Amended Final Report on the Safety Assessment of PPG-40 Butyl Ether with an Addendum to Include PPG-2, -4, -5, -9, -12, -14, -15, -16, -17, -18, -20, -22, -24, -26, -30, -33, -52, and -53 Butyl Ethers[1]

The Polypropylene Glycol (PPG) Butyl Ethers function as skin- and hair-conditioning agents in cosmetics. Intestinal absorption of the PPG Butyl Ethers was inversely proportional to the molecular weight. In general, the toxicity of the PPG Butyl Ethers decreased as the molecular weight increased. In acute studies, moderate intraperitoneal (IP) doses of various PPG Butyl Ethers caused convulsive seizures in mice and anesthetized dogs, and large oral doses caused decreased activity, anuria, renal tubular swelling and necrosis, and hepatic swelling and necrosis. PPG-2 Butyl Ether vapors were nontoxic by the inhalation route. PPG-2 Butyl Ether was nontoxic in short-term feeding and dermal exposure studies in rats. In animal irritation studies, PPG-2 Butyl Ether caused minor, transient erythema and desquamation; in addition, erythema, edema, ecchymosis, necrosis, and other changes were observed during an acute percutaneous study. PPG-2 Butyl Ether also caused minor to moderate conjunctival irritation and minor corneal injury. PPG-2 Butyl Ether when dermally applied was nontoxic to pregnant rats and was nonteratogenic at doses up to 1.0 ml/kg/day. PPG BE800 at concentrations of 0.001% to 0.26% in feed was noncarcinogenic to rats after 2 years of treatment. In clinical studies, PPG BE800 was nonirritating and nonsensitizing to the skin when tested using 200 subjects. PPG-40 Butyl Ether was neither an irritant nor a sensitizer in a repeat-insult patch test using 112 subjects. Although clinical testing did not indicate significant skin irritation is produced by these ingredients, the animal test data did indicate the potential that these ingredients can be irritating. Therefore, it was concluded that the PPG Butyl Ethers can be used safely in cosmetic products if they are formulated to avoid irritation. Data on the component ingredients, Propylene Glycol, PPG, and n-Butyl Alcohol, from previous cosmetic ingredient safety assessments were also considered and found to support the safety of PPG Butyl Ethers.

INTRODUCTION

The PPG Butyl Ethers are the polypropylene glycol (PPG) ethers of n-Butyl Alcohol that function as skin- and hair-conditioning agents in cosmetics. The Cosmetic Ingredient Review (CIR) Expert Panel previously assessed the safety of PPG-40 Butyl Ether in cosmetics and found the available data insufficient to support the safety of this ingredient in cosmetics (Andersen 1993). Based on the evaluation of additional safety test data on PPG-40 Butyl Ether, on ingredients of other PPG Butyl Ethers, and on previous safety assessments of propylene (PG) and PPG and n-Butyl Alcohol, the safety assessment of PPG-40 Butyl Ether was reevaluated.

This report is both an addendum to the CIR safety assessment of PPG-40 Butyl Ether to include PPG-2, -4, -5, -9, -12, -14, -15, -16, -17, -18, -20, -22, -24, -26, -30, -33, -52, and -53 Butyl Ethers and an amendment of the previous report on the safety assessment of PPG-40 Butyl Ether. Relevant data from the previous CIR safety assessments of PG and PPG and n-Butyl Alcohol have been added to this review as further basis for assessing the safety of PPG Butyl Ethers in cosmetics.

CHEMISTRY

Definition and Structure

The PPG Butyl Ethers (generic CAS No. 9003-13-8) are the PPG ethers of n- Butyl Alcohol that conform generally to the formula in Figure 1, where the average value of "*n*" equals the number in the name; e.g., "*n*" equals 40 in PPG-40 Butyl Ether.

Although most of the available information uses the PPG-n Butyl Ether naming convention, these ingredients also may be referred to as PPG BE*mw*, where *mw* equals the average molecular weight in the name. For example, a PPG Butyl Ether of molecular weight 770 Da may be called PPG BE770 (Table 1).

Other synonyms for these ingredients are Polyoxypropylene (n) Butyl Ether; Polypropylene Glycol (n) Butyl Ether (Wenninger and McEwen 1995a); and Butoxypolypropylene Glycol (Layton et al. 1987).

Chemical and Physical Properties

The approximate molecular weights of the PPGs Butyl Ether are listed in Table 1.

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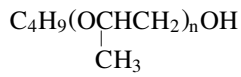

FIGURE 1
Formula for PPG-n Butyl Ether.

PPG-14 Butyl Ether is a clear, almost colorless, slightly viscous liquid. It is soluble in alcohol and other organic solvents. The specific gravity of PPG-14 Butyl Ether at 75°C is approximately 0.985, and the viscosity at 25°C is 84 to 105 cps. The minimum flash point is 400°F. Upon assay, the minimum purity is 99.5%. The maximum acid, ash, and moisture values are 0.5%, 0.005%, and 0.25%, respectively (Nikitakis and McEwen 1990).

The volatility of two PPGs Butyl Ether (PPG BE400 and PPG BE800) were low; the vapor pressure of each was <0.1 mm Hg at 20°C. The specific gravity of the lower molecular weight compound was 0.973 at 20°C, and was soluble in water "to an extent of about 0.2% at 20°C." The larger molecular weight compound had a specific gravity of 0.99 and a water solubility of ~0.1% at the same temperature. Both compounds were soluble in most organic solvents, which included alcohols, ketones, toluene, and gasoline, and were miscible in petroleum distillates and methylated naphthalene (Granett et al. 1949; Carpenter et al. 1951, 1959).

TABLE 1
Approximate molecular weights of PPG Butyl Ethers

Compound	Approximate molecular weight (Da)
PPG-2 Butyl Ether	190
PPG-4 Butyl Ether	306
PPG-5 Butyl Ether	364*
PPG-9 Butyl Ether	596
PPG-12 Butyl Ether	770
PPG-14 Butyl Ether	886
PPG-15 Butyl Ether	944
PPG-16 Butyl Ether	1002
PPG-17 Butyl Ether	1060
PPG-18 Butyl Ether	1118
PPG-20 Butyl Ether	1234
PPG-22 Butyl Ether	1350
PPG-24 Butyl Ether	1466
PPG-26 Butyl Ether	1582
PPG-30 Butyl Ether	1814
PPG-33 Butyl Ether	1988*
PPG-40 Butyl Ether	2394
PPG-52 Butyl Ether	3090
PPG-53 Butyl Ether	3148*

*Union Carbide Corp. (1990) reported molecular weights of 360 Da for PPG-5 Butyl Ether; 2050 Da for PPG-33 Butyl Ether, a range of 3000 to 4000 Da for PPG-53 Butyl Ether.

Method of Manufacture and Impurities

The PPG Butyl Ethers are produced by the reaction of excess Propylene Glycol with n-Butyl Alcohol (Hazardous Substances Data Base [HSDB] 1997), and can contain propylene oxide (Food and Drug Administration [FDA] 1991).

Food- and cosmetic-grade PG can contain up to 0.07% sulfated ash, 0.2% water, and 3 ppm arsenic (as As). Food- and cosmetic-grade PPG can contain up to 3 ppm arsenic (as As), 5 ppm heavy metals (as Pb), and 0.02% propylene oxide. In cosmetic products, the purity of PG is specified as a minimum of 97.5%. One supplier recommends that United States Pharmacopeia (USP)-grade PG be used for cosmetics. USP-grade PG has a typical assay of 99.9% and a specification of 99.5% minimum purity. The supplier recognizes that the USP allows up to 5 ppm propylene oxide in PG, but is of the opinion that typical amounts present in products today are less than detectable (Andersen 1994).

USE

Cosmetic

The PPG Butyl Ethers are used as hair-conditioning agents and skin-conditioning agents—miscellaneous in cosmetic products (Wenninger and McEwen 1995b). In 1998, PPG-2, -14, -16, -18, -33, and -40 Butyl Ethers were used in a total of 100 cosmetic formulations; PPG-4, -5, -9, -12, -15, -17, -20, -22, -24, -26, -30, -52, and -53 were not reported to be used in cosmetics (FDA 1998). Table 2 presents the product types in which each ingredient in current use is found. For example, 1 out of 10 products in the "other personal cleanliness product" category would be expected to have PPG-14 Butyl Ether, but only around 1 out of 100 products in the "skin freshener" category would have the ingredient.

Current concentrations at which these ingredients are used were not available. In 1984, PPG-5 Butyl Ether was used at concentrations of 1% to 5%; PPG-14 Butyl Ether was used at concentrations up to 25%, but was used mostly at 0.1% to 1%; PPG-15 and -18 Butyl Ethers were used at 1% to 5%; PPG-24 Butyl Ether was used at concentrations of 10% to 25%; PPG-33 Butyl Ether was used at concentrations up to 25%, but was used mostly at 1% to 5%; PPG-40 Butyl Ether was used at concentrations of 50%+, but was used mostly at 0.1% to 1%; and PPG-53 Butyl Ether was used at concentrations of 10% to 25% (FDA 1984).

Noncosmetic

The FDA approved the use of PPG-n Butyl Ether (minimum molecular weight = 1000 Da; $n > 16$) as viscosity enhancers in surface lubricants (at concentrations not to exceed 20%) for the manufacture of metallic articles that contact food (FDA 1991).

PPG BE400 and PPG BE800 are used as fly repellents for livestock (Granett et al. 1949, 1951; Carpenter et al. 1951, 1959). The repellents are applied at a concentration of ~5% to dairy cattle in the form of water emulsions or solutions in petroleum

TABLE 2
Product formulation data (FDA 1998)

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
	PPG-2 Butyl Ether	
Nail polish and enamel	80	1
1998 total		**1**
	PPG-14 Butyl Ether	
Colognes and toilet waters	656	9
Deodorants (underarm)	250	2
Other personal cleanliness products	291	29
Body and hand (excluding shaving)	796	1
Moisturizing preparations	769	2
Skin fresheners	184	2
1998 total		**45**
	PPG-16 Butyl Ether	
Shaving cream	139	1
1998 total		**1**
	PPG-18 Butyl Ether	
Shaving cream	139	1
1998 total		**1**
	PPG-33 Butyl Ether	
Colognes and toilet waters	656	5
Moisturizing preparations	769	1
1998 total		**6**
	PPG-40 Butyl Ether	
Tonics, dressings, and other hair-grooming aids	549	5
Other hair preparations	276	1
Hair dyes and colors	1572	39
Moisturizing preparations	769	1
1998 total		**46**

base oils (i.e., kerosene). The repellents are seldom applied more often than every other day (Carpenter et al. 1951), and were effective against stable, horse, and horn flies (Granett et al. 1951).

International

Polyoxypropylene (2, 4, 12, 15, 17, 20, 24, 26, 30, 33, and 52) Butyl Ethers are listed in the Japanese *Comprehensive Licensing Standards of Cosmetics by Category (CLS)* (Rempe and Santucci 1997). The PPG Butyl Ethers that conform to the specifications of the *Japanese Cosmetic Ingredient Codex* have precedents for use without restriction in all *CLS* categories except eyeliner preparations, lip preparations, and/or oral preparations, for which there are no precedents for use.

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

The short-chain length ("*n*" of five or less) PPG Butyl Ethers were completely absorbed from the rabbit or rat digestive tract, and the long-chain compounds ("*n*" of 30 or more) were "little absorbed." Typical absorption values ranged from 100% to 2%, depending upon the chain length (Union Carbide Corp. 1989).

Carpenter et al. (1951) investigated the gastrointestinal (GI) absorption and excretion of PPG BE400 and PPG BE800 (single oral doses of 2 g/kg) using adult albino rabbits. The lower molecular weight compound was absorbed "practically completely" from the GI tract such that <5% of the dose was found in the feces 72 hours after dosing. Within 24 hours of treatment, an unspecified metabolite equivalent to 40% to 55% of the dose was excreted in the urine of three of the four treated rabbits. The fourth rabbit was anuric during this time period, and the urine it excreted during the last 2 days of the collection period contained <3% of the administered dose. The investigators concluded that a substantial proportion of the ingested ether underwent "nearly complete metabolic destruction." The investigators were unable to purify and characterize the metabolite, but an infrared spectral analysis of the original material and the metabolite established that the butyl group had been removed. The larger molecular

weight ether was less well absorbed and as much as 50% or more of a single dose was excreted unchanged in the feces. In another test using albino rabbits, a greater proportion of PPG BE800 was eliminated in the feces than in the urine following single oral doses of the compound. Total recoveries were 45% to 66% (feces) and 8% to 16% (urine) of the administered dose.

Carpenter et al. (1951) also analyzed the livers and carcasses of four groups of rats (five per group) that had been fed 5% of PPG BE400 for 30 days. In three trials, 87%, 88%, and 96% of the ether was recovered, respectively, after the compound was added to hepatic tissue in 100 mg amounts. When the ether was added to the rat carcass, 76%, 82%, and 83% was recovered, respectively.

The same investigators fed a basal diet plus 5% PPG BE400 to four groups of five rats each. The mean feed consumption was 9.7 g/rat/day, and the total ingestion was 14.5 g. After 30 days of treatment, the rats were killed and the livers were analyzed for the ether (four test livers and four control livers). One carcass was selected at random from each group and similarly analyzed. The value for total PPG BE400 did not differ significantly from the blank values from the control group. The mean value for total PPG BE400 was 9.6 ± 4.2 mg, and the mean control value was 2.0 ± 0.8 mg; the difference in means was significant statistically. The investigators concluded that the amount was "so small in proportion to the daily intake of about 500 mg" that the material was in the process of passing through the body, rather than accumulating in the body.

Once absorbed, the butyl group was removed and oxidized, then was partly or completely excreted as carbon dioxide by the lungs. The chains appeared "to be split into random length fragments" and were eliminated in the urine as weak acids after oxidation of the terminal hydroxyls to carboxyl groups (Union Carbide Corp. 1989).

Carpenter et al. (1959) reported that PPG BE800 penetrated rabbit skin slowly, if at all (see "Animal Toxicology-Dermal Toxicity"), and passed poorly through internal tissue barriers. PPG BE800 was absorbed poorly from the gut of rats, mice, guinea pigs, and rabbits.

In a review of the safety of PG and PPG in cosmetics, Andersen (1994) reported that the major route of PG metabolism in mammals is to lactaldehyde and then lactate via hepatic alcohol and aldehyde dehydrogenases. When PG was administered intravenously to humans, dose-related elimination occurred. In animal studies, PPGs 425, 1025, and 2025 were readily absorbed from the GI tract and were excreted in the urine and feces (Andersen 1994).

In a review of the safety of n-Butyl Alcohol in cosmetics, Elder (1987) reported that n-Butyl Alcohol penetrated human epidermis and dermis during in vitro diffusion cell studies. It also penetrated rabbit corneas. When administered orally to rats and humans, dermally to dogs, and by inhalation to dogs and humans, n-Butyl Alcohol was eliminated rapidly and primarily in the expired air and in the urine. It is rapidly oxidized in vivo. *n*-Butyl Alcohol is a substrate for alcohol dehydrogenase and can completely inhibit the metabolism of ethanol by this enzyme. n-Butyl Alcohol is also oxidized by two microsomal pathways in the rat liver and can be oxidized nonenzymatically (Elder 1987).

Miscellaneous Effects

PPG BE400 and PPG BE800 cause ventricular extrasystoles when injected intravenously in anesthetized dogs at doses of 10 to 90 mg/kg. The duration depended on the total amount of PPG administered, not the size of the single dose. Once extrasystoles were produced, further dosing with PPG or epinephrine did not cause ventricular fibrillation. The investigators concluded that the sensitivity of the heart to treatment with PPG was "dependent in some way on a relative anoxia" (Shideman and Moe 1949).

This effect has also been observed after oral administration of 0.1 g/kg of a PPG with a molecular weight of 425 Da. When PPG BE400 was similarly tested, an oral dose of 1 g/kg had no effect on the cardiogram 15 minutes after treatment (Carpenter et al. 1951).

Carpenter et al. (1959) reported that PPG BE800 was a respiratory stimulant in anesthetized dogs at concentrations of 0.15 to 0.3 ml/kg (intravenous [IV]) and 1.0–4.0 ml/kg (intramuscular). The butyl ether acted upon the central nervous system in a parasympathomimetic manner. The investigators reported that the butyl ether increased blood clotting time, and observed slow, steady decreases in blood pressure and the presence of "pinpoint" pupils, cardiac irregularity (increased force, decreased rate), severe tonoclonic convulsive seizures, increased respiratory volume, decreased respiratory rate, eventual respiratory cessation, and cardiac arrest. The investigators stated that these results were caused by parenteral doses that were greater than the amounts "likely to enter the body through the topical application" of the butyl ether as a fly repellent.

ANIMAL TOXICOLOGY

Large oral doses (not specified) of the PPG Butyl Ethers caused decreased activity and anuria. Renal injury from nonfatal doses was rapidly reversible. Sufficiently large, repeated oral doses produced tubular cloudy swelling and focal necrosis of the renal tubules as well as cloudy swelling and focal hepatic cell necrosis. Smaller multiple doses increased hepatic and renal weights and reduced growth of female rats. Convulsive seizures were observed in mice and anesthetized dogs after moderate intraperitoneal (IP) doses of various PPG Butyl Ethers (Union Carbide Corp. 1989).

Acute Toxicity

The Union Carbide Corp. (1989) reported that the single dose rat peroral LD_{50} values ranged from 17.0 ml/kg for PPG BE1020 to 45.3 ml/kg for PPG BE2760.

The Union Carbide Corp. (1990) determined the peroral and cutaneous toxicity of several PPG Butyl Ethers using rats and rabbits, respectively. The peroral LD_{50} of PPG-5 Butyl Ether

was approximately 4.85 ml/kg and the cutaneous LD_{50} was >20 ml/kg. The LD_{50} values of PPG-33 Butyl Ether were 49.4 ml/kg (peroral) and >20 ml/kg (cutaneous). For PPG-53 Butyl Ether, the peroral LD_{50} was 45.2 ml/kg and the cutaneous LD_{50} was >16 ml/kg.

The acute oral LD_{50} in rats of PPG BE800 was 9.1 g/kg (Weil and McCollister 1963). In a study using five adult, albino rats per sex per group, the acute oral LD_{50} was 12.5 ± 3.58 g/kg for a silicone mixture containing 0.13% of an unspecified PPG Butyl Ether (General Electric Co. 1992).

The single-dose oral LD_{50} values of undiluted PPG-9, -15, and -18 Butyl Ethers were determined using rats. The LD_{50} values were 8.2, 9.6, and 14.9 g/kg for the three ethers, respectively. Undiluted PPG-9, -15, -18, -22, and -33 Butyl Ethers were applied to the trunks of rabbits under occlusive patches for 24 hours. The dermal LD_{50} values were 11.9 ml/kg for PPG-9 Butyl Ether, and 20 ml/kg (the maximum retainable dosage; i.e., the maximum that could be applied to the skin) for the other ethers; none of the four rats died after treatment with PPG-15, -18, or -33 Butyl Ethers and one rabbit died after treatment with PPG-33 Butyl Ether. An unidentified PPG Butyl Ether (chain length between 9 and 15; undiluted) had a dermal LD_{50} of 13.4 ml/kg (Mellon Institute of Industrial Research 1952a).

When male Sherman rats were treated via stomach tube with single doses of PPG-33 Butyl Ether, the LD_{50} was 41.3 ml/kg. After dosing, the rats were "somewhat sluggish and unkempt in appearance because of the oily character of the fecal contents after such large doses." Congested or hemorrhagic lungs, mottled liver, and pale kidneys were observed at necropsy. The investigators concluded that PPG-33 Butyl Ether was the least toxic of the ingredient family ranging in molecular weight from 60 1145 Da. In general, as the molecular weight increased, the acute oral toxicity of the PPG Butyl Ethers decreased (Mellon Institute of Industrial Research 1952b).

Undiluted PPG-33 Butyl Ether had an "extremely low order of toxicity" after percutaneous exposure using four male New Zealand white rabbits. The dose was applied to the clipped skin of the trunk, the treatment site was covered with Vinylite sheeting, and the rabbits were immobilized for the duration of the 24 hours treatment period. All of the rabbits survived after treatment with 20 ml/kg of the test compound (Mellon Institute of Industrial Research 1952b).

Two to five fasted rats per group were treated via peroral intubation with 0.5 to 8.0 ml/kg PPG-2 Butyl Ether (clear, low-viscosity liquid; as received); the LD_{50} in males was 2.8 ml/kg and in females was 1.6 ml/kg. Signs of toxicity included sluggishness, lacrimation, kyphosis, piloerection, unsteady gait, and prostration. One rat had a moribund appearance and another had both a yellow discharge on the periurogenital fur (positive for blood) and a red crust on the perinasal fur. Deaths occurred at 45 minutes to 1 day after dosing, and survivors recovered in 1 to 2 days. Dark-red or mottled lungs, discolored stomachs, stomachs filled with red or clear liquid, red or yellow intestines, dark-red livers and kidneys, and/or gas-filled cecums were observed at necropsy. PPG-2 Butyl Ether was classified as moderately toxic by the peroral route (Bushy Run Research Center 1989a).

When tested using five rabbits per group, the percutaneous LD_{50} of PPG-2 Butyl Ether was 7.13 ml/kg for males and 5.86 ml/kg for females. Erythema, edema, ecchymosis, necrosis, fissuring, ulceration, desquamation, alopecia, and scabs were observed. The animals also had sluggishness, prostration, abdominal distention, diarrhea, emaciation, and/or a red-brown discharge on the perinasal fur. The majority of deaths occurred at 3.5 hours to 2 days. Two females died at 11 days, but the investigators attributed this to a gastrointestinal disorder rather than a direct toxic effect of the test material. All rabbits of the low-dose group (4.00 ml/kg) survived. Findings at necropsy included in individual rabbits discolored lungs, red thymus and dark-red trachea, stomach with loose contents, foci of the stomach or thymus, and/or mottled kidneys (Bushy Run Research Center 1989a).

Carpenter et al. (1951) investigated the acute toxicities of PPGs BE400 and BE800. The results of the studies, which are summarized below, indicated that PPG BE400 was 1.5-times more toxic for rats, 2.7-times as toxic for guinea pigs, and 7-times as toxic for rabbits as PPG BE800 when administered orally. When administered intraperitoneally to the rat, PPG BE400 was 3-times more toxic as PPG BE800.

When a 50% aqueous dilution of PPG BE400 was administered by gavage to male albino Sherman rats, the mean LD_{50} was 5.8 g/kg. As the dosage was increased, the signs of distress included sluggishness, gasping, tremors, and convulsions. At the high dose, death occurred within 4 hours of treatment. At necropsy, congestion of the liver and GI tract were observed. When a 50% dispersion of PPG BE800 (in 1% aqueous nonoxynol-7) was fed to rats, the LD_{50} was 9.2 g/kg. Deaths occurred within 24 hours, but the signs were not as severe. At necropsy, congestion or hemorrhages of the lungs, GI tract irritation, and congestion of the liver and pancreas were observed. The PPG Butyl Ethers were considered slightly toxic in this study.

When the undiluted compounds were fed in the diet to male albino New Zealand white rabbits, the mean LD_{50} values were 3.3 g/kg for PPG BE400 and 23.7 g/kg for PPG BE800. For the former, convulsions and death occurred within 24 hours of treatment; pale liver and kidneys, irritation of the GI tract, and watery feces were observed at necropsy. When PPG BE800 was administered, most of the deaths occurred within 24 hours without signs of distress. Rabbits that died at doses near to the LD_{50} had congested and hemorrhagic lungs, pale liver and kidneys, and excessive fluid in the peritoneal cavity. PPG BE400 was considered moderately toxic and PPG BE800 had an "extremely low order of toxicity."

In male albino guinea pigs, 50% dispersions of the two ethers (in 1% aqueous nonoxynol - 7) resulted in LD_{50} values of 2.5 g/kg and 6.8 g/kg, respectively. For PPG BE400, most of the deaths occurred within 1 hour of treatment and followed violent convulsions. The principal finding at necropsy was irritation of the

GI tract. In guinea pigs fed PPG BE800, lung hemorrhages, GI tract irritation, and congestion of the peritoneum were observed. PPG BE400 was considered moderately toxic and PPG BE800 was considered slightly toxic.

The LD_{50} in rats for PPG BE400 was 0.32 g/kg when given intraperitoneally. All deaths but one occurred within 4 hours of dosing. A dose of 1.0 g/kg caused paroxysms, retching, frothing at the mouth, and death within 15 minutes of treatment. A dose of 0.5 g/kg caused tremors and death within 4 hours. At necropsy, the blood was considered darker than normal, and the liver, peritoneal wall, and the adrenal glands were congested. When PPG BE800 was injected intraperitoneally, the LD_{50} was 0.9 g/kg. No signs of toxicity were apparent when a dose of 1.0 g/kg was injected. When treated with 2.0 g/kg, the rats were "narcose," and when treated with 4.0 g/kg, the rats had violent convulsions and frothing at the mouth (Carpenter et al. 1951).

Carpenter et al. (1959) used Carworth Farms-Wistar or Nelson specific pathogen–free rats (five per group) to determine the acute toxicity of PPG BE800. The oral LD_{50} values ranged from 8.9 to 17.3 ml/kg for undiluted PPG BE800 and was 17.2 ml/kg for a 50% dilution of the ether in corn oil. In guinea pigs, rabbits, and C3H/Jax mice (number not stated) the LD_{50} values were 9.5 to 22.5 ml/kg, 5 to 28.3 ml/kg, and 6.7 ml/kg, respectively, when the animals were dosed orally with undiluted PPG BE800. When rats were given single IP injections of PPG BE800, the LD_{50} was 0.8 to 2.2 ml/kg. After groups of four rats were given multiple injections of PPG BE800 (doses = 0.125, 0.25, and 0.5 ml/kg/day for 10 days), the rats survived and had normal weight gains. When rats were given IV injections of the butyl ether, the LD_{50} was 0.22 ml/kg; in rabbits, the LD_{50} was approximately 0.09 ml/kg. Death was preceded by convulsions after parenteral administration of the undiluted ether. The most common finding at necropsy was capillary breakdown and hemorrhages in the lungs. Convulsions did not occur in rats treated orally with PPG BE800 until the dosage equaled or exceeded the LD_{50}.

The acute oral LD_{50} of PPG-40 Butyl Ether was 48.7 ml/kg in a study using five male Sherman rats. Sluggishness and fine tremors sometimes preceded death, which occurred within a few hours of dosing. Weight gain of the survivors was not adversely affected by treatment with the ether. When necropsied, the animals that died prematurely had congestion and hemorrhage of the lungs, congested kidneys, and mottled liver. PPG-40 Butyl Ether was considered less toxic than PPG Butyl Ethers with molecular weights below 400 Da (Mellon Institute of Industrial Research 1952c).

Four New Zealand white rabbits were treated dermally with 20.0 ml/kg of undiluted PPG-40 Butyl Ether. The test compound was applied to the clipped skin of the trunk. Erythema was observed 24 hours after treatment, and all the rabbits survived and had normal weight gain. The investigators concluded that PPG-40 Butyl Ether had a "low order of toxicity by the cutaneous route" (Mellon Institute of Industrial Research 1952c).

The approximate IV LD_{50} for rats of undiluted PPG-40 Butyl Ether was 0.5 ml/kg. When dosed via the IP route, the LD_{50} was 14.8 ml/kg (Mellon Institute of Industrial Research 1952c).

In acute oral toxicity studies using rats, the LD_{50} of PG was 21 g/kg. For PPGs (molecular weights = 300–3900 Da), the LD_{50} values were 0.5 to >40 g/kg for rats (Andersen 1994).

The single oral dose LD_{50} of n-Butyl Alcohol for rats was 0.79 to 4.36 g/kg (Elder 1987).

Short-Term Toxicity

Sprague-Dawley rats (6/sex/group) were fed 100, 200, and 400 mg/kg/day PPG-2 Butyl Ether (purity >95%) for 14 consecutive days. All rats survived to the end of the treatment period, and no systemic toxicity was observed. No test substance–related changes were observed (organ weights, organ/body weights, clinical chemistry and hematologic parameters, and gross and microscopic lesions) (NOTOX 1987).

Groups of eight albino rabbits were given five dermal inunctions per week of 80% PPG-33 Butyl Ether in ethanol, for a maximum of 30 inunctions. The doses were 0.875 or 2.5 ml/kg/day (0.7 or 2.0 g/kg/day). A separate group was started at a later date and received doses of 0.3125 ml/kg/day (0.25 g/kg/day). Rabbits of the control group were treated with 2.5 ml/kg/day of 80% castor oil in ethanol. The doses were applied to 100-cm^2 areas on the clipped belly, were massaged into the skin for 1 minute every 15 minutes during a 1-hour period. The skin was blotted after the 1 hour exposure period and the rabbits were weighed weekly. No deleterious effect was observed on body weight, although rabbits of the test groups gained more weight than controls. None of the rabbits of the high-dose group died, and one of the rabbits treated with 0.875 ml/kg/day died. Five of the eight rabbits in the separate group that started treatment later and received doses of 0.3125 ml/kg/day died. In the control group for the 0.875-or 2.5-ml/kg/day doses, none of the eight rabbits/group died. In the control group for the 0.3125-ml/kg/day dose group, two of the eight rabbits/group died. All deaths were attributed to infections of the lungs and were not considered test compound related. Cloudy swelling of the renal tubules was observed in three rabbits of the group treated later, but this was discounted as an artifact. Reversible, cloudy swelling of the liver was observed in rabbits of the high-dose group; it was concluded that the no-observable-effect level (NOEL) was at least 2.0 g/kg/day (Mellon Institute of Industrial Research 1952b).

In a study using the same test concentrations, groups of 10 albino rabbits were treated with 80% PPG-40 Butyl Ether. One rabbit of the group that started treatment later died of an intestinal infection, and another was killed due to a middle ear infection. Body weight gains did not differ statistically among groups. No micropathologic changes were observed in the liver or skin from the test site. Reversible, cloudy swelling of the renal tubules was observed, but was not considered related to the test concentration as the majority of these findings were in the low-dose group. The investigators concluded that 0.25 g/kg/day had no effect on

mortality, weight change, or microscopic findings in the lung, liver, or kidneys, and that slight effects were noted with doses of 0.7 or 2.0 g/kg/day (Mellon Institute of Industrial Research 1952c).

Subchronic Toxicity

Wistar rats (10/sex/group) were treated topically with 0.1, 0.5, and1.0 ml/kg/day, 5 days/week, PPG-2 Butyl Ether for 13 weeks. Skin reactions (erythema, edema, scaliness, wounds, and incrustations) were observed in all groups, including the control group; however, the findings were more pronounced in the test groups. Other signs of systemic toxicity were not observed, and treatment-related changes were not noted upon ophthalmoscopic examination. Males of the mid- and high-dose groups had decreased body weights, but feed consumption did not differ among the groups. Both sexes of the high-dose group and males of the mid-dose group had increased numbers of the neutrophils. Males of the high-dose group had increased glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) activities, and females had increased triglyceride concentration and decreased glucose concentration; both sexes had increased relative liver weights. Treatment-related changes in urinalysis values and lesions at necropsy were not observed. At microscopic examination, changes of the treated skin were observed in all groups. In particular, females of the high-dose group had more severe acanthosis. No treatment-related microscopic changes were observed in organs or tissues other than the skin. The investigators concluded that the dermal NOEL was 0.1 ml/kg/day PPG-2 Butyl Ether, which was equivalent to a dose of 91 mg/kg/day (CIVO Institutes TNO 1988).

When rats were fed PPG BE800 for 90 days, the minimum effect dose was 0.25% and the maximum NOEL was 0.0625%, or 46.9 mg/kg/day (Weil and McCollister 1963). In another 90-day feeding study using rats (Union Carbide Corp. 1989), the NOELs of PPG BE910 and PPG BE1020 were 0.25% and 0.0625% of the diet, respectively.

PPG BE400 was added to the feed of rats at concentrations of 0.25% (0.16 g/kg/day), 1.0% (0.67 g/kg/day), and 4.0% (3.28 g/kg/day) for 90 days. There were nine rats in each group. Two of nine rats fed the high-dose group died as a result of treatment; the mean number of days to death was 73.5. At microscopic examination of the kidneys of rats that died, slight, cloudy swelling of the renal tubules was observed. The surviving male rats of the high-dose group had decreased weight gains, and significantly increased hepatic and renal weights, compared to the 10 rats of the control group. Surviving female rats of the same group had significantly increased renal weights. Two rats fed the median dose had persistent weight loss and died after 21 and 77 days, respectively. The males of this group had significantly increased renal and hepatic weights, and the females did not differ from controls. One of 10 rats treated with the 0.25% dose died with severe weight loss after 49 days. The males of this group had increased hepatic weights and all rats had increased renal weights, compared to controls, but no other effects were noted at gross and microscopic examinations. The investigators concluded that the 90-day NOEL was 0.16 to 0.67 g/kg/day or between 0.25-1.0% of the diet (Carpenter et al. 1951).

A similar study was performed using PPG BE800. The rats were fed 0.12 (0.25%), 0.52 (1.0%), and 1.48 g/kg/day (4.0%) of the ether. Twenty-two of the 40 treated rats died of pneumonia during the course of the investigation. The percent survivals were 20%, 80%, and 40% for rats of the 0.25%, 1.0%, and 4.0% treatment groups, respectively. Forty percent of the rats of the control group survived. Rats of the high-dose group had reduced feed intake (by 50%) and significantly decreased growth. No microscopic changes were apparent among the survivors. All doses increased hepatic weights. As mortality was great, the results were considered of doubtful value. The investigators concluded that a dose of 0.52 g/kg/day for 90 days was "too great to be tolerated by rats," but could make no further definite statements about the toxicity of PPG BE800 (Carpenter et al. 1951).

In subchronic oral toxicity studies, 3% PPG 2000 induced, at most, slight decreases in body weight in rats; no adverse reactions were noted at concentrations of 0.1% to 1.0% PPG 2000. PPG 750 (1%) caused slight increases in hepatic and renal weights in rats. Rats fed diets containing 50,000 ppm PG (2.5 g/kg/day) for 15 weeks had no test substance–related lesions. When dogs were given 5% PG in drinking water for 5 to 9 months, tests evaluating hepatic and renal impairment were negative. When cats were given feed containing PG, concentrations of $\geq$6% caused erythrocyte destruction (Andersen 1994).

Chronic Toxicity

Weil and McCollister (1963) stated that the NOEL for PPG BE800 was 480 mg/kg body weight per day (0.64%) during a 2-year feeding study using rats, but no study details were provided.

When dogs were fed PPG BE910 for 1 year, the NOEL was approximately 130 mg/kg body weight per day. In a 2-year study of the same compound using rats, the NOEL was 0.016% of the diet. In 6 of 10 long-term feeding studies using rats and dogs, the highest dose tested, 0.5 g/kg body weight per day, produced no adverse, treatment-related effects (Union Carbide Corp. 1989).

Carpenter et al. (1959) reported that the feeding of PPG BE800 to Carworth-Wistar rats had no adverse effects on mortality, body weight gain of males, or incidence of microscopic abnormalities after 2 years of treatment. Each group was comprised of 20 males and 20 females. The test concentrations ranged from 0.001% to 0.256% of the diet. Mortality and the incidence of neoplasms were not increased in any treatment group compared to controls. PPG BE800 at 0.256% in the diet caused a transient increase in the liver weight of females, both at 6 months and during the entire study. Males and females fed 0.064% and 0.0256% PPG BE800 diets had swelling of the renal convoluted tubules at 6 months, but not after 1 year. No lesions were observed in the liver and other organs at microscopic examination. The

investigators concluded that the concentration of PPG BE800 "that was without permanent significant effect on the health of the rats when included in their diet for two years was between 0.064 and 0.256%."

The same investigators fed 0.0008 to 0.013 g/kg/day PPG BE800 (in corn oil) to dogs. The mean concentrations were 47 to 890 ppm. The ether was fed in gelatin capsules 5 days per week for 1 year. The low dose (0.0008 g/kg) was 0.016 ml/kg of a 5% dilution; the middle dose (0.0032 g/kg) was 0.02 ml/kg of a 16% dilution; and the high-dose (0.0128 g/kg) was 0.025 ml/kg of a 51.2% dilution. Animals of the control group were given capsules containing 0.3 ml of corn oil. After 1 year of treatment, no significant differences of hematologic parameters were observed among the control and treatment groups. Liver and kidneys weights did not differ significantly among the groups, and no degenerative changes were noted at microscopic examination. The investigators concluded that treatment of dogs with up to 0.0128 g/kg/day of butyl ethers for 1 year had no deleterious effects (Carpenter et al. 1959).

Rats fed up to 50,000 ppm PG for 2 years had no treatment-related lesions. Similar results were reported after dogs were fed 2 or 5 g/kg PG for ~103 weeks (Andersen 1994).

Dermal Toxicity

Undiluted PPG BE400 was applied to the hair-free skin of the trunk of male New Zealand white rabbits. The test site was covered with an occlusive patch for 24 hours. The mean LD_{50} was 13.3 ml/kg. The investigators concluded that the compound penetrated the skin poorly. Deaths occurred several days or more after dosing, and most of the survivors had decreased body weights. Erythema and "desquamation of the skin," pale liver, pale kidneys with pitted surfaces, and congestion of the intestinal blood vessels were observed. When PPG BE800 was applied using the same method, only 1 of 10 rabbits died after treatment with the maximum dose, 20 ml/kg, of the undiluted compound (Carpenter et al. 1951).

In another study by the same investigators, undiluted PPG BE400 and PPG BE800 were applied by gentle inunction to the skin of groups of rabbits. The dosages were 0.1 and 1.0 ml/kg/day; the smaller molecular weight compound was also applied at a dosage of 0.3 ml/kg/day. The liquid test compounds were massaged into the clipped skin of the belly (test site area = 100 cm^2) for 1 minute every 15 minutes during a 1-hour period. The skin was blotted after the 1-hour exposure period and the rabbits were weighed weekly.

For PPG BE400, 10 rabbits (3 to 4 kg each) per group were treated 5 days/week for 6 weeks. Seven rabbits treated with either 0.3 or 1.0 ml/kg survived 30 inunctions, although mean body weight was reduced. Six rabbits given the low dose survived to the end of treatment; again the mean body weight was reduced. All rabbits of the control group survived; the mean body weight increased. In three of the seven survivors of the high-dose group, the liver was swollen. One of the seven survivors of the median dose group had swelling and fatty degeneration of the liver, as did one survivor of the low-dose group. No renal lesions were observed in survivors of any dose group. The clinical cutaneous effects observed, which were apparent after the second dose, included erythema, fissures, pustules, and desquamation of the epidermis. The investigators concluded that the pustules (similar to appearance of boils on human skin) were likely caused by staphylococcal infection. All of the deaths were attributed to pneumonia, but the weight losses and pathologic changes of the liver indicated that the 30-day NOEL was <0.1 ml/kg/day.

For study of PPG BE800, eight rabbits per group were treated 5 days/week for 18 weeks. One rabbit died of pneumonia in each treatment group. The mean body weight gains of the survivors were 602.8 g and 454.8 g for the low- and high-dose groups, respectively. No abnormalities were observed during microscopic examination of the kidneys, liver, and skin. Mild erythema and "desquamation of the skin" were observed during the experiment; the alternations of skin irritation were less severe later in the study, but were noticeable after 90 doses. The 30- day NOEL was "1.0 ml/kg/day or more" (Carpenter et al. 1951).

Carpenter et al. (1959) also performed skin penetration studies using undiluted PPG BE800. The LD_{50} values for these studies ranged from 18.8 to 21.2 ml/kg after the ether was applied under an occlusive wrap for 24 hours to the clipped skin of the rabbit belly. The investigators concluded that PPG BE800 did not pass the intact skin barrier in physiologically significant amounts.

The same investigators administered undiluted PPG BE800 to rats via subcutaneous (SC) injections under the loose skin of the dorsal scapular area. The LD_{50} was 25.9 ml/kg; necrosis of the skin over the injection site was observed, but the rats gained weight normally during the 14-day observation period. When rabbits were used in place of rats, the SC LD_{50} was 3.6 ml/kg (Carpenter et al. 1959).

Dermal Irritation and Sensitization

The Union Carbide Corp. (1989) reported that the primary skin irritation and skin sensitization potential of the PPGs Butyl Ether was low.

A volume of 0.5 ml PPG-2 Butyl Ether was applied to the skin during a 4-hour occlusive patch test using six rabbits. One rabbit had minor, transient erythema that cleared by day 7. Four rabbits had epidermal desquamation within 7 days of dosing. Edema was not observed in any of the treated animals (Bushy Run Research Center 1989a).

Undiluted PPG BE400 and PPG BE800 were applied to the skin of five rabbits in a 4-hour rabbit belly irritation test. The rabbits had sensitive skin, as determined by screening with 8-ethyl-3,6-dioxydodecanol-1; only rabbits that had moderate to marked erythema within 30 minutes of application were used in the remainder of the study. The PPG Butyl Ethers were applied to the clipped skin of the belly in 0.01 ml volumes at 30-minute intervals for 4 hours. The reactions were scored

24 hours later using a 4-point system, 1 = causing "moderate injection" and 4 = causing marked erythema. PPG BE400 produced a total score of 11 to 15 out of a possible total 20 and PPG BE800 resulted in a total score of 6 to 10 out of a possible total of 20. The smaller molecular weight compound was considered slightly more irritating than the larger molecular weight compound to the skin, but neither caused damage more severe than erythema after repeated application (Carpenter et al. 1951).

PPG BE800 was not a primary irritant when 0.01 ml of the undiluted ether was applied, uncovered, to the clipped skin of the rabbit belly during a 24-hour test (Carpenter et al., 1959). No reactions were observed during a 3-day repeated application test, when a 0.01-ml volume of undiluted PPG BE800 was applied at 3-hour intervals, three times daily. Four of five treated rabbits had no reactions after nine applications, and the fifth had only "minimal capillary injection."

Undiluted PPG-9, -15, -18, and -33 Butyl Ethers, as well as an unidentified member of this family of ingredients (chain length between 9 and 15), were assayed for dermal effects using the rabbit belly vesicant test. The unidentified PPG Butyl Ether, and PPG-15 Butyl Ether, had grade 1 effects (no response). PPG-18 Butyl Ether caused grade 2 reactions (minor capillary injection), and PPG-9 Butyl Ether caused grade 3 reactions (definite capillary injection) (Mellon Institute of Industrial Research 1951).

PPG-33 Butyl Ether produced no irritation (grade 1) in the skin of rabbits during the vesicant test and 4-hour irritation test. During a 3-day repeated-application study in which the compound was applied to the skin three times daily, two rabbits did not react to the ether and one had slight epidermal desquamation of the treatment site (Mellon Institute of Industrial Research 1952b).

Two of five rabbits treated with PPG-40 Butyl Ether had minimal detectable capillary injection after a single uncovered application of 0.01 ml undiluted PPG-40 Butyl Ether. The ether was classified as a grade 2 irritant (comparable to irritancy of dimethyl phthalate). During a 4-hour rabbit belly irritation test (eight applications of 0.01 ml at 30-minute intervals), marked capillary injection, but no other responses, were observed. PPG-40 Butyl Ether was classified as a grade B irritant, where grade E members induce edema or necrosis. When the ether (0.01 ml) was applied to the skin of three rabbits three times daily for three days, no detectable irritation was observed after day 1, capillary injection was observed on two of the three rabbits after day 2, and one of three rabbits had capillary injection after day 3. Under the conditions of this study, PPG-40 Butyl Ether had an "extremely low order of irritation to rabbit skin" (Mellon Institute of Industrial Research 1952c).

During a 24-hour skin irritation test using nude mice, no reactions were observed after treatment with 10% PG; PG at a concentration of 50% caused hypertrophy, dermal inflammation, and proliferation. Undiluted PG was, at most, a mild skin irritant when applied to the skin of guinea pigs and rabbits for 48 hours under open and closed patches. In 48-hour and 21-day open and closed patch tests using Gottingen swine, no reactions to undiluted PG were observed. In a mouse external ear swelling test, 100% PG did not cause sensitization reactions. PG at a concentration of 70% was nonsensitizing during guinea pig maximization, open epicutaneous, and Finn chamber tests. In a maximization test, PG was classified as a potentially weak sensitizer. In six other guinea pig sensitization tests, PG was not an allergen. Single and repeated applications of PPGs 425, 1025, and 2025 did not cause skin irritation in rabbits. Repeated applications of PPG 1200 to rabbits produced mild reactions at abraded skin sites and no reactions at intact skin sites (Andersen 1994).

n-Butyl Alcohol did not cause skin irritation in rabbits (Elder 1987).

Ocular Irritation

The Union Carbide Corp. (1989) reported that the ocular irritancy potential of the PPG Butyl Ethers was low. In studies using rabbits, PPG-9, -15, -18, and -22 Butyl Ethers, as well as an unidentified member of this family of ingredients (chain length between 9 and 15), caused "minor injury from an excess" and was classified as a grade 1 irritant.

Minor corneal injury (opacity) occurred in six of six treated rabbits after instillation of 0.1 ml PPG-2 Butyl Ether. Iritis and moderate conjunctival irritation, with a "substantial amount of discharge" were also observed in the six animals. Two eyes appeared normal at 72 hours, and all six eyes recovered by day 7. In a study using 0.01 ml volumes of the test material, opacity was not observed. Iritis occurred in four rabbits, and all six had minor to moderate conjunctival irritation and substantial discharge. All eyes recovered within 48 hours of treatment (Bushy Run Research Center 1989a).

When an excess amount of PPG-33 Butyl Ether was instilled into the eyes of five rabbits, traces of corneal necrosis were observed in two of the rabbits. PPG-33 Butyl Ether was considered "among the compounds least harmful to eyes." PPG-40 Butyl Ether, when instilled in 0.5-ml volumes, produced no detectable damage to the rabbit eye (Mellon Research Institute of Industrial Research, 1952b, 1952c).

In a 24-hour ocular toxicity study, 0.5 ml PPG-15 Butyl Ether (as received) produced traces of diffuse corneal necrosis in the eyes of four rabbits and no injury to the eye of one rabbit. A volume of 0.5 ml PPG-33 Butyl Ether (as received) caused no injury to the eyes of five rabbits (Mellon Institute 1965).

Carpenter et al. (1951) reported that undiluted PPGs 400 and BE800 caused only minimal corneal injury to the eyes of rabbits when the ingredients were applied using a 0.5-ml volume. The ethers were "no worse than glycerin or liquid petrolatum USP in their irritative action on rabbit eyes." Carpenter et al. (1959) reported that the instillation of undiluted PPG BE800 to the eyes of rabbits caused no harmful effects.

PG did not induce corneal damage in rabbits in one Draize test and was classified as a slight ocular irritant in a second

test. PPGs 425, 1025, and 2025 were nonirritating to the eyes of rabbits; PPG 1200 induced slight, transient ocular irritation in an albino rabbit (Andersen 1994).

n-Butyl Alcohol caused severe ocular irritation in rabbits (Elder 1987).

Inhalation Toxicity

The low volatility of the ethers limited toxicity by inhalation at room temperature, but the ethers were more readily oxidized at higher temperatures and were somewhat toxic after inhalation of the resultant mist (Union Carbide Corp. 1989).

During a 6-hour inhalation study, all rats (five per sex) survived after exposure to a statically generated, substantially saturated vapor of PPG-2 Butyl Ether (room temperature). No signs of toxicity were observed, and no gross lesions were evident at necropsy (Bushy Run Research Center 1989a).

The Bushy Run Research Center (1989b) performed several toxicity studies on PPG-5, -33, and -53 Butyl Ethers. In a preliminary, range-finding study (Table 3), the PPGs Butyl Ether in saline were dosed directly into the lungs of anesthetized, male Sprague-Dawley rats (one or two per group). Rats of the control group were treated with saline alone. In the final study, 15 rats/group were given a single endotracheal dose of the highest nonlethal concentration determined in the range-finding study. The 15 rats of the control group were given a 2.0 ml/kg dose of saline. The animals were observed daily for signs of toxicity and were weighed weekly. Three rats/group were killed for necropsy at 1, 2, 3, 7, and 14 days after dosing; the lungs were then removed and microscopic examination was performed on stained lung tissue. No signs of toxicity were observed in rats treated with saline, 0.005 ml/kg (0.25%) PPG-5 Butyl Ether, or 1.0 ml/kg (50%) PPG-53 Butyl Ether. Rats treated with 2.0 ml/kg (100%) PPG-33 Butyl Ether had piloerection and tremors within 7 minutes of dosing. At necropsy, lungs of the control group were discolored and had hemorrhages. At microscopic examination, the control lungs had minimal grade perivascular infiltrates, interstitial pneumonitis, and one instance of interstitial fibrosis (low severity). Similar lesions were observed in lungs of rats treated with PPG-5 Butyl Ether (low severity). Both PPG-33 and -53 Butyl Ethers caused increased perivascular infiltrates (similar to controls) and interstitial pneumonitis (moderate severity). None of the PPG Butyl Ethers caused discolorations of the lungs. The investigators concluded that the least toxic (endotracheally) of the materials tested were those with molecular weights of >2000 Da and with water solubilities of $<0.1\%$. The peroral toxicity was inversely proportional to the molecular weight, and the incidence of pulmonary lesions following endotracheal dosing was directly proportional to the molecular weight (Bushy Run Research Center 1989b).

Groups of six female rats were exposed for 8 hours to saturated vapors of PPGs BE400 and BE800, and were observed for 14 days for signs of toxicity. The vapors were produced by passing an air stream through 50 ml of the ethers, which were contained in 250-ml gas-washing bottles. The rats were unaffected by the treatment, and no gross organ damage was observed. In a related study, similar number of rats were exposed for 8 hours to fogs of the ethers by means of a nebulizer. The exposure concentrations were $\sim$0.005 ml/l of the smaller molecular weight compound and $\sim$0.004 ml/l of the larger molecular weight compound. None of the rats died as a result of treatment, and the only effect noted was a slight reduction in body weight gains (Carpenter et al. 1951).

No signs of toxicity were observed when six male and six female albino rats were exposed to PPG BE800 vapors for 4 hours daily for 5 consecutive days (Carpenter et al. 1959). The exposure concentration was approximately 0.005 ml/l, and was administered using a nebulizer (particle diameter $= 2$ μm). In an 8-hour study, six male rats were exposed to a dense fog of the ether with a test concentration of 0.02 ml/l. Five of the six rats had normal weight gains during the 14-day observation period, and no treatment-related effects were observed.

When rats inhaled saturated vapors (room temperature) of PPG-18 Butyl Ether for 8 hours, all six of the rats survived. In another study, six rats per group were exposed to mist and oxidation products from cooling PPG-9, -18, or -24 Butyl Ether vapors (saturated at 170°C). None of the rats were killed after 15 minutes of exposure. At 30 minutes, two rats treated with

TABLE 3
Preliminary endotracheal study (Bushy Run Research Center 1989b)

Dose	Concentration (*v*/*v* in saline)	Dead/dosed	Time to death
PPG-5 Butyl Ether (molecular weight = 360 Da)			
0.02 ml/kg	1.0%	1/1	30 sec
0.01 ml/kg	0.5%	1/1	30 sec
0.005 ml/kg	0.25%	0/2	—
PPG-33 Butyl Ether (molecular weight = 2050 Da)			
2.0 ml/kg	100%	0/2	—
PPG-53 Butyl Ether (molecular weight = 3000–4000 Da)			
2.0 ml/kg	100%	1/2	30 min
1.0 ml/kg	50%	0/2	—

PPG-9 Butyl Ether, one rat treated with PPG-18 Butyl Ether, and five rats treated with PPG-24 Butyl Ether had died. All of the rats had died within 1 hour (Mellon Institute of Industrial Research 1952a).

A substantially saturated vapor was generated at room temperature by passing air at 2.5 l/min through a fritted glass disc immersed in 50 ml of PPG-33 Butyl Ether. Six adult male rats were exposed to the vapor for 8 hour and were observed for 14 days after treatment. The only response noted was slight ocular irritation. A mist of PPG-33 Butyl Ether (produced in the same manner except that the bubbler was immersed in a silicone bath at 170°C) killed six of six rats in 4 hour and one of six rats in 2 hour. Irritation of the eyes and extremities was observed. The investigators concluded that the "inhalation of mist evolved at this temperature constitutes a moderate hazard and should not be tolerated" (Mellon Institute of Industrial Research 1952b).

Inhalation of n-Butyl Alcohol vapors caused intoxication of laboratory animals, and high concentrations were sometimes fatal (Elder 1987).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Two groups of 20 pregnant Wistar rats were treated topically with 0.3 and 1.0 ml/kg/day PPG-2 Butyl Ether (in PG) on gestational days (GDs) 6 to 16. Rats of the control group were treated with 1.5 ml/kg/day of the vehicle alone. No mortality occurred in any of the test or control groups, and no behavioral effects or signs of systemic toxicity were observed. Minor local skin reactions were observed in both test groups, but the investigators did not consider the test material a dermal irritant. Maternal performance was comparable in all groups, and no statistically significant differences were observed in body or organ weights, feed consumption, gross lesions, or litter data between the test and control groups. Compound-related malformations, anomalies, or variants of the offspring were not observed; however, offspring of the high dose group had a minor, but nonsignificant increase in the incidence of supernumerary ribs. The investigators concluded that PPG-2 Butyl Ether was nontoxic to pregnant rats and that dermal application during gestation was nonteratogenic at doses up to 1.0 ml/kg/day (TNO-CIVO Institutes 1988).

PG was not teratogenic in CD-1 mice when administered at a concentration of 10,000 ppm during days 8 to 12 of gestation. Malformations were observed in 5 of 226 living fetuses from female mice injected subcutaneously with 0.1 ml/g PG on days 9 to 11 of gestation; in comparison, 3 of 1026 living fetuses of the untreated control group had malformations. In a continuous breeding reproduction study, no significant differences were observed between control and experimental groups of albino mice with respect to mating index, fertility index, mean number of live pups per litter, proportion of pups born alive, and sex of pups born alive. Embryonic development was decreased in cultures of mouse zygotes exposed to 3.0 M PG and was inhibited completely in cultures exposed to 6.0 M PG for 20 minutes (Andersen 1994).

GENOTOXICITY AND CARCINOGENICITY

PPG BE800 (0.001% to 0.26% of the diet) was not carcinogenic to rats after 2 years of treatment (Carpenter et al. 1959).

PG was nonmutagenic in the Ames test in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100, with and without metabolic activation. PG caused a dose-dependent increase in the frequency of sister-chromatid exchanges (SCEs) in Chinese hamster cells, and was classified as a weak inducer of SCEs. In another study, PG was not mutagenic in an SCE assay using human cultured fibroblasts and a cultured Chinese hamster cell line both with and without metabolic activation. PG induced chromosomal aberrations in one assay, but was not mutagenic in other in vitro tests: chromosomal aberrations, mitotic recombination, basepair substitution, micronucleus test, reverse mutation, and DNA damage.

PG disturbed the proliferation of urinary bladder epithelial cells from the rat, having reduced DNA production in tetraploid cells 1 and 2 months after the rats received SC injections of PG. This effect was not observed at 3 months. When PG was tested in the hamster ovary cell transformation bioassay, the results were negative. PG (50,000 ppm) was not carcinogenic during a 2-year feeding study using CD rats. In a lifetime dermal carcinogenicity study using Swiss mice, 10% to 100% PG did not increase the incidence of neoplasms, and skin tumors were not observed (Andersen 1994).

n-Butyl Alcohol was not mutagenic in the *Salmonella*/mammalian-microsome mutagenicity assay, did not induce SCEs or chromosome breakage in chick embryo cells or Chinese hamster ovary cells, and did not induce micronuclei formation in V79 Chinese hamster cells. Carcinogenicity data were not available (Elder 1987).

CLINICAL ASSESSMENT OF SAFETY

PPG BE800 did not cause primary skin irritation when applied undiluted to the skin of 200 subjects in a 5-day patch test. Upon retest, 3 weeks after the first application, none of the subjects had signs of sensitization (Carpenter et al. 1951, 1959).

In a clinical test of 112 subjects, a volume of approximately 0.2 ml of 7% PPG-40 Butyl Ether was applied to the 1 × 1-inch portion of an adhesive dressing and was allowed to volatilize for several minute prior to application. The semiocclusive dressing was applied to the upper back (between the scapulae) of each subject, 109 of whom completed the study. This procedure was repeated three times per week for a total of 10th induction applications. A challenge patch was applied to the original and an untreated site on the volar forearm 14 days after the 10th induction exposure. The test sites were evaluated at 24 and 48 hours after application. None of the participants reacted to the test material, and PPG-40 Butyl Ether was not considered a potential irritant or sensitizer (CPTC, Inc. 1992).

PG induced skin irritation and sensitization reactions in normal subjects and patients. The test concentrations ranged from 2% to 100%, and reactions were observed at concentrations of

≥10% in predictive tests and ≥2% in provocative tests. PG increased the allergic responses in 43 patients patch-tested with 50 μg of 1% nickel sulfate solution. Neither skin irritation nor sensitization reactions were observed in 300 subjects who received continuous and repeated dermal applications of undiluted PPG 2000 (Andersen 1994).

During repeat-insult patch tests using 105 to 558 subjects, a nail enamel and nail color (each containing 3.0% n-Butyl Alcohol) were neither irritants nor sensitizers. The nail enamel was also not a phototoxin or photoallergen. When 105 dermatologic patients were tested for reactions to n-Butyl Alcohol using the chamber test method, four patients had positive reactions (edema). Inhalation of n-Butyl Alcohol can cause human nose, throat, and ocular irritation (Elder 1987).

SUMMARY

The PPGs Butyl Ether function as skin- and hair-conditioning agents in cosmetics. In 1998, these ingredients were used in 100 cosmetic formulations. Current concentration of use are not available, but in 1984, these ingredients were typically used at concentrations from 0.1% to 25%. PPG-40 Butyl Ether was generally used at concentrations of 0.1% to 1%, but a concentration of 50%+ was reported for one formulation (tonics, dressings, other hair grooming aids).

Absorption of the PPGs Butyl Ether was inversely proportional to the molecular weight; typical gastric absorption values ranged from 2% to 100%, depending upon the chain length. PPG BE800 (~PPG-13 Butyl Ether) penetrated rabbit skin slowly, if at all, and passed poorly through internal tissue barriers. Once absorbed, the butyl group was removed and oxidized, then was partly or completely excreted as CO_2 by the lungs. The chains were apparently split into random length fragments and eliminated in urine as weak acids after oxidation of the terminal hydroxyls to carboxyl groups.

In general, the toxicity of the PPG Butyl Ethers decreased as the molecular weight increased. Moderate IP doses of various PPG Butyl Ethers caused convulsive seizures in mice and anesthetized dogs, and large oral doses caused decreased activity, anuria, renal tubular swelling and necrosis, and hepatic swelling and necrosis. In rats, the acute oral LD_{50} values of the ethers ranged from 1.6 to 2.9 ml/kg (PPG-2 Butyl Ether) to 48.7 ml/kg (PPG-40 Butyl Ether). For rabbits, the cutaneous LD_{50} values were 5.9 to 7.1 ml/kg (PPG-2 Butyl Ether) to >20 ml/kg (PPG-40 Butyl Ether). The SC LD_{50} of PPG BE800 was 3.6 ml/kg.

PPG-2 Butyl Ether vapors were nontoxic by the inhalation route. A room-temperature mist of PPG-33 Butyl Ether was nontoxic when inhaled by rats, but when the mist was evolved at 170°C, the ether was moderately toxic. Rats that inhaled vapors of PPG-9, -18, and -24 Butyl Ethers for 1 hour died, but none were killed during a 15-minute exposure period.

PPG-2 Butyl Ether at a dose of 0.40 g/kg/day was nontoxic to rats during a 14-day feeding study. In 90-day feeding studies, the NOELs of PPG BE400, 800, 910, and 1020 were 0.047 g/kg/day, 0.16 to 0.67 g/kg/day, 0.25% of the diet, and 0.0625% of the diet, respectively. When rats were treated topically with PPG-2 Butyl Ether 5 days/week for 13 weeks, the dermal NOEL was 0.1 ml/kg/day, which was equivalent to a dose of 91 mg/kg/day. Doses of 0.25 g/kg/day 80% PPG-40 Butyl Ether, 2.0 g/kg/day 80% PPG-33 Butyl Ether, and 1.0 ml/kg/day PPG BE800 had no effect on mortality, weight change, or microscopic findings when applied to the skin of rabbits 5 days/week for 6 weeks, but the 30-day dermal NOEL for PPG BE400 was <0.1 ml/kg/day. When dogs and rats were fed PPG BE800 and 910 for up to two years, the NOELs were up to 0.5 g/kg/day.

In a 4-hour occlusive patch test using rabbits, PPG-2 Butyl Ether caused minor, transient erythema and desquamation, but not edema. PPG-33 Butyl Ether was nonirritating in a vesicant, 4-hour irritation, and 3-day repeated application tests. Undiluted PPG-40 Butyl Ether was minimally irritating to the skin of rabbits. Rabbits treated with PPG BE800 had minimal capillary injection during a 3-day repeated application test, and PPG-40 Butyl Ether was slightly less irritating than PPG BE400 (caused erythema) in a 4-hour belly irritation test. PPG-9 and -18 Butyl Ethers caused capillary injection, whereas PPG-15, -33, and ~9–15 Butyl Ethers caused no response during a rabbit belly vesicant test.

Rabbits treated with 0.1 ml PPG-2 Butyl Ether had minor corneal injury (opacity), iritis, and moderate conjunctival irritation; rabbits treated with 0.01 ml of the ether had iritis and minor to moderate conjunctival irritation. In an ocular toxicity study, PPG-15 Butyl Ether produced traces of diffuse corneal necrosis in four of five rabbits and PPG-33 Butyl Ether was not irritating. PPG-9, ~9–15, -15, -18, -22, and -33 Butyl Ethers caused minor injury to the eyes of rabbits.

PPG-2 Butyl Ether when dermally applied was nontoxic to pregnant rats and was nonteratogenic at doses up to 1.0 ml/kg/day. PPG BE800 at concentrations of 0.001% to 0.26% in feed was noncarcinogenic to rats after 2 years of treatment.

In clinical studies, PPG BE800 was nonirritating and nonsensitizing to the skin when tested using 200 subjects. PPG-40 Butyl Ether was neither an irritant nor a sensitizer in a repeat insult patch test using 112 subjects.

Acute, subchronic, and short-term animal studies using PG and PPG suggested little toxicity beyond a slight decrease of body weight. Little ocular or skin irritation, and no sensitization, were observed in animals. Mice injected subcutaneously with PG had slight increases in fetal malformations, but no reproductive toxicity occurred in a multigeneration feeding study. PG was nonmutagenic in mammalian and microbial assays and noncarcinogenic in studies using mice and rats. Skin irritation and sensitization were observed in normal subjects treated with 10% PG and in dermatitic patients treated with 2% PG.

In vitro studies indicated that human epidermis and dermis were permeable to n-Butyl Alcohol. Acute oral and dermal LD_{50} values were 0.8 to 4 g/kg and 4.2 g/kg, respectively, in rats.

n-Butyl Alcohol was nonirritating to the skin of rabbits, but was a severe ocular irritant. Inhalation of n-Butyl Alcohol vapors caused intoxication, and high concentration were sometimes fatal. n-Butyl Alcohol was nongenotoxic in mammalian and microbial assays. Nail formulations containing 3.0% n-Butyl Alcohol were nonirritating and nonsensitizing in studies using 979 subjects, but the alcohol produced edema in 4 of 105 dermatologic patients. Nail enamel formulations containing the alcohol were neither irritants, sensitizers, nor photoallergens. Inhalation by humans of n-Butyl Alcohol caused irritation of the nose, throat, and eyes.

DISCUSSION

In general, the toxicity of the PPGs Butyl Ether decreased with increasing molecular weight; for example, PPG-40 Butyl Ether was less toxic than PPG-2 Butyl Ether. Mutagenicity data were not found on the PPGs Butyl Ether. However, an ether of molecular weight 800 Da (~PPG-13 Butyl Ether) was noncarcinogenic when fed to rats for 2 years.

Because the PPGs Butyl Ethers undergo metabolic degradation; i.e., the butyl group are removed and oxidized, the PPG chains are split into random length fragments, the genotoxicity of the component chemicals, PG and n-Butyl Alcohol, were also considered. Both PG and n-Butyl Alcohol were nonmutagenic in mammalian and microbial assays. PG was noncarcinogenic in a 2-year feeding study using rats and in a lifetime dermal study using mice. These studies effectively eliminated the need for genotoxicity data on the PPG Butyl Ethers.

The Panel was concerned about the irritancy potential of PPG-2 Butyl Ether. In animal irritation studies, the ingredient caused minor, transient erythema and desquamation; in addition, erythema, edema, ecchymosis, necrosis, and other changes were observed during an acute percutaneous study. PPG-2 Butyl Ether also caused minor to moderate conjunctival irritation and minor corneal injury. The Panel concluded that the PPG Butyl Ethers were safe for use in cosmetics when formulated to avoid irritation.

The CIR Expert Panel previously reviewed the safety of PPG-40 Butyl Ether and found the data to be insufficient to support safety. Because the data on the lower molecular weight PPG Butyl Ethers can be considered relevant to PPG-40 Butyl Ether, and because additional data on PPG-40 Butyl Ether itself were provided, this report amends the conclusion reached in that report.

CONCLUSION

Based on the available data, the CIR Expert Panel concludes that PPG-2, -4, -5, -9, -12, -14, - 15, -16, -17, -18, -20, -22, -24, -26, -30, -33, -40, -52, and -53 Butyl Ethers are safe for use in cosmetics when formulated to avoid irritation. (Note: This presents a revised conclusion for PPG-40 Butyl Ether.)

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