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## AMENDED FINAL REPORT

# Safety Assessment of PPG-9-Buteth-12, PPG-12-Buteth-16, PPG-26-Buteth-26, and PPG-28-Buteth-35

## ABSTRACT

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PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-26-Buteth-26, and PPG-28-Buteth-35 are polyoxypropylene, polyoxyethylene ethers of butyl alcohol that function as hair conditioning agents, miscellaneous skin conditioning agents, surfactant/emulsifying agents. In addition, PEG-12-Buteth-16 is used as a solvent in cosmetic formulations. This latter ingredient is used at concentrations up to 31% in hair grooming aids (e.g., hair tonics), 1-4% in shampoos, and less than 1% in other types of cosmetics. PPG-28-Buteth-35 is used at concentrations up to 1% in shampoos. Uses in cosmetic products have been reported for PPG-9-Buteth-12 and PPG-26-Buteth-26, but no current concentration of use data are available. All of the PPG Buteths in this safety assessment are highly water soluble and have molecular weights above 1000. Very little acute toxicity was seen in rats, mice, and rabbits with oral exposure to various PPG Buteths. 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. Acute, short-term, and subchronic inhalation studies with various PPG Buteths were negative as well. 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. While 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 produced 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. Clinical testing of PPG-12-Buteth-16 likewise produced no skin irritation or sensitization. Based on its large molecular weight alone, it is unlikely that PPG-28-Buteth-35 would be associated with any skin irritation or sensitization. PPG-9-Buteth-12 has a lower molecular weight than the PPG Buteths for which there has been shown an absence of skin sensitization and irritation, but it is highly soluble in water and has a molecular weight over 1000. These factors suggest that skin absorption would be very limited and it would be unlikely that PPG-9-Buteth-12 would produce 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. Based on the available data, it may be concluded that PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-26-Buteth-26, and PPG-28-Buteth-35 are safe as used in cosmetic formulations.

## INTRODUCTION

The toxicity of PPG-9-Buteth-12, PPG-12-Buteth-16, PPG-26-Buteth-26, and PPG-28-Buteth-35 is reviewed in this report. In 1997, the Cosmetic Ingredient Review (CIR) Expert Panel issued a final safety assessment (CIR, 1997) in which PPG-26-Buteth-26 and PPG-28-Buteth-35 were found safe as used in cosmetic products. The available data, however, were found insufficient to support the safety of PPG-9-Buteth-12 and PPG-12-Buteth-16 as used in cosmetics.

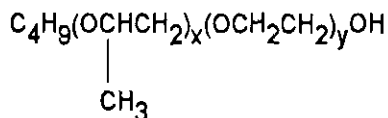
In 2000, the CIR Expert Panel received human repeat insult patch test (RIPT) data on PPG-12-Buteth-16 and updated information on the concentrations at which this ingredient is used in cosmetic formulations. These data have been incorporated into this amended final safety assessment.

Because the PPG Buteths have the same basic chemical structure, data on other chemicals in this family are included in this report to contribute to the safety assessment of these four cosmetic ingredients. The additional data are on the following chemicals, none of which is 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

The PPG Buteths (CAS Numbers 9038-95-3 and 9065-63-8) are polyoxypropylene, polyoxyethylene ethers of butyl alcohol that conform to the formula (Wenninger et al, 2000):



For PPG Buteths listed in the International Cosmetic Ingredient Dictionary, 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).

Other names for PPG Buteths include: *Polyoxyethylene (y) Polyoxypropylene (x) Monobutyl Ether* and *Polyoxypropylene (x) Polyoxyethylene (y) Monobutyl Ether*.

Thus, PPG-12-Buteth-16 would also be known as Polyoxyethylene (16) Polyoxypropylene (12) Monobutyl Ether and Polyoxypropylene (12) Polyoxyethylene (16) Monobutyl Ether (Wenninger et al, 2000).

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 -1.054 (at 20°/20°C); refractive index of 1.450 -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 IR spectrum with no indication of foreign materials (Nikitakis and McEwen, 1990).

Properties of PPG-7-Buteth-10, PPG-9-Buteth-12, PPG-12-Buteth-16, PPG-20-Buteth-30, PPG-28-Buteth-35, and PPG-33-Buteth-45 and specifications for PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-20-Buteth-30, PPG-28-Buteth-35, and PPG-33-Buteth-45 provided by suppliers are summarized in Table 1.

### 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; Nikitakis and McEwen, 1990 Hoffman et al., 1991).

### Impurities

According to the CTFA cosmetic ingredient description, 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

**Table 1. PPG Buteths Properties (Union Carbide Chemicals and Plastics Company, Inc. 1992a, b, c, d, e, f) and Specifications (Union Carbide Corporation, 1994; Amerchol Corporation, 1994a, b, c, d).**

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
Form Specification	---	---	---	---	---	Viscous, clear liquid
Viscosity Specification	630 to 690 cps	---	380 to 420 cps	1900 to 2100 cps	3370 to 3670 cps	4850 to 5350 cps
Appearance	Transparent, colorless	Transparent, colorless to pale yellow	Transparent, colorless to white	Transparent, colorless	Transparent, colorless	Transparent, colorless to pale yellow
Color Specification	---	---	100 platinum, max	200 platinum, max	200 platinum, max	200 platinum, max
Clarity Specification	Free from haze or turbidity	Free from haze or turbidity	Free from haze or turbidity	Free from haze or turbidity	Free from haze or turbidity	Free from haze or turbidity
Particulates Specification	Substantially free	---	Substantially free	Substantially free	Substantially free	Substantially free
Dilution test Specification	Clear	---	Clear	Clear	Passes	Clear
Odor	Characteristic	Characteristic	Mild	Characteristic	Characteristic	Characteristic
Odor Specification	---	---	Characteristic	Low, characteristic	Characteristic	Low, characteristic
Molecular Weight	1700	970	1230	2660	3380	3930
pH Specification	5.5 - 7.5 (10% aq at 25°C)	---	---	---	---	---
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 (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
Water/moisture Specification	0.13% by weight, max	---	0.3% max	0.3% max	0.3% max	0.3% max
Solubility in water by weight	100%	100%	100% at 20°C	100%	100%	100%

chromatography (detection limit = 1 ppm) and solid phase micro extraction (SPME) with gas chromatography (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 et al, 2000).

### Scope and Extent of Use in Cosmetics

Information on use of ingredients in cosmetic formulations is available from the Food and Drug Administration (FDA) as part of a voluntary industry reporting program. The product formulation data submitted to FDA in 1997 indicated that all of the PPG Buteths were used in cosmetics (FDA, 1997). Information on the types of products in which these ingredients were reportedly used is shown in Table 2. The number in parenthesis in the first column represents how many of this type of product were reported to FDA (e.g. 241 underarm deodorants) and the second column tells how many of those products contained the ingredient in question. Thus, out of 241 underarm deodorants, only one was reported to contain PPG-26-Buteth-26.

Table 2 also presents current information as provided by the industry on the concentrations at which PPG Buteths are used (CTFA, 1995, 1999). Concentration of use values are no longer reported to FDA by the cosmetics industry (FDA, 1992a). No maximum use concentration data are available for PPG-9-Buteth-12 because all participating companies indicated that they were not using that chemical in current formulations

(CTFA, 1999). For comparison purposes, historical data (reported to FDA in 1984) include the following concentration ranges: PPG-12-Buteth-16 (0.1-25%); PPG-9-Buteth-12 (0.1-1%); and PPG-28-Buteth-35 (0.1-1%) (FDA, 1984).

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 Use

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 anglicized Japanese name for PPG Buteths is Polyoxyethylene Polyoxypropylene Butyl Ethers. Polyoxyethylene Polyoxypropylene Butyl Ethers are specified in all 11 Japanese Comprehensive Licensing System (CLS) categories without limits. These categories are cleansing preparations, hair care preparations, treatment, makeup preparations, fragrant preparations, suntan/sunscreen preparations, nail preparations, makeup preparations, eyeliner preparations, lip preparations, oral preparations, and bath preparations. Where a specific Polyoxyethylene Polyoxypropylene Butyl Ethers is listed (e.g., PPG-28-Buteth-35) it is listed as "not used" in eyeliner preparations, lip preparations, or oral preparations (Santucci, 1999).

### 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:

**Table 2. Ingredient Usage as a Function of Product Type.**

Product Category (Total number reported to FDA 1997)	Number of Formulations with the Ingredient (FDA, 1997)	Current Concentration of Use (CTFA, 1995, 1999)
<b>PPG-12-Buteth-16</b>		
Baby Shampoos (19)	1	-
Bubble Baths (186)	8	0.6%
Other Bath Preparations (141)	14	0.7%
Other Eye Makeup Preparations (116)	1	-
Hair Conditioners (596)	4	-
Non-coloring Shampoos (825)	6	1-4%
Tonics, Dressings, and Other Hair Grooming Aids (512)	7	1-31%
Wave Sets (55)	1	-
Face Powders	-	1%
Nail Creams and Lotions (17)	1	-
Bath Soaps and Detergents (341)	4	0.6%
Other Personal Cleanliness Products (262)	1	-
Aftershave lotions	-	0.5%
Skin cleansing creams, lotions, liquids, pads	-	1%
Foot Powders and Sprays (32)	1	-
Skin Fresheners	-	0.5-0.6%
Other Skin Care Preparations (683)	1	-
Indoor Tanning Preparations (50)	3	1%
<b>1997 Total for PPG-12-Buteth-16</b>	<b>63</b>	
<b>PPG-9-BUTETH-12</b>		
Other Bath Preparations (141)	2	-
<b>1997 Total for PPG-9-Buteth-12</b>	<b>2</b>	
<b>PPG-26-BUTETH-26</b>		
Underarm Deodorants (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	-
<b>1997 Total for PPG-26-Buteth-26</b>	<b>13</b>	
<b>PPG-28-BUTETH-35</b>		
Non-coloring Rinses (42)	3	-
Non-coloring Shampoos (825)	4	1%
Bath Soaps and Detergents (341)	1	-
Underarm Deodorants (241)	1	-
Cleansing Skin Care Preparations (630)	1	-
<b>1997 Total for PPG-28-Buteth-35</b>	<b>10</b>	

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).

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, 1992b).

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  $^{14}\text{C}$ -PPG-7-Buteth-10 (67 mg/kg). Three samples of this chemical were radio-labeled at the butoxy, ethylene oxide, and propylene oxide groups, respectively. Radioactivity was not detected in the carcass of any animal at day 7 post-dosing. The urine and feces accounted for 46.4% and 26.7% of the total

radioactivity detected within seven 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  $^{14}\text{C}$ -ethylene oxide and least was from the  $^{14}\text{C}$ -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  $^{14}\text{C}$ -PPG-7-Buteth-10 had occurred at the ether linkages (Smyth et al., 1970).

#### PPG-33-Buteth-45

Following the oral administration of  $^{14}\text{C}$ -PPG-33-Buteth-45 ( $^{14}\text{C}$ -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 seven days after dosing. No radioactivity was found in expired carbon dioxide (Smyth et al., 1970).

## TOXICOLOGY

### Acute Inhalation Toxicity

The results of acute inhalation toxicity studies on the PPG Buteths are summarized in Table 3. A wide range of LC50 values and morbidity was observed.

Table 3. 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. The aerosol size was not stated	No deaths	Union Carbide Corporation, 1952a
PPG-12-Buteth-16	6 rats	Exposure to mists from saturated vapors for 2 h. The aerosol size was not stated	All animals died	Union Carbide Corporation, 1952a

**Table 3 (con't.). Acute Inhalation Toxicity of PPG Buteths**

Test Substance	Animals Tested	Procedure	Results	References
PPG-12-Buteth-16	Groups of 10 Wistar Albino rats (5 males, 5 females per group). Weights = 200 to 300 g	Single 4 h exposures up to a mean chamber concentration of 5230 mg/m <sup>3</sup> . The aerosol had a mass median aerodynamic particle size of 1.1 microns with a geometric standard deviation of 3.3	LC50 - males; 4670 mg/m <sup>3</sup> ; LC50 - females; > 5230 mg/m <sup>3</sup> . 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 to 300 g)	Endotracheal administration at dose of 0.1 ml/kg. The aerosol size was not stated	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 to 236 g (males) and 129 to 185 g (females)	Single 4 h exposures up to a mean concentration of 4.92 mg/L. The aerosol had a mass median aerodynamic particle size between 6.0 to 7.9 microns with geometric standard deviations of 5.0 to 5.5	Mean LC50 (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 wks post-exposure	Bushy Run Research Center, 1988
PPG-7-Buteth-10 (1% v/v in saline)	15 male rats (weights = 250 to 300 g)	Endotracheal administration at dose of 0.02 ml/kg. The aerosol size was not stated	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. The aerosol size was not stated	2 deaths	Union Carbide Corporation, 1952b
PPG-20-Buteth-30	6 rats	Exposure to mists from saturated vapors for 2 h. The aerosol size was not stated	All animals died	Union Carbide Corporation, 1952b
PPG-20-Buteth-30	6 rats	Exposure to mists from saturated vapors for 8 h. The aerosol size was not stated	No deaths	Union Carbide Corporation, 1952b
PPG-20-Buteth-30	Groups of ten Wistar Albino rats (5 males, 5 females per group). Weights = 200 to 300 g	Single 4 h exposures up to a mean chamber concentration of 992 mg/m <sup>3</sup> . The aerosol had a mass median aerodynamic particle size of 1.1 microns with a geometric standard deviation of 3.3	LC50 = 330 mg/m <sup>3</sup> (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 to 300 g)	Endotracheal administration at dose of 0.02 ml/kg. The aerosol had a mass median aerodynamic particle size of 1.1 microns with a geometric standard deviation of 3.3	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. The aerosol size was not stated	2 deaths	Union Carbide Corporation, 1952b
PPG-33-Buteth-45	6 rats	Exposure to mists from saturated vapors for 2 h. The aerosol size was not stated	No deaths	Union Carbide Corporation, 1952b
PPG-33-Buteth-45	6 rats	Exposure to mists from saturated vapors for 8 h. The aerosol size was not stated	No deaths	Union Carbide Corporation, 1952b

**Table 3 (con't.). Acute Inhalation Toxicity of PPG Buteths**

Test Substance	Animals Tested	Procedure	Results	References
PPG-33-Buteth-45	10 Sprague -Dawley rats (weights = 279 to 387 g)	Exposure to aerosol at concentrations up to 2,400 mg/m <sup>3</sup> for 4 h. The aerosol had a mass median aerodynamic particle size between 2.0 and 2.7 microns	Mean LC50 = 147 mg/m <sup>3</sup> . Significant increases in mean lung weight at concentrations of 54, 100, and 200 mg/m <sup>3</sup> . Gross pulmonary changes included emphysema and edema	Hoffman et al., 1991
PPG-33-Buteth-45	Groups of ten Wistar Albino rats 5 males, 5 females per group. (Weights = 200 to 300 g)	Single 4 h exposures up to a mean chamber concentration of 940 mg/m <sup>3</sup> . The aerosol had a mass median aerodynamic particle size of 1.1 microns with a geometric standard deviation of 3.3	LC50 = 106 mg/m <sup>3</sup> (males and females). Mottled lungs and livers most common necropsy findings	Klonne et al., 1987
PPG-33-Buteth-45	Groups of 12 male Hsd/Ola (Wistar derived) Albino rats. (Weights = 180 to 220 g)	Single exposures (nose only) to a target concentration of 75 mg/m <sup>3</sup> for 2, 4, or 6 h, yielding mean equivalent 4 h concentrations of 36.3, 74.4, and 113.3 mg/m <sup>3</sup> , respectively. The aerosol had a mass median aerodynamic particle size between .068 to 1.08 microns with a geometric standard deviations from 1.48 to 2.87	Toxicologically significant increases in lung weights at 74.4 and 113.3 mg/m <sup>3</sup> . 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 <sup>3</sup> . The aerosol had a mass median aerodynamic particle size between 1.1 to 1.3 microns	50 mg/m <sup>3</sup> (no deaths); 84 mg/m <sup>3</sup> (1 of 6 died); 111 mg/m <sup>3</sup> (4 of 6 died); and 185 mg/m <sup>3</sup> (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 to 250 g)	Single 4 h exposures at mean chamber concentrations up to 0.74 mg/L. The aerosol had a mass median aerodynamic particle size between 0.8 to 1.6 microns with geometric standard deviations from 1.8 to 6.1	Mean LC50 = 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 to 300 g)	Endotracheal administration at dose of 0.02 ml/g. The aerosol size was not stated	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 to 33 g)	Exposure to aerosol at concentrations up to 2,400 mg/m <sup>3</sup> for 4 h. The aerosol had a mass median aerodynamic particle size between 2.0 and 2.7 microns	Mean LC50 = 174 mg/m <sup>3</sup> . Significant increases in mean lung weight at concentrations of 54 and 200 mg/m <sup>3</sup> . Gross pulmonary changes included emphysema and edema.	Hoffman et al., 1991



**Table 3 (con't.). Acute Inhalation Toxicity of PPG Buteths**

Test Substance	Animals Tested	Procedure	Results	References
PPG-33-Buteth-45	10 male Golden Syrian hamsters (weights = 77 to 110 g)	Exposure to aerosol at concentrations up to 2,400 mg/m <sup>3</sup> for 4 h. The aerosol had a mass median aerodynamic particle size between 2.0 and 2.7 microns	Mean LC50 = 511 mg/m <sup>3</sup> . Significant increases in mean lung weight at concentrations of 140, 320, 940, and 2,400 mg/m <sup>3</sup> . Gross pulmonary changes included emphysema and edema	Hoffman et al., 1991
PPG-33-Buteth-35	10 male Hartley Albino guinea pigs (weights = 355 to 507 g)	Exposure to aerosol at concentrations up to 2,400 mg/m <sup>3</sup> for 4 h. The aerosol had a mass median aerodynamic particle size between 2.0 and 2.7 microns	Mean LC50 = 293 mg/m <sup>3</sup> . Significant increase in lung weight at a concentration of 940 mg/m <sup>3</sup> . 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 3,200 mg/m <sup>3</sup> for 4 h. The aerosol had a mass median aerodynamic particle size between 2.0 and 2.7 microns	No deaths. Gross pulmonary changes included emphysema and edema	Hoffman et al., 1991

## Short-term Inhalation Toxicity

Studies on the short-term inhalation toxicity of PPG Buteths are described below and summarized in Table 4 at the end of this section.

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 evaluated by Bushy Run Research Center (1989) (see subheading PPG-33-Buteth-45 under short-term inhalation toxicity for comparative data); untreated rats served as negative controls. The strain and weight range of the animals tested were not stated. The aerosol particle size was not provided.

### PPG-12-Buteth-16

Groups (males and females) were exposed to PPG-12-Buteth-16 aerosol concentrations of 500, 1000, and 2500 mg/m<sup>3</sup>, respectively. In rats exposed to 2500 mg/m<sup>3</sup> PPG-12-Buteth-16 (all of which died), the principal pulmonary lesions were: congestion, hemorrhage, pulmonary edema, interstitial pneumonia, and intraalveolar cellular debris. Neither congestion nor pulmonary edema was observed in rats of the 500 and 1,000 mg/m<sup>3</sup> 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 1,000 mg/m<sup>3</sup> dose groups. Rats exposed to PPG-12-Buteth-16 had up to ten affected rats per group (interstitial pneumonia and perivascular infiltrates) (Bushy Run Research Center, 1989).

Klonne (1993) evaluated the short-term inhalation toxicity of PPG-12-Buteth-16 using Fischer 344 rats (8 weeks old, groups of 10 rats per sex) in two studies. Mean body weights for males and females were 180 and 120 g, respectively in both studies.

In the first study, rats were exposed to PPG-12-Buteth-16 at mean chamber aerosol concentrations of 504 ± 44 mg/m<sup>3</sup>, 982 ± 68 mg/m<sup>3</sup>, and 2460 ± 104 mg/m<sup>3</sup>, 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. The aerosol had a mass median aerodynamic particle size of 3.0 microns with a geometric standard deviation of 3.2.

Untreated rats (10 males, 10 females) served as negative controls. All animals exposed to the

high concentration died. All surviving animals were killed on day 12; necropsy was performed on all rats. Hematological determinations also were made.

Histopathologic evaluations were conducted on control animals and animals of the 982 mg/m<sup>3</sup> exposure group. The following observations were made for rats of the 2460 mg/m<sup>3</sup> 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<sup>3</sup> 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 ( $p < 0.05$ ) 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 at 504 and 982 mg/m<sup>3</sup>: 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<sup>3</sup> concentration 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 ( $p < 0.01$ ) were also noted in both concentration groups. Histopathological evaluation was performed only on the respiratory tract of rats of the 504 and 2460 mg/m<sup>3</sup> groups, because the lungs were the only site of exposure-related histopathological changes that were identified in rats of the 982 mg/m<sup>3</sup> exposure group.

The following pulmonary changes were noted in rats of the 2460 mg/m<sup>3</sup> concentration group: mild to moderate pulmonary congestion, mild to moderate interstitial pneumonitis, 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 histopathological changes was actually greater in rats of the 982 mg/m<sup>3</sup> concentration group. Minimal to mild alveolar histiocytosis, interstitial pneumonitis, and bronchioalveolar cell hyperplasia were the principal microscopic lesions in rats of the 504 mg/m<sup>3</sup> dose group (Klonne et al., 1993).

In the second study, four groups of Fischer-344 rats were exposed to PPG-12-Buteth-16 at mean chamber aerosol concentrations of  $5 \pm 0.05$  mg/m<sup>3</sup>,  $51 \pm 2$  mg/m<sup>3</sup>,  $98 \pm 3$  mg/m<sup>3</sup>, and  $492 \pm 23$  mg/m<sup>3</sup>, respectively, according to the procedures outlined in the preceding paragraph. The aerosol had a mass median aerodynamic particle size of 2.5 microns with a geometric standard deviation of 3.5. The incorporation of a six-week 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<sup>3</sup> concentration 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<sup>3</sup> concentration group. However, body weights returned to normal during the six-week recovery period. Slight decreases in body weight gain were reported for female rats of the 98 mg/m<sup>3</sup> concentration group. The changes in hematologic parameters were consistent with those noted in the preceding study. Most of the hematological changes were observed in rats of the 492 mg/m<sup>3</sup> concentration group. In male rats of the 51, 98, and 492 mg/m<sup>3</sup> concentration groups and female rats of the 98 and 492 mg/m<sup>3</sup> concentration 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<sup>3</sup> 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<sup>3</sup> exposure group. An increased incidence of alveolar histiocytosis was observed in male rats exposed to 51 mg/m<sup>3</sup> or higher concentrations. Exposure-related microscopic lesions were not observed in male or female rats at the end of the six-week recovery period (Klönne et al., 1993).

#### PPG-7-Buteth-10

Klönne (1993) evaluated the short-term inhalation toxicity of PPG-7-Buteth-10 using Fischer 344 rats (8 weeks old, groups of 10 rats per sex). The mean body weights for males and females were 180 and 120 g, respectively.

Three groups of Fischer-344 rats were exposed to PPG-7-Buteth-10 at mean chamber aerosol concentrations of  $5 \pm 0.4$  mg/m<sup>3</sup>,  $52 \pm 2$  mg/m<sup>3</sup>, and  $512 \pm 13$  mg/m<sup>3</sup>, respectively, according to the procedures outlined in the preceding paragraph. The aerosol had a mass median aerodynamic particle size of 2.7 microns with a geometric standard deviation of 2.7. 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<sup>3</sup> exposure group included perinasal encrustation and urogenital wetness.

The incidence of these changes in the 52 mg/m<sup>3</sup> exposure group was only slightly greater than that in the control group. Clinical signs of toxicity were not evident in the 5 mg/m<sup>3</sup> exposure group. Statistically significant decreases in absolute body weight were noted in the 512 mg/m<sup>3</sup> exposure group; however, values returned to normal during the recovery period. In the 52 mg/m<sup>3</sup> 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<sup>3</sup> concentration group. In the 52 and 512 mg/m<sup>3</sup> concentration groups, both sexes had a statistically significant decrease in body weight gain ( $p < 0.05$ ); the decreases were concentration-related.

A transient decrease in body weight gain was noted for rats in the 5 mg/m<sup>3</sup> concentration group. At ophthalmic examination, none of the findings were considered compound-related. The following statistically significant changes in hematologic parameters were reported for rats of

the 512 mg/m<sup>3</sup> concentration 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<sup>3</sup> concentration 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 (Klönne et al., 1993).

#### PPG-20-Buteth-30

Ulrich et al. (1977) evaluated the toxicity of PPG-20-Buteth-30 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<sup>3</sup>. The aerosol had a mass median aerodynamic particle size of 2.2 microns (standard deviation of 0.04) with a geometric standard deviation of 1.87 (standard deviation of 0.044). The positive control group (10 rats) was exposed to PPG-33-Buteth-45 at a chamber concentration of 55 mg/m<sup>3</sup> according to the same procedure, and the negative control group (10 rats) was exposed to air. The aerosol had a mass median aerodynamic particle size of 2.3 microns (standard deviation of 0.13) and a geometric standard deviation of 1.87 (standard deviation of 0.113). At the end of the two-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 two-week post-exposure recovery period.

Six rats exposed to PPG-20-Buteth-30 died after a total of three exposures; deaths occurred on days three to five 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 ( $p < 0.05$ ) in body weight was noted in surviving animals from the experimental group after five and six 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; intraalveolar 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 three exposed rats (Ulrich et al., 1977).

#### PPG-33-Buteth-45

Ulrich et al. (1977) evaluated the 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<sup>3</sup>. The PPG-20-Buteth-30 aerosol had a mass median aerodynamic particle size of 2.2 microns (standard deviation of 0.04) with a geometric standard deviation of 1.87 (standard deviation of 0.044). The positive control group (10 rats) was exposed to PPG-33-Buteth-45 at a chamber concentration of 55 mg/m<sup>3</sup> according to the same procedure, and the negative control group (10 rats) was exposed to air. The PPG-33-Buteth-45 aerosol had a mass median aerodynamic particle size of 2.3 microns (standard deviation of 0.13) and a geometric standard deviation of 1.87 (standard deviation of 0.113). At the end of the two-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 two-week post-exposure recovery period.

Nine rats exposed to PPG-33-Buteth-45 (positive control) died after a total of three exposures;

deaths occurred on days three to five of the study. Due to the number of deaths, the survivors were killed after the first week 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; intraalveolar 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 (Ulrich et al., 1977).

Klönne et al. (1987) evaluated the short-term inhalation toxicity of PPG-33-Buteth-45 using four groups of Fischer 344 rats ( $\approx$  7 weeks old). Twenty rats per sex were assigned to control and high concentration ( $49.5 \pm 1.6$  mg/m<sup>3</sup>, mean chamber atmosphere concentration) groups and ten rats per sex were assigned to the low ( $4.8 \pm 0.6$  mg/m<sup>3</sup>) and intermediate ( $25.5 \pm 2.5$  mg/m<sup>3</sup>) concentration groups. The aerosol had a mass median aerodynamic particle size of 1.1 microns with a geometric standard deviation of 3.3. The rats were exposed 6 h per day over a period of 11 days; exposures did not exceed five days per week. Each animal was subjected to nine exposures, and no exposures occurred on days 5 and 6. In each group, ten rats per sex were killed on the morning after the ninth exposure. The remaining ten rats per sex in control and high concentration groups were killed after a two-week recovery period.

Signs noted only in the high exposure group included unkempt appearance, nasal discharge, and urogenital wetness (females only). Statistically significant differences in body weight gain were observed only in high ( $p < 0.01$ ) and intermediate ( $p < 0.05$ ) exposure 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 exposure 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 hematologic parameters were not observed after the recovery period. Biologically significant changes in serum chemistry or hematologic 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 exposure group, when compared to animals in this group that were killed on the morning after the ninth exposure (Klonne et al., 1987).

Three short-term (9 days) inhalation toxicity studies were conducted at the Bushy Run Research Center (1989). 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 were evaluated; untreated rats served as negative controls. The strain and weight range of the animals tested were not stated. The aerosol particle size was not provided.

In the first Bushy Run Research Center (1989) study, groups (males and females) were exposed to PPG-12-Buteth-16 aerosol concentrations of 500, 1000, and 2500 mg/m<sup>3</sup>, 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<sup>3</sup>, respectively. In the third study, two groups of ten

male rats were exposed to PPG-33-Buteth-45 at aerosol concentrations of 1.0 and 5.0 mg/m<sup>3</sup>, respectively. In the second and third studies, controls and rats from the highest exposure group were evaluated after a two-week recovery period.

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, groups exposed to PPG-33-Buteth-45 that were killed on day 9 had a maximum of four to seven affected rats per group (interstitial pneumonia and perivascular infiltrates, respectively); in comparison, rats exposed to PPG-12-Buteth-16 had up to ten affected rats per group (both lesions).

The investigators concluded that in the preceding three Bushy Run Research Center 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 greater 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).

The preceding short-term inhalation toxicity studies are summarized in Table 4.

## **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.

**Table 4. Short-term Inhalation Toxicity of PPG Buteths**

Test Substance	Animals Tested	Procedure	Results	Reference
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 <sup>3</sup> . The aerosol size was not stated	Main pulmonary lesions in rats exposed to 2500 mg/m <sup>3</sup> included congestion, hemorrhage, edema, interstitial pneumonitis, and intraalveolar cellular debris. Pulmonary hemorrhage and inflammation only at lower concentrations (500 and 1,000 mg/m <sup>3</sup> )	Bushy Run Research Center, 1989
PPG-12-Buteth-16	Groups of 20 Fischer 344 rats (10 males, 10 females) 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 <sup>3</sup> . The aerosol had a mass median aerodynamic particle size of 3.0 microns with a geometric standard deviation of 3.2	All of the 20 rats exposed to 2460 mg/m <sup>3</sup> died. Interstitial pneumonitis and bronchioalveolar cell hyperplasia observed in all three exposure groups (504, 982, and 2460 mg/m <sup>3</sup> )	Klönne 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 <sup>3</sup> . The aerosol had a mass median aerodynamic particle size of 2.5 microns with a geometric standard deviation of 3.5	No mortalities. Minimal to moderate intraalveolar cellular debris and interstitial pneumonitis in the 492 mg/m <sup>3</sup> exposure group. Increased incidence of alveolar histiocytosis in male rats exposed to ≥ 52 mg/m <sup>3</sup> . All lesions had cleared by end of 6 wk recovery period	Klönne 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 <sup>3</sup> . The aerosol had a mass median aerodynamic particle size of 2.7 microns with a geometric standard deviation of 2.7	No exposure-related deaths in any of the groups (5, 52, and 512 mg/m <sup>3</sup> ). No exposure-related alterations (microscopic lesions)	Klönne et al., 1993
PPG-20-Buteth-30	10 male Sprague-Dawley Albino rats (5 weeks old)	10-day inhalation toxicity test. Exposure to chamber aerosol concentration of 100 mg/m <sup>3</sup> . The aerosol had a mass median aerodynamic particle size of 2.2 microns	6 rats died after three exposures. Alveolar lesions consisted of hyperemia, intraalveolar 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 weeks old)	10-day inhalation toxicity test. Exposure to chamber aerosol concentration of 55 mg/m <sup>3</sup> . The aerosol had a mass median aerodynamic particle size of 2.3 microns	9 rats died after three exposures. Alveolar lesions consisted of hyperemia, intraalveolar 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 wks old; males and females)	9-day inhalation toxicity test. Exposure to mean chamber concentrations up to 49.5 mg/m <sup>3</sup> . The aerosol had a mass median aerodynamic particle size of 1.1 microns with a geometric standard deviation of 3.3	Irregular red foci in lungs of males and females noted in group (20 rats) exposed to 25 mg/m <sup>3</sup> and in group (40 rats) exposed to 49.5 mg/m <sup>3</sup> . Irregular red foci in lungs of males in group (20 rats) exposed to 4.8 mg/m <sup>3</sup> . Foci also in rats killed after 2 wk recovery period	Klönne et al., 1987

Three groups of rats (20/sex/group) were exposed to PPG-33-Buteth-45 aerosol at mean chamber concentrations of  $0.30 \pm 0.039 \text{ mg/m}^3$ ,  $1.1 \pm 0.13 \text{ mg/m}^3$ , and  $5.2 \pm 0.26 \text{ mg/m}^3$ , respectively, 6 h per day (5 days/week) for thirteen weeks. The aerosol had a mass median aerodynamic particle size of 1.1 microns with a geometric standard deviation of 3.3. Exposure concentrations were determined at the conclusion of a two-week range-finding study. The control group was exposed only to filtered air. During week 14, ten rats/sex/group were killed after at least two days of exposure. The remaining animals (10 rats/sex/group) were killed after a five-week recovery period.

Statistically significant decreases in body weight gain were observed only in male rats of the  $5.2 \text{ mg/m}^3$  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  $1.1 \text{ mg/m}^3$  exposure group and in males of the  $5.2 \text{ mg/m}^3$  exposure group. Biologically significant alterations in the hematologic profile or in the serum or urine chemistries were not observed at any time during the study.

The lungs were the only organ with toxicologically significant organ weight changes and toxicologically significant macroscopic lesions. Female rats of the  $1.1 \text{ mg/m}^3$  exposure group and rats of both sexes in the  $5.2 \text{ mg/m}^3$  exposure group had statistically significant increases ( $p < 0.01$ ) in absolute and relative (as a percentage of both body weight and brain weight) lung weights. A significant increase ( $p < 0.05$ ) in the lung/body weight ratio was also noted in male rats. All absolute and relative lung weights for males and females of the  $5.2 \text{ mg/m}^3$  group remained significantly increased at the end of the five-week recovery period. Values for absolute lung weight and lung/body weight also remained significantly increased in males of the  $1.1 \text{ mg/m}^3$  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  $0.3 \text{ mg/m}^3$  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  $5.2 \text{ mg/m}^3$  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  $5.2 \text{ mg/m}^3$  groups), alveolar histiocytosis, and focal or multifocal fibrosis; the lesions were minimal to severe (Klonne et al., 1988).

## Acute Oral Toxicity

Studies on the acute oral toxicity of PPG Buteths are presented below and summarized in Table 5 at the end of this section.

### PPG-7-Buteth-10

The acute oral toxicity of undiluted PPG-7-Buteth-10 was evaluated using male and female albino rats (number not stated). The test substance was 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 LD50 for PPG-7-Buteth-10 in rats were as follows: 7.07 ml/kg (males, weights = 90 to 120 g), 5.95 ml/kg (males, weights = 120 to 170 g), 8.57 ml/kg (females, weights = 90 to 120 g), and 4.49 ml/kg (females, weights = 300 to 400 g) (Smyth et al., 1970).

In rabbits (number and strain not stated; weights = 2200 to 2900 g), the mean oral LD50 for PPG-7-Buteth-10 was 1.77 ml/kg (Smyth et al., 1970).

The acute oral toxicity of PPG-7-Buteth-10 was evaluated using female mice (number and strain not stated; weights = 23 to 36 g); PPG-7-Buteth-10 was administered by oral intubation. The mean acute oral LD50 for PPG-7-Buteth-10 was 7.46 ml/kg (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 to 33 g).

The mean acute oral LD50 for PPG-33-Buteth-45 was 49.4 ml/kg (range = 39.9 to 61.0 ml/kg) (Union Carbide Corporation, 1964).

#### PPG-12-Buteth-16

The acute oral toxicity of PPG-12-Buteth-16 in rats (number, strain, and weights not stated) was evaluated. In each test, undiluted PPG-12-Buteth-16 was administered to fasted rats by gavage. The mean acute oral LD50 was 18.3 g/kg (range = 15 to 22.4 g/kg) for PPG-12-Buteth-16 (Union Carbide Corporation, 1952b).

#### PPG-20-Buteth-30

The acute oral toxicity of PPG-20-Buteth-30 in rats (number, strain, and weights not stated) was evaluated. In each test, undiluted PPG-20-Buteth-30 was administered to fasted rats by gavage. The mean acute oral LD50 was 20.6 g/kg (range = 16.7 to 25.5 g/kg) for PPG-20-Buteth-30 (Union Carbide Corporation, 1952b).

#### PPG-24-Buteth-27

The acute oral toxicity of undiluted PPG-24-Buteth-27 was evaluated using Sprague-Dawley albino rats (5 males, 5 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 evaluated using ten hooded Long Evans rats (5 males, 5 females; weights = 200 to 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 at the end of the study. The LD50 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).

Safeparm Laboratories Ltd. (1987a) evaluated the acute oral toxicity of a solubilizing system containing PPG-26-Buteth-26 (as supplied) 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 h post-dosing 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 post-dosing: hunched posture, pilo-erection, lethargy, and decreased respiratory rate. Surviving animals appeared normal from day 2 post-dosing to the end of the study.

On necropsy of the two rats that died the authors found abnormally red lungs, congestion of the small intestines, and patchy pallor of the liver. Except for one female with an ulcerated area on the non-glandular 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 (LD50) was greater than 5000 mg/kg body weight (Safeparm Laboratories Ltd., 1987a).

#### PPG-33-Buteth-45

The acute oral toxicity of PPG-33-Buteth-45 in rats (number, strain, and weights not stated) was evaluated. In each test, the undiluted PPG-33-Buteth-45 was administered to fasted rats by gavage. The mean acute oral LD50 was 48.7 g/kg (range = 42.3 to 55.9 g/kg) for PPG-33-Buteth-45 (Union Carbide Corporation, 1952b). The acute oral toxicity of undiluted PPG-33-Buteth-45 was evaluated using male and female albino rats (number not stated). The test substance was 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 LD50 for PPG-33-Buteth-45 in rats was 45.2 ml/kg (females, weights = 300 to 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).

The acute oral toxicity of PPG-33-Buteth-45 was evaluated using female mice (number and strain not stated; weights = 23 to 36 g); PPG-33-Buteth-45 was administered by oral intubation. The mean acute oral LD50 for PPG-33-Buteth-45



**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 LD50 = 18.3 g/kg	Klonne et al., 1987
PPG-7-Buteth-10	Male Albino rats (weights = 90 to 120 g)	Single dose by oral intubation	Oral LD50 = 7.07 ml/kg	Smyth et al., 1970
PPG-7-Buteth-10	Male Albino rats (weights = 120 to 170 g)	Single dose by oral intubation	Oral LD50 = 5.95 ml/kg	Smyth et al., 1970
PPG-7-Buteth-10	Female Albino rats (weights = 90 to 120 g)	Single dose by oral intubation	Oral LD50 = 8.57 ml/kg	Smyth et al., 1970
PPG-7-Buteth-10	Female Albino rats (weights = 300 to 400 g)	Single dose by oral intubation	Oral LD50 = 4.49 ml/kg	Smyth et al., 1970
PPG-7-Buteth-10	Female mice (weights = 23 to 36 g)	Single dose by oral intubation	Oral LD50 = 7.46 ml/kg	Smyth et al., 1970
PPG-7-Buteth-10	Rabbits (weights = 2200 to 2900 g)	Single oral dose	Oral LD50 = 1.77 ml/kg	Smyth et al., 1970
PPG-20-Buteth-30	Rats (number not stated)	Single dose by gavage	Oral LD50 = 20.6 g/kg	Klonne et al., 1977
PPG-24-Buteth-27	Sprague-Dawley Albino rats (5 males, 5 females). Weights = between 200 and 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 to 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 to 147 g)	Single dose (4.81 ml/kg)	Two deaths	Safepharm Laboratories, Ltd., 1987a
PPG-33-Buteth-45	Female Albino rats (weights = 300 to 400 g)	Single dose by oral intubation	Oral LD50 = 45.2 ml/kg	Smyth et al., 1970
PPG-33-Buteth-45	Albino rats (males and females). Weights = 90 to 120 g	Single dose by oral intubation	No deaths	Smyth et al., 1970
PPG-33-Buteth-45	Female mice (weights = 23 to 36 g)	Single dose by oral intubation	LD50 = 49.4 ml/kg	Smyth et al., 1970
PPG-33-Buteth-45	10 female Swiss albino mice (weights = 26 to 33 g)	Single oral dose	LD50 = 49.4 ml/kg	Union Carbide Corporation, 1964
PPG-33-Buteth-45	Rabbits (weights = 2200 to 2900 g)	Single oral dose	LD50 = 15.8 ml/kg	Smyth et al., 1970
PPG-33-Buteth-45	8 male New Zealand albino rabbits (weights = 2308 to 2848 g)	Single oral dose	LD50 = 15.8 ml/kg	Union Carbide Corporation, 1964

was 49.4 ml/kg (Smyth et al., 1970).

The acute oral toxicity of PPG-33-Buteth-45 was evaluated using 10 fasted, female Swiss albino mice (weights = 26 to 33 g). The mean acute oral LD50 for PPG-33-Buteth-45 was 49.4 ml/kg (range = 39.9 to 61.0 ml/kg) (Union Carbide Corporation, 1964).

In rabbits (number and strain not stated; weights = 2200 to 2900 g), the mean oral LD50 for PPG-33-Buteth-45 was 15.8 ml/kg (Smyth et al., 1970).

In another study, the acute oral toxicity of PPG-33-Buteth-45 was evaluated using 8 fasted, male New Zealand albino rabbits (weights = 2308 to 2848 g). The mean acute oral LD50 for PPG-33-Buteth-45 was 15.8 ml/kg (range = 11.6 to 21.3 ml/kg) (Union Carbide Corporation, 1964).

The acute oral toxicity studies presented above are summarized in Table 5.

## Subchronic Oral Toxicity

### PPG-24-Buteth-27

The subchronic oral toxicity of PPG-24-Buteth-27 was evaluated by the Union Carbide Corporation (1961) 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 three 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 moribund and killed 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 % of body weight) were significantly lower in males fed PPG-24-Buteth-27 at dietary concentrations of 0.01 ( $p$  = between 0.05 and 0.01) and 1.25% ( $p$  < 0.0001), 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 % of body weight) between controls and females from any of the treatment groups.

The mean value for liver weight (as % 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 % 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 by Klonne et al. (1987), 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, Smyth et al. (1970) fed PPG-7-Buteth-10 at doses of 0.004, 0.02, 0.1, and 0.5 g/kg/day, respectively, to four groups of 36 male and 36 female CF-E albino rats (weights not stated) for two years. Dietary concentrations were adjusted every two weeks for six months and, then, every four 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) also fed PPG-7-Buteth-10 at doses of 0.0043, 0.043, and 0.62 g/kg/day, respectively, to three groups of beagle dogs (3 males and 3 females/group; weights not stated) were fed for two 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-min bromsulphalein retention, and gross and microscopic lesions in 18 tissues.

### PPG-33-Buteth-45

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

PPG-33-Buteth-45 produced little toxicity when administered in the diet to three groups of 3 male

and 3 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

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. Undiluted test substance was applied to intact skin, after which the test sites were covered with an impermeable wrap for 24 h. One of the four animals died (Klonne et al., 1987).

### PPG-20-Buteth-30

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

### 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-33-Buteth-45. Undiluted test substance was applied to intact skin, after which the test sites were covered with an impermeable wrap for 24 h. One of the four animals died (Klonne et al., 1987).

### PPG-26-Buteth-26

Stillmeadow Inc. (1977) evaluated the acute dermal toxicity of undiluted PPG-26-Buteth-26 using ten New Zealand Albino rabbits (5 males, 5 females; weights = 2.3 to 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 h post-application 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 pharmacologic effects daily for up to two 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 pharmacologic effects were observed. No abnormalities were observed at necropsy. The acute dermal LD50 was not achieved at a dose of 2.0 g/kg (1.89 ml/kg), and PPG-26-Buteth-26 was considered non-toxic (Stillmeadow Inc., 1977).

#### PPG-24-Buteth-27

The Bushy Run Research Center (1986) evaluated the acute dermal toxicity of undiluted PPG-24-Buteth-27 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 h. Ten rabbits (5 males, 5 females) received 8 and 16 ml/kg doses and four rabbits (2 males, 2 females) received 2 and 4 ml/kg doses. Excess fluid was removed at the end of the 24 h contact period in order to diminish ingestion.

The animals were observed for skin reactions at 1 h and days 7 and 14 after the 24 h 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 presented below are summarized in Table 6 at the end of this section.

#### PPG-12-Buteth-16

The Bushy Run Research Center, (1990b) studied the acute intravenous toxicity of the

PPG-12-Buteth-16 (100%) using groups of ten (5 males, 5 females/group) 7 to 13-week-old, Sprague-Dawley albino rats that weighed between 200 and 300 g.

For PPG-12-Buteth-16 (100%), no more than 2.0 ml was injected into the tail vein of each rat (10 rats). All rats were necropsied and microscopic examination was performed on the lungs of selected rats (those that died and those killed). Study results are summarized as follows: the acute intravenous LD50's for 100% PPG-12-Buteth-16 were 0.41 ml/kg in male rats (5 individuals) and 0.64 ml/kg in female rats (5 individuals).

In the acute intravenous toxicity tests, the most toxic substances were those with low molecular weights (< 2000), PPG-12-Buteth-16 and PPG-7-Buteth-10. Relatively few lung lesions were produced by PPG-12-Buteth-16. At microscopic examination, the most significant treatment-related lesions were pulmonary inflammation, alveolar histiocytosis, and fibrosis. 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-7-Buteth-10

The Bushy Run Research Center (1990b) studied the acute intravenous toxicity of PPG-7-Buteth-10 (10% in saline) using groups of ten (5 males, 5 females/group) 7 to 13-week-old, Sprague-Dawley albino rats that weighed between 200 and 300 g.

For PPG-7-Buteth-10 (10% in saline), no more than 2.0 ml was injected into the tail vein of each rat (10 rats). All rats were necropsied and microscopic examination was performed on the lungs of selected rats (those that died and those killed). The acute intravenous LD50's for 10% PPG-7-Buteth-10 were 0.20 ml/kg (5 male rats) and 0.21 ml/kg (5 female rats).

In the acute intravenous toxicity tests, the most toxic substances were those with low molecular weights (< 2000), PPG-12-Buteth-16 and PPG-7-Buteth-10. Relatively few lung lesions were produced by PPG-7-Buteth-10. At microscopic examination, the most significant treatment-related lesions were pulmonary inflammation, alveolar histiocytosis, and fibrosis. 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-20-Buteth-30

The Bushy Run Research Center (1990b) studied the acute intravenous toxicity of PPG-20-Buteth-30 (100%) using groups of ten (5 males, 5 females/group) 7 to 13-week-old, Sprague-Dawley albino rats that weighed between 200 and 300 g.

For PPG-20-Buteth-30 (100%), no more than 2.0 ml was injected into the tail vein of each rat (10 rats). All rats were necropsied and microscopic examination was performed on the lungs of selected rats (those that died and those killed). The acute intravenous LD50's for 100% PPG-20-Buteth-30 were 1.62 ml/kg (5 male rats) and 2.0 ml/kg (5 female rats).

In the acute intravenous toxicity tests, PPG-20-Buteth-30 (100%) had low toxicity compared to the PPG Buteths with low molecular weights (< 2000), PPG-12-Buteth-16 and PPG-7-Buteth-10. Relatively few lung lesions were produced by PPG-20-Buteth-30. At microscopic examination, the most significant treatment-related lesions were pulmonary inflammation, alveolar histiocytosis, and fibrosis. 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

The Bushy Run Research Center (1990b) studied the acute intravenous toxicity of the following chemicals using groups of ten (5 males, 5 females/group) 7 to 13-week-old, Sprague-Dawley albino rats that weighed between 200 and 300 g: PPG-33-Buteth-45 (60% in saline), and PPG-33-Buteth-45 reduced (60% in saline). The authors reported that PPG-33-Buteth-45 reduced means that the unsaturated level in PPG-33-Buteth-45 was decreased from 0.034 meq/g to 0.019 meq/g by reducing the alkyl end group.

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).

Acute intravenous LD50's for 60% PPG-33-Buteth-45 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).

In the preceding series of acute intravenous toxicity tests, the most toxic substances were those with low molecular weights (< 2000), 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).

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 post-injection; other animals were killed sequentially on days 1, 2, 3, and 14 post-injection. Pulmonary lesions were noted as early as day 1 post-injection and included congestion, hemorrhages, perivascular inflammatory 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 of the pilot study summarized above, Union Carbide Corporation (1992) dosed 53 rats 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

(treated and controls included) that were originally included in the study died between days 3 and 6 post-injection; 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 treated, 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 treated, 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 post-injection. 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 intravenous toxicity studies presented above are summarized in Table 6.

### **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 to 120 g). An LD50 of 2.46 ml/kg (range = 1.79 to 3.39 ml/kg) was reported (Union Carbide Corporation, 1967a).

### **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**

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

#### **PPG-33-Buteth-45**

The ocular irritation potential of PPG-33-Buteth-45 in rabbits (number and strain not stated) was evaluated. In the study, the test substance (0.1 ml) was instilled into the conjunctival sac of each animal. PPG-33-Buteth-45 was not an ocular irritant 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 h and days 1, 2, 3, and 7 post-instillation. 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 two days post-instillation (Bushy Run Research Center, 1986).

#### **PPG-26-Buteth-26**

The ocular irritation potential of undiluted PPG-26-Buteth-26 was evaluated by 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 h and on days 4 and 7 post-instillation 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 non-irritant (Stillmeadow Inc., 1977).

**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 = between 200 and 300 g	Single injection into tail vein	LD50's = 0.41 ml/kg (males) and 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 = between 200 and 300 g	Single injection into tail vein	LD50's = 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 = between 200 and 300 g	Single injection into tail vein	LD50's = 1.62 ml/kg (males) and 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 = between 200 and 300 g	Single injection into tail vein	LD50's = 2.14 ml/kg (males) and 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 = between 200 and 300 g	Single injection into tail vein	LD50's = 2.14 ml/kg (males) and 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 post-injection. Pulmonary lesions noted as early as day 1 post-injection included congestion, hemorrhage, and interstitial pneumonitis	Union Carbide Corporation, 1992
PPG-33-Buteth-45	53 Sprague-Dawley rats in treatment group; equal number in control group	Single intravenous dose of 1.75 ml/kg	17 of the 106 rats at the beginning of the study died. Lung lesions in treatment group included: hemorrhage, perivascular infiltrates, interstitial pneumonitis, emphysema, and alveolar edema. Renal toxicity was also noted in 5 treated rats. Microscopic changes included edema, necrosis, and atrophy of the proximal renal tubules	Union Carbide Corporation, 1992

Safeparm Laboratories, Ltd. (1987b) evaluated the ocular irritation potential of a solubilizing system containing PPG-26-Buteth-26 (as supplied) using three New Zealand White rabbits (weights = 2.72 to 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 sec after instillation. Untreated eyes served as controls.

Ocular reactions were scored at 1, 24, 48, and 72

h post-instillation. At 1 h post-instillation, 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 of all animals; reactions had cleared by day 7 post-instillation. The solubilizing system was classified as a mild ocular irritant (score = 4; scale of 1 to 8) (Safeparm 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 h. 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 h; excess test substance was then removed. Sites were covered with a gauze patch and impervious sheeting during the 4 h contact period. At 1 h 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 two days (Bushy Run Research Center, 1986).

### PPG-26-Buteth-26

Stillmeadow Inc. (1977) evaluated the skin irritation potential of undiluted PPG-26-Buteth-26 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 (1 abraded, 1 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 h contact period. Reactions were scored at 24 and 72 h post-application 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 h readings) at intact and abraded sites (total of 4 scores) and mean scores for edema formation (24 and 72 h readings) at intact and abraded sites (total of 4 scores) were calculated. The sum of the eight mean scores was divided by 4 to yield a dermal irritation score of 3.12 (max = 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).

Safepharm Laboratories Ltd. (1987c) evaluated the skin irritation potential of a solubilizing system containing PPG-26-Buteth-26 (as supplied) using three New Zealand White rabbits (weights = 2.57 to 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 h; the trunk was also wrapped with an elasticated corset. At 4 h post-application, patches and any residual test material were removed.

Reactions were scored 1 h after patch removal and 24, 48, and 72 h 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 h post-removal, 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 h observation.

Desquamation was observed in two rabbits at the 24 and 72 h observations. The solubilizing system was classified as a mild skin irritant (primary irritation index = 0.3) (Safepharm Laboratories Ltd., 1987c).

## GENOTOXICITY

No genotoxicity information was available in the



published literature.

## CARCINOGENICITY

### PPG-7-Buteth-10

In a chronic feeding study, four groups of 36 male and 36 female CF-E albino rats (weights not stated) were fed PPG-7-Buteth-10 at doses of 0.004, 0.02, 0.1, or 0.5 g/kg/day for two years. Dietary concentrations were adjusted every two weeks for six months and, then, every four 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. Female rats (0.5 g/kg/day dose group) with growth rates less than those for controls and no statistically significant differences were observed in the incidence of neoplasms (Smyth et al., 1970).

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 Union Carbide Corporation (1967b) evaluated the tumorigenicity and tumor promotion activity of PPG-24-Buteth-27 using groups of 35 to 40 CAF<sub>1</sub> 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.

In the first experiment, 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 dimethyl-benzanthracene (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 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-12-Buteth-16

Clinical Research Laboratories, Inc. (1997) conducted a repeat insult patch test using PPG-12-Buteth-16 at 0.75% with 117 subjects. Eight subjects discontinued, reportedly for reasons unrelated to the study. Prior to application of the patch, the test area (upper back) was wiped with 70% isopropyl alcohol and allowed to air dry. The test material (volume not specified) was applied and allowed to volatilize. A semi-occlusive patch was applied and the material remained in direct skin contact for 24 h. Patches were applied to the same site on Monday, Wednesday, and Friday for three weeks (the induction period). Sites were graded for dermal irritation and sensitization 24 h after removal of the patches by the subjects on Tuesday and Thursday, and 48 h after subjects removed the patches on Saturday. Sites were graded on a 0-4+ scale, with 0 being no visible skin reaction and 4+ being erythema and edema with vesiculation. No signs of irritation or sensitization were found during the induction period.

Following a 2 week rest period, challenge patches were applied to previously untreated areas of the back of each subject. Challenge sites were evaluated as above at 24, 48, and 72 h. One subject exhibited barely perceptible erythema at 24 h, which disappeared at 48 and 72 h. No other subjects exhibited any visible skin reaction at any

time. Based on these results, PPG-12-Buteth-16 was described by the authors as having no potential for eliciting either dermal irritation or sensitization (Clinical Research Laboratories, Inc., 1997).

#### PPG-26-Buteth-26

Harrison Research Laboratories, Inc. (1995) evaluated the skin irritation and sensitization potential of a test aftershave lotion containing 2.5% PPG-26-Buteth-26 in a 21-day use test involving 54 male subjects (18 to 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 one 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 pre-screened using a semi-occlusive patch test (< 24 h 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 semi-occlusive patch test (pre-screen), 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 ten 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 & 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 to 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 irritation 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**

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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). Maximum use concentrations reported for PPG-12-Buteth-16 were 0.6 % in bubble baths, 0.7% in other bath preparations, 1-4% in noncoloring shampoos, 1-31% in hair grooming aids, 1% in face powders, 0.6% in bath soaps and detergents, 0.5% in aftershave lotions, 0.6% in shaving cream, 1% in skin cleansers, 0.5-0.6% in skin fresheners, and 1% in indoor tanning preparations. PPG-28-Buteth-35 was used at concentrations up to 1% in shampoos. No use concentration data were available for PPG-9-Buteth-12 because all participating companies indicated that they were not using that chemical in current formulations.

In rats dosed orally with  $^{14}\text{C}$ -PPG-7-Buteth-10, most of the administered radioactivity was excreted (urine, feces, and expired  $\text{CO}_2$ ) within seven days post-dosing. Similar observations were reported for rats dosed orally with  $^{14}\text{C}$ -PPG-33-Buteth-45; however, radioactivity was not detected in expired  $\text{CO}_2$ .

Acute inhalation LC50 values for PPG Buteths that have been reported for rats are as follows: 4670  $\text{mg}/\text{m}^3$  and  $> 5230 \text{ mg}/\text{m}^3$  for males and females, respectively (PPG-12-Buteth-16); 4.77  $\text{mg}/\text{m}^3$  (males and females) for PPG-7-Buteth-10; 330  $\text{mg}/\text{m}^3$  (males and females) for PPG-20-Buteth-30; and 147  $\text{mg}/\text{m}^3$  for PPG-33-Buteth-45. LC50 values of 174  $\text{mg}/\text{m}^3$  (mice); 511  $\text{mg}/\text{m}^3$  (hamsters); and 293  $\text{mg}/\text{m}^3$  (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  $\text{mg}/\text{m}^3$ . Pulmonary lesions were also noted in rats exposed to PPG-20-Buteth-30 (100  $\text{mg}/\text{m}^3$ ) and PPG-33-Buteth-45 (55  $\text{mg}/\text{m}^3$ ) for 10 days and in rats exposed to PPG-33-Buteth-45 at concentrations ranging from 4.8 to 50  $\text{mg}/\text{m}^3$  for 9 days. No exposure-related microscopic lesions were found in rats exposed for nine days to

PPG-7-Buteth-10 at concentrations ranging from 5 to 512  $\text{mg}/\text{m}^3$ .

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  $\text{mg}/\text{m}^3$  for 13 weeks. The lesions consisted of hemorrhage and interstitial pneumonia (only in 1.1 and 5.2  $\text{mg}/\text{m}^3$  groups), alveolar histiocytosis, and focal or multifocal fibrosis.

An LD50 of 18.3 g/kg for PPG-12-Buteth-16 was reported in an acute oral toxicity study involving rats. Acute oral LD50's ranging from 4.49 to 8.57 ml/kg have been reported for PPG-7-Buteth-10 in studies involving rats. Oral LD50's of 7.46 ml/kg (mice) and 1.77 ml/kg (rabbits) for PPG-7-Buteth-10 also have been reported.

The oral LD50 for PPG-20-Buteth-30 in rats was 20.6 g/kg, and,  $> 16 \text{ ml}/\text{kg}$ , in rats dosed with PPG-24-Buteth-27. An oral LD50 of  $> 5.01 \text{ g}/\text{kg}$  (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 LD50 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, LD50's of 45.2 ml/kg and 49.4 ml/kg, respectively, were reported. In studies using rabbits, an LD50 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 statistically significant 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: 1 of 4 rabbits (PPG-12-Buteth-16); 1 of 4 rabbits (PPG-20-Buteth-30); and 1 of 4 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 LD50 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 non-reduced 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 LD50 values, PPG-12-Buteth-16 (LD50's = 0.41 ml/kg -males; 0.64 ml/kg -females) and PPG-7-Buteth-10 (LD50's = 0.20 ml/kg -males; 0.21 ml/kg -females) were the most toxic chemicals.

The acute intraperitoneal LD50 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 post-instillation. 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 post-application. 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 dimethylbenzanthracene (DMBA), 70% PPG-24-Buteth-27 acted as a tumor promoter; however, 5% PPG-24-Buteth-27 did not act as a tumor promoter.

AnRIPT study in 109 subjects found no irritation or sensitization associated with the application of 0.75% PPG-12-Buteth-16 under semioclusive patches. 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

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. n-butyl alcohol is a reproductive and developmental toxin. Data were available addressing the presence of n-butyl alcohol in PPG-26-Buteth-26. 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. There was no other basis for suspecting that PPG Buteths presented a reproductive or developmental toxicity risk, so additional data were not needed.

The data provided on irritation and sensitization for PPG-26-Buteth-26 and PPG-12-Buteth-16 demonstrated that these members of the PPG Buteth family would not be irritating or sensitizing at their current concentrations of use.

Based on its large molecular weight alone, it is unlikely that PPG-28-Buteth-35 would be associated with any skin irritation or sensitization, but 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. Because PPG-9-Buteth-12 has a lower molecular weight than the PPG Buteths for which irritation/sensitization data are available, the Panel considered whether additional data were needed. Because all the PPG Buteths are highly water soluble, and large molecules and its rates of absorption into the skin should be sufficiently limited to make it unlikely that they would be skin sensitizers in their current uses.

The Panel further considered the question of dermal absorption by noting that all of the ingredients in this report have molecular weights above 1000 and are unlikely, on that basis, to penetrate skin. The Panel then reconsidered the import of the several studies of the smaller PPG-7-Buteth-10 (MW 970) that are included in this safety assessment. No evidence of toxicity of PPG-7-Buteth-10 was seen in chronic oral toxicity studies in rats. In addition, a lifetime skin painting study in mice found neither papillomas nor carcinomas in any animals in the vehicle control or the PPG-7-Buteth-10 groups, but did find neoplasms in all the animals in the group receiving a known carcinogen, methyl cholanthrene. As stated above, PPG-7-Buteth-10 was not toxic when delivered orally. These results support that all the members of the PPG Buteth family considered in this safety assessment are unlikely to penetrate skin to any significant degree to cause toxicity.

## CONCLUSION

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Based on the available animal and clinical data included in this report, the CIR Expert Panel concluded that PPG-9-Buteth-12, PPG-12-Buteth-16, PPG-26-Buteth-26 and PPG-28-Buteth-35 are safe as used in cosmetic products.

**ACKNOWLEDGEMENT:** The original safety assessment was prepared by Wilbur Johnson, Jr., Senior Scientific Analyst and Writer.

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