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Amended Safety Assessment of Butyl Polyoxyalkylene Ethers as Used in Cosmetics

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Abstract

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 46 butyl polyoxyalkylene ethers that share a common structural motif, namely a butyl chain (4 carbon alkyl chain) bound to a polyoxyalkylene (PPG, PEG, or both); 23 of these ethers were previously reviewed by the Panel, and 23 are reviewed herein for the first time. Most of the butyl polyoxyalkylene ethers have several functions in cosmetics, but the most common reported functions include hair conditioning agent and skin conditioning agent, and many reportedly function as solvents. Upon review of new data, including frequency and concentration of use, and data from previous Panel reports and on read-across analogs, the Panel concluded that these ingredients are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating.

Keywords

butyl polyoxyalkylene ethers, safety, cosmetics

Introduction

The Expert Panel for Cosmetic Ingredient Safety (Panel) published the Amended Final Report on the Safety Assessment of PPG-40 Butyl Ether with an Addendum to Include PPG-2, -4, -5, -9, -12, -14, -15, -16, -17, -18, -20, -22, -24, -26, -30, -33, -52, and -53 Butyl Ethers in 2001.[1] Based on the available data, the Panel concluded that these butyl PPG ethers were safe for use in cosmetics when formulated to avoid irritation. This was a revised conclusion for PPG-40 Butyl Ether; in 1993, the Panel concluded that the safety of PPG-40 Butyl Ether was not documented or substantiated.[2]

In 2000, the Panel published the Final Report on the Safety Assessment of PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-26-Buteth-26, and PPG-28-Buteth-35.[3] Based on the information included in that published report, the Panel concluded that PPG-26-Buteth-26 and PPG-28-Buteth-35 are safe as used in cosmetic products, and that the data were insufficient to support the safety of PPG-12-Buteth-16 and PPG-9-Buteth-12 as used in cosmetics. However, that same year, the Panel issued an Amended Final Report on these butyl PPG/PEG ethers, and concluded that all four ingredients are safe as used in cosmetic products.[4]

The Panel usually evaluates the conclusions of previously-issued reports every 15 years, and it has been at least 15 years since the last assessments have been issued on the ingredients named above. Because the ingredients included in the reports on the butyl PPG ethers and the butyl PPG/PEG ethers share a common structural motif, namely a butyl chain (4 carbon alkyl chain) bound to a polyoxyalkylene (PPG, PEG, or both), the Panel determined that the butyl PPG ethers and butyl PPG/PEG ethers could be re-reviewed together in one report; this family is referred to as the butyl polyoxyalkylene ethers.

Included in this assessment are butyl polyoxyalkylene ethers named in the *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*) that have not yet been reviewed:

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Buteth-3
PPG-3 Butyl Ether
PPG-2-Buteth-1
PPG-2-Buteth-2
PPG-2-Buteth-3
PPG-3-Buteth-5
PPG-4-Buteth-4
PPG-5-Buteth-5
PPG-5-Buteth-7
PPG-7-Buteth-4
PPG-7-Buteth-10
PPG-10-Buteth-9
PPG-12-Buteth-12
PPG-15-Buteth-20
PPG-17-Buteth-17
PPG-19-Buteth-19
PPG-20-Buteth-30
PPG-24-Buteth-27
PPG-30-Buteth-30
PPG-33-Buteth-45
PPG-36-Buteth-36
PPG-38-Buteth-37

Therefore, this safety assessment includes 23 butyl polyoxyalkylene ethers that were evaluated in two previous reports and 23 butyl polyoxyalkylene ethers that were not yet reviewed by the Panel. A list of all 46 ingredients included in this review is provided in Table 1.

The two groups of ingredients that are being combined in this report have similar functions in cosmetics. According to the *Dictionary*, both the butyl PPG/PEG ethers and the butyl PPG ethers are reported to function as hair conditioning agents and skin conditioning agents (Table 2).[5] Other functions for some butyl PPG/PEG ethers include fragrance ingredients, surfactants, or solvents. Buteth-3 is reported to function as a solvent.

The Panel has reviewed similar groups of ingredients. Previously, the Panel concluded alkyl PEG ethers (reaction products of an alkyl alcohol and one or more equivalents of ethylene oxide) are safe in the present practices of use and concentration (as described in the safety assessment) when formulated to be non-irritating.[6] The Panel also found the alkyl PEG/PPG ethers (reaction products of an alkyl alcohol and one or more equivalents each of ethylene oxide and propylene oxide) safe in the present practices of use and concentration (as described in the safety assessment) when formulated to be non-irritating.[7] These reports are available on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/ingredients).

Much of the new data included in this safety assessment was found on the European Chemicals Agency (ECHA) website[8] and in an Organisation for Economic Co-operation and Development (OECD) Screening Information Data Set (SIDS).[9]

ECHA dossiers[10,11] and the SIDS document[9] also provided information that is useful for read-across. The justifications for the use of information on (butoxymethylethoxy)methylethoxy] propan-1-ol, poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy-, and 1-(2-butoxy-1-methylethoxy)-propan-2-ol for read across are provided in Table 3; test data on these compounds are included in the body of the report. Additionally, excerpts from the summaries of previous reports (issued in 2000 and 2001) on butyl PPG/PEG ethers and the butyl PPG ethers are disseminated throughout the text of this re-review document, as appropriate.

Chemistry

Definition and Structure

The definitions and structures of the butyl polyoxyalkylene ethers are provided in Table 2.

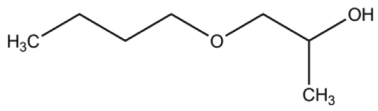
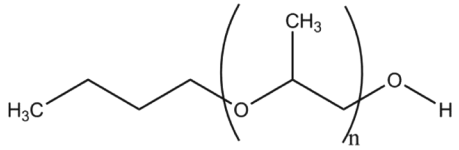
The butyl polyoxyalkylene ethers in this report share a common core structure comprising a linear, four carbon alkyl chain (butyl) connected, through an ether linkage, to a polyether chain comprising a polyethylene glycol (PEG, or an "eth"

Table 1. Butyl Polyoxyalkylene Ethers Included in This Report.

Buteth-3	PPG-19-Buteth-19	PPG-15 Butyl Ether
PPG-2-Buteth-1	PPG-20-Buteth-30	PPG-16 Butyl Ether
PPG-2-Buteth-2	PPG-24-Buteth-27	PPG-17 Butyl Ether
PPG-2-Buteth-3	PPG-26-Buteth-26	PPG-18 Butyl Ether
PPG-3-Buteth-5	PPG-28-Buteth-35	PPG-20 Butyl Ether
PPG-4-Buteth-4	PPG-30-Buteth-30	PPG-22 Butyl Ether
PPG-5-Buteth-5	PPG-33-Buteth-45	PPG-24 Butyl Ether
PPG-5-Buteth-7	PPG-36-Buteth-36	PPG-26 Butyl Ether
PPG-7-Buteth-4	PPG-38-Buteth-37	PPG-30 Butyl Ether
PPG-7-Buteth-10	PPG-2 Butyl Ether	PPG-33 Butyl Ether
PPG-9-Buteth-12	PPG-3 Butyl Ether	PPG-40 Butyl Ether
PPG-10-Buteth-9	PPG-4 Butyl Ether	PPG-52 Butyl Ether
PPG-12-Buteth-12	PPG-5 Butyl Ether	PPG-53 Butyl Ether
PPG-12-Buteth-16	PPG-9 Butyl Ether	Propylene Glycol Butyl Ether
PPG-15-Buteth-20	PPG-12 Butyl Ether	
PPG-17-Buteth-17	PPG-14 Butyl Ether	

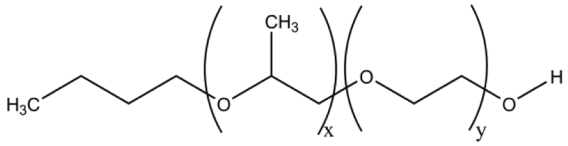
Note: ingredients that were reviewed previously are indicated in blue.

Table 2. Definitions, Structures, and Reported Functions of Butyl Polyoxyalkylene Ethers [5; CIR Staff].

Ingredient CAS no *Butyl Propylene Glycol Ether*	Definition and Structure	Function
Propylene Glycol Butyl Ether 29387-86-8 (mixture); 5131-66-8 (α-isomer); 15821-83-7 (β-isomer)[9]	Propylene Glycol Butyl Ether is the propylene glycol ether of n-butyl alcohol that conforms to the formula 	fragrance ingredient; solvent
Butyl PPG Ethers	The butyl PPG ethers included in this report all conform generally to the formula:  the value of "n" varies for each ingredient, and this value is specified with each definition	
PPG-2 Butyl Ether 9003-13-8 (generic)	PPG-2 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 2	hair conditioning agent; skin-conditioning agent – misc; solvent
PPG-3 Butyl Ether 55934-93-5	PPG-3 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 3	hair conditioning agent; skin-conditioning agent – misc; solvent
PPG-4 Butyl Ether 9003-13-8 (generic)	PPG-4 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 4	hair conditioning agent; skin-conditioning agent – misc
PPG-5 Butyl Ether 9003-13-8 (generic)	PPG-5 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 5	hair conditioning agent; skin-conditioning agent – misc
PPG-9 Butyl Ether 9003-13-8 (generic)	PPG-9 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 9	hair conditioning agent; skin-conditioning agent – misc
PPG-12 Butyl Ether 9003-13-8 (generic)	PPG-12 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 12	hair conditioning agent; skin-conditioning agent – misc
PPG-14 Butyl Ether 9003-13-8 (generic)	PPG-14 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 14	hair conditioning agent; skin-conditioning agent – misc
PPG-15 Butyl Ether 9003-13-8 (generic)	PPG-15 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 15	hair conditioning agent; skin-conditioning agent – misc
PPG-16 Butyl Ether 9003-13-8 (generic)	PPG-16 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 16	hair conditioning agent; skin-conditioning agent – misc
PPG-17 Butyl Ether 9003-13-8 (generic)	PPG-17 Butyl Ether is the polypropylene glycol ether of butyl alcohol conforms generally to the formula depicted above, where n has an average value of 17	hair conditioning agent; skin-conditioning agent – misc
PPG-18 Butyl Ether 9003-13-8 (generic)	PPG-18 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 18	hair conditioning agent; skin-conditioning agent – misc
PPG-20 Butyl Ether 9003-13-8 (generic)	PPG-20 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 20	hair conditioning agent; skin-conditioning agent – misc
PPG-22 Butyl Ether 9003-13-8 (generic)	PPG-22 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 22	hair conditioning agent; skin-conditioning agent – misc
PPG-24 Butyl Ether 9003-13-8 (generic)	PPG-24 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 24	hair conditioning agent; skin-conditioning agent – misc

(continued)

Table 2. (continued)

Ingredient CAS no *Butyl Propylene Glycol Ether*	Definition and Structure	Function
PPG-26 Butyl Ether 9003-13-8 (generic)	PPG-26 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 26	hair conditioning agent; skin-conditioning agent – misc
PPG-30 Butyl Ether 9003-13-8 (generic)	PPG-30 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 30	hair conditioning agent; skin-conditioning agent – misc
PPG-33 Butyl Ether 9003-13-8 (generic)	PPG-33 Butyl Ether is the polypropylene glycol ether of butyl alcohol conforms generally to the formula depicted above, where n has an average value of 33	hair conditioning agent; skin-conditioning agent – misc
PPG-40 Butyl Ether 9003-13-8 (generic)	PPG-40 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 40	hair conditioning agent; skin-conditioning agent – misc
PPG-52 Butyl Ether 9003-13-8 (generic)	PPG-52 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 52	hair conditioning agent; skin-conditioning agent – misc
PPG-53 Butyl Ether 9003-13-8 (generic)	PPG-53 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 53	hair conditioning agent; skin-conditioning agent – misc
Butyl PPG/PEG Ethers		
The butyl PPG/PEG ethers included in this report all conform generally to the formula:  the value of "x" and "y" varies for each ingredient, and these values are specified with each definition		
PPG-2-Buteth-1 9038-95-3 (generic) 9065-63-8 (generic)	PPG-2-Buteth-1 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 2 and y has an average value of 1	hair conditioning agent; skin-conditioning agent – misc
PPG-2-Buteth-2 9038-95-3 (generic) 9065-63-8 (generic)	PPG-2-Buteth-2 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 2 and y has an average value of 2	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; surfactant – emulsifying agent
PPG-2-Buteth-3 9038-95-3 (generic) 9065-63-8 (generic)	PPG-2-Buteth-3 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 2 and y has an average value of 3	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; solvent
PPG-3-Buteth-5 9038-95-3 (generic) 9065-63-8 (generic)	PPG-3-Buteth-5 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 3 and y has as average value of 5	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; solvent
PPG-4-Buteth-4 9038-95-3 (generic) 9065-63-8 (generic)	PPG-4-Buteth-4 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 4 and y has an average value of 4	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; surfactant – emulsifying agent
PPG-5-Buteth-5 9038-95-3 (generic) 9065-63-8 (generic)	PPG-5-Buteth-5 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 5 and y has an average value of 5	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; surfactant – emulsifying agent
PPG-5-Buteth-7 9038-95-3 (generic) 9065-63-8 (generic)	PPG-5-Buteth-7 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 5 and y has an average value of 7	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; solvent
PPG-7-Buteth-4 9038-95-3 (generic) 9065-63-8 (generic)	PPG-7-Buteth-4 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 7 and y has an average value of 4	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; solvent; surfactant – emulsifying agent
PPG-7-Buteth-10 9038-95-3 (generic) 9065-63-8 (generic)	PPG-7-Buteth-10 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 7 and y has an average value of 10	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; solvent; surfactant – emulsifying agent

(continued)

Table 2. (continued)

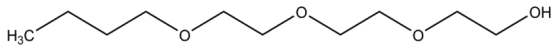
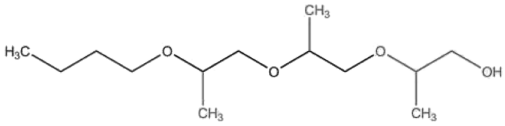
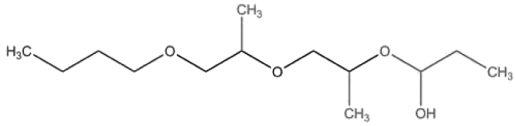
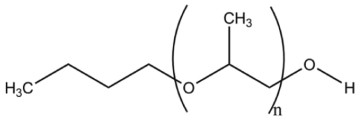
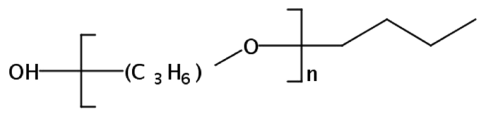
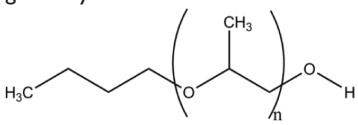
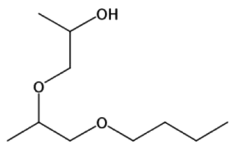
Ingredient CAS no *Butyl Propylene Glycol Ether*	Definition and Structure	Function
PPG-9-Buteth-12 9038-95-3 (generic) 9065-63-8 (generic)	PPG-9-Buteth-12 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 9 and y has an average value of 12	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; surfactant - emulsifying agent
PPG-10-Buteth-9 9038-95-3 (generic) 9065-63-8 (generic)	PPG-10-Buteth-9 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 10 and y has an average value of 9	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; surfactant – emulsifying agent
PPG-12-Buteth-12 9038-95-3 (generic) 9065-63-8 (generic)	PPG-12-Buteth-12 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 12 and y has an average value of 12	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; surfactant – emulsifying agent
PPG-12-Buteth-16 9038-95-3 (generic) 9065-63-8 (generic)	PPG-12-Buteth-16 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 12 and y has an average value of 16	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; solvent; surfactant – emulsifying agent
PPG-15-Buteth-20 9038-95-3 (generic) 9065-63-8 (generic)	PPG-15-Buteth-20 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 15 and y has an average value of 20	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; solvent; surfactant – emulsifying agent
PPG-17-Buteth-17 9038-95-3 (generic) 9065-63-8 (generic)	PPG-17-Buteth-17 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 17 and y has an average value of 17	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; surfactant – emulsifying agent
PPG-19-Buteth-19 9038-95-3 (generic) |9065-63-8 (generic)	PPG-19-Buteth-19 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 19 and y has an average value of 19	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; surfactant – emulsifying agent
PPG-20-Buteth-30 9038-95-3 (generic) 9065-63-8 (generic)	PPG-20-Buteth-30 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 20 and y has an average value of 30	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; solvent; surfactant – emulsifying agent
PPG-24-Buteth-27 9038-95-3 (generic) 9065-63-8 (generic)	PPG-24-Buteth-27 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 24 and y has an average value of 27	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; surfactant – emulsifying agent
PPG-26-Buteth-26 9038-95-3 (generic) 9065-63-8 (generic)	PPG-26-Buteth-26 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 26 and y has an average value of 26	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; surfactant – emulsifying agent
PPG-28-Buteth-35 9038-95-3 (generic) 9065-63-8 (generic)	PPG-28-Buteth-35 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 28 and y has an average value of 35	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; surfactant – emulsifying agent
PPG-30-Buteth-30 9038-95-3 (generic) 9065-63-8 (generic)	PPG-30-Buteth-30 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 30 and y has an average value of 30	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; surfactant – cleansing agent; surfactant – solubilizing agent
PPG-33-Buteth-45 9038-95-3 (generic) 9065-63-8 (generic)	PPG-33-Buteth-45 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 33 and y has an average value of 45	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc
PPG-36-Buteth-36 9038-95-3 (generic) 9065-63-8 (generic)	PPG-36-Buteth-36 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 36 and y has an average value of 36	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; surfactant – cleansing agent; surfactant – solubilizing agent
PPG-38-Buteth-37 9038-95-3 (generic) 9065-63-8 (generic)	PPG-38-Buteth-37 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 38 and y has an average value of 37	fragrance ingredient; hair conditioning agent; skin-conditioning agent – misc; surfactant – cleansing agent; surfactant – solubilizing agent
Butyl PEG Ether		
Buteth-3 [143-22-6]	Buteth-3 is the polyethylene glycol ether of butyl alcohol that conforms generally to the formula: 	solvent

Table 3. Read Across Justification.

	Target material	Read-across material
Name	***PPG-3 Butyl Ether***	***[(Butoxymethylethoxy)methylethoxy]propan-1-ol***[10]
CAS no.	55934-93-5	55934-93-5
Structure		
Read-across endpoints		•acute toxicity; dermal, oral •short-term toxicity – oral •subchronic toxicity; oral •genotoxicity; in vitro, in vivo •dermal irritation; animal •dermal sensitization; animal •ocular irritation; animal
Justification	chemical properties, physical properties and metabolism are expected to be essentially identical for these two positional isomers	
Name	***PPG-n Butyl Ether***	***Poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy-***[11]
CAS no.	9003-13-8 (generic)	9003-13-8
Structure	the butyl PPG ethers included in this report all conform generally to the formula:  the value of "n" varies for each ingredient, as specified in each definition	
Read-across endpoints		•acute toxicity; dermal, oral •short-term; oral •DART •genotoxicity; in vitro •dermal irritation; in vitro
Justification	the common core structure (butoxy) and the polyol repeat units (propylene glycol residues) of the butyl PPG ethers are identical to those of α-butyl-ω-hydroxy-poly[oxy(methyl-1,2-ethanediyl)]	
Name	***PPG-n Butyl Ether***	***1-(2-Butoxy-1-methylethoxy)-propan-2-ol***[9]
CAS no.	9003-13-8 (generic)	
Structure	the butyl PPG ethers included in this report all conform generally to the formula:  the value of "n" varies for each ingredient, as specified in each definition	 (produced as a 4-isomer mixture)
Mol. Wt (avg)		190.29
Read-across endpoints		•ADME •acute toxicity; dermal, oral; inhalation •short-term toxicity – oral; inhalation •subchronic toxicity; dermal, oral •DART •genotoxicity; in vitro, in vivo •dermal irritation; animal •dermal sensitization; animal, human •ocular irritation; animal
Justification	potential metabolite of positional isomers of the butyl PPG ethers	

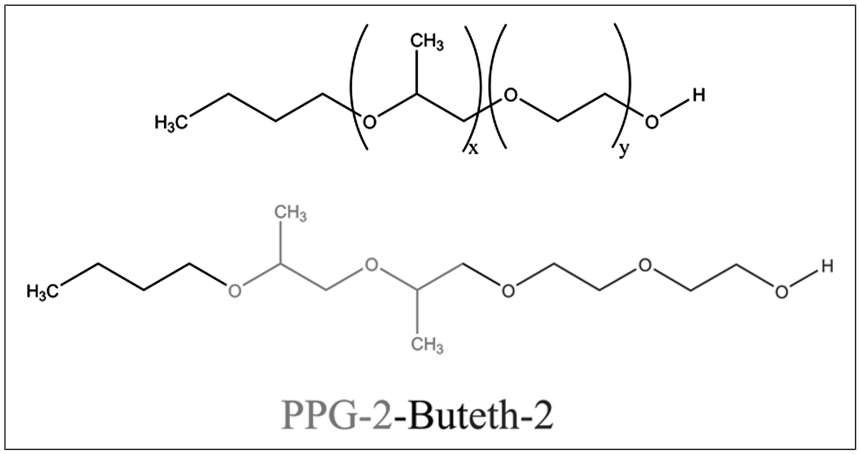


Figure 1. Generic and specific butyl polyoxyalkylene ether structures.

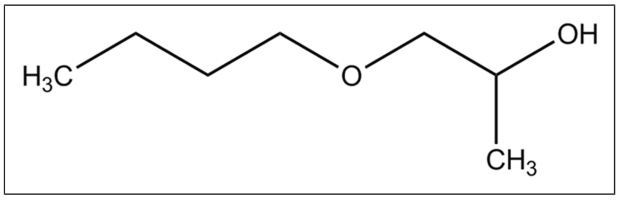


Figure 2. Propylene glycol butyl ether.

suffix), polypropylene glycol (PPG), or both. These polyether chains vary in length from just 1 repeat unit (i.e., Propylene Glycol Butyl Ether, MW = 132.20 g/mol) to 75 repeat units (i.e., PPG-38-Buteth-37, mean MW = 3911.12 g/mol). Accordingly, the butyl polyoxyalkylene ethers may be represented generically as a butyl terminated polyether, as shown in Figure 1.

Propylene Glycol Butyl Ether represents the smallest ingredient in this report, and is simply the ether of butanol and one propylene glycol residue.[12] While the *Dictionary* recites the structures of all of the other propylene glycol containing ingredients in this report as the β-isomers (terminal alcohol is primary (1°)), as shown in Figure 1, Propylene Glycol Butyl Ether is recited as the α-isomer (terminal alcohol is secondary (2°)) (Figure 2).

Physical and Chemical Properties

Propylene Glycol Butyl Ether[13,14] and PPG-3 Butyl Ether,[10] a hydrophobic glycol ether,[15] are colorless liquids (Table 4). Also described in Table 4 are physical and chemical properties of Buteth-3, a water-soluble crystalline compound with low volatility,[16] and those of an undefined polypropylene glycol butyl ether.

Methods of Manufacture

PPG-12-Buteth-16 and other ethylene oxide/propylene oxide polymers of this series, are butanol-initiated, random linear copolymers that are produced from equal amounts (by weight) of ethylene and propylene oxide.[4]

The PPG Butyl Ethers are produced by the reaction of excess propylene glycol with n-butyl alcohol.[1]

Generally, propylene glycol ethers are prepared commercially by reacting propylene oxide with an alcohol in the presence of a catalyst[17] in a closed continuous system.[9] This reaction can produce glycol ethers of varying chain lengths that depend on the stoichiometric ratio of reactants and the temperatures and pressures used in the reaction. Milder conditions and lower stoichiometric ratios of propylene oxide to alcohol yields the monopropylene glycol ethers, while using more propylene oxide and higher temperatures and pressures produces the di-, tri-, and poly-propylene glycol, mono-alkyl ethers. The products are purified by distillation.

The α-isomer and a β-isomer are usually formed during the synthesis of Propylene Glycol Butyl Ether. A technical product generally comprises 95–99% of the α-isomer and only traces of the β-isomer (the α-isomer is a secondary alcohol, and the β-isomer is a primary alcohol).[17]

Impurities

The concentration of residual ethylene oxide and propylene oxide in PPG-33-Buteth-45 is less than 1 ppm.[4] The PPG Butyl Ethers can contain propylene oxide.[1] It was reported (by two suppliers in 2010) that a maximum of 10 ppm propylene oxide was present in PPGs used to make finished products.[18] A tradename mixture containing PPG-26-Buteth-26 contained <5 ppm dioxane and <1 ppm ethylene oxide.[3]

Some of the butyl polyoxyalkylene ethers are ethoxylated and therefore may contain trace amounts of 1,4-dioxane, which is a by-product of ethoxylation and a known animal carcinogen.[19]

Table 4. Physical and Chemical Properties.

Property		
Propylene Glycol Butyl Ether	Value	Reference
Physical form	Clear liquid	13,14
Color	Colorless	13,14
Molecular wt.	132.23	14
Density (@ 20°C)	0.88 g/cm^3	13
(@ 25°C)	0.87 g/cm^3	
Relative density (water =1; @ 25°C)	0.879	14
Viscosity (@ 25°C)	2.9 mm^2/s	14
Vapor pressure	0.6 mmHg (20°C)	49
	1.40 mmHg (25°C)	14
Relative vapor density (air = 1)	4.55	14
Melting point	Below −75°C	14
Boiling point	171°C	14
Solubility	6g/100 mL water (moderate)	14
Log P_{ow}	1.2 (experimental)	13
	1.15 (estimated)	14
PPG-3 Butyl Ether		
Physical form	Liquid	10,15
Color	Colorless	10,15
Odor	Practically none mild	15,10
Molecular wt.	248.4 g/mol	15
Density (@ 20°C) (@ 25°C)	0.930 g/cm^3	15
	0.927 g/cm^3	
Specific gravity (@ 25°C)	0.930	
Viscosity (mm^2/s @ 25°C)	7	15
Vapor pressure (@ 20°C – extrapolated)	<0.01 mmHg	15
Vapor density (air = 1)	>6	15
Boiling point (@ 760 mmHg)	275°C	10,15
Water solubility (25°C)	40.2 g/L	15
log P_{ow}	1.9	10,15
Buteth-3		
Physical form	Clear crystalline substance	16
Vapor pressure (@ 25°C)	0.0025 mmHg	16
Solubility	Water soluble	16
Poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy-		
Physical form	Liquid	11
Color	Brown	11
Density (@ 20°C)	0.949 g/cm^3	11
Viscosity (@ 20°C) (@ 40°C)	19 mPa·s 16 mPa·s	11
Vapor pressure (@ 20°C)	0.0006 mmHg	11
Melting point	< −20°C	11
Boiling point (@ ~760 mmHg)	306°C	11
Solubility (solvent in water @ 25°C)	42.3 g/L; very soluble	11
log P_{ow} (@ 28°C)	1.18–4.37	11

Use

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics.

Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

Table 5. Frequency and Concentration of Use of Previously Reviewed Butyl Polyoxyalkylene Ethers According to Duration and Exposure[20-22].

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	PPG-9-Buteth-12				PPG-12-Buteth-16			
	2017	1997	2015	1995; 1999[#]	2017	1997	2015	1995; 1999[#]
Totals*	**2**	**2**	**NR**	**NR**	**436**	**53**	**0.001-2**	**0.5-31**
Duration of use								
Leave-on	*0*	*0*	*NR*	*NR*	*7*	*15*	*0.15-1*	*0.5-31*
Rinse-off	*0*	*0*	*NR*	*NR*	*424*	*16*	*0.0001-2*	*0.6-4*
Diluted for (bath) use	*2*	*2*	*NR*	*NR*	*5*	*22*	*0.8-1.3*	*0.6-0.7*
Exposure type								
Eye area	NR	NR	NR	NR	0	1	NR	NR
Incidental ingestion	NR	NR	NR	NR	0	NR	NR	NR
Incidental inhalation – spray	NR	NR	NR	NR	1; 4[a]	10[b]; 1[b]	0.53; 0.5[b]	0.5-31[b]
Incidental inhalation – powder	NR	NR	NR	NR	NR	1[b]	NR	1
Dermal contact	2	2	NR	NR	392	34	0.15-1.3	0.5-1
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair – non-coloring	NR	NR	NR	NR	42	18	0.0001-2	1-31
Hair – coloring	NR	NR	NR	NR	2	NR	0.05	NR
Nail	NR	NR	NR	NR	NR	1	NR	NR
Mucous membrane	2	2	NR	NR	385	27	0.8-1.3	0.6-0.7
Baby products	NR	NR	NR	NR	NR	1	NR	NR
	PPG-26-Buteth-26				**PPG-28-Buteth-35**			
	2017	**1997**	**2015**	**1995; 1999[#]**	**2017**	**1997**	**2015**	**1995; 1999[#]**
Totals*	**1332**	**13**	**0.000025-8**	**NR**	**9**	**10**	**NR**	**1**
Duration of use								
Leave-on	*738*	*7*	*0.000025-8*	*NR*	*6*	*1*	*NR*	*NR*
Rinse-off	*584*	*6*	*0.01-8*	*NR*	*3*	*9*	*NR*	*1*
Diluted for (bath) use	*10*	*0*	*0.025*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure type								
Eye area	27	NR	0.002-3.6	NR	NR	NR	NR	NR
Incidental ingestion	1	NR	NR	NR	NR	NR	NR	NR
Incidental inhalation – spray	448; 93[b]; 112[b]	5[a]; 1[b]	0.000025-6.2; 0.06-1.8[b]	NR	5[b]	NR	NR	NR
Incidental inhalation – powder	112[b]; 1[c]	NR	8[c]	NR	NR	NR	NR	NR
Dermal contact	1215	13	0.000025-8	NR	4	3	NR	NR
Deodorant (underarm)	7[a]	1[b]	Spray: 0.099	NR	1[b]	NR	NR	NR
Hair – non-coloring	107	NR	0.0001-8	NR	5	7	NR	1
Hair – coloring	3	NR	0.055-0.9	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous membrane	463	2	0.01-2	NR	NR	1	NR	NR
Baby products	3	NR	0.9	NR	NR	NR	NR	NR
	PPG-2 Butyl Ether				**PPG-14 Butyl Ether**			
	2017	**1998**	**2015**	**1998**	**2017**	**1998**	**2015**	**1998**
Totals*	**7**	**1**	**2-8**	**	**29**	**45**	**0.05-17.5**	**
Duration of use								
Leave-on	*1*	*1*	*2*	**	*28*	*16*	*1-17.5*	**
Rinse-off	*6*	*NR*	*3-8*	**	*1*	*29*	*0.05-8*	**
Diluted for (bath) use	*NR*	*NR*	*NR*	**	*NR*	*NR*	*NR*	**
Exposure type								
Eye area	1	NR	NR	**	1	NR	1.9	**

(continued)

Table 5. (continued)

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	PPG-9-Buteth-12				PPG-12-Buteth-16			
	2017	1997	2015	1995; 1999[#]	2017	1997	2015	1995; 1999[#]
Incidental ingestion	NR	NR	NR	**	NR	NR	NR	**
Incidental inhalation – spray	NR	NR	NR	**	6; 2[b]; 5[b]	9; 4[b]; 1[b]	1-10	**
Incidental inhalation – powder	NR	NR	NR	**	5[b]	1[b]	4-4.5[c]	**
Dermal contact	5	NR	2-8	**	29	45	1-17.5	**
Deodorant (underarm)	NR	NR	NR	**	13[a]	2[b]	6-17.5	**
Hair – non-coloring	NR	NR	NR	**	NR	NR	0.05-8	**
Hair – coloring	2	NR	5	**	NR	NR	NR	**
Nail	NR	1	NR	**	NR	NR	NR	**
Mucous membrane	4	NR	NR	**	1	29	NR	**
Baby products	NR	NR	NR	**	NR	NR	0.05	**
	PPG-16-Butyl Ether				**PPG-18 Butyl Ether**			
	2017	**1998**	**2015**	**1998**	**2017**	**1998**	**2015**	**1998**
Totals*	**NR**	**1**	**NR**	**	**NR**	**1**	**NR**	**
Duration of use								
Leave-on	*NR*	*NR*	*NR*	**	*NR*	*NR*	*NR*	**
Rinse-off	*NR*	*1*	*NR*	**	*NR*	*1*	*NR*	**
Diluted for (bath) use	*NR*	*NR*	*NR*	**	*NR*	*NR*	*NR*	**
Exposure type								
Eye area	NR	NR	NR	**	NR	NR	NR	**
Incidental ingestion	NR	NR	NR	**	NR	NR	NR	**
Incidental inhalation – spray	NR	NR	NR	**	NR	NR	NR	**
Incidental inhalation – powder	NR	NR	NR	**	NR	NR	NR	**
Dermal contact	NR	1	NR	**	NR	1	NR	**
Deodorant (underarm)	NR	NR	NR	**	NR	NR	NR	**
Hair – non-coloring	NR	NR	NR	**	NR	NR	NR	**
Hair – coloring	NR	NR	NR	**	NR	NR	NR	**
Nail	NR	NR	NR	**	NR	NR	NR	**
Mucous membrane	NR	NR	NR	**	NR	NR	NR	**
Baby products	NR	NR	NR	**	NR	NR	NR	**
	PPG-33 Butyl Ether				**PPG-40 Butyl Ether**			
	2017	**1998**	**2015**	**1998**	**2017**	**1998**	**2015**	**1998**
Totals*	**2**	**6**	**1-10**	**	**6**	**46**	**0.75-73.5**	**
Duration of use								
Leave-on	*1*	*6*	*1-10*	**	*6*	*7*	*0.75-71*	**
Rinse-off	*1*	*NR*	*NR*	**	*0*	*39*	*2-73.5*	**
Diluted for (bath) use	*NR*	*NR*	*NR*	**	*NR*	*NR*	*NR*	**
Exposure type								
Eye area	NR	NR	NR	**	NR	NR	NR	**
Incidental ingestion	NR	NR	NR	**	NR	NR	NR	**
Incidental inhalation – spray	1	5; 1[b]	2-2.1; 10[b]	**	6[b]	6[b]	0.75-10; 7-23[b]	**
Incidental inhalation – powder	NR	NR	NR	**	NR	NR	NR	**
Dermal contact	2	6	1-2.1	**	NR	1	NR	**
Deodorant (underarm)	NR	NR	NR	**	NR	NR	NR	**
Hair – non-coloring	NR	NR	10	**	6	6	0.75-71	**
Hair – coloring	NR	NR	NR	**	NR	39	73.5	**

(continued)

Table 5. (continued)

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	PPG-9-Buteth-12				PPG-12-Buteth-16			
	2017	1997	2015	1995; 1999[#]	2017	1997	2015	1995; 1999[#]
Nail	NR	NR	NR	**	NR	NR	NR	**
Mucous membrane	NR	NR	NR	**	NR	NR	NR	**
Baby products	NR	NR	NR	**	NR	NR	NR	**
	PPG-52 Butyl Ether							
	2017	**1998**	**2015**	**1998**				
Totals*	**NR**	**NR**	**3-23**	**				
Duration of use								
Leave-on	*NR*	*NR*	*23*	**				
Rinse-off	*NR*	*NR*	*3*	**				
Diluted for (bath) use	*NR*	*NR*	*NR*	**				
Exposure type								
Eye area	NR	NR	NR	**				
Incidental ingestion	NR	NR	NR	**				
Incidental inhalation – spray	NR	NR	23[a]	**				
Incidental inhalation – powder	NR	NR	NR	**				
Dermal contact	NR	NR	NR	**				
Deodorant (underarm)	NR	NR	NR	**				
Hair – non-coloring	NR	NR	3-23	**				
Hair – coloring	NR	NR	NR	**				
Nail	NR	NR	NR	**				
Mucous membrane	NR	NR	NR	**				
Baby products	NR	NR	NR	**				

Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
**At the time of the original safety assessment, concentration of use data were not reported by the FDA.
NR, no reported use.
[#]Some concentration of use data was reported at that time.
[a]It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b]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.
[c]It is possible these products are powders, but it is not specified whether the reported uses are powders.

According to information from the VCRP and the Council, 18 of the 46 ingredients assessed in this report are in use.[20-22] PPG-26-Buteth-26 has the highest frequency of use; according to the 2017 VCRP data, it is used in 1332 cosmetic formulations.[20] Buteth-3 and PPG-12-Buteth-16 have the next highest frequency of use, with 446 and 436 reported uses, respectively (Tables 5 and 6).

The results of the concentration of use survey conducted by the Council in 2015 indicate that PPG-40 Butyl Ether has the highest maximum use concentration in both leave-on (71% in a hair wax listed under tonics, dressings, and other hair grooming aids) and rinse-off formulations (73.5% in hair tints)[23] PPG-14 Butyl Ether has the greatest maximum leave-on concentration of use that results in dermal exposure; it is used at up to 17.5% in deodorants (Tables 5 and 6).

Approximately half of the in-use ingredients have been reviewed previously by the Panel.[3,4] The current frequency of use for the majority of these ingredients is similar to that reported at the time of the original review. However, there has been a large increase in the frequency of use of PPG-26-Buteth-26; in 1997, this ingredient was reported to be used in 13 formulations, and it is now used in 1332 formulations. Concentrations of use were not reported by the FDA at the time of the previous safety assessments, so it is not known if the concentrations of use have changed.

The 28 butyl polyoxyalkylene ethers not currently reported to be in use according to VCRP data and industry survey are listed in Table 7.

In some cases, reports of uses were received from the VCRP, but no concentration of use data was provided. For example, PPG-28-Buteth-35 is reported to be used in 9 formulations, but no use concentration data were submitted. In other cases, no uses were reported to the VCRP, but a maximum use concentration was provided in the industry survey. For example, PPG-52 Butyl Ether was not reported to be in use in the VCRP database, but the industry survey indicated that it is used in at least 2 hair product categories; it should be presumed that PPG-52 Butyl Ether

Table 6. Frequency (2017) and Concentration of Use (2015) of Previously Unreviewed Butyl Polyoxyalkylene Ethers.

	# of Uses[20]	Max Conc of Use (%)[23]	# of Uses[20]	Max Conc of Use (%)[23]	# of Uses[20]	Max Conc of Use (%)[23]
	PPG-5-Buteth-5		PPG-7-Buteth-4		PPG-7-Buteth-10	
Totals*	NR	0.05-0.5	NR	0.1-4	1	0.023
Duration of use						
Leave-on	*NR*	*0.05-0.5*	*NR*	*NR*	*1*	*0.023*
Rinse-off	*NR*	*0.05-0.2*	*NR*	*0.1-4*	*NR*	*NR*
Diluted for (bath) use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure type						
Eye area	NR	NR	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation – spray	NR	0.05; 0.5[a]	NR	NR	NR	NR
Incidental inhalation – powder	NR	0.05[b]	NR	NR	NR	NR
Dermal contact	NR	0.05	NR	4	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair – non-coloring	NR	0.05-0.5	NR	0.1	1	0.023
Hair – coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	NR	NR	NR	NR
Baby products	NR	NR	NR	NR	NR	NR
	PPG-15-Buteth-20		**PPG-17-Buteth-17**		**PPG-20-Buteth-30**	
Totals*	**1**	**2-6.2**	**NR**	**1.3-2**	**1**	**NR**
Duration of use						
Leave-on	1	2-6.2	NR	2	NR	NR
Rinse-off	NR	2	NR	1.3	1	NR
Diluted for (bath) use	NR	NR	NR	NR	NR	NR
Exposure type						
Eye area	NR	NR	NR	NR	1	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation – spray	1[a]	NR	NR	2	NR	NR
Incidental inhalation – powder	NR	6.2[b]	NR	NR	NR	NR
Dermal contact	1	2-6.2	NR	1.3	1	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair – non-coloring	NR	NR	NR	2	NR	NR
Hair – coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	NR	NR	NR	NR
Baby products	NR	NR	NR	NR	NR	NR
	PPG-33-Buteth-45		**PPG-38-Buteth-37**		**Buteth-3**	
Totals*	**5**	**0.03**	**4**	**0.4-0.8**	**446**	**0.00043-0.33**
Duration of use						
Leave-on	NR	NR	*NR*	*0.8*	*51*	*0.0005-0.33*
Rinse-off	5	0.03	*4*	*0.4-0.8*	*366*	*0.00043-0.33*
Diluted for (bath) use	NR	NR	*NR*	*NR*	*29*	*0.065-0.33*
Exposure type						
Eye area	NR	NR	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation – spray	NR	NR	NR	NR	6; 32[a]; 9[c]	0.065-0.13; 0.065[a]
Incidental inhalation – powder	NR	NR	NR	NR	1[b]9[c]	0.065[b]
Dermal contact	NR	NR	2	NR	363	0.00043-0.33

(continued)

Table 6. (continued)

	# of Uses[20]	Max Conc of Use (%)[23]	# of Uses[20]	Max Conc of Use (%)[23]	# of Uses[20]	Max Conc of Use (%)[23]
	PPG-5-Buteth-5		PPG-7-Buteth-4		PPG-7-Buteth-10	
Totals*	NR	0.05-0.5	NR	0.1-4	1	0.023
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair – non-coloring	5	0.03	NR	0.8	19	0.0005-0.33
Hair – coloring	NR	NR	2	0.4	63	0.02-0.1
Nail	NR	NR	NR	NR	1	0.33
Mucous membrane	NR	NR	NR	NR	313	0.00043-0.33
Baby products	NR	NR	NR	NR	1	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[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.

Table 7. Ingredients Not Reported to be in Use.

PPG-2-Buteth-1	PPG-30-Buteth-30	PPG-18 Butyl Ether
PPG-2-Buteth-2	PPG-36-Buteth-36	PPG-20 Butyl Ether
PPG-2-Buteth-3	PPG-3 Butyl Ether	PPG-22 Butyl Ether
PPG-3-Buteth-5	PPG-4 Butyl Ether	PPG-24 Butyl Ether
PPG-4-Buteth-4	PPG-5 Butyl Ether	PPG-26 Butyl Ether
PPG-5-Buteth-7	PPG-9 Butyl Ether	PPG-30 Butyl Ether
PPG-10-Buteth-9	PPG-12 Butyl Ether	PPG-53 Butyl Ether
PPG-12-Buteth-12	PPG-15 Butyl Ether	Propylene Glycol Butyl Ether
PPG-19-Buteth-19	PPG-16 Butyl Ether	
PPG-24-Buteth-27	PPG-17 Butyl Ether	

is used in at least one cosmetic formulation in each category.

A few of the butyl polyoxyalkylene ethers are used in products that can be used near the eye (e.g., 3.6% PPG-26-Buteth-26 in eyeliner and eye shadow) or come in contact with mucous membranes (e.g., 2% PPG-26-Buteth-26 in bath soaps and detergents). Additionally, some of these ingredients are used in cosmetic sprays and could possibly be inhaled; for example, PPG-40 Butyl Ether is reported to be used at a maximum concentration of 10% in hair sprays. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles <10 μm compared with pump sprays.[24,25] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[26,27] PPG-26-Buteth-26 has reported use in spray deodorant at a concentration of 0.099%. There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[27] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

The butyl polyoxyalkylene ethers described in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union (EU).[28]

Non-Cosmetic

Most of the butyl polyoxyalkylene ethers are approved for use as secondary direct food additives or as indirect food additives (Table 8).

Propylene glycol ethers are coalescing, coupling and dispersing agents.[17] These ethers are used in solvents and have a wide range of applications. For example, they are used in paints, lacquers, resins, surface coatings, dyes, and other related products.

Propylene Glycol Butyl Ether

Propylene Glycol Butyl Ether is used as a coupling agent and solvent due to its high solvency, oil solubility, high formulating flexibility, and low viscosity.[29] It has been used in household and commercial degreasers and hard surface cleaners.

Table 8. Food Additive Use Status.

Substance as Named in the CFR	Status	Cfr citation
monobutyl ethers of polyethylene-polypropylene glycol produced by random condensation of a 1:1 mixture by wt of ethylene oxide and propylene oxide with butanol; minimum mol. wt. of 1500 Da	Secondary direct food additives permitted in food for human consumption when used as boiler water additives	21CFR173.310
n-butoxypoly(oxyethylene)-poly (oxypropylene)glycol; viscosity range of 4850-5350	Secondary direct food additive permitted in food for human consumption when used as a defoaming agent in processing beet sugar	21CFR173.340
butoxy polyethylene polypropylene glycol; mol. wt. 900-4200 Da	Indirect food additive permitted in adhesives	21CFR175.105
polyoxybutylene-polyoxypropylene-polyoxyethylene glycol; minimum mol. wt. 3700	Indirect food additive permitted as a defoaming agent used in coatings	21CFR176.200
butoxy polyethylene polypropylene glycol; mol. wt. 900-4200 Da	Indirect food additive permitted as a defoaming agent used in the manufacture of paper and paperboard	21CFR176.210
[alpha]-butyl-omega-hydroxypoly (oxyethylene) poly(oxypropylene) produced by random condensation of a 1:1 mixture by wt of ethylene oxide and propylene oxide with butanol; minimum mol. wt. 1500 Da (CAS No. 9038-95-3)	Indirect food additive permitted for use in surface lubricants with incidental food contact; addition to food not to exceed 10 ppm	21CFR178.3570
[alpha]-butyl-omega-hydroxypoly (oxypropylene); minimum mol. wt. 1500 Da (CAS No. 9003-13-8)		
[alpha]-Butyl-[omega]-hydroxypoly (oxyethylene)-poly (oxypropylene) (CAS No. 9038-95-3), produced by random condensation of a 1:1 mixture by weight of ethylene oxide and propylene oxide with butanol; minimum mol. wt. of 1000 Da	Indirect food additive permitted for use in surface lubricants used in the manufacture of metallic articles	21CFR178.3910
oxirane, methyl-, polymer with oxirane, monobutyl ether	Residues resulting from the use of the polymer as an inert ingredient in a pesticide chemical formulation, including antimicrobial pesticide chemical formulations, are exempted from the requirement of a tolerance under FFDCA section 408, if such use is in accordance with good agricultural or manufacturing practices	40CFR180.960

FFDCA, Federal Food, Drug, and Cosmetic Act; mol. wt., molecular weight.

PPG-3 Butyl Ether

PPG-3 Butyl Ether is a solvent and coalescing agent used in architectural and industrial coatings, and in indoor decorative paints.[30] It is also used as a solvent in heavy-duty cleaning formulations, oven cleaners, inks for ball-point and felt-tip pens and stamp pads, and in textile printing pastes.

Buteth-3

Buteth-3 is used as a component of hydraulic brake fluid, as a solvent in paint stripping formulations, and as a dye carrier for textile dye processes.[16]

Toxicokinetics Studies

Dermal Penetration

Buteth-3. The dermal penetration of Buteth-3 through human skin was measured in vitro.[31] Epidermal samples were mounted in a glass diffusion apparatus; the exposure area was 2.54 cm^2. (The composition of the receptor fluid was not described.) Undiluted Buteth-3 (99.9% pure) was placed in contact with the epidermis for 12 h; 5 runs were performed. Tritiated water was used as a control. The diffusion rate was 22 $\mu g/cm^2/h$. Additionally, the epidermal damage caused by exposure to Buteth-3 was examined by measuring the increase in tritiated water diffusion following exposure. Buteth-3 had no significant effect on skin barrier function; the damage ratio (i.e., the ratio of permeability constants determined from tritiated water diffusion after chemical exposure compared to before exposure) was 1.26.

Absorption, Distribution, Metabolism, and Excretion (ADME). In rats dosed orally with [^{14}C]PPG-7-Buteth-10, most of the administered radioactivity was excreted (urine, feces, and expired CO_2) within seven days post-dosing. Similar observations were reported for rats dosed orally with [^{14}C]PPG-33-Buteth-45; however, radioactivity was not detected in expired carbon dioxide.[4]

Absorption of the PPGs Butyl Ether was inversely proportional to the molecular weight; typical gastric absorption

Table 9. Acute Toxicity Studies.

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/ Procedure	Results	Reference
Dermal						
Propylene Glycol Butyl Etder	Wistar rats	5/sex	None	In Accord witd OECD Guideline 402; 24-h semi-occlusive patch 2 g/kg bw	LD_{50} >2 g/kg	9,13,32
Propylene Glycol Butyl Ether	NZW rabbits	4 males	None	In accord with OECD guideline 402; 24-h occlusive patch	LD_{50} 1.4 g/kg (estimated)	13
Propylene Glycol Butyl Ether	NZW rabbits	4 males	None	In accord with OECD guideline 402; 24-h occlusive patch	LD_{50} 3.1 g/kg (estimated)	13
[(butoxymethylethoxy) methylethoxy]propan-1-ol (read across to PPG-3 Butyl Ether) (99% pure)	Wistar rats	5/sex	None	In accord with OECD Guideline 402; 25-h semi-occlusive patch 2 g/kg	LD50 >2 g/kg	10
[(butoxymethylethoxy) methylethoxy]propan-1-ol (read across to PPG-3 Butyl Ether) (85% pure)	NZW rabbits	2 males	None	In accord with OECD Guideline 402; 24-h patch; type of coverage not stated 2 g/kg	LD50 >2 g/kg no dermal effects	10
poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy- (read across for PPG-n Butyl Ether)	Fischer 344 rats	5/sex	None	In accord with OECD Guideline 402; 24-h application using an occlusive 2″ x 3″ patch (10% of body area) 2 g/kg	LD_{50} >2 g/kg bw; no animals died; no signs of gross toxicity, dermal irritation, adverse toxicological effects, or abnormal behavior	11
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	Wistar rats	5/sex	None	In accord with OECD Guideline 402; 24-h semi-occlusive patch to intact skin 2 g/kg	LD_{50} >2 mg/kg bw	9
Buteth-3	Rats	Not specified	Not specified	Details not provided	LD_{50} 3.5 g/kg	16
Oral						
Propylene Glycol Butyl Ether	Wistar rats	5/sex	None	In accord with OECD Guideline 401; single dose by gavage 1.8, 2.4, 3.2 g/kg bw	LD_{50} 3.3 g/kg (calculated) 1 female of the mid dose group, and 4 females and 1 male of the high dose group, died	9,13
Propylene Glycol Butyl Ether	Wistar rats	5/sex	None	In accord with OECD Guideline 401; single dose by gavage	LD_{50} 5.2 g/kg (estimated)	13
Propylene Glycol Butyl Ether	Wistar rats	6/sex	CMC	In accord with OECD Guideline 401; single dose by gavage 2 g/kg	LD_{50} >2 g/kg	13
[(butoxymethylethoxy) methylethoxy]propan-1-ol (read across to PPG-3 Butyl Ether) (85% pure)	Fischer rats	3 females	None	In accord with OECD Guideline 401; single dose by gavage 2 g/kg	>2 g/kg 1 animal died	10
[(butoxymethylethoxy) methylethoxy]propan-1-ol (read across to PPG-3 Butyl Ether)	Wistar rats	6/sex	CMC	In accord with OECD guideline 423; single dose by gavage 2 g/kg	>2 g/kg 1 female died	10
[(butoxymethylethoxy) methylethoxy]propan-1-ol (read across to PPG-3 Butyl Ether) (99% pure)	Wistar rats	1/sex	None	2.5, 4, and 5 mg/kg bw in accord with OECD Guideline 401; single dose by gavage	Both animals of the 4 and 5 g/kg group died within 24 h of dosing	10
[(butoxymethylethoxy) methylethoxy]propan-1-ol (read across to PPG-3 Butyl Ether) (99% pure)	Wistar rats	5/sex	None	In accord with OECD Guideline 401; single dose by gavage 2.4, 3.2, and 4.2 g/kg	LD_{50} ~2.8 mg/kg bw (combined) 3.1 g/kg bw (males) 2.6 g/kg bw (females) 3, 6, and 10 animals of the low, mid- and high-dose died	10

(continued)

Table 9. (continued)

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/ Procedure	Results	Reference
Dermal						
poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy- (read across for PPG-n Butyl Ether)	Fisher rats	3 female	None	In accord with OECD Guideline 423 gavage study 0.3 (2 groups) or 2.0 g/kg bw	LD_{50} between 0.3 and 2 g/kg bw 2/3 high dose animals died; 0/6 low dose animals died	11
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	CD-1 mice	4 males	None	In accord with OECD Guideline 401; 0.1, 0.316, 1.0, and 10 mL	LD_{50} 2160 mg/kg bw (calculated)	9
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	Wistar rats	5/sex	None	In accord with OECD Guideline 401; single dose by gavage 3200, 4200, or 5600 mg/kg	LD_{50} combined – 4000 mg/kg LD50 males – 4400 mg/kg LD50 females – 3700 mg/kg	9
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	Rats	Not specified	None	In feed; dose not specified	LD_{50} 1850 mg/kg bw	9
Buteth-3	Rats	Not specified	Not specified	Details not provided	LD_{50} 6.6 g/kg	16
Inhalation						
Propylene Glycol Butyl Ether	Fischer 344 rats	5/sex	None	In accord with OECD Guideline 403; 4-h whole-body exposure 3251 mg/m^3	LC_{50} >3251 mg/m^3	9,13
Propylene Glycol Butyl Ether	Rats	6	None	In accord with OECD Guideline 403; 8-h whole-body exposure saturated vapor	No mortality	13
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether) (99.33% pure)	Fischer 344 rats	5/sex	None	In accord with OECD Guideline 403; 4 h whole body exposure 328 mg/m^3	LC_{50} >328 mg/m^3	9

CMC, carboxymethylcellulose; NZW, New Zealand White; OECD, Organisation for Economic Co-operation and Development.

values ranged from 2% to 100%, depending upon the chain length. PPG BE800 (PPG BE refers to the molecular weight of the substance; PPG BE800 is ~PPG-13 Butyl Ether) penetrated rabbit skin slowly, if at all, and passed poorly through internal tissue barriers. Once absorbed, the butyl group was removed and oxidized, then was partly or completely excreted as carbon dioxide by the lungs. The chains were apparently split into random length fragments and eliminated in urine as weak acids after oxidation of the terminal hydroxyls to carboxyl groups.[1]

Propylene glycol butyl ether. As a class, the propylene glycol ethers are rapidly absorbed and distributed throughout the body following oral and inhalation exposure.[9] The primary routes of excretion are via the urine and expired air; a small amount is excreted in the feces.

Absorption via the dermal route is slower, but subsequent distribution is rapid.[9] Additionally, Propylene Glycol Butyl Ether (a monoglycol ether) is expected to be absorbed more rapidly than diglycol and triglycol ethers.[12] However, diglycol and triglycol ethers may be present on the skin much longer than monoglycol ethers because of lower vapor pressures.

Animal

Oral

1-(2-Butoxy-1-methylethoxy)-propan-2-ol (read-across for PPG-n Butyl Ethers)

New ADME data were not available for the PPG Butyl Ethers. But an appropriate read across material was identified; an ADME study was conducted in accord with OECD Guideline 417 with 1-(2-butoxy-1-methylethoxy)-propan-2-ol.[9] Groups of four male Fischer 344 rats were given a single dose by gavage of 0.4 or 4.4 mmol/kg bw [^{14}C]1-(2-butoxy-1-methylethoxy)-propan-2-ol in 1% methylcellulose. Urine, feces, expired air, blood, and tissues were collected for 48 h and analyzed for total [^{14}C]-activity. In the low dose group, 42% of the dose was excreted in urine, 4% in the feces, and 42% as $^{14}CO_2$; the tissues, carcass, and skin retained 11% of the radioactivity. In the high-dose group, 51% of the dose was excreted in urine, 11% in the feces, and 35% as $^{14}CO_2$; the tissues, carcass, and skin retained 7% of the dose. Peak blood levels of [^{14}C]-activity occurred 0.5 h after dosing in the low dose group and 4 h after dosing in the high dose group. The distribution of [^{14}C]-activity in tissues was similar between dose groups, with liver, bone marrow, and

Table 10. Short-Term and Subchronic Toxicity Studies.

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Procedure	Results	Reference
SHORT-TERM TOXICITY STUDIES							
Dermal							
Propylene Glycol Butyl Ether	5 NZW rabbits/ sex	4 wks	50/50 ethanol/ water	0, 0.569, 5.69, and 56.9%; 2 mL/kg	Open 7-h applications 5 days/wk for 4 wks to clipped abraded skin; collars were used to prevent ingestion	-The mid-dose produced slight erythema (6 animals), the high-dose resulted in moderate erythema and desquamation (n=10), slight edema (n=9) and atonia (n=5), and slight (n=6) to moderate (n=4) fissuring -No clinical signs of toxicity, and no changes in body, liver, or kidney wts	33
Propylene Glycol Butyl Ether	5 NZW rabbits/ sex	28 days	Distilled water	0, 50, and 100%; 2 mL/kg	Open 7-h applications 5 days/wk for 4 wks to clipped abraded skin; collars were used to prevent ingestion	-No clinical, gross, or microscopic signs of toxicity -Slight to moderate (low dose group) and slight to severe (high dose group) erythema, slight atonia, and slight desquamation; no edema, fissuring, eschar, or exfoliation	34
Buteth-3 (99.9% pure)	5 NZW rabbits/ sex	21 days	None	0 (water) or 1000 mg/ kg/day	6-h occlusive application to a shaved area of the back 1x/day, 5 days/wk; collars used to prevent ingestion during dosing; test sites were rinsed following dosing animals were killed within 1 day of termination of dosing	-No clinical signs of toxicity; no effect on body wt gain; no mortality -slight erythema and edema on day 6 and day 7, respectively; both were reported in all test animals as of day 11; desquamation in 1-8 animals on days 10-17; fissuring in 3-5 animals on days 8-16; no signs of irritation in controls -N treatment-related effects on hematology or clinical chemistry parameters -no gross lesions at necropsy; a statistically significant increase in brain wts was not considered treatment-related; other organ wts were comparable to controls -microscopic examination of skin from the test site found trace acanthosis and moderate dermatitis	31
Oral							
Propylene Glycol Butyl Ether	2 Sprague-Dawley rats/ sex	8 days	Propylene glycol	0, 200, 500, and 1000 mg/kg bw	In accord with OECD Guideline 407 dosed by gavage 1x daily	1 mid-dose male and 1 high-dose female died	13

(continued)

Table 10. (continued)

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Procedure	Results	Reference
Propylene Glycol Butyl Ether	6 Sprague-Dawley rats/sex	14 days	Propylene glycol	0, 100, 200, and 400 mg/kg bw	In accord with OECD Guideline 407 dosed by gavage 1x daily	NOAEL and LOAEL – 400 mg/kg bw -No signs of toxicity; no effect of body weights, organ weights, hematology, or clinical chemistry	9,13,37
[(butoxymethylethoxy) methylethoxy] propan-1-ol (read across to PPG-3 Butyl Ether) purity – 80.67%	5 Fischer 344 rats/sex	28 days	Corn oil	0, 100, 350, or 1000 mg/kg bw	In accord with OECD Guideline 407 dosed 1x/day, 5 days/wk by gavage	NOAEL – 1000 mg/kg bw -No treatment-related effects on body wt, hematology parameters -Statistically significant increase in absolute and relative liver wts for mid- and high-dose animals, with increased hepatocellular size and "altered" staining of the cytoplasm in high dose animals	10
poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy- (read across for PPG-n Butyl Ether)	12 Crj: CD (SD rats/sex	46 day, males 53 days, females	CMC	0, 20, 100, or 500 mg/kg bw/day	In accord with OECD Guideline 422 (combined repeated dose toxicity study with the reproduction/develop-mental toxicity screening test) -Males dosed by gavage 1x/day for 14 days prior to and throughout mating, for 32 days -Females dosed 1x/day for 14 days prior to mating and continuing through breeding (2 wks), gestation (3 wks), and lactation (4 days)	NOEL – 100 mg/kg bw/day, for clinical observations, higher absolute and relative liver wts, and increased incidence of liver and thyroid gland hypertrophy 500 mg/kg/day: treatment-related transient clinical observations in males and females during all phases of the study, including perioral soiling (all animals), muscle twitches (6/12 males, 11/12 females), uncoordinated gait (0/12 males, 6/12 females), and decreased activity (0/12 males, 3/12 females); all effects resolved within 1 h of dosing -No significant effects on body wt or body wt gain, feed consumption, hematology, clinical chemistry, urinalysis	11
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	6 Sprague-Dawley rats/sex	2 wks	Propylene glycol	0, 100, 200, or 400 mg/kg bw	In accord with OECD guideline 407; by gavage	NOAEL – 400 mg/kg	9
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	5 Sprague-Dawley rats/sex	2-wk	In feed	0, 250, 500, or 750 mg/kg bw	In accord with OECD guideline 407; feed study	NOAEL – >750 mg/kg	9

(continued)

Table 10. (continued)

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Procedure	Results	Reference
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether) (99.34% pure)	12 Crl:CD (SD) rats/sex	43 days (males) 53 days (females)	0.5% methylcellulose	0, 100, 300, or 1000 mg/kg bw/day	In accord with OECD guideline 422 -Males dosed by gavage 1x/day for 14 days prior to and during, mating; males were killed on day 29 -Females were dosed 1x/day for 14 days prior to breeding, and continuing through mating, gestation, and 4 days of lactation; females were killed 5 days after parturition (53 total days)	NOAEL for systemic toxicity – 100 mg/kg/day, based on very slight to slight hepatocellular hypertrophy with no corresponding increases in liver weights in low-dose males -Treatment-related increases in the incidence of hepatocellular hypertrophy in males of all dose groups and in mid- and high-dose females, correlated with increased liver weights in mid- and high-dose males and high dose females; considered to be adaptive changes associated with increased hepatic metabolism -Treatment-related increases in absolute and relative kidney weights in high-dose animals; hyaline droplet formation in the proximal renal tubules in mid- and high-dose males; histopathologic correlation with the higher kidney weights not evident in females	[10]
Inhalation							
Propylene Glycol Butyl Ether (98.8% pure)	Main study: 10 Fischer 344 and 5 Sprague-Dawley rats/sex recovery: additional 10 sex/strain control and high dose	11 days	None	0, 540, 1622, and 3244 mg/m^3	In accord with OECD Guideline 412 9 whole body exposure; 6 h/day, 5 days/wk; a 4-wk recovery group was used with each strain hematologic, clinical chemistry, and urinalysis parameters were examined	NOAEL 3244 mg/m^3 Fischer 344 rats: statistically significant increase in absolute and relative liver (to body and to brain) weights (3244 mg/m^3 males) and relative liver to body weights (244 mg/m^3 females) without microscopic changes; low incidence of mild eye lesions 1622 and 3244 mg/m^3 groups) Sprague Dawley rats: no exposure-related effects	[13,49]
Propylene Glycol Butyl Ether	5 Fischer 344 rats/sex	2 wks	None	0, 270, 1081, and 3785 mg/m^3	In accord with OECD Guideline 412 9 whole body exposure; 6 h/day, 5 days/wk	NOAEL and LOAEL >3785 mg/m^3 -slightly increased relative liver weight in high dose males and females without microscopic effects	[9,13,38]

(continued)

Table 10. (continued)

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Procedure	Results	Reference
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	5 Fischer 344 rats/sex	2 wks	None	0, 160, 320 mg/m^3	In accord with OECD Guideline 412; 9–6/h nose-only exposures	NOAEL – 320 mg/m^3	9
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	5 Fischer 344 rats/sex	2 wks	None	0, 200, 810, or 2010 mg/m^3	In accord with OECD Guideline 412; 9–6/h nose-only exposures	NOAEL – 200 mg/m^3 LOAEL – 810 mg/m^3	9
SUBCHRONIC TOXICITY STUDIES							
Dermal							
Propylene Glycol Butyl Ether	10 Wistar rats/sex	13 wks	Propylene glycol	0, 88, 264, 880 mg/kg	In accord with OECD Guideline 411 1 open 24-h application/day, 5 days/wk; collars were used to prevent grooming	NOAEL – 880 mg/kg bw -Irritation at all application sites, including controls; focal necrosis of the epidermis, crust formation, mild inflammatory changes, and acanthosis; difference in severity between treated and control animals was not significant -No clinical, gross, or microscopic signs of toxicity	9,13,36
Propylene Glycol Butyl Ether	5 NZW rabbits/sex	91 days	Water	2 mL/kg bw	In accord with OECD Guideline 411 1 open 7-h application/day, 5 days/wk; collars were used to prevent grooming	NOEL – 1.76 mg/kg bw/day -Mild to moderate irritation at the application site -No clinical signs of toxicity	13
Propylene Glycol Butyl Ether	5 NZW rabbits/sex	13 wks	50/50 ethanol/water	0, 10, 100, or 1000 mg/kg bw/day; 2 mL/kg bw	In accord with OECD Guideline 411 1 7-h application/day, 5 days/wk; collars were used to prevent grooming	NOAEL/local skin irritation – 10 mg/kg bw/day LOAEL/local skin irritation – 100 mg/kg bw/day NOAEL/systemic toxicity – 1000 mg/kg bw/day -Dermal irritation in the mid and high dose groups; in the high dose group, severe erythema, slight to moderate edema, slight to moderate atonia, moderate desquamation, and slight to moderate fissuring. -Skin lesions were considered to be a direct, local effect from the solvents and the clipping procedure. -No clinical signs of toxicity	9

(continued)

Table 10. (continued)

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Procedure	Results	Reference
Propylene Glycol Butyl Ether	5 NZW rabbits/sex	13 wks	50/50 ethanol/water	0, 0.569, 5.69, and 56.9 2 mL/kg	Open 7-h applications to intact skin of the back, 5 days/wk for 13 wks; collars were used to prevent grooming	-Slight erythema and severe erythema in the mid- and high-dose groups, respectively -No significant differences in body wt parameters or absolute organ or relative organ wts of the test animals compared to the vehicle control group	35
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	10 Wistar rats/sex	13 wks	Propylene glycol	0, 91, 273, or 910 mg/kg bw/day	In accord with OECD Guideline 411; 5 open applications/wk; animals wore collars to prevent ingestion	NOAEL – 91 mg/kg/day LOAEL – 273 mg/kg/day (based on body weight -changes and increased neutrophil count) -Skin irritation at all test sites (including controls)	9
Oral							
Propylene Glycol Butyl Ether (99.4% pure)	10 Fischer 344 rats/sex	13 wks	None	0, 100, 350, and 1000 mg/kg bw recovery groups: 0 and 1000 mg/kg bw	In accord with OECD Guideline 408 administered in drinking water recovery groups given untreated water for 4 wks following dosing	NOAEL – 350 mg/kg bw; LOAEL – 1000 mg/kg -Absolute and relative liver weights increased in high dose males ad absolute and relative kidney weights increased in high dose females with no accompanying histopathology -No changes in organs selected for examination, including the testes	9,13
PPG-3 Butyl Ether	10 Fischer 344 rats/sex	13 wks	None	0, 100, 350, or 1000 mg/kg bw	Administered in drinking water	NOAEL – 350 mg/kg bw; LOAEL – 1000 mg/kg bw -Histopathological and organ weight alterations of liver and kidney (males) and liver (females) (details not provided)	30

(continued)

Table 10. (continued)

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Procedure	Results	Reference
[(butoxymethylethoxy) methylethoxy] propan-1-ol (read across to PPG-3 Butyl Ether) (97.7% pure)	10 Fischer 344 rats/sex	13 wks	None	0, 100, 350, or 1000 mg/kg bw; 0 and 1000 mg/kg (recovery group)	In accord with OECD Guideline 40 8 90-day study administered in drinking water	NOAEL – 1000 mg/kg bw -No clinical signs of toxicity; statistically significant changes included: decrease in body wts and feed consumption of high dose animals; treatment-related increases in absolute and relative liver weights in males of all dose groups and females of the mid- and high-dose groups; absolute and relative kidney weights were increased in high-dose males mid- and high-dose females -Changes in hematology, clinical chemistry, and urinalysis parameters not considered toxicologically significant	10
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	20 Sprague-dawley rats/sex; additional 5 for interim sacrifice	13 wks	In feed	0, 200, 450, or 1000 mg/kg bw	In accord with OECD Guideline 408; feed study	NOAEL – 450 mg/kg LOAEL – 1000 mg/kg -High-dose males: slight but statistically significant decrease in body wts, enlarged livers with histopathological changes, increased absolute, and relative liver weights; some changes in clinical chemistry corroborated liver changes -High-dose females: absolute and relative kidney weights were increased in high dose females with no accompanying histopathology	9

CMC, carboxymethylcellulose; LOAEL, lowest-observed adverse effect level; NOAEL, no-observed adverse effect level; NOEL, no-observed effect level; NZW, New Zealand White.

Table 11. Developmental and Reproductive Toxicity Studies.

Test article						
Dermal	Animals/Group	Vehicle	Dose/Concentration	Procedure	Results	Reference
Propylene Glycol Butyl Ether (>98% pure)	25 gravid Wistar rats	Propylene glycol (test article was provided as 2 mixtures in vehicle at ratios 12:60 [sic] and 40:60)	0, 0.3 and 1.0 mL/kg bw/day (equivalent to 0, 264, and 880 mg/kg bw/day)	In accord with OECD Guideline 414 open applications (20 cm2) on days 6-16 of gestation; collars were used to prevent ingestion; animals were killed on day 21 of gestation	NOAEL for maternal toxicity, embryotoxicity, and teratogenicity – 880 mg/kg/day -Not embryotoxic, fetotoxic, or teratogenic -Minor skin reactions not considered toxicologically relevant -No clinical signs of toxicity; no mortality; no statistically significant differences in body weight, feed consumption -Ovaries, uterus, kidneys, and liver wts comparable for test and control groups. -No test-article related visceral and skeletal malformations, anomalies, or variants	9,11,17
Propylene Glycol Butyl Ether (100% pure)	Gravid NZW rabbits; 19/ test group, 17 control	Water	0, 10, 40, and 100 mg/kg bw/ day	In accord with OECD Guideline 414 6-h applications to a 10 cm x 20 cm shaved area of the dorsal trunk on days 7-18 of gestation; collars were used to prevent ingestion; animals were killed on day 29 of gestation	Developmental NOEL – >100 mg/ kg bw/day -No maternal toxicity -No embryotoxic or teratogenic effects -Mild erythema in the high dose group occurred at a greater incidence and severity compared to other groups	9,10,17
PPG-2 Butyl Ether	20 gravid Wistar rats	Not stated	0, 0.3, 1 mL/kg	The test substance was applied dermally on days 6-16 of gestation; details were not provided	Maternal and developmental NOEL – > 1 mL/kg -Local skin reactions observed in all treated animals; no signs of maternal toxicity -No reproductive or teratogenic effects	17

(continued)

Table 11. (continued)

Test article						
Dermal	Animals/Group	Vehicle	Dose/Concentration	Procedure	Results	Reference
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	22 (control), 21 (low-dose), and 25 (high-dose) gravid Wistar rats	Propylene glycol	0, 0.3 or 1.0 mL/kg bw/day (0, 273, or 910 mg/kg bw/day, respectively) applied volumes of 1.5 mL (control), 1.8 mL, and 2.5 mL test solution/kg bw, respectively	In accord with OECD Guideline 414 open applications (20 cm2) on days 6-15 of gestation; collars were used to prevent ingestion; animals were killed on day 21 of gestation	-Minor skin reactions were not considered toxicologically relevant; no clinical signs of toxicity; no mortality; organ weights comparable for test and control groups - Pre- and post-implantation loss, number of viable fetuses, and fetal weights and lengths comparable between treatment and control groups, no signs of developmental toxicity - Not embryotoxic, fetotoxic, or teratogenic	[9-11]
Oral						
poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy- (read across for PPG-n Butyl Ether)	12 Crj: CD (SD) rats/sex	CMC	0, 20, 100, or 500 mg/kg bw/day	Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (described previously in Table 10)	NOEL for reproductive effects – 500 mg/kg/day no indication of reproductive toxicity at any dose; no adverse effects on prenatal/early neonatal growth and survival of the offspring	[11]
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether) (99.34% pure)	12 Crl:CD (SD) rats/sex	0.5% methylcellulose	0, 100, 300, or 1000 mg/kg bw/day	Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (described previously in Table 10	NOEL for reproductive effects – 1000 mg/kg/day - No treatment-related effects on any reproductive parameters	10
Buteth-3	10 gravid rats/group	Water	0, 250, or 1000 mg/kg	Animals dosed by gavage on days 7-16 of gestation	-No clinical signs of toxicity or effects on maternal body wts -No developmental or reproductive toxicity -No effect on number of live pups, mean pup body wts, or mean pup body wt gains on day 1 and day 5 post-partum	[31]

CMC, carboxymethylcellulose; LOAEL, lowest-observable adverse effect level; NOAEL, no-observed adverse effect level; NOEL, no-observed-effect level; NZW, New Zealand White; OECD, Organisation for Economic Co-operation and Development; PND, post-natal day.

Table 12. Genotoxicity Studies.

Test article					
In Vitro	Concentration/Vehicle	Procedure	Test System	Results	Reference
Propylene Glycol Butyl Ether	1.0-20 μl/plate in DMSO	Ames test	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538; solvent and appropriate positive controls were used	Negative	39
Propylene Glycol Butyl Ether	0-4500 μg/ml with and of 0-6000 μg/ml without metabolic activation in culture medium	Mammalian chromosome aberration assay, in accord with OECD Guideline 473	CHO cells	Negative	9,13
Propylene Glycol Butyl Ether	500, 1667, and 5000 μg/ml with and without metabolic activation in culture medium	Mammalian chromosome aberration assay, in accord with OECD Guideline 473	CHO cells	Negative	40
Propylene Glycol Butyl Ether	Dose-range finding study: 0.005–100 μl/ml in 50% solution of 95% ethanol	Mouse lymphoma cell assay, with and without metabolic activation		Dose-range finding study: no growth with ≥5.0 μl/ml	41
	Main study: 0.5–5.0 μl/ml in 50% solution of 95% ethanol		T5178Y TK+/- lymphoma cells	Main study: negative results	
Propylene Glycol Butyl Ether	0-6000 μg/ml	Mouse lymphoma cell assay, with and without metabolic activation, in accord with OECD Guideline 476	T5178Y TK+/- lymphoma cells	Negative	9
Propylene Glycol Butyl Ether	0.01-0.80 μl/ml in ethanol/water (50:50)	UDS assay; appropriate negative and positive controls were used	Primary rat hepatocytes	Negative doses >0.65 μl/ml were too toxic to score	42
Propylene Glycol Butyl Ether	0-6000 μg/ml in culture medium	UDS assay, with and without metabolic activation, in accord with OECD Guideline 482	Primary rat hepatocytes	Negative	9
[(butoxymethylethoxy) methylethoxy]propan-1-ol (read across to PPG-3 Butyl Ether) (96.12% pure)	50-5000 μg/plate, +/− metabolic activation in DMSO	In accord with OECD Guideline 471 Ames test, with and without metabolic activation negative and positive controls were included	*S.typhimurium* TA1535, TA1537, TA98, TA100	Negative controls gave expected results	10
poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy- (read across for PPG-n Butyl Ether)	1.5-5000 μg/plate	In accord with OECD Guideline 471 Ames test, negative and positive controls were included	*S.typhimurium* TA1535, TA1537, TA98, TA100 *Escherichia coli* WP2 uvr A	Negative controls gave expected results	11
poly[oxy(methyl-1,2-ethane-diyl)],α-butyl-ω-hydroxy- (read across for PPG-n Butyl Ether)	78.1-5000 μg/ml with, 39.1-5000 μg/ml without, metabolic activation	In accord with OECD guideline 473 mammalian chromosomal aberration assay (4 h exposure); negative and positive controls	Rat lymphocytes	Negative controls gave expected results	11

(continued)

Table 12. (continued)

Test article					
In Vitro	Concentration/Vehicle	Procedure	Test System	Results	Reference
poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy- (read across for PPG-n Butyl Ether)	500-2500 μg/ml +/− activation (initial assay) 1400-2400 μg/ml with and 1000-2000 μg/ml without activation	In accord with OECD guideline 476 mammalian cell mutation assay; negative and positive controls	CHO cells	Negative controls gave expected results	11
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	279-5000 μg/ml in DMSO	In accord with OECD guideline 471, Ames test, with and without metabolic activation	*S.typhimurium* TA98, TA100, TA1535, TA1527, TA1538	Negative	9
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	0, 333, 1000, or 3333 μg/ml with and 0, 1000, 2000, 3000, and 4000 μg/ml without activation in culture medium	In accord with OECD Guideline 473, chromosomal aberration assay	CHO-K1, S1B cells	Positive chromatid and chromosome gaps and breaks and fragments detected in all groups, including negative control; the frequency of these aberrations increased significantly in some of the treated groups at the 9 and 13-hour incubation (fixation) times	9
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	0 and 3500 μg/ml with and 0 and 4500 μg/ml without activation in culture medium	In accord with OECD guideline 473, chromosomal aberration assay	CHO-K1, S1B cells	Positive chromatid and chromosome gaps and breaks and fragments detected in all groups, including negative control; treated groups showed increased frequencies in these aberrations and occasional exchanges and pulverized chromosomes	9
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	0, 500, 1000, 2000, and 3000 μg/ml with and 0, 500, 1000, 2000, 3500, and 5000 μg/ml without activation in culture medium	In accord with OECD Guideline 473, chromosomal aberration assay	CHO-K1, S1B cells	Positive chromatid and chromosome gaps and breaks and fragments detected in all groups, including negative controls, in cells with activation; a dose-response increase was not evident without activation, a more pronounced increase observed in cells, significant to a higher *P* value at the highest dose; but a dose-response still was not apparent	9

(continued)

Table 12. (continued)

Test article					
In Vitro	Concentration/Vehicle	Procedure	Test System	Results	Reference
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	0, 500, 1667, and 5000 μg in culture medium	In accord with OECD Guideline 473, chromosomal aberration assay with and without metabolic activation	CHO-K1, CCL61cells	Negative	9
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	0, 500, 1667, and 5000 μg in culture medium	In accord with OECD Guideline 473, chromosomal aberration assay with and without metabolic activation	CHO-K1, S1B cells	Negative	9
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether) (98.97% pure)	279-5000 μg/ml in DMSO	In accord with OECD Guideline 476; mammalian CHO/HGPRT forward mutation assay with and without metabolic activation	CHO cells	Negative	9,10
In vivo					
[(butoxymethylethoxy) methylethoxy]propan-1-ol (read across to PPG-3 Butyl Ether) (96.12% pure)	0, 187.5, 625, and 1875 mg/kg bw in corn oil	In accord with OECD Guideline 474 mammalian erythrocyte micronucleus test animals were given a single dose by gavage solvent and positive controls were used	5 CD-1 mice/sex/group	Negative controls gave expected results	10
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	0, 250, 833, and 2500 mg/kg bw	In accord with OECD Guideline 475, micronucleus assay; single dose by gavage	5 CD-1 mice/sex	Negative	9

CHO, Chinese hamster ovary; DMSO, dimethyl sulfoxide; OECD, Organisation for Economic Co-operation and Development; UDS, unscheduled DNA synthesis.

Table 13. Dermal Irritation and Sensitization Studies.

Test Article					
In VITRO	Concentration/Dose	Test Population	Procedure	Results	Reference
poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy- (read across for PPG-n Butyl Ether)			EpiDerm™ study to evaluate skin corrosivity	Classified as non-corrosive; mean tissue viability following the 3 min and 1 h exposure periods was 89.2% and 92.6%, respectively	11
ANIMAL					
Irritation					
Propylene Glycol Butyl Ether	25, 50, and 75% in water; 0.5 mL	3 female NZW rabbits	In accord with OECD Guideline 404 semi-occlusive 4 h patch to 6 cm^2 area of clipped unabraded skin	25%: non-irritating; PDII – 0 no significant irritation 50%: slightly irritating; PDII – 0.8 very slight erythema in 3 animals, edema in 1 animal; all resolved by day 7 75%: moderately irritating; PDII –2.5 well-defined erythema in 2 animals; eschar in 1 animal; very slight edema in 3 animals; all resolved by day 7	9,13,43
Propylene Glycol Butyl Ether	Undiluted; 0.5 mL	3 female NZW rabbits	In accord with OECD Guideline 404 semi-occlusive 4 h patch to 6 cm^2 area of clipped unabraded skin	Moderately irritating; PDII – 4; erythema/eschar 2.66, edema – 1.33 on day 1, eschar formation in 1 animal that mostly resolved on day 14; well defined erythema and slight edema in 2 rabbits with some scaliness (days 2 and 3) resolved by day 14	9,13,44
Propylene Glycol Butyl Ether	Undiluted; 0.5 mL	3 NZW rabbits	In accord with OECD Guideline 404, EU method B.4, and EPA OPPTS 870.2500 semi-occlusive 4 h patch to 2.5 cm^2 area of clipped unabraded skin	Not irritating mean 24-72 h erythema score – 1.6/4 erythema scores of 2 in all animals at 1 and 24 h, 2 in 2 animals and 1 in 1 animal at 48 h, 1 in all animals at 72 h, 0 in all animals on day 8 edema was not observed in any of the animals	13
Propylene Glycol Butyl Ether	Undiluted; 0.01 mL	5 albino rabbits	In accord with OECD Guideline 404 open 24 h application to clipped skin	Irritating PDII – 2/10	13
Propylene Glycol Butyl Ether	Undiluted; 0.01 mL	5 albino rabbits	In accord with OECD Guideline 404 open 24 h application to clipped skin	Irritating PDII –3/10	13
Propylene Glycol Butyl Ether (purity >98%)	100%, 5, 10, and 50% in propylene glycol	Hartley guinea pigs, # not stated	Preliminary dose-range finding study for a sensitization test	Minimal irritation with undiluted material; no irritation at lower concentrations	9
[(butoxymethylethoxy) methylethoxy]propan-1-ol (read across to PPG-3 Butyl Ether)	Not provided	3 NZW rabbits	In accord with OECD Guideline 4044-h semi-occlusive patch	Not irritating mean erythema score of 1.6; erythema scores of 1-2 reported in all animals, and erythema extended beyond the application area in 1 animal; fully reversible within 9 days; no edema	10

(continued)

Table 13. (continued)

Test Article					
In VITRO	Concentration/Dose	Test Population	Procedure	Results	Reference
[(butoxymethylethoxy) methylethoxy]propan-1-ol (read across to PPG-3 Butyl Ether) (99% pure)	0.5 mL	3 female NZW rabbits	In accord with OECD Guideline 404 4-h semi-occlusive patch to shaved skin	Not irritating; PII = 1.2 slight erythema (score = 1) in all animals; slight edema (score = 0.7) in 1 animal; fully reversible in 1 wk	10
[(butoxymethylethoxy) methylethoxy]propan-1-ol (read across to PPG-3 Butyl Ether) (85% pure)	0.5 mL (semi-occlusive application) 0.1 mL (open applications)	1 male NZW rabbit	In accord with OECD Guideline 404 24-h semi-occlusive patches to intact and abraded skin of the abdomen; 3 applications to abraded skin and 5 to intact skin 5 daily open applications to intact skin on the medial surface of the left ear pinna	Not irritating repeated contact resulted in very slight to slight erythema and exfoliation	10
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	0.5 mL	3 female NZW rabbits	4-h semi-occlusive patch	PDII – 2; slightly irritating EU classification – not irritating	9
Sensitization					
Propylene Glycol Butyl Ether (purity >98%)	Induction: 80% Challenge: 40% 0.3 mL vehicle – propylene glycol	Hartley Guinea pigs 10/sex – test and 5/sex – control	In accord with OECD Guideline 406 Buehler test; occlusive patches induction: 3, 6-h occlusive patches over 3 wks Challenge: 1, 6-h application after a 10-day non-treatment period	Non-sensitizing and non-irritating	9,13,45
[(butoxymethylethoxy) methylethoxy]propan-1-ol (read across to PPG-3 Butyl Ether) (98.47% pure)	Undiluted in petrolatum; 0.5% (w/w); dose volume not provided	female Hartley guinea pigs; 20 test, 10 control	In accord with OECD Guideline 406 Buehler test; epicutaneous induction and challenge induction: 9, 6-h applications over 3 wks Challenge: 1, 6-h application after a 10-day non-treatment period	Not sensitizing	10
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	80% for induction; 40% for at challenge vehicle – propylene glycol	10 Guinea pigs/sex	In accord with OECD Guideline 406; 3, 6-h induction applications (1/wk); 6 h challenge patch applied after a 12-day non-treatment period	Not a sensitizer	9
HUMAN					
Sensitization					
PPG-14 Butyl Ether	Undiluted; 0.2 mL	199 subjects	RIPT; nine 24-h occlusive patches (2 cm^2) applied over a 3 wk period for induction -Challenge was performed after a 2-wk non-treatment period at a previously unpatched site	Not a sensitizer	46

(continued)

Table 13. (continued)

Test Article					
In VITRO	Concentration/Dose	Test Population	Procedure	Results	Reference
hair Styling wax containing 71% PPG-40 Butyl Ether	Applied neat; 0.1–0.15 g ~25-38 μg/cm^2	48 subjects	RIPT; nine 24-h semi-occlusive patches (2 cm^2) applied over a 3 wk period for induction -Challenge was performed after a 2-wk non-treatment period at a previously unpatched site	Not an irritant or a sensitizer No reactions during induction or at challenge	[47]
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	0.4 mL	82 human subjects	RIPT; 24 h patches	Not a sensitizer	[9]

EPA, Environmental Protection Agency; NZW, New Zealand White; OECD, Organisation for Economic Co-operation and Development; OPPTS, Office of Prevention, Pesticides and Toxic Substances; PDII, primary dermal irritation index; RIPT, repeat insult patch test.

Table 14. Ocular Irritation Studies.

Test Article	Concentration/ Dose	Test Population	Procedure	Results	Reference
Propylene Glycol Butyl Ether	Undiluted; 0.1 mL	3 NZW rabbits	In accord with OECD Guideline 405, EU Method B.5, and EPA OPPTS 870.2400; eyes scored after 24 h; contralateral eye served as a control	Irritating at 24 h, mean scores: 1/4 for corneal opacity; 0.9/2 for effects on the iris; 2.7/3 for conjunctival redness; 0.7/4 for chemosis. -Only chemosis was fully reversible by day 7	[13]
Propylene Glycol Butyl Ether	Undiluted; 0.1 mL	3 female NZW rabbits	In accord with OECD Guideline 405; eyes were not rinsed; contralateral eye served as a control	Not irritating according to EU criteria, mean 24-72 h scores: 0.3 for corneal opacity; 0.2 for effects on the iris; 2.2 for conjunctival redness; 1 for chemosis -All fully reversible by day 7	[13]
Propylene Glycol Butyl Ether	Undiluted; 0.1 mL	3 female NZW rabbits	In accord with OECD Guideline 405; eyes were not rinsed; contralateral eye served as a control	Moderately irritating; 1-h Draize score – 34/110; classifiable as an "eye irritant" according to European criteria mean 24-72 h scores: 0 for corneal opacity; 0.2 for iridial damage; 2.2 for conjunctival redness; 1 for chemosis -All effects were fully reversible by day 7	[9,48]
Propylene Glycol Butyl Ether	Undiluted; 0.1 mL	Rabbits; # not specified	In accord with OECD Guideline 405; eyes were not rinsed	Not irritating according to EU criteria corneal opacity was 7/10	[13]
[(butoxymethylethoxy) methylethoxy]propan-1-ol (read across to PPG-3 Butyl Ether) (99% pure)	Undiluted; 0.1 mL	3 female NZW rabbits	In accord with OECD guideline 405; eyes were not rinsed; contralateral eye served as a control	Not irritating; Draize score = 12 (60 min)slight conjunctival redness and obvious to moderate chemosis; 1 animal with slight injection of the iris after 24 h; no adverse effects on the cornea, except for epithelial damage in 2 animals visualized with fluorescein	[10]
[(butoxymethylethoxy) methylethoxy]propan-1-ol (read across to PPG-3 Butyl Ether)	Undiluted; 0.1 mL	3 NZW rabbits	In accord with OECD guideline 405; eyes were not rinsed; contralateral eye served as a control	Not irritating; no corneal or iridial irritation; conjunctival redness (score = 2) was reversible within 48 h	[10]
[(butoxymethylethoxy) methylethoxy]propan-1-ol (read across to PPG-3 Butyl Ether) (85% pure)	Undiluted; 0.1 mL	1 NZW rabbits	In accord with OECD guideline 405; test instilled into both eyes; one eye was rinsed after 30 sec, the other after 1 h	Not irritating; moderate conjunctival redness and swelling, and slight to moderate reddening of the iris; corneal effects included very slight, transient haziness and moderate corneal injury	[10]
1-(2-butoxy-1-methylethoxy)-propan-2-ol (read across for PPG-n Butyl Ether)	Undiluted; 0.1 mL	3 female NZW rabbits	In accord with OECD guideline 405; eyes were not rinsed	Draize score (1 h) – 12.7/110, slightly irritating (EC classification – not irritating)	

NZW, New Zealand White; OECD, Organisation for Economic Co-operation and Development.

kidneys retaining the greatest percentage of [^{14}C]. Urinary metabolites included propylene glycol n-butyl ether, dipropylene glycol, propylene glycol, and the sulfate conjugate of 1-(2-butoxy-1-methylethoxy)-propan-2-ol. The parent material was present in the urine.

Human

Inhalation

Propylene glycol butyl ether. A cleaning solution containing 3.5% Propylene Glycol Butyl Ether was applied in a simulated cleaning procedure in 7 offices where 8 individuals were employed.[12] The office floor spaces ranged from 41 to 55 m^2 and the room volumes ranged from 33 to 50 m^3. Each office contained wooden furnishings and linoleum flooring and was naturally ventilated. The furniture was wetted with 40 mL of undiluted cleaning solution in the morning; application of the cleaner resulted in a Propylene Glycol Butyl Ether concentration of 0.55 ppm (average; standard deviation 0.17 ppm) in the office air. Seven of the subjects were exposed for approximately 8 h, and one was exposed for approximately 5 h.

Subjects collected daily urine the day before, the day of, and the day after exposure. Urine samples were collected by unexposed individuals and analyzed to determine background levels of glycol ether metabolites. 2-Butoxypropionic acid, a metabolite of Propylene Glycol Butyl Ether, could not be quantified in control urine samples. In all test subjects, the concentration of 2-butoxypropionic acid in the urine was below the limit of quantification (LOQ; 0.01 ppm) the day before exposure; it was present at an average concentration of 0.06 ppm (standard deviation 0.9 ppm) in samples collected on the day of exposure. In three subjects, 2-butoxypropionic acid was detected in the urine samples collected on the day after exposure at concentrations slightly above the LOQ (0.012–0.014 ppm).

Toxicological Studies

Acute Toxicity Studies

Mortality rates for rabbits dosed with PPG Buteths (dose = 21 g/kg) in acute dermal toxicity studies are summarized as follows: 1 of 4 rabbits (PPG-12-Buteth-16); 1 of 4 rabbits (PPG-20-Buteth-30); and 1 of 4 rabbits (PPG-33-Buteth-45). In another acute dermal toxicity study, no deaths occurred in groups of rabbits dosed with PPG-24-Buteth-27 (2, 4, 8, and 16 mL/kg). Erythema, edema, ecchymosis, and desquamation were noted in this study. Pulmonary lesions were noted at necropsy. In New Zealand Albino rabbits dosed with PPG-26-Buteth-26, the acute cutaneous LD_{50} was not achieved at a dose of 2.0 g/kg (1.89 mL/kg).[4]

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

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

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

Acute inhalation LC_{50} values for PPG Buteths that have been reported for rats are as follows: 4670 mg/m^3 and >5230 mg/m^3 for males and females, respectively (PPG-12-Buteth-16); 4.77 mg/m^3 (males and females) for PPG-7-Buteth-10; 330 mg/m^3 (males and females) for PPG-20-Buteth-30; and 14 7 mg/m^3 for PPG-33-Buteth-45. LC_{50} values of 174 mg/m^3 (mice); 511 mg/m^3 (hamsters); and 293 mg/m^3 (guinea pigs) have also been reported for PPG-33-Buteth-45 in other acute inhalation toxicity studies.

In general, the lethality of the PPG Butyl Ethers decreased as the molecular weight increased. In rats, the acute oral LD_{50} values of the PPG butyl ethers ranged from 1.6 to 2.9 mL/kg (PPG-2 Butyl Ether) to 48.7 mL/kg (PPG-40 Butyl Ether). For rabbits, the cutaneous LD_{50} values were 5.9–7.1 mL/kg (PPG-2 Butyl Ether) to >20 mL/kg (PPG-40 Butyl Ether).[1]

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

The acute dermal, oral, and inhalation toxicity studies summarized below are described in Table 9. No new acute toxicity data were available for PPG-3 Butyl Ether. But appropriate read across materials were identified for dermal, oral, and inhalation acute toxicity testing, and those data are included in this table.

In rats, the dermal LD_{50} was 3.5 g/kg for Buteth-3[16] and >2 g/kg for Propylene Glycol Butyl Ether,[9,13,32] [(butoxymethylethoxy) methylethoxy]-propan-1-ol,[10] poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy-,[11] and 1-(2-butoxy-1-methylethoxy)-propan-2-ol.[9] In rabbits, the dermal LD_{50} was ≥1.4 g/kg for Propylene Glycol Butyl Ether[13] and >2 g/kg for [(butoxymethylethoxy)methylethoxy]-propan-1-ol.[10]

In rats, the oral LD_{50} was 6.6 g/kg for Buteth-3,[16] > 2 g/kg for Propylene Glycol Butyl Ether,[13] [(butoxymethylethoxy) methylethoxy]-propan-1-ol,[10] and 1-(2-butoxy-1-methylethoxy)-propan-2-ol, and between 0.3 and 2 g/kg poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy-.[11] In rats, inhalation LC_{50}s were >3251 mg/m^3 Propylene Glycol Butyl Ether[10,11,16] and >328 mg/m^3 1-(2-butoxy-1-methylethoxy)-propan-2-ol.[9]

Short-Term, Subchronic and Chronic Toxicity Studies

The subchronic (3 mo) oral toxicity of PPG-24-Buteth-27 in rats was evaluated at concentrations of 0.01 to 1.25% in the diet. Acute pneumonia was the primary cause of death in one of the two rats (highest exposure group) that died. Lesions were observed in the livers and kidneys of rats from the 0.05, 0.25, or 1.25% treatment groups. The changes observed in the 0.05% treatment group were regarded as transitory, and tissues from rats in the 0.01% group differed little from those of the control group.[4]

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

In a 2-yr feeding study involving rats, no statistically significant differences were found in the incidence of neoplasms and other lesions (20 tissues) between rats fed PPG-7-Buteth-10 (0.004, 0.02, 0.1, and 0.5 g/kg/d) and control groups. Similar results were reported for PPG-33-Buteth-45, following administration to groups of rats at dietary concentrations of 0.02, 0.1, and 0.5 g/kg/d, respectively.

In a chronic 2-yr feeding study involving dogs, no statistically significant differences in the incidence of gross or microscopic lesions (18 tissues) between groups of animals fed PPG-7-Buteth-10 (0.004, 0.02, 0.1, and 0.5 g/kg/d) and control groups were observed. Similar results were reported for PPG-33-Buteth-45, following administration to groups of dogs at dietary doses of 0.023, 0.11, and 0.61 g/kg/day.

PPG-2 Butyl Ether at a dose of 0.40 g/kg/day was nontoxic to rats during a 14-d feeding study. In 90-d feeding studies, the no-observed effect levels (NOELs) of PPG BE400, 800, 910, and 1020 were 0.047 g/kg/d, 0.16 to 0.67 g/kg/d, 0.25% of the diet, and 0.0625% of the diet, respectively. When rats were treated topically with PPG-2 Butyl Ether 5 d/wk for 13 wk, the dermal NOEL was 0.1 mL/kg/d, which was equivalent to a dose of 91 mg/kg/d. Doses of 0.25 g/kg/d 80% PPG-40 Butyl Ether, 2.0 g/kg/d 80% PPG-33 Butyl Ether, and 1.0 mL/kg/d PPG BE800 had no effect on mortality, weight change, or microscopic findings when applied to the skin of rabbits 5 d/wk for 6 wk, but the 30-d dermal NOEL for PPG BE400 was <0.1 mL/kg/d. When dogs and rats were fed PPG BE800 and 910 for up to 2 yr, the NOELs were up to 0.5 g/kg/d.[1]

The short-term and subchronic toxicity studies summarized below are described in Table 10. No new repeated-dose dermal, oral, or inhalation toxicity data were available for PPG-3 Butyl Ether. Appropriate read-across materials were identified for dermal subchronic toxicity, oral short-term and subchronic toxicity, and short-term inhalation toxicity testing, and those data are included in this table.

In dermal studies, effects on rabbit skin were reported in a 21-d toxicity study of Buteth-3 (1000 mg/kg, occlusive application),[31] in 28-d (at concentrations of ≥5.69%, open applications)[33,34] and 91 d (NOEL of 1.76 mg/kg bw/d) studies of Propylene Glycol Butyl Ether,[9,35] and in a 13-wk study of 1-(2-butoxy-1-methylethoxy)-propan-2-ol (≥91 mg/kg bw/d). Clinical signs of toxicity generally were not observed. Irritation was also observed in a 13-wk study of Propylene Glycol Butyl Ether in rats (≥88 mg/kg).[9,13,36]

In short-term oral toxicity studies in rats, a no-observed adverse effect level (NOAEL) of 400 mg/kg was reported in 14-d gavage studies of Propylene Glycol Butyl Ether[9,13,37] and 1-(2-butoxy-1-methylethoxy)-propan-2-ol,[9] and of 1000 mg/kg in a 28-d gavage study with [(butoxymethylethoxy)methylethoxy]-propan-1-ol.[10] In oral combined repeated dose toxicity studies with the reproduction/developmental toxicity screening test in rats, the NOEL was 100 mg/kg bw/d in rats exposed to either poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy-[11] or 1-(2-butoxy-1-methylethoxy)-propan-2-ol.[10] In subchronic (13-wk) drinking water studies in rats, both Propylene Glycol Butyl Ether[9,13] and PPG-3 Butyl Ether[30] had a NOAEL of 350 mg/kg, and [(butoxymethylethoxy)methylethoxy]-propan-1-ol had a NOAEL of 1000 mg/kg.[10] A NOAEL of 450 mg/kg was reported in rats fed a diet containing 1-(2-butoxy-1-methylethoxy)-propan-2-ol for 13 wk.[9]

In short-term inhalation studies (nine 6-h exposures) in rats, the NOAEL for Propylene Glycol Butyl Ether was 3785 mg/m^3[39,13,38] and for 1-(2-butoxy-1-methylethoxy)-propan-2-ol was ≥200 mg/m^3.[9]

Developmental and Reproductive Toxicity Studies

PPG-2 Butyl Ether when dermally applied was nontoxic to pregnant rats and was non-teratogenic at doses up to 1.0 mL/kg/d.[1]

The developmental and reproductive toxicity (DART) studies summarized below are described in Table 11. Appropriate read-across materials were identified for dermal and oral DART testing, and those data are included in this table.

Dermal application of PPG-2 Butyl Ether to rats during days 6–16 of gestation produced local skin reactions, but not reproductive or teratogenic effects (NOEL >1 mL/kg).[17] Dermally applied Propylene Glycol Butyl Ether was not embryotoxic or teratogenic to rats (≤1.0 mL/kg bw/d applied on days 6–16 of gestation)[9,11,17] or rabbits (≤100 mg/kg bw/d applied on days 7–18 of gestation).[9,10,17] Dermal application of up to 910 mg/kg bw/d 1-(2-butoxy-1-methylethoxy)-propan-2-ol was not embryotoxic, fetotoxic, or teratogenic in rats.[9-11]

No test-article related adverse developmental or reproductive effects were observed in rats dosed by gavage (days 7–16 of gestation) with up to 1000 mg/kg Buteth-3.[31] No effects on reproduction were observed in rats dosed orally prior to and during mating with up to 500 mg/kg bw/d poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy-[11] or up to 1000 mg/kg bw/d 1-(2-butoxy-1-methylethoxy)-propan-2-ol.[10]

Genotoxicity Studies

The genotoxicity studies summarized below are described in Table 12. No genotoxicity data were available for PPG-3 Butyl Ether. Appropriate read-across materials were identified for which Ames tests, mammalian chromosomal aberration assays, and a mammalian cell mutation assay were conducted in vitro and micronucleus tests were conducted in vivo. Those data are included in this table.

Propylene Glycol Butyl Ether,[39] [(butoxymethylethoxy) methylethoxy]-propan-1-ol,[10] poly[oxy(methyl-1,2-ethanediyl)], α-butyl-ω-hydroxy-,[11] and 1-(2-butoxy-1-methylethoxy)-propan-2-ol[9] were not mutagenic in Ames tests. Propylene Glycol Butyl Ether was not mutagenic in numerous other genotoxicity studies, including mammalian chromosomal aberration assays in Chinese hamster ovary (CHO) cells (≤6000 μg/ml),[9,13,40] mouse lymphoma cell assays in T5178Y TK+/- lymphoma cells (≤6000 μg/ml),[9,41] and unscheduled DNA synthesis (UDS) assays in primary rat hepatocytes (≤6000 μg/ml).[42] Poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy-was not genotoxic in a mammalian chromosomal assay in rat lymphocytes (≤5000 μg/ml), or a mammalian cell mutation assay in CHO cells (≤2500 μg/ml).[11] 1-(2-Butoxy-1-methylethoxy)-propan-2-ol was positive, with chromatid and chromosome gaps and breaks, in chromosomal aberration assays in CHO-K1, S1B cells but not in CHO-K1, CCL61 cells, or CHO cells.[9] Gaps and breaks were also reported in negative controls in the tests using CHO-K1, S1B cells.

Both [(butoxymethylethoxy)methylethoxy]-propan-1-ol and 1-(2-butoxy-1-methylethoxy)-propan-2-ol were negative in vivo in the mouse micronucleus assay following a single oral dose of 1875 mg/kg bw[10] and 2500 mg/kg bw,[9] respectively.

Carcinogenicity Studies

In two lifetime skin painting studies, PPG-7-Buteth-10 and PPG-33-Buteth-45, respectively, did not induce papillomas or carcinomas in mice. When administered following either one or two initiator doses of dimethylbenzanthracene (DMBA), 70% PPG-24-Buteth-27 acted as a tumor promoter; however, 5% PPG-24-Buteth-27 did not act as a tumor promoter.[4]

PPG BE800 at concentrations of 0.001% to 0.26% in feed was non-carcinogenic to rats after 2 yr of treatment.[1]

Dermal Irritation and Sensitization Studies

In a skin irritation test of PPG-12-Buteth-16, PPG-20-Buteth-30, and PPG-33-Buteth-45, capillary injection was observed in rabbits only after the application of PPG-12-Buteth-16. The results of another study indicated that PPG-24-Buteth-27 induced minor erythema and moderate edema in rabbits. Reactions were not observed after day 2 post-application. PPG-26-Buteth-26 induced very slight to slight skin irritation in New Zealand albino rabbits. A solubilizing system containing PPG-26-Buteth-26 (concentration not stated) was classified as a mild skin irritant in New Zealand White rabbits.[4]

A human repeated insult patch tests (HRIPT) study in 109 subjects found no irritation or sensitization associated with the application of 0.75% PPG-12-Buteth-16 under semi-occlusive patches. Aftershave formulations containing 2.5% PPG-26-Buteth-26 were not skin irritants or sensitizers when evaluated in two 21-d home use tests. The skin irritation and/or sensitization use test and the skin irritation use test involved 52 and 54 subjects, respectively.

In a 4-h occlusive patch test using rabbits, PPG-2 Butyl Ether caused minor, transient erythema and desquamation, but not edema. PPG-33 Butyl Ether was nonirritating in a vesicant, 4-h irritation, and 3-d repeated application tests. Undiluted PPG-40 Butyl Ether was minimally irritating to the skin of rabbits. Rabbits treated with PPG BE800 had minimal capillary injection during a 3-d repeated application test, and PPG-40 Butyl Ether was slightly less irritating than PPG BE400 (caused erythema) in a 4-h belly irritation test. PPG-9 and -18 Butyl Ethers caused capillary injection, whereas PPG-15, -33, and ~9-15 Butyl Ethers caused no response during a rabbit belly vesicant test.[1]

In clinical studies, PPG BE800 was nonirritating and nonsensitizing to the skin when tested using 200 subjects. PPG-40 Butyl Ether was neither an irritant nor a sensitizer in a repeat insult patch test using 112 subjects.

The dermal irritation and sensitization studies summarized below are described in Table 13. No new dermal irritation or sensitization data were available for PPG-3 Butyl Ether. Studies on appropriate read-across materials were identified for in vitro irritation testing, irritation and sensitization testing in animals, and sensitization testing in humans. Those data are included in this table.

Poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy- was classified as non-corrosive based on the results of an EpiDerm™ test.[11] In rabbits, Propylene Glycol Butyl Ether was slightly irritating at a concentration of 50%[9,13,43] and was generally irritating when applied undiluted.[9,13,44] In guinea pigs, undiluted Propylene Glycol Butyl Ether was a minimal irritant in one study[9]; however, it was not irritating or sensitizing in a Buehler test (three induction patches with 80% and a challenge with 40%).[9,13,45] Undiluted [(butoxymethylethoxy) methylethoxy]-propan-1-ol was not irritating to rabbit skin and was not a sensitizer in guinea pigs in a Buehler test.[10] 1-(2-Butoxy-1-methylethoxy)-propan-2-ol produced some slight irritation in rabbit skin, but was not irritating according to EU classification criteria; also, it was not a sensitizer in guinea pigs (three induction patches with 80% and a challenge with 40%).[9]

In HRIPT, undiluted PPG-14 Butyl Ether,[46] hair styling wax containing 71% PPG-40 Butyl Ether (applied neat),[47] and 1-(2-butoxy-1-methylethoxy)-propan-2-ol[9] were not sensitizers.

Ocular Irritation Studies

Buteth-27 induced iritis and minor to moderate conjunctival irritation. All reactions had cleared by day 2 post-instillation. PPG-26-Buteth-26 did not induce ocular irritation in New

Zealand albino rabbits. Mild ocular irritation was induced in New Zealand White rabbits tested with a solubilizing system containing PPG-26-Buteth-26 (concentration not stated).[4]

Rabbits treated with 0.1 mL PPG-2 Butyl Ether had minor corneal injury (opacity), iritis, and moderate conjunctival irritation; rabbits treated with 0.01 mL of the ether had iritis and minor to moderate conjunctival irritation. In an ocular toxicity study, PPG-15 Butyl Ether produced traces of diffuse corneal necrosis in four of five rabbits and PPG-33 Butyl Ether was not irritating. PPG-9, ~9-15, −15, -18, -22, and -33 Butyl Ethers caused minor injury to the eyes of rabbits.[1]

The ocular irritation studies summarized below are described in Table 14. No new ocular irritation data were available for PPG-3 Butyl Ether. Ocular irritation studies in rabbits for appropriate read-across materials were identified, and those data are included in this table.

The classification of undiluted Propylene Glycol Butyl Ether in rabbit eyes ranged from not irritating (according to criteria established by the EU) to moderately irritating (according the Draize scores).[9,13,48] Undiluted [(butoxymethylethoxy) methylethoxy]-propan-1-ol[10] and 1-(2-butoxy-1-methylethoxy)-propan-2-ol[9] were not irritating and slightly irritating to rabbit eyes, respectively.

Summary

The Panel previously issued final reports on the safety of 19 butyl PPG ethers (2001; safe for use in cosmetics when formulated to avoid irritation) and four butyl PPG/PEG ethers (2000; safe as used in cosmetic products). The ingredients reviewed in those two reports share a common structural motif, namely a butyl chain (4 carbon alkyl chain) bound to a polyoxyalkylene (PPG, PEG, or both). This safety assessment combines the 23 butyl polyoxyalkylene ethers named in those two reports with 23 butyl polyoxyalkylene ethers that were not previously reviewed by the Panel. Most of the ingredients included in this safety assessment are reported to function as hair conditioning agents and skin conditioning agents and several are also reported to function as fragrance ingredients, surfactants, or solvents.

Eighteen of the 46 ingredients assessed in this report are currently reported as used in cosmetic formulations. According to 2017 VCRP data, PPG-26-Buteth-26 has the highest frequency of use, with 1332 reported uses. Buteth-3 and PPG-12-Buteth-16 have the next highest frequency of use, with 446 and 436 reported uses, respectively. PPG-40 Butyl Ether has the highest maximum use concentration in both leave-on (71% in tonics, dressings, and other hair grooming aids) and rinse-off formulations (73.5% in hair tints). Approximately half of the ingredients that are in use have been reviewed previously by the Panel, and for the majority of these ingredients, the frequency of use has not changed. However, there has been a large increase in the frequency of use of PPG-26-Buteth-26, from 13 reported uses in 1997 to 1332 uses reported in 2017.

Most of the butyl polyoxyalkylene ethers are approved for use as secondary direct food additives or as indirect food additives.

The in vitro diffusion rate of Buteth-3 through human skin samples following a 12-h exposure was 22 μg/cm^2/h. Buteth-3 did not have a significant effect on skin barrier function.

Small propylene glycol ethers are rapidly absorbed and distributed throughout the body following oral and inhalation exposures. Excretion is primarily via the urine and expired air; a small amount is excreted in the feces. Absorption via the dermal route is slower, but subsequent distribution is rapid. Additionally, Propylene Glycol Butyl Ether (a monoglycol ether) is absorbed through the skin better than diglycol and triglycol ethers. However, diglycol and triglycol ethers may be present on the skin much longer than monoglycol ethers because of their lower vapor pressures.

Following a single oral dose of [^{14}C]1-(2-butoxy-1-methylethoxy)-propan-2-ol in 1% methylcellulose in rats, 42–51% of the dose was excreted in the urine and 42–35% in carbon dioxide (0.4 or 4.4 mmol/kg bw, respectively) within 48 h. Metabolites and the parent compound were present in the urine.

2-Butoxypropionic acid, a metabolite of Propylene Glycol Butyl Ether, appeared in the urine (at a concentration of 0.06 ppm) of 6 subjects who were exposed to vapors from a cleaning solution containing 3.5% Propylene Glycol Butyl Ether. The day after the exposure, 2-butoxypropionic acid was detected in the urine samples of 3 subjects at slightly over the LOQ (0.012–0.014 ppm).

In rats, the dermal LD_{50} was 3.5 g/kg for Buteth-3 and >2 g/kg for Propylene Glycol Butyl Ether, [(butoxymethylethoxy) methylethoxy]-propan-1-ol, poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy-, and 1-(2-butoxy-1-methylethoxy)-propan-2-ol. In rabbits, the dermal LD_{50} was ≥1.4 g/kg for Propylene Glycol Butyl Ether and >2 g/kg for [(butoxymethylethoxy) methylethoxy]-propan-1-ol.

In rats, the oral LD_{50} was 6.6 g/kg Buteth-3, >2 g/kg for Propylene Glycol Butyl Ether, [(butoxymethylethoxy) methylethoxy]-propan-1-ol, and 1-(2-butoxy-1-methylethoxy)-propan-2-ol, and between 0.3 and 2 g/kg poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy-. In rats, inhalation LC_{50}s were >3251 mg/m^3 Propylene Glycol Butyl Ether and >328 mg/m^3 1-(2-butoxy-1-methylethoxy)-propan-2-ol.

In dermal studies, effects on rabbit skin were reported in a 21-d toxicity study of Buteth-3 (1000 mg/kg, occlusive application), in 28-d (at concentrations of ≥5.69%, open applications) and 13-wk (NOEL of 1.76 mg/kg bw/d) studies of Propylene Glycol Butyl Ether, and in a 13-wk study of 1-(2-butoxy-1-methylethoxy)-propan-2-ol (≥91 mg/kg bw/d). Clinical signs of toxicity generally were not observed. Irritation was also observed in a 13-wk study of Propylene Glycol Butyl Ether in rats (≥88 mg/kg).

In short-term oral toxicity studies in rats, a NOAEL of 400 mg/kg was reported in 14-d gavage studies of Propylene Glycol Butyl Ether and 1-(2-butoxy-1-methylethoxy)-propan-2-ol, and of 1000 mg/kg in a 28-d gavage study with [(butoxymethylethoxy)methylethoxy]-propan-1-ol. In oral combined repeated dose toxicity studies with the reproduction/developmental toxicity screening test, the NOEL was 100 mg/kg bw/d in rats exposed to either poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy- or 1-(2-butoxy-1-methylethoxy)-propan-2-ol. In subchronic (13-wk) drinking water studies in rats, both Propylene Glycol Butyl Ether and PPG-3 Butyl Ether[30] had a NOAEL of 350 mg/kg, and [(butoxymethylethoxy) methylethoxy]-propan-1-ol had a NOAEL of 1000 mg/kg. A NOAEL of 450 mg/kg was reported in rats fed a diet containing 1-(2-butoxy-1-methylethoxy)-propan-2-ol.

In short-term inhalation studies (nine 6-h exposures) in rats, the NOAEL for Propylene Glycol Butyl Ether was 3785 mg/m^3 and for 1-(2-butoxy-1-methylethoxy)-propan-2-ol was ≥200 mg/m^3. Dermal application of PPG-2 Butyl Ether to rats during days 6–16 of gestation produced local skin reactions, but it did not produce reproductive or teratogenic effects (NOEL >1 mL/kg). Dermally applied Propylene Glycol Butyl Ether was not embryotoxic or teratogenic to rats (≤1.0 mL/kg bw/d applied on days 6–16 of gestation) or rabbits (≤100 mg/kg bw/d applied on days 7–18 of gestation). Dermal application of up to 910 mg/kg bw/d 1-(2-butoxy-1-methylethoxy)-propan-2-ol was not embryotoxic, fetotoxic, or teratogenic in rats.

No test-article related adverse developmental or reproductive effects were observed in rats dosed by gavage (days 7–16 of gestation) with up to 1000 mg/kg Buteth-3. No effects on reproduction were observed in rats dosed orally prior to and during mating with up to 500 mg/kg bw/d poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy- or up to 1000 mg/kg bw/d 1-(2-butoxy-1-methylethoxy)-propan-2-ol.

Propylene Glycol Butyl Ether, [(butoxymethylethoxy) methylethoxy]-propan-1-ol, poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy-, and 1-(2-butoxy-1-methylethoxy)-propan-2-ol were not mutagenic in Ames tests. Propylene Glycol Butyl Ether was not mutagenic in numerous other genotoxicity studies, including mammalian chromosomal aberration assays in CHO cells (≤6000 μg/ml), mouse lymphoma cell assays in T5178Y TK+/- lymphoma cells (≤6000 μg/ml), and UDS assays in primary rat hepatocytes (≤6000 μg/ml). Poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy-was not genotoxic in a mammalian chromosomal assay in rat lymphocytes (≤5000 μg/ml), or a mammalian cell mutation assay in CHO cells (≤2500 μg/ml). 1-(2-Butoxy-1-methylethoxy)-propan-2-ol was positive, with chromatid and chromosome gaps and breaks, in chromosomal aberration assays in CHO-K1, S1B cells but not in CHO-K1, CCL61 cells, or CHO cells. Gaps and breaks were also reported in negative controls in the tests using CHO-K1, S1B cells. Both [(butoxymethylethoxy) methylethoxy]-propan-1-ol and 1-(2-butoxy-1-methylethoxy)-propan-2-ol were negative in the mouse micronucleus assay following a single oral dose of 1875 mg/kg bw and 2500 mg/kg bw, respectively.

Poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy- was classified as non-corrosive in an EpiDerm^{TM} study. In rabbits, Propylene Glycol Butyl Ether was slightly irritating at a concentration of 50% and was generally irritating when applied undiluted. In guinea pigs, undiluted Propylene Glycol Butyl Ether was a minimal irritant in one study; it was not irritating or sensitizing in a Buehler test (three induction patches with 80% and a challenge with 40%). Undiluted [(butoxymethylethoxy)methylethoxy]-propan-1-ol was not irritating to rabbit skin, and was not a sensitizer in guinea pigs in a Buehler test. 1-(2-Butoxy-1-methylethoxy)-propan-2-ol produced some slight irritation in rabbit skin, but was not irritating according to the EU classification, and it was not a sensitizer in guinea pigs (three induction patches with 80% and a challenge with 40%). In HRIPTs, undiluted PPG-14 Butyl Ether, hair styling wax containing 71% PPG-40 Butyl Ether (applied neat), and 1-(2-butoxy-1-methylethoxy)-propan-2-ol were not sensitizers.

The classification of undiluted Propylene Glycol Butyl Ether in rabbit eyes ranged from not irritating (according to criteria established by the EU) to moderately irritating (according the Draize scores). Undiluted [(butoxymethylethoxy) methylethoxy]-propan-1-ol and 1-(2-butoxy-1-methylethoxy)-propan-2-ol were not irritating and slightly irritating to rabbit eyes, respectively.

Discussion

The Panel previously issued final reports on the safety of 19 butyl PPG ethers (2001; safe for use in cosmetics when formulated to avoid irritation) and four butyl PPG/PEG ethers (2000; safe as used in cosmetic products). In accordance with its Procedures, the Panel evaluates the conclusions of previously-issued reports every 15 yr to determine whether the conclusion should be reaffirmed. Because the ingredients included in the reports on the butyl PPG ethers and the butyl PPG/PEG ethers share a common structural motif, the Panel determined that the butyl PPG ethers and butyl PPG/PEG ethers should be combined in one report for the re-review. Additionally, the Panel determined that it was appropriate to include 23 butyl polyoxyalkylene ethers that have not yet been reviewed, because these ingredients also share the same structural motif.

The Panel addressed the use of chemicals for read-across, and determined that information reported for [(butoxymethylethoxy) methylethoxy]propan-1-ol, poly[oxy(methyl-1,2-ethanediyl)], α-butyl-ω-hydroxy-, and 1-(2-butoxy-1-methylethoxy)-propan-2-ol (see Table 3) is appropriate for read-across. [(Butoxymethylethoxy)methylethoxy]propan-1-ol and PPG-3 Butyl Ether are positional isomers. The Panel stated that, because the chemical and physical properties and metabolism of these two compounds should be similar, the information on [(butoxymethylethoxy)methylethoxy]propan-1-ol is useful for

evaluating the safety of ingredients included in this assessment. Poly[oxy(methyl-1,2-ethanediyl)],α-butyl-ω-hydroxy- contains the common core structure of the butyl polyoxyalkylene ethers; therefore, the information on this chemical supports the safety of the butyl PPG ethers named in this report. 1-(2-Butoxy-1-methylethoxy)-propan-2-ol is a potential metabolite of the butyl PPG ethers; accordingly, data on this ingredient are included to strengthen the toxicity profile.

For many of the ingredients included in this report, the frequency of use has increased some since the Panel's original review; however, the frequency of use of PPG-26-Buteth-26 has increased notably, from 13 reported uses in 1997 to the 1332 uses reported in 2017. Additionally, at the time of the original review, concentrations of use were not reported. It is now known that PPG-14 Butyl Ether has the greatest maximum concentration of use that results in dermal exposure (up to 17.5% in deodorants), and that the overall maximum use concentrations are for PPG-40-Butyl Ether, that is, up to 71% for leave-on formulations (in a hair wax) and 73.5% in rinse-off formulations (hair tint).

The Panel noted that the smaller compounds are more rapidly absorbed than the larger compounds in the group. However, because there is a strong weight of evidence for low systemic toxicity across the group, the Panel was generally not concerned about the use of these ingredients in cosmetics.

Because some of these ingredients are ethoxylated, the Panel was concerned about the possible presence of 1,4-dioxane and ethylene oxide impurities. The Panel stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities from the butyl polyoxyalkylene ethers before blending them into cosmetic formulations.

The Panel was also concerned that the potential exists for dermal irritation with the use of products formulated with butyl polyoxyalkylene ethers. Therefore, the Panel specified that products containing these ingredients must be formulated to be non-irritating.

Finally, the Panel discussed the issue of incidental inhalation exposure, as some of the butyl polyoxyalkylene ethers are used in cosmetic sprays and could possibly be inhaled. For example, PPG-40 Butyl Ether is reported to be used at a maximum concentration of 10% in hair sprays. The inhalation study data included in the safety assessment did not concern the Panel. Additionally, the Panel noted that droplets/particles from spray cosmetic products would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings

Conclusion

The Expert Panel for Cosmetic Ingredient Safety concluded that the following butyl polyoxyalkylene ethers safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating:

Buteth-3
PPG-2-Buteth-1*
PPG-2-Buteth-2*
PPG-2-Buteth-3*
PPG-3-Buteth-5*
PPG-4-Buteth-4*
PPG-5-Buteth-5
PPG-5-Buteth-7*
PPG-7-Buteth-4
PPG-7-Buteth-10
PPG-9-Buteth-12
PPG-10-Buteth-9*
PPG-12-Buteth-12*
PPG-12-Buteth-16
PPG-15-Buteth-20
PPG-17-Buteth-17
PPG-19-Buteth-19*
PPG-20-Buteth-30
PPG-24-Buteth-27*
PPG-26-Buteth-26
PPG-28-Buteth-35
PPG-30-Buteth-30*
PPG-33-Buteth-45
PPG-36-Buteth-36*
PPG-38-Buteth-37
PPG-2 Butyl Ether
PPG-3 Butyl Ether*
PPG-4 Butyl Ether*
PPG-5 Butyl Ether*
PPG-9 Butyl Ether*
PPG-12 Butyl Ether*
PPG-14 Butyl Ether
PPG-15 Butyl Ether*
PPG-16 Butyl Ether*
PPG-17 Butyl Ether*
PPG-18 Butyl Ether*
PPG-20 Butyl Ether*
PPG-22 Butyl Ether*
PPG-24 Butyl Ether*
PPG-26 Butyl Ether*
PPG-30 Butyl Ether*
PPG-33 Butyl Ether
PPG-40 Butyl Ether
PPG-52 Butyl Ether
PPG-53 Butyl Ether*
Propylene Glycol Butyl Ether*

*Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group

Author's Note

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Author Contribution

Fiume, M. contributed to conception and design, contributed to acquisition, analysis, and interpretation, drafted manuscript, and critically revised manuscript; Heldreth, B. contributed to conception and design, contributed to acquisition, analysis, and interpretation, drafted manuscript, and critically revised manuscript; Gill, LJ, Bergfeld, W., Belsito, D., Hill, R., Klaassen, C., Liebler, D., Marks, J., Shank, R., Slaga, T., and Snyder, P. contributed to conception and design, contributed to analysis and interpretation, and critically revised manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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