Final Report of the Cosmetic Ingredient Review Expert Panel

On the Safety Assessment of

1,2-Glycols as Used in Cosmetics

June 28, 2011

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ABSTRACT: Caprylyl glycol and related 1,2-glycols are used mostly as skin and hair conditioning agents and viscosity agents in cosmetic products, and caprylyl glycol and pentylene glycol also function as cosmetic preservatives. The Expert Panel noted that these ingredients are dermally absorbed and that modeling data predict decreased skin penetration of longer-chain 1,2-glycols. The Panel concluded that negative oral toxicity data on shorter-chain 1,2-glycols and genotoxicity data support the safety of all of the 1,2-glycols reviewed in this safety assessment. Thus, it was concluded that these ingredients are safe in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

This report assesses the safety of 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, and caprylyl glycol and pentylene glycol are also used as preservatives. 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, 5 are being used in personal care products: caprylyl glycol, pentylene glycol, 1,2-hexanediol, and C15-18 glycol. The remaining 12 ingredients are not reported to be in current use.

A CIR final safety assessment on propylene glycol (PG), short-chain 1,2-glycol, and polypropylene glycols was published in 1994.[1,1] 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 June 28-29, 2010 meeting, the Expert Panel issued an amended final safety assessment on propylene glycol, tripropylene glycol, and polypropylene glycols with the following conclusion: The CIR Expert Panel concluded that propylene glycol, tripropylene glycol, PPG-3, -7, -9, -12, -13, -15, -16, -17, -20, -26, -30, -33, -34, -51, -52, -69, and any PPG ≥3, are safe as cosmetic ingredients in the present practices of use and concentration as described in this safety assessment when formulated to be non-irritating.[2]

In the absence of safety test data on many of the 1,2-glycols reviewed in this safety assessment, data on PG from both the CIR published final safety assessment and amended final safety assessment are included to support the safety of these ingredients in personal care products.

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 compounds that conform to a structure or formula. The fundamental carbon backbone contains a hydroxyl group at the 1 and 2 positions, and the length of the carbon backbone varies from one structure to another. 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. The solubility of these ingredients in water ranges from highly soluble (1,2-butanediol, octanol/water partition coefficient of -0.8) to poorly soluble (octacosanyl glycol, octanol/water partition coefficient of approximately 11.9).

No information on the chemical and physical properties of C14-18, C15-18, C18-30, and C20-30 glycols were found, but because these ingredients are mixtures of various length glycols, their chemical and physical properties are expected to reflect their individual components.

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 alkene 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]

Composition/Impurities

The heavy metals specification for > 98% caprylyl glycol (Dermosoft® Octiol) is 5 ppm max (as Pb).[8] Decylene glycol (as SymClariol®) contains 98% to 100% decylene glycol.[9] 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 spectrometry.[10,11] Decylene glycol has been analyzed via gas chromatography, and has been identified using mass, IR, and NMR spectroscopy**.** [11, 12] 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 spectrometry and IR or NMR spectroscopy. [11]

UV absorption data on caprylyl glycol or any of the other 1,2-glycols reviewed in this safety assessment were not provided or found in the published literature. Based on the chemical formulas included in Figure 1, there is no reason to suspect that any UV absorption would be associated with these 1,2-glycols.

Reactivity

For 1,2-butanediol at temperatures above 90°C, explosive vapor/air mixtures may be formed.[13] Additional information on the reactivity of 1,2-butanediol, in relation to the EPA-proposed national rule on the reduction of ozone formation, is included in the section on Noncosmetic Use later in the report text.

USE

Purpose In Cosmetics

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

Scope and Extent Of Use In Cosmetics

According to information supplied by industry as part of the Voluntary Cosmetic Registration Program (VCRP), obtained from the Food and Drug Administration (FDA) in 2011, the following ingredients were being used in personal care products: caprylyl glycol, decylene glycol, pentylene glycol, 1,2-hexanediol, and C15-18 glycol.[14] These data are summarized in Table 3. Independent of these data, the results of a survey of ingredient use concentrations that was conducted by the Personal Care Products Council in 2010, also in Table 3, indicate that three 1,2-glycols were being used at the following concentrations: caprylyl glycol (0.00003 to 5%), pentylene glycol (0.001 to 5%), and 1,2-hexanediol (0.00005 to 10%).[15] According to FDA's VCRP data, there was no indication that the following remaining ingredients in this safety assessment were being used in cosmetic products in 2011: arachidyl glycol, cetyl glycol, hexacosyl glycol, lauryl glycol, myristyl glycol, octacosanyl glycol, stearyl glycol, 1,2-butanediol, C14-18 glycol, C18-30 glycol, and C20-30 glycol.

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

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.[16]

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 the EPA proposal to amend the aerosol coatings reactivity rule by adding compounds and associated reactivity factors based on petitions that were received. The 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.[17]

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.[18]

Stearyl Glycol

Stearyl Glycol has been used as a surfactant (in octanol/water microemulsion) in a transdermal delivery system for the drug, 8-methoxypsoralen.[19]

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

Information on the metabolism, distribution, and excretion of 1,2-butanediol following i.v. dosing indicate that, in rabbits, this chemical is metabolized slowly and excreted in the urine either as the glucuronide or unchanged; there was no evidence of tissue accumulation. Metabolites were not identified in the urine of rabbits fed 1,2-butanediol in the diet. Based on metabolism modeling data on caprylyl glycol (1,2-octanediol), 1,2-hexanediol, decylene glycol(1,2-decanediol), and lauryl glycol (1,2-dodecanediol), it is likely that C-oxidation, C-hydroxylation, glucuronidation, and beta-oxidation may take place to form corresponding metabolites. C-hydroxylation and beta-oxidation are more likely to be favored metabolic pathways for the longer alkyl chain compounds, 1,2-decanediol and 1,2-dodecanediol, than for the shorter alkyl chain length compounds, 1,2-hexanediol and 1,2-octanediol.

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

A metabolism assessment for the following 1,2-glycols (C6 – C12) was provided by the Personal Care Products Council: caprylyl glycol (1,2-octanediol, C8), 1,2-hexanediol (C6), decylene glycol (1,2-decanediol, C10), and lauryl glycol (1,2-dodecanediol, C12).[20] Because metabolism database searches did not yield information on these four compounds, the possible metabolic fates of each were determined based on structural features, a substructure search, and a Meteor™ (9.0) metabolism prediction. The results of this assessment indicated that it is likely that *C*-oxidation, *C*-hydroxylation, glucuronidation, and beta-oxidation may take place to form corresponding metabolites. Furthermore, *C*-hydroxylation and beta-oxidation are more likely to be favored metabolic pathways for the longer alkyl chain compounds, 1,2-decanediol and 1,2-dodecanediol, than for the shorter alkyl chain length compounds, 1,2-hexanediol and 1,2-octanediol.

1,2-Butanediol

1,2-Butanediol was infused i.v. into rabbits at a dose of 1 g/kg body weight. Metabolism was described as slow, and 1,2-butanediol was excreted in the urine either as the glucuronide or unchanged.[21] Accumulation in the tissues was not observed. Metabolites were not isolated from the urine of rabbits fed 1,2-butanediol at a dose of 0.2 g/kg body weight.

Propylene Glycol

> The original 1994 CIR final safety assessment reported that, in mammals, the pathway of PG metabolism is to lactaldehyde and then lactate via hepatic alcohol and aldehyde dehydrogenases. When PG was administered i.v. to human subjects (patients), elimination from the body occurred in a dose-dependent manner.
> From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

Percutaneous Absorption

Dermal penetration of PG from a ternary cosolvent solution through hairless mouse skin was 57% over a 24 h period. Using thermal emission decay (TED)-Fourier transform infrared (FTIR) spectroscopy, it appeared that PG did not reach the dermis. After PG was applied dermally to the fingertip of a human subject, the concentration of PG remaining at the surface of the stratum corneum decreased over time. Following topical application of 5% caprylyl glycol in 70% ethanol/30% propylene glycol (5% Dermosoft Octiol in alcoholic solution) to female pig skin in vitro, approximately 97% of the test

solution was found in the skin within 24 h post-application. Based on dermal penetration modeling data on caprylyl glycol (1,2-octanediol), 1,2-hexanediol, decylene glycol (1,2-decanediol), and lauryl glycol (1,2-dodecanediol), the default values for % dose absorbed per 24 h were 80% for 1,2-hexanediol and 1,2-octanediol and 40% for 1,2-decanediol and 1,2-dodecanediol. Also, because of the limited percutaneous absorption data on 1,2-glycols, 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).

Caprylyl Glycol

The dermal absorption and skin penetration of 5% Dermosoft Octiol in alcoholic solution (5% caprylyl glycol in 70% ethanol/30% propylene glycol) *in vitro* was evaluated using skin from the backs of female pigs (~ 130 days old) in Franz diffusion cells. The partition coefficient of caprylyl glycol was estimated using an appropriate computer program (ACD logD-Suite) to be log $P_{ow} \approx 1$ (pH 3 to 7.4). The solution was applied topically to excised pig skin for 24 h. The investigators used an analytical method that only measured the parent compound, caprylyl glycol, and the total recovery was only 55%.

Approximately 97% of the recovered material was found in the skin within 24 h post-application, and the following distribution (as % of dermal absorbed caprylyl glycol) was reported: ~10% in stratum corneum, ~9% in epidermis, and ~81% in dermis. Caprylyl glycol was not detected in the receptor fluid, and this was likely a result of metabolism in the skin. The authors noted that, normally, the metabolism of caprylyl glycol takes place mainly in the epidermis/dermis. Therefore, undetectable amounts of the unchanged substances (below the detection limit) may penetrate into the receptor fluid. Because size of the sample (N = 2; taken from same pig) was very small and considered non-representative, it was not possible to perform an inductive statistical analysis. Therefore, according to the authors, the descriptive results achieved in this study have to be considered as a trend and interpreted as such.[22]

In addition to the dermal penetration study, a study in which caprylyl glycol was incubated with and without cut up pig skin for 24 h was completed. [22] Compared to the sample without pig skin, 50% of the caprylyl glycol was lost in the presence of skin during the 24 h incubation. The investigators attributed this loss to chemical or metabolic degradation, and suggested that the poor recovery in the dermal penetration study was likely a result of the metabolism.

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

Dermal penetration modeling information on the following 1,2-glycols (C6 – C12) was provided by the Personal Care Products Council: caprylyl glycol (1,2-octanediol, C8), 1,2-hexanediol (C6), decylene glycol (1,2-decanediol, C10), and lauryl glycol (1,2-dodecanediol, C12).[23] Dermal penetration predictions were made on the basis of Jmax (maximal flux) values calculated from Kp estimations and calculated water solubility. Based on the calculated Jmax values, assignment of default % absorption values was done, as described by Kroes et al.[24] Utilizing this approach, the default values for % dose absorbed per 24 h were 80% for 1,2-hexanediol and 1,2-octanediol and 40% for 1,2-decanediol and 1,2-dodecanediol.

Propylene Glycol

> The dermal penetration of [^{14}C]PG through excised female hairless mouse skin from the ternary cosolvent containing 10 mol% oleic acid and 6 mol% dimethyl isosorbide in 84% PG was determined. Over a 24-h period, the cumulative penetration of PG was 57.1% of the applied amount.
> From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

> The dermal absorption of PG was determined in the outermost layers of skin (1 human subject), after application to the fingertip, using TED-FTIR spectroscopy.[25] The concentration of PG remaining at the surface of the stratum corneum decreased over time. The authors suggested that PG molecules diffuse into stratum corneum only to a depth of 6-7 μm, approximately, and do not reach the dermis.
> From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[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. Skin penetration of the following was enhanced: ^{3}H-corticosterone, ^{3}H-triethanolamine, and dihydrovenanthramide D. PG can act as a penetration enhancer for some chemicals and under some conditions. Often, it works synergistically with other enhancers. The mechanism by which PG enhances penetration has not been definitively identified.

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

Warner et al.[12] 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.

1,2-Butanediol and Pentylene Glycol

In a study by Heuschkel et al.,[26] 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.

Propylene Glycol

> PG has been described as a penetration enhancer. Proposed mechanisms of penetration enhancement by PG include alteration of barrier function by its effects on a keratin structure or a PG-induced increase in the solution capacity within the stratum corneum.
>
> From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

ANIMAL TOXICOLOGY

Acute Inhalation Toxicity

1,2-Butanediol

According to a data summary available from Dow Chemical Company, there were no obvious toxic effects in rats exposed for 7 h to an atmosphere saturated with 1,2-butanediol.[21] Further details relating to this study were not available.

Acute Oral Toxicity

Acute oral toxicity data on Caprylyl glycol, propylene 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). Reportedly, high (unspecified) oral doses of 1,2-butanediol caused narcosis, dilation of the blood vessels, and kidney damage in rats.

Caprylyl Glycol

The acute oral toxicity of caprylyl glycol was evaluated using male and female rats (number and strain not stated).[27] Doses of $\geq$ 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.

In another study (OECD 423 test procedure) involving rats, the LD50 for caprylyl glycol was > 2500 mg/kg.[28,28]

1,2-Butanediol

An acute oral LD50 of 4,192 mg/kg was reported for 1,2-butanediol in a study involving female Swiss albino mice/ICR.[29] Study details were not provided.

According to a data summary available from Dow Chemical Company, the acute oral LD50 for 1,2-butanediol in rats was 16 g/kg body weight.[30] Also, high (unspecified) doses caused narcosis in rats (often leading to death in a few hours), dilation of the blood vessels, and kidney damage.

1,2-Butanediol administered orally to rats (ethanol-dependent) at a dose of 2.74 g/kg did not induce any overt toxic effects.[21]

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).[31]

Stearyl Glycol

An LD50 of > 5,000 mg/kg was reported for rats dosed orally with stearyl glycol.[31]

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. Oral LD50 values (rats) of up to 27 g/kg body weight have been reported in other studies.
> From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

Acute Dermal Toxicity

1,2-Butanediol

According to a data summary provided by Dow Chemical Company, prolonged application of 1,2-butanediol to the skin of rabbits did not result in overt toxic effects.[21] Details relating to the test procedure were not provided; however, it was presumed that neat material was tested.

Decylene Glycol

In an acute dermal toxicity study involving rats, the LD50 for decylene glycol (SymClariol®) was > 2,000 mg/kg.[28]

Propylene Glycol

> The dermal LD50 for PG was > 11.2 g/kg in mice and was 13 g/kg in rats.
> From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

Acute Intraperitoneal Toxicity

The available data suggest that 1,2-Butanediol (LD50s up to 5990 mg/kg) and pentylene glycol (TDLo = 3,510 mg/kg) are not significant acute i.p. toxicants. However, muscle incoordination was observed in rats at an i.p. dose of ~ 2.94 g/kg. In an i.p. dosing study in which ED_3 values for caprylyl glycol (1,2-octanediol), pentylene glycol (1,2-pentanediol), 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. Mortalities were observed in mice at the highest i.p. dose of PG (10,400 mg/kg).

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

In a report by Shoemaker,[32] 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-pentanediol), 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).[32]

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 (~5.99 g/kg) and 144 h LD50 of 46.5 mmol/kg (~ 4.19 mg/kg).[33]

Muscle incoordination was observed in rats at an i.p. dose of ~ 2.94 g/kg 1,2-butanediol.[21] An i.p. TDLo of 3,510 mg/kg has been reported for pentylene glycol in rats.[31]

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.
> From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

> An acute study was performed in which female ICR mice were dosed i.p. with 2600, 5200, or 10400 mg/kg PG.[34] All except the high dose mice survived 6 days after dosing. Signs of toxicity, such as lethargy and ruffled hair coats, were not observed in the 2600 and 5200 groups.
> From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Other Acute Parenteral Toxicity Studies

Propylene Glycol

> Acute i.v. LD50's of 6.2 ml/kg (rats) and 6.4 ml/kg (mice) have been reported for PG**.** 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.
> From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

Short-Term Oral and Parenteral Toxicity

A no-observed effect level (NOEL) of 50 mg/kg/day and a no-observed adverse-effect-level (NOAEL) of 300 mg/kg/day for systemic toxicity in rats were reported in a 28-day oral toxicity study on > 98% caprylyl glycol (Dermosoft® Octiol). The NOAEL was based on findings of irritation on the pars non-glandularis and limiting ridge of the stomach; analogous structures do not exist in man. An NOAEL of 100 mg/kg/day was reported for rats in a 28-day oral toxicity study on 98% to 100% decylene glycol (SymClariol®); squamous epithelial hyperplasia of the forestomach was observed at higher doses. Short-term oral administration of 1,2-butanediol to rats (males [42 days]; females [day 14 before mating to day 3 of lactation] yielded an NOAEL of 200 mg/kg/day. In rats fed 1,2-butanediol at concentrations of 5% to 40% in the diet for 8 weeks, death was not noted at 5% in the diet (~2.9 g/kg/day), but dietary concentrations ≥ 10% were fatal. Large (unspecified) doses of 1,2-butanediol did not cause irritation of the gastrointestinal tract in rats. All mice survived in a short-term study in which 10% PG was administered in drinking water for 14 days, and all rats and mongrel dogs survived oral dosing with up to 3.0 ml 100% PG 3 times per day for 3 days. Similarly, cats survived dosing 12% PG in the diet for 5 weeks and 41% PG in the diet for 22 days. Intravenous dosing with PG over a 2-week period resulted in little toxicity in rats.

Caprylyl Glycol

In a 28-day oral toxicity study, > 98% caprylyl glycol (Dermosoft® Octiol) was administered to groups of Wistar rats at doses of 50, 300, and 1000 mg/kg/day, respectively, according to OECD guidelines.[35] The number of animals per group was not stated and the control group was not identified. The authors reported no test substance-related mortalities or toxicologically relevant clinical signs during weeks 1 through 3 or week 4 (functional observational battery). Additionally, there were no differences in feed consumption, body weight, hematological/clinical biochemistry parameters, or macroscopic findings that were considered toxicologically relevant. Test substance-related findings (males and females) included slightly reduced locomotor activity and increased mean absolute and relative kidney weights at the highest dose. Whether or not microscopic changes were observed in the kidneys was not stated.

Systemic effects were not observed at doses up to 300 mg/kg/day. Test substance-related microscopic changes were observed in the stomachs of rats in 300 and 1000 mg/kg/day dose groups. These findings were considered indicative of an irritative potential of the test substance on the pars non-glandularis and limiting ridge of the stomach. The authors noted that analogous structures do not exist in humans. Study results indicated a no-observed effect level (NOEL) of 50 mg/kg/day, and a no-observed adverse-effect-level (NOAEL) of 300 mg/kg/day for systemic toxicity. The NOAEL was based on findings (irritation) in the stomach likely due to local irritation effects.[35]

1,2-Butanediol

In an 8-week oral study, groups of rats were fed 1,2-butanediol at concentrations ranging from 5 to 40% in the basic diet (one dose level per group).[21] A control group only received basic diet. There were no mortalities at the lowest dose (~ 2.9 g/kg body weight/day); however, doses $\geq$ 10% were classified as fatal. The following signs of toxicity were noted at the highest dose of 22 g/kg/day: weight loss, fatigue, reduced responsiveness, diarrhea, and rapid, shallow breathing. No abnormalities were observed in tissues of major organs from 2 rats at each of the 5 dose levels.

The following study 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.[36] 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 weights, feed 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. [36]

According to a summary of data provided by Dow Chemical Company, the administration of large (unspecified) doses of 1,2-butanediol to rats caused irritation of the gastrointestinal tract.[21]

Decylene Glycol

In a 28-day oral toxicity study, 98% to 100% decylene glycol (SymClariol®) was administered to groups of SPF-bred Wistar rats (5 males, 5 females/group) at doses of 100, 300, and 1000 mg/kg/day, respectively, according to OECD guidelines.[37] The vehicle control group received 2.5% ethanol in distilled water. Rats in each group were killed after day 28. Two additional groups (same composition) were untreated and dosed with 1000 mg/kg/day, respectively, for 28 days. The animals in these groups were killed after a 14-day non-treatment period. In all groups, a functional observational battery was performed (week 4) before animals were killed. All of the animals survived the 28-day dosing period, and there were no toxicologically-relevant clinical signs during the study. Mean locomotor activity was significantly reduced in males and females in the 1000 mg/kg/day dose group, and this finding was deemed test substance-related. Decreased feed consumption was also noted in females at this dose level. Mean body weights of males and females were similar to those of negative control animals.

There were no test-substance-related differences in hematological or clinical biochemical parameters that were of toxicological relevance. The presence of ketone in the urine of males and females of the 1000 mg/kg/day dose group was considered likely representative of metabolic adaptation to the test substance. Both absolute and relative organ weights of dosed animals were comparable to those of negative control rats. Toxicologically-relevant macroscopic findings were not observed. Squamous epithelial hyperplasia, ulceration, and inflammation of the forestomach were observed at doses of 1000 mg/kg/day, and squamous epithelial hyperplasia of the forestomach was less severe and occurred at a lower incidence in the of 300 mg/kg/day dose group. After a 14-day recovery period, squamous epithelial hyperplasia remained in the animals previously dosed with 1000 mg/kg/day, but the severity and incidence of this finding after the treatment period was largely reversible. Both the NOEL and the NOAEL in this study was 100 mg/kg body weight/day.[37]

Propylene Glycol

No significant toxicity was observed in short-term oral tests on PG inolving 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. 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.
From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

Groups of 8 male and 8 female CD-1 mice were given 0.5, 1.0, 2.5, 5.0, and 10.0% PG in the drinking water for 14 days. Body weight gains of test animals were similar to or greater than controls. No animals died during the study.
From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Subchronic Inhalation Toxicity

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 (0.16 to 2.2 mg/liter of air) for 13 weeks.

Propylene Glycol

Male and female Sprague-Dawley rats (number per group not given) were exposed to 0.16, 1.0, or 2.2 mg PG/l air for 6 h/day, 5 days/wk, for 13 wks in a nose-only inhalation study. Relevant differences occurred in some hematological parameters, serum enzyme activities, and lung, spleen, liver, and kidney weights; however these differences were inconsistent and without dose-response trends.
From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Subchronic and Chronic Oral Toxicity

A TDLo of 2,450mg/kg was reported for pentylene glycol in rats dosed orally over a 28-week period. In subchronic oral toxicity studies involving rats, PG (50,000 ppm in diet) given in feed for 15 wks did not produce any lesions. The same was true for dogs that received 5% or 10% PG in drinking water in subchronic studies. Toxic effects were not observed in PG chronic feeding studies involving rats or dogs. In a 92- to 97-day oral toxicity study involving mice, rats, dogs, and monkeys dosed with a formulation containing 1000 mg/kg propylene glycol, there were no adverse effects on body weight, food consumption, clinical pathology, histopathology, or adverse clinical observations.

Pentylene Glycol

Pentylene glycol was administered orally to rats, intermittently over a 28-week period. A TDLo of 2,450mg/kg was reported.[31]

Propylene Glycol

A 92- to 97-day study was conducted to assess the safety and tolerability of propylene glycol as an alternative formulation vehicle in general toxicology studies in the mouse, rat, dog, and monkey.[38] In Sprague-Dawley (Crl:CD[SD]VAF/Plus) rats (10/sex; 6 ± 1 weeks old) and CD1 (Crl:CD1[Icr]VAF/Plus) mice (10/sex; 6 ± 1 weeks old), the vehicle was administered orally via gavage at dose volumes of 5 ml/kg (rats) and 10 ml/kg (mice) for 92 to 93 days. In Beagle dogs (4/sex; 7 to17 months old) and cynomolgus monkeys (*Macaca fascicularis*, 4/sex; juvenile to young adult), the vehicle was administered orally by gavage (dose = 1,000 mg/kg; dose volume of 5 ml/kg) for 95–97 days. Effects on clinical observations, body weight and food consumption parameters, clinical pathology, and histopathology were evaluated across all species. The

suitability of formulations containing up to 1000 mg/kg propylene glycol for use in preclinical safety studies was confirmed by a lack of effects on all parameters examined.[38]

> There was no evidence of toxic effects in subchronic oral toxicity studies in which rats were fed 50,000 ppm 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. Toxic effects were not observed in rats that received up to 50,000 ppm PG in the diet for 104 weeks or in dogs that received 2 g/kg PG in the diet for 104 weeks.
>
> From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

Repeated Dose Dermal Toxicity

1,2-Butanediol

According to a data summary provided by Dow Chemical Company, repeated applications of 1,2-butanediol to the skin of rabbits did not result in overt toxic effects.[21] Details relating to the test procedure were not provided; however, it is presumed that neat material was tested.

Cytotoxicity

The cytotoxicity of cetyl glycol, lauryl glycol, and pentylene glycol has been demonstrated in vitro. Cetyl glycol(130 µg/ml) had a cytocidal effect on Ehrlich ascites carcinoma cells, lauryl glycol (99 µM) had a hemolytic effect on human erythrocytes, and pentylene glycol (5%) induced apoptosis in a human promyeolcytic leukemia cell line. Propylene glycol was moderately cytotoxic to human fibroblasts and keratinocytes in vitro.

Pentylene Glycol

Anselmi et al.[39] 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.

Lauryl Glycol

Osorio e Castro et al.[40] 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).

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.[41]

Propylene Glycol

> PG was found to be cytotoxic in assays that measured inhibition of human foreskin fibroblasts and keratinocytes, inhibition of collagen contraction by fibroblasts, and changes in cell morphology of fibroblasts and keratinocytes. Changes in morphology included detachment of cells from the culture and changes in cell shape.
>
> From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Ocular Irritation

Based on Draize test results, lauryl glycol has been classified as a severe ocular irritant. Undiluted 1,2-butanediol , but not 10% aqueous, induced ocular irritation in rabbits. Undiluted decylene glycol induced corrosion when instilled into the eyes of rabbits. In an in vitro ocular irritation assay (HET-CAM), 1% decylene glycol in neutral oil and caprylyl glycol (1% and 3%) in neutral oil were classified as non-irritants; however, a 50:50 (w/w) mixture of caprylyl glycol and 1,2-hexanediol was classified as a severe ocular irritant when evaluated at a concentration of 1% aqueous (effective concentration per ingredient = 0.5%) in the same assay. Together, the results of a neutral red release (NRR) assay, the HET-CAM assay, and the reconstituted human epithelial culture (REC) assay indicated that a lash gel serum containing 3% pentylene glycol might be a slight ocular irritant. In other studies, undiluted PG was, at most, a slight ocular irritant.

Caprylyl Glycol

In an *in vitro* assay (hen's egg test on the chorioallantoic membrane [HET-CAM]) for evaluating ocular irritation potential, caprylyl glycol was classified as a non-irritant at test concentrations of 1% and 3% in neutral oil.[42]

Caprylyl Glycol and 1,2-Hexanediol

A 50:50 (w/w) mixture of 1,2-hexanediol and caprylyl glycol (Symdiol® 68) was also tested in the HET-CAM assay. The mixture was classified as a severe eye irritant at a test concentration of 1% aqueous (effective concentration per ingredient = 0.5%).[43]

1,2-Butanediol

According to a summary of data provided by Dow Chemical Company, undiluted 1,2-butanediol was irritating to the eyes of rabbits, but was a non-irritant when tested as a 10% aqueous solution. [21]

Pentylene Glycol

The ocular irritation potential of a lash gel serum containing 3% pentylene glycol was evaluated using the following in vitro assays: neutral red release (NRR) assay using rabbit cornea fibroblasts, HET-CAM, and the reconstituted human epithelial culture (REC) assay.[44] In the NPR assay, the undiluted product and dilutions (in hydrophilic or lipophilic substance) ranging from 0.1% to 60% were tested. Sodium dodecyl sulfate served as the positive control. The test product concentration that gave rise to the release of 50% neutral red dye (NR_{50}) was used as an endpoint to reflect cytotoxicity. Data were expressed as a percentage of cytotoxicity, compared to the negative control (dilution 0%), and the NR_{50} was calculated by interpolation from the curve representing the percentage of viability versus the concentration of test product. An NR50 of > 50% (slightly cytotoxic) was reported for the lash gel serum.

In the HET-CAM assay, the undiluted product (0.3 ml) was applied to the chorioallantoic membrane and classified as moderately irritating. In the REC assay, the product (neat or diluted) was applied to the apical surface of the epithelial culture. Hexadecylpyridinum bromide solution in saline and saline solution served as positive and negative controls, respectively. Results were expressed as a percentage of cytoxicity, compared to the negative control. The product was classified as slightly cytotoxic. Together, the results for the 3 in vitro assays indicate that the lash gel serum might be a slight ocular irritant, with a Draize score that might range from 0 to 15. The conclusion for this study (slight ocular irritant) is from a global assessment conducted by the International Research and Development Center that was based on results of the 3 methods used, because no single alternative method can predict ocular irritation with a sufficient level of safety.[44]

Decylene Glycol

In an ocular irritation study (OECD 405 protocol) involving rabbits, decylene glycol (SymClariol®) induced corrosion when tested at a concentration of 100%. Additionally, the ocular irritation potential of 1% SymClariol® in neutral oil was evaluated in the HET-CAM assay, and results were negative.[28]

Lauryl Glycol

According to Worth and Cronin,[45] 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 the Draize eye test has been used for the identification of R41 chemicals. Actual Draize test results for lauryl glycol were not included. This classification of lauryl glycol as a severe ocular irritant is included in a study by the preceding authors to explore the possibility of distinguishing between eye irritants and non-irritants by using *in vitro* endpoints of the HET-CAM assay and the neutral red uptake (NRU) test.

According to one of the prediction models for eye irritation potential, a chemical is more likely to be an eye irritant if its log (TH10) value is low (i.e., if a 10% solution of the chemical produces rapid hemorrhaging of the chorioallantoic membrane) and if its log (IC 50) value is low (i.e., if the chemical is cytotoxic to 3T3 cells). TH10 is defined as the mean detection time (units not stated) for hemorrhage in the vascularized chorioallantoic membrane of embryonated chicken eggs. The IC50 is defined as the concentration of test chemical (mg/ml) resulting in 50% inhibition of neutral red uptake in 3T3 cells. The TH10 and IC50 values for lauryl glycol were 171.0 and 0.02, respectively.[45] Using a logarithm calculator, log 0.02 = -1.70 and log 171.0 = 2.23.

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.
> From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

> The ocular irritation potential of PG was determined using groups of 6 male and female New Zealand white albino rabbits. Following instillation of a single drop and multiple instillations, slight to moderate conjunctival hyperemia was observed and all reactions had cleared by day 3.
> From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Skin Irritation and Sensitization

In the guinea pig maximization test, results were negative for caprylyl glycol at a challenge concentration of 50% in petrolatum. Undiluted decylene glycol (SymClariol®) was classified as a moderate skin irritant in rabbits, but did not induce sensitization in the guinea pig maximization test at challenge concentrations of 2% and 5% in arachis oil or in the mouse local lymph node assay at concentrations of 5% to 50% in acetone/olive oil (4:1). Repeated applications of 1,2-butanediol to the skin of rabbits did not result in skin irritation, and results were negative for 1,2-hexanediol (10% to 100%) in the mouse local lymph node assay for evaluating sensitization potential . Dermal irritation/sensitization studies on PG were reported in the 1994 CIR final safety assessment and the amended final safety assessment. Both mild and no skin irritation were observed following the application of undiluted PG in animal studies. The application of 50% PG resulted in skin irritation/dermal inflammation. PG induced reactions ranging from no sensitization to mild sensitization.

Caprylyl Glycol

The skin sensitization potential of caprylyl glycol was evaluated in the guinea pig maximization test (OECD 406 protocol) using 20 animals. During intradermal and topical induction, caprylyl glycol was applied at concentrations of 5% (in peanut oil) and 50% (in petrolatum). The challenge concentration was 50% in petrolatum. Sensitization was not observed in any of the animals tested.[42]

1,2-Butanediol

According to a summary of data provided by Dow Chemical Company, 1,2-butanediol did not induce skin irritation in rabbits, following prolonged and repeated application.[21] Details regarding the test procedure were not provided; however, it was presumed that neat material was used.

1,2-Hexanediol

The sensitization potential of 1,2-hexanediol was evaluated at concentrations of 10%, 50%, and 100% in acetone/olive (3:1) using the mouse local lymph node assay (OECD 429 protocol). Study results were negative for skin sensitization.[46]

Decylene Glycol

In a skin irritation study (OECD 404 protocol) involving rabbits, 100% decylene glycol (SymClariol®) was classified as a moderate skin irritant (PII = 3.2). SymClariol® was evaluated at the following concentrations in the guinea pig maximization test: 1% in arachis oil (intradermal induction), 5% in arachis oil (topical induction), and 2% and 5% in arachis oil (challenge). Sensitization was not observed in any of the 19 guinea pigs tested.[28]

The skin sensitization potential of SymClariol® was also evaluated at the following test concentrations in the mouse local lymph node assay: 5%, 10%, 25%, and 50% in acetone/olive oil (4:1). Sensitization was not recorded at any of the concentrations tested.[28]

Propylene Glycol

> PG (50%) may have caused skin irritation in nude mice, while, in another study, 100% PG was minimally irritating to hairless mouse skin. In nude mice, hypertrophy, dermal inflammation, and proliferation were observed with 50% PG. Undiluted PG was, at most, a mild dermal irritant in a Draize test using rabbits with intact and abraded skin. No reactions to undiluted PG were observed with guinea pigs, rabbits, or Gottingen swine. PG (concentrations not given) was negative in a number of sensitization/allergenicity assays using guinea pigs, but, in another study, PG (0.5 ml) was a weak sensitizer in guinea pigs.
>
> From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

> The dermal irritation potential of 100% PG was evaluated using male hairless SKH1 *hr/hr* mice. PG was minimally irritating, with a total score of 7 (maximum score =77).
>
> From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

An oral NOAEL of 1,000 mg/kg for reproductive/developmental toxicity has been reported for 1,2-butanediol in rats. In a developmental toxicity study involving rats dosed with 1,2-hexanediol , an oral NOEL of 300 mg/kg was reported. In other studies, no significant adverse reproductive or developmental effects in oral studies when evaluated in mice at concentrations of ≤5.0% PG, rats at doses of ≤1600 mg/kg PG, rabbits at doses of ≤1230 mg/kg PG, or hamsters at doses of ≤1550 mg/kg PG. 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 in mice reported an increase in the frequency of premature centromere separation (PCS) with 1300-5200 mg/kg PG. In zygotes from PG-dosed mice, hyperploidy was increased.

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.[36] The estimated dose of low concern (EDCL) for this study was calculated as 10 mg/kg/day, using an NOAEL of 1,000 mg/kg/day and a reproductive toxicity uncertainty factor of 100.[7]

1,2-Hexanediol

The developmental toxicity of Hydrolite-6 (99% 1,2-hexanediol) was evaluated using groups of 24 mated Sprague-Dawley rats of the Crl:CD strain.[47] Three groups received oral doses (gavage) of 30, 100, and 300 mg/kg/day, respectively, between days 5 and 19 of gestation. The negative control group received vehicle (not stated) only. Pregnant females were killed on day 20 of gestation and subjected to macroscopic necropsy. Doses up to 300 mg/kg/day were well-tolerated, and did not induce any effects on clinical condition, body weight, body weight change, food intake, or necropsy observations. There were also no effects on embryo-fetal survival, growth, or development at doses up to 300 mg/kg/day. It was concluded that Hydrolite-6 at doses up to 300 mg/kg/day was not associated with any adverse effect on the pregnant rat or the developing conceptus. The Hydrolite-6 (1,2-hexanediol) NOEL for the pregnant female and for embryo-fetal survival, growth, and development was considered to be 300 mg/kg/day.

Propylene Glycol

A continuous breeding reproductive study was conducted using COBS Crl:CD-1 (ICR)BR outbred Swiss albino mice (6 weeks old). The 3 experimental groups received the following doses (in feed or water), respectively, during a 7-day pre-mating period: 1.0% propylene glycol (daily dose of 1.82 g/kg), 2.5% propylene glycol (daily dose of 4.80 g/kg), and 5.0% propylene glycol (daily dose of 10.10 g/kg). PG was not a reproductive toxicant in this study.
From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

The reproductive and developmental effects of PG were evaluated using mice, rats, rabbits, and hamsters. Groups of 25 or 28 female albino CD-1 outbred mice were mated and 22, 22, 22, 20, and 23 gravid mice were dosed by oral intubation with 0.0, 16.0, 74.3, 345.0, and 1600.0 mg/kg aq. PG on days 6-15 of gestation. Groups of 25-28 female albino Wistar rats were mated and 22, 23, 22, 20, and 24 were dosed as above, respectively. PG was not a reproductive or developmental toxicant in this study.
From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Groups of 11, 11, 12, 14, and 13 gravid female Dutch-belted rabbits were dosed by oral intubation with 0, 12.3, 57.1, 267.0, or 1230.0 mg/kg aq. PG on days 6-18 of gestation, respectively. Administration of PG did not cause reproductive or developmental toxicity.
From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Groups of 24-27 female golden hamsters were mated and 21, 24, 25, 22, and 22 gravid hamsters were dosed by oral intubation with 0.0, 15.5, 72.0, 334.5, and 1550.0 mg/kg aq. PG on days 6-10 of gestation, respectively. PG was not a reproductive or developmental toxicant in this study.
From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

PG was used as a vehicle in a reproductive and behavioral development study. It was administered to 15 gravid Sprague-Dawley rats orally by gavage on days 7-18 of gestation at a volume of 2 ml/kg. PG did not have any effects on reproductive or behavioral development parameters.
From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Embryonic development was reduced or inhibited completely in cultures of mouse zygotes exposed to 3.0 or 6.0 M PG, respectively.
From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

A study was performed to determine whether PG induced cytogenetic aberrations in mouse metaphase II (MII) oocytes that predispose zygotes to aneuploidy. In the MII portion of the study, female ICR mice were dosed i.p. with 1300, 2600, or 5200 mg/kg PG in distilled water after dosing with hCG. A statistically significant change in hyperploidy, hypoploidy, or single chromatids was not observed. An increase in the frequency of PCS at each dose was statistically significant, and the incidence of premature anaphase was significantly greater in the 5200 mg/kg dose group as compared to controls.

In the zygote portion of the study, female mice were dosed i.p. with 1300, 2600, or 5200 mg/kg PG 3 h after hCG administration. There were 30, 40, 49, and 66 mice in the control, 1300, 2600, and 5200 mg/kg groups, respectively. The increase in hyperploidy was statistically significant in all test groups compared to controls. A statistically significant change was not seen for polyploidy or hypoploidy, and zygotes containing PCS, premature anaphase, or single chromatids were not found. There was not a statistically significant difference in the proportion of zygotes collected for each group compared to oocytes. However, the number of zygotes analyzed compared to the number placed on slides was significantly decreased in the test groups; a relatively large portion of these zygotes had clumped chromosomes.
From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

GENOTOXICITY

Caprylyl glycol (Dermosoft® Octiol) did not induce gene mutations in Chinese hamster V79 cells (test concentrations up to 1489 µg/ml) and >98% caprylyl glycol (ADEKA NOL OG) did not induce chromosomal aberrations in Chinese hamster lung cells in vitro with or without metabolic activation at concentrations up to700 µg/ml. Decylene glycol (SymClariol®) was non-genotoxic in the Ames test. 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). In the 1994 CIR final safety assessment, PG was not mutagenic in bacterial assays, but positive and negative results were reported in assays involving mammalian cells.

Caprylyl Glycol

The genotoxicity of > 98% caprylyl glycol (Dermosoft® Octiol) was evaluated in a gene mutation assay involving Chinese hamster V79 cells *in vitro* according to OECD and European Commission guidelines.[48] Test concentrations up to 1480 µg/ml were evaluated. The first experiment (with and without metabolic activation) involved a 4-h treatment period, whereas, the second experiment involved 4-h and 24-h treatment periods (without activation). A substantial or reproducible dose-dependent increase in the mutation frequency was not observed in either of the 2 experiments. Appropriate reference mutagens (positive controls, unnamed) induced a distinct increase in mutant colonies. Negative control cultures were not described. Caprylyl glycol, > 98% (Dermosoft® Octiol) did not induce gene mutations under the experimental conditions reported, and therefore, was considered non-mutagenic.

The genotoxicity of > 98% caprylyl glycol (ADEKA NOL OG) was evaluated in the chromosome aberrations assay using Chinese hamster lung (CHL/IU) cells *in vitro* according to Ministry of Health and Welfare (Japan) genotoxicity test guidelines.[49] Short-term treatment of cultures (with and without metabolic activation) involved concentrations up to 700 µg/ml and continuous treatment involved concentrations up to 180 µg/ml, both with and without metabolic activation. Negative and positive control cultures were not identified. In all test cultures, the number of structural and numerical chromosomal aberrations was not increased when compared to negative control cultures. The positive control was genotoxic. The test substance did not induce chromosomal aberrations with or without metabolic activation.

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.[50]

Decylene Glycol

In the Ames test (OECD 471 protocol), decylene glycol (SymClariol®) was classified as non-mutagenic. Test concentrations were not stated.

Propylene Glycol

> PG (≤10,000 µg/plate) was not mutagenic in Ames tests with or without metabolic activation**.** PG, tested at concentrations of 3.8-22.8 mg/ml, was a weak, but potential, inducer of sister chromatid exchanges (SCEs), causing a dose-dependent 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. PG, 32 mg/ml, induced chromosomal aberrations in a Chinese hamster fibroblast line, but not in human embryonic cells. PG was not mutagenic in mitotic recombination or basepair substitution assays, or in a micronucleus test or a hamster embryo cell transformation assay (concentration used not specified).
>
> From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

CARCINOGENICITY

Propylene Glycol

PG was non-carcinogenic in a 2-year bioassay in which rats were given ≤50,000 ppm PG in the diet (feeding schedule not included). The dermal application of undiluted PG (volume not stated) to Swiss mice in a lifetime study was non-carcinogenic. PG was non-carcinogenic in other oral, dermal, and subcutaneous studies.

From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

CLINICAL ASSESSMENT OF SAFETY

Skin Penetration Enhancement

Combined exposure to PG and oleic acid synergistically enhanced the dermal penetration of both compounds.

Propylene Glycol

By evaluating transepidermal water loss (TEWL) and determining attenuated total reflectance (ATR)-FTIR, PG dermal penetration was found to be enhanced by the addition of fatty acids, such as oleic acid. TEWL was determined using 10 subjects (number of males and females not specified) with application of occlusive chambers containing nothing, 300 µl PG, or 300 µl 0.16 M oleic acid in PG, for 3 or 24 h. To determine ATR-FTIR, an occlusion system containing PG or oleic acid/PG was applied to the forearm of each subject for 3 h.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Predictive Testing - Irritation and Sensitization

A 1,2-hexanediol/caprylyl glycol preservative mixture tested at concentrations up to 15% did not induce sensitization. Decylene glycol (20%) did not induce skin irritation/sensitization when applied to intact skin; however, decylene glycol (1%) had low skin irritation potential when applied to scarified skin. Results were negative for skin irritation/sensitization in RIPTs on products containing 1,2-glycols at concentrations ranging from 0.112% pentylene glycol to 0.5% caprylyl glycol or 1,2-hexanediol. In an in-use test of a products containing 0.15% 1,2-hexanediol, neither skin irritation nor sensitization was observed. PG was a slight skin irritant, but not a sensitizer, in human subjects. Deodorants or antiperspirant products containing 35 to 86% PG have been tested in HRIPTs and use tests. Although irritation was reported in some subjects exposed to the PG-containing products, studies including a reference deodorant or antiperspirant product without PG found that the PG-containing product did not result in more irritation than the reference product.

Caprylyl Glycol and 1,2-Hexanediol

A lipstick containing 0.5% caprylyl glycol was evaluated in an RIPT using 105 healthy subjects (males and females). The product was applied to the upper back of each subject and application sites were covered with a semi-occlusive patch for 24 h. It was concluded that the product did not demonstrate a potential for eliciting skin irritation or sensitization.[51]

Levy et al.[52] studied the potential for delayed type IV dermal sensitivity following exposure to a new preservative 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 preservative (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.[52]

A 50:50 (w/w) mixture of 1,2-hexanediol and caprylyl glycol (Symdiol® 68) was evaluated in an RIPT involving 56 subjects. At a test concentration of 20% in gel (effective concentration per ingredient = 10%), the mixture did not induce skin sensitization in any of the subjects tested.[43]

A leg and foot gel containing 0.5% 1,2-hexanediol was applied to the upper back of each of 101 healthy subjects (males and females) in an RIPT. Each site was covered with a semi-occlusive patch that remained in place for 24 h. The product did not induce skin irritation or sensitization in this study.[53]

In an in-use safety evaluation for skin irritation and sensitization potential, 28 subjects (males and females) were instructed to use a body wash containing 0.15% 1,2-hexanediol for a minimum of 3 times per week over a 30-day period. There was no evidence of erythema, edema, or dryness of application sites in any of the subjects, and it was concluded that the product did not demonstrate a potential for eliciting skin irritation or sensitization.[54]

Pentylene Glycol

A foundation containing 0.112% pentylene glycol was evaluated in an RIPT using 101 subjects (males and females). A 1" x 1" semi-occlusive patch containing 0.2 g of the product was applied repeatedly (24 h applications) to the upper back. It was concluded that the product did not have a potential for inducing skin irritation or allergic contact sensitization.[55]

Decylene Glycol

The skin irritation potential of decylene glycol (SymClariol®) was evaluated using 52 subjects in a 48 h semi-occluded patch test. At a concentration of 20% in petrolatum, the test substance did not induce skin irritation. SymClariol® (1% in neutral oil) had low skin irritation potential when applied to scarified skin sites on 10 subjects. In an HRIPT, SymClariol® (20% in petrolatum) did not induce skin sensitization in any of the 55 subjects tested. [28]

In a facial stinging test, SymClariol® was classified as having very slight stinging potential when applied at concentrations of 1% and 2% (in neutral oil) in a group of 10 subjects.[28]

Propylene Glycol

> PG induced skin irritation reactions in normal subjects. Reactions were observed at concentrations as low as 10% in predictive 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 (0.2 ml; concentration not stated) induced 19 cutaneous reactions at challenge.
>
> From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

> The effect of the addition of PG to an isopropanol vehicle on the irritant reaction of benzoic acid was determined in a non-occlusive test using 15 subjects, 7 males and 8 females. Benzoic acid in isopropanol was tested at concentrations of 31, 62, 125, and 250 mM without PG as well as with the addition of 1, 2, 5, 10, and 25% PG. Visual appearance, laser Doppler flowmetry, and skin color (using a Minolta chromameter) were measured. PG enhanced the strength of the reactions to 125 and 250 mM benzoic acid, but not to 31 or 62 mM benzoic acid. Enhancement was observed with the addition of 1% PG, and maximal enhancement was attained with 5%.
>
> From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

> It has been reported that intradermal injection of 0.02 ml undiluted PG produces a wheal-and-flare reaction within minutes, while the same volume applied epidermally does not produce any reaction. It has also been stated that subjective or sensory irritation sometimes occurs in volunteers after application of various concentrations of PG.
>
> From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

A 24-h single insult occlusive patch test (SIOPT) was performed on an undiluted deodorant formulation containing 69.15% PG using 20 subjects (gender not specified). Four subjects had a score of ± (minimal faint uniform or spotty erythema) and 3 subjects had a score of 1 (pink-red erythema visibly uniform in the entire contact area.) The primary irritation index (PII) was 0.25.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

In another SIOPT, a deodorant formulation containing 68.06% PG was tested undiluted using 20 subjects (gender not specified). Three subjects had a score of ± and 1 had a score of 1 to the test formulation. The PII was 0.13.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

The irritation index for PG and 0.16 M oleic acid/PG was determined using 12 subjects (number per gender not specified) by applying occlusive chambers containing these 2 test substance to the volar forearm for 3 or 24 h. Visually, the 24-h application of PG produced only slight erythema, while the 24-h application of oleic acid/PG produced clearly visible irritation.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Thirty-day use studies were completed with 26 male, 40 female, and 24 male subjects to evaluate the potential for deodorant sticks containing 35, 65.2, and 73% PG, respectively, to induce dermal irritation and/or sensitization. The subjects were instructed to apply the product to the underarm once daily for 30 days. None of the subjects had any irritation or sensitization reactions. In a 4-wk use study completed with 26 male subjects following the same procedure, a deodorant stick containing 65.8% PG also did not demonstrate a potential for eliciting dermal irritation or sensitization.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

A maximization test was completed with 25 subjects, 18 male and 7 female, to determine the sensitization potential of a deodorant containing 69.15% PG. Sensitization reactions were not observed.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

An RIPT was completed with 101 subjects, 30 male and 71 female, to determine the sensitization potential of a stick deodorant formulation containing 73% PG. Scores of + (barely perceptible or spotty erythema) to 2, with some dryness, were observed throughout the study. While the authors stated that a stick deodorant formulation containing 73% PG "did not indicate a clinically significant potential for dermal irritation or allergic contact sensitization," the Expert Panel questioned that conclusion since repeated reactions were observed.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Another RIPT was completed with 99 subjects to determine the sensitization potential of a stick antiperspirant formulation containing 86% PG. One "+" reaction was observed during the entire study, and there was no evidence of sensitization.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Provocative Testing – Irritation and Sensitization

PG induced skin irritation reactions in patients at concentrations as low as 2%. Patients with chronic venous insufficiency (CVI) had sensitization reactions to PG, whereas contact dermatitis patients did not.

Propylene Glycol

PG induced skin irritation reactions in patients. Reactions were observed at concentrations as low as 2% in provocative tests.

From the Final Report on Propylene Glycol and Polypropylene Glycols[1]

Thirty-six patients with CVI were patch tested with 5% PG in petrolatum by application to the back for 2 days. Twelve patients were male; 2, 5, and 5, had 1st, 2nd, and 3rd degree CVI, respectively. Twenty-four patients were

female; 5 and 19 had 2nd and 3rd degree CVI, respectively. The sensitization rate as a percentage of all patients was 8.3%. The sensitization rate of patients with 2nd and 3rd degree CVI tested with PG was 10 and 8.3%, respectively.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

During the period 2000-2004, 308 patients, 111 males and 197 females, with contact dermatitis were patch-tested using the European standard series and some additional chemicals, including PG. PG, 5% in petrolatum, did not cause any positive reactions.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Photoallergenicity

PG did not produce a photoallergic response in a provocative photopatch test.

Propylene Glycol

Over a 2-yr period, 30 males and 52 females with photoallergic contact dermatitis were photopatch tested with a standard series of sunscreens as well as some additional chemicals, including PG (dose not given). The allergens were applied in duplicate on the back and covered with opaque tape for 24 h. One set of test sites was irradiated with a UVA (320-400 nm) dose of 5 J/cm^2. PG did not produce a photoallergenic or contact allergy response.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

Retrospective Analysis

Propylene Glycol

The NACDG performed a number of retrospective analyses on various dermatological conditions, and data on the relevance of positive reactions to PG were presented. These studies are summarized in Table 5.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

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. A few case reports concerning PG and hand dermatitis or atopic dermatitis have been described, and positive reactions were reported.

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.[56]

Propylene Glycol

A few case reports have been described concerning PG and hand dermatitis or atopic dermatitis. The cases generally had positive patch test reactions to PG. Improvement was seen with the avoidance of PG-containing products.

From the Amended Final Report on Propylene Glycol, Tripropylene Glycol, and Polypropylene Glycols[2]

SUMMARY

The sixteen 1,2-glycols included in this safety assessment function primarily as skin and hair conditioning agents and viscosity increasing agents in personal care products, although caprylyl glycol and pentylene glycol also function as preservatives. The following five 1,2-glycols were reported to FDA as being used: caprylyl glycol, decylene glycol,

pentylene glycol, 1,2-hexanediol, and C15-18 glycol. The results of a Personal Care Products Council industry survey indicate that ingredient use concentrations have range from 0.00003% (caprylyl glycol) to 10% (1,2-hexanediol). Use concentrations of pentylene glycol (up to 5%) were also included in this survey. C15-18 glycol was included in this survey, but no uses or use concentrations were reported.

Safety test data from the CIR safety assessment on propylene glycol have been reviewed and are 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.

Stearyl glycol is 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 metabolism, distribution, and excretion of 1,2-butanediol following i.v. dosing indicate that, in rabbits, this chemical is metabolized slowly and excreted in the urine either as the glucuronide or unchanged; there was no evidence of tissue accumulation. Metabolites were not isolated from the urine of rabbits fed 1,2-butanediol in the diet. Based on metabolism modeling information on caprylyl glycol, 1,2-hexanediol, decylene glycol, and lauryl glycol, it is likely that *C*-oxidation, *C*-hydroxylation, glucuronidation, and beta-oxidation may take place to form corresponding metabolites. *C*-hydroxylation and beta-oxidation are more likely to be favored metabolic pathways for the longer alkyl chain compounds, 1,2-decanediol and 1,2-dodecanediol, than for the shorter alkyl chain length compounds, 1,2-hexanediol and 1,2-octanediol.

Following topical application of 5% caprylyl glycol in 70% ethanol/30% propylene glycol (5% Dermosoft Octiol in alcoholic solution) to female pig skin *in vitro*, approximately 97% of the test solution was dermally absorbed within 24 h post-application. Based on dermal penetration modeling information on caprylyl glycol, 1,2-hexanediol, decylene glycol, and lauryl glycol, the default values for % dose absorbed per 24 h were 80% for 1,2-hexanediol and 1,2-octanediol and 40% for 1,2-decanediol and 1,2-dodecanediol.

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

There were no significant toxic effects in rats exposed for 7 h to an atmosphere saturated with 1,2-butanediol. 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 (LD50 range: 2200 to > 20,000 mg/kg). Reportedly, high (unspecified) oral doses of 1,2-butanediol caused narcosis, dilation of the blood vessels, and kidney damage in rats. Overt toxic effects were not observed in ethanol-dependent rats dosed orally with 2.74 g/kg 1,2-butanediol.

The available data suggest that 1,2-butanediol (LD50s up to 5.99 g/kg) and pentylene glycol (TDLo = 3.51 g/kg) are not significant acute i.p. toxicants. However, muscle incoordination was observed in rats at an i.p. dose of ~ 2.94 g/kg. In an i.p. dosing study in which ED_3 values for caprylyl glycol (1,2-octanediol), pentylene glycol (1,2-pentanediol), 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. In an acute dermal toxicity study involving rats, the LD50 for decylene glycol (SymClariol®) was > 2,000 mg/kg. Prolonged application or repeated applications of 1,2-butanediol to the skin of rabbits did not result in overt toxic effects.

A no-observed effect level (NOEL) of 50 mg/kg/day and a no-observed adverse-effect-level (NOAEL) of 300 mg/kg/day for systemic toxicity in rats were reported in a 28-day oral toxicity study on > 98% caprylyl glycol (Dermosoft® Octiol). The NOAEL was based on findings of irritation on the pars non-glandularis and limiting ridge of the stomach; analogous structures do not exist in man. An NOAEL of 100 mg/kg/day was reported for rats in a 28-day oral toxicity study on decylene glycol (SymClariol®). Short-term oral administration of 1,2-butanediol to rats yielded an NOAEL of 200 mg/kg/day. Reportedly, in another repeated dose study, the administration of large (unspecified) doses of 1,2-butanediol to rats, caused irritation of the gastrointestinal tract. Signs of toxicity were noted at the highest dose of 22 g/kg/day in rats receiving 1,2-butanediol in the diet for up to 8 weeks; abnormalities were not observed in tissues from major organs.

Intermittent oral administration of pentylene glycol to rats over a 28-week period yielded a TDLo of 2,450mg/kg. In a 92- to 97-day oral toxicity study involving mice, rats, dogs, and monkeys dosed with a formulation containing propylene glycol (dose = 1000 mg/kg), there were no adverse effects on body weight, feed consumption, clinical pathology, histopathology, or adverse clinical observations.

Cetyl glycol (130 µg/ml) had a cytocidal effect on Ehrlich ascites carcinoma cells, lauryl glycol (99 µM) had a hemolytic effect on human erythrocytes, and pentylene glycol (5%) induced apoptosis in a human promyelocytic leukemia cell line *in vitro*.

Based on Draize test results, lauryl glycol has been classified as a severe ocular irritant. Undiluted 1,2-butanediol , but not 10% aqueous, induced ocular irritation in rabbits. Undiluted decylene glycol (SymClariol®) induced corrosion when instilled into the eyes of rabbits. In an in vitro ocular irritation assay (HET-CAM), 1% SymClariol® in neutral oil and caprylyl glycol (1% and 3%) in neutral oil were classified as non-irritants; however, a 50:50 (w/w) mixture of caprylyl glycol and 1,2-hexanediol was classified as a severe ocular irritant when evaluated at a concentration of 1% aqueous (effective concentration per ingredient = 0.5%) in the same assay. Together, the results of a neutral red release (NRR) assay, the HET-CAM assay, and the reconstituted human epithelial culture (REC) assay indicated that a lash gel serum containing 3% pentylene glycol might be a slight ocular irritant.

In the guinea pig maximization test, results were negative for caprylyl glycol at a challenge concentration of 50% in petrolatum. Undiluted decylene glycol (SymClariol®) was classified as a moderate skin irritant in rabbits, but did not induce sensitization in the guinea pig maximization test at challenge concentrations of 2% and 5% in arachis oil or in the mouse local lymph node assay at concentrations of 5% to 50% in acetone/olive oil (4:1). Repeated applications of 1,2-butylene glycol to the skin of rabbits did not result in skin irritation, and results were negative for 1,2-hexanediol (10% to 100%) in the mouse local lymph node assay for evaluating sensitization potential.

An NOAEL of 1,000 mg/kg for reproductive/developmental toxicity has been reported for 1,2-butanediol in rats dosed orally. In a prenatal developmental toxicity study involving rats, an NOEL of 300 mg/kg was reported for 1,2-hexanediol.

Caprylyl glycol, > 98% (Dermosoft® Octiol) did not induce gene mutations in Chinese hamster V79 cells (concentrations up to 1480 µg/ml) and >98% caprylyl glycol (ADEKA NOL OG) did not induce chromosomal aberrations in Chinese hamster lung cells (concentrations up to 700 µg/ml) *in vitro*. Decylene glycol (SymClariol®) was non-genotoxic in the Ames test, and 1,2-Butanediol was not genotoxic in assays involving bacterial cells (doses up to 5,000µg/plate) or mammalian cells (doses up to 0.9 mg/ml). Marked antitumor effects of cetyl glycol were observed in mice *in vivo* following i.p. doses of 80 mg/kg/day. Cetyl glycol (130 µg/ml) was found to have a cytocidal effect (irreversible cell degeneration) on cultured EAC cells.

Results were negative for skin irritation and sensitization potential in RIPTs in which 105 subjects were patch tested with a lipstick containing 0.5% caprylyl glycol and 101 subjects were patch tested with a leg and foot gel containing 0.5% 1,2-hexanediol. An in-use test of a body wash containing 0.15% 1,2-hexanediol did not result in skin irritation or sensitization reactions in 28 subjects. 1,2-hexanediol/caprylyl glycol mixture (in preservative system) was non-sensitizing at a concentration of 0.5% or 15% in an RIPT involving 205 human subjects. Skin sensitization also was not observed in another RIPT in which 56 subjects were tested with a 50:50 (w/w) mixture of 1,2-hexanediol and caprylyl glycol (Symdiol® 68; effective concentration per ingredient = 10%). Decylene glycol (SymClariol®) did not induce skin irritation in 52 subjects or sensitization (RIPT) in 55 subjects patch tested at a concentration of 20% in petrolatum. However, SymClariol® (1% in neutral oil) had low skin irritation potential when applied to scarified skin in a group of 10 subject, and very slight stinging potential when tested at concentrations of 1% and 2% in neutral oil in 10 subjects. A foundation containing 0.112% pentylene glycol did not induce skin irritation or sensitization in an RIPT involving 101 subjects.Positive reactions were observed in a patient patch tested with 0.5% and 5% 1,2-pentylene glycol, but not in the control group.

Propylene Glycol

In mammals, the major pathway of PG metabolism is to lactaldehyde and then lactate via hepatic alcohol and aldehyde dehydrogenases. When PG was administered i.v. to human subjects (patients), elimination from the body occurred in a dose-dependent manner.

Dermal penetration of PG from a ternary cosolvent solution through hairless mouse skin was 57% over a 24 h period. Using thermal emission decay (TED)-Fourier transform infrared (FTIR) spectroscopy, it appeared that PG did not reach the dermis.

PG is a penetration enhancer for some chemicals and, under some conditions, in human subjects, and can act synergistically with other enhancers. The mechanism by which PG enhances penetration has not been identified.

Based on the 1994 safety assessment and more recent information, few toxic effects were seen in dosing with PG. The oral LD_{50} of PG was >21 g/ kg for rats. The dermal LD_{50} of PG was >11.2 g/kg for mice and was 13 g/kg for rats. Mortalities were observed in mice at the highest i.p. dose of PG (10,400 mg/kg). All mice survived in a short-term study in which mice were given 10% PG in drinking water for 14 days, and all rats and mongrel dogs survived oral dosing with up to 3.0 ml 100% PG, 3 times per day, for 3 days. In a subchronic study, a dose of ≤50,000 ppm PG given in the feed for 15 wks did not produce any lesions. Subchronic inhalation data reported some effects in rats due to PG exposure of 2.2 mg/l air for 6 h/day, 5 days/wk, for 13 wks, but these effects were inconsistent and without dose-response trends. In the 1994 safety assessment, no toxic effects were reported in chronic studies when rats or dogs were given feed containing 50 g/kg or 5 g/kg, respectively, PG.

Undiluted PG was, at most, a slight ocular irritant. Dermal irritation studies were reported in the 1994 CIR final safety assessment and in the amended final safety assessment. In one study using nude mice, 50% PG may have caused skin irritation, while in another study, 100% PG was minimally irritating to hairless mice. Hypertrophy, dermal inflammation, and proliferation were also observed with 50% PG in nude mice. These effects were not seen in hairless mice with undiluted PG. Undiluted PG was at most a mild dermal irritant in a Draize test using rabbits with intact and abraded skin. No reactions to undiluted PG were observed with guinea pigs, rabbits, or Gottingen swine. PG (concentrations not given) was negative in a number of sensitization assays using guinea pigs. In a study using guinea pigs, 0.5 ml PG was a weak sensitizer.

Oral administration of PG did not have any adverse reproductive or developmental effects when evaluated in mice at concentrations of ≤5%, rats at doses of ≤1600 mg/kg, rabbits at doses of ≤1230 mg/kg, or hamsters at doses of ≤1550 mg/kg. 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 in mice reported an increase in the frequency of premature centrosphere separation with 1300-5200 mg/kg PG. In zygotes from PG-dosed mice, hyperploidy was increased.

PG, ≤10,000 μg/plate, was not mutagenic in Ames tests with or without metabolic activation. PG, tested at concentrations of 3.8-22.8 mg/ml, was a weak but potential inducer of sister chromatid exchanges (SCEs), causing a dose-dependent 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. PG, 32 mg/ml, induced chromosomal aberrations in a Chinese hamster fibroblast line, but not in human embryonic cells. PG was not mutagenic in mitotic recombination or base pair substitution assays, or in a micronucleus test or a hamster embryo cell transformation assay.

PG was not carcinogenic in a 2-yr chronic 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.

Combined exposure to PG and oleic acid synergistically enhanced the dermal penetration of both compounds. Addition of PG to an isopropanol vehicle enhanced the irritant reactions of benzoic acid; maximal enhancement was seen with 5% PG.

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%, although results were questionable in a RIPT of a deodorant containing 73% PG. Additionally, in a modified Draize sensitization study with 203 subjects, PG (0.2 ml, concentration not stated) induced 19 cutaneous reactions at challenge. PG did not produce a photoallergic response in a provocative photopatch test. Retrospective analysis of pools of patient patch test data indicated that ≤6.0% of patients tested had positive reactions to 30% aq. PG. A few case reports concerning PG and hand dermatitis or atopic dermatitis have been described, and positive reactions were reported.

DISCUSSION

The available safety test data for 1,2-glycols indicate that they are not significant acute toxicants, are not significantly genotoxic, are non-carcinogenic, and are not significant dermal irritants, sensitizers or photosensitizers. Data on the following 1,2-glycols were reviewed: caprylyl glycol, lauryl glycol, stearyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, 1,2-hexanediol, C15-18 glycol, and propylene glycol. Many of the studies included in this safety assessment are on propylene glycol. However, because increasing the chain length of the carbon backbone likely will not increase the potential for toxicity of longer-chain 1,2-glycols, data on propylene glycol may be used to support the safety of all 1,2-glycols reviewed in this safety assessment.

Results from an *in vitro* skin penetration study on 5% caprylyl glycol in 70% ethanol/30% propylene glycol (5% Dermosoft Octiol) using female pig skin indicated significant percutaneous absorption of caprylyl glycol. Dermal penetration modeling data on caprylyl glycol (C8), 1,2-hexanediol (C6), decylene glycol (C10), and lauryl glycol (C12) predicted that skin penetration would decrease with increasing chain length. Acknowledging the dermal absorption of these compounds, the Expert Panel determined that evaluation of reproductive/developmental toxicity data would be key to determining a safe level. The results of oral reproductive/developmental toxicity studies on propylene glycol (C3), 1,2-butanediol (C4), and 1,2-hexanediol (C6) were negative, and there was no evidence of systemic toxicity in other oral repeated dose toxicity studies involving caprylyl glycol (C8), propylene glycol (C3), 1,2-butanediol (C4), pentylene glycol (C5), and decylene glycol (C10). Additionally, the available repeated dose toxicity data included some 28-day oral toxicity studies, but no 28-day dermal toxicity data, and dermal reproductive/developmental toxicity data also were not available. However, the Expert Panel agreed that these oral toxicity data could be used to evaluate the safety of 1,2-glycols in products applied to the skin in the absence of dermal studies, because 1,2-glycol blood levels following oral exposure would be higher when compared to dermal exposure and systemic toxicity was absent in the oral studies.

Dermal absorption modeling data predicted that skin penetration decreases with increasing chain length, significant dermal penetration of the longer chain 1,2 glycols may occur. Metabolism modeling data on caprylyl glycol, 1,2-hexandiol, decylene glycol and lauryl glycol predicted that *C*-oxidation, *C*-hydroxylation, glucuronidation, and beta-oxidation may take place to form corresponding metabolites. The Expert Panel agreed that the negative oral reproductive/developmental toxicity (up to C6) and other negative oral repeated dose toxicity data (up to C10) may be extrapolated to longer –chain 1,2-glycols. The negative results of bacterial/mammalian genotoxicity assays on caprylyl glycol, 1,2-butanediol, and decylene glycol were also considered, and the Expert Panel agreed that these data can also be extrapolated to longer-chain 1,2-glycols as well. Thus, the modeling data predictions of decreased skin penetration of longer-chain 1,2-glycols and those relating to their metabolic fate, together with the negative oral toxicity data on shorter-chain 1,2-glycols and genotoxicity data, support the safety of all of the 1,2-glycols reviewed in this safety assessment in products applied to the skin.

The Expert Panel noted the potential for caprylyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol to be penetration enhancers. Some cosmetic ingredients have been regarded as safe based on the fact that they do not penetrate the skin. If caprylyl glycol, decylene glycol, pentylene glycol, 1,2-butanediol, and 1,2-hexanediol enhance the penetration of such ingredients, then industry is advised to consider the impact of the penetration enhancing activity of these ingredients on the safety of other ingredients in formulation.

CONCLUSION

The CIR Expert Panel concluded that the following cosmetic ingredients are safe in the present practices of use and concentration described in this safety assessment:

- 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*

*Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the 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; preservative
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; preservative
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[57]
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[57]
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[58]
Boiling point	356.1 ± 10.0°C (760 Torr)	ACD/Labs[57]
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[57]
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[59]
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)	″
Myristyl glycol		
Molecular weight	230.39	ACD/Labs[57]
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)	″

Table 2. Chemical and Physical Properties

Property	Values	Reference
Mass intrinsic solubility	0.0015 g/l (25°C)	ACD/Labs[57]
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[57]
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[57]
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[60]
Boiling point	377.2 ± 10.0°C (760 Torr)	ACD/Labs[57]
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		
Form	Specification: Colorless liquid with mild odor (as > 98% caprylyl glycol [Dermosoft® Octiol])	Straetmans[8]
Molecular weight	146.23	ACD/Labs[57]
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)	″
Mass intrinsic solubility	4.2 g/l (25°C)	″
Mass solubility	4.4 g/l (pH 7, 25°C)	″
Molar intrinsic	0.029 mol/l (25°C)	″

Table 2. Chemical and Physical Properties

Property	Values	Reference
solubility		
Molar solubility	0.030 mol/l (pH 7, 25°C)	″
Glycol value	Specification: 740 to 770 (as Dermosoft® Octiol)	Straetmans[8]
Melting point	36 to 37°C (not calculated)	Fringuelli[61]
Boiling point	137 to 139°C (not calculated); 243.0 ± 8.0°C (760 Torr)	Mugdan[62]
Flash point	109.1 ± 13.0°C	ACD/Labs[57]
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		
Form	Whitish to white waxy mass (as 98% to 100% decylene glycol [SymClariol®])	Symrise[9]
Molecular weight	174.28	STN[11]
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[59]
Melting point	42 to 52°C	Symrise[9]
Boiling point	93 to 96°C (0.5 Torr) - not calculated; 255.0 ± 0.0°C (760 Torr)	Orito[63]
Flash point	122.4 ± 13.0°C	ACD/Labs[57]
Flash point	>100ºC (as SymClariol®)	Symrise[9]
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[57]
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[64]
Refractive index	1.4400 (20°C, λ = 589.3 nm) – not calculated	Emmons[65]
Mass intrinsic solubility	95 g/l (25°C)	ACD/Labs[57]
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[64]; Emmons[65]
Flash point	104.4 ± 0.0°C	ACD/Labs[57]
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[57]
Molar volume	89.9 ± 3.0 cm^3/mol (20°C, 760 Torr)	″

Table 2. Chemical and Physical Properties

Property	Values	Reference
Density	1.0205 g/cm^3 (20°C) – not calculated; 1.001 ± 0.06 g/cm^3 (20°C)	Mamedov[66]; Tishchenko[67]
Refractive index	1.4380 (20°C, λ = 589.3 nm)	ACD/Labs[57]
Mass intrinsic solubility	230 g/l (25°C)	″
Solubility	Very soluble in water	NIOSH[13]
Mass solubility	230 g/l (pH 7, 25°C)	ACD/Labs[57]
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[11]
Boiling point	132 to 133°C (760 Torr) – not calculated; 190.3 ± 8.0°C (760 Torr)	Clendenning[64]; Hill[68]
Flash point	93.3 ± 0.0°C	ACD/Labs[57]
Enthalpy of vaporization	49.64 ± 6.0 kJ/mol (760 Torr)	″
Vapor pressure	1.48E-01 Torr 10 (20ºC)	″ NIOSH[13]
pKA	14.27 ± 0.20 (25°C)	STN[11]
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		
Form	Colorless to light yellow liquid with a characteristic odor (as Hydrolite-6, 99% 1,2-hexanediol)	Symrise[69]
Molecular weight	118.17	ACD/Labs[57]
Molar volume	122.9 ± 3.0 cm^3/mol (20°C, 760 Torr)	″
Density	0.961 ± 0.06 g/cm^3 (20°C)	″
Relative density (D20/4)	0.9490 to 0.9540 (as Hydrolite-6)	Symrise[69]
Refractive index	1.4518 (25°C, λ = 589.3 nm) – not calculated	Zelinski[70]
Refractive index (n20/D)	1.4400 (as Hydrolite-6)	Symrise[69]
Solubility	Readily soluble in water and oil	
Mass intrinsic solubility	37 g/l (25°C)	ACD/Labs[57]
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[71]
Flash point	95.8 ± 13.0°C	″
Flash point	>100ºC (as Hydrolite-6)	Symrise[69]
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 Frequency and Concentration of Use According to Duration and Type of Exposure[14,15]

	Caprylyl Glycol		**Decylene Glycol**		**Pentylene Glycol**	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Exposure Type						
Eye Area	269	0.3 to 5	NR	NR	114	0.005 to 4
Possible Ingestion	NR	NR	NR	NR	6	NR
Inhalation	27	0.2 to 0.5	NR	NR	6	1
Dermal Contact	1843	0.0003 to 5	1	NR	775	0.001 to 5

Deodorant (underarm)	36	0.03 to 2	NR	NR	3	0.2
Hair - Non-Coloring	101	0.0002 to 2	NR	NR	8	0.001
Hair-Coloring	1	0.002 to 5	NR	NR	NR	NR
Nail	8	0.0004 to 0.5	NR	NR	1	4 to 5
Mucous Membrane	NR	NR	NR	NR	6	0.001 to 5
Bath Products	63	0.0004 to 1	NR	NR	1	NR
Baby Products	11	0.6	NR	NR	NR	NR
Duration of Use						
Leave-On	1721	0.00003 to 5	1	NR	713	0.005 to 5
Rinse off	416	0.0004 to 2	NR	NR	105	0.001 to 5
Totals/Conc. Range	2137	0.00003 to 5	1	NR	818	0.001 to 5
	1,2-Hexanediol		**C15-18 Glycol**			
	# of Uses	Conc. (%)	# of Uses	Conc. (%)		
Exposure Type						
Eye Area	35	0.3 to 0.7	NR	NR		
Possible Ingestion	39	0.3	NR	NR		
Inhalation	2	10	NR	NR		
Dermal Contact	215	0.00005 to 10	1	NR		
Deodorant (underarm)	3	NR	NR	NR		
Hair - Non-Coloring	4	0.0003 to 0.3	NR	NR		
Hair-Coloring	NR	NR	NR	NR		
Nail	1	0.4	NR	NR		
Mucous Membrane	14	0.3	NR	NR		
Bath products	2	0.2	NR	NR		
Baby Products	3	NR	NR	NR		
Duration of Use						
Leave-On	182	0.2 to 10	1	NR		
Rinse off	51	0.00005 to 0.8	NR	NR		
Totals/Conc. Range	233	0.00005 to 10	1	NR		

NR = Not Reported; NS = Not Surveyed; Totals = Rinse-off + Leave-on Product Uses.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

Table 4. Corticosterone and TEA Permeability Coefficients in the Presence of Permeation Enhancers[12]

Enhancer	**Enhancer Concentration (M)**	**Permeability Coefficient of CS$^{\alpha}$ (cm/s x 10^{7})**	**Permeability Coefficient of TEA$^{\alpha}$ (cm/s x 10^{8})**
PBS – control		2.2 ± 0.8	1.35 ± 0.65
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	
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 2. Octanol/Water Partitioning Coefficient (log P)

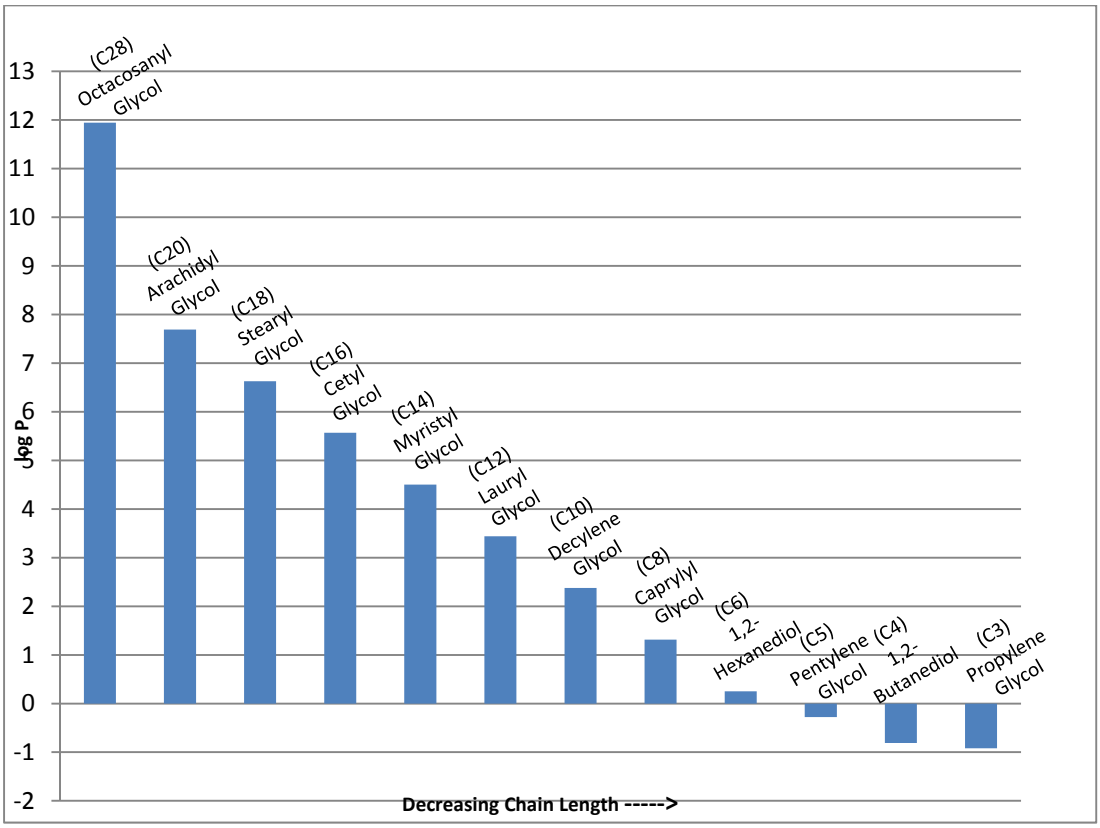
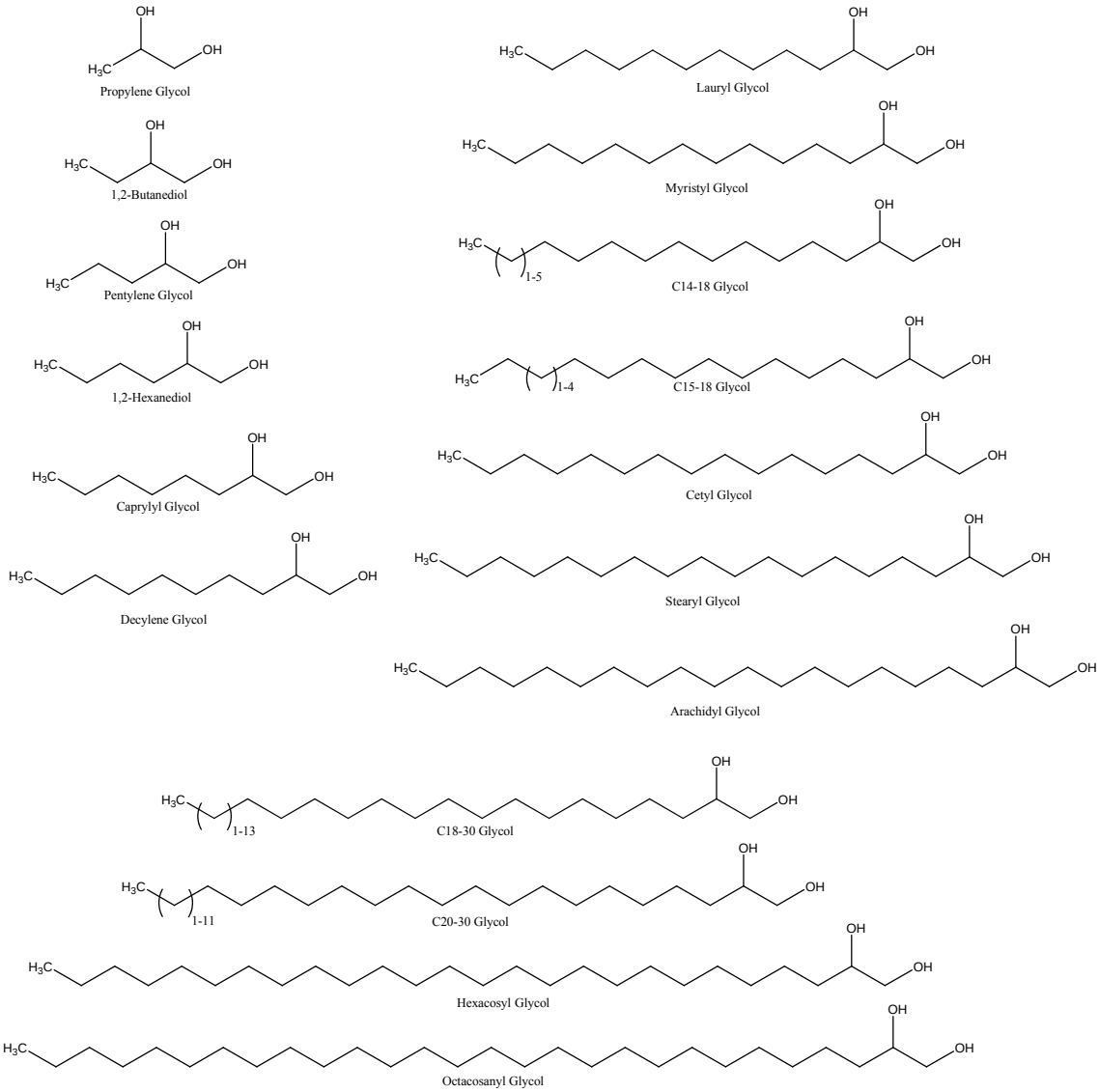


Table 5. Retrospective analyses with propylene glycol

No. of patients	Years studied	% PG	Methods	Findings
not given	1984-1996	10 aq.	data were collected from NACDG-reported studies; the SPIN for each allergen was calculated as the proportion of the population allergic by the weighted clinician-assessed likelihood of relevance of the reaction	the SPIN rank for PG has changed over time: 23 in 1984-1985; 40 in 1992-1994; 41 in 1994-1996[72]
45138 patients (16210 males; 28928 females)	1992-2002	20 aq.	analysis of a large pool of IVDK patch-test data, examining possible relevance of patient characteristics	- 1044 patients (2.3%), 412 males and 632 females, had positive reactions; 895, 129, and 20 patients had 1+, 2+, and 3+ reactions, respectively; of the 895 1+ reactions, 114 were to PG only - 1041 doubtful, 43 follicular, and 271 irritant reactions were observed - there were little difference between patients with positive and negative reactions to PG; the greatest difference was the high portion (27.2% vs. 13.1%) of patients with leg dermatitis – this was the only sig. risk factor - the most common concomitant reactions were with fragrance mix, balsam of Peru, lanolin alcohol, amerchol L-101, and nickel sulfate[73]
23359 patients	1996-2006	30 aq.	retrospective cross-sectional analysis of NACDG patch-test data to evaluate the patient characteristics, clinical relevance (definite – positive reaction to a PG-containing item; probable – PG was present in the skin contactants; possible – skin contact with PG-containing material was likely), source of exposure, and occupational relationship	- 810 patients (3.5%) had reactions to PG; 12.8% of the reactions were definitely relevant, 88.3% were currently relative (definite, probable or possible relevance), 4.2% were occupation related - 135 patients were positive to only PG; in these patients, the face was the most commonly-affected area (25.9%), a scattered or generalized pattern was next (23.7%) - the most common concomitant reactions were with balsam of Peru, fragrance mix, formaldehyde, nickel sulfate, and bacitracin[74]
1494 patients w/ SGD (patient pop. 10061)	2001-2004	30 aq.	retrospective analysis of cross-sectional NACDG data using only patients with SGD as the sole site affected	89 patients (6.0%) had positive reactions to PG 94% of the reactions were currently relative, with 30.3, 20.2, and 42.7% being of definite, probable, and possible relevance[75]
10061 patients	2001-2004	30 aq.	retrospective analysis of cross-sectional NACDG data to determine reactions to foods	109 patients (1.1%), 37 males and 72 females, had 122 reactions to foods; of those 122 reactions, 5 were to PG[76]

IVDK – Information Network of Departments of Dermatology
NACDG – North America Contact Dermatitis Group
SGD – scattered generalized distribution
SPIN – significance-prevalence index number, a parameter that assesses the relative importance of different allergens. SPIN for nickel (among the most clinically important allergens) = 894.[77]

Figure 1. Formulas of 1,2-Glycols



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