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Final Report on the Safety Assessment of Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol

Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol are viscous liquids used in the cosmetic industry as humectants, emulsifiers, plasticizers, and solvents.

The results of acute, subchronic, and chronic oral toxicity studies using a variety of animal species indicate a low order of toxicity for the Glycols. Results of parenteral injection, inhalation, and acute and subchronic cutaneous toxicity studies likewise support a low order of toxicity. Butylene Glycol, Ethoxydiglycol, and Dipropylene Glycol caused minimal to mild irritation of rabbit skin, whereas Hexylene Glycol was moderately irritating. The Glycols produced mild to severe ocular irritation when tested in rabbits, with Hexylene Glycol producing the most severe irritation. Although undiluted Hexylene Glycol produced severe ocular irritation, a 25 percent aqueous solution produced no signs of irritation. Undiluted Butylene Glycol was not an eye irritant to rabbits but was to humans.

Human skin patch tests on undiluted Butylene Glycol and undiluted Hexylene Glycol produced a very low order of primary skin irritation. A repeated insult patch test on Butylene Glycol produced no evidence of skin sensitization.

Based on the available data it is concluded the Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol are safe as presently used in cosmetics.

INTRODUCTION

Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol are viscous liquids used in the cosmetic industry as humectants, emulsifiers, plasticizers, and solvents.

CHEMICAL AND PHYSICAL PROPERTIES

Structure/Composition

1. Butylene Glycol is an aliphatic diol. It conforms to the formula:

$$\mathrm{HOCH_2CH_2\underset{\underset{OH}{|}}{C}HCH_3}$$

CAS Number: 107-88-0

Other names include 1,3-Butanediol and 1,3-Butylene Glycol.[1]

2. Hexylene Glycol is the aliphatic alcohol that conforms to the formula:

$$\mathrm{CH_3{-}\overset{\overset{CH_3}{|}}{\underset{\underset{OH}{|}}{C}}{-}CH_2{-}\underset{\underset{OH}{|}}{C}HCH_3}$$

CAS Number: 107-41-5

Other names are 2-Methyl-2,4-Pentanediol and 2,4-Pentanediol,2-Methyl-.[1]

3. Ethoxydiglycol is the ether alcohol that conforms to the formula:

$$\mathrm{CH_3CH_2OCH_2CH_2OCH_2CH_2OH}$$

CAS Number: 111-90-0

Other names include Diethylene Glycol Monoethyl Ether; Ethanol, 2-(2-Ethoxyethoxy)-; 2-(2-Ethoxyethoxy)Ethanol.[1]

4. Dipropylene Glycol is a mixture of diols that conforms generally to the formula:

$$\mathrm{CH_3\underset{\underset{OH}{|}}{C}HCH_2{-}O{-}CH_2\underset{\underset{OH}{|}}{C}HCH_3}$$

The material of commerce is primarily a mixture of 3 isomers, with the majority being disecondary (85 to 90 percent). Primary-secondary and diprimary isomers, along with up to 5 percent unidentified material, make up the remainder.

CAS Number: 110-98-5

Other names are: Di-1,2-Propylene Glycol; 1,1′-Oxybis-2-Propanol; 2-Propanol,1,1′-Oxybis-.[1,2]

Properties

Butylene Glycol is a clear, practically colorless, viscous, hygroscopic liquid. It is odorless and has a slightly sweet, characteristic taste. Butylene Glycol is miscible in all proportions with water, acetone, and alcohol. It is immiscible with fixed oils and insoluble in aliphatic hydrocarbons, benzene, toluene, and carbon tetrachloride. This glycol does dissolve most essential oils and synthetic flavoring substances.[3-7]

Hexylene Glycol is a clear hygroscopic liquid with a mild, sweet odor. It exhibits exceptional solvency for a variety of materials and is miscible with aliphatic and aromatic hydrocarbons as well as with such polar substances as water, fatty acids, and alcohols. It is combustible.[5,6,8]

Ethoxydiglycol is a colorless hygroscopic liquid, soluble in water and most organic solvents.[4,9]

Dipropylene Glycol is a colorless, slightly viscous liquid that is soluble in water, ethanol, and acetone.[5]

Other physical and chemical properties of the glycols are shown in Table 1.

Production

Butylene Glycol is produced by the catalytic hydrogenation of acetaldehyde using as catalysts Raney nickel, copper, or platinum oxide. It is purified by distillation.[6,7,10]

TABLE 1. Properties of Glycols

Property	*Butylene Glycol*	*Hexylene Glycol*	*Ethoxydiglycol*	*Dipropylene Glycol*	*Reference*
Molecular weight	90.12	188.18	134.18	134.18	4
Boiling point (°C)	208 (0.8 atm)	$197^{(760mm)}$	$195^{(760mm)}$	229–32	4
	207.5	$197.1^{(760mm)}$	–	$222–38^{(760mm)}$	2, 7, 8
Freezing point (°C)	−50	–	−105	Supercools	2, 6, 7, 9
Specific gravity (g/ml)	1.0053^{20}_{4}	0.9254^{17}_{4}	0.9881^{20}_{4}	1.0224^{20}_{20}	4
	1.0053^{20}_{20}	0.9233^{20}_{20}	0.988^{25}_{25}	$1.020–1.030^{20}_{20}$	2, 7–9
Refractive index n^{20}_{D}	1.4418	1.4250	1.4300	–	4
	1.4412	1.4276	–	1.439	2, 7, 8
Vapor pressure	0.06 mm	–	0.26 mm	0.01 mm	2, 4, 5, 9
Viscosity (cps)	103.9 (25°C)	41.7 (20°C)	–	–	7,8
Solubility					
Water	Soluble	Soluble	Soluble	Soluble	3, 4
Alcohol	Soluble	Soluble	Soluble	Soluble	3, 4
Ether	Insoluble	Soluble	Soluble	–	4
Acetone	Soluble	–	Soluble	Soluble	2, 4, 7
Benzene	Insoluble	–	Soluble	–	4, 7
Carbon tetrachloride	Insoluble	–	–	–	7
Aliphatic hydrocarbons	Insoluble	Soluble	–	–	7,8
Aromatic hydrocarbons	–	Soluble	–	–	8
Fatty acids	–	Soluble	–	–	8

Hexylene Glycol is manufactured by the condensation of 2 molecules of acetone to produce diacetone alcohol, which is further hydrogenated to produce Hexylene Glycol. This is then purified by distillation.[8]

Ethoxydiglycol is prepared from the reaction of ethylene oxide with ethanol followed by purification by distillation.[9]

Dipropylene Glyol is the reaction product of propylene glycol and propylene oxide.[2,11]

Analytical Methods

Chemical and chromatographic methods may be used for the identification and separation of the glycols. Chemical methods involve oxidation of the glycols with subsequent reaction with a reagent.[12] Gas chromatography may be used for the identification of glycols.[13,14]

Impurities

Butylene Glycol has a minimum gas chromatographic assay of 99.5 percent by weight. It contains a maximum of 0.5 percent water, up to 0.005 percent acetic acid, and trace amounts of branched 1,3-Butylene Glycol.[7]

Hexylene Glycol contains a maximum of 0.1 percent water and 0.005 percent acetic acid.[8]

Ethoxydiglycol has a minimum gas chromatographic assay of 99.0 percent and contains water and acetic acid to maximums of 0.1 and 0.01 percent, respectively. Known impurities include diethylene glycol and triethylene glycol.[9]

The isomer distribution of Dipropylene Glycol is as specified by the commercial buyer. It contains up to 0.1 percent water, up to 0.01 percent acetic acid, and up to 0.001 percent inorganic chlorides. The maximum combustion residue of Dipropylene Glycol should not exceed 0.005 percent.[2]

USE

Noncosmetic Use

Butylene Glycol has been tested as a parenteral drug solvent,[11] in the manufacture of polyester plasticizers, and as a humectant for cellophane and tobacco.[6] It serves as a surfactant, coupling agent, and solvent.[5] Butylene Glycol has both indirect food additive (IFA) and direct food additive (DFA) status with the Food and Drug Administration when used as a solvent for flavors,[15] as an antioxidant and stabilizer, and as a component of packaging (21 Code of Federal Regulations [CFR] 173.220; 177.1200; 175.105; 177.1680; 177.1210; 178.2010).[16]

Hexylene Glycol has IFA status as a defoaming agent (21 CFR 176.210).[16] It is also used in hydraulic brake fluids, printing inks, and textile dye vehicles. Hexylene Glycol serves as a coupling agent, as a fuel and lubricant additive and as an emulsifying agent.[5,11]

Exthoxydiglycol has IFA status for use as a component of paperboard and adhesives (21 CFR 175.105; 176.180).[16]

Dipropylene Glycol is an IFA ingredient for use in adhesives, lubricants, and as a defoaming agent (21 CFR 175.105; 178.3910; 176.200).[16] It is also used as a solvent for nitrocellulose and shellac and as a partial solvent for cellulose acetate. Other applications include solvent mixtures, lacquers, coatings, and printing inks.[5]

Cosmetic Use

The glycols generally are used as cosmetic emulsifiers, solidifiers, plasticizers, cosolvents, and film producers.[17,18] Butylene Glycol is used as a humectant, especially in hair sprays and setting lotions.[18-20] It helps retard the loss of aromas from essential oils, preserves against spoilage by microorganisms, and is used as a solvent for benzoates. Special grades of Dipropylene Glycol (based on odor quality) are used as carriers for perfume oils.[2]

Cosmetic product formulation data on the use and occurrence of the glycols in finished products are made available by the Food and Drug Administration (FDA) and compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations. Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100 percent concentration, the value reported by the cosmetic formulator may not necessarily reflect the true concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. Since data are only submitted within the framework of preset concentration ranges, the opportunity exists for a 2- to 10-fold overestimation of the actual concentration of an ingredient in a particular product (Table 2).[21]

Butylene Glycol is used in 165 products at concentrations from less than 0.1 percent to greater than 50 percent. It is used in hair and bath products, eye and facial makeup, fragrances, personal cleanliness products, and shaving and skin care preparations.[21]

Hexylene Glycol is used in 85 cosmetic formulations at concentrations of use ranging from less than 0.1 percent to 25 percent. The types of products in which Hexylene Glycol is used include bath and hair preparations, eye makeup, soaps, and skin care preparations.[21]

Ethoxydiglycol has been reported as an ingredient in 80 product formulations at concentrations from less than 0.1 percent to 50 percent. The types of products include eye makeup, fragrances, hair and nail preparations, and shaving and skin care preparations.[21]

Dipropylene Glycol is reported as an ingredient in 50 cosmetic formulations in concentrations ranging from less than 0.1 percent to 50 percent. It is used in hair care and bath products, perfumes, facial makeup, doedorants, and shaving and skin care preparations.[21]

The Glycols may contact all parts of the integument to which the products are applied and may remain in contact for several hours daily.[21]

TABLE 2. Product Formulation Data[21]

*Product Category**	*Total No. Containing Ingredient*	*No. Product Formulations Within Each Concentration Range (%)*					
		>50	*>10–25*	*>5–10*	*>1–5*	*>0.1–1*	*≤0.1*
Butylene Glycol							
Bath oils, tablets, and salts	1	–	–	1	–	–	–
Other bath preparations	4	1	–	3	–	–	–
Eyeliner	3	–	–	–	3	–	–
Eye shadow	13	–	12	1	–	–	–
Eye makeup remover	4	–	–	–	4	–	–
Mascara	34	–	–	5	29	–	–
Other eye makeup preparations	1	–	–	–	1	–	–
Colognes and toilet waters	3	–	1	–	–	2	–
Perfumes	2	–	–	–	2	–	–
Other fragrance preparations	1	–	–	1	–	–	–
Hair conditioners	5	–	–	2	1	1	1
Hair shampoos (noncoloring)	1	–	–	–	–	–	1
Tonics, dressings, and other hair grooming aids	1	–	–	–	1	–	–
Blushers (all types)	7	–	1	3	3	–	–
Face powders	1	–	–	–	1	–	–
Makeup foundations	19	–	3	16	–	–	–
Makeup bases	1	–	–	1	–	–	–
Rouges	2	1	–	1	–	–	–
Other makeup preparations (not eye)	2	–	1	1	–	–	–
Cuticle softeners	1	–	–	1	–	–	–
Bath soaps and detergents	1	–	–	1	–	–	–
Deodorants (underarm)	1	–	1	–	–	–	–
Other personal cleanliness products	1	–	–	–	1	–	–
Aftershave lotions	4	–	–	–	2	2	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	13	–	–	2	10	–	1
Face, body, and hand skin care preparations (excluding shaving preparations)	8	–	1	2	2	1	2
Moisturizing skin care preparations	11	–	3	2	6	–	–
Night skin care preparations	1	–	–	–	–	–	1
Paste masks (mudpacks)	3	–	–	1	1	1	–
Skin fresheners	6	–	–	–	4	1	1
Wrinkle smoothers (removers)	2	–	–	–	1	–	1
Other skin care preparations	7	–	–	2	3	1	1
Suntan gels, creams, and liquids	1	–	–	–	1	–	–
1981 TOTALS	165	2	23	46	76	9	9

TABLE 2. (Continued)

*Product Category**	*Total No. Containing Ingredient*	*No. Product Formulations Within Each Concentration Range (%)*				
		>10–25	*>5–10*	*>1–5*	*>0.1–1*	*≤0.1*
Hexylene Glycol						
Bath oils, tablets, and salts	4	1	3	–	–	–
Bubble baths	3	–	–	2	1	–
Eye makeup remover	1	–	–	–	1	–
Hair conditioners	7	–	1	2	4	–
Permanent waves	1	1	–	–	–	–
Hair rinses (noncoloring)	1	1	–	–	–	–
Hair shampoos (noncoloring)	29	–	10	13	5	1
Hair dyes and colors (all types requiring caution statement and patch test)	20	17	–	3	–	–
Hair bleaches	1	–	–	1	–	–
Bath soaps and detergents	3	–	–	3	–	–
Deodorants (underarm)	2	–	–	–	2	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	4	–	–	3	1	–
Face, body, and hand skin care preparations (excluding shaving preparations)	1	–	–	1	–	–
Moisturizing skin care preparations	3	–	–	2	1	–
Paste masks (mudpacks)	1	–	1	–	–	–
Skin fresheners	3	–	–	1	2	–
Other skin care preparations	1	–	–	1	–	–
1981 TOTALS	85	20	15	32	17	1

*Product Category**	*Total No. Containing Ingredient*	*No. Product Formulations Within Each Concentration Range (%)*					
		>25–50	*>10–25*	*>5–10*	*>1–5*	*>0.1–1*	*≤0.1*
Ethoxydiglycol							
Mascara	1	–	–	–	–	1	–
Colognes and toilet waters	3	–	–	2	–	1	–
Hair conditioners	4	–	–	–	2	2	–
Hair shampoos (noncoloring)	1	–	–	–	–	1	–
Wave sets	1	–	–	–	1	–	–
Hair dyes and colors (all types requiring caution statement and patch test)	14	–	–	4	10	–	–
Hair tints	13	–	–	–	13	–	–
Hair bleaches	5	–	–	–	5	–	–
Other hair coloring preparations	1	–	–	–	1	–	–
Nail polish and enamel remover	1	–	–	1	–	–	–
Aftershave lotions	2	–	–	–	–	2	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	14	1	–	1	8	3	1

TABLE 2. (Continued)

*Product Category**	*Total No. Containing Ingredient*	*No. Product Formulations Within Each Concentration Range (%)*					
		>25–50	*>10–25*	*>5–10*	*>1–5*	*>0.1–1*	*≤0.1*
Face, body, and hand skin care preparations (excluding shaving preparations)	3	–	–	–	1	1	1
Moisturizing skin care preparations	3	–	–	2	1	–	–
Night skin care preparations	2	–	–	–	1	–	1
Paste masks (mudpacks)	3	–	1	–	1	1	–
Skin lighteners	1	–	–	–	1	–	–
Skin fresheners	3	–	–	–	2	–	1
Other skin care preparations	5	–	–	1	3	1	–
1981 TOTALS	80	1	1	11	50	13	4

*Product Category**	*Total No. Containing Ingredient*	*No. Product Formulations Within Each Concentration Range (%)*					
		>50	*>10–25*	*>5–10*	*>1–5*	*>0.1–1*	*≤0.1*
Dipropylene Glycol							
Bath oils, tablets, and salts	1	1	–	–	–	–	–
Colognes and toilet waters	2	–	–	2	–	–	–
Perfumes	12	6	4	–	1	1	–
Sachets	1	1	–	–	–	–	–
Other fragrance preparations	1	1	–	–	–	–	–
Hair sprays (aerosol fixatives)	1	–	–	–	–	–	1
Hair shampoos (noncoloring)	1	–	–	1	–	–	–
Tonics, dressings, and other hair grooming aids	1	–	1	–	–	–	–
Wave sets	4	–	–	4	–	–	–
Lipstick	4	–	–	1	1	–	2
Makeup bases	1	–	–	–	1	–	–
Deodorants (underarm)	4	–	–	–	4	–	–
Aftershave lotions	2	–	–	–	1	1	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	4	–	–	–	–	–	4
Face, body, and hand skin care preparations (excluding shaving preparations)	3	–	–	–	3	–	–
Foot powders and sprays	1	–	–	–	–	1	–
Moisturizing skin care preparations	3	–	–	1	2	–	–
Skin fresheners	2	–	1	–	–	1	–
Wrinkle smoothers (removers)	1	–	–	–	1	–	–
Other skin care preparations	1	–	–	1	–	–	–
1981 TOTALS	50	9	6	10	14	4	7

*Preset product categories and concentration ranges in accordance with federal filing regulations (21 CFR 720.4).

BIOLOGICAL PROPERTIES

Absorption, Metabolism, and Excretion

Romsos and associates[22] investigated the effects of Butylene Glycol on lipid metabolism in rats, pigs, and chicks. The animals were fed a basal high carbohydrate diet that contained approximately 20 percent protein and 5 percent fat. In the test diets, Butylene Glycol was substituted isocalorically for the carbohydrate. The diets were offered ad lib except for 1 experiment in which pigs were fed to satiety twice daily. Controls received the basal diet. Addition of up to 20 percent Butylene Glycol to the diet did not affect body weight gain of the 3 species. Blood β-hydroxybutyrate content increased in all 3 species. Plasma triglyceride concentrations decreased in the rat, increased in pigs, and remained the same in chicks. Plasma glucose decreased in the rat and remained stable in pigs and chicks. Dietary Butylene Glycol decreased the rate of fatty acid synthesis in the liver of rats, but there was no such effect in pigs or chicks.

Mehlman et al.[23] studied the metabolic fate of Butylene Glycol in the rat. Two groups of 14 rats each were fed for up to 7 weeks either a control diet of 70 percent carbohydrate and 30 percent fat or 45 percent carbohydrate, 30 percent fat, and 25 percent Butylene Glycol. Body weight gain and epididymal fat pad weight decreased in test animals receiving the test diet. Blood acetoacetate and β-hydroxybutyrate concentrations were increased significantly. Blood pyruvate concentration was decreased significantly in animals fed this glycol for 7 weeks. The metabolism of glucose and Butylene Glycol to ketones by hepatic tissue taken from test animals was also studied. The conversion of glucose to lactate and pyruvate was decreased, as was the concentration of ketones. In liver slices, Butylene Glycol was metabolized to acetoacetate and β-hydroxybutyrate. Butylene Glycol, therefore, is metabolized in the cytosol and converted by the liver to ketones; it is then oxidized in the tricarboxylic acid cycle.

Tate et al.[24] also studied the metabolic fate of Butylene Glycol in rats. They found that the conversion of the glycol to β-hydroxybutyrate in the liver was dependent on NAD^+ and inhibited by pyrazole. They found that hepatic alcohol dehydrogenase was the catalyst in the catabolism of the glycol to an intermediate aldol and then to β-hydroxybutyrate.

Mehlman et al.[25] also reported that hepatic alcohol dehydrogenase was the enzyme responsible for the initial oxidation of Butylene Glycol.

The metabolites of Butylene Glycol in the brain of rats were determined by Morris et al.[26] The animals were fed diets containing 1 of the following: 47 percent dietary calories as glucose, 47 percent calories as Butylene Glycol, or 47 percent calories as ethanol for 62 days. The animals were killed and metabolites in the brain were determined. Butylene Glycol significantly decreased glutamate, lactate, and pyruvate concentrations. Glucose concentrations and the NADP/$NADPH_{IDH}$ ratios were also decreased.

Rats and mice excreted up to 40 percent of a 200 mg daily oral dose of Hexylene Glycol in the urine.[27] An oral 1 mmol/kg dose of Hexylene Glycol administered to rabbits was excreted as glucuronate (67 percent of original dose).[28]

When administered orally or by subcutaneous injection to rabbits, Ethoxydiglycol was oxidized in the body or excreted as glucuronate. Such administration was followed by a marked increase in the urinary content of glucuronic acid.[29]

Reproductive Physiology

The effect of the ingestion of Butylene Glycol on pregnant rats and on the metabolism of their offspring was studied.[30] Groups of pregnant rats were given water (control) or Butylene Glycol (9 percent w/v) in drinking water. Treatment was continued throughout the period of gestation and lactation. The length of gestation was not affected by the glycol. The investigators found that rats that ingested Butylene Glycol through gestation bore offspring with a slight increase in RNA content in neurones taken from the cerebral cortex at 18 days. In 8- and 18-day-old pups, protein synthesis in the liver was significantly reduced. In amino acid incorporation studies, neuronal perikarya from 8-day-old pups incorporated 45 percent more amino acids into acid-insoluble polypeptides than did controls. However, protein synthesis in neurons from 18-day-old pups was severely inhibited by maternal ingestion of the glycol. Therefore, maternal treatment with the glycol exerted opposite effects on neuronal protein synthesis at different stages of postnatal development of progeny. Amino acid incorporation by free and membrane-bound ribosomes from liver of 8- and 18-day-old pups was increased by Butylene Glycol.

Neuropharmacology and Behavior

Ayers and Isgrig[31] studied the effect of Butylene Glycol on the behavior of rats in several experiments. To study its effect on voluntary activity (running), the compound was administered intragastrically in a 3.5 g/kg dose, once a week for 3 weeks. Glycerol, water, sucrose, or a sham was administered on 4 other days in the week. Butylene Glycol depressed voluntary running activity; this finding might be due to the glycol's interference with hunger motivation, since intubation of the compound depressed food and water intake. These investigators also studied the dose-effect of Butylene Glycol on food and water intake and urine output in several different experiments. In one study, groups of 8 male Charles River Sprague-Dawley rats were fed Butylene Glycol in doses of 0, 1.75, 3.5, 5.25, or 7.0 g/kg. Corn oil was added to the last 4 dosages to produce a constant caloric value. Distilled water and lecithin (emulsifier) were also added to produce a constant dose volume of 11.4 ml/kg. Each dose was administered to each animal daily over a 5-day period. Ingestion of the glycol produced a dose-related depression of activity and food and water intake. In another experiment, 10 male Charles River Sprague-Dawley rats were trained to balance on a rotating dowel. Butylene Glycol (7.0 g/kg) was administered once a week for 3 weeks. Other animals received glycerol, sucrose, or ethanol. The glycol produced more falls than any of the other test compounds. The glycol-treated rats were barely able to stand, and Butylene Glycol apparently acted as a CNS depressant or a muscle relaxant.

The effects of Butylene Glycol on neuropharmacology, behavior, and CNS function were studied in male and female Sprague-Dawley rats, which were given IP doses of 0.2 g/ml of Butylene Glycol in sterile 0.15 M saline.[32] Control animals were given equal volumes of saline. Another group of rats was fed a liquid diet containing Butylene Glycol in increasing concentrations (0.07 g/ml for 2 days; 0.08 g/ml for 2 days; 0.09 g/ml for 3 days; then 0.1 g/ml for 5 days). The IP administration of the glycol caused a dose-related impairment of motor coordination 1 hour after treatment as measured by aerial righting reflex. Administration of the compound depressed cGMP content in the cerebellum but did not alter plasma-leuteinizing hormone. "Conflict behavior," as measured by the number of electrical shocks accepted by rats, was attenuated after treatment with glycol, i.e., more shocks were accepted by treated rats than by control rats. Compound treatment also caused a decrease in blood pH and blood pressure. When ethanol-withdrawn rats were acutely treated with Butylene Glycol, a dose-related decrease in tremors was observed. Feeding of rats caused no significant motor coordination impairment, and all rats gained weight. After 12 days, the glycol was removed from the diet. No tremors developed after 1 hour, but 1 of 9 rats developed seizures. After 7.5 hours, tremors increased, and 33 percent of the rats developed seizures; 1 died.

Microbiological Effects

Butylene Glycol can be used as the sole carbon source by some strains of mycobacteria.[33] However, other investigators found it to be toxic to some microorganisms and useful as a cosmetic preservative.[19] Harb and Toama[34] reported that Butylene Glycol is the most efficient polyol as an antimicrobial agent. It inhibits both gram-positive and gram-negative microorganisms, as well as molds and yeast. However, it is not sporicidal. Those microbes against which Butylene Glycol is effective include *Escherichia coli, Pseudomonas aeroginosa, Staphylococcus aureus, Corynebacterium hofmanii, Aspergillus niger, Aspergillus fumigatus, Pityrosporum oxalicum, Fusarium sp.,* and *Candida albicans.*

Animal Toxicology

Oral Toxicity

Acute Studies

The acute oral LD_{50} of Butylene Glycol was 23 g/kg in rats[6,35] and 11 g/kg in guinea pigs.[35] A nail lotion containing 5.0 percent Butylene Glycol had an LD_{50} of >5 g/kg in rats,[36] and a product containing 21.35 percent Butylene Glycol produced no deaths when fed to rats at 15 g/kg.[37]

Windholz[6] reported the acute oral LD_{50} of Hexylene Glycol in rats was 4.70 g/kg. Other sources reported an oral LD_{50} of 4000 mg/kg for rats,[35] 3200 mg/kg for rabbits,[38] 2800 mg/kg for guinea pigs,[38] and 3900 mg/kg for mice.[35] A skin care product formulation containing 1.6 percent Hexylene Glycol was found to be "slightly toxic" or "practically nontoxic" when administered orally to groups of 10 rats in 4 separate assays.[39] An eye makeup remover containing 1.0 percent Hexylene Glycol caused no deaths when administered orally to 10 mice at 15 ml/kg.[40]

The acute oral LD_{50} values for Ethoxydiglycol are: in rats, 5.54 g/kg; in mice, 6.58 g/kg; and in guinea pigs, 3.87 g/kg.[41] A paste mask product formulation containing 2 percent Ethoxydiglycol caused no signs of toxicity when administered orally to 10 rats at 13 ml/kg.[42] A body lotion containing 1.0 percent Ethoxydiglycol caused no deaths when 15 ml/kg oral doses were administered to 10 mice.[43]

The acute oral LD_{50} of Dipropylene Glycol in rats was 15 g/kg.(35) A shaving preparation containing 7.2 percent Dipropylene Glycol had an oral LD_{50} of >5 g/kg.(44)

Subchronic Studies

For subchronic effects of Butylene Glycol, see also the Metabolism section of this report.

Larsen(27) reported that Hexylene Glycol fed to mice daily at 5, 10, or 20 mg Hexylene Glycol for 57 to 81 days produced no effect on growth curves. Also, rats receiving up to 150 mg of this glycol in the diet daily for 4 months had no abnormality in growth, behavior, or fertility; some changes were present in renal tissue of rats of the 200 mg/day group.(27)

No effect was caused by the daily consumption of 0.49 g/kg Ethoxydiglycol by each of 5 rats for 30 days. However, 0.87 g/kg caused reduced feed consumption.(45)

Four groups of Charles River Wistar rats, each consisting of 12 males and 12 females, were fed diets containing 0 (control), 0.25, 1.0, or 5.0 percent Ethoxydiglycol for periods up to 90 days. Observations were made of body weight, food intake, hematological parameters at 6 and 12 weeks, kidney function, blood urea concentration, and urine composition. Organs examined were the liver, kidneys, brain, spleen, heart, adrenals, and gonads. The investigators found that throughout the 90 days, the general conditions remained good. One male rat in the 5 percent group died on Day 23; there was weight loss and degeneration of renal tubules and liver. Growth rates of male and female rats were reduced when fed the 5 percent diet, and this was associated with a decrease in food consumption. No hematological changes were produced by any diet. However, activity of urinary glutamic-oxaloacetic transaminase was increased in both sexes fed the 5 percent diet, which was indicative of impaired renal function. An increase in weight of the kidneys occurred in both sexes fed the 5 percent diet. No other important changes were found.(46)

The effect of subchronic ingestion of Ethoxydiglycol was studied in rats, mice, and pigs. The glycol was fed for 90 days to groups of 15 male and 15 female rats at dietary concentrations of 0 (control), 0.5, or 5 percent and to groups of 20 male and 20 female mice at dietary concentrations of 0 (control), 0.2, 0.6, 1.8, or 5.4 percent. Three groups of 4 male and 4 female pigs were fed daily oral doses of 0 (control), 167, 500, or 1500 mg/kg. There was a reduction of growth in rats and mice at the highest concentrations. All 3 species had reduced hemoglobin concentration at the highest doses administered. Oxaluria occurred in rats and mice at highest concentrations. Three pigs given 1500 mg/kg per day for up to 21 days died with signs of uremia. For the surviving pigs, the dose was then reduced to 1000 mg/kg per day. Six of the 20 male mice fed the 5.4 percent diet died of renal damage. The relative weights of the kidneys was increased in all 3 species fed the highest concentration of glycol and in mice fed the 1.8 percent diet. Microscopic changes were hydropic degeneration of the proximal renal tubules in all 3 species fed the highest dosage and in pigs receiving 500 mg/kg per day. Hydropic degeneration of the hepatocytes was observed in those pigs above a dose of 500 mg/kg. Hepatic cell enlargement was found in those mice fed the 1.8 and 5.4 percent diets. The "no effect" level for Ethoxydiglycol in rats was 0.5 percent of the diet. In mice it was 0.6 percent of the diet, and in pigs it was 167 mg/kg per day.[47]

Chronic Studies

Butylene Glycol was fed to Sprague-Dawley weanling rats and beagle dogs for 2 years. In the rat study, 60 male and 60 female control rats were fed a basal diet and water ad lib. Three test groups of 30 male and 30 female rats each were fed diets containing 1.0, 3.0, or 10.0 percent Butylene Glycol for 2 years. Observations were made on body weight, food consumption, compound consumption, pharmacological effects, urinalysis, and gross appearance. Erythrocyte and leukocyte counts, packed cell volume, and hemoglobin values were determined. At 1 year, 10 animals from each group were killed, and all survivors were killed at the end of 2 years. Representative organs were weighed and examined microscopically. These tests were negative for deleterious or toxic effects due to the ingestion of Butylene Glycol at any dietary concentration.[48]

In the study using beagle dogs, a control group of 4 males and 4 females were fed a basal diet, and 3 similar groups received diets containing 0.5, 1.0, or 3.0 percent Butylene Glycol. Daily or weekly observations were made of feed intake, elimination, clinical appearance, pharmacological effects, and feed and compound consumption. The blood, urine, and representative organs were examined as with the rat portion of the study described above. Two animals from each group were killed after 1 year and the remainder after 2 years. As with the rats, no toxic effects were produced by the ingestion of Butylene Glycol at any dietary concentration.[48]

Ethoxydiglycol was fed to rats at 1.0 g/kg per day for 2 years. The rats had slight hepatic damage, some interstitial edema in the testes, and in 1 animal, oxalate crystals in the kidney.[26]

Parenteral Toxicity

The subcutaneous LD_{50} of Butylene Glycol in mice and rats was 16.5 ml/kg and 20.1 ml/kg, respectively.[11] No deaths were caused by intraperitoneal injection of 1.0 g/kg Butylene Glycol into 5 mice.[49] Butylene Glycol was evaluated for tissue irritation using chicken pectoral muscle. Injections of 0.5 ml of the glycol, 1.3 cm deep into the right and left pectoral muscle of each of 6 chickens, caused only minimal tissue irritation.[50]

Hexylene Glycol had a subcutaneous LD_{50} of 13 g/kg in rabbits and rodents.[38] The intraperitoneal LD_{50} of Hexylene Glycol in the mouse was 4.5 ml/kg.[51] NIOSH[35] lists the intraperitoneal LD_{50} in mice as 1299 mg/kg.

The subcutaneous LD_{50} of Ethoxydiglycol in mice was 5500 mg/kg.[38] In rats and rabbits, it was 3.4 ml/kg and 2.0 ml/kg, respectively.[52] The intraperitoneal LD_{50} of Ethoxydiglycol in rats was 6310 mg/kg.[38] The intravenous LD_{50} in dogs was 3000 mg/kg and in cats, 5000 mg/kg.[38] Other investigators report intravenous LD_{50}s in mice, rats, and rabbits as 3.9, 2.9, and 0.9 ml/kg, respectively.[52]

The intraperitoneal LD_{50} of Dipropylene Glycol in rats and mice was 10 g/kg and 4600 mg/kg, respectively.[35] The intravenous LD_{50} in rats and dogs was 5800 mg/kg and 11,500 mg/kg, respectively.[35]

Inhalation Toxicity

Rats survived an 8-hour exposure to the saturated, room temperature vapors of Hexylene Glycol.[45]

Cutaneous Toxicity

Acute Studies

The cutaneous LD_{50} of Hexylene Glycol in rabbits and rodents was 13.2 g/kg.[38] A product formulation containing 5.0 percent Butylene Glycol had a cutaneous LD_{50} of >2 g/kg when tested in rabbits.[36]

The cutaneous LD_{50} of Ethoxydiglycol was 6 g/kg in rats[38] and 10.3 g/kg in rabbits.[53]

A product formulation containing 7.2 percent Dipropylene Glycol produced a cutaneous LD_{50} of >2 g/kg when tested in rabbits.[44]

Subchronic Studies

A product formulation containing 3 percent Butylene Glycol was applied daily at 500 mg/kg to the clipped intact and abraded skin of each of 8 albino rabbits for 4 weeks. A control group of 8 rabbits remained untreated. All of the animals survived the duration of the study. Clinical observations of compound-related importance were confined to the skin, which had slight erythema with drying and flaking. No systemic effects as evidenced by microscopic tissue examination were attributable to the test material.[54]

Skin Irritation

Primary Irritation

Undiluted Butylene Glycol produced no more than minimal skin irritation when tested under occlusion on the skin of rabbits for 24 hours[55] or daily for 4 consecutive days.[56]

Undiluted Hexylene Glycol produced moderate irritation when 465 or 500 mg was applied to the skin of rabbits for 24 hours.[38] A 24-hour application of 1.84 g/kg undiluted Hexylene Glycol to the skin of rabbits caused mild edema and erythema.[57]

Undiluted Ethoxydiglycol was a mild irritant when applied to rabbit skin (500 mg for 24 hours).[38] According to Rowe,[57] it is a nonirritant to rabbits.

Undiluted Dipropylene Glycol caused mild irritation when 500 mg was applied to rabbit skin for 24 hours.[38]

Several product formulations containing 5.0 to 21.4 percent Butylene Glycol, 1.0 to 1.6 percent Hexylene Glycol, 1.0 percent Ethoxydiglycol, or 7.2 percent Dipropylene Glycol were tested for 24 hours under occlusion on rabbit skin (Leberco Labs).[36,44,58-64] The products produced no irritation to moderate irritation, depending upon the particular formulation tested. The degree of irritation did not correlate with the concentration of glycol.

Cumulative Irritation

A daily dose of 0.5 ml of a paste mask product formulation containing 2 percent Ethoxydiglycol was applied to the backs of 3 albino rabbits for 14 consecutive days. Each treatment site was rinsed with warm tap water 30 minutes after treatment. There was slight erythema 24 hours after the initial application that had disappeared by 48 hours. There were no other signs of irritation.[42]

Ocular irritation

According to NIOSH,[35] 505 mg of undiluted Butylene Glycol applied to the rabbit eye was an irritant. No irritation was observed when 0.1 ml of undiluted Butylene Glycol[65] or a 40 percent aqueous solution of Butylene Glycol[66] was instilled into 1 eye of each of 6 rabbits.

Irritation was severe when 93 mg undiluted Hexylene Glycol was instilled into the eyes of rabbits,[38] and Rowe[57] reported that this glycol caused corneal damage in a rabbit. A 25 percent aqueous solution of Hexylene Glycol caused no ocular irritation when tested in the rabbit.[67]

Moderate toxic effects were found in the eyes of rabbits instilled with 500 mg undiluted Ethoxydiglycol. Mild effects were caused by 125 mg.[38]

Laillier et al.[68] studied the ocular effects of Ethoxydiglycol and other chemicals using the rabbit. The chemicals were applied to a series of 4 animals at application frequencies of 1, 3, 6, 7, and 13 times over periods of 2, 4, 7, 26, and 58 hours. The chemicals were used either pure or as a 25 percent dilution in distilled water in 0.1 ml volumes. Ocular edema was measured by the following formula:

$$\frac{\text{mg dry tissue weight}}{\text{mg wet tissue weight}} \times 100$$

In addition, aqueous humor and conjunctival content were assayed for effects 1 hour after Evans blue solution was injected into the rabbit's marginal ear vein. Ethoxydiglycol was very irritating to the rabbit's eye in this assay system (Table 3).

Undiluted Dipropylene Glycol is an irritant in the rabbit eye in an amount of 510 mg.[35]

Several product formulations containing 5.0 to 21.35 percent Butylene Glycol, 1.0 percent Hexylene Glycol, 1.0 to 2.0 percent Ethoxydiglycol, or 7.2 percent Dipropylene Glycol produced no more than minimal, transient irritation when instilled into the eyes of rabbits.[36,42,44,69-72] Another product formulation containing 1.6 percent Hexylene Glycol produced mild to moderate irritation in the eyes of rabbits.[73] This formulation had also produced mild to moderate irritation when applied to the skin of rabbits.

Clinical Assessment of Safety

Nutritional and Metabolic Studies

Tobin and associates[74] investigated the nutritional and human metabolic effect of Butylene Glycol. Three studies were conducted.

In the first experiment, the effect of Butylene Glycol and urea in the nutrition of 12 men and women was studied. The volunteers went through a 2-day depletion period in which nitrogen intake was 1.23 g/day. Caloric intake was evaluated and adjusted so that during the 4- to 7-day test periods subjects consumed diets with constant caloric content. Dietary variation was randomly distributed during

TABLE 3. Ocular Irritation in Rabbits by Measuring Tissue Edema: Ethoxydiglycol[68]

	No. of Instillations (4 Rabbits Each)	Time* (hours)	Conjunctivae (% Dry Weight)	Conjunctivae (μg Evans Blue/g Dry Weight)	Corneas (% Dry Weight)	Aqueous Humors (μg Evans Blue/ml)
Ethoxydiglycol (undiluted)	1	2	13.9 ± 0.8†	439 ± 88†	24.1 ± 1.2†	135.1 ± 69.1†
	3	4	12.7 ± 1.3†	439 ± 92†	21.2 ± 2.0†	21.7 ± 16.0†
	6	7	13.1 ± 0.6†	497 ± 168†	18.6 ± 1.9†	9.0 ± 4.9†
	7	26	16.4 ± 1.9†	906 ± 171†	17.1 ± 1.5†	10.9 ± 8.0†
	13	58	15.9 ± 1.0†	988 ± 283†	15.8 ± 1.4†	29.5 ± 22.9†
25% Ethoxydiglycol in distilled water	1	2	17.7 ± 1.1†	189 ± 28†	24.8 ± 1.3	3.3 ± 2.6†
	3	4	20.7 ± 0.8	91 ± 23	25.9 ± 1.5	0.8 ± 0.25
	6	7	18.6 ± 1.4	178 ± 34†	25.3 ± 1.2	11.6 ± 8.6†
	7	26	20.8 ± 0.4	177 ± 32†	25.5 ± 1.5	12.8 ± 11.9†
	13	58	19.4 ± 1.4	139 ± 27	27.1 ± 1.0	5.6 ± 3.0†

*Time in hours over which instillations made.
†Significantly different from controls (Student's *t*-test).
Mean ± 95% confidence limits.

the 4 experimental periods: 1 in which the glycol (15 g) was substituted isocalorically for starch in the diet, 1 in which starch without the glycol was ingested, 1 in which urea (4 g of nitrogen/day) was added to the diet, and the fourth and final period in which the glycol and urea were added to the diet. Butylene Glycol, as compared to starch, caused a significant decrease of urinary nitrogen excretion. Subjects fed urea or glycol plus urea had a significant increase in urinary excretion of nitrogen. The glycol did not increase fecal nitrogen excretion, but urea feeding did. Feeding the glycol or urea or the combination caused a less negative nitrogen balance than did the starch feeding. The glycol caused a lowering of blood glucose and no increase in blood ketones. The investigators concluded that Butylene Glycol can be used as a caloric source by human beings.

The second study investigated the effect of Butylene Glycol on endocrine function and its influence on glucose homeostasis. Twenty-seven women volunteered for a 15-day experiment in which one half were fed 40 g of Butylene Glycol per day for 5 days or a calorically equivalent quantity of sucrose for 5 days. At the end of 5 days, the diets were switched. Mean blood glucose concentrations and serum insulin concentrations were lower in the second and third weeks of ingestion. The glycol had no effect on triglyceride or cholesterol concentrations. Fasting insulin and growth hormone concentrations were somewhat increased by the glycol.

In the third study, 10 adult male and female volunteers were fed for 12 days 6 g of nitrogen per day, starch, and vitamin and mineral supplements. The Butylene Glycol was substituted isocalorically for sucrose to provide 10 percent of the total caloric intake. Glucose tolerance tests were performed on the sixth and twelfth days of the test. Glucose concentrations were normal, as were free fatty acid and growth hormone values. Serum insulin values and blood pyruvate and lactate values were normal, and β-hydroxybutyrate, acetoacetate and triglyceride values were likewise normal. Butylene Glycol was nontoxic in these tests.[74]

Skin Irritation/Sensitization

A Shelanski and Shelanski repeated insult patch test was conducted on 200 volunteers (80 male, 120 female) to assess the irritation and sensitization potentials of Butylene Glycol. The compound was diluted to 50 percent in water, and 0.9 ml of the mixture was applied under occlusion to sites on the upper arm. After 24 hours of contact, the patches were removed and the sites were graded on a scale of 0 (no reactions) to 4+ (erythema, edema, vesicles, and extensions beyond the site of contact). After 24 hours, the sites were reexamined. If no changes occurred, a second patch was reapplied to the same site. This cycle was repeated each Monday, Wednesday, and Friday. After the fifteenth application, sites were not treated for a 2-week period, and then 24-hour occlusive patches were applied to the same sites. Test areas were graded immediately and then at 24 and 48 hours after patch removal. The investigator reported visible skin change in one subject after applications 4–6 and in another after applications 13–15. No reactions were caused by the challenge patch. Butylene Glycol was a mild fatiguing agent in 2 of 200 test subjects. With statistical extrapolation, greater than 98 percent of the general population would not be sensitized to Butylene Glycol[19] (Table 4).

Undiluted Butylene Glycol was applied to the volar skin of the forearms or

TABLE 4. Clinical Skin Patch Tests with Butylene Glycol and Hexylene Glycol

Test Method	*Material Tested*	*Concentration (%)*	*No. of Subjects*	*Results*	*Reference*
24-hour single insult occlusive or semiocclusive patch	Butylene Glycol	100	37	Occlusive patch; no reactions	75
			39	Semiocclusive patch; 1 subject with mild irritation	
	Hexylene Glycol	100	37	Occlusive patch; minimal irritation (primary irritation index 0.11; max, 4.0)	76
			39	Semiocclusive patch; minimal irritation (primary irritation index 0.02; max, 4.0)	
Shelanski and Shelanski repeated insult patch test (24-hour occlusive patches 3 days/week for 15 induction patches; challenge patch after 2-week rest)	Butylene Glycol	50 (in water)	200	Mild skin irritation in 2 subjects; no sensitization	19

medial arms of 37 human subjects under occlusion and 39 subjects under semioccluded conditions for 24 hours. One subject in the semioccluded panel had evidence of mild irritation; no other reactions were observed in either panel[75] (Table 4). Hexylene Glycol was tested in an identical fashion, producing primary irritation indices of 0.11 (scale 0 to 4) for the occluded patch and 0.02 for the semioccluded patch. These scores are indicative of only minimal irritation[76] (Table 4).

Fisher[18] reported that cross-reactivity (sensitivity) may occur between Butylene Glycol and propylene glycol.

A number of product formulations containing 1 of the glycols at concentrations of 0.016 to 21.4 percent have also been tested for skin irritation and sensitization in humans (Table 5). In single insult occlusive patch tests, products con-taining 3.0 to 21.4 percent Butylene Glycol produced no more than minimal irritation.[77-80] Several multiple insult tests were conducted on products containing a glycol in which no irritation to moderate irritation was found depending upon the particular product tested. There was no correlation between the degree of irritation and the concentration of glycol (Table 5). Results indicative of irritation cannot be interpreted without knowledge of the other ingredients in a formulation. Of the 1087 subjects tested in skin sensitization assays (Schwartz-Peck and Draize-Shelanski tests), there were no reactions indicative of sensitization to any of the glycols (Table 5).

Photoreactivity

Four studies included exposure to ultraviolet light as a supplement to the Schwartz-Peck prophetic patch tests and Draize-Shelanski repeated insult patch tests on a nail lotion containing 5.0 percent Butylene Glycol[81] and on a shaving preparation containing 7.2 percent Dipropylene Glycol[82] (Table 5). The ultraviolet light exposure was to a Hanovia Tanette Mark I quartz lamp at a distance of 12 inches for 1 minute. This lamp has a wavelength coverage of 240 to 370 nM, with a peak at 365 nM. None of the subjects in the Schwartz-Peck tests had reactions when a single UV exposure was made after the second insult. The Draize-Shelanski tests included UV exposure after induction patches 1, 4, 7, and 10 and after the challenge patch; there were no reactions (Table 5).

Ocular Irritation

A drop of Butylene Glycol applied to the eyes of humans caused immediate severe stinging similar to that induced by propylene glycol. Irrigation with water brought rapid relief.[83]

When human subjects were exposed for 15 minutes to a vapor concentration of 50 ppm of Hexylene Glycol, ocular irritation occurred.[57]

Inhalation Toxicity

Nasal and respiratory discomfort occurred from a concentration of 100 ppm aerosolized Hexylene Glycol, and at 1000 ppm irritation of the eyes, nose, throat, and respiratory tract were noted.[57]

Industry Complaint Experience

A skin care product containing 1.6 percent Hexylene Glycol had 43 safety-related complaints in 4 years with 243 million units distributed.[97] A shaving preparation containing 7.2 percent Dipropylene Glycol had 7 safety-related complaints in 3 years with 2.3 million units sold; 2 of these were listed as "rash" and 5 as "irritated skin."[98]

SUMMARY

Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol are viscous liquids used in the cosmetic industry as humectants, emulsifiers, plasticizers, and solvents. They are added to various types of cosmetic products at concentrations up to 50 percent. The Glycols also have many noncosmetic uses and have been given Direct and/or Indirect Food Additive status by the FDA.

Various animal species and man metabolize Butylene Glycol and use it as a source of calories. The results of acute, subchronic, and chronic oral toxicity studies using a variety of animal species indicate a low order of toxicity for the Glycols. Results of parenteral injection, inhalation, and acute and subchronic cutaneous toxicity studies likewise support a low order of toxicity. Butylene Glycol, Ethoxydiglycol, and Dipropylene Glycol caused minimal to mild irritation of rabbit skin, whereas Hexylene Glycol was moderately irritating. The Glycols produced mild to severe ocular irritation when tested in rabbits, and Hexylene Glycol produced the most severe irritation. Although undiluted Hexylene Glycol

TABLE 5. Clinical Skin Patch Tests with Product Formulations Containing Glycols

Test Method	*Material Tested*	*Concentration (%)*	*No. of Subjects*	*Results*	*Reference*
24-hour single insult occlusive patch	Eye shadow	21.35 Butylene Glycol	20	Minimal irritation	79
	Foundation makeup	16.0 Butylene Glycol	19	Minimal irritation. Also included semiocclusive patch with minimal irritation	78
	Mascara	8.0 Butylene Glycol	20	Minimal irritation	80
	Rouge	3.0 Butylene Glycol	20	No signs of irritation	77
"Soap chamber test:" 1 24-hour followed by 4 daily 6-hour applications in Duhring chambers on volar forearm	Personal cleanliness product	0.13 Hexylene Glycol (8% aqueous dilution of product containing 1.6%)	10	Moderate irritation	84
Cumulative irritancy test (daily 23-hour occlusive patch for 21 days)	Eye shadow	21.35 Butylene Glycol	10	Slight irritation; total composite score was 70/630 max	85
	Paste mask	2.0 Ethoxydiglycol	12	Essentially nonirritating; total composite score was 36/630 max	86
Schwartz-Peck prophetic patch test (open and closed 48-hour patches, repeated after 2 weeks)	Nail lotion	5.0 Butylene Glycol	104	No reactions; supplemental UV exposure at open patch after second insult produced no reactions	81
	Shaving preparation	7.2 Dipropylene Glycol	101	Mild irritation with closed patch in 6 subjects at first exposure and in 8 subjects at second; open patches and supplemental UV exposure after second insult produced no reactions	82
Draize-Shelanski repeated insult patch test (24- or 48-hour patches 3 days/week for 9 or 10 induction patches; challenge patch after 2-week rest)	Foundation makeup	16.0 Butylene Glycol	108	Mild irritation; no sensitization	87

	Nail lotion	5.0 Butylene Glycol	49	No irritation; no sensitization. Supplemental UV exposure after induction patches 1, 4, 7, and 10 and after challenge showed no photosensitization	81
	Rouge	3.0 Butylene Glycol	108	Slight irritation; no sensitization	88
	Eye makeup remover	1.0 Hexylene Glycol	103	Mild irritation; no sensitization	89
	Personal cleanliness product	0.048 Hexylene Glycol (3% aqueous dilution of product containing 1.6%)	52	Mild irritation with fatiguing during induction; 4 reactions on challenge at original site with 2 persisting and 3 reactions on challenge at alternate site with 1 persisting. Reactions at challenge consistent with induction irritation reactions. Test sites exposed to 30 minutes natural sunlight 24 hours after each application	90
	Personal cleanliness product	0.016 Hexylene Glycol (1% aqueous dilution of product containing 1.6%)	52	Mild irritation; no sensitization	90
		0.016 Hexylene Glycol (1% aqueous dilution of product containing 1.6%)	106	No significant irritation; no sensitization	91
	Paste mask	2.0 Ethoxydiglycol	213	Minimal irritation; no sensitization	92
	Body lotion	1.0 Ethoxydiglycol	93	Minimal irritation; no sensitization	93
	Shaving preparation	7.2 Dipropylene Glycol	50	Mild irritation with probable fatiguing; no sensitization. Supplemental UV exposure after induction patches 1, 4, 7, and 10 and after challenge showed no photosensitization	82
Controlled use test: 4 weeks	Mascara	8.0 Butylene Glycol	50	No reactions	94
	Shaving preparation	7.2 Dipropylene Glycol	59	No reactions	95
Controlled use test: 2 weeks	Personal cleanliness product	1.6 Hexylene Glycol	80	Minimal irritation	96

produced severe ocular irritation, a 25 percent aqueous solution produced no signs of irritation.

Feeding studies in man indicated that Butylene Glycol was metabolized and nontoxic. Single insult 24-hour skin patch tests on undiluted Butylene Glycol and undiluted Hexylene Glycol showed a very low order of primary skin irritation potential for these ingredients. In a repeated insult patch test, Butylene Glycol produced mild skin fatigue in 2 of 200 test subjects but no evidence of skin sensitization. A number of product formulations containing the Glycols at concentrations up to 21.4 percent have been tested in various human skin irritation and sensitization assays (Table 5). The degree of irritation produced depended upon the particular formation. There was no correlation between the degree of irritation and the concentration of the Glycol present in the formulation. There were no reactions indicative of skin sensitization to the Glycols in any of the 1087 subjects tested under skin sensitization assays. Supplemental exposure to ultraviolet light in some of the skin sensitization tests on product formulations produced no reactions suggestive of phototoxicity or photosensitization. Butylene Glycol and Hexylene Glycol were irritating to the human eye. And Hexylene Glycol was irritating to the respiratory tract at concentrations significantly higher than those generally found in cosmetic products.

CONCLUSION

Based on the available data, Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol are safe as presently used in cosmetics.

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