International Journal of Toxicology
28(6S) 162S-174S

DOI: 10.1177/1091581809350933
http://ijt.sagepub.com
SAGE

Final Report on the Safety Assessment of PPG-2 Methyl Ether, PPG-3 Methyl Ether, and PPG-2 Methyl Ether Acetate

Valerie Robinson,[1] Wilma F. Bergfeld,[1] Donald V. Belsito,[1] Curtis D. Klaassen,[1] James G. Marks Jr,[1] Ronald C. Shank,[1] Thomas J. Slaga,[1] Paul W. Snyder,[1] Cosmetic Ingredient Review Expert Panel, and F. Alan Andersen[1]

Abstract

PPG-2 methyl ether, PPG-3 methyl ether, and PPG-2 methyl ether acetate are used in cosmetics as fragrance ingredients and/or solvents at concentrations of 0.4% to 2%. Propylene glycol ethers are rapidly absorbed and distributed throughout the body when introduced by inhalation or oral exposure, but the inhalation toxicity of PPG-2 methyl ether vapor, for example, is low. Aerosols, such as found with hair sprays, produce particle sizes that are not respirable. Because these ingredients are highly water-soluble, they are likely to be absorbed through the human skin only at slow rates, resulting in low blood concentrations and rapid removal by the kidney. These ingredients are not genotoxic and are not reproductive or developmental toxicants. Overall the data are sufficient to conclude that PPG-2 methyl ether, PPG-3 methyl ether, and PPG-2 methyl ether acetate are safe as used in cosmetics.

Keywords

PPG-2 methyl ether, PPG-3 methyl ether, PPG-2 methyl ether acetate, cosmetics, safety

This safety assessment considers published and unpublished data pertinent to the safety of PPG-2 methyl ether (dipropylene glycol methyl ether), PPG-3 methyl ether (tripropylene glycol methyl ether), and PPG-2 methyl ether acetate (dipropylene glycol monomethyl ether acetate) as used in cosmetics. Propylene glycol has been reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel and found to be safe for use in cosmetic products at concentrations up to 50.0%.[1] Dipropylene glycol was found safe as presently used in cosmetics, a conclusion that was reaffirmed in 2004.[2]

Chemistry

Definition and Structure

PPG-2 methyl ether (CAS nos. 13429-07-7 and 34590-94-8) is the polypropylene glycol ether of methyl alcohol that conforms to the formula in Figure 1.[3]

PPG-3 methyl ether (CAS no. 25498-49-1 is the polypropylene glycol ether of methyl alcohol that conforms to the formula in Figure 2.[3]

PPG-2 methyl ether acetate (CAS no. 88917-22-0) is the ester of PPG-2 methyl ether (qv) and acetic acid (qv), with the following empirical formula: $C_9H_{18}O_4$.

Physical and Chemical Properties

Glycol ethers are a class of materials that are categorized as ethylene, monopropylene, dipropylene, or tripropylene glycol ethers.[4] The ether function may be bound to methyl, ethyl, *n*-propyl, *n*-butyl, or *t*-butyl groups. In some instances, the alcohol groups are bound in the form of their acetate esters. Because of the ease and rapidity of ester hydrolysis in vivo, there is no reason to assume that the toxicities of the esters differ from those of the unesterified glycols. Propylene glycol ethers have generally low to moderate volatility and possess high aqueous solubilities, low octanol-water partition coefficients (K_{ow}), and bioconcentration factor values of less than 10. The octanol-water coefficients for PPG-2 methyl ether acetate and PPG-3 methyl ether are 0.803 and 0.309, respectively.[5]

PPG-2 methyl ether is a colorless liquid with a mild, pleasant odor.[6] PPG-2 methyl ether exists in 3 structural forms and there are a total of 12 possible isomers. The 12 consist of

[1] Cosmetic Ingredient Review, Washington, DC, USA

Corresponding author:
Valerie C. Robinson, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036
Email: cirinfo@cir-safety.org

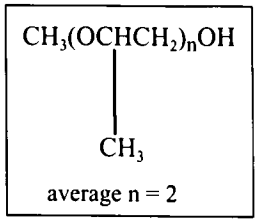

Figure 1. PPG-2 methyl ether.

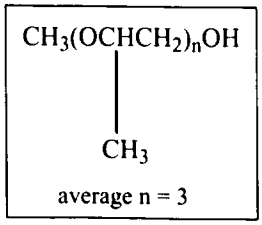

Figure 2. PPG-3 methyl ether.

4 enantiomer pairs and 2 meso-compounds.[7] PPG-2 methyl ether is a mid-to-slow evaporating solvent.[8] It is considered to be a hydrophilic solvent with 100% water solubility. The features of this chemical include powerful solvency, moderate evaporation rate, low viscosity, high dilution ratio, low surface tension, and coupling ability.[8]

PPG-3 methyl ether has 4 structural isomers, and each structural isomer has 3 asymmetric carbons. Therefore, each structural isomer has 8 possible stereochemical isomers or a total of 32 isomers of PPG-3 methyl ether.[7] Dow Chemical Company reported that PPG-3 methyl ether is a strong solvent and has a low evaporation rate and viscosity, high dilution ratio, and coupling ability. [8]

Table 1 presents properties and synonyms of PPG-2 methyl ether, PPG-3 methyl ether, and PPG-2 methyl ether acetate.

Solubility

According to Dow Chemical Company, glycols are soluble in water. Many water-immiscible materials can be incorporated into clear water solutions by means of the coupling actions of glycol.[9] Glycols are hygroscopic, and if placed in an atmosphere containing water vapor they will pick up and retain moisture. This property is responsible for the various applications of glycols as humectants and dehydrating agents.

Reactivity

No data were available on the reactivity of PPG-3 methyl ether or PPG-2 methyl ether acetate.

PPG-2 methyl ether. PPG-2 methyl ether is stable, combustible, and incompatible with strong oxidizing agents.[10] Heat or flame contributes to the instability of PPG-2 methyl ether.[11] Contact with strong oxidizing agents may cause fires and explosions. Toxic vapors and gases, such as oxides of carbon, may be released in a fire involving PPG-2 methyl ether. The National Fire Protection Association has issued a flammability rating of 2 for this chemical, which is indicative of a moderate fire hazard.

Method of Manufacture

According to Dow Chemical Company, the DOWANOL*P-series are produced by reacting propylene oxide with different alcohols, such as methanol and phenol.[12] DOWANOL PM propylene glycol methyl ether is produced when propylene oxide reacts with methanol. DOWANOL PM has an alcohol group and may be reacted with additional propylene oxide to produce PPG-2 methyl ether. Similarly, PPG-2 methyl ether can be reacted with additional propylene oxide to produce PPG-3 methyl ether. DOWANOL PMA propylene glycol methyl ether acetate is the reaction product of DOWANOL PM with acetic acid or anhydride. Other sources confirm that this general methodology is widely used.[13,14]

Commercial PPG-2 methyl ether and PPG-2 methyl ether acetate are each produced only as a 4-isomer mixture. The 4 individual isomers are not separated or produced as individual chemicals. Likewise, commercial PPG-3 methyl ether is produced only as an 8-isomer mixture. The 8 individual isomers are not separated or produced as individual chemicals.[15]

Analytical Methods

Gas chromatography is used to identify glycerol ethers.[16]

USE

Cosmetic

Table 2 summarizes the uses reported by industry to the U.S. Food and Drug Administration (FDA) for PPG-2 methyl ether and PPG-3 methyl ether.[17] The highest number of uses (18) is reported in hair conditioners for PPG-2 methyl ether, followed by hair dyes and colors (5). Based on an industry survey of current use concentrations, the range is 0.4% to 2%.[18]

PPG-3 methyl ether has 1 reported use in hair dyes and colors.[17] Current use concentration data were reported.[18] There were no reported uses found for PPG-2 methyl ether acetate.[17] No current use concentration data were reported.[18]

PPG-2 methyl ether. PPG-2 methyl ether is currently used in a variety of cosmetics as a solvent, dispersing agent, coupling agent, emollient, and fragrance in cosmetic formulations.[3,19,20]

PPG-3 methyl ether and PPG-2 methyl ether acetate are used in a wide variety of cosmetics and function as a solvent.[3]

Noncosmetic

PPG-2 methyl ether, PPG-3 methyl ether, and PPG-2 methyl ether acetate are used in a wide variety of industrial and consumer applications, such as resin solvents, dye solvents in textile and leather treatments, and ingredients in brake fluids and

Table 1. Synonyms for and Properties of PPG-2, PPG-3 Methyl Ether, Methyl Ether, PPG-2 Methyl Ether Acetate[3,8,11,21,35]

Synonym/Property	Reported Information
PPG-2 methyl ether	
Technical names	Dipropylene glycol monomethyl ether Methoxy dipropylene glycol (2-methoxymethylethoxy) propanol 1-(2-methoxypropoxy)-2-propanol Polyoxypropylene (2) methyl ether; propanol, (2-methoxymethylethoxy)- 2-Propanol, 1-(2-methoxypropoxy)- Dowanol 50B Propasol Solvent DM Polysolv; DPM solvent; UCAR solvent 2 LM arcosolv DOWANOL DPM glycol ether
Trade names	DOWANOL DPM (Dow Chemical) Hisolve DPM (Toho)
Description	Colorless liquid with a weak, ether-like odor
Molecular weight, g/mol	148.20
Boiling point, °C, at 760 mm Hg	189
Density, g/mL	0.950
Vapor pressure, mm Hg, at 25°C	0.36
Vapor density	5.11
Flash point (closed cup), °C (°F)	75 (167)
Freezing point, °C (°F)	–83 (–117)
Melting point, °C (°F)	–80 (–112)
Specific gravity (25°C/25°C)	0.951
Viscosity, cP or mPaćs @ 25°C	3.7
Surface tension, dyne/cm or mN/m @ 25°C	3.7
Specific heat, J/g/°C @ 25°C	2.25
Heat of vaporization, J/g, at normal boiling point	267
Net heat of combustion, kJ/g—predicted @ 25°C	27.2
Autoignition temperature, °C (°F)	207 (405)
Evaporation rate	0.035 (n-butyl acetate = 1.0) 351 (diethyl ether = 1.0)
Hansen solubility parameters, $(J/cm^3)^{1/2}$	
_d (dispersion)	15.5
_p (polar)	4
_h (hydrogen bonding)	10.3
Solubility	Completely miscible with water, acetone, ethanol, benzene, carbon tetrachloride, ether, methanol, monochlorobenzene, petroleum ether, and VM&P naphtha
Flammability limits, vol% in air	Lower (measured @ 100°C) = 1.10 Upper (measured @ 150°C) = 14.00
PPG-3 methyl ether acetate	
Technical names	Polyoxypropylene (3) methyl ether Polypropylene glycol (3) methyl ether Tripropylene glycol monomethyl ether
Trade names	DOWANOL TPM (Dow Chemical)
Molecular weight, g/mol	206.28
Chemical family	Aliphatic ether alcohol/aliphatic glycol ether/aliphatic triglycol ether/aliphatic triglycol mono ether/propylene glycol ether/tripropylene glycol monoether
Description	Clear, colorless liquid with a slight sweetish ether odor
Boiling point, °C, at 760 mm Hg	242.4
Density, g/mL	0.965
Vapor pressure, mm Hg, at 25°C	0.022
Flash point (closed cup), °C (°F)	121 (250)
Freezing point, °C (°F)	–78 (–108)
Specific gravity (25°C/25°C)	0.965
Viscosity, cP or mPaćs @ 25°C	5.5

(continued)

Table 1. (continued)

Synonym/Property	Reported Information
Surface tension, dyne/cm or mN/m @ 25°C	30.0
Specific heat, J/g/°C @ 25°C	2.12
Heat of vaporization, J/g, at normal boiling point	210
Net heat of combustion, kJ/g—predicted @ 25°C	27.8
Autoignition temperature, °C (°F)	277 (531)
Evaporation rate	0.0026 (n-butyl alcohol = 1.0)
	>1200 (diethyl ether = 1.0)
Solubility, g/100 g @ 25°C	∞
	∞
Hansen solubility parameters, $(J/cm^3)^{1/2}$	15.1
	2.5
	8.7
Flammability limits, vol% in air	
Lower	0.7
Upper	14.8
Octanol-water coefficient	.309
PPG-2 methyl ether acetate	
Technical name	Dipropylene glycol monomethyl ether acetate
Trade name	DOWANOL DPMA (Dow Chemical)
Molecular weight, g/mol	190.2
Boiling point, °C @ 760 mm Hg	209
Freezing point, °C (°F)	−25 (−117)
Flash point, °F/°C	187/86[2]
Evaporation rate, n-BuAc = 1	0.015
Specific gravity (25°C/25°C)	0.977
Density, lb/gal (25°C)	8.13
Density, g/cc (25°C)	0.974
Viscosity, cP (@ 25°C)	1.7
Vapor pressure, mmHg @ 20°C	0.08
Surface tension (dyne/cm)	27.3
Specific heat, J/g/°C @ 25°C	1.94
Heat of vaporization, J/g, at normal boiling point	241
Net heat of combustion, kJ/g—predicted @ 25°C	25.4
Autoignition temperature, °C (°F)	285 (545)
Evaporation rate	0.015 (n-butyl acetate = 1.0)
	791 (diethyl ether = 1.0)
Solubility @ 25°C	Solvent in water (wt%), 16.0; water in solvent (wt%), 3.5
Hansen solubility parameters, $(J/cm^3)^{1/2}$	
_d (dispersion)	16.3
_p (polar)	4.9
_h (hydrogen bonding)	6.0
Flammability limits (vol % in air)	1.21 lower (measured @ 150°C)
	5.35 upper (measured @ 150°C)
Octanol-water coefficient	.803

antifreeze products.[21] Because the methyl ethers of propylene glycol have mutual solvencies in water and oils, they are useful as coupling and dispersing agents as well as solvents for lacquers, paints, resins, dyes, oils, and greases.[20]

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

Propylene glycol ethers are rapidly absorbed and distributed throughout the body following inhalation or oral exposure.[15] Dermal absorption is somewhat slower, but subsequent distribution is rapid. Most excretion of propylene glycols is via the urine and expired air. A small portion is excreted in the feces. PPG-2 methyl ether acetate hydrolysis studies indicated that the acetate rapidly hydrolyzes in plasma to yield PPG-2 methyl ether. Metabolism of propylene glycols occurs primarily in the liver, where mixed function oxidase cleaves the ether linkage, yielding propylene glycol and an alcohol. These 2 by-products may be consumed in intermediary metabolism to CO_2 and water, with the former ultimately being excreted in expired air. Alternatively, the parent PGE (or intermediate

Table 2. Current Cosmetic Product Uses and Concentrations for PPG-2 Methyl Ether and PPG-3 Methyl Ether[17,18]

Product Category (Total No. of Products in Each Category)	Ingredient Uses in Each Product Category	Use Concentrations, %
PPG-2 methyl ether		
Noncoloring hair care products		
Conditioners (651)	18	0.5
Sprays/aerosol fixatives (275)	—	0.6
Tonics, dressings (598)	2	0.5
Other hair preparations (277)	1	—
Hair coloring products		
Dyes and colors (1690)	5	—
Makeup		
Leg and body paints (4)	1	—
Nail care products		
Nail polishes and enamels (123)	—	0.4
Other manicuring preparation (55)	—	2[a]
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (775)	2	—
Total uses/ranges for ingredient PPG-2 methyl ether	29	0.4-2
PPG-3 methyl ether		
Noncoloring hair preparations		
Hair sprays/aerosol fixatives (275)	1	—
Total uses/ranges for ingredient PPG-3 methyl ether	1	—

[a] Nail treatment.

metabolite) may be conjugated in the liver with liver with glucuronic acid and sulfate, for ultimate excretion, primarily in the urine.[15]

Miller et al[20] studied the metabolism and disposition of PPG-2 methyl ether in male Fischer 344 rats weighing 175 to 200 g.[20] The animals were given a single oral dose of approximately 1289 mg/kg (8.7 mmol/kg) of [^{14}C] PPG-2 methyl ether. The labeled material was diluted to provide a dosing solution with a specific activity of approximately 5 fCi/mmol and was given 2:3:1 in water. Each animal was given about 10 μCi in a volume that did not exceed 0.5 mL.

Following administration, the expired air, excreta, and tissues were analyzed for activity, and metabolites in urine were isolated and identified. About 60% of the administered ^{14}C activity was excreted in the urine, whereas 27% was eliminated as $^{14}CO_2$ within 48 hours after dosing. PPG-2 methyl ether, propylene glycol monomethyl ether, dipropylene glycol, propylene glycol, and sulfate and glucuronide conjugates of PPG-2 methyl ether were identified in the urine of animals given [^{14}C] PPG-2 methyl ether. The authors concluded that PPG-2 methyl ether is metabolized by the same routes to the same general types of metabolites as previously identified for propylene glycol monomethyl ether.[20]

An in vitro liver slice metabolism assay was used to investigate the formation of 2-methoxypropionic acid (2-MPA), a putative developmental toxicant, from 6 propylene glycol ethers including β-propylene glycol methyl ether, propylene glycol dimethyl ether, dipropylene glycol dimethyl ether, propylene glycol methyl butyl ether, dipropylene glycol methyl butyl ether, and tripropylene glycol methyl butyl ether. Formation of 2-MPA by liver slices from both female F344 rat and female NZW rabbit liver was quantitatively determined for each substrate, using gas chromatography/negative chemical ionization/mass spectroscopy and a d3-labeled internal standard.[22] Ethoxycoumarin-O-deethylase activity, a measure of microsomal mixed function oxidase activity, was assayed in representative slices for each experiment as an indication of metabolic capacity of the system. Liver slice protein was assayed. Comparison of species differences in formation of 2-MPA from these propylene glycol ethers demonstrated that in vitro metabolism of β-propylene glycol monomethyl ether led to formation of much greater amounts of 2-MPA than any other propylene glycol ethers investigated. Additionally, rat liver slices were from 3- to 10-fold more effective at producing 2-MPA from β-propylene glycol monomethyl ether than were rabbit liver slices under these conditions. The calculated in vitro rate of 2-MPA formation from PPG-2 methyl ether of 14 μg of 2-MPA per gram of liver per hour was in fairly good agreement with the in vivo rate of 7.3 μg of 2-MPA per gram of liver per hour.

The authors concluded that the in vitro metabolism of PPG-2 methyl ether to 2-MPA, quantified with the liver slice technique, was representative of in vivo formation of 2-MPA from PPG-2 methyl ether. Also, these in vitro results suggest that the species difference in sensitivity to β-propylene glycol monomethyl ether–induced developmental toxicity demonstrated in vivo between rat and rabbit was not due to increased formation of 2-MPA by rabbit compared with rat.[22]

The metabolism of propylene glycol ethers in rats is rapid. The ether bond may be broken via O-dealkylation by mixed function oxidase to yield mono-, di-, or tripropylene glycol (depending on the parent compound) and the alkyl alcohol. The

Table 3. Acute Mammalian Toxicity Studies[15]

Chemical	Acute Rat Oral LD_{50}	Acute Rat Inhalation LC_{50} (4 h)[a]	Acute Dermal LD_{50} (24 h)
PPG-2 methyl ether acetate	Females: 5448 mg/kg (95% confidence interval, 4071-7635 mg/kg) (2/6 female deaths at 5000 mg/kg). Males: >5000 mg/kg (no deaths).	>5700 mg/m^{3-1} (=733 ppm) (no deaths)	>5000 mg/kg (no deaths)
PPG-3 methyl ether	3500 mg/kg	>200 000 mg/m^3 (no deaths)	15 400 mg/kg (2/4 deaths) (no deaths at next lower dose of 7720 mg/kg)
PPG-2 methyl ether	Males: 5230 mg/kg. Females: 5180 mg/kg.	500 ppm (supersaturated) ≡3031 mg/m^3 (no deaths)	≥10 000 mg/kg

[a] Inhalation exposure was for 4 hours.

mono-, di-, or tripropylene glycol released may then undergo further metabolism to yield CO_2. Because of its molecular structure, the secondary (α) alcohol isomer is not oxidized to the carboxylic acid. The acetate, PPG-2 methyl ether acetate, is also expected to be rapidly hydrolyzed to yield PPG-2 methyl ether, which would then be metabolized similarly to the nonacetate PPG-2 methyl ether.[15]

The excretion of [^{14}C]-PPG-3 methyl ether administered as a single gavage dose (1 or 4 mmol/kg at 41.3 and 11.1 μCi/mmol, respectively) to male rats (3 per dose) was measured.[15] Rats were housed in metabolism cages where urine, feces, and expired air were collected in varying time increments over a total period of 48 hours and monitored for radioactivity. Urine was collected in 12-hour increments and feces in 24-hour increments; expired air was collected at 4-hour intervals for the first 12 hours and at 12-hour intervals thereafter.

At the end of 48 hours, brain, muscle, perirenal fat, skin, kidneys, liver, and the remaining carcass were analyzed for total radioactivity. Urine samples were fractionated using liquid chromatography, and fractions containing radioactivity were analyzed using gas chromatography mass spectroscopy to identify the structures of the metabolites.

After 48 hours, 75% of the dose was excreted in urine and 16% as [^{14}C]-CO_2 at 1 mmol/kg body weight, whereas the high-dose rats excreted 69% in urine and 16% as ^{14}C-CO_2. Fecal excretion accounted for approximately 5% of the dose at both dose levels. Less than 1% of the dose was eliminated as expired volatile organics at both dose levels. The carcass retained between 1% and 2% of either dose. The distribution of radiolabel in tissues was similar between dose groups, with liver, kidneys, and skin containing the highest percentage after 48 hours; all values were less than 0.5% of the total dose.[15]

ANIMAL TOXICOLOGY

Acute Toxicity

Summaries of acute animal toxicity studies of PPG-2 methyl ether, PPG-3 methyl ether, and PPG-2 methyl ether acetate are shown in Table 3.[15]

Rabbits were treated with various doses of PPG-2 methyl ether, and mortality was evaluated following a single 24-hour application to the intact skin. All doses of glycol methyl ether caused some loss in body weight. There was a slight loss of body weight at all dosage levels, but the rabbits recovered quickly and in most cases showed weight increase within 2 days. PPG-3 methyl ether caused 1 death at a dose of 15 mL/kg after 4 days but no deaths at 20 mL/kg. There was a significant loss in body weight, and recovery was sometimes prolonged for a week or more, even at the 10-mL/kg level. Narcosis resulted a few hours after application of the material at all dosage levels but was not usually apparent at the end of the 24-hour exposure period.

Short-Term Toxicity

PPG-2 methyl ether. The percutaneous toxicity of ethylene glycol monomethyl ether and PPG-2 methyl ether was studied in 80 male Porton-Wistar rats.[23] The subacute percutaneous toxicity of PPG-2 methyl ether in male rats dosed 5 days per week for 4 weeks under both occluded and unoccluded conditions was compared with the percutaneous toxicity of ethylene glycol monomethyl ether (EGM). Eighty rats were randomly divided into 10 groups of 8. Prior to the first dose, the fur was removed from the dorsal skin of all of the animals. The appropriate dose of PPG-2 methyl ether, EGM, or water was applied to the clipped area daily, 5 days per week, for 28 days. The individual body weights and food intake were monitored on a daily basis. Before the first dose and at 18 and 28 days, blood samples (0.5 mL of lithium heparin) were taken from the caudal tail vein of each rat. The samples were assayed for total protein, creatinine, glucose, blood urea nitrogen, 5′-nucleotidase, creatine kinase, aspartate aminotransferase, and alkaline phosphatase. A 0.25-mL dipotassium-EDTA blood sample was taken from the caudal vein of each rat for analysis of differential leukocyte and reticulocyte counts.

At the postmortem examination, bone marrow fragments were removed from the left femur of each rat and placed in tubes containing 20% bovine serum albumin in saline. The marrow films were prepared, air dried, and fixed in methanol for 10 minutes each in May-Grunwald and Giemsa stains. The

films were differentiated for 10 minutes in dilute phosphate buffer (pH 6.8) and blotted dry. One femur from each animal was decalcified with a 10% solution of formic acid in formalin for a week and stained with hematoxylin and eosin. PPG-2 methyl ether caused no changes in the clinical chemistry, hematology, or pathology, whereas ethylene glycol monomethyl ether caused changes in the hematology and clinical chemistry as well as testicular and bone marrow damage at doses of 1000 mg/kg/d. According to the authors, the difference in toxicity between the 2 glycol ethers may be due to different routes of metabolism. EGM is a primary alcohol that is metabolized to methoxyacetic acid, which is considered to be the ultimate toxicant. In contrast, PPG-2 methyl ether is metabolized to propylene glycol, which is relatively nontoxic.[23]

An oral repeated-dose 4-week toxicity study of PPG-2 methyl ether in rats and a 2-week recovery study were conducted to assess the systemic toxicity of PPG-2 methyl ether to the rat by oral administration, once daily for 28 days, to 3 groups of 5 male and 5 female rats at dosage levels of 40, 200, and 1000 mg/kg/d. A negative control group was included. Five males and 5 females were additionally assigned to both the control group and high-dose group for the observation of the recovery from toxic symptoms (if any).

Clinical observations, body weights, food consumption, and urinalysis were recorded for toxicological effects during the 28 days of treatment. At the end of the administration period, blood samples were taken from rats of the 28-day treatment group and sent to the laboratory for analysis. The animals were euthanized and subsequently examined macroscopically; specified tissues were then prepared for the histopathological examination. The extra animals added to the highest dose and the control groups for observation were retained for a 2-week recovery period after which they were killed and examined.

Transient salivation was recorded in the male and female animals treated with 1000 mg/kg from day 11 onward, which appeared immediately after oral administration of the test material. Absolute and relative liver weights of male and female animals treated with 1000 mg/kg were still significantly elevated after the recovery period.

Histopathological examination revealed centrilobular hypertrophy of liver in the animals treated with 1000 mg/kg PPG-2 methyl ether. There were no other changes that were considered to be related to the treatment.

The authors concluded that 200 mg/kg/d represents the no observable adverse effect level (NOAEL) for PPG-2 methyl ether in the rat because there was transient salivation immediately after the oral administration of PPG-2 methyl ether at 1000 mg/kg, increased liver weight, and centrilobular hypertrophy of liver.[24]

Mice and rats exposed to PPG-2 methyl ether via inhalation had reportedly mild symptoms of toxicity, including central nervous system effects (sedation), adaptive hepatic changes, and decreases in body weight gain at concentrations of 140 to 400 ppm (849-2425 mg/m^3). NOAELs ranged from 50 to 400 ppm in experiments in rats lasting 2 to 28 weeks. For mice, a no observable effect level (NOEL) of 50 ppm (303 mg/m^3) and a lowest observable effect level (LOEL) of 140 ppm (849 mg/m^3) in an experiment lasting 2 weeks were reported. According to the authors, because the NOEL and LOEL were based on increased liver weights without accompanying histopathology, the response may be considered adaptive rather than a toxic effect. In experiments in rabbits lasting 13 to 31 weeks, NOAELs of 200 ppm (highest dose tested) and 300 to 400 ppm were observed, respectively. In the 31-week study, however, changes in liver histology were observed at doses of 300 to 400 ppm.[15]

PPG-3 methyl ether. Groups of rats and mice (5 per species per sex per dose) were exposed to PPG-3 methyl ether aerosol 6 hours per day, 5 days per week at concentrations of 0, 150, 360, or 1010 mg/m^3 (0, 18, 43, or 120 ppm) over a 2-week period for a total of 9 exposures.[15] Animals were observed for mortality and clinical signs, body weight changes, clinical chemistry and hematology effects, gross lesions and organ weights at necropsy, and histopathological changes. In rats, the only effect found was increased liver weights without accompanying histopathology in the mid- and high-exposure groups. Similarly, the only effect found in mice was increased liver weights at all exposure levels in males and at the high level only in females. Liver weight increases were not accompanied by histologically observable damage, except in the high-dose males (increased eosinophilia; necrosis not reported). According to the authors, if liver weight increases without cellular damage in mice at the lower dose levels are considered adaptive in nature (ie, not "adverse"), this establishes a NOAEL of 360 mg/m^3 and a LOAEL of 1010 mg/m^3 based on liver changes with histopathology in mice and a NOAEL in rats of 1010 mg/m^3.[15]

Table 4 presents some repeated-dose toxicity study outcomes for PPG-3 methyl ether and PPG-2 methyl ether included in the OECD SIDS document.[15]

Subchronic Toxicity

Various doses of PPG-2 methyl ether and PPG-3 methyl ether were applied over the clipped, shaven abdominal skin of male rabbits, divided into groups of at least 5 animals each.[25] The doses were applied 5 times a week over a 90-day period. In the first experiment, each compound was tested at 4 unstated dosage levels. A separate group of 5 served as the control animals for each compound. In a second experiment, the 2 intermediate dosage levels of PPG-2 methyl ether were evaluated in the same manner as in the first experiment with a separate control group being used. The control animals received the same treatment as the experimental animals, except that distilled water was substituted for the test material. The authors stated that narcosis generally led to death at high doses and that the loss in body weight was caused by decreased food consumption.

A subchronic inhalation study examined the effects of PPG-2 in which male and female Fischer 344 rats and New Zealand White rabbits (7 per sex per exposure concentration) were exposed to 0, 15, 50, or 200 ppm (0, 91, 303, or 1212 mg/m^3).[26] The animals were exposed for 6 hours per day, 5 days

Table 4. Repeated-Dose Toxicity Studies for PPG-2 Methyl Ether and PPG-3 Methyl Ether[15]

Chemical	Oral	Inhalation	Dermal
PPG-3 methyl ether	No studies	2 wk using rats and mice: NOAEL for rats 1010 mg/m^3 (120 ppm).[a] For mice, NOAEL 360 mg/m^3 (42.7 ppm) and LOAEL 1010 mg/m^3 (120 ppm).	90 d using rabbits: NOAEL 965 mg/kg/d and LOAEL ~2895 mg/kg/d.
PPG-2 methyl ether	28 d using rats: NOAEL 200 mg/kg/d and LOAEL 1000 mg/kg/d.	90 d using rats and rabbits: NOAEL for rats >200 ppm (1212 mg/m^3).[a] NOAEL for rabbits >200 ppm (1212 mg/m^3).[a] 2 wk using mice: NOEL 303 mg/m^3 and LOEL 849 mg/m^3.	90 d using rabbits: NOAEL 4750 mg/kg/d (5 mL/kg/d) and LOAEL 9500 mg/kg/d) (10 mL/kg/d).

NOAEL, no observable adverse effect level; LOAEL, lowest observable effect level.
[a] Highest dose or exposure level used in the study.

Table 5. Eye/Skin Irritation (Rabbits)[15]

Chemical	Eye Irritation (Rabbits)	Skin Irritation (Rabbits)
PPG-2 methyl ether acetate	Nonirritating: 24 h, PII = 1.0/110; 48 h, PII = 0.3/110	Nonirritating (PII = 0.04/8)
PPG-3 methyl ether	Moderately irritating (PII = 4/10)	Nonirritating (PII = 1.0/10)
PPG-2 methyl ether	Slightly irritating	Nonirritating

PII, primary irritation index.

per week for 13 weeks. Responses recorded included general observations, body weights, clinical chemistry, hematology, urinalyses (rats only), necropsy, organ weights, and histopathology. No effects (including terminal body and organ weights summary, clinical chemistry and urine specific gravity, and hematology results) were observed in any of the animals at any of the exposure concentrations. Because the highest concentration tested (200 ppm) was approximately 40% of the theoretical saturated minimum, PPG-2 methyl ether, according to the authors, has a low degree of hazard via the inhalation route of exposure.

Chronic Toxicity

No chronic toxicity data on PPG-2 methyl ether, PPG-3 methyl ether, or PPG-2 methyl ether acetate were available.

Ocular Irritation

Rowe et al[25] reported a study in which undiluted propylene glycol methyl ether, PPG-2 methyl ether, and PPG-3 methyl ether were each placed (1 drop) into the eyes of rabbits everyday for 5 consecutive days. A mild transitory irritation of the conjunctival membranes appeared after each dose. There was no cumulative effect, and fluorescein staining revealed no corneal injury.

Ballantyne[27] studied the ocular effect of PPG-2 methyl ether in 132 adult female New Zealand albino rabbits. Eighteen of the animals were used for subjective assessment of eye irritation, 60 for intraocular tension measurements, and 54 for in vivo measurement of corneal thickness. The effects of 20% and 40% (vol/vol) dilutions of PPG-2 methyl ether in distilled water, as well as on the undiluted material, were examined. Each concentration was tested in 1 eye of each of 6 rabbits. The contralateral eye served as a control. The eyes were examined for up to 14 days after administration of the test material. The undiluted PPG-2 methyl ether produced rapid development of conjunctoblepharitis in all animals, which the authors termed moderately severe. This effect peaked at approximately 6 hours and disappeared within a week. Conjunctival hemorrhages and sloughing were not observed. Slight keratitis was found in 2 of the 6 rabbits by 24 hours but disappeared within 4 days. The animals showing keratitis also had detectable injection of iris vessels, noticeable with 24 hours and disappearing within 3 days. A 40% aqueous solution of PPG-2 methyl ether resulted in injection of conjunctival vessels in all animals, which was observed at 1 hour and disappeared by day 2. Minimal chemosis (lasting <24 hours) occurred in half the animals. No adverse effects were noted in the cornea or iris. The 20% solution of PPG-2 methyl ether did not produce any inflammatory effects on the eye or surrounding tissues. To determine the effect of PPG-2 methyl ether on corneal thickness, this same author instilled 0.1 mL of the following concentrations of PPG-2 methyl ether in water into the inferior conjunctival sac of rabbits: 10%, 20%, 40%, and 80% (vol/vol).

Corneal thickness increased after the instillation of 0.1 mL of differing concentrations of PPG-2 methyl ether into the conjunctival sac. Thickness returned to control values within 2 hours for PPG-2 methyl ether (10%), by 24 hours for PPG-2 methyl ether (20%), and by 48 hours with PPG-2 methyl ether (40%) and PPG-2 methyl ether (80%).

A summary of rabbit eye and skin irritation data for PPG2 methyl ether, PPG-3 methyl ether, and PPG-2 methyl ether acetate is shown in Table 5.[15]

Reproductive and Developmental Toxicity

Monopropylene, dipropylene, and tripropylene glycol ethers do not share the potent reproductive toxicity shown by ethylene

Table 6. In Vitro Genotoxicity Testing[15]

Chemical	In Vitro Testing
PPG-2 methyl ether acetate	Ames test negative
PPG-3 methyl ether	Ames test negative
	Unscheduled DNA synthesis negative
PPG-2 methyl ether	Ames test negative
	Escherichia coli negative
	Unscheduled DNA synthesis negative
	CHO cytogenetics negative

glycol regardless of administration route (oral, inhalation, or dermal). However, some embryo or fetal toxicity may have been observed at the highest doses. No dose produced birth defects, testicular atrophy, or damage to blood or thymic tissues.[4]

Breslin et al[28] evaluated the developmental toxicity of inhaled PPG-2 methyl ether in pregnant Fischer 344 rats and New Zealand White rabbits. The PPG-2 methyl ether used was a commercial mixture of 4 isomers with a maximum theoretical yield of 61.8% β-propylene glycol monomethyl ether (β-PGME). Groups of 16 inseminated rabbits or 32 to 37 bred rats were exposed via inhalation to 0 (control, filtered air), 50, 150, or 300 ppm PPG-2 methyl ether for 6 hours per day on days 7 through 19 (rabbits) or 6 through 15 (rats) of gestation. The exposure levels were 0, 32, 97, and 193 mg of PPG-2 methyl ether/kg/d for rabbits and 0, 107, 322, and 644 mg of PPG-2 methyl ether/kg/d for rats. The animals were observed for changes in behavior, feed and water consumption (rats only), body weight gain, liver weight, and various reproductive parameters. Fetuses were removed by cesarean section on day 28 (rabbits) or day 21 (rats) of gestation. The fetuses were then weighed and examined for external, visceral, and skeleton alterations. There were no significant treatment-related effects on any maternal, embryonal, or fetal parameters in rabbits or rats at any exposure level. According to the authors, these results indicated that a commercial grade of PPG-2 ethyl ether is not embryofetotoxic or teratogenic in rats or rabbits when administered by inhalation exposure at the highest concentration (300 ppm) that is practically attainable at room temperature and pressure.

Genotoxicity

Results of in vitro genotoxicity testing on the propylene glycols is shown in Table 6. Ames tests were conducted with a minimum of 4 tester strains, including TA 98, TA100, TA1535, TA1537, and/or TA1538, with and without Aroclor-induced rat S-9 activation systems, with appropriate positive and negative controls, and evaluated propylene glycol ethers at concentrations up to 5000 μg per plate and higher.[12] All test results were negative.

PPG-2 Methyl Ether

Kirkland and Varley[29] tested PPG-2 methyl ether in a bacterial reverse mutation assay (Ames test) on *Salmonella typhimurium* with and without metabolic activation. PPG-2 methyl ether was negative for genotoxic effects.

Dow Chemical Japan reported on a reverse mutation assay using PPG-2 methyl ether.[30] PPG-2 methyl ether was tested for mutagenic potential using histidine-dependent autotrophic mutants of *S typhimurium* strains TA98, TA1537, and TA100 as well as a tryptophan-dependent mutants of *Escherichia coli*, strain WP2*uvrA*, in 2 independent mutation tests in the presence (with metabolic activity) of liver preparations (S9-mix) by preincubation method. PPG-2 methyl ether was dissolved in the distilled water for testing at concentrations up to 5000 μg per plate, based on a dose range–finding study. According to the authors, there was no evidence of mutagenic activity, and the calculated values for the concurrent negative and positive controls of each strain were within the range of the background data. The authors concluded that PPG-2 methyl ether shows no evidence of mutagenic activity in this bacterial system.

Dow Chemical Japan performed another study to assess the ability of PPG-2 methyl ether (molecular weight 148.2) to induce chromosomal aberrations in CHL/IU cells derived from the female Chinese hamster lung cultured in vitro by 3 different treatment methods, that is, the pulse (short time) treatment method in both the absence and presence of metabolic activation or continuous treatment for 25 hours. The cell growth inhibition study and the chromosomal aberration study were conducted serially.[24]

CHL/IU cells in culture plates were exposed to various concentrations of the test substance.[24] The highest concentration was 1.482 mg/mL (equivalent to 10 mmol/L concentration). There was no clear cell growth inhibition in this first series of tests for assessing the toxicity of PPG-2 methyl ether to CHL cells.

On the basis of these data, 3 concentrations (1.482, 0.741, and 0.371 mg/mL) were selected for metaphase analysis along with negative controls (solvent) and positive controls (methyl methanesulfonate and dimethylnitrosamine). The pulse (short time) treatment method in both the absence and presence of metabolic activation or continuous treatment was used to assess chromosomal aberrations using the microscope.

No increases in the proportion of cells showing structural aberrations, exceeding 5% of the control values, including concentration-dependent increases, were seen at any concentration used in 3 different treatment methods.

Because the incidences of structural abnormalities in negative and positive controls were less than 2.5% and 32.5% to 37.0%, respectively, it was concluded that this study was valid.

The authors concluded that PPG-2 methyl ether shows no potential to cause structural and numerical abnormalities in chromosomes of CHL/IU cells.[24]

Carcinogenicity

No carcinogenicity data for PPG-2 methyl ether, PPG-3 methyl ether, or PPG-2 methyl ether acetate were found.

Clinical Assessment of Safety

Dermal Sensitization

No clinical dermal sensitization data for PPG-3 methyl ether and PPG-2 methyl ether acetate were available.

PPG-2 methyl ether. PPG-2 methyl ether was tested by a repeat insult patch technique on 100 humans (50 males, 50 females).[25] The material was applied to the backs of the subjects for 4 to 8 hours every other day until 10 applications had been made. After a 3-week lapse, the material was reapplied for a 24- to 48-hour period. None of the human subjects exhibited any evidence of irritation or sensitization at any time.

Ocular Irritation

PPG-2 methyl ether. Ballantyne[27] observed the effects of controlled applications of PPG-2 methyl ether solutions to the human eye. Ten male volunteers, 18 to 26 years of age, participated in the experiment. A droplet of 20% (vol/vol) aqueous PPG-2 methyl ether (0.04 mL in volume) was instilled into the left eye using a micrometer syringe. The subjects were asked to identify any symptoms experienced and their duration. Intraocular tension was measured a few minutes prior to applying PPG-2 methyl ether to the eye and at 2 to 4, 30, and 60 minutes after contaminating the eye.

PPG-2 methyl ether caused a minor stinging sensation when applied to 1 eye of each of the 10 subjects. The stinging lasted for 30 to 45 seconds and was accompanied by slight excess of lachrymation and intermittent blepharospasm, which lasted for about 1 minute. A mild swelling of the conjunctival vessels developed within 2 minutes and persisted for 30 to 40 minutes. Increases in intraocular tension, measured at 5 minutes, ranged from 2 to 8 mm Hg. Intraocular tension returned to control levels by 1 hour in 9 of the subjects and by 2 hours in the remaining subject.[27]

Inhalation

PPG-2 methyl ether. According to Patty,[31] PPG-2 methyl ether is low in toxicity by inhalation. However, protective respirators must be worn for concentrations above 5000 ppm. Concentrations exceeding 5000 ppm are unlikely to be encountered in the workplace given the high boiling point and low vapor pressure of this substance.

Exposure Limits

The current Occupational Safety and Health Administration permissible exposure limit (PEL) for PPG-2 methyl ether is 100 ppm parts of air (600 mg/m^3) as an 8-hour weighted average concentration.[32] The OSHA PEL includes a notation which indicates that the cutaneous route of exposure (including mucous membranes and eyes) contributes to overall exposure.

Particle Size

PPG-2 methyl ether is used in hair sprays, and effects on the lungs that may be induced by aerosolized products containing this ingredient may be of concern. Jensen and O'Brien[33] reviewed the potential adverse effects of inhaled aerosols, which depend on the specific chemical species, the concentration, the duration of the exposure, and the site of deposition within the respiratory system. The aerosol properties associated with the location of deposition in the respiratory system are particle size and density. The parameter most closely associated with this regional deposition is the aerodynamic diameter, $\mathbf{d_a}$, defined as the diameter of a sphere of unit density possessing the same terminal setting velocity as the particle in question. These authors reported a mean aerodynamic diameter of 4.25 $\pm$ 1.5 μm for respirable particles that could result in lung exposure.[33]

Bower[34] reported diameters of anhydrous hair spray particles of 60 to 80 μm and pump hair sprays with particle diameters of 80 μm or greater. Johnsen reported that the mean particle diameter is around 38 μm in a typical aerosol spray.[35] He stated that in practice, aerosols should have at least 99% of particle diameters in the 10- to 110-μm range. This means that most aerosol particles are deposited in the nasopharyngeal region and are not respirable.

Summary

Data relevant to assessing the safety of PPG-2 methyl ether, PPG-3 methyl ether, and PPG-2 methyl ether acetate as cosmetic ingredients were evaluated in this report.

PPG-2 methyl ether (PPG refers to polypropylene glycol) is currently used in cosmetics as a fragrance ingredient and solvent at concentrations of 0.4% to 2%. PPG-2 methyl ether also is known as dipropylene glycol monomethyl ether, often referred to by its acronym, DGME.

PPG-3 methyl ether and PPG-2 methyl ether acetate both function as solvents in cosmetics. PPG-3 methyl ether has 1 reported use in hair dyes and colors, but the use concentration is not known. There were no reported uses for PPG-2 methyl ether acetate in cosmetics.

Although PPG-3 methyl ether reportedly is used, the concentration of use is not available and for some uses of PPG-2 methyl ether, information regarding use concentration for specific product categories is provided but the number of such products is unknown. In both cases, uses are likely to be in the overall concentration range and in the types of products described.

Polypropylene glycol and dipropylene glycol also are cosmetic ingredients. Earlier safety assessments concluded that polypropylene glycol was safe as a cosmetic ingredient at concentrations up to 50% and that dipropylene glycol is safe as used.

PPG-2 methyl ether is the polypropylene glycol ether of methyl alcohol, PPG-3 methyl ether is the polypropylene glycol ether of methyl alcohol, and PPG-2 methyl ether acetate is the ester of PPG-2 methyl ether (qv) and acetic acid (qv).

PPG-2 methyl ether and PPG-3 methyl ether are commercially prepared by reacting propylene oxide with methanol.

PPG-2 methyl ether has a vapor pressure of 0.36 at 25°C and is 100% soluble in water. PPG-3 methyl ether has an even lower vapor pressure, 0.022 at 25°C, and is completely soluble in water. PPG-2 methyl ether acetate has a vapor pressure of 0.08 at 20°C and an octanol/water partition coefficient of 0.803.

The propylene glycol ethers are rapidly absorbed and distributed throughout the body, including the brain, liver, and kidneys, following inhalation or oral exposure. Dermal absorption is somewhat slower, but subsequent distribution and excretion are rapid via the urine and expired air. A small portion is excreted in the feces.

PPG-2 methyl ether acetate rapidly hydrolyzes in plasma to yield PPG-2 methyl ether. Metabolism of propylene glycol ethers occurs primarily in the liver, where mixed function oxidases cleave the ether linkage, yielding propylene glycol and an alcohol. This is in contrast to ethylene glycol monomethyl ether, which is metabolized to methoxyacetic acid, which is considered to be a toxicant.

The acute rat oral LD_{50} for PPG-2 methyl ether acetate in females is ~5 g/kg and in males greater than 5 g/kg. The acute rat oral LD_{50} for PPG-2 methyl ether is ~5 g/kg for both sexes. The acute rat oral LD_{50} for PPG-3 methyl ether is ~3.5 g/kg for both sexes. The acute rat dermal LD_{50} for PPG-3 methyl ether is 15 g/kg, for PPG-2 methyl ether is greater than 10 g/kg, and for PPG-2 methyl ether acetate is greater than 5 g/kg. Acute inhalation LC_{50} values using rats were greater than 5 g/m^3 for PPG-2 methyl ether acetate, greater than 200 g/kg for PPG-3 methyl ether, and ~3 g/kg for PPG-2 methyl ether.

In a rat short-term oral toxicity test, PPG-2 methyl ether at 40, 200, and 1000 mg/kg/d resulted in significant, persistent increases of absolute and relative liver weight in the high-dose group only. Centrilobular hypertrophy of the liver was seen in high-dose rats on histological examination.

In a rat short-term dermal toxicity study, PPG-2 methyl ether at 100 and 1000 mg/kg did not produce any adverse effects; in a 90-day dermal study using rabbits, a NOAEL of 4750 mg/kg was reported.

In short-term inhalation toxicity studies, the NOAEL for PPG-3 methyl ether was 1010 mg/m^3 for rats and 360 mg/m^3 for mice.

In a subchronic dermal toxicity study using rabbits, exposures to PPG-2 methyl ether and PPG-3 methyl ether up to 5 mL/kg were not toxic.

A subchronic inhalation toxicity study using rats and rabbits exposed to PPG-2 methyl ether at doses of 0, 91, 303, or 1212 mg/m^3 did not produce any adverse effects.

No chronic toxicity data were available on these ingredients, but in a chronic inhalation toxicity study of the closely related PGME in mice and rats at levels up to 3000 ppm, initial sedation in all animals, increased eosinophilic foci of altered hepatocytes in male rats, and elevated mortality in mice and rats, all at the high dose, were reported. No significant differences in neoplasia in any animals were reported.

Undiluted PPG-2 methyl ether and PPG-3 methyl ether were mild ocular irritants in 1 rabbit study and undiluted PPG-2 methyl ether produced conjunctoblepharitis in all rabbits in another study. In the latter study, slight keratitis was found in 2 of the 6 rabbits by 24 hours but disappeared within 4 days. The animals showing keratitis also had detectable infection of iris vessels, noticeable within 24 hours and disappearing within 3 days. A 20% solution of PPG-2 methyl ether did not produce any effects on the eye or surrounding tissues in rabbits.

PPG-2 methyl ether and PGME were not reproductive or developmental toxicants. It was noted that the monopropylene, dipropylene, and tripropylene glycol ethers do not share the potent reproductive toxicity shown by ethylene glycol regardless of administration route.

PPG-2 methyl ether was not genotoxic in bacterial or mammalian test systems.

Undiluted PPG-2 methyl ether applied to the skin of 200 human subjects was not irritating, nor was there any sensitization at any time. Instillation of a droplet of 20% PPG-2 methyl ether into the eye of 10 human subjects resulted in transient irritation.

Recommended occupational exposure limits of 100 ppm as a time-weighted average for up to a 10-hour workday and a 40-hour work week and 150 ppm as a short-term exposure limit have been established.

Discussion

The CIR Expert Panel recognizes that certain ingredients in this group are reportedly used in a given product category, but the concentration of use is not available. For other ingredients in this group, information regarding use concentration for specific product categories is provided, but the number of such products is unknown. Overall, however, a range of use concentrations and types of products is established, within which these ingredients may be expected to be used.

Monopropylene, dipropylene, and tripropylene glycol ethers do not share the potent reproductive toxicity shown by ethylene glycol regardless of administration route (oral, inhalation, or dermal).

PPG-2 methyl ether has a low inhalation toxicity suggesting that its use in hair sprays presents no concern. The panel determined that PPG-2 methyl ether, PPG-3 methyl ether, and PPG-2 methyl ether acetate can be used safely in hair sprays because the ingredient particle size is not respirable. The panel reasoned that the particle size of aerosol hair sprays (~38 μm) and pump hair sprays (>80 μm) is large compared with respirable particulate sizes (≤10 μm).

PPG-2 methyl ether, PPG-3 methyl ether, and PPG-2 methyl ether acetate are water soluble and likely to be absorbed through the human skin only at slow rates, resulting in low blood concentrations and rapid removal by the kidney. With this in mind, and given the lack of sensitization and irritation at use concentrations, the data are sufficient to conclude that PPG-2 methyl ether, PPG-3 methyl ether, and PPG-2 methyl ether acetate are safe as used in cosmetics.

The Expert Panel also reviewed safety test data available for PGME and found that these data were consistent with the polypropylene glycol methyl ethers included in this safety assessment.

Conclusion

The CIR Expert Panel concluded that PPG-2 methyl ether, PPG-3 methyl ether, and PPG-2 methyl ether acetate are safe as cosmetic ingredients in the practices of use and concentration as described in this safety assessment.

Authors' Note

The 2009 Cosmetic Ingredient Review Expert Panel members Wilma F. Bergfeld, MD, FACP, Chair; Donald V. Belsito, MD; Curtis D. Klaassen, PhD; James G. Marks Jr, MD; Ronald C. Shank, PhD; Thomas J. Slaga, PhD; and Paul W. Snyder, DVM, PhD. The CIR Director is F. Alan Andersen, PhD. Valerie Robinson, CIR Scientific Analyst, prepared this report.

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1101 17th Street, Suite 412, Washington, DC 20036, USA.

Conflict of Interest

No potential conflict of interest relevant to this article was reported. F. Alan Andersen, PhD, and Valerie Robinson are employed by the Cosmetic Ingredient Review.

Financial Disclosure/Funding

The articles in this supplement were sponsored by the Cosmetic Ingredient Review. The Cosmetic Ingredient Review Program is financially supported by the Personal Care Products Council. No potential conflict of interest relevant to this article was reported

References

1. Andersen FA. Final report on the safety assessment of propylene glycol and prolypropylene glycol. *J Am Coll Toxicol.* 1994;13: 437-491.
2. Elder RL. Final report on the safety assessment of butylene glycol, hexlyene glycol, ethoxydiglycol, and diproplyene glycol. *J Am Coll Toxicol.* 1985;4:223-248.
3. Gottschalck TE, McEwen GN Jr. *International Cosmetic Ingredient Dictionary and Handbook.* 11th ed. Washington, DC: CTFA; 2006.
4. Snyder R, Andrews LS. Glycol ethers. In: *Casarett & Doull's Toxicology: The Basic Science of Poisons.* New York: The McGraw-Hill Companies; 1996, 759-760.
5. Staples CA, Davis JW. An examination of the physical properties, fate, ecotoxicity and potential environmental risks for a series of propylene glycol ethers. *Chemosphere.* 2002;49:61-73.
6. New Jersy Department of Health and Senior Services (NJDHSS). Hazardous subsances fact sheet: dipropelyne glycol methyl ether. TRK substance no. 0804. 1998.
7. Kroschwitz J. *Kirk-Othmer Encyclopedia of Chemical Technology.* 4th ed. New York, NY: John Wiley; 1999.
8. Dow Chemical Company. Material safety data sheet—DOWANOL Form 110-00618-03-4. 2004.
9. Dow Chemical Company. A guide to glycols. 117-01682-0804XSI. 2003.
10. Physical and Theoretical Chemistry Lab. Safety (MSDS) data for dipropylene glycol methyl ether. Oxford University; 2004. http://ptcl.chem.ox.ac.uk/MSDS/DI/dipropylene_glycol_methyl_ether.html. Accessed August 30, 2005.
11. Occupational Safety and Health Administration (OSHA). Dipropylene glycol methyl ether. 2005. http://www.cdc.gov/niosh/pel88/34590-94.html. Accessed November 11, 2005.
12. Dow Chemical Company. Propylene Glycols. 2006. http://www.dow.com/propyleneglycol/pprod/pguspep.htm.
13. Antczakm G, Antczakm S. PG-3 methy ether in cosmetics unmasked. 2004. http://www.gina.antczak.btinternet.co.uk. Accessed August 30, 2005.
14. Shell Chemicals. Propylene glycols. 2006. http://www.shellchemicals.com/propylene_glycol/1.1098.589.00.html. Accessed July 12, 2006.
15. Organisation for Economic Co-operation and Development Screening Information Data Set (OECD SIDS). OECD SIDS Initial Assesment Report: Propylene Glycol Ether. Unpublished data submitted by the American Chemistry Council; 2003.
16. NIOSH. Glycol ethers. *NIOSH Manual of Analytical Methods (NMAM),* 4th ed. Cincinnati, Ohio: NIOSH; 2003.
17. Food and Drug Administration. *Frequency of Use of Cosmetic Ingredients. FDA Database.* Washington, DC: Food and Drug Administration; 2005.
18. Cosmetic, Toiletry and Fragrance Association. Industry data on PPG-2 methyl ether, ppg-3 methyl ether and ppg-3 methyl ether acetate use concentrations. Unpublished data submitted by CTFA on March 13, 2006.
19. Dow Chemical Company. Material Safety Data Sheet—DOWANOL DPMA Form 110-00587-03-04. 2002.
20. Miller RR, Hermann EA, Calhoun LL, Kastl PE, Zackett D. Metabolism and disposition of dipropelyne glycol monomethyl ether (PPG-2 methy ether) in male rats. *Fundam Appl Toxicol.* 1985;5:721-726.
21. Langhorst ML. Glycol ethers—validation procedures for tube/pump and dosimeter monitoring methods. *Am Ind Hyg Assoc J.* 1984;45:416-424.
22. Pottenger LH, Bus JS, McNett DA. In vitro metabolism of propylene glycol ethers. Unpublished report of the Dow Chemical Company, Midland, Mich; 1995.
23. Fairhurst S, Knight R, Marrs TC, Scawin JW, Spurlock MS, Swantston DW. Percutaneous toxicity of ethylene glycol monomethyl ether and of dipropylene glycol monomethyl ether in the rat. *Toxicology.* 1989;57:209-215.
24. Dow Chemical Japan. Unpublished report FBM 00-8026. Final report: DPM: bacterial reverse mutation assay. May 31, 2000.
25. Rowe VK, McCollister DD, Spencer HC, Hollingsworth RL, Drill VA. Toxicology of mono-, di-, and tripropylene glycol methyl ethers. *A M A Arch Ind Hyg Occup Med.* 1954;9:509-525.
26. Landry TD, Yano BL. Dipropelyn glycol monomethyl ether: a 13-week inhalation toxicity study in rats and rabbits. *Fundam Appl Toxicol.* 1984;4:612-617.

27. Ballantyne B. Local opthalmic effects of dipropylene glycol monomethyl ether. *J Toxicol Cutaneous Ocul Toxicol.* 1984;2:229-242.
28. Breslin WJ, Cieszlak FS, Zablotny CL, Corley RA, Verschuuren HG, Yano BL. Evaluation of the developmental toxicity of inhaled dipropylene glycol monomethyl ether (PPG-2 methyl ether) in rabbits and rats. *Occup Hyg.* 1996;6:161-170.
29. Kirkland DY, Varley R. Bacterial mutagenicity test on DOWANOL DPM. Unpublished report of the Dow Chemical Company; 1983.
30. Dow Chemical Japan. Unpublished report FBM00-8-27. Final report: DPM: chromosomal aberration test in cultured mammmalian cells. May 31, 2000.
31. Patty FA. *Industrial Hygiene and Toxicology.* Vol 2. 2nd rev. ed. New York, NY: Interscience; 1963:1573.
32. OSHA. *Dipropylene Glycol Monomethyl Ether.* 2006.
33. Jensen PA, Obrien D. Industrial hygiene. In: Willeke K, Baron PA, eds. *Aerosol Measurement. Principles, Techniques and Applications.* New York, NY: John Wiley; 1993:538-540.
34. Bower D. Unpublished information on hair spray particle sizes provided at the September 9, 1999 CIR Expert Panel meeting.
35. Johnsen MA. The Influence of Particle Size. *Spray Technology and Marketing.* 2004;(November):24-27.