Final Report of the Cosmetic Ingredient Review Expert Panel

Amended Safety Assessment of Triethylene Glycol and Polyethylene Glycols (PEGs)-4, -6, -7, -8, -9, -10, -12, -14, -16, -18, -20, -32, -33, -40, -45, -55, -60, -75, -80, -90, -100, -135, -150, -180, -200, -220, -240, -350, -400, -450, -500, -800, -2M, -5M, -7M, -9M, -14M, -20M, -23M, -25M, -45M, -65M, -90M, -115M, -160M and -180M and any PEGs ≥ 4 as used in Cosmetics

June 29, 2010

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Cosmetic Ingredient Review

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ABSTRACT

The safety of Polyethylene Glycols (PEGs) as used in cosmetics was reviewed. In general, PEGs are not oral toxicants, exhibit little ocular irritation, and have minimal dermal irritation and sensitization. PEGs are not genotoxic or carcinogenic. PEGs are not reproductive or developmental toxicants. Use of antimicrobial creams with a PEG vehicle was associated with renal toxicity when applied to burned skin, but studies of extensively tape stripped skin demonstrated that the levels of PEGs that could penetrate in a worst case analysis are >100 times less than the renal toxicity no observable effect level, providing a margin of safety. Triethylene Glycol and PEGs ≥ 4 are considered safe for use in cosmetics in the present practices of use and concentration.

INTRODUCTION

Polyethylene Glycols (PEGs) are condensation polymers of ethylene oxide used for a wide range of purposes in cosmetics depending on molecular weight (see Table 1). The Cosmetic Ingredient Review (CIR) Expert Panel previously evaluated (Andersen 1993) the safety of Polyethylene Glycol (PEGs) -6, -8, -32, -75, -150, -14M and -20M, concluding that these ingredients are safe for use in cosmetics at the use concentrations and in the product categories included in the report, except that the Expert Panel stated that cosmetic formulations containing these PEGs should not be used on damaged skin. The CIR Expert Panel also reviewed the safety of Triethylene Glycol and PEG-4, concluded that these two ingredients are safe as cosmetic ingredients in the practices of use and concentration described in the safety assessment. Additional data have been evaluated that address the "damaged skin" caveat.

In addition, other PEGs now listed as cosmetic ingredients have been added to the group. Ingredients in this safety assessment include: Triethylene Glycol and Polyethylene Glycols (PEGs) -4, -6, -7, -8, -9, -10, -12, -14, -16, -18, -20, -32, -33, -40, -45, -55, -60, -75, -80, -90, -100, -135, -150, -180, -200, -220, -240, -350, -400, -450, -500, -800, -2M, -5M, -7M, -9M, -14M, -20M, -23M, -25M, -45M, -65M, -90M, -115M, -160M and -180M and any PEG ≥ 4 that may be used as a cosmetic ingredient in the future.

There is a mixture of terminology for PEGs because Triethylene Glycol is a specific chain length polymer (three ethylene oxide units only, no PEG-2, PEG-4, etc.), whereas, for example, PEG-4 is a mixture where the average chain length of polymers is four, but which can contain polymers ranging from two to eight repeated units.

PEG derivatives previously have been reviewed by the CIR Expert panel, with following conclusions:

- *PEG-30, -33, -35, -and -40 Castor Oils are safe for use in cosmetics at concentrations up to 50% and PEG-30 and -40 Hydrogenated Castor Oil are safe for use at concentrations up to 100% as cosmetic ingredients in the present practices of concentration and use (Andersen 1999a).*
- *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), except that the Expert Panel stated that cosmetic formulations containing these PEGs should not be used on damaged skin.*
- *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 2000a), except that the Expert Panel expressed concern regarding sensitization and toxicity when applied to damaged skin.*
- *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 1999c), except that the Expert Panel stated that cosmetic formulations containing these PEGs should not be used on damaged skin.*
- *PEG-7, -30, -40, -78, and -80 Glyceryl Cocoate are safe as used in rinse-off products and safe up to 10% in leave-on products (Andersen 1999d), except that the Expert Panel stated that cosmetic formulations containing these PEGs should not be used on damaged skin.*
- *PEG-20, -27, -30, -40, -50, -60, -75, and -85 Lanolin are safe as presently used in cosmetic products (Elder 1982).*
- *PEG-5, -10, -24, -25, -35, -55, -100, and -150 Lanolin; PEG-5, -10, -20, -24, -30, and -70 Hydrogenated Lanolin; PEG-75 Lanolin Oil; and PEG-75 Lanolin Wax (Andersen 1999e) are safe for use in cosmetic products under the present practices of use , except that the Expert Panel expressed concern regarding sensitization and toxicity when applied to damaged skin.*
- *PEG-10 Propylene Glcol; PEG-8 Propylene Glycol Cocoate; PEG-55 PropyleneGlycol Oleate; and PEG-25, -75, and -120 Propylene Glycol Stearate are safe as used in cosmetic products (Andersen 2001a), except that the Expert Panel stated that cosmetic formulations containing these PEGs should not be used on damaged skin.*
- *PEG-20 Sorbitan Cocoate, PEG-40 Sorbitan Diisostearate, PEG-2, -5, -20 Sorbitan Isostearate, PEG-40 and -75 Sorbitan Lanolate, PEG-10, -40, -44, -75, and -80 Sorbitan Laurate, PEG-3 and -6 Sorbitan Oleate, PEG-80 Sorbitan Palmitate, PEG-40 Sorbitan Perisostearate, PEG-40 Sorbitan Peroleate, PEG-3, -6, -40, and -60 Sorbitan Stearate, PEG-20, -30, -40, and -60 Sorbitan Tetraoleate, PEG-60 Sorbitan Tetrastearate, PEG-20 and -160 Sorbitan Triisostearate, PEG-18 Sorbitan Trioleate, PEG-40 and -50 Sorbitan Hexaoleate, PEG-30 Sorbitol Tetraoleate Laurate, and PEG-60 Sorbitol Tetrastearate are safe for use under the present practices of use (Andersen 2000b), except that the Expert Panel stated that cosmetic formulations containing these PEGs should not be used on damaged skin.*

- *PEG-5, -10, -16, -25, -30, and -40 Soy Sterol are safe as used in cosmetic products (Andersen 2004), except that the cosmetic industry is advised to avoid using PEGs Soy Sterol in cosmetic formulations that may be used on damaged skin.*
- *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).*
- *Sorbeth-6, -8, and -20 Beeswax (formerly PEG-6, -8, and -20 Sorbitan Beeswax) are safe for use as cosmetic ingredients under the present practices of use (Andersen 2001b), but the Expert Panel recommends that cosmetic formulations containing the PEG-6, PEG-20, and PEG-75 not be used on damaged skin.*

The "damaged skin" caveat from the original safety assessment of PEGs was carried over to the safety assessments of PEG esters in which it appeared in either the discussion or the conclusion, including:

- PEG-2, -3, -5, -10, -15, and -20 Cocamine;
- 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;
- PEG-2, -3, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150 and -175 Distearate;
- PEG-7, -30, -40, -78, and -80 Glyceryl Cocoate;
- PEG-5, -10, -24, -25, -35, -55, -100, and -150 Lanolin; PEG-5, -10, -20, -24, -30, and -70 Hydrogenated Lanolin; PEG-75 Lanolin Oil; and PEG-75 Lanolin Wax;
- PEG-10 Propylene Glycol; PEG-8 Propylene Glycol Cocoate; PEG-55 PropyleneGlycol Oleate; and PEG-25, -75, and -120 Propylene Glycol Stearate;
- PEG-20 Sorbitan Cocoate, PEG-40 Sorbitan Diisostearate, PEG-2, -5, -20 Sorbitan Isostearate, PEG-40 and -75 Sorbitan Lanolate, PEG-10, -40, -44, -75, and -80 Sorbitan Laurate, PEG-3 and -6 Sorbitan Oleate, PEG-80 Sorbitan Palmitate, PEG-40 Sorbitan Perisostearate, PEG-40 Sorbitan Peroleate, PEG-3, -6, -40, and -60 Sorbitan Stearate, PEG-20, -30, -40, and -60 Sorbitan Tetraoleate, PEG-60 Sorbitan Tetrastearate, PEG-20 and -160 Sorbitan Triisostearate, PEG-18 Sorbitan Trioleate, PEG-40 and -50 Sorbitan Hexaoleate, PEG-30 Sorbitol Tetraoleate Laurate, and PEG-60 Sorbitol Tetrastearate;
- PEG-5, -10, -16, -25, -30, and -40 Soy Sterol; and
- PEG-6, -8, and -20 Sorbitan Beeswax

Based on the amended conclusion for this safety assessment, conforming changes in each of these safety assessments will be made to remove the "damaged skin" caveat.

CHEMISTRY

DEFINITION AND STRUCTURE

Table 1 summarizes the CAS numbers, definitions, functions and synonyms for PEGs included in this safety assessment.

As two different naming conventions are commonly used for these ingredients, the potential exists for some confusion. The official name for each ingredient is that given in the International Cosmetic Ingredient Dictionary and Handbook, the INCI name (e.g. PEG-4), but it is also common to use the molecular weight name (e.g. PEG 200) for the same ingredient. Table 2 gives the official INCI name, the molecular weight name, and the corresponding molecular weight. All INCI names include dashes and the numbers represent the average number of moles of ethylene oxide. When the PEG name does not include a dash, the number is the average molecular weight.

PHYSICAL AND CHEMICAL PROPERTIES

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 several individual PEGs are listed in Tables 3 and 4. "Carbowax" 1500 is a solid blend of equal weights of PEG-6 and PEG-32 (Smyth et al. 1950).

Tensile data show a maximum in extensibility at a polyethylene glycol (PEG) molecular weight of 1450, while ultimate strength increases with increasing segment length (Silver et al. 1994). When the PEGs are hydrated, there is a significant drop in the modulus, ultimate stress and ultimate elongation. Dynamic contact angle measurements show that surface hydrophobicity decreases as the soft segment molecular weight increases. Using electron spectroscopy for chemical analysis (ESCA) to determine the surface composition, it was found that the hard segment content at the surface increases as the polyol block length decreases.

With increasing molecular weight, PEGs can have some degree of branching (Webster et al. 2007).

METHODS OF MANUFACTURE

PEGs are the condensation products of ethylene oxide and water, with the chain length controlled by number of moles of ethylene oxide that are polymerized (Hunting 1983). 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).

ANALYTICAL METHODS

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

According to Robinson et al. (2006), the combination of high-field asymmetric waveform ion mobility spectrometry (FAIMS) with Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS) can be used in the analysis of PEG samples of low molecular weight. The high ion transmission obtained using FAIMS combined with the high sensitivity of FTICR-MS detection make possible separation of multiple gas-phase conformers of PEG molecular cations that have low abundance (less than 0.2% relative abundance) and that have not been detected previously.

PEG-4

Triethylene Glycol and PEG-4 may be analyzed using gas chromatography-mass spectrometry (Kawai et al. 1978) and gas-liquid chromatography (Sigma-Adldrich 2001a, b). 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).

PEG-8

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).

PEG-12

A high-performance liquid chromatographic (HPLC) method has been developed for the determination of PEG-12 in human urine, which includes a pre-column dibenzoate derivatisation step. The dibenzoate derivatives of PEG-12 can be quantitatively prepared, and this, coupled with ultraviolet detection at 230 nm, has greatly improved the limit of detection for the determination of PEGs by HPLC. A suitable extraction procedure has also been developed which enabled PEG levels in urine to be monitored with much greater sensitivity than any previously reported method (Kinahan and Smyth 1991).

IMPURITIES

Silverstein et al. (1984) reported that PEG-6 may contain small amounts of ethylene oxide monomer and dimers. The amounts were not quantified.

Peroxides, formed as a result of autoxidation, 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 thiosuIfate/mI glycol. PEG-8 had concentrations ranging from 3.24 to 5.7 μEq thiosulfate/ml glycol. The specific peroxides present in the PEGs were not determined, but they were thought to be organic peroxides rather than hydrogen peroxide (McGinity et al. 1975).

PEGs may contain trace amounts of 1,4-dioxane, a by-product of ethoxylation (Robinson and Ciurczak 1980). 1,4-Dioxane is a known animal carcinogen (Kociba et al. 1974). Commercial grade Triethylene Glycol has been found to contain < 1 ppm dioxane (Union Carbide 1990a). 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

Functions in cosmetics of Triethylene Glycol and other PEGs are shown in Table 1.

The CIR Expert Panel recognized that certain ingredients in this group are reportedly used in a given product category, but the concentration of use was not available. For other ingredients in this group, information regarding use concentration for specific product categories was provided, but the number of such products was unknown. In still other cases, an ingredient was not in current use, but may be used in the future. The information available on the types of products and at what concentration indicate a pattern of use, within which some of these ingredients likely would be used.

Table 5 presents the available product use information provided by manufacturers to the Food and Drug Administration (FDA) under the Voluntary Cosmetic Registration Program (VCRP) for the various PEGs (FDA 2008), along with recent information on the concentration of use provided to the Personal Care Products Council (Council 2009). There are gaps in the available data. For example, 2 uses of PEG-45M were reported in the VCRP in the other baby products category, but no use concentration data were available. Also, use concentrations were provided for PEG-180M in non-coloring hair products, but no uses were reported in the VCRP. The following are reported to be in use: Triethylene Glycol and PEGs -4, -6, -8, -9, -10, -12, -14, -20, -32, -40, -75, -90, -150,

-180, -220, -240, -350, -400, -450, -2M, -5M, -7M, -14M, -23M, -45M, -90M, and -180M, with the highest reported use concentration of 85% in a non-coloring hair product for PEG-8.

The ingredients in this safety assessment are not restricted in Japan (Ministry of Health, Labor and Welfare (MHLW) 2001a, b). These ingredients are not restricted in any way under the rules governing cosmetic products in the European Union (European Commission 2002).

NON-COSMETIC

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.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 cell fusion of plant protoplasts, bacterial protoplasts, plant protoplasts with animal cells, and animal cells in culture (Blow et al. 1978).

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 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 1989). 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).

PEG 3350 is an approved OTC laxative (Miralax, GlycoLax) (Cerner Multum 2008).

GENERAL BIOLOGY

ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION

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). In reported cases of renal tubular necrosis resulting in the the death of burn patients treated with topical ointments containing PEGs, PEG and its metabolites were present in the serum of these patients (Sturgill et al. 1982). Additional data relevant to dermal penetration of PEGs through damaged skin is provided in the Clinical Assessment Safety section.

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 hours. 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 Triethylene Glycol-C^{14}. The rats were then placed in a metabolic chamber in which urine, feces, and expired air were collected over a period of five 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).

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 (Borron et al. 1997; Vassiliadis 1999).

PEG-6 and PEG-8

Shaffer et al. (1950) studied the intestinal absorption of PEG-8 in the rat. PEG-8 was administered by stomach tube. For a 25% solution of PEG-8, approximately 62% of the dose was absorbed into the intestines in 5 h.

Metabolic fate of PEG-8 in the dog was also demonstrated by Shaffer et al. (1950). Three dogs were intravenously 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. The authors stated that ethylene glycol was not a metabolite of PEG-8.

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

In a study using PEG-8 to determine the intestinal permeability in humans, Chadwick et al. (1977) evaluated the absorption, metabolic fate, 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 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 further investigated in vitro by incubating 1g of PEG-8 with 20g 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 0.4g or 0.75g PEG-8, and urine was collected for 24 h. The groups eliminated an average of 47% and 67% of the total dose, respectively. The disposition of the remaining dose was unknown (Shaffer et al. 1950).

Urinary excretion of PEG-8 was studied using human subjects. Three subjects given intravenous injections of 1g 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.

PEG-6, PEG-12, and PEG-20

The dependence of permeability on molecular weight (MW) in acetone-disrupted female hairless mouse (strain SKH1-hr) skin in contrast to normal skin was investigated (Tsai et al. 2001). The number of animals used was not provided. Penetration of PEG-6, PEG-12, and PEG-20 over 12 h was measured using diffusion cells. High-performance liquid chromatographic methods with refractive index detection were used to separate and quantitate the individual oligomeric species in the PEG samples. Percutaneous penetration of PEGs exhibited slightly steeper MW dependency at a transepidermal water loss (TEWL) of 30-41 g/m2 per h in comparison with TEWLs of 0-10 (control skin), 10-20, and 20-30 g/m2 per h, with a higher percentage of smaller oligomer PEGs penetrating than larger ones. Increasing the TEWL of the skin increased the penetration of all the PEG oligomers, and the degree of the enhancement relative to penetration through control skin increased with MW and was maximal for oligomers with a MW ranging from 326 to 414 Da. Within the limit of quantitation of the assay, the MW cut-off for PEG penetration across mouse skin with TEWLs of 0-10, 10-20, and 20-30 g/m2 per h was 414, 590, and 942 Da, respectively, while all the measurable oligomers up to MW 1,074 Da were able to penetrate skin with TEWLs in the range 30-41 g/m^2 per h. There was no mention of a change in absorption rate or percent PEG absorbed after damage by the study authors.

The dependence of permeability on MW with different forms of barrier disruption was investigated in female hairless mice (strain SKH1-hr) using a series of PEGs ranging in MW from near 300 to over 1000 Da (Tsai et al. 2003). The number of animals used was not provided. PEGs were used to determine the effects of tape stripping and sodium dodecyl sulfate (SDS) treatment on the MW permeability profiles of mouse skin in vitro. The 12-h percutaneous penetration of all the PEG-6, PEG-12, and PEG-20 generally increased as a function of transepidermal water loss (TEWL) of the skin, either tape-stripped or SDS-treated. In addition, the total penetration of PEG oligomers across control skin, and skin tape-stripped and SDS-treated to different degrees of barrier disruption progressively decreased with increasing MW. There were no significant differences in the percutaneous penetration of the PEG oligomers between skin tape-stripped and SDS-treated to the same degree of barrier disruption. The penetration enhancement relative to control skin was more prominent with larger molecules. The MW cutoff for skin penetration increased with the degree of barrier disruption irrespective of the treatment applied, and was 986 Da (tape stripping) and 766 Da (SDS treatment) at TEWL levels in the range 10-20 g/m(2) per h in comparison with 414 Da for control skin. There was no mention of a change in absorption rate or percent PEG absorbed after damage by the study authors. In accordance with previous findings in acetone-treated mouse skin, the results strongly suggest that, irrespective of the form of barrier disruption applied, not only higher amounts but also more varieties of chemicals (larger molecules) may penetrate skin with a compromised barrier than normal skin.

According to Moolenar et al. (1981), a rectal solution using PEG-12 as a solvent produced a slow, but continuous absorption (of PEG-12) over at least 8 hours in humans.

PEG-32, PEG-75, PEG-150

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 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).

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 (the disposition of the remaining dose is unknown. Most of the radioactivity was excreted in the urine within 24 h (Carpenter et al. 1971).

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.

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).

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 tissues (Shaffer and Critchfield 1947b).

HEMATOLOGIC EFFECTS

PEG-8

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 EC_{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-12

PEG-12 at 1% was thrombogenic in an ex vivo canine blood-contacting model (Silver et al. 1994).

PEG-75 and PEG-150

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).

RADIOPROTECTION

PEG-4, PEG-8, PEG-12, PEG-20, PEG-80, and PEG-450

PEG of molecular weights 200 (PEG-4), 400 (PEG-8), and 600 (PEG-12) afforded significant levels of radioprotection against x-rays; PEG of molecular weights 1000 (PEG-20), 1450, 4000 (PEG-80), and 20,000 (PEG-450) when given at maximum tolerated doses (approximately 0.5 LD_{50}) did not (Shaeffer and Schellenberg 1984). The degree of radioprotection by PEG-4 given 20 min before irradiation increased with dose up to the maximum tolerated dose of 6.4 g/Kg.

USE AS DRUG VEHICLE

PEG-6 and PEG-8

The biochemical effects of a series of commonly used drug carrier vehicles, including PEG-6, were investigated in the rat using ^{1}H NMR spectroscopic and pattern recognition based metabonomic analysis (Beckwith-Hall et al. 2002). PEG-6 induced changes in the biochemical composition of urine including increased concentrations of dicarboxylic acids, creatinine, taurine, and sugars. The authors concluded that PEG-6 was bioactive in its own right and that this might confound interpretation of biochemical effects of weakly toxic drugs dosed in this carrier.

ANTICONVULSANT PROPERTIES

PEG-8 and PEG-75

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 mI/hr). Prior to and after this treatment, the monkeys were administered saline (1 mI/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, 5 of the animals had statistically significant decreases in seizure frequency. The 3 other monkeys were removed from the study because of signs of toxicity. Follow-up studies confirmed that at concentrations between 35% and 60% PEG-8 had anticonvulsant activity (Lockard and Levy 1978; Lockard et al. 1979).

ANIMAL TOXICOLOGY

ACUTE TOXICITY

Oral

Acute oral toxicity LD_{50} values for Triethylene Glycol and PEGs are summarized in Table 6, with values ranging from 6.4 g/kg in the mouse to >50 g/kg in rats.

PEG-75

Smyth et al. (1942) also determined that 31.6 g/kg was the smallest single oral dose of PEG-75 to cause microscopic renal or hepatic lesions in rats. Since it appeared that only 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 concentration and caused slight hepatic cell swelling. Since the intestines were unobstructed, the authors suggested that the increase in urea concentration was due to the direct action of PEG-75 on the kidneys.

Parenteral

Triethylene Glycol

Lauter and Vrla (1940) administered adult albino rats (body weights = 120 - 145 g) 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 showed only mild signs of toxicity, but all were normal 48 hours after the injection. All animals of the 8.4 g/kg group showed signs of toxicity, three died within 36 hours, and the two surviving animals in this group recovered three days after the injection. All animals of the 11.3 g/kg dose group died with 16 to 36 hours after dosing.

Karel et al. (1947) reported an intraperitoneal LD_{50} of 8.15 g/kg in female mice (strain not provided). Toxic effects observed in Triethylene Glycol-treated mice included 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 five to seven days had signs of regeneration of splenic and lymphoid tissues.

Budavari (1989) stated that the intravenous LD_{50} value for Triethylene Glycol in rats is in the range from 7.3 to 9.5 g/kg .

PEG-6

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

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. 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 6 rats received subcutaneous injections of 2.5, 5, and 10 ml/kg PEG-6. Tissue reactions were monitored, and necropsy was performed on 2 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 6 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).

PEG-8, PEG-32, PEG-75, PEG-150

In an acute intraperitoneal toxicity study using rats, 8% or less PEG-8 did not cause any deaths, but the weight of the kidneys of treated rats was less than that of control rats (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 was 12.9 ml/kg and 13.1 ml/kg for mice and rats, respectively.

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).

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).

Groups of 2 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 mI/min. All animals survived to termination (day 14). One rabbit given PEG-150 had renal tubular cell swelling (Smyth et al. 1947).

Dermal

Triethylene Glycol

Union Carbide (1990c) dosed five male and five female rabbits with a single percutaneous dose of 16 mg/kg Triethylene Glycol. No signs of dermal irritation were observed, but one female was emaciated on the fourth day after dosing. Two females showed abdominal distention four 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.

PEG-6 and PEG-8

The acute dermal toxicity of undiluted PEG-6 and PEG-8 was tested on New Zealand white 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).

PEG-75 and PEG-20M

Two groups of 4 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).

Intratracheal

PEG-75

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 increased. The lung weights relative to the body weights were increased 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 different from 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 weights, 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 the incidence was not statistically significant compared to the controls (Bushy Run Research Center 1988b).

SHORT-TERM TOXICITY

Oral

Triethylene Glycol

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

In another 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 had signs of severe toxicity, and one animal died on day 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 had signs of toxicity and died by day 12.

In the last 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 had signs of toxicity in the first two weeks of exposure but showed improvement thereafter. Body weight gains were decreased, 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).

Preliminary to a subchronic exposure reported later in this report, Van Miller and Ballantyne (2001) conducted a probe 14-d study using rats given dietary concentrations of 0 ppm (control), 10,000, 20,000 or 50,000 ppm Triethylene Glycol daily. Triethylene Glycol consumptions were determined to be 1132, 2311 or 5916 mg/kg with males, and 1177, 2411 or 6209 mg/kg with females for the treatment groups, respectively. There were no mortalities or adverse clinical signs, and no effects on body weight, hematology, serum chemistry, organ weights, and gross or microscopic pathology. Feed consumption was increased at the high dosage. Urinalysis showed increased urine volume and decreased pH with high dose males and females, and increased volume with mid-dose males.

PEG-4

Union Carbide Corp. (1994) exposed male Fischer 344 rats to 0, 5000, 25,000, or 50,000 ppm PEG-4 (as tetraethylene glycol) in drinking water for five consecutive days in a Dominant Lethal Assay. The respective daily consumption levels 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 fifth day of PEG-4 exposure. At the end of the five-day exposure period, the PEG-4 drinking water was replaced with regular water. The males were then mated with ten 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 decreased body weights on the fifth day of treatment, but at one week after removal of PEG-4 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.

Schladt et al. (1998) dosed Wistar rats at 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, feed 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 killed for necropsy and histology at the end of the dosing period. There were no treatment-related effects on clinical signs, mortality, feed and water consumption, body weights, hematology parameters, gross necropsy, or histopathology. There were no toxicologically relevant effects on serum chemistry. Urine pH was decreased 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 NOAEL of PEG-4 in this study was the highest oral dose, 2000 mg/kg/day.

PEG-75

A 5-week study of the effects of PEG-75 on the kidneys of rabbits was conducted (Smyth et al. 1942). 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.

Inhalation

Triethylene Glycol

Union Carbide (1992) exposed Sprague-Dawley rats to Triethylene Glycol by aerosol inhalation for six hours a day for nine days over a two-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 of many organs and tissues (pituitary gland, brain, nasal mucosa, kidney, thymus and lungs). Rats exposed to 2011 or 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 decreased body weights. Feed (females only) and water consumption were increased in the mid- and low-dose groups. Hematological analysis showed increased erythrocyte counts (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 2011mg/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 hours/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 gains was observed for the mid dose group. No changes in feed 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).

Intravenous

PEG-6, PEG-8, PEG-32, PEG-75 and PEG-150

Three of eight chronically epileptic monkeys given intravenous infusions of 60% PEG-8 in water (1 ml/h) for 3 weeks had decreased 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).

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 dose was 350 mg/kg/day. No deaths occurred in the groups receiving PEG-6 and PEG-32, but 1 of 5 rabbits died in the PEG-8 group, 1 of 9 died in the PEG-75 group, and 1 of 5 died in the PEG-150 group. One PEG-8 rabbit and four PEG-75 rabbits had hepatic cell and renal tubular cell swelling.

Dermal

Groups of 8 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. Mean body weight gains were greater in 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 2 paravertebral skin excisions (2.5 **x** 15 cm) were made on 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 8 rabbits treated with the antimicrobial cream and 3 of the 4 rabbits treated with the PEG-vehicle died during the study. They had increased total serum calcium, increased 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).

SUBCHRONIC TOXICITY

Oral Studies

Triethylene Glycol

Van Miller and Ballantyne (2001) studied the potential for Triethylene Glycol to produce nephrotoxicity, or other organ/tissue injury, in a subchronic (90-d) study conducted by continuous inclusion of Triethylene Glycol in the diet of Fischer 344 rats (20 males and 20 females). The dietary concentrations were 0 ppm (control), 10,000, 20,000 or 50,000 ppm Triethylene Glycol, daily. Triethylene Glycol consumption was determined to be 748, 1522 or 3849 mg/kg (males), and 848, 1699 or 4360 mg/kg (females).

There was neither mortality nor signs of toxicity, and no dose-response effects in serum chemistry, gross and microscopic pathology. Body weights were decreased during the dosing period with both males and females at the high dose. Body weight gains were decreased at all dosages with males and females. No hematological effects were seen with females, but males of the mid- and high-dose groups had slightly decreased erythrocyte counts and hematocrits, and high-dose males had decreased hemoglobin concentration with increased mean corpuscular volumes. These were considered to reflect a mild hemodilution related to the absorption of large Triethylene Glycol doses. Urinalysis showed dosage-related decreased pH, and increased urine volume mainly at the high dose. These were probably related to the renal excretion of absorbed Triethylene Glycol and/or metabolites. Kidney weights were increased for high-dose females, and increased relative (to body) weight of kidneys for males and females from the mid- and high-dose groups were observed, probably related to the renal excretion of the absorbed Triethylene Glycol and/or its metabolites. These findings indicate that the subchronic continuous oral dosing of Triethylene Glycol to rats does not result in local or systemic specific organ or tissue toxicity. These findings contrast with the known repeated oral toxicity, notably nephrotoxicity, produced by ethylene and diethylene glycols. Therefore, Triethylene Glycol had significantly lesser potential for systemic toxicity by the oral route than its lower molecular weight homologues (Van Miller and Ballantyne 2001).

PEG-6 and PEG-8

Groups of 5 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 for 90 days. Ten control rats received 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.

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, swollen livers were 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 of the study (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 (Smyth et al. 1950).

Hermansky et al. (1995) studied the effects of PEG-8 following 13 weeks (65 doses) of gavage treatment in Fischer 344 rats (10/group/sex) at doses of 1.0, 2.5 or 5.0 ml/kg (1.1, 2.8 and 5.6 g/kg, respectively) body weight/day for 5 days/week. The control animals received water by gavage (5.0 ml/kg b.w./treatment day). An additional 10 rats/sex/group were assigned to the control and high-dose groups for a 6-week recovery period. Potential renal toxicity was evaluated; there was no mortality or changes in hematology or clinical chemistry measurements attributed to PEG-8 toxicity.

Loose feces in the mid- and/or high-dose group of both sexes were attributed to bulk cathartic effects of PEG-8. Slight decreases in feed consumption and body weights in the mid- and/or high-dose group of male and female rats were attributed to the physical presence of PEG-8 in the intestinal tract. The authors noted, however, that a direct effect of PEG-8 on the intestinal tract was not ruled out. Increased water consumption occurred as a result of a possible increase in serum osmolality due to the absorption of the PEG-8 or a reflection of the water dosing received by the control animals. Increased urinary concentration and decreased urinary pH were at least partially attributed to absorption, possible metabolism, and urinary excretion of PEG-8.

Small increases in absolute and/or relative kidney weights, observed in various dose groups, were attributed to the osmotic effect of the test substance and/or metabolites in the urine. The significance of a slight increase in relative kidney weights in female rats following the recovery period was unknown. Although no microscopic changes were observed in the kidneys or urinary bladder, a slight, reversible renal toxicity may have resulted in male rats treated by gavage with 2.5 ml/kg/day and rats of both sexes treated by gavage with 5.0 ml PEG-8 kg/day (Hermansky et al. 1995).

PEG-6, PEG-8, PEG-32, PEG-75, and PEG-150

Smyth et al. (1942) conducted a 90-day oral toxicity study of PEG-6, PEG-32 and PEG-75. Groups of five rats were given 1-16% (0.88-22.9 g/kg/day) PEG-6, PEG-32 or 0.05-16% (0.04-19.0 g/kg/day) PEG-75 in their drinking water. No deaths were caused by any of the dosages, and blood cytology and hemoglobin were normal. The animals drinking PEG-6 and PEG-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 PEG-6 dosage groups: 4.05, 8.1, and 22.9 g/kg/day. Lower doses 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. A PEG-75 dose 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.

Smyth et al. (1950) reported that 0.04 g/kg/day PEG-75 in drinking water could be administered to rats without causing adverse effects. These authors noted 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. (1955) investigated the relationship between the molecular weight of PEGs and subacute toxicity. Groups of 10 rats (5 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) in drinking water 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.

PEG-20M

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 decreased 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 dose (Mellon Institute of Industrial Research 1956).

Intravenous

PEG-75

Three groups of 9 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).

Dermal Studies

PEG-6, PEG-8, PEG-20, PEG-32, PEG-75, PEG-150, and PEG-20M

Fifteen female Sprague-Dawley rats received 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. Daily applications were made 5 times a week. All of the animals survived the test period, and no changes in body weight gains, 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 organ

weights were found. 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 gains 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 increased neutrophiI/lymphocyte ratio for male rats, and increased 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 weights 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 decreased body weights of the treated animals and the increased neutrophil to lymphocyte ratios 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).

An 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, PEG-32 and 50% aqueous PEG-75 also were nontoxic when applied to the skin for prolonged periods of time. Dosages of 10 g/kg of the “Carbowax” compounds 1500 and 4000 (the latter in the form of a 50% aqueous solution), placed on thin cotton pads, 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).

Tusing et al. (1954) evaluated the dermal toxicity of PEGs -6, -8, -75, and -150 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 5 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 5 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 study termination and all of the control animals survived, the authors noted that the deaths appeared to be due to an incidental coccidial infection. A parasitic infection was also found among the control and surviving test animals.

CHRONIC TOXICITY

Oral

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 two years (n = 12/group). Body weights and feed consumption were measured weekly. There were no toxic effects observed in the Triethylene Glycol group. Feed 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.

PEG-6, PEG-8, PEG-32, and PEG-75

A 2-year oral toxicity study of PEG-6 and PEG-32 and PEG-75 was conducted using Wistar albino rats (Smyth et al. 1947). Four groups of 16 rats (8 of each gender) were given solutions of PEG-6 or PEG-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 and PEG-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 decreased rate of growth in the animals given the two highest doses of PEG-6 and PEG-32 (1.69 and 0.27 g/kg/day), and the high 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 urinary bladder, but these changes were also found in the control rats and were considered typical manifestations of aging (Smyth et al. 1947).

The results of this study were reinterpreted by Smyth et al. (1950), who 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 decrease in growth. The authors concluded that the greatest doses of PEG-6 and PEG-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).

Smyth et al. (1955) 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) in their feed 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 4 dogs were given 2% dietary concentrations of PEG-8, PEG-32, and PEG-75 for 1 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 dogs and those of controls; at necropsy, no abnormalities or microscopic lesions were observed in any of the major organs (Smyth et al. 1955).

OCULAR IRRITATION

Triethylene Glycol

Union Carbide (1990c) reported that ocular exposure to 0.1 ml Triethylene Glycol in six rabbits did not produce corneal injury, however all rabbits displayed acute iritis and minor transient conjunctival irritation. The affected tissues returned to normal within 24 hours after exposure.

PEG-6, PEG-8, PEG-32, PEG-75

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 instilled into the conjunctival sac of rabbits, and 18-24 h later fluorescein staining was used to determine corneal changes. Traces of diffuse corneal necrosis were found in one to two of the five eyes tested for each ingredient. No corneal necrosis was observed when 15% solutions of either PEG were administered (Smyth et al. 1945).

Carpenter and Smyth (1946) reported that 0.5 ml undiluted PEG-6, PEG-8, PEG-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 instilled into 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 Republique, Francaise 1973). 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.

Laillier et al. (1976) instilled a 35% solution of PEG-8 (0.1 ml) into 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.

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).

DERMAL IRRITATION/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 four hours in an occluded patch test (Union Carbide 1990c).

PEG-6, PEG-8, PEG-32, PEG-75, and PEG-20M

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 Republique Francaise 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 for the two lots, respectively. These authors also reported that PEG-8 was 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.

Smyth et al. (1942) applied 3 g PEG-6 and PEG-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 and PEG-32 was irritating to the abdominal skin of rabbits, but was less irritating than petrolatum. Fifty percent PEG-75 (40 ml) caused no irritation.

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 (3 per week). A challenge of 0.05 ml was administered after 3 weeks of no treatment. None of the animals were sensitized.

INHALATION TOXICITY

Triethylene Glycol

Robertson et al. (1947) placed 24 male and 12 female rats in a chamber containing supersaturated Triethylene Glycol vapor. Four male and two female control rats were kept in a separate chamber containing normal air. Animals remained in the respective chambers for six to 13 months. Triethylene Glycol exposure by inhalation of saturated vapor in 24 hours was 0.004 cc/kg/day. The growth rates of adult and offspring rats in the Triethylene Glycol inhalation group was similar to growth in the control group. General health of the rats were not affected by the Triethylene Glycol as vapor. Hematology was likewise similar between control and treated animals. Necropsies showed no treatment-related lesions.

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

Union Carbide (1990b) exposed four groups of Sprague-Dawley rats, five of each sex per group, to an aerosol atmosphere of Triethylene Glycol for four hours. 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 rats 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 post-exposure 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 second day after exposure, and two females died on the third 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. While these additional rats exhibited the same clinical signs observed in the other exposure conditions, none died prematurely. The only treatment-related gross lesions found in 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 (1 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.

PEG-75

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) (Klonne et al. 1989). The approximate mass median aerodynamic diameters of the particles for each of the treatment groups were 6.1, 5.0, and 3.8 μm, 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 of the study. 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 or 1008 mg/m^3 PEG-75 had decreased body weight gains, and the latter group also had a 50% increase in neutrophil counts. 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).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

In a special report on the reproductive and developmental toxicity of ethylene glycol and its ethers, the CIR Expert Panel noted that metabolites of ethylene glycol monoalkyl ethers, such as methoxyethanol and ethoxyethanol (but not butoxyethanol) are reproductive and developmental toxicants, but not ethylene glycol monoalkyl ethers themselves (Andersen 1999c). NTP (2004) concluded that ethylene glycol itself was not a reproductive/developmental toxicant.

Triethylene Glycol

Triethylene glycol and two of its derivatives were evaluated for reproductive toxicity in a continuous breeding protocol with Swiss CD-1 mice (Bossert et al. 1992). Triethylene Glycol (0, 0.3, 1.5, and 3%) was administered in drinking water to breeding pairs (20 pairs per treatment group, 40 control pairs) during a 98-day cohabitation period. Reproductive function was assessed by the number of litters per pair, live pups per litter, proportion of pups born alive, and pup weights. There were no apparent effects on reproductive function in the animals receiving Triethylene Glycol at doses up to 3% in the drinking water. However, some developmental toxicity was demonstrated for Triethylene Glycol. Continuous exposure of dams to 1.5 or 3% Triethylene Glycol significantly decreased live pup weights at birth compared to control and 0.3% Triethylene Glycol. Reproductive toxicity was not demonstrated in mice receiving Triethylene Glycol at doses up to 6.78 g/kg.

Union Carbide (1990d) dosed pregnant CD-1 mice with 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). The Triethylene Glycol doses were of neat undiluted Triethylene Glycol, calculated based on most recent body weight measurements, and the negative control dose was 10 ml/kg/day deionized water. Feed 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 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 feed or water consumption.

Maternal toxicity observed in the 10 ml/kg/day group included hyperactivity with audible and rapid respiration. Necropsy revealed no differences between the treated and control groups, except that relative (but not absolute) kidney weights were increased in the high dose group. Pregnancy outcomes (number of corpora lutea, viable and non-viable implantations, and sex ratio) were not affected by Triethylene Glycol treatment. The sum of fetal body weights per litter were significantly decreased in the 5 and 10 ml/kg/day groups. There were no treatment related malformations noted in the external or visceral examinations.

The lowest observable effect level for skeletal abnormalities seen at gestation day 18 (cervical centra #1, #2, #3, or #4 poorly ossified; reduced number of caudal segments; unossifed proximal phlalanges of hindlimb; and poorly ossified proximal phlalanges of hindlimb) was 10 ml/kg/day and for poorly ossified frontal and supraoccipital bones was 5 ml/kg/day.

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 (Union Carbide 1990d).

Union Carbide (1991) dosed pregnant Sprague-Dawley rats with Triethylene Glycol by oral gavage on gestation days 6 through 15. The doses were 0, 1, 5, or 10 ml/kg/day (n = 55 rats per group). The Triethylene Glycol doses were of neat undiluted Triethylene Glycol, calculated based on most recent body weight measurements, and the negative control dose was 10 ml/kg/day deionized water. Feed and water consumption as well as body weights and clinical observations were recorded throughout the study. Dams were killed on gestation day 21. 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 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 decreased on gestation days 9 through 18, feed consumption was decreased on gestation days 6 through 15, and water consumption was increased on gestation days 6 through 18. Clinical observations in the 10 mg/kg/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 feed consumption on gestation days 6 through 9, and increased water consumption on gestation days 6-15. Animals treated with 1 ml/kg/day had no observations different from controls. At necropsy maternal body weights (adjusted for gravid uterine weight) were decreased and relative (but not absolute) kidney weights were increased in the high-dose group compared to controls. There were no treatment-related effects 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 # 10) in the high-dose group. While 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).

PEG-6, PEG-32, and PEG-75

Smyth et al. (1947) investigated the reproductive toxicity of PEG-6, PEG-32 and PEG-75 during the 2-year oral toxicity studies (described earlier in this report). The animals at each dose (0.015, 0.059, 0.27, and 1.69 g/kg/day PEG-6, PEG-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.

In the 90-day oral toxicity study conducted by Smyth et al. (1942) described earlier, 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.

GENOTOXICITY

Triethylene Glycol

Union Carbide (1986b) evaluated Triethylene Glycol in a 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 microsomal activation.

Triethylene Glycol at doses of up to 50 mg/ml tested negative for genotoxicity in the Chinese Hamster Ovary Mutation (Union Carbide, 1986c) and Sister Chromatid Exchange (Union Carbide 1986d) assays in CHO cells.

PEG-4

Mortelmans et al. (1986) reported that PEG-4 (concentrations up to 10000 μg/plate) was negative for mutagenicity in *Salmonella typhimurium* strains TA100, TA 1535, TA 1537, and TA 98 with and without S9 rat or hamster liver microsome activation.

Union Carbide Corp. (1988) used an *in vivo* bone marrow chromosome aberration assay was used to evaluate the clastogenic (chromosome breaking) potential of PEG-4. Sprague-Dawley rats received 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 non-toxic up to 5000 mg/kg. A positive control group received an 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 hours 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 Corp. 1988).

Union Carbide Corp. (1994) exposed male Fischer 344 rats (n = 20 rats per group) to 0, 5000, 25,000, or 50,000 ppm PEG-4 in drinking water for five consecutive days in a dominant lethal assay. 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 five-day dosing period, the PEG-4 drinking water was replaced with regular water. Beginning 24 hours 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 ten females or until ten weeks had passed. At the end of the tenth week after PEG-4 exposure, males were killed for necropsy (observations of male toxicity are described in the Short-Term Toxicity section 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 Corp. 1994).

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).

Rat hepatocytes were treated with PEG-8 in DMSO at concentrations ranging from 0.0001% to 0.1% (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. While there was a trend to 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 precipitated DNA of the cells treated with the highest concentration. No dose-response relationship was apparent in the precipitated DNA measurement and there was no significant elevation of UDS levels measured in the nuclei (Bushy Run Research Center 1980).

PEG-150

PEG-150 was tested in the mouse lymphoma TK+/-+TK-/- forward mutation assay without metabolic activation at concentrations of 50.1, 75.2, 100.0, 125.0, and 150.0 μm/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

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).

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).

TUMOR GROWTH INHIBITION

PEG-75

Hartveit (1969a) reported that oral administration of PEG-75 significantly decreased 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).

PEG-150

lntraperitoneal 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 1969a).

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).

CLINICAL ASSESSMENT OF SAFETY

Hammer et al. (1989) reported that PEG ingestion induces diarrhea in normal human volunteers.

DERMAL IRRITATION AND SENSITIZATION

PEG-6, PEG-8, PEG-20, PEG-32, PEG-75, and PEG-150

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).

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, for the two samples tested (Hill Top Research, Inc. 1979).

In a number of repeat insult patch tests, PEG-8 did not exhibit a potential for inducing allergic contact dermatitis. These studies, completed on products containing PEG-8, are detailed in Table 7. 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 non-treatment 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 undiluted PEG-6 and PEG-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 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 re-application period, PEG-6 and PEG-32 caused 3 sensitization reactions, and PEG-75 caused four reactions. All reactions were mild.

Smyth et al. (1945) reported that undiluted 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.

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, PEG-32 and PEG-150. The author concluded that group sensitization of the PEGs only occurred with polymers of similar molecular weight (Braun 1969).

A human repeat insult patch test with challenge of masque containing 66% PEG-8 was conducted in 54 subjects (44 males and 19 females; 18-65 years of age) (TKL Research, Inc. 2007). During the induction phase, the test material was applied to 1 side of the infrascapular area of the back. The application sites were assessed for erythema, edema and other signs of cutaneous irritation. Following induction, subjects had a 2-week rest period, after which they entered the challenge phase that consisted of one 48-h patch application to the original site and a naive site on the opposite side of the back. Observations at the naive site during challenge and the

patterns of reactivity during the induction period were analyzed for contact allergic response. Under the conditions of this study, there was no evidence of sensitization or significant irritation.

A cytotoxicity study was performed on an Episkinc reconstructed human epidermis model (MTT conversion assay) on a mask containing 66% PEG-8 (Episkin SNC 2007). The negative control in the study was the untreated epidermis, solvent control was 150 μL of water used to dilute the products, and the positive control was 150 μL of an aqueous solution of sodium dodecyl sulfate at a concentration of 20 mg/mL. Based on the the conditions of this study, it was concluded that on a reconstructed human epidermis model, the product was a non-irritant.

A cutaneous study was conducted using a purifying mask (containing 66% PEG-8) following a single dermal application (Peritesco 2007). Fifty female subjects (19 - 67 years of age) participated in the study. No signs of irritation were observed in any of the subjects. The authors concluded that this product was non-irritating.

RENAL TOXICITY

PEG-6, PEG-20, and PEG-75

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).

These data formed the basis for the "damaged skin" caveat discussed in the introduction. The nephrotoxicity seen in burn patients presumably resulted because no intact skin barrier remained to prevent the entry of PEGs into the circulation. The question remained about the degree of dermal penetration of PEGs (and concern regarding nephrotoxicity) with less severely damaged skin.

DERMAL PENETRATION OF PEGs

Raabe and Norman (2009) at the Institute for In Vitro Sciences developed an in vitro model of damaged skin representative of the degree of damage that would be seen in the consumer population. Levels of skin damage and disease states from published studies were correlated with increases in transepidermal water loss (TEWL). Increases in TEWL of 3.5 to 6.5 were determined to reflect moderate skin damage.

A clinical study was performed to determine the degree of skin damage (as measured using TEWL) from either sodium lauryl sulfate (SLS) at 1, 5, and 10% or 1, 20 or 30 successive tape-strippings. Tape-stripping produced more reproducible results and more of a defined dose-response. SLS again was compared to tape-stripping in a pilot study of cadaver skin using ^3H_2O penetration to assess barrier function disruption. The use of 20 successive tape-strips was chosen as indicative of moderate skin damage and clear disruption of barrier function in a reproducible manner.

PEG-4 was selected as the test article because its low molecular weight range (120-210) would maximize dermal penetration and because [^{14} C] PEG-4 was readily available. A rinse-off (surfactant based) and a leave-on (water in oil emulsion) formulation were used as vehicles in which PEG-4 was tested using cadaver skin mounted in flow-through diffusion cells and samples of receptor fluid taken each 1.5 h. For the rinse-off formulation, exposure was 5 min followed by rinsing. For leave-on formulations, the material was left on the skin sample for 24 h. Three cadaver skin donors were used, with two minimum replicate tissues from each donor per group. The integrity of the skin samples was determined using ^3H_2O.

Absorption of PEG-4 from the rinse-off formulation was 0.37 ± 0.22% in intact skin and 2.30 ± 4.21% for skin that had been tape-stripped 20 times. The absorption of PEG-4 from the leave-on formulation was 8.42 ± 1.56% for intact skin and 33.72 ± 20.11% for skin that had been tape-stripped 20 times. Study results are summarized in Table 8. These data were used in a risk assessment for PEG renal toxicity.

RENAL TOXICITY RISK ASSESSMENT

The Personal Care Products Council (2009b) provided a risk assessment for Kidney Effects of PEGs. In addition, the Council (2009c) summarized the data from the Raabe and Norman study above.

The Council stated that the best available oral NOEL for renal toxicity for PEGs is 1.1 g/kg (Hermansky et al. 1995).

Highest Exposure from a Leave-On Product

Of the reported uses of PEGs, the product type potentially applied to the largest body surface at the highest concentration contains 12% PEG-6 in the "body and hand creams, lotions and powders" category. Assuming this is a whole body product (resulting in higher exposure than a hand-only product), the amount of product used per day from Loretz et al. (2005) is 7.63 g (50^{th} percentile body lotion use) or 14.39 g (90^{th} percentile body lotion use).

Using data from the dermal penetration study by Raabe and Norman (2009), the average total absorption of PEG-4 from a leave-on formulation in a) intact and b) damaged skin, with exposure expressed as a percentage of the applied dose using data from all acceptable trials, is a) 8.42% and b) 33.72%, respectively. Resulting exposure from the leave-on product (amount of cosmetic applied ***x*** concentration of PEG-6 ***x*** units conversion factor ***x*** PEG-4 penetration percent ÷ body weight) would be:

- ***50% percentile:***
  Intact skin: 7.63 g/day x 0.12 x 1000 mg/g x 0.0842 ÷ 60 kg = 1.3 mg/kg/day
  Damaged skin: 7.63 g/day x 0.12 x 1000 mg/g x 0.3372 ÷ 60 kg = 5.1 mg/kg/day
- ***90% percentile:***
  Intact skin: 14.39 g/day x 0.12 x 1000 mg/g x 0.0842 ÷ 60 kg = 2.4 mg/kg/day
  Damaged skin: 14.39 g/day x 0.12 x 1000 mg/g x 0.3372 ÷ 60 kg = 9.7 mg/kg/day

Highest Exposure from a Rinse-off Product

Of the reported uses of PEGs, the rinse-off product type with potentially the highest exposure is a shampoo (noncoloring) containing 62% PEG-8. The amount of product used per day from Loretz et al. (2006) is 10.75 g (50 th percentile shampoo use) or 23.63 (90th percentile shampoo use).

The average total absorption of PEG-4 from a rinse-off formulation in a) intact and b) damaged skin was a) 0.37% and b) 2.30%, respectively (Raabe and Norman 2009),. Resulting exposure from the rinse-off product would be:

- ***50% percentile:***
  Intact skin: 10.75 g/day x 0.62 x 1000 mg/g x 0.0037 ÷ 60 kg = 0.41 mg/kg/day
  Damaged skin: 10.75 g/day x 0.62 x 1000 mg/g x 0.023 ÷ 60 kg = 2.6 mg/kg/day
- ***90% percentile:***
  Intact skin: 23.63 g/day x 0.62 x 1000 mg/g x 0.0037 ÷ 60 kg = 0.90 mg/kg/day
  Damaged skin: 23.63 g/day x 0.62 x 1000 mg/g x 0.023 ÷ 60 kg = 5.4 mg/kg/day

The Council noted that these calculations overestimate exposure because 1) PEG-4 was used in the dermal penetration studies but PEG-6 and PEG-8 were used in the reported products; due to their larger size, penetration of PEG-6 and PEG-8 is likely to be lower than PEG-4; and 2) for damaged skin, 100% of exposed skin is assumed to be damaged.

Comparison of Exposure to NOEL (Margin of Safety)

Leave-on, 50th percentile:

Assuming PEG-6 is 100% metabolized to ethylene glycol, comparison of the highest exposure product in intact (1.3 mg/kg/day) and damaged (5.1 mg/kg/day) skin to the NOEL for kidney toxicity (1.1 g/kg/day) results is Margins of Safety of 846 and 216, respectively.

Leave-on, 90th percentile:

Assuming PEG-6 is 100% metabolized to ethylene glycol, comparison of the highest exposure product in intact (2.4 mg/kg/day) and damaged (9.7 mg/kg/day) skin to the NOEL for kidney toxicity (1.1 g/kg/day) results is Margins of Safety of 458 and 113, respectively.

Rinse-off, 50th percentile:

Assuming PEG-8 is 100% metabolized to ethylene glycol, comparison of the highest exposure product in intact (0.41 mg/kg/day) and damaged (2.6 mg/kg/day) skin to the NOEL for kidney toxicity (1.1 g/kg/day) results is Margins of Safety of 2,683 and 423, respectively.

Rinse-off, 90th percentile:

Assuming PEG-8 is 100% metabolized to ethylene glycol, comparison of the highest exposure product in intact (0.90 mg/kg/day) and damaged (5.4 mg/kg/day) skin to the NOEL for kidney toxicity (1.1 g/kg/day) results is Margins of Safety of 1,222 and 204, respectively.

The Council noted that these calculations underestimate the MOS because 1) it is assumed that 100% of PEG is metabolized to ethylene glycol; and 2) exposure is overestimated.

CASE REPORTS

PEG-6, PEG-8, PEG-20, and PEG-75

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).

Two cases of delayed allergic eczematous contact dermatitis caused by PEGs used in a soluble dressing to treat patients with second-degree burns was reported (Fisher 1978). 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. 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.

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).

SUMMARY

Polyethylene Glycols (PEGs) are condensation polymers of ethylene oxide that perform a wide variety of functions in cosmetics depending on molecular weight. Ingredients in this safety assessment include: Triethylene Glycol and Polyethylene Glycols (PEGs) -4, -6, -7, -8, -9, -10, -12, -14, -16, -18, -20, -32, -33, -40, -45, -55, -60, -75, -80, -90, -100, -135, -150, -180, -200, -220, -240, -350, -400, -450, -500, -800, -2M, -5M, -7M, -9M, -14M, -20M, -23M, -25M, -45M, -65M, -90M, -115M, -160M and -180M and any PEG $\geq$ 4 that may become a cosmetic ingredient in the future.

The physical and biological properties of the individual PEGs are dependent on their molecular weight. PEGs may also contain trace amounts of 1,4-dioxane, a by-product of ethoxylation and small quantities of ethylene oxide.

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. For example, PEG-8 is rapidly absorbed by the GI tracts of several mammalian species and excreted primarily in the urine with less excretion in the feces and PEG-150 in water was not absorbed from the gastrointestinal tract of humans.

PEGs are used in the pharmaceutical industry as vehicles for drugs and as ointment bases.

The following are reported to be in use to the FDA's VCRP or reported in an industry survey of use concentrations: Triethylene Glycol and PEGs -4, -6, -8, -9, -10, -12, -14, -20, -32, -40, -75, -90, -150, -180, -220, -240, -350, -400, -450, -2M, -5M, -7M, -14M, -23M, -45M, -90M, and -180M, with the highest reported use (299) in PEG-8 at concentrations up to 85%.

Several studies reported effects of minimal toxicological significance, including crenation and clumping of rabbit erythrocytes. In a study of PEGs radioprotection, low molecular weight were effective, while PEG-20 and above were not. In a study of the biochemical effects of a series of commonly used drug carrier vehicles, PEG-6 was bioactive in its own right, increasing urine concentrations of dicarboxylic acids, creatinine, taurine, and sugars.

In general, PEGs had low acute oral toxicity. The higher-molecular-weight PEGs appeared to be less toxic than the lower PEGs in oral studies. Oral LD_{50} values in rodents ranged from 15 to 22 g/kg, and the intravenous LD_{50} in rodents ranged from 7.3 to 9.5 g/kg. The LC_{50} of aerosolized Triethylene Glycol in rats was greater than 3.9 mg/L.

PEG-8 administered for 13 weeks of gavage treatment in Fischer 344 rats at doses of 1.1, 2.8 and 5.6 g/kg/day for resulted in no mortality or changes in hematology or clinical chemistry measurements attributed to PEG-8 toxicity.

Dermal exposure to PEGs was not irritating in rabbits in several studies. Overall, PEGs were not irritating to the skin of rabbits and guinea pigs. PEG-75 was not a sensitizer in guinea pigs.

Ocular exposure to Triethylene Glycol in rabbits produced no corneal injury, however all rabbits displayed acute iritis and minor transient conjunctival irritation. Overall, PEGs cause mild, transient ocular irritation in rabbits.

Inhalation of aerosolized PEG-75 at concentrations up to 1008 mg/m^3 caused little or no toxicity in rats.

In reproductive and developmental toxicity studies in rats and mice, PEGs did not produce biologically significant embryotoxicity or teratogenicity.

PEGs were not mutagenic or genotoxic in the Ames assay, a Chinese Hamster ovary cell mutation assay, an *in vivo* bone marrow assay, a dominant lethal assay, the mouse TK+/-+TK-/- forward mutation assay, or a sister chromosome exchange assay. PEG-8 was not carcinogenic when administered orally, intraperitoneally, or subcutaneously to various test animals.

In clinical studies, PEG-6 and PEG-8 caused mild cases of immediate hypersensitivity. Extensive clinical studies of patients with normal skin demonstrate that PEG-8 was not a sensitizer and one large study in patients with eczematous skin, only 0.3% positive reactions were seen to PEG-8. Cases of delayed allergic contact dermatitis have been reported in burn patients treated with antimicrobial creams with a PEG vehicle.

Use of antimicrobial creams with a PEG vehicle have been associated with renal toxicity when applied to burned skin. Measured values for dermal penetration of PEG-4 as a function of number of tape strippings demonstrated that tape stripping can increase dermal penetration. Exposure estimates that combined type and use quantity of cosmetic product, concentration of PEGs, and dermal penetration were used to determine exposures to skin in which tape stripping had removed the stratum corneum. These exposures were used with the renal toxicity NOEL to develop a margin of safety calculation, with values ranging from 113 to over 2,600.

DISCUSSION

The available acute, short-term, and chronic toxicity data support the safety of PEGs at the concentrations used in cosmetic products. Likewise, these ingredients are not genotoxic or carcinogenic, nor are they reproductive or developmental toxicants. While there is some suggestion of minor ocular irritation, these ingredients are not dermal irritants or sensitizers in individuals with normal skin. While there are case reports of allergic contact dermatitis in burn patients treated with an antimicrobial agent in a PEG vehicle, there also one clinical study of over 1,500 patients with eczematous skin in which positive reactions were seen in less than one-third of one percent of individuals, suggesting that sensitization is not a significant concern for individuals with damaged skin.

The CIR Expert Panel has further considered one issue of concern --- that PEGs use on severely damaged skin, as in burned skin, can be associated with renal toxicity. Clearly, the available data demonstrate an absence of renal toxicity when PEGs are applied to normal skin. The Panel then considered the newly available dermal penetration data for normal skin and for skin in which the stratum corneum substantially has been removed. These data demonstrated that the dermal penetration of lower molecular weight PEGs is increased when the stratum corneum barrier is removed. The question the Panel then addressed was the significance of that finding. Using assumptions that would maximize the risk (e.g., whole body use of a hand lotion containing 12% PEG-6), a margin of safety of over 100 was maintained between the renal toxicity no observable effect level (the level at which no adverse effects are seen) and the exposure that could result from use of leave-on cosmetics. Even higher margins of safety were found for rinse-off cosmetics, suggesting no reason for concern for PEGs use in rinse-off products in the current practices of use and concentration.

The CIR Expert Panel further reasoned that the almost total removal of the stratum corneum was not unlike the damaged skin seen in certain skin diseases such as atopic dermatitis. Were a user to have such a condition and use a cosmetic product containing PEGs (e.g. the hand lotion containing 12% PEGs noted above), even at the 90th percentile of use quantities, the Panel was reassured that there is a large margin of safety between exposure to PEGs from use of leave-on cosmetics and any concern about adverse effects.

The Panel did note that, were the stratum corneum and the epidermis both absent (as in partial and full thickness burns), then penetration of PEGs into the dermis is likely, leading to systemic exposure and possible renal toxicity as seen with burn patients. The Expert Panel strongly asserted that it is inappropriate to apply cosmetic products containing high concentrations of PEGs to individuals exhibiting barrier skin disruption through both the stratum corneum and the epidermis, or greater.

The Expert Panel also expressed concern regarding the possible presence of ethylene oxide and trace amounts of 1,4-dioxane 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.

The potential adverse effects of inhaled aerosols depend on the specific chemical species, the concentration and the duration of the exposure and their site of deposition within the respiratory system. In practice, aerosols should have at least 99% of their particle diameters in the 10 – 110 μm range and the mean particle diameter in a typical aerosol spray has been reported as ~38 μm. Particles with an aerodynamic diameter of $\leq$ 10μm are respirable. In addition to inhalation toxicity data, the panel determined that PEGs can be used safely in hair sprays, because the product particle size is not respirable.

The CIR Expert Panel also acknowledged that the "damaged skin" caveat from the original safety assessment of PEGs was carried over to safety assessments of PEGs and PEG esters in which it appeared in either the discussion or the conclusion, including:

- PEG-2, -3, -5, -10, -15, and -20 Cocamine;
- 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;
- PEG-2, -3, -6, -8, -9, -12, -20, -32, -50, -75, -120, -150 and -175 Distearate;
- PEG-7, -30, -40, -78, and -80 Glyceryl Cocoate;
- PEG-5, -10, -24, -25, -35, -55, -100, and -150 Lanolin; PEG-5, -10, -20, -24, -30, and -70 Hydrogenated Lanolin; PEG-75 Lanolin Oil; and PEG-75 Lanolin Wax;
- PEG-10 Propylene Glycol; PEG-8 Propylene Glycol Cocoate; PEG-55 PropyleneGlycol Oleate; and PEG-25, -75, and -120 Propylene Glycol Stearate;

- PEG-20 Sorbitan Cocoate, PEG-40 Sorbitan Diisostearate, PEG-2, -5, -20 Sorbitan Isostearate, PEG-40 and -75 Sorbitan Lanolate, PEG-10, -40, -44, -75, and -80 Sorbitan Laurate, PEG-3 and -6 Sorbitan Oleate, PEG-80 Sorbitan Palmitate, PEG-40 Sorbitan Perisostearate, PEG-40 Sorbitan Peroleate, PEG-3, -6, -40, and -60 Sorbitan Stearate, PEG-20, -30, -40, and -60 Sorbitan Tetraoleate, PEG-60 Sorbitan Tetrastearate, PEG-20 and -160 Sorbitan Triisostearate, PEG-18 Sorbitan Trioleate, PEG-40 and -50 Sorbitan Hexaoleate, PEG-30 Sorbitol Tetraoleate Laurate, and PEG-60 Sorbitol Tetrastearate;
- PEG-5, -10, -16, -25, -30, and -40 Soy Sterol; and
- PEG-6, -8, and -20 Sorbitan Beeswax

Accordingly, conforming changes in each of these safety assessments are made to remove the "damaged skin" caveat from each of them.

CONCLUSION

On the basis of the data presented in this report, the CIR Expert Panel concluded that Triethylene Glycol and Polyethylene Glycols (PEGs))-4, -6, -7, -8, -9, -10, -12, -14, -16, -18, -20, -32, -33, -40, -45, -55, -60, -75, -80, -90, -100, -135, -150, -180, -200, -220, -240, -350, -400, -450, -500, -800, -2M, -5M, -7M, -9M, -14M, -20M, -23M, -25M, -45M, -65M, -90M, -115M, -160M and -180M and any PEG $\geq$ 4 are safe in the present practices of use and concentration.[1]

[1]Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group. This conclusion effectively amends the safety assessments of PEG derivatives and removes the caveat regarding use on damaged skin for those ingredients as listed in the discussion.

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Table 1. CAS numbers, cosmetic ingredient definitions and functions, and technical/other names as given in the International Cosmetic Ingredient Dictionary and Handbook (Gottschalck and Bailey 2008) for Triethylene Glycol (1a) and Polyethylene Glycols (1b)

Table 1a

Ingredient	CAS No.	Definition - aliphatic alcohol[a]	Function	Technical/Other Names
Triethylene Glycol	112-27-6	n equals 3	fragrance ingredient; viscosity decreasing agent	2,2'-[1,2-ethanediylbis(oxy)] bisethanol ethanol, 2,2'-[1,2-ethanediylbis(oxy)] bis

Table 1b

Ingredient		Polymers of ethylene oxide where n has an average value[a]	Function	Technical/Other Names[c]
PEG-4	112-60-7	average value of 4	humectant; solvent	2,2'-[oxybis(2,1-ethanediyloxy)] bisethanol ethanol, 2,2'-[oxybis(2,1-ethanediyloxy)] bis polyethylene glycol 200 polyoxyethylene (4) tetraethylene glycol
PEG-6	2615-15-8	average value of 6	humectant; solvent	3,6,9,12,15-pentaoxaheptadecane-1,17-diol polyethylene glycol 300 polyoxyethylene (6) hexaethylene glycol
PEG-7	25322-68-3[b]	average value of 7	humectant; solvent	polyethylene glycol (7) polyoxyethylene (7)
PEG-8	5117-19-1	average value of 8	humectant; solvent	3,6,9,12,15,18,21-heptaoxatricosane-1,23-diol octaethylene glycol polyethylene glycol 400 polyoxyethylene (8)
PEG-9	-[b]	average value of 9	humectant; solvent	3,6,9,12,15,18,21,24-octaoxahexacosane-1,26-diol nonaethylene glycol polyoxyethylene (9)
PEG-10	5579-66-8	average value of 10	humectant; solvent	decaethylene glycol 3,6,9,12,18,21,24-nonaoxahexacosane-1,29-diol polyoxyethylene (10)
PEG-12	6790-09-6	average value of 12	humectant; solvent	dodecaethylene glycol 3,6,9,12,15,18,21,24,27,30,33-undecaoxapentatriacontane-1,35-diol 3,6,9,12,15,18,21,24,27,30,33-undecaoxapentatricontane-1,35-diol polyethylene glycol (12) polyethylene glycol 600
PEG-14	-[b]	average value of 14	humectant; solvent	polyoxyethylene (14) polyethylene glycol (14)
PEG-16	-[b]	average value of 16	humectant; solvent	polyethylene glycol (16) polyoxyethylene (16)
PEG-18	-[b]	average value of 18	humectant; solvent	polyethylene glycol (18) polyoxyethylene (18)
PEG-20	-[b]	average value of 20	humectant; solvent	polyethylene glycol 1000 polyoxyethylene (20)
PEG-32	-[b]	average value of 32	binder; humectant; solvent	polyethylene glycol 1540 polyoxyethylene (32)
PEG-33	-[b]	average value of 33	binder; humectant; solvent	polyoxyethylene (33) polyethylene glycol (33)
PEG-40	-[b]	average value of 40	binder; humectant; solvent	polyethylene glycol 2000 polyoxyethylene (40)
PEG-45	-[b]	average value of 45	binder; humectant; solvent	polyethylene glycol (45) polyoxyethylene (45)
PEG-55	-[b]	average value of 55	binder; humectant; solvent	polyethylene glycol (55) polyoxyethylene (55)
PEG-60	-[b]	average value of 60	binder; humectant; solvent	polyethylene glycol 3000 polyoxyethylene (60)
PEG-75	-[b]	average value of 75	binder; humectant; solvent	polyethylene glycol 4000 polyoxyethylene (75)
PEG-80	-[b]	average value of 80	binder; humectant; solvent	polyethylene glycol 4000

				polyoxyethylene (80) polyethylene glycol (80)
PEG-90	-[b]	average value of 90	binder; humectant; solvent	polyoxyethylene (90) polyethylene glycol (90)
PEG-100	-[b]	average value of 100	binder; humectant; solvent	polyoxyethylene (100) polyethylene glycol (100)
PEG-135	-[b]	average value of 135	binder; humectant; solvent	polyoxyethylene (135) polyethylene glycol (135)
PEG-150	-[b]	average value of 150	binder; humectant; solvent	polyoxyethylene (150) polyethylene glycol 6000
PEG-180	-[b]	average value of 180	binder; humectant; solvent	polyoxyethylene (180) polyethylene glycol (180)
PEG-200	-[b]	average value of 200	binder; humectant; solvent	polyoxyethylene (200) polyethylene glycol 9000
PEG-220	-[b]	average value of 220	binder; humectant; solvent	polyoxyethylene (220) polyethylene glycol (220)
PEG-240	-[b]	average value of 240	binder; humectant; solvent	polyoxyethylene (240) polyethylene glycol (240) polyethylene glycol 11000
PEG-350	-[b]	average value of 350	binder; emulsion stabilizer; solvent	polyoxyethylene (350) polyethylene glycol 20000
PEG-400	-[b]	average value of 400	binder; emulsion stabilizer; solvent	polyoxyethylene (400) polyethylene glycol (400)
PEG-450	-[b]	average value of 450	binder; emulsion stabilizer; solvent	polyoxyethylene (450) polyethylene glycol 20000
PEG-500	-[b]	average value of 500	binder; emulsion stabilizer; solvent	polyoxyethylene (500) polyethylene glycol (500)
PEG-800	-[b]	average value of 800	anticaking agent; binder; humectant; plasticizer; viscosity increasing agent-aqueous	polyoxyethylene (800) polyethylene glycol (800)
PEG-2M	-[b]	average value of 2000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (2000) polyethylene glycol (2000) PEG-2000
PEG-5M	-[b]	average value of 5000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (5000) polyethylene glycol (5000) PEG-5000
PEG-7M	-[b]	average value of 7000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (7000) polyethylene glycol (7000) PEG-7000
PEG-9M	-[b]	average value of 9000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (9000) polyethylene glycol (9000) PEG-9000
PEG-14M	-[b]	average value of 14000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (14000) polyethylene glycol (14000) PEG-14000
PEG-20M	-[b]	average value of 20000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (20000) polyethylene glycol (20000) PEG-20000
PEG-23M	-[b]	average value of 23000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (23000) polyethylene glycol (23000) PEG-23000
PEG-25M	-[b]	average value of 25000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (25000) polyethylene glycol (25000) PEG-25000
PEG-45M	-[b]	average value of 45000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (45000) polyethylene glycol (45000) PEG-45000
PEG-65M	-[b]	average value of 65000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (65000) polyethylene glycol (65000) PEG-65000
PEG-90M	-[b]	average value of 90000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (90000) polyethylene glycol (90000) PEG-90000
PEG-115M	-[b]	average value of 115000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyoxyethylene (115000) polyethylene glycol (115000) PEG-115000
PEG-160M	-[b]	average value of 160000	binder; emulsion stabilizer;	polyoxyethylene (160000)

			viscosity increasing agent-aqueous	polyethylene glycol (160000)
PEG-180M	-[b]	average value of 180000	binder; emulsion stabilizer; viscosity increasing agent-aqueous	polyethylene glycol (180000)

[a] The formula for all PEGs is: $H(OCH_2CH_2)_nOH$. This column gives the value/average value for "n."

[b] The generic CAS No. for PEGs is 25322-68-3.

[c] The *International Nonproprietary Names for Pharmaceutical Substances* for PEGs is macrogol.

Table 2. Ingredient names, molecular weight names as given in the International Cosmetic Ingredient Dictionary and Handbook (Gottschalck and Bailey 2008) and corresponding average molecular weights (Personal Care Products Council 2009).

Ingredient name	Molecular weight name	Calculated average molecular weight ((n x 44) +18)
Triethylene Glycol		150
PEG-4	polyethylene glycol 200	194
PEG-6	polyethylene glycol 300	282
PEG-7		326
PEG-8	polyethylene glycol 400	370
PEG-9		414
PEG-10	polyethylene glycol 500	458
PEG-12	polyethylene glycol 600	546
PEG-14		634
PEG-16		722
PEG-18		810
PEG-20	polyethylene glycol 1000	898
PEG-32	polyethylene glycol 1540	1426
PEG-33		1470
PEG-40	polyethylene glycol 2000	1778
PEG-45		1998
PEG-55		2438
PEG-60	polyethylene glycol 3000	2658
PEG-75		3318
PEG-80	polyethylene glycol 4000	3538
PEG-90		4068
PEG-100		4418
PEG-135		5958
PEG-150	polyethylene glycol 6000	6618
PEG-180	polyethylene glycol 8000	7938
PEG-200	polyethylene glycol 9000	8818
PEG-220		9698
PEG-240	polyethylene glycol 11000	10578
PEG-350	polyethylene glycol 20000	15418
PEG-400		17618
PEG-450	polyethylene glycol 20000	19818
PEG-500		22018
PEG-800		35218
PEG-2M (2000)		88018
PEG-5M (5000)		220018

Ingredient name	Molecular weight name	Calculated average molecular weight ((n x 44) +18)
PEG-7M (7000)		308018
PEG-9M (9000)		396018
PEG-14M (14000)		616018
PEG-20M (20000)		880018
PEG-23M (23000)		1012018
PEG-25M (25000)		1100018
PEG-45M (45000)		1980018
PEG-65M (65000)		2860018
PEG-90M (90000)		3960018
PEG-115M (115000)		5060018
PEG-160M (160000)		7040018
PEG-180M (180000)		7920018

Table 3. Chemical and Physical Properties of PEGs -6, -8, -32, -75, -150, -14M, and -20M (Patty 1963, Sax 1979, FAO 1983, Hunting 1983, Windholz 1983, Silverstein et al. 1984).

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
Soluble in:	Water	Water	-	-	Water	Water	-
Molecular Weight	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 Point	-15 to -6°C	4 - 10°C	43 - 46°C	53 - 58°C	56 - 63°C	-	-
Viscosity at 210°F	-	7.3[a]	-	76 – 110[a]	470 – 900[a]	-	-

[a] centistokes

Table 4. Chemical and physical properties of Triethylene Glycol and PEG-4 (Budavari 1989, Union Carbide 1990a, Ashford 1994, NTP 2001a).

Property	Triethylene Glycol (Reference)	PEG-4 (Reference)
Molecular Weight	150.17	190 - 210
Relative Density	1.1274	1.127
Specific Gravity	1.126	1.125
Freezing Point	-4.3 C	
Boiling Point	285 C (283 C @ 760 mmHg)	327 C
Flash Point	330 to 342 F	171.1 to 182.2 C
Refractive Index	1.4578 @ 15 C	1.459 @ 25 C
Viscosity	47.8 cp @ 20 C	4.3 centistrokes @ 210 C
Vapor Pressure	< 0.01 mmHg @ 20 C	low
Vapor Density (air = 1)	5.2	

Table 5. Frequency of use and use concentration for Triethylene Glycol and PEGs -4, -6, -8, -9, -10, -12, -14, -20, -32, -40, -75, -90, -150, -180, -220, -240, -350, -400, -450, -2M, -5M, -7M, -14M, -20M, -23M, -45M, -90M, and -180M as a function of cosmetic product category.

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
	Triethylene Glycol	
Shaving Products		
Aftershave lotions	-	0.2%
Shaving creams	3	-
Skin Care Products		
Cleansers	-	0.0006%
Face and neck creams, lotions, powders and sprays	-	0.03%
Body and hand creams, lotions powders and sprays	-	0.2%
Bath Products		
Oils, tablets and salts	1	-
Bubble baths	1	-
Others	4	-
Noncoloring Hair Products		
Conditioners	1	-
Hair Products (coloring)		
Tints	1	-
Bath Products		
Soaps and detergents	1	-
Personal Hygiene Products		
Others	19	-
Total uses/ranges for Triethylene Glycol	**31**	**0.0006 - 0.2%**
	PEG-4	
Bath products		
Oils, tablets, and salts	-	67%
Soaps and detergents	2	0.2 - 2%
Others	1	-
Eye makeup		
Eye shadows	2	3 - 5%
Eye lotions	-	0.1%
Eye makeup removers	1	0.2 - 2%
Fragrance products		
Others	3	-
Noncoloring hair care products		
Conditioners	6	-
Shampoos	2	5%
Tonics, dressings, etc.	2	-
Wave sets	-	0.5 - 2%
Makeup		
Blushers	-	7
Foundations	3	-
Lipsticks	-	0.3%
Nail care products		
Cuticle softeners	-	20%
Others	-	0.3%
Oral hygiene products		
Dentifrices	-	1 - 8%
Personal hygiene products		
Underarm deodorants	3	20%
Shaving products		
Aftershave lotions	6	1%
Preshave lotions	1	-
Shaving creams	-	0.03 - 17%
Others	2	-
Skin care products		
Cleansers	4	1 - 8%
Face and neck creams, lotions, powders and sprays	1	2 - 3%
Body and hand creams, lotions, powders and sprays	21	3 - 4%
Moisturizers	8	4 - 5%
Night creams, lotions, powders and sprays	1	5%
Skin fresheners	1	5%
Others	2	-
Suntan products		
Suntan gels, creams, liquids and sprays	-	0.01%
Indoor tanning preparations	-	6%
Others	-	2%

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
Total uses/ranges for PEG-4	**72**	**0.01 - 67%**
	PEG-6	
Baby products		
Others	1	-
Bath products		
Oils, tablets, and salts		11%
Soaps and detergents	18	0.01 - 23%
Bubble baths	1	
Others	1	1%
Eye makeup		
Eyeliners	-	3%
Mascara	-	0.03%
Eye lotions	1	0.2%
Eye makeup removers	1	-
Others[a]	-	0.2 - 0.6%
Fragrance products		
Colognes and toilet waters	-	2 - 3%
Others	1	-
Nail care products		
Nail creams and lotions	-	1%
Noncoloring hair care products		
Shampoos	-	2%
Conditioners	1	3 - 4%
Hair sprays (aerosol fixatives)	-	0.2%
Tonics, dressings, etc.	1	1 - 51%
Others	1	-
Makeup		
Face powders	-	4%
Foundations	-	0.8 - 2%
Makeup bases	-	3%
Makeup fixatives	2	-
Others	3	-
Shaving products		
Aftershave lotions	1	0.8 - 2%
Shaving creams	-	0.5%
Others[b]	-	5%
Oral hygiene products		
Dentifrices	-	3%
Personal hygiene products		
Underarm deodorants	1	2%
Feminine hygiene products	-	0.2%
Others	2	-
Skin care products		
Cleansers	26	5 - 10%
Face and neck creams, lotions, powders and sprays	20	3 - 45%[j]
Body and hand creams, lotions, powder and sprays	5	2 - 12%
Moisturizers	32	2 - 14%
Night creams, lotions, powders and sprays	1	2%
Paste masks/mud packs	2	6 - 10%
Skin fresheners	1	-
Foot powders and sprays	-	1%
Others	9	-
Suntan products		
Suntan gels, creams, liquids and sprays	5	2%
Indoor tanning preparations	2	-
Others	1	-
Total uses/ranges for PEG-6	**140**	**0.01 - 51%**
	PEG-8	
Baby products		
Baby lotions, oils, powders and creams	-	5%
Others	1	-
Bath products		
Oils, tablets, and salts	1	-
Soaps and detergents	5	2 - 15%
Others	4	30%
Fragrance products		
Colognes and toilet waters	-	2 - 10%
Eye makeup		
Eyebrow pencils	1	-
Eye shadows	2	0.5%
Eye lotions	-	0.1 - 3%

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
Eye makeup removers	4	3%
Others	1	1%
Noncoloring hair care products		-
Conditioners	12	3 - 12%
Rinses	-	10%
Shampoos	1	62%
Tonics, dressings, etc.	6	0.0002 - 62%
Others	2	10 - 85%
Makeup		
Blushers	1	-
Face powders	-	8%
Foundations	14	0.03 - 10%
Lipsticks	16	0.1%
Makeup bases	56	-
Others	9	0.1%
Oral hygiene products		
Dentifrices	3	3%
Personal hygiene products		
Underarm deodorants	14	2 - 13%
Others	2	4 - 46%
Shaving products		
Aftershave lotions	4	2 - 5%
Shaving creams	2	-
Others[c]	1	10%
Skin care products		
Cleansers	41	0.5 - 66%
Face and neck creams, lotions, powders and sprays	14	0.002 - 10%[k]
Body and hand creams, lotions, powders and sprays [i]	26	0.3 - 6%[l]
Moisturizers	17	2 - 6%
Depilatories	-	0.9%
Foot powders and sprays	-	20%
Night creams, lotions, powders and sprays	7	0.01 - 6%
Paste masks/mud packs	10	0.003 - 59%
Skin fresheners	5	-
Others[d]	-	0.01 - 46%
Suntan products		1 - 5%
Indoor tanning preparations	1	-
Suntan gels, creams and liquids	-	0.5 - 5%
Others	16	-
Total uses/ranges for PEG-8	**288**	**0.0002 - 85%**

PEG-9

Noncoloring Hair Products		
Conditioners	10	-
Others	-	0.9%
Makeup Products		
Foundations	2	0.04%
Makeup bases	-	0.02%
Total uses/ranges for PEG-9	**12**	**0.02% - 0.9%**

PEG-10

Makeup Products		
Foundations	-	0.2%
Lipsticks	-	0.1%
Suntan Products		
Suntan gels, creams and liquids	-	0.2%
Total uses/ranges for PEG-10	**-**	**0.1 - 0.2%**

PEG-12

Makeup Products		
Mascara		4%
Foundations		8%
Eye Makeup Products		
Eye makeup removers	4	-
Fragrance Products		
Colognes and toilet waters	-	4%
Others	1	-
Noncoloring Hair Products		
Tonics, dressings, etc.	3	4%
Others	1	9 - 56%
Oral Hygiene Products		
Dentifrices	2	
Bath Products		

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
Soaps and detergents	12	-
Personal Hygiene Products		
Others	1	-
Skin Care Products		
Face and neck creams, lotions, powders and sprays	1	-
Moisturizers	5	
Foot powders and sprays		30%
Others	1	0.04%
Suntan Products		
Indoor tanning preparations	1	-
Total uses/ranges for PEG-12	**32**	**0.04 - 56%**

PEG-14

Bath Products		
Bubble baths	-	0.3%
Others	-	2%
Fragrance Products		
Perfumes	-	2%
Others	2	-
Eye Makeup Products		
Others	1	-
Noncoloring Hair Products		
Shampoos	1	0.3%
Shaving Products		
Shaving creams	1	-
Bath Products		
Bath oils, tablets and salts	1	-
Skin Care Products	-	-
Cleansers	-	0.3%
Face and neck creams, lotions, powders and sprays	1	-
Body and hand creams, lotions, powders and sprays	-	0.1 - 2%[m]
Moisturizers	1	-
Night creams, lotions, powders and sprays	1	-
Total uses/ranges for PEG-14	**10**	**0.1 - 2%**

PEG-20

Bath products		
Soaps and detergents	-	0.02 - 2%
Eye makeup		
Eyeliners	-	1 - 18%
Eye lotions	-	2%
Eye makeup removers	-	2%
Noncoloring hair care products		
Tonics, dressings, etc.	-	18%
Others	-	27%
Makeup		
Blushers	-	2%
Foundations	-	2%
Makeup bases	-	2%
Personal hygiene products		
Underarm deodorants	-	0.8%
Shaving products		
Aftershave lotions	-	20%
Skin care products		
Face and neck creams, lotions, powders and sprays	-	4 - 8%
Body and hand creams, lotions, powders and sprays	-	2%
Moisturizers	-	5%
Night creams, lotions, powders and sprays	-	3%
Paste masks/mud packs	-	6%
Others[f]	-	0.4 - 8%
Suntan products		
Suntan gels, creams, liquids and sprays	-	3 - 4%
Total uses/ranges for PEG-20	**-**	**0.02 - 27%**

PEG-32

Baby products		
Shampoos	1	-
Bath products		
Oils, tablets, and salts		11%
Soaps and detergents	4	11%
Bubble baths	1	-
Eye makeup		
Eyeliners	1	-

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
Eye lotions	1	1 - 4%
Eye makeup removers	1	2 - 3%
Mascara	2	0.03 - 2%
Fragrance products		
Colognes and toilet waters	-	2%
Others	1	-
Noncoloring hair care products		
Shampoos	-	2%
Hair conditioners	-	3%
Hair sprays (aerosol fixatives)	-	0.2%
Tonics, dressings, etc.	3	2%
Others	1	15%
Makeup		
Face powders	-	4%
Foundations	2	2%
Makeup bases	-	3%
Makeup fixatives	2	-
Others	1	-
Nail care products		
Cuticle softeners	-	2%
Nail creams and lotions	-	1%
Others	1	-
Shaving products		
Aftershave lotions	-	0.8%
Shaving creams	-	0.1%
Others[b]	-	5%
Oral Hygiene products		
Dentifrices	-	2%
Skin care products		
Cleansers	35	0.8 - 11%
Face and neck creams, lotions, powders and sprays	17	0.5 - 12%
Body and hand creams, lotions, powders and sprays	4	2 - 12%
Moisturizers	31	0.5 - 14%
Night creams, lotions, powders and sprays	2	0.5 - 10%
Paste masks/mud packs	4	2 - 6%
Skin fresheners	-	0.5 - 4%
Others	10	0.5 - 1%
Suntan products		
Indoor tanning preparations	1	-
Suntan gels, creams and liquids	-	2%
Others	1	-
Total uses/ranges for PEG-32	**127**	**0.03 - 15%**

PEG-40

Noncoloring hair care products		
Conditioners	1	-
Tonics, dressings, etc.	3	-
Others	21	-
Makeup		
Foundations	-	0.2%
Oral hygiene products		
Dentifrices	-	6%
Mouthwashes and breath freshener sprays	1	-
Shaving products		
Aftershave lotions	1	-
Skin care products		
Cleansers	-	0.001 - 6%
Face and neck creams, lotions, powders and sprays	-	3%
Body and hand creams, lotions, powders and sprays	-	3%
Moisturizers	1	-
Night creams, lotions, powders and sprays	-	0.001 - 3%
Paste masks/mud packs	-	0.001 - 3%
Skin fresheners	-	0.6%
Others	-	0.005%
Total uses/ranges for PEG-40	**28**	**0.001 - 6%**

PEG-75

Bath products		
Oils, tablets, and salts	1	-
Soaps and detergents	-	2 - 5%
Makeup products		
Foundations	-	7%
Eye makeup		

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
Eyeliners	4	11%
Mascara	10	-
Others	1	-
Noncoloring hair care products		
Tonics, dressings, etc.	1	2 - 16%
Rinses	-	3%
Others	1	29%
Personal hygiene products		
Underarm deodorants	-	0.5 - 0.8%
Shaving products		
Aftershave lotions	-	6%
Shaving creams	-	3%
Others	1	-
Skin care products		
Cleansers	4	0.5 - 7%
Face and neck creams, lotions, powders and sprays	2	0.4 - 4%
Body and hand creams, lotions, powders and sprays	1	0.2 - 36%
Foot powders and sprays	-	0.5 - 7%
Moisturizers	6	4 - 7%
Night creams, lotions, powders and sprays	1	-
Paste masks/mud packs	8	3%
Skin fresheners	1	-
Other	7	0.4%
Total uses/ranges for PEG-75	**49**	**0.2 - 36%**
	PEG-90	
Bath Products		
Soaps and detergents	6	-
Others	-	0.05%
Noncoloring Hair Products		
Tonics, dressings, etc.	1	0.2%
Others	-	21%
Personal Hygiene Products		
Underarm deodorants	7	-
Shaving Products		
Aftershave lotions	-	0.2%
Skin Care Products		
Face and neck creams, lotions, powders and sprays	5	-
Body and hand creams, lotions, powders and sprays	5	-
Paste masks	1	-
Total uses/ranges for PEG-90	**25**	**0.05 - 21%**
	PEG-150	
Bath products		
Oils, tablets, and salts	9	2 - 5%
Soaps and detergents	-	1%
Bubble baths	-	2%
Capsules	1	-
Others	1	1 - 4%
Eye makeup		
Eye lotions	1	-
Noncoloring hair care products		
Conditioners	2	1%
Hair sprays (aerosol fixatives)	-	0.3%
Rinses	-	0.5%
Tonics, dressings, etc.	3	0.5%
Others	1	-
Makeup		
Makeup bases	1	2%
Foundations	-	0.0009 - 2%
Lipsticks	-	1%
Personal hygiene products		
Underarm deodorants	3	-
Others	2	-
Nail Products		
Nail creams and lotions	-	1%
Skin care products		
Cleansers	-	0.03 - 3%
Face and neck creams, lotions, powders and sprays	5	0.009 - 6%
Body and hand creams, lotions, powders and sprays	1	2%
Foot powders and sprays	1	-
Moisturizers	5	0.009 - 6%
Night creams, lotions, powders and sprays	1	-

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
Paste masks/mud packs	1	1%
Skin fresheners	1	-
Others	4	0.009 - 3%
Suntan products		
Suntan gels, creams and liquids	-	2%
Total uses/ranges for PEG-150	**43**	**0.0009 - 6%**

PEG-180

Baby Products		
Shampoos	-	2%
Bath Products		
Oils, tablets, and salts	-	4%
Others	-	6
Eye Makeup Products		
Eyeliners	-	4%
Noncoloring Hair Products		
Conditioners	-	0.5 - 3%
Tonics, dressings and other hair grooming aids	-	1%
Others	-	5%
Makeup Products		
Lipsticks	-	4%
Nail Products		
Nail cream and lotions	-	2%
Shaving Products		
Shaving creams	-	0.05%
Skin Care Products		
Cleansers	-	5%
Face and neck creams, lotions, powders and sprays	-	1 - 2%
Skin fresheners	-	0.5%
Total uses/ranges for PEG-180	**-**	**0.05 - 5%**

PEG-220

Bath Products		
Others	1	-
Personal Hygiene Products		
Others[g]	-	0.4%
Skin Care Products		
Cleansers	-	0.3%
Total uses/ranges for PEG-220	**-**	**0.3 - 0.4%**

PEG-240

Makeup Products		
Face powders	-	10%
Bath Products		
Soaps and detergents	-	5%
Skin Care Products		
Face and neck creams, lotions, powders and sprays	-	4%
Moisturizers	1	
Total uses/ranges for PEG-240	**1**	**4 - 10%**

PEG-350

Makeup Products		
Foundations	-	1%
Eye makeup products	-	-
Eye lotions	1	-
Skin Care Products		
Face and neck creams, lotions, powders and sprays	3	1%
Body and hand creams, lotions, powders and sprays	2	1%
Moisturizers	2	-
Night creams, lotions, powders and sprays	1	-
Skin fresheners	1	-
Total uses/ranges for PEG-350	**10**	**1%**

PEG-400

Makeup Products		
Foundations	-	1%
Makeup bases	-	3%
Eye Makeup Products		
Eye lotions	3	-
Bath Products		
Soaps and detergents	-	2%
Shaving Products		

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
Aftershave lotions	-	3%
Skin Care Products		
Face and neck creams, lotions, powders and sprays	2	3%
Body and hand creams, lotions, powders and sprays	-	3%
Moisturizers	1	2%
Paste masks	-	2%
Suntan Products		
Suntan gels, creams and liquids	-	2%
Total uses/ranges for PEG-400	**6**	**1 - 3%**

PEG-450		
Noncoloring Hair Products		
Others	1	-
Skin Care Products		
Face and neck creams, lotions, powders and sprays	-	1%
Body and hand creams, lotions, powders and sprays	2	1%
Moisturizers	2	1%
Total uses/ranges for PEG-450	**5**	**1%**

PEG-2M		
Fragrance Products		
Others	1	-
Noncoloring Hair Products		
Conditioners	3	0.5%
Tonics, dressings, etc.	3	-
Skin Care Products		
Others	1	-
Total uses/ranges for PEG-2M	**8**	**0.5%**

PEG-5M		
Noncoloring Hair Products		
Conditioners	-	0.01%
Tonics, dressings, etc.	1	0.01%
Skin Care Products		
Cleansers	1	-
Total uses/ranges for PEG-5M	**2**	**0.01%**

PEG-7M		
Bath Products		
Oils, Tablets and salts	2	0.5%
Noncoloring Hair Products		
Conditioners	1	-
Shampoos	41	-
Others	-	0.2%
Shaving Products		
Shaving creams	1	0.2 - 0.5%
Shaving soaps	1	-
Skin Care Products		
Moisturizers	1	0.05 - 0.1%
Face and neck creams, lotions, powders and sprays	-	0.1%
Total uses/ranges for PEG-7M	**47**	**0.05 - 0.5%**

PEG-14M		
Baby products		
Shampoos	1	0.1%
Lotions, oils, powders, and creams	-	0.05%
Others	5	-
Bath products		
Oils, tablets, and salts	-	0.1%
Soaps and detergents	8	0.05 - 0.5%
Bubble baths	-	0.1%
Others	2	0.1%
Noncoloring hair care products		
Conditioners	6	0.2%
Shampoos	10	0.03%
Tonics, dressings, etc.	3	0.5%
Others	2	-
Hair coloring products		
Shampoos	1	-
Bleaches	1	-
Makeup		
Makeup bases	-	0.2%

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
Shaving products		
Shaving creams	6	0.2 - 0.3%
Others[e]	13	0.1%
Skin care products		
Cleansers	13	0.05 - 0.5%
Face and neck creams, lotions, powder and sprays	-	0.05%
Body and hand creams, lotions, powder and sprays	-	0.1%
Skin fresheners	1	-
Others	3	-
Total uses/ranges for PEG-14M	**75**	**0.05 - 0.5%**
	PEG-20M	
Noncoloring hair care products		
Conditioners	-	1%
Makeup		
Face powders	-	3%
Personal hygiene products		
Underarm deodorants	-	0.4%
Skin care products		
Cleansers	-	0.4%
Total uses/ranges for PEG-20M	**-**	**0.4 - 3%**
	PEG-23M	
Eye Makeup Products		
Others	1	-
Noncoloring Hair Products		
Shampoos	1	0.05%
Tonics, dressings, etc.	1	-
Shaving Products		
Others	13	-
Total uses/ranges for PEG-23M	**16**	**0.05%**
	PEG-45M	
Baby Products		
Others	2	
Noncoloring Hair Products		
Conditioners	1	0.03 - 0.3%
Shampoos	2	0.05%
Tonics, dressing, etc.	3	0.1 - 0.3%
Bath Products		
Soaps and detergents	1	0.05 - 0.08%
Personal Hygiene Products		
Others	3	-
Shaving Products		
Shaving creams	1	0.2%
Shaving soaps	1	-
Skin Care Products		
Body and hand creams, lotions, powders and sprays	-	0.1%
Total uses/ranges for PEG-45M	**14**	**0.03 - 0.3%**
PEG-90M		
Noncoloring Hair Products		
Conditioners	4	0.05 - 0.1%
Shampoos	3	0.0002%
Rinses	-	0.08%
Tonics, dressings, etc.	22	0.3 - 1%
Others	19	-
Hair Products (Coloring)		
Hair dyes and colors	-	0.5%
Others[h]	-	0.02 - 0.05%
Makeup Products		
Foundations	-	0.01%
Bath Products		
Soaps and detergents	14	0.05%
Personal Hygiene Products		
Others	-	0.3%
Shaving Products		
Shaving creams	2	0.01 - 0.2%
Shaving soaps	1	2%
Others	24	-
Skin Care Products		
Cleansers	-	0.05%
Face and neck creams, lotions, powders and sprays	3	0.1%

Product Category	Number of uses reported under the Voluntary Cosmetic Registration Program (FDA 2008)	Concentration of use (%) (Personal Care Products Council 2009a)
Moisturizers	2	-
Total uses/ranges for PEG-90M	**94**	**0.0002 - 0.3%**
	PEG-180M	
Noncoloring Hair Products		
Conditioners	-	0.05%
Shampoos	-	0.08%
Total uses/ranges for PEG-180M	**-**	**0.05 - 0.08%**

[a] 0.2% in an eye gel, 0.6% in an eye mask
[b] 5% in a shaving gel
[c] 10% in a shaving gel
[d] 10% in a foot/leg massage gel, 40% in a body peel
[e] 0.1% in a shaving gel
[f] 0.4% in a bronzer
[g] 0.4% in a body scrub
[h] 0.02% in a hair color remover
[i] a prototype body and hand product containing 20% PEG-8 is not currently on the market
[j] includes a face and neck spray at 3%
[k] includes a face and neck spray at 0.002%
[l] includes body and hand sprays in the 1 - 3% range
[m] includes a body and hand spray at 2%

Table 6. Acute Oral LD_{50} values for Triethylene Glycol and PEGs.

Ingredient (concentration)	Species (No.)	LD_{50} (g/kg)	Reference
Triethylene Glycol	Rat	22.06	Smyth et al (1941)
	Guinea pig	14.66	Smyth et al (1941)
	Mouse	18.5	Smyth et al (1941)
	Rat	15 - 22	Budavari (1989)
	Rat	>16 ml/kg	Union Carbide (1990c)
PEG-4 (100%)	Mouse	6.4	Shaeffer and Schellenberg (1984)
	Rat	32.77	Smyth et al. (1941)
PEG-6 (100%)	Albino Wistar rat	31.7	Smyth et al. (1945)
	Rabbit	17.3	Smyth et al. (1950)
PEG-6 (50%)	White rat	45.6	Smyth et al. (1960)
	White rat	38.9	Smyth et al. (1950)
	White rat (10)	31.6	Smyth et al. (1941)
	Albino rabbit	20.7	Smyth et al. (1945)
	Guinea pig (10)	19.6	Smyth et al. (1941)
PEG-8 (100%)	Albino Wistar rat	32.8	Smyth et al. (1945)
PEG-8 (50%)	White rat	43.6	Smyth et al. (1950)
	White rat (10)	37.4	Smyth et al. (1941)
	Albino rabbit	26.8	Smyth et al. (1945)
PEG-32 (50%)	White rat	51.2	Smyth et al. (1950)
	Rat	>16	Bushy Run Research Center (1987)
PEG-75 (100%)	Rabbit	76	Smyth et al. (1950)
PEG-75 (50%)	White rat	>50	Smyth et al. (1950)
	White rat	59	Smyth et al. (1950)
PEG-150 (50%)	White rat	>50	Smyth et al. (1950)
PEG-20M (30%)	Rat	31.6	Mellon Institute of Industrial Research (1956)

Table 7. Results of Human Repeat Insult Patch Tests with Formulas Containing PEG-8.

No. of test subjects	Dose delivery	Results	References
90	Induction patches (0.1 ml of test material) 1 and 2 had 3.0% in formulation, and the rest of the patches contained a 50% aq. dilution of the formulation containing 3%	Based on irritant reactions with the first two patches, the formulation was diluted for the remainder of the patches. 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	Induction patches (0.1 ml of test material) containing 1.0 % in formulation	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	Induction patches (0.1 ml of test material) containing 1.0 % in formulation	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	Induction patches (0.1 ml of test material) containing 1.0 % in formulation	Three subjects had minimal to mild reactions during the induction phase. No reactions were evoked during the challenge phase.	CTFA 1982c
109	Induction patches (0.1 ml of test material) containing 1.0 % in formulation	Four panelists had barely perceptible erythema at least once during induction. No sensitization reactions were observed.	CTFA 1982d
100	Induction patches (0.1 ml of test material) containing 1.0 % in formulation	Four panelists had minimal erythema once during induction. None of the panelists had reactions during the challenge phase.	CTFA 1983a
102	Induction patches (0.1 ml of test material) containing 1.0 % in formulation	Minimal irritation was observed in 18 panelists during induction. No reactions were evoked during the challenge phase.	CTFA 1983b
106	Induction patches (0.1 ml of test material) containing 1.0 % in formulation	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	Induction patches (0.1 ml of test material) containing 1.0 % in formulation	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

Table 8. Dermal penetration of PEG-4 in rinse-off and leave-on formulation for intact skin samples and skin samples tape-stripped 20 times. (Raabe and Norman 2009).

Treatment Group	**Parameter**		**Line Purge**	**Upper stratum corneum**	**Lower stratum corneum**	**Epidermis**	**Dermis**	**Cumulative in Receptor Fluid (24h)**	**Tissue Handling Residues**	**Total Absorption**
PEG-4 in rinse-off formulation in intact skin	% [a]	Mean	0.00%	0.06%	0.01%	0.14%	0.09%	0.06%	0.01%	0.37%
		s.d.	0.00%	0.04%	0.01%	0.14%	0.16%	0.03%	0.01%	0.22%
	µg/cm^2	Mean	0.00	0.15	0.03	0.35	0.23	0.14	0.02	0.93
		s.d.	0.01	0.10	0.03	0.35	0.41	0.07	0.02	0.55
PEG-4 in rinse-off formulation in tape-stripped skin	% [a]	Mean	0.00%	ND [b]	ND	0.18%	0.06%	2.03%	0.02%	2.30%
		s.d.	0.00%	ND	ND	0.13%	0.07%	4.26%	0.02%	4.21%
	µg/cm^2	Mean	0.01	ND	ND	0.45	0.16	5.07	0.05	5.74
		s.d.	0.01	ND	ND	0.33	0.17	10.64	0.04	10.52
PEG-4 in leave-on formulation in intact skin	% [a]	Mean	0.04%	3.02%	1.52%	1.80%	0.34%	1.44%	0.26%	8.42%
		s.d.	0.02%	0.96%	0.70%	0.69%	0.26%	0.54%	0.24%	1.56%
	µg/cm^2	Mean	0.10	7.54	3.80	4.51	0.85	3.61	0.64	21.05
		s.d.	0.04	2.39	1.76	1.74	0.65	1.34	0.61	3.89
PEG-4 in leave-on formulation in tape-stripped skin	% [a]	Mean	0.45%	ND	ND	10.68%	1.27%	20.27%	1.06%	33.72%
		s.d.	0.43%	ND	ND	3.90%	0.84%	21.24%	0.42%	20.11%
	µg/cm^2	Mean	1.12	ND	ND	26.70	3.18	50.66	2.65	84.31
		s.d.	1.07	ND	ND	9.75	2.10	53.10	1.05	50.29

[a] % applied dose

[b] not determined