Final Report on the Safety Assessment of PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-26-Buteth-26, and PPG-28-Buteth-35[1]

Currently, PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-26-Buteth-26, and PPG-28-Buteth-35 are reported to be used in cosmetic formulations. PPG is the acronym used by the cosmetics industry for polypropylene glycol. Very little acute toxicity was seen in rats, mice, and rabbits with oral exposure to various PPG Buteths. Hepatic and renal lesions were observed in subchronic oral toxicity studies of PPG-24-Buteth-27 and PPG-33-Buteth-45 in rats. In a chronic feeding study involving rats and one involving dogs, no significantly different incidence of neoplasms or other lesions were seen with PPG-7-Buteth-10 and PPG-33-Buteth-45. Acute, short-term, and subchronic inhalation studies with various PPG Buteths were negative. Some deaths were seen in acute dermal toxicity studies in rabbits using various PPG Buteths, but even the surviving animals exhibited erythema, edema, ecchymosis, and desquamation. Although PPG-24-Buteth-27 produced mild ocular toxicity, mixed results were seen with PPG-26-Buteth-26, and no irritation with several other PPG Buteths. PPG Buteths produce skin irritation in animal tests. In two lifetime skin painting studies in mice, PPG-7-Buteth-10 and PPG-33-Buteth-45 did not induce papillomas or carcinomas. Some evidence was found that PPG-24-Buteth-27 could act as a tumor promotor, but only at high concentrations. Clinical testing of PPG-26-Buteth-26 produced no skin irritation or sensitization. Because PPG Buteths are butanol-initiated random linear copolymers, there is a concern that a reproductive and developmental toxin, n-butyl alcohol, could be present. Data were provided showing the absence of n-butyl alcohol in PPG-26-Buteth-26 from which it may be inferred that this compound is not found in other PPG Buteths. Although the available data on skin irritation and sensitization of PPG-26-Buteth-26 were considered applicable to the larger molecular weight PPG-28-Buteth-35, these data were not considered applicable to PPG Buteths with molecular weights lower than that of PPG-26- Buteth-26. Experience suggested to the CIR Expert Panel that lower molecular weight members of a chemical family can be absorbed through the skin differently compared to higher molecular weight compounds. Absent any data on the dermal absorption of a low-molecular-weight PPG Buteth, or actual data on skin irritation and sensitization, it was concluded that the available data are insufficient to support the safety of PPG-9-Buteth-12 or PPG-12-Buteth-16 in cosmetic products. Based on the available data, PPG-26-Buteth-26 and PPG-28-Buteth-35 are considered safe as used in cosmetic products.

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INTRODUCTION

This report assesses the safety of the use of PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-26-Buteth-26, and PPG-28-Buteth-35 in cosmetic formulations. These PPG (polypropylene) Buteths are polyoxypropylene, polyoxyethylene ethers of butyl alcohol that conform to the formula shown in Figure 1. Other PPG Buteths are listed in the *International Cosmetic Ingredient Dictionary* (Wenninger, Canterbery, and McEwen 2000), but they are currently not reported to the Food and Drug Administration (FDA) as being used (FDA 1997), and are not included in this safety assessment. Because the PPG Buteths have the same basic chemical structure, however, data on other chemicals in this family are included in this report as they may contribute to the safety assessment of the currently used PPG Buteth cosmetic ingredients. The additional data are on the following chemicals (again, none of these are currently being used in cosmetic products): PPG-7-Buteth-10, PPG-20-Buteth-30, PPG-24-Buteth-27, and PPG-33-Buteth-45.

CHEMISTRY

Chemical and Physical Properties

PPG Buteths (CAS Numbers 9038-95-3 and 9065-63-8) conform to the formula shown in Figure 1 where average values for x range from 2 to 38 and average values for y range from 2 to 45; e.g., PPG-12-Buteth-16 has average x and y values of 12 and 16, respectively (Wenninger, Canterbery, and McEwen 2000).

Other names for PPG Buteths include: Polyoxyethylene (y) Polyoxypropylene (x) Monobutyl Ether and Polyoxypropylene (x) Polyoxyethylene (y) Monobutyl Ether. For example, PPG-12-Buteth-16 is also known as Polyoxyethylene (16) Polyoxypropylene (12) Monobutyl Ether and Polyoxypropylene (12) Polyoxyethylene (16) Monobutyl Ether (Wenninger, Canterbery, and McEwen 2000).

According to the CTFA (Cosmetic, Toiletry and Fragrance Association) cosmetic ingredient description, PPG-12-Buteth-16 is a clear, colorless slightly viscous liquid with the following properties: no apparent odor; soluble in water or ethanol; specific gravity of 1.050 to 1.054 (at 20°/20°C); refractive index of 1.450 to 1.462 (at 25°C); pH of 5.5 to 8.5 (10% aqueous solution); viscosity (Saybolt) of 630 to 690 cps at 100°F; and with a close match to a standard infrared (IR) spectrum with no indication of foreign materials (Nikitakis and McEwen 1990).

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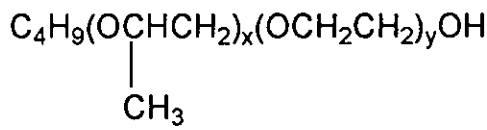

FIGURE 1
Chemical formula for PPG Buteths where average values for x range from 2 to 38 and for y range from 2 to 45; e.g., PPG-12-Buteth-16 has average x and y values of 12 and 16, respectively (Wenninger, Canterbery, and McEwen 2000).

Additional chemical and physical properties of PPG-12-Buteth-16, PPG-7-Buteth-10, PPG-9-Buteth-12, PPG-20-Buteth-30, PPG-28-Buteth-35, and PPG-33-Buteth-45 are summarized in Table 1. Chemical specifications provided by ingredient suppliers for PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-20-Buteth-30, PPG-28-Buteth-35, and PPG-33-Buteth-45 are summarized in Table 2.

Methods of Production

PPG-12-Buteth-16 and other ethylene oxide/propylene oxide polymers of this series, which includes the other PPG Buteths reviewed in this report, are butanol-initiated, random linear copolymers that are produced from equal amounts (by weight) of ethylene and propylene oxide (Klonne et al. 1987; Hoffman et al. 1991). PPG-12-Buteth-16 is prepared by etherification of a 50:50 copolymer of ethylene and propylene oxides (Nikitakis and McEwen 1990).

Impurities

PPG-12-Buteth-16 contains ash (0.01% maximum) and moisture (0.3% maximum) (Nikitakis and McEwen 1990). Two batches of PPG-26-Buteth-26 and two batches of a trade name mixture containing PPG-26-Buteth-26 (Solubilisant LRI) were assayed for the percentage of residual n-butyl alcohol using head space with gas chromatography (detection limit = 1 ppm) and solid phase micro extraction (SPME) with gas chromatography (GC) (detection limit = 1 ppb) techniques. For each sample tested, there was no signal indicating the presence of n-butyl alcohol. Solubilisant LRI was also assayed for dioxane and ethylene oxide content using the SPME with GC technique. Dioxane content was below 5 ppm and ethylene oxide content was below 1 ppm (Les Colorants Wackherr 1996). The concentration of residual ethylene oxide and propylene oxide in PPG-33-Buteth-45 is less than 1 ppm (Union Carbide Corporation 1987).

USE

Purpose in Cosmetics

PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-26-Buteth-26, and PPG-28-Buteth-35 have the following uses in cosmetics: hair conditioning agent; skin conditioning agent—miscellaneous; and surfactant—emulsifying agent. PPG-12-Buteth-16 is also used as a solvent for cosmetic products (Wenninger, Canterbery, and McEwen 2000).

Scope and Extent of Use in Cosmetics

United States

The product formulation data submitted to the FDA in 1997 indicated that the following PPG Buteths were used in cosmetics at the following use frequencies: PPG-12-Buteth-16 (53 products); PPG-9-Buteth-12 (2 products); PPG-26-Buteth-26 (13 products); and PPG-28-Buteth-35 (10 products) (FDA 1997).

The types of cosmetic products in which PPG-12-Buteth-16 is used are shown in Table 3. Similar information on the other PPG Buteths is included in Table 4.

Concentration of use values are no longer reported to FDA by the cosmetics industry (FDA 1992a). However, product formulation data submitted to FDA in 1984 indicated that PPG Buteths were used at the following concentrations: PPG-12-Buteth-16 (0.1–25%); PPG-9-Buteth-12 (0.1–1%); and PPG-28-Buteth-35 (0.1–1%). PPG-26-Buteth-26 was not reported as being used in cosmetics in 1984 (FDA 1984). More recent data submitted to The Cosmetic, Toiletry, and Fragrance Association, Inc. (CTFA) in 1995 indicated the following maximum use concentrations for PPG-12-Buteth-16: 22% (hair dressings); 2% (self-tanners); 1% (hair styling lotions); and 0.1% to 1% (astringents). PPG-28-Buteth-35 was used at concentrations up to 1% in shampoos (CTFA 1995).

Cosmetic products containing PPG-12-Buteth-16, PPG-9-Buteth-12, and PPG-26-Buteth-26 are applied to the skin, hair, and nails and could come in contact with the eyes, nasal mucosa, and other parts of the body. Products containing PPG-28-Buteth-35 are applied only to the hair, and could come in contact with facial skin, the eyes, and nasal mucosa.

Products containing the PPG Buteths could be used on a daily basis and potentially can be applied many times over a period of several years.

International

The PPG Buteths are not included in the list of substances that are prohibited from use in cosmetic products that are marketed in the European Union (European Economic Community 1995).

The following PPG Buteths are included in the *Japanese Comprehensive Licensing Standards of Cosmetics by Category (CLS)* (Rempe and Santucci 1997): PPG-2-Buteth-2, PPG-4-Buteth-4, PPG-5-Buteth-5, PPG-7-Buteth-10, PPG-10-Buteth-9, PPG-12-Buteth-12, PPG-15-Buteth-20, PPG-17-Buteth-17, PPG-28-Buteth-35, PPG-30-Buteth-30, PPG-33-Buteth-45, PPG-36-Buteth-36, and PPG-38-Buteth-37. All of these ingredients conform to the specifications of the *Japanese Cosmetic Ingredients Codex*, and have precedent for use without restriction in all CLS categories except eyeliner, lip, and oral preparations, for which there is no precedent for use.

TABLE 1
Properties of PPG Buteths (Union Carbide Chemicals and Plastics Company, Inc. 1992a, b, c, d, e, f)

Properties	Ingredients					
	PPG-12-Buteth-16	PPG-7-Buteth-10	PPG-9-Buteth-12	PPG-20-Buteth-30	PPG-28-Buteth-35	PPG-33-Buteth-45
Physical State	Liquid	Liquid	Liquid	Liquid	Liquid	Liquid
Appearance	Transparent, colorless	Transparent, colorless to pale yellow	Transparent, colorless to white	Transparent, colorless	Transparent, colorless	Transparent, colorless to pale yellow
Odor	Characteristic	Characteristic	Mild	Characteristic	Characteristic	Characteristic
Molecular weight	1700	970	1230	2660	3380	3930
Specific gravity	1.051 at 20°/20°C	1.033 at 20°/20°C	1.041 at 20°/20°C	1.056 at 20°/20°C	1.056 at 20°/20°C	1.013 at 20°/20°C
Freezing point	Pour point, −34.4°C	Pour point, −40°C	Pour point, −41°C	Pour point, −31.7°C	Pour point, −28.9°C	Pour point, −51.1°C
Boiling point (at 760 mm Hg)	Decomposes at >200°C	Decomposes at >200°C	Decomposes at >291°C	Decomposes at >200°C	Decomposes at >200°C	Decomposes at 200°C
Flash point	202°C, closed cup 229°C, open cup	350°C, closed cup 238°C, open cup	204°C, closed cup 249°C, open cup	177°C, closed cup 249°C, open cup	182°C, closed cup 243°C, open cup	141°C, closed cup 196°C, open cup
Vapor pressure (at 20°C)	<0.01 mm Hg	<0.01 mm Hg	<0.01 mm Hg	<0.01 mm Hg	<0.01 mm Hg	<0.01 mm Hg
Vapor density	>1	>1	42.41	>1	>1	>1
Evaporation rate	Nil	Nil	<0.01	Nil	Nil	Nil
Solubility in water by weight	100%	100%	100% at 20°C	100%	100%	100%

TABLE 2
Specifications for PPG Buteths (Union Carbide Corporation 1994; Amerchol Corporation 1994a, b, c, d)

Property	Ingredients				
	PPG-12-Buteth-16	PPG-9-Buteth-12	PPG-20-Buteth-30	PPG-28-Buteth-35	PPG-33-Buteth-45
Color	—	100 platinum, max	200 platinum, max	200 platinum, max	200 platinum, max
Odor	—	Characteristic	Low, characteristic	Characteristic	Low, characteristic
Form	—	—	—	—	Viscous, clear liquid
Clarity	Free of haze or turbidity	Free from haze or turbidity	Free from turbidity	Free from haze or turbidity	Free from haze or turbidity
Dilution test	Clear	Clear	Clear	Passes	Clear
Viscosity (at 100°F)	630–690 cps	380–420 cps	1900–2100 cps	3370–3670 cps	4850–5350 cps
pH (10% aqueous solution at 25°C)	5.5–7.5	—	—	—	—
Moisture	—	0.3% max	0.3% max	0.3% max	0.3% max
Water	0.13% by weight, max	—	—	—	—
Particulates	Substantially free	Substantially free	Substantially free	Substantially free	Substantially free

Noncosmetic Use

In general, PPG Buteths have had the following uses: components of adhesives; defoaming agents in paper manufacture, animal glue, and beet sugar; as components of paperboard for packaging dry food; rubber lubrication; heat transfer fluids; and specialty solvents (Smyth et al. 1970).

According to the Code of Federal Regulations (CFR), the following food uses of PPG-33-Buteth-45 have been approved by FDA: additive to steam boilers used to generate steam that will contact food (21 CFR 173.310); component of defoaming agents used in the processing of beet sugar (21 CFR 173.340); component of adhesives used in articles intended for packaging, transporting, or holding food (21 CFR 175.105); component of defoaming agents used in the preparation and application of coatings for paper and paperboard (21 CFR 176.200); component of defoaming agents used in the manufacture of paper and paperboard (21 CFR 176.210); and component of lubricants for use on machinery used for producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food (limitation of 10 ppm in food) (21 CFR 178.3570).

TABLE 3
Product formulation data on PPG-12-Buteth-16 (FDA 1997)

Product category	Total no. of formulations in category	Total no. containing ingredient
Baby shampoos	19	1
Bubble baths	186	8
Other bath preparations	141	14
Other eye makeup preparations	116	1
Hair conditioners	596	4
Shampoos (noncoloring)	825	6
Tonics, dressings, and other hair grooming aids	512	7
Wave sets	55	1
Nail creams and lotions	17	1
Bath soaps and detergents	341	4
Other personal cleanliness products	262	1
Foot powders and sprays	32	1
Other skin care preparations	683	1
Indoor tanning preparations	50	3
1997 totals		**53**

Poly(oxyethylene/oxypropylene)monobutylether (PPG-12-Buteth-16 is Polyoxyethylene [16] Polyoxypropylene [12] Monobutyl Ether) has been approved for use as an optional adjuvant substance in the processing and finishing of poly(*p*-phenyleneterephthalamide) resins that are intended to produce articles for repeated use in the processing and handling of food (FDA 1992).

PPG-12-Buteth-16 and PPG-20-Buteth-30 have been used to coat the walls of polar glass capillary columns used by analytical chemists (Higgins 1981).

BIOLOGICAL PROPERTIES

Metabolism and Excretion

PPG-7-Buteth-10

Rats (number, weights, and strain not stated) were dosed orally with ^{14}C-PPG-7-Buteth-10 (67 mg/kg). Three samples of this chemical were radiolabeled at the butoxy, ethylene oxide, and propylene oxide groups, respectively. Radioactivity was not detected in the carcass of any animal at day 7 postdosing.

TABLE 4
Product formulation data on PPG Buteths (FDA 1997)

Product category	Total no. of formulations in category	Total no. containing ingredient
PPG-9-Buteth-12		
Other bath preparations	141	2
1997 totals		**2**
PPG-26-Buteth-26		
Deodorants (underarm)	241	1
Other personal cleanliness products	262	2
Other shaving preparation products	60	1
Cleansing skin care preparations	630	3
Body and hand (Excluding shaving) skin care preparations	776	1
Moisturizing skin care preparations	743	1
Skin fresheners	181	4
1997 totals		**13**
PPG-28-Buteth-35		
Rinses (noncoloring)	42	3
Shampoos (noncoloring)	825	4
Bath soaps and detergents	341	1
Deodorants (underarm)	241	1
Cleansing skin care preparations	630	1
1997 totals		**10**

The urine and feces accounted for 46.4% and 26.7% of the total radioactivity detected within 7 days after dosing; radioactivity (12.5% of total) was also detected in expired carbon dioxide. The greater part of expired radioactivity originated in the terminal butoxy groups and half as much originated in the propylene oxide groups distributed at random in the chain; almost no radioactivity was detected in the ethylene oxide groups in the chain. Also, the proportions of radioactivity in the three samples that appeared in the feces differed. Most radioactivity was from the ^{14}C-ethylene oxide and least was from the ^{14}C-butanol. The investigators noted that these proportions are the reverse of what was observed in expired carbon dioxide and that these differences could have occurred only if cleavage of ^{14}C-PPG-7-Buteth-10 had occurred at the ether linkages (Smyth et al. 1970).

PPG-33-Buteth-45

Following the oral administration of ^{14}C-PPG-33-Buteth-45 (^{14}C was only at the ethylene oxide groups) according to the same procedures of the preceding experiment, the urine and feces accounted for 5.3% and 89.0% of the total radioactivity detected within 7 days after dosing. No radioactivity was found in expired carbon dioxide (Smyth et al. 1970).

TOXICOLOGY

Acute Oral Toxicity

Studies on the acute oral toxicity of PPG Buteths are summarized in Table 5. The results show a range of LD_{50} values.

PPG-12-Buteth-16, PPG-20-Buteth-30, and PPG-33-Buteth-45

The acute oral toxicity of PPG-12-Buteth-16, PPG-20-Buteth-30, and PPG-33-Buteth-45 in rats (number, strain, and weights not stated) was evaluated by administering undiluted test substance to fasted rats by gavage. The mean acute oral LD_{50} values were as follows: 18.3 g/kg (15 to 22.4 g/kg) for PPG-12-Buteth-16, 20.6 g/kg (16.7 to 25.5 g/kg) for PPG-20-Buteth-30, and 48.7 g/kg (42.3 to 55.9 g/kg) for PPG-33-Buteth-45 (Union Carbide Corporation 1952).

PPG-7-Buteth-10 and PPG-33-Buteth-45

The acute oral toxicity of undiluted PPG-7-Buteth-10 and PPG-33-Buteth-45 was evaluated using male and female albino rats (number not stated). The test substances were administered by oral intubation. The two weight ranges for male rats were 90 to 120 g and 120 to 170 g and the two weight ranges for female rats were 90 to 120 g and 300 to 400 g. The mean oral LD_{50} values for PPG-7-Buteth-10 in rats were as follows: 7.07 ml/kg (males, weights = 90–120 g), 5.95 ml/kg (males, weights = 120–170 g), 8.57 ml/kg (females, weights = 90–120 g), and 4.49 ml/kg (females, weights = 300–400 g) (Smyth et al. 1970).

For PPG-33-Buteth-45, the mean oral LD_{50} in rats was 45.2 ml/kg (females, weights = 300–400 g). No deaths occurred in males and females weighing 90 to 120 g; males in the 120 to 170 g weight range were not dosed with PPG-33-Buteth-45 (Smyth et al. 1970).

PPG-24-Buteth-27

The acute oral toxicity of undiluted PPG-24-Buteth-27 was evaluated using Sprague-Dawley albino rats (five males, five females; weights between 200 and 300 g). The test substance was melted and then administered to each animal, by gastric intubation, at a dose of 16.0 ml/kg. None of the animals died. The only sign of toxicity was diarrhea at day 1, followed by recovery at day 2. With the exception of enlarged uterine horns in one female, gross lesions were not observed at necropsy (Bushy Run Research Center 1986).

PPG-26-Buteth-26

The acute oral toxicity of undiluted PPG-26-Buteth-26 was evalauted using ten hooded Long Evans rats (five males, five females; weights = 200–300 g). The test substance was warmed and then administered via oral intubation to each animal. Necropsy was performed on each rat at the time of death or

TABLE 5
Acute oral toxicity of PPG Buteths

Test substance	Animals tested	Procedure	Results	References
PPG-12-Buteth-16	Rats (number not stated)	Single dose by gavage	Oral LD_{50} = 18.3 g/kg	Klonne et al. 1987
PPG-7-Buteth-10	Male albino rats (weights = 90–120 g)	Single dose by oral intubation	Oral LD_{50} = 7.07 ml/kg	Smyth et al. 1970
PPG-7-Buteth-10	Male albino rats (weights = 120–170 g)	Single dose by oral intubation	Oral LD_{50} = 5.95 ml/kg	Smyth et al. 1970
PPG-7-Buteth-10	Female albino rats (weights = 90–120 g)	Single dose by oral intubation	Oral LD_{50} = 8.57 ml/kg	Smyth et al. 1970
PPG-7-Buteth-10	Female albino rats (weights = 300–400 g)	Single dose by oral intubation	Oral LD_{50} = 4.49 ml/kg	Smyth et al. 1970
PPG-7-Buteth-10	Female mice (weights = 23–36 g)	Single dose by oral intubation	Oral LD_{50} = 7.46 ml/kg	Smyth et al. 1970
PPG-7-Buteth-10	Rabbits (weights = 2200–2900 g)	Single oral dose	Oral LD_{50} = 1.77 ml/kg	Smyth et al. 1970
PPG-20-Buteth-30	Rats (number not stated)	Single dose by gavage	Oral LD_{50} = 20.6 g/kg	Klonne et al. 1987
PPG-24-Buteth-27	Sprague-Dawley albino rats (5 males, 5 females) (weights = 200–300 g)	Single dose (16 ml/kg) by gastric intubation	No deaths	Bushy Run Research Center 1986
PPG-26-Buteth-26	10 Long Evans hooded rats (5 males, 5 females) (weights = 200–300 g)	Single dose (4.72 ml/kg)	No deaths	Stillmeadow, Inc. 1977
Solubilizing system containing PPG-26-Buteth-26	Sprague-Dawley CFY rats (5 males, 5 females) (weights = 120–147 g)	Single dose (4.81 ml/kg)	Two deaths	Safepharm Laboratories, Ltd. 1987a
PPG-33-Buteth-45	Female albino rats (weights = 300–400 g)	Single dose by oral intubation	Oral LD_{50} = 45.2 ml/kg	Smyth et al. 1970
PPG-33-Buteth-45	Albino rats (males and females) (weights = 90–120 g)	Single dose by oral intubation	No deaths	Smyth et al. 1970
PPG-33-Buteth-45	Female mice (weights = 23–36 g)	Single dose by oral intubation	LD_{50} = 49.4 ml/kg	Smyth et al. 1970
PPG-33-Buteth-45	10 female Swiss albino mice (weights = 26–33 g)	Single oral dose	LD_{50} = 49.4 ml/kg	Union Carbide Corporation 1964
PPG-33-Buteth-45	Rabbits (weights = 2200–2900 g)	Single oral dose	LD_{50} = 15.8 ml/kg	Smyth et al. 1970
PPG-33-Buteth-45	8 male New Zealand albino rabbits (weights = 2308–2848 g)	Single oral dose	LD_{50} = 15.8 ml/kg	Union Carbide Corporation 1964

at the end of the study. The LD_{50} was not achieved at a dose of 5.01 g/kg (4.72 ml/kg), and PPG-26-Buteth-26 was considered nontoxic. No lesions were observed at necropsy (Stillmeadow Inc. 1977).

The acute oral toxicity of a solubilizing system containing PPG-26-Buteth-26 (as supplied) was evaluated using five male and five female Sprague-Dawley CFY rats. The concentration of PPG-26-Buteth-26 in this system was not stated. The weight ranges for the animals tested were 120 to 147 g (males) and 121 to 128 g (females). Each rat received a single dose (5000 mg/kg; dose volume = 4.81 ml/kg) of the test substance by gavage. The animals were observed at 1 and 4 hours postdosing and then once daily for 14 days. Necropsy was performed on each animal. Two rats died during the study; one female rat died on day 1, and another female on day 2. The following signs were noted up to day 1 postdosing: hunched posture, piloerection, lethargy, and decreased respiratory rate. Surviving animals appeared normal from day 2 postdosing to the end of the study. The following necropsy findings for the two rats that died were reported: abnormally red lungs, congestion of the small intestines, and patchy

pallor of the liver. Except for one female with an ulcerated area on the nonglandular region of the stomach, no abnormalities were noted at necropsy of surviving animals killed at the end of the study. It was concluded that the acute oral median lethal dose (LD_{50}) was greater than 5000 mg/kg body weight (Safepharm Laboratories Ltd. 1987a).

PPG-7-Buteth-10 and PPG-33-Buteth-45

The acute oral toxicity of PPG-7-Buteth-10 and PPG-33-Buteth-45 was evaluated using female mice (number and strain not stated; weights = 23–36 g); each test substance was administered by oral intubation. The mean acute oral LD_{50} values for PPG-7-Buteth-10 and PPG-33-Buteth-45 were 7.46 ml/kg and 49.4 ml/kg, respectively (Smyth et al. 1970).

In another study, the acute oral toxicity of PPG-33-Buteth-45 was evaluated using 10 fasted, female Swiss albino mice (weights = 26–33 g). The mean acute oral LD_{50} for PPG-33-Buteth-45 was 49.4 ml/kg (range = 39.9–61.0 ml/kg) (Union Carbide Corporation 1964).

PPG-7-Buteth-10 and PPG-33-Buteth-45

In rabbits (number and strain not stated; weights = 2200–2900 g), the mean oral LD_{50} values for PPG-7-Buteth-10 and PPG-33-Buteth-45 were 1.77 ml/kg and 15.8 ml/kg, respectively (Smyth et al. 1970).

In another study, the acute oral toxicity of PPG-33-Buteth-45 was evaluated using eight fasted, male New Zealand albino rabbits (weights = 2308–2848 g). The mean acute oral LD_{50} for PPG-33-Buteth-45 was 15.8 ml/kg (range = 11.6–21.3 ml/kg) (Union Carbide Corporation 1964).

Subchronic Oral Toxicity

PPG-24-Buteth-27

The subchronic oral toxicity of PPG-24-Buteth-27 was evaluated using groups of male and female CF-E albino rats (10 males, 10 females/group). Four groups of rats were fed PPG-24-Buteth-27 at concentrations of 0.01%, 0.05%, 0.25%, and 1.25%, respectively, for 3 months. Negative-control rats were fed laboratory chow only. Only two rats (males) died during the study. One of the two died after consuming 1.25% PPG-24-Buteth-27 in the diet for 51 days; at necropsy, acute pneumonia was the primary cause of death. The other male rat, from the same group, was killed moribund on the 52nd day.

Bilateral hydronephrosis with markedly dilated ureters and urinary bladder were noted. Compared to controls, group mean values for kidney weight (as percent of body weight) were significantly lower in males fed PPG-24-Buteth-27 at dietary concentrations of 0.01 (p = value between .05 and .01) and 1.25% ($p < .0001$), respectively. Kidney weights of rats of 0.05% and 0.25% treatment groups were not significantly different from controls; however, the values reported were lower. No significant differences were found in kidney weight (as percent of body weight) between controls and females from any of the treatment groups. The mean value for liver weight (as percent of body weight) in females was significantly different from controls only in the group that was fed 1.25% PPG-24-Buteth-27 in the diet. No significant differences were found in liver weight (as percent of body weight) between controls and males from any of the treatment groups. Microscopic changes in kidneys from rats of the 0.05%, 0.25%, or 1.25% PPG-24-Buteth-27 treatment groups included focal tubular necrosis and cloudy swelling of the proximal convoluted tubules. Microscopic changes in livers from rats in 0.05%, 0.25%, or 1.25% treatment groups included focal hepatic cell necrosis, and diffuse parenchymatous cloudy swelling. It was concluded that toxicological tissue changes were significant in selected rats fed diets containing 0.05%, 0.25%, or 1.25% PPG-24-Buteth-27. All changes that were observed in the 0.05% treatment group were considered transitory. Tissues from representative animals of the 0.01% treatment group differed little from controls (Union Carbide Corporation 1961).

PPG-33-Buteth-45

In a 90-day feeding study, PPG-33-Buteth-45 was fed to groups of 20 CFE albino rats (10 males, 10 females/group) at dietary concentrations of 0.04%, 0.2%, 1.0%, and 5.0% (0.03, 0.15, 0.7, and 4.0 g/kg/day), respectively. Male rats ranged in weight from 122 to 217 g and body weights of females ranged from 131 to 164 g. Effects were not observed on mortality, body weight, feed consumption, and on absolute and relative kidney and liver weights in all treatment groups. At microscopic examination, lesions of the kidneys and liver were observed in rats of 0.7 and 4.0 g/kg/day dose groups. Primarily, the renal lesions consisted of a diffuse, cloudy swelling and focal necrosis of the proximal convoluted tubule, swollen glomeruli, and diffuse capillary congestion. The hepatic lesions consisted of focal hepatic cell necrosis and diffuse, cloudy swelling. Pulmonary lesions were not observed in any of the treatment groups (Klonne et al. 1987).

Chronic Oral Toxicity

PPG-7-Buteth-10

In a chronic feeding study, four groups of 36 male and 36 female CFE albino rats (weights not stated) were fed PPG-7-Buteth-10 at doses of 0.004, 0.02, 0.1, and 0.5 g/kg/day, respectively, for 2 years. Dietary concentrations were adjusted every 2 weeks for 6 months and, then, every 4 weeks to keep the dosage essentially constant (in terms of g/kg/day) as body weights increased. The negative-control group was fed laboratory chow only. With the exception of female rats (0.5 g/kg/day dose group) with growth rates less than those for controls, no statistically significant differences were observed with respect to the following: behavior, diet consumption, mortality, life span, incidence of infections, terminal liver and kidney to body weight ratios, body weight gain, hematocrit, total red blood cell count, incidence of neoplasms, and microscopic lesions in 20 tissues (Smyth et al. 1970).

Three groups of beagle dogs (three males and three females/group; weights not stated) were fed PPG-7-Buteth-10 at doses

of 0.0043, 0.043, and 0.62 g/kg/day, respectively, for 2 years. The three doses represented average equivalent g/kg/day based on the percentage of PPG-7-Buteth-10 that was administered in the diet for each group. The control group received meal only. No statistically valid differences were found between control and experimental groups with respect to the following: appetite, body weight change, mortality, terminal liver and kidney to body weight ratios, hematocrit, hemoglobin, red and white blood cell total counts, differential white cell counts, serum urea nitrogen, activity of serum alkaline phosphatase, 15-minute bromsulphalein retention, and gross and microscopic lesions in 18 tissues (Smyth et al. 1970).

PPG-33-Buteth-45

As with PPG-7-Buteth-10, Smyth et al. (1970) found no toxicological or pathological changes were observed after PPG-33-Buteth-45 was administered to three groups of 36 male and female CFE albino rats (same procedure; weights not stated) at dietary concentrations of 0.02, 0.1, and 0.5 g/kg/day, respectively (Smyth et al. 1970).

PPG-33-Buteth-45 produced little toxicity when administered in the diet to three groups of three male and three female beagle dogs (weights not stated; same procedure) at doses of 0.023, 0.11, and 0.61 g/kg/day, respectively (Smyth et al. 1970).

Acute Dermal Toxicity

PPG-12-Buteth-16, PPG-20-Buteth-30, PPG-33-Buteth-45

In an acute dermal toxicity study involving rabbits (strain and weights not stated), groups of four animals were dosed with 21 g/kg PPG-12-Buteth-16, PPG-20-Buteth-30, or PPG-33-Buteth-45. Undiluted test substance was applied to intact skin, after which the test sites were covered with an impermeable wrap for 24 hours. In each case, one of four animals died (Klonne et al. 1987).

PPG-26-Buteth-26

The acute dermal toxicity of undiluted PPG-26-Buteth-26 was evaluated using ten New Zealand Albino rabbits (five males, five females; weights = 2.3–3.0 kg). Feed and water were made available ad libitum throughout the study. Prior to test substance administration, skin of the trunk was clipped free of hair (10 rabbits) and clipped free of hair and abraded (5 rabbits). The trunk of each animal was covered with a sleeve made of plastic sheeting, which served as a reservoir for the test substance. The test substance was introduced under the sleeve, which was then resealed with adhesive tape, and then massaged into the exposure area. The sleeves were removed at 24 hours postapplication and reactions were scored according to the following scales: 0 (no erythema) to 4 (severe erythema to slight eschar formation) and 0 (no edema) to 4 (severe edema, raised more than 1 mm and extending beyond the area of exposure). Observations for necrosis and ulceration were also made. The animals were observed for any toxic or pharmacological effects daily for up to 2 weeks after sleeve removal.

Necropsy was performed on each animal at the time of death or at the end of the study. Skin irritation was observed in all rabbits. Erythema scores ranged from 1 (very slight) to 3 (moderate to severe). Scores for edema ranged from 1 (no edema) to 3 (moderate, raised approximately 1 mm). Throughout the study, no toxic or pharmacological effects were observed. No abnormalities were observed at necropsy. The acute dermal LD_{50} was not achieved at a dose of 2.0 g/kg (1.89 ml/kg), and PPG-26-Buteth-26 was considered nontoxic (Stillmeadow Inc. 1977).

PPG-24-Buteth-27

The acute dermal toxicity of undiluted PPG-24-Buteth-27 was evaluated using 14 New Zealand white rabbits that weighed between 2.0 and 3.0 kg. The test substance was applied (doses of 2, 4, 8, and 16 ml/kg) to clipped, intact skin of the trunk and sites were covered with impervious sheeting for 24 hours. Ten rabbits (5 males, 5 females) received 8 and 16 ml/kg doses and 4 rabbits (2 males, 2 females) received 2 and 4 ml/kg doses. Excess fluid was removed at the end of the 24-hour contact period in order to diminish ingestion. The animals were observed for skin reactions at 1 hour and days 7 and 14 after the 24-hour contact period. None of the animals died. Cutaneous lesions included erythema, edema, ecchymoses, and desquamation. All of the animals had one or more of these cutaneous lesions. Sluggishness (transient) was noted in rabbits given doses of 8 and 16 ml/kg. Necropsy findings included mottled and pink to red lungs, and, in a few animals, nodules were found in the lungs (Bushy Run Research Center 1986).

Acute Intravenous Toxicity

Studies on the acute intravenous toxicity of PPG Buteths are presented below and are summarized in Table 6. The results show a range of LD_{50} values.

PPG-12-Buteth-16, PPG-7-Buteth-10, PPG-20-Buteth-30, and PPG-33-Buteth-45

The acute intravenous toxicity of the following chemicals was evaluated at the Bushy Run Research Center (1990b) using groups of 10 (5 males, 5 females/group) 7- to 13-week-old, Sprague-Dawley albino rats that weighed between 200 and 300 g: PPG-12-Buteth-16 (100%), PPG-7-Buteth-10 (10% in saline), PPG-20-Buteth-30 (100%), PPG-33-Buteth-45 (60% in saline), and PPG-33-Buteth-45 reduced (60% in saline). PPG-33-Buteth-45 reduced means that the unsaturation level in PPG-33-Buteth-45 was decreased from 0.034 to 0.019 meq/g by reducing the alkyl end group. The formula for PPG-33-Buteth-45 reduced (molecular weight = 4000 Da) was given as: C_4H_9 $(OCH_2\ CH_2)_n$ $(OCH_2\ CH\ (CH_3))_n$ OH. For each test substance, no more than 2.0 ml was injected into the tail vein of each rat (10 rats per test substance). All rats were necropsied and microscopic examination was performed on the lungs of selected rats (those that died and those killed).

The acute intravenous LD_{50} values for 100% PPG-12-Buteth-16 were 0.41 ml/kg (5 male rats) and 0.64 ml/kg (5 female rats).

TABLE 6
Acute intravenous toxicity of PPG Buteths

Test substance	Animals tested	Procedure	Results	References
PPG-12-Buteth-16	10 Sprague-Dawley albino rats (5 males, 5 females) (weights = 200–300 g)	Single injection into tail vein	LD_{50} = 0.41 ml/kg (males); 0.64 ml/kg (females). Relatively little lung pathology	Bushy Run Research Center 1990b
PPG-7-Buteth-10 (10% in saline)	10 Sprague-Dawley albino rats (5 males, 5 females) (weights = 200–300 g)	Single injection into tail vein	LD_{50} = 0.20 ml/kg (males); 0.21 ml/kg (females). Relatively little lung pathology	Bushy Run Research Center 1990b
PPG-20-Buteth-30	10 Sprague-Dawley albino rats (5 males, 5 females) (weights = 200–300 g)	Single injection into tail vein	LD_{50} = 1.62 ml/kg (males); 2.0 ml/kg (females). Relatively little lung pathology	Bushy Run Research Center 1990b
PPG-33-Buteth-45 (60% in saline)	10 Sprague-Dawley albino rats (5 males, 5 females) (weights = 200–300 g)	Single injection into tail vein	LD_{50} = 2.14 ml/kg (males); 2.0 ml/kg (females). Inflammation, alveolar histiocytosis, and fibrosis most significant treatment-related findings in lungs	Bushy Run Research Center 1990b
PPG-33-Buteth-45 (reduced form, 60% in saline)	10 Sprague-Dawley albino rats (5 males, 5 females) (weights = 200–300 g)	Single injection into tail vein	LD_{50} = 2.14 ml/kg (males); 1.66 ml/kg (females). Inflammation, alveolar histiocytosis, and fibrosis most significant treatment-related findings in lungs	Bushy Run Research Center 1990b
PPG-33-Buteth-45 (60% in saline)	20 Sprague-Dawley rats	Single intravenous dose of 1.75 ml/kg	One rat died on day 3 postinjection. Pulmonary lesions noted as early as day 1 postinjection and included congestion, hemorrhage, and interstitial pneumonitis	Union Carbide Corporation 1992
PPG-33-Buteth-45	53 Sprague-Dawley rats	Single intravenous dose of 1.75 ml/kg	17 (experimentals and controls included) of the 106 rats at the beginning of the study died. The lesions in lungs from most of the 53 rats that survived included: hemorrhage, perivascular infiltrates, interstitial pneumonitis, emphysema, and alveolar edema. Renal toxicity was also noted in 5 rats. Microscopic changes included edema, necrosis, and atrophy of the proximal renal tubules	Union Carbide Corporation 1992

Acute intravenous LD_{50} values for 100% PPG-20-Buteth-30 were 1.62 ml/kg (5 male rats) and 2.0 ml/kg (5 female rats). For 60% PPG-33-Buteth-45, acute intravenous LD_{50} values were 2.14 ml/kg (5 male rats) and 2.0 ml/kg (5 female rats). Values for 60% PPG-33-Buteth-45 reduced were 2.14 ml/kg (5 males) and 1.66 ml/kg (5 females). Acute intravenous LD_{50} values for 10% PPG-7-Buteth-10 were 0.20 ml/kg (5 male rats) and 0.21 ml/kg (5 female rats). The most toxic substances were those with low molecular weights (<2000 Da), PPG-12-Buteth-16 and PPG-7-Buteth-10; the remaining chemicals had low toxicity. At microscopic examination, the most significant treatment-related lesions were pulmonary inflammation, alveolar histiocytosis, and fibrosis. These lesions were most prevalent among rats dosed with PPG-33-Buteth-45 (reduced and non-reduced). Relatively few lung lesions were produced by PPG-7-Buteth-10, PPG-12-Buteth-16 or PPG-20-Buteth-30. The investigators noted that the lungs were sites of significant toxicologic activity, induced especially by the larger molecular weight substances (Bushy Run Research Center 1990b).

PPG-33-Buteth-45

In a pilot study, the acute intravenous toxicity of PPG-33-Buteth-45 was evaluated using 20 Sprague-Dawley rats (weights not stated). Thirteen rats served as controls. Each of the experimental rats received a single intravenous dose (1.75 ml/kg) of 60% PPG-33-Buteth-45 in physiological saline. Control rats were dosed with 2.92 ml/kg saline. One rat died on day 3 postinjection; other animals were killed sequentially on days 1, 2, 3, and 14 postinjection. Pulmonary lesions were noted as early as day 1 postinjection and included congestion, hemorrhages, perivascular inflamatory cell infiltrates, and interstitial pneumonia. The severest lung lesions were observed in the five rats that

were killed on day 3 and consisted of moderate or marked hemorrhages and mild to marked inflammatory cell infiltrates. Lesions were less severe in animals that survived to day 14; minimal to mild residual inflammatory lesions included granulomas, interstitial fibrosis, interstitial pneumonia, and perivascular infiltrates (Union Carbide Corporation 1992).

In the definitive study (pilot study summarized above), 53 rats were dosed with 60% PPG-33-Buteth-45 in physiological saline (1.75 ml/kg) and 36 control rats were dosed with physiological saline (2.92 ml/kg) according to the procedures in the preceding study. Seventeen of the 106 rats (experimentals and controls included) that were originally included in the study died between days 3 and 6 postinjection; thus, 89 rats completed the study.

Deaths were attributed to hypoxia caused by pulmonary edema and epithelial cell necrosis. After day 14, the lungs of 30 rats (15 experimentals, 15 controls) were weighed and fixed for microscopic examination, and bronchioalveolar lavage was performed on 45 rats (27 experimentals, 18 controls). The remaining rats (11 experimentals, 3 controls) were perfused, and lungs were collected for electron microscopy. Evidence of damage to the lungs (presence of leukocytes, increased enzyme activity, and protein in pulmonary lavage fluid) of experimental animals was detected as early as day 1 postinjection. Peak leukocyte infiltration and enzyme and protein leakage from cells were noted on days 3 to 4, and only a slight increase in leukocytes was noted on day 14. Microscopic lesions in weighed and lavaged lungs were classified as follows: hemorrhage, perivascular infiltrates, interstitial pneumonia, interstitial fibrosis, emphysema, and pulmonary (alveolar) edema. These lesions were observed on days 1 to 4 and had decreased in severity by day 7. However, lesions were still evident, although sparse, in most of the experimental animals that were killed on day 14. Changes that were identified using electron microscopy included edema and damage to cells of alveolar walls. The kidneys were also identified as a target organ for PPG-33-Buteth-45 induced toxicity. Gross lesions (color change) were observed in five rats. The following lesions were observed at microscopic examination: edema, necrosis, dilation, proteinosis, basophilia, and atrophy of the proximal tubules (Union Carbide Corporation 1992).

Acute Intraperitoneal Toxicity

PPG-12-Buteth-16

The acute intraperitoneal toxicity of undiluted PPG-12-Buteth-16 was evaluated using 15 male albino rats (weights = 90–120 g). An LD_{50} of 2.46 ml/kg (range = 1.79–3.39 ml/kg) was reported (Union Carbide Corporation 1967a).

Acute Inhalation Toxicity

The results of acute inhalation toxicity studies on the PPG Buteths are summarized in Table 7. A wide range was observed for both LC_{50} values and morbidity.

Short-Term Inhalation Toxicity

Studies on the short-term inhalation toxicity of PPG Buteths are summarized in Table 8. Klonne et al. (1993) evaluated the short-term inhalation toxicity of PPG-12-Buteth-16 and PPG-7-Buteth-10 using Fischer 344 rats (8 weeks old, groups of 10 rats per sex). PPG-12-Buteth-16 was tested in two studies and PPG-7-Buteth-10 was tested in one study. In all three studies, mean body weights for males and females were 180 and 120 g, respectively. The results for each PPG Buteth follow.

PPG-12-Buteth-16

In the first study by Klonne et al. (1993), rats were exposed to PPG-12-Buteth-16 at mean chamber aerosol concentrations of 504 ± 44, 982 ± 68, and 2460 ± 104 mg/m^3, respectively. The animals received a total of nine exposures (6 h/day, 5 days/week) over a period of 11 days; no exposures were made on days 6 and 7. Untreated rats (10 males, 10 females) served as negative controls. All of the high dose animals died. All surviving animals were killed on day 12; necropsy was performed on all rats. Hematological determinations also were made. Histopathological evaluations were conducted on control animals and animals of the 982 mg/m^3 exposure group.

The following observations were made for rats of the 2460 mg/m^3 exposure group, all of which died: unkempt and emaciated appearance, ataxia, prostration, and respiratory difficulties. Ocular and nasal irritation were also observed in some of the animals. With the exception of ataxia and prostration, rats exposed to 504 and 982 mg/m^3 had many of the same signs that were observed in the highest dose group. The incidence and severity of these signs decreased with decreasing dose. In all exposure groups, statistically significant decreases ($p < .05$) in absolute body weight and body weight gain were observed; the decrease in body weight gain was concentration-related.

The following concentration-related, statistically significant blood alterations were noted in rats of the 504 and 982 mg/m^3 dose groups: decreased platelet count in females, decreased mean corpuscular hemoglobin in males, decreased total protein in females, increased activities of aspartate aminotransferase, alkaline phosphatase, and alanine aminotransferase in females, decreased glucose in females, and decreased serum calcium in males. An increased leukocyte count ($\approx$23%) was also reported for both sexes of the 504 and 982 mg/m^3 dose groups.

Necropsy findings indicated that many of the absolute and organ/brain weight values in these two dose groups were significantly different from control values, and the same was true for every organ/body weight value. Significantly increased absolute lung weights ($p < .01$) were also noted in both dose groups. Histopathological evaluation was performed only on the respiratory tract of rats of the 504 and 2460 mg/m^3 groups, because the lungs were the only sites of exposure-related histopathological changes that were identified in rats of the 982 mg/m^3 exposure group. The following pulmonary changes were noted in rats of the 2460 mg/m^3 dose group: mild to moderate pulmonary congestion, mild to moderate interstitial pneumonitis,

TABLE 7
Acute inhalation toxicity of PPG Buteths

Test substance	Animals tested	Procedure	Results	References
PPG-12-Buteth-16	6 rats	Exposure to mists from saturated vapors for 1 h	No deaths	Klonne et al. 1987
PPG-12-Buteth-16	6 rats	Exposure to mists from saturated vapors for 2 h	All animals died	Klonne et al. 1987
PPG-12-Buteth-16	Groups of 10 Wistar albino rats (5 males, 5 females per group) (weights = 200–300 g)	Single 4 h exposures up to a mean chamber concentration of 5230 mg/m^3	LC_{50}–males: 4670 mg/m^3; LC_{50}–females: >5230 mg/m^3. Mottled lungs and livers most common necropsy findings	Klonne et al. 1987
PPG-12-Buteth-16 (0.5% *v/v* in saline)	15 male rats (weights = 250–300 g)	Endotracheal administration at dose of 0.1 ml/kg	No overt signs of toxicity. Microscopic changes in lungs moderate in severity	Myers et al. 1990
PPG-7-Buteth-10	Groups of 10 Sprague-Dawley albino rats (5 males, 5 females per group) (weights = 170–236 g [males] and 129–185 g [females])	Single 4-h exposures up to a mean concentration of 4.92 mg/L	Mean LC_{50} (males and females combined) = 4.77 mg/L. Dark red discoloration of lungs in rats that died. No such observations in rats killed at 2 wk postexposure	Bushy Run Research Center 1988
PPG-7-Buteth-10 (1% *v/v* in saline)	15 male rats (weights = 250–300 g)	Endotracheal administration at dose of 0.02 ml/kg	No overt signs of toxicity or gross pathological changes. Microscopic lung changes similar to those in controls	Myers et al. 1990
PPG-20-Buteth-30	6 rats	Exposure to mists from saturated vapors for 1 h	2 deaths	Klonne et al. 1987
PPG-20-Buteth-30	6 rats	Exposure to mists from saturated vapors for 2 h	All animals died	Klonne et al. 1987
PPG-20-Buteth-30	6 rats	Exposure to mists from saturated vapors for 8 h	No deaths	Klonne et al. 1987
PPG-20-Buteth-30	Groups of 10 Wistar albino rats (5 males, 5 females per group) (weights = 200–300 g)	Single 4-h exposures up to a mean chamber concentration of 992 mg/m^3	LC_{50} = 330 mg/m^3 (males and females). Mottled lungs and livers most common necropsy findings	Klonne et al. 1987
PPG-20-Buteth-30 (1% *v/v* in saline)	15 male rats (weights = 250–300 g)	Endotracheal administration at dose of 0.02 ml/kg	5 rats died. Microscopic lung changes, classified as severe, included emphysema and interstitial pneumonitis	Klonne et al. 1987
PPG-33-Buteth-45	6 rats	Exposure to mists from saturated vapors for 1 h	2 deaths	Klonne et al. 1987
PPG-33-Buteth-45	6 rats	Exposure to mists from saturated vapors for 2 h	No deaths	Klonne et al. 1987
PPG-33-Buteth-45	6 rats	Exposure to mists from saturated vapors for 8 h	No deaths	Klonne et al. 1987
PPG-33-Buteth-45	10 Sprague-Dawley rats (weights = 279–387 g)	Exposure to aerosol at concentrations up to 2400 mg/m^3 for 4 h	Mean LC_{50} = 147 mg/m^3. Significant increases in mean lung weight at concentrations of 54, 100, and 200 mg/m^3. Gross pulmonary changes included emphysema and edema	Hoffman et al. 1991
PPG-33-Buteth-45	Groups of 10 Wistar albino rats (5 males, 5 females per group) (weights = 200–300 g)	Single 4-h exposures up to a mean chamber concentration of 940 mg/m^3	LC_{50} = 106 mg/m^3 (males and females). Mottled lungs and livers most common necropsy findings	Klonne et al. 1987

(Continued on next page)

TABLE 7
Acute inhalation toxicity of PPG Buteths *(Continued)*

Test substance	Animals tested	Procedure	Results	References
PPG-33-Buteth-45	Groups of 12 male Hsd/Ola (Wistar derived) albino rats (weights = 180–220 g)	Single exposures (nose only) to a target concentration of 75 mg/m^3 for 2, 4, or 6 h, yielding mean equivalent 4-h concentrations of 36.3, 74.4, and 113.3 mg/m^3, respectively	Toxicologically significant increases in lung weights at 74.4 and 113.3 mg/m^3. Principal lung lesion was perivascular edema	ICI Central Toxicology Laboratory 1992
PPG-33-Buteth-45	Groups of 6 male rats (weights ≈ 250 g)	Single 4-h exposures (nose only) at mean concentrations of 50, 84, 111, and 185 mg/m^3	50 mg/m^3(no deaths); 84 mg/m^3 (1 of 6 died); 111 mg/m^3 (4 of 6 died); and 185 mg/m^3 (all rats died)	E.I. DuPont De Nemours & Company 1984
PPG-33-Buteth-45 (reduced)	Groups of 10 Sprague-Dawley albino rats (5 males and 5 females per group) (weights = 200–250 g)	Single 4-h exposures at mean chamber concentrations up to 0.74 mg/L	Mean LC_{50} = 0.14 mg/L (males) and 0.16 mg/L (females). Red discoloration of the lungs in all rats that died. No gross lesions at lowest test concentration (0.08 mg/L)	Bushy Run Research Center 1990a
PPG-33-Buteth-45 (1% *v/v* in saline)	15 male rats (weights = 250–300 g)	Endotracheal administration at dose of 0.02 ml/g	7 rats died. Signs of toxicity included lethargy and labored breathing. Bronchopneumonia and interstitial pneumonitis noted at microscopic examination	Myers et al. 1990
PPG-33-Buteth-45	10 male CD-1, COBS Swiss albino mice (weights = 26–33 g)	Exposure to aerosol at concentrations up to 2400 mg/m^3 for 4 h	Mean LC_{50} = 174 mg/m^3. Significant increases in mean lung weight at concentrations of 54 and 200 mg/m^3. Gross pulmonary changes included emphysema and edema.	Hoffman et al. 1991
PPG-33-Buteth-45	10 male Golden Syrian hamsters (weights = 77–110 g)	Exposure to aerosol at concentrations up to 2400 mg/m^3 for 4 h	Mean LC_{50} = 511 mg/m^3. Significant increases in mean lung weight at concentrations of 140, 320, 940, and 2400 mg/m^3. Gross pulmonary changes included emphysema and edema	Hoffman et al. 1991
PPG-33-Buteth-35	10 male Hartley albino guinea pigs (weights = 355–507 g)	Exposure to aerosol at concentrations up to 2400 mg/m^3 for 4 h	Mean LC_{50} = 293 mg/m^3. Significant increase in lung weight at a concentration of 940 mg/m^3. Gross pulmonary changes included emphysema and edema	Hoffman et al. 1991
PPG-33-Buteth-45	2 male beagle dogs (weights = 10.1 and 11.5 kg)	Exposure to aerosol at mean gravimetric concentrations up to 3200 mg/m^3 for 4 h	No deaths. Gross pulmonary changes included emphysema and edema	Hoffman et al. 1991

and small foci of hemorrhage (females only), with a lesser incidence of bronchioalveolar cell hyperplasia, macrophage infiltration into alveoli (alveolar histiocytosis) and around blood vessels, and bronchopneumonia. The incidence of several of these histopathological changes was actually greater in rats of the 982 mg/m^3 dose group. Minimal to mild alveolar histiocytosis, interstitial pneumonitis, and bronchioalveolar cell hyperplasia were the principal microscopic lesions in rats of the 504 mg/m^3 dose group.

In the second study by Klonne et al. (1993), four groups of Fischer-344 rats were exposed to PPG-12-Buteth-16 at mean chamber aerosol concentrations of 5 ± 0.05, 51 ± 2, 98 ± 3, and 492 ± 23 mg/m^3, respectively, according to the procedures outlined in the preceding paragraph. The incorporation of a 6-week

TABLE 8
Short-term inhalation toxicity of PPG Buteths

Test substance	Animals tested	Procedure	Results	References
PPG-12-Buteth-16	20 rats (10 males, 10 females)	9-Day inhalation toxicity test. Exposure to aerosol at concentrations up to 2500 mg/m^3	Main pulmonary lesions in rats exposed to 2500 mg/m^3 included congestion, hemorrhage, edema, interstitial pneumonitis, and intraalveolar cellular debris. Pulmonary hemorrhage and inflammation only at lower concentrations (500 and 1000 mg/m^3)	Bushy Run Research Center 1989
PPG-12-Buteth-16	Groups of 20 Fischer 344 rats (10 males, 10 females per group). Mean weights = 180 g (males) and 120 g (females)	9-Day inhalation toxicity test. Exposure to mean chamber aerosol concentrations up to 2460 mg/m^3	All of the 20 rats exposed to 2460 mg/m^3 died. Interstitial pneumonitis and bronchioalveolar cell hyperplasia observed in all three exposure groups (504, 982, and 2460 mg/m^3)	Klonne et al. 1993
PPG-12-Buteth-16	Groups of 20 Fischer 344 rats (10 males, 10 females per group). Mean weights = 180 g (males) and 120 g (females)	9-Day inhalation toxicity test. Exposure to mean chamber aerosol concentrations up to 492 mg/m^3	No mortalities. Minimal to moderate intraalveolar cellular debris and interstitial pneumonitis in the 492 mg/m^3 exposure group. Increased incidence of alveolar histiocytosis in male rats exposed to $\geq$52 mg/m^3. All lesions had cleared by end of 6-wk recovery period	Klonne et al. 1993
PPG-7-Buteth-10	Groups of 20 Fischer 344 rats (10 males, 10 females per group). Mean weights = 180 g (males) and 120 g (females)	9-Day inhalation toxicity test. Exposure to mean chamber aerosol concentrations of up to 512 mg/m^3	No exposure-related deaths in any of the groups (5, 52, and 512 mg/m^3). No exposure-related alterations (microscopic lesions)	Klonne et al. 1993
PPG-20-Buteth-30	10 male Sprague-Dawley albino rats (5 wk old)	10-Day inhalation toxicity test. Exposure to chamber aerosol concentration of 100 mg/m^3	6 rats died after three exposures. Alveolar lesions consisted of hyperemia, intra-alveolar edema, and hemorrhage. Laryngeal hyperplasia in three rats	Ulrich et al. 1977
PPG-33-Buteth-45 (positive control in preceding study)	10 male Sprague-Dawley albino rats (5 wk old)	10-Day inhalation toxicity test. Exposure to chamber aerosol concentration of 55 mg/m^3	9 rats died after three exposures. Alveolar lesions consisted of hyperemia, intra-alveolar edema, and hemorrhage. Laryngeal hyperplasia in 2 rats	Ulrich et al. 1977
PPG-33-Buteth-45	Groups of 40 and 20 Fischer 344 rats (7 wk old; males and females)	9-Day inhalation toxicity test. Exposure to mean chamber concentrations up to 49.5 mg/m^3	Irregular red foci in lungs of males and females noted in group (20 rats) exposed to 25 mg/m^3 and in group (40 rats) exposed to 49.5 mg/m^3. Irregular red foci in lungs of males in group (20 rats) exposed to 4.8 mg/m^3. Foci also in rats killed after 2-wk recovery period	Klonne et al. 1987

recovery period was the only modification of this procedure. Untreated rats served as negative controls.

No deaths occurred throughout the duration of the study. Clinical signs were noted in rats of the 492 mg/m^3 dose group, and included rapid respiration, staining of the urogenital area, perinasal encrustation, and swollen periocular tissue. Exposure-related ophthalmic lesions were not observed. Decreases in absolute body weight and body weight gain were noted in male and female rats of the 492 mg/m^3 dose group. However, body weights returned to normal during the 6-week recovery period. Slight decreases in body weight gain were reported for female rats of the 98 mg/m^3 dose group.

The changes in hematological parameters were consistent with those noted in the preceding study. Most of the hematological changes were observed in rats of the 492 mg/m^3 dose group. In male rats of the 51, 98, and 492 mg/m^3 dose groups and

female rats of the 98 and 492 mg/m^3 dose groups, concentration-related increases in absolute and/or relative (both to body and brain weight) lung weight were noted. An increase in absolute and/or relative kidney weights was also noted in female rats of the 98 and 492 mg/m^3 exposure groups. At microscopic examination, lesions were observed only in the lungs. Minimal to moderate intra-alveolar cellular debris and interstitial pneumonia were observed in animals of the 492 mg/m^3 exposure group. An increased incidence of alveolar histiocytosis was observed in male rats exposed to 51 mg/m^3 or higher concentrations. Exposure-related microscopic lesions were not observed in male or female rats at the end of the 6-week recovery period.

PPG-7-Buteth-10

In a third study by Klonne et al. (1993), three groups of Fischer-344 rats were exposed to PPG-7-Buteth-10 at mean chamber aerosol concentrations of 5 ± 0.4, 52 ± 2, and 512 ± 13 mg/m^3, respectively, according to the procedures outlined in the preceding section on PPG-12-Buteth-16. Untreated rats served as negative controls. No deaths that were related to test substance exposure occurred in any of the three experimental groups. Clinical signs observed in rats of the 512 mg/m^3 exposure group included perinasal encrustation and urogenital wetness. The incidence of these changes in the 52 mg/m^3 exposure group was only slightly greater than that in the control group. Clinical signs of toxicity were not evident in the 5 mg/m^3 exposure group. Statistically significant decreases in absolute body weight were noted in the 512 mg/m^3 exposure group; however, values returned to normal during the recovery period. In the 52 mg/m^3 exposure group, a decrease in body weight was noted in female rats only on the last day of exposure. No effect on body weight was observed in the 5 mg/m^3 dose group. In the 52 and 512 mg/m^3 dose groups, both sexes had a statistically significant decrease in body weight gain ($p < .05$); the decreases were concentration related. A transient decrease in body weight gain was noted for rats in the 5 mg/m^3 dose group. At ophthalmic examination, none of the findings was considered compound-related. The following statistically significant changes in hematological parameters were reported for rats of the 512 mg/m^3 dose group: increased red blood cells, increased hemoglobin concentration, and decreased mean corpuscular volume. However, the biological significance of these changes was unclear. At necropsy, crusted and/or swollen periocular/perinasal tissue was observed in some of the rats of the 512 mg/m^3 dose group. Statistically significant increases in absolute kidney weights were also noted in this group (males and females); however, values were similar to those of controls at the end of the recovery period. Compound-related changes in organ weights were not observed at lower concentrations. No histopathological changes related to the compound were observed in any of the experimental groups. In particular, no lesions were found in the lungs and kidneys.

PPG-20-Buteth-30 and PPG-33-Buteth-45

Ulrich et al. (1977) evaluated the inhalation toxicity of PPG-20-Buteth-30 and PPG-33-Buteth-45 in rats. Ten male Sprague-Dawley albino rats (5 weeks old) were exposed to PPG-20-Buteth-30 aerosol over a period of two weeks (10 exposures, 6 h/day) at a chamber concentration of 100 mg/m^3. The positive control group (10 rats) was exposed to PPG-33-Buteth-45 at a chamber concentration of 55 mg/m^3 according to the same procedure, and the negative-control group (10 rats) was exposed to air. At the end of the 2-week period, five rats from each group were to have been killed. The remaining five per group were to have been killed at the end of a 2-week postexposure recovery period.

Six rats exposed to PPG-20-Buteth-30 and nine rats exposed to PPG-33-Buteth-45 (positive control) died after a total of three exposures; deaths occurred on days 3 to 5 of the study. Due to the number of deaths, the survivors were killed after the first week of exposure. The following signs of toxicity were observed in some of the rats during exposure to PPG-20-Buteth-30 aerosol: lethargy, soft stool, and prolapsed penis. Compared to negative controls, a statistically significant depression ($p < .05$) in body weight was noted in surviving animals from the experimental group after 5 and 6 days of exposure. Compound-related pulmonary lesions were observed in experimental and positive-control groups. The changes consisted of moderate to severe multifocal to generalized areas of alveolar inflammation (alveolitis), and involved terminal airways. The bronchi and bronchioles were essentially unaffected. Specifically, the alveolar lesions consisted of the following changes: hyperemia; intra-alveolar edema; hemorrhage; intraalveolar inflammatory cellular exudate (mostly alveolar macrophages and neutrophils); some areas of intense type II pneumocyte hyperplasia; some foci of early alveolar organization of exudates; and thickened, hypercellular alveolar interstices. Although pulmonary fibrosis was not observed, the organization of alveolar exudate and interstitial thickening were compatible with prefibrotic changes. Laryngeal epithelial hyperplasia was observed in two positive-control rats and three exposed rats.

PPG-33-Buteth-45

Klonne et al. (1987) evaluated the short-term inhalation toxicity of PPG-33-Buteth-45 using four groups of Fischer 344 rats (≈7 weeks old). Twenty rats per sex were assigned to control and high-dose (49.5 ± 1.6 mg/m^3, mean chamber atmosphere concentration) groups and 10 rats per sex were assigned to the low- (4.8 ± 0.6 mg/m^3) and intermediate- (25.5 ± 2.5 mg/m^3) dose groups. The rats were exposed 6 hours per day over a period of 11 days; exposures did not exceed 5 days per week. Each animal was subjected to nine exposures, and no exposures occurred on days 5 and 6. In each group, 10 rats per sex were killed on the morning after the ninth exposure. The remaining 10 rats per sex in control and high concentration groups were killed after a 2-week recovery period.

Clinical signs noted only in the high-dose group included unkempt appearance, nasal discharge, and urogenital wetness (females only). Statistically significant differences in body weight gain were observed only in high ($p < .01$) and intermediate ($p < .05$) dose groups. The results of hematological evaluations indicated statistically significant decreases in the serum concentrations of total protein, albumin, and globulin in females of the high dose group. An increase in alanine aminotransferase activity was also observed in intermediate- and high-dose groups. An increase in the number of white blood cells (neutrophils and eosinophils) was also observed for high-dose female rats. Compound related differences in the serum chemistries or hematological parameters were not observed after the recovery period. Biologically significant changes in serum chemistry or hematological parameters were not observed in male rats of the high dose group. Compound-related effects on the urinalysis parameters were not observed in any of the test groups. At necropsy, compound-related macroscopic lesions (irregular red foci) were noted only in the lungs. These lesions were reported for male and female rats in intermediate- and high-dose groups and only in males from the low-dose group. Lesions were noted primarily in the pulmonary capillaries and the epithelial cells of the alveoli, and were characterized by congestion and areas of hemorrhage, with mild to moderate necrosis and exfoliation of cells lining the alveoli and an increased number of macrophages phagocytizing debris within the alveolar spaces. Pulmonary foci were also observed in rats that were killed after the recovery period. The severity of the pulmonary lesions was considerably less in animals from the high-dose group, when compared to animals in this group that were killed on the morning after the ninth exposure (Klonne et al. 1987).

A series of inhalation toxicity studies was conducted by the Bushy Run Research Center (1989). In the first study, groups (males and females) were exposed to PPG-12-Buteth-16 aerosol concentrations of 500, 1000, and 2500 mg/m^3, respectively. The second study involved the exposure of groups of male and female rats to PPG-33-Buteth-45 at aerosol concentrations of 5, 25, and 50 mg/m^3, respectively. In the third study, two groups of 10 male rats were exposed to PPG-33-Buteth-45 at aerosol concentrations of 1.0 and 5.0 mg/m^3, respectively. In the second and third studies, controls and rats from the highest exposure group were evaluated after a 2-week recovery period. The results of microscopic examination of groups of 20 rats (10 males, 10 females/group) exposed to PPG-12-Buteth-16 or PPG-33-Buteth-45 in three short-term (9 days) inhalation toxicity studies were compared; untreated rats served as negative controls. The strain and weight range of the animals tested were not stated.

PPG-12-Buteth-16

In rats exposed to 2500 mg/m^3 PPG-12-Buteth-16 (all of which died), the principal pulmonary lesions were: congestion, hemorrhage, pulmonary edema, interstitial pneumonia, and intra-alveolar cellular debris. Neither congestion nor pulmonary edema was observed in rats of the 500 and 1000 mg/m^3 groups that survived exposure; however, hemorrhage and inflammation were noted. Inflammatory lesions included alveolar histiocytosis, perivascular infiltrates, and intraalveolar cellular debris. A concentration-related effect on frequency and/or the severity of most lesions was observed between the 500 and 1000 mg/m^3 dose groups.

PPG-33-Buteth-45

Compared to rats exposed to PPG-12-Buteth-16, the lesions that resulted from exposure to PPG-33-Buteth-45 were similar, but less severe. No deaths occurred in any of the groups exposed to PPG-33-Buteth-45. In most animals, lesions were minimal to mild and the frequency of lesions was related more to compound concentration than the severity of the lesions. The most consistent lesions in rats exposed to PPG-33-Buteth-45 were hemorrhage and intraalveolar cellular debris of minimal to moderate severity and alveolar histiocytosis of minimal to mild severity. Inflammatory infiltrates, particularly perivascular infiltrates and interstitial pneumonia, were less prominent in rats exposed to PPG-33-Buteth-45 than in rats exposed to PPG-12-Buteth-16. Specifically, a maximum of four to seven affected rats per group (interstitial pneumonia and perivascular infiltrates, respectively) was observed in rats exposed to PPG-33-Buteth-45 that were killed on day 9, compared to up to 10 per group (both lesions) for rats exposed to PPG-12-Buteth-16.

The investigators concluded that in the preceding three studies, PPG-12-Buteth-16 and PPG-33-Buteth-45 produced similar pulmonary lesions. It was also concluded that the greater severity of lesions and the greaterer mortality produced by PPG-12-Buteth-16 could have been due to the greater exposure concentrations rather than to an innate greater toxicity of the chemical (Bushy Run Research Center 1989).

Subchronic Inhalation Toxicity

PPG-33-Buteth-45

Klonne et al. (1988) evaluated the subchronic inhalation toxicity of PPG-33-Buteth-45 using Fischer-344 rats (8 weeks old). Male and female rats had mean body weights of 174 and 122 g, respectively. Three groups of rats (20/sex/group) were exposed to PPG-33-Buteth-45 aerosol at mean chamber concentrations of 0.30 ± 0.039, 1.1 ± 0.13, and 5.2 ± 0.26 mg/m^3, respectively, 6 hours per day (5 days/week) for 13 weeks. Exposure concentrations were determined at the conclusion of a 2-week range-finding study. The control group was exposed only to filtered air. During week 14, 10 rats/sex/group were killed after at least 2 days of exposure. The remaining animals (10 rats/sex/group) were killed after a 5-week recovery period.

Statistically significant decreases in body weight gain were observed only in male rats of the 5.2 mg/m^3 exposure group. No exposure-related clinical signs, ophthalmic changes, or deaths were observed during the study. At the end of exposure, a

statistically significant increase in the neutrophil count was noted in females of the 1.1 mg/m^3 exposure group and in males of the 5.2 mg/m^3 exposure group. Biologically significant alterations in the hematological profile or in the serum or urine chemistries were not observed at any time during the study. The lungs were the only organs with toxicologically significant organ weight changes and toxicologically significant macroscopic lesions. Female rats of the 1.1 mg/m^3 exposure group and rats of both sexes in the 5.2 mg/m^3 exposure group had statistically significant increases ($p < .01$) in absolute and relative (as a percentage of both body weight and brain weight) lung weights. A significant increase ($p < .05$) in the lung/body weight ratio was also noted in male rats. All absolute and relative lung weights for males and females of the 5.2 mg/m^3 group remained significantly increased at the end of the 5-week recovery period. Values for absolute lung weight and lung/body weight also remained significantly increased in males of the 1.1 mg/m^3 exposure group that were killed at the end of the recovery period; no similar effect was observed in female rats. Statistically significant differences in absolute or relative lung weights were not observed in the 0.3 mg/m^3 exposure group. However, a concentration-related increase in absolute and relative lung weights was noted across all exposure groups at the end of exposure. In all exposure groups, macroscopic lesions were gray or tan foci that were scattered across the lung surface. This was true for animals that were killed at the end of exposure or after the recovery period. Multifocal petechial hemorrhages were observed mainly in rats that were exposed to 5.2 mg/m^3 and killed at the end of exposure. Microscopic lesions were also observed only in the lungs and the occurrence of these lesions was concentration-related. The microscopic lesions consisted of hemorrhages and interstitial pneumonia (only in the 1.1 and 5.2 mg/m^3 groups), alveolar histiocytosis, and focal or multifocal fibrosis; the lesions were minimal to marked in severity.

Ocular Irritation

PPG-12-Buteth-16

PPG-12-Buteth-16 was not an ocular irritant in rabbits (number not stated). The test substance (0.1 ml) was instilled into the conjunctival sac of each animal (Klonne et al. 1987).

PPG-20-Buteth-30 and PPG-33-Buteth-45

The ocular irritation potential of PPG-20-Buteth-30 and PPG-33-Buteth-45 in rabbits (number and strain not stated) was evaluated in two studies, respectively. In each study, the test substance (0.1 ml) was instilled into the conjunctival sac of each animal. PPG-20-Buteth-30 and PPG-33-Buteth-45 were not ocular irritants in rabbits (Klonne et al. 1987).

PPG-24-Buteth-27

The ocular irritation potential of undiluted PPG-24-Buteth-27 was evaluated using six New Zealand white rabbits. The test substance (0.1 ml) was instilled into the conjunctival sac of one eye of each rabbit. Ocular reactions were scored at 1 and 4 hours and days 1, 2, 3, and 7 postinstillation. Corneal injury (opacity) was not observed in any of the rabbits. Iritis was observed in four rabbits, and six rabbits had minor to moderate conjunctival irritation. All reactions had cleared by 2 days postinstillation (Bushy Run Research Center 1986).

PPG-26-Buteth-26

The ocular irritation potential of undiluted PPG-26-Buteth-26 was evaluated using six New Zealand albino rabbits. The test substance was warmed to approximately 30°C and then instilled (0.1 ml) into the conjunctival sac of one eye per animal. The lids were held together for approximately 1 second and then released. Contralateral eyes (untreated) served as controls. The eyes were evaluated for irritation reactions at 24, 48, and 72 hours and on days 4 and 7 postinstillation using the Draize scale: (0 to 110). Ocular irritation was not observed in any of the animals tested, and PPG-26-Buteth-26 was considered a nonirritant (Stillmeadow Inc. 1977).

The ocular irritation potential of a solubilizing system containing PPG-26-Buteth-26 (as supplied) was evaluated using three New Zealand white rabbits (weights = 2.72–3.08 kg). The concentration of PPG-26-Buteth-26 in this system was not stated. The test material (0.1 ml) was instilled into the right eye of each animal; the upper and lower eyelids were held together for approximately 1 second after instillation. Untreated eyes served as controls.

Ocular reactions were scored at 1, 24, 48, and 72 hours postinstillation. At 1 hour postinstillation, iridial inflammation and a dulling of the normal luster of the cornea were confined to the eye of one animal. These represented the only adverse corneal or iridial effects that were observed in the study. Moderate conjunctival irritation was observed in the eyes all animals; reactions had cleared by day 7 postinstillation. The solubilizing system was classified as a mild ocular irritant (score = 4; scale of 1 to 8) (Safepharm Laboratories, Ltd. 1987b).

Skin Irritation

The skin irritation potential of PPG-12-Buteth-16, PPG-20-Buteth-30, and PPG-33-Buteth-45 was evaluated using rabbits (number, weights, and strain not stated). In each of the three experiments, the test substance (0.5 ml) was applied to the under belly of each rabbit, after which the test site was covered with an impermeable wrap for 4 hour. PPG-12-Buteth-16 caused capillary injection in rabbits, whereas PPG-20-Buteth-30 and PPG-33-Buteth-45 did not (Klonne et al. 1987).

PPG-24-Buteth-27

The skin irritation potential of undiluted PPG-24-Buteth-27 was evaluated using six New Zealand white rabbits. The test substance was applied (0.5 ml) to clipped, intact skin for 4 hours; excess test substance was then removed. Sites were covered

with a gauze patch and impervious sheeting during the 4-hour contact period. At 1 hour and on days 2, 3, and 7, skin reactions were scored according to the Draize scale: 0 (no erythema) to 4 (severe erythema to slight eschar formation) and 0 (no edema) to 4 (severe erythema, raised more than 1 mm and extending beyond the area of exposure). Slight erythema was noted in three rabbits, and four rabbits had moderate edema. Reactions were not observed after 2 days (Bushy Run Research Center 1986).

PPG-26-Buteth-26

The skin irritation potential of undiluted PPG-26-Buteth-26 was evaluated using three male and three female New Zealand albino rabbits. The test substance was warmed to approximately 30°C and applied (0.5 ml, under surgical gauze) to sites on the back (one abraded, one intact) that had been clipped free of hair. The two test sites per animal were to the right and left of the spinal column, respectively. The surgical gauze was secured with an adhesive tape and the entire trunk of each animal was wrapped with an impervious material. The coverings were removed at the end of the 24-hour contact period. Reactions were scored at 24 and 72 hours postapplication according to the following scales: 0 (no erythema) to 4 (severe erythema to slight eschar formation) and 0 (no edema) to 4 (severe edema, raised more than 1 mm and extending beyond the area of exposure). Sites were also observed for the presence of either ulceration or necrosis. Because of the possibility of percutaneous absorption, the rabbits were observed for any generalized signs of pharmacological or toxicological effects. Mean scores for erythema (24- and 72-hour readings) at intact and abraded sites (total of four scores) and mean scores for edema formation (24- and 72-hour readings) at intact and abraded sites (total of four scores) were calculated. The sum of the eight mean scores was divided by 4 to yield a dermal irritation score of 3.12 (maximum = 8) for PPG-26-Buteth-26. It was concluded that PPG-26-Buteth-26 induced very slight to slight dermal irritation. Neither pharmacological nor toxicological effects were observed during the study. Ulceration or necrosis were not observed at any of the test sites (Stillmeadow Inc. 1977).

The skin irritation potential of a solubilizing system containing PPG-26-Buteth-26 (as supplied) was evaluated using three New Zealand white rabbits (weights = 2.57–2.79 kg). The concentration of PPG-26-Buteth-26 in this system was not stated. The test substance (0.5 ml) was applied to dorsal/flank skin that had been clipped free of hair. The test site of each animal was covered with a gauze patch secured with surgical adhesive tape for 4 hours; the trunk was also wrapped with an elasticated corset. At 4 hours postapplication, patches and any residual test material were removed. Reactions were scored 1 hour after patch removal and 24, 48, and 72 hours later according to the following scales: 0 (no erythema) to 4 (severe erythema to slight eschar formation); 0 (no edema) to 4 (severe edema, raised more than 1 mm and extending beyond the area of exposure). At 1 hour postremoval, very slight erythema, with or without very slight edema, was observed at all test sites. Very slight erythema was also noted in two rabbits at the 24-hour observation. Desquamation was observed in two rabbits at the 24- and 72-hour observations. The solubilizing system was classified as a mild skin irritant (primary irritation index = 0.3) (Safepharm Laboratories Ltd. 1987c).

Carcinogenicity

PPG-7-Buteth-10

Undiluted PPG-7-Buteth-10 was painted on clipped skin of the backs of 40 or more (exact number not stated) C3H/HeJ mice (weights not stated) three times per week until death. The time intervals between the initiation of application and death were not stated. Negative-control mice were painted with acetone and positive-control mice were painted with 0.2% methyl cholanthrene according to the same procedure. The test substance produced neither papillomas nor carcinomas in experimental animals, and the same was true for acetone in the negative-control group. Neoplasms were observed in all positive-control mice (Smyth et al. 1970).

PPG-33-Buteth-45

No neoplasms were produced after undiluted PPG-33-Buteth-45 was painted on the skin of mice (same strain as above) (Smyth et al. 1970).

PPG-24-Buteth-27

The tumorigenicity and tumor promotion activity of PPG-24-Buteth-27 were evaluated (Union Carbide Corporation 1967a) using groups of 35 to 40 CAF_1 mice (7 to 8 weeks old). PPG-24-Buteth-27 (70% in acetone) was painted onto dorsal skin of each mouse five days per week for life. The test sites were clipped free of hair prior to skin painting. PPG-24-Buteth-27 (70% in acetone) alone neither induced papillomas nor carcinomas in any of the 35 mice tested. In additional groups, skin paintings were done after preparation of the dorsal skin for tumor promotion by initiator treatment with dimethylbenzanthracene (DMBA). In these experiments, an increased incidence of carcinomas was noted when two initiator doses of DMBA preceded skin paintings with 70% PPG-24-Buteth-27.

In another experiment, an increased incidence of papillomas (and, perhaps, carcinomas) was noted when skin painting with PPG-24-Buteth-27 was preceded by only one initiator dose. The results of skin paintings with 5% PPG-24-Buteth-27 following dimethylbenzanthracene (DMBA) initiation were negative. The investigators concluded that PPG-24-Buteth -27 was neither a tumorigen nor a carcinogen, but did act as a tumor promoter (Union Carbide Corporation 1967b).

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation and Sensitization

PPG-26-Buteth-26

The skin irritation and sensitization potential of a test aftershave lotion containing 2.5% PPG-26-Buteth-26 was evaluated in a 21-day use test involving 54 male subjects (18–68 years old) with no history of allergic reactions to soaps, sunscreens, moisturizers, shaving products or aftershaves. All subjects shaved at least five times per week and were habitual users of aftershave. None of the subjects had participated in a use test for at least 1 week prior to this study, or had been treated with antihistamines or corticosteroids within one week of study initiation. On day 0 (baseline) of the use test, subjects were prescreened using a semiocclusive patch test (≤24 hours application period) of the aftershave lotion; results were negative. The patch test was conducted in order to rule out empaneling any subject who had an individual idiosyncratic reaction to the aftershave lotion. Upon completion of the semiocclusive patch test (prescreen), each subject was instructed to use the test aftershave lotion at least once daily. Subjects were also instructed to continue their normal cleansing regimen; no new toiletries were to be used. Reactions were scored by a dermatologist on days 0 (baseline), 7, 14, and 21 according to the following scale: 0 (reactions within normal limits) to 3 (severe erythema/edema). Subjective irritation was graded according to the scale: 0 (within normal limits) to 3 (severe). Fifty-two of the original 54 subjects completed the study. Transient redness of the facial area (mild, very slight; score = 1) was observed in 15 subjects. Reactions persisted through day 21 in 10 of the 15 subjects. Subjective irritation was not noted for any of the subjects tested. Additionally, all 52 subjects had a score of 0 (within normal limits) for edema. It was concluded that no significant dermal facial irritation or sensitization was elicited by the test aftershave lotion in the use test (Harrison Research Laboratories, Inc. 1995).

The Education and Research Foundation, Inc. (1995) evaluated the skin irritation potential of an aftershave lotion containing 2.5% PPG-26-Buteth-26 in another 21-day use test involving 54 male subjects (18–69 years old). These subjects were described as daily shavers, and generally shaved at least five times per week. Subjects with skin disorders or allergies that could have interfered with the evaluation of study results, and subjects with any existing skin irritation or history of skin irritation were excluded from the study. Study participants were asked to identify the cosmetic and toiletry products (including soap) normally used, and were instructed not to change brands during the course of the study. On day 1 of the study, each subject was screened by a dermatologist to confirm that the skin and upper body areas were free of skin irritation. After shaving on day 1 and throughout the remainder of the 21-day test, the aftershave lotion was applied to shaved skin. The face was dried prior to product application. Subjects visited the testing facility on Tuesday of each week for facial and upper body examinations, conducted by a dermatologist. Reactions (erythema, scaling, and edema) were evaluated according to the following scale: 0 (no reaction) to 3 (severe reaction). Any visual signs of irritancy or subjective comments relating to adverse effects (i.e., itching, burning, stinging, etc.) were reported. Itching and irritation reactions, as described by the subjects tested, were scored according to the same grading scale. Subjects were also instructed to report any delayed reactions. Three subjects reported irritation and/or itching. One of the three had a score of 1 (slight) for erythema, and another had a score of 1 for scaling. Scaling (score = 1) was also observed in an additional subject who did not report irritation and/or itching. Finally, another subject experienced congestion after use of the lotion; no other reactions were reported. It was concluded that the aftershave lotion did not cause skin irritation, was well tolerated, and is safe for human use (Education & Research Foundation, Inc. 1995).

SUMMARY

The PPG Buteths are polyoxypropylene, polyoxyethylene ethers of butyl alcohol. They are butanol-initiated, random linear copolymers that are produced from equal amounts (by weight) of ethylene and propylene oxide.

The following PPG Buteths were reported as being used in cosmetics in 1997: PPG-12-Buteth-16 (53 products), PPG-9-Buteth-12 (2 products), PPG-26-Buteth-26 (13 products), and PPG-28-Buteth-35 (10 products). Data submitted to the CTFA in 1995 indicated the following maximum use concentrations for PPG-12-Buteth-16, the PPG Buteth that is most frequently used in cosmetics: 22% (hairdressings); 2% (self-tanners); 1% (hair styling lotion); and 0.1 to 1% (astringent). PPG-28-Buteth-35 was used at concentrations up to 1% in shampoos.

In rats dosed orally with ^{14}C-PPG-7-Buteth-10, most of the administered radioactivity was excreted (urine, feces, and expired CO_2) within 7 days postdosing. Similar observations were reported for rats dosed orally with ^{14}C-PPG-33-Buteth-45; however, radioactivity was not detected in expired CO_2.

Acute inhalation LC_{50} values for PPG Buteths that have been reported for rats are as follows: 4670 and >5230 mg/m^3 for males and females, respectively (PPG-12-Buteth-16); 4.77 mg/L (males and females) for PPG-7-Buteth-10; 330 mg/m^3 (males and females) for PPG-20-Buteth-30; and 147 mg/m^3 for PPG-33-Buteth-45. LC_{50} values of 174 mg/m^3 (mice); 511 mg/m^3 (hamsters); and 293 mg/m^3 (guinea pigs) have also been reported for PPG-33-Buteth-45 in other acute inhalation toxicity studies.

In short-term (9-day) inhalation toxicity studies using rats, pulmonary lesions were observed at exposure concentrations of PPG-12-Buteth-16 ranging from 492 to 2500 mg/m^3. Pulmonary lesions were also noted in rats exposed to PPG-20-Buteth-30 (100 mg/m^3) and PPG-33-Buteth-45 (55 mg/m^3) for 10 days and in rats exposed to PPG-33-Buteth-45 at concentrations ranging from 4.8 to 50 mg/m^3 for 9 days. No exposure-related microscopic lesions were found in rats exposed for 9 days to PPG-7-Buteth-10 at concentrations ranging from 5 to 512 mg/m^3.

In a subchronic inhalation toxicity study, microscopic lesions were observed in the lungs of rats exposed to PPG-33-Buteth-45 at concentrations of 0.3, 1.1, and 5.2 mg/m^3 for 13 weeks. The lesions consisted of hemorrhage and interstitial pneumonia (only in 1.1 and 5.2 mg/m^3 groups), alveolar histiocytosis, and focal or multifocal fibrosis.

An LD_{50} of 18.3 g/kg for PPG-12-Buteth-16 was reported in an acute oral toxicity study involving rats. Acute oral LD_{50} values ranging from 4.49 to 8.57 ml/kg have been reported for PPG-7-Buteth-10 in acute oral toxicity studies involving rats. Oral LD_{50} values of 7.46 ml/kg (mice) and 1.77 ml/kg (rabbits) for PPG-7-Buteth-10 also have been reported.

The oral LD_{50} for PPG-20-Buteth-30 in rats was 20.6 g/kg, and >16 ml/kg in rats dosed with PPG-24-Buteth-27. An oral LD_{50} of >5.01 g/kg (4.72 ml/kg) was reported for PPG-26-Buteth-26 in Long Evans rats. Similar results were reported for Sprague-Dawley rats dosed with a solubilizing system containing PPG-26-Buteth-26 (concentration not stated); the LD_{50} was greater than 5.0 g/kg (4.81 ml/kg).

In acute oral toxicity studies on PPG-33-Buteth-45 using rats and mice, LD_{50} values of 45.2 ml/kg and 49.4 ml/kg, respectively, were reported. In studies using rabbits, an LD_{50} of 15.8 ml/kg was reported for PPG-33-Buteth-45.

The subchronic (3 months) oral toxicity of PPG-24-Buteth-27 in rats was evaluated at concentrations of 0.01% to 1.25% in the diet. Acute pneumonia was the primary cause of death in one of the two rats (highest exposure group) that died. Lesions were observed in the livers and kidneys of rats from the 0.05%, 0.25%, or 1.25% treatment groups. The changes observed in the 0.05% treatment group were regarded as transitory, and tissues from rats in the 0.01% group differed little from those of the control group.

Hepatic and renal lesions were also observed in another subchronic study (90 days) in which groups of rats were fed PPG-33-Buteth-45 at dietary doses of 0.7 and 4.0 g/kg/day for 90 days. These lesions were not observed in rats fed lower doses (0.03 or 0.15 g/kg/day).

In a chronic feeding study involving rats, no statistically significant differences were found in the incidence of neoplasms and other lesions (20 tissues) between rats fed PPG-7-Buteth-10 (0.004, 0.02, 0.1, and 0.5 g/kg/day) and control groups. Similar results were reported for PPG-33-Buteth-45, following administration to groups of rats at dietary concentrations of 0.02, 0.1, and 0.5 g/kg/day, respectively.

In a chronic feeding study involving dogs, no statistical differences in the incidence of gross or microscopic lesions (18 tissues) between groups of animals fed PPG-7-Buteth-10 (0.004, 0.02, 0.1, and 0.5 g/kg/day) and control groups were observed. Similar results were reported for PPG-33-Buteth-45, following administration to groups of dogs at dietary doses of 0.023, 0.11, and 0.61 g/kg/day.

Mortality rates for rabbits dosed with PPG Buteths (dose = 21 g/kg) in acute dermal toxicity studies are summarized as follows: one of four rabbits (PPG-12-Buteth-16); one of four rabbits (PPG-20-Buteth-30); and one of four rabbits (PPG-33-Buteth-45). In another acute dermal toxicity study, no deaths occurred in groups of rabbits dosed with PPG-24-Buteth-27 (2, 4, 8, and 16 ml/kg). Erythema, edema, ecchymosis, and desquamation were noted in this study. Pulmonary lesions were noted at necropsy. In New Zealand albino rabbits dosed with PPG-26-Buteth-26, the acute cutaneous LD_{50} was not achieved at a dose of 2.0 g/kg (1.89 ml/kg).

In acute intravenous toxicity studies involving rats, pulmonary lesions were most prevalent among rats dosed with PPG-33-Buteth-45 (reduced and nonreduced forms). Relatively few pulmonary lesions were produced by PPG-7-Buteth-10, PPG-12-Buteth-16, or PPG-20-Buteth-30. Overall, based on acute intravenous LD_{50} values, PPG-12-Buteth-16 (LD_{50} values = 0.41 ml/kg, males; 0.64 ml/kg, females) and PPG-7-Buteth-10 (LD_{50} values = 0.20 ml/kg, males; 0.21 ml/kg, females) were the most toxic chemicals.

The acute intraperitoneal LD_{50} for PPG-12-Buteth-16 in rats was 2.46 ml/kg.

PPG-12-Buteth-16, PPG-20-Buteth-30, and PPG-33-Buteth-45 were not classified as ocular irritants after instillation into the conjunctival sac of the eyes of rabbits. However, PPG-24-Buteth-27 induced iritis and minor to moderate conjunctival irritation. All reactions had cleared by day 2 postinstillation. PPG-26-Buteth-26 did not induce ocular irritation in New Zealand albino rabbits. Mild ocular irritation was induced in New Zealand white rabbits tested with a solubilizing system containing PPG-26-Buteth-26 (concentration not stated).

In a skin irritation test of PPG-12-Buteth-16, PPG-20-Buteth-30, and PPG-33-Buteth-45, capillary injection was observed in rabbits only after the application of PPG-12-Buteth-16. The results of another study indicated that PPG-24-Buteth-27 induced minor erythema and moderate edema in rabbits. Reactions were not observed after day 2 postapplication. PPG-26-Buteth-26 induced very slight to slight skin irritation in New Zealand albino rabbits. A solubilizing system containing PPG-26-Buteth-26 (concentration not stated) was classified as a mild skin irritant in New Zealand white rabbits.

In two lifetime skin painting studies, PPG-7-Buteth-10 and PPG-33-Buteth-45, respectively, did not induce papillomas or carcinomas in mice. When administered following either one or two initiator doses of DMBA, 70% PPG-24-Buteth-27 acted as a tumor promoter; however, 5% PPG-24-Buteth-27 did not act as a tumor promoter.

Aftershave formulations containing 2.5% PPG-26-Buteth-26 were not skin irritants or sensitizers when evaluated in two 21-day home use tests. The skin irritation and/or sensitization use test and the skin irritation use test involved 52 and 54 subjects, respectively.

DISCUSSION

Section 1, paragraph (p) of the CIR Procedures states that "A lack of information about an ingredient shall not be sufficient

to justify a determination of safety." In accordance with Section 30(j)(2)(A) of the Procedures, the Expert Panel informed the public of its decision that the data on PPG Buteths were not sufficient for determining whether the ingredients, under relevant conditions of use, were either safe or unsafe. The Panel released for public comment a Tentative Report with an insufficient data conclusion on these ingredients (June 4, 1996).

In reaching its tentative conclusion that the available data were insufficient to support safety, the Expert Panel was particularly concerned that PPG Buteths are butanol-initiated random linear copolymers and that n-butyl alcohol could be present as an impurity in the finished product. Information was lacking on the amount of n-butyl alcohol that could be present in the finished product. Because n-butyl alcohol is a reproductive and developmental toxin, data confirming its absence were considered important. Alternatively, dermal reproductive and developmental toxicity tests of the lowest molecular weight PPG Buteth in this group would have sufficed. If that data were not available, dermal absorption data indicating no significant absorption would have resolved this concern. In addition, the Expert Panel needed human dermal irritation and sensitization data. Complicating this request for data was the fact that there are lower molecular weight PPG Buteths (i.e., PPG-2-Buteth-2) listed as cosmetic ingredients than are included in this safety assessment. The Expert Panel provided the option to expand the family of ingredients by submitting the above data on the lowest molecular weight PPG Buteth.

During the 90-day public comment period after the Tentative Report was issued, data were received addressing the presence of n-butyl alcohol and clinical data were provided on dermal irritation and sensitization -all for PPG-26-Buteth-26. The following specific data were received from the cosmetics industry: acute oral/dermal toxicity and skin/ocular irritation studies on undiluted PPG-26-Buteth-26; home use tests evaluating the skin irritation and sensitization potential of a shaving lotion containing 2.5% PPG-26-Buteth-26; and an impurities analysis on PPG-26-Buteth-26 and a trade mixture (solubilizing system) containing this ingredient. Data on the skin/ocular irritation potential of this trade mixture were also received. The concentration of PPG-26-Buteth-26 was not indicated; however, study results indicated that the skin and ocular irritation potential of this mixture in rabbits was less when compared to undiluted PPG-26-Buteth-26 (classified as mild irritant).

In its review of these data, the Expert Panel considered that the absence of n-butyl alcohol as an impurity in PPG-26-Buteth-26 was an indication that n-butyl alcohol would not be an impurity in any of the PPG Buteths. Therefore, the need for dermal reproductive and developmental toxicity data is eliminated.

The data provided on irritation and sensitization, however, were not considered applicable to PPG Buteths with molecular weights lower than PPG-26-Buteth-26, the ingredient actually tested. The experience of the Panel is that lower molecular weight members of a chemical family can be absorbed differently compared to higher molecular weight compounds. Absent any data on the dermal absorption of a low molecular weight PPG Buteth, or actual data on skin irritation and sensitization, the Expert Panel could not consider the available data sufficient to support the safety of PPG-9-Buteth-12 or PPG-12-Buteth-16. Accordingly, the Panel has identified the following data which are still needed in order to complete the safety assessment of PPG-9-Buteth-12 and PPG-12-Buteth-16 (and possibly, to evaluate the safety of even lower molecular weight PPG Buteths):

1. Dermal absorption of PPG-9-Buteth-12[2]
2. Human dermal irritation and sensitization of PPG-9-Buteth-12.[2a]

When new data are available, the Expert Panel will reconsider the Final Report in accordance with Section 46 of the CIR Procedures, Amendment of a Final Report.

The data were considered sufficient to complete the safety assessment for PPG-26-Buteth-26 and PPG-28-Buteth-35. The absence of n-butyl alcohol impurities and the negative findings in clinical testing support that these ingredients are safe as used in cosmetic products.

CONCLUSION

The CIR Expert Panel concluded that PPG-26-Buteth-26 and PPG-28-Buteth-35 are safe as used in cosmetic products, and that the available data are insufficient to support the safety of PPG-12-Buteth-16 and PPG-9-Buteth-12 as used in cosmetics.

REFERENCES

Amerchol Corporation. 1994a. Specifications on UCON 50-HB-400 (PPG-9-Buteth-12). Edison, NJ: Amerchol Corporation.

Amerchol Corporation. 1994b. Specifications on UCON 50-HB-2000 (PPG-20-Buteth-30). Edison, NJ: Amerchol Corporation.

Amerchol Corporation. 1994c. Specifications on UCON 50-HB-3520 (PPG-28-Buteth-35). Edison, NJ: Amerchol Corporation.

Amerchol Corporation. 1994d. Specifications on UCON 50-HB-5100 (PPG-33-Buteth-45). Edison, NJ: Amerchol Corporation.

Bushy Run Research Center. 1986. *Tergitol Nonionic Surfactant XD. Acute toxicity and primary irritancy studies.* BRRC Report No. 49-161. Export, PA: Union Carbide Corporation.

Bushy Run Research Center. 1988. *UCON 50-HB-260: Acute aerosol inhalation toxicity test in rats.* (BRRC Report No. 50-108.) NTIS Report No. OTS0536524.

Bushy Run Research Center. 1989. *A comparison of microscopic lung lesions between UCON 50-HB-5100 and UCON 50-HB-660.* (BRRC Report No. 52-103.) NTIS Report No. OTS051057611.

Bushy Run Research Center. 1990a. *Experimental lubricant 50-HB-5100 reduced: Acute aerosol inhalation toxicity test in rats.* (BRRC Report No. 52-139.) NTIS Report No. OTS051057615.

[2]Additional data addressing the needs identified above have been received and the CIR Expert Panel is currently considering revising its insufficient data conclusion for PPG-9-Buteth-12 and PPG-12-Buteth-16.

[2a]Studies on the lowest molecular weight PPG Buteth listed in the *International Cosmetic Ingredient Dictionary* (PPG-2-Buteth-2) are acceptable and could provide a basis for expanding this family of ingredients to include all of the PPG Buteths.

Bushy Run Research Center. 1990b. *UCON lubricant samples. Assessment of toxicity and pulmonary effects in the rat following single intravenous injection.* (BRRC Report No. 53-83.) NTIS Report No. OTS0537537.

Cosmetic, Toiletry, and Fragrance Association (CTFA). 1995. Use levels for various ingredients. Data on PPG-12-Buteth-16 and PPG-28-Buteth-35. Unpublished data submitted by CTFA. (1 page.)[3]

Education & Research Foundation, Inc. 1995. Use-irritancy test—dermatologist tested. Evaluation of dermal irritation potential of an aftershave lotion containing 2.5% PPG-26-Buteth-26 in human male subjects. (Final Report No. GMEH-3570.) Unpublished data submitted by CTFA. (10 pages.)[3]

E. I. Du Pont De Nemours & Company. 1984. Letter to the Environmental Protection Agency, dated July 5, 1984. Experimental procedure and results for acute inhalation toxicity study on PPG-33-Buteth-45. NTIS Report No. OTS000335-0.

European Economic Community (EEC). 1995. *EEC Cosmetics Directive 76/768/EEC, as amended, Annexes I through VII.* Brussels: EEC.

Food and Drug Administration (FDA). 1984. Frequency and concentration of use of cosmetic ingredients. *FDA database.* Washington, DC: FDA.

FDA. 1992a. Indirect food additives; poly(phenylene-terephthalamide) resins. *Fed. Register* 57:3123–3126.

FDA. 1997. Frequency of use of cosmetic ingredients. *FDA database.* Washington, DC: FDA.

Harrison Research Laboratories, Inc. 1995. Aftershave lotion use test. Evaluation of dermal irritation and/or sensitization potential of an aftershave lotion containing 2.5% PPG-26-Buteth-26 in human male subjects. HRL Panel #95-2503. Final Report. Unpublished data submitted by CTFA, August, 1996. (11 pages.)[3]

Higgins, C. E. 1981. Preparation of polar glass capillary columns. *Anal. Chem.* 53:732–734.

Hoffman, G. M., P. E. Newton, W. C. Thomas, H. A. Birnbaum, and G. L. Kennedy. 1991. Acute inhalation toxicity studies in several animal species of an ethylene oxide/propylene oxide copolymer (UCON 50-HB-5100). *Drug Chem. Toxicol.* 14:243–256.

ICI Central Toxicology Laboratory. 1992. *Acute inhalation toxicity study in the rat of ethylene oxide/propylene oxide copolymers UCON 50 HB-5100, EMKAROX VG680W and EMKAROX VG1050W.* (Report No. CTL/L/4427.) NTIS No. OTS0534745-1.

Klonne, D. R., H. D. Burleigh-Flayer, D. E. Dodd, P. E. Losco, and T. R. Tyler. 1993. Acute and 2-week aerosol inhalation studies on 970 and 1700 molecular weight ethylene oxide/propylene oxide (EO/PO) polymers. *Inhal. Toxicol.* 5:189–201.

Klonne, D. R., D. E. Dodd, P. E. Losco, C. M. Troup, and T. R. Tyler. 1988. Pulmonary fibrosis produced in F-344 rats by subchronic inhalation of aerosols of a 4000 molecular weight ethylene oxide/propylene oxide polymer. *Fundam. Appl. Toxicol.* 10:682–690.

Klonne, D. R., D. J. Nachreiner, D. E. Dodd, P. E. Losco, and T. R. Tyler. 1987. Acute and 2-week inhalation toxicity studies on aerosols of selected ethylene oxide/propylene oxide polymers in rats. *Fundam. Appl. Toxicol.* 9:773–784.

Les Colorants Wackherr. 1996. Impurities analysis of PPG-26-Buteth-26 and Solubilisant LRI. Unpublished data submitted by CTFA, September, 1996. (12 pages.)[3]

Myers, R. C., S. M. Christopher, P. E. Losco, and T. R. Tyler. 1990. Acute toxicity and pulmonary pathology from selected polyalkylene glycols following intratracheal administration to rats. Presented at the Annual Meeting of the Society of Toxicology at Miami Beach, Florida.

Nikitakis, J. M., and G. N. McEwen, Jr., eds. 1990. *CTFA compendium of cosmetic ingredient composition—Descriptions II.* Washington, DC: CTFA.

Rempe, J. M., and L. G. Santucci, eds. 1997. *CTFA list of Japanese cosmetic ingredients*, 3rd ed., 88–89. Washington, DC: CTFA.

Safepharm Laboratories, Ltd. 1987a. LRI solubilizing system. OECD 401 acute oral toxicity (limit test) in the rat. (Project Number 124/1.) Unpublished data submitted by CTFA. (10 pages.)[3]

Safepharm Laboratories, Ltd. 1987b. Submission of unpublished data by CTFA. LRI solubilizing system: OECD 405 acute eye irritation/corrosion test in the rabbit. Project Number 124/3. (10 pages.)[3]

Safepharm Laboratories, Ltd. 1987c. Submission of unpublished data by CTFA. LRI solubilizing system: OECD 404 acute dermal irritation/corrosion test in the rabbit. Project Number 124/2. (6 pages.)[3]

Smyth, H. F., C. S. Weil, J. M. King, J. B. Knaak, L. J. Sullivan, and C. P. Carpenter. 1970. Oral toxicity and excretion of four commercial polyoxyalkylene glycol compounds. *Toxicol. Appl. Pharmacol.* 16:675–680.

Stillmeadow, Inc. 1977. Submission of unpublished data by CTFA. Acute oral toxicity, acute dermal toxicity, skin irritation, and ocular irritation studies on PPG-26-Buteth-26, Project No. 288-77.[3]

Ulrich, C. E., R. G. Geil, T. R. Tyler, G. L. Kennedy, and H. A. Birnbaum. 1977. Two-week aerosol inhalation study in rats of ethylene oxide/propylene oxide copolymers. *Drug Chem. Toxicol.* 15:15–31.

Union Carbide Chemicals and Plastics Company, Inc. 1992a. *Material safety data sheet on UCON lubricant 50-HB-660 (PPG-12-Buteth-16).* Bound Broom, NJ: Union Carbide Chemicals and Plastics Company, Inc.

Union Carbide Chemicals and Plastics Company, Inc. 1992b. *Material safety data sheet on UCON lubricant 50-HB-260 (PPG-7-Buteth-10).* Bound Broom, NJ: Union Carbide Chemicals and Plastics Company, Inc.

Union Carbide Chemicals and Plastics Company, Inc. 1992c. *Material safety data sheet on UCON lubricant 50-HB-400 (PPG-9-Buteth-12).* Bound Broom, NJ: Union Carbide Chemicals and Plastics Company, Inc.

Union Carbide Chemicals and Plastics Company, Inc. 1992d. *Material safety data sheet on UCON lubricant 50-HB-2000 (PPG-20-Buteth-30).* Bound Broom, NJ: Union Carbide Chemicals and Plastics Company, Inc.

Union Carbide Chemicals and Plastics Company, Inc. 1992e. *Material safety data sheet on UCON lubricant 50-HB-3520 (PPG-28-Buteth-35).* Bound Broom, NJ: Union Carbide Chemicals and Plastics Company, Inc.

Union Carbide Chemicals and Plastics Company, Inc. 1992f. *Material safety data sheet on UCON lubricant 50-HB-5100 (PPG-33-Buteth-45).* Bound Broom, NJ: Union Carbide Chemicals and Plastics Company, Inc.

Union Carbide Corporation. 1952. *Progress report for the month that ended on June 30, 1952. Inhalation toxicity.* (Mellon Institute of Industrial Research Report No. 15-54.) Danbury, CT: Union Carbide Corporation.

Union Carbide Corporation. 1961. *Results of including TERGITOL Nonionic XD (PPG-24-Buteth-27) in the diet of rats for three months.* (Mellon Institute of Industrial Research Special Report No. 24-87.) Danbury, CT: Union Carbide Corporation.

Union Carbide Corporation. 1964. *Acute peroral toxicity of UCON lubricant 50-HB-5100.* (Mellon Institute Special Report No. 27-85.) Danbury, CT: Union Carbide Corporation.

Union Carbide Corporation. 1967a. *UCON Lubricant 50-HB-660. Range-finding toxicity studies. Intraperitoneal toxicity.* (Mellon Institute Special Report No. 30-6a.) Danbury, CT: Union Carbide Corporation.

Union Carbide Corporation. 1967b. *Results of testing TERGITOL Nonionic XD for tumorigenicity as well as for its potential tumor-promoter action.* (Mellon Institute Report No. 30-127.) NTIS Report No. OTS0540075.

Union Carbide Corporation. 1987. Letter to the Environmental Protection Agency dated May 1, 1987. Response to question about unreacted monomer content of PPG-33-Buteth-45. NTIS Report No. OTS0510576-2.

Union Carbide Corporation. 1992. *Draft report summary: Investigation of pathogenesis of pulmonary toxicity following a single intravenous injection of UCON lubricant 50-HB-5100 (PPG-33-Buteth-45).* (Bushy Run Research Center Report No. 9100019.) NTIS Report No. OTS0537537.

Union Carbide Corporation. 1994. *Product specification on "UCON" lubricant 50-HB-660 (PPG-12-Buteth-16).* Tarrytown, NY: Union Carbide Corporation. Research and Development Department, UCON fluids and lubricants.

Wenninger, J. A., R. C. Canterbery, and G. N. McEwen, Jr., eds. 2000. *International cosmetic ingredient dictionary and handbook.* 8th ed., Vol 2., 1177-1180. Washington, DC: CTFA.

[3]Available for review from the Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.