Three dogs were infused at a constant rate with a 5% solution of PEG-8 in saline, and the rate of excretion was compared with the rate of infusion. For every 100 mg of PEG-8 infused, 75–88 mg was excreted. Ethylene glycol was not a metabolite of PEG-8.

In a study using PEG-8 to determine the intestinal permeability in humans, the absorption, metabolic fate, and excretion of PEG-8 was evaluated. Five normal human subjects (males or postmenopausal women) ingested 1, 5, or 15 g of PEG-8 in a liquid concoction randomly on three different occasions. Urine and feces were collected regularly for 48 h after each dose. Gas–liquid chromatography indicated that the amount of PEG-8 recovered in the wastes was directly proportional to the ingested dose. Most of the dose was excreted rapidly in the urine; 55.6% was eliminated in 48 h, and, of this, 94.4% was eliminated within 24 h. In a separate study, four individuals ingested 10 g PEG-8 mixed with 500 ml water in a liquid concoction. The mean recovery of

Table 7. Cosmetic Product Formulation Data for PEG-14M (FDA, 1992)[a]

Product category	Total no. of formulations in category (FDA, 1992)	Total no. of formulations containing ingredient (FDA, 1992)	Maximum concentration of use (FDA, 1984)
Mascara	247	6	1%
Hair conditioners	666	3	1%
Hair shampoos (noncoloring)	953	30	5%
Bath soaps and detergents	324	3	1%
Other shaving preparations	47	4	Category not reported in 1984
Total		46	

[a]CIR requests that the cosmetic industry provide current formulation data on each product category.

PEG-8 in the urine and feces after 4 days was 92.8% (58.5% in the urine and 34.3% in the feces). The authors suggested that PEG-8 was not metabolized after absorption (Chadwick et al., 1977).

This suggestion was investigated *in vitro* by incubating 1 g of PEG-8 with 20 g aliquots of human feces, or with pure cultures of *Pseudomonas aeruginosa* for 1 wk periods. The mean recovery of PEG-8 in these studies was 96.2% and the percentage composition of PEG-8 was not changed, supporting the suggestion that PEG-8 was not degraded by intestinal bacteria (Chadwick et al., 1977).

The elimination of PEG-8 after oral administration was studied in the rabbit. Two groups of three rabbits were given either 5.7 g or 8.5 g of PEG-8 by stomach tube. Urine and feces were collected and gravimetric methods were used to analyze the amount of PEG-8. The low-dose rabbits eliminated approximately 9% of the dose in their feces, and 20% in their urine after 4 days. The majority of the PEG-8 found in the urine was eliminated within the first 24 h. The same trend was observed in the high-dose rabbits; an average of 36% of the initial PEG dose was eliminated in the urine, and 18% in the feces (Shaffer et al., 1950).

Further investigation was done on renal excretion using intravenous administration of PEG-8. Two groups of three rabbits were given intravenous injections of 0.4 g or 0.75 g PEG-8, and urine was collected for 24 h. The groups eliminated an average of 47% and 67% of the total dose, respectively (Shaffer et al., 1950).

Carpenter and Shaffer (1952) later demonstrated with rats that subcutaneous and intramuscular injections (2 ml/kg) of PEG-6 and PEG-8 were rapidly removed from the sites of injection and eliminated in the urine. An average of 85% or more of the PEGs was eliminated within 24 h.

The route of PEG-75 excretion after intravenous injection was studied in rats using ^{14}C-PEG-75. Ten rats were given 10 mg (approx. 70 mg/kg) intravenous injections of ^{14}C-PEG-75. After 7 days, the mean cumulative recovery of radioactivity was 81%: 61% was recovered in the urine, and 20% in the feces. Most of the radioactivity was excreted in the urine within 24 h (Carpenter et al., 1971).

In a study with dogs, PEG-150 had an identical rate of excretion to creatinine, which indicated that this PEG was excreted by the same mechanism as creatinine: glomerular filtration without tubular participation (Shaffer et al., 1948).

Urinary excretion of PEG-8 was studied using human subjects. Three subjects given intravenous injections of 1 g PEG-8 in 20 ml of saline solution eliminated an average of 77% of the dose in 12 h. Two subjects injected with 10 g PEG-8 eliminated an average of 47%, and one individual given 5 g eliminated 40% of the dose in 24 h (Shaffer et al., 1950).

In a study of the excretion of PEG-150, six men were injected intravenously with 20 ml of 5% PEG-150, and urine samples were collected from them at timed intervals for 12 h. Approximately 63% of the injected dose was found in the urine after 1 h, and 96% was recovered after 12 h. The authors found that a PEG of lower molecular weight (PEG-20) was excreted at a slower rate and in smaller quantities. They attributed this observation to the lower molecular weight polymer's ability to diffuse more quickly through the tissues (Shaffer and Critchfield, 1947b).

In a report on burn patients treated with a PEG-based antimicrobial cream (described later in this report), "appreciable" amounts of monomeric ethylene glycol were found in the serum of the patients. The authors noted that high concentrations of PEG were probably absorbed through the damaged skin, since only 0.01% ethylene glycol was present in the burn cream (Bruns et al., 1982).

Effects on the Blood

Since PEGs are used as vehicles for intravenous drug administration, studies were conducted to determine their hemolytic potential. Reed and Yalkowsky (1985) reported that the LD_{50} value for lysis of human erythrocytes by PEG-8 was 30.0% (total volume percent of cosolvent in whole blood). Others have reported that the hemolytic potential of PEG-8 was reduced when combined with various combinations of ethanol, polypropylene glycol, water, and/or saline (Fort et al., 1984; Smith and Cadwaller, 1967).

PEG-75 caused crenation and clumping of erythrocytes of rabbits at concentrations of 10% or greater. This observation was tested *in vivo* by administering intravenous infusions of 10% PEG-75 to rabbits. Blood from animals that died from pulmonary hemorrhages contained numerous clumps of cellular elements. Animals tested with 5% PEG-150 solutions did not have this reaction (Smyth et al., 1947).

Pharmacodynamic Effects

In a study of the muscle relaxant properties of drug solvents, the recommended tolerable concentration of PEG-8 as a drug solvent was determined to be 6.0% (w/v) using the Rota-Rod Test. Groups of four male NMRI mice were trained to run continuously for 5 min on a rotating rod. The minimum oral dose producing premature drop-off was 0.6 g/kg (Budden et al., 1979).

PEG-8 and PEG-75 were tested for anticonvulsant properties using mice in the electroshock, pentetrazole, and strychnine tests. Data from the later two tests indicated that intraperitoneal injection of PEG-8 had slight anticonvulsant activity, and PEG-75 had even more pronounced anticonvulsant activity at dosages considered inert (6.84 and 3.42 g/kg PEG-8; and 6.03 and 3.01 g/kg PEG-75). Neither solvent was active in the electroshock test. Oral administration of the PEGs did not alter the time of seizure onset or death (Bartoli Klugmann et al., 1986).

Lockard and Levy (1978) demonstrated in several studies with monkeys that PEG-8 had anticonvulsant properties. In one study, four chronically epileptic rhesus monkeys were given intravenous infusions of 60% PEG-8 in water solution for 4 wks (1 ml/hr). Prior to and after this treatment, the monkeys were administered saline (1 ml/hr) for 3 wks in order to establish baseline seizure frequency. During PEG-8 administration, a significant decrease in seizure frequency was observed compared to baseline periods. In another group of eight monkeys given the same treatment, five of the animals had statistically significant decreases in seizure frequency. The three other monkeys were removed from the study because of signs of toxicity. Their signs are described in the section on 'Subchronic Toxicity—Parenteral' included in this report. Follow-up studies confirmed that at concentrations between 35% and 60% PEG-8 had anticonvulsant activity (Lockard and Levy, 1978; Lockard et al., 1979).

Hartveit (1969a) reported that oral administration of PEG-75 significantly reduced subcutaneous tumor growth in female mice. Thirteen mice were injected with Ehrlich's ascites carcinoma and given drinking water containing 20% PEG-75 for 8 days. Control animals were given untreated water after injection. The treated rats had a marked reduction in the inflammatory response around the tumor transplants, and tumor growth was reduced by 84%. These tumors were not infiltrative. Lymph node hypertrophy and splenic atrophy also occurred. Female control animals had inflammatory responses and tumor growth was infiltrative. Since *in vitro* studies indicated that PEG-75 was not directly toxic to these tumor cells (Hartveit, 1967), the author suggested that PEG-75 ". . .upset the immunological balance in host–tumor relationship and that

subsequent changes in response may be ultimately responsible for the difference in the subcutaneous growth of the tumor transplants."

In similar studies using male rats, 20% PEG-75 reduced subcutaneous tumor growth by 48% compared to that seen in untreated controls. However, the tumor growth in male mice treated with 10% PEG-75 was not inhibited and was similar to that seen in the control rats (Hartveit, 1969a).

Intraperitoneal injection (1 ml) of 10% PEG-75 in physiological saline inhibited the growth of Ehrlich's ascites carcinoma transplants in female mice. The mean tumor diameter was reduced by 15% in short-term studies (9–12 days), and by 30% in studies of greater duration (3–7 weeks) compared to untreated control mice (Hartveit, 1969b).

In vitro studies of PEG-150 indicated that PEG-150 augmented the generation of antitumor cytotoxicity by MOPC-315 tumor-bearer splenic cells (Mokyr et al., 1982), and potentiated mitogen-induced lymphocyte stimulation (Bessler et al., 1977). PEG-150 also enhanced the murine T-cell proliferative response against autologous non-T stimulator cells (Ponzio, 1980).

ANIMAL TOXICOLOGY

Acute Toxicity

Oral Studies

Smyth et al. (1941, 1945, and 1950) conducted acute oral toxicity studies with different animals (see Table 8). The PEGs were administered either undiluted or as 50% solutions by stomach tube and the animals were observed for 14 days. The majority of the animals that died did so within 24 h. Digestive tract congestion was reported in some of these animals. Smyth et al. (1950) reviewed these studies and noted ". . . a clear tendency for a slight decrease in acute toxicity with large increases in molecular weight."

Smyth et al. (1942) also determined that 31.6 g/kg was the smallest single dose of PEG-75 to cause microscopic renal or hepatic lesions in rats. Since it appeared that only

Table 8. Acute Oral Toxicity of PEGs-6, -8, -32, -75, and -150

Ingredient (conc.)	*Species (no.)*	*LD_{50}*	*Reference*
PEG-6 (100%)	Albino Wistar rat	31.7 g/kg	Smyth et al. (1945)
	Rabbit	17.3 g/kg	Smyth et al. (1950)
PEG-6 (50%)	White rat	45.6 g/kg	Smyth et al. (1950)
	White rat	38.9 g/kg	Smyth et al. (1950)
	White rat (10)	31.6 g/kg	Smyth et al. (1941)
	Albino rabbits	20.7 g/kg	Smyth et al. (1945)
	Guinea pigs (10)	19.6 g/kg	Smyth et al. (1941)
PEG-8 (100%)	Albino wistar rat	32.8 g/kg	Smyth et al. (1945)
PEG-8 (50%)	White rat	43.6 g/kg	Smyth et al. (1950)
	White rat (10)	37.4 g/kg	Smyth et al. (1941)
	Albino rabbit	26.8 g/kg	Smyth et al. (1945)
PEG-32 (50%)	White rat	51.2 g/kg	Smyth et al. (1950)
PEG-75 (100%)	Rabbit	76 g/kg	Smyth et al. (1950)
PEG-75 (50%)	White rat	>50 g/kg	Smyth et al. (1950)
	White rat	59 g/kg	Smyth et al. (1950)
PEG-150 (50%)	White rat	>50 g/kg	Smyth et al. (1950)

very large single doses affected the liver and kidneys, the authors conducted another large dose study using rabbits. A dose of 50 g/kg PEG-75 greatly increased blood urea and caused slight hepatic cell swelling. Since the intestines were unobstructed, the authors suggested that the elevation in urea concentration was due to the direct action of PEG-75 on the kidneys (Smyth et al., 1942).

The LD_{50} for 30% PEG-20M was reported to be >31.6 g/kg (Mellon Institute of Industrial Research, 1956).

In a more recent study, no deaths occurred after 10 rats were administered 16.0 g/kg of 50% PEG-32 (melted in a water bath) orally. The rats had diarrhea and red crusting on their perinasal hair. At necropsy, the lungs were mottled, and single cases of distended stomach, dilated uterus, and small testes were observed (Bushy Run Research Center, 1987).

Parenteral Studies

The acute intraperitoneal toxicity of 50% PEG-6 for rats was 17.0 g/kg (Smyth et al., 1950).

Bartsch et al. (1976) administered PEG-8 in 0.9% NaCl solution intraperitoneally (10 ml/kg) to SPF-NMRI strain mice and SPF-Sprague-Dawley rats. The median lethal dose for each species was 12.9 ml/kg and 13.1 ml/kg, respectively.

The LD_{50} values for 50% aqueous solutions of PEGs -32, -75, and -150 administered by intraperitoneal injection to male Wistar albino rats were 15.39, 11.55, and 6.79 g/kg, respectively. Eighty-percent of the rats that died did so within 30 h of the dose. The remaining rats were observed for 14 days. At necropsy, a few of the rats had swollen livers (Smyth et al., 1947).

In a follow-up study, the toxicity of a different production lot of PEG-75 was tested in rats. The LD_{50} for a 50% solution was 13.0 g/kg. Eighty-percent of the deaths occurred within 30 h of the injection, and the surviving rats were observed for 14 days. No PEG-75 remained in the peritoneal cavity at the end of this period (Smyth et al., 1950).

The intraperitoneal toxicity of PEG-8 and PEG-75 was tested in two groups of 50 albino mice. The LD_{50}s for each PEG were 9200 mg/kg and 8000 mg/kg, respectively (Shideman and Procita, 1951).

Carpenter and Shaffer (1952) determined that the intravenous LD_{50} for undiluted PEG-6 in rats was 7.1 ml/kg. This dosage was based upon mortality during a 14-day period.

Bartsch et al. (1976) administered PEG-8 in 0.9% NaCl solution intravenously (10 ml/kg) to SPF-NMRI strain mice and SPF-Sprague-Dawley rats. The median lethal dose for each species was 7.6 ml/kg and 6.5 ml/kg, respectively.

Groups of two rabbits received 5% solutions of PEGs -32, -75, and -150 by slow intravenous injection (10 g/kg) via the ear vein. The infusion rate was 2.5 ml/min. All animals survived to termination (day 14). One rabbit given PEG-150 had renal tubular cell swelling (Smyth et al., 1947).

Groups of six dogs were given intravenous injections of PEG-8 and PEG-75 at doses ranging from 2 to 3 g/kg. This treatment caused a minor reduction in blood pressure and a transient depression in respiration. At doses of 3 g/kg and greater, a gradual decline in blood pressure and periodic apnea were observed, and the animals eventually suffered from complete respiratory arrest. At necropsy, these dogs had pulmonary edema and small infarcts in the lungs. No adverse changes occurred in the heart or kidneys (Shideman and Procita, 1951).

Undiluted PEG-6 was injected into Sherman strain albino rats either subcutaneously in the abdominal region or intramuscularly into the multifidus muscle in the right lumbo-sacral region. Groups of six rats received subcutaneous injections of 2.5, 5, and 10 ml/kg PEG-6. Tissue reactions were monitored, and necropsy was performed on two rats from each group on days 2, 4 (or 7), and 14. All dosages caused the skin to blanch and scabs to form on the overlying dermis within 2 days. Increased vascularization and fibroblastic repair tissue were present after 4 days, the extent of which was reduced after 14 days.

Two groups of six rats were intramuscularly injected with 0.5 and 2 ml/kg PEG-6, and the same observation schedule was used as in the subcutaneous study. Both dosages caused ischemic necrosis of the muscle fibers when the PEG-6 was deposited within the muscle bundles. When PEG-6 was placed subcutaneously, increased vascularization and fibroblastic proliferation were observed. These responses were transient; no evidence of injury was found after 14 days (Carpenter and Shaffer, 1952).

No deaths occurred when 10 rats were administered 16.0 g/kg PEG-32 (melted in a water bath) subcutaneously. Erythema and edema were evident, but no signs of toxicity were observed. At necropsy, two animals had red or mottled lungs, and the stomach and intestines of one rat were filled with a gray–green liquid (Bushy Run Research Center, 1987).

Dermal Studies

The acute dermal toxicity of undiluted PEG-6 and PEG-8 was tested on rabbits using modified FDA cuff testing. Six rabbits had 20 ml/kg of either PEG applied to their skin. No deaths resulted from this treatment (Smyth et al., 1945).

Two groups of four male, albino, New Zealand rabbits had 20.0 ml/kg of 40% PEG-75 or 40% PEG-20M applied to their skin for 24 h. No deaths occurred during the 14-day observation period (Mellon Institute of Industrial Research, 1956).

Pulmonary Studies

The pulmonary effects of PEG-75 on rats following endotracheal injection was investigated. Five male and five female Sprague-Dawley rats were lightly anesthetized and 1.0 g/kg of 50% PEG-75 (the highest nonlethal dose determined during initial tests) was injected endotracheally into their lungs. A positive control group was administered kerosine, and a negative control group was administered saline. Rats of each sex were killed on days 1, 2, and 3, and the remaining survivors were killed on day 14. No treatment-related deaths occurred during the study. A clear to light red discharge from the nose was observed 10–30 min following administration in the male rats only. The rats experienced an initial decrease in weight, but weight gain increased after 3 or 7 days. The absolute lung weights of both male and female rats were statistically higher than that seen in the negative control animals. The lung weights relative to the body weights were higher for the females only. The only significant histologic change was alveolar histiocytosis in male rats. However, microscopic lesions in the rats killed on day 14 were not statistically greater than that seen in the negative control group (Bushy Run Research Center, 1988a).

In another study, groups of 10 male and female Sprague-Dawley rats were slightly anesthetized and had 2.0 ml/kg of 7.5% (w/v) PEG-75 (0.15 g/kg PEG-75) injected into their lungs endotracheally. A control group of rats was treated with 2.0 ml/kg of saline. The rats were monitored regularly for toxic effects. Two rats per gender were killed on days 1, 2, and 3, and the remaining survivors were killed on day 14. Necropsies were

performed on all of the animals. There were no treatment-related deaths or signs of toxicity during the study. The rats experienced an initial decrease in body weight, but gained weight steadily after day 3. The lung weights of the treated animals (in terms of both absolute weight and weight relative to body weight) were normal. A few of the lungs had a change in color, which was not observed in the control rats, but the incidence of these changes was not statistically significant. A few of the rats also had interstitial pneumonitis, but its incidence was not statistically higher than that found in the controls (Bushy Run Research Center, 1988b).

Subchronic Toxicity

Oral Studies

Groups of five male albino rats received either PEG-6 or PEG-8 in their drinking water at concentrations of 0.06, 0.25, 1, 4, and 16 g/100 ml. Ten control rats were given untreated water. The rats were observed for 90 days. All animals drinking 4% solutions (5.4 g/kg/day PEG-6 and 4.8 g/kg/day PEG-8) or less survived to termination. No changes in behavior, growth, body fluid chemistry, or lesions were observed in any of the them. The rats given 16% solutions (20.5 g/kg/day PEG-6 and 16.4 g/kg/day PEG-8) drank 25–75% less than the control rats. Three rats died from both treatment groups before termination; the rats drinking PEG-6 died within 9 days, and the rats consuming PEG-8 died in 80–84 days. At necropsy, a swollen liver was found in all of the PEG-6 treated rats, and microscopic examination showed dilated renal glomeruli, which the authors attributed to low water intake. Animals that died before termination (from both treatment groups) also had necrosis of epithelial cells of the convoluted renal tubules. No organ abnormalities were reported in the PEG-8 rats surviving to termination (Smyth et al., 1945).

A similar study confirmed these results. Sixteen percent concentrations of PEG-6 and PEG-8 killed all treated rats within 7 and 13 days, respectively. Eight percent PEG-6 killed two of 10 rats in 30 days. Concentrations of 4% or less had no effect. PEG-8, at concentrations of 8% or less, did not cause any deaths, but the weight of the kidneys of these rats was less than that of control rats (Smyth et al., 1950).

Smyth et al. (1942) conducted a 90-day oral toxicity study of PEG-6-32 and PEG-75. Groups of five rats were given 1–16% PEG-6-32 or 0.05–16% PEG-75 in their drinking water. The average doses ranged from 0.88–22.9 g/kg/day and 0.04–19.0 g/kg/day, respectively. No deaths were caused by any of the dosages, and blood cytology and hemoglobin were normal. The animals drinking PEG-6-32 grew normally, and at necropsy the only abnormality found was in the kidneys. Microscopically, the Bowman's capsule was dilated in one rat in each of the following dosage groups: 4.05, 8.1, and 22.9 g/kg/day. Lower dosages did not cause such changes. The growth of rats drinking 7.0 and 19.0 g/kg/day PEG-75 was reduced 25% compared to controls. Dosages of 19.0 g/kg/day caused renal lesions, such as distension of the Bowman's capsule, granular detritus, secretion of albuminoid, and cloudy swelling of the convoluted tubules.

In this study, the authors reported that 0.04 g/kg/day PEG-75 could be administered to rats without causing adverse effects. Later, it was reported in a similar study that the safe oral dose of PEG-75 for rats was 1.6 g/kg. The authors noted that the PEG-75 used in the study was from a later year of production, and explained that the discrepancy in results was probably due to better manufacturing methods (Smyth et al., 1950).

These investigators also conducted a 5 week study of the effects of PEG-75 on the kidneys of rabbits. Groups of five rabbits were given 5, 10, or 20 g/kg PEG-75 by stomach tube 6 days per week. Blood urea concentrations monitored throughout the study were normal, and at necropsy and microscopic examination, no abnormalities were found in the kidneys. Slightly retarded growth was reported in the animals receiving 20 g/kg, but the authors attributed this to appetite reduction as a result of the large volume of inert material in the stomach (Smyth et al., 1942).

Smyth et al. (1955) investigated the relationship between the molecular weight of PEGs and subacute toxicity. Groups of 10 rats (five of each sex) were given 2, 4, 8, 16, and 24% PEGs ranging in molecular weight from 200 to 6000 (which includes PEGs -6, -8, -32, -75, and -150) for 90 days. For PEGs -6, -8, -32, and -75, toxicity was dose dependent. The rats had reduced body weight gain and increased renal and hepatic weights. In the group receiving PEG-150, only the rats fed a concentration of 24% had signs of toxicity. For PEGs ranging from 200 to 4000 in molecular weight, there was no relationship between molecular weight and toxicity. PEG-150 was distinctly less toxic than the lower molecular weight PEGs (Smyth et al., 1955).

PEG-20M was tested for toxicity in a 90-day study using CT-Wistar albino rats. Groups of 10 rats were fed PEG-20M as 0.5, 1.0, 2.0, 4.0, and 10.0% of their diets. A control group of rats was fed the diet alone. The rats were weighed weekly, and their kidneys and livers were weighed at necropsy. No treatment-related deaths occurred. The only sign of toxicity caused by the diet of 10.0% PEG-20M was reduced liver weights. No signs of toxicity were observed in the 4.0% PEG-20M treatment group. In the lower-dose groups, scattered, barely significant differences in body weight gain, appetite, and organ weights were associated, but not correlated, with dosage (Mellon Institute of Industrial Research, 1956).

Parenteral Studies

Smyth et al. (1947) studied the effects of intravenous injections of PEGs -6, -8, -32, -75, and -150 in rabbits. The animals were given 1 g injections via the ear vein of 5% PEG solutions in 0.85% sodium chloride 6 days a week for 5 weeks. The average dosage was 350 mg/kg/day. No deaths occurred in the groups receiving PEG-6 and PEG-32, but one of five rabbits died in the PEG-8 group, one of nine died in the PEG-75 group, and one of five died in the PEG-150 group. One PEG-8 rabbit and four PEG-75 rabbits had hepatic cell and renal tubular cell swelling.

Three groups of nine beagle dogs were given intravenous injections of 10% PEG-75 in 0.85% aqueous sodium chloride at dosages of 10, 30, and 90 mg/kg/day. A corresponding group of dogs, injected with the sodium chloride vehicle alone, served as a control. Two dogs from each group were killed after 43 daily injections, and another two dogs were killed after 99 daily injections. The remaining dogs were killed after 178 injections. During the course of the study, no changes were observed in the general behavior, appetite, body weight, or bodily functions of the dogs. At necropsy, none of the dogs had gross lesions or microscopic changes in any of their tissues or organs that could be attributed to PEG-75. No statistically significant differences were found between the experimental and control animals either in the organ weights or biochemical tests (Carpenter et al., 1971).

Three of eight chronically epileptic monkeys given intravenous infusions of 60% PEG-8 in water (1 ml/h) for 3 weeks had reduced appetites, a greasy texture to their lower extremities, edema of their genitals and legs, and deteriorating infusion sites

(Lockard and Levy, 1978). Similar reactions occurred in other epileptic monkeys and normal monkeys treated with 60% and 65% PEG-8 (Lockard and Levy, 1978; Lockard et al., 1979).

Dermal Studies

Fifteen female Sprague-Dawley rats had 886 mg/kg of a formulation containing 3% PEG-8 applied to the shaved skin of their backs for 13 weeks. The treatment site was 10–15% of the total surface area, and the site was shaved once a week throughout the study. Applications were made once a day five times a week. All of the animals survived the test period, and no changes in body weight gain, appearance, or behavior were observed. Most of the animals had moderate irritation and a brown discoloration of the skin at the treatment site, and hyperkeratosis and parakeratosis was found upon histopathologic examination. Serum chemistry, hematology, and urinalysis parameters taken during the study were similar to those seen in the untreated control group, or fell between the range of normal values established in this laboratory for the Sprague-Dawley rat. At necropsy, no gross abnormalities or changes in weight were found in the major organs or glands. The rats had a pulmonary infection, but this was not considered treatment-related since the formulation was not volatile (CTFA, 1981).

In another study, Sprague-Dawley rats (number unspecified) were given daily dermal applications (2400 mg/kg) of a formulation containing 5% PEG-8 for 13 weeks. All of the animals survived to the end of the study, and no change in their behavior was noted. There was a significant decrease in body weight gain of the treated rats compared to the untreated controls, and minimal irritation and desquamation and scabbing were observed at the application sites. There were statistically significant changes in the various hematology parameters investigated. However, the authors noted that these changes were within the historical limits for untreated control rats. The only toxicologically significant changes were an elevated neutrophil/lymphocyte ratio for male rats, and elevated activities of serum glutamic pyruvic transaminase (SGPT), serum alkaline phosphatase (SAP), and serum glutamic oxaloacetic transaminase (SGOT) for male rats, and SGPT and SGOT for female rats.

At necropsy, both male and female rats had hyperemia of the stomach and small and large intestines, and an apparent smoothing of the gastric mucosa. The relative weights of the brain, heart, and testes of the male rats were increased, and the absolute weight of the spleens from male rats was decreased. Histopathologic alterations included acanthosis, hyperkeratosis, sebaceous gland hyperplasia, and chronic inflammation in the dermis; all were indicative of dermal irritation. Submucosal edema and inflammation, and mucosal hyperemia were observed, but these changes were also present in the female rats of the control group. The presence of a black material, subsequently determined to be iron, was detected in the connective tissue of the denuded tips of the villi of the small intestine of the experimental male rats.

The authors suggested that the reduced body weights of the treated animals and the elevated neutrophil/lymphocyte ratio in male rats were related to the skin changes. Since there were no significant gross or microscopic changes in the brain, heart, testes, or spleen, the changes in their weight were not considered to be evidence of toxicity. Similarly, the livers had no microscopic lesions to indicate that the increased enzyme activities were treatment related. The changes in the gastrointestinal tract were thought to be related to the ingestion of the formulation, since the applications were not made under occlusive patches. The authors concluded that the formulation containing 5% PEG-8 did not produce cumulative systemic toxic effects (CTFA, 1985a).

In a much earlier 18-week toxicity study of skin absorption conducted by Smyth et al. (1945), two groups of six albino white rabbits received dermal applications (2 ml/kg/day) of PEG-6 or PEG-8 on their clipped abdomens 5 days a week. All animals survived to termination, and no evidence of toxicity was observed during the study or at necropsy.

Undiluted PEG-6-32 and 50% aqueous PEG-75 also were nontoxic when applied to the skin for prolonged periods of time. Patches covered with 10 g/kg of each compound were applied to the abdominal skin of rabbits 5 days a week for 13 weeks. Control animals were given applications of petrolatum or water. Very little or none of the experimental compounds was absorbed, and no interference with renal function or microscopic renal changes were observed (Smyth et al., 1942).

The dermal toxicity of PEGs -6, -8, -75, and -150 was tested using albino white rabbits. Groups of 10 rabbits were given the following treatments for 12–13 weeks: two groups had 2.0 ml/kg PEG-6 and PEG-8 bound to the skin of their clipped abdomens five times a week; and two groups had 10 g/kg PEG-75 and PEG-150 applied to their abdominal skin for 5 consecutive days. Two groups of five animals served as controls, and were subjected to the bandaging procedures without the PEGs.

No significant skin reactions or evidence of systemic toxicity were caused by any of the PEGs. Although 14 test animals died before termination and all of the control animals survived, the authors noted that the deaths appeared to be due to an incidental coccidial infection. Parasitic infection was also found among the control and surviving test animals. Microscopic examination of skin sections indicated that some of the experimental rats had mild irritation; however, similar lesions were also found in control animals. The major organs and glands, and the blood and urine specimens were normal (Tusing et al., 1954).

Groups of eight male albino rabbits had 0.4 or 0.8 g/kg PEG-75 or PEG-20M applied to their clipped abdomens for 1 h a day for 30 days. A control group of rabbits was treated with distilled water. All of the rabbits were weighed weekly and observed for signs of toxicity. No treatment-related deaths occurred. The mean body weight gain was greater in both treatment groups receiving 0.8 g/kg (735.1 g for PEG-75; 701.0 g for PEG-20M) than in the control group (671.8 g). Mild, transient erythema was observed at the application sites (Mellon Institute of Industrial Research, 1956).

Herold et al. (1982) developed an animal model to study the potential toxicity of repeated applications of a PEG-based antimicrobial cream to burn patients. The hair of New Zealand white rabbits was removed, and two paravertebral skin excisions (2.5 × 15 cm) were made on each of their backs. The experimental rabbits had either the antimicrobial cream or the PEG-vehicle (63% PEG-6, 5% PEG-20, and 32% PEG-75) alone applied to their lesions. The dressings of all the rabbits were changed every 12 h for 7 days. In the control group only the bandaging procedures were used.

Seven of the eight rabbits treated with the antimicrobial cream and three of the four rabbits treated with the PEG-vehicle died during the study. They showed elevated total serum calcium, elevated osmolality gap, high anion gap metabolic acidosis, and renal failure. These alterations were consistent with that seen in burn patients treated with the antimicrobial cream. All six of the control animals survived. The authors suggested that the syndrome observed in the experimental animals was a form of systemic toxicity as a result of the absorption of the PEGs, which were metabolized into nephrotoxic compounds, acid alcohols, and diacids (Herold et al., 1982).

Chronic Oral Toxicity

A 2-year oral toxicity study of PEG-6-32 and PEG-75 was conducted using Wistar albino rats. Four groups of 16 rats (eight of each gender) were given solutions of PEG-6-32 in place of their water supply at concentrations of 0.02, 0.08, 0.4, and 2%. An identical set of rats was given 0.00125, 0.005, 0.02, and 0.08% solutions of PEG-75. The control group of rats were given untreated water. The animals were monitored for adverse behavioral or physiological changes throughout the study, and were killed and examined at the end of 2 years.

The weighted mean dosages during the study were calculated to be 0.015, 0.059, 0.27, and 1.69 g/kg/day for PEG-6-32, and 0.00085, 0.0036, 0.017, and 0.062 g/kg/day for PEG-75. Fifty-five percent of the rats died before termination of the study. The only sign of toxicity was a reduced rate of growth in the animals given the two largest doses of PEG-6-32 (1.69 and 0.27 g/kg/day), and the largest dose of PEG-75 (0.062 g/kg/day). After 1 year, a 9% difference was found between the weights of the treated animals and that of the controls (including the animals given smaller doses of the PEG). At necropsy, the treated rats had several neoplasms and soft aggregates of protein in the bladder, but these changes were also found in the control rats and were considered typical manifestations of aging (Smyth et al., 1947).

Later, the results of this paper were reinterpreted by Smyth et al. (1950). This group pointed out that only one untreated control rat survived the 1947 experiment, so a synthetic control group consisting of this rat and the rats receiving the lowest dosages was established for comparative purposes. They compared the weights of the dosed rats with untreated animals and noted a trend of effect associated with dosage; however, they could find no direct indication that PEGs caused a reduction in growth. The authors concluded that the greatest doses of PEG-6-32 (1.69 g/kg/day) and PEG-75 (0.062 g/kg/day) did not cause any toxic effects in rats (Smyth et al., 1950).

In 1955, Smyth et al. conducted 2 year toxicity studies of PEGs -8, -32, and -75. Groups of Wistar-derived rats (20 of each gender) were administered 0, 1, 2, 4, and 8% PEG-8, or 0, 0.5, 1, 2, 4, and 8% PEG-75 in their feed. PEG-32 was administered to Sherman strain rats (35 of each sex) at concentrations of 0, 0.02, 0.08, 0.4, 2, 4, and 8%. Evidence of toxicity was minor. PEG-8 at concentrations of 4% and 8% caused a slight reduction in the growth rate of male rats, and rats of both sexes fed 8% PEG-75 grew slightly less than control rats. PEG-32 administered at 8% slightly increased the incidence of renal cell swelling (Smyth et al., 1955).

The chronic toxicity of these PEGs was also investigated using dogs. Groups of four dogs were given 2% solutions of PEG-8, PEG-32, and PEG-75 in their diets for one year. Body weight, blood cytology, bromsulfalein retention, and prothrombin time were evaluated throughout the study. There was no significant difference between these measurements in treated rats and those of controls; at necropsy, no abnormalities or microscopic lesions were observed in any of the major organs (Smyth et al., 1955).

Dermal Irritation and Sensitization

When undiluted PEG-6 and PEG-8 (amount not specified) were applied to the clipped abdomens of albino rabbits (six rabbits for each PEG) for 4 h, no signs of irritation were found in 24 h (Smyth et al., 1945).

No irritation was observed during the acute dermal toxicity study (described earlier in this report), in which 20 ml/kg of undiluted PEG-6 and PEG-8 were applied to the skin of six rabbits (Smyth et al., 1945).

Cutaneous tolerance tests of PEG-8 were conducted by Guillot et al. (1982) following official French methods (Journal Officiel de la République Française, 1971a, 1973a, 1980). Two different production lots of PEG-8 were tested using rabbits and occlusive patch testing. The primary irritation indices were 0.04 and 0. PEG-8 was not a cutaneous irritant.

PEG-8 was also nonirritating to rabbits during a 6 -week cutaneous study. The mean maximum cutaneous index for both production lots of PEG-8 was 0.67. No significant lesions were found during macroscopic and microscopic examination (Guillot et al., 1982).

Smyth et al. (1942) applied 3 g PEG-6-32 or 6 ml 50% PEG-75 to the clipped abdomens of guinea pigs (10 animals per treatment group) for 4 days. The PEGs did not irritate the skin.

In the 13 week dermal toxicity study described earlier in this report, the investigators reported that repeated applications (5 days per week) of 20 g undiluted PEG-6-32 was irritating to the abdominal skin of rabbits, but was less irritating than petrolatum. Fifty percent PEG-75 (40 ml) caused no irritation (Smyth et al., 1942).

Six rabbits had 0.5 ml of PEG-32 (melted in a water bath) applied under occlusive patch to their skin for 4 h. No irritation was observed during the 7 day observation period (Bushy Run Research Center, 1987).

In a 30 day dermal toxicity study (described earlier in this report), PEG-75 and PEG-20M at doses of 0.4 and 0.8 g/kg/day caused mild erythema. All signs of irritation disappeared by the last application (Mellon Institute of Industrial Research, 1956).

Carpenter et al. (1971) used a modified Landsteiner intradermal sensitization test to determine the parenteral sensitization potential of PEG-75. Twenty male albino guinea pigs were given eight doses (0.1 ml) of 0.1% PEG-75 in 0.85% NaCl on alternate days (three per week). A challenge of 0.05 ml was administered after 3 weeks of no treatment. None of the animals were sensitized.

Ocular Irritation

Smyth et al. (1945) reported that 20% PEG-6 and undiluted PEG-8 were slightly more or equally irritating to the conjunctiva of rabbits than a 10% solution of glycerine in saline.

An investigation of corneal necrosis produced by contact with undiluted PEG-6 or PEG-8 was also conducted. The PEGs (amount not specified) were placed in the conjunctival sac of rabbits, and 18–24 h later fluorescein staining was used to determine conjunctival changes. Traces of diffuse necrosis were found in one to two of the five eyes tested for each ingredient. No necrosis was observed when 15% solutions of either PEG were administered (Smyth et al., 1945).

When 0.1 ml PEG-32 (melted in a water bath) was instilled into the conjunctival sac of six rabbits, mild conjunctival irritation was observed in all of the eyes and iritis was observed in three rabbits. All signs of irritation disappeared by 48 h (Bushy Run Research Center, 1987).

A 2% solution of PEG-75 caused congestion of the lower eye lid of rabbits for 5 min. The length of irritation increased with concentration. Solutions of 28% and 42% caused congestion for 30 min and 60 min, respectively. It was reported that a 10% solution of PEG-75 was as irritating as 2% glycerol, 2% boric acid, or 5% ethyl alcohol. The irritancy of a 50% solution was equal to 5% sodium chloride. The authors attributed the irritancy to hypotonicity (Smyth et al., 1942).

Carpenter and Smyth (1946) reported that 0.5 ml undiluted PEG-6, PEG-8, PEG-6-32, and PEG-75 did not cause corneal injuries to the eyes of rabbits 24 h after application.

A 35% solution of PEG-8 (0.1 ml) was placed in the conjunctival sac of four albino rabbits 1, 3, 6, 7, and 13 times over 2, 4, 7, 26, and 50 h. The eyes were monitored for corneal and conjunctival edema, serum extravasion in conjunctivae, and blood/aqueous humor barrier disruption. PEG-8 caused little or no irritation to the eyes (Laillier et al., 1975).

Guillot et al. (1982) conducted ocular tolerance tests of PEG-8 following official French methods (Journal Officiel de la République, Française, 1971b, 1973b). Two different production lots of PEG-8 were tested using the eyes of rabbits. Evaluations were made 1 h after administration, after 24 h, and on days 2, 3, 4, and 7. Fluorescein staining was used to detect corneal ulceration. The ocular irritation indices were 8.50 and 9.83, and no corneal opacity was observed. PEG-8 was not an ocular irritant.

Inhalation Toxicity

Groups of 10 male and 10 female Fischer 344 rats were exposed to aerosols of PEG-75 (20% w:w in water) at 0, 109, 567, or 1008 mg/m^3 for 6 h five times per week for 2 weeks (total of nine exposures). The approximate mass median aerodynamic diameters of the particles for each of the treatment groups were 6.1, 5.0, and 3.8, respectively. The rats were necropsied after nine exposures. Separate groups of control rats and high-dose rats were necropsied after a 2-week recovery period.

All of the rats survived to termination. Parameters of ophthalmology, serum chemistry, urinalysis, and gross lesions of the experimental rats were comparable to those of the control animals. Male rats exposed to 567 and 1008 mg/m^3 PEG-75 had decreased body weight gain, and the latter group also had a 50% increase in neutrophil count. These changes did not occur in the male rats killed after a 2 week recovery period or in any of the female rats killed at either interval. For both sexes, there was a 10% and 18% increase in absolute weights of the lungs for the 567 and 1008 mg/m^3 groups, respectively. The only microscopic changes were in the lungs. There was a concentration-dependent increase in the number of macrophages in the alveoli of rats of both treatment schedules (Klonne et al., 1989).

Reproduction Studies

In the 90-day oral toxicity study conducted by Smyth et al. (1942) (described earlier in this report), the authors reported that rats drinking dosages of 0.23 g/kg/day or more of PEG-75 had testicular tubule degeneration and scant or degenerated sperm. They noted that although none of their control rats had these conditions, historical control rats have had such changes.

Smyth et al. (1947) investigated the reproductive toxicity of PEG-6-32 and PEG-75 during the 2-year oral toxicity studies (described earlier in this report). The animals at each dosage (0.015, 0.059, 0.27, and 1.69 g/kg/day PEG-6-32; and 0.00085, 0.0036, 0.017, and 0.062 g/kg/day PEG-75) were allowed to breed during the study and records were kept of the F_1 and F_2 generations. No changes or adverse responses to either compound occurred in the three generations.

MUTAGENICITY

PEG-8 was tested for mutagenic activity with the Chinese hamster ovary (CHO) mutation test. CHO cells were incubated with PEG-8 at concentrations ranging from 1.0–6.25 $\times 10^{-2}$% (by volume) for 5 h both with and without S9 metabolic activation. Cell survival was determined after 24 h, and the mutant fraction was determined after 7 days. Dimethylnitrosamine (DMN) and ethylmethanesulfonate (EMS) were used as positive controls both with and without metabolic activation. These agents had highly statistically significant mutation frequencies that were within the normally expected range of values observed in historical controls. The mutation frequencies for the solvent (dimethylsulfoxide [DMSO]) and negative controls both with and without metabolic activation were in an acceptable and low range based upon historical control values. PEG-8 was relatively nontoxic at all concentrations tested, and there was no dose-related increase in the frequency of mutants/10^6 viable cells either with or without metabolic activation (Bushy Run Research Center, 1980).

The sister chromatid exchange (SCE) test was used to evaluate the mutagenic potential of PEG-8. CHO cells were incubated with PEG-8 at concentrations ranging from 1.0 to 0.0625% (by volume) for 5 h without metabolic activation, or for 2 h using S9 metabolic activation. EMS was used as a positive control. In the absence of metabolic activation, no statistically significant increases occurred in the SCE frequency at any of the doses of PEG-8. In the presence of a metabolic activation system, the only SCE value that was statistically significant from the solvent control group occurred at the 0.5% dose level. However, there was no indication of a correlation between dose and SCE induction (Bushy Run Research Center, 1980).

PEG-8 was also tested in the unscheduled DNA synthesis (UDS) assay. Rat hepatocytes were treated with PEG-8 prepared in DMSO at concentrations ranging from 100 $\times 10^{-3}$ to 0.1 $\times 10^{-3}$% (by volume) for 2 h in a culture medium containing [^{3}H]thymidine and hydroxyurea. UDS activity was determined by analyzing radioactive incorporation into isolated hepatocyte nuclei or in precipitated DNA. The positive controls used were DMN and 4-nitroquinoline oxide. At concentrations of 3 $\times 10^{-3}$ and 100 $\times 10^{-3}$%, PEG-8 induced elevated levels of UDS measured in the nuclei and DNA of the hepatocytes. The only statistically significant increase in radioactive thymidine incorporation was measured in the DNA of the cells treated with the high dose. However, concentrations between 3 $\times 10^{-3}$ and 100 $\times 10^{-3}$% did not indicate a dose–response relationship, since there was no significant elevation of UDS levels measured in either the nuclei or DNA (Bushy Run Research Center, 1980).

PEG-150 was tested in the mouse lymphoma $TK^{+/-} \rightarrow TK^{-/-}$ forward mutation assay without metabolic activation at concentrations of 50.1, 75.2, 100.0, 125.0, and 150.0 g/l. The mutation frequencies (mutants/10^6 surviving cells) at these concentrations were 46, 65, 61, 60, and 126, respectively. Two control cultures had mutation frequencies of 51 and 60. The mutation index (mutation frequency of treated culture/average mutation frequency of control cultures) ranged from 0.8 to 2.3 (Wangenheim and Bolcsfoldi, 1988).

CARCINOGENICITY

The following carcinogenicity data on PEG-8 were obtained from experiments testing the carcinogenicity of other materials, in which PEG-8 was used as a solvent control.

Twenty Swiss male mice fed 0.30 ml PEG-8 weekly for 30 weeks did not have tumors (Berenblum and Haran, 1955).

PEG-8 (0.05 ml) was injected into the ventral wall of the gastric antrum of 12 guinea pigs. The animals were killed for necropsy after 8 months. No gastric lesions were found (Zaldivar, 1963).

Male CB stock rats were injected intraperitoneally with 0.25 ml PEG-8 once a week for 6 months. Among the 24 animals, one case of hepatoma was reported (Boyland et al., 1968).

Twenty Chester Beatty Stock mice were given weekly subcutaneous injections of PEG-8 (0.2 ml) for 1 year. No neoplasms developed in these animals (Roe et al., 1966).

Subcutaneous injections of PEG-8 (0.25 ml) were administered weekly to 20 male and 20 female Sprague-Dawley rats for 20 weeks. The mice were killed for necropsy after 106 weeks. No sarcomas or fibromas developed in the subcutaneous tissues. Mammary fibroadenomas and carcinomas were observed. However, the incidence of these neoplasms did not differ significantly from that of the untreated control rats (Carter, 1969).

CLINICAL ASSESSMENT OF SAFETY

Systemic Toxicity

Sturgill et al. (1982) reported cases of renal tubular necrosis resulting in the death of burn patients treated with topical ointments containing PEGs. Over a 2-year period, 40 patients with burns over 20–70% of their bodies were treated with a PEG-based antimicrobial cream. The active ingredient in the dressing was 0.2% nitrofurazone, and the PEG-base consisted of 63% PEG-6, 5% PEG-20, and 32% PEG-75. Nine patients died from a syndrome of renal failure, metabolic acidosis, and osmolal gaps. The ointment was identified as the toxic agent. PEG and its metabolites were present in the serum of the patients and, at autopsy, six of the patients had extremely swollen kidneys, with hydropic degeneration and necrosis of proximal tubules. Two individuals had oxalate crystals. Such changes were not present in 14 comparable burn patients not treated with the PEG-based ointment. The investigators noted that the renal changes were similar to that seen in ethylene glycol poisoning.

The same syndrome as described in the patients above occurred in three other burn patients who died from renal failure after being treated with the same antimicrobial cream. These patients also had a markedly decreased ratio of ionized calcium to total calcium in their serum. These changes were linked to the presence of PEGs and their metabolites in the circulation (Bruns et al., 1982).

The animal model developed to assess the potential toxicity of PEG to burn patients was discussed earlier in this report. (See the section on 'Subchronic Toxicity—Dermal' on page 444, paragraph 6 [Herold et al., 1982]).

Dermal Irritation and Sensitization

The irritation potential of a formulation containing 3.0% PEG-8 was determined using 10 volunteers. Each of the panelists had two 0.3 ml samples of the formulation applied to their back under an occlusive patch for 23 h, the sites were scored at 24 h, and new patches were applied to the same sites. Applications were made daily for 3

weeks. The 3.0% PEG-8 formulation caused evidence of a moderate potential for mild cumulative irritation. Composite scores for this panel were 208 and 411 out of a maximum possible score of 630, and the average end point day (the day patching was discontinued because of maximum irritation) was 14.90 and 8.80, respectively (Hill Top Research, Inc., 1979).

In a Draize test, one of 200 individuals was sensitized to an experimental bar of soap. PEG-6 (3% in petrolatum) was determined to be the component in the soap causing this reaction. Challenges with 1% and 3% PEG-75 and PEG-150 also produced positive results. However, the individual was not sensitive to an open test with 3% PEG-6 (Maibach, 1975).

In a number of repeat insult patch tests, PEG-8 did not exhibit a potential for inducing allergic contact dermatitis. These studies are detailed in Table 9. In general, the following procedures were used: a formulation containing PEG-8 was applied under an occlusive patch to the backs of the panelists for 24 h every Monday, Wednesday, and Friday for 3 weeks. The sites were scored 48 or 72 h after application, and new samples were applied to the same site. After a 3 week nontreatment period, a challenge patch was applied to a previously untreated site for 24 h. The sites were scored 24 and 48 h after the patch removal (CTFA, 1980, 1982a, b, c, d, 1983b, c, 1984, 1985b).

Smyth et al. (1942) applied PEG-6-32 and 50% aqueous PEG-75 to the backs of 100 men for 7 days. After 10 days, the patients were reapplied with the PEGs for 2 days. Three cases of irritation occurred in both treatment groups during the initial 7 day exposure. The authors attributed these reactions to previous hypersensitivity or to direct irritation of the compound. During the 2 day reapplication period, PEG-6-32 caused three sensitization reactions, and PEG-75 caused four reactions. All reactions were mild.

Smyth et al. (1945) reported that PEG-6 and PEG-8 caused mild sensitization reactions. Using the same method as above, PEG-6 and PEG-8 were applied to the backs of 23 men. PEG-6 and PEG-8 caused erythema in 9% and 4% of the subjects, respectively.

Later production lots of PEG-8 and PEG-75 were also tested using patch tests and human subjects. No reactions occurred in the 100 male and 100 female subjects tested (Smyth et al., 1950).

Hannuksela et al. (1975) tested 1,556 eczema patients with PEG-8 using the chamber test method. Testing was done throughout the year. PEG-8 was applied for 20–24 h and readings were made 1, 2, and 4–5 days later. Positive reactions occurred in 0.3% of the patients.

A commercial solution for treatment of tinea infection of the toe webs containing PEG-8 as a solvent caused immediate urticaria in a 50-year-old man. A similar product also containing PEG-8 also caused the same symptoms. The two solutions and PEG-8 caused contact urticaria within 15 min when tested for immediate reactions on the patient's forearms. Five control subjects treated with PEG-8 did not have this reaction. The irritation was not a result of delayed type hypersensitivity, since patch test results after 48 h for both products and PEG-8 were negative (Fisher, 1977).

Another case of immediate urticarial reaction was linked to PEG-6 in an ear medication. Patch tests of the medication and PEG-6 were negative, but when they were tested for immediate reactions on this patient's forearms urticarial reaction occurred within 20 min. Five control patients did not have this reaction (Fisher, 1978).

Table 9. Results of Human Repeated Insult Patch Tests with PEG-8

Number of panelists	*PEG-8 concentration and dose*	*Results*	*References*
90	Induction patches 1 and 2 had 3.0% PEG-8 in formulation, and the rest of the patches contained a 50% aq. 3% PEG-8 formulation. Dose: 0.1 ml	Since a fair number of irritant reactions were caused by the first two patches, the formulation was diluted. Minimal to mild irritation was noted in over 75% of the panelists during induction. Twenty-two of the panelists had a response at the 24 h challenge reading. Some of these individuals also had reactions at the 48 h reading. The most severe reaction was mild erythema.	CTFA (1980)
84	Formulation containing 1.0% PEG-8 Dose: 0.1 ml	Seventeen individuals had minimal to mild erythema at least once during the induction phase. One panelist had barely perceptible erythema at the 24 h challenge reading. No reactions were observed at 48 h.	CTFA (1982a)
84	Formulation containing 1.0% PEG-8 Dose: 0.1 ml	Minimal to mild irritation was observed in 25 panelists at least once during induction. Minimal erythema was observed in one panelist during the 24 h challenge reading. No reactions were observed at 48 h.	CTFA (1982b)
98	Formulation containing 1.0% PEG-8 Dose: 0.1 ml	Three subjects had minimal to mild reactions during the induction phase. No reactions were evoked during the challenge phase.	CTFA (1982c)
109	Formulation containing 1.0% PEG-8 Dose: 0.1 ml	Four panelists had barely perceptible erythema at least once during induction. No sensitization reactions were observed.	CTFA (1982d)
100	Formulation containing 1.0% PEG-8 Dose: 0.1 ml	Four panelists had minimal erythema once during induction. None of the panelists had reactions during the challenge phase.	CTFA (1983b)
102	Formulation containing 1.0% PEG-8 dose: 0.1 ml	Minimal irritation was observed in 18 panelists during induction. No reactions were evoked during the challenge phase.	CTFA (1983c)
106	Formulation containing 1.0% PEG-8 Dose: 0.1 ml	Thirty-eight panelists had minimal erythema at least once during the induction phase. Only one case of mild erythema was observed at the 24 h challenge reading. In a follow-up study, this subject showed no signs of sensitization.	CTFA (1984)
97	Formulation containing 1.0% PEG-8 Dose: 0.1 ml	Twenty subjects had minimal to mild erythema during induction. Five subjects had minimal responses during the challenge phase. Reactivity was not confirmed in three subjects tested in a follow-up study.	CTFA (1985b)
106	Formulation containing 1.0% PEG-8 Dose: 0.3 ml	Fifty percent of the panelists had mild erythema at least once during the induction phase of the experiment. Three of 106 panelist had mild reactions at the 24 h challenge evaluation. None of the 106 subjects who completed the study had reactions at the 48 h challenge reading.	Hill Top Research, Inc. (1982)
107	Formulation containing 1.0% PEG-8 Dose: 0.3 ml	Five panelists had mild reactions during the induction period. Two mild reactions were observed at the 24 h challenge reading, and one reaction was observed at the 48 h reading.	Hill Top Research, Inc. (1983)

Cases of delayed allergic eczematous contact dermatitis were caused by PEGs used in a soluble dressing to treat patients with second-degree burns. The dressing contained the active ingredient nitrofurazone in a base composed of PEGs -6, -20, and -75. In one case, a woman treating burns on her leg suffered from erythema and edema 48 h after application. After a patch test, she had strong reactions to the dressing, PEG-6, and PEG-8. No reactions occurred in six control patients. PEG-20 and PEG-75 were negative for sensitization in patch tests (Fisher, 1978).

In another case, a man receiving treatment for burns on his chest suffered severe, edematous, vesicular, and crusted contact dermatitis on his burns. Patch tests of the dressing, PEG-6, and PEG-8 were strongly positive. PEG-20 and PEG-75 did not cause any reactions (Fisher, 1978).

Individuals with delayed allergic contact sensitivity from a topical medication were tested with both the active ingredient, nitrofural, and the solvent, PEG-6. Three of the 40 cases were caused by PEG-6 (Braun, 1969).

When 92 dermatologic patients were tested with PEG-6, 4% had positive reactions. Of 12 sensitized patients, five reacted to PEG-8, and only one reacted to PEG-6-32 and PEG-150. The author concluded that group sensitization of the PEGs only occurred with polymers of similar molecular weight (Braun, 1969).

SUMMARY

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

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

In general, PEGs have low oral and dermal toxicity. The greater-molecular-weight PEGs appear to be less toxic than the lighter PEGs in oral studies.

The PEGs were not irritating to the skin of rabbits or guinea pigs. PEG-75 was not a sensitizer.

PEGs cause mild, transient ocular irritation in rabbits.

Inhalation of aerosolized PEG-75 (20% w:w in water) at concentrations up to 1008 mg/m^3 caused little or no toxicity in rats.

No adverse reproductive effects occurred during subchronic and chronic oral toxicity studies of PEG-6-32 and PEG-75. PEG-8 was negative in the Chinese hamster ovary cell mutation test, the sister chromatid exchange test, and the unscheduled DNA synthesis assay. PEG-150 was not mutagenic in the mouse $TK^{+/-} \rightarrow TK^{-/-}$ forward mutation assay. The mutation index ranged from 0.8 to 2.3.

PEG-8 was not carcinogenic when administered orally, intraperitoneally, or subcutaneously to various test animals.

Cases of systemic toxicity and contact dermatitis in burn patients were attributed to a PEG-based topical ointment.

In clinical studies, PEG-6 and PEG-8 caused mild cases of immediate hypersensitivity. However, PEG-8, PEG-6-32, and PEG-75 were not sensitizers.

DISCUSSION

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

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

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

CONCLUSION

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

ACKNOWLEDGMENT

Susan N.J. Pang, Scientific Analyst and Writer, prepared this report.

REFERENCES

ARGUS, M.F., ARCOS, J.C., and HOCH-LIGETI, C. (1965). Studies on the carcinogenic activity of protein-denaturing agents: hepatocarcinogenicity of dioxane. J. Natl. Cancer Inst. **35**:949–58.

BARTOLI KLUGMANN, F., DECORTI, G., CANDUSSIO, L., and BALDINI, L. (1986). Anticonvulsant activity of two polyethylene glycols in mice. Pharmacol. Res. Commun. **18**(2):149–54.

BARTSCH, W., SPONER, G., DIETMANN, K., and FUCHS, G. (1976). Acute toxicity of various solvents in the mouse and rat. Arzneimittelforsch. **26**:1581–3.

BERENBLUM, I. and HARAN, N. (1955). The influence of croton oil and of polyethylene glycol-400 on carcinogenesis in the forestomach of the mouse. Cancer Res. **15**:501–6.

BESSLER, W.G., SCHIMMELPFENG, L., and PETERS, J.H. (1977). Potentiation of mitogen-induced lymphocyte stimulation by polyethylene glycols. Biochem. Biophys. Res. Commun. **76**(4):1253–60.

BLOW, A.M.J., BOTHAM, G.M., FISHER, D., GOODALL, A.H., TILCOCK, C.P.S., and LUCY, J.A. (1978). Water and calcium ions in cell fusion induced by poly(ethylene glycol). FEBS Lett. **94**(2):305–10.

BOYLAND, E., CARTER, R.L., GORROD, J.W., and ROE, F.J.C. (1968). Carcinogenic properties of certain rubber additives. Eur. J. Cancer **4**:233–9.

BRAUN, W. (1969). Contact allergies to polyethylene glycols. Z. Hautkr. **44**:385. (Secondary referee from Fisher, 1978.)

BRUNS, D.E., HEROLD, D.A., RODEHEAVER, G.T., and EDLICH, R.F. (1982). Polyethylene glycol intoxication in burn patients. Burns **9**:49–52.

BUDDEN, R., KUHL, U.G., and BAHLSEN, J. (1979). Experiments on the toxic, sedative and muscle relaxant potency of various drug solvents in mice. Pharmacol. Ther. **5**:467–74.

BUSHY RUN RESEARCH CENTER. (1980). Submission of unpublished data by CTFA. Polyethylene glycol-400 Carbowax. *In vitro* mutagenesis studies: 3-test battery. (15 pages).*

BUSHY RUN RESEARCH CENTER. (1987). Submission of unpublished data by CTFA. Carbowax PEG-1450 NMW. Acute toxicity and primary irritancy studies. (3 pages).*

BUSHY RUN RESEARCH CENTER. (1988a). Submission of unpublished data by CTFA. Tergitol and Carbowax samples. Assessment of toxicity and pulmonary effects in the rat following single endotracheal injection. (13 pages).*

BUSHY RUN RESEARCH CENTER. (1988b). Submission of unpublished data by CTFA. Carbowax PEG 600, PEG 3350 and MPEG 2000. Assessment of pulmonary effects in the rat following single endotracheal injection. (5 pages).*

CARPENTER, C.P. and SHAFFER, C.B. (1952). A study of the polyethylene glycols as vehicles for intramuscular and subcutaneous injection. J. Am. Pharm. Assoc. Sci. Ed. **41**:27–9.

CARPENTER, C.P. and SMYTH, H.F. (1946). Chemical burns of the rabbit cornea. Am. J. Ophthalmol. **29**:1363–72.

CARPENTER, C.P., WOODSIDE, M.D., KINKEAD, E.R., KING, J.M., and SULLIVAN, L.J. (1971) Response of dogs to repeated intravenous injection of polyethylene glycol 4000 with notes on excretion and sensitization. Toxicol. Appl. Pharmacol. **18**:35–40.

CARTER, R.L. (1969). Early development of injection site sarcomas in rats: A study of tumors induced by a rubber additive. Br. J. Cancer. **23**:408–16.

CHADWICK, V.S., PHILLIPS, S.F., and HOFMANN, A.F. (1977) Measurement of intestinal permeability using low molecular weight polyethylene glycols (PEG 400). I. Chemical analysis and biological properties of PEG 400. Gastroenterology **73**(2):241–6.

CORI, C.F. (1925). The fate of sugar in the animal body. I. The rate of absorption of hexoses and pentoses from the intestinal tract. J. Biol. Chem. **66**:691–75.

COSMETIC, TOILETRY, AND FRAGRANCE ASSOCIATION (CTFA). (1980). Submission of unpublished data by CTFA. Allergic contact sensitization test. 14A/16427-14 containing 3.0% PEG-8 (RI 0639). (11 pages).*

CTFA (1981). Submission of unpublished data by CTFA. The safety evaluation of 14A/16427-14 containing 3.0% PEG-8 RI 0639/Group 6. 13 week subchronic dermal toxicity study using male and female albino rats. Study project: AT0173. (15 pages).*

CTFA (1982a). Submission of unpublished data by CTFA. Allergic contact sensitization test. 12A/23379-04 containing 1.0% PEG-8 (RI 0639). (8 pages).*

CTFA (1982b). Submission of unpublished data by CTFA. Allergic contact sensitization test. 12J/22879-07 containing 1.0% PEG-8 (RI 0639). (8 pages).*

CTFA (1982c). Submission of unpublished data by CTFA. Allergic contact sensitization test. 12J/12829-19 containing 1.0% PEG-8 (RI 0639). (7 pages).*

CTFA (1982d). Submission of unpublished data by CTFA. Allergic contact sensitization test. 12J/25402-16 containing 1.0% PEG-8 (RI 0639). (7 pages).*

CTFA (1983a). CTFA List of Japanese Cosmetic Ingredients. Washington, DC: CTFA, pp. 60–2.

CTFA (1983b). Submission of unpublished data by CTFA. Allergic contact sensitization test. 12C/25613-05 containing 1.0% PEG-8 (RI 0639). (7 pages).*

CTFA (1983c). Submission of unpublished data by CTFA. Allergic contact sensitization test. 12F/27764-06 containing 1.0% PEG-8 (RI 0639). (8 pages).*

CTFA (1984). Submission of unpublished data by CTFA. Allergic contact sensitization test. 12F/30612-03 containing 1.0% PEG-8 (RI 0639). (9 pages).*

CTFA (1985a). Submission of unpublished data by CTFA. The safety evaluation of 14A/25363-17 containing 5.0% PEG-8 (RI 0639)/Group 6. 13 week subchronic dermal toxicity study using male and female albino rats. Study project code 219. (14 pages).*

CTFA (1985b). Submission of unpublished data by CTFA. Allergic contact sensitization test. 12G/34562-12 containing 1.0% PEG-8 (RI 0639). (10 pages).*

*Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, N.W., Suite 310, Washington, DC 20036.

DELAHUNTY, T. and HOLLANDER, D. (1986). New liquid-chromato-graphic method for measuring polyethylene glycol in urine. Clin. Chem. **32**(2):351–3.

ELDER, R.L. (Ed.). (1983). Final report on the safety assessment of PEG-2, -6, -8, -12, -20, -32, -40, -50, -100, and -150 Stearates. J. Am. Coll. Toxicol. **2**(7):17–34.

ESTRIN, N.F., CROSLEY, P.A., and HAYNES, C.R. (Editors). (1982). CTFA Cosmetic Ingredient Dictionary. Third Edition. Washington, DC: The Cosmetic, Toiletry and Fragrance Association, pp. 202–3.

FAO. (1983). Polyethylene glycols. FAO Food and Nutrition Paper No. 28.

FEDERAL REGISTER. (1992). Modification in voluntary filing of cosmetic product ingredient and cosmetic raw material composition statements. Final rule. **57**(18):3128–30.

FISHER, A.A. (1977). Contact urticaria due to polyethylene glycol. Cutis **19**(4):409–12.

FISHER, A.A. (1978). Immediate and delayed allergic contact reactions to polyethylene glycol. Contact Derm. **43**(3):135–8.

FOOD AND DRUG ADMINISTRATION (FDA). (1981). Cosmetic product formulation data. FDA computer printout. Washington, DC: FDA.

FDA. (1984). Cosmetic product formulation data: ingredients used in each product category. FDA computer printout. Washington, DC: FDA.

FDA. (1991). Cosmetic product formulation data. FDA computer printout. Washington, DC: FDA.

FDA. (1992). Cosmetic product formulation data. FDA computer printout. Washington, DC: FDA.

FORT, F.L., HEYMAN, I.A., and KESTERSON, J.W. (1984). Hemolysis study of aqueous polyethylene glycol 400, propylene glycol and ethanol combinations *in vivo* and *in vitro*. J. Parenter. Sci. Technol. **38**:82–7.

GUILLOT, J.P., MARTINI, M.C., GIAUFFRET, J.Y., GONNET, J.F., and GUYOT, J.Y. (1982). Safety evaluation of some humectants and moisturizers used in cosmetic formulations. Int. J. Cosmet. Sci. **4**:67–79.

HAMBURGER, R., AZAZ, E., and DONDROW, M. (1975). Autoxidation of polyoxyethylenic non-ionic surfactants and of polyethylene glycols. Pharm. Acta Helv. **50**:10–7.

HANNUKSELA, M., PIRILA, V., and SALO, O.P. (1975). Skin reactions to propylene glycol. Contact Derm. **1**:112–6.

HARTVEIT, F. (1967). *In-vitro* potentiation of immune oncolysis by polyethylene glycol and by polyvinylpyrrolidone. J Pathol. Bacteriol. **94**(1):200–4.

HARTVEIT, F. (1969a). Oral polyethylene glycol's inhibitory effect on the subcutaneous growth of Ehrlich's carcinoma in mice, and on the local inflammatory responses to the tumor. Acta Pathol. Microbiol. Scand. **77**:623–38.

HARTVEIT, F. (1969b). Inhibition of the subcutaneous growth of Ehrlich's ascites carcinoma in female mice by polyethylene glycol 4000. J. Pathol. **97**(1):145–8.

HAWLEY, G.G. (Editor). (1971). The Condensed Chemical Dictionary. 8th Edition. New York: Van Nostrand Reinhold Company, p. 706.

HEROLD, D.A., RODEHEAVER, G.T., BELLAMY, W.T., FITTON, L.A., BRUNS, D.E., and EDLICH R.F. (1982). Toxicity of topical polyethylene glycol. Toxicol. Appl. Pharmacol. **65**(2):329–35.

HILL TOP RESEARCH, INC. (1979). Unpublished data submitted by CTFA. The study of cumulative irritant properties of a series of test materials. 14A/16427-09 containing 3.0% PEG-8 (RI 0639). (14 pages).*

HILL TOP RESEARCH, INC. (1982). Unpublished data submitted by CTFA. Repeated insult patch test. 12J/25402-09 containing 1.0% PEG-8 (RI 0639). (13 pages).*

HILL TOP RESEARCH, INC. (1983). Unpublished data submitted by CTFA. Repeated insult patch test. 12J/25402-16 containing 1.0% PEG-8 (RI 0639). (20 pages).*

HOCH-LIGETI, C., ARGUS, M.F., and ARCOS, J.C. (1970). Induction of carcinomas in the nasal cavity of rats by dioxane. Br. J. Cancer. **24**:164–7.

HUNTING, A.L.L. (1983). Encyclopedia of Shampoo Ingredients. Cranford, NJ: Micelle Press Inc., pp. 308–10, 321.

JOURNAL OFFICIEL DE LA RÉPUBLIQUE FRANÇAISE DU 21/4/71 (Ed. Lois de Décrets). (1971a). Arrêté du 5/4/71 relatif aux méthodes officielles d'analyses des cosmétiques et produits de beauté. Annexe I: Détermination de l'indice d'irritation primaire.

JOURNAL OFFICIEL DE LA RÉPUBLIQUE FRANÇAISE DU 21/4/71. (1971b). Arrêté du 5/4/71 relatif aux méthodes officielles d'analyses des cosmétiques et produits de beauté. Annexe II: Détermination de l'indice d'irritation oculaire.

JOURNAL OFFICIEL DE LA RÉPUBLIQUE FRANÇAISE DU 5/6/73. (1973a). Arrêté du 16/4/73 relatif aux méthodes officielles d'analyses des cosmétiques et produits de beauté. Annexe I: Détermination de l'indice d'irritation primaire.

JOURNAL OFFICIEL DE LA RÉPUBLIQUE FRANÇAISE DU 5/6/73. (1973b). Arrêté du 16/4/73 relatif aux méthodes officielles d'analyses des cosmétiques et produits de beauté. Annexe II: Détermination de l'indice d'irritation oculaire.

JOURNAL OFFICIEL DE LA RÉPUBLIQUE FRANÇAISE DU 29/1/1980. (1980). Arrêté du 18/12/79, relatif à la méthode officielles pour l'appréciation de l'aggressivité superficielle cutanée par applications itératives pendant 6 semaines d'un produit cosmétique ou d'hygiène corporelle.

*Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, N.W., Suite 310, Washington, DC 20036.

KLONNE, D.R., DODD, D.E., LOSCO, P.E., and TROUP, C.M. (1989). Two-week aerosol inhalation study on polyethylene glycol (PEG) 3350 in F-344 rats. Drug Chem. Toxicol. **12**(1):39–48.

KOCIBA, R.J., MCCOLLISTER, S.B., PARK, C., TORKELSON, T.R., and GEHRING, P.J. (1974). 1,4-Dioxane. I. Results of a 2-year ingestion study in rats. Toxicol. Appl. Pharmacol. **30:**275–86.

KRUGLIAK, P., HOLLANDER, D., MA, T.Y., TRAN, D., DADUFALZA, V.D., KATZ, K.D., and LE, K. (1989). Mechanisms of polyethylene glycol 400 permeability of perfused rat intestine. Gastroenterology **97:**1164–70.

LAILLIER, J., PLAZONNET, B., and LE DOUAREC, J.C. (1976). Evaluation of ocular irritation in the rabbit: development of an objective method of studying eye irritation. Proc. Eur. Soc. Toxicol. **17**(Predict. Chronic. Toxic. Short Term Stud., Proc. Meet., 1975):336–50.

LOCKARD, J.S. and LEVY, R.H. (1978). Polyethylene glycol 400: Solvent and anticonvulsant? Life Sci. **23**(25):2499–502.

LOCKARD, J.S., LEVY, R.H., CONGDON, W.C., and DUCHARME, L.L. (1979). Efficacy and toxicity of the solvent polyethylene glycol 400 in monkey model. Epilepsia **20**(1):77–84.

MAIBACH, H.I. (1975). Polyethyleneglycol: Allergic contact dermatitis potential. Contact Derm. **1:**247.

MCGINITY, J.W., HILL, J.A., and LA VIA, A.L. (1975). Influence of peroxide impurities in polyethylene glycols on drug stability. J. Pharm. Sci. **64**(2):356–7.

MELLON INSTITUTE OF INDUSTRIAL RESEARCH. (1956). Unpublished data submitted by CTFA. Gross results of 90-day feeding of Carbowax compound 20-M to rats and of 30-dose rabbit inunction and single skin penetration of 20-M and Carbowax compound 4000. (5 pages).*

MOKYR, M.B., PRZEPIORKA, D., and DRAY, S. (1982). Mode of action of polyethylene glycol 6000 in potentiating the *in vitro* generation of antitumor cytotoxicity by MOPC-315 tumor bearer spleen cells. Cancer Res. **42**(7):2537–43.

NIKITAKIS, J.M. (Editor). (1988). CTFA Cosmetic Ingredient Handbook. First Edition. Washington, DC: The Cosmetic, Toiletry and Fragrance Association, pp. 149–50. 281-2, 289-91, 293-4, 297-8, and 304.

PATTY, F.A. (Editor). (1963). Industrial Hygiene and Toxicology. Second Revised Edition. Vol. II. New York: Interscience Publishers, p. 1511.

PONZIO, N.M. (1980). Lymphocyte responses to syngeneic antigens. I. Enhancement of the murine autologous mixed lymphocyte response by polyethylene glycol. Cell. Immunol. **49:**266–82.

REED, K.W. and YALKOWSKY, S.H. (1985) Lysis of human red blood cells in the presence of various cosolvents. J. Parenter. Sci. Technol. **39:**64–9.

ROBINSON, J.J. and CIURCZAK, E.W. (1980). Direct gas chromatographic determination of 1,4-dioxane in ethoxylated surfactants. J. Soc. Cosmet. Chem. **31:**329–37.

ROE, F.J.C., ROSS, W.C.J., and MITCHLEY, B.C.V. (1966). Carcinogenicity of certain glycidal derivatives. Fd. Cosmet. Toxicol. **4:**365–7.

SAX, N.I. (1979). Dangerous Properties of Industrial Materials. 5th Edition. New York: Van Nostrand Reinhold Company, p. 921.

SHAFFER, C.B AND CRITCHFIELD, F.H. (1947a). Solid polyethylene glycols (Carbowax compounds). Quantitative determination in biological materials. Ind. Eng. Chem., Anal. Ed. **19**(1):32–4.

SHAFFER, C.B. and CRITCHFIELD, F.H. (1947b). The absorption and excretion of the solid polyethylene glycols (Carbowax compounds). J. Am. Pharm. Assoc. Sci. Ed. **36:**152–7.

SHAFFER, C.B., CRITCHFIELD, F.H., and CARPENTER, C.P. (1948). Renal excretion and volume distribution of some polyethylene glycols in the dog. Am. J. Physiol. **152:**93–9.

SHAFFER, C.B., CRITCHFIELD, F.H., and NAIR, J.H. III. (1950). The absorption and excretion of a liquid polyethylene glycol. J. Am. Pharm. Sci. Ed. **39:**340–4.

SHIDEMAN, F.E. and PROCITA, I. (1951). Some pharmacological actions of polypropylene glycols of average molecular weight 400, 750, 1200 and 2000. Pharmacol. Exp. Ther. **103:**293–305.

SILVERSTEIN, B.D., FURCINITTI, P.S., CAMERON, W.A., BROWER, J.E., and WHITE, O., Jr. (1984). Biological effects summary report—polyethylene glycol. Government Reports Announcements & Index. Issue 15. NTIS/DE84007984. 27 pp.

SMITH, B.L. and CADWALLER, D.E. (1967). Behavior of erythrocytes in various solvent systems III. Water—polyethylene glycols. J. Pharm. Sci. **56:**351–5.

SMYTH, H.F., Jr., CARPENTER, C.P., and SHAFFER, C.B. (1945). The subacute toxicity and irritation of polyethylene glycols of approximate molecular weights of 200, 300, and 400. J. Am. Pharm. Assoc. **34:**172–4.

SMYTH, H.F., Jr., CARPENTER, C.P., and SHAFFER, C.B. (1947). The toxicity of high molecular weight polyethylene glycols; chronic oral and parenteral administration. J. Am. Pharm. Assoc. Sci. Ed. **36:**157–60.

SMYTH, H.F., Jr., CARPENTER, C.P., SHAFFER, C.B., SEATON, J., and FISCHER, L. (1942). Some pharmacological properties of polyethylene glycols of high molecular weight ("Carbowax" compounds). J. Ind. Hyg. Toxicol. **24:**281–4.

*Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, N.W., Suite 310, Washington, DC 20036.

SMYTH, H.F., Jr., CARPENTER, C.P., and WEIL, C.S. (1950). The toxicology of the polyethylene glycols. J. Am. Pharm. Assoc. Sci. Ed. **39:**349–54.

SMYTH, H.F., Jr., CARPENTER, C.P., and WEIL, C.S. (1955). The chronic oral toxicology of the polyethylene glycols. J. Am. Pharm. Assoc. Sci. Ed. **44:**27–30.

SMYTH, H.F., Jr., SEATON, J., and FISCHER, L. (1941). The single dose toxicity of some glycols and derivatives. J. Ind. Hyg. Toxicol. **23:**259–68.

STURGILL, B.C., HEROLD, D.A., and BRUNS, D.E. (1982). Renal tubular necrosis in burn patients treated with topical polyethylene glycol. Lab. Invest. **46:**81A (abstract).

TUSING, T.W., ELSEA, J.R., and SAUVEUR, A.B. (1954). The chronic dermal toxicity of a series of polyethylene glycols. J. Am. Pharm. Assoc. **43:**489–90.

WANGENHEIM, J. and BOLCSFOLDI, G. (1988). Mouse lymphoma L5178Y thymidine kinase locus assay of 50 compounds. Mutagenesis **3**(3):193–206.

WINDHOLZ, M. (Editor). (1983). The Merck Index. 10th Edition. Rahway, NJ: Merck & Co., Inc. p. 1092.

ZALDIVAR, R.S.D. (1963). Precancerous lesions in guinea-pigs after intramural injections of 3-methylcholanthrene. Naturwissenschaften **50:**380–1.