GREEN BOOK 2

Caprylyl Glycol

CIR EXPERT PANEL MEETING
JUNE 28-29, 2010

Cosmetic Ingredient Review
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June 28, 2010

Memorandum

To: CIR Expert Panel

From: Wilbur Johnson, Jr.
Senior Scientific Analyst

Subject: Caprylyl Glycol and Other 1,2-Glycols

The availability of a scientific literature review (SLR) on caprylyl glycol and other 1,2-glycols was announced on April 23, 2010. A copy of the draft safety assessment on these ingredients is included along with the following: CIR report history, literature search strategy, and comments from the Personal Care Products industry.

The CIR Expert Panel has evaluated the safety of the 1,2-glycol, propylene glycol and polypropylene glycols and concluded that these ingredients are safe for use in cosmetic products at concentrations up to 50.0%. At its April 5-6 2010 meeting, the Expert Panel issued a tentative amended safety assessment on propylene glycol, tripropylene glycol, and polypropylene glycols with a conclusion stating that these ingredients are safe in the present practices of use and concentration as described in the safety assessment, when formulated to be non-irritating. Study summaries from these safety assessments are italicized under Propylene Glycol subheadings in the draft safety assessment.

After reviewing the data included in the draft safety assessment, the Expert Panel needs to determine whether data on propylene glycol can be used to evaluate the safety of other 1,2-glycols, in the absence of data on these ingredients. The Expert Panel also needs to determine whether additional data are needed in order to arrive at a conclusion on the safety of caprylyl glycol and other 1,2-glycols in personal care products.

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CIR History of:

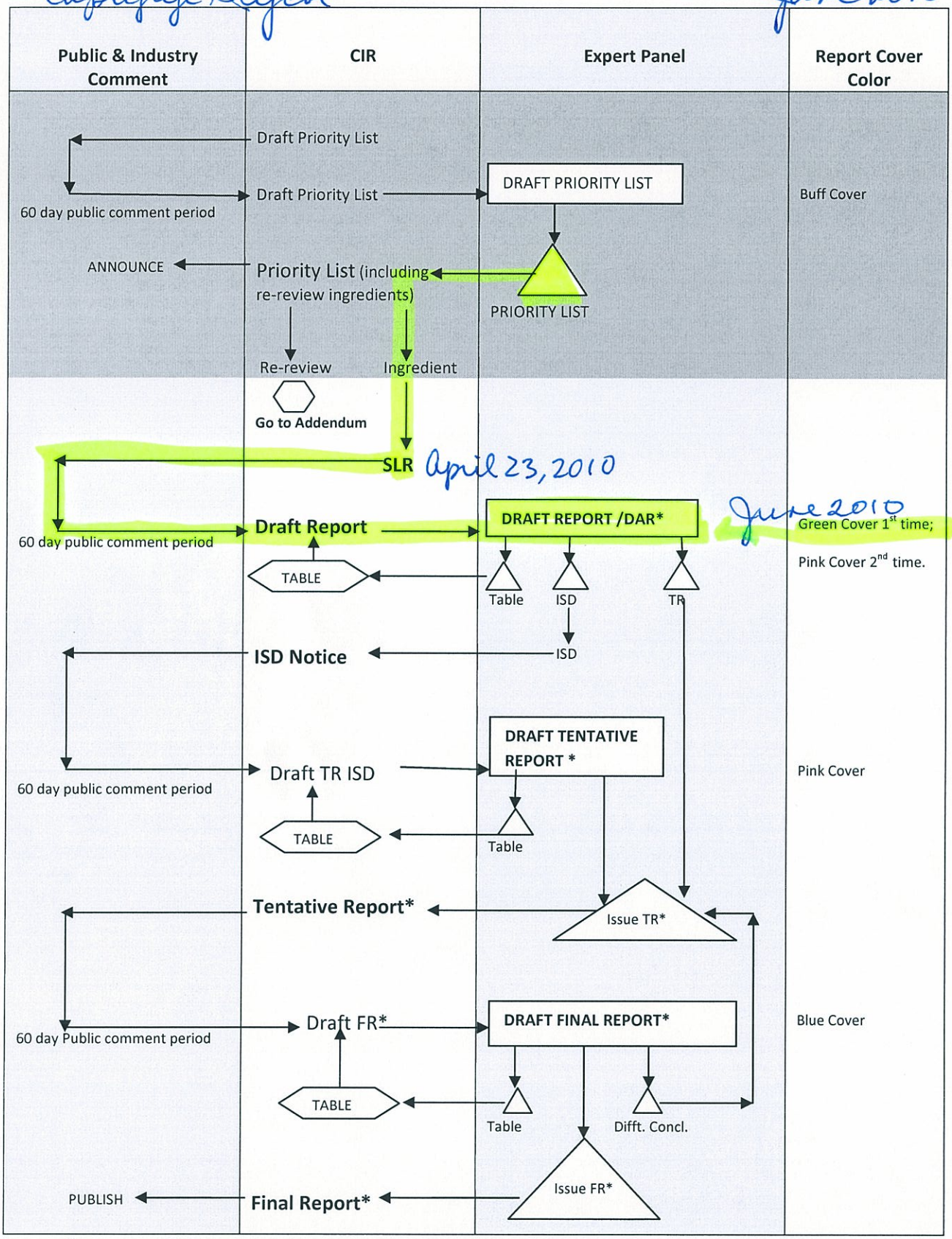
Caprylyl Glycol and other 1,2-Glycols

The availability of a scientific literature review (SLR) on this group of ingredients was announced on April 23, 2009. Comments from the Personal Care Products industry were received during the 60-day comment period.

1st Review, Belsito and Marks Teams/Panel: June 28-29, 2010

SAFETY ASSESSMENT FLOW CHART

Capryly Glycol June 2010



* For ingredient groups originating as Re-Reviews, add word "Amended" before Report; (DAR: Draft Amended Report).

△ Expert Panel Decision

▭ Document for Panel Review

Literature Search on Caprylyl Glycol and Related Ingredients*

Ingre-dients	Toxline &PubMed	ChemIDplus	Multidatabase (See legend*)	DART	Household Products	Beilstein	Registry	Kosmet	Napralert	RTECS	CAplus
AG	0	1	0	0	0	0	1	0	0	0	0
CG	3	**1**	0	0	0	0	1	0	0	0	13
HG	0	0	0	0	0	0	0	0	0	0	0
LG	6	1	0	0	0	0	1	0	0	0	7
MG	15	1	0	0	0	0	1	0	0	0	5
OG	0	1	0	0	0	0	1	0	0	0	1
SG	0	1	0	0	0	0	1	0	0	0	5
CPG	9	1	0	0	1	0	1	0	0	0	17
DG	5	1	0	0	0	0	1	0	0	0	14
PG	28	1	0	0	0	0	1	0	0	1	24
12B	67	1	0	0	0	0	1	1	0	1	46
12H	6	1	0	0	1	0	1	0	0	0	24
C4G	1	0	0	0	0	0	29	0	0	0	0
C5G	0	2	0	0	0	0	1	0	0	0	0
C8G	1	0	0	0	0	0	1	0	0	0	0
C2G	0	0	0	0	0	0	1	0	0	0	0
NG	55	1	1 - CCRIS	0	0	0	1	0	0	1	50
BEP	0	1	0	0	0	0	1	0	0	1	8
IP	0	1	0	0	0	0	1	0	0	0	5
TP	147	1	1 - HSDB	1	1	0	1	0	0	1	10
MP	7	1	1 – HSDB	0	0	0	1	0	0	1	9
14B	253, with limitations	1	1 – CCRIS; 1 – HSDB; 1-Genetox	10	1	0	1	0	1	1	225
11D	4	1	0	0	0	0	1	0	0	1	27
HD	313	2	1 – HSDB; 1 - CCRIS	1	0	0	1	0	0	1	78
OD	14	1	0	1	0	0	1	0	1	0	27
15P	38	1	0	0	1	0	1	0	0	1	62
PD	80, with limitations	1	0	1	1	0	1	0	1	1	186

*Data in Table: Publications used (Total no. in search); Multidatabase = HSDB, CCRIS, ITER, IRIS, Gene-Tox, and LacMed;

Searches Performed on 3/8-12/2010

Ingredients

1,2-glycols

(AG) Arachidyl Glycol OR 1,2-Eicosanediol OR 39825-93-9

(CG) Cetyl Glycol OR 1,2-Dihydroxyhexadecane OR 1,2-Hexadecanediol OR 1,2-Hexadecylene Glycol OR 2-Hydroxycetyl Alcohol OR 6920-24-7

(HG) Hexacosyl Glycol OR Hexacosil glicol

(LG) Lauryl Glycol OR1,2-Dihydroxydodecane OR 1,2-Dodecanediol OR 1,2-Dodecylene Glycol OR 1119-87-5

(MG) Myristyl Glycol OR 1,2-Tetradecanediol OR 21129-09-9

(OG) Octacosanyl Glycol OR 1,2-Octacosanediol OR 97338-11-9

(SG) Stearyl Glycol OR 1,2-Dihydroxyoctadecane OR 1,2-Octadecanediol OR 20294-76-2

(CPG) Caprylyl Glycol OR Capryl Glycol OR 1,2-Dihydroxyoctane OR 1,2-Octanediol OR 1,2-Octylene Glycol OR 1117-86-8

(DG) Decylene Glycol OR 1,2-Decanediol OR 1119-86-4

(PG) Pentylene Glycol OR 1,2-Dihydroxypentane OR 1,2-Pentanediol OR 5343-92-0

(12B) 1,2-Butanediol OR 1,2-Butylene Glycol OR 1,2-Dihydroxybutane OR 584-03-2

(12H) 1,2-Hexanediol OR 1,2-Dihydroxyhexane OR 6920-22-5

(C4G) C14-18 Glycol OR Ethylene Glycol Fatty Acid Ester (2)

(C5G) C15-18 Glycol OR Alkylene (15-18) Glycol OR Cetyl Stearyl Vicinal Glycol OR Glycols, C15-18 OR 70750-40-2 OR 92128-52-4

(C8G) C18-30 Glycol OR Ethylene Glycol Fatty Acid Ester (1)

(C2G) C20-30 Glycol OR Alkylene (20-30) Glycol

Branched 1,3-glycols

(NG) Neopentyl Glycol OR 2,2-Dimethyl-1,3-Dihydroxypropane OR Dimethylolpropane OR 2,2-Dimethyltrimethylene Glycol OR Neopentanediol OR Neopentylene Glycol OR 1,3-Propanediol, 2,2-Dimethyl- OR 126-30-7

(BEP) Butyl Ethyl Propanediol OR 1,3-Propanediol, 2-Butyl-2-Ethyl OR 115-84-4

(IP) Isopentyldiol OR 1,3-Butanediol, 3-Methyl- OR 1,1-Diemthyl-1,3-propanediol OR 3-Hydroxy-3-Methylbutanol OR Isoprene Glycol OR 3-Methyl-1,3-Butanediol OR 3-Methyl-1,3-butylene Glycol OR 2568-33-4

(TP) Trimethyl-1,3-Pentanediol OR 1,3-Pentanediol, 2,2,4-Trimethyl- OR TMPD (alcohol) OR 144-19-4

(MP) Methylpropanediol OR β-Hydroxyisobutanol OR 2-Methyl-1,3-Propanediol OR 2163-42-0

Terminal glycols

(14B) 1,4-Butanediol OR Butane-1,4-diol OR Tetramethylene Glycol OR 110-63-4

(11D) 1,10-Decanediol OR Decamethylene Glycol OR 112-47-0

(HD) Hexanediol OR 1,6-Dihydroxyhexane OR Hexamethylenediol OR Hexamethylene Glycol OR 1,6-Hexanediol OR 629-11-8 OR 26762-52-7

(OD) Octanediol OR 1,8-Octanediol OR 629-41-4

(15P) 1,5-Pentanediol OR 1,5-pentylene glycol OR 111-29-5

(PD) Propanediol OR 1,3-Propanediol OR 1,3-Dihydroxypropane OR 1,3-Propylene Glycol OR Trimethylene Glycol OR 504-63-2 OR 6264-14-2

″Arachidyl Glycol″ OR 39825-93-9 OR ″Cetyl Glycol″ OR 6920-24-7 OR ″Hexacosyl Glycol″ OR ″Lauryl Glycol″ OR 119-87-5 OR ″Myristyl Glycol″ OR 21129-09-9 OR ″Octacosanyl Glycol″ OR 97338-11-9 OR ″Stearyl Glycol″ OR 20294-76-2 OR ″Caprylyl Glycol″ OR 1117-86-8 OR ″Decylene Glycol″ OR 1119-86-4 OR ″Pentylene Glycol″ OR 5343-92-0 OR ″1,2-Butanediol″ OR ″1,2-Butylene Glycol″ OR 584-03-2 OR ″1,2-Hexanediol″ OR 6920-22-5 OR ″C14-18 Glycol″ OR ″Ethylene Glycol Fatty Acid Ester″ OR ″C15-18 Glycol″ OR 70750-40-2 OR 92128-52-4 OR ″C18-30 Glycol″ OR ″C20-30 Glycol″

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Draft Report on the Safety Assesment of the Cosmetic Ingredient Review Expert Panel

On the Safety Assessment of

Caprylyl Glycol and Other 1,2-Glycols

June 28, 2010

The 2010 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 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 F. Alan Andersen, Ph.D. This report was prepared by Wilbur Johnson, Jr., Senior Scientific Analyst/Writer.

Cosmetic Ingredient Review

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INTRODUCTION

This is a safety assessment of caprylyl glycol and other 1,2-glycols, as used in cosmetic products. The 1,2-glycols are used mostly as skin and hair conditioning agents and viscosity increasing agents in these products. This safety assessment includes the following 1,2-glycols :

- caprylyl glycol
- arachidyl glycol
- cetyl glycol
- hexacosyl glycol
- lauryl glycol
- myristyl glycol
- octacosanyl glycol
- stearyl glycol
- decylene glycol
- pentylene glycol
- 1,2-butanediol
- 1,2-hexanediol
- C14-18 glycol
- C15-18 glycol
- C18-30 glycol
- C20-30 glycol

Of the 16 ingredients that are being reviewed in this safety assessment, the following 4 are being used in personal care products: caprylyl glycol, pentylene glycol, 1,2-hexanediol, and C15-18 glycol.

A CIR final safety assessment on propylene glycol (PG) and polypropylene glycols was published in 1994. [1] PG is a very short chain 1,2-glycol, and is therefore very similar to the ingredients reviewed in this safety assessment. The CIR Expert Panel concluded that PG and polypropylene glycols are safe for use in cosmetic products at concentrations up to 50.0%. At its April 5-6 2010 meeting, the Expert Panel issued a tentative amended safety assessment on propylene glycol, tripropylene glycol, and polypropylene glycols with the following conclusion: These ingredients are safe as cosmetic ingredients in the present practices of use and concentration as described in this safety assessment, when formulated to be non-iritating.[2] Individual study summaries on PG are included in italics in the report text.

CHEMISTRY

Definition and Structure

Other chemical names and cosmetic ingredient functions for the ingredients reviewed in this safety assessment are included in Table 1.[3] Caprylyl glycol and other 1,2-glycols are generally defined as the compound that conforms to a structure or formula. Chemical structures for the 1,2-glycols that are being reviewed are included in Figure 1.

Chemical and Physical Properties

Available data on the properties of the following ingredients are included in Table 2: caprylyl glycol, arachidyl glycol, cetyl glycol, lauryl glycol, myristyl glycol, octacosanyl glycol, stearyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol. Information on hexacosyl glycol was not found. No information on the chemical and physical properties of C14-18, C15-18, C18-30, and C20-30 glycols were found. Because these ingredients are mixtures of various length glycols, their chemical and physical properties are expected to be an average of their individual components. UV

absorption data on caprylyl glycol or any of the other 1,2-glycols reviewed in this safety assessment were not found in the published literature.

Methods of Production

The commercially practiced synthesis of ethylene glycol, the simplest of the 1,2-glycols, commonly occurs via a thermal oxidation of ethylene oxide with water.[4] The commercial production of other 1,2-glycols, including those currently under review herein, are commonly synthesized via either catalytic oxidation of the corresponding alkylene oxide, or reduction of the corresponding 2-hydroxy acid**.**

C15-18 glycol, for example, has been prepared via oxidation of the corresponding C15-C18 1,2-alkylene oxides (and the 1,2-alkylene oxides have been synthesized via epoxidation of the corresponding 1,2-alkenes). [5]

Stearyl glycol has been prepared via the reduction of 2-hydroxyoctadecanoic acid with lithium aluminum hydride.[6] This reaction is followed by the quenching of any unchanged lithium aluminum hydride with excess ethyl acetate, filtering of salt, and subsequent drying of the resulting solution.

The production of 1,2-butanediol, much like the synthesis of ethylene glycol, is commonly carried out via a continuous reaction and distillation operation. [7]

Impurities

1,2-butanediol is $\geq$ 99% pure and also contains water, 1,4-butanediol, and 1-acetoxy-2-hydroxybutane. [7]

Analytical Methods

Cetyl glycol has been analyzed using silica gel thin-layer chromatography, and has been identified using IR and mass spectroscopy. [8,9] Decylene glycol has been analyzed via gas chromatography, and has been identified using mass, IR, and NMR spectroscopy**.** [9, 10] Gas chromatography-mass spectrometry (GC-MS) has been used in the analysis of stearyl glycol**.**[6]

Lauryl glycol, myristyl glycol, caprylyl glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol have been identified using mass, IR, or NMR spectroscopy. [9]

Reactivity

For 1,2-butanediol at temperatures above 90°C, explosive vapor/air mixtures may be formed.[11] Additional information on the reactivity of 1,2-butanediol, in relation to EPA's proposed national rule on the reduction of ozone formation, is included in the section on Noncosmetic Use later in the report text.

USE

Most of the ingredients reviewed in this safety assessment function as skin and hair conditioning agents and viscosity increasing agents in cosmetic products in personal care products.[3]

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) in 2009, the following ingredients are being used in personal care products: caprylyl glycol, pentylene glycol, 1,2-hexanediol, and C15-18 glycol. [12] These data are summarized in Table 3. Ingredient use concentration data from the Personal Care Products industry are anticipated. However, it should be noted that the Personal Care Products Council concentration of use survey has not been conducted, and that it is likely that the results will not be available until after the June 28-29 2010 CIR Expert Panel meeting.

Personal care products containing these ingredients may be applied to the skin, nails, or hair, or, incidentally, may come in contact with eyes and mucous membranes. Products containing these ingredients may be applied as frequently as several

times per day and may come in contact with the skin, nails, or hair for variable periods following application. Daily or occasional use may extend over many years.

Noncosmetic Use

Cetyl Glycol

Some colloidal nanoparticles of Sm-Co alloys are made in octyl ether using samarium acetylacetonate and dicobalt octacarbonyl as precursors in a mixture of 1,2-hexadecanediol (cetyl glycol), oleic acid, and trioctylphospine oxide.[13]

Stearyl Glycol

Stearyl Glycol has been used as a surfactant (in octanol/water microemulsion) in a transdermal delivery system for the drug, 8-methoxysalen. [14]

Caprylyl Glycol

Study results support the notion that treatment of glutaraldehyde-treated tissue with a short-chain alcohol (ethanolic buffered solution) and long-chain alcohol (caprylyl glycol) combination will reduce both extractable phospholipids and the propensity for *in vivo* calcification. The use of glutaraldehyde-treated biological tissue in heart valve substitutes is an important option in the treatment of heart valve disease; however, the durability of these devices is limited, in part, because of tissue calcification. [15]

1,2-Butanediol

The Environmental Protection Agency (EPA) lists 1,2-Butanediol as one of the reactive compounds in aerosol coatings (i.e., aerosol spray paints) that contributes to ozone (O_3) formation. It is listed as having a reactivity factor of 2.21 g O_3/g 1,2-butanediol. Reactivity factor is defined as a measure of the change in mass of ozone formed by adding a gram of a volatile organic compound (VOC) to the ambient atmosphere. This listing of compounds, such as 1,2-butanediol, is in keeping with EPA's proposal to amend the aerosol coatings reactivity rule by adding compounds and associated reactivity factors based on petitions that were received. EPA has concluded that a national rule based on the relative reactivity approach achieves more reduction in ozone formation than would be achieved by a mass-based approach for this specific product category. States have previously promulgated rules for aerosol spray paints based upon reductions of VOC by mass.[16]

According to EPA, a risk assessment on 1,2-butanediol and data resulting from a voluntary testing agreement may be available. A freedom of information act (FOIA) request was submitted to EPA to obtain these data. [17]

Butanediol (1,2- or 1,3- not specified)

Esterified butylene glycol (formed with reconstituted oils from triglycerides or fatty acids derived from the oils) is among the chemicals used in the production of resinous and polymeric coatings that may be safely used as the food-contact surface of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food. Also, esterified butylene glycol (formed with fatty triglycerides and marine oils, and the fatty acids and alcohols derived from them) is among the chemicals permitted for use in the formulation of defoaming agents that may be safely used in the manufacture of paper and paperboard intended for use in packaging, transporting, or holding food. [18]

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

Information on absorption, distribution, metabolism, and excretion of the ingredients reviewed in this safety assessment were not identified in the published literature. However, in the absence of percutaneous absorption data, octanol/water partition

coefficients (logP values) for most of the ingredients in this safety assessment are presented in a graph of logP versus 1,2-glycol chain length (Figure 2).

Skin Penetration Enhancement

The skin penetration enhancement effect of caprylyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol has been demonstrated in vitro.

Caprylyl Glycol, Decylene Glycol, and 1,2-Hexanediol

Warner et al.[10] studied ^{3}H-corticosterone (CS) and ^{3}H-triethanolamine flux (TEA) enhancement across full-thickness hairless mouse (SKH-HR1 strain) skin in the presence of 1,2-octanediol (caprylyl glycol), 1,2-decanediol (decylene glycol), and 1,2-hexanediol, each in phosphate buffered saline (PBS). Permeability experiments were performed using a two–chamber diffusion cell, and results are presented in Table 4. Each of the 3 chemicals enhanced the skin penetration of CS and TEA in a concentration-dependent manner.

Pentylene Glycol and 1,2-Butanediol

In a study by Heuschkel et al.,[19] the influence of pentylene glycol and 1,2-butanediol on the skin penetration of the drug, dihydrovenavenanthramide D (DHAvD, 0.2% in hydrophilic cream) across full thickness human skin (from breast, females) was investigated using Franz-type diffusion cells. Relative amounts of DHAvD in different skin compartments (stratum corneum, viable epidermis, and dermis) following penetration from a hydrophilic cream and from a hydrophilic cream containing a 4% pentylene glycol/1,2-butanediol mixture were compared. Within 30 min, the amount of DHAvD that penetrated into the viable skin layers doubled in the presence of the glycol mixture. After 300 min, 12% of the applied dose was detected in the viable epidermis and dermis after application of DHAvD in hydrophilic cream, compared to 41% after application in the cream with the glycol mixture.

ANIMAL TOXICOLOGY

Acute Oral Toxicity

Oral toxicity data on Caprylyl glycol and other 1,2-glycols for which data are available suggest that death (rats) would occur at relatively high doses (LD50 range: 2200 to > 20,000 mg/kg).

Stearyl Glycol

A median LD50 of > 5,000 mg/kg was reported for rats dosed orally with stearyl glycol.[20]

Caprylyl Glycol

The acute oral toxicity of caprylyl glycol was evaluated using male and female rats (number and strain not stated).[21] Doses of ≥ 464 mg/kg caused sedation and ataxia. Specifically, loss of muscle tone and dyspnea were observed at a dose of 1000 mg/kg, and lateral position, coma, and death were observed at a dose of 1470 mg/kg. Deaths occurred within 2 h post-administration; at necropsy, pale parenchymal organs were observed in 3160 and 4640 mg/kg dose groups. Surviving animals recovered within 24 h, and 215 mg/kg was the nontoxic dose in this study. LD50 values of 2240 (males) and 2200 (females) were reported.

Pentylene Glycol (1,2-Pentanediol)

The following acute oral LD50 values have been reported for pentylene glycol: 1.2700 E + 04 mg/kg (rats); 7,400 mg/kg (mice); 3,700 mg/kg (rabbits); and 5,200 mg/kg (guinea pigs).[20] Efforts to obtain the primary references for these studies are underway.

1,2-Butanediol

The following acute oral LD50s have been reported for 1,2-butanediol: 16,000 mg/kg (rats) and 3,720 mg/kg (mice).[20] Efforts to obtain the primary reference for this study are underway.

The Cosmetic Ingredient Review (CIR) is aware of a report by the British Industrial Biological Research Association (BIBRA) that contains acute oral toxicity data on 1,2-butanediol.[22] This report was ordered from the National Technical Information Service (NTIS).

C15-18 Glycol

The acute oral toxicity of C15-18 glycol was evaluated using adult male Sprague-Dawley rats, and an LD50 of > 20.0 g/kg body weight was reported.[5]

Propylene Glycol

The 24 h oral LD50 for PG was 22.8 g/kg body weight in a study involving 5 female Fischer rats. The lowest recorded 24 h oral lethal dose in this study was 20.9 g/kg body weight. Oral LD50 values (rats) of up to 27 g/kg body weight have been reported in other studies.

Acute Intraperitoneal Toxicity

1,2-Butanediol (LD50s up to 5990 mg/kg; TDLo = 2,940 mg/kg) and pentylene glycol (TDLo = 3,510 mg/kg) are not significant acute i.p. toxicants. In an i.p. dosing study in which ED_3 values for caprylyl glycol (1,2-octanediol), pentylene glycol (1,2-propanediol), and 1,2-butanediol were compared, caprylyl glycol had the lowest ED_3 value (1.5 mmole/kg), suggesting that its intoxication potency (i.e., ability to induce ataxia) was greatest.

Caprylyl Glycol, Pentylene Glycol, and 1,2-Butanediol

In a report by Shoemaker,[23] the intoxicating potency of alcohols, some of which were straight-chain primary alcohols and straight-chain diols, was determined. Data on the following 3 diols reviewed in this safety assessment were included: caprylyl glycol (1,2-octanediol), pentylene glycol (1,2-propanediol), and 1,2-butanediol. Doses of each alcohol were injected (intraperitoneally [i.p.]) into male Sprague-Dawley rats, and intoxicating scores were recorded based on the following rating scale: 0 (normal) to 7 (death).

An ED_3 value for each chemical was determined. The ED_3 was defined as the dose (mmole/kg body weight) required to obtain a score of 3 (ataxia) on the intoxication rating scale (0 to 7 [death]). The following ED_3 values were reported: 1.5 mmole/kg (caprylyl glycol), 256.0 mmole/kg (pentylene glycol), and 32.6 mmole/kg (1,2-butanediol).[23]

1,2-Butanediol

Groups of 6 adult female, ICR Swiss albino mice were injected i.p. with increasing doses of 1,2-butanediol (geometric factor of 1.2) in distilled water (injection volume = 0.01 ml/g body weight). Mean LD50 values and 95% confidence limits were calculated from cumulative mortality curves at 24 h and 144 h. The following values were reported for 1,2-butanediol: 24 h LD50 of 66.5 mmol/kg (~5,990 mg/kg) and 144 h LD50 of 46.5 mmol/kg (~ 4,185 mg/kg).[24]

According to another study, a lowest published i.p. toxic dose (TDLo) of 2,940 mg/kg has been reported for 1,2-butanediol in rats.[20] Efforts to obtain the primary reference for this study are underway.

Pentylene Glycol (1,2-Pentanediol)

An i.p. TDLo of 3,510 mg/kg has been reported for pentylene glycol in rats.[20] Efforts to obtain the primary reference for this study are underway.

Propylene Glycol

Following i.p. dosing with PG (5 ml/kg), none of the 5 female C3H mice died, but peritonitis was observed at necropsy. In other studies, i.p. LD 50 values up to 13.7 ml/kg (rats) and 11.2 g/kg (mice) have been reported.

Acute Intravenous Toxicity

Propylene Glycol

Acute i.v. LD50's of 6.2 ml/kg (rats) and 6.4 ml/kg (mice) have been reported for PG.

Acute Parenteral Toxicity

Propylene Glycol

In other parenteral toxicity studies, acute i.m. LD50 (20 g/kg - rats) and acute s.c. LD50 (18.5 g/kg – mice) values have been reported.

Short-term Oral Toxicity

Short-term oral administration of 1,2-butanediol to rats yielded an NOAEL of 200 mg/kg/day.

1,2-Butanediol

The study summarized in this section is actually a combined repeated dose/reproductive and developmental toxicity study, and results relating to reproductive and developmental toxicity appear in that section later in the report text.[25] Groups of Crj-CD(SD) rats (10 males, 10 females) were dosed orally, by gavage, with aqueous 1,2-butanediol at doses of 40, 200, or 1,000 mg/kg/day. Males were dosed daily for 42 days, and females were dosed from day 14 before mating to day 3 of lactation. Control rats (10 males, 10 females) were dosed with distilled water.

None of the animals died, and there were no differences in histopathological findings or the following parameters between test and control animals: body weight, food consumption, hematology parameters, clinical chemistry parameters, and organ weights. However, transient hypolocomotion and hypopnea (slight clinical signs) were observed in females that received 1,000 mg/kg doses. No observable effect levels (NOELs) for repeat dose toxicity were 1,000 mg/kg/day (males) and 200 mg/kg/day (females). The no observable adverse effect level (NOAEL) was 200 mg/kg body weight/day in this study. [25] The estimated dose of low concern (EDCL) for this study was calculated as 0.2 mg/kg/day.[7]

Propylene Glycol

Little or no toxicity was observed in short-term oral tests on PG inolving mice, dogs and cats. Dogs received 3.0 ml/kg doses of undiluted PG over a 3- day period, and cats received 12% PG in the diet for 5 weeks and 41% PG in the diet for 22 days. Mice received up to 10% PG in drinking water for 14 days.

Short-Term Intravenous Toxicity

Propylene Glycol

Short-term i.v. dosing with PG resulted in little toxicity in rats. Groups of rats received i.v. infusions of PG/ethanol/water (5:1:4) over a 2-week period.

Repeated Dose Toxicity

1,2-Butanediol

CIR is aware of a report by BIBRA that contains oral toxicity data (multiple doses) on 1,2-butanediol.[22] This report was ordered from the National Technical Information Service (NTIS).

Subchronic Inhalation Toxicity

Propylene Glycol

Subchronic inhalation data reported some effects due to PG administration, but these effects were inconsistent and without dose-response trends. Rats were exposed (nose-only) to PG at concentrations up to 22 mg/liter of air for 13 weeks.

Subchronic Oral Toxicity

Pentylene Glycol

Pentylene glycol was administered orally to rats, intermittently over a 28-week period. A TDLo of 2,450mg/kg was reported.[20] Efforts to obtain the primary reference for this study are underway.

Propylene Glycol

No toxic effects were seen in a subchronic oral toxicity studies in which rats were fed 50,000 PG in the diet for 15 weeks, and dogs received 5% PG in drinking water for 9 months and 10% PG in drinking water for 6 months.

Chronic Oral Toxicity

Propylene Glycol

No toxic effects were reported when rats or dogs were given feed containing PG in chronic studies. Rats received up to 50,000 ppm PG in the diet for 104 weeks, and, in another study, dogs received 2 g/kg PG in the diet for 104 weeks.

Cytotoxicity

The cytotoxicity of cetyl glycol (130 µg/ml), lauryl glycol (99 µM*), and pentylene glycol (5%) has been demonstrated in vitro. Marked antitumor effects were observed in mice in vivo following i.p. doses of 80 mg/kg/day*.

Cetyl Glycol

In an antitumor activity test, 1,2-hexadecanediol (cetyl glycol) was injected intraperitoneally (i.p.) into 8 inbred C57BL/6 mice in which Ehrlich ascites carcinoma (EAC) cells had been implanted. Doses of 80/mg/kg/day were injected for 10 consecutive days. The survival of mice was monitored over a 2-month period. Compared to control mice, dosing with cetyl glycol prolonged the lifespan of animals more than 2.7-fold. Antitumor effects were described as marked, in that 4 of 8 mice injected were alive, with scarce tumor proliferation, at 60 days. Cetyl glycol (130 µg/ml) was found to have a cytocidal effect (irreversible cell degeneration) on cultured EAC cells.[26]

Lauryl Glycol

Osorio e Castro et al.[27] studied hemolysis rates (at 37ºC) of human erythrocytes induced by C_2 and C_8-C_{14} straight chain 1-alkanols, 1,2-alkanediols, and the corresponding benzilidene derivatives (benzaldehyde acetals). The most active compound was 1-dodecanol (50% hemolysis at 15 µM), followed by 1,2-dodecanedol (lauryl glycol, 50% hemolysis at 99 µM) and the C_{10} benzylidene acetal (50% hemolysis at 151 µM).

Pentylene Glycol

Anselmi et al.[28] conducted an *in vitro* DNA fragmentation assay (human promyelocytic leukemia cell line [HL60]) to investigate the apoptosis- and necrosis-inducing potential of brief, 10 min applications of the preservative, pentylene glycol (between 0.01 and 5% [usual concentration as a preservative]). Cells treated with phosphate buffered saline served as controls. The percentage of apoptotic cells was quantified by analysis of DNA content. Pentylene glycol induced apoptosis only at a concentration of 5%. Externalization of phosphatidyl serine, a hallmark of apoptosis, was concomitant with the subdiploid DNA peak in HL60 cells treated with pentylene glycol.

Ocular Irritation

Based on Draize test results, lauryl glycol has been classified as a severe ocular irritant.

Lauryl Glycol

According to Worth and Cronin,[29] the European Union has classified 1,2-dodecanediol (lauryl glycol) as a severe ocular irritant. The European classification system has allowed 2 classes of acute eye toxicity, R36 for moderate irritants and R41 for severe irritants, and th Draize eye test has been used for the identification of R41 chemicals. Actual Draize test results for lauryl glycol were not included.

1,2-Butanediol

CIR is aware of a report by BIBRA that contains ocular irritation data on 1,2-butanediol.[22] This report was ordered from the National Technical Information Service (NTIS).

Propylene Glycol

PG (0.1 ml, pH 8.8) was a slight ocular irritant in rabbits in one study, but PG (0.1 ml, pH unknown) did not induce ocular irritation in another study involving rabbits.

Skin Irritation and Sensitization

Propylene Glycol

PG (concentration not stated) was at most a mild dermal irritant in a Draize test using rabbits with intact and abraded skin. No reactions were observed with guinea pigs or Gottingen swine. Using nude mice, hypertrophy, dermal inflammation and proliferation were observed with 50% PG. These effects were not seen in hairless mice with undiluted PG. PG was negative in a number of sensitization assays.

Cross Reactivity

There was no evidence of cross reactivity between antipanaxytriol antibody and decylene glycol.

Decylene Glycol

Saita et al.[30] studied the cross reactivities of antipanaxytriol antibody with panaxytriol analogues using the enzyme-linked immunosorbent assay (ELISA). Panaxytriol is an antitumor polyacetylenic alcohol that has been isolated from the roots of *Panax ginseng* C. A. Meyer. The antibody had a high affinity for 1,16-heptadecadiene-4,6-diyne-3,9,10-triol, which is structurally different from panaxytriol only in the C-16,17 positions. The antibody had very limited reactivity with the other panaxytriol analogues, which are different only in the D9,10 positions. No reactivity was found between the antibody and a 1,2-decanediol (decylene glycol). The authors noted that these results indicate that the antibody recognition sites are both the glycol and moiety and the diacetylene moiety of the panaxytriol molecule.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

An NOAEL of 1,000 mg/kg for reproductive/developmental toxicity has been reported for 1,2-butanediol in rats dosed orally.

1,2-Butanediol

The test procedure for the combined repeated dose and reproductive/developmental toxicity study (Crj-CD(SD) rats) and results relating to oral toxicity are included in the Short-Term Oral Toxicity section earlier in the report text. All of the animals were killed on day 4 of lactation. Neither effects on reproduction (copulation, implantation, pregnancy, parturition, or lactation) nor developmental toxicity effects on offspring were observed. The NOAEL was 1,000 mg/kg for parental animals and the F_1 generation.[25] The estimated dose of low concern (EDCL) for this study was calculated as 10 mg/kg/day.[7]

Propylene Glycol

PG did not have any adverse reproductive or developmental effects when evaluated in mice (doses of 1.69 and 10.1 g/kgday), rats (1.69 g/kg/day), rabbits (1.23 g/kg/day), or hamsters (1.55 g/kg/day) in vivo. In the original safety assessment, embryonic development was reduced or inhibited completely in cultures of mouse zygotes exposed to 3.0 or 6.0 M PG, respectively. A study examining induction of cytogenetic aberrations found an increase in the frequency of premature centrosphere separation (PCS) with PG (1.3 to 5.2 g/kg i.p.). In zygotes from PG-dosed mice, hyperploidy was increased (1.3 to 5.2 g/kg i.p.).

GENOTOXICITY

1*,2-Butatnediol was not genotoxic in assays involving bacterial cells (doses up to 5,000µg/plate) or mammalian cells (doses up to 0.9 mg/ml)*.

1,2-Butanediol

1.2-Butanediol was not mutagenic to *Salmonella typhimurium* strains TA100, TA98, TA97, and TA102 at doses up to 5,000 µg/plate with or without metabolic activation. The test substance also induced neither chromosomal aberrations nor polyploidy in Chinese hamster CHL cells at doses up to 0.9 mg/ml either with or without metabolic activation.[31]

Propylene Glycol

PG was not mutagenic in Ames tests with or without metabolic activation (doses up to 10 mg/plate). PG was a weak inducer of sister chromatid exchanges (SCEs), causing a dose-dependent (up to 22.83 mg/ml) increase in SCEs in a Chinese hamster cell line. However in another SCE assay using human cultured fibroblasts and Chinese hamster cells with and without metabolic activation, PG was not mutagenic (concentration not stated). PG (32 mg/ml) induced chromosomal aberrations in a Chinese hamster fibroblast line, but not in human embryonic cells (PG concentration not stated). PG (concentration not stated) was not mutagenic in mitotic recombination or base pair substitution assays or in a micronucleus test or a hamster embryo cell transformation assay.

CARCINOGENICITY

Propylene Glycol

PG was not carcinogenic in a study in which rats were given ≤50 000 ppm PG in the diet. Dermal application of undiluted PG to Swiss mice in a lifetime study produced no significant carcinogenic effects. PG was not carcinogenic in other oral, dermal, and subcutaneous studies (concentrations not stated).

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation and Sensitization

A 1,2-hexanediol/caprylyl glycol mixture (in preservative system) did not induce sensitization at a concentration of 0.5% or 15% in human subjects.

Caprylyl Glycol and 1,2-Hexanediol

Levy et al.[32] studied the potential for delayed type IV dermal sensitivity following exposure to a new preservative system containing 1,2-hexanediol and caprylyl glycol. In a repeat insult patch test, a 15% mixture of 1,2-hexanediol and caprylyl glycol (equal parts of the 2 ingredients) in carbomer gel (total volume = 20 µl) was applied to each of 205 subjects (163 females, 42 males; 18 to 70 years old). The mixture was applied under 48 h occlusive patches (Finn chambers) during induction and challenge phases. Challenge application involved a new test site and reactions were scored at 48 and 72 h post-application according to the following scale: + (definite erythema without edema) to +++ (definite erythema, edema, and vesiculation). One of the subjects had a D reaction (damage to the epidermis: oozing, crusting, and/or superficial erosions) to the mixture; however, no reactions were observed in a subsequent 4-day repeat open application test. The reaction observed was indicative of irritation.

A cosmetic formulation containing the same preservation system (gel vehicle) at an actual use concentration (0.5%) was evaluated in an additional group of 224 subjects (176 females, 48 males; 19 to 70 years old) according to the same test procedure. None of the subjects had a delayed type IV dermal reaction.[32]

Propylene Glycol

PG induced skin irritation reactions in normal subjects and in patients. Reactions were observed at concentrations as low as 10% in predictive tests and 2% in provocative tests. Use studies of deodorants containing 35-73% PG did not report any potential for eliciting irritation or sensitization. PG generally did not induce sensitization reactions when tested at 12-86%. In a modified Draize sensitization study with 203 subjects, PG induced 19 cutaneous reactions at challenge.

Case Reports

Positive reactions were observed in a patient patch tested with 0.5% and 5% 1,2-pentylene glycol, but not in the control group.

Pentylene Glycol (1,2-Pentanediol)

A 68-year-old, non-atopic female developed facial dermatitis after using an eye cream that contained pentylene glycol (1,2-pentanediol), and patch test results were positive. Positive patch test reactions (+1) to 0.5% and 5% aqueous pentylene glycol were also reported. Except for one control subject with a follicular reaction to 5% pentylene glycol, reactions to 0.5% and 5.0% aqueous pentylene glycol were negative in a control group of 29 subjects.[33]

SUMMARY

The sixteen 1,2-glycols included in this safety assessment function mostly as skin and hair conditioning agents and viscosity increasing agents in personal care products, and the following 4 are reported as being used: caprylyl glycol, pentylene glycol, 1,2-hexanediol, and C15-18 glycol.

Safety test data from the CIR safety assessment on propylene glycol have been reviewed and should be considered relevant to the safety assessment of other 1,2-glycols included in this report, based on structural similarities.

The Environmental Protection Agency (EPA) lists 1,2-butanediol as one of the reactive compounds in aerosol coatings (i.e., aerosol spray paints) that contributes to ozone (O_3) formation. Esterified butanediol (1,2- or 1,3- not specified) is used in the production of resinous and polymeric coatings that comprise the food contact surface of packaged food products.

Stearyl glycol has been prepared via the reaction of 2-hydroxyoctadecanoic acid with lithium aluminum hydride in dry tetrahydrofuran, and the production of 1,2-butanediol is via a continuous reaction and distillation operation. The available impurities data indicate that 1,2-butanediol is $\geq$ 99% pure and also contains water, 1,4-butanediol, and 1-acetoxy-2-hydroxybutane.

Information on the absorption, distribution, metabolism, excretion of the ingredients reviewed in this safety assessment were not identified in the published literature. However, the available octanol/water partitition coefficients on 1,2-glycols are being considered in the absence of percutaneous absorption data.

The skin penetration enhancement effect of caprylyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol has been demonstrated *in vitro*.

Acute oral toxicity data on caprylyl glycol and other 1,2-glycols for which data are available suggest that death would occur at relatively high doses, and the same is true for 1,2-butanediol and pentylene glycol when administered i.p. In an i.p. dosing study in which ED_3 values for caprylyl glycol (1,2-octanediol), pentylene glycol (1,2-propanediol), and 1,2-butanediol were compared, caprylyl glycol had the lowest ED_3 value (1.5 mmole/kg), suggesting that its intoxication potency (i.e., ability to induce ataxia) was greatest.

Short-term oral administration of 1,2-butanediol to rats yielded an NOAEL of 200 mg/kg/day. Intermittent oral administration of pentylene glycol to rats over a 28-week period yielded a TDLo of 2,450mg/kg. The cytotoxicity of lauryl glycol (99 µM) and pentylene glycol (5%) has been demonstrated *in vitro*.

Based on Draize test results, lauryl glycol has been classified as a severe ocular irritant. There was no evidence of cross reactivity between antipanaxytriol antibody and decylene glycol.

An NOAEL of 1,000 mg/kg for reproductive/developmental toxicity has been reported for 1,2-butanediol in rats dosed orally. 1,2-Butatnediol was not genotoxic in assays involving bacterial or mammalian cells, and cetyl glycol (130 µg/ml) had a cytocidal effect on cultured Ehrlich ascites carcinoma cells. Marked antitumor effects of cetyl glycol were observed in mice *in vivo* following i.p. doses of 80 mg/kg/day.

A 1,2-hexanediol/caprylyl glycol mixture (in preservative system) did not induce sensitization at a concentration of 0.5% or 15% in human subjects. In a case report, positive reactions were observed in a patient patch tested with 0.5% and 5% 1,2-pentylene glycol, but not in the control group.

Table 1. Caprylyl Glycol and Other 1,2-Glycols[3]

Chemical Names/CAS Nos.	Functions in Cosmetics
Arachidyl Glycol 1,2-Eicosanediol; CAS No. 39825-93-9	Viscosity Increasing Agents - Aqueous; Viscosity Increasing Agents - Nonaqueous
Cetyl Glycol 1,2-Dihydroxyhexadecane; 1,2-Hexadecanediol; 1,2-Hexadecylene Glycol; 2-Hydroxycetyl Alcohol; CAS No. 6920-24-7	Hair Conditioning Agents; Skin-Conditioning Agents - Emollient; Viscosity Increasing Agents - Aqueous; Viscosity Increasing Agents - Nonaqueous
Hexacosyl Glycol	Skin-Conditioning Agents - Emollient; Viscosity Increasing Agents - Nonaqueous
Lauryl Glycol 1,2-Dihydroxydodecane; 1,2-Dodecanediol; 1,2-Dodecylene Glycol; CAS No. 1119-87-5	Hair Conditioning Agents; Skin-Conditioning Agents - Emollient
Myristyl Glycol 1,2-Tetradecanediol; CAS No. 21129-09-9	Hair Conditioning Agents; Skin-Conditioning Agents - Emollient; Surfactants - Foam Boosters; Viscosity Increasing Agents - Aqueous
Octacosanyl glycol 1,2-Octacosanediol; CAS No. 97338-11-9	Emulsion Stabilizers; Viscosity Increasing Agents - Nonaqueous
Stearyl Glycol 1,2-Dihydroxyoctadecane; 1,2-Octadecanediol; CAS No. 20294-76-2	Emulsion Stabilizers; Skin-Conditioning Agents - Emollient; Viscosity Increasing Agents - Nonaqueous
Caprylyl Glycol Capryl Glycol; 1,2-Dihydroxyoctane; 1,2-Octanediol; 1,2-Octylene Glycol; CAS No. 1117-86-8	Hair Conditioning Agents; Skin-Conditioning Agents - Emollient
Decylene Glycol 1,2-Decanediol; CAS No. 1119-86-4	Skin-Conditioning Agents - Miscellaneous
Pentylene Glycol 1,2-Dihydroxypentane; 1,2-Pentanediol; CAS No. 5343-92-0	Skin-Conditioning Agents - Miscellaneous; Solvents
1,2-Butanediol 1,2-Butylene Glycol; 1,2-Dihydroxybutane; CAS No. 584-03-2	Skin-Conditioning Agents - Humectant; Solvents; Viscosity Decreasing Agents
1,2-Hexanediol 1,2-Dihydroxyhexane; CAS No. 6920-22-5	Solvents
C14-18 Glycol Ethylene Glycol Fatty Acid Ester (2)	Emulsion Stabilizers; Skin-Conditioning Agents - Emollient
C15-18 Glycol Alkylene (15-18) Glycol; Cetyl Stearyl Vicinal Glycol; Glycols, C15-18; CAS Nos. 70750-40-2 and 92128-52-4	Emulsion Stabilizers; Skin-Conditioning Agents - Emollient
C18-30 Glycol Ethylene Glycol Fatty Acid Ester (1)	Emulsion Stabilizers; Skin-Conditioning Agents - Emollient
C20-30 Glycol Alkylene (20-30) Glycol	Emulsion Stabilizers; Skin-Conditioning Agents - Occlusive

Table 2. Chemical and Physical Properties

Property	Values	Reference
Arachidyl Glycol		
Molecular weight	314.55	ACD/Labs[34]
Molar volume	354.0 ± 3.0 cm^3/mole (20°C, 760 Torr)	″
Density	0.888 ± 0.6 g/cm^3 (20°C, 760 Torr)	″
Mass intrinsic solubility	0.000000063 g/l (25°C)	″
Mass solubility	0.000000063 g/l (pH 7, 25°C)	″
Molar intrinsic solubility	0.00000000020 mol/l (25°C)	″
Molar solubility	0.00000000020 mol/l (pH 7, 25°C)	″
Melting point	84.3 to 84.8°C	″
Boiling point	435.2 ± 18.0°C (760 Torr)	″
Flash point	183.7 ± 15.8°C	″
Enthalpy of vaporization	79.83 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	2.11E-09 Torr	″
pKA	14.19 ± 0.20 (25°C)	″
logP	7.692 ± 0.216 (25°C)	″
Cetyl glycol		
Molecular weight	258.44	ACD/Labs[34]
Molar volume	288.0 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.897 ± 0.06 g/cm^3 (20°C, 760 Torr)	″
Mass intrinsic solubility	0.000067 g/l (25°C)	″
Mass solubility	0.000067 g/l (pH 7, 25°C)	″
Molar intrinsic solubility	0.00000026 mol/l (25°C)	″
Molar solubility	0.00000026 mol/l (pH 7, 25°C)	″
Melting point	75 to 76°C (not calculated)	Bryun[35]
Boiling point	356.1 ± 10.0°C (760 Torr)	ACD/Labs[34]
Flash point	151.9 ± 13.6°C	″
Enthalpy of vaporization	69.61 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	1.69E-06 Torr (25°C)	″
pKA	14.19 ± 0.20 (25°C)	″
logP	5.567 ± 0.216 (25°C)	″
Lauryl glycol		
Molecular weight	202.33	ACD/Labs[34]
Molar volume	222.0 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.911 ± 0.06 g/cm3 (20°C, 760 Torr)	″
Refractive index	1.4558 (20°C, λ = 589.3 nm)	″
Mass intrinsic solubility	0.028 g/l (25°C)	″
Mass solubility	0.028 g/l (pH 7, 25°C)	″
Molar intrinsic solubility	0.00014 mol/l (25°C)	″
Molar solubility	0.00014 mol/l (pH7, 25°C)	″
Melting point	60 to 61°C (not calculated)	Swern[36]
Boiling point	179 to 181°C (4 Torr) – not calculated; 304.3 ± 10°C (760 Torr)	″
Flash point	134.3 ± 13.6 °C	″
Enthalpy of vaporization	63.17 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	8.40E-05 Torr	″
pKA	14.19 ± 0.20 (25°C)	″
logP	3.441 ± 0.216 (25°C)	″

Table 2. Chemical and Physical Properties

Property	Values	Reference
Myristyl glycol		
Molecular weight	230.39	ACD/Labs[34]
Molar volume	255.0 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.903 ± 0.06 g/cm^3 (20°C, 760 Torr)	″
Mass intrinsic solubility	0.0015 g/l (25°C)	ACD/Labs[34]
Mass solubility	0.0015 g/l (pH 7, 25°C)	″
Molar intrinsic solubility	0.0000067 mol/l (25°C)	″
Molar solubility	0.0000067 mol/l (pH 7, 25°C)	″
Melting point	68 to 68.5 °C	″
Boiling point	152 to 154 °C (0.2 Torr); 333.1 ± 10.0°C (760 Torr)	″
Flash point	143.8 ± 13.6 °C	″
Enthalpy of vaporization	66.48 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	1.16E-05 Torr (25°C)	″
pKA	14.19 ± 0.20 (25°C)	″
logP	0.4504 ± 0.216 (25°C)	″
Octacosanyl Glycol		
Molecular weight	426.76	ACD/Labs[34]
Molar volume	486.1 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.877 ± 0.06 g/cm^3 (20°C, 760 Torr)	″
Mass intrinsic solubility	0.0000032 g/l (25°C)	″
Mass solubility	0.0000032 g/l (pH 7, 25°C)	″
Molar intrinsic solubility	0.0000000076 mol/l (25°C)	″
Molar solubility	0.0000000076 mol/l (pH 7, 25°C)	″
Boiling point	536.3 ± 23.0°C (760 Torr)	″
Flash point	210.9 ± 17.2°C	″
Enthalpy of vaporization	93.49 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	9.74E-14 Torr (25°C)	″
pKA	14.19 ± 0.20 (25°C)	″
logP	11.943 ± 0.217 (25°C)	″
Stearyl Glycol		
Molecular weight	286.49	ACD/Labs[34]
Molar volume	321.0 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.892 ± 0.06 g/cm^3 (20°C, 760 Torr)	″
Mass intrinsic solubility	0.0000023 g/l (25°C)	″
Mass solubility	0.0000023 g/l (pH 7, 25°C)	″
Molar intrinsic solubility	0.0000000080 mol/l (25°C)	″
Molar solubility	0.0000000081 mol/l (pH 7, 25°C)	″
Melting point	79 to 79.5°C (not calculated)	Niemann[37]
Boiling point	377.2 ± 10.0°C (760 Torr)	ACD/Labs[34]
Flash point	157.6 ± 13.6°C	″
Enthalpy of vaporization	72.30 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	3.09E-07 Torr (25°C)	″
pKA	14.19 ± 0.20 (25°C)	″
logP	6.629 ± 0.216 (25°C)	″
Caprylyl Glycol		
Molecular weight	146.23	ACD/Labs[34]
Molar volume	155.9 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.937 ± 0.06 g/cm^3 (20°C, 760 Torr)	″

Table 2. Chemical and Physical Properties

Property	Values	Reference
Mass intrinsic solubility	4.2 g/l (25°C)	″
Mass solubility	4.4 g/l (pH 7, 25°C)	″
Molar intrinsic solubility	0.029 mol/l (25°C)	″
Molar solubility	0.030 mol/l (pH 7, 25°C)	″
Melting point	36 to 37°C (not calculated)	Fringuelli[38]
Boiling point	137 to 139°C (not calculated); 243.0 ± 8.0°C (760 Torr)	Mugdan[39]
Flash point	109.1 ± 13.0°C	ACD/Labs[34]
Enthalpy of vaporization	55.78 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	5.59E-03 Torr	″
pKA	14.31 ± 0.10 (25°C)	″
logP	1.316 ± 0.215 (25°C)	″
Decylene Glycol		
Molecular weight	174.28	STN[9]
Molar volume	188.9 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.922 ± 0.06 g/cm^3 (20°C, 760 Torr)	″
Mass intrinsic solubility	0.40 g/l (25°C)	″
Mass solubility	0.40 g/l (pH 7, 25°C)	″
Molar intrinsic solubility	0.0023 mol/l (25°C)	″
Molar solubility	0.0023 mol/l (pH 7, 25°C)	″
Melting point	48-49°C	Swern[36]
Boiling point	93 to 96°C (0.5 Torr) - not calculated; 255.0 ± 0.0°C (760 Torr)	Orito[40]
Flash point	122.4 ± 13.0°C	ACD/Labs[34]
Enthalpy of vaporization	57.21 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	2.54E-03 Torr (25°C)	″
pKA	14.21 ± 0.20 (25°C)	″
logP	2.378 ± 0.216 (25°C)	″
Pentylene Glycol		
Molecular weight	104.15	ACD/Labs[34]
Molar volume	106.4 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.9723 g/cm^3 (20°C) – not calculated; 0.978 ± 0.06 g/cm^3 (20°C, 760 Torr)	Clendenning[41]
Refractive index	1.4400 (20°C, λ = 589.3 nm) – not calculated	Emmons[42]
Mass intrinsic solubility	95 g/l (25°C)	ACD/Labs[34]
Mass solubility	95 g/l (pH 7, 25°C)	″
Molar intrinsic solubility	0.91 mol/l (25°C)	″
Molar solubility	0.91 mol/l (25°C)	″
Boiling point	78 to 80°C (0.3 Torr) – not calculated ; 206.0 ± 0.0°C (760 Torr)	Clendenning[41]; Emmons[42]
Flash point	104.4 ± 0.0°C	ACD/Labs[34]
Enthalpy of vaporization	51.45 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	5.75E-02 Torr (25°C)	″
pKA	14.22 ± 0.20 (25°C)	″
logP	-0.278 ± 0.215 (25°C)	″
1,2-Butanediol		
Molecular weight	90.12	ACD/Labs[34]
Molar volume	89.9 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	1.0205 g/cm^3 (20°C) – not calculated; 1.001 ±	Mamedov[43];

Table 2. Chemical and Physical Properties

Property	Values	Reference
	0.06 g/cm^3 (20°C)	Tishchenko[44]
Refractive index	1.4380 (20°C, λ = 589.3 nm)	ACD/Labs[34]
Mass intrinsic solubility	230 g/l (25°C)	″
Solubility	Very soluble in water	NIOSH[11]
Mass solubility	230 g/l (pH 7, 25°C)	ACD/Labs[34]
Molar intrinsic solubility	2.55 mol/l (25°C)	″
Molar solubility	2.55 mol/l (pH 7, 25°C)	″
Melting point	-50°C and -114°C (not calculated)	STN[9]
Boiling point	132 to 133°C (760 Torr) – not calculated; 190.3 ± 8.0°C (760 Torr)	Clendenning[41]; Hill[45]
Flash point	93.3 ± 0.0°C	ACD/Labs[34]
Enthalpy of vaporization	49.64 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	1.48E-01 Torr 10 (20ºC)	″ NIOSH[11]
pKA	14.27 ± 0.20 (25°C)	STN[9]
logP	-0.810 ± 0.215 (25°C)	″
Stability	Stable in neutral, acidic, or alkaline solutions	OECD[7]
Half life	≥ 1 year (25ºC; pH: 4, 7, and 9)	″
1,2-Hexanediol		
Molecular weight	118.17	ACD/Labs[34]
Molar volume	122.9 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.961 ± 0.06 g/cm^3 (20°C)	″
Refractive index	1.4518 (25°C, λ = 589.3 nm) – not calculated	Zelinski[46]
Mass intrinsic solubility	37 g/l (25°C)	ACD/Labs[34]
Mass solubility	37 g/l (pH7, 25°C)	″
Molar intrinsic solubility	0.31 mol/l (25°C)	″
Molar solubility	0.31 mol/l (pH 7, 25°C)	″
Melting point		″
Boiling point	112 to 113°C (12 Torr) – not calculated; 223.5 ± 0.0°C (760 Torr)	Lapporte[47]
Flash point	95.8 ± 13.0°C	″
Enthalpy of vaporization	53.48 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	1.94E-02 Torr	″
pKA	14.22 ± 0.20 (25°C)	″
logP	0.253 ± 0.215 (25°C)	″

Table 3. Current Cosmetic Product Uses[12] and Concentrations of 1,2-Glycols[48]

Product category	2009 uses (total number of products in category)	2010 concentrations
caprylyl glycol		
Baby products		
Shampoos	2 (56)	
Lotions, oils, powders, and creams	2 (137)	
Other	5 (143)	
Bath Products		
Oils, Tablets, and Salts	6 (314)	
Bubble Baths	3 (169)	
Soaps and Detergents	24 (1,665)	
Other	6 (234)	
Eye makeup		
Eyebrow pencil	1 (144)	
Eyeliner	7 (754)	
Eye shadow	25 (1,215)	
Eye lotion	39 (254)	
Eye makeup remover	4 (128)	
Mascara	35 (499)	
Other	19 (365)	
Fragrance products		
Powders	5 (666)	
Other	11 (566)	
Noncoloring hair care products		
Conditioners	6 (1,226)	
Rinses	2 (33)	
Shampoos	2 (1,361)	
Tonics, dressings, etc.	12 (1,205)	
Other	6 (807)	
Hair coloring products		
Other	2 (168)	
Makeup		
Blushers	21 (434)	
Face powders	35 (661)	
Foundations	27 (589)	
Lipstick	114 (1,883)	
Makeup bases	4 (117)	
Other	21 (485)	
Nail care products		
Creams and Lotions	1 (14)	
Personal Cleanliness Products		
Deodorants (underarm)	26 (580)	
Other	21 (792)	
Shaving products		
Aftershave lotion	9 (367)	
Shaving cream	2 (122)	
Other	3 (134)	
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	67 (1,446)	
Face and neck lotions	104 (1,583)	
Body and hand lotions	115 (1,744)	
Foot powders and sprays	2 (47)	
Moisturizers	167 (2,508)	
Night creams and lotions	38 (353)	
Paste masks (mud packs)	26 (441)	

Table 3. Current Cosmetic Product Uses[12] and Concentrations of 1,2-Glycols[48]

Product category	2009 uses (total number of products in category)	2010 concentrations
Skin fresheners	5 (259)	
Other	41 (1,308)	
Suntan products		
Indoor tanning preparations	8 (240)	
Other	4 (62)	
Total uses/ranges for caprylyl glycol	1084	
Pentylene glycol		
Bath products		
Bubble baths	1 (169)	
Other	2 (234)	
Soaps and detergents	16 (1,665)	
Eye makeup		
Eyeliner	3 (754)	
Eye shadow	8 (1,215)	
Eye lotion	30 (254)	
Eye makeup remover	4 (128)	
Mascara	5 (499)	
Other	15 (365)	
Fragrance products		
Cologne and toilet waters	1 (1,377)	
Other	2 (566)	
Noncoloring hair care products		
Conditioners	3 (1,226)	
Shampoos	2 (1,361)	
Tonics, dressings, etc.	6 (1,205)	
Other	1 (807)	
Makeup		
Blushers	1 (434)	
Face powders	6 (661)	
Foundations	22 (589)	
Lipstick	4 (1,883)	
Makeup bases	1 (117)	
Makeup fixatives	2 (45)	
Other	2 (485)	
Personal hygiene products		
Deodorants (underarm)	3 (580)	
Other	5 (792)	
Shaving products		
Other	4 (134)	
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	34 (1,446)	
Face and neck lotions	88 (1,583)	
Body and hand lotions	39 (1,744)	
Foot powders and sprays	1 (47)	
Moisturizers	95 (2,508)	
Night creams and lotions	13 (353)	
Paste masks (mud packs)	10 (441)	
Skin fresheners	12 (259)	
Other	54 (1,308)	
Suntan products		
Indoor tanning preparations	10 (240)	
Other	1 (62)	
Total uses/ranges for pentylene glycol	506	

Table 3. Current Cosmetic Product Uses[12] and Concentrations of 1,2-Glycols[48]

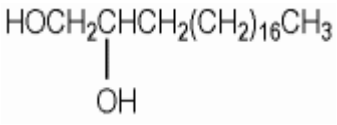
Product category	2009 uses (total number of products in category)	2010 concentrations
1,2-hexanediol		
Baby products		
Shampoos	1 (56)	
Lotions, oils, powders, and creams	2 (137)	
Bath products		
Soaps and detergents	3 (1,665)	
Other	1 (234)	
Eye makeup		
Eye shadow	2 (1,215)	
Eye lotion	4 (254)	
Eye makeup remover	2 (128)	
Mascara	12 (499)	
Other	3 (365)	
Makeup		
Face powders	1 (661)	
Foundations	2 (589)	
Lipstick	16 (1,883)	
Other	1 (485)	
Personal hygiene products		
Deodorants (underarm)	3 (580)	
Other	7 (792)	
Shaving products		
Aftershave lotion	2 (367)	
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	14 (1,446)	
Face and neck lotions	11 (1,583)	
Body and hand lotions	4 (1,744)	
Moisturizers	22 (2,508)	
Night creams and lotions	4 (353)	
Paste masks (mud packs)	2 (441)	
Skin fresheners	1 (259)	
Other	4 (1,308)	
Total uses/ranges for 1,2-hexanediol	124	
C15-18 glycol		
Makeup		
Other	1 (485)	
Total uses/ranges for C15-18 glycol	1	

Table 4. Corticosterone and TEA Permeability Coefficients in the Presence of Permeation Enhancers[10]

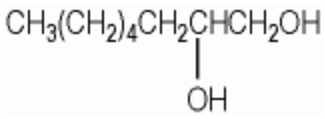
Enhancer	Enhancer Concentration (M)	Permeability Coefficient of CS[α] (cm/s x 10^7)	Permeability Coefficient of TEA[α] (cm/s x 10^8)
PBS – control		2.2 ± 0.8	1.35 ± 0.65
Caprylyl glycol (1,2-octanediol)	0.005	6.2 ± 1.1	
	0.0104	7.4 ± 1.4	4.2 ± 1.3
	0.02	30 ± 3	12 ± 8
	0.024	27 ± 9	20 ± 5
	0.035	110 ± 10	
Decylene glycol (1,2-decanediol)	0.0006	5 ± 1	
	0.001	11 ± 3	4.7 ± 2.1
	0.00141	28 ± 7	
	0.00192	80 ± 20	7.1 ± 0.7
	0.0024	110 ± 1	63 ± 16
1,2-hexanediol	0.09	6.5 ± 2.7	
	0.145	13 ± 3	2 ± 1
	0.25	23 ± 5	
	0.35	65 ± 23	9.2 ± 4.1

[α]Mean ± SD (n = 3)

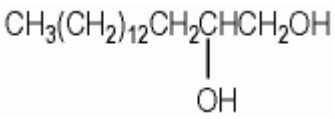
Figure 1. Formulas of 1,2-glycols



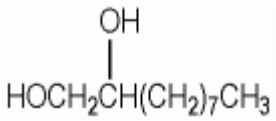
Arachidyl Glycol



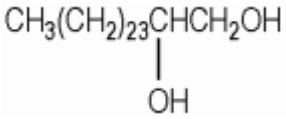
Caprylyl Glycol



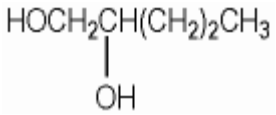
Cetyl Glycol



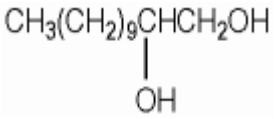
Decylene Glycol



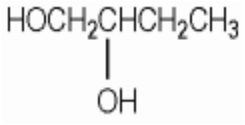
Hexacosyl Glycol



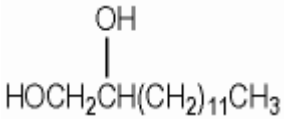
Pentylene Glycol



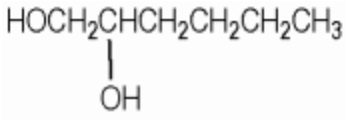
Lauryl Glycol



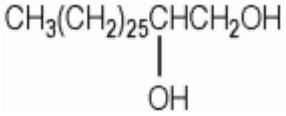
1,2-Butanediol



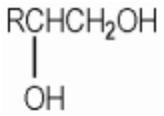
Myristyl Glycol



1,2-Hexanediol

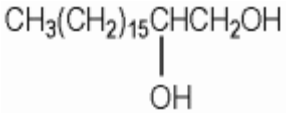


Octacosanyl Glycol



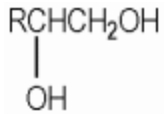
C14-18 Glycol

(wherein R is C12-C16)



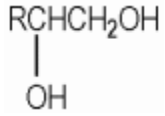
Stearyl Glycol

Figure 1. Formulas of 1,2-glycols



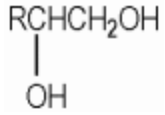
C15-18 Glycol

(wherein R is C13-C16)



C18-30 Glycol

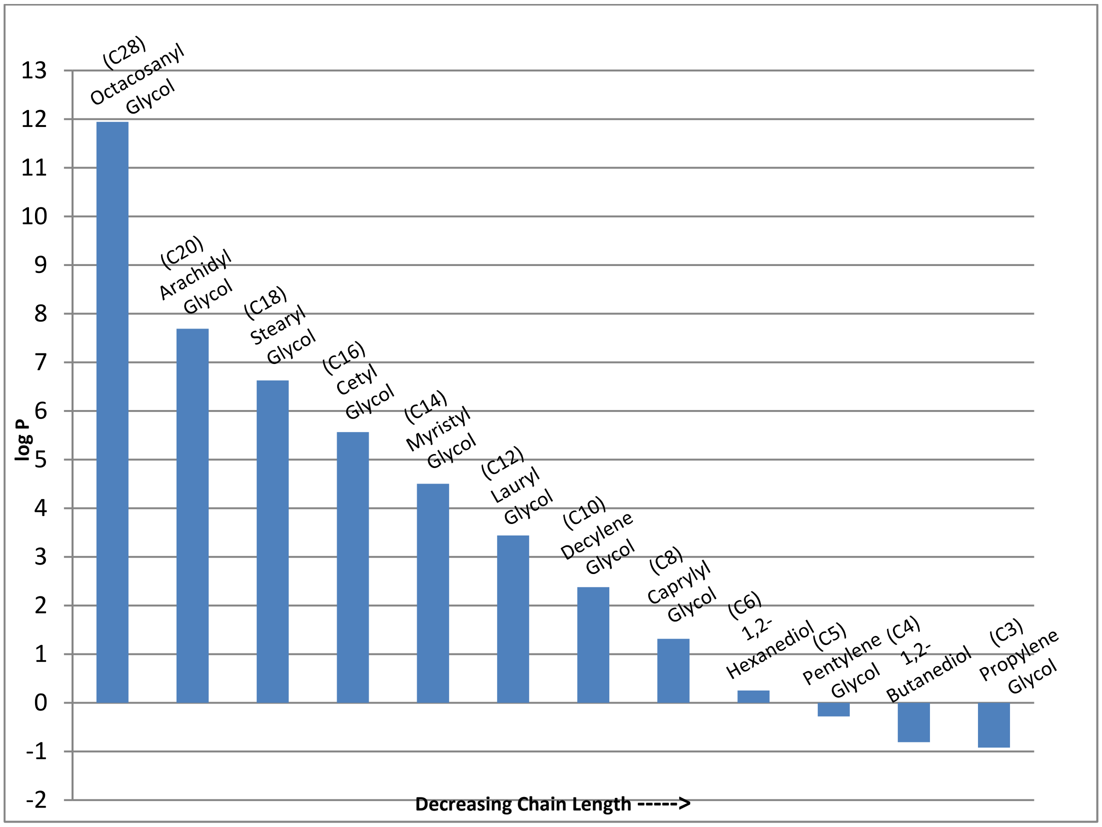
(wherein R is C16-C28)



C20-30 Glycol

(wherein R is C18-C28)

Figure 2. Octanol/Water Partitioning Coefficient (log P)



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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: John Bailey, Ph.D. 5/3/10
Industry Liaison to the CIR Expert Panel

DATE: May 3, 2010

SUBJECT: Comments on the Scientific Literature Review on Caprylyl Glycol and Other 1,2-Glycols

p.1 - It should state that the use information is from the FDA VCRP as the Council concentration of use survey has not yet been sent out. Council concentration of use information is not likely to be available until after the June 28-29, 2010 CIR Expert Panel meeting.

p.1 - Please update the conclusion for Propylene Glycol to the current tentative report. At the April, 2010 meeting, The CIR Expert Panel concluded that Propylene Glycol, Tripropylene Glycol and the PPG ingredients are safe in the present practices of use and concentration as described in this safety assessment when formulated to be nonirritating. In addition to adding ingredients, this report was opened to increase the use concentration.

p.3, 19, Table 5 - This "Table" is actually a figure, and should be given a title of Figure rather than Table.

p.4, 10 - What is meant by "not significant oral toxicants"? If this means that death occurs at relatively high doses, that is what should be stated. Ataxia in a human would be considered a significant effect.

p.5 - In the summary regarding Propylene Glycol, what is meant by "harmless"? In some studies, high doses caused convulsions. Is that harmless? Because the Propylene Glycol summary includes several routes of exposure, it should not be presented in the Acute Oral Exposure section. It would be helpful to provide the doses that resulted in effects.

p.6 - The 28-week study of Pentylene Glycol in rats should be moved to a Subchronic Oral Exposure section. Chronic studies are considered to be 1 year or longer.

p.6 - In the summary of the Cytotoxicity section, please include the concentrations or doses that were tested. The *in vivo* study of Cetyl Glycol should also be mentioned in the summary.

p.6 - What concentration of Cetyl Glycol "was found to have a cytocidal effect (irreversible cell degeneration) on cultured EAC cells"?

p.7 - If available, please provide the concentration of Lauryl Glycol tested in the Draize study reported by Worth and Cronin (2001).

p.7 - What concentration of Propylene Glycol was a slight ocular irritant?

p.7 - What concentration of Propylene Glycol was a mild dermal irritant?

p.8 - What doses of Propylene Glycol did not cause reproductive or developmental effects in mice, rats, rabbits or hamsters? What concentrations of Propylene Glycol increased the frequency of premature centrosphere separation? What dose increased hyperploidy in zygotes from Propylene Glycol treated mice?

p.8, 10 - Please include the doses/concentrations of 1,2-Butanediol that were not genotoxic.

p.8 - What concentrations of Propylene Glycol were not mutagenic?

p.8 - What doses of Propylene Glycol were not carcinogenic?

p.10 - What concentrations of Lauryl Glycol and Pentylene Glycol were cytotoxic?

p.10 - What doses of Cetyl Alcohol had a cytocidal effect on Ehrlich ascites carcinoma cells implanted in mice?

p.19, Table 4 - Did the study indicate which values were statistically different from controls?

p.22, Reference 4 - What is meant by REF?