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Final Report on the Safety Assessment of Triethylene Glycol and PEG-4[1]

Triethylene Glycol and PEG-4 (polyethylene glycol) are polymers of ethylene oxide alcohol. Triethylene Glycol is a specific three-unit chain, whereas PEG-4 is a polymer with an average of four units, but may contain polymers ranging from two to eight ethylene oxide units. In the same manner, other PEG compounds, e.g., PEG-6, are mixtures and likely contain some Triethylene Glycol and PEG-4. *Triethylene Glycol* is a fragrance ingredient and viscosity decreasing agent in cosmetic formulations, with a maximum concentration of use of 0.08% in skin-cleansing products. Following oral doses, Triethylene Glycol and its metabolites are excreted primarily in urine, with small amounts released in feces and expired air. With oral LD_{50} values in rodents from 15 to 22 g/kg, this compound has little acute toxicity. Rats given short term oral doses of 3% in water showed no signs of toxicity, whereas all rats given 10% died by the 12th day of exposure. At levels up to 1 g/m^3, rats exposed to aerosolized Triethylene Glycol for 6 h per day for 9 days showed no signs of toxicity. Rats fed a diet containing 4% Triethylene Glycol for 2 years showed no signs of toxicity. There were no treatment-related effects on rats exposed to supersaturated Triethylene Glycol vapor for 13 months nor in rats that consumed 0.533 cc Triethylene Glycol per day in drinking water for 13 months. Triethylene Glycol was not irritating to the skin of rabbits and produced only minimal injury to the eye. In reproductive and developmental toxicity studies in rats and mice, Triethylene Glycol did not produce biologically significant embryotoxicity or teratogenicity. However, some maternal toxicity was seen in dams given 10 ml/kg/day during gestation. Triethylene Glycol was not mutagenic or genotoxic in Ames-type assays, the Chinese hamster ovary mutation assay, and the sister chromatid exchange assays. PEG-4 is a humectant and solvent in cosmetic products, with a maximum concentration of use of 20% in the "other manicuring preparations" product category. This ingredient, with an oral LD_{50} in rats of 32.77 g/kg, has low acute toxicity. Rats given up to 50,000 ppm PEG-4 in drinking water for 5 days showed no permanent signs of toxicity. Rats given daily oral doses up to 2 g/kg/day of PEG-4 for 33 days showed no signs of toxicity. Undiluted PEG-4 produced only minimal injury to the rabbit eye. PEG-4 was not mutagenic in Ames-type assays, did not induce chromosome aberration in an in vivo bone marrow assay, and was negative for genotoxicity in a dominant lethal assay using rats. Other PEG compounds, which have previously been reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel, e.g., PEG-6, are mixtures that likely include Triethylene Glycol and PEG-4, so these data were also considered. PEG-6 and PEG-8 were not dermal irritants in several rabbit studies. PEG-2 Stearate had a potential for slight irritation in rabbits but was not a sensitizer in guinea pigs. PEG-2 Cocamine was a moderate irritant in rabbits, producing severe erythema. In one dermal study, PEG-2 Cocamine was determined to be corrosive to rabbit skin, causing eschar and necrosis. PEG-6 and PEG-8 caused little to no ocular irritation. PEG-8 was not mutagenic or genotoxic in a Chinese hamster ovary assay, a sister-chromatid exchange assay, and in an unscheduled DNA synthesis assay. In clinical studies on normal skin, PEG-6 and PEG-8 caused mild cases of immediate hypersensitivity; PEG-8 was not a sensitizer; PEG-2 Stearate was not an irritant, a sensitizer, or a photosensitizer; and PEG-6 Stearate was not an irritant or sensitizer. In damaged skin, cases of systemic toxicity and contact dermatitis in burn patients were attributed to a PEG-based topical ointment. The CIR Expert Panel acknowledged the lack of dermal sensitization data for Triethylene Glycol and dermal irritation and sensitization data for PEG-4. That PEG-6, PEG-8, and PEG-2 Stearate were not irritants or sensitizers suggested that Triethylene Glycol and PEG-4 also would not be irritants or sensitizers, and the absence of any reported reactions in the case literature and the professional experience of the Expert Panel further supported the absence of any significant sensitization potential. The need for additional data to demonstrate the safety of PEGs Cocamine was related to the Cocamine moiety and is not relevant here. The Panel reminded formulators of cosmetic products that, as with other PEG compounds, Triethylene Glycol and PEG-4 should not be used on damaged skin because of cases of systemic toxicity and contact dermatitis in burn patients have been attributed to a PEG-based topical ointment. Based on its consideration of the available information, the CIR Expert Panel concluded that Triethylene Glycol and PEG-4 are safe as cosmetic ingredients in the present practices and concentrations of use as described in this safety assessment.

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INTRODUCTION

Triethylene Glycol is a fragrance ingredient and viscosity decreasing agent and PEG-4 (Polyethylene Glycol) is a humectant and solvent in cosmetic formulations. Triethylene Glycol and PEG-4 are polymers of ethylene oxide alcohol. Triethylene is a specific three-unit chain, whereas PEG-4 is a polymer with an average of four units, but which may contain polymers ranging from two to eight repeated ethylene oxide units. In the same manner, other PEG compounds, e.g., PEG-6, are mixtures and likely contain some Triethylene Glycol and PEG-4.

It is relevant, therefore, that related chemicals, including PEG-6 through -20M, PEGs Stearate, PEGs Distearate, PEGs Laurate, PEGs Dilaurate, and PEGs Cocamine, have been previously reviewed by the CIR Expert panel. The following conclusions were made:

PEG-6, -8, -32, -75, 150, -14M, and -20M are safe for use at the concentrations reflected in the Cosmetic Use section and in the product formulation safety test data included in the Final Report. The Expert Panel recommends that cosmetic formulations containing these PEGs not be used on damaged skin (Andersen 1993).

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

PEG-2, -3, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150, and -175 Distearate are safe for use in cosmetic formulations under the present practices of use (Andersen 1999a).

PEG-2, -4, -6, -8, -12, -20, -32, -75, and -150 Dilaurate and PEG-2, -4, -6, -8, -9, -10, -12, -14, -20, -32, -75, -150, and -200 Laurate are safe for use in cosmetics at concentrations up to 25% (Andersen 2000).

The available data are insufficient to support the safety of **PEG-2, -3, -5, -10, -15, and -20 Cocamine** for use in cosmetic products (Andersen 1999b). The need for additional data was related to the Cocamine moiety.

The relevant data from the previous Final Reports have been summarized in this review as a further basis for the assessment of safety of Triethylene Glycol and PEG-4 .

CHEMISTRY

Definition and Structure

Triethylene Glycol (CAS No. 112-27-6) is the aliphatic alcohol that conforms generally to the formula H-(O-CH_2-CH_2)$_3$-OH. It is also known as 2,2′-[1,2-Ethanediylbis(Oxy)]Bisethanol and Ethanol, 2,2′-[1,2-Ethanediylbis(Oxy)]Bis (Pepe et al. 2002).

Polyethylene Glycol-4 (CAS Nos. 112-60-7 and 25322-68-3) is the polymer of ethylene oxide that conforms generally to the formula H-(O-CH_2-CH_2)$_n$-OH, in which n has an average value of 4 (Pepe et al. 2002) and a range of 2 to 8 ethylene oxide units (Schick 1966). The pure polymer which conforms to the formula above and in which n is equal to 4 (and is not a mixture) is called tetraethylene glycol. Synonyms of PEG-4 include Ethanol, 2,2′-[Oxybis(2,1-Ethanediyloxy) Bis-;2,2′-[Oxybis(2,1-ethanediyloxy) Bisethanol; Polyethylene Glycol 200 (PEG200); and Polyoxyethylene (4) (Pepe et al. 2002). Commercial names for PEG-4 include Carbowax 200, Emkapol 200, Gafanol E 200, Pluriol E 200, and Polydiol 200 (NTP 2001a).

Physical and Chemical Properties

Triethylene Glycol is a colorless hygroscopic, odorless liquid. It is miscible in water, alcohol, benzene, and toluene; sparingly soluble in ether; and insoluble in petroleum ether (Budavari et al. 1989). The quantitative chemical and physical properties of Triethylene Glycol and PEG-4 are summarized in Table 1.

Triethylene Glycol is stable in long-term storage. Combination with strong acids or strong bases at high temperatures may result in explosive decomposition. Burning of Triethylene Glycol can produce carbon dioxide and/or carbon monoxide (NTP 2001b).

PEG-4 is heat-stable and inert to many chemical agents, and it will not hydrolyze or deteriorate under normal conditions. PEG-4 has a solvent action on some plastics (NTP 2001a).

Method of Manufacture

Triethylene Glycol is prepared from ethylene oxide and ethylene. It is manufactured by forming a ether-ester of $HOCH_2COOH$ with glycol and then hydrogenating (Budavari 1989).

According to the Kirk-Othmer Encyclopedia of Chemical Technology (Kroschwitz 1999), Triethylene Glycol is described as an oligomer of ethylene glycol. So-called polyglycols are higher molecular weight adducts of ethylene oxide and distinguished by intervening ether linkages in the hydrocarbon chain.

TABLE 1
Chemical and physical properties of Triethylene Glycol and PEG-4

Property	Triethylene Glycol	PEG-4
Molecular weight	150.17 (Budavari 1989)	190–210 (Budavari 1989)
Relative density	1.1274 (Budavari 1989)	1.127 (Budavari 1989)
Specific gravity	1.126 (Union Carbide 1990a)	1.125 (NTP 2001a)
Freezing point	−4.3°C (Union Carbide 1990a)	Not available
Boiling point	285°C (Budavari 1989) 283°C at 760 mm Hg (Union Carbide 1990a)	327°C (Ashford 1994)
Flash point	330–342°F (Union Carbide 1990a)	171.1–182.2°C (NTP 2001a)
Refractive index	1.4578 at 15°C (Budavari 1989)	1.459 at 25°C (NTP 2001a)
Viscosity	47.8 cp at 20°C (Budavari 1989)	4.3 centistrokes at 210°C (Budavari 1989)
Vapor pressure	<0.01 mm Hg at 20°C (Union Carbide 1990a)	"Relatively low" (NTP 2001a)
Vapor density (air = 1)	5.2 (Union Carbide 1990a)	Not available

Analytical Methods

Triethylene Glycol and PEG-4 have been determined by gas chromatography-mass spectrometry (Kawai et al. 1978) and gas-liquid chromatography (Sigma-Adldrich 2001a, 2001b).

Triethylene Glycol has been measured in rat and rabbit urine using vapor phase chromatography and colorimetry (McKennis et al. 1962).

PEG-4 has been identified from a mixture of low-molecular-weight PEGs using thin-layer and gel permutation chromatography (Sloan et al. 1983).

Impurities

Commercial grade Triethylene Glycol has been found to contain <1 ppm dioxane (Union Carbide 1990a). Twenty-six samples of 99.9% pure Triethylene Glycol were found to contain 0.02% to 0.13% diethylene glycol (McKennis et al. 1962).

USE

Cosmetic

Triethylene Glycol functions in cosmetic products as a fragrance ingredient and as a viscosity-decreasing agent. Frequency of use data for Triethylene Glycol in cosmetic products, as provided by industry to the Food and Drug Administration (FDA) in 2001 as part of a voluntary program, are shown in Table 2. The maximum concentration of use of Triethylene Glycol reported to CTFA (2002) was 0.08% in skin-cleansing products.

TABLE 3
Concentrations of use of Triethylene Glycol (Opdyke 1979)

	Soap	Detergent	Creams, lotion	Perfume
Usual	0.05%	0.005%	0.025%	0.8%
Maximum	0.6%	0.06%	0.2%	2.0%

Opdyke (1979) reported the uses of Triethylene Glycol in cosmetic products as described in Table 3.

PEG-4 functions in cosmetic products as a solvent and as a humectant. Frequency of use data for PEG-4 used in cosmetic products, as reported to the FDA in 2001, are shown in Table 4. The maximum concentration of use of PEG-4 reported to CTFA (2002) was 20% in the "other manicuring preparations" product category.

The use of neither Triethylene Glycol nor PEG-4 in cosmetic products is restricted in Japan (Ministry of Health, Labor and Welfare [MHLW] 2001a, 2001b). Neither ingredient is restricted in any way under the rules governing cosmetic products in the European Union (European Commission 2002).

Noncosmetic

Triethylene Glycol is used in various plastics to increase pliability; in air disinfectants; as a solvent and plasticizer in vinyl, polyester, and polyurethane resins; in dehydration of natural gas; as a humectant in printing inks; as an extraction solvent; and as

TABLE 2
Current and historical use of Triethylene Glycol in cosmetic products

Product category	Total products in each category (FDA 2001)	Number of products with Triethylene Glycol (FDA 2001)	2002 use concentration (%) (CTFA 2002)
Noncoloring hair care			
Conditioners	630	1	
Sprays	267	—	0.0001
Hair coloring			
Tints	54	4	—
Makeup			
Face powders	301	—	0.0001
Lipstick	942	—	0.0001
Makeup bases	136	—	0.001
Rouges	16	—	0.0001
Nail care			
Other manicuring preparations	57	—	0.03
Personal hygiene			
Underarm deodorants	247	—	0.002
Other personal hygiene	291	1	—
Skin care			
Cleansing creams, lotions, etc.	653	—	0.0001–0.08
Total uses/ranges of Triethylene Glycol		6	0.0001–0.08

TABLE 4
Current and historical use of PEG-4 in cosmetic products (FDA 1984, 2001)

Product category	Total products in each category (FDA 2001)	Number of products with PEG-4 (FDA 2001)	2002 use concentration (%) (CTFA 2002)
Bath			
Soaps and detergents	405	—	0.2
Eye makeup			
Eye makeup remover	99	1	0.08
Fragrances			
Perfumes	195	2	0.3
Other fragrance preparations	148	2	—
Noncoloring hair care			
Conditioners	636	5	0.09–3
Shampoos	860	3	0.2
Other hair care	276	2	—
Face powders	250	—	—
Makeup			
Foundations	287	2	—
Lipstick	942	—	0.3
Other makeup	135	1	—
Nail care			
Cuticle softeners	19	1	0.3
Other manicuring preparations	57	1	0.3–20
Personal hygiene			
Underarm deodorants	250	2	—
Other personal hygiene	291	—	—
Shaving			
Aftershave lotion	216	7	0.1
Skin care			
Cleansing creams, lotions, etc.	—	—	0.3
Body and hand skin care	796	15	—
Moisturizers	769	7	—
Skin fresheners	184	1	—
Other skin care preparations	692	5	—
Suntan			
Suntan gels, creams, and liquids	131	—	1
Other suntan preparations	37	—	1
Total use/concentration range of PEG-4		57	0.08–20

a fungicide and solvent for nitrocellulose (NTP 2001b). Triethylene Glycol has also been identified as a main ingredient (99.9% Triethylene Glycol) in a brake fluid (Vassiliadis et al. 1999).

The largest industrial use (about 50%) of PEG-4 is in oil refineries as part of a process of aromatic extraction from refined products. The second largest use (about 40%) of PEG-4 is in the production of plasticizers (Union Carbide 1989b). PEG-4 is also used as a water-soluble lubricant for rubber molds, textile fabrics, and metal-forming operations; in food and food packaging; as a chemical intermediate; in the manufacture of plasticizers, softeners and ointments; in water-based paints; in paper coatings; in polishes; in ceramics; and in pharmaceuticals (NTP 2001a).

ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION

Triethylene Glycol

McKennis et al. (1962) gave two female New Zealand white rabbits 200 or 2000 mg/kg Triethylene Glycol by stomach tube. Urine from the dosed animals was subsequently collected for 24 h. Rabbits dosed with 200 or 2000 mg/kg Triethylene Glycol

respectively excreted 34.3% or 28% of the dose amount as unchanged Triethylene Glycol. The urine of one rabbit contained 35.2% of the administered dose as a hydroxyacid form of Triethylene Glycol.

These same authors also gave four male albino rats weighing 112 to 145 g a single oral dose of 22.5 mg randomly radiolabeled ^{14}C-Triethylene Glycol. The rats were then placed in a metabolic chamber in which urine, feces, and expired air were collected over a period of 5 days. The radioactivity recovered (in percent of the administered dose) amounted to 0.8% to 1.2% in expired air, 2.0% to 5.3% in feces, and 86.1% to 94.0% in urine. The total recovery of radioactivity was 90.6% to 98.3% of the administered dose (McKennis et al. 1962).

In discussing treatment of Triethylene Glycol poisoning, Borron et al. (1997) and Vassiliadis (1999) stated that Triethylene Glycol is believed to be metabolized in mammals by alcohol dehydrogenase to acidic products causing metabolic acidosis. Triethylene Glycol metabolism by alcohol dehydrogenase can be inhibited by 4-methyl pyrazole or ethanol.

PEG-4

Bacterial metabolism of PEG-4 (as tetraethylene glycol) by PEG dehydrogenase in a mixture of *Flavobacterium* and *Pseudomonas* species produced Triethylene Glycol and PEG-4-monocarboxilic acid plus small amounts of PEG-4-dicarboxilic acid, diethylene glycol, and ethylene glycol. The K_M of PEG-4 metabolism in this bacterial mixture was 11 mM (Kawai et al. 1978).

PEG-8

Shaffer et al. (1950) studied the intestinal absorption of PEG-8 in rats, dogs, rabbits, and humans. In the rat, a known amount of PEG-8 was administered by stomach 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.

To examine metabolic destruction of PEG-8 in the dog, 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 to 88 mg was excreted. Ethylene glycol was not a metabolite of PEG-8.

Two groups of three rabbits were given either 5.7 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.

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 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.

These authors also studied urinary excretion of PEG-8 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).

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.

Chadwick et al. (1977) evaluated the intestinal permeability in humans, the absorption, metabolic rate, and excretion of PEG-8. 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 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.

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-week 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).

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

ANIMAL TOXICOLOGY

Acute Toxicity

Triethylene Glycol

Lauter and Vrla (1940) reported that adult albino rats (body weights = 120–145 g) were given a single intramuscular injection of 5.6, 8.4, or 11.3 g/kg Triethylene Glycol ($n = 5$ animals per group; sex unspecified). Animals in the 5.6 g/kg dose group showed only mild signs of toxicity, but all were normal 48 h after the injection. All animals of the 8.4 g/kg group showed signs of toxicity, 3 died within 36 h, and the two surviving animals in

this group recovered 3 days after the injection. All animals of the 11.3 g/kg dose group died with 16 to 36 h after dosing.

Smyth et al. (1941) stated that the oral LD_{50} of Triethylene Glycol had been reported to be 22.06, 14.66, and 18.5 g/kg in rats, guinea pigs, and mice, respectively.

According to *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals* (Budavari 1989), the respective oral and intravenous LD_{50} values for Triethylene Glycol in rats are 15 to 22 and 7.3 to 9.5 g/kg.

Karel et al. (1947) reports an intraperitoneal LD_{50} of 8.15 g/kg in female mice. Toxic effects observed in Triethylene Glycol–treated mice include damage to the spleen, thymus, renal tubules, and glomeruli, as well as high white blood cell counts, pulmonary congestion, and atelectasis (collapse or incomplete expansion of the lung). Animals surviving 5 to 7 days showed signs of regeneration of splenic and lymphoid tissues.

Union Carbide (1986a) exposed five male and five female rats to a single 6-h inhalation treatment of saturated Triethylene Glycol vapor at 21°C. None of the rats died or showed any signs of toxicity as a result of the treatment.

Union Carbide (1990b) exposed four groups of rats, five of each sex per group, once to an aerosol atmosphere of Triethylene Glycol for 4 h. The aerosol concentrations were 2.6, 3.9, 5.0, and 6.7 mg/L Triethylene Glycol. The median aerosol particle diameters per group ranged from 4.4 to 9.3 μm. Animals were observed for signs of toxicity after exposure and for several days following.

Immediately after exposure all rabbits had wet/oily fur and perinasal and periocular encrustation. In the 6.7 and 5.0 mg/L groups, clinical signs included bright red discoloration of the eyes, ears, and feet, blepharospasm, and an absence of toe and tail pinch reflexes. Audible respiration and decreased motor activity were observed in the 5.0 mg/L group on postexposure day 1. For the first 2 to 5 days after exposure, periocular and perinasal encrustation and discolored and unkempt fur were observed. In the 5.0 mg/L group three females died on the 2nd day after exposure, and two females died on the 3rd day. The cause of death for these rats could not be determined upon necropsy and microscopic examinations.

The treatment of 5.0 mg/L Triethylene Glycol exposure was repeated in five additional female rats. Although these additional rats exhibited the same clinical signs observed in the other exposure conditions, none died prematurely. The only treatment-related gross lesions found at necropsy were brown discoloration of the kidneys (two males in the 5.0 mg/L group) and discoloration of the caudate lobe of the liver (one female in the 3.9 mg/L group). The authors determined that the LC_{50} for Triethylene Glycol aerosol in Sprague-Dawley rats is greater than 3.9 mg/L (Union Carbide 1990b).

In a later report (Union Carbide 1990d), five male and five female fasted rats were each given a single oral dose of 16 ml/kg of Triethylene Glycol. No animals died in the 14 days following dosing. One male and one female showed signs of unsteady gait about 30 to 60 min after dosing but returned to normal within 3 to 24 h. No lesions were observed at necropsy 14 days after dosing.

Also described in this report was a study in which five male and five female rabbits were exposed to a single percutaneous application of 16 mg/kg Triethylene Glycol. No signs of dermal irritation were observed, but one female was emaciated on the 4th day after dosing. Two females showed abdominal distention 4 and 14 days after dosing, and one of them died. Necropsy of the dead rabbit showed a gas-filled intestine. Necropsy on day 14 revealed slight skin vascularization of the treated skin in one male. In one surviving female the lungs were tan, and the stomach was filled with liquid (Union Carbide 1990d).

PEG-4

Smyth et al. (1941) stated that the oral LD_{50} of PEG-4 (as tetraethylene glycol) in rats is 32.77 g/kg, with respective upper and lower 95% confidence limits of 36.4 and 28.22 g/kg.

Short-Term Toxicity

Triethylene Glycol

Lauter and Vrla (1940) reported a series of studies using rats. In the first study, albino rats received daily doses of Triethylene Glycol via stomach tube for 30 consecutive days. The dosing groups were 0.1 ml/kg of a 5% aqueous solution, 3.0 ml/kg of a 30% aqueous solution, 10.0 ml/kg of undiluted Triethylene Glycol, and 20.0 mg/kg of undiluted Triethylene Glycol (n = 5 rats per group; sex unspecified). Animals in the lower two dose groups showed normal weight gain and no signs of toxicity. Animals in the 10 mg/kg dose group had slowed weight gain had hair loss and diarrhea. Of the animals in the 20 mg/kg dose group, three died within the first 24 h after the first dose, and the remaining two died before the 3rd day of the study.

In the second study, mature albino rats received drinking water containing 5% or 10% by volume of Triethylene Glycol for 30 days (n = 5 rats per group; sex unspecified). All animals in the 5% dose group showed signs of "severe toxicity," and one animal died on days 8, 21, and 28. The remaining two animals in the group survived to study completion and recovered after exposure ended. All animals in the 10% dose group showed signs of toxicity and died by day 12.

In the third study, young (3-week-old) rats were exposed to drinking water containing 3% or 5% by volume of Triethylene Glycol for 30 days (n = 5 rats per group; sex unspecified). All animals in the 3% dose group survived to study completion without signs of toxicity. Animals in the 5% dose group showed signs of toxicity (weight loss, alopecia, and poor grooming) in the first 2 weeks of exposure but showed improvement thereafter. Body weight gains were reduced, but weights returned to normal after the exposure period ended. One animal in the 5% dose group died on day 25 (Lauter and Vrla 1940).

Union Carbide (1989) reported a study in which Fischer 344 rats received Triethylene Glycol mixed in the diet for 14 days. Triethylene Glycol concentrations in the feed were 0, 10,000,

20,000, or 50,000 ppm ($n = 20$/sex/group). The mean consumption rates of Triethylene Glycol were 1132, 2311, and 3916 mg/kg/day for males and 1177, 2411, and 6209 mg/kg/day for females in the 10,000, 20,000, or 50,000 ppm groups, respectively. No treatment-related effects were observed in food consumption, body weights, body weight gains, hematology, clinical chemistry, gross pathology, histology, or organ weights. The only treatment-related effect seen was in urinalysis. Males and females of the 50,000 ppm group had increased urine volumes, decreased urine pH, and decreased urine triple phosphate crystals. Males of the 20,000 ppm group had a slightly increased urine volume.

Union Carbide (1992) exposed Sprague-Dawley rats to Triethylene Glycol by aerosol inhalation for 6 h a day for 9 days over a 2-week period. The target Triethylene Glycol exposure levels were 0 (filtered air control), 500, 2000, and 5000 mg/m^3. The actual Triethylene Glycol exposure levels were 494, 2011, and 4842 mg/m^3 ($n = 10$/sex/group). Five additional rats were added to the control and 5000 mg/m^3 group for planned postexposure recovery observations. The mean particle size for aerosolized Triethylene Glycol was 2.48 microns.

All rats in the 5000 mg/m^3 dose group died or were euthanized moribund on or before exposure day 5. Prior to their deaths, clinical observations of the animals in this group included ataxia, prostration, unkempt fur, labored respiration (males only), ocular discharge, swollen periocular tissue, perinasal and perioral encrustation, blepharospasm, and reduced body weights. Necropsies of the high-dose animals revealed hyperinflation of the lungs (failure of the lungs to collapse when the chest cavity was opened), ocular opacity, congestion, and hemorrhage in many organs and tissues (pituitary gland, brain, nasal mucosa, kidney, thymus, and lungs).

Rats exposed to 2011 and 494 mg/m^3 Triethylene Glycol survived to the study's completion, and the only clinical observations noted were swollen periocular tissue and perinasal encrustation. After the fifth exposure the males in the 2011 mg/m^3 group had reduced body weights. Food (females only) and water consumption were increased in the mid- and low-dose groups. Hematological analysis showed increased erythrocyte count (females only), decreased red corpuscle volume, increased albumin aminotransferase activity, increased alkaline phosphatase activity, and increased blood urea nitrogen in rats of the 2011 and 494 mg/m^3 groups. Analysis of the urine revealed increased urine volume, decreased urine osmolarity and pH, and decreased *N*-acetyl-β-D-glucoseaminidase activity in the 2011 mg/m^3 group.

At necropsy the mid-dose rats had increased relative and absolute liver and kidney weights. The only remarkable microscopic finding was minimal to mild alveolar histiocytosis. The authors stated that these findings indicate impaired liver function without morphological evidence of organ injury. The threshold exposure concentration for hepatotoxicity from inhalation of aerosol Triethylene Glycol was approximately 494 mg/m^3. There were no consistent findings to suggest renal injury.

Because exposed animals ingested (preened) Triethylene Glycol from wet fur, contributing (unknown quantity) to the total dose received by the animals, a nose-only study was conducted. Male and female CR rats ($n = 10$/sex/group) were exposed to aerosols of Triethylene Glycol for 6 h/day for 9 days over an 11-day period by nose-only exposure. Mean exposure concentrations were 0, 102, 517, or 1036 mg/m^3.

No exposure-related clinical signs were observed. Non–statistically significant decreases in female body weight gains were reported in the mid- and high-concentration groups. The apparent decrease in the mid-dose group was determined to be due to the inclusion of an outlier in the control group with a much higher weight. When this animal was excluded, no decrease in weight gain was observed for the mid-dose group. No changes in food and water consumption were noted. No clinical pathology findings were related to Triethylene Glycol exposure, and no exposure-related organ weight changes were noted in any group (Union Carbide 1992).

PEG-4

Union Carbide (1994) reported a study in which male Fischer 344 rats were exposed to 0, 5000, 25,000, or 50,000 ppm PEG-4 (as tetraethylene glycol) in drinking water for 5 consecutive days in a dominant lethal assay. The respective daily consumption levels of the three doses of PEG-4 were 425 ± 45, 2441 ± 328, and 5699 ± 1341 mg/kg. Males were observed for clinical toxicity, and urine was collected on the 5th day of PEG-4 exposure. At the end of the 5-day dosing period, the PEG-4 drinking water was replaced with regular water. The males were then mated with 10 naive females (reproductive results of the dominant lethal assay are described in the Genotoxicity section later in this report). Ten weeks after the end of dosing the males were killed and necropsied.

Males in the 50,000 ppm group had reduced body weights on the 5th day of treatment, but at 1 week after removal of PEG-4 all body weights were similar to controls. Water consumption was increased in males of the 25,000 and 50,000 ppm groups during the treatment period, and urinalysis indicated increased urine volume and decreased urine pH in all PEG-4 dose groups. Males of the 50,000 ppm group also had decreased urine osmolarity. Necropsy of the males revealed no treatment-related gross or histological effects (Union Carbide 1994).

Schladt et al. (1998) exposed Wistar rats to 0, 220, 660, or 2000 mg/kg/day PEG-4 (as tetraethylene glycol) ($n = 10$/sex/dose) by oral gavage for 33 days. The dosing volume was 5 ml/kg. Animals were observed daily for clinical signs of toxicity. Body weights, food consumption and water consumption were recorded weekly. Blood was collected for hematology and clinical chemistry at week 4. Urine was collected for urinalysis at weeks 2 and 5. Urine was collected for determination of oxalic acid on days 2 and 25 of dosing. Animals were sacrificed for necropsy and histology at the end of the dosing period.

There were no treatment-related effects on clinical signs, mortality, food and water consumption, body weights,

hematology parameters, gross necropsy, or histopathology. There were no toxicologically relevant effects on serum chemistry. Urine pH was reduced and urine osmolarity was increased in the 660 mg/kg males and 2000 mg/kg females; however, these findings were considered not toxicologically relevant. The content of urine oxalic acid was not affected by the PEG-4 doses tested. The no-observed adverse effect level (NOAEL) of PEG-4 in this study was the highest oral dose, 2000 mg/kg/day (Schladt et al. 1998).

Subchronic Toxicity

Triethylene Glycol

Union Carbide (1990c) reported a study in which Fischer 344 rats were fed Triethylene Glycol mixed in the diet for 13 weeks. Triethylene Glycol concentrations in the feed were 0, 10,000, 20,000, or 50,000 ppm. The sample sizes were 20/sex/group for the 10,000 and 20,000 ppm groups and 30/sex/group in the control and 50,000 ppm groups. The mean daily consumption rates of Triethylene Glycol were 748, 1522, and 3849 mg/kg/day for males and 848, 1699, and 4360 mg/kg/day for females. At the end of the 13-week dosing period 20 rats per sex per group were sacrificed for necropsy and histological examinations. The remaining animals in the control and high-dose groups were monitored without treatment for an additional 6 weeks of recovery.

There were no treatment-related findings in clinical observations, ophthalmic examination, food consumption, clinical chemistry, necropsy, or histology. Body weights were reduced in high-dose males throughout the treatment period and in high-dose females beginning the 8th week and continuing to the end of the exposure period. In the 6-week recovery period the body weights of the high-dose males increased to those of control males; however, the body weights of high-dose females in the recovery period remained lower than the body weights of control females.

Males of the 20,000 and 50,000 ppm Triethylene Glycol doses had decreased erythrocytes and hematocrit and increased mean corpuscular volume; these effects were not seen in females. Urine pH was decreased in all dosed males and in the 20,000 and 50,000 ppm Triethylene Glycol females. Urine volume was increased in high-dose males. Relative kidney weights were increased in males and females of the mid and high Triethylene Glycol doses. The authors attributed the increased urine volumes to excretion of large amounts of the test material or metabolites (Union Carbide 1990c).

Chronic Toxicity

Triethylene Glycol

Fitzhugh and Nelson (1946) fed Osborne-Mendel rats diet (ground commercial rat biscuits with 1% added cod liver oil) containing 0%, 1%, 2%, or 4% Triethylene Glycol for 2 years ($n = 12$/group). Body weights and food consumption were measured weekly. There were no toxic effects observed in the Triethylene Glycol group. Food consumption, growth rate, mortality, incidence of bladder stones, incidence of bladder tumors, and incidence of kidney and liver damage were all similar between the Triethylene Glycol and control groups. The same doses of diethylene glycol produced dose-dependent toxicity in all parameters noted above.

Robertson et al. (1947) placed 24 male and 12 female rats in a chamber containing supersaturated Triethylene Glycol vapor (maintained by a glycostat device) in the air. Four male and two female control rats were kept in a separate chamber containing normal air. Animals remained in the respective chambers for 6 to 13 months. Due to breeding during the test period, the populations increased in the Triethylene Glycol and control chambers to 60 and 14, respectively. Additional set of treatment groups consumed 0.028, 0.065, or 0.533 cc Triethylene Glycol per day in the drinking water ($n = 8$/group). These doses were chosen as 35, 80, and 7000 times the maximum possible Triethylene Glycol exposure by inhalation of saturated vapor in 24 h (determined to be 0.004 cc/kg/day). The water dosing groups were exposed to the respective levels of Triethylene Glycol for 5 to 13 months.

The growth rates of adult and offspring rats in the Triethylene Glycol inhalation and drinking groups were similar to growth in the control group. General health of the rats were not affected by the Triethylene Glycol as vapor or in water. Hematology was likewise similar between control and treated animals. Necropsies showed no treatment-related lesions (Robertson et al. 1947).

DERMAL IRRITATION AND SENSITIZATION

Triethylene Glycol

Triethylene Glycol did not produce any erythema, edema, or other dermal reactions in six rabbits that had been exposed to 0.5 ml Triethylene Glycol for 4 h in an occluded patch test (Union Carbide 1990d).

PEG-6 and -8

Smyth et al. (1945) reported that 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.

Likewise, no irritation was observed during an acute dermal toxicity study, 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). 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).

PEG-2 Stearate

Inolex (1975) reported a study in which PEG-2 Stearate (0.5 ml) was applied to intact and abraded skin sites on the back of each of six rabbits. Following 24 h of exposure, the sites were scored and again at 72 h according to the Federal Hazardous Substances Labeling Act (FHSLA) scale. The primary irritation index (PII) was found to be 0.08/8.00 indicating that the ingredient has a potential for slight irritation.

The same protocol and scoring procedure were used in another experiment. The resulting PII was 0.1718.00 indicating the same low level of skin irritation potential for PEG-2 Stearate (Armak 1972).

Inolex (1975) used two guinea pigs to evaluate the effects of a 0.1% suspension of PEG-2 Stearate. Intracutaneous injections were made three times per week for a total of 10 exposures. The first induction injection was 0.05 ml whereas the remaining nine were 0.1 ml each. After 2 weeks, a challenge injection of 0.05 ml was made. The exposure sites were scored 24 h after each injection. The average score for the 10 sensitizing injections was compared with the score for the challenge. PEG-2 Stearate was considered to be a nonsensitizer.

PEG Cocamine

CTFA (1978a) reported a study in which six New Zealand white rabbits were treated topically with 0.5 ml PEG-2 Cocamine on both abraded and intact sites on their back and flanks. Applications were covered with gauze patches and taped to the skin. Irritation scores were determined at 24 and 72 h following application. Irritation was observed on all the rabbits. The primary skin irritation index (PII) was 3.9 out of a maximum of 8.

In similar studies, the PIIs for PEG-2 Cocamine and PEG-15 Cocamine were 2.4 and 1.4, respectively. The irritation score of PEG-2 Cocamine was due to severe erythema which was observed at 72 h. Erythema was also observed with PEG-15 Cocamine. However, no edema was observed with either ingredient. PEG-2 Cocamine was classified as a moderate irritant, and PEG-15 Cocamine was considered a mild irritant (CTFA 1978b and 1978c).

Hazelton Laboratories America, Inc. (1985) applied semiocclusive patches of 0.5 ml PEG-2 Cocamine (concentration not stated) to the intact skin of six New Zealand white rabbits. The patches were kept in contact with the skin for 4 h, after which the skin was rinsed. Examinations of the skin were made at the time of patch removal and at 24 and 48 h later. The PII for time intervals were 6.2 at 4 h, 7.2 at 24 h, and 7.3 at 48 h. Subcutaneous hemorrhaging and blanching was observed in all of the animals at 24 h and in one rabbit at 48 h. Eschar and necrotic areas were observed at both the 24- and 48-h readings. The investigators concluded that PEG-2 Cocamine was corrosive to the skin.

OCULAR IRRITATION

Triethylene Glycol

Carpenter and Smyth (1946) applied undiluted Triethylene Glycol (0.5 ml) to one eye of each of five albino rabbits. The eyes were then stained with fluorescein and scored for injury 18 to 24 h after dose application. The scoring system was based on corneal opacity, keratoconus, iritis, and necrosis. Triethylene Glycol produced zero to minimal injury to the rabbit eye.

Union Carbide (1990d) reported that ocular exposure to 0.1 ml Triethylene Glycol in six rabbits produced no corneal injury; however, all rabbits displayed acute iritis and minor transient conjunctival irritation. The affected tissues had healed and were back to normal within 24 h after exposure.

PEG-4

Carpenter and Smyth (1946) applied undiluted PEG-4 (0.5 ml) was applied to one eye of each of five albino rabbits. The eyes were then stained with fluorescein and scored for injury 18 to 24 h after dose application. The scoring system was based on corneal opacity, keratoconus, iritis, and necrosis. PEG-4 produced zero to minimal injury to the rabbit eye.

PEG-6 and -8

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 to 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.

Laillier et al. (1975) placed a 35% solution of PEG-8 (0.1 ml) 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.

Guillot et al. (1982) conducted ocular tolerance tests of PEG-8. 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.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

In considering the safety assessments of other polyethylene glycol derivatives (Andersen 1999c), the CIR Expert Panel expressed concern over the teratogenicity and testicular toxicity of ethylene glycol. In this special report on the reproductive and developmental toxicity of ethylene glycol and its ethers, the

CIR Expert Panel concluded that "metabolites of ethylene glycol monoalkyl ethers are reproductive and developmental toxins. In general, these metabolites of concern are not expected to be formed in cosmetic formulations that contain polymers of ethylene glycol."

Triethylene Glycol

Union Carbide (1990e) reported a study in which pregnant CD-1 mice were exposed to Triethylene Glycol by oral gavage daily on gestation days 6 through 15. The Triethylene Glycol doses were 0, 0.5, 5, or 10 ml/kg/day ($n = 30$ mice per group). Triethylene Glycol doses were neat and undiluted, calculated based on most recent body weight measurements, and the negative control dose was 10 ml/kg/day deionized water. Food and water consumption as well as body weights and clinical observations were recorded throughout the study. Dams were killed on gestation day 18. At this time uteri containing fetuses were removed for evaluation, and the dams underwent gross necropsy and microscopic evaluation of certain tissues. Measures of pregnancy outcome were evaluated. Live fetuses were counted, sexed, and weighed before being fixed and stained for evaluations of visceral and skeletal morphology. Half of the live fetuses were decapitated and examined by serial sections for soft-tissue craniofacial malformations.

There were no treatment-related maternal deaths, and no dams aborted. Maternal body weights and body weight gains were similar between all dose groups. There were no affects of treatment on food or water consumption. Maternal clinical signs observed in the 10 ml/kg/day group included hyperactivity with audible and rapid respiration. Necropsy revealed no differences between the doses and control groups, except that relative (but not absolute) kidney weights were increased in the high-dose group. Pregnancy outcome (number of corpora lutea, viable and nonviable implantations, and sex ratio) were not affected by Triethylene Glycol treatment.

The sum of fetal body weights per litter were significantly reduced in the 5 and 10 ml/kg/day groups.

There were no-treatment related malformations noted in the external or visceral examinations. Table 5 lists the remarkable findings of the skeletal examinations. The authors concluded that Triethylene Glycol exposure during organogenesis resulted in evidence of slight maternal toxicity at 10 ml/kg/day and consistent evidence of developmental delay at 5 and 10 ml/kg/day. The authors concluded that no biologically significant embryotoxicity or teratogenicity was observed at the doses tested (Union Carbide 1990e).

Union Carbide (1991) reported a study in which pregnant Sprague-Dawley rats were exposed to Triethylene Glycol by oral gavage on gestation days 6 through 15. The exposure levels were 0, 1, 5, or 10 ml/kg/day ($n = 55$ rats per group). The Triethylene Glycol doses were of undiluted Triethylene Glycol, calculated based on most recent body weight measurements, and the negative control dose was 10 ml/kg/day deionized water. Food and water consumption as well as body weights and clinical observations were recorded throughout the study. Dams were killed on gestation day 21. Uteri containing fetuses were removed for evaluation, and the dams underwent gross necropsy and microscopic evaluation of certain tissues. Measures of pregnancy outcome were evaluated. Live fetuses were counted, sexed, and weighed before being fixed and stained for evaluations of visceral and skeletal morphology. Half of the live fetuses were decapitated and examined by serial sections for soft-tissue craniofacial malformations.

There were no maternal deaths and no aborted pregnancies. In the 10 ml/kg/day group maternal body weights were reduced on gestation days 9 through 18, food consumption was reduced on gestation days 6 through 15, and water consumption was increased on gestation days 6 through 18. Clinical observations in the 10 mg/ml/day group included audible respiration, urine stains, periocular encrustation, and perioral wetness. Dams in the 5 ml/kg/day group had decreased body weights on gestation day 18, decreased food consumption on gestation days 6 through 9, and increased water consumption on gestation days 6 to 15.

Animals treated with 1 ml/kg/day had no observations different from controls. At necropsy maternal body weights (adjusted for gravid uterine weight) were reduced and relative (but not absolute) kidney weights were increased in the high-dose group compared to controls. There were no treatment-related effects

TABLE 5

Summary of fetal developmental observations in mice with lowest observed effect level (LOEL) at which the effect was seen for Triethylene Glycol exposure during pregnancy (Union Carbide 1990e)

Subjects	Dosing	Observations on gestation day 18	LOEL
Pregnant CD-1 mice; 30/dose	0, 0.5, 5, 10 ml/kg/day neat Triethylene Glycol by oral gavage on gestation days 6 through 15	Cervical centra 1, 2, 3, or 4 poorly ossified	10 ml/kg/day
		Reduced number of caudal segments	10 ml/kg/day
		Poorly ossified frontal bone	10 ml/kg/day
		Poorly ossified supraoccipital bone	10 ml/kg/day
		Unossifed proximal phalanges of hindlimb	10 ml/kg/day
		Poorly ossified proximal phalanges of hindlimb	10 ml/kg/day
		Poorly ossified frontal and supraoccipital bones	5 ml/kg/day

on pregnancy outcome with the exception of a decrease in the sum of fetal body weights per litter in the 10 ml/kg/day. There were no significant increases in the incidence of external, visceral, or skeletal malformations. There was an increase in the incidence of one skeletal variation (bilobed thoracic centrum no. 10) in the high-dose group. Although there was some evidence of maternal toxicity, no biologically significant embryotoxiciy or teratogenicity was observed at the doses administered in this study (Union Carbide 1991). These conclusions agree with the above study (Union Carbide 1990e).

In the reports of Lamb et al. (1997) and Bossert et al. (1992), Swiss CD-1 mice were exposed to 0%, 0.3%, 1.5%, or 3.0% Triethylene Glycol in the drinking water in a continuous breeding protocol (n = 20 pairs per treatment group and 40 pairs in control group). There were no signs of treatment-related toxicity in any dose groups. Triethylene Glycol exposure had no effect on the number of litters per breeding pair nor on the number of live pups per litter. The mean live pup weight adjusted for litter size was reduced in the 1.5% and 3.0% Triethylene Glycol groups. Second generation mice in the control and 3.0% Triethylene Glycol groups were evaluated and bred within their dose groups.

Mice in the 3% Triethylene Glycol group consumed 16% more fluid than control mice, but there were no remarkable differences in the pregnancy outcomes of the treated and control groups. Relative liver weights of second generation treated mice were increased; however, there were no other differences noted between treated and control groups. Sperm concentration, motility, and morphology were unaffected by the exposure. Triethylene Glycol was considered not to be a reproductive toxicant when administered to mice in drinking water at concentrations of up to 3% (Lamb et al. 1997; Bossert et al. 1992).

GENOTOXICITY

Triethylene Glycol

Union Carbide (1986b) reported that Triethylene Glycol was evaluated in an Ames bacterial mutagenicity assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538. Triethylene Glycol at concentrations of 1 to 112.6 mg/plate was not mutagenic in any of the strains tested with or without the presence of S9 miscrosomal activation.

In other reports, Triethylene Glycol at dose concentrations of up to 50 mg/ml tested negative for genotoxicity in the Chinese hamster ovary (CHO) mutation and sister-chromatid exchange assays (Union Carbide 1986c, 1986d).

PEG-4

Mortelmans et al. (1986) found that PEG-4 (concentrations up to 10000 μg/plate) was negative for mutagenicity in *S. typhimurium* strains TA100, TA1535, TA1537, and TA98 with and without S9 rat or hamster liver microsome activation in an Ames-type bacterial mutagenicity assay.

Union Carbide (1988) reported that an in vivo bone marrow chromosome aberration assay was used to evaluate the clastogenic (chromosome breaking) potential of PEG-4. Sprague-Dawley rats were given a single 10 ml/kg oral dose of 0, 1250, 2500, or 5000 mg/kg PEG-4 (n = 5/sex/group) diluted in water. The dose levels were selected based on a preliminary test in which PEG-4 was nontoxic up to 5000 mg/kg. A positive-control group received an intraperitoneal (i.p.) injection of 30 mg/kg cyclophosphamide to demonstrate the responsiveness of the animals to a recognized clastogenic agent. Animals were killed at 12, 24, or 48 h after dosing. Bone marrow tissue from the femur of each rat was isolated and prepared for staining of the chromosomes of mitotic cells on slides. Cells were evaluated for chromosome number, specific type of chromosome- or chromatid-type aberrations, and further classified for deletions and exchanges.

None of the three dose levels of PEG-4 tested produced statistically significant or dose-related increases in relative numbers of chromosome aberrations compared to negative-control values. Simple chromatid breaks and fragments were observed, but the frequencies were within the range of spontaneous incidence for the test system. The positive control (cyclophosphamide) group exhibited significant increases in the numbers and types of chromosomal damage in both male and female rats, demonstrating the effectiveness of the test system in detecting clastogenic agents (Union Carbide 1988).

In another study, Union Carbide (1994) reported that male Fischer 344 rats were exposed to 0, 5000, 25,000, or 50,000 ppm PEG-4 in drinking water for 5 consecutive days in a dominant lethal assay (n = 20 rats per group). The respective daily consumption levels of the three doses of PEG-4 were 425 $\pm$ 45, 2441 $\pm$ 328, and 5699 $\pm$ 1341 mg/kg. At the end of the 5-day dosing period, the PEG-4 drinking water was replaced with regular water. Beginning 24 h after the last PEG-4 exposure, the males were mated with two naive (nontreated) virgin females. When those females showed evidence of copulation, they were replaced with two more females, until each male had mated with 10 females or until 10 weeks had passed. At the end of the 10th week after PEG-4 exposure, males were killed for necropsy (observations of male toxicity are described in Short-Term Toxicity earlier in this report). The females were observed and killed on gestation day 15, at which time corpora lutea and implantation sites (resorptions and live embryos) were counted.

Reproductive parameters, including number of fertile males and number of gravid females with viable implants, were not affected by PEG-4 treatment. There were no significant preimplantation losses or dominant lethal effects observed. A concurrent positive control group of males receiving an i.p. injection of 0.5 mg/kg triethylenemelamine (TEM) were bred with naive females in a similar manner described above. The TEM group showed increased pre- and postimplantation loss, increased early resorptions, and significant dominant lethal effects, verifying the validity of the test system (Union Carbide 1994).

PEG-6 and -8

The Bushy Run Research Center (1980) conducted a series of genotoxicity assays.

PEG-8 was tested for mutagenic activity with the CHO mutation test. CHO cells were incubated with PEG-8 at concentrations ranging from 0.01%–0.0625% (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 ethylmethane sulfonate (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).

A 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 100×10^{-3}% to 0.1×10^{-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 3×10^{-3}% and 100×10^{-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, for concentrations between 3×10^{-3}% and 100×10^{-3}%, there was no significant elevation of UDS levels measured in either the nuclei or DNA and the authors concluded that these results did not indicate a dose-response relationship (Bushy Run Research Center 1980).

CARCINOGENICITY

PEG-8

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).

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).

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).

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

Dermal Irritation, Sensitization, and Photosensitization

PEGs

Smyth et al. (1945) reported that PEG-6 and PEG-8 caused mild sensitization reactions. 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).

Braun (1969) tested individuals with delayed allergic contact sensitivity from a topical medication with both the active ingredient, nitrofural, and the solvent, PEG-6. Three of the 40 cases were caused by PEG-6. When 92 dermatologic patients were tested with PEG-6, 4% had positive reactions. Of 12 sensitized patients, 5 reacted to PEG-8, and only 1 reacted to PEG-6 to 32 and PEG-l50. The author concluded that group sensitization of the PEGs only occurred with polymers of similar molecular weight.

Hannuksela et al. (1975) tested 1556 eczema patients with PEG-8 using the chamber test method. Testing was done throughout the year. PEG-8 was applied for 20 to 24 h and readings were made 1, 2, and 4 to 5 days later. Positive reactions occurred in 0.3% of the patients.

In a Draize test, Maibach (1975) reported that 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.

Hill Top Research, Inc. (1979) determined the irritation potential of a formulation containing 3.0% PEG-8 in 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.

In a number of repeat insult patch tests, CTFA (1980, 1982a, 1982b, 1982c, 1982d, 1983a, 1983b, 1984, 1985) reported that PEG-8 did not exhibit a potential for inducing allergic contact dermatitis. These results are detailed in Table 6. 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.

PEGs Stearate

CTFA (1979) reported that a 1.5% PEG-6 Stearate hair cream was tested on 48 subjects for potential skin irritancy/sensitization. Four occlusive patches per week for 2 weeks were applied for 18 to 24 h each, after which the patch was removed and the sites scored on a scale of 0 to 8. Two weeks after the last induction patch, a challenge patch was applied to an adjacent area of the arm. These sites were scored 24 and 48 h later. All irritation scores were zero following the first five exposures. For insults 6, 7, and 8, there were 1, 4, and 7 reactors, respectively. All challenge scores were zero.

The Food and Drug Research Labs (1982) performed a repeated insult patch test on 168 subjects (115 females, 53 males) using 0.1 ml of a 25% water solution of PEG-2 Stearate. The test material was applied at 48-h intervals, three times per week for 3 weeks on the backs of the subjects. The test area was occluded for 24 h before removal, and washed with distilled water. The test sites were read at 48 h, after which fresh test material and the occlusive patch were reapplied. After a 3-week rest period, the test area, as well as an untreated site, were challenged using the same procedure as previously noted. The sites were scored for sensitization at 24, 48, and 72 h. The investigator noted that only transient reactions were observed during the test and that PEG-2 Stearate was neither an irritant nor a sensitizer.

Twenty-eight of the 168 subjects tested for irritation and sensitization discussed above were randomly selected to test the ability of PEG-2 Stearate to induce a phototoxic or photosensitive reaction following ultraviolet (UV) exposure. The test protocols were the same except that the forearm was used as a test site. The 28 subjects were divided into two groups; 19 received only UVA and 9 received both UVA and UVB. The UVA (320 to 400 nm) light was applied for 15 min to the 19 subjects (4.4 $pWIcm^2$ at the skin surface measured at a 360-nm wavelength peak). The UVB was applied at two times mean erythema dose (MED) to nine subjects from a 150-watt xenon arc solar simulator emitting at 280 to 320 nm. The subjects receiving the UVB exposure were also exposed for 5 min to UVA as previously described. The investigator noted that only transient reactions were observed, and that PEG-2 Stearate was not a photosensitizer (Food and Drug Research Labs 1982).

Case Reports

Triethylene Glycol

A 23-year-old woman was brought to an emergency room after intentionally ingesting one gulp (volume unspecified) of Caltex® brake fluid containing 99.9% Triethylene Glycol. The patient was given milk to drink by her family and subsequently vomited. Upon arrival to the emergency room, she was unconscious and had metabolic acidosis (pH 7.03, PCO_2 44 mm Hg, bicarbonate 11 mmol/L, anion gap 30 mmol/L, serum creatinine 90 μmol/L). She was intubated and given 100 mmol of intravenous sodium bicarbonate. Triethylene Glycol is thought to be metabolized by alcohol dehydrogenase to acidic products resulting in metabolic acidosis. To act as a competitor of the alcohol dehydrogenase enzyme, ethanol was administered to maintain a serum ethanol level of 100 mg/dl. The blood pH returned to normal over the next eight hours, and ethanol infusion continued for 22 h. At 36 h post ingestion, the patient was discharged to a psychiatric ward. Analysis of blood drawn upon admission did not detect the presence of ethanol, ethylene glycol, or methanol. At the time of publication the authors knew of no other cases of pure Triethylene Glycol poisoning in humans (Vassiliadis et al. 1999).

The above case study described the Caltex® brake fluid as 99.9% Triethylene Glycol. The material safety data sheet for Caltex® brake fluid, however, lists its ingredients as 30.00–60.00% polyglycol ethers; 30.00–60.00% borate of triethylene glycol monomethyl ether; 30.00–60.00% polyglycol; 0–10.00% corrosion inhibitor; and 0–10.00% dye (Caltex Australia Petroleum Pty, Ltd. 1997).

PEGs

Fisher (1977) reported that 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

TABLE 6
Results of human repeated-insult patch tests with PEG-8

No. of panelists	PEG-8 concentration and dose	Results	References
90	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	Because 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 1983a
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 1983b
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 1985

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 (1978) linked a series of cases to PEGs. A 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.

Cases of delayed allergic eczematous contact dermatitis were linked to 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).

SUMMARY

Triethylene Glycol and PEG-4 are polymers of ethylene oxide alcohol without ester linkages to fatty acids. Triethylene is a single compound, whereas PEG-4 is a mixture that may contain polymers of two to eight repeated ethylene oxide units. Other Polyethylene Glycol compounds that have previously been reviewed by the CIR Expert Panel are mixtures that may include Triethylene Glycol and PEG-4.

Triethylene Glycol

Triethylene Glycol is a fragrance ingredient and viscosity decreasing agent in cosmetic formulations. The maximum concentration of use of Triethylene Glycol is 0.08% in Skin Cleansing Products.

Following oral doses, Triethylene Glycol and its metabolites are excreted primarily in the urine, with small amounts released in the feces and expired air.

Oral LD_{50} values in rodents range from 15 to 22 g/kg, and the intravenous LD_{50} in rodents ranges from 7.3 to 9.5 g/kg. The LC_{50} of aerosolized Triethylene Glycol in rats is greater than 3.9 mg/L.

Rats given drinking water that contained 5% Triethylene Glycol for 30 days showed signs of toxicity (weight loss, alopecia, and poor grooming). Surviving animals recovered to normal health after Triethylene Glycol treatment ended. A lower dose of 3% Triethylene glycol in water showed no signs of toxicity, whereas all animals in a higher dose (10%) died by the 12th day of exposure.

Rats exposed to up to 1036 mg/m^3 aerosolized Triethylene Glycol via a nose-only apparatus for 6 h per day for 9 days showed no signs of toxicity.

Triethylene Glycol mixed in the feed of rats at 50,000 ppm for 13 weeks caused increased kidney weights and transient effects on urine volume and chemistry. Rats fed a diet containing 4% Triethylene Glycol for 2 years showed no signs of toxicity. There were no treatment-related effects in rats exposed to supersaturated Triethylene Glycol vapor for 13 months nor in rats that consumed 0.533 cc Triethylene Glycol per day in drinking water for 13 months.

Dermal exposure of rabbits to Triethylene Glycol (0.5 ml) under occlusive patch for four hours was not irritating. Ocular exposure to 0.1 ml Triethylene Glycol in rabbits produced no corneal injury, however all rabbits displayed acute iritis and minor transient conjunctival irritation. Undiluted Triethylene Glycol (0.5 ml) applied to the eyes of rabbits produced only minimal injury to the eye.

In reproductive and developmental toxicity studies in rats and mice, Triethylene Glycol did not produce biologically significant embryotoxicity or teratogenicity. However, some maternal toxicity was seen in dams given 10 ml/kg/day during gestation.

Triethylene Glycol was not mutagenic or genotoxic in Ames-type assays using *S. typhimurium*, the Chinese hamster ovary mutation assay, and sister-chromatid exchange assays.

PEG-4

Polyethylene Glycol-4 (PEG-4) is a humectant and solvent in cosmetic products. The maximum concentration of use of PEG-4 in cosmetics is 20% in other manicuring preparations.

The oral LD_{50} of PEG-4 in rats is 32.77 g/kg.

Rats exposed to 5000 to 50000 ppm PEG-4 in drinking water for 5 days showed no permanent signs of toxicity. Decreased body weights and altered urine chemistry in the 50000 ppm group were returned to normal after the dosing period. Rats given daily oral doses of 220 to 2000 mg/kg/day of PEG-4 for 33 days showed no signs of toxicity.

Undiluted PEG-4 (0.5 ml) produced only minimal injury to the rabbit eye.

PEG-4 was not mutagenic in Ames-type assays using *S. typhimurium*. PEG-4 did not induce chromosome aberration in an in vivo bone marrow assay. PEG-4 was negative for genotoxicity in a dominant lethal assay using rats.

Other PEG Groups

In the absence of specific safety data on Triethylene Glycol and PEG-4, data from related polyethylene glycol compounds are presented.

PEG-8 is rapidly absorbed by the gastrointestinal (GI) tract of several mammalian species and excreted primarily in the urine with less excretion in the feces. Excretion of PEG-8 is rapid, 40% to 67% of oral doses are eliminated within 24 h. Ethylene glycol was not a metabolite of PEG-8 in dogs.

PEG-6 and PEG-8 were not dermal irritants in several rabbit studies. PEG-2 Stearate had a potential for slight irritation in rabbits but was not a sensitizer in guinea pigs. PEG-2 Cocamine was a moderate irritant in rabbits, producing severe erythema. In one dermal study, PEG-2 Cocamine was determined to be corrosive to rabbit skin, causing eschar and necrosis. PEG-6 and PEG-8 caused little to no ocular irritation.

PEG-8 was not mutagenic or genotoxic in a Chinese hamster ovary assay, a sister-chromatid exchange assay, and in an unscheduled DNA synthesis (UDS) assay.

In clinical studies, PEG-6 and PEG-8 caused mild cases of immediate hypersensitivity. However, PEG-8 was not a sensitizer. PEG-2 Stearate was not an irritant, a sensitizer, or a photosensitizer. PEG-6 Stearate was not an irritant or sensitizer. Cases of systemic toxicity and contact dermatitis in burn patients were attributed to a PEG-based topical ointment.

DISCUSSION

The CIR Expert Panel acknowledged the lack of dermal sensitization data for Triethylene Glycol and dermal irritation and sensitization data for PEG-4. Because Triethylene Glycol and PEG-4 produced zero to minimal eye irritation, however, the Panel considered that they are not likely to be dermal irritants. The lack of significant dermal irritation with all PEG-6 and -8 supports this view. The need for additional data to demonstrate the safety of PEGs Cocamine was related to the Cocamine moiety and is not relevant here. The Panel also noted that PEG-6, PEG-8, and PEG-2 Stearate were not sensitizers, which suggested that Triethylene Glycol and PEG-4 also would not be sensitizers. In addition, the absence of reports in the case literature and the professional experience of the CIR Expert Panel suggested that there is no significant sensitization potential.

Because cases of systemic toxicity and contact dermatitis in burn patients were attributed to a PEG-based topical ointment, the Panel alerted formulators of cosmetic products that, as with other PEG compounds, Triethylene Glycol and PEG-4 should not be used on damaged skin.

CONCLUSION

The CIR Expert Panel concluded that Triethylene Glycol and PEG-4 are safe as cosmetic ingredients in the present practices and concentrations of use as described in this safety assessment.

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