Amended Safety Assessment of Butyl Polyoxyalkylene Ethers as Used in Cosmetics

Status: Re-Review for Panel Review
Release Date: May 13, 2016
Panel Meeting Date: June 6-7, 2016

The 2016 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This safety assessment was prepared by Monice M. Fiume, Assistant Director/Senior Scientific Analyst/Writer.

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Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume MMF
Assistant Director/Senior Scientific Analyst
Date: May 13, 2016
Subject: Amended Safety Assessment of Butyl Polyoxyalkylene Ethers as Used in Cosmetics

Enclosed is the Re-Review of the Amended Safety Assessment of Butyl Polyoxyalkylene Ethers as Used in Cosmetics. (It is identified as *butype062016rep* in the pdf document.) In 2001, the 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." 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.

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." 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

It has been at least 15 years since the last assessments on these groups of ingredients have been issued. Last year during the priority list discussions, that Panel agreed with a strategy memo that suggested combining these two reports into one re-review because the reports are comprised of ingredients that all share a common structural motif, (a butyl connected to a simple polyoxyalkylene (PPG, PEG, or both)). In addition, there was agreement to include 22 additional butyl polyoxyalkylene ethers that have not yet been reviewed. This report reflects the Panel's agreement to combine the two reports and to add the additional butyl polyoxyalkylene ethers.

Concentration of use data were received from the Council and are included (*butype062016data*). Also included are the 2016 VCRP data (*butype062016FDA*). The current frequency of use for the majority of these ingredients is similar to that at the time of the original review. However, there has been a remarkable increase in the frequency of use of PPG-26-Buteth-26 – from 13 uses in 1997 to 1091 reported uses in 2016.

The four safety assessments referred to above are provided as identified here:

- *butype062016prev_1*: 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 Ether (2001)
- *butype062016prev_2*: Final Report on the Safety Assessment of PPG-40 Butyl Ether (1993)
- *butype062016prev_3*: Amended Final Report of the Safety Assessment of PPG-9-Buteth-12, PPG-12-Buteth-16, PPG-26-Buteth-26, and PPG-28-Buteth-35 (2000)
- *butype062016prev_4*: Final Report on the Safety Assessment of PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-26-Buteth-26, and PPG-28-Buteth-35 (2000)

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Also included are minutes that were available from the original proceedings:

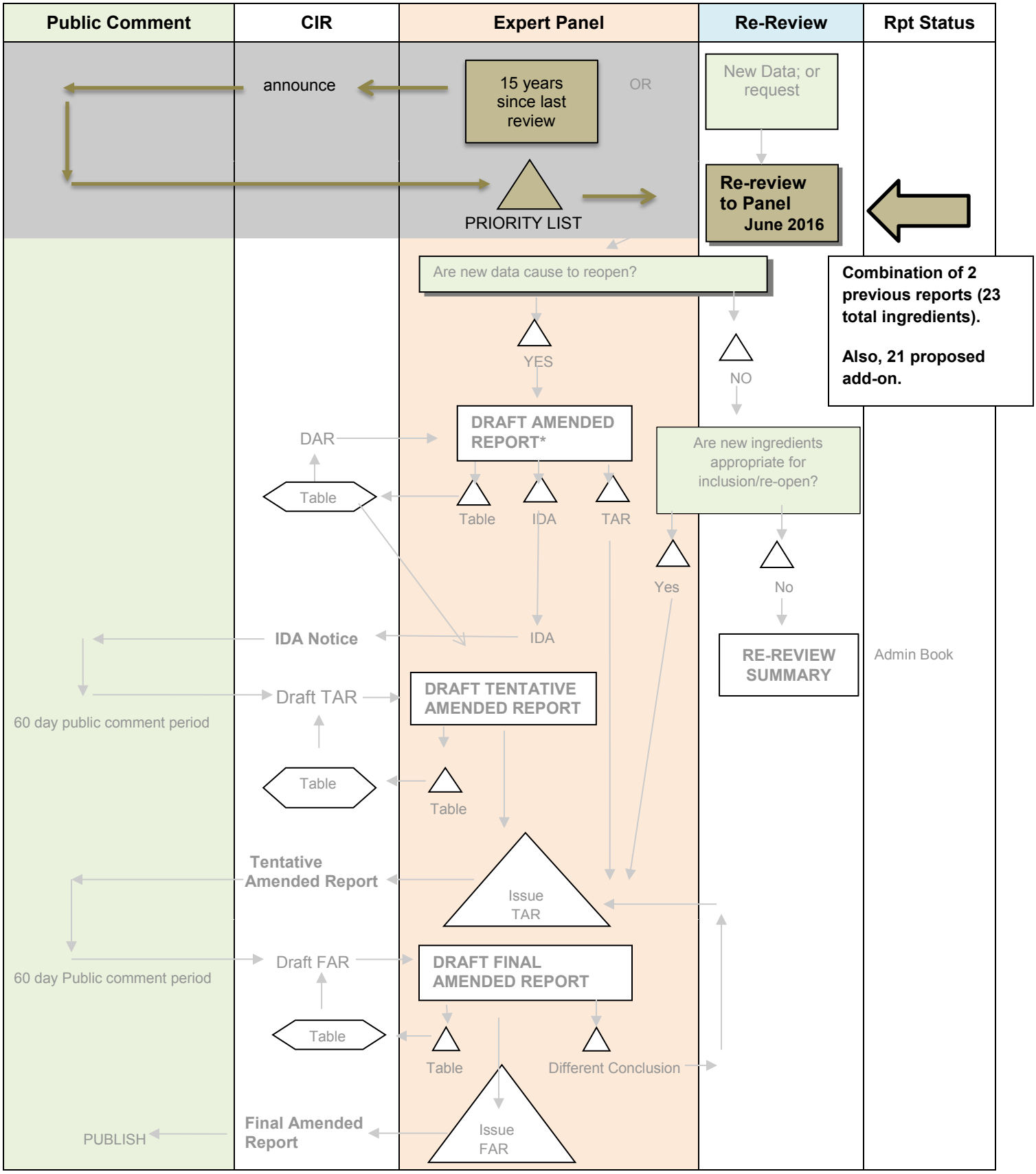
- *butype062016min_1*: discussions of PPG-2, -4, -5, -9, -12, -14, -15, -16, -17, -18, -20 -22, -24, -26, -30, -33, -52, and -53 Butyl Ether (Addendum To PPG-40 Butyl Ether Report)
- *butype062016min_2*: discussions of PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-26-Buteth-26, and PPG-28-Buteth-35

If the existing and new data presented in the report are sufficient, the Panel should be prepared to issue a Tentative Amended Report.

RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Butylated Polyoxyalkylene Ethers

MEETING June 2016



*If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

Butyl Polyoxyalkylene Ethers

Butyl PPG Ethers
2001: The Panel published a safety assessment with the conclusion that PPG-2 , -4, -5 , -9, -12 , -14, -15 , -16, -17, -18, -20, -22, -24, -26, -30, -33, -40, -52, and -53 Butyl Ethers are safe for use in cosmetics when formulated to avoid irritation
1993: The Panel published a final report on PPRG-40 Butyl Ether with a conclusion of insufficient data

Butyl PPG/PEG Ethers
2000: the Panel issued an Amended Final Report on PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-26-Buteth-26, and PPG-28-Buteth-35 with a conclusion that all 4 ingredients are safe as used in cosmetic products; this superseded the conclusion that was published that year
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 with a conclusion that stated 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

2015 Priorities Strategy Memo: the Panel agreed to combine the 2 sets of ingredients into one report, as a family named Butyl Polyoxyalkylene Ethers, and to add 22 previously unreviewed Butyl Polyoxyalkylene Ethers

June 2016: Re-Review
The re-review document was presented to Panel.

Butyl Polyoxyalkylene Ethers_ (new data only) – June 2016 – Monice Fiume

	Reported Use - current	Method of Mfg	Impurities	Toxicokinetics	Dermal Penetration	Animal Tox – Acute, Dermal	Animal Tox – Acute, Oral	Animal Tox, Acute, Inhalation	Animal Tox – Rptd Dose, Dermal	Animal Tox, Rptd Dose, Oral	Animal Tox – Rptd Dose, Inhalation	Repro/Dev Toxicity	Genotoxicity	Carcinogenicity	Dermal Irr/Sens	Case Reports	Ocular Irritation	Mucous Membrane Irr
PPG-2-Buteth-1																		
PPG-2-Buteth-2																		
PPG-2-Buteth-3																		
PPG-3-Buteth-5																		
PPG-4-Buteth-4																		
PPG-5-Buteth-	X																	
PPG-5-Buteth-7																		
PPG-7-Buteth-4	X																	
PPG-7-Buteth-10	X																	
PPG-9-Buteth-12	X																	
PPG-10-Buteth-9																		
PPG-12-Buteth-12																		
PPG-12-Buteth-16	X																	
PPG-15-Buteth-20	X																	
PPG-17-Buteth-17	X																	
PPG-19-Buteth-19																		
PPG-20-Buteth-30																		
PPG-24-Buteth-27																		
PPG-26-Buteth-26	X																	
PPG-28-Buteth-35	X																	
PPG-30-Buteth-30																		
PPG-33-Buteth-45	X																	
PPG-36-Buteth-36																		
PPG-38-Buteth-37	X																	
PPG-2 Butyl Ether	X																	
PPG-3 Butyl Ether						X	X			X			X		X		X	
PPG-4 Butyl Ether																		
PPG-5 Butyl Ether																		

Butyl Polyoxyalkylene Ethers_ (new data only) – June 2016 – Monice Fiume																		
	Reported Use - current	Method of Mfg	Impurities	Toxicokinetics	Dermal Penetration	Animal Tox – Acute, Dermal	Animal Tox – Acute, Oral	Animal Tox, Acute, Inhalation	Animal Tox – Rptd Dose, Dermal	Animal Tox, Rptd Dose, Oral	Animal Tox – Rptd Dose, Inhalation	Repro/Dev Toxicity	Genotoxicity	Carcinogenicity	Dermal Irr/Sens	Case Reports	Ocular Irritation	Mucous Membrane Irr
PPG-9 Butyl Ether																		
PPG-12 Butyl Ether																		
PPG-14 Butyl Ether	X																	
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	X																	
PPG-40 Butyl Ether	X																	
PPG-52 Butyl Ether	X																	
PPG-53 Butyl Ether																		
Buteth-3	X			X		X	X		X			X						
Read Across Ingredients																		
polypropylene glycol butyl ethers										X		X			X			
propylene glycol butyl ether												X	X		X			
1-(2-butoxy-1-methylethoxy)propan-2-ol										X		X	X					
methoxyisopropanol											X	X		X				
PPG-3 Methyl Ether												X						

PREVIOUS REPORTS

	Method of Manufacture	Impurities/Composition	Toxicokinetics	Dermal Absorption	Animal Tox – Acute, Dermal	Animal Tox – Acute, Oral	Animal Tox, Acute, Inhal.	Animal Tox – Rptd Dose, Derm	Animal Tox, Rptd Dose, Oral	Animal Tox – Rptd Dose, Inhal	Repro/Dev Toxicity	Genotoxicity	Carcinogenicity	Dermal Irr/Sens	Ocular Irritation	Mucous Membrane Irr	Phototoxicity
Amended Final Report on the Safety Assessment of PPG-40 Butyl Ether with an Addendum to Include PPG-2 , etc - 2001																	
PPG Butyl Ethers (not defined)	X	X	X			X											
PPG-2 Butyl Ether					X			X	X	X	X			X	X		
PPG-4 Butyl Ether																	
PPG-5 Butyl Ether						X											
PPG-9 Butyl Ether					X	X	X							X	X		
PPG-12 Butyl Ether																	
PPG-14 Butyl Ether																	
PPG-15 Butyl Ether					X	X								X	X		
PPG-16 Butyl Ether																	
PPG-17 Butyl Ether																	
PPG-18 Butyl Ether					X	X	X							X	X		
PPG-20 Butyl Ether																	
PPG-22 Butyl Ether					X										X		
PPG-24 Butyl Ether							X										
PPG-26 Butyl Ether																	
PPG-30 Butyl Ether																	
PPG-33 Butyl Ether					X	X	X	X						X	X		
PPG-40 Butyl Ether					X	X		X						X			
PPG-52 Butyl Ether																	
PPG-53 Butyl Ether						X											
Final Report on the Safety Assessment of PPG-40 Butyl Ether																	
PPG-40 Butyl Ether						X											

PREVIOUS REPORTS

	Method of Manufacture	Impurities/Composition	Toxicokinetics	Dermal Absorption	Animal Tox – Acute, Dermal	Animal Tox – Acute, Oral	Animal Tox, Acute, Inhal.	Animal Tox – Rptd Dose, Derm	Animal Tox, Rptd Dose, Oral	Animal Tox – Rptd Dose, Inhal	Repro/Dev Toxicity	Genotoxicity	Carcinogenicity	Dermal Irr/Sens	Ocular Irritation	Mucous Membrane Irr	Phototoxicity
Amended Final Report of the Safety Assessment of PPG-9-Buteth-12, PPG-12-Buteth-16, PPG-26-Buteth-26, and PPG-28-Buteth-35(final 2000)																	
General – not defined		X															
PPG-9-Buteth-12																	
PPG-12-Buteth-16	X	X			X	X	X			X				X	X		
PPG-26-Buteth-26		X			X	X								X	X		
PPG-28-Buteth-35																	
PPG-7-Buteth-10			X			X	X			X			X				
PPG-20-Buteth-30					X	X	X			X					X		
PPG-24-Buteth-27					X	X							X	X	X		
PPG-33-Buteth-45			X		X	X	X			X			X		X		
Final Report of the Safety Assessment of PPG-9-Buteth-12, PPG-12-Buteth-16, PPG-26-Buteth-26, and PPG-28-Buteth-35 (published 2000)																	
General - not defined	X	X															
PPG-9-Buteth-12																	
PPG-12-Buteth-16					X	X	X			X					X		
PPG-26-Buteth-26					X	X								X	X		
PPG-28-Buteth-35																	
PPG-7-Buteth-10			X			X	X		X	X			X				
PPG-20-Buteth-30					X	X	X			X							
PPG-24-Buteth-27					X	X			X				X	X			
PPG-33-Buteth-45			X		X	X	X		X	X			X				

Butyl Polyoxyalkylene Ethers

	CAS #	Use	InfoBase	PubMed	SciFinder	ChemID	NTIS	FDA	ECHA	HPV	IUCLID/ SIDS	WHO/ JEFCA	EU	NICNAS	Web
PPG-26-Buteth-26	9038-95-3 (generic) 9065-63-8 (generic)			0 hits	3 new hits			21CFR173.310; 21CFR173.340; 21CFR175.105; 21CFR176.210; 21CFR178.3570; 21CFR178.3910; 40CFR180.960	9038-95-3 – preR 9065-63-8 – no						
PPG-28-Buteth-35															
PPG-12-Buteth-16															
PPG-9-Buteth-12															
PPG-2 Butyl Ether	9003-13-8 (generic)								yes						
PPG-3 Butyl Ether	55934-93-5								yes						
PPG-4 Butyl Ether	9003-13-8 (generic)								yes						
PPG-5 Butyl Ether															
PPG-9 Butyl Ether															
PPG-12 Butyl Ether															
PPG-14 Butyl Ether								21CFR178.3910							
PPG-15 Butyl Ether															
PPG-16 Butyl Ether															
PPG-17 Butyl Ether															
PPG-18 Butyl Ether								21CFR175.105; 21CFR176.210; 21CFR178.3910							
PPG-20 Butyl Ether								21CFR175.105; 21CFR176.200.; 21CFR176.210; 21CFR178.3910							
PPG-22 Butyl Ether															
PPG-24 Butyl Ether															
PPG-26 Butyl Ether															
PPG-30 Butyl Ether															
PPG-33 Butyl Ether															
PPG-40 Butyl Ether								21CFR175.105; 21CFR176.200.; 21CFR176.210; 21CFR178.3570; 21CFR178.3910							
PPG-52 Butyl Ether								21CFR176.200.; 21CFR178.3570; 21CFR178.3910							
PPG-53 Butyl Ether															
Buteth-3	[143-22-6]								maybe						
PPG-2-Buteth-1	9038-95-3 (generic) 9065-63-8 (generic)							21CFR173.310; 21CFR173.340; 21CFR175.105; 21CFR176.210; 21CFR178.3570; 21CFR178.3910; 40CFR180.960	9038-95-3 – preR 9065-63-8 – no						
PPG-2-Buteth-2															
PPG-2-Buteth-3															
PPG-3-Buteth-5															
PPG-4-Buteth-4															
PPG-5-Buteth-5															
PPG-5-Buteth-7															

	CAS #	Use	InfoBase	PubMed	SciFinder	ChemID	NTIS	FDA	ECHA	HPV	IUCLID/ SIDS	WHO/ JEFCA	EU	NICNAS	Web
PPG-7-Buteth-4															
PPG-7-Buteth-10															
PPG-10-Buteth-9															
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-30-Buteth-30															
PPG-33-Buteth-45															
PPG-36-Buteth-36															
PPG-38-Buteth-37															

PPG-40 Butyl Ether IJT 19(S1): 47-67, 2000
Amended Report on PPG-40 Butyl Ether IJT 20(S4): 39-52, 2001

PubMed
(((((9038-95-3[EC/RN Number]) OR 9065-63-8[EC/RN Number]) OR 9003-13-8[EC/RN Number]) OR 55934-93-5[EC/RN Number]) OR 143-22-6[EC/RN Number]) OR (PPG AND Buteth) OR (PPG AND Butyl AND Ether) OR buteth – 88 hits

SciFinder
9038-95-3; 9065-63-8; 9003-13-8; 55934-93-5; 143-22-6; Buteth-3 – 602 hits

FDA Citations
21CFR173.310 - Secondary Direct Food Additives Permitted In Food For Human Consumption; Specific Usage Additives; Boiler water additives
21CFR173.340 - Secondary Direct Food Additives Permitted In Food For Human Consumption; Specific Usage Additives; Defoaming agents
21CFR175.105 – Indirect Food Additive; Adhesives
21CFR176.200 – Indirect Food Additive; Defoaming Agent Used in Coatings
21CFR176.210 – Indirect Food Additive; Defoaming Agent Used in the Manufacture of Paper And Paperboard
21CFR178.3570 – Indriect Food Additive; Lubricants with Incidental Food Contact
21CFR178.3910 – Indirect Food Additive; Surface Lubricants Used In The Manufacture Of Metallic Articles
40CFR180.960 - Polymers; exemptions from the requirement of a tolerance; 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 the Federal Food, Drug, and Cosmetic Act (FFDCA) section 408, if such use is in accordance with good agricultural or manufacturing practices.

PPG-2, -4, -5, -9, -12, -14, -15, -16, -17, -18, -20 -22, -24, -26, -30, -33, -52, AND -53 BUTYL ETHER (ADDENDUM TO PPG-40 BUTYL ETHER REPORT)

May 18-19, 1998

Dr. Schroeter noted that his Team concluded that these ingredients are safe as used, but that concern in the area of genotoxicity was expressed during the Team review, which should be discussed.

Dr. Belsito said that his Team concluded that these ingredients are safe for use when formulated to avoid skin irritation.

Dr. Schroeter agreed with the Belsito Team's amendment of the safe as used conclusion that was proposed.

Dr. Shank noted that neither the methods of manufacture, impurities data, nor genotoxicity data were made available on the PPG Butyl Ethers. He indicated that two genotoxicity assays on PPG-2 Butyl Ether are needed.

Dr. Shank wanted to know how the Belsito Team addressed the issue of genotoxicity.

Dr. Belsito noted that his Team considered that the PPG Butyl Ethers would be broken down to propylene glycol and butanol.

Dr. Shank said that it is not the breakdown of the PPG Butyl Ethers that is of concern. Specifically, he noted that the manufacturing process may yield some byproduct that has not been anticipated, and that the Panel does not have data to indicate otherwise.

Dr. Belsito stated that the Panel received a report from Union Carbide indicating that the potential for PPG Butyl Ether-induced skin cancer is low. He also noted that PPG Butyl Ether 800, fed to rats at a concentration of 0.26% of the diet, was not carcinogenic after two years of dosing. Dr. Belsito noted that his Team is comfortable with these data.

Dr. Belsito added that it was clarified that the PPG Butyl Ethers are produced from n-butyl alcohol. With this in mind, he said that in addition to the Schroeter Team's request to delete references to the brake-coating fluid study that was done using an unknown concentration of PPG Butyl Ether, his Team requested that the references to t-butyl alcohol be deleted as well.

Dr. Belsito wanted to know the method by which PPG-40 Butyl Ether can be incorporated into the present document such that the Panel's conclusion on PPG Butyl Ethers that will be generated today will be applicable. Dr. Belsito recalled that the Panel previously issued an insufficient data conclusion on PPG-40 Butyl Ether, published in 1993.

Dr. Andersen said that PPG-40 Butyl Ether could be added to the title of the current report on PPG Butyl Ethers, and that the public could be alerted to the fact that the current conclusion amends the Panel's previous conclusion on PPG-40 Butyl Ether.

The Panel voted unanimously in favor of issuing a Tentative Report with the following conclusion: Based on the available data, the CIR Expert Panel concludes that PPG-2, -4, -5, -9, -12, -14, -15, -16, -17, -18, -20, -22, -24, -26, -30, -33, -40, -52, and -53 Butyl Ether are safe for use in cosmetics when formulated to avoid irritation. (Note: This tentative conclusion would amend the conclusion previously reached for PPG-40 Butyl Ether.)

December 2-3, 1998

Dr. Belsito noted that the Panel issued a Tentative Report with the following conclusion at the May 18-19, 1998 Panel meeting: Based on the available data, the CIR Expert Panel concludes that PPG-2, -4, -5, -9, -12, -14, -15, -16, -17, -18, -20, -22, -24, -26, -30, -33, -40, -52, and -53 Butyl Ether are safe for use in cosmetics when formulated to avoid irritation. (Note: This tentative conclusion would amend the conclusion previously reached for PPG-40 Butyl Ether.)

Dr. Belsito also recalled that the Panel had previously reviewed a significant amount of data that was received just prior to the May Panel meeting as well as additional new data that were received. He noted that these data have been incorporated into the CIR report and do not warrant any change in the Panel's tentative conclusion.

The Panel voted unanimously in favor of issuing a Final Report with the conclusion stated in the first paragraph of this section.

PPG-12-BUTETH-16, PPG-9-BUTETH-12, PPG-26-BUTETH-26, AND PPG-28-BUTETH-35

December 11-12, 1995

The Panel voted unanimously in favor of issuing an Insufficient Data Announcement on the PPG Buteths, with the following data requests:

(1) Percutaneous absorption data, preferably on the lowest molecular weight PPG Buteth that is being used in cosmetics (PPG-9-Buteth-12); if absorption occurs, then a dermal teratogenicity study may be needed

(2) Skin irritation and sensitization data on PPG-9-Buteth-12, preferably involving human subjects

(3) UV spectral analysis on PPG-9-Buteth-12; if there is absorption in the UVA or UVB range, then photosensitization data will be requested.

June 3-4, 1996

Dr. Schroeter noted that neither of the following studies requested in the Insufficient Data Announcement issued at the December 11-12, 1995 Panel meeting has been received: (1) Percutaneous absorption data, preferably on the lowest molecular weight PPG Buteth that is being used in cosmetics (PPG-9-Buteth-12); if absorption occurs, then a dermal teratogenicity study may be needed; (2) Skin irritation and sensitization data on PPG-9-Buteth-12, preferably involving human subjects; and (3) UV spectral analysis on PPG-9-Buteth-12; if there is absorption in the UVA or UVB range, then photosensitization data will be requested. Dr. Schroeter then proposed that the Panel approve the issuance of a Tentative Report with an insufficient data conclusion and a discussion section that includes the preceding data requests.

Dr. Belsito said that his Team determined that the Panel's data needs could be met by requesting one of the following three items: (1) dermal absorption, assuming that this would be low or negligible, or (2) teratogenicity of n-butyl alcohol, or (3) the amount of n-butyl alcohol impurity in the finished product. He also said that if either of the three was found to be negative (i.e., no dermal absorption, n-butyl alcohol not teratogenic, or no significant amount of n-butyl alcohol contaminating the finished product), his Team would be able to rule on the safety of the PPG Buteths.

Dr. Bergfeld confirmed that Dr. Belsito's Team also agreed that the UV spectral analysis and skin irritation and sensitization study included in the Insufficient Data Announcement are not needed.

Dr. Belsito noted that deletion of the request for skin irritation and sensitization data is based on the observation that, historically, PPG Buteths have not been recognized as sensitizers under use conditions, along with data from an earlier CIR Report indicating that n-butyl alcohol was not a sensitizer at test concentrations of 2 to 3%. He acknowledged that though significantly higher amounts of n-butyl alcohol are conjugated with the PPG's, it is not believed that 2 to 3% n-butyl alcohol will actually be released into the skin.

Dr. Schroeter noted that the Panel does not have any data to support either his or Dr.Belsito's assumption that the PPG Buteths are not sensitizers, and recommended that the Panel's request for skin irritation and sensitization data remain.

Given the large number of inhalation toxicity studies included in the Tentative Report draft, Dr. Belsito requested clarification of the reason why these studies were performed. He wanted to know whether there was some concern relating to pulmonary toxicity.

Dr. Andersen noted that the report on PPG Buteths has been updated to include the following studies on PPG-26-Buteth-26 that were received from industry: acute oral toxicity, acute dermal toxicity, skin irritation, and ocular irritation. It was also noted that these studies do not address any of the Panel's current concerns relating to the safety of PPG Buteths in cosmetics.

Dr. McEwen noted that there had been a discussion in Teams relating to the possibility of adding more PPG Buteths to the current report. He also recalled that the Panel had requested that PPG-9-Buteth-12 be tested in the skin irritation and sensitization and percutaneous absorption studies listed in the Insufficient Data Announcement that was issued. With this in mind, Dr. McEwen wanted to know whether it would be appropriate to discuss using the lowest molecular weight PPG Buteth (PPG-2-Buteth-2) that is listed for use in cosmetics in the International

Cosmetic Ingredient Dictionary for these tests. He also wanted to know if other PPG Buteths listed in the dictionary that are not reported to FDA as being used should be added to the current report.

Dr. Andersen said that such a discussion, as proposed by Dr. McEwen above, holds the potential for two things: (1) If the data were provided, then the basic insufficiencies could be satisfied; and (2) if the data were provided on the lowest molecular weight PPG Buteth, the Panel would be on record as saying that this would support expanding the group of ingredients reviewed in the present report to include the range encompassing PPG-2-Buteth-2 (lowest molecular weight) up to PPG-38-Buteth-37 (highest molecular weight).

In response to Dr. Bergfeld's question, the Panel agreed that data on the lowest molecular weight PPG Buteth (PPG-2-Buteth-2) would satisfy the Panel's request for skin irritation and sensitization and percutaneous absorption data.

Dr. Andersen recommended that it be indicated in the report discussion that the results of studies involving PPG-2-Buteth-2 may serve as the basis for expanding the group of PPG Buteths reviewed in the present report to include all PPG Buteths listed in the International Cosmetic Ingredient Dictionary.

The Expert Panel concluded that the available data are insufficient to support the safety of PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-26-Buteth-26, and PPG-28-Buteth-35 as used in cosmetics, and voted unanimously in favor of issuing a Tentative Report. Based on today's discussion, the data needed in order for the Panel to complete its safety assessment will be included in the discussion section of the Tentative Report as follows:

(1) Dermal absorption of lowest molecular weight PPG Buteth in this group*;
alternatively, data on n-butyl alcohol teratology or the amount of n-butyl alcohol as an impurity in the finished product could be provided
(2) Human dermal irritation and sensitization*

*Studies on the lowest molecular weight PPG Buteth listed in the International Cosmetic Ingredient Dictionary (PPG-2-Buteth-2) are acceptable and may provide a basis for expanding this family of ingredients to include all of the PPG Buteths.

December 16-17, 1996

Dr. Schroeter noted that a Tentative Report with an insufficient data conclusion was issued at the June 3-4, 1996 Panel meeting. However, since this Panel meeting, data on human skin irritation and sensitization data and an impurities analysis, all on PPG-26-Buteth-26, were received. In recognition of the new study results on PPG-26-Buteth-26, Dr. Schroeter said that his Team concluded that PPG-26-Buteth-26 and PPG-28-Buteth-35 are safe as used. It was also concluded that the available data are insufficient for arriving at a conclusion on the safety of PPG-12-Buteth-16 and PPG-9-Buteth-12 in cosmetics. The data needed for completion of the safety assessment of these two ingredients were stated as follows: (1) Human dermal irritation and sensitization; (2) Dermal absorption of the lowest molecular weight PPG Buteth in this group; and (3) n-butyl alcohol impurities in the finished compounds.

Dr. Shank noted that the Panel does not have data on the toxicity of the lower molecular weight PPG Buteths, and, furthermore, lower molecular weight compounds usually have a higher biological activity than higher molecular weight compounds.

Dr. Belsito noted that the Panel received data indicating that the PPG Buteths do not contain n-butyl alcohol as an impurity, and requested that data from the CIR Final Report on n-butyl alcohol be deleted from the present report on PPG Buteths.

Dr. Belsito also said that based on the Panel's prior review of PPG's and other PPG-containing compounds, the existing report probably could be broadened to include additional PPG Buteths listed in the International Cosmetic Ingredient Dictionary.

Dr. Klaassen said that he would not suspect that there would be any tremendous differences in absorption between PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-26-Buteth-26, and PPG-28-Buteth-35, based on molecular weights. He also noted that the Panel is quite knowledgeable of the PPG's. With this in mind, he said that additional lower molecular weight PPG Buteths from the International Cosmetic Ingredient Dictionary could probably be grouped together for review.

Dr. McEwen brought to the Panel's attention that data on a representative low molecular weight PPG Buteth (compared to the four ingredients being reviewed) are included in the present review: acute oral toxicity, chronic oral toxicity, intravenous toxicity, and dermal carcinogenicity studies on PPG-7-Buteth-10.

Dr. Shank noted that the exact number of mice tested in the carcinogenicity study on PPG-7-Buteth-10 was not stated.

In response to Dr. McEwen's question regarding additional data needed to complete the present safety assessment, Dr. Shank noted that very minimal impurities data are available and that there are no skin irritation or sensitization data on the lower molecular weight compounds. He reiterated that lower molecular weight compounds usually have more biological activity than higher molecular weight compounds, and the extent of penetration into the skin may be greater for lower molecular weight compounds.

Dr. Shank said that his concerns about the lower molecular weight PPG Buteths relate to dermal effects, not systemic effects. He expressed interest in knowing the changes that occur when the lower molecular weight compounds are applied to the skin.

Dr. Belsito recalled that the Panel has approved Propylene Glycol and Polypropylene Glycols (PPG's) for use in cosmetics.

In response to Dr. Belsito's comments, Dr. Shank noted that the PPG Buteths are different compounds with, perhaps, different impurities.

The Panel voted in favor of issuing the following conclusion on PPG Buteths: The CIR Expert Panel concluded that PPG-26-Buteth-26 and PPG-28-Buteth-35 are safe as used in cosmetic products, and that the available data are insufficient to support the safety of PPG-12-Buteth-16 and PPG-9-Buteth-12 as used in cosmetics.

There was one abstention, Dr. Belsito.

The Panel also determined that the following data are needed in order to complete the safety assessment of PPG-9-Buteth-12 and PPG-12-Buteth-16, and, possibly, to evaluate the safety of even lower molecular weight PPG Buteths:

(1) Dermal absorption of PPG-9-Buteth-12*
(2) Human dermal irritation and sensitization of PPG-9-Buteth-12*

* Studies on the lowest molecular weight PPG Buteth listed in the International Cosmetic Ingredient Dictionary (PPG-2-Buteth-2) are acceptable and could provide a basis for expanding this family of ingredients to include all of the PPG Buteths.

The preceding data requests will be included in the report discussion.

Dr. Andersen noted that because the conclusion reached at the present meeting is substantially different from the one included in the Tentative Report, the current document will be re-issued as a Tentative Report with the new conclusion that was approved today. Announcement of the Tentative Report will be followed by a 90-day comment period. The Panel had previously issued a tentative insufficient data conclusion on PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-26-Buteth-26, and PPG-28-Buteth-35.

June 5-6, 1997

Dr. Schroeter noted that a Tentative Report with the following conclusion was issued at the December 16-17, 1997 Panel meeting: The CIR Expert Panel concluded that PPG-26-Buteth-26 and PPG-28-Buteth-35 are safe as used in cosmetic products, and that the available data are insufficient to support the safety of PPG-12-Buteth-16 and PPG-9-Buteth-12 in cosmetics.

The data needed in order for the Panel to complete its safety assessment of PPG-12-Buteth-16 and PPG-9-Buteth-12 were stated as follows:

(1) Dermal absorption of PPG-9-Buteth-12*
(2) Human dermal irritation and sensitization of PPG-9-Buteth-12*

*Studies on the lowest molecular weight PPG Buteth listed in the International Cosmetic Ingredient Dictionary (PPG-2-Buteth-2) are acceptable and could provide a basis for expanding this family of ingredients to include all of the PPG Buteths.

Dr. Schroeter noted that no information was received in response to the Panel's data requests on PPG-12-Buteth-16 and PPG-9-Buteth-12.

The Panel voted unanimously in favor of issuing a Final Report with the conclusion and data requests (in report discussion) stated above.

May 18-19, 2000

Dr. Schroeter recalled that a Final Report with the following conclusions was issued in 1997: The CIR Expert Panel concluded that PPG-26-Buteth-26 and PPG-28-Buteth-35 are safe as used in cosmetic products, and that the available data are insufficient to support the safety of PPG-12-Buteth-16 and PPG-9-Buteth-12 as used in cosmetics. He noted that the Panel has identified the following data that are still needed in order to complete the safety assessment of PPG-9-Buteth-12 and PPG-12-Buteth-16 (and possibly, to evaluate the safety of even lower molecular weight PPG Buteths):

(1) Dermal absorption of PPG-9-Buteth 121
(2) Human dermal irritation and sensitization of PPG-9-Buteth-121

1 Studies on the lowest molecular weight PPG Buteth listed in the International Cosmetic Ingredient Dictionary (PPG-2-Buteth-2) are acceptable and could provide a basis for expanding this family of ingredients to include all of the PPG Buteths.

Dr. Schroeter indicated that the Panel recently received negative repeated insult patch test data on PPG-12-Buteth-16, which was tested at a concentration of 0.75%, and that these data are acceptable. However, he said that his Team noted that the question relating to the dermal absorption of PPG-9-Buteth-12 remains and that these data are still needed.

Dr. Schroeter also requested confirmation that the carcinogencity study on PPG-7-Buteth-10 is a skin-painting study, because the reference for this study is indicative of oral toxicity testing. He said that if the study is a skin-painting study, then the Panel would have good documentation that the lower and higher molecular weight PPG Buteths are safe. Dr. Schroeter requested that review of the Final Report be tabled until the September 2000 Panel meeting, pending confirmation of the route of administration of PPG-7-Buteth-10 in the carcinogenicity study.

Dr. Belsito noted that his Team agreed that a Final Report with a safe as used conclusion on the two lower molecular weight PPG Buteths should be issued at this meeting, assuming that the carcinogenicity study is a skin-painting study and that this will be verified. Dr. Belsito also said that if it is determined that the study is not a dermal carcinogenicity study, then further discussion of the report by the Panel would be necessary.

Dr. Andersen said that if it is determined that the carcinogenicity study is a dermal carcinogenicity study, then the Final Report will be revised and issued as a Tentative Amended Final Report. He added that if further consideration of the study is required, then a Draft Report along with the carcinogenicity study will be provided for consideration at the September 11-12, 2000 Panel meeting.

The Panel voted unanimously in favor of issuing a Tentative Amended Final Conclusion on PPG-9-Buteth-12, PPG-12-Buteth-16, PPG-26-Buteth-26, and PPG-28-Buteth-35 indicating that these ingredients are safe as used in cosmetic formulations, with the caveat that the study on PPG-7-Buteth-10 is reexamined and found to be a robust evaluation of long-term, chronic toxicity.

Dr. Bailey asked who would be making the determination that is referred to in the caveat.

Dr. Andersen said that the chair, Panel members designated by the chair, or the entire Panel could make the determination.

Dr. Bergfeld said that the study could be submitted to toxicologists on the Panel for review and comment, and that any concerns raised would result in the report being tabled for review at the September Panel meeting.

Amended Safety Assessment of Butyl Polyoxyalkylene Ethers as Used in Cosmetics

Status: Re-Review for Panel Review
Release Date: May 13, 2016
Panel Meeting Date: June 6-7, 2016

The 2016 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This safety assessment was prepared by Monice M. Fiume, Assistant Director/Senior Scientific Analyst/Writer.

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INTRODUCTION

The Cosmetic Ingredient Review (CIR) Expert Panel (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]

CIR evaluates the conclusions of previously-issued reports every 15 years, and it has been at least 15 years since the last assessments on the ingredients named above have been issued. Because the reports on the butyl PPG ethers and the butyl PPG/PEG ethers are comprised of ingredients that all share a common structural motif, namely a butyl chain (4 carbon alkyl chain) connected to a simple 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.

Several butyl polyoxyalkylene ethers included in the *International Cosmetic Ingredient Dictionary and Handbook* have not yet been reviewed. These ingredients are included in this safety assessment:

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

A list of all the 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. 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. 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 described in the safety assessment, when formulated to be non-irritating.[7] These reports are available on the CIR website. (http://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] In several instances test articles were deemed appropriate for read-across in those dossiers; that read-across data is included in this report.

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, and are identified by *italicized text*. (This information is not included in the tables or the summary section.) Additionally, the Discussions from these reports are also included in this document.

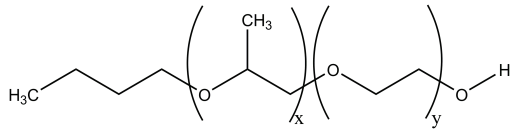
CHEMISTRY

Definition and Structure

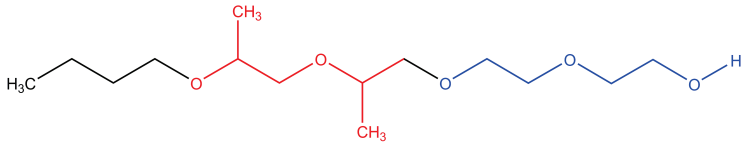
The definitions and structures of the butyl polyoxyalkylene ethers are provided in Table 2.

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" suffix), polypropylene glycol (PPG), or both. These polyether chains vary in length from just 2 repeat units (i.e. PPG-2 Butyl Ether,

MW=190.28 g/mol) up to 75 repeat units (i.e. PPG-38-Buteth-37, MW=3911.12 g/mol). Accordingly, the butyl polyoxyalkylene ethers may be represented generically as a butyl terminated polyether as shown in Figure 1.



wherein "x" may be any integer from 0 to 53 and "y" may be any integer from 0 to 45



PPG-2-Buteth-2

Figure 1. Generic and specific butyl polyoxyalkylene ether structures

Physical and Chemical Properties

PPG-3 Butyl Ether, a hydrophobic glycol ether,[9] is a colorless liquid (Table 3). Also described are physical and chemical properties of Buteth-3, a water-soluble crystalline compound with low volatility,[10] 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]

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]

USE

Cosmetic

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

According to information from the VCRP and that received from the Council, 17 of the 45 ingredients assessed in this report are in use.[11,12] PPG-26-Buteth-26 has the highest frequency of use; according to the 2016 VCRP data, it is used in 1091 cosmetic formulations.[11] Buteth-3 has the next highest frequency of use, with 433 reported uses (Table 4, Table 5).

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 (60.5% in tonics, dressings, and other hair grooming aids) and rinse-off formulations (73.5% in hair tints)[12] (Table 4).

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 at the time of the original review. However, there has been a remarkable 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 1091 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 6.

In some cases, reports of uses were received from the VCRP, but no concentration of use data were 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 in the VCRP database to be in use, 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 is used in at least one cosmetic formulation for 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.[13,14] 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.[15,16] PPG-26-Butth-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.[16] 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).[17]

Non-Cosmetic

Most of the butyl polyoxyalkylene ethers are approved for use as secondary direct food additives or as indirect food additives. (Table 7)

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.[18] 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.[10]

TOXICOKINETIC STUDIES

Dermal Penetration

Buteth-3

The dermal penetration of Buteth-3 through human skin was measured *in vitro*.[19] Epidermal samples were mounted in a glass diffusion apparatus; the exposure area was 2.54 cm^2. Undiluted Buteth-3 (99.9% pure) was placed in contact with the epidermis; 5 runs were performed. Tritiated water was used as a control. The diffusion rate was 22 $\mu g/cm^2/h$. The epidermal damage caused by exposure to Buteth-3 was also 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., ratio of permeability constants determined from tritiated water diffusion after chemical exposure compared to before exposure) was 1.26.

Absorption, Distribution, Metabolism, and Excretion

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 CO_2.[4]

Absorption of the PPGs Butyl Ether was inversely proportional to the molecular weight; typical gastric absorption values ranged from 2% to 100%, depending upon the chain length. PPG BE800 (~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 $C0_2$ 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]

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 LD50 of 18.3 g/kg for PPG-12-Buteth-16 was reported in an acute oral toxicity study involving rats. Acute oral LD50's ranging from 4.49 to 8.57 ml/kg have been reported for PPG-7-Buteth-10 in studies involving rats. Oral LD50's of 7.46 ml/kg (mice) and 1. 77 ml/kg (rabbits) for PPG-7- Buteth-10 also have been reported.

The oral 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 LD50 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 17 4 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 toxicity 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 - 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 nontoxic 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 inhaled vapors of PPG-9, -18, and -24 Butyl Ethers for 1 hour died, but none were killed during a 15-minute exposure period.

The dermal LD_{50} of PPG-3 Butyl Ether was >2 g/kg in rats and rabbits, and the dermal LD_{50} of Buteth-3 in rats was 3.5 g/kg. The oral LD_{50} of PPG-3 Butyl Ether and Buteth-3 in rats was >2 g/kg and 6.6 g/kg, respectively. Polypropylene glycol butyl ethers (not defined) had a dermal and oral LD_{50} of >2 g/kg and 0.3-2 g/kg bw, respectively, in mice (Table 8).[10,20,21]

Short-Term, Subchronic and Chronic Toxicity Studies

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

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

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

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

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

Buteth-3 (1000 mg/kg/day) was not toxic to rabbits in a 21-day dermal study; erythema, desquamation, and fissuring were observed. In short-term oral toxicity studies in rats, PPG-3 Butyl Ether had a NOAEL of 1000 mg/kg bw; polypropylene glycol butyl ethers had a NOEL of 100 mg/kg bw/day for clinical observations, higher absolute and relative liver weights, and an increased incidence of liver and thyroid gland hypertrophy; and 1-(2-butoxy-1-methylethoxy)propan-2-ol had a NOAEL of 100 mg/kg/day based on very slight to slight hepatocellular hypertrophy with no corresponding increases in liver weights in low-dose males. In a 90-day oral toxicity study, administration of up to 1000 mg/kg bw/day PPG-3 Butyl Ether to rats in drinking water produced treatment-related increases in absolute and relative liver and kidney weights. The NOAELs in rats and mice exposed to ≤3000 ppm methoxyisopropanol via inhalation for 2 yrs were 1000 ppm (based on slight body wt decreases in males and females) and 300 ppm (based on altered hepatocellular foci in males), respectively (Table 9).[18-21]

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/ day.[1]

Dermal application of propylene glycol butyl ether was not embryotoxic or teratogenic to rabbits (≤100 mg/kg bw/day applied on days 7-18 of gestation) or rats (≤1.0 ml/kg bw/day applied on days 6-16 of gestation). 1-(2-Butoxy-1-methyl-ethoxy)propan-2-ol (applied on days 6-16 or 6-15 of gestation) also was not embryotoxic or teratogenic in rats. No test-article related adverse developmental or reproductive effects were observed in rats dosed by gavage with up to 1000 mg/kg Buteth-3 or 1-(2-butoxy-1-methylethoxy)propan-2-ol or up to 500 mg/kg bw/day polypropylene glycol butyl ethers. In inhalation studies, exposure of rats to ≤1.0 mg/l air PPG-3 Methyl Ether did not have any teratogenic or reproductive effects. Exposure to 1000 and 3000 ppm methoxyisopropanol produced some adverse effects in a two-generation study in rats; adverse effects were not observed with 300 ppm (Table 10).[19-21]

GENOTOXICITY STUDIES

PPG-3 Butyl Ether was not genotoxic *in vitro* in the Ames test or *in vivo* in a mouse micronucleus assay. Propylene glycol butyl ether was not genotoxic in an Ames test or a mammalian chromosomal aberration assay, in rat lymphocytes and neither propylene glycol butyl ether or 1-(2-butoxy-1-methylethoxy)propan-2-ol were genotoxic in a mammalian cell mutation assay in Chinese hamster ovary (CHO) cells (Table 11).[20,21]

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 years of treatment.[1]

Inhalation

Provided as Read-Across

The carcinogenic potential of methoxyisopropanol (composed of >97% 1-methoxy-2-propanol; <3% 2- methoxy-1-propanol) was evaluated as a surrogate for PPG-3 Butyl Ether in accordance with OECD guideline 453.[20] Groups of 50 male and female $B6C3F_1$ mice were exposed by whole body to 300, 1000, or 3000 ppm methoxyisopropanol for 6 h/day, 5days/wk for 2 yrs. There was an increase in S-phase DNA synthesis and in mixed function oxidase (MFO) activity in the livers of high-dose males. An increase in renal epithelial tumors was not observed at any dose level, and no treatment-related neoplastic or non-neoplastic microscopic findings were reported. The NOEL for carcinogenicity was 3000 ppm for male and female mice.

The carcinogenic potential of methoxyisopropanol was determined in groups of 50 male and 50 female Fischer 344 rats following the same protocol with the same exposure levels.[20] At gross necropsy, a slight increase in the incidence of dark foci in the liver of mid-and high-dose males was reported; this increase correlated with the presence of altered hepatocellular foci observed upon microscopic examination. Other gross pathological observations and the occurrence of palpable masses that were observed in all groups were not treatment-related. Eosinophilic hepatocellular foci and cystic degeneration were noted in mid- and high-dose male rats at microscopic examination, and an increase in S-phase DNA synthesis (not significant) and in MFO activity in the liver was reported for high-dose males. Mid- and high dose males also had an increase in 2μ-globulin nephropathy; no increase in renal epithelial tumors was observed. The NOEL for carcinogenicity was 3000 ppm for male and female rats.

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]

An RIPT 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-day 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-hour 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-hour irritation, and 3-day 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-day repeated application test, and PPG-40 Butyl Ether was slightly less irritating than PPG BE400 (caused erythema) in a 4-hour 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 non-sensitizing 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.

Undiluted PPG-3 Butyl Ether was not irritating to rabbit skin and was not an irritant or sensitizer in guinea pigs. Polypropylene glycol butyl ethers was classified as non-corrosive in an EpiDerm™ study (Table 12).[20,21]

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]

PPG- Butyl Ether was not irritating to rabbit eyes (Table 13).[20]

SUMMARY

The Panel has 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 that were reviewed in those two reports all share a common structural motif, namely a butyl chain (4 carbon alkyl chain) connected to a simple polyoxyalkylene (PPG, PEG, or both). This safety assessment is a compilation of the 23 butyl polyoxyalkylene ethers named in those two reports, as well as an additional 22 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.

Seventeen of the 45 ingredients assessed in this report are used in cosmetic formulations. PPG-26-Buteth-26 has the highest frequency of use, with 1091 reported uses. Buteth-3 has the next highest frequency of use, with 433 reported uses. PPG-40 Butyl Ether has the highest maximum use concentration in both leave-on (60.5% 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 remarkable increase in the frequency of use of PPG-26-Buteth-26, from 13 reported uses in 1997 to the 1091 uses reported in 2016.

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 was 22 $\mu g/cm^2/h$. Buteth-3 did not have a significant effect on skin barrier function.

The dermal LD_{50} of PPG-3 Butyl Ether was >2 g/kg in rats and rabbits, and the dermal LD_{50} of Buteth-3 in rats was 3.5 g/kg. The oral LD_{50} of PPG-3 Butyl Ether and of Buteth-3 in rats was >2 g/kg and 6.6 g/kg, respectively. Polypropylene glycol butyl ethers (not defined) had a dermal and an oral LD_{50} of >2 g/kg and 0.3-2 g/kg bw, respectively, in mice.

Buteth-3 (1000 mg/kg/day) was not toxic to rabbits in a 21-day dermal study; erythema, desquamation, and fissuring were observed. In short-term oral toxicity studies in rats, PPG-3 Butyl Ether had a NOAEL of 1000 mg/kg bw; polypropylene glycol butyl ethers had a NOEL of 100 mg/kg bw/day for clinical observations, higher absolute and relative liver weights, and an increased incidence of liver and thyroid gland hypertrophy; and 1-(2-butoxy-1-methylethoxy)propan-2-ol had a NOAEL of 100 mg/kg/day based on very slight to slight hepatocellular hypertrophy with no corresponding increases in liver weights in low-dose males. In a 90-day oral toxicity study, administration of up to 1000 mg/kg bw/day PPG-3 Butyl Ether to rats in drinking water produced treatment-related increases in absolute and relative liver and kidney weights. The NOAELs in rats and mice exposed to ≤3000 ppm methoxyisopropanol via inhalation for 2 yrs were 1000 ppm (based on slight body wt decreases in males and females) and 300 ppm (based on altered hepatocellular foci in males), respectively.

Dermal application of propylene glycol butyl ether was not embryotoxic or teratogenic to rabbits (≤100 mg/kg bw/day applied on days 7-18 of gestation) or rats (≤1.0 ml/kg bw/day applied on days 6-16 of gestation). 1-(2-Butoxy-1-methyl-ethoxy)propan-2-ol (applied on days 6-16 or 6-15 of gestation) also was not embryotoxic or teratogenic in rats. No test-article related adverse developmental or reproductive effects were observed in rats dosed by gavage with up to 1000 mg/kg Buteth-3 or 1-(2-butoxy-1-methylethoxy)propan-2-ol or up to 500 mg/kg bw/day polypropylene glycol butyl ethers. In inhalation studies, exposure of rats to ≤1.0 mg/l air PPG-3 Methyl Ether did not have any teratogenic or reproductive effects. Exposure to 1000 and 3000 ppm methoxyisopropanol produced some adverse effects in a two-generation study in rats; adverse effects were not observed with 300 ppm.

PPG-3 Butyl Ether was not genotoxic *in vitro* in the Ames test or *in vivo* in a mouse micronucleus assay. Propylene glycol butyl ether was not genotoxic in an Ames test or a mammalian chromosomal aberration assay in rat lymphocytes, and neither propylene glycol butyl ether or 1-(2-butoxy-1-methylethoxy)propan-2-ol were genotoxic in a mammalian cell mutation assay in CHO cells.

In inhalation carcinogenicity studies, mice and rats were exposed by whole body exposure to ≤3000 ppm methoxyisopropanol for 2 yrs. An increase in S-phase DNA synthesis and in MFO activity in the liver was observed in high-dose male mice and rats. Renal epithelial tumors were not observed, and the NOEL for carcinogenicity was 3000 ppm for mice and rats.

Undiluted PPG-3 Butyl Ether was not irritating to rabbit skin or eyes, and it was not an irritant or sensitizer in guinea pigs. Polypropylene glycol butyl ethers were classified as non-corrosive in an EpiDerm™ study.

DISCUSSION FROM THE AMENDED FINAL SAFETY ASSESSMENT OF PPG-9-BUTETH-12, etc[4]

The Expert Panel was particularly concerned that PPG Buteths are butanol-initiated random linear copolymers and that n-butyl alcohol could be present as an impurity in the finished product. n-Butyl alcohol is a reproductive and developmental toxin. Data were available addressing the presence of n-butyl alcohol in PPG-26-Buteth-26. In its review of these data, the Expert Panel considered that the absence of n-butyl alcohol as an impurity in PPG-26- Buteth-26 was an indication that n-butyl alcohol would not be an impurity in any of the PPG Buteths. There was no other basis for suspecting that PPG Buteths presented a reproductive or developmental toxicity risk, so additional data were not needed.

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

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

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

DISCUSSION FROM THE AMENDED FINAL REPORT ON PPG BUTYL ETHERS[1]

In general, the toxicity of the PPGs Butyl Ether decreased with increasing molecular weight; for example, PPG-40 Butyl Ether was less toxic than PPG-2 Butyl Ether. Mutagenicity data were not found on the PPGs Butyl Ether. However, an ether of molecular weight 800 Da (~PPG-13 Butyl Ether) was non-carcinogenic when fed to rats for 2 years.

Because the PPGs Butyl Ethers undergo metabolic degradation; i.e., the butyl group are removed and oxidized, the PPG chains are split into random length fragments, the genotoxicity of the component chemicals, propylene glycol (PG) and n-Butyl Alcohol, were also considered. Both PG and n-Butyl Alcohol were non-mutagenic in mammalian and microbial assays. PG was non-carcinogenic in a 2-year feeding study using rats and in a lifetime dermal study using mice. These studies effectively eliminated the need for genotoxicity data on the PPG Butyl Ethers. The Panel was concerned about the irritancy potential of PPG-2 Butyl Ether. In animal irritation studies, the ingredient caused minor, transient erythema and desquamation; in addition, erythema, edema, ecchymosis, necrosis, and other changes were observed during an acute percutaneous study. PPG-2 Butyl Ether also caused minor to moderate conjunctival irritation and minor corneal injury. The Panel concluded that the PPG Butyl Ethers were safe for use in cosmetics when formulated to avoid irritation.

The CIR Expert Panel previously reviewed the safety of PPG-40 Butyl Ether and found the data to be insufficient to support safety. Because the data on the lower molecular weight PPG Butyl Ethers can be considered relevant to PPG-40 Butyl Ether, and because additional data on PPG-40 Butyl Ether itself were provided, this report amends the conclusion reached in that report.

DISCUSSION

To be developed.

CONCLUSION

To be determined.

TABLES

Table 1. Butyl polyoxyalkylene ethers included in this report

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

Note; ingredients that were previously reviewed are indicated in blue

Table 2. Definitions, structures, and functions of butyl polyoxyalkylene ethers [5; CIR Staff]

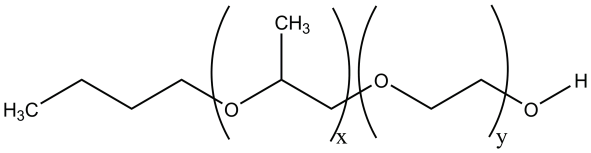
Ingredient CAS No.	Definition & Structure	Function
Butyl PPG/PEG Ethers		
	the butyl PPG/PEG ethers included in this report all conform generally to the formula:  the value of "x" and "y" varies for each ingredient, and these values are specified with each definition	
PPG-2-Buteth-1 9038-95-3 (generic) 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
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

Table 2. Definitions, structures, and functions of butyl polyoxyalkylene ethers [5; CIR Staff]

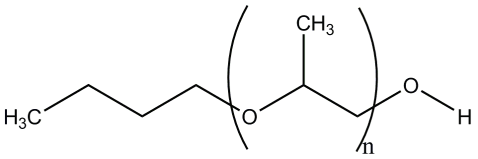
Ingredient CAS No.	Definition & Structure	Function
PPG-12-Buteth-16 9038-95-3 (generic) 9065-63-8 (generic)	PPG-12-Buteth-16 is the polyoxypropylene, polyoxyethylene ether of butyl alcohol that conforms generally to the formula depicted above, where x has an average value of 12 and y has an average value 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 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

Table 2. Definitions, structures, and functions of butyl polyoxyalkylene ethers [5; CIR Staff]

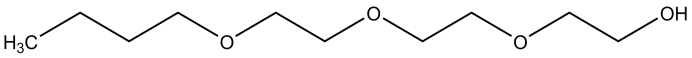
Ingredient CAS No.	Definition & Structure	Function
PPG-15 Butyl Ether 9003-13-8 (generic)	PPG-15 Butyl Ether is the polypropylene glycol ether of butyl alcohol that conforms generally to the formula depicted above, where n has an average value of 15	hair conditioning agent; skin-conditioning agent – 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
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 PEG Ether		
Buteth-3 [143-22-6]	Buteth-3 is the polyethylene glycol ether of butyl alcohol that conforms generally to the formula:  where n has an average value of 3	solvent

Table 3. Physical and Chemical Properties

Property	Value	Reference
	PPG-3 Butyl Ether	
Physical Form	liquid	9,20
Color	colorless	9,20
Odor	practically none mild	9 20
Molecular Wt	248.4 g/mol	9
Density (20ºC) (25ºC)	0.930 g/cm^3 0.927 g/cm^3	9
Specific Gravity (25/25ºC)	0.930	
Viscosity (mm^2/s @ 25ºC)	7	9
Vapor Pressure (20ºC – extrapolated)	<0.01 mm Hg	9
Vapor Density (air = 1)	>6	9
Boiling Point (760 mm Hg)	275ºC	9,20
Water Solubility (25ºC)	40.2 g/l	9
log P_{ow}	1.9	9,20
	Buteth-3	
Physical Form	clear crystalline substance	10
Vapor Pressure (25ºC)	0.0025 mm Hg	10
Solubility	water soluble	10
	polypropylene glycol butyl ethers (not defined)	
Physical Form	liquid	21
Color	brown	21
Density (20ºC)	0.949 g/cm^3	21
Viscosity (20ºC) (40ºC)	19 mPa·s 16 mPa·s	21
Vapor Pressure (20ºC)	0.0006 mm Hg	21
Melting Point	< -20ºC	21
Boiling Point (~760 mm Hg)	306ºC	21
Solubility (solvent in water @ 25ºC)	42.3 g/l; very soluble	21
log P_{ow} (28°C)	1.18 – 4.37	21

Table 4. Current and historical frequency and concentration of use of butyl polyoxyalkylene ethers according to duration and exposure[1,4,11,12]

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	PPG-9-Buteth-12				**PPG-12-Buteth-16**			
	2016	**1997**	**2015**	**1995; 1999[#]**	**2016**	**1997**	**2015**	**1995; 1999[#]**
Totals*	**2**	**2**	**NR**	**NR**	**340**	**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*	*328*	*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[a]; 1[b]	0.53; 0.5[a]	0.5-31[a]
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	1[b]	NR	1
Dermal Contact	2	2	NR	NR	295	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	43	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	288	27	0.8-1.3	0.6-0.7
Baby Products	NR	NR	NR	NR	1	1	NR	NR
	PPG-26-Buteth-26				**PPG-28-Buteth-35**			
	2016	**1997**	**2015**	**1995; 1999[#]**	**2016**	**1997**	**2015**	**1995; 1999[#]**
Totals*	**1091**	**13**	**0.000025-8**	**NR**	**9**	**10**	**NR**	**1**
Duration of Use								
Leave-On	*660*	*7*	*0.000025-8*	*NR*	*6*	*1*	*NR*	*NR*
Rinse-Off	*422*	*6*	*0.01-8*	*NR*	*3*	*9*	*NR*	*1*
Diluted for (Bath) Use	*9*	*0*	*0.025*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	25	NR	0.002-3.6	NR	NR	NR	NR	NR
Incidental Ingestion	1	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	396; 92[a]; 100[b]	5[a]; 1[b]	0.000025-6.2; 0.06-1.8[a]	NR	5[a]	NR	NR	NR
Incidental Inhalation-Powder	1; 100[b]	NR	8[c]	NR	NR	NR	NR	NR
Dermal Contact	986	13	0.000025-8	NR	4	3	NR	NR
Deodorant (underarm)	8[a]	1[a]	spray: 0.099	NR	1[a]	NR	NR	NR
Hair - Non-Coloring	96	NR	0.0001-8	NR	5	7	NR	1
Hair-Coloring	2	NR	0.055-0.9	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	351	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**			
	2016	**1998**	**2015**	**1998**	**2016**	**1998**	**2015**	**1998**
Totals*	**6**	**1**	**2-8**	**	**50**	**45**	**0.05-7.5**	**
Duration of Use								
Leave-On	*1*	*1*	*2*	**	*35*	*16*	*1-17.5*	**
Rinse-Off	*5*	*NR*	*3-8*	**	*15*	*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	**
Incidental Ingestion	NR	NR	NR	**	NR	NR	NR	**
Incidental Inhalation-Spray	NR	NR	NR	**	6; 1[a]; 2[b]	9; 4[a]; 1[b]	1-10	**
Incidental Inhalation-Powder	NR	NR	NR	**	2[b]	1[b]	4-4.5[c]	**
Dermal Contact	4	NR	2-8	**	50	45	1-17.5	**
Deodorant (underarm)	NR	NR	NR	**	24[a]	2[a]	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	3	NR	NR	**	15	29	NR	**
Baby Products	NR	NR	NR	**	NR	NR	0.05	**

Table 4. Current and historical frequency and concentration of use of butyl polyoxyalkylene ethers according to duration and exposure[1,4,11,12]

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	PPG-16-Butyl Ether				**PPG-18 Butyl Ether**			
	2016	**1998**	**2015**	**1998**	**2016**	**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**			
	2016	**1998**	**2015**	**1998**	**2016**	**1998**	**2015**	**1998**
Totals*	**1**	**6**	**1-10**	**	**13**	**46**	**0.75-73.5**	**
Duration of Use								
Leave-On	*NR*	*6*	*1-10*	**	*6*	*7*	*0.75-60.5*	**
Rinse-Off	*1*	*NR*	*NR*	**	*7*	*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	NR	5; 1[a]	2-2.1; 10[a]	**	6[a]	6[a]	0.75-10; 7-23[a]	**
Incidental Inhalation-Powder	NR	NR	NR	**	NR	NR	NR	**
Dermal Contact	1	6	1-2.1	**	NR	1	NR	**
Deodorant (underarm)	NR	NR	NR	**	NR	NR	NR	**
Hair - Non-Coloring	NR	NR	10	**	6	6	0.75-60.5	**
Hair-Coloring	NR	NR	NR	**	7	39	73.5	**
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							
	2016	**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.
[#] some concentration of use data were reported
[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
NR – no reported use

Table 5. Frequency and concentration of use previously unreviewed butyl polyoxyalkylene ethers

	# of Uses[11]	*Max Conc of Use (%)*[12]	*# of Uses*[11]	*Max Conc of Use (%)*[12]	*# of Uses*[11]	*Max Conc of Use (%)*[12]
	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-33-Buteth-45**	
Totals*	**1**	**2-6.2**	**NR**	**1.3-2**	**5**	**0.03**
Duration of Use						
Leave-On	1	2-6.2	NR	2	NR	NR
Rinse Off	NR	2	NR	1.3	5	0.03
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[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	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	2	5	0.03
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-38-Buteth-37		**Buteth-3**			
Totals*	**2**	**0.4-0.8**	**433**	**0.00043-0.33**		
Duration of Use						
Leave-On	*NR*	*0.8*	*48*	*0.0005-0.33*		
Rinse-Off	*2*	*0.4-0.8*	*356*	*0.00043-0.33*		
Diluted for (Bath) Use	*NR*	*NR*	*29*	*0.065-0.33*		
Exposure Type						
Eye Area	NR	NR	NR	NR		
Incidental Ingestion	NR	NR	NR	NR		
Incidental Inhalation-Spray	NR	NR	6; 32[a]; 6[c]	0.065-0.13; 0.065[a]		
Incidental Inhalation-Powder	NR	NR	1; 6[c]	0.065[b]		
Dermal Contact	NR	NR	354	0.00043-0.33		
Deodorant (underarm)	NR	NR	NR	NR		
Hair - Non-Coloring	NR	0.8	17	0.0005-0.33		
Hair-Coloring	2	0.4	61	0.02-0.1		
Nail	NR	NR	1	0.33		
Mucous Membrane	NR	NR	307	0.00043-0.33		
Baby Products	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 6. Ingredients not reported to be in use

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

Table 7. 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

Abbreviations: FFDCA - Federal Food, Drug, and Cosmetic Act ; mol. wt. – molecular weight

Table 8. Acute Toxicity Studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Procedure	LD_{50}/Results	Reference
DERMAL						
PPG-3 Butyl Ether	Wistar rats	5/sex	neat	2 g/kg ; 25 h semi-occlusive patch	>2 g/kg	[20]
PPG-3 Butyl Ether	NZW rabbits	2 males	neat	2 g/kg; 24h patch; type of coverage not stated	>2 g/kg no dermal effects	[20]
Buteth-3	rats	not specified	not specified	details not provided	3.5 g/kg	[10]
Read-Across						
polypropylene glycol butyl ethers (not defined)	Fischer344 rats	5/sex	neat	OECD guideline 402 2 g/kg applied for 24-h using an occlusive 2" x 3" patch (10% of body area)	> 2 g/kg bw; no animals died; no signs of gross toxicity, dermal irritation, adverse toxicologic effects, or abnormal behavior	[21]
ORAL						
PPG-3 Butyl Ether	Fischer rats	3 females	none	2 g/kg bw	>2 g/kg bw 1 animal died	[20]
PPG-3 Butyl Ether	Wistar rats	6/sex	CMC	2 g/kg bw	>2 g/kg bw 1 female died	[20]
PPG-3 Butyl Ether	Wistar rats	5/sex	undiluted	2.4, 3.2, and 4.2 g/kg bw by gavage	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	[20]
Buteth-3	rats	not specified	not specified	details not provided	6.6 g/kg	[10]
Read-Across						
polypropylene glycol butyl ethers (not defined)	Fischer344 rats	3 females	undiluted	OECD Guideline 423 gavage study; 0.3 (2 groups) or 2.0 g/kg bw	0.3 – 2.0 g/kg bw 2/3 high dose animals died 0/6 low dose animals died	[21]

Abbreviations: CMC – carboxymethylcellulose; NZW – New Zealand White; OECD – Organisation for Economic Co-operation and Development

Table 9. Short-Term, Subchronic, and Chronic Toxicity Studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose	Procedure	Results	Reference
SHORT-TERM TOXICITY STUDIES							
Dermal							
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 were used to prevent ingestion during dosing; the test sites were rinsed following dosing the animals were killed within 1 day of termination of dosing	there were no clinical signs of toxicity, and no effect on body wt gains; no mortality slight erythema and edema were observed starting at day 6 and day 7 respectively; both were reported in all test animals as of day 11; desquamation was observed in 1-8 animals on days 10-17; fissuring was reported in 3-5 animals on days 8-16; no signs of irritation were observed in controls there were no treatment-related effects on hematology or clinical chemistry parameters no gross lesions were observed 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	[19]
Oral							
PPG-3 Butyl Ether (80.67% pure)	5 F344 rats/sex	4 wks	corn oil	0, 100, 350, or 1000 mg/kg bw	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 in high dose animals	[20]
Read-Across							
polypropylene glycol butyl ethers (not defined)	12 Crj: CD(SD)/sex	males – 46 days females – 53 days	CMC	0, 20, 100, or 500 mg/kg bw/day	OECD Guideline 422 Males were dosed daily by gavage for 14 days prior to mating and continuing throughout mating for 32 days; females were dosed once daily 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 weights, and an increased incidence of liver and thyroid gland hypertrophy 500 mg/kg/day: treatment-related transient clinical observations were observed in males and females during all phases of the study and included 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 there were not significant effects on body wt or body wt gains, feed consumption, hematology, clinical chemistry, urinalysis (effects on reproduction are described in that respective section)	[21]

Table 9. Short-Term, Subchronic, and Chronic Toxicity Studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose	Procedure	Results	Reference
1-(2-butoxy-1-methylethoxy)-propan-2-ol (99.34% pure)	12 Crl:CD(SD) rats/sex	males – 29 days females – 53 days	0.5% methylcellulose	0, 100, 300, or 1000 mg/kg bw/day	OECD guideline 422 Males were 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	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 that occurred 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; these changes were considered to be an adaptive response associated with increased hepatic metabolism treatment-related increases in absolute and relative kidney weights also were reported in high-dose animals; hyaline droplet formation in the proximal renal tubules was observed in mid- and high-dose males; a histopathologic correlation to the higher kidney weights was not evident for females (Effects on toxicity were described previously)	20
SUBCHRONIC TOXICITY STUDIES							
Oral							
PPG-3 Butyl Ether	10 F344 rats/sex	13 wks	none	0, 100, 350, or 1000 mg/kg bw	administered in drinking water	Histopathological and organ weight alterations of liver and kidney (males) and liver (females) NOAEL – 350 mg/kg bw; LOAEL – 1000 mg/kg bw	18
PPG-3 Butyl Ether (97.7% pure)	10 Fischer 344 rats/sex	90 days	none	0, 100, 350, or 1000 mg/kg bw; 0 and 1000 mg/kg (recovery group)	OECD Guideline 408 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 were not considered toxicologically significant	20
CHRONIC TOXICITY STUDIES							
Inhalation							
Read-Across							
methoxyisopropanol (>97% 1-methoxy-2-propanol; <3% 2-methoxy-1-propanol)	50 B6C3F1 mice/sex	2 yrs	none	0, 300, 1000, or 3000 ppm	OECD Guideline 453 (Combined Chronic Toxicity / Carcinogenicity Studies) animals were exposed by whole body exposure for 6 h/day, 5days/wk	NOAEL – 1000 ppm based on slight body wt decreases in males and females high dose males had increased mortality after 18 mos; high-dose animals exhibited decreased activity, incoordination, and transient sedation during wk 1of exposure; “large” but not statistically significant decreases in body wts in the mid- and high-dose groups liver wts were increased in high dose animals no treatment-related effects on clinical chemistry, hematology, or urinalysis parameters	20

Table 9. Short-Term, Subchronic, and Chronic Toxicity Studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose	Procedure	Results	Reference
methoxyisopropanol (>97% 1-methoxy-2-propanol; <3% 2-methoxy-1-propanol)	50 Fischer 344 rats/sex	2 yrs	none	0, 300, 1000, or 3000 ppm	OECD Guideline 453 animals were exposed by whole body exposure for 6 h/day, 5days/wk	NOAEL – 300 ppm based on altered hepatocellular foci in males high dose males had increased mortality after 18 mos; high-dose animals exhibited decreased activity, incoordination, and transient sedation during wk 1of exposure, these signs reappeared at 12-18 mos; statistically significant decreases in body wts in the high-dose groups liver and kidney wts were increased in high dose animals; no treatment-related effects on hematology or urinalysis parameters; some clinical chemistry parameters were affected in high dose males statistically significant increased labeling indices for hepatic cell proliferation were observed in high dose males; no changes in renal cell proliferation	20

Abbreviations: CMC – carboxymethylcellulose; LOAEL – lowest-observed adverse effect level; NOAEL – no-observed adverse effect level; NOEL – no-observed effect level; NZW – New Zealand White

Table 10. Developmental and Reproductive Toxicity Studies

Test Article	Animals/Group	Vehicle	Dose/Concentration	Procedure	Results	Reference
				Dermal		
Read-Across						
propylene glycol n-butyl ether (98% pure)	25 gravid Wistar rats	propylene glycol (test article was provided as 2 mixtures vehicle at ratios 12:60 and 40:60)	0, 0.3 and 1.0 ml/kg bw/day	OECD guideline 414 open applications (20 cm^2) were made on days 6-16 of gestation; collars were used to prevent ingestion; animals were killed on day 21 of gestation	Not embryotoxic or teratogenic Minor skin reactions were 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 were comparable for test and control groups. No test-article related visceral and skeletal malformations, anomalies or variants	20,21
propylene glycol butyl ether (100% pure)	gravid NZW rabbits; 19/test group, 17 control	water	0, 10, 40, and 100 mg/kg bw/day	OECD guideline 414 6-h applications were made to a 10 cm x 20cm 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 the other groups	20
1-(2-butoxy-1-methyl-ethoxy)propan-2-ol (>95% pure)	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)	OECD guideline 414 open applications (20 cm^2) were made 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 were comparable for test and control groups pre- and post-implantation loss, number of viable fetuses, and fetal weights and lengths were comparable between treatment and control groups, and there were no signs of developmental toxicity not embryotoxic, fetotoxic, or teratogenic	20,21

Table 10. Developmental and Reproductive Toxicity Studies

Test Article	Animals/Group	Vehicle	Dose/Concentration	Procedure	Results	Reference
ORAL						
Buteth-3	10 gravid rats/group	water	0, 250, or 1000 mg/kg	animals were 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	[19]
Read-Across						
polypropylene glycol butyl ethers (not defined)	12 Crj:CD(SD) rats/sex	CMC	0, 20, 100, or 500 mg/kg bw/day	OECD Guideline 422 Males were dosed by gavage 1x/day for 14 days prior to mating, and continuing throughout the mating for 32 days; males were killed on day 39 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	No indication of reproductive toxicity at any dose No adverse effects on prenatal/early neonatal growth and survival of the offspring. NOEL for reproductive effects was 500 mg/kg/day (Effects on toxicity were described previously)	[21]
1-(2-butoxy-1-methyl-ethoxy)propan-2-ol	12 Crl:CD(SD) rats/sex	0.5% methylcellulose	0, 100, 300, or 1000 mg/kg bw/day	OECD guideline 422 Males were 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	NOEL for reproductive effects was 1000 mg/kg/day There were no treatment-related effects on any reproductive parameters (Effects on toxicity were described previously)	[20]
INHALATION						
Read-Across						
PPG-3 Methyl Ether	25 gravid female Sprague-Dawley rats		0, 0.1, 0.3, or 1.0 mg/l air; avg. average mass median particle diameter ranged from 2.47 - 3.75 µm	Animals were dosed via whole body exposure (length of daily exposure not specified) on days 6-15 of gestation	Not embryotoxic, fetotoxic, or teratogenic NOAEL and LOAEL were 1.02 and >1.02 mg/l, respectively, for developmental toxicity NOAEL and LOAEL were 0.29 and 1.02 mg/l, respectively, for maternal toxicity; a "high incidence" of muzzle staining was observed in the 1.0 mg/l group	[21]

Table 10. Developmental and Reproductive Toxicity Studies

Test Article	Animals/Group	Vehicle	Dose/Concentration	Procedure	Results	Reference
Methoxyisopropanol (98% α-isomer)	30 Sprague-Dawley rats/sex	none	0, 300, 1000 or 3000 ppm	OECD guideline 416; 2-generation study Animals were exposed via whole body exposure for 6 h/day, 5 days/wk prior to mating and 6 h/day, 7 days/wk during mating, gestation and lactation breeding of the P_1 adults P_2 adults (i.e., 30 F_{1b} weanlings/sex/group; first exposed on PND 28) commenced after approximately 10 wks of treatment; each female was placed with a male from the same exposure group (1:1 mating); P_1 rats were mated twice to produce F_{1a} and F_{1b} litters; P_2 adults produced F_2 litters maternal rats were not exposed from day 20 of gestation through day 4 post-partum	parental NOAEL – 300 ppm; F_1 and F_2 NOAEL – 1000 ppm toxicity in high dose P_1 and P_2 animals was evidenced primarily as an increased incidence of sedation for several weeks early in the exposure regimen and significant decreases in body wts; decreased body wts persisted throughout the pre-breeding, gestation and lactation phases of the study lengthened estrous cycles, decreased fertility, decreased ovary wts and an increased incidence of ovarian atrophy was observed in high-dose P_1 and P_2 females no treatment-related differences in sperm counts or motility were observed among P1 or P2 adult males neonatal effects observed in the high-dose group consisted of decreased pup body wts, reduced pup survival and litter size, increased time to vaginal opening or preputial separation, and histopathologic observations in the liver and thymus of weanling rats; these neonatal effects were considered secondary to maternal toxicity mild parental toxicity was evidenced in the mid-dose group by slightly decreased pre-mating body weights among P1 and P2 females, but was not accompanied by any statistically significant effects on parental reproduction or neonatal survival, growth or development there were no treatment-related parental or neonatal effects in the low dose group	[20]

Abbreviations: 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 11. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
			IN VITRO			
PPG-3 Butyl Ether (96.12% pure)	50 - 5000 µg/plate, +/- metabolic activation	DMSO	*Salmonella typhimurium* TA1535, TA1537, TA98, TA100	OECD guideline 471; Ames test; solvent and positive controls were included	negative controls gave expected results	[20]
Read-Across						
polypropylene glycol butyl ethers (not defined)	1.5-5000 µg/plate, +/- metabolic activation	DMSO	*S. typhimurium* TA1535, TA1537, TA98, TA100 Escherichia coli WP2 uvr A	OECD guideline 471; Ames test; negative and positive controls were included	negative controls gave expected results	[21]
polypropylene glycol butyl ethers (not defined)	78.1-5000 µg/ml with, 39.1- 5000 µg/ml without, metabolic activation	DMSO	rat lymphocytes	OECD guideline 473; mammalian chromo-somal aberration assay (4 h exposure) ; negative and positive controls were included	negative controls gave expected results	[21]
polypropylene glycol butyl ethers (not defined)	500-2500 µg/ml +/- activation (initial assay) 1400-2400 µg/ml with and 1000-2000 µg/ml without activation (confirmatory assay)	DMSO	CHO cells	OECD guideline 476; mammalian cell mutation assay; negative and positive controls were included	negative controls gave expected results	[21]
1-(2-butoxy-1-methyl-ethoxy)propan-2-ol (98.97% pure)	279 - 5000 µg/ml, +/- metabolic activation	DMSO	CHO cells	OECD guideline 476; mammalian cell mutation assay; solvent and positive controls were included	negative controls gave expected results	
			IN VIVO			
PPG-3 Butyl Ether (96.12% pure)	0, 187.5, 625, and 1875 mg/kg bw	corn oil	5 CD-1 mice/sex/group	OECD guideline 474; mammalian erythrocyte micronucleus test animals were given a single dose by gavage solvent and positive controls were included	negative controls gave expected results	[20]

Abbreviations: CHO – Chinese hamster ovary; DMSO – dimethyl sulfoxide; OECD – Organisation for Economic Co-operation and Development

Table 12. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			IN VITRO		
Read Across					
polypropylene glycol butyl ethers (not defined)	undiluted		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.	[21]
			ANIMAL		
PPG-3 Butyl Ether (98.47% pure)	undiluted	1 female Hartley guinea pig	0.5 ml applied to the flank for 24 h	not irritating	[20]
PPG-3 Butyl Ether (98.47% pure)	10, 25, 50,and 100% in propylene glycol	4 female Hartley guinea pigs	0.05 ml applied to the flank of each animal for 6 h	no systemic toxicity	[20]
PPG-3 Butyl Ether	undiluted	3 NZW rabbits	OECD Guideline 404 4-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 was reported	[20]

Table 12. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
PPG-3 Butyl Ether (99% pure)	undiluted; 0.5 ml	3 female NZW rabbits	OECD Guideline 404 4-h semi-occlusive patch applied 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	[20]
PPG-3 Butyl Ether (85% pure)	undiluted	1 male NZW rabbit	OECD Guideline 404 24-h semi-occlusive patches of 0.5 ml were applied to intact and abraded skin of the abdomen; 3 applications were made to abraded skin and 5 to intact skin 5 daily 0.1 ml applications open applications were made to intact skin on the medial surface of the left ear pinna, received	not irritating repeated contact resulted in very slight to slight erythema and exfoliation	[20]
PPG-3 Butyl Ether (98.47% pure)	undiluted in petrolatum	female Hartley guinea pigs; 20 test, 10 control	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	[20]

Abbreviations: NZW – New Zealand White; OECD – Organisation for Economic Co-operation and Development; PII – primary irritation index

Table 13. Ocular irritation studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
PPG-3 Butyl Ether (99% pure)	undiluted; 0.1 ml	3 female NZW rabbits	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 showed slight injection of the iris after 24 h; no adverse effects on the cornea, except for epithelial damage in 2 animals visualized with fluorescein	[20]
PPG-3 Butyl Ether	undiluted; 0.1 ml	3 NZW rabbits	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	[20]
PPG-3 Butyl Ether (85% pure)	undiluted; 0.1 ml	1 NZW rabbits	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	[20]

Abbreviations: NZW – New Zealand White; OECD – Organisation for Economic Co-operation and Development

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The following previous CIR reports mentioned in this packet are available by search at http://www.cir-safety.org/ingredients

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

Final Report on the Safety Assessment of PPG-40 Butyl Ether

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

Final Report on the Safety Assessment of PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-26-Buteth-26, and PPG-28-Buteth-35

BUTETH-3	01B - Baby Lotions, Oils, Powders, and Creams	1
BUTETH-3	02A - Bath Oils, Tablets, and Salts	4
BUTETH-3	02B - Bubble Baths	13
BUTETH-3	02D - Other Bath Preparations	12
BUTETH-3	04A - Cologne and Toilet waters	4
BUTETH-3	04E - Other Fragrance Preparation	2
BUTETH-3	05A - Hair Conditioner	3
BUTETH-3	05F - Shampoos (non-coloring)	10
BUTETH-3	05G - Tonics, Dressings, and Other Hair Grooming Aic	4
BUTETH-3	06A - Hair Dyes and Colors (all types requiring cautior	61
BUTETH-3	08G - Other Manicuring Preparations	1
BUTETH-3	10A - Bath Soaps and Detergents	32
BUTETH-3	10E - Other Personal Cleanliness Products	246
BUTETH-3	12A - Cleansing	4
BUTETH-3	12C - Face and Neck (exc shave)	2
BUTETH-3	12D - Body and Hand (exc shave)	4
BUTETH-3	12F - Moisturizing	28
BUTETH-3	12J - Other Skin Care Preps	2
PPG-12-BUTETH-16	01A - Baby Shampoos	1
PPG-12-BUTETH-16	02B - Bubble Baths	5
PPG-12-BUTETH-16	05B - Hair Spray (aerosol fixatives)	1
PPG-12-BUTETH-16	05F - Shampoos (non-coloring)	40
PPG-12-BUTETH-16	05G - Tonics, Dressings, and Other Hair Grooming Aic	1
PPG-12-BUTETH-16	06H - Other Hair Coloring Preparation	2
PPG-12-BUTETH-16	10A - Bath Soaps and Detergents	260
PPG-12-BUTETH-16	10E - Other Personal Cleanliness Products	23
PPG-12-BUTETH-16	12A - Cleansing	2
PPG-12-BUTETH-16	12I - Skin Fresheners	1
PPG-12-BUTETH-16	12J - Other Skin Care Preps	2
PPG-12-BUTETH-16	13B - Indoor Tanning Preparations	2
PPG-15-BUTETH-20	12F - Moisturizing	1
PPG-26-BUTETH-26	01B - Baby Lotions, Oils, Powders, and Creams	1
PPG-26-BUTETH-26	01C - Other Baby Products	2
PPG-26-BUTETH-26	02B - Bubble Baths	9
PPG-26-BUTETH-26	03B - Eyeliner	1
PPG-26-BUTETH-26	03C - Eye Shadow	3
PPG-26-BUTETH-26	03D - Eye Lotion	3
PPG-26-BUTETH-26	03E - Eye Makeup Remover	4
PPG-26-BUTETH-26	03F - Mascara	6
PPG-26-BUTETH-26	03G - Other Eye Makeup Preparations	8
PPG-26-BUTETH-26	04A - Cologne and Toilet waters	196
PPG-26-BUTETH-26	04B - Perfumes	26
PPG-26-BUTETH-26	04E - Other Fragrance Preparation	161
PPG-26-BUTETH-26	05A - Hair Conditioner	6
PPG-26-BUTETH-26	05B - Hair Spray (aerosol fixatives)	13
PPG-26-BUTETH-26	05F - Shampoos (non-coloring)	17
PPG-26-BUTETH-26	05G - Tonics, Dressings, and Other Hair Grooming Aic	43
PPG-26-BUTETH-26	05H - Wave Sets	2
PPG-26-BUTETH-26	05I - Other Hair Preparations	15
PPG-26-BUTETH-26	06D - Hair Shampoos (coloring)	2
PPG-26-BUTETH-26	07C - Foundations	1
PPG-26-BUTETH-26	07E - Lipstick	1
PPG-26-BUTETH-26	07H - Makeup Fixatives	1

PPG-26-BUTETH-26	10A - Bath Soaps and Detergents	222
PPG-26-BUTETH-26	10B - Deodorants (underarm)	8
PPG-26-BUTETH-26	10E - Other Personal Cleanliness Products	119
PPG-26-BUTETH-26	11A - Aftershave Lotion	4
PPG-26-BUTETH-26	11G - Other Shaving Preparation Products	1
PPG-26-BUTETH-26	12A - Cleansing	40
PPG-26-BUTETH-26	12C - Face and Neck (exc shave)	83
PPG-26-BUTETH-26	12D - Body and Hand (exc shave)	16
PPG-26-BUTETH-26	12E - Foot Powders and Sprays	1
PPG-26-BUTETH-26	12F - Moisturizing	24
PPG-26-BUTETH-26	12G - Night	2
PPG-26-BUTETH-26	12H - Paste Masks (mud packs)	9
PPG-26-BUTETH-26	12I - Skin Fresheners	16
PPG-26-BUTETH-26	12J - Other Skin Care Preps	18
PPG-26-BUTETH-26	13B - Indoor Tanning Preparations	7
PPG-28-BUTETH-35	05G - Tonics, Dressings, and Other Hair Grooming Aic	5
PPG-28-BUTETH-35	10B - Deodorants (underarm)	1
PPG-28-BUTETH-35	12A - Cleansing	3
PPG-33-BUTETH-45	05F - Shampoos (non-coloring)	5
PPG-38-BUTETH-37	06A - Hair Dyes and Colors (all types requiring cautior	1
PPG-38-BUTETH-37	06H - Other Hair Coloring Preparation	1
PPG-7-BUTETH-10	05I - Other Hair Preparations	1
PPG-9-BUTETH-12	02D - Other Bath Preparations	2
PPG-14 BUTYL ETHER	03G - Other Eye Makeup Preparations	1
PPG-14 BUTYL ETHER	04A - Cologne and Toilet waters	5
PPG-14 BUTYL ETHER	04E - Other Fragrance Preparation	1
PPG-14 BUTYL ETHER	10B - Deodorants (underarm)	24
PPG-14 BUTYL ETHER	10E - Other Personal Cleanliness Products	15
PPG-14 BUTYL ETHER	12C - Face and Neck (exc shave)	2
PPG-14 BUTYL ETHER	12F - Moisturizing	1
PPG-14 BUTYL ETHER	12J - Other Skin Care Preps	1
PPG-2 BUTYL ETHER	03B - Eyeliner	1
PPG-2 BUTYL ETHER	06A - Hair Dyes and Colors (all types requiring cautior	2
PPG-2 BUTYL ETHER	10A - Bath Soaps and Detergents	2
PPG-2 BUTYL ETHER	10E - Other Personal Cleanliness Products	1
PPG-33 BUTYL ETHER	12A - Cleansing	1
PPG-40 BUTYL ETHER	05G - Tonics, Dressings, and Other Hair Grooming Aic	6
PPG-40 BUTYL ETHER	06A - Hair Dyes and Colors (all types requiring cautior	7

Concentration of Use by FDA Product Category – Butyl Polyoxyalkylene Ethers*

PPG-26-Buteth-26
PPG-28-Buteth-35
PPG-12-Buteth-16
PPG-9-Buteth-12
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
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-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

Ingredient	Product Category	Maximum Concentration of Use
PPG-26-Buteth-26	Other baby products Leave-on	 0.9%
PPG-26-Buteth-26	Bubble baths	0.025%
PPG-26-Buteth-26	Eyeliner	0.06-3.6%
PPG-26-Buteth-26	Eye shadow	0.18-3.6%
PPG-26-Buteth-26	Eye lotion	0.18-1.5%
PPG-26-Buteth-26	Mascara	0.002-0.27%
PPG-26-Buteth-26	Other eye makeup preparations	0.06%
PPG-26-Buteth-26	Colognes and toilet waters	0.05-2.5%
PPG-26-Buteth-26	Perfumes	0.000025-6.2%
PPG-26-Buteth-26	Other fragrance preparations	2.3%
PPG-26-Buteth-26	Hair conditioners	0.05-8%
PPG-26-Buteth-26	Hair spray Aerosol Pump spray	 0.0001% 0.34%
PPG-26-Buteth-26	Shampoos (noncoloring)	0.002-1%
PPG-26-Buteth-26	Tonics, dressings and other hair grooming aids	0.06-1.8%
PPG-26-Buteth-26	Other hair preparations (noncoloring)	0.16%
PPG-26-Buteth-26	Hair dyes and colors	0.055-0.9%
PPG-26-Buteth-26	Foundations	1.3%
PPG-26-Buteth-26	Bath soaps and detergents	1.2-2%
PPG-26-Buteth-26	Deodorants Pump spray	 0.099%
PPG-26-Buteth-26	Other personal cleanliness products	0.01-0.038%
PPG-26-Buteth-26	Aftershave lotions	0.77%

PPG-26-Buteth-26	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.025-4.5%
PPG-26-Buteth-26	Face and neck products Not spray Spray	 0.001-8% 0.23-0.36%
PPG-26-Buteth-26	Body and hand products Not spray Spray	 0.025-1.2% 5.4%
PPG-26-Buteth-26	Foot products Spray	8% 2%
PPG-26-Buteth-26	Moisturizing products Not spray	 1.5-8%
PPG-26-Buteth-26	Paste masks and mud packs	0.09-0.56%
PPG-26-Buteth-26	Skin fresheners	0.45-2%
PPG-26-Buteth-26	Other skin care preparations	0.36-1.7%
PPG-12-Buteth-16	Bubble baths	1.3%
PPG-12-Buteth-16	Other bath preparations	0.8%
PPG-12-Buteth-16	Hair conditioners	0.0001%
PPG-12-Buteth-16	Shampoos (noncoloring)	0.05-2%
PPG-12-Buteth-16	Tonics, dressings and other hair grooming aids	1%
PPG-12-Buteth-16	Hair shampoos (coloring)	0.05%
PPG-12-Buteth-16	Bath soaps and detergents	0.8%
PPG-12-Buteth-16	Aftershave lotion	0.62%
PPG-12-Buteth-16	Shaving cream	1%
PPG-12-Buteth-16	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	1%
PPG-12-Buteth-16	Body and hand products Spray	 0.62%
PPG-12-Buteth-16	Foot products Spray	 0.53%
PPG-12-Buteth-16	Other skin care preparations Not spray	 0.15%
PPG-12-Buteth-16	Indoor tanning preparations	0.5%
PPG-2 Butyl Ether	Eyeliner	2%
PPG-2 Butyl Ether	Hair dyes and colors	5%
PPG-2 Butyl Ether	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	3-8%
PPG-14 Butyl Ether	Baby shampoo	0.05%
PPG-14 Butyl Ether	Eyeliner	1.9%
PPG-14 Butyl Ether	Colognes and toilet waters	10%
PPG-14 Butyl Ether	Other fragrance preparations	1%
PPG-14 Butyl Ether	Shampoos (noncoloring)	8%
PPG-14 Butyl Ether	Deodorants Not spray	 6-17.5%
PPG-14 Butyl Ether	Aftershave lotion	2%
PPG-14 Butyl Ether	Face and neck products Not spray	 4-4.5%

PPG-14 Butyl Ether	Night products Not spray	 5%
PPG-14 Butyl Ether	Other skin care preparations	6%
PPG-33 Butyl Ether	Colognes and toilet water	2%
PPG-33 Butyl Ether	Other fragrance preparations	2.1%
PPG-33 Butyl Ether	Tonics, dressings and other hair grooming aids	10%
PPG-33 Butyl Ether	Other skin care preparations Leave-on	 1%
PPG-40 Butyl Ether	Hair sprays Aerosol Pump spray	 0.75% 2-10%
PPG-40 Butyl Ether	Rinses (noncoloring)	2%
PPG-40 Butyl Ether	Tonics, dressings and other hair grooming aids Not spray	7-23% 60.5%
PPG-40 Butyl Ether	Hair tints	73.5%
PPG-52 Butyl Ether	Hair conditioners	3%
PPG-52 Butyl Ether	Tonics, dressings and other hair grooming aids	23%
Buteth-3	Bubble baths	0.33%
Buteth-3	Other bath preparations	0.065%
Buteth-3	Colognes and toilet waters	0.13%
Buteth-3	Perfumes	0.13%
Buteth-3	Hair conditioners	0.001%
Buteth-3	Shampoos (noncoloring)	0.33%
Buteth-3	Other hair preparations (noncoloring)	0.0005%
Buteth-3	Hair dyes and colors	0.1%
Buteth-3	Hair shampoos (coloring)	0.02%
Buteth-3	Other manicuring preparations	0.33%
Buteth-3	Bath soaps and detergents	0.00043-0.33%
Buteth-3	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.065%
Buteth-3	Depilatories	0.065%
Buteth-3	Body and hand products Not spray Spray	 0.065% 0.065%
Buteth-3	Paste masks and mud packs	0.065%
Buteth-3	Other skin care preparations Rinse-off	 0.065%
Buteth-3	Indoor tanning preparations	0.065%
PPG-5-Buteth-5	Hair sprays Pump spray	 0.05%
PPG-5-Buteth-5	Permanent waves	0.2%
PPG-5-Buteth-5	Shampoos (noncoloring)	0.05%
PPG-5-Buteth-5	Tonics, dressings and other hair grooming aids	0.5%
PPG-5-Buteth-5	Face and neck products Not spray	 0.05%

PPG-7-Buteth-4	Shampoos (noncoloring)	0.1%
PPG-7-Buteth-4	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	4%
PPG-7-Buteth-10	Tonics, dressings and other hair grooming aids Not spray	0.023%
PPG-15-Buteth-20	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	2%
PPG-15-Buteth-20	Face and neck products Not spray	6.2%
PPG-15-Buteth-20	Other skin care preparations	2%
PPG-17-Buteth-17	Hair sprays Pump spray	2%
PPG-17-Buteth-17	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	1.3%
PPG-33-Buteth-45	Shampoos (noncoloring)	0.03%
PPG-38-Buteth-37	Other hair preparations (noncoloring)	0.8%
PPG-38-Buteth-37	Hair dyes and colors	0.4%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2015
Table prepared October 13, 2015