Safety Assessment of PPG-11 and PPG-15 Stearyl Ether as Used in Cosmetics

Status:	Re-Review for Panel Consideration
Release Date:	May 23, 2022
Panel Meeting Date:	June 16-17, 2022

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Senior Scientific Analyst/Writer, CIR.

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, Senior Scientific Analyst/Writer
Date: May 23, 2022
Subject: Re-Review of the Safety Assessment of PPG-11 and PPG-15 Stearyl Ether

The Expert Panel for Cosmetic Ingredient Safety (Panel) first published a review of the safety of PPG-11 and PPG-15 Stearyl Ether in 2001, with the conclusion that these ingredients are safe as used in cosmetics, as described in the safety assessment. The original report is included for your use (identified as *originalreport_PPGStearylEthers_062022* in the pdf).

Because it has been at least 15 years since the previous safety assessment was published, in accord with Cosmetic Ingredient Review (CIR) Procedures, the Panel should consider whether the safety assessment of PPG-11 and PPG-15 Stearyl Ether should be re-opened. An exhaustive search of the world's literature was performed from the year 1994 forward. An historical overview, comparison of original and new use data, the search strategy used, and a synopsis of notable new data are enclosed herein (*newdata_PPGStearylEthers_062022)*.

A study was found evaluating the effect of PPG-15 Stearyl Ether (2.5, 5, and 10%) on the skin permeation of a psoriasis medication in pig ear skin. PPG-15 Stearyl Ether, at a concentration of 2.5%, resulted in notably increased skin permeation compared to isopropyl myristate, a common drug solvent. However, increasing concentrations of PPG-15 Stearyl Ether resulted in lower amounts of skin permeation, suggesting an inverse relationship between skin permeation enhancement and PPG-15 Stearyl Ether concentration.

Also included for your review is a table of current and historical use data (*usetable_PPGStearylEthers_062022*). The frequencies of use of PPG-11 and PPG-15 Stearyl Ether have decreased since the original report was issued. Compared to 1998 concentration of use data, the maximum concentration of use of PPG-11 Stearyl Ether has decreased from 10% to 5%; however, the maximum concentration of use for PPG-15 Stearyl Ether has increased from 10 to 18%.

If upon review of the new studies and updated use data the Panel determines that a re-review is warranted, a draft amended report will be presented at an upcoming meeting.

Re-Review - PPG-11 and PPG-15 Stearyl Ether- History and New Data

(Priya Cherian – June 2022 meeting)

Ingredients (2)	Citation	Conclusion	Use - New Data	Use - Historical Data	Notes
PPG-11 Stearyl Ether **PPG-15 Stearyl Ether**	IJT 20(S4):53-60 (2001)	safe as used	PPG-11 Stearyl Ether frequency of use (2022): 16 uses conc of use (2022): ≤ 5% PPG-15 Stearyl Ether frequency of use (2022): 100 uses conc of use (2022): ≤ 18%	PPG-11 Stearyl Ether frequency of use (1998): 15 uses conc of use (1998): ≤ 10% PPG-15 Stearyl Ether frequency of use (1998): 41 uses conc of use (1998): ≤ 10%	Frequency of use is similar between 2001 and 2022; concentration of use has decreased Frequency of use has decreased; concentration of use has increased

NOTABLE NEW DATA			
Publication	**Study Type**	**Results – Brief Overview**	**Different from Existing Data?**
Turi JS, Danielson D, Woltersom JW. Effects of polyoxypropylene 15 stearyl ether and propylene glycol on percutaneous penetration rate of diflorasone diacetate. J Pharm Sci. 1979 Mar;68(3):275-80.	Penetration Enhancement	-the effect of PPG-15 Stearyl Ether on skin permeability was evaluated to determine potential solvents for psoriasis medication (i.e., calcipotriol and betamethasone dipropionate) -pig ear skin was used; mounted to Franz-type diffusion cells -treatments containing PPG-15 Stearyl Ether (2.5%) caused significant increased amounts of skin permeability of the drug substances compared to isopropyl myristate -increasing the amount of PPG-15 Stearyl Ether (5-10%) caused a decrease in the normalized flux ratio of the drug substances, suggesting an inverse relationship between skin permeability and increasing PPG-15 Stearyl Ether concentration	Penetration enhancement data were not provided in the previous report

Search (from 1994 forward)

PubMed

(((“PPG-11 stearyl ether”) OR (Polyoxypropylene (11) Stearyl Ether) OR (Polypropylene Glycol (11) Stearyl Ether) OR (25231-21-4 [CAS NO]) – 2 hits; none useful

(((“PPG-15 stearyl ether”) OR (Polyoxypropylene (15) Stearyl Ether) OR (Polypropylene Glycol (15) Stearyl Ether) OR (25231-21-4 [CAS NO]) – 6 hits; 1 useful

Current and historical frequency and concentration of use according to duration and exposure

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	PPG-11 Stearyl Ether				**PPG-15 Stearyl Ether**			
	2022[1]	**1998[2]**	**2022[3]**	**1998[2]**	**2022[1]**	**1998[2]**	**2022[3]**	**1998[2]**
Totals*	**16**	**15**	**2 – 5**	**2 - 10**	**100**	**41**	**1 – 18**	**2 - 10**
Duration of Use								
Leave-On	*1*	*NR*	*2.5 – 5*	*NR*	*78*	*29*	*3 – 18*	*NR*
Rinse-Off	*14*	*14*	*2*	*NR*	*22*	*11*	*1 – 8*	*NR*
Diluted for (Bath) Use	*1*	*1*	*NR*	*NR*	*NR*	*1*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	11	1	4.5	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1	NR	2.5[c]	NR	27[a]; 20[c]	3; 17[a]; 3[c]	NR	NR
Incidental Inhalation-Powder	NR	NR	2.5[c]	NR	20[c]	1[b]; 3[c]	5 – 18[b]	NR
Dermal Contact	16	15	2 – 5	NR	94	38	2 – 18	NR
Deodorant (underarm)	NR	NR	3 – 4.4	NR	6[a]	NR	3 – 4.4	NR
Hair - Non-Coloring	NR	NR	NR	NR	4	3	1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	13	13	2.5	NR	2	5	NR	NR
Baby Products	NR	NR	NR	NR	NR	1	NR	NR

*Ingredient concentrations were not presented by specific product category in the original 2001 report; therefore, concentrations of these ingredients are only stated in the "totals" column. In addition, concentrations were provided for multiple years (1984 and 1998). The concentration range presented in the "total" column represents the concentration range for the ingredient reported by ICI Surfactants in 1998.

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[b] It is possible these products are powders, but it is not specified whether the reported uses are powders.

[c] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

NR – no reported use

References

1. US Food and Drug Administration (FDA) Center for Food Safety & Applied Nutrition (CFSAN). 2022. Voluntary Cosmetic Registration Program - Frequency of Use of Cosmetic Ingredients. (Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 4, 2022; received January 11, 2022). College Park, MD.

2. Andersen FA (ed). Final report on the safety assessment of PPG-11 and PPG-15 stearyl ethers. *Int J Toxicol.* 2001;20 Suppl 4:53-59.

3. Personal Care Products Council. 2022. Concentration of Use by FDA Product Category: PPG-11 and PPG-15 Stearyl Ethers. (Unpublished data submitted to Personal Care Products Council on March 31, 2022.)

Final Report on the Safety Assessment of PPG-11 and PPG-15 Stearyl Ethers[1]

The Polypropylene Glycol (PPG) Stearyl Ethers are polypropylene ethers of stearyl ether that function as skin-conditioning agent in cosmetic formulations. Few data on the PPG Stearyl Ethers were available. Data on chemically related PPG Butyl Ethers were reviewed as a further basis for the assessment of safety. The amounts of PPG Butyl Ethers absorbed from the digestive tract were inversely proportional to the molecular weights on the compounds; skin penetration was slow to nil. During metabolism, the butyl group was removed and oxidized, and the chains were fragmented, oxidized to weak acids, and eliminated in the urine. Little acute oral toxicity was seen in animal studies. In general, the PPG Butyl Ethers were very toxic by the intravenous route and were slightly toxic to nontoxic by the intraperitoneal and subcutaneous routes. The smaller molecular weight ethers were generally more toxic than the larger molecular weight ethers. PPG-2 Butyl Ether vapor was nontoxic by the inhalation route. Undiluted PPG-15 Stearyl Ether was practically nonirritating to the eyes of rabbits, and PPG Butyl Ethers had minor to moderate conjunctival irritation, opacity, and iritis. PPG-15 Stearyl Ether was slightly irritating to rabbit skin. PPG-2 Butyl Ether caused minor, transient erythema and desquamation during a 4-hour occlusive patch test. PPG-2 Butyl Ether did not irritate the skin of pregnant mice, was nontoxic to dams, and was not teratogenic. PPG-9–13 Butyl Ether was noncarcinogenic when fed to rats. PPG-40 Butyl Ether was nonsensitizing in clinical tests. These data were considered by the Cosmetic Ingredient Review Expert Panel to support the safety of PPG Stearyl Ethers at their current use concentrations (2% to 10%, but not greater than 25%). Data on the component ingredients, Propylene Glycol, PPG, and Steraryl Alcohol, from previous cosmetic ingredient safety assessments were also considered and found to support the safety of PPG Stearyl Ethers.

INTRODUCTION

PPG-11 and -15 Stearyl Ethers are the polypropylene glycol (PPG) ethers of stearyl alcohol that function as skin-conditioning agents—emollient in cosmetic formulations.

The Cosmetic Ingredient Review (CIR) Expert Panel previously reviewed the safety of the Propylene Glycol (PG), PPG, and Stearyl Alcohol, finding that PG and PPG are safe for use in cosmetic products at concentrations up to 50.0% (Andersen 1994), and that Stearyl Alcohol is safe as currently used in cosmetics (Elder 1985). In a review of the safety of PPG Butyl Ethers (also appearing in this issue) the Panel found that PPG Butyl Ethers are safe for use in cosmetics when formulated to avoid irritation.

Few data on PPG-11 and -15 Stearyl Ethers were found; however, data on the PPG Butyl Ethers, a structurally similar group of ingredients, were considered relevant in that the smaller ethers (particularly PPG-2 Butyl Ether) are likely more toxic than the stearyl ethers. Data from the relevant reports have been included as a further basis for the assessment of safety.

CHEMISTRY

Definition and Structure

PPG-11 and -15 Stearyl Ethers (CAS No. 25231-21-4) are the PPG ethers of stearyl alcohol that conform generally to the formula in Figure 1, where the average value of *n* equals the number in the name.

The PPG Stearyl Ethers are also known as Polyoxypropylene (n) Stearyl Ether; Polypropylene Glycol (n) Stearyl Ether (Wenninger and McEwen 1997); Glycols, Polypropylene, Monooctadecyl Ether; Poly(Oxy(Methyl-1,2-Ethanediyl))-, α-Octadecyl-(gr v)-Hydroxy-; Poly(Oxy(Methyl-1,2-Ethanediyl)), α-Octadecyl-ω-Hydroxy-; Poly(Oxypropylene)Stearyl Ether; Polypropylene Glycol Monooctadecyl Ether; and Stearyl Alcohol, Propoxylated (Chemline 1997).

Chemical and Physical Properties

PPG-11 and -15 Stearyl Ethers are colorless or light yellow, oily liquids. They are soluble in mineral oil and ethyl alcohol, but are insoluble in water, propylene glycol, and glycerin. The specific gravity of PPG-11 Stearyl Ether is 0.939–0.947 at 25°C/25°C. The hydroxy value is 58 to 72. The specific gravity of PPG-15 Stearyl Ether is 0.948 to 0.964. For both ingredients, the maximum iodine value is 3.0, the maximum acid value is 2.0, and the maximum water content is 0.7% (Nikitakis and McEwen 1990).

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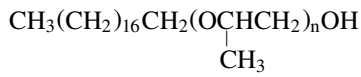

FIGURE 1
PPG-n Stearyl Ether.

Method of Manufacture

ICI Surfactants (1998) reported that these ingredients were produced by the alkoxylation of stearyl alcohol with propylene oxide. This is similar to the production of PPG Butyl Ethers, which are produced by the reaction of excess propylene oxide with n-butyl alcohol (Andersen 2001).

Impurities

Food- and cosmetic-grade PG can contain up to 0.07% sulfated ash, 0.2% water, and 3 ppm arsenic (as As). Food- and cosmetic-grade PPG can contain up to 3 ppm arsenic (as As), 5 ppm heavy metals (as Pb), and 0.02% propylene oxide. In cosmetic products, the purity of PG is specified as a minimum of 97.5%.

A supplier recommends that United States Pharmacopeia (USP)-grade PG be used for cosmetics. USP-grade PG has a typical assay of 99.9% and a specification of 99.5% minimum purity. The supplier recognizes that the USP now allows up to 5 ppm propylene oxide in PG, but is of the opinion that typical levels contained in products today are less than detectable amounts (Andersen 1994).

Stearyl Alcohol consists of not less than 90% Stearyl Alcohol. The remainder consists chiefly of cetyl alcohol, oleyl alcohol, palmityl alcohol, and other alcohols. The known major consitiuents and minor impurities are: n-octadecanol (90% minimum), n-hexadecanol (variable), n-tetradecanol (variable), n-eriosanol (variable), n-dodecanol (variable), stearyl stearate (2% maximum), octadecane (1% maximum), stearic acid (0.5% maximum), and hydrocarbons (~1.8%) (Elder 1985).

Cosmetic Use

The PPG Stearyl Ethers are skin-conditioning agents—emolient in cosmetic formulations (Wenninger and McEwen 1997). In 1998 (Table 1), PPG-11 Stearyl Ether and PPG-15 Stearyl Ether were used in 15 and 41 cosmetic formulations, respectively (Food and Drug Administration [FDA] 1998).

Data submitted to the FDA in 1984 indicated that the PPG-11 Stearyl Ether was used at concentrations of 1% to 5%. PPG-15 Stearyl Ether was used primarily at concentrations of 1% to 5%, but was also used at concentrations within the range of 0% to 25% (FDA 1984). ICI Surfactants (1998) reported that PPG-11 and -15 Stearyl Ethers currently are used at concentrations of 2% to 10%.

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

Short-chain length PPG Butyl Ethers were completely absorbed from the rabbit or rat digestive tract and long-chain PPG Butyl Ethers were "little absorbed." Typical absorption values were 2% to 100%, depending on the chain length. Once absorbed, the butyl group was removed and oxidized, then was partly or completely excreted as carbon dioxide via the lungs. The chains were split into random-length fragments and eliminated in the urine as weak acids after oxidation of the terminal hydroxyls to carboxyl groups. A PPG Butyl Ether of molecular weight 800 Da (chain length between 9 and 13) penetrated the skin of rabbits slowly or not at all and passed poorly through internal tissue barriers. It was also absorbed poorly from the gut of rats, mice, guinea pigs, and rabbits. In a study using rabbits, 45% to 66% was excreted unchanged in feces and 8% to 16% in urine. In contrast, a PPG Butyl Ether of molecular weight 400 Da (chain length between 5 and 9) was absorbed almost completely such that <5% of the dose was found in the feces after 72 hours, and a metabolite was found in the urine that corresponded to 40% to 55% of the dose (Andersen 2001).

In mammals, the major route of PG metabolism is to lactaldehyde and then lactate via hepatic alcohol and aldehyde dehydrogenases. When PG was administered intravenously to human subjects (patients), elimination from the body occurred in a dose-related manner. The results of animal studies on PPGs 425, 1025, and 2025 indicate that they are readily absorbed from the gastrointestinal (GI) tract and are excreted in the urine and feces (Andersen 1994).

The metabolism of Stearyl Alcohol and oleyl alcohol in rats is well described. They are used in the biosynthesis of lipids and other naturally occurring cellular constituents or enter metabolic pathways for energy production (Elder 1985).

Cytotoxic Effects

The cytotoxicity of human natural killer cells was decreased significantly in an assay in which target cells (cultured K562 erythroleukemia cells) were incubated with 1% PG (Andersen 1994).

ANIMAL TOXICOLOGY

Acute Toxicity

PPG-15 Stearyl Ether

Twenty-five rats per sex were orally given PPG-15 Stearyl Ether; the LD_{50} was 6.31 g/kg. The investigators observed signs of intoxication, including intermittent tremors, depression, and ataxia. Deaths were observed within 24 hours of dosing, and at necropsy these animals had pinpoint foci on the thymus and kidneys, pelvic dilatation, and ovarian hyperemia. These changes were sporadic and were not caused by the test compound. The investigators classified PPG-15 Stearyl Ether as "practically

TABLE 1
Frequency of use of PPG Stearyl Ethers (FDA 1998)

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
	PPG-11 Stearyl Ether	
Bath oils, tablets, and salts	124	1
Other personal cleanliness products	291	12
Shaving cream	139	1
Cleansing preparations	653	1
1998 total for PPG-11 Stearyl Ether		**15**
	PPG-15 Stearyl Ether	
Baby lotions, oils, powders, and creams	53	1
Bubble baths	200	1
Other eye makeup preparations	120	1
Colognes and toilet waters	656	1
Other fragrance preparations	148	2
Hair conditioners	636	1
Tonics, dressings, and other hair-grooming aids	549	2
Foundations	287	1
Other personal cleanliness products	291	4
Preshave lotions (all types)	14	2
Cleansing preparations	653	4
Face and neck (excluding shaving)	263	1
Body and hand (excluding shaving)	796	2
Moisturizing preparations	769	13
Night preparations	188	2
Other skin care preparations	692	3
1998 total for PPG-15 Stearyl Ether		**41**

harmless" (Cosmetic, Toiletry, and Fragrance Association [CTFA] 1998).

During a 24-hour dermal toxicity study, 5.25 cc/kg PPG-15 Stearyl was applied to the abraded skin of six male and six female rabbits. No signs of toxicity were observed during the study; the LD_{50} was >5g/kg, and the investigators classified the test compound as "practically harmless" (CTFA 1998).

PPG Butyl Ethers

Large oral doses of the PPG Butyl Ethers caused decreased activity and anuria. Renal and hepatic injury from nonfatal doses was rapidly reversible. Smaller multiple doses increased hepatic and renal weights and reduced growth of female rats. Convulsive seizures were observed in mice, rabbits, and anesthestized dogs after moderate intraperitoneal (IP) or intravenous (IV) doses of various PPG Buty Ethers. The PPG Butyl Ethers were very toxic after IV dosing, but had low toxic potential after IP and subcutaneous dosing. After IP administration, PPG-33 Butyl Ether was the least toxic of the ingredient family ranging in molecular weight from 60 to 1145 Da. In general, the acute oral toxicity of the PPG Butyl Ethers increased as the molecular weight decreased. Skin penetration and toxicity were low. The percutaneous LD_{50} of PPG-2 Butyl Ether was 7.13 ml/kg for male rabbits and 5.86 ml/kg for females. In this study, the rabbits had erythema, edema, ecchymosis, fissuring, ulceration, desquamation, alopecia, and scabs, as well as other clinical signs of toxicity; discolored lungs, red thymuses and tracheas, stomachs with loose contents, foci of the stomach and thymus, and/or mottled kidneys were observed at necropsy. In contrast, slight effects were observed when the clipped skin of rabbits was treated thirty times with 0.7 to 2.0 g/kg/day 80% PPG-40 Butyl Ether. Doses of 0.25 g/kg/day PPG-40 Butyl Ether had no effect on mortality, weight change, or microscopic findings of the lungs, liver, and kidneys.

Propylene Glycol and Polypropylene Glycols

PG was relatively harmless ($LD_{50} = 21$ g/kg) in acute oral toxicity studies involving rats. Acute oral toxicity studies on PPGs of various molecular weights (300 to 3900 Da) have indicated LD_{50} values (rats) ranging from 0.5 to >40g/kg.

The acute dermal toxicity studies involving groups of five albino rabbits, doses of PPG 1025 (20 ml/kg) and PPG 2025 (20 ml/kg) did not cause death. Two of five rabbits dosed with 20 ml/kg PPG 425 and one of five dosed with 10 ml/kg PPG 425 died (Andersen 1994).

Stearyl Alcohol

The results of acute oral toxicity studies of rats of undiluted Stearyl Alcohol indicated a very low order of toxicity. Results of percutaneous toxicity studies with products containing 8.0% Stearyl Alcohol also indicated a low order of toxicity (Elder 1985).

Subchronic And Chronic Toxicity

PPG Butyl Ethers

Wistar rats (10/sex/group) were treated topically with 0.1 to 1.0 ml/kg/day, 5 days/week, PPG-2 Butyl Ether for 13 weeks. Skin reactions (erythema, edema, scaliness, wounds, and incrustations) were observed in all groups, including the control group; however, the findings were more pronounced in the test groups. Other signs of systemic toxicity were not observed, and treatment-related changes were not noted upon ophthalmoscopic examination. Males of the mid- and high-dose groups had decreased body weights, but feed consumption did not differ among the groups. Both sexes of the high-dose group and males of the mid-dose group had increased numbers of the neutrophil granulocytes. Males of the high-dose group had increased plasma Glutamine-Oxaloacetic Transaminase (GOT) and Glutamic-Pyruvic Transaminase (GPT) activities, and females had increased plasma triglyceride concentration and decreased glucose concentration; both sexes had increased relative liver weights. Treatment-related changes in urinalysis values and gross pathology were not observed. At microscopic examination, changes of the treated skin were observed in all groups, including the controls. In particular, females of the high-dose group had more severe acanthosis. No treatment-related microscopic changes were observed in organs or tissues other than the skin. The investigators concluded that the dermal no-observable-effect level (NOEL) was 0.1 ml/kg/day PPG-2 Butyl Ether, which was equivalent to a dose of 91 mg/kg/day (Andersen 2001).

Propylene Glycol and Polypropylene Glycols

In subchronic oral toxicity studies, PPG 2000 induced, at most, slight reductions in growth and body weight of rats. PPG 750 caused slight increases in liver and kidney weights in rats. Following the subchronic oral administration of PPG 750 to dogs, slight increases in liver and kidney weights were noted.

In a subchronic dermal toxicity study (rabbits), PPG 2000 did not cause any adverse effects at doses of 1 ml/kg. Slight depression of growth was observed after the administration of 5- and 10-ml/kg doses. Test substance–related lesions were not observed in rats that were fed diets containing 50,000 ppm PG (2.5 g/kg/day) for 15 weeks or in rats that were fed PG concentrations up to 50,000 ppm in the diet for 2 years. Similar results were reported in a study in which dogs were fed 2 or 5 g/kg PG in the diet for ~103 weeks. In another subchronic study, dogs received 5% PG in drinking water for 5 to 9 months. The results of tests for hepatic and renal impairment were negative. However, in cats fed diets containing PG, erythrocyte destruction was noted at concentrations as low as 6% PG (Andersen 1994).

Inhalation Toxicity

PPG Butyl Ethers

When five rats/sex were treated to saturated PPG-2 Butyl Ether vapor, all of the rats survived and no clinical signs of toxicity or gross lesions were observed. A mist of PPG-33 Butyl Ether (evolved at 170°C) killed six of six rats in 4 hours and one of six rats in 6 hours, and was classified as moderately hazardous. In contrast, vapors evolved at room temperature only produced slight ocular irritation.

No signs of toxicity were observed in rats treated via endotracheal injection with saline, 0.005 ml/kg (0.25%) PPG-5 Butyl Ether, or 1.0 ml/kg (50%) PPG-53 Butyl Ether. Rats treated with 2.0 ml/kg (100%) PPG-33 Butyl Ether had piloerection and tremors within 7 minutes of dosing. At necropsy, lungs of the control group were discolored and had hemorrhages. At microscopic examination, the control lungs had minimal grade perivascular infiltrates, interstitial pneumonitis, and one instance of interstitial fibrosis (low severity). Similar lesions were observed in lungs of rats treated with PPG-5 Butyl Ether (low severity). Both PPG-33 and -53 Butyl Ethers caused increased perivascular infiltrates (similar to controls) and interstitial pneumonitis (moderate severity). None of the PPG Butyl Ethers caused discolorations of the lungs. The investigators concluded that the least toxic (endotracheally) of the materials tested were those with molecular weights of >2000 Da and with water solubilities of <0.1%. The peroral toxicity was inversely proportional to the molecular weight, and the incidence of pulmonary lesions following endotracheal dosing was directly proportional to the molecular weight (Andersen 2001).

Ocular Toxicity

PPG Stearyl Ethers

Undiluted PPG-15 Stearyl Ether was practically nonirritating (score = 1.7/110) when instilled into the conjunctival sac of five rabbits (CTFA 1998).

PPG Butyl Ethers

PPG-2 Butyl Ether caused minor corneal injury (opacity), iritis, moderate conjunctival irritation, and a discharge when a 0.1-ml volume was instilled into the conjunctival sac of six rabbits. When rabbits were treated with 0.01 ml of the test material, opacity was not observed, but four rabbits had iritis and all six had minor to moderate conjunctival irritation and discharge. In another study, 0.5 ml PPG-15 Butyl Ether caused traces of diffuse corneal necrosis in the eyes of four rabbits and no injury to the eye of one rabbit; 0.5 ml PPG-33 Butyl Ether caused no signs of ocular toxicity (Andersen 2001).

Propylene Glycol and Polypropylene Glycols

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

irritation studies. PPGs 425, 1025, and 2025 were classified as harmless agents in rabbits in another ocular irritation study; PPG 1200 induced slight, transient ocular irritation in an albino rabbit (Andersen 1994).

Stearyl Alcohol

In rabbit irritation tests, Stearyl Alcohol produced minimal ocular irritation (Elder 1985).

Skin Irritation and Sensitization

PPG Stearyl Ethers

When applied to the intact and abraded skin of six New Zealand white rabbits, PPG-15 Stearyl Ether (concentration not specified) was slightly irritating; the primary irritation index (PII) was 0.42/8 (CTFA 1998).

PPG Butyl Ethers

During a 4-hour occlusive patch test, PPG-2 Butyl Ether caused minor, transient erythema in one of six rabbits and desquamation in four rabbits. PPG-33 Butyl Ether was nonirritating in a vesicant test and a 4-hour irritation test using rabbits. During a 3-day repeated-application study, one of three treated rabbits had desquamation of the treatment site. In studies using rabbits, undiluted PPG-40 Butyl Ether caused minimal to marked capillary injection (Andersen 2001).

Propylene Glycol and Polypropylene Glycols

In a 24-hour skin irritation test involving nude mice, no reactions were observed after administration of 10% PG. Hypertrophy, dermal inflammation, and epidermal proliferation were observed when a concentration of 50% PG was similarly tested. Draize test results indicated that PG was, at most, a mild skin irritant when applied for 24 hours to abraded and intact skin of rabbits. When PG was applied to the skin of guinea pigs and rabbits (guinea pigs and rabbits lack sweat glands) for 48 hours using open and closed patches, no reactions were observed. The results of 48-hour and 21-day open and closed patch tests involving Gottingen swine (no sweat glands) indicated no reactions to PG. Single and repeated applications of PPG 425, PPG 1025, and PPG 2025 did not cause skin irritation in the rabbit. Repeated applications of PPG 1200 to rabbits caused mild reactions at abraded skin sites and no reactions at intact sites. Results were negative for 100% PG in a mouse external ear swelling sensitization test. The results of a guinea pig maximization, open epicutaneous, and Finn chamber tests indicated no sensitization reactions to 70% PG. In another maximization test, PG was classified as a potentially weak sensitizer. The results of six other guinea pig sensitization tests indicated that PG was not an allergen (Andersen 1994).

Stearyl Alcohol

In rabbit irritation tests, Stearyl Alcohol produced minimal to mild primary cutaneous irritation. A product containing 24% Stearyl Alcohol produced no evidence of contact sensitization in the guinea pig. A rabbit ear comedogenicity test on Stearyl Alcohol was negative (Elder 1985).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

PPG Butyl Ethers

Two groups of twenty pregnant Wistar rats were treated topically with 0.3 and 1.0 ml/kg/day PPG-2 Butyl Ether (in propylene glycol) on gestational days (GDs) 6 to 16. Rats of the control group were treated with 1.5 ml/kg/day of the vehicle alone. No mortality occurred in any of the test or control groups, and no behavioral effects or signs of systemic toxicity were observed. Minor local skin reactions were observed in both test groups, but the investigators did not consider the test material a dermal irritant. Maternal performance was comparable in all groups, and no statistically significant differences were observed in body or organ weights, feed consumption, gross pathology, or litter data between the test and control groups. Compound-related malformations, anomalies, or variants of the offspring were not observed; however, offspring of the high dose group had a minor, but nonsignificant increase in the incidence of supernumerary ribs. The investigators concluded that PPG-2 Butyl Ether was nontoxic to pregnant rats and that dermal application during gestation was nonteratogenic at doses up to 1.0 ml/kg/day (Andersen 2001).

Propylene Glycol and Polypropylene Glycols

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

GENOTOXICITY

Propylene Glycol and Polypropylene Glycols

In the Ames test, PG was not mutagenic in strains TA1535, TA1537, TA1538, TA98, and TA100 of *Salmonella typhimurium* with and without metabolic activation. PG caused a dose-dependent increase in the frequency of sister-chromatid exchanges (SCEs) in a Chinese hamster cell line and was classified as a weak inducer of SCEs. In another study, PG was not mutagenic when tested in a SCE assay involving human cultured fibroblasts and a cultured Chinese hamster cell line both with and without metabolic activation. Chromosomal aberrations were induced in

Chinese hamster fibroblasts in another assay. PG was not mutagenic in additional in vitro tests: chromosomal aberrations, mitotic recombination, basepair substitution, micronucleus test, reverse mutation, and DNA damage (Andersen 1994).

Stearyl Alcohol

Stearyl Alcohol was not mutagenic in the Ames Assay (Elder 1985).

CARCINOGENICITY

PPG Butyl Ethers

A PPG Butyl Ether of chain length ~9 to 13 (0.001% to 0.26% of the diet) was not carcinogenic to rats after 2 years of treatment (Andersen 2001).

Propylene Glycol and Polypropylene Glycols

PG disturbed the proliferation of urinary bladder epithelial cells from the rat, having reduced DNA production in tetraploid cells 1 and 2 months after the rats were injected subcutaneously. This effect was not observed at 3 months.

The results were negative when PG was tested in the hamster ovary cell transformation bioassay. In a 2-year feeding study involving CD strain rats, PG was not carcinogenic when concentrations up to 50,000 ppm were administered in the diet. In a lifetime dermal carcinogenicity study, three groups of Swiss mice received dermal applications of 10%, 50%, and 100% PG, respectively. The tumor incidence in each of the three groups did not differ from that noted in the negative control group; skin tumors were not observed (Andersen 1994).

Stearyl Alcohol

Stearyl Alcohol did not promote tumor formation when tested with dimethylbenzanthracene (DMBA) (Elder 1985).

CLINICAL ASSESSMENT OF SAFETY

PPG Butyl Ethers

PPG-40 Butyl Ether at a concentration of 7% (test volume = 0.2 ml) was nonsensitizing when applied to the upper back of 112 subjects (Andersen 2001).

Propylene Glycol and Polypropylene Glycols

PG induced skin irritation and sensitization reactions in normal subjects and in patients. In these studies, test concentrations ranged from 2% to 100% PG. Reactions were observed at concentrations as low as 10% PG in predictive tests and as low as 2% in provocative tests. PG also increased the allergic responses in 43 patients patch tested with 50 μg of 1% nickel sulfate solution. Neither skin irritation nor sensitization reactions were observed in 300 subjects who received continuous and repeated dermal applications of undiluted PPG 2000 (Andersen 1994).

Stearyl Alcohol

The results of single-insult clinical patch testing indicate a very low order of skin irritation potential for undiluted Stearyl Alcohol. The rate of contact sensitization in a large population was 19 of 3740 (0.51%) for Stearyl Alcohol. Reports of isolated cases of contact dermatitis from Stearyl Alcohol are available (Elder 1985).

SUMMARY

The PPG Stearyl Ethers are polypropylene ethers of stearyl ether that function as skin-conditioning agents in cosmetic formulations. In 1998, they were reported used in 56 cosmetic formulations. Data submitted to FDA in 1984 indicated that concentrations up to 25% were used in cosmetics, and one supplier (ICI surfactants, 1998) reported that the concentration of use were 2% to 10%.

Few data on the PPG Stearyl Ethers were available. Data on PPG Butyl Ethers, PG and PPG, and Stearyl Alcohol were reviewed as a further basis for the assessment of safety.

The amounts of the PPG Butyl Ethers that were absorbed were inversely proportional to the molecular weights on the compounds. Little to no penetration occurred when a PPG Butyl Ether of molecular weight 800 Da (approximate chain length = 9–13) was applied to the skin of rabbits, and was absorbed poorly from the intestine of rats, rabbits, guinea pigs, and mice. During metabolism, the butyl group was removed and oxidized, and the chains were fragmented, oxidized to weak acids, and eliminated in the urine. The major route of mammalian PG metabolism is to lactaldehyde and lactate via hepatic alcohol and aldehyde dehydrogenases. Elimination in humans after IV injection was dose related. PPGs were readily absorbed from the GI tract and were excreted in the urine and feces. Stearyl Alcohol is used in the biosynthesis of lipids and other constituents, or enters metabolic pathways for energy production.

The acute oral LD_{50} (rats) of PPG-15 Stearyl Ether was 6.31 g/kg. The compound was classified as "practically harmless," as the observed changes were not considered direct effects of the test compound. During an acute dermal toxicity study, 5.25 ml/kg PPG-15 Stearyl Ether was nontoxic to rabbits. In general, the PPG Butyl Ethers were very toxic by the IV route and were slightly toxic to nontoxic by the IP and subcutaneous routes. The smaller molecular weight ethers were generally more toxic than the larger molecular weight ethers. In rats, the acute oral LD_{50} of the ethers ranged from 1.62 to 2.93 ml/kg (PPG-2 Butyl Ether) to 48.7 ml/kg (PPG-40 Butyl Ether). For rabbits, the cutaneous LD_{50} values were 5.86 to 7.13 ml/kg (PPG-2 Butyl Ether) to >20 ml/kg (PPG-40 Butyl Ether). The oral LD_{50} of PG was 21 g/kg in studies using rats. PPG (20 ml/kg) was nontoxic during acute dermal studies. Stearyl Alcohol was nontoxic during acute oral or percutaneous toxicity studies. The 13-week dermal no-effect level of PPG-2 Butyl Ether in rats was 0.1 ml/kg/day, which corresponded to a dose of 91 mg/kg/day. During subchronic studies, PPG caused slight reductions in growth and slight increases of liver and kidney weights. Compound-related lesions were not observed in rats fed 2.5 g/kg/day PG for 15 weeks to 2 years, or in dogs fed 2 or 5 g/kg/day PG for 103 weeks.

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

Undiluted PPG-15 Stearyl Ether was practically nonirritating to the eyes of rabbits (Draize score = 1.7/110). Rabbits treated with PPG-2 Butyl Ether had minor to moderate conjunctival irritation, opacity, and iritis. PPG-33 Butyl Ether was not an ocular irritant. Other PPG Butyl Ethers caused only minor injury to the eyes of rabbits. PG and PPG were nonirritating or slightly irritating, and Stearyl Alcohol was minimally irritating. During dermal studies using rabbits, PPG- 15 Stearyl Ether was slightly irritating (PII = 0.42/8). PPG-2 Butyl Ether caused minor, transient erythema and desquamation during a 4-hour occlusive patch test. PPG-9, ~9–15, -15, -18, and -33 Butyl Ethers caused, at most, capillary injection. PG and PPG were, at most, mild irritants to the skin of rabbits. PG caused no to weak sensitization in a mouse external ear swelling test and guinea pig maximization test. Stearyl Alcohol caused minimal to mild primary cutaneous irritation, but no evidence of contact sensitization, in the skin of rabbits. Stearyl Alcohol was noncomedogenic in a study using the ears of rabbits.

At a topical dose of 1.0 ml/kg/day on GDs 6 to 16, PPG-2 Butyl Ether did not irritate the skin of pregnant mice and was both nontoxic to dams and nonteratogenic. PG (10,000 ppm) was not teratogenic in offspring of CD-1 mice treated during gestation. PG inhibited embryonic development in vitro, however.

PPG-9–13 Butyl Ether was noncarcinogenic when fed to rats at a concentration of 0.001% to 0.26% in the diet for 2 years. PG was generally nongenotoxic. In two studies, however, PG induced chromosomal aberrations or was a weak inducer of SCEs in Chinese hamster cells. Stearyl Alcohol was nonmutagenic in the Ames test. PG was noncarcinogenic during studies using hamster ovary cells, CD rats, and Swiss mice. Stearyl Alcohol did not promote tumor formation when tested with DMBA.

In a clinical study using 112 subjects, 7% PPG-40 Butyl Ether was nonsensitizing. Concentrations of 2% to 100% PG induced skin irritation and sensitization. PG increased the allergic responses of nickel–sensitive patients. Skin irritation and sensitization were not observed in 300 subjects treated with undiluted PPG 2000. Undiluted Stearyl Alcohol had a very low order of skin irritation potential and had a 0.51% rate of contact sensitization in a population of 3740 subjects.

DISCUSSION

Although few data on the PPG Stearyl Ethers were available, the CIR Expert Panel expected the ethers to be metabolized to PG and stearyl alcohol, both of which have been previously reviewed and found safe for use in cosmetics. Because of the chemical similarity of the PPG Stearyl Ethers and the PPG Butyl Ethers, the view was taken that safety test data on the latter group of ingredients would be an indication of the toxicity of the former group. Absorption of the PPG Butyl Ethers was inversely related to the molecular weight and, overall, these compounds were poorly absorbed through skin. In general, compounds of high molecular weight are less toxic than compounds of low molecular weight; therefore, PPG-11 and -15 Stearyl Ethers (average molecular weights = 638–870 Da) are likely less toxic than PPG-2 Butyl Ether (average molecular weight = 190 Da).

The Expert Panel's "safe as used" in cosmetics conclusion is based on historical data on concentration of use. The Expert Panel does not expect uses of PPG Stearyl Ethers to exceed 25%.

The available data do not suggest any significant toxicity. PPG-15 Stearyl Ether was classified as "practically harmless" in acute oral and dermal studies, and did not produce cutaneous or ocular irritation. PPG-2 Butyl Ether was nontoxic by the inhalation route. In a 13-week dermal application study, topical doses of up to 1.0 ml/kg/day PPG-2 Butyl Ether did not produce adverse reproductive and developmental effects. A PPG Butyl Ether of chain length ~9 to 13 was not carcinogenic. In a primary irritation study, PPG-2 Butyl Ether caused minor, transient erythema and epithelial cell desquamation, but not edema. The ether also caused iritis and minor to moderate conjunctival irritation during an ocular irritation study using rabbits. Based on these studies, as well as data on the component chemicals, the Expert Panel concluded that PPG-11 and -15 Stearyl Ethers are safe as used in cosmetics.

CONCLUSION

Based on the available data, the CIR Expert Panel concludes that PPG-11 and -15 Stearyl Ethers are safe as used in cosmetics.

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