Safety Assessment of Alkane Diols as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	March 17, 2017
Panel Meeting Date:	April 10-11, 2017

The 2017 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This safety assessment was prepared by Laura N. Scott, Scientific Writer/Analyst.

1620 L Street, NW, Suite 1200 ◊ Washington, DC 20036-4702 ◊ ph 202.331.0651 ◊ fax 202.331.0088 ◊
cirinfo@cir-safety.org

Commitment & Credibility since 1976

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Laura N. Scott
Senior Scientific Writer
Date: March 17, 2017
Subject: Draft Tentative Report of the Safety Assessment of Alkane Diols as Used in Cosmetics

Enclosed is the Draft Tentative Report of the Safety Assessment of Alkane Diols as Used in Cosmetics (identified as *ADIOLS042017rep* in the pdf document). At the September 26-27th, 2016 meeting, the Panel issued an Insufficient Data Announcement for all of the alkane diols with requested data needs as follows: method of manufacturing (all ingredients), impurities (all ingredients), penetration enhancement (all ingredients), neurotoxicity (Isopentydiol), and concentration of use (1,4-Butanediol).

The CIR report history (*ADIOLS042017hist*), Process Flow Chart (*ADIOLS042017flow*), Literature Search Strategy (*ADIOLS042017strat*), 2017 VCRP data (*ADIOLS042017FDA*), Ingredient Data Profile (*ADIOLS042017prof*), and Minutes from the Sept 2016 Meeting (*ADIOLS042017min*) are enclosed for the Panel's review. Council comments on the Draft Report from the Sept 2016 Meeting (*ADIOLS042017pcpc*) were received and have been addressed. Industry data submitted to the Council were received by CIR and have been incorporated into the report as appropriate (*ADIOLS042017data_1; ADIOLS042017data_2; ADIOLS042017data_3; ADIOLS042017data_4; ADIOLS042017data_5*).

The following have been added (highlighted in Tables and │bracketed│ in text) to the safety assessment since the September 2016 Meeting:

1. Unpublished ADME and phototoxicity data for 1,5-Pentanediol, which was presented to the Panel in Wave 2 at Sept 2016 Meeting.
2. Penetration enhancement and clinical studies data for 1,5-Pentanediol (from 3 journal articles referenced in Wave 2 from Sept 2016 Meeting).
3. Unpublished toxicity studies for 1,10-Decanediol (*ADIOLS042017data_1*); hardcopies were made available at the Sept Panel Meeting because it was received after Wave 2.
4. Impurities data for Propanediol; 1,4-Butanediol; 1,5-Pentanediol; Hexanediol; Methylpropanediol; and Isopentyldiol.
5. Penetration enhancement data (journal article) for Propanediol, 1,4-Butanediol, and 1,5-Pentanediol and method of manufacture for Propanediol (unpublished data from industry).
6. Chronic Toxicity study for 1,4-Butanediol (OECD-SIDS report).
7. Human dermal irritation/sensitization and phototoxicity data (unpublished data from industry) and a case report (journal article) for 1,5-Pentanediol.
8. Human sensitization data at maximum concentration of use for Methylpropanediol (21.2%, unpublished from industry).

1620 L Street, NW Suite 1200, Washington, DC 20036
(Main) 202-331-0651 (Fax) 202-331-0088
(Email) cirinfo@cir-safety.org (Website) www.cir-safety.org

Please consider for discussion the following:

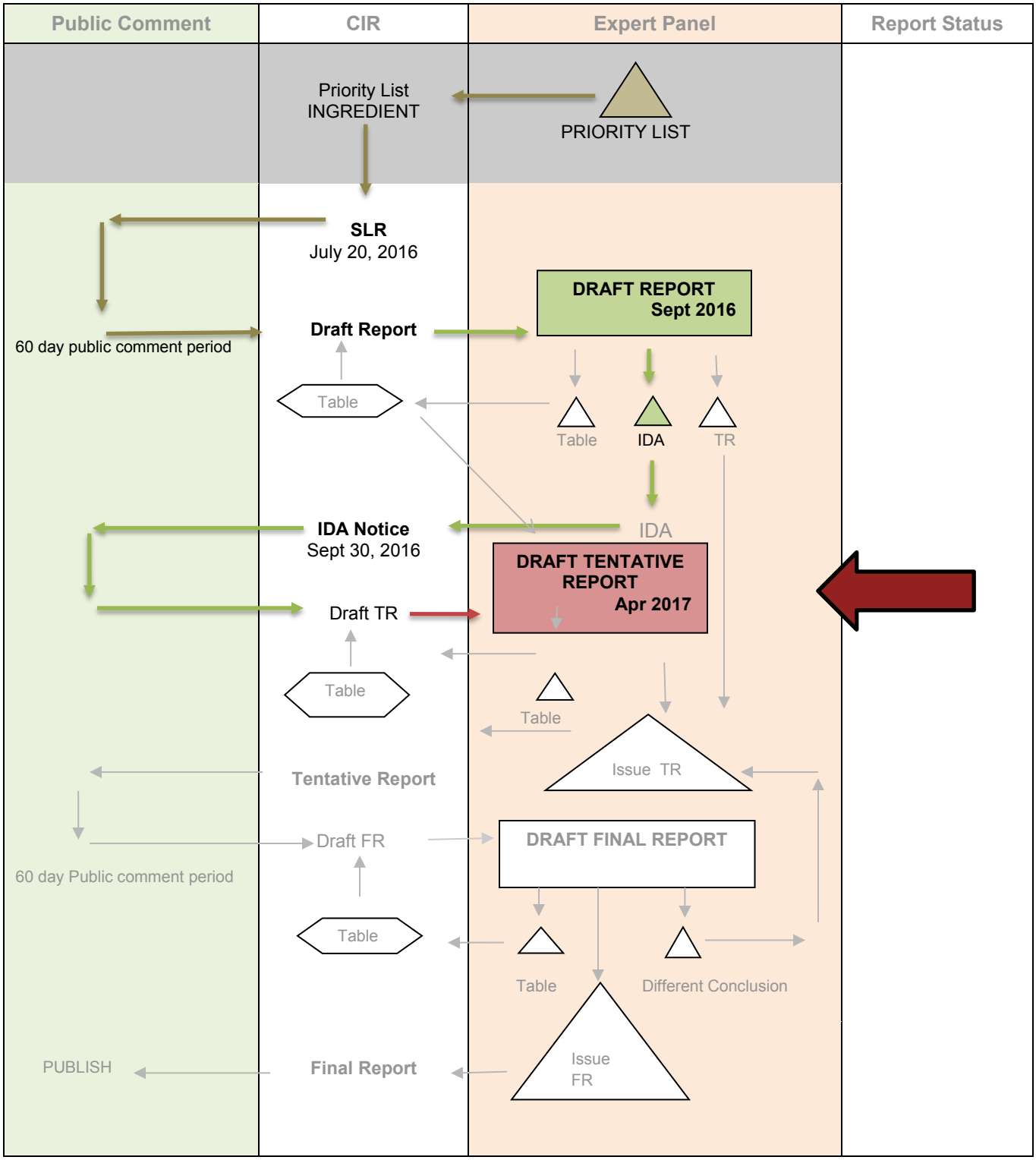
A. Additional data in #'s 4-8 above.
B. Should the Discussion section of the report include analysis of the differences in toxicity between the alkane diol ingredients based on their regiochemistry?
C. Should the Discussion section mention the systemic toxicity observed following dermal, oral, and inhalation exposure to high doses/concentrations of alkane diols in acute, short-term, and subchronic animal studies?
D. Does the *in vivo* genotoxicity study indicating that Propanediol is converted to malondialdehyde, subsequently causing damage to rat DNA (liver and testicular homogenates were tested), need to be addressed in the Discussion section?
E. In *ADIOLS042017data_4* (last paragraph on pdf page 3) there is an industry synopsis of the English abstract for a reference to a Chinese article (abstract only in English with limited details) evaluating the ability of Propanediol to increase the in vitro skin penetration of diphenhydramine hydrochloride. A Google search produced this link to the English version of the abstract http://en.cnki.com.cn/Article_en/CJFDTOTAL-ZGYA200831009.htm. The abstract indicates that Propanediol is a penetration enhancer for diphenhydramine hydrochloride. Does the Panel recommend including any of these abstract details in the report and if so, should the abstract in the above link or the industry submission (in *ADIOLS042017data_4)* be cited?

If the data included in this report adequately address the safety of the alkane diols, the Panel should be prepared to formulate a tentative conclusion, provide the rationale to be described in the Discussion, and issue a Tentative Report for public comment. If the data are not sufficient for making a determination of safety, then an Insufficient Data Announcement should be issued with a listing of the additional data that are needed.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Alkane Diols

MEETING April 2017



Report History-Alkane Diols

July 20th, 2016-The Alkane Diols Scientific Literature Review was posted at www.cir-safety.org for public comment.

September 26-27th, 2016-This was the first time the Expert Panel saw this safety assessment. The Panel issued an Insufficient Data Announcement for the Alkane Diols Draft Report presented at this meeting.

December 5th-6th, 2016-This report was not reviewed at the December Panel Meeting.

Alkane Diols Data Profile for April 10-11, 2017. Writer – Laura Scott

	Used in Cosmetics?	Safety Data Available?	*In Vitro*-Dermal Penetration	Penetration Enhancement			ADME					Acute Toxicity				Short-Term Toxicity		Sub-chron. Tox.		Chronic Tox.	DART	Geno-tox		Carcin-ogenicity	Neuro-tox	Dermal Irr.			Dermal Sen.		Photo-Irr/Sen		Ocular Irr.	
				In Vitro	Animal	Human	In Vitro	Animal-Oral	Animal-Other	Human-Dermal	Human-Oral & IV	Animal-Dermal	Animal-Oral	Animal-Inhalation	Animal-IV	Animal-Oral	Animal-Inhalation	Animal-Oral	Animal-Inhalation	Animal-Oral	Animal-Oral	In Vitro	In Vivo-Oral	Animal	Animal	In Vitro	Animal	Human	Animal	Human	Animal	Human	In Vitro	Animal
Propanediol (1,3-Propanediol)	Y	Y	X	X				X				X	X	X	X	X	X	X			X	X	X				X	X	X	X				X
1,4-Butanediol	Y	Y		X			X	X			X	X	X	X		X	X		X	X	X	X		X *	X		X	X	X	X				X
2,3-Butanediol	N	Y					X	X	X				X	X								X					X		X					X
1,5-Pentanediol	N	Y		X				X		X		X	X	X								X					X	X		X		X		X
Hexanediol (1,6-Hexanediol)	Y	Y						X				X	X	X		X		X			X	X					X		X					X
Octanediol (1,8-Octanediol)	Y	N																																
1,10-Decanediol	Y	Y											X									X				X	X	X	X		X		X	X
Methylpropanediol (2-Methyl-1,3-Propanediol)	Y	Y					X	X				X	X	X		X		X			X	X					X	X	X	X				X
Butyl Ethyl Propanediol	Y	Y										X	X			X		X			X	X	X				X		X					X
Isopentyldiol	Y	Y											X									X					X	X	X		X			X

X indicates available, relevant studies included in this safety assessment in each applicable category. Blank boxes indicate no available, relevant data were found in the literature or submitted.

*This study evaluated gamma-butyrolactone, which converts to gamma-hydroxybutyrate (GHB) in the body as does 1,4-Butanediol.

Alkane Diols Search Strategy Info

Ingredient	Cas No.	Prev Rev	in Use	NTIS	FDA/ CFR	NTP	TOXNET	WHO	ECHA	EPA	OECD/ SIDS	EU	NICNAS	Web
Propanediol (26264-14-2); 1,3-Propanediol (504-63-2)	**26264-14-2; 504-63-2**	No	Yes	X	X	-	X	-	X	X	-	-	-	X
1,4-Butanediol	**110-63-4**	No	Yes	X	X	X	X	X	X	X	X	-	X*	X
1,5-Pentanediol	**111-29-5**	No	No	X	X	-	X	-	X	-	-	-	-	X
Hexanediol (1,6-Hexanediol)	**26762-52-7; 629-11-8**	No	Yes	-	X	-	X	-	X	-	X	-	-	X
Octanediol (1,8-Octanediol)	**629-41-4**	No	No	X	-	-	-	-	-	-	-	-	-	X
1,10-Decanediol	**112-47-0**	No	Yes	-	-	X	X	-	-	-	-	-	-	X
Methylpropanediol (2-Methyl-1,3-Propanediol)	**2163-42-0**	No	Yes	-	-	-	X	-	X	X	-	-	X**	X
2,3-Butanediol	**513-85-9**	No	No	-	-	-	X	-	X	-	-	-	-	X
Butyl Ethyl Propanediol	**115-84-4**	No	Yes	-	-	-	X	-	X	-	-	-	-	X
Isopentyldiol	**2568-33-4**	No	Yes	-	-	-	-	-	-	-	-	-	X**	X

X indicates data were available; - indicates no relevant data were available; * indicates ingredients are in the Australian Inventory of Chemical Substances (AICS) and secondary notification conditions do not apply; ** indicates ingredients are in the Australian Inventory of Chemical Substances (AICS) and secondary notification conditions *do* apply

PubMed:

12-9-2015 Searched: ((((((((((toxicity or irritation or sensitization and (propanediol or 26264-14-2 or 504-63-2))) OR (toxicity or irritation or sensitization and (1,4-butanediol or 110-63-4))) OR (toxicity or irritation or sensitization and (1,5-pentanediol or 111-29-5))) OR (toxicity or irritation or sensitization and (hexanediol or 26762-52-7 or 629-11-8))) OR (toxicity or irritation or sensitization and (octanediol or 629-41-4))) OR (toxicity or irritation or sensitization and (1,10-decanediol or 112-47-0))) OR (toxicity or irritation or sensitization and (methylpropanediol or 2163-42-0))) OR (toxicity or irritation or sensitization and (2,3-butanediol or 513-85-9))) OR (toxicity or irritation or sensitization and (butyl ethyl propanediol or 115-84-4))) OR (toxicity or irritation or sensitization and (isopentyldiol or 2568-33-4)) *(353 hits/ 14useful that were not already discovered in SciFinder)*

Email updates are received when new articles (using similar search parameters as above) become available.

1-25-2017 Searched: structure activity relationship and penetration enhancement *(60 hits/ 1 potentially useful, but it was also found in SciFinder)*

SciFinder:

12-7-2015 Searched: propanediol toxicity, propanediol toxicokinetics, propanediol sensitization, propanediol irritation, 26264-14-2 toxicity, 504-63-2 toxicity, 1,4-Butanediol toxicity, 1,4-Butanediol irritation, 1,4-Butanediol sensitization, 110-63-4 toxicity, 110-63-4 irritation, 110-63-4 sensitization, 1,5-Pentanediol toxicity, 1,5 Pentanediol irritation, 1,5-Pentanediol sensitization, 111-29-5 toxicity, 111-29-5 irritation, 111-29-5 sensitization, Hexanediol toxicity, Hexanediol irritation, Hexanediol sensitization, 26762-52-7 toxicity, 26762-52-7 irritation, 26762-52-7 sensitization, 26762-52-7, 629-11-8 toxicity, 629-11-8 irritation, 629-11-8 sensitization, Octanediol toxicity, Octanediol irritation, Octanediol sensitization, 629-41-4 toxicity, 629-41-4 irritation, 629-41-4 sensitization, 629-41-4, 1,10-Decanediol toxicity, 1,10-Decanediol irritation, 1,10-Decanediol sensitization, 112-47-0 toxicity, 112-47-0 irritation, 112-47-0 sensitization, Methylpropanediol toxicity, Methylpropanediol irritation, Methylpropanediol sensitization, 2163-42-0, 2163-42-0 toxicity, 2163-42-0 irritation, 2163-42-0 sensitization, 2,3-Butanediol toxicity, 2,3-Butanediol irritation, 2,3-Butanediol sensitization, 513-85-9 toxicity, 513-85-9 irritation, 513-85-9 sensitization, Butyl Ethyl Propanediol, Butyl Ethyl Propanediol toxicity, Butyl Ethyl Propanediol irritation, Butyl Ethyl Propanediol sensitization, 115-84-4, 115-84-4 toxicity, 115-84-4 irritation, 115-84-4 sensitization, Isopentyldiol, Isopentyldiol toxicity, Isopentyldiol irritation, Isopentyldiol sensitization, 2568-33-4, 2568-33-4 toxicity, 2568-33-4 irritation, 2568-33-4 sensitization *(1702 hits/84 useful)*

"Keep Me Posted" (started 12-7-2015) for email updates when new articles (using similar search parameters as above) become available.

1-25-2017 Searched: structure activity relationship and penetration enhancement *(46 hits/ 2 potentially useful)*

ECHA Citations

Date Accessed 2-22-2016 Searched CAS #'s: 26264-14-2 (Propanediol = 0 hits); 2568-33-4 (Isopentyldiol = 0 hits);

504-63-2 (Propane-1,3-diol = *1 hit* http://echa.europa.eu/registration-dossier/-/registered-dossier/2099);

110-63-4 (Butane-1,4-diol = *1 hit* http://echa.europa.eu/registration-dossier/-/registered-dossier/15496);

111-29-5 (Pentane-1,5-diol = 1 hit http://echa.europa.eu/registration-dossier/-/registered-dossier/14818);

629-11-8 (Hexane-1,6-diol = *1 hit* http://echa.europa.eu/registration-dossier/-/registered-dossier/15109);

629-41-4 (Octanediol = 0 hits); 112-47-0 (1,10-Decanediol = 0 hits); 2163-42-0 (Methylpropanediol = 0 hits);

513-85-9 (Butane-2,3-diol = *1 hit* http://echa.europa.eu/registration-dossier/-/registered-dossier/10060);

115-84-4 (2-Butyl-2-Ethylpropanediol = *1 hit* http://echa.europa.eu/registration-dossier/-/registered-dossier/12725)

12-10-15 and 12-11-15 Searched for Alkane Diols by CAS#'s, names above, and synonyms (when applicable) in NTP, NICNAS, ECHA, HPVIS/EPA, OECD/SIDS, WHO, and EU

12-15-15 and 12-16-15 Searched for Alkane Diols by CAS#'s, names above, and synonyms (when applicable) in NTIS, TOXNET, FDA/CFR

Daily Med

3-2-2016 Searched for Alkane Diols by names above and synonyms at http://dailymed.nlm.nih.gov/dailymed/ ; None of the Alkane Diol ingredients above appeared on prescription medication labels

Drug Enforcement Agency

3-2-2016 Searched for 1,4-Butanediol because it is known to be an illicit drug of abuse and analog to gamma-hydroxybutyric acid (GHB; also known as "the date rape drug" for its intoxicating and sedative effects); 1,4-Butanediol and GHB share very similar metabolism in the human body as 1,4-Butanediol is rapidly converted to GHB after oral administration. Found several hits on DEA website under the Controlled Substances Act at http://www.deadiversion.usdoj.gov/21cfr/21usc/index.html when 1,4-Butanediol was the search term used; 1,4-Butanediol was considered by the FDA to be a Class I Health Hazard in 1999 because it is an analog of GHB; the warning letter issued by FDA in 1999 for 1,4-Butanediol, GHB, and another GHB analog gamma-butyrolactone (GBL) indicated that these possess a significant health hazard; DEA search hits from 2000, 2003, 2005, and 2013 indicate that 1,4-Butanediol and GBL are considered controlled substance analogs and treated as Schedule I substances if they are intended for human consumption

FDA

3-2-2016 Searched for Alkane Diols by names above and synonyms at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm for FDA approved drug products containing the Alkane Diol ingredients; no hits found

3-29-2016 Searched for Alkane Diols by names above and synonyms at http://www.accessdata.fda.gov/scripts/cder/iig/ for inactive ingredients in FDA approved drug products; no hits found

CFR Citations

21CFR74.3045 (*1,4-Butanediol*): Part 74-Listing of Color Additives Subject to Certification; Subpart D-Medical Devices; Section 74.3045 [Phthalocyaninato(2-1)] copper.

(a) Identity. The color additive is [phthalocyaninato (2-1)] copper…
(b) Specifications. The color additive…shall conform to the following specifications and shall be free from impurities other than those named to the extent that such impurities may be avoided by current good manufacturing practices…
(c) Uses and restrictions. (1) The color additive…may be safely used to color polypropylene sutures, polybutester (the generic designation for the suture fabricated from 1,4-benzenedicaroxylic acid, polymer with ***1,4-butanediol*** and alpha-hydro-omega-hydroxypoly(oxy-1,4-butanediyl)…

21CFR175.105 (*1,4-Butanediol; Hexanediol*): Part 175-Indirect Food Additives: Adhesives and Components of Coatings; Subpart B-Substances for Use Only as Components of Adhesives; Section 175.105 Adhesives. (a) Adhesives may be safely used as components of articles intended for use in packaging, transporting, or holding food in accordance with the following prescribed conditions: (1) The adhesive is prepared from one or more of the optional substances named in paragraph (c) of this section, subject to any prescribed limitations…(c) Subject to any limitations prescribed in this section and in any other regulations promulgated under section 409 of the Act which prescribes safe conditions of use for substances that may be employed as constituents of adhesives, the optional substances used in the formulation of adhesives may include the following: (1) Substances generally recognized as safe for use in food or food packaging. (2) Substances permitted for use in adhesives by prior sanction or approval….(3) Flavoring substances permitted for use in food by regulations in this part…(4) Color additives approved for use in food. (5) Substances permitted for use in adhesives by other regulations in this subchapter and substances named in this subparagraph…: ***1,4-Butanediol***; Alcohols: ***1,6-Hexanediol***

21CFR177.1210 (*1,4-Butanediol*): Part 177-Indirect Food Additives: Polymers; Subpart B-Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces; Section 177.1210 Closures with sealing gaskets for food containers; Closures with sealing gaskets may be safely used on containers intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food in accordance with the following prescribed conditions:

(a) Closures for food containers are manufactured from substances generally recognized as safe for contact with food…
(b) Closure-sealing gaskets and overall discs are formulated from substances identified in 175.300(b)…and from other optional substances, including the following:
    (1) Substances generally recognized as safe in food
    (2) Substances used in accordance with the provisions of a prior sanction or approval within the meaning of section 201(s)…
    (3) Substances that are the subject of regulations in parts 174, 176, 177, 178 and 179.45 of this chapter…
    (4) Substances identified in….this section, used in amounts not to exceed those required to accomplish the intended physical or technical effect and in conformance with any limitation provided…
    (5) Substances that may be employed in the manufacture of closure-sealing gaskets include: Polyurethane resins manufactured from diphenylmethane diisocyanate, ***1,4-butanediol***, and adipic acid (CAS Reg. No. 26375-23-5)….For use only: No

limitation on amount used, but for use only in closure gasket compositions used in contact with food types VI-A and VI-C (up to 15 percent alcohol) under conditions of use D, E, F, and G, as described in 176.170(c) of this chapter, tables 1 and 2, respectively

21CFR177.1390 (*Hexanediol*): Part 177-Indirect Food Additives: Polymers; Subpart B-Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces; Section 177.1390 Laminate structures for use at temperatures of 250 deg. F and above…(c) Subject to the provisions of this paragraph, food-contact articles produced from high-temperature laminates may be safely used to package all food types except those containing more than 8 percent ethyl alcohol. (2) Adhesives. The use of adhesives in these containers is optional. Adhesives may be formulated from the following substances, subject to the prescribed limitations…(vi) Polyurethane-polyester resin-epoxy adhesives formulated from the following mixture: (2) Polyester resin formed by the reaction of polybasic acids and polyhydric alcohols listed in 175.300(b) (3) (vii) of this chapter. Additionally, azelaic acid and ***1,6-Hexanedi***ol may also be used as reactants in lieu of a polyhydric alcohol…(vii) Polyester-polyurethane resin-acid dianhydride adhesives for use at temperatures not to exceed 121 deg. C (250 deg. F), in contact only with food Types I, II, VIA, VIB, VIIB, and VIII….(a) (1) Polyesterpolyurethanediol resins prepared by the reaction of a mixture of polybasic acids and polyhydric alcohols….Additionally, dimethylol propionic acid and ***1,6-Hexanediol*** may be used alone or in combination as reactants in lieu of a polybasic acid and a polyhydric alcohol.

21CFR177.1500 (*1,4-Butanediol*): Part 177-Indirect Food Additives: Polymers; Subpart B-Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces; Section 177.1500 Nylon resins. The nylon resins listed in paragraph (a) of this section may be safely used to produce articles intended for use in processing, handling, and packaging food…(c) Nylon modifier-(1) Identity. Copolyester-graft-acrylate copolymer is the substance of 1,4-benzenedicarboxylic acid, polymer with ***1,4-Butanediol***, (E)-2-butenedioic acid, 1,2-ethanediol, ethyl 2-propenoate, hexanedioic acid and 2-propenoic acid, graft…and is derived from grating of 25 weight percent of acrylic polymer with 75 weight percent of copolyester. The copolyester is polymerized terephthalic acid (55 mol%), adipic acid (40 mol%), and fumaric acid (5 mol%) with ethylene glycol (40 mol%) and ***1,4-Butanediol*** (60 mol%).

21CFR177.1590 (*1,4-Butanediol*): Part 177-Indirect Food Additives: Polymers; Subpart B-Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces; Section 177.1590 Polyester elastsomers. The polyester elastomers identified in paragraph (a) of this section may be safely used as the food-contact surface of articles intended for use in contact with bulk quantities of dry food of the type identified in 176.170(c) of this chapter, table 1, under Type VIII, in accordance with the following prescribed conditions: (a) For the purpose of this section, polyester elastomers are those produced by the ester exchange reaction when one or more of the following phthalates-dimethyl terephthalate, dimethyl orthophthalate, and dimethyl isophthalate-is made to react with alpha-hydroomega-hydroxypoly (oxytetrmethylene) and/or ***1,4-Butanediol*** such that the finished elastomer has a number average molecular weight between 20,000 and 30,000.

21CFR177.1630 (*1,4-Butanediol*): Part 177-Indirect Food Additives: Polymers; Subpart B-Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces; Section 177.1630 Polyethylene phthalate polymers. Polyethylene phthalate polymers identified in this section may be safely used as, or components of plastics (films, articles, or fabric) intended for use in contact with food in accordance with the following prescribed conditions…List of Substances and Limitations…(v) Modifier: 1,4-Benzenedicarboxylic acid, dimethyl ester, polymer with ***1,4-Butanediol*** and [alpha]-hydro-omega-hydroxypoly(oxy-1,4-butanediyl)…meeting the following specifications: Melting point: 200 deg. To 215 deg. C…Density: 1.15 to 1.20…The modifier is used at a level not to exceed 5 percent by weight of polyethylene terephthalate film. The average thickness of the finished film shall not exceed 0.016 millimeter…

21CFR177.1660 (*1,4-Butanediol*): Part 177-Indirect Food Additives: Polymers; Subpart B-Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces: Section 177.1660 Poly (tetramethylene terephthalate). Poly (tetramethylene terephthalate) (poly (oxytetramethyleneoxyter-ephthaloyl))…identified in this section may be safely used as articles or components of articles intended to contact food, in accordance with the following prescribed conditions: (a) Identity. For the purpose of this section, poly (tetramethylene terephthalate) is the reaction product of dimethyl terephthalate with ***1,4-Butanediol*** to which may have been added certain optional substances to impart desired technological properties to the polymer.

21CFR177.1680 (*1,4-Butanediol; Hexanediol*): Part 177-Indirect Food Additives: Polymers; Subpart B-Substances for Use as Basic Components of Single and Repeated Use Food Contact Surfaces; Section 177.1680 Polyurethane resins. The polyurethane resins identified in paragraph (a) of this section may be safely used as the food-contact surface of articles intended for use in contact with bulk quantities of dry food of the type identified in 176.170(c) of this chapter, table 1, under Type VIII, in accordance with the following prescribed conditions: (a) For the purpose of this section, polyurethane resins are those produced when one or more of the isocyanates listed in paragraph (a) (1) of this section is made to react with one or more of the substances listed in paragraph (a) (2) of this section: (2) List of substances: ***1,4-Butanediol***. ***1,6-Hexanediol*** (CAS Reg. No. 629-11-8)…

21CFR177.2600 (*1,4-Butanediol*): Part 177-Indirect Food Additives: Polymers; Subpart C-Substances for Use Only as Components of Articles Intended for Repeated Use; Section 177.2600 Rubber articles intended for repeated use. Rubber articles intended for repeated use may be safely used in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food, subject to the provisions of this section…(c) Substances employed in the preparation of rubber articles include the following, subject to any limitations prescribed…(4) Substances identified in this paragraph (c) (4), provided that any substance that is the subject of a regulation in parts 174, 175, 176, 177, 178, and 179.45 of this chapter conforms with any specification in such regulation. (i) Elastomers.

Polybutadiene. Polyester elastomers derived from the reaction of dimethyl terephthalate, ***1,4-Butanediol***, and [alpha]-hydro-omega-hydroxypoly (oxytetramethylene). Additionally, trimethyl trimetllitate may be used as a reactant. The polyester elastomers may be used only in contact with foods containing not more than 8 percent alcohol and limited to use in contact with food at temperatures not exceeding 150 deg. F.

Polyisoprene. Polyurethane resins…derived from the reaction of diphenylmethane diisocyanate with ***1,4-Butanediol*** and polytetramethylene ether glycol. Polyurethane resins derived from reactions of diphenylethane diisocyanate with adipic acid and ***1,4-Butanediol***.

DR. MARKS: Okay, great. Any other comments? Okay, our next ingredient with be the alkane diols.

MRS. SCOTMS. SCOTT [MS. SCOTT]: Unpublished data came in after (inaudible).

DR. MARKS: Laura, I am probably going to ask you to summarize the unpublished data then. Once you pass that to the other team members so what we are handing is something that is -- data that has come in after wave two. I guess there are two ways to handle this, one would be Laura, you just summarize, we can kind of look at the table and the other would be postpone the review of this until say after lunch but I'd rather we just review it now.

So -- this is the first review of these ingredients. There are 10 and the first thing Tom, Ron, and Ron, are these ten ingredients, okay?

DR. SHACK [SHANK]: No, I see there is insufficient data and identified some data needs which did not include the 10 --

DR. HILL: I think he is asking about the grouping?

DR. MARKS: Yes, correct, and then we'll go -- yeah, I always like to start with are the ingredients

(inaudible) as they are an outlier which should be in this. Are the 10 ingredients okay and

then we'll go to the needs.

DR. SHACK [SHANK]: The 10 ingredients as a group is fine for me.

DR. SLAGA: Same here.

DR. HILL: So I had a nice active debate with myself the whole time and ever since, I let my left brain work on this and I agree that it's a reasonable grouping even though I certainly read the comment by Dr. Fergemant. I am not sure exactly how you say that but it should be close, at Gothenburg in Switzerland about just restricting to the terminal one, two dials but I felt like leaving in the ingredients as you have them is better.

I'll have some qualifying statements about that later but in terms of ingredients, in terms of both administratively keeping them together because there's enough similarity and second of all the thought that we might get some structure property relationships and structure toxicity relationships out of this, particularly because of an issue raise with one of them, keeping them together is a good idea but then I'll have some qualifying things to say in a little bit.

DR. MARKS: So since we got more data, Laura do you want to just briefly review table one or more than table one?

MS. SCOTT: No, the table at the front is just a summary table I created from the data that follows so it's an

anonymous submission. It's all for one, ten decane diol [1,10-Decanediol] which we don't have.

We really don't have data on that one so this is basically acute oral genotox dermal irritation in vitro and in vivo including human. Dermal sensitization, phototox and ocular irritation and what's highlighted are the main outcomes so basically dermal irritation was non-irritating except in humans there is mild erothema [erythema], sensitization was non-sensitizing, non-phototoxic.

Occular irritation was either non-irritating in vitro or slightly irritating in rabbits but it was reversible and the acute oral tox is an LD 50 that's greater than 20 milliliters per kilogram. That's basically the sum of it.

DR. HILL: We don't have any chronic dermal tox of any kind?

MS. SCOTT: On this particular ingredient?

DR. HILL: Or any chronic toxide --

MS. SCOTT: No, there is only sub-chronic --

DR. EISENMANN: But note they sell this material in propalin glycol and butelyn glycol so it's mostly propolin glycol or butelyn glycol. I don't remember the percentage that came down but I think it was fairly small.

MS. SCOTT: It's. 006. This data is actually reporting it at 1.2 percent so what the council industry survey

says is a little lower than what this data -- was submitted.

DR. MARKS: So, Tom, in wave two, were you okay with what we received in wave two?

DR. SLAGA: Well it was actually between wave two and that -- and now with the additional, there is a good bit of non-irritating, non-sensitizing and non-genotoxic data.

DR. MARKS: Okay, good. And then Ron Shank, we'll get your (inaudible). I wanted to comment the butanadiol poisoning that occurs and whether we feel that it's okay for use in cosmetics. I wanted to address that issue, that there would be enough absorbed that there would be any issues.

There are uses and we don't know the concentration in cosmetics, is that correct we didn't have the use.

MS. SCOTT: Correct, we only have frequency of use.

DR. SLAGA: Because not knowing the concentration, I would leave it out.

DR. MARKS: You would leave the ingredient out or insufficient?

DR. SLAGA: If we don't have any concentration to deal with in one four butane diol, how can we say --

DR. MARKS: We can say it's insufficient.

DR. SLAGA: To get in and that's enough --

DR. MARKS: RIF.

DR. SLAGA: Blackness to it that I would just get rid

of it.

DR. MARKS: So then you would recommend that we do nine ingredients and not ten?

DR. SLAGA: Right.

DR. MARKS: Ron and Ron, let's sort of reverse what we first said.

DR. SHACK [SHANK]: Why drop them? Why not just say insufficient?

DR. SLAGA: Well that's the same thing -- well not quite.

DR. MARKS: Well Ron Shank. I like the idea of insufficient and then we get the concentration and we can always say the margin of safety, if we can calculate that.

DR. SLAGA: Okay.

DR. MARKS: Ron Shank, is that good with you then?

DR. SHACK [SHANK]: That's all right but I have more.

DR. MARKS: Okay, so this would be an insufficient data notice then, it sounds like.

DR. BERGFIELD: Or final, tentative final with insufficient.

DR. MARKS: Normally when we see it the first time, we put in an insufficient data announcement and then - -

DR. HILL: I have other needs anyway.

DR. MARKS: Okay, let me -- that was the next part,

what are the needs? So we have one need is the concentration of use for one, four butane diol [1,4-Butanediol], okay. Ron Shank, you were chomping at the bit here for other needs.

DR. SHACK [SHANK]: We have on the list the name hexane diol [Hexanediol] and I think I am right. In every case, that is 1.6 hexane diol [1,6-Hexanediol] which is important because 2.5 hexane diol [2,5-Hexanediol] is a known neurotoxin. It's a precursor to the neurotoxin which is the dione, the deoxidation product so I would like to know if there is any 2.5 hexane diol [2,5-Hexanediol] in the cosmetic ingredient that would be an impurity or a specific request.

Then I think we needed the methods of manufacture for hexane diol [Hexanediol], octane diol [Octanediol] --

DR. MARKS: Hold on a second, so any 2.5 [2,5] impurity because the 2.5 [2,5] is a neurotoxin?

DR. SHACK [SHANK]: Yes, a precursor to the neurotoxin.

DR. BERGFIELD: Is it 2.5 [2,5] or 2.4 [2,4]?

DR. SHACK [SHANK]: It's 2.5 [2,5] and it's a very specific structure activity relationship there and a lot of toxicology information.

DR. MARKS: So, Ron, you would expect in manufacturing there could be some impurity with the 2.5 [2,5] so you're going to want to know the impurity, the level of 2.5

[2,5], not just -- if it's clarified, this means -- the hexane diol [Hexanediol] is 1.6 [1,6], you aren't going to be satisfied with that. You want to know what the 2.5 [2,5] impurity is?

DR. SHACK [SHANK]: Yes.

DR. MARKS: Okay.

DR. SLAGA: If it's present.

DR. MARKS: Yeah. Okay.

DR. SHACK [SHANK]: And methods of manufacture for the hexane diol [Hexanediol].

DR. MARKS: Okay. And do you want to leave it as hexane diol [Hexanediol] or do you want to be specific and say method of manufacture 1.6 [1,6]?

DR. SHACK [SHANK]: Well the report says hexane diol [Hexanediol]. Now if that's always 1.6 hexane diol [1,6-Hexaneidol], then it would be ask for method of manufacture for 1.6 [1,6]

DR. MARKS: Okay.

DR. HELDRETH: That is what the cosmetic ingredient is defined as, that's 1.6 [1,6].

DR. SHACK [SHANK]: Why don't we just say -- because hexane raises red flags in toxicology circle.

DR. MARKS: So in the --

DR. SHACK [SHANK]: It used to be used to textures proteins so you could make bacon out of soybeans and things like

that and they have some problems.

DR. MARKS: Bart, in the cosmetic ingredient dictionary, is it listed just as hexane diol [Hexanediol] or 1.6 [1,6]?

DR. HELDRETH: That is the INCI name and they define it by giving the structure of the 1.6 hexane diol [1,6-Hexanediol].

DR. MARKS: Okay, so it sounds like that clarifies what is in the -- what material is or what ingredient but we still want to know what the impurity -- if 2.5 [2,5] is an impurity and that's in method of manufacture and then obviously in the discussion, we are going to want to clarify that the hexane diol [Hexanediol] is indeed the 1.6 [1,6]. we don't want to leave that uncertain.

DR. SHACK [SHANK]: Would the hexane itself be a likely impurity in 1.6 [1,6]?

DR. HILL: Well, what I wrote down here is we have no real impurities data for any of these. Only one statement on reference that would seem to be the writer's reasonable but unsubstantiated conjecture and I don't think that getting impurities because what I know is typically with these low molecular weight kind of compounds depending on the production process that's used, the mixtures are not unreasonable expectation and I don't think we have any information to be

assured of that so I don't know if hexane -- I doubt that hexane is based on what I see and how these -- but we don't even have a solid -- this is the way these things are made industrially across the globe for cosmetic ingredient streams --

DR. MARKS: So did we want method manufacture for all the ingredients?

DR. HILL: Yes, sir.

DR. MARKS: Not just the 1.6 hexane diol [1,6-Hexanediol].

DR. HILL: Right, and then of course we won't necessarily get them if they are not but --

DR. MARKS: And impurities for all the ingredients?

DR. HILL: Yes and then the 2.3 butane diol 2,3-Butanediol], he still had the floor so I didn't want to --

DR. MARKS: We'll let Ron --

DR. HILL: Let Dr. Hill go.

DR. MARKS: Go ahead, Ron Hill.

DR. HILL: I was going to say the 2.3 butane diol [2,3-Butanediol] can be any of three (inaudible) isomers. We have mizo [miso], which is RS, which is equivalent to SR and I don't like the DNL [D and L] nomenclature here because this is not a sugar and it's not an amino acid but we have RR and SS which are not equivalent so then the question is are commercial 2.3 butane diol [2,3-Butanediol] mizo [miso], or a mixture of all

three or a mixture of two of the three and it's actually important because there's a lot of writing in the report and I'm glad that it's there talking about the role of 2.3 butane diol [2,3-Butanediol] and biochemistry but that would be in human biochemistry almost exclusively one of those three stereo isomers and so that's the significance of that particular piece of information.

Finally, while we are all on the same subject and this wraps up and now I've got two. We have several places in the table and we are getting an estimated value for the molecular weight whereas if it is singly that substance, we would know, no question exactly what that molecular weight is so the fact that the table does have an estimated value for molecular weight suggests we are not getting that information from the horse's mouth, so to speak and for me it raises the flag that we might in fact have mixtures with these ingredients so need to know that and then since I have one more datum, do you want me to give it now or --

DR. MARKS: Sure.

DR. HILL: We really need something about penetration enhancement for any of these -- all of these ingredients and it would be helpful because we can probably get at least a sketchy SPR, structural property relationship if we have it. And I don't know whether we have it but it's an issue with any of these,

especially the one that's the deck hand that's used at very low concentrations, I think that worries but the ones that -- in formulations, above 10 percent and is genuine concern.

So we could say just the ones that are in formulation above 10 percent and I'd be comfortable with that. Leave on about 10 percent -- 10 percent is arbitrary but that's in my mind the sort of threshold where I'd get really interested.

DR. MARKS: Which actually is propyl diol is close to 40 percent, the methyl propanediol is 21 percent, the isopenthyl diol is 15 percent so at least that is

(inaudible). Ron Shank, did you have any other needs?

DR. SHACK [SHANK]: Yes. I'd like to ask for neurotoxicity data on isopentyl diol.

DR. MARKS: Neuro --

DR. SHACK [SHANK]: Toxicity because it can be metabolized to the diaketone, similar to 2.4 hexane diol [2,4-Hexanediol] which is known so the industry could address that.

DR. MARKS: Which one was that again, Ron?

DR. SHACK [SHANK]: Isopentyl diol.

DR. MARKS: Okay. And anything else, Ron Shank?

DR. SHACK [SHANK]: That's it.

DR. MARKS: Okay --

DR. HILL: I have some --

DR. MARKS: Okay.

DR. HILL: Those were my needs, I have a couple of other issues.

DR. MARKS: Which would not be in the insufficient data?

DR. HILL: They would not be in the insufficient data so if you want to wait?

DR. MARKS: No, let's see them tomorrow when we have a discussion if you want to bring them up again, Ron Hill, this way Ron Shank and Tom can react. Yeah, and nobody brought up the irritation sensitization. I thought that was fine and the data that we received this morning is fine.

DR. HILL: So I am going to consult with the toxicologist here for a moment. We have this strange -- seemingly strange piece of information that without activation, we're seeing some sign of genotox with the 1.3 propane diol [1,3-Propanediol]. With activation, we don't see and I can easily explain that as a possibility and then we have some additional in vivo date [data] as I remember, that also flags this a little bit because if we are going to have any genetox with this molecule, it will be crosslinking through a dialdehyde.

If you give this alcohol to the cells, they may be able to make a dialdahyde and they might not have enough alcohol

dehydrogenase to convert those (inaudible) further to carboxylic acid and we cross link but if you put in the presence of activating enzymes, it might convert at least one of those two dialdehydes to carboxylic acid, in which case we can no longer cross link and we don't have the concern so I looked at this from both the en vivo and en vitro data and said this could be real and have we investigated this enough to definitely write it off because it is ingredients that large concentration that are used on wide areas of the skin.

DR. MARKS: Okay, so tomorrow -- again, I expect to second a motion with an insufficient data announcement and the needs (inaudible) concentration used for the 1.4 butane diol [1,4-Butanediol] and I think we've had it clarified now that the hexane diol [Hexanediol] does refer to 1.6 [1,6](inaudible) and a 2.5 [2,5] impurity because of its precursor of the neurotoxin so we want concentration of that and then we want two, the method of manufacture at 1.6 hexane diol [1,6-Hexanediol] and all the ingredients.

The impurities for all penetration enhancement of about 10 percent on (inaudible) and then for neurotoxicity data on the isopentyl diol, does that capture it?

And then I think also in the discussion, we need the pesticide boilerplate plant sources --

DR. BERGFIELD: Could Tom address the question that

was raised by Ron Hill?

DR. HILL: I have a follow up before the then speaks to it which is I know we have this micronucleus data that's negative but we are talking about oral administration to rodents so the chances, under those circumstances, that we'd end up generating dialdahyde in bone marrow is small because rodents are very aggressive at further metabolizing so if we make an aldahyde systemically in the gut even before we get there, that's converted to carboxylic acid and we're done so the question is if you give this thing dermally at high concentrations, do we have enough add me [ADME] data to know that it's not going to reach bone marrow or any place else where this could be a concern so that was that.

Is it -- I could also explain why the en [in] vivo result was negative even in the face of that, without activation -- a genotox test based on the nature of rodents and oral administration and I know I am always saying this but oral administration is not an assurance when you've got things you use dermally at high concentration, particularly rodents because they are really aggressive at first pass metabolism. You lose a lot of compound unless you're given really high doses, saturating everything in site [in situ?] and even then, I am concerned and the micronucleus test, that's not the case.

And I know this is a big deal but I at least want to

raise it and make sure it gets put to bed.

DR. MARKS: Tom, did you want to make any coments [comments]?

DR. SLAGA: No.

DR. MARKS: Okay --

MS. SCOTT: Can I just ask to clarify on the penetration enhancement?

DR. MARKS: Sure.

MS. SCOTT: So we have 1.5 pentane diol [1,5-Pentanediol] penetration enhancement data for that indermal [in dermal] penetration data for the propane dial and so we're -- what we're asking for just generally penetration enhancement data for all of - -

DR. HILL: I'd like to have that, some sense of that for all of them --

MS. SCOTT: Okay.

DR. HILL: And I feel like that might be known unless it's not an ingredient that's in use.

MS. SCOTT: Okay.

DR. HILL: I want to make sure we comb the literature and look specifically if there is any science done where somebody might have an SAR on that particular attribute.

MS. SCOTT: Thank you.

DR. HILL: The other question is just a question

before we leave. Do we have clarification on which is 1.2 pentane diol [1,2-Pentanediol] or 1.5 [1,5] that's in that hydrogel wound dressing that was approved by FDA? He might not have it yet but --

MS. SCOTT: I'll look into it and see.

MINUTES FROM SEPTEMBER 2016 PANEL MEETING-ALKANE DIOLS-(Day 1) DR. BELSITO'S TEAM

DR. BELSITO: So then we're moving on to alkane diols.

MS. SCOTT: Here's some data that came in after Wave 2.

DR. LIEBLER: Oh, Wave 3, the dreaded Wave 3.

MS. SCOTT: It's summarized in a table on the first page.

DR. BELSITO: Okay, and remember we also had data in Wave 2 on the alkane diols as well. We also got information that 1,5-pentanediol was used in other products and it wasn't listed as having uses in the VCRP data and Council survey. It was in this resveratrol and then the Wave 2 data showed that it's in a number of other --

DR. SNYDER: It's a penetration enhancer.

DR. BELSITO: Yeah, it's a penetration enhancer. So I don't understand why that wasn't picked up. I was just concerned going up in this metabolism section. Where is it?

It's on PDF page 19 when we're talking about "detoxification of acetaldehyde through aldehyde dehydrogenase to form acetate." And, Dan, you can comment on whether you think this is relevant. But the third sentence says, "Acetoin can interconvert between diacetyl and 2,3-butanediol." And as you know, diacetyl was a huge disaster. It makes me very nervous when I start mentioning diacetyl in any cosmetic product report, you know, from the buttered popcorn fiasco with both lung and skin sensitization. So are we keeping this in this report because when I see diacetyl, I freak out?

DR. KLAASSEN: What page are you on?

DR. BELSITO: I'm on PDF page 19 under the 2,3- butanediol, the second paragraph. It's the acetaldehyde. I don't even know why that's in here. I mean I don't follow the chemistry of the link between butanediol and acetaldehyde.

DR. LIEBLER: I had cut this whole section down a lot. I had recommended removing the entire first paragraph. I thought there was just a lot of unnecessary information here. And so the first paragraph under 2,3-butanediol that starts with "2,3-Butanediol plays an integral part in the metabolism of alcohol." I thought -- in fact, I'm trying to remember the reference here because this is all based on this reference 50. What the heck was that again? I'm scrolling down. Oh, okay. "Blood and Urinary Levels of Ethanol, Acetaldehyde, and C4

Compounds Such as Diacetyl, Acetoin, and 2,3-Butanediol in Normal Male Students After Ethanol Ingestion." I didn't look at the paper, but they evidently made measures of these things and then speculated about the metabolic relationships. But they speculated about the metabolic relationships.

DR. SNYDER: So is diacetyl an issue?

MS. SCOTT: There's another experiment in the admin [ADME] section on page 19 also, "a liver perfusion experiment in rats in vivo, which also discusses diacetyl and acetoin."

DR. LIEBLER: Just small amounts of diacetyl and acetoin. So to get to Don's point, I'm not sure that this is a pathway for the formation of significant amounts of diacetyl. You're concerned about diacetyl?

DR. BELSITO: Yes. So we leave this in, but talk about diacetyl in the discussion, or it's so small we don't?

DR. KLAASSEN: Well, I thought most of this was relatively irrelevant. I mean we're talking about the metabolism of ethanol. They're basically -- in these studies we're looking at the metabolism of ethanol, which is what we drink. And apparently you get a little teeny bit of this 2,3-butanediol when you drink it, although it must be in tremendously small amounts.

DR. BELSITO: Should we measure our levels tonight?

DR. ANSELL: So it's high ethanol being converted into acetaldehyde, which can then undergo further reactions to

form acetate. And then the acetate itself can undergo further transformations.

DR. LIEBLER: Well, acetaldehyde can have alternate reactions, and I think this is all taken from this reference 50. I mean reference 50 is interesting because this entire second paragraph is also taken from reference 50. Essentially they say, "In male human subjects," at the bottom of that paragraph, "In male human subjects, endogenous levels of acetaldehyde were determined to be" in the small numbers. In other words these are endogenous metabolites. These are endogenously present compounds, including the butanediol, the diacetyl. I mean they're present in anybody, not just because you sniffed hot buttered popcorn. These are commonly present. These are metabolites that are commonly present in small amounts. I disagreed -- as soon as I saw that first sentence that said, "2,3-butanediol plays an integral part of the metabolism of alcohol." No, not really. In this context it shares some metabolic pathways with intermediates and ethanol metabolism, which would be a more correct thing to say. But it's kind of a digression into this one study that it tells you a little bit about the biotransformation of butanediol, and I think that's really the only information we need to retain from this reference. They're really just talking about the metabolism of these compounds. So I would -- rather than get it tied up with

all the baggage about interaction with ethanol, the data in the paper -- I can take another look at the paper. I probably can't pull it up here, but if you can pull up the PDF and email it to me, I'll double check this before tomorrow. But I think essentially what they're going to be able to say is that we can simplify this down to what is the metabolism of butanediol in vivo, which is the thing that we need to summarize here. And if there are small amounts of diacetyl and acetoin, those are intermediates on the way to other things.

DR. BELSITO: So, Dan, you're going to look at the 2,3-butanediol report and smooth out that language?

DR. LIEBLER: Yeah.

DR. GILL: And, Dan, you wanted to add something for the discussion?

DR. LIEBLER: Yeah, I'm going to. Yes, as soon as I get -- if you can just pull up the PDF. Send me the PDF and I'll take a quick look at it. I'll do that this afternoon.

DR. ANSELL: And that's after 24 grams of alcohol.

DR. SNYDER: They must have had fun. Those male subjects must have had fun.

MS. LORETZ: A typical Saturday night, right?

DR. SNYDER: So can we go back to the introduction?

DR. BELSITO: No. Yes.

DR. SNYDER: I'm being a nemesis here, but in the

second paragraph after the listing of the ingredients, "The alkane diol ingredients in this report are structurally related to each other as simple, small diols." And so simple means what and small means what, molecular weight- wise? And then are there other larger diols that are in the dictionary that we're not reviewing? My question was, are there only simple, small diols in the dictionary? So why are we just looking at -- I wasn't quite certain there on that.

MS. FIUME: That's probably a question Bart can answer because I believe that comes from some of the language he develops. I know he's sitting in on the other meetings.

DR. GILL: Yeah, he answered that one.

DR. SNYDER: Well, I'm just wondering is there a larger group? What was the reasoning why we pulled out these? And does small mean molecular weight?

MS. FIUME: Under chemistry, definition and structure in the first line, he has it identified as three to ten.

DR. SNYDER: Three to ten, and is that --

DR. ANSELL: Well, then you don't need to characterize it qualitatively when you defined it quantitatively, right?

DR. SNYDER: And then in the last paragraph there, the last sentence, "The above references are cited when data from these sources is summarized and the primary references were not

readily obtainable." But we don't have any references. You don't have any reference indications there, any numbers. And so I guess -- how are we handling -- I had a note here that the statement regarding the ECHA references needs to be similar to other reports. So I haven't seen that come up yet in another report, but somehow one of the writers did it differently in one of the other reports that I thought was maybe a little better way rather than stating -- I think we should actually reference these things.

MS. SCOTT: Sure, I can put references in.

DR. SNYDER: And then we have to be a little bit careful about using summary data stuff as a primary reference when in fact it's not a primary reference because if we don't have the data, we don't know it. We need to be a little bit careful about that.

DR. LIEBLER: I think you just delete that last sentence, "The above references" because you already say some of the data in this report comes from these sources and then you cite them in the appropriate places.

DR. SNYDER: Fine.

MS. SCOTT: They are summary data then.

DR. SNYDER: Right. Yeah, I understand what they are, but I just thought that wording was just --

MS. SCOTT: Okay, I can.

DR. BELSITO: So you're happy if we just delete the last sentence, Paul?

DR. SNYDER: Yes, but I want to try to find out -- because I made a notation to myself how it was referred to, particularly the ECHA data, in another report. Hopefully I'll come across that between now and tomorrow.

MS. SCOTT: That'd be great.

DR. BELSITO: Well, we used summary data from the other reports in numerous reports previous to this as well.

DR. SNYDER: But I don't know how we referenced it.

DR. BELSITO: Summary data, and normally it comes with the number of animals not known and other data endpoints that we don't know because it was just summarized.

DR. SNYDER: So where's an example where we had a study report versus a data summary from one of those?

DR. BELSITO: Multiple ingredients that we've done previously and there are several in this report, in this series of reports, that you'll see where we just summarize ECHA data. And then when you start looking at the specifics of the study, the number of animals isn't known, sometimes the concentrations aren't known. I mean the various aspects of what we look for are not known, it's just summarized.

DR. SNYDER: Okay.

MS. FIUME: It's more than just -- so we had OECD

because the information that's cited is the actual laboratory report that was done, and we don't have that.

DR. SNYDER: The whole report, okay. But I was just wondering how that translated from there into our document. So where's an example of where we credit one of those as a source?

MS. FIUME [MS. SCOTT]: Oh, okay, so numerous reports are in various tables. Let me see if I can quickly pull something up.

DR. SNYDER: Because I went through and I didn't see any references to those things.

MS. FIUME [MS. SCOTT]: Are you sure? Oh, here they are.

DR. SNYDER: Because I didn't see any as reported in, you know what I mean?

MS. FIUME [MS. SCOTT]: So you're looking for the text? I'm thinking reference like the number.

DR. BELSITO: It's referenced in the tables.

MS. FIUME [MS. SCOTT]: So I think number 38 happens to be --

DR. SNYDER: Part of that was because you didn't have any numbers up there for me to know that those were references.

MS. FIUME [MS. SCOTT]: I see what you're saying, sure. In the intro I didn't have numbers, but other places I do. So I'll add them to the intro. And if I need to add

clarification wording, that's --

DR. SNYDER: You may not. I was trying to relate where that data was being referred to in the report.

MS. FIUME [MS. SCOTT]: Oh, okay. I see.

DR. SNYDER: I didn't think about the tables to be honest. I didn't even look at the tables.

DR. BELSITO: Yeah, because the verbiage was really summary and then the tables were like details on the studies.

MS. FIUME [MS. SCOTT]: Correct.

DR. BELSITO: So the ECHA studies are sort of referred to in the tables. They're referenced in the tables.

DR. SNYDER: Okay. That was my mistake not to look at the tables.

DR. GILL: Paul, on page 50 of the Word document there's one, reference 38.

DR. SNYDER: Okay.

MS. SCOTT: There's several for this report, 38 happens to be one of them.

DR. BELSITO: 38, 60, 61, 62, 63 are all ECHA studies.

DR. SNYDER: Okay, thank you. I just raise the point for discussion about the structure related to each other is simple small diols and so two points on that. What constitutes a simple small diol beyond just the number of carbons, alkyls? And

then number two is, are there other diols in the dictionary that we're not including in here that are larger, more complex?

DR. HELDRETH: I think when I said small, my intention was to separate these from something like larger polyols that are common ingredients in the dictionary. And then these are all simple alkanes so there's no groups here, there's no heteroatoms here outside of oxygen. They're just simple, small alkanes. So those were my intentions, but if you want different nomenclature, we can certainly --

DR. SNYDER: No, I just didn't know what constituted it. If that's acceptable, understood language, then it's fine.

DR. LIEBLER: I don't think it needs to be changed at all.

DR. BELSITO: So from Wave 2 and now Wave 3 I think we're going to solve the diacetyl problem when Dan does the metabolism. Discussion really penetration enhancement. Did anyone have any other discussion points here since we're getting rid of diacetyl? And then safe as used.

DR. LIEBLER: Discussion points I had were high likelihood of dermal absorption, 1,4-butanediol not safe based on potential of systemic neurotox, and previous FDA evaluation. Others have a very good safety profile.

DR. BELSITO: Okay, so you're saying the 1,4- butanediol is not safe.

DR. LIEBLER: Right. I think that's what our conclusion will have to be. Safe as used when formulated to be nonirritating, 1,4-butanediol unsafe.

DR. ANSELL: Insufficient, unsafe.

DR. LIEBLER: Isn't that the one with the FDA warning?

MS. SCOTT: Yes.

DR. LIEBLER: An FDA warning in my neighborhood -- a high likelihood of dermal absorption.

DR. ANSELL: Its uses are in illegal drugs.

DR. LIEBLER: And it's unsafe when you do that, right. So, therefore --

DR. ANSELL: Well, it's illegal when you do that. I'm not sure it's unsafe, but it's a date-rape drug.

DR. LIEBLER: Right.

DR. KLAASSEN: I wouldn't really call that a neurotoxin in contrast to -- I mean a 2,5 is a known neurotoxic, but you're talking about the 1,4, right?

DR. LIEBLER: Correct.

DR. KLAASSEN: I mean it does something to the central nervous system, I'll agree. It's almost --

DR. LIEBLER: After undergoing metabolism it became a hydroxybutyrate.

DR. KLAASSEN: Right.

DR. LIEBLER: And that's the problem. And so it undergoes metabolism to a metabolite. You can call it a neuroactive metabolite or a neurodepressive metabolite, but in this context it's an adverse effect.

DR. KLAASSEN: It's not good, right.

DR. LIEBLER: It's well known and you combine that with the fact that this could be easily absorbed through the skin because this is relatively small. It's got the right mix of polar and nonpolar features, it zooms right through.

DR. SNYDER: But it's not a toxic then. It's a modulator, right?

DR. BELSITO: Well, it's only reported to be used in possibly three sprays and one eye area, and we have no reported concentrations.

DR. LIEBLER: Right. I think there's good reason for that.

DR. BELSITO: So I mean we certainly can -- I don't know that we can go unsafe because someone could say we use it at 10 parts per million and then at that point, even if it was 100 percent absorbed, are you concerned? I think we need to go insufficient.

DR. LIEBLER: So we're not presented with that situation.

DR. BELSITO: We don't know a concentration of use,

so I think we can only say insufficient for concentration of use.

DR. ANSELL: That's what I would suggest at this point.

DR. BELSITO: Because we can't say it's unsafe. I mean if someone comes back and goes oh, well, it's an incidental contaminant in something or it's present in 2 parts per million. We don't have any reported case studies.

DR. LIEBLER: I'm okay with insufficient at concentrated use [concentration of use?].

DR. BELSITO: For concentration of use, okay.

DR. KLAASEN: You can probably ask Bill Cosby.

DR. BELSITO: Oh, Curt.

MS. SCOTT: So for the discussion, 4,1-butanediol [1,4-Butanediol] -- so basically we're still going to just go with insufficient for concentration of use and not mention -- we're still mentioning that it's absorbed?

DR. BELSITO: We're saying there's a high likelihood of absorption; the metabolism to GPA or whatever it is; and, therefore, in the absence of known concentration of use, the safety of this material in cosmetics cannot be assessed.

MS. SCOTT: Okay.

DR. LIEBLER: GHB?

DR. BELSITO: GHB. So we need to include the data from Wave 2, the data from Wave 3, penetration enhancement in the

discussion, high likelihood of dermal absorption in the discussion, lack of concentration for 1,4-butanediol, and the potential that it could be metabolized to GHB. And then in the discussion they're all safe as used except for 1,4-butanediol, insufficient for concentration of use.

MS. SCOTT: Is it safe when formulated to be nonirritating for the others?

DR. BELSITO: Where did you get the irritation? I didn't see that there. And potential for -- it may be there. It's used up to -- I had a note that it was used up to 39.9 percent in ancillary products, but then I didn't say I was concerned about irritation.

DR. LIEBLER: "Overall, the alkane diols were non- to-mildly irritating to animal skin." That's the last sentence of PDF 22. And then the first paragraph of PDF 23, "Isopentyldiol (concentration not specified) and 1,3- Butanediol (concentration not specified) were slightly irritating. Generally the alkane diols evaluated were non- to-slightly irritating." So if I saw any irritation, that's why I put that in. But I'm fine.

DR. SNYDER: I'll defer to the data on irritation here. So I'll defer to a dermatologist.

DR. BELSITO: So I'm fine with when formulated to be nonirritating. That covers it.

DR. LIEBLER: My conclusion irritates you.

DR. BELSITO: Dan, your conclusions never irritate me.

DR. BERGFELD: That's accepted. I'll call the question then.

All those in favor of moving forward as an insufficient data announcement?

Thank you. Unanimous. Then moving on to the last ingredient for today's

consideration, Dr. Belsito presenting an alkane diol.

DR. BELSITO: Okay. So this is the first time the panel's looking at these 10 cosmetic ingredients that are small diols. We received a lot of information initially in Wave 2 and then yesterday in Wave 3.

And we noted that these materials were penetration enhancers with a high likelihood of dermal absorption. Based on that and the information we had, we felt that they were all safe as used when formulated to be non-irritating except for the one for butanediol, which was insufficient for concentration of use and potential formation of GHB.

DR. BERGFELD: Dr. Marks?

DR. MARKS: Yes, we had a slightly different

conclusion. We felt to move on with an insufficient data announcement. We have the same concentration of use for the one for butanediol. We wanted to clarify the hexanediol: 1,6 is the INCI name. Are there any 2,5 impurities in that? Because it's a precursor to a neurotoxin.

We wanted method of manufacture of 1,6-hexanediol and all the ingredients. We wanted the impurities for all. And then, as you mentioned, Don, the penetration enhancement. And we wanted also neurotoxicity data on isopentyldiol. So we had a number of data needs.

Ron, did I capture that correctly?

DR. SHANK: You did.

DR. BERGFELD: Any further comments by Belsito's team?

DR. BELSITO: I would go to Dan and the toxicologists.

DR. BERGFELD: Paul?

DR. LIEBLER: Yes, I think it's reasonable to request that information on the hexanediol.

DR. BERGFELD: Paul, did you have a comment?

DR. SNYDER: No, no.

DR. BERGFELD: Curt?

DR. KLAASEN: No, that's fine.

DR. BERGFELD: Okay. Ron Hill?

DR. HILL: No, I just raised one or two other chemistry issues yesterday, but it's captured and I don't think we need to discuss it today.

DR. BERGFELD: Okay. So I'm coming around the table. Ron?

DR. SHANK: I'm fine.

DR. BERGFELD: Okay. Tom?

DR. SLAGA: Fine.

DR. BERGFELD: Okay. So restate your motion.

DR. MARKS: Well, I think the other motion needs to be retracted before.

DR. BERGFELD: Okay.

DR. BELSITO: Well, we're still going insufficient.

DR. MARKS: Oh, yes, absolutely.

DR. BELSITO: So it's --

DR. MARKS: It's just insufficient data announcement versus --

DR. BELSITO: You've added additional data.

DR. MARKS: Yes, I think your move was a tentative report with a safe and insufficient data.

DR. BELSITO: Well, in a way it was. You know, I mean, I think perhaps I overstated it. We're basically saying that at this point we felt all were sufficient except for the 1,4-butanediol where we needed concentration of use and the

potential formation of GHB. We weren't saying that that was unsafe. We were saying the data was insufficient there.

DR. MARKS: Yes.

DR. BELSITO: So essentially, it was an insufficient conclusion on this group. I think you just added some additional insufficiencies, and I'm fine with that.

DR. MARKS: Yes, and it would go out as an announcement rather than as a tentative report.

DR. BERGFELD: All right, I think that has been resolved then. We're going with Dr. Marks' proposal, a motion of insufficient with all the listed insufficiencies.

All those in favor, please indicate by raising your hand.

Thank you. Unanimous. We've come to the end of this 15-character list of

ingredients. I thank you very much for all the time spent and certainly to all the staff that supported this effort.

And again, congratulations on 40 good years. See you in December. Happy Thanksgiving.

Any other comments?

DR. MARKS: Thank you.

DR. BERGFELD: We're adjourned.

Safety Assessment of Alkane Diols as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	March 17, 2017
Panel Meeting Date:	April 10-11, 2017

The 2017 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This safety assessment was prepared by Laura N. Scott, Scientific Writer/Analyst.

1620 L Street, NW, Suite 1200 ◊ Washington, DC 20036-4702 ◊ ph 202.331.0651 ◊ fax 202.331.0088 ◊
cirinfo@cir-safety.org

ABSTRACT

This is a safety assessment of 10 alkane diol ingredients as used in cosmetics. The alkane diols function in cosmetics as, solvents, viscosity decreasing agents, humectants, skin-conditioning agents, and plasticizers. The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the relevant data for these ingredients. The Panel concluded that…(conclusion to be added).

INTRODUCTION

This assessment reviews the safety of 10 alkane diols as used in cosmetic formulations (with systematic nomenclature in parenthesis when different from the ingredient name). Throughout this report, the information on these ingredients is presented in order of increasing chain length as follows:

Propanediol (1,3-Propanediol)
1,4-Butanediol
2,3-Butanediol
1,5-Pentanediol
Hexanediol (1,6-Hexanediol)
Octanediol (1,8-Octanediol)
1,10-Decanediol
Methylpropanediol (2-Methyl-1,3-Propanediol)
Butyl Ethyl Propanediol
Isopentyldiol

The alkane diols reviewed in this safety assessment have various reported functions in cosmetics (Table 1), as indicated in the *International Cosmetic Ingredient Dictionary and Handbook (Dictionary)*, including uses as solvents, humectants, skin conditioning agents, plasticizers, fragrance ingredients, and viscosity decreasing agents.[1] Propanediol, for example, is used as a solvent and viscosity decreasing agent; Butyl Ethyl Propanediol is used as a skin-conditioning agent and humectant.

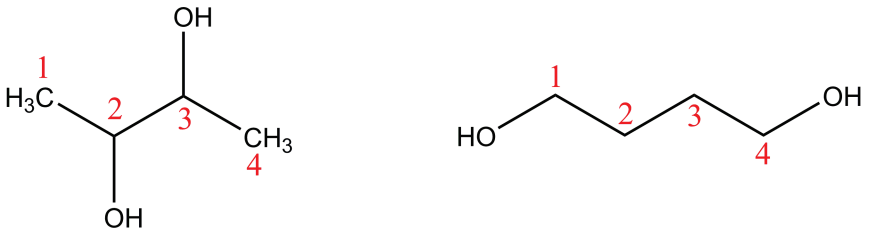
The alkane diol ingredients in this report are structurally related to each other as small diols. Diols with 1,2-substitution regiochemistry (e.g., 1,2-Butanediol) have been reviewed previously by the Panel, and the conclusion for each is summarized in Table 2.[2-10] Almost all of these previously-reviewed diols were assessed to be safe as used; Propylene Glycol (i.e., 1,2-Propanediol) was deemed to be safe as used when formulated to be non-irritating.

The European Chemicals Agency (ECHA)[11-16] website and the Australian Government Department of Health National Industrial Chemicals Notification and Assessment Scheme (NICNAS)[17-19] website provide summaries of data generated by industry, and ECHA and NICNAS are cited as the sources of the summary data in this safety assessment as appropriate. Also referenced in this safety assessment are summary data found in reports published by the World Health Organization (WHO),[20] the Organization for Economic Co-operation and Development Screening Information Data Sets (OECD SIDS),[21] the National Toxicology Program (NTP),[22,23] and in reports made publically available by the Food and Drug Administration (FDA),[24-31] the Environmental Protection Agency (EPA),[32-35] and the National Technical Information Service (NTIS).[36-40]

CHEMISTRY

Definition and Structure

All of the ingredients in this report are structurally related to each other as small diols (i.e., three to ten carbon alkyl diols). The ingredients in this report include regiochemistry other than 1,2-substitution. For example, 2,3-Butanediol is a vicinal diol with the first hydroxyl substitution at the 2-position and 1,4-Butanediol is a terminal diol with substitution at the 1- and 4-positions (Figure 1).



2,3-Butanediol 1,4-Butanediol

Figure 1. 2,3-Butanediol and 1,4-Butanediol

Variations in the regiochemistry of small alkane diols may lead to significant differences in toxicity. For example, 2,5-hexanediol, which is not a cosmetic ingredient, is known to be a neurotoxic metabolite of hexane.[41,42] However, the structurally similar cosmetic ingredient, Hexanediol (i.e., 1,6-Hexanediol), is not a neurotoxin.

Physical and Chemical Properties

Alkane diols can be liquids or crystalline solids. Most are soluble in alcohol and have variable solubility in water, depending largely on molecular weight (Table 3). All of the terminal diols are soluble or somewhat soluble in water, except for the longest chain compound, 1,10-Decanediol, which is nearly insoluble in water. The branched alkane diols among these ingredients are very soluble in water, with the exception that Butyl Ethyl Propanediol is only slightly soluble.

Method of Manufacture

Propanediol

Propanediol may be prepared from corn-derived glucose using a biocatalyst (non-pathogenic strain of *Escherichia coli* K-12);[43] it is also prepared by glucose fermentation with subsequent distillation.[44] Propanediol can be manufactured by heating γ,γ-dihydroxy-dipropyl ether with hydrobromic acid, followed by hydrolysis with sodium hydroxide. It is also obtained from plants that produce glycerol.[40] Propanediol can be prepared by reducing ethyl glycidate with lithium aluminum hydride.[45]

1,4-Butanediol

Some industrial chemical companies manufacture 1,4-Butanediol using cupric acetylide catalysts in the condensation reaction of acetylene with formaldehyde.[40] Some manufacturers convert propylene oxide to allyl alcohol, which is then hydroformylated to 4-hydroxybutyraldehyde.[20] 1,4-Butanediol can be produced by the hydrogenolysis of 4-hydroxybutyraldehyde. Maleic acid and succinic acid can be used to manufacture 1,4-Butanediol during the vapor phase hydrogenation of their corresponding esters and anhydrides. *E. coli* can be genetically engineered to metabolize sugar to produce 1,4-Butanediol.[46]

2,3-Butanediol

2,3-Butanediol has been commercially produced by fermentation of molasses or sugar using *Mesentericus*, *Aerobacter*, *Klebsiella*, and *Serratia* bacteria; *Bacillus polymyxa*, *Lactobacilli* and *Staphylococci* strains and filamentous fungi (e.g., *Rhizopus nigricans*, *Penicillium expansum*) produce 2,3-Butanediol.[40] Fermentation of potatoes or wheat mash also yields 2,3-Butanediol. Mixtures of gases containing isobutylene and normal butenes, when combined with hydrogen peroxide and formic acid, yield a product containing 2,3-Butanediol, fractions of which are collected by distillation. The *meso*-form of 2,3-Butanediol can be prepared from *trans*-2,3-epoxybutane; the D-form can be prepared by fermenting carbohydrate solutions with *Bacillus subtilis* organisms.[45]

1,5-Pentanediol

1,5-Pentanediol can be prepared in the presence of copper chromite by hydrogenolysis of tetrahydrofurfuryl alcohol.[45]

1,10-Decanediol

1,10-Decanediol may be prepared by reducing diethyl or dimethyl sebacate with sodium in ethyl alcohol. It is also prepared by catalytic hydrogenation of sebacic esters.[45]

Methylpropanediol

In industry, carbon monoxide and hydrogen can be used in the hydroformylation of allyl alcohol to produce the intermediate hydroxymethylpropionaldehyde, which then undergoes hydrogenation to yield Methylpropanediol.[35]

Impurities

Propanediol

The following Food Chemicals Codex acceptance criteria apply for Propanediol in relation to food preparation: cobalt (not more than-(NMT) 1.0 mg/kg or 1 ppm); lead (NMT 1.0 mg/kg or 1 ppm); nickel (NMT 1.0 mg/kg or 1 ppm).[43] The purity of Propanediol should not be less than 99.9% and water content should be NMT 0.1%. A manufacturer reported Propanediol to be 99.8% pure (impurities were not provided) and stated that the product did not contain added preservatives, animal by-products, or petroleum ingredients.[47] Propanediol was reported to be ≥ 99.98% pure and no other substance > 0.10%; water was listed as an impurity, but no heavy metals, monomers, or amines were known to be present.[44]

1,4-Butanediol

Maleic acid and succinic acid may be potential residual impurities because they are sometimes used as starting materials in the manufacture of 1,4-Butanediol, as mentioned above. 1,4-Butanediol has been reported to be 98% pure (impurities were not specified).[21]

1,5-Pentanediol

A gas chromatographic/mass-spectrometry analysis was performed to determine the impurities in 1,5-Pentanediol.[48] 1,5-Pentanediol was found to be 98.1% pure with a total of 0.28% unknown impurities, stated by the authors not to be diols. Contamination by water, 1,5-hexanediol, and 1,6-Hexanediol was found to be 0.02%, 1.02%, and 0.56%, respectively. Other diol impurities, including 1,4-Butanediol, 2,5-Hexanediol, and cyclic diols, were below the limit of detection (< 0.05%).

Hexanediol

Hexanediol has been reported to be > 96% pure (impurities were not specified).[49]

Methylpropanediol

Methylpropanediol has been reported to be 98% pure (2% maximum impurities) by a manufacturer.[50]

Isopentyldiol

Isopentyldiol has been reported to be 97% pure with 3% of impurities and residual monomers (no further details provided).[18] Isopentyldiol is > 99% pure as reported by a cosmetics industry supplier.[51]

Natural Occurrence

2,3-Butanediol

2,3-Butanediol occurs naturally in certain foods: some examples include "0.006 mg/kg in fish (lean), up to 90 mg/kg in cheddar cheese, up to 2.3 mg/kg in raspberry, up to 850 mg/kg in vinegar, 1.9 mg/kg in sherry and up to 2900 mg/kg in various types of wine."[52]

USE

Cosmetic

The CIR Expert Panel evaluated the safety of the cosmetic ingredients included in this assessment based on the expected use of and potential exposure to the ingredients in cosmetics. The data received from the FDA are collected from manufacturers through the FDA Voluntary Cosmetic Registration Program (VCRP), and include the use of individual ingredients in cosmetics by cosmetic product category. The data received from the cosmetic industry are collected by the Personal Care Products Council (Council) in response to a survey of the maximum reported use concentrations by product category.

VCRP data obtained from the FDA in 2017[27] indicated that some of the alkane diols are being used in cosmetic formulations (Table 4). Among the ingredients most frequently reported to be used are Propanediol (1138 reported uses), Methylpropanediol (541 reported uses), and Isopentyldiol (135 reported uses). Concentration of use survey data in 2015[53] (Table 4) indicated that the highest maximum reported concentrations of use were as follows: 39.9% Propanediol (in non-spray deodorants); 21.2% Methylpropanediol (in non-spray body and hand products); 15% Isopentyldiol (in hair conditioners, non-coloring shampoo, and other hair preparations, non-coloring).

In some cases, uses of alkane diols were reported in the VCRP, but concentration of use data were not provided in the Council survey. For example, 1,4-Butanediol is reported to be used in 4 cosmetic formulations, but no use concentration data were reported.[27] Conversely, there were instances in which no uses were reported in the VCRP, but use concentrations were provided in the industry survey. For example, Butyl Ethyl Propanediol was not reported to be in use in the VCRP, but the Council survey indicated that it is used at concentrations of 0.29% (tonics, dressings and other hair grooming aids) in leave-on formulations.[53] It should be presumed in these cases that there is at least one use in every category for which a concentration of use is reported.

There are no frequency of use, or concentration of use, reported for 2,3-Butanediol and 1,5-Pentanediol.[27,53]

Alkane diols were reported to be used in cosmetic sprays, including perfumes, hair sprays, and deodorants, and could possibly be inhaled. For example, Propanediol was reportedly used in aerosol and pump hair sprays at concentrations up to 0.12% and 1.5%, respectively.[53] Propanediol was used in face and neck sprays at concentrations up to 3%. Isopentyldiol was reportedly used in perfumes and aerosol deodorants at concentrations up to 5% and up to 1%, respectively. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles below 10 μm compared with pump sprays.[54-57] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[54,56] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[56] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. Isopentyldiol was reportedly used in face powders at concentrations up to 0.33%[53] and could possibly be inhaled. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[58-60]

Alkane diols were reported to be used in cosmetic formulations indicative of potential eye exposure (Propanediol up to 10% in eye makeup removers) and possible mucous membrane exposure and ingestion (Propanediol up to 10% in dentifrices). Propanediol was reported to be used in baby shampoos, baby lotions, oils, powders, and creams (no concentrations of use were reported).

None of the alkane diols named in this report are restricted from use in any way under the rules governing cosmetic products in the European Union.[61]

Non-Cosmetic

The non-cosmetic uses of the alkane diols (see Table 5), as specified in the Code of Federal Regulations Title 21, are largely as indirect food additives.

1,4-Butanediol

1,4-Butanediol is known to be an illicit drug of abuse because of its conversion to gamma-hydroxybutyric acid (GHB, aka-the "date rape drug") after oral administration.[62] GHB, occurring endogenously in mammals, is a neurotransmitter with a high affinity for pre- and postsynaptic neuron GHB-receptors.[63] In 1999, the FDA issued a warning about products (i.e., dietary supplements advertised as a sleep aid) containing 1,4-Butanediol and gamma-butyrolactone because of reports linking these compounds to adverse health effects (e.g., decreased respiration) and 3 deaths.[29] In this warning, the FDA noted 1,4-Butanediol to be a Class I Health Hazard (potentially life-threatening risk). GHB has been used in dietary supplements because it can increase physiological concentrations of growth hormone, leading to an increase in lean muscle mass; weight control and sedation were other effects of GHB ingestion advertised by health food stores.[63] In 1997, the FDA re-issued a warning for GHB used recreationally and in body building because it caused serious adverse health effects.[29] As of 2000, the Drug Enforcement Agency (DEA) reported GHB to be a Schedule I Controlled Substance and 1,4-Butanediol and gamma-butyrolactone (GBL) to be controlled substance analogs if they are intended for human consumption pursuant to 21 U.S.C §§802(32)(A) and 813.[62] Sodium oxybate (the sodium salt form of GHB) is an FDA-approved prescription drug product (schedule III controlled substance)[62] used to treat attacks of muscle weakness and daytime sleepiness in narcolepsy patients.[24,25,30] The warnings and regulatory actions listed above pertain to oral administration.

Pentylene Glycol

Pentylene Glycol is listed as an ingredient in a prescription hydrogel wound dressing (medical device classified under 21CFR878.4022), which was approved by the FDA (Section 510(k)).[31,64] Sources did not specifiy whether 1,2-Pentanediol or 1,5-Pentanediol was used or the concentration used.

1,5-Pentanediol

1,5-Pentanediol has been reported to have antimicrobial and antifungal properties in pharmaceutical applications.[48,69,70] Additionally, 1,5-Pentanediol is used in therapeutic products for hair loss, cold sores, nail problems, dry and scaly feet, and eczema; it can be used as a moisturizing substance and solvent.[70]

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

Propanediol

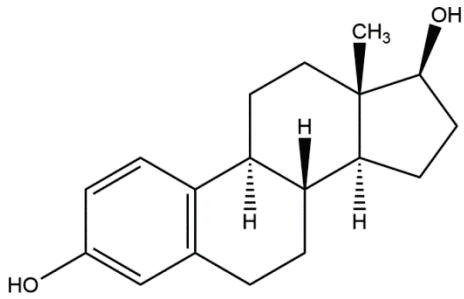
A dermal penetration study conducted using human cadaver skin evaluated the penetration of Propanediol.[11] The stratum corneum (abdominal region of human cadaver skin, n=6 representing 3 donors) was mounted on an in vitro static diffusion cell (skin surface area 0.64 cm^2). The experiment was conducted using Good Laboratory Practice (GLP) and in accordance with OECD Test Guideline (TG) 428 (Skin Absorption: in vitro Method). A solution containing 1.059 g/ml Propanediol (purity 99.953%) was applied to the skin (1200 µl/cm^2, infinite dose) in the donor chamber (opening to chamber was occluded). The receptor fluid (0.9% saline) was maintained at 32°C in a recirculating water bath and was sampled at time zero and every 4-6 hours up to 48 hours post-application. The permeability coefficient was calculated to be 1.50×10^{-5} cm/h, based on the slope at steady state (15.9 µg/cm^2/h) and the concentration of Propanediol applied (test solution density 1,059,700 µg/cm^3). The percentage of the applied Propanediol recovered from the receptor chamber 48 hours post-application was 0.12%.

Penetration Enhancement

In Vitro

Provided below is a summary of penetration experiments that are presented in greater detail in Table 6.

The ability of Propanediol, 1,4-Butanediol, and 1,5-Pentanediol to enhance the penetration of the drug estradiol (Figure 2) in human skin was evaluated in an in vitro experiment using a Franz diffusion cell.[71] The test substance (100 µl of 0.12% [^{3}H]estradiol in 1:10 Propanediol, 1,4-Butanediol, or 1,5-Pentanediol/ethanol solution) was applied to the dermis, which faced the receptor side of the cell. Receptor fluid samples were collected at various time points. The steady-state flux of Propanediol, 1,4-Butanediol, and 1,5-Pentanediol was determined to be 0.11, 0.017, and 0.005 µg/cm^2/h, respectively, indicating a decrease in steady-state flux with increasing alkyl chain length. After ~ 85-90 minutes the permeability of [^{3}H]estradiol in human skin was ~ 5-6 µg/cm^2 with Propanediol and < 1 µg/cm^2 with 1,4-Butanediol or 1,5-Pentanediol.



estradiol

Figure 2. Estradiol

Penetration enhancement tests in vitro showed 1,5-Pentanediol to be a penetration enhancer for certain pharmaceutical drugs.[72,73] Test cream formulations containing 0.1% tri-iodothyroacetic acid (TRIAC; a thyroid hormone analog, Figure 3) and either 1,5-Pentanediol (10%) or 1,2-Propanediol (10%) showed 1,5-Pentanediol to be a more effective penetration enhancer than 1,2-Propanediol for TRIAC in a multilayer membrane system (MMS) experiment.[72]

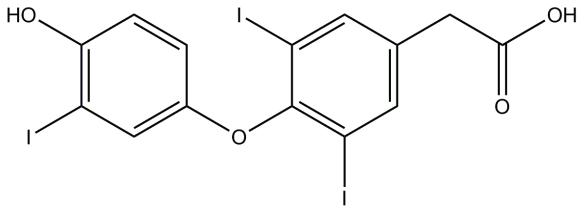


Figure 3. TRIAC

Results for 1,5-Pentanediol indicated that 33% of the TRIAC (pharmacologically active agent) was released from the carrier vehicle, or formulation (in MMS), to enable TRIAC to contact the skin at the epidermal surface by 30 minutes post-application; 62% TRIAC was released from the formulation by 300 minutes.[72] In a separate experiment, test cream formulations containing 1% hydrocortisone (Figure 4) and either 1,5-Pentanediol (25%) or 1,2-Propanediol (25%) were evaluated using human breast skin.

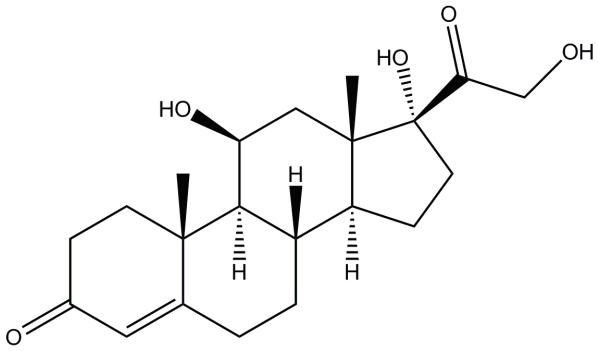


Figure 4. Hydrocortisone

Both 1,5-Pentanediol (increased drug absorption 4-fold, compared to controls) and 1,2-Propanediol (increased drug absorption 13-fold, compared to controls) were shown to be penetration enhancers.[72] However, 1,2-Propanediol enhanced the transfer of the drug through the skin more effectively and 1,5-Pentanediol increased retention of the drug in the skin more effectively (receptor fluid collected up to 60 hours post-application). Another experiment evaluating test cream formulations containing 0.1% mometasone furoate (Figure 5) and either 1,5-Pentanediol (25%) or Hexylene Glycol (12%) revealed that both formulations were percutaneous absorption enhancers in human breast skin (receptor fluid collected up to 60 hours post-application). The absorption of 0.1% mometasone furoate into the skin was 6% using 1,5-Pentanediol and 7% using Hexylene Glycol as penetration enhancers.

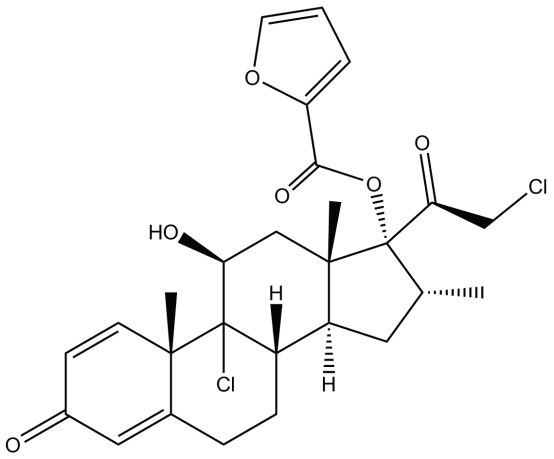


Figure 5. Mometasone furoate

1,5-Pentanediol (5% and 20%) and 1,2-Propanediol (5% and 20%) were also evaluated in an in vitro experiment investigating the penetration enhancement of 1% terbinafine, a lipophilic drug used to treat foot and nail fungus (Figure 6), in a hydrogel formulation.[73] Both alkane diols were found to be percutaneous absorption enhancers in human breast skin (receptor fluid collected up to 60 hours post-application). Results indicated that 21% and 11% terbinafine was absorbed into the skin with 20% 1,2-Propanediol or 20% 1,5-Pentanediol, respectively. The 5% 1,2-Propanediol or 5% 1,5-Pentanediol yielded 19% and 52% terbinafine absorption into skin, respectively. For comparison, the control (1% terbinafine in hydrogel without either alkane diol) resulted in 8% drug absorption into the skin.

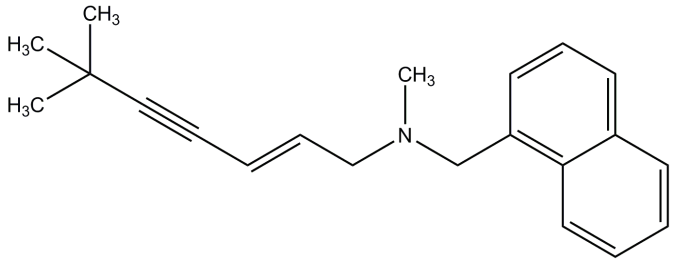


Figure 6. Terbinafine

Absorption, Distribution, Metabolism, Excretion

Absorption, distribution, metabolism, and excretion studies are summarized below under the subheadings; details are presented in Table 7.

In Vitro

Competitive inhibition between 1,4-Butanediol (0.5 mM) and ethanol (0.5 mM) occurred in a test performed using horse liver alcohol dehydrogenase.[74] In rat liver homogenates, 10 nmol of diacetyl, acetoin, and 2,3-Butanediol were interconvertible with a molar equilibrium ratio of 0:3:7, respectively.[75] Methylpropanediol was a substrate for rat liver alcohol dehydrogenase.[35]

Animal

Metabolism experiments conducted using homogenates from rats that were fed 500 ppm Propanediol in the diet for 15 weeks and control rats (fed a plain diet) revealed that Propanediol was converted to malondialdehyde (5.6 nmol/h/100 mg tissue) in the liver homogenates (of Propanediol exposed rats and controls), but little-to-no conversion occurred in the testicular homogenates of treated or control rats.[76] Experiments in rabbits administered single doses of alkane diols via stomach tube revealed metabolites isolated from the urine 1 to 3 days post-dosing. Propanediol glucuronic acid conjugation accounted for up to 2% of the administered dose (4 mmol/kg); 1,4-Butanediol (9 g) was metabolized to succinic acid (7% of administered dose); 2,3-Butanediol glucuronic acid conjugation accounted for up to 26% of the administered dose (4 mmol/kg); phenacyl glutarate (0.5% of dose) was identified after 1,5-Pentanediol (8.5 g) administration; Hexanediol glucuronic acid conjugation accounted for up to 9% of the administered dose (2 mmol/kg) and adipic acid was detected.[77]

Rats were intragastrically exposed to a single dose of 1 g/kg 1,4-Butanediol; 75 minutes post-dosing 96 µg/g were measured in the brain, 52 µg/g in the liver, and 58 µg/g in the kidney; endogenous levels of 1,4-Butanediol in rats dosed with ethanol were found to be 0.02 to 0.05 µg/g, by comparison; 1,4-Butanediol levels in the liver peaked at 50 µg/g 1.5 to 3 hours post-dosing; sedation and ataxia were observed 30 minutes post-dosing and, by 60 minutes, catalepsy was noted (these effects were synergistically intensified when ethanol was concurrently administered).[74] In rats orally administered up to 400 mg/kg, 1,4-Butanediol (radiolabels on C1 and

C4), >75% of the radioactivity was excreted as $^{14}CO_2$ (by 24 hours post-administration), up to 6% of the radioactivity was excreted in urine (by 72 hours post-administration), and up to 0.6% of the radioactivity was excreted in feces (by 72 hours post-administration).[23] Endogenous concentrations of 1,4-Butanediol in rats were found to be 165 ng/g (stomach) and 30 ng/g (liver) in aqueous phase tissues (i.e., aqueous portion of supernatant of homogenized tissues) and in lipid phase tissues (i.e., lipid portion of supernatant of homogenized tissues) were 150 to 180 ng/g.[78]

Experiments in rats orally administered 1 M diacetyl, acetoin, or 2,3-Butanediol showed that these compounds interconvert.[75] Methylpropanediol orally administered to rats (100 or 1000 mg/kg, ^{14}C-labled) was rapidly metabolized and eliminated in the urine as 3-hydroxybutyric acid (31%-45% of dosed radioactivity), in the exhaled breath as CO_2 (42%-57% of dosed radioactivity), and in the feces (< 1% of dosed radioactivity).[34,35,79]

In liver perfusion experiments in rats (in vivo), perfusion with 1 mM 2,3-Butanediol resulted in the oxidation of 2,3-Butanediol to small amounts of diacetyl and acetoin; 33% of the perfused 2,3-Butanediol was metabolized or conjugated in the liver.[75]

Human

In human subjects dermally exposed to 25% 1,5-Pentanediol (2 applications, 12 hours apart), increasing levels of glutaric acid were detected in urine and serum (no concentrations were provided).[70] The study authors reported that the risk of 1,5-Pentanediol accumulation at the concentration tested (therapeutic dose) was low.

Human subjects orally exposed to 1,4-Butanediol (single 25 mg/kg dosage) in fruit juice exhibited measurable plasma concentrations of GHB between 5 and 30 minutes post-dosing, indicating rapid conversion of 1,4-Butanediol to GHB; 4 hours post-dosing plasma levels were below the limit of quantitation (1 mg/l).[80] Clearance of 1,4-Butanediol was rapid in some subjects and relatively slow in subjects who were confirmed to have a genetic mutation of variant alleles (G143A single nucleotide-polymorphism of ADH-1B). Lightheadedness, headaches, and increased blood pressure were observed 15 minutes post-dosing, and reports of subjects feeling dizzy or less alert were expressed for up to 4 hours post-dosing. A study in which human subjects were injected intravenously with 1,4-Butanediol (15 or 30 mg/kg) showed rapid and nearly 100% conversion of 1,4-Butanediol to GHB; 1,4-Butanediol and GHB had essentially the same decay curves when equal doses of each were administered.[23] In another study, human subjects were orally administered GHB (single 25 mg/kg dosage) in water; absorption and elimination (linear kinetics) of GHB were rapid.[81] Terminal plasma elimination half-life was 17.4 to 42.5 min. The majority of subjects showed the highest concentrations in urine 60 minutes post-dosing; by 24 hours post-dosing, up to 2% of the administered dose was recovered in the urine. Confusion, sleepiness, and dizziness were observed, with substantial variation among the subjects.

Metabolic Pathway

1,4-Butanediol

In mammals, 1,4-Butanediol is metabolized endogenously to gamma-hydroxybutyraldehyde by alcohol dehydrogenase and then by aldehyde dehydrogenase to GHB.[63] This metabolism has been reported to occur in rat brain and liver.[78] Ethanol, a competitive substrate for alcohol dehydrogenase, can inhibit 1,4-Butanediol metabolism.[63,74] GHB is metabolized to succinic semialdehyde by GHB dehydrogenase, and then to succinic acid by succinic semialdehyde dehydrogenase; succinic acid then enters the Krebs cycle.[63] Alternatively, succinic semialdehyde can be metabolized by gamma-aminobutyric acid (GABA) transaminase to produce the neurotransmitter GABA.

TOXICOLOGICAL STUDIES

Acute Toxicity

Provided below is a summary of the acute toxicity studies; details are presented in Table 8.

Animal

Dermal

Dermal exposure animal studies evaluating the toxicity of the alkane diols indicated an LD_{50} > 20 g/kg in rats for Propanediol,[82] > 20 ml/kg in rabbits for 1,5-Pentanediol,[83] > 10 g/kg in rabbits for Hexanediol,[83,84] and > 2 g/kg in rabbits for Butyl Ethyl Propanediol.[85] The LD_{50}s reported for 1,4-Butanediol and Methylpropanediol were > 2 g/kg in dermally exposed rats[12] and rabbits.[19] After dermal exposure to 1,4-Butanediol (5 g/kg) in rats, findings included dermal lesions (48 h post-application) and abnormalities in the liver (14 days post-application), but no mortality.[86] Clinical signs observed in rats within 2 hours of exposure to 2 g/kg 1,4-Butanediol were dyspnea and poor general state; slight erythema was noted 24 hours post-exposure.[12] One source reported that 1,4-Butanediol was toxic on the skin, however the quality of the test material was questionable; the same source noted that there was no indication of absorption of acutely toxic quantities of 1,4-Butanediol in rabbit skin (no further details provided).[87] Clinical signs reported following dermal exposure to 2 g/kg Methylpropanediol (time between exposure and appearance of signs not specified) were slight erythema, diarrhea, yellow nasal discharge, bloated abdomen, soiling of anogenital area, gastrointestinal tract abnormalities, and lung and liver abnormalities.[19] By 14 days post-application (2 g/kg Methylpropanediol), abnormalities in kidney and gastrointestinal tract of rabbits were reported at necropsy; there were no treatment-related mortalities.

Oral

Propanediol, 1,4-Butanediol, 2,3-Butanediol, 1,5-Pentanediol, Hexanediol, 1,10-Decanediol, Methylpropanediol, Butyl Ethyl Propanediol, and Isopentyldiol were evaluated for toxicity in acute oral exposure studies in animals. An LD_{50} of 14.9 ml/kg was reported for Propanediol in rats; clinical signs were sluggishness, sedation, ataxia, and unconsciousness followed by the death of some of the animals.[11] An approximate lethal dosage (ALD) of 17 g/kg (70% purity) and > 25 g/kg (99.8% purity) were also reported in rats dosed with Propanediol; clinical effects noted from dosages between 2.25 g/kg and 17 g/kg were pallor, irregular respiration, salivation, chewing motion, and belly crawling.[38] Various animal studies reported an LD_{50} between 1.2 and 2.5 g/kg for 1,4-Butanediol.[12,21,23,37,40,86] Findings at necropsy in one rat study (animals killed 48 h post-dosing with 1.8 g/kg 1,4-Butanediol) were fluid-filled gastrointestinal tract and congestion of internal organs, histopathological changes in liver and kidneys, extensive vacuolar degeneration of hepatic parenchyma, granular clusters of desquamated cells, and interstitial infiltration of mononuclear kidney cells.[86] In another rat study, 14-days post dosing (1 to 2.5 g/kg 1,4-Butanediol), the animals that survived to necropsy showed no abnormal findings and an LD_{50} of 1.5 g/kg was reported.[12] Clinical signs observed after 1,4-Butanediol (1.35 to 2 g/kg dosage) administration in rats included irregular, decreased respiration and catalepsy, dyspnea, apathy, abnormal position, staggering, spastic gait, atony, and unusual pain reflex.[12,37,86] Rats dosed intragastrically with a single dosage of 1 g/kg 1,4-Butanediol showed hyperemia in the brain, liver, and kidney 24 hours post-administration.[74] Animals that were administered 1,4-Butanediol (LD_{50}s of 1.2 to 2.5 g/kg) exhibited lethargy, lateral posture and hyperemia of the mucosa, brain, and internal organs.[21] The mortality rate of rats 24 hours after administration of a single 1 g/kg 1,4-Butanediol dosage was 1 death per 18 rats. For the following alkane diols, LD_{50}s in rats and/or mice were reported as: > 5 g/kg and 9 g/kg 2,3-Butanediol,[15,52] 10 g/kg 1,5-Pentanediol,[13] 3 g/kg Hexanediol,[14] >20 ml/kg 1,10-Decanediol (in a test substance mixture also containing unspecified amounts of Propylene Glycol),[88] > 5 g/kg Methylpropanediol,[19] 2.9 g/kg and 5 g/kg Butyl Ethyl Propanediol,[16,85] and > 5 g/kg Isopentyldiol.[18] Clinical signs reported after dosing with 2,3-Butanediol, 1,5-Pentanediol, Hexanediol, Methylpropanediol, or Butyl Ethyl Propanediol included: staggering, spastic gait, salivation, exsiccosis, paresis, apathy, narcotic state, increased urination, diarrhea, chromorhinorrhea, dyspnea, piloerection, erythema, and pallor.[13-16,19] Noted at necropsy were dilation of the heart and congestive hyperemia, bloody stomach ulcerations, and abnormal bladder content in rats dosed with 1,5-Pentanediol.[13] After dosing with Methylpropanediol (5 g/kg), 1 rat (n=10) showed pink bladder fluid at necropsy.[19] There were no clinical signs reported in mice dosed with Isopentyldiol;[18] at necropsy, rats and/or mice dosed with Hexanediol, 1,10-Decanediol, Butyl Ethyl Propanediol, or Isopentyldiol showed no abnormalities.[14,16,18,88] In mice (n=2/sex/dosage) dosed with Butyl Ethyl Propanediol, 2 deaths were reported at 1.25 g/kg; 2 deaths at 1.5 g/kg; 3 deaths at 2 g/kg.[16]

Inhalation

Studies evaluating the toxicity of Propanediol, 1,4-Butanediol, 2,3-Butanediol, 1,5-Pentanediol, Hexanediol, and Methylpropanediol were conducted in rats exposed by inhalation. An approximate lethal concentration (ALC) was estimated by the authors to be > 5 mg/l for Propanediol (4 h exposure time, 3.2 µm mass median aerodynamic diameter); clinical signs were wet fur/perineum and ocular discharge.[11] Rats survived a 4-hour exposure to 2000 to 5000 mg/l Propanediol.[82] Rats exposed to 1,4-Butanediol (4.6 to 15 mg/l) by inhalation showed lethargy, labored breathing, red discharge in perineal area, weight loss within 24 hours post-exposure, followed by resumption of normal weight gain, and lung noise/dry nasal discharge 1 to 9 days post-dosing; 1 death (15 mg/l) occurred 1 day post-dosing.[89] In another rat study, an LC_{50} > 5.1 mg/l 1,4-Butanediol (4 hour exposure time) was reported; no mortality or abnormalities during gross pathology examination were reported and clinical signs, which resolved within 48 hours post-exposure, included shallow breathing, nasal discharge, ruffled fur, staggering gait, and deterioration.[12,21] The results for other alkane diols evaluated were: no deaths after 7 to 8 hours of exposure to 2,3-Butanediol (up to 0.85 mg/l in air);[15] 1,5-Pentanediol (concentrated vapor),[83] Hexanediol (concentrated vapor),[83,84] or an LC_{50} > 5.1 g/l was reported for inhalation of Methylpropanediol.[35]

Short-Term Toxicity

Below is a summary of the short-term toxicity studies that are presented in detail in Table 9.

Animal

Oral

Short-term oral exposure studies were conducted in animals to investigate the toxicity of Propanediol, 1,4-Butanediol, Hexanediol, Methylpropanediol, and Butyl Ethyl Propanediol. A no-observed-effect-level (NOEL) of 1000 mg/kg/day was reported for Propanediol in a 14-day rat study.[11] A 28-day experiment in rats evaluating the toxicity of 1,4-Butanediol revealed liver abnormalities; NOELs of 500 mg/kg/day (females) and 50 mg/kg/day (males) were reported.[90] Another rat study (approximately 42 days exposure duration) examining 1,4-Butanediol, showed lower body weight gains and food consumption (400 and 800 mg/kg/day), a statistically significant dose-related decrease of blood glucose (male treated animals), and bladder abnormalities (400 and 800 mg/kg/day); a NOAEL of 200 mg/kg/day was reported.[12] The results of testing Hexanediol in rats (up to 1000 mg/kg/day for 28 days)[14] and rabbits (up to 2000 mg/kg for 25 doses, duration unknown)[39] yielded a reported NOEL of 1000 mg/kg/day for the rats[14] and observations of thrombosis and treatment-related effects (unspecified) on the liver and kidneys in the rabbits.[39] Results of testing Methylpropanediol in rats up to 1000 mg/kg/day for 14 days were reported to be unremarkable.[19] A NOAEL of 1000

mg/kg/day was reported for Butyl Ethyl Propanediol in a 28-day rat experiment; rats exhibited liver abnormalities (in males at 1000 mg/kg/day) and kidney abnormalities (in males at 150 or 1000 mg/kg/day).[16]

Inhalation

Short-term inhalation exposure studies were conducted in animals to evaluate the toxicity of Propanediol and 1,4-Butanediol. A rat study evaluating exposure to Propanediol, up to 1800 mg/l, 6 h/day for 2 weeks (9 exposures total), reported no remarkable results.[82] A study in which rats were exposed to 1,4-Butanediol (up to 5.2 mg/l), 6 h/day, 5 days/week for 2 weeks showed red nasal discharge, lower body weights, and abnormal blood chemistry parameters.[89]

Subchronic Toxicity

Below is a synopsis of the subchronic toxicity studies that are presented in detail in Table 9.

Animal

Oral

Propanediol, Hexanediol, Methylpropanediol, and Butyl Ethyl Propanediol were evaluated for toxicity in subchronic (approximately 3-month) studies in rats with oral exposure. A NOEL of 1000 mg/kg/day was reported for Propanediol;[91] another evaluation of 5 or 10 ml/kg of Propanediol resulted in 100% mortality (5 deaths) at 10 ml/kg and 2 deaths at 5 ml/kg.[11] NOAELs for Hexanediol were reported to be 400 mg/kg/day (males) and 1000 mg/kg/day (females); a treatment-related decrease (in males at 1000 mg/kg/day) in mean body weights and a statistically significant increase in relative adrenal gland weights (in males at 400 and 1000 mg/kg/day) and in relative weights of the brain, epididymides, and testes (in males at 1000 mg/kg/day) were observed.[14] A NOEL of 600 mg/kg/day was reported for Methylpropanediol; abnormalities seen were decreased liver enzymes and inorganic phosphate (at 1000 mg/kg/day).[19] NOAELs of 150 mg/kg/day (females) and 15 mg/kg/day (males) were reported for Butyl Ethyl Propanediol; there were 4 treatment-related deaths (males at 150 or 1000 mg/kg/day), abnormal locomotion and respiration 1 to 2 hours post-dosing (after which animals returned to normal), hunched body, urinary abnormalities (at 150 and 1000 mg/kg/day), and kidney abnormalities (at $\geq$ 15 mg/kg/day) reported.[16]

Inhalation

In rat studies of 4-month durations (2 h/day exposure time) evaluating 1,4-Butanediol, a NOAEC of 500 mg/l (or NOAEL of 23 mg/kg/day) and a lowest-observed-adverse-effect-concentration (LOAEC) of 1500 mg/l (or LOAEL of 85 mg/kg/day) were reported; observations in the study reporting the LOAEC of 1500 mg/l included a sleepy condition 20 minutes post-exposure and pulmonary abnormalities.[21]

Chronic Toxicity

Oral

1,4-Butanediol

Experimental details for one chronic toxicity study found in the literature were limited.[21,92] In this study male rats (n=6/group) were orally exposed to 0.25, 3, or 30 mg/kg 1,4-Butanediol for 6 months. Controls were used (no further details). At the 30 mg/kg dosage, blood cholinesterase activity was reduced, the ratio of blood serum protein fractions changed, the -SH (thiol) groups in whole blood and the brain decreased, liver glycogen and choline esterase activity decreased, vitamin C in organs decreased, and there was an increase in blood serum transaminases. A substantial increase in the auto-diffusion coefficient of tissue fluid was found in the liver and brain with the 3 and 30 mg/kg dosages. Incipient morphological changes were noted with the 3 mg/kg dosage. At the 30 mg/kg dosage, the morphological changes observed were a reduction in Nissl bodies, glial element growth in cerebral tissue, fatty dystrophy, hyperemia in organs, and sclerotic growth in liver.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Provided below is a summary of DART studies that are presented in detail in Table 10.

In Vivo

Oral

Developmental and reproductive toxicity studies were conducted in animals that were orally exposed to Propanediol, 1,4-Butanediol, Hexanediol, Methylpropanediol, and Butyl Ethyl Propanediol. In rat studies evaluating Propanediol at dose rates up to 1000 mg/kg/day, spermatogenic endpoints were unaffected (90-day exposure duration)[91] and no maternal (dosing on days 6-15 of gestation) or fetal toxic effects were observed (maternal and fetal NOAEL 1000 mg/kg/day).[11] In a mouse study evaluating 1,4-Butanediol at up to 600 mg/kg/day (dosing on days 6-15 of gestation), a maternal and developmental NOAEL of 100 mg/kg/day and a LOAEL of 300 mg/kg/day were reported; maternal central nervous system intoxication (300-600 mg/kg/day) and maternal and fetal body weight reduction (maternal 300-600 mg/kg/day) were observed.[93] For males and females dosed with up to 800 mg/kg/day 1,4-Butanediol (14 days prior to mating and for females through day 3 of lactation), the following were reported: developmental NOEL of 400 mg/kg/day (pup weight slightly but statistically significantly decreased on lactation day 4 at 800

mg/kg/day, secondary to maternal reduction in body weight), parental transient hyperactivity (200 and 400 mg/kg/day) and reversible parental hypoactivity (≥ 400 mg/kg/day), but no parental reproductive parameters were changed by treatment.[12,21] A maternal and developmental NOAEL of 1000 mg/kg/day was reported in animal studies on Hexanediol (rats dosed on days 6-19 of gestation)[14] and for Methylpropanediol (rats dosed on days 0-20 of gestation; rabbits on days 0-29).[34,35] In a rat study evaluating Butyl Ethyl Propanediol (up to 1000 mg/kg/day on days 6-19 of gestation), a maternal NOAEL of 150 mg/kg/day (reduced activity, staggering, limb dragging, slow respiration, and reduced food consumption/body weight at 1000 mg/kg dose) and a developmental NOAEL of 1000 mg/kg/day were reported.[16]

GENOTOXICITY

Provided below is a summary of genotoxicity studies that are presented in detail in Table 11.

In Vitro

Genotoxicity data are available for Propanediol, 1,4-Butanediol, 2,3-Butanediol, 1,5-Pentanediol, Hexanediol, 1,10-Decanediol, Methylpropanediol, Butyl Ethyl Propanediol and Isopentyldiol. Experiments conducted in vitro evaluating Propanediol were negative for genotoxicity in a mammalian cell gene mutation assay (up to 5000 µg/ml), a chromosomal aberration test (up to 5000 µg/ml), and an Ames test (up to 5000 µg/plate).[11] A mammalian chromosomal aberration test (2500 µg/ml) evaluating Propanediol resulted in positive responses for genotoxicity without metabolic activation, but was negative with metabolic activation.[11] 1,4-Butanediol was negative for genotoxicity in a *Salmonella typhimurium* mutagenicity test (up to 10,000 µg/plate),[94] in an Ames test (up to 10,000 µg/plate),[12] in a mammalian cell gene mutation assay (up to 5000 µg/ml),[12] and in a chromosomal aberration test (up to 5000 µg/ml).[12] 2,3-Butanediol was negative in an Ames II™ test (up to 5000 µg/ml).[15] In an Ames test (up to 5000 µg/plate) 1,5-Pentanediol was negative for genotoxicity.[13] Hexanediol was negative for genotoxicity in an Ames test (up to 5000 µg/plate), in a mammalian chromosomal aberration test (up to 1.2 µg/ml), and in a mammalian cell gene mutation assay (up to 5000 µg/ml).[14] 1,10-Decanediol (in a test substance mixture also containing unspecified amounts of Propylene Glycol or Butylene Glycol) was non-mutagenic in an Ames test (up to 10,000 µg/plate).[88] Methylpropanediol was negative in a reverse mutation assay (up to 5000 µg/plate) and in a chromosomal aberration test (up to 5000 µg/plate).[19] Butyl Ethyl Propanediol was negative for genotoxicity in an Ames test (up to 5000 µg/plate) and in a mammalian cell gene mutation assay (up to 7.2 mmol/l).[16] Isopentyldiol was negative for genotoxicity in an Ames test (up to 10,000 µg/plate) and in a liquid suspension assay (up to 100 mg/plate).[18]

In Vivo

Oral

Tests performed in rat liver and testicular homogenates from rats that were fed 500 ppm Propanediol in the diet for 15 weeks (controls fed plain diet), showed that the DNA-protein and interstrand DNA-crosslinking in the hepatic DNA at 10 and 15 weeks were greater than in controls, and the DNA-protein and interstrand crosslinking in testicular DNA of treated rats were slightly greater than in controls at 15 weeks.[76] The study authors concluded that Propanediol was converted to malondialdehyde in vivo, causing damage to rat DNA. Mouse micronucleus tests conducted in vivo were negative for Propanediol (single dose of 2150 mg/kg)[11] and for Butyl Ethyl Propanediol (single dosage up to 1250 mg/kg).[16]

CARCINOGENICITY

In Vivo

Oral

1,4-Butanediol (gamma-butyrolactone)

No carcinogenicity studies for the alkane diols reviewed in this safety assessment were found in the literature. However, a 2-year oral bioassay (NTP study) evaluated the carcinogenic potential of gamma-butyrolactone in rats (males dosed by gavage up to 225 mg/kg, females dosed up to 450 mg/kg for 5 days/week for 102 weeks) and mice (both sexes dosed by gavage up to 525 mg/kg for 5 days/week for 102 weeks).[22,23,95] There were no carcinogenic responses reported in either sex of rat or in female mice; there was an increase in focal hyperplasia and a slight increase in adrenal gland pheochromocytoma in male mice, however these findings were considered to be equivocal. This study was essentially an evaluation of GHB. In the body 1,4-Butanediol is rapidly metabolized to form GHB, as is the cyclic lactone of GHB, gamma-butyrolactone.[95] In a two-step process, 1,4-Butanediol is metabolized to form GHB (as described previously in the Toxicokinetics Section above); in a one-step process, gamma-butyrolactone is converted to GHB through lactonase catalysis.

OTHER RELEVANT STUDIES

Cytotoxicity

1,10-Decanediol

An Agarose Overlay Test was performed by evaluating the diffusion in an agarose gel of a test mixture containing 1.2% of 1,10-Decanediol and an unspecified amount of Butylene Glycol. Average diameters (total score) were 1.075 cm; results indicated that cytotoxicity was low. No further details were provided.[88]

Neurotoxicity

1,4-Butanediol

Central nervous system effects have been reported for exposures to 1,4-Butanediol.[23] Central nervous system depression, anesthetic effect, loss of righting reflex, struggle response, and voluntary motor activity were documented in rats administered 496 mg/kg 1,4-Butanediol (no further details were provided). During oral, intraperitoneal, or intravenous exposure, neuropharmacologic responses have been reported. These effects were also observed after administration of GHB. Endogenous levels of GHB in the brain of mammals are in micromolar concentrations, while in the liver, heart, and kidneys concentrations are 5 to 10 times higher. Although 1,4-Butanediol can be converted to GHB in the brain, liver, kidney, and heart, the liver has the greatest capacity (per gram of tissue) to metabolize GHB. When GHB was administered at dosages exceeding 150 mg/kg in rats, a state of behavioral arrest was observed, with bilaterally synchronous electroencephalogram readings resembling those of humans undergoing seizures (non-epileptic).

DERMAL IRRITATION AND SENSITIZATION STUDIES

A summary of dermal irritation, sensitization, and photoirritation/photosensitization studies is provided below; details are presented in Table 12.

Irritation

In Vitro

1,10-Decanediol (1.2% in a test substance mixture also containing an unspecified amount of Butylene Glycol) was non-irritating in an in vitro test evaluating the test substance on reconstructed human epidermis.[88]

Animal

Skin irritation testing of Propanediol, 1,4-Butanediol, 2,3-Butanediol, 1,5-Pentanediol, Hexanediol, 1,10-Decanediol, Methylpropanediol, Butyl Ethyl Propanediol, and Isopentyldiol was conducted. Results indicated the following observations: Propanediol (undiluted) was mildly irritating to rabbit skin in 24-hour occlusive patch tests;[11] 1,4-Butanediol (undiluted) caused only minimal redness after application to rabbit ears and no irritation was observed in a 24-hour occlusive patch test on intact and abraded rabbit skin;[86] 2,3-Butanediol (undiluted) was non-irritating to rabbit skin in a 24-hour occlusive patch test;[15] 1,5-Pentanediol (undiluted) was non-irritating to rabbit skin in both a 24-hour non-occlusive skin test[83] and a 20-hour occlusive patch test on intact and scarified skin;[13] Hexanediol (45% to 80%) was non-irritating to animal skin in both non-occlusive and occlusive tests performed with approximately 24-hour dermal exposure;[14,83,84,96] 1,10-Decanediol (1.2% in a test substance mixture also containing an unspecified amount of Propylene Glycol) was non-irritating to rabbit skin in a 24 h occlusive patch test;[88] Methylpropanediol (concentration not specified) was non-irritating to animal skin;[19,19,35] Butyl Ethyl Propanediol (undiluted) was non-to-minimally irritating to rabbit skin in 4-hour semi-occlusive patch tests;[16] Isopentyldiol (undiluted) was non-to-slightly irritating to rabbit skin in 24-hour occlusive and semi-occlusive patch tests.[18] Overall, the alkane diols were non-to-mildly irritating to animal skin.

Human

Skin irritation testing of Propanediol, 1,4-Butanediol, 1,5-Pentanediol, 1,10-Decanediol, Methylpropanediol, and Isopentyldiol in human subjects showed the following: Propanediol (25% to 75% and undiluted) was non-to-slightly irritating in 24-hour occlusive patch tests;[97] 1,4-Butanediol (concentration not specified) was non-irritating in a patch test (no additional details provided);[21] 1,5-Pentanediol (5%) was non-irritating in an occlusive patch test;[48] 1,10-Decanediol (1.2% in a test substance mixture also containing an unspecified amount of Butylene Glycol) was well-tolerated, according to study authors (2 subjects showed mild erythema 1 h following patch removal) in a 48 h occlusive patch test;[88] Methylpropanediol (100%, 50% aqueous dilution) was non-irritating to subjects with sensitive skin in a 14-day cumulative irritation study;[35,79] Isopentyldiol (concentration not specified) and 1,3-Butanediol (concentration not specified) were slightly irritating in a 48-hour Finn chamber skin test.[18] Generally the alkane diols evaluated were non-to-slightly irritating to human skin.

Sensitization

Animal

Skin sensitization testing of Propanediol, 1,4-Butanediol, 2,3-Butanediol, Hexanediol, 1,10-Decanediol, Methylpropanediol, Butyl Ethyl Propanediol, and Isopentyldiol was performed. The following observations were reported: Propanediol (2.5% intradermal and 100% epicutaneous concentrations applied at induction, 50% epicutaneous and semi-occlusive at challenge) was non-sensitizing to guinea pig skin;[11] 1,4-Butanediol (10% intradermal and 30% topical concentrations applied at induction and challenge) was non-

sensitizing to guinea pig skin.[86] 2,3-Butanediol (5% intradermal and 50% epicutaneous concentrations applied at induction, 25% at challenge) was non-sensitizing to guinea pig skin, although during epicutaneous induction animals showed incrustation and confluent erythema with swelling.[15] Hexanediol (5% intradermal and 50% epicutaneous concentrations applied at induction, 25% at challenge) was non-sensitizing to guinea pig skin in one test.[14] In another test, strong erythema was reported in guinea pigs with Hexanediol challenge (no concentration specified) following induction (sensitization) with another compound (0.2% hydroxyethyl methacrylate). However no Hexanediol induction (0.2%)/ Hexanediol challenge (no concentration specified) tests showed a positive sensitization reaction.[96] 1,10-Decanediol (1.2% in a test substance mixture containing an unspecified amount of Propylene Glycol or Butylene Glycol) was non-sensitizing to guinea pig skin in a Buehler test (100% test substance mixture at induction and 25% at challenge).[88] Methylpropanediol showed mild sensitization potential in guinea pigs (10% intradermal to 100% epidermal concentrations applied at induction, up to 100% at challenge).[19] Butyl Ethyl Propanediol (2.5% intradermal and 100% topical concentrations applied at induction, 50% and 100% at challenge) was non-sensitizing in guinea pigs.[16] Isopentyldiol (10% intradermal and 100% topical concentrations applied at induction, 50% at challenge) was non-sensitizing in guinea pigs. However, during intradermal injection at induction and topical induction, moderate and confluent erythema were observed.[18] Sensitization results were mixed, with no-to-mild sensitization potential and some positive skin reactions observed during induction.

Human

Skin sensitization studies of Propanediol, 1,4-Butanediol, 1,5-Pentanediol, and Methylpropanediol showed the following results: Propanediol was non-sensitizing (5% to 75% concentrations applied at induction and at challenge);[97] 1,4-Butanediol (concentration not specified) was non-sensitizing;[21] 1,5-Pentanediol (5% and 25% in different tests) was non-sensitizing;[48] Methylpropanediol (concentration not specified) was non-sensitizing in one test;[35] in another test Methylpropanediol (50% aqueous dilution applied at induction and challenge) showed mild skin sensitization potential, however the study authors concluded that it was unclear as to whether or not the skin reactions were caused by irritation, allergic response, or an atopic condtion.[35,79] An additional test showed that Methylpropanediol (21.2% applied at induction and challenge) caused erythema and damage to epidermis in some subjects during the induction phase. However, the reactions were not reproducible after a new skin site was tested on those subjects under semi-occlusive conditions; Methylpropanediol was non-sensitizing in this study.[98] Generally, the alkane diols evaluated were non-sensitizing in human skin.

Photoirritation /Photosensitization

Animal

1,10-Decanediol (1.2% in a test substance mixture also containing an unspecified amount of Butylene Glycol) was non-phototoxic in guinea pig skin.[88] Isopentyldiol (undiluted) was neither a photo-irritant nor a photo-sensitizer when tested in guinea pig skin; positive controls were used in both experiments and yielded expected results.[18]

Human

1,5-Pentanediol (5%) was not phototoxic and not photosensitizing in a 24-hour occlusive patch test performed following UV-A/ UV-B exposure to the treated skin; study authors stated that it does not absorb in the long-wave ultra-violet range.[48,70]

OCULAR IRRITATION

Below is a synopsis of ocular irritation studies that are presented in detail in Table 13.

In Vitro

1,10-Decanediol (1.2% in a test substance mixture also containing an unspecified amount of Butylene Glycol) was evaluated in a hen's egg experiment and found to have moderate irritation potential when tested on the chorioallantoic membrane.[88] The same 1,10-Decanediol test substance was also evaluated on reconstructed human corneal epithelium in vitro and found to be non-irritating.

Animal

Ocular irritation was evaluated in rabbit eyes for Propanediol, 1,4-Butanediol, 2,3-Butanediol, 1,5-Pentanediol, Hexanediol, 1,10-Decanediol, Methylpropanediol, Butyl Ethyl Propanediol, and Isopentyldiol; results were mixed. No-to-slight irritation (resolved within 48 hours post-application) was reported for undiluted Propanediol.[11] Undiluted 1,4-Butanediol was slightly irritating.[40,86] Undiluted 2,3-Butanediol was non-irritating to rabbit eyes.[15] No-to-mild irritation was observed for undiluted 1,5-Pentanediol[13,36,83] and undiluted Hexanediol.[14,83,84] 1,10-Decanediol (1.2% in a test substance mixture also containing an unspecified amount of Propylene Glycol) was slightly irritating.[88] Methylpropanediol (concentration not specified) was non-irritating to rabbit eyes.[19,35] Butyl Ethyl Propanediol (concentration not specified) resulted in severe eye injury in one test.[85] In another experiment, undiluted Butyl Ethyl Propanediol was considered to be irritating, with corneal opacification and diffuse crimson conjunctiva coloration, swelling, and partial eyelid eversion; the rabbit eyes returned to normal by 14 days post-application.[16] Isopentyldiol (concentration not specified) was non-irritating.[18]

CLINICAL STUDIES

A controlled, double-blind comparative study was conducted to evaluate the treatment of atopic dermatitis with hydrocortisone and 1,5-Pentanediol.[99] Patients with atopic dermatitis were treated 2x/day with either 1% hydrocortisone (n=31) or 1% hydrocortisone with 25% 1,5-Pentanediol (n=32) in a cream formulation for 6 weeks. Quantitative bacteria cultures were taken for *Staphylococcus aureus* (commonly seen in the skin of atopic dermatitis patients) from the lesional skin prior to treatment and at weeks 2, 4, and 6 of treatment. The results indicated that the hydrocortisone-only formulation was effective for 68% of the patients in that test group; the hydrocortisone plus 1,5-Pentanediol formulation was effective for 69% in that group. There was a statistically significant reduction in *S. aureus* (baseline to week 2 and baseline to week 6) in the hydrocortisone plus 1,5-Pentanediol group, which was not observed in the hydrocortisone-only group. There were 2 instances in each treatment group of "slight burning sensation" following cream application. The study authors noted that bacteria are not likely to develop resistance to 1,5-Pentanediol because of the interaction of diols on membranes.

The therapeutic effect of 1,5-Pentanediol was investigated for the treatment of herpes simplex labialis (cold sore virus) in a placebo-controlled, randomized, double-blind clinical trial.[100] Patients included in the trial were those with known, frequent recurrences of herpes labialis. The treatment group (n=53) received 25% 1,5-Pentanediol in a gel formulation, which was applied to both lips (0.04 g total/day) during the 26-week prophylactic evaluation. The placebo group (n=52) received the same gel formulation without 1,5-Pentanediol for 26 weeks. During the occurrence of herpes labialis episodes the treatment gel or placebo was applied to both lips (0.16 g total/day) for 5 days and then the prophylactic treatment resumed until the next herpes episode. The herpes episodes reported during the trial were 109 for the treatment group and 120 for the placebo group. 1,5-Pentanediol did not demonstrate a prophylactic effect, compared to the placebo, in preventing the recurrence of herpes labialis. However, there was a statistically significant improvement in blistering, swelling, and pain for the therapeutic use of 1,5-Pentanediol as compared to the placebo. There were no treatment-related adverse events attributable to 1,5-Pentanediol or the placebo reported. In the treatment and placebo groups, body weight and temperature, heart rate, and clinical parameters were nearly unchanged.

Case Reports

Below is a synopsis of case reports that are presented in detail in Table 14.

Information from case reports for the alkane diols included allergic contact dermatitis as a result of dermal exposure to 1,5-Pentanediol (0.5% to 10%) in various creams include[101,102] a recommendation by study researchers for dental professionals exposed to Hexanediol in dentin primers to take precautions because of the potential to cause contact dermatitis following repeated occupational exposure[96] and adverse effects reported in adults (including death) and poisoning in children from oral exposure to 1,4-Butanediol (varying doses).[12,21,37,103,104]

RISK ASSESSMENT

Occupational Standards

International occupational inhalation exposure limits for 1,4-Butanediol are 100 mg/m^3 (Italy and Portugal) and 200 mg/m^3 (Austria and Germany); short-term exposure value is 800 mg/m^3 (Austria).[17]

SUMMARY

The 10 alkane diols included in this safety assessment reportedly function in cosmetics as solvents, humectants, and skin conditioning agents.

VCRP data received from the FDA in 2017 indicated that the highest reported uses are for Propanediol (1138 uses), Methylpropanediol (541 uses), and Isopentyldiol (135 uses). The Council industry survey data from 2015 indicated that the highest maximum use concentration in leave-on products was 39.9% for Propanediol in non-spray deodorants.

The alkane diols are indirect food additives. The FDA has issued warnings about dietary supplements containing 1,4-Butanediol because of associated adverse health effects, including death. 1,4-Butanediol is considered to be a Class I Health Hazard by the FDA, as well as a Schedule I Controlled Substance Analog by the DEA if illicit human consumption is intended.

A permeability coefficient of 1.50 x 10^{-5} cm/h was calculated for Propanediol after abdominal skin from human cadavers was exposed for 48 hours in a static diffusion cell to a 1.059 g/ml Propanediol solution (infinite dose, 99.953% purity).

The ability of Propanediol, 1,4-Butanediol, or 1,5-Pentanediol to enhance the penetration of the drug estradiol (0.12% [^{3}H]estradiol in 1:10 alkane diol/ ethanol solution) in human skin was evaluated in an in vitro experiment using a Franz diffusion cell. After ~ 85-90 minutes the permeability of [^{3}H]estradiol in human skin was determined to be ~ 5-6 µg/cm^2 with Propanediol and < 1 µg/cm^2 with 1,4-Butanediol or 1,5-Pentanediol. In vitro tests of pharmaceutical formulations containing 0.1% mometasone furoate and 25% 1,5-Pentanediol or 1% hydrocortisone and 25% 1,5-Pentanediol or 1% terbinafine and either 5% or 20% 1,5-Pentanediol, showed that 1,5-Pentanediol was a penetration enhancer in human breast skin samples exposed to the formulations for 60 hours.

1,4-Butanediol was a competitive inhibitor of ethanol metabolism by alcohol dehydrogenase. Diacetyl, acetoin, and 2,3-Butanediol were interconvertible with a molar equilibrium ratio of 0:3:7, respectively, in rat liver homogenates. Methylpropanediol was demonstrated to be a substrate for alcohol dehydrogenase in vitro.

Rat liver homogenates metabolized Propanediol to yield malondialdehyde in treated rats (500 ppm in the diet for 15 weeks) and in control rats (plain diet). A single dose of Propanediol, 1,4-Butanediol, 2,3-Butanediol, or Hexanediol administered orally to rabbits yielded the corresponding glucuronic acid conjugates in the urine representing 2% to 26% of the administered dose. Orally administered 1,4-Butanediol and 1,5-Pentanediol produced succinic acid and phenacyl glutarate, respectively, in the urine.

Endogenous concentrations of 1,4-Butanediol in rats were 30 to 165 ng/g in aqueous phase tissues (aqueous portion of supernatant generated from homogenized tissues) and 150 to 180 ng/g in lipid phase tissues (lipid portion of supernatant generated from homogenized tissues). 1,4-Butanediol concentrations were 96 µg/g, 52 µg/g, and 58 µg/g in the brain, liver, and kidney, respectively, of rats 75 minutes after oral exposure to 1 g/kg 1,4-Butanediol. In rats orally exposed to up to 400 mg/kg 1,4-Butanediol (radiolabels on C1 and C4), >75% of the radioactivity was excreted as $^{14}CO_2$ by 24 hours post-dosing; up to 6% was eliminated in feces 72 hours post-dosing. Experiments in rats orally administered 1M diacetyl, acetoin, or 2,3-Butanediol showed interconversion among these compounds in vivo. Methylpropanediol (100 or 1000 mg/kg, ^{14}C-labeled) orally administered to rats was reported to be rapidly metabolized and eliminated as 3-hydroxybutyric acid in the urine (31%-45% dosed radioactivity), as CO_2 in exhaled breath (42%-57%), and in the feces (< 1% dosed radioactivity).

In human subjects dermally exposed to 25% 1,5-Pentanediol (2 applications, 12 hours apart), increasing levels of glutaric acid were detected in urine and serum (no concentrations were provided). Oral exposure to 25 mg/kg 1,4-Butanediol resulted in measurable plasma concentrations of GHB in human subjects within 5 to 30 minutes after exposure, indicating rapid conversion of 1,4-Butanediol to GHB; GHB concentrations were below the limit of quantitation within 4 hours. Clearance of 1,4-Butanediol was rapid in some subjects and relatively slow in others; the latter were confirmed to have a genetic mutation of variant alleles of ADH-1B. Nearly 100% of 1,4-Butanediol was rapidly converted to GHB in a study in which 15 or 30 mg/kg 1,4-Butanediol was intravenously injected into human subjects.

The toxicity of acute dermal exposure in animals to Propanediol, 1,5-Pentanediol, Hexanediol, and Butyl Ethyl Propanediol was evaluated, and reported LD_{50}s ranged from > 2 g/kg to > 20 g/kg. A single dermal exposure to 5 g/kg 1,4-Butanediol caused dermal lesions within 48 hours and liver abnormalities within 14 days, but no mortalities in rats. In rabbits, a single 2 g/kg dermal application of Methylpropanediol caused kidney, lung, liver, and gastrointestinal tract abnormalities, among other effects, but no mortalities.

Acute oral LD_{50}s reported in multiple studies of mammalian test species included 14.9 ml/kg Propanediol, 1.2 to 2.5 g/kg 1,4-Butanediol, 10 g/kg 1,5-Pentanediol, 3 g/kg Hexanediol, 3 to 5 g/kg Butyl Ethyl Propanediol, > 20ml/kg 1,10-Decanediol (in a test substance mixture also containing unspecified amounts of Propylene Glycol), and ≥ 5 g/kg for 2,3-Butanediol, Methylpropanediol and Isopentyldiol. Clinical signs in the affected animals included ataxia, paresis, dyspnea, and exsiccosis in these studies. Necropsy and histological examinations revealed bloody stomach ulcerations, abnormal bladder contents, congestive hyperemia, and changes in the liver and kidneys in the affected animals.

A single, 4-hour inhalation exposure to 2000 to 5000 mg/l Propanediol caused moderate weight loss but no deaths in rats. A single 4.6 to 15 mg/l exposure to 1,4-Butanediol resulted in lethargy, labored breathing, and lung noise/dry nasal discharge in rats 1 to 9 days post-dosing, and 1 death at 15 mg/l 1 day post-dosing. Rats exposed for 4 hours to 5.1 mg/l 1,4-Butanediol exhibited shallow respiration that resolved within 48 hours post-exposure; gross pathology examination revealed no abnormalities. No deaths were reported after a single 7- to 8- hour inhalation exposure to 2,3-Butanediol (up to 0.85 mg/l in air), 1,5-Pentanediol (concentrated vapor), or Hexanediol (concentrated vapor). An LC_{50} > 5.1 g/l for inhalation was reported for Methylpropanediol.

Reported NOELs and NOAELs for short-term oral exposures in rats included 200 mg/kg/day 1,4-Butanediol (~42 days), 500 mg/kg/day 1,4-Butanediol (28 days), and 1000 mg/kg/day Propanediol and Methylpropanediol (14 days) or Hexanediol and Butyl Ethyl Propanediol (28 days). Effects observed at dose rates exceeding the NOEL or NOAEL in these studies included decreased food consumption and body weight gains, liver and bladder abnormalities, and decrease in blood glucose concentrations. Rabbits, orally exposed to twenty-five 200 mg/kg dosages exhibited thrombosis and unspecified effects in the liver and kidneys.

Results were unremarkable in a study in which rats inhaled up to 1800 mg/l Propanediol, 6 h/day, for 2 weeks (9 total exposures). Rats exposed to up to 5.2 mg/l 1,4-Butanediol, 6 h/day, 5 days/week, for 2 weeks, showed red nasal discharge, lower body weights, and abnormal blood chemistry parameters.

NOELs and NOAELs in subchronic, oral exposure studies ranged from 15 mg/kg/day and 150 mg/kg/day Butyl Ethyl Propanediol in male and female rats, respectively. In rats, a NOAEL of 600 mg/kg/day was reported for Methyl Propanediol and NOAELs of 1000 mg/kg/day were reported for Propanediol and Hexanediol. Effects reported in rats exposed to oral doses exceeding the NOAELs included decreased body weights, increased organ weights, decreased liver enzymes and inorganic phosphate levels, and renal and urinary abnormalities. In subchronic inhalation studies, rats were exposed to 1,4-Butanediol 2 hours/day for 4 months; a NOAEC of 500 mg/l (equivalent to approximately 23 mg/kg/day) and a LOAEC of 1500 mg/l (equivalent to about 85 mg/kg/day)

were reported. Effects at the reported LOAEC included a sleepy condition 20 minutes after each exposure and pulmonary abnormalities.

In a chronic study, rats were orally exposed to 0.25, 3, or 30 mg/kg 1,4-Butanediol for 6 months. At the 30 mg/kg dosage, blood cholinesterase activity was reduced, the ratio of blood serum protein fractions changed, the –SH (thiol) groups in whole blood and the brain decreased, liver glycogen and choline esterase activity decreased, vitamin C in organs decreased, and there was an increase in blood serum transaminases. A substantial increase in the autodiffusion coefficient of tissue fluid was found in the liver and brain with the 3 and 30 mg/kg dosages. At the 30 mg/kg dosage, the morphological changes were observed.

In rat studies evaluating oral Propanediol exposures up to 1000 mg/kg/day, spermatogenic endpoints were unaffected (90-day exposure) and no maternal or fetal toxic effects were observed (dosing on days 6-15 of gestation). A NOAEL of 100 mg/kg/day and a LOAEL of 300 mg/kg/day 1,4-Butanediol were reported for maternal (dosing on days 6-15 of gestation) and developmental toxicity in a mouse study; maternal central nervous system intoxication and maternal and fetal body weight reduction were observed at the LOAEL. Results reported in male and female rats exposed to 1,4-Butanediol for 14 days before mating and, with dosing continuing in females through day 3 of lactation, included a developmental NOEL of 400 mg/kg/day (pup weight was slightly, but statistically significantly decreased on lactation day 4 at 800 mg/kg/day, effect was secondary to maternal reduction in body weight), parental transient hyperactivity (at 200 and 400 mg/kg/day) and reversible parental hypoactivity (≥ 400 mg/kg/day), but no parental reproductive parameters were changed by treatment. A NOAEL of 1000 mg/kg/day Hexanediol (dosing on days 6-19 of gestation) and Methylpropanediol (dosing on days 0-29 of gestation) was reported for maternal and developmental effects in animals. The NOAEL for maternal effects was 150 mg/kg/day Butyl Ethyl Propanediol in rats (dosing on days 6-19 of gestation); 1000 mg/kg/day caused staggering, slow respiration, and reduced food consumption and body weights in the dams. The NOAEL for developmental effects was 1000 mg/kg/day Butyl Ethyl Propanediol in this study.

No carcinogenicity studies of the alkane diols reviewed in this safety assessment were found in the literature. However, one review article referred to an NTP 2-year oral bioassay of gamma-butyrolactone in rats (dosing 5 days/week for 102 weeks, 5 males at up to 225 mg/kg/day, females at up to 450 mg/kg/day) and mice (at up to 525 mg/kg/day). Both 1,4-Butanediol and gamma-butyrolactone are metabolized to produce GHB in the body. The results were generally negative for the carcinogenicity of gamma-butyrolactone. There were increased incidences of focal hyperplasia and a slight increase in adrenal gland pheochromocytoma in male mice in this study, however these findings were considered to be equivocal.

Genotoxicity experiments conducted in vitro evaluating Propanediol were negative in a mammalian cell gene mutation assay (up to 5000 µg/ml), a chromosomal aberration test (up to 5000 µg/ml), and an Ames test (up to 5000 µg/plate). Another mammalian chromosomal aberration test (2500 µg/ml, without metabolic activation) that evaluated Propanediol resulted in positive responses for genotoxicity, however the same test (up to 5000 µg/ml Propanediol) performed with metabolic activation yielded negative results. 1,4-Butanediol was negative for genotoxicity in a *Salmonella typhimurium* mutagenicity test (up to 10,000 µg/plate), in an Ames test (up to 10,000 µg/plate), in a mammalian cell gene mutation assay (up to 5000 µg/ml), and in a chromosomal aberration test (up to 5000 µg/ml). 2,3-Butanediol was negative in an Ames II™ test (up to 5000 µg/ml). In an Ames test (up to 5000 µg/plate) 1,5-Pentanediol was negative for genotoxicity. Hexanediol was negative for genotoxicity in an Ames test (up to 5000 µg/plate), in a mammalian chromosomal aberration test (up to 1.2 µg/ml), and in a mammalian cell gene mutation assay (up to 5000 µg/ml). 1,10-Decanediol (in a test substance mixture also containing unspecified amounts of Propylene Glycol or Butylene Glycol) was negative in an Ames test (up to 10,000 µg/plate). Methylpropanediol was negative in a reverse mutation assay (up to 5000 µg/plate) and in a chromosomal aberration test (up to 5000 µg/plate). Butyl Ethyl Propanediol was negative for genotoxicity in an Ames test (up to 5000 µg/plate) and in a mammalian cell gene mutation assay (up to 7.2 mmol/l); Isopentyldiol was negative for genotoxicity in an Ames test (up to 10,000 µg/plate) and in a liquid suspension assay (up to 100 mg/plate). Tests performed in rat liver and testicular homogenates from rats that were fed 500 ppm Propanediol in the diet for 15 weeks (controls fed plain diet), showed that the hepatic DNA-protein and DNA-crosslinking at 10 and 15 weeks were higher than controls, and the testicular DNA-protein and DNA-crosslinking of treated rats were slightly higher than controls at 15 weeks. The study authors concluded that Propanediol was converted to malondialdehyde in vivo, causing damage to rat DNA. Mouse micronucleus tests conducted in vivo were non-mutagenic for Propanediol (single dose of 2150 mg/kg bw) and for Butyl Ethyl Propanediol (single dose up to 1250 mg/kg).

1,10-Decanediol (1.2% in a test substance mixture also containing an unspecified amount of Butylene Glycol) was non-irritating in an in vitro test evaluating the test substance on reconstructed human epidermis.

Undiluted Propanediol, 1,4-Butanediol, 2,3-Butanediol, 1,5-Pentanediol, or Isopentyldiol was non-irritating to slightly or minimally irritating to the skin of rabbits in 20-to 24-hour patch tests. Undiluted 1,4-Butanediol was minimally irritating when applied to rabbit ears. Hexanediol was non-irritating to guinea pig skin (45% test substance applied) and rabbit skin (80% test substance applied) in 24-hour patch tests. 1,10-Decanediol (1.2% in a test substance mixture also containing an unspecified amount of Propylene Glycol) was non-irritating to rabbit skin in a 24 h occlusive patch test. Methylpropanediol (concentration not specified) was non-irritating to rabbit skin. Undiluted Butyl Ethyl Propanediol was non-to-mildly irritating to rabbit skin in 4-hour semi-occlusive patch tests.

Propanediol tested at concentrations ranging from 25% to 100% was non-to-slightly irritating in 24-hour occlusive patch tests in human subjects. 1,4-Butanediol was non-irritating in a patch test on human subjects (concentration not specified). 1,5-Pentanediol (5%) was non-irritating in a 24-hour occlusive patch test in human subjects. 1,10-Decanediol (1.2% in a test substance mixture also containing an unspecified amount of Butylene Glycol) was well-tolerated, according to study authors (2 subjects showed mild erythema 1 h following patch removal) in a 48-hour occlusive patch test. Methylpropanediol (100%, 50% aqueous dilution) was non-irritating to subjects with sensitive skin in a 14-day cumulative irritation study. Slight irritation was observed in a 48-hour Finn chamber skin test evaluating unspecified concentrations of Isopentyldiol.

The following treatments were negative in tests for the induction of dermal sensitization in guinea pigs: Propanediol (2.5% intradermal and 100% epicutaneous concentrations applied at induction, 50% at challenge), 1,4-Butanediol (10% intradermal and 30% topical concentrations applied at induction and challenge), 2,3-Butanediol (5% intradermal and 50% epicutaneous concentrations applied at induction, 25% at challenge), Hexanediol (5% intradermal and 50% epicutaneous concentrations applied at induction, 25% at challenge), 1,10-Decanediol (1.2% in a test substance mixture containing an unspecified amount of Proplyene Glycol or Butylene Glycol) in a Buehler test (100% test substance mixture at induction and 25% at challenge), Butyl Ethyl Propanediol (2.5% intradermal and 100% topical concentrations applied at induction, 50% and 100% at challenge), and Isopentyldiol (10% intradermal and 100% topical concentrations applied at induction, 50% at challenge). In another test, strong erythema was reported in guinea pigs with Hexanediol challenge (no concentration specified) following induction (sensitization) with another compound (0.2% hydroxyethyl methacrylate); however no Hexanediol induction (0.2%)/ Hexanediol challenge (no concentration specified) tests showed a positive sensitization reaction. Methylpropanediol showed mild sensitization potential in guinea pigs (10% intradermal to 100% epidermal concentrations applied at induction, up to 100% at challenge).

Propanediol (5% to 75% concentrations applied at induction and challenge), 1,4-Butanediol (concentration not specified), and 1,5-Pentanediol (5% or 25% in different tests) were non-sensitizing in human subjects. Methylpropanediol (concentration not specified) was non-sensitizing in one test and showed mild skin sensitization potential in another test (50% aqueous dilution applied at induction and challenge). However, the study authors concluded that it was unclear as to whether or not the skin reactions were caused by irritation, allergy, or an atopic condition. An additional study showed that Methylpropanediol (21.2% applied at induction and challenge) induced erythema and damage to epidermis in some subjects during induction, however the reactions discontinued after a new skin site in those subjects was tested under semi-occlusive conditions; Methylpropanediol was non-sensitizing in that study.

1,10-Decanediol (1.2% in a test substance mixture also containing an unspecified amount of Butylene Glycol) was non-phototoxic in guinea pig skin. Undiluted Isopentyldiol was neither a photo-irritant nor a photo-sensitizer when tested in guinea pig skin.

Human subjects were treated with 1,5-Pentanediol (5%) on the forearms, followed by UV-A/ UV-B exposure. Results from a 24-hour occlusive patch test to the treated skin revealed that the test substance was non-phototoxic and non-photosensitizing.

Experiments evaluating 1,10-Decanediol (1.2% in a test substance mixture also containing an unspecified amount of Butylene Glycol) performed in vitro showed moderate irritation potential in a hen's egg test, and was non-irritating in a test on reconstructed human corneal epithelium.

Undiluted Propanediol, 1,4-Butanediol, 2,3-Butanediol, 1,5-Pentanediol, and Hexanediol were non-to-slightly irritating or mildly irritating in rabbit eyes. 1,10-Decanediol (1.2% in a test substance mixture also containing an unspecified amount of Propylene Glycol) was slightly irritating to rabbit eyes. Methylpropanediol and Isopentyldiol were also non-irritating to rabbit eyes in studies for which the concentrations of the substances tested were not specified. In contrast, undiluted Butyl Ethyl Propanediol caused severe injury in rabbit eyes, including irritation, corneal opacification, partial eyelid eversion, all of which were reversible.

In a 6-week study investigating the therapeutic effect of 1,5-Pentanediol (25% in a cream formulation) plus hydrocortisone (1%) compared to only hydrocortisone (1%) on patients with atopic dermatitis, there were 2 instances in each treatment group of a slight skin burning sensation after application. In the group treated with hydrocortisone and 1,5-Pentanediol, a statistically significant decrease in *S. aureus* colonies at weeks 2 and 6 of treatment was observed, which was not seen with treatment of hydrocortisone alone.

In a 6-month clinical trial evaluating the therapeutic effect of 1,5-Pentanediol (25% in a gel formulation) on herpes labialis in patients with recurrent herpes episodes, there were no treatment-related adverse events reported; body weight and temperature, heart rate, and clinical parameters were nearly unchanged.

Information from case reports for the alkane diols included allergic contact dermatitis as a result of dermal exposure to 1,5-Pentanediol (0.5% to 10%) in various creams; recommendation by study researchers for dental professionals exposed to Hexanediol in dentin primers to take precautions because of the potential to cause contact dermatitis following repeated occupational exposure; the adverse effects in adults (non-fatal cases occurred with doses between 1 to 14 g, fatalities occurred with 5.4 to 20 g doses) and poisoning in children (with 14% 1,4-Butanediol by weight) from oral exposure to 1,4-Butanediol.

DISCUSSION

(Under Development, pending submission of additional data needs)

At the 2016 September CIR Expert Panel Meeting, the Panel issued an insufficient data announcement with the following data requests:

- Method of manufacturing (for all ingredients);
- Impurities data for all ingredients (particularly indicating whether or not 2,5-Hexanediol, a known neurotoxin, is an impurity of Hexanediol);
- Additional penetration enhancement data for all ingredients;
- Neurotoxicity data for Isopentyldiol;
- Concentration of use data for 1,4-Butanediol.

The Expert Panel recognized that alkane diols can enhance the penetration of other ingredients through the skin. The Panel cautioned that care should be taken in formulating cosmetic products that may contain these ingredients, in combination with any ingredients for which safety was based on data supporting a lack of dermal absorption, or when dermal absorption was a concern. The Panel discussed that alkane diols have a high potential to be dermally absorbed, especially considering their low molecular weights.

Propanediol and 2,3-Butanediol are derived from plant sources. The Panel expressed concern about pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

The Panel was concerned about the potential for dermal irritation with the use of products formulated using several of the alkane diols (e.g., Propanediol, Butyl Ethyl Propanediol, Isopentyldiol). The Panel specified that products containing alkane diols must be formulated to be non-irritating. Similarly, the potential exists for ocular irritation for many of the alkane diols that were evaluated in animal studies (e.g., Propanediol, 1,4-Butanediol, 1,5-Pentanediol, Hexanediol, 1,10-Decanediol, Butyl Ethyl Propanediol). The alkane diols are used in cosmetic products with possible eye area exposure, thereby affirming the need for cosmetic formulations to be non-irritating.

The Panel discussed the issue of incidental inhalation exposure from perfumes, hair sprays, deodorant sprays, and face powders. The data available from animal inhalation studies, including acute and short-term exposure data, suggest little potential for respiratory effects at relevant doses. International occupational inhalation exposure limits for 1,4-Butanediol range from 100 to 800 mg/m^3. Propanediol and Isopentyldiol are reportedly used at concentrations up to 3.0% in cosmetic products that may be aerosolized and Isopentyldiol is used up to 0.33% in face powder that may become airborne. The Panel noted that 95% to 99% of the droplets/particles produced in cosmetic aerosols and loose-powder cosmetic products would not be respirable to any appreciable amount. The potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. In principle, inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. However, coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

The Panel noted that the mammalian chromosomal aberration test evaluating Propanediol at 2500 µg/ml (without metabolic activation), which was positive for genotoxicity, was not of concern because mammalian chromosomal aberration tests performed at concentrations up to 5000 µg/ml Propanediol, with and without metabolic activation, were negative. Additionally, these high concentrations tested are not relevant to the concentrations used in cosmetic formulations. Lower doses of Propanediol examined in mammalian chromosomal aberration tests, both with and without metabolic activation, were also negative for genotoxicity.

CONCLUSION

To be determined…

TABLES

Table 1. Definitions, structures, and functions of the ingredients in this safety assessment. [1;CIR Staff]

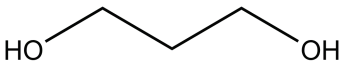
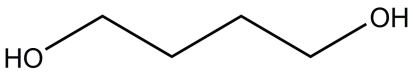
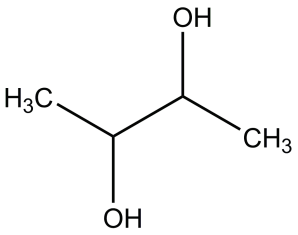
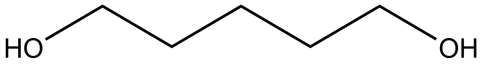
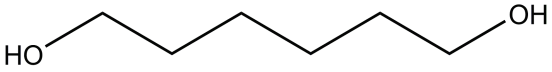
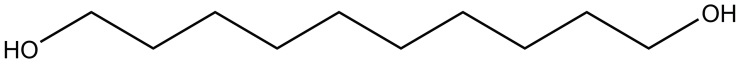
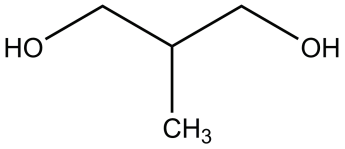
Ingredient Name & CAS No.	Definition & Structure	Function
Propanediol 26264-14-2 504-63-2	Propanediol is the organic compound that conforms to the formula: 	Solvent; Viscosity Decreasing Agent
1,4-Butanediol 110-63-4	1,4-Butanediol is the organic compound that conforms to the formula: 	Solvent
2,3-Butanediol 513-85-9	2,3-Butanediol is the organic compound that conforms to the formula: 	Fragrance Ingredient; Humectant; Skin-Conditioning Agent-Humectant; Solvent
1,5-Pentanediol 111-29-5	1,5-Pentanediol is the organic compound that conforms to the formula: 	Solvent
Hexanediol 26762-52-7 629-11-8	Hexanediol is the organic compound that conforms to the formula: 	Solvent
Octanediol 629-41-4	Octanediol is the organic compound that conforms to the formula: 	Plasticizer
1,10-Decanediol 112-47-0	1,10-Decanediol is the organic compound that conforms to the formula: 	Solvent
Methylpropanediol 2163-42-0	Methylpropanediol is the organic compound that conforms to the formula: 	Solvent

Table 1. Definitions, structures, and functions of the ingredients in this safety assessment. [1;CIR Staff]

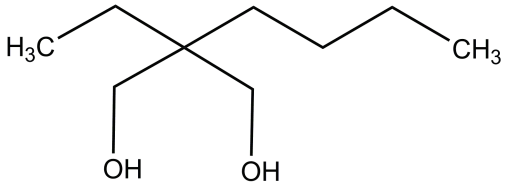
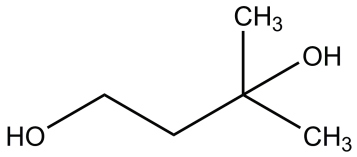
Ingredient Name & CAS No.	Definition & Structure	Function
Butyl Ethyl Propanediol 115-84-4	Butyl Ethyl Propanediol is the organic compound that conforms to the formula: 	Skin-Conditioning Agent; Humectant
Isopentyldiol 2568-33-4	Isopentyldiol is the diol that conforms to the formula: 	Solvent

Table 2. Aliphatic diols and constituent acids previously reviewed by the Panel

Ingredient	Conclusion (year issued; maximum use concentration reported)	Reference
1,2-ALKANE DIOLS (aliphatic diols)		
Propylene Glycol (i.e., 1,2-Propanediol)	Safe as used when formulated to be non-irritating (2012; up to 73% in leave-ons; up to 42% in rinse-offs)	3,4
1,2-Butanediol	Safe as used (2012; no reported uses)	2
Pentylene Glycol (i.e., 1,2-Pentanediol)	Safe as used (2012; up to 5% in leave-ons; up to 5% in rinse-offs)	2
1,2-Hexanediol	Safe as used (2012; 10% in leave-ons; 0.8% in rinse-offs)	2
Ethyl Hexanediol (i.e., 2-Ethyl-1,3-Hexanediol)	Safe as used (1994; no reported use concentrations, but product formulation data submitted to FDA in 1984 stated concentration of use up to 5%); reaffirmed in 2011 (no reported use concentrations)	5,6
Caprylyl Glycol (i.e., 1,2-Octanediol)	Safe as used (2012; up to 5% in leave-ons; up to 2% in rinse-offs)	2
Decylene Glycol (i.e., 1,2-Decanediol)	Safe as used (2012; no reported use concentrations; 1 reported use in leave-ons)	2,3
OTHER ALIPHATIC DIOLS		
Butylene Glycol (i.e., 1,3-Butanediol)	Safe as used (1985); reaffirmed in 2006 (up to 89% in leave-ons; up to 20% in rinse-offs)	7,8
Hexylene Glycol (i.e., 2-Methyl-2,4-Pentanediol)	Safe as used (1985); reaffirmed in 2006 (up to 4% in leave-ons; up to 6% in rinse-offs)	7,8
SYNTHETIC STARTING MATERIALS		
Maleic Acid (sometimes used in the synthesis of 1,4-Butanediol)	Safe for use in cosmetic formulations as a pH adjuster (2007; no reported concentrations or uses in leave-ons; 0.004% in diluted for bath use)	9
Succinic Acid (sometimes used in the synthesis of 1,4-Butanediol)	Safe as used (2012; up to 0.2% in leave-ons; up to 26% in rinse-offs)	10

Table 3. Physical and Chemical Properties

Property	Value	Reference
Propanediol		
Physical Form	Hygroscopic liquid; viscid (sticky) liquid	43,45
Color	Colorless; Colorless to pale yellow	43,45
Odor	Mild, sweet	43,45
Molecular Weight (g/mol)	76.10	45
Density (g/ml)	1.0597	45
Melting Point (°C)	146-147	105
Boiling Point (°C)	210-212	45
Water Solubility	Slightly soluble	43
Other Solubility	Soluble in alcohols and acetone; miscible with many polar solvents	43
Log P @ 25 °C	-1.093±0.458 calculated	106
pKa @ 25 °C	14.46±0.10 calculated	106

Table 3. Physical and Chemical Properties

Property	Value	Reference
1,4-Butanediol		
Physical Form	Viscous liquid	45
Color	Colorless	45
Molecular Weight (g/mol)	90.12	45
Density g/ml @ 20 °C	1.069	105
Melting Point (°C)	19-19.5	45
Boiling Point (°C)	230	45
Water Solubility	Soluble	45
Other Solubility	Soluble in DMSO, acetone, 95% ethanol	45
Log P @ 25 °C	-0.767±0.187 calculated	106
pKa @ 25 °C	14.73±0.10 calculated	106
2,3-Butanediol		
Physical Form	Hygroscopic crystals (*meso*-form)	45
Molecular Weight (g/mol)	90.12	45
Density (g/ml) @ 25 °C	0.9873	105
Melting Point °C (meso-Form)	34.4	45
Boiling Point (°C)	181.7	45
Water Solubility (pH 6.90) (g/l) in unbuffered @ 25 °C	245 calculated	106
Other Solubility	Moderately soluble in diisopropyl ether	45
Log P @ 25 °C	-0.655±0.221 calculated	106
pKa @ 25 °C	14.67±0.20 calculated	106
1,5-Pentanediol		
Physical Form	Viscous, oily liquid; bitter taste	45
Odor	Odorless	70
Molecular Weight (g/mol)	104.15	45
Density (g/ml)	0.9941	45
Melting Point (°C)	-18	45
Boiling Point (°C)	239	45
Water Solubility	Miscible with water	45
Other Solubility	Miscible with methanol, alcohol, acetone, ethyl acetate; Soluble in ether (25°C, 11% w/w); Limited solubility in benzene, trichloroethylene, methylene chloride, petroleum ether, heptane	45
Log P @ 25 °C	-0.559±0.185 calculated	106
pKa @ 25 °C	14.83±0.10 calculated	106
Hexanediol		
Physical Form	Crystals	45
Molecular Weight (g/mol)	118.18	45
Density (g/ml) @ 0°C	0.967	105
Melting Point (°C)	42.8	45
Boiling Point (°C) @ 760 mmHg	208	105
Water Solubility	Soluble	45
Other Solubility	Soluble in alcohol; Sparingly soluble in hot ether	45
Log P @ 25 °C	-0.049±0.185 calculated	106
pKa @ 25 °C	14.87±0.10 calculated	106
Octanediol		
Molecular Weight (g/mol)	146.23 calculated	106
Density (g/ml)	0.939±0.06 calculated	106
Melting Point (°C)	61-62	105
Boiling Point (°C)	140-150	105
Water Solubility (pH 7.00) (g/l) in unbuffered water @ 25 °C	4.8 calculated	106
Log P @ 25 °C	0.970±0.186 calculated	106
pKa @ 25 °C	14.89±0.10 calculated	106
1,10-Decanediol		
Physical Form	Needles from water or diluted alcohol	45
Molecular Weight (g/mol)	174.28	45
Density (g/ml) @ 20 °C, 760 mmHg	0.923±0.06 calculated	106
Melting Point (°C)	74	45
Boiling Point (°C)	71.5	105
Water Solubility	Almost insoluble	45
Other Solubility	Freely soluble in alcohol, warm ether; almost insoluble in petroleum ether	45
Log P @ 25 °C	1.989±0.186 calculated	106
pKa @ 25 °C	14.89±0.10 calculated	106

Table 3. Physical and Chemical Properties

Property	Value	Reference
Methylpropanediol		
Physical Form	Viscous liquid	35
Molecular Weight (g/mol)	90.12 calculated	106
Density (g/ml) @ 20 °C	1.020	105
Vapor Pressure (mmHg) @ 25 °C	0.021	35
Melting Point (°C)	-91	105
Boiling Point (°C)	195	105
Water Solubility (pH 6.88) (g/l) in unbuffered water @ 25 °C	215 calculated	106
Log P @ 25 °C	-0.740±0.462 calculated	106
pKa @ 25 °C	14.51±0.10 calculated	106
Butyl Ethyl Propanediol		
Molecular Weight (g/mol)	160.25 calculated	106
Density (g/ml) @ 20 °C, 760 mmHg	0.930±0.06 calculated	106
Melting Point (°C)	41.4-41.9	105
Boiling Point (°C)	262	105
Water Solubility (pH 7.00) (g/l) in unbuffered @ 25 °C	1.9 calculated	106
Log P @ 25 °C	1.709±0.470 calculated	106
pKa @ 25 °C	14.54±0.10 calculated	106
Isopentyldiol		
Molecular Weight (g/mol)	104.15 calculated	106
Density (g/ml) @ 20 °C	0.9867	105
Boiling Point (°C) @ 760 mmHg	202	105
Water Solubility (pH 6.96) (g/l) in unbuffered @ 25 °C	122 calculated	106
Log P @ 25 °C	-0.329±0.470 calculated	106
pKa @ 25 °C	14.90±0.29 calculated	106

Table 4. Current frequency and concentration of use of alkane diols[27,53]

	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)
	Propanediol		**1,4-Butanediol**		**Hexanediol**	
	2017	**2015**	**2017**	**2015**	**2017**	**2015**
Totals*	**1138**	**0.0001-39.9**	**4**	**NR**	**1**	**0.011-0.5**
Duration of Use						
Leave-On	*453*	*0.0001-39.9*	*4*	*NR*	*1*	*0.011-0.5*
Rinse-Off	*685*	*0.005-12*	*NR*	*NR*	*NR*	*0.02-0.45*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	43	0.002-10	1	NR	NR	0.011-0.08
Incidental Ingestion	1	3-10	NR	NR	NR	NR
Incidental Inhalation-Spray	spray: 18 possible: 171[a]; 145[b]	spray: 0.0001-3 possible: 2-38[a]	possible: 3[a]	NR	NR	NR
Incidental Inhalation-Powder	possible: 145[b]; 4[c]	possible: 0.0071-24[c]	NR	NR	NR	possible: 0.38[c]
Dermal Contact	1066	0.0001-39.9	4	NR	NR	0.011-0.5
Deodorant (underarm)	11[a]	not spray: 5-39.9	NR	NR	NR	NR
Hair - Non-Coloring	56	0.005-38	NR	NR	NR	NR
Hair-Coloring	9	0.17-12	NR	NR	NR	NR
Nail	NR	5	NR	NR	1	NR
Mucous Membrane	562	0.5-10	NR	NR	NR	NR
Baby Products	7	NR	NR	NR	NR	NR

	Octanediol		**1,10-Decanediol**		**Methylpropanediol**	
	2017	**2015**	**2017**	**2015**	**2017**	**2015**
Totals*	**3**	**NR**	**15**	**0.006**	**541**	**0.025-21.2**
Duration of Use						
Leave-On	*3*	*NR*	*14*	*0.006*	*336*	*0.025-21.2*
Rinse-Off	*NR*	*NR*	*1*	*NR*	*203*	*5-12*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*2*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	47	0.71-5
Incidental Ingestion	NR	NR	NR	NR	2	NR
Incidental Inhalation-Spray	possible: 3[a]	NR	possible: 12[a]; 2[b]	NR	spray: 6 possible: 100[a]; 140[b]	NR
Incidental Inhalation-Powder	NR	NR	possible: 2[b]	possible: 0.006[c]	possible: 140[b]	possible: 0.8-21.2[c]
Dermal Contact	3	NR	15	0.006	504	0.025-21.2
Deodorant (underarm)	NR	NR	NR	NR	NR	not spray: 0.025
Hair - Non-Coloring	NR	NR	NR	NR	15	NR
Hair-Coloring	NR	NR	NR	NR	8	NR
Nail	NR	NR	NR	NR	1	0.04-12
Mucous Membrane	NR	NR	NR	NR	124	5
Baby Products	NR	NR	NR	NR	NR	NR

	Butyl Ethyl Propanediol		**Isopentyldiol**	
	2017	**2015**	**2017**	**2015**
Totals*	**NR**	**0.29**	**135**	**0.13-15**
Duration of Use				
Leave-On	*NR*	*0.29*	*132*	*0.13-15*
Rinse-Off	*NR*	*NR*	*3*	*3-15*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*
Exposure Type				
Eye Area	NR	NR	25	0.13-5
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	possible: 0.29[a]	spray: 4 possible: 74[a]; 10[b]	spray: 3-5 possible: 2-5[a]
Incidental Inhalation-Powder	NR	NR	powder: 3 possible: 10[b]	powder: 0.33 possible: 1-10[c]
Dermal Contact	NR	NR	133	0.33-10
Deodorant (underarm)	NR	NR	NR	spray: 1
Hair - Non-Coloring	NR	0.29	1	3-15
Hair-Coloring	NR	NR	NR	5
Nail	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR

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

[a]Includes products that can be sprays, but it is not known whether the reported uses are sprays

[b]Not specified whether this product is a spray or a powder or neither, but it is possible it may be a spray or a powder, so this information is captured for both categories of incidental inhalation

[c]Includes products that can be powders, but it is not known whether the reported uses are powders

NR – no reported use

Table 5. Non-Cosmetic Uses

Ingredient	Non-Cosmetic Use	References
1,4-Butanediol	– Polymer component used in fabricating non-absorbable sutures for use in general and ophthalmic surgery – Indirect food additive used as a component of adhesives – Indirect food additive used as a component in polyurethane resins (no limit on amount used, but only to be used in closure gasket compositions in contact with certain food types), which are used in the manufacturing of closure-sealing gaskets for food containers – Indirect food additive used in the formation of copolyester-graft-acrylate copolymer used as a nylon modifier in nylon resins, which are used as basic components of food contact surfaces – Indirect food additive used as a reactant in the formation of polyester elastomers, which are used as basic components of food contact surfaces – Indirect food additive used as a reactant to modify polyethylene phthalate polymers used as components of plastics in contact with food – Indirect food additive used as a reactant in the formation of poly (tetramethylene terephthalate), which is used as a component in food contact surfaces – Indirect food additive used as a reactant in the formation of polyurethane resins, which are used as components of food contact surfaces – Indirect food additive used as a reactant in the formation of polyester elastomers (polybutadiene) and polyurethane resins (polyisoprene), which are rubber articles intended for repeat use in food packaging, processing, etc. – FDA estimated exposure to 1,4-Butanediol as a migrant in polyurethane resins (indirect food additive-21CFR177) would be not more than 90 µg/person/day, which FDA concluded was safe based on available toxicological data and estimated dietary exposure	21CFR74.3045; 21CFR175.105; 21CFR177.1210; 21CFR177.1500; 21CFR177.1590; 21CFR177.1630; 21CFR177.1660; 21CFR177.1680; 21CFR177.2600; [28]
Hexanediol	– Indirect food additive used as a component of adhesives – Indirect food additive used as a reactant in the formation of polyester resins and polyesterpolyurethanediol resins in adhesives, which are used in high-temperature laminate structures for food contact surfaces – Indirect food additive used as a reactant in the formation of polyurethane resins, which are used as components of food contact surfaces	21CFR175.105; 21CFR177.1390; 21CFR177.1680
Methylpropanediol	– Exemption from requirement of a tolerance for 2-Methyl-Propanediol residues (40CFR180.940a) was established when "…used as an inert ingredient component of food contact sanitizing solutions applied to all food contact surfaces in public eating places, diary-processing equipment, and food-processing equipment and utensils."-Based on EPA's review of toxicity data, especially that which showed no systemic toxicity or adverse reproductive/developmental effects at doses up to 1,000 mg/kg/day in animals, and potential for aggregate exposure – Exemption from requirement of a tolerance for 2-Methyl-Propanediol (40CFR180.910 and 40CFR180.930) when "…used as an inert ingredient in pesticide formulations applied to growing crops, raw agricultural commodities after harvest, and to animals (used for food)."	40CFR180.940(a); 40CFR180.910; 40CFR180.930;[32,33]

Table 6. Penetration Enhancement Studies

Test Substance(s)	Species	Sample Type or Test Population-Sex	Concentration (Vehicle)	Exposure Route	Procedure	Results	Reference
			IN VITRO				
Propanediol; 1,4-Butanediol; 1,5-Pentanediol	Human	Abdominal skin from cadavers (with subcutaneous fat removed)	0.12% [^{3}H]estradiol in 1:10 test substance/ ethanol solution	1.8 cm^2 diffusion area in open glass Franz diffusion cell	Experiment performed with dermis facing receptor fluid (0.05 M isotonic phosphate buffer, pH 7.4 with 0.01% mercury chloride), cells equilibrated for 1 h prior to addition of test substance; 100 µl of test substance was applied to skin sample and allowed to sit for a few minutes while ethanol evaporated (drug and vehicle remained on skin); diffusion cell incubated at 37 °C; receptor cell samples were collected at various time intervals (not specified) and fresh replacement fluid was added; steady-state flux was determined	Permeation of estradiol in skin after ~ 85 to 90 min was ~ 5 to 6 µg [^{3}H]estradiol/cm^2 for Propanediol and < 1 µg [^{3}H]estradiol/cm^2 for 1,4-Butanediol and 1,5-Pentanediol; steady-state flux for Propanediol, 1,4-Butanediol, and 1,5-Pentanediol was 0.11, 0.017, and 0.005 µg/cm^2·h, respectively	[71]
1,5-Pentanediol; 1,2-Propanediol*	Human	Cells of a multilayer membrane system comprised 3 dodecanol collodion membranes functioning as acceptors	Test cream formulations (semisolid) containing: 0.1% TRIAC (a thyroid hormone analog) + 10% 1,5-Pentanediol or 0.1% TRIAC + 6% 1,2-Propanediol or 0.1% TRIAC + 10% 1,2-Propanediol	membrane area 4 cm^2; dodecanol membrane content was 2.5 mg/ 4 cm^2	10 mg test cream applied to membrane area; beaker @ 32°C used to perform experiments; penetration cells were removed from beaker at 30, 100, and 300 min; membranes separated and TRIAC extracted and analyzed by High Performance Liquid Chromatography (HPLC)	1,5-Pentanediol was a more effective penetration enhancer for TRIAC than 1,2-Propanediol; 33% TRIAC released from formulation @ 30 min, 57% released @ 100 min, 62% released @ 300 min 1,2-Propanediol (6%) was a penetration enhancer for TRIAC; 11% TRIAC released from formulation @ 30 min, 25% released @ 100 min, 37% released @ 300 min 1,2-Propanediol (10%) was a penetration enhancer for TRIAC; 14% TRIAC released from formulation @ 30 min, 37% released @ 100 min, 41% released @ 300 min	[72]

Table 6. Penetration Enhancement Studies

Test Substance(s)	Species	Sample Type or Test Population-Sex	Concentration (Vehicle)	Exposure Route	Procedure	Results	Reference
1,5-Pentanediol; 1,2-Propanediol*	Human	Breast skin was surgically removed with a dermatome during reconstructive surgery; 3x6 cm; epidermal/dermal sample 400-500 µm thick; skin used immediately or stored in Eagle's minimum essential medium for up to 5 days; n=2 per formulation	Test cream formulations containing: 1% hydrocortisone + 25% 1,5-Pentanediol or 1% hydrocortisone + 25% 1,2-Propanediol or 1% hydrocortisone were prepared following Good Laboratory Practice (GLP)	Stratum corneum (1 cm^2) mounted on an in vitro continuous flow diffusion cell	50 mg test cream applied to top of skin in diffusion cell, receptor fluid (ethanol/phosphate buffered saline, 30:70 pumped through cell @ 2 ml/h) samples taken every 30 min between 0 and 60 h post-application; portion of test cream that was not absorbed was removed and weighed; fractions of test substance that diffused through skin were analyzed by HPLC; amount of test substance absorbed into skin was assayed separately; negative control (1% hydrocortisone) used in receptor fluid analysis	Absorption of hydrocortisone through skin increased by 4.4 times using 1,5-Pentanediol (has lipophilic characteristics) as compared to control (no penetration enhancer); hydrocortisone absorbed into skin was 58% (control not used in this part of experiment); the authors' speculated that 1,5-Pentanediol was potentially better absorbed into skin than 1,2-Propanediol (results below) because of the ability of 1,5-Pentanediol to bind to lipophilic structures in skin, slowing down drug transfer Absorption of hydrocortisone through skin increased by 12.6 times using 1,2-Propanediol (less lipophilic than 1,5-Pentanediol) compared to control; hydrocortisone absorbed into skin was 37% (control not used in this part of the experiments)	[72]
1,5-Pentanediol; 2-Methyl-Pentane-2,4-Diol (Hexylene Glycol)	Human	Breast skin was surgically removed with a dermatome during reconstructive surgery; 3x6 cm; epidermal/dermal sample 400-500 µm thick; skin used immediately or stored in Eagle's minimum essential medium for up to 5 days; n=5 per formulation	Test cream formulations containing: 0.1% mometasone furoate + 25% 1,5-Pentanediol or 0.1% mometasone furoate + 12% 2-Methyl-Pentane-2,4-Diol were prepared (GLP)	Stratum corneum (1 cm^2) mounted on an in vitro continuous flow diffusion cell	50 mg test cream applied to top of skin in donor chamber, receptor fluid (ethanol/phosphate buffered saline, 30:70 pumped through cell @ 2 ml/h) samples taken every 30 min between 0 and 60 h post-application; portion of test cream that was not absorbed was removed and weighed; fractions of test substance that diffused through skin were analyzed by HPLC; amount of test substance absorbed into skin was assayed separately	1,5-Pentanediol was a percutaneous absorption enhancer increasing the mometasone furoate absorbed through skin (4% mometasone furoate in receptor fluid) and into skin (6% mometasone furoate); 12 mg of cream remained on skin at completion of experiment 2-Methyl-Pentane-2,4-Diol was a percutaneous absorption enhancer increasing mometasone furoate absorbed through skin (5% in receptor fluid) and into skin (7%); 29 mg of cream remained on skin; the authors' speculated that the increase amount in remaining cream was possibly related to the greasiness of the formulation compared to cream containing 1,5-Pentanediol	[72]

Table 6. Penetration Enhancement Studies

Test Substance(s)	Species	Sample Type or Test Population-Sex	Concentration (Vehicle)	Exposure Route	Procedure	Results	Reference
1,5-Pentanediol; 1,2-Propanediol*	Human	Breast skin was surgically removed with a dermatome during reconstructive surgery; 3x6 cm; epidermal/dermal sample 300-400 µm thick; skin used immediately or stored in Eagle's minimum essential medium for up to 1 h before use in experiment; n=5 per test condition	Test substance hydrogels (1.5% Chremophor RH40 INCI and water, pH 6) containing: 1% terbinafine only (control); 1% terbinafine + 5% or 20% 1,5-Pentanediol; 1% terbinafine + 5% or 20% 1,2-Propanediol	Stratum corneum (1 cm^2) mounted on an in vitro continuous flow diffusion cell	50 mg test substance applied to top of skin in donor chamber, receptor fluid (ethanol/phosphate buffered saline, 30:70 pumped through cell @ 2 ml/h) samples taken every 30 min between 0 and 60 h post-application; portion of test substance that was not absorbed was removed and weighed; fractions of test substance that diffused through skin were analyzed by HPLC; amount of test substance absorbed into skin was assayed separately	1,5-Pentanediol and 1,2-Propanediol were percutaneous absorption enhancers for terbinafine (lipophilic drug); peak concentration of terbinafine in receptor fluid occurred at ~15 h for 5% 1,5-Pentanediol and at ~25 h for 5% 1,2-Propanediol with both curve profiles dropping off quickly after that; the 20% formulations had a more consistent profile at lower peak concentrations Control: 8% terbinafine absorbed into skin, 0.35% in receptor fluid, 11 µg gel not absorbed 20% 1,2-Propanediol + 1% terbinafine: 21% terbinafine absorbed into skin, 2% in receptor fluid, 19 µg gel not absorbed 20% 1,5-Pentanediol + 1% terbinafine: 11% terbinafine absorbed into skin, 3% in receptor fluid, 76 µg gel not absorbed 5% 1,2-Propanediol + 1% terbinafine: 19% terbinafine absorbed into skin, 2.5% in receptor fluid, 34 µg gel not absorbed 5% 1,5-Pentanediol + 1% terbinafine: 52% terbinafine absorbed into skin, 3% in receptor fluid, 14 µg gel not absorbed	[73]

GLP=Good Laboratory Practice; HPLC=High Performance Liquid Chromatography; TRIAC= tri-iodothyroacetic acid; **Dictionary* name is Propylene Glycol

Table 7. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
			IN VITRO			
1,4-Butanediol	Horse	Horse liver alcohol dehydrogenase	0.5 mM 1,4-Butanediol and 0.5 mM ethanol (no further details provided)	1,4-Butanediol and ethanol were combined with 80 mM potassium phosphate (pH 7.6), 0.5 mM NAD, and 10 µg crystalline horse liver alcohol dehydrogenase in a mixture (3 ml total volume) and incubated at 37°C	Competitive inhibition of the metabolism of 1,4-Butanediol occurred with ethanol; oxidation of 1,4-Butanediol was inhibited in the presence of 0.5 mM ethanol; oxidation of ethanol was inhibited in the presence of 0.5 mM 1,4-Butanediol	[74]

Table 7. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
2,3-Butanediol	Rat, Wistar	Males, rat liver homogenates	10 nmol diacetyl, 10 nmol acetoin, or 10 nmol 2,3-Butanediol were added to homogenate mixture described in Procedure column	Rat liver was homogenized in sodium phosphate buffer, centrifuged, and a mixture of 10 nmol diacetyl, acetoin or 2,3-Butanediol plus NADH, nicotinamide, 0.1 ml homogenate supernatant, and buffer were incubated for 10 min @ 37°C; reaction stopped by adding $HClO_4$, sample centrifuged, and supernatant was assayed for diacetyl, acetoin, or 2,3-Butanediol	Diacetyl, acetoin, and 2,3-Butanediol were interconvertible; they became equilibrated at a molar ratio of 0:3:7, respectively (diacetyl and acetoin were used as substrates)	[75]
Methylpropanediol	Rat	Rat liver cells	Not specified	Not specified	Metabolism studies showed that Methylpropanediol is a substrate for rat liver alcohol dehydrogenase, no further details provided (this data was submitted by industry to the EPA for the High Production Volume Challenge Program)	[35]
IN VIVO						
ANIMAL						
Oral						
Propanediol	Rat, Sprague-Dawley	Rat liver and testicular homogenates	0 or 10 mM Propanediol in 100 mg of homogenized tissue mixture	For 15 weeks rats were dosed with 500 ppm Propanediol in the diet (control rats were fed a plain diet); rats were killed and livers and testes of 2 rats/group were homogenized; a reaction mixture of either liver or testes homogenates from treated or control rats, 0 or 10 mM Propanediol, buffer, sodium pyruvate, lactic dehydrogenase, and NAD (nicotinamide adenine dinucleotide) was prepared (in duplicate) and incubated at 37°C for 3 h; 2-thiobarbituric acid in buffer and trichloroacetic acid were added, mixture heated at 95°C for 1 h, and absorbance measured at 532 nm	Propanediol was converted to malondialdehyde (~5.6 nmol/h/100 mg of tissue) by rat liver homogenates from both the control (plain diet) and Propanediol-exposed rats; testicular homogenates from control and treated rats showed little to no ability to convert Propanediol to malondialdehyde This study focused on DNA cross-linking in liver and testes of rats orally administered Propanediol (data presented in the Genotoxicity Studies section of this safety assessment)	[76]
Propanediol; 1,4-Butanediol; 2,3-Butanediol; 1,5-Pentanediol; Hexanediol;	Rabbit, Chinchilla	n=variable, see Procedure column	1.0-1.5 g/kg test substances in water is specified in the reference with the total g administered listed in the Procedure column	Single doses administered via stomach tube as follows (details regarding frequency of administration were not provided): 16 g total Propanediol fed to 4 rabbits; 9 g total 1,4-Butanediol fed to 4 rabbits; 1.2-1.5 g total 2,3-Butanediol fed to rabbits and 2 g total 2,3-Butanediol fed to 4 rabbits; 8.5 g total 1,5-Pentanediol fed to 4 rabbits; 2.8 g total Hexanediol fed to 1 rabbit; Rabbits were fed 60 g of rat cubes and 100 mL water/day; urine was treated, extracted, and assayed by various methods for metabolites 1-3 days post-dosing	Propanediol: neither malonic acid nor unchanged diol was isolated from urine 1,4-Butanediol: 0.81 g (7% of dose) of succinic acid was isolated 2,3-Butanediol: neither diacetyl nor acetoin were detected in urine or breath of rabbits (1.2-1.5 g dose); a glucuronide (triacetyl methyl ester) was isolated from urine of 2-g dosed rabbits 1,5-Pentanediol: phenacyl glutarate (0.5% of dose) was isolated from the urine Hexanediol: unchanged diol was not isolated from urine, from the carboxylic acid fraction of urine adipic acid was isolated	[77]

Table 7. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
Propanediol; 1,4-Butanediol; 2,3-Butanediol;1,5-Pentanediol; Hexanediol	Rabbit, Chinchilla	n=3	4 mmol/kg Propanediol 4 mmol/kg 1,4-Butanediol 2 mmol/kg 1,5-Pentanediol 2 mmol/kg Hexanediol 4 mmol/kg 2,3-Butanediol	Single dose administered via stomach tube; rabbits were fed 60 g of rat cubes and 100 mL water/day; 1-3 days post-dosing urine was treated, extracted, and assayed by various methods for metabolites of glycols and glucuronic acid conjugation	Propanediol glucuronic acid conjugation was 0-2% of dose, no other urinary metabolites were reported; the authors' surmised that Propanediol is likely oxidized completely to CO_2 in body; 1,4-Butanediol glucuronic acid conjugation was 0-2% of dose, urinary metabolite identified was succinic acid; 2,3-Butanediol glucuronic acid conjugation was 20%-26% of dose, glucuronide of the glycol (triacetyl methyl ester) was the urinary metabolite identified; 1,5-Pentanediol had no glucuronic acid conjugation reported, urinary metabolite identified was glutaric acid (glutaric acid is metabolized to CO_2 in body); Hexanediol glucuronic acid conjugation was 4%-9% of dose, urinary metabolite identified was adipic acid	[77]
1,4-Butanediol	Rat	Not specified	1 g/kg (no further details specified)	Animals were dosed via stomach tube and the concentrations of 1,4-Butanediol in brain, liver, kidney, stomach, and pancreas were determined by Gas Chromatography/ Mass Spectrometry (GC/MS) analysis 75 min post-dosing; the same organ concentrations of 1,4-Butanediol in control rats (naïve) were determined similarly	In naïve rats concentrations were 165 ng/g (stomach) and 30 ng/g (liver) in aqueous phase tissues (aqueous portion of supernatant generated from homogenized tissues); in lipid phase tissues (lipid portion of supernatant generated from homogenized tissues) concentrations ranged from 150 to 180 ng/g in all organs tested; at 75 min post-dosing 1,4-Butanediol was distributed through all organ systems evenly (no further details regarding concentrations of 1,4-Butanediol in organs of naïve or treated animals were provided in the abstract that is referenced); 1,4-Butanediol is ubiquitous in lipid membranes and aqueous phase fractions of the organs analyzed, implying 1,4-Butanediol may be an extraneuronal source for GHB; 1,4-Butanediol is an endogenous hepatoxin relevant to alcohol induced liver damage	[74,78]

Table 7. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
1,4-Butanediol	Rat, F344/N	Male, n=4 per dosage level	4, 40, 120, or 400 mg/kg ^{14}C-1,4-Butanediol (C1 and C4 labeled)	Single doses administered via gavage; rats housed individually in metabolism chambers; urine and feces collected @ 8, 24, 48, and 72 h post-dosing; breath samples were collected by various traps and analyzed 2, 4, 8, 12, 24, 32, 48, 56, and 72 h post-dosing; blood drawn by cardiac puncture from anesthetized rats at completion of experiment (72 h); adipose tissue, muscle, skin, liver, and brain were removed from rats dosed with 40 mg/kg ^{14}C-1,4-Butanediol and assayed for ^{14}C; the carcasses of 2 rats each dosed with 4 or 400 mg/kg ^{14}C-1,4-Butandiol were assayed for ^{14}C; no controls used	>75% of dosed radioactivity was excreted as $^{14}CO_2$ 24 h post-dosing; with 400 mg/kg capacity-limited metabolism observed at 26-30% lower $^{14}CO_2$ production 2 h post-dosing compared to other dose levels but differences decreased over time; by 72 h post-administration 3%-6% of dosed radioactivity was excreted in urine and 0.04%-0.6% of dosed radioactivity excreted in feces; ≤1% of ^{14}C were recovered in volatile compounds in breath after 4 or 400 mg/kg exposures so volatile compounds were not collected at remaining dosages; accumulation of ^{14}C after the 40 mg/kg exposures was 0.9% of dosed radioactivity in muscle tissue, 0.5% of dosed radioactivity in liver tissue, 0.1% of dosed radioactivity in blood, 0.01% of dosed radioactivity in brain, 0.15% of dosed radioactivity in adipose tissue; ^{14}C in carcass was 2.2% of 4 mg/kg dosed radioactivity and 2.8% of 400 mg/kg dosed radioactivity	[23]
1,4-Butanediol	Rat, Sprague-Dawley	n=4/cage (no further details specified)	1 g/kg 1,4-Butanediol and/or 3 g/kg ethanol (in 38% v/v water)	Single doses of 1,4-Butanediol (intragastrically) and ethanol (intraperitoneally) administered; food and water available ad libitum; rats were killed 75 min after dosing with ethanol and/or 1,4-Butanediol (maximal behavioral effects of drugs were observed at this time)	Blood ethanol levels were no different between 1,4-Butanediol and ethanol administered together compared to ethanol administered alone; concentrations of 1,4-Butanediol in brain (338 µg/g), liver (315 µg/g), and kidney (347 µg/g) tissues of rats dosed with both 1,4-Butanediol and ethanol together were statistically significantly higher than in rats administered 1,4-Butanediol alone in brain (96 µg/g), liver (52 µg/g), and kidney tissues (58 µg/g); endogenous 1,4-Butanediol in animals dosed only with ethanol was 0.02-0.05 µg/g of tissue (type of tissue not specified); liver 1,4-Butanediol concentrations were maximal 1.5-3 h post-administration of 1,4-Butanediol alone (50 µg/g) or when administered together with ethanol (>300 µg/g); by 30 min post-dosing with 1,4-Butanediol alone sedation and ataxia were observed and by 60 min catalepsy was noted, these types of effects were intensified with administration of 1,4-Butanediol and ethanol together	[74]
1,4-Butanediol	Rat, Sprague-Dawley	n=10	1 g/kg 1,4-Butanediol and 20% ethanol (v/v) in water	Ethanol administered intragastrically 6x/day for 4 days, then 10-11 h after last ethanol exposure 1,4-Butanediol was administered to 5 rats and 5 rats received saline	1,4-Butanediol had no effect on ethanol elimination	[74]

Table 7. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
2,3-Butanediol	Rat, Wistar	Male	1 M diacetyl, acetoin, or 2,3-Butanediol dissolved in saline administered at 5 mmol/kg	Single dose administered orally (control rats administered saline); 1 h post-dosing rats were intraperitoneally injected with pentobarbital and liver, kidney, and brain were removed and perfused with ice-cold saline; organs homogenized @ 4°C, centrifuged, and supernatants analyzed for diacetyl, acetoin, and 2,3-Butanediol	Diacetyl, acetoin, and 2,3-Butanediol interconvert; reduced 2,3-Butanediol was found in liver, kidney, and brain at a total of 2.3% of the administered dose of diacetyl; reduced 2,3-Butanediol was found in liver, kidney, and brain at a total of 2.6% of the administered dose of acetoin; small amounts of 2,3-Butanediol were oxidized to diacetyl and acetoin (these accumulated in liver) and 2,3-Butanediol was located in liver, kidney, and brain tissues at a total of 3% of administered dose	[75]
Methylpropanediol	Rat	n=4 per group	100 or 1000 mg/kg (each animal received ~ 10.5-13.0 µCi, ^{14}C-labeled)	Gavage administration (no further details provided)	Rapid metabolism and elimination in the urine as 3-hydroxybutyric acid and exhaled air as CO_2 (42%-57% of dosed radioactivity mostly recovered within 24 h post-dosing) were observed; 31%-45% of dosed radioactivity eliminated by renal excretion and cage wash; <1% of dose excreted in feces; dosed radioactivity remaining 7 days post-dosing was 0.1% in blood, 0.3% in liver and kidney, and 5% in carcass; > 60% of dosed radioactivity eliminated in 6 h and 83% by 24 h; half-life was calculated to be 3.57 h (high dose) and 3.87 h (low dose); alcohol dehydrogenase catalyzed metabolism to S- and R- stereoisomers of 3-hydrobutyric acid and CO_2, R-stereoisomer of 3-hydrobutyric acid largely excreted in urine (this data was submitted by industry to the EPA for the High Production Volume Challenge Program)	[34,35,79]
				Other		

Table 7. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
2,3-Butanediol	Rat, Wistar	Male	1 mM diacetyl, acetoin, or 2,3-Butanediol	Rats were administered pentobarbital, liver perfusion performed through portal vein to inferior vena cava @ 37°C; substrate added to buffer 30 min after perfusion began; perfusion was conducted without recirculation; perfusates collected every 10 min for 1 h, then liver was removed, homogenized, deproteinized, and assayed for diacetyl, acetoin, and 2,3-Butanediol	Diacetyl was reduced to acetoin and 2,3-Butanediol in liver (mole ratio diacetyl: acetoin: 2,3-Butanediol was 5:39:100; perfusate showed 45, 15, and 10% of diacetyl dose, respectively); diacetyl in perfused liver was 0.1% of perfused diacetyl dose so ~30% was metabolized or underwent glucuronidation in liver Acetoin was reduced to 2,3-Butanediol and small amount oxidized to diacetyl in liver (mole ratio diacetyl: acetoin: 2,3-Butanediol was 1:38:100; perfusate showed 1:15:45 of acetoin dose, respectively); acetoin in perfused liver was 0.1% of perfused acetoin dose, therefore ~30% was metabolized or conjugated in liver 2,3-Butanediol was oxidized in small amounts to diacetyl and acetoin; ~33% of perfused 2,3-Butanediol was metabolized or conjugated in liver; when only buffer was perfused none of the test compounds were detected in the perfusate	[75]

Table 7. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
2,3-Butanediol	Rat, Sprague-Dawley	Male Exp. 1, n=6 livers/substrate Exp. 2, n=2 Exp. 3, n=1	Exp. 1: 2 mM 2R,3R-Butanediol or 2 mM 2S,3S-Butanediol or Racemic 2,3-Butanediol (0.8 mM RR-,SS-forms and 1.2 mM *meso*-forms); 2 mM 2R,3R-[2-^{14}C]Butanediol or 1 mM *meso*-[2-^{14}C]2,3-Butanediol	Exp. 1-Rats were fed ad libitum. Livers were perfused with 150 ml of bicarbonate buffer containing bovine serum albumin and 15 mM glucose for 30 min, then various forms of labeled, unlabeled, or racemic 2,3-Butanediol were added to perfusate Exp. 2-To determine if isomer interconversion occurred, buffer (in deuterium oxide, 99.9% ^{2}H) solution containing 15 mM glucose and 2 mM 2R,3R-Butanediol or 2 mM 2S,3S-Butanediol was perfused through the liver Exp. 3-To examine whether the liver would convert ethanol to 2,3-Butanediol, 15 mM glucose and 20 mM ethanol were perfused through the liver for 2 h; 5 mM pyruvate was added to perfusate after 1 h (no exogenous 2,3-Butanediol was added) In a control experiment the livers of fed rats were perfused with 15 mM glucose	Exp. 1-In unlabeled 2,3-Butanediol experiments, the uptake rate (linear) of the RR- form was greater than for the SS- form; uptake rate for either labeled or unlabeled RR- form was double that of the labeled *meso*- form; rate of formation of *meso*- form from labeled RR- form was approx. double the rate of formation of labeled RR-, SS- forms produced from *meso*-form; uptake of labeled RR- and meso- forms resulted in formation of $^{14}CO_2$, acetate, ketone bodies, acetoin, and isomers of 2,3-Butanediol, which is attributed to approx. 1/3 of label uptake; results indicate the oxidation of 2,3-Butanediol to acetyl-CoA via acetoin Exp. 2-10 µM *meso*-[$^{2}H_1$]2,3-Butanediol and 3 µM of RR,SS-[$^{2}H_1$]2,3-Butanediol were produced 60 min after start of perfusion of RR-form; no *meso*-[$^{2}H_1$]2,3-Butanediol was detected and no RR,SS-2,3-Butanediol showed deuterium present in the perfusion of the SS-form Exp. 3-No 2,3-Butanediol or acetoin were produced from ethanol perfusion 1 h after the start of perfusion, but during the 2nd h 2,3-Butanediol and acetoin were reported to be 15 µM Controls did not show any detectable 2,3-Butanediol (<1 µM) after the start of the perfusion	[107]
HUMAN						
Dermal						
1,5-Pentanediol	Human	n=12	Therapeutic concentration of 25% (gel)	Test substance was applied 2x (12 h apart) to backs of subjects; plasma, serum, and urine samples were collected at varying times points (no further details provided)	Study authors reported a medium-long elimination time (no further details provided) of 1,5-Pentanediol, which was eliminated (after biotransformation) as glutaric acid in urine; glutaric acid was noted in subjects' urine prior to treatment (concentrations were not specified); by 24 h after first application of test substance, glutaric acid was detected in serum (concentrations not specified, increased over time in serum and urine); authors stated low risk of accumulation of 1,5-Pentanediol at concentration tested	[48,70]
Oral						

Table 7. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
1,4-Butanediol	Human	n=5 males, 3 females (22 to 35 yrs old)	25 mg/kg in orange or cranberry juice	Subjects were not GHB-naïve (GHB-naïve= not once ingested GHB, 1,4-Butanediol, or gamma-butyrolactone) or illicit drug or prescription drug (except for oral contraceptives) users; they were not heavy alcohol consumers (not > 3 drinks/week) and consumed no alcohol 3 days prior to the study and only light users of GHB (no more than 2 x in 6 months); design of study was randomized double-blinded, placebo-controlled, two arm, crossover; subjects were orally administered a single dose of placebo (plain juice) or 1,4-Butanediol after fasting overnight; subjects allowed to eat 3 h post-dosing; 2 day washout period between treatments; heart rate, blood pressure, respiratory rate, and skin temperature were measured 30 and 15 min prior to and every 15 min for the first 2 h after dosing; blood samples collected prior to and at 5, 15, 30, 45, 60, and 90 min and 2, 3, 4, 5, 6, 12, and 24 h after dosing; blood sample analysis done by GC/MS; subjects completed a visual analog scale questionnaire and a computerized cognitive battery to evaluate drug effects prior to and 1, 2, and 4 h after dosing; subjects' DNA was tested for the G143A single-nucleotide polymorphism of ADH-IB (non-synonymous mutation of an amino acid 48 substitution from arginine to histidine, R48H, associated with 40-fold increase in ethanol metabolism)	Extensive conversion of 1,4-Butanediol to GHB was observed ; average C_{max} (maximum concentration) for GHB was 45.6 mg/l and for 1,4-Butanediol was 3.8 mg/l in blood plasma; 5 of 8 subjects had measurable plasma GHB levels 5 min post-dosing, the 3 other subjects did not, potentially because of slower gastrointestinal absorption; at 30 min post-dosing all subjects had measurable plasma GHB levels; elimination half-life for GHB was 32 min and for 1,4-Butanediol was 39 min; at 4 h post-dosing plasma levels were below the limit of quantitation (1 mg/l); 4 subjects showed rapid clearance and 4 showed relatively slower clearance (3 of 4 subjects with slower metabolism had variant alleles for G143A and 3 of 4 with faster metabolism had normal wild-type ADH-IB); 2 subjects experienced lightheadedness and 2 had headaches; blood pressure increased 15 min post-dosing compared to placebo; O_2 saturation was statistically significantly decreased compared to placebo, but only by 1%; heart rate or rhythm and body temperature were unaffected; some subjects reported feeling less awake and alert, less able to concentrate, more lightheaded or dizzy up to 4 h post-dosing with effects at a max 60-90 min post-dosing	[80]
GHB sodium salt (a metabolite of 1,4-Butanediol)	Human	n=4 males, 4 females (27 to 47 yrs old); subjects were GHB naive	25 mg/kg in water	Single dose of freshly prepared solution administered orally through a drinking straw on an empty stomach; subjects not allowed to consume medication, alcohol, or drugs 48 h prior to and 24 h after study; blood samples were collected just before dosing and at 10, 15, 20, 25, 30, 45, 60, 69, 90, 120, 150, 180, 240, and 360 min post-dosing; urine samples were collected 10 min pre- and 120, 240, 360, 480, 720, and 1440 min post-dosing; oral fluid was collected up to 360 min post-dosing; above samples were assayed and quantitative analysis performed using GC/MS; blood pressure, heart rate, and hemoglobin oxygen saturation were measured when blood was drawn	GHB plasma levels ranged from < LOD to 76.3 µg/ml with C_{max} between 4.70 and 76.3 µg/ml occurring 20-45 min post-dosing; terminal plasma elimination half-lives were 17.4 to 42.5 min indicating oral absorption and elimination of GHB were rapid; mean residence time was 43.7 to 194 min; total clearance was 476 to 2520 ml/min; linear elimination kinetics were observed; GHB in oral fluid ranged from < LOD to 778 µg/ml (mean highest values of 203 to 101 µg/ml observed 10 to 15 min post-dosing, respectively); GHB in urine ranged from <LOD to 840 µg/ml (most subjects excreted highest GHB concentrations 60 min post-dosing, no GHB was detected in baseline urine or in urine samples collected 1440 min post-dosing; within 24 h, 0.2%-2.1% of administered dose was recovered in urine; no severe psychotropic side effects noted or vital functions substantially affected; confusion, sleepiness, and some dizziness were observed; substantial inter-individual variation noted	[81]

Table 7. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
			Intravenous			
1,4-Butanediol	Human	Not specified	15 or 30 mg/kg (no further details specified)	Either dose level was administered by IV, additionally gamma-hydroxybutyric acid was administered for comparison (1,4-Butanediol converts to gamma-hydroxybutyric acid or GHB in the body); no further details provided	Within 2 min post-administration of 1,4-Butanediol, GHB blood levels peaked and began to decay; 1,4-Butanediol and GHB had nearly identical decay curves when equal doses of each were administered, showing a rapid and almost 100% conversion of 1,4-Butanediol to GHB (no further details provided)	[23]

C_{max}=maximum concentration; GC/MS=Gas Chromatography/Mass Spectrometry; GHB=gamma-hydroxybutyric acid or gamma-hydroxybutyrate; LOD=limit of detection; NAD= nicotinamide adenine dinucleotide

Table 8. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
			ANIMAL			
			Dermal			
Propanediol	Rat, Wistar	n=2/sex/group	1.0, 2.0, or 4.0 ml/kg (undiluted, no vehicle)	Dorso-lumbar skin shaved free of hair; test substance applied to dorso-lumbar skin and occlusively covered for 24 h (rats fasted during exposure); at 24 h post-application covering removed and skin washed with detergent; rats observed for 9 days post-application	LD_{50} > 4ml/kg (or 4.2 g/kg); no mortalities reported	[11]
Propanediol	Rabbit	Not specified	Not specified	No details specified	LD_{50}> 20 g/kg	[82]
1,4-Butanediol	Rat, Wistar Imp: DAK	Female, n=12	5 g/kg (undiluted liquid)	Food and water were available ad libitum; sides and dorsum clipped free of hair; single application of test substance to dorsum and occlusively covered for 24 h, then covering was removed; rats were observed for 48 h (n=4) or daily for 14 days (n=8) post-application and then killed	No mortality; 48 h post-application dermal lesions (segmentary acanthosis, single microcrusts with granulocytes infiltrations, slight collagen edema, mononuclear cell infiltrations in hypodermis) were observed in 2 of 4 rats and in the liver of all 4 rats extensive vacuolar degeneration of hepatocyte cytoplasm was noted; 14 days post-application rats showed small, single desquamating crusts on skin and focal granulocyte infiltrations in epidermis and in the liver moderate periportal vacuolization of hepatocytes cytoplasm was noted; the pathological lesions observed were similar to those noted following acute oral doses	[86]

Table 8. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
1,4-Butanediol	Rat, Sprague-Dawley	n=5/sex	2 g/kg (vehicle=water)	Test substance applied (whether skin was shaved or not was not specified) to a 50 cm^2 area and skin occlusively covered for 24 h post-dosing, at that time skin washed with warm water; animals observed for 14 days post-dosing	LD_{50} > 2g/kg for males and females; no mortalities; animals gained weight; gross pathology revealed no abnormalities; clinical signs: dyspnea, poor general state within 2 h post-exposure, slight erythema after removing test substance	[12]
1,5-Pentanediol	Rabbit, New Zealand (albino)	Male, n=4	20 ml/kg	Rabbit trunk was clipped free of hair; single application of test substance to hairless skin and covered with occlusive plastic film for 24 h, at which point plastic film was removed; rabbits were observed for 14 days; researchers noted that doses >20 ml/kg could not be "retained in contact with the skin"	LD_{50} >20 ml/kg was reported	[83]
Hexanediol	Rabbit, New Zealand (albino)	Male, n=4	10 g/kg in a "suitable vehicle"	Rabbit trunk was clipped free of hair; single application of test substance to hairless skin and covered with occlusive plastic film for 24 h, at which point plastic film was removed; rabbits were observed for 14 days	LD_{50}>10 g/kg was reported	[83,84]
Hexanediol	Rabbit, Vienna White	n=5/sex	2.5 g/kg (vehicle = 0.5% carboxymethyl cellulose)	Procedures followed were in accordance with OECD Test Guideline (TG) 402 (Acute Dermal Toxicity); rabbit dorsal and lateral back area and flanks were clipped free of hair; single application of test substance to hairless skin and occlusively covered for 24 h then skin was washed with warm water; animals observed for 8 days post-application; necropsy performed	LD_{50} > 2.5 g/kg for males and females; no mortalities; gross pathology revealed no abnormalities; clinical signs: within 20-30 min slight apathy in 1 male and 1 female, slight skin irritation in 1 male (resolved after 5 days) and in 1 female (cleared within 48 h)	[14]
Methylpropanediol	Rabbit, New Zealand	n=5/sex	2 g/kg	Procedure followed was in accordance with OECD TG for Testing Chemicals; single application of test substance (semi-occlusive) for 24 h; animals observed for 14 days post-application; necropsy performed	LD_{50} > 2 g/kg; 1 death on day 12 (deemed not treatment-related because there were no signs observed previously); no-to-slight dermal reaction in 2 rabbits on day 1, but cleared by day 7; 5 of 9 animals showed abnormal kidneys and gastrointestinal tract at necropsy; a tissue mass and hemorrhagic areas on dorsal abdominal cavity of 1 animal were noted; weight loss in 2 animals observed; clinical signs: slight erythema, diarrhea, yellow nasal discharge, few feces, bloated abdomen and soiling of anogenital area; abnormalities in lungs, pleural cavity, liver and gastrointestinal tract	[19]
Methylpropanediol	Rabbit	Not specified	Not specified	Not Specified	LD_{50} > 2 g/kg	[35]
Butyl Ethyl Propanediol	Rat, CD(SD)BR VAF/Plus	n=5/sex	2 g/kg (no vehicle, test substance in powder form and moistened with distilled water before application)	Procedures followed (non-GLP) were in accordance with OECD TG 402 (Acute Dermal Toxicity); rat skin was clipped free of hair; a single application of test substance to hairless skin and occlusively covered for 24 h then skin was washed with water; animals were observed for 14 days post-application; necropsy performed	LD_{50} > 2 g/kg for males and females; no mortalities; no abnormal clinical signs; rats gained weight; gross pathology revealed no treatment-related observations	[16]
Butyl Ethyl Propanediol	Rabbit	Not specified	Not specified	Single application of test substance to skin (no further details provided)	LD_{50} was reported to be 3.81 ml/kg	[85]

Table 8. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
			Oral			
Propanediol	Rat, Wistar (albino)	n=5/sex/dose	9.0, 10.8, 13.0, 15.6, 18.7 ml/kg (no vehicle was used)	Procedures followed were in accordance with OECD TG 401 (Acute Oral Toxicity) but no controls; animals were fasted overnight; single doses administered by gavage; animals observed for 14 days post-dosing, necropsy performed on survivors	LD_{50} was calculated (Weil method) to be 14.9 ml/kg; clinical signs within a few hours post-dosing were sluggishness, sedation, ataxia, and unconsciousness preceding death; animals that survived recovered to good health by 14 days post-dosing; no gross pathology changes in survivors were reported; mortality was as follows: 1 female (10.8 ml/kg), 2 males (13.0 ml/kg), 3 males and 2 females (15.6 ml/kg); 5 males and 5 females (18.7 ml/kg)	[11]
Propanediol	Rat	n=at least 5/dose	1-9, 11, 12, 13, 14, 15, 16, 17, 18, 19 ml/kg (no vehicle specified)	Dose administered by gavage (no further details provided)	Mortality rates were as follows: 10%-18% (11-14 ml/kg); 64% (15 ml/kg); 50% (16 ml/kg); 40% (17 ml/kg); 100% (18-19 ml/kg) Authors' speculated that the variable mortality was potentially related to gastrointestinal absorption variability No mortality observed with 1-9 ml/kg	[11]
Propanediol	Cat	n=3	3 ml/kg	Dose administered by gavage (no further details provided)	At 48 h post-dosing no effects observed; by 72 h post-dosing cats vomited after drinking water and would not eat; weight loss and death reported within 1 week post-dosing	[11]
Propanediol	Rat, Wistar	n=8/sex	10.5 g/kg equivalent to 10 ml/kg (no vehicle used)	Dose administered by gavage (no further details provided)	LD_{50} reported to be 10 ml/kg; piloerection noted 24 h post-dosing in some animals; 4 of 16 animals died	[11]
Propanediol	Rat, ChR-CD	n=1 male/dose	2.25, 3.4, 5, 7.5, 11, 17, 25 g/kg; two different grades of Propanediol were evaluated undiluted at the above dosages (refined 99.8% and crude 70%)	Single dose administered by intragastric intubation; rats observed for 14 days post-dosing	ALD > 25 g/kg for 99.8% purity; no mortalities at any dosages; clinical signs observed at all dosages 1-2 days post-dosing included pallor, irregular respiration, belly-crawling, chewing motion, and salivation ALD of 17 g/kg for 70% purity; rats died within 24 h of dosing with 17 or 25 g/kg; no mortalities at remaining dosages; clinical signs at dosages below 17 g/kg observed on days 1-6 post-dosing were pallor, irregular respiration, salivation, chewing motions, belly-crawling, and diuresis	[38]
Propanediol	Rat	Preliminary Test: n=1/sex/group Definitive Test: n=4/sex	Preliminary Test: 0.63, 1.25, 2.5, 5, 10 ml/kg Definitive Test: 10 ml/kg	Preliminary Test: Single dose administered by gavage; animals observed through 9 days post-dosing (no further details provided) Definitive Test: Single dose administered by gavage (no further details provided)	Preliminary Test: 2 deaths (females) by 2 days post-dosing (no details as to which dose was lethal), other animals survived until 9 days post-dosing; piloerection noted 24 h post-dosing Definitive Test: LD_{50} of 10 ml/kg (or 10.5 g/kg)	[26]

Table 8. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
1,4-Butanediol	Rat, Sprague-Dawley	No further details specified	1 g/kg 1,4-Butanediol or 3 g/kg ethanol or both together	A single dose of 1,4-Butanediol, ethanol, or both together were administered	Mortality rate 24 h post-administration of 1,4-Butanediol was 1 of 18 rats, for ethanol was 0 of 18 rats, and for both administered together was 9 of 18 rats; 1,4-Butandiol concentrations in liver tissues of 2 of 9 animals (dosed with both compounds) that died 1.5 to 2.5 h after dosing were 1450-1600 µg/g shortly after death; the remaining 7 of 9 died 12 to 24 h post-dosing when liver concentrations of 1,4-Butanediol were low	[74]
1,4-Butanediol	Rat, Sprague-Dawley	n=5 per group	1 g/kg 1,4-Butanediol or 3 g/kg ethanol or both together	A single dose of 1,4-Butanediol (intragastrically), ethanol (intraperitoneally), or both together were administered; rats killed 24 h post-dosing; gross and microscopic studies of brain, liver and kidney were conducted	No histological changes were noted in kidney, liver, or brain 24 h post-dosing with ethanol only; 1,4-Butanediol dosed rats showed hyperemia in all organs examined; in rats dosed with ethanol and 1,4-Butanediol the following results were observed: ascites and liver congestion, microscopic liver (fatty infiltration and necrosis) and kidney changes (medullary necrosis)	[74]
1,4-Butanediol	Rat, Wistar Imp: DAK	n=4/sex/dose group; n=5/sex/dose group	1.5 to 2.5 g/kg at increasing doses; 1.8 g/kg	Food and water were available ad libitum; animals fasted for 16 h prior to dosing; single doses of 1.5 to 2.5 g/kg were administered by gavage and rats observed daily for 14 days; single doses of 1.8 g/kg administered, rats killed 48 h (n=8) or 14 days (n=8) post-dosing and examined for pathological lesions	Estimated LD_{50} of 1.83 g/kg (1.7-1.98 g/kg range) for males and 2.00 g/kg (1.8-2.22 g/kg range) for females 48 h post-dosing: unspecified number of deaths were reported (pathological findings were fluid-filled gastrointestinal tract and congestion of internal organs); in both sexes irregular, decreased respiration and catalepsy were observed; histopathological changes in liver and kidneys were noted (1.8 g/kg dose); extensive vacuolar degeneration of hepatic parenchyma noted in liver of all rats; 1 male showed periportal fatty changes in liver; hyaline or granular casts/clusters of desquamated cells (renal tubule lumen of subcortical zone and outer medulla), tubules with regeneration, and interstitial infiltration of mononuclear cells in kidneys were noted 14 days post-dosing: periportal vacuolization of hepatocytes cytoplasm and cells in mitosis were observed in liver; in 3 of 3 males and 2 of 5 females hyaline casts, single tubules regenerations, and dispersed interstitial infiltration with lymphocytes were seen in kidneys; liver and kidney changes were reversible	[86]

Table 8. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
1,4-Butanediol	Rat, Sprague-Dawley	n=5/sex/dose	1, 1.3, 1.5, 2, 2.5 g/kg (vehicle=water)	Procedures followed were in accordance with OECD TG 401(Acute Oral Toxicity); single dose administered by gavage and animals observed for 14 days post-dosing; necropsy was performed	LD_{50} estimated to be 1.5 g/kg for males and females; at 24 h post-dosing 27 animals dead (≥1.3 g/kg); deaths attributed to congestive hyperemia; animals killed after 14 days showed no abnormalities; clinical signs reported: dyspnea, apathy, abnormal position, staggering, atony, unusual pain reflex, unusual cornea reflex, narcotic-like state, tremor, spastic gait, scrubby fur, hair loss, exsiccosis, exophthalamus, poor general state; animals that survived to 14 days gained weight	[12]
1,4-Butanediol	Rat	n=5/sex	Dosage not specified (vehicle=water)	Single dose administered by gavage; animals observed for 14 days post-dosing; necropsy performed	LD_{50}s of 1.67 g/kg (females) and 1.35 g/kg (males) were reported; clinical signs included: dyspnea, apathy, abnormal position, staggering, atony, unusual pain reflex, unusual cornea reflex, narcotic-like state, tremor, spastic gait, scrubby fur, loss of hair, exsiccosis, exophthalamus, poor general state	[37]
1,4-Butanediol	Rat, albino	n=25/sex	Not specified	Not specified	LD_{50} of 1.55 g/kg	[23]
1,4-Butanediol	Rat	Not specified	Not specified	Not specified	LD_{50} of 1.78 g/kg	[40]
1,4-Butanediol	Rat, Wistar	Not specified	Not specified	Not specified	LD_{50} of 1.5 g/kg; deaths on days 1-2; signs of poisoning 10 to 15 min post-dosing; lateral posture, hyperemia of mucosa, and lethargy observed; hyperemia in brain and internal organs noted during necropsy	[21,40]
1,4-Butanediol	Mouse	Not specified	Not specified	Not specified	LD_{50} of 2.1 g/kg; animal deaths occurred on days 1-2; signs of poisoning were noted 10 to 15 min post-dosing; lateral posture, hyperemia of mucosa, and lethargy were observed; hyperemia in brain and internal organs noted during necropsy	[21,40]
1,4-Butanediol	Mouse	Not specified	Not specified	Not specified	LD_{50} of 2.2 g/kg (24 h post-dosing)	[40]
1,4-Butanediol	Guinea Pig	Not specified	Not specified	Not specified	LD_{50} of 1.2 g/kg; animal deaths occurred on days 1-2; signs of poisoning were noted 10 to 15 min post-dosing; lateral posture, hyperemia of mucosa, and lethargy were observed; hyperemia in brain and internal organs noted during necropsy	[21,40]
1,4-Butanediol	Rabbit	Not specified	Not specified	Not specified	LD_{50} of 2.5 g/kg; animal deaths occurred on days 1-2; signs of poisoning were noted 10 to 15 min post-dosing; lateral posture, hyperemia of mucosa, and lethargy were observed; hyperemia in brain and internal organs noted during necropsy	[21,40]
2,3-Butanediol	Mouse	Not specified	Not specified	Oral administration, details were not provided	LD_{50} of 9 g/kg	[52]

Table 8. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
2,3-Butanediol	Rat, Sprague-Dawley	n=5/sex	5 g/kg (vehicle=water)	Procedures followed were in accordance with OECD TG 401 (Acute Oral Toxicity)	LD_{50} > 5 g/kg for males and females; no mortality; clinical signs: dyspnea, apathy, staggering, piloerection, erythema, exophthalmos, poor general state	[15]
1,5-Pentanediol	Rat, Carworth-Wistar	n=5	Dose not specified, a "suitable vehicle" (e.g. water, corn oil, or semi-sold agar suspension) was used	Single dose administered by gastric intubation to non-fasted rats; rats observed for 14 days post-dosing	An estimated LD_{50} of 5.89 g/kg ±1.96 standard deviations was reported, LD_{50} range reported was 5.38 to 6.44 g/kg	[83]
1,5-Pentanediol	Rat, Sprague-Dawley	n=12 total (males and females)	1, 4.64, 6.81, 10 g/kg (vehicle=water)	Procedures followed were in accordance with OECD TG 401 (Acute Oral Toxicity); single dose administered by gavage; animals observed for 14 days post-dosing	LD_{50} of 10 g/kg for males and females; 1 death in 24 h (6.81 g/kg dose), 3 deaths in 24 h (10 g/kg dose), no deaths at two lower doses; reduced weight gain early in study; gross pathology revealed acute dilation of the heart and congestive hyperemia, bloody stomach ulcerations, diarrhetic and hematonic gut content, and abnormal bladder content; clinical signs: reduced state, staggering, paresis, spastic gait, salivation, exsiccosis	[13]
1,5-Pentanediol	Guinea Pig	Not Specified	Not Specified	Not Specified	LD_{50} of 4.6 g/kg; somnolence, excitement, and muscle weakness noted (no further details provided)	[108]
1,5-Pentanediol	Mouse	Not Specified	Not Specified	Not Specified	LD50 of 6.3 g/kg; somnolence, excitement, and muscle weakness noted (no further details provided)	[108]
1,5-Pentanediol	Rabbit	Not Specified	Not Specified	Not Specified	LD50 of 6.3 g/kg; somnolence, excitement, and muscle weakness noted (no further details provided)	[108]
Hexanediol	Rat, Carworth-Wistar	n=5	Dose not specified, a "suitable vehicle" (e.g. water, corn oil, or semi-sold agar suspension) was used	Single oral dose administered by gastric intubation to non-fasted rats; rats observed for 14 days post-dosing	An estimated LD_{50} of 3.73 g/kg was reported, LD_{50} range reported was 2.68 to 5.21 g/kg	[83,84]
Hexanediol	Rat	n= 20 total (males and females)	2.5, 3.2, 6.4 g/kg (vehicle=water)	Procedures followed were in accordance with OECD TG 401 (Acute Oral Toxicity); dose administered by gavage; animals observed for 7 days (2.5 and 6.4 g/kg dose) or 14 days (3.2 g/kg dose); necropsy performed	LD_{50} of 3 g/kg for males and females; mortality as follows: none in 7 days (2.5 g/kg dose), 7 deaths in 24 h (3.2 g/kg dose), 4 deaths in 24 h and 5 deaths in 7 days (6.4 g/kg dose); gross pathology revealed no abnormalities; clinical signs: staggering (within 24 h of 2.5 g/kg dose); apathy (within 1 h of 3.2 g/kg dose), lateral position, narcotic state, and atonia, constant urination (within 3 h of 3.2 g/kg dose); apathy and atonia (within 1 h of 6.4 g/kg dose), lateral position, increased urination (within 3 h of 6.4 g/kg dose), piloerection (within 24 h of 6.4 g/kg dose)	[14]

Table 8. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
1,10-Decanediol (supplier reported > 98% pure); Propylene Glycol	Mice, IFFA CREDO of 1	n=10 males	Test substance: 1.2% 1,10-Decanediol in a trade name mixture containing unspecified amount of Propylene Glycol; 20 ml/kg test substance was used	Single dose was administered; animals were observed for 8 days post-exposure and then necropsies were performed	LD_{50} > 20 ml/kg; clinical signs, behavior, and gross pathology were unaffected by test substance	[88]
1,10-Decanediol (supplier reported > 98% pure); Butylene Glycol	Mice, IFFA CREDO of 1	n=10 males	Test substance: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Butylene Glycol; 20 ml/kg of test substance was used	Single dose was administered; animals were observed for 8 days and then necropsies were performed	Normal animal behavior observed; no clinical signs; no changes to main organs (no digestive tract necrosis or ulceration) seen at necropsy	[88]
Methylpropanediol	Rat, Wistar	n=5/sex	5 g/kg	Procedures followed were in accordance with OECD TG for Testing of Chemicals; dose administered orally by a syringe and animals observed for 14 days post-dosing; negative controls used; necropsy performed	LD_{50} > 5 g/kg; no mortality; body weight not different from controls; 1 male had pink fluid in bladder at necropsy; clinical signs: diarrhea and chromorhinorrhea observed in 3 animals	[19]
Methylpropanediol	Rat	Not specified	Not specified	Not specified	LD_{50} > 5g/kg	[35]
Butyl Ethyl Propanediol	Rat, Sprague-Dawley	n=5/sex/dose	2, 3.2, and 5 g/kg (vehicle=aqueous methylcellulose 1% w/v)	Procedures followed were in accordance with (Good Laboratory Practice-GLP), and similar to European Union Method B.1 (Acute Toxicity Oral); single dose administered by gavage; animals observed for 15 days post-dosing; necropsy performed	LD_{50} calculated to be 2.9 g/kg for males and females; mortality as follows (most within 2 h post-dosing): 1 male (2 g/kg dose), 2 males and 5 females (3.2 g/kg dose), 5 males and 4 females (5 g/kg dose); gross pathology revealed no abnormalities; normal weight gain for rats except for 2 females with low weight gain; clinical signs (all dose levels): piloerection, hunched posture, waddling, lethargy, decreased respiration, ptosis, pallor-these resolved within 48 h post-dosing	[16]
Butyl Ethyl Propanediol	Rat	Not specified	Not specified	Single oral dose administered (no further details provided)	LD_{50} of 5.04 g/kg	[85]
Butyl Ethyl Propanediol	Mouse, NMRI	n=2/sex/dose	0.313, 0.625, 1.25 g/kg (vehicle=PEG 400)	Single dose administered by gavage; animals were observed for toxicity 1, 2-4, 6, 24, 30, and 48 h post-dosing (this acute study was performed in conjunction with a genotoxicity study; summary data from the genotoxicity study is presented in the Genotoxicity Table 11)	No mortality below 1.25 g/kg; 2 male deaths (4 h post-dosing) with 1.25 g/kg dose; clinical signs at all dose levels included reduced activity, eyelid closure, ruffled fur-these resolved by 24 h post-dosing	[16]

Table 8. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Butyl Ethyl Propanediol	Mouse	n=2/sex/dose	1, 1.25, 1.5, 2 g/kg	Single dose administered by gavage; animals were observed for up to 48 h post-dosing for toxicity; this was a range-finding study used to determine dosages for a genotoxicity study (summary data is presented in Genotoxicity Table 11)	No mortality below 1.5 g/kg; 1 male death (4 h post-dosing) and 1 female death (6 h post-dosing) with 1.5 g/kg; 1 male death (6 h post-dosing) and 2 female deaths (4 h post-dosing) with 2 g/kg; clinical signs observed throughout all dosages included reduced activity, abdominal position, ruffled fur, closed eyelids (most signs resolved within 24 h or less post-dosing)	[16]
Isopentyldiol	Mouse, CD-1	n=5/sex/dose	2 g/kg and 5 g/kg (vehicle= water)	Procedures followed were in accordance with OECD TG 401 (Acute Oral Toxicity); necropsy performed	LD_{50} > 5 g/kg; no mortality; gross necropsy revealed no abnormalities; no signs of toxicity reported	[18]
				Inhalation		
Propanediol	Rat, Crl:CD (SD)BR	n= 6 males	5 mg/l mean aerosol concentration (vehicle=air)	Animals were restrained in test chamber with conical nose pieces; airflow rate 15 L/min; mass median aerodynamic diameter/ geometric standard deviation = 3.2 µm/ 2.1µm; animals exposed for 4 h and observed for 14 days post-exposure	Authors reported an ALC > 5.0 mg/l; no mortalities reported; after animals were removed from chamber all had wet fur/ perineum and 1 animal had ocular discharge; 24 h post-exposure weight loss observed in all rats, but all rats gained weight by 14 days post-exposure	[11]
Propanediol	Rat	Not specified	2000 to 5000 mg/l	Animals were exposed to concentration for 4 hours (no further details provided)	Rats survived; slight-to-moderate weight loss observed the day following exposure	[82]
1,4-Butanediol	Rat, Crl:CD (SD) BR	Male, n=10/group (3 groups total)	4.6 (± 0.4), 9.4 (± 1.1), or 15.0 (± 4.2) mg/l	Food and water were available to rats ad libitum except during exposure; animal noses were positioned in a chamber where aerosolized liquid was present for inhalation of a single, 4 h duration; chamber samples were collected every 30 min; particle size (mass median diameter) was evaluated; rats were observed and weighed daily for 14 days post-exposure and then killed	Particle sizes were 3.0 to 3.6 µm mass median diameter; 1 rat died 1 day after exposure to 15.0 (±4.2) mg/l; lethargy and labored breathing were reported with 4.6 and 9.4 mg/l concentrations; red discharge was observed in perineal area with 15.0 mg/l concentration; slight (seen with 4.6 mg/l concentration) to severe (seen with 15.0 mg/l concentration) weight loss noted 24 h post-exposure, but then normal weight gain resumed; with 9.4 and 15.0 mg/l concentrations rats exhibited lung noise and dry, red nasal discharge 1 to 9 days post-exposure	[89]
1,4-Butanediol	Rat, Wistar	n=5/sex	5.1 mg/l (no vehicle)	GLP procedures were followed in accordance with OECD TG 403 (Acute Inhalation Toxicity); animals were restrained in test chamber with conical nose pieces; animals were exposed to a single concentration for 4 h; rate of air 1500 l/h; mass median aerodynamic diameter 1.9 µm; animals were observed for 14 days post-exposure; necropsy performed	LC_{50} > 5.1 mg/l (in air) for 4 h for males and females; no mortality; animals gained weight; gross pathology revealed no abnormalities; clinical signs: during exposure and on test day shallow breathing reported; on test day nasal discharge, ruffled fur, staggering gait, and deterioration observed; by 48 h post-exposure all animals were symptom free	[12,21]
2,3-Butanediol	Rat	n=12 total	Saturated atmosphere @ 20°C (up to 0.85 mg/l in air)	Animals exposed for 7 h (no further details specified)	LC_{50} > 0.85 mg/l (in air) for males and females; no mortality	[15]

Table 8. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
1,5-Pentanediol	Rat, albino	n=6/sex	Concentrated vapor (concentration in air not specified)	Rats were exposed to a stream of air containing the concentrated vapor; vapor was produced by passing dried air (2.5 liters/min) through a glass disc immersed in 1 inch of 50 ml 1,5-Pentanediol; duration of inhalation exposure was up to 8 h; rats observed for 14 days post-exposure	No deaths were reported for up to 8 h of inhalation exposure	[83]
1,5-Pentanediol	Rat, Sprague-Dawley	n=6/sex	0.11 g (no vehicle)	Procedures followed were in accordance with OECD TG 403 (Acute Inhalation Toxicity); animals exposed for 7 h; animals observed for 14 days post-exposure; necropsy performed	LC_0 of 0.078 mg/l air for 7 h for males and females was reported; no mortality; gross pathology revealed no findings	[13]
Hexanediol	Rat, albino	n=6/sex	Concentrated vapor (concentration in air not specified)	Rats were exposed to a stream of air containing the concentrated vapor; vapor was produced by passing dried air (2.5 liters/min) through a glass disc immersed in 1 inch of 50 ml Hexanediol; duration of inhalation exposure was up to 8 h; rats observed for 14 days post-exposure	No deaths were reported for up to 8 h of inhalation exposure	[83,84]
Hexanediol	Rat, Fischer 344	n=3/sex	3.3 mg/l (no vehicle used)	Procedures followed were in accordance with OECD TG 403 (Acute Inhalation Toxicity); animals exposed for 8 h; animals observed for 14 days post-exposure; necropsy performed	LC_0 of 3.3 mg/l (in air) for 8 h for males and females was reported; no mortality; gross pathology revealed no abnormalities; no clinical signs reported	[14]
Methylpropanediol	Rat	Not specified	Not specified	Not specified	LC_{50}> 5.1 g/l	[35]
				Intravenous		
Propanediol	Rabbit	n=3/dose	3, 4, 5, 6, 7, ml/kg (vehicle=water)	Dose was injected by IV into marginal ear vein (no further details provided)	LD_{50} of 4-5 ml/kg; mortality rate as follows: 40% (4 ml/kg), 60% (5 ml/kg), 100% (6-7 ml/kg); no mortality reported at 3 ml/kg	[11]

ALC=Approximate Lethal Concentration; ALD=Approximate Lethal Dose; GLP=Good Laboratory Practice; NOAEL=No Observed Adverse Effect Level; OECD TG= Organization for Economic Co-operation and Development Test Guideline

Table 9. Short-Term and Subchronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
SHORT-TERM (< 3 MONTHS)							
ANIMAL							
				Oral			
Propanediol	Rat, Crl:CD(SD)BR	n=5/sex/dose	0, 100, 250, 500, 1000 mg/kg (vehicle=deionized water)	14 days	Animals were dosed daily by gavage as indicated; necropsy performed at study termination	NOEL of 1000 mg/kg/day; no mortality; no clinical signs; body weight, food consumption, organ weights were no different than control group; neither gross necropsy nor microscopic examination revealed any treatment-related findings different from control group	[11]

Table 9. Short-Term and Subchronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
1,4-Butanediol	Rat, Wistar Imp: DAK	n=8/sex/group	0, 5, 50, 500 mg/kg/day (control group received distilled water)	28 days	Food and water were available ad libitum; dose administered by gavage 1 time per day for 28 consecutive days; blood samples (fasting) were collected just prior to necropsy	NOEL of 500 mg/kg/day (females) and NOEL of 50 mg/kg/day (males) for clinical chemistry parameters; NOEL of 50 mg/kg/day and LOEL of 500 mg/kg/day for histopathological changes; no mortality; unremarkable clinical observations; body weight, food consumption, and organ weights were unaffected; hematology parameters showed statistically significant differences compared to controls as follows: decrease in red blood cells and elevated hemoglobin (in various treatment groups, not dose dependent), lower hematocrit (males with 500 mg/kg dose), other parameters were statistically significantly different from controls (erythrocytic mean corpuscular volume, mean corpuscular hemoglobin, platelets, thrombocytes) but were not dose dependent; statistically significant increase in alanine aminotransferase and sorbitol dehydrogenase and decrease in total protein (males with 500 mg/kg dose); pronounced proliferation of bile ducts with 500 mg/kg dose (statistically significant compared to controls) and periportal infiltrations in the liver were noted in treated animals	[90]
1,4-Butanediol	Rat, Sprague-Dawley	n=13/sex/dose	200, 400, 800 mg/kg/day (vehicle=water); controls received water	42 days (males), from 14 days prior to mating until day 3 of lactation (females)	Food and water were available ad libitum; procedures followed were in accordance with OECD TG 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test); dose administered by gavage daily as indicated; hematology and clinical chemistry samples were collected at study termination; necropsy performed	NOAEL of 200 mg/kg/day for males and females; dose dependent toxic central nervous system signs observed in both sexes; hyperactivity immediately following administration (200 mg/kg/day); hyperactivity observed after a few 400 mg/kg/day doses; some animals exhibited hypoactivity or were recumbent prior to becoming comatose (800 mg/kg/day) but this resolved 5 h post-dosing and animals recovered to normal; lower body weight gains and food consumption earlier in study (at 400 and 800 mg/kg/day) that remained through study termination; statistically significant (dose-related) decrease of blood glucose in treated animals (males); gross pathology revealed no treatment-related lesions; diffuse transitional epithelial hyperplasia and fibrosis in lamina propria of bladder (400 and 800 mg/kg/day) were noted	[12]

Table 9. Short-Term and Subchronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
1,4-Butanediol and Hexanediol	Rat, Sprague-Dawley	n=4 (1,4-Butanediol), n=6 (Hexanediol)	0.5% 1,4-Butanediol or 0.5% Hexanediol (control animals received untreated water)	10 weeks (1,4-Butanediol) and 12 weeks (Hexanediol)	Food and water were available ad libitum for test and control animals; each test substance was dissolved in the treated animals' drinking water; at study termination 2 to 4 animals/group were necropsied	1,4-Butanediol: animals lost weight 6 weeks into the study, but gradually resumed weight gain; histology results revealed no changes in tissues compared to controls Hexanediol: weight gain and clinical signs were unaffected; histology results revealed no changes in tissues compared to controls	[42]
Hexanediol	Rabbit	Not specified	50 to 2000 mg/kg	Not specified	Up to 25 doses were administered by gavage as indicated (no further details provided)	Increase in clotting observed leading to thrombosis; liver and kidney were affected by treatment (no further details provided)	[39]
Hexanediol	Rat, Wistar	n=5/sex/dose	100, 400, 1000 mg/kg/day (controls were dosed with water vehicle only)	28 days	Procedures followed were in accordance with GLP and OECD TG 407 (Repeated Dose 28-Day Oral Toxicity in Rodents); animals were dosed daily by gavage as indicated; blood and urine samples were collected throughout study	NOEL of 1000 mg/kg/day for males and females was reported; statistically significant decrease in female body weights was not considered to be treatment-related because of the lack of dose-response relationship and was consistent with historical controls (food consumption was similarly affected); clinical observations, clinical chemistry, gross pathology, and histopathology were unaffected by treatment	[14]
Methylpropanediol	Rat, Wistar	n=5/sex/dose	0, 300, 600, 1000 mg/kg/day	14 days	Procedures followed were in accordance with OECD Guidelines for Testing Chemicals; doses administered daily by gavage as indicated	There were no treatment-related clinical signs and histopathology; clinical chemistry and hematology parameters were unaffected	[19]
Butyl Ethyl Propanediol	Rat, Sprague-Dawley (CD)	n=5/sex/dose	15, 150, 1000 mg/kg/day (controls were dosed with methylcellulose vehicle only, 1% w/v aqueous)	28 days	Procedures followed were in accordance with OECD TG 407 (Repeated Dose 28-Day Oral Toxicity in Rodents); animals were dosed daily by gavage as indicated; blood samples collected; necropsy performed	NOAEL of 1000 mg/kg/day (males and females); NOEL of 15 mg/kg/day (males and females); no mortalities; no treatment-related effects were correlated with clinical signs, body weight and weight gain, food/water consumption, hematology, clinical chemistry, and organ weights; gross pathology revealed liver and kidney enlargement (males with 1000 mg/kg/day) and pale, mottled kidneys (males with 150 or 1000 mg/kg/day); an adaptive liver effect noted (males with 1000 mg/kg/day); dose-related increase in renal cortical tubular eosinophilic inclusions (males with 150 or 1000 mg/kg/day)	[16]

Table 9. Short-Term and Subchronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
				Inhalation			
Propane diol	Rat, CRl:CD(SD)BR	n=10 males/group	0, 41, 650, 1800 mg/l (analytical concentrations verified the nominal concentrations 0, 60, 600, 1800 mg/l)	6 h/day for 2 weeks (9 exposures total)	Rats were restrained and fitted with conical nose pieces extending into a chamber during exposure; mass median aerodynamic diameter 2.2-2.4 µm at 2 higher concentrations and vapor at lower concentration; concluding the 2- week exposure period urine and fasting blood samples were collected, 5 rats/group were killed and pathological exam performed; concluding the 2-week exposure an 18-day recovery was allowed for remainder of animals prior to urine and fasting blood analysis and pathological exams	No mortalities during exposure and/or recovery period; no treatment-related clinical signs or clinical chemistry or hematology changes were reported; no abnormalities during microscopic or gross pathological exam (other than incidental or typical of occurring in this strain); NOEL for body weights was 1800 mg/l; vapor phase concentration achieved at 41 mg/l	[82]
1,4-Butanediol	Rat, Crl:CD BR	n=10 males/group (4 groups total including a control group)	0.2, 1.1, 5.2 mg/l (control group was exposed to air only); particle size was 2.5 to 3.6 µm (mass median diameter)	6 h/day, 5 days/wk for 2 weeks (10 exposures total)	Food and water were available to rats ad libitum except during exposure; animal noses were positioned in a chamber where aerosolized liquid was present for inhalation; chamber samples were collected every 30 min; particle size (mass median diameter) was evaluated; rats were observed and weighed daily for 14 days post-exposure; 5 rats/group were killed and necropsied at the end of the 2-week exposure period; the remainder were killed and necropsied concluding the 14-day post-exposure recovery period; clinical laboratory and urine analysis were performed on all rats (both after 2-wk exposure period and after 14-day post exposure period)	NOAEC reported for 0.2 and 1.1 mg/l; no mortality at any level; only clinical sign noted for some rats in all groups was slight, red nasal discharge during inhalation exposure; body weights (5.2 mg/l) were statistically significantly lower than controls; serum cholesterol concentrations (5.2 mg/l) were statistically significantly lower in rats killed after 10^{th} exposure compared to controls (not seen in 14-day post-exposure rats at 5.2 mg/l); statistically significantly higher erythrocyte counts and hematocrits (5.2 mg/l) in rats killed after 10^{th} exposure compared to controls (not seen in 14-day post-exposure rats at 5.2 mg/l); urine analysis and organ weights were unaffected by treatment; in lymphoid cells from thymus slight atrophy was noted (5.2 mg/l), but was not present in the 14-day post exposure rats with 5.2 mg/l	[89]
SUBCHRONIC (≥ 3 to < 6 MONTHS)							
ANIMAL							
				Oral			
Propanediol	Rat, Crl:CD(SD)BR	n=10/sex/group	0, 100, 300, 1000 mg/kg/day (control group received water)	90 days	Procedures followed (GLP) were in accordance with EPA Toxic Substances Control Act Health Effects Testing Guidelines (40CFR1989); single doses were administered daily by gastric intubation for 91-92 days; food and water were available ad libitum; blood samples (fasting) were collected for clinical pathology analysis (evaluated at 4 weeks post-dosing and at study termination); necropsy performed	NOEL of 1000 mg/kg/day for males and females; no mortality; no treatment-related clinical signs; no treatment-related hematology or chemistry parameter changes; neither microscopic nor gross pathology change related to treatment were observed (only incidental lesions typically seen in laboratory rats were noted)	[91]

Table 9. Short-Term and Subchronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
Propanediol	Rat	n=5/group (7 groups total)	5% or 12% in diet; 5 ml/kg or 10 ml/kg (gavage); control diet; control diet + 10 ml water (gavage); control diet + 10 ml 1,2-Propanediol* (gavage)	15 weeks	Animals were dosed by gavage or in the diet as indicated (no further details provided)	100% mortality prior to study termination for animals dosed with 10 ml/kg Propanediol; 2 rats died (5 ml/kg group); reduced growth weights were noted in groups dosed with Propanediol	[11]
Hexanediol	Rat, Wistar	n =10/sex/dose	100, 400, 1000 mg/kg/day (controls were dosed with water vehicle only)	91-92 days	Procedures followed were in accordance with GLP and OECD TG 408 (Repeated Dose 90-Day Oral Toxicity in Rodents); animals were dosed daily by gavage as indicated; blood and urine samples were collected	NOAEL of 400 mg/kg/day (males) and NOAEL of 1000 mg/kg/day (females); no mortality; treatment-related decrease with 1000 mg/kg/day (males only) in mean body weight (-10.5%) and mean body weight change (-18.7%); no treatment-related effects were reported for food/water consumption, ophthalmoscopic exam, hematology, clinical chemistry, histopathology, estrous cycle, sperm parameters, gross pathology; non-adverse treatment-related effects for urinalysis (decreased urine volume and pH and increased specific gravity in males with 1000 mg/kg/day); non-adverse treatment-related decrease in grip strength of hindlimbs (males 1000 mg/kg/day); statistically significant increase (compared to controls) in absolute (males 400 mg/kg/day) and relative (males 400 and 1000 mg/kg/day) adrenal gland weight; statistically significant increase in relative brain, epididymides, and testes weights (males 1000 mg/kg/day); statistically significant decrease in absolute weights of heart, seminal vesicle, and spleen (males 1000 mg/kg/day) and absolute and relative spleen weight (females 1000 mg/kg/day)	[14]
Methylpropanediol	Rat, Wistar	n=10/sex/dose	0, 300, 600, 1000 mg/kg/day	90 days	Procedures followed were in accordance with OECD Guidelines for Testing Chemicals; doses administered daily by gavage as indicated	NOEL of 600 mg/kg/day; no treatment-related clinical signs or histopathology were reported; small increase in partial thromboplastin time (females with 1000 mg/kg/day); decrease (10%-14%) in ALT and aspartate aminotransferase AST in males with 1000 mg/kg/day; decrease in inorganic phosphate (males and females with 1000 mg/kg/day)	[19]

Table 9. Short-Term and Subchronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
Butyl Ethyl Propanediol	Rat, Wistar	n=10/sex/dose	15, 150, 1000 mg/kg/day (controls received hydroxypropyl methylcellulose vehicle only)	90 days	Procedures (GLP) followed were in accordance with OECD TG 408 (Repeated Dose 90-Day Oral Toxicity in Rodents); dose administered daily by gavage as indicated; blood and urine samples collected; necropsy performed	NOAEL of 15 mg/kg/day (males) and NOAEL of 150 mg/kg/day (females); treatment-related deaths of 3 males (1000 mg/kg/day) and 1 male (150 mg/kg/day); the following were unaffected by treatment: body weight and weight gain, food/water consumption, ophthalmoscopic exam, hematology, and gross pathology; clinical signs (with 1000 mg/kg/day) were reduced activity, abnormal locomotion and respiration up to 1-2 hours post-dosing after which animals returned to normal, piloerection, hunched body posture, and partially closed eyes were observed; compared to controls a statistically significant increase in urea (males with 150 or 1000 mg/kg/day) and protein and globulin levels (males with 1000 mg/kg/day); statistically significant decrease in urinary pH (males and females with 1000 mg/kg/day); statistically significant increase in urinary specific gravity (males with 1000 mg/kg/day); higher kidney weights (males with ≥ 150 mg/kg/day) and corresponding tubular dilation (males with ≥ 150 ng/kg/day) and nephropathy (males with ≥ 15 mg/kg/day)	[14]
				Inhalation			
1,4-Butanediol	Rat	Males	1500 to 2000 mg/l	2 h/day each day for 4 months	Animals were exposed daily as indicated (no further details provided)	LOAEC of 1500 mg/l (or LOAEL 85 of mg/kg/day); around 3-4 weeks into the study a sleepy condition was induced 10-20 min post-exposure; noted on histopathological exam were pulmonary emphysema, mild lung edema, treatment-related inflammatory changes of single alveolar cell and weak hyperplasia of alveolar septum (lymphocytes and histiocytes were present)	[21]
1,4-Butanediol	Rat	Males	300 to 500 mg/l	2 h/day for 6 days/week for 4 months	Animals were exposed as indicated (no further details provided)	NOAEC of 500 mg/l (or 23 mg/kg/day); body weight, neuromuscular response, hemogenesis, liver and kidney function were unaffected	[21]

ALT=alanine transaminase; AST=aspartate aminotransferase; GLP=Good Laboratory Practice; LOAEC=Lowest Observed Adverse Effect Concentration; LOAEL=Lowest Observed Adverse Effect Level; LOEL=Lowest Observed Effect Level; NOAEC=No Observed Adverse Effect Concentration; NOAEL=No Observed Adverse Effect Level; NOEL=No Observed Effect Level; OECD TG= Organization for Economic Co-operation and Development Test Guideline; **Dictionary* name is Propylene Glycol

Table 10. Developmental and Reproductive Toxicity (DART) Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Dosage (Vehicle)	Procedure	Results	Reference
			Oral			
Propanediol	Rat, Crl:CD(SD)BR	n=10 males/group	0, 100, 300, 1000 mg/kg/day (control group received water)	Procedures followed were in accordance with GLP and EPA Toxic Substances Control Act Health Effects Testing Guidelines (40CFR1989); single doses were administered daily by gastric intubation for about 90 days; food and water were available ad libitum; at study termination the animals were killed and epididymis excised and weighed; sperm motility was measured; sperm assessed for morphology; testis and epididymis were homogenized and examined for sperm production rates	Spermatogenic endpoints (mean testicular and epididymal sperm counts, sperm production rate, sperm motility and morphology) were unaffected by treatment at all dose rates	[91]
Propanediol	Rat, Sprague-Dawley	n=20 females	0, 250 or 1000 mg/kg/day (vehicle=0.8% aqueous hydroxypropyl-methylcellulose gel)	Procedures followed (GLP) were in accordance with OECD TG 414 (Prenatal Developmental Toxicity Study); females were dosed by gavage on days 6 through 15 of gestation	Maternal and fetal toxicity NOAEL of 1000 mg/kg/day; no maternal toxic effects from treatment (fertility rate was 91% for all dose rates); no embryotoxic or teratogenic effects on fetuses from treatment	[11]
1,4-Butanediol	Mouse, Swiss (CD-1)	n=28-32/group	0, 100, 300, 600 mg/kg/day	Pregnant mice were dosed by gavage during days 6 through 15 of gestation	Maternal and developmental NOAEL of 100 mg/kg/day; maternal and developmental LOAEL of 300 mg/kg/day ; no maternal mortality; maternal central nervous system intoxication was observed (300-600 mg/kg/day) 4 h after daily dosing; reduced food consumption and body weight/weight gain noted (maternal with 300-600 mg/kg/day); developmental toxicity observed was reduced fetal body weight (300-600 mg/kg/day maternal dose)	[93]
1,4-Butanediol	Rat, Sprague-Dawley	n=13/sex/dose	200, 400, 800 mg/kg/day (vehicle=water); controls received water	Food and water were available ad libitum; procedures followed were in accordance with GLP and OECD TG 422 (Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test); dose administered daily by gavage for 42 days (males) and from 14 days prior to mating until day 3 of lactation (females); non-fasting blood samples collected after final exposure	Offspring male/female NOEL of 400 mg/kg/day (pup weight slightly, but statistically significantly decreased on lactation day 4 at 800 mg/kg/day, effect was secondary to maternal reduced food consumption and body weight); Transient hyperactivity (with 200 and 400 mg/kg/day in parents) was observed following administration; neurological effects (hypoactivity and recumbency followed by coma in some animals) observed at ≥ 400 mg/kg/day but reversed 5 h post-dosing; no parental reproductive parameters were changed by treatment; offspring viability and morphological abnormalities were unaffected by treatment	[12,21]

Table 10. Developmental and Reproductive Toxicity (DART) Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Dosage (Vehicle)	Procedure	Results	Reference
Hexanediol	Rat, Wistar	n=10/sex/dose	0, 100, 400, or 1000 mg/kg/day, controls received water vehicle only	Food and water available ad libitum; procedures followed were in accordance with GLP and OECD TG 421 (Reproduction/Developmental Toxicity Screening Test; animals dosed daily by gavage; duration of treatment for males was approximately 4 weeks (2 weeks premating); duration of treatment for females was about 6 weeks (2 weeks premating); study termination was post-partum day 4; animals killed at study conclusion and necropsy performed	Parental (female) NOAEL of 1000 mg/kg/day; parental (male) NOAEL of 400 mg/kg/day; offspring (male/female) NOAEL of 1000 mg/kg/day; male parents (1000 mg/kg/day) showed treatment-related (stat. sig) decrease in food consumption and body weight; male fertility index was 90%-100%; female mating index was 90%-100% and fertility index was 100%; offspring exhibited no treatment-related effects	[14]
Hexanediol	Rat, Wistar	n=25 females	0, 100, 400,1000 mg/kg/day (controls received water vehicle only)	Food and water were available ad libitum; procedures followed were in accordance with GLP and OECD TG 414 (Prenatal Developmental Toxicity Study); animals were dosed by gavage during days 6 through 19 of gestation; on day 20 of gestation females were killed and necropsies performed	Maternal and developmental NOAEL of 1000 mg/kg/day; no maternal mortalities or clinical signs; maternal body weight and food consumption unaffected; maternal necropsies revealed no findings; conception rate 96%-100%; female fetus weight (1000 mg/kg dose) was slightly but statistically-significantly decreased, and still within historical control range; a few external malformation were reported in test groups and the control group, but agreed with historical control data; 2 fetal soft tissue malformations (1000 mg/kg) and skeletal malformations (all test groups) occurred, but data were not significantly different from controls and agreed with historical control data	[14]
Hexanediol	Rat, Wistar	n=10/sex/dose	0, 100, 400, 1000 mg/kg/day (controls received water vehicle)	Food and water were available ad libitum: procedures were in accordance with GLP and OECD TG 421 (Reproduction/Developmental Toxicity Screening Test); animals were dosed by gavage; duration of treatment for males was approximately 4 weeks (2 weeks premating); duration of treatment for females was about 6 weeks (2 weeks premating); test duration of treatment and exposure was until day 4 postpartum of F1 generation; at study termination uterus, ovaries, and offspring were examined	Maternal and developmental NOAEL of 1000 mg/kg/day; no maternal toxic or embryotoxic effects were observed	[14]
Methylpropanediol	Rat, Sprague-Dawley	n=10/sex/dose	0, 100, 300, 1000 mg/kg/day	A 2-generation reproduction study was conducted; animals were dosed by gavage (no further details provided)	Maternal and neonatal NOAEL of 1000 mg/kg/day	[34]

Table 10. Developmental and Reproductive Toxicity (DART) Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Dosage (Vehicle)	Procedure	Results	Reference
Methylpropanediol	Rat, Wistar	Females	Up to 1000 mg/kg, negative controls were used (no further details specified)	Animals were dosed by gavage on days 0 through 20 of gestation (no further details specified); this study was repeated due to possibly skewed results (outcomes of both studies are summarized in the Results column)	No maternal toxicity or changes in fetal development were reported; potential embryotoxicity reported because of a statistically significant increase (compared to controls) in early absorptions (maternal 600 and 1000 g/kg/day doses), but results may have been skewed by 1 female at those dose levels with atypically high incidences so the study was repeated; the follow-up study results were unremarkable and indicated that interuterine growth and survival were unaffected by treatment (with up to 1000 mg/kg/day maternal dose)	[35]
Methylpropanediol	Rabbit, New Zealand White	Females	0, 250, 500, 1000 mg/kg	Animals were dosed by gavage on days 0 through 29 of gestation (no further details provided)	Maternal toxicity, fetotoxicity, and teratogenic effects NOAEL of 1000 mg/kg/day; intrauterine growth and survival was not affected by treatment, no treatment-related effects were observed for malformations or changes in soft or skeletal tissues	[34]
Butyl Ethyl Propanediol	Rat, Sprague-Dawley	n=24 females	0, 15, 150, 1000 mg/kg/day (controls received the aqueous hydroxypropyl methylcellulose vehicle only)	Food and water were available ad libitum; procedures followed were in accordance with GLP and OECD TG 414 (Prenatal Development Toxicity Study); dose administered by gavage on days 6 through 19 of gestation; animals were killed on gestation day 20; necropsy performed	Maternal NOAEL of 150 mg/kg/day; Developmental NOAEL of 1000 mg/kg/day; maternal clinical signs included subdued behavior, reduced activity, staggering, limb dragging, slow/wheezing respiration, excess salivation, piloerection, partially closed eyes (1000 mg/kg); small decrease in maternal body weights/food consumption (day 7-8 of gestation, 1000 mg/kg) which returned to normal by gestation days 9-12; no embryotoxic/teratogenic effects were observed	[16]

GLP=good laboratory practice; LOAEL=lowest observed adverse effect level; NOAEL=no observed adverse effect level; OECD TG= Organization for Economic Co-operation and Development Test Guideline

Table 11. Genotoxicity Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
			IN VITRO			
Propanediol	*Salmonella typhimurium*	TA1535, TA1537, TA98, TA100, TA102	33.3, 100, 333.3, 1000, 2500, 5000 µg/plate (vehicle=water)	Bacterial reverse mutation assay (Ames Test) was performed, with and without metabolic activation, in accordance with GLP and OECD TG 471 (Bacterial Reverse Mutation Assay); negative, vehicle, and positive controls were used	Negative; controls performed as expected	[11]
Propanediol	Hamster	Chinese Hamster Lung Fibroblasts (V79)/ Hypoxanthine-guanine phosphoribosyl transferase (HPRT)	0, 250, 1000, 2500, 5000 µg/ml	Mammalian cell gene mutation assay was performed, with and without metabolic activation, in accordance with GLP and OECD TG 476 (In vitro Mammalian Cell Gene Mutation Test); 2 independent experiments using the same test conditions were performed; negative, vehicle, and positive controls were used	Negative; controls performed as expected; cytotoxicity was reported (low survival) at 5000 µg/ml without using metabolic activation	[11]
Propanediol	Hamster	Chinese Hamster Lung Fibroblasts (V79)	625, 1250, 2500, 5000 µg/ml (vehicle=water)	Mammalian chromosomal aberration test was performed, with (4 h exposure) and without (4 or 20 h exposure) metabolic activation, in accordance with GLP and OECD TG 473 (In vitro Mammalian Chromosome Aberration Test); vehicle and positive controls were used	Negative; controls performed as expected; cytotoxicity was noted at 5000 µg/ml without metabolic activation (20 h exposure)	[11]
Propanediol	Hamster	Chinese Hamster Lung Fibroblasts (V79)	250, 1000, 2500 µg/ml (18 h, without activation); 500, 2500, 5000 µg/ml (18 h, with activation); 375, 1250, 2500 µg/ml (18 h, without activation); 1250 µg/ml (28 h, without activation); 2500, 3750, 5000 µg/ml (18 h, with activation); 5000 µg/ml (28 h, with activation)	Mammalian chromosomal aberration test was performed, with and without metabolic activation, in accordance with GLP and OECD TG for Testing of Chemicals, section 4, No. 473); vehicle and positive controls were used	Positive for genotoxicity (18 h interval with 2500 µg/ml concentration) without metabolic activation (controls performed as expected); negative for genotoxicity with metabolic activation (controls performed as expected)	[11]
1,4-Butanediol	*Salmonella typhimurium* and *Escherichia coli*	*S. typhimurium*: TA98, TA100, TA1535, TA1537; *E. coli*: WP2 uvrA	0, 313, 625, 1250, 2500, 5000 µg/plate	Ames Test was performed, with and without metabolic activation, in accordance with GLP and OECD TG 471 (Bacterial Reverse Mutation Assay) and 472 (Genetic Toxicology: *E. coli*, Reverse Mutation Assay); vehicle and positive controls were used	Negative; controls performed as expected	[12]

Table 11. Genotoxicity Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
1,4-Butanediol	*Salmonella typhimurium*	TA1535, TA1537, TA1538, TA98, TA100	500, 1000, 2500, 5000, 7500, and 10,000 µg/plate (vehicle=distilled water)	Ames Test was performed with and without metabolic activation; negative, vehicle, and positive controls were used	Negative: controls performed as expected	[12]
1,4-Butanediol	*Salmonella typhimurium*	TA98, TA100, TA1535, TA97	0, 1, 3, 10, 33, 100, 333, 1000, 3333, and 10,000 µg/plate	Mutagenicity test performed; 0.05 ml of test compound was incubated @ 37°C with *S. typhimurium* and a buffer; tests were performed with and without metabolic activation; negative and positive controls were used	Negative	[94]
1,4-Butanediol	Hamster	Chinese Hamster Ovary cells	20, 60, 200, 600, 2000, 5000 µg/ml (vehicle=Ham's F12 cell culture medium)	Mammalian cell gene mutation assay was performed, with and without metabolic activation in accordance with GLP and OECD TG 476 (In vitro Mammalian Cell Gene Mutation Test); vehicle, negative, and positive controls were used	Negative; controls were validated	[12]
1,4-Butanediol	Hamster	Chinese Hamster Lung Fibroblasts (V79)	400, 3000, 5000 µg/ml (vehicle=MEM cell culture medium)	Chromosomal aberration test was performed, with and without metabolic activation, in accordance with GLP and OECD TG 473 (In vitro Mammalian Chromosome Aberration Test); vehicle and positive controls were used	Negative; controls performed as expected	[12]
1,4-Butanediol	Hamster	Chinese Hamster Lung (CHL/IU) cells	0, 230, 450, 900 µg/ml (vehicle=distilled water)	Chromosomal aberration test was performed, with and without metabolic activation, in accordance with GLP and OECD TG 473 (In vitro Mammalian Chromosome Aberration Test); vehicle and positive controls were used	Negative; controls performed as expected	[12]
2,3-Butanediol	*Salmonella typhimurium*	TA98 and TA mix (TA7001-7006)	4 to 5000 µg/ml	Ames II™ Assay test was performed (GLP), with and without metabolic activation; negative, vehicle, and positive controls were used	Negative; controls performed as expected	[15]
1,5-Pentanediol	*Salmonella typhimurium*	TA1535, TA1537, TA98, TA100	0, 20, 100, 500, 2500, 5000 µg/plate (vehicle=water; application by agar plate incorporation)	Ames Test was performed, with and without metabolic activation, in accordance with GLP and OECD TG 471 (Bacterial Reverse Mutation Assay); negative, vehicle, and positive controls were used	Negative; controls performed as expected	[13]
1,5-Pentanediol	*Salmonella typhimurium*	TA1535, TA1537, TA98, TA100	0, 20, 100, 500, 2500, 5000 µg/plate (vehicle=water; application by preincubation @ 37°C for 20 min)	Ames Test was performed, with and without metabolic activation, in accordance with GLP and OECD TG 471 (Bacterial Reverse Mutation Assay); negative, vehicle, and positive controls were used	Negative; controls performed as expected	[13]
Hexanediol	*Salmonella typhimurium*	TA1535, TA1537, TA98, TA100	20, 100, 500, 2500, 5000 µg/plate (vehicle=dimethyl sulfoxide or DMSO; application by agar plate incorporation)	Ames Test was performed (non-GLP), with and without metabolic activation, in accordance with OECD TG 471 (Bacterial Reverse Mutation Assay); negative, vehicle, and positive controls were used	Negative; controls performed as expected	[14]

Table 11. Genotoxicity Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Hexanediol	*Salmonella typhimurium*	TA1535, TA1537, TA98, TA100	20, 100, 500, 2500, 5000 µg/plate (vehicle=DMSO; application by preincubation @ 37°C for 20 min)	Ames Test was performed (non-GLP), with and without metabolic activation, in accordance with OECD TG 471 (Bacterial Reverse Mutation Assay); negative, vehicle, and positive controls were used	Negative; controls performed as expected	[14]
Hexanediol	Hamster	Chinese Hamster V79 cells	0.3, 0.6, 1.2 µg/ml (vehicle=MEM; application by agar plate incorporation and preincubation in suspension)	Mammalian chromosomal aberration test was performed, with and without metabolic activation, in accordance with GLP and OECD TG 473 (In vitro Mammalian Chromosome Aberration Test); negative, vehicle, and positive controls were used	Negative; controls performed as expected	[14]
Hexanediol	Hamster	Chinese Hamster (V79)/ Hypoxanthine-guanine phosphoribosyl transferase (HPRT)	500, 1000, 2500, 5000 µg/ml	Mammalian cell gene mutation assay was performed, with and without metabolic activation, in accordance with GLP and OECD TG 476 (In vitro Mammalian Cell Gene Mutation Test); negative, vehicle, and positive controls were used	Negative; controls performed as expected	[14]
1,10-Decanediol (supplier reported > 98% pure); Propylene Glycol	*Salmonella typhimurium*	TA98, TA100, TA1537	Test substance: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Propylene Glycol; Test substance was evaluated up to 10,000 µg/plate	Ames test was performed with and without metabolic activation	Non-mutagenic; no cytotoxicity observed	[88]
1,10-Decanediol (supplier reported > 98% pure); Butylene Glycol	*Salmonella typhimurium*	TA98, TA100, TA1535, TA1537, TA1538	Test substance: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Butylene Glycol; Test substance was evaluated at 10, 50, 100, 1,000, 5,000 µg/plate	Assay was performed, with and without metabolic activation, to evaluate mutagenicity (positive and vehicle controls were used)	Non-mutagenic (revertant frequencies of test substance were similar to controls); no cytotoxicity observed	[88]
Methylpropanediol	*Salmonella typhimurium*	TA98, TA100, TA1535, TA1537	100 to 5000 µg/plate	Reverse mutation assay was performed, with and without metabolic activation, in accordance with OECD Guidelines for Testing of Chemicals (no further details)	Negative	[19]
Methylpropanediol	Hamster	Chinese Hamster V79 cells	333 to 5000 µg/plate	Chromosomal aberration test was performed, with and without metabolic activation, in accordance with OECD Guidelines for Testing Chemicals; positive controls were used	Negative; controls performed as expected	[19]

Table 11. Genotoxicity Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Methylpropanediol	Human	Human lymphocytes	333 to 5000 µg/plate (3 h, with metabolic activation); 10 to 5000 µg/plate (24 and 48 h, without metabolic activation) Vehicle=F10 medium buffered with 20 mM HEPES	Chromosomal aberration test was performed, with and without metabolic activation, in accordance with OECD Guidelines for Testing Chemicals; positive controls were used	Negative; controls performed as expected	[19]
Butyl Ethyl Propanediol	*Salmonella typhimurium*	TA1535, TA1537, TA98, TA100	0, 50, 150, 500, 1500, 5000 µg/plate (vehicle=ethanol; application by plate incorporation)	Ames Test was performed (non-GLP), with and without metabolic activation, in accordance with OECD TG 471 (Bacterial Reverse Mutation Assay); Ames Test was conducted independently 2x (for initial assessment and then for confirmation); vehicle, and positive controls were used	Negative; controls performed as expected; cytotoxicity was reported at 5000 µg/plate with TA98 without activation in both initial and confirmatory experiments	[16]
Butyl Ethyl Propanediol	Mouse	Thymidine kinase locus in mouse lymphoma L5178Y cells	0.03, 0.06, 0.11, 0.22, 0.45, 0.90, 1.3, 1.8, 2.6, 3.1, 3.6, 4.2, 5.0 mmol/l (24 h, without activation); 0.06, 0.11, 0.22, 0.45, 0.9, 1.8, 2.6, 3.7, 5.2, 6.1, 7.2, 8.5, 10 mmol/l (4 h, with activation); 0.06, 0.11, 0.22, 0.45, .9, 1.8, 2.6, 3.7, 5.2, 6.1, 7.2, 8.5, 10 mmol/l (4 h in a confirmatory assay with and without activation)	Mammalian cell gene mutation assay was performed, with and without metabolic activation, in accordance with GLP and OECD TG 476 (In vitro Mammalian Cell Gene Mutation Test); negative and positive controls were used	Negative for genotoxicity; cytotoxicity (with and without activation) limited the confirmation assay to a maximum concentration of 7.2 mmol/l; controls performed as expected	[16]
Isopentyldiol (purity 97%)	*Salmonella typhimurium* and *Escherichia coli*	*S. typhimurium*: TA98, TA100, TA1535, TA1537; *E. coli*: WP2 uvrA (pKM101)	33 to 10,000 µg/plate (vehicle=DMSO)	Bacterial reverse mutation assay was performed , with and without metabolic activation, in accordance with OECD TG 471 (Bacterial Reverse Mutation Test) and EC Directive 2000/32/EC B.12/14 Mutagenicity-Reverse Mutation Test using Bacteria; 10,000 µg/plate exceeds the 5000 µg/plate limit recommended for non-cytotoxic substances; positive controls were used	Negative; controls performed as expected	[18]
Isopentyldiol	*Bacillus subtilis*	M45, H17	6.25, 12.5, 25, 50, 100 mg/plate (vehicle=DMSO)	Preliminary rapid streak test was conducted to determine dose levels; liquid suspension assay was performed with and without metabolic activation; negative, vehicle, and positive controls were used	No toxicity reported in preliminary test; liquid suspension assay was negative for genotoxicity; controls performed as expected	[18]

Table 11. Genotoxicity Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
			IN VIVO			
			Oral			
Propanediol	Rat, Sprague-Dawley	Rat liver and testicular homogenates	500 ppm Propanediol in the diet	For up to 15 weeks, rats were dosed in the diet (control rats were fed a plain diet); 3 rats/group were killed at 5, 10, and 15 weeks; tissues from the liver and one testicle from each rat were homogenized and assayed to isolate the DNA; bound tryptophan was measured (effect of DNA concentration on fluorescence was evaluated); DNA template activity was determined; hepatic and testicular DNA was assayed for cross-linking	The metabolism results from the homogenized liver and testes are summarized in the Toxicokinetics Section of this safety assessment. No substantial difference in control vs. treated rats was observed in the evaluation of lipid-soluble testicular fluorophores; tryptophan bound to testicular DNA of treated rats was not different from the controls; tryptophan bound to hepatic DNA in treated rats killed at 5 and 15 weeks was statistically significantly higher than in corresponding controls; treated rats showed a statistically significantly lower template activity in hepatic DNA in rats killed at 10 and 15 weeks compared to controls; template activities of testicular DNA showed no difference from controls; in treated rats the hepatic DNA-protein and DNA-crosslinking at 10 and 15 weeks were higher than controls; testicular DNA-protein and DNA-crosslinking of treated rats were slightly higher than controls at 15 weeks; given the above results and the toxicokinetics results presented in Table 8 (rat liver homogenates converted Propanediol to malondialdehyde) the authors concluded that there were indications that Propanediol produced malondialdehyde in vivo, resulting in damage to rat DNA	[76]
Propanediol	Mouse, Hsd/Win: NMRI	n=14/sex/dose (main test), n=6/sex/dose (repeated test)	Main Test: single dose of 2150 mg/kg Repeated Test: single dose of 1000, 1470, or 2150 mg/kg (vehicle=water)	Micronucleus assay to test for chromosomal aberrations was performed in accordance with GLP and European Commission ECC Directive 92/69/EEC Part B: Methods for the Determination of Toxicity, B.12. Micronucleus Test); single dose administered orally; positive controls were used for each test; mice were killed 24 or 48 h post-exposure	Genotoxicity results were negative (non-mutagenic) for males and females; controls performed as expected; in the main test a statistically significant increase in micronucleated polychromatic erythrocytes at 48 h sampling was reported. Therefore, as per the method, a repeat test was performed; repeat test did not verify findings from the main test (findings were considered incidental)	[11]

Table 11. Genotoxicity Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Butyl Ethyl Propanediol	Mouse, NMRI	n=6/sex/dose (1250 mg/kg dose was performed 2x, reason why not specified); only n=5/sex/dose were evaluated (no further details)	312.5, 625, 1250 mg/kg (controls received PEG 400 vehicle only)	Micronucleus assay was performed in accordance with GLP and OECD TG 474 (Mammalian Erythrocyte Micronucleus Test); single dose administered by oral gavage; negative, vehicle, and positive controls were used; bone marrow smears were prepared from each femur	Negative for genotoxicity; controls performed as expected; clinical signs of toxicity were observed (summary data is presented in the Acute Toxicity Table 8)	[16]

DMSO=dimethyl sulfoxide; GLP (or non-GLP)=good laboratory practice; OECD TG= Organization for Economic Co-operation and Development Test Guideline

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
IRRITATION						
In Vitro						
1,10-Decanediol (supplier reported > 98% pure); Butylene Glycol	Human	Epidermis (RhE)	Test substance: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Butylene Glycol	10 µl of test substance was applied to top of reconstructed human epidermis for 15 min; % viability was evaluated compared to untreated controls; IL1-α concentration released at 15 min post-application and 42 h culture was also assessed	Non-irritating; average % viability (compared to controls) was 92%; IL1-α concentration released was < 5 pg/ml	[88]
Animal						
Propanediol	Rabbit, New Zealand White	n=6 (abraded skin), n=6 (intact skin)	Undiluted	Procedures followed were in accordance with OECD TG 404 (Acute Dermal Irritation/ Corrosion); 0.5 ml test compound was applied (1 x1 cm patch) to shaved back skin (abraded and intact) and occlusively covered for 24 h; at 24 h post-application patch was removed; skin examined immediately and 48 h after patch removal (72 h post-application); no controls were used	Slightly irritating (well-defined erythema); mean Draize scores for intact skin at 24 h post-application was 1.3 and at 72 h was 0.3; mean Draize score for abraded skin at 24 h post-application was 1.3 and at 72 h was 0.8; these effects were reversible and cleared up in 48 h	[11]
Propanediol	Rabbit	n=8	Undiluted	Procedures followed (non-GLP) were in accordance with OECD TG 404 (Acute Dermal Irritation/ Corrosion); test substance was applied to shaved skin (abraded and non-abraded) and occlusively covered for 24 h; skin was observed for 7 days post-application	Mild erythema and edema were reported on abraded and non-abraded skin for 7 of 8 rabbits; this cleared by 3 days post-exposure	[11]

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
1,4-Butanediol	Rabbit, Vienna White	n=4	Undiluted; control areas of skin were untreated and treated with water	Food and water were available ad libitum; fur was clipped and shaved from sides of trunk; 0.3 ml test substance was applied to hair-free skin (intact on right side and abraded on left side) and occlusively covered with a 2 x 2 cm patch for 24 h; at 24 h post-exposure the patch was removed and skin examined at 1, 24, 48, and 72 h following patch removal Additionally, the rabbits' right ears (internal area) were coated with undiluted or 50% (water dilution) 1,4-Butanediol for 10 days; controls used were left ears coated with water; the 1st day after applying coating the ears were examined	No reactions were observed on the intact or abraded trunk skin test sites; minimal redness was noted 10 days post-application of undiluted 1,4-Butanediol to the right ears of 2 of 4 rabbits; no reaction in rabbit ears was observed with 50% test solution	86
1,4-Butanediol	Rabbit	Unknown	Unknown	Repeated treatments were applied to abraded and intact skin (no further details provided)	No irritation observed; no signs of absorption of toxic quantities of 1,4-Butanediol	21,40
2,3-Butanediol	Rabbit, Vienna White	n=6 (no controls)	Undiluted	An irritation/ corrosion test (non-GLP) was performed; test substance was applied to skin and covered occlusively (no further details provided); skin was examined at 24 h post-application and for up to 8 days	Non-irritating; erythema and edema reactions were reported, but were reversible within 8 days	15
1,5-Pentanediol	Rabbit, albino	n=5	Undiluted or in solutions of water, propylene glycol, or acetone (no further specifications provided)	Fur was clipped from skin; 0.1 ml test substance was applied and left uncovered for 24 h, at which point skin was examined	Non-irritating (rated grade 1 on a scale from 1-non-irritating to 10-necrosis)	83
1,5-Pentanediol	Rabbit, Vienna White	n= 6 total (1 male, 5 females); no controls	Undiluted	Procedures followed (non-GLP) were in accordance with OECD TG 404 (Acute Dermal Irritation/ Corrosion); 1 ml of test substance saturated on a cotton patch (2.5 x 2.5 cm area) was applied to intact or scarified back skin and occlusively covered for 20 h, then patch was removed and skin was washed with 50% polyethylenglycol in water; skin was examined for irritation 24, 48, and 72 h post-application and also 7 days post-application	Non-irritating: For the 24, 48, and 72 h post-application time points the mean erythema score was 0.5 (very slight effect) and mean edema score was 0.1 (very slight effect); this erythema and edema were reversible within 48 h; additional findings were at 48 h spotted appearance (scarified skin of 2 animals), at 72 h desquamation (scarified skin of 3 animals), and at 7 days observation desquamation (scarified skin of 4 animal)	13
Hexanediol	Rabbit, albino	n=5	Test substance was applied in an appropriate vehicle (no further specifications provided)	Fur was clipped from skin; 0.1 ml test substance was applied and left uncovered for 24 h, at which point skin was examined	Estimated reaction was a grade 2 on a scale from 1-non-irritating to 10-necrosis	83,84
Hexanediol	Rabbit, Vienna White	n=2	80% solution; vehicle=water	A non-GLP irritation test was performed; 1 ml of test substance was applied to intact back skin and occlusively covered (2.5 x 2.5 cm) for 1 min, 5 min, 15 min, or 20 h, then the patch was removed and test substance washed off with a Lutrol®-water mixture; skin was examined at various points over a 3 day period	Non-irritating; mean erythema and edema scores were 0 out of 4	14

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
Hexanediol; Ethylene Glycol	Guinea Pig; Hartley	Primary Skin Irritation Test: n=3/test concentration Cumulative Skin Irritation Test: n=3/test concentration	62.5 wt % (Ethylene Glycol); 45 wt % (Hexanediol)	Primary Skin Irritation Test: To the shaved flank skin of animals, 200 µl of test solutions soaked into filter paper were applied and occlusively covered for 24 h; at 24, 48, and 72 h post-application the skin was examined and rated based on criteria of the ICDRG Cumulative Skin Irritation Test: To the shaved flank skin of animals, 200 µl of test solutions soaked into filter paper were applied and left uncovered; 1x/day for 5 days the test solution was reapplied; 5 days post-application the skin was examined and rated based on criteria of the ICDRG	No irritation for primary or cumulative skin irritation test for either compound	96
1,10-Decanediol (supplier reported > 98% pure); Propylene Glycol	Rabbit	n=?	Test substance: 1.2% 1,10-Decanediol in trade name mixture containing unspecified amount of Propylene Glycol; 0.5 ml of 100% test substance used	Test substance was occlusively applied for 24 h; skin was examined at 25, 48, and 72 h after application	Non-irritating; transient erythema was seen 48 h post-application, but resolved by 72 h	88
Methylpropanediol	Rabbit, New Zealand White	n=6	Not specified	0.5 ml test substance was applied and semi-occlusively covered for 24 h for each of 4 sites/animal (2 abraded and 2 intact); period of observation was 72 h (no further details provided); procedures followed were in accordance with OECD Guidelines for Testing Chemicals	Non-irritating (no erythema or edema reported)	19
Methylpropanediol	Animal	Unknown	Not specified	Irritation testing was conducted (no further details were provided)	Non-irritating	35
Butyl Ethyl Propanediol	Rabbit, New Zealand White	n=3 (no controls)	Undiluted	To the shaved dorsum skin, 0.5 ml of heated (44°C) test substance was applied (6 cm^2 area) and covered with a bandage (semi-occluded) for 4 h then covering was removed, skin was washed with water and dried; skin was examined at 24, 48, and 72 h post-application	Non-irritating; mild erythema was reported up to 48 h post- application but cleared within 72 h; no edema observed	16
Butyl Ethyl Propanediol	Rabbit, New Zealand White	n=3 (no controls)	Undiluted	An irritation test was performed in accordance with GLP and OECD TG 404 (Acute Dermal Irritation/ Corrosion); to the shaved dorsal skin 0.5 g of crystalline test substance moistened with water was applied and covered with a bandage (semi-occlusively) for 4 h; covering was removed after 4 h and skin washed; skin was examined at 24, 48, and 72 h post-application	Minimally irritating; very slight, transient reactions (erythema and edema) were noted in all animals 30 min after removing covering, but skin cleared by 48 to 72 h post-application	16
Butyl Ethyl Propanediol	Rabbit	Unknown	Unknown	Ingredient was tested on rabbit skin (no further details provided)	Non-irritating	85
Isopentyldiol	Rabbit, New Zealand White	n=3/sex	Undiluted	Procedures followed were a variation of OECD TG 404 (Acute Dermal Irritation/Corrosion); test substance was applied and occlusively covered for 24 h, then the patch was removed; skin was examined at 24 and 72 h post-application	Non-irritating	18

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
Isopentyldiol	Rabbit, New Zealand White	n=9 males	Not specified	15 µl of test substance was applied to dorsal trunk area (clipped) while another site in the vicinity was used as a control; sites were covered (semi-occlusively) for 24 h, then patches were removed and skin examined; another treatment of test substance was applied to the same site and procedures used during the first application were repeated each day for 28 days; at the completion of the study the animals were killed and skin cells examined	No substantial irritation with repeated skin application On day 10 of study an animal died (cause was gastrointestinal disease and unrelated to treatment) and another was added to test group; an animal died on day 22, but cause was unknown On days 15, 18, and 27 slight erythema and/or edema was observed in 4 animals, but by the following day irritation had resolved At the treatment site of 4 animals, mild inflammatory cell infiltration was reported, but in 2 of those 4 animals the control sites yielded similar results	18
			Human			
Propanediol	Human	n=40	Undiluted	Single treatment of test substance was applied (no further details provided)	No substantial irritation	97
Propanediol	Human	n=100	5%, 25%, 50%; controls used water vehicle only	For the induction phase 0.1 ml of test solution was applied to pad (1 inch),covered with clear adhesive, and pressed onto left arm; this patch was removed 24 h post-application to examine skin (skin examined again at 48 h post-application); at 48 h post-application a new patch was applied to the same site and the procedure above repeated for 9 applications total; a 2 week rest period was allowed prior to challenge; application of test solution for challenge was the same as for the induction phase; to a previously untreated site on the other arm, a duplicate challenge treatment was applied; after 24 h the challenge patches were removed and skin examined immediately and again 48 h after patch removal (72 h post-application)	No skin reactions or irritation at any concentration levels nor with controls were observed	97
Propanediol; 1,2-Propanediol*	Human	n=200	Propanediol: 25% (pH 7), 50% (pH 7), and 75% (pH 4, 7, 9); 1,2-Propanediol: 25% (pH 7); 50% (pH 7); 75% (pH 7); vehicle=water; negative controls were used at pH 4, 7, and 9	For the induction phase, 0.1 ml of test solution was applied to pad (1 inch), covered with clear adhesive, and pressed onto the upper back; this patch was removed 24 h post-application to examine skin (skin examined again at 48 h post-application); at 48 h post-application a new patch was applied to the same site and the procedure above repeated for 9 applications total; a 2 week rest period was allowed prior to challenge; application of test solution for challenge was the same as for the induction phase; to a previously untreated site on the back, a duplicate challenge treatment was applied; after 24 h the challenge patches were removed and skin examined immediately and again 48 h after patch removal (72 h post-application)	Propanediol: Very slight erythema at test sites was noted 24 or 72 h post-challenge application in a few subjects (at all concentration levels), however these findings were considered clinically insignificant; during induction 4 subjects showed mild erythema after the 1st of 9 applications (with 75% only) 1,2-Propanediol: During 9 applications of induction phase and 24 and 72 h post-challenge, mild to moderate skin irritation and cumulative skin irritation were observed in 8.2% of subjects treated with 25%, 21.7% of subjects with 50%, and 22.7% of subjects with 75%	97
1,4-Butanediol	Human	n=200	Unknown	A patch test was performed (no further details provided)	Non-irritating	21

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
1,5-Pentanediol	Human	n=30	5% in a topical formulation	Patch test was performed; test substance was applied (single application) to inner forearms and occlusively covered with a patch; 24 h post-application the patch was removed and skin was immediately assessed and assessed again 48 and 72 h after patch removal; standard light conditions used	Non-irritating, no indications of hypersensitivity or photo-sensitivity	[48]
1,10-Decanediol (supplier reported > 98% pure); Butylene Glycol	Human	n=10	Test substance: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Butylene Glycol	Test substance was occlusively applied to inside upper arm for 48 h; skin was examined at 1, 24, and 48 h after patch removal	Study authors reported that test substance was well-tolerated; placebo treated sites showed erythema throughout experiment; 2 subjects showed mild erythema 1 h following patch removal; no other observations were reported	[88]
Methylpropanediol	Human	n=25 (sensitive skin subjects, male and female, 18-70 yr)	100%, 50% aqueous dilution	0.2 ml test substance was applied to 0.75 x 0.75 in^2 occlusive dressing and secured between the scapulae; test substance applied for 5 consecutive days and patch left in place on weekends for 14-day total cumulative irritation study; patch sites were examined prior to each application	Non-irritating; all treated areas were normal	[35,79]
Isopentyldiol; 1,3-Butanediol	Human	n= 13 males and 17 females (20 to 66 yrs old)	Not specified	An unspecified concentration of Isopentyldiol, 1,3-Butanediol, and water (control) were soaked into filter paper and applied to medial brachium area of skin and covered with a Finn chamber; 48 h post-application the test substance/Finn chamber were removed and skin examined at 30 min, 24 h, and up to 7 days	Slightly irritating; slight erythema reported 30 min after Finn chamber removal (in 66 yr old female and in 49 yr old female), but this resolved within 24 h	[18]
SENSITIZATION						
Animal						
Propanediol	Guinea Pig, SPF albino	Males, n=8/ concentration	Induction Phases 1 & 2: 25%; Challenge: 10% (vehicle=water for all dilutions)	A Landsteiner/ Draize test was performed (time lapse between induction and challenge was not specified) Induction Phase 1: 0.05 ml of test substance was intradermally injected (1st injection) Induction Phase 2: 0.01 ml of test substance was intradermally injected (2nd through 10th injections) Challenge: 0.05 ml of test substance was intradermally injected skin examined 24 h post-challenge Negative controls were used (0.05 ml of 10% at challenge with no treatment during induction)	Non-sensitizing; reactions at challenge were very mild or mild and were not considered to vary substantially from controls; during repeated induction phase exposures mild to severe reactions were reported	[11]

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
Propanediol	Guinea Pig	n=2/sex (preliminary test); n=10/sex (test animals); n=5/sex (controls used at induction and challenge)	Induction: 2.5% (intradermal) and undiluted (epicutaneous) Challenge: 50% (epicutaneous and semi-occlusive) vehicle=water	A guinea pig maximization test was performed (non-GLP) in accordance with OECD TG 406 (Skin Sensitization) Preliminary Test: conducted to find the concentrations for intradermal and topical challenge Induction: 6 intradermal injections (within a 4 x 4 cm area) were made on shaved back of each animal; 1 week later, to the same back skin site (freshly shaved), a test substance (undiluted) soaked filter paper patch was applied and occlusively covered for 48 h Challenge: 2 weeks after induction,50% test substance soaked filter paper patch (2.5 x 2.5 cm) was applied to shaved flanks and covered by adhesive tape and a bandage for 24 h; at 24 h post-application bandage was removed and skin was examined immediately and 24 h (site shaved 3 h prior to 24 h reading) and 48 h after patch removal	Non-sensitizing; no reactions in any tests	[11]
1,4-Butanediol	Guinea Pig, Hartley albino	n=30 (male and female) total: 10 used for controls and 20 used for test substance evaluation	Both induction and challenge phase concentrations were 10% (intradermal injection) and 30% (topical application)	Food and water (containing 400 mg/l vitamin C) were available ad libitum; a Magnusson and Kligman guinea pig maximization test was performed	Non-sensitizing	[86]

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
2,3-Butanediol	Guinea Pig	n=10 females	Intradermal Induction: 5% test substance in Freund's adjuvant/0.9% aqueous sodium chloride solution Epicutaneous Induction: 50% test substance in distilled water Topical Challenge: 25% test substance in distilled water	A guinea pig maximization test was performed (GLP) in accordance with OECD TG 406 (Skin Sensitization); controls were used Intradermal Induction: injections were as follows (no volumes provided): Freund's adjuvant/ 0.9% aqueous sodium chloride; 0.9% aqueous sodium chloride; test substance in Freund's adjuvant/0.9% aqueous sodium chloride solution; test substance in 0.9% aqueous sodium chloride solution Epicutaneous Induction: no further details were provided explaining this induction other than concentration Challenge: no further details were provided explaining challenge other than concentration	Non-sensitizing The following reactions were reported: -All animals injected with only Freund's adjuvant/ 0.9% aqueous sodium chloride showed erythema and swelling at injection sites -Animals injected with only 0.9% aqueous sodium chloride had no skin reactions -Test group animals injected with 5% test substance in Freund's adjuvant/ 0.9% aqueous sodium chloride showed erythema and swelling at injection sites -Test group animals injected with 5% test substance in 0.9% aqueous sodium chloride showed moderate and confluent erythema and swelling -Test group animals epicutaneously exposed to 50% test substance during induction showed incrustation and confluent erythema with swelling -Test group animals exposed to 25% test substance at challenge showed no reactions	[15]

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
Hexanediol	Guinea Pig, Pirbright-Hartley	Range-finding study n=4; in main study n=10 females, n=5 controls	Intradermal Induction: 5% Hexanediol in 0.9% aqueous sodium chloride solution containing Freund's adjuvant Epicutaneous Induction: 50% Hexanediol in aqua bidest. solution Challenge: 25% Hexanediol in aqua bidest. solution	Food and water were available ad libitum; A guinea pig maximization test was performed (GLP) in accordance with European Union (EU) Method B.6 (Skin Sensitization) Range-finding study was conducted (2 x 2 cm filter paper soaked in approximately 0.15 g of test substance was applied 2x to flank skin and occlusively covered for 24 h; skin was examined at 24 and 48 h post-application) Intradermal Induction: 6 injections total (2 injections/animal) as follows: 2 injections each of 0.1 ml Freund's adjuvant emulsified with 0.9% sodium chloride (1:1) not containing test substance; 2 injections each of 0.1 ml Freund's adjuvant emulsified with 0.9% sodium chloride (1:1) containing test substance; 2 injections each of 0.1 ml test substance only Epicutaneous Induction: 1 week following intradermal induction; 2 x 4 cm filter paper soaked in 0.3 g of test substance was applied to shoulder skin and occlusively covered for 48 h Challenge: 21 days following induction; 2 x2 cm filter paper soaked in 0.15 g of test substance was applied to flank skin (hair clipped) and occlusively covered for 24 h; then patch was removed and skin was examined at 24 and 48 h post-application	Non-sensitizing	[14]
Hexanediol; Ethylene Glycol	Guinea Pig, Hartley	n=19 total	Induction Phases 1 & 2: Test solutions (% by wt) were experimental dentin primers: 0.2% 2-HEMA; 0.2% Ethylene Glycol; or 0.2% Hexanediol (vehicle=7:3, v/v, olive oil: acetone)	A Magnusson and Kligman guinea pig maximization test was performed; below are the compounds used as the sensitizer followed by test substance used at challenge (neither time lapse between induction and challenge nor challenge concentrations were specified): 2-HEMA sensitizer/ Ethylene Glycol challenge (n=5) 2-HEMA sensitizer/ Hexanediol challenge (n=5) Ethylene Glycol sensitizer/ Ethylene Glycol challenge (n=2) Hexanediol sensitizer/ Hexanediol challenge (n=2) 2-HEMA sensitizer/ 2-HEMA challenge (n=5) Induction Phase 1: 50 µl of each test solution was intradermally injected (also injected was 50:50 Freund's complete adjuvant: distilled water) into back skin Induction Phase 2: 1 week after Phase 1, 0.2 ml (100%) of test solution soaked into filter paper was applied to shaved back; 0.1 ml (100%) test solution soaked into filter paper was applied to 2 skin sites and occlusively covered for 24 h	There were positive results for 2-HEMA sensitizer/ Hexanediol challenge with a mean response of 1.5 (24 h) and 0.8 (48 h) indicating strong erythema (no vesicles present); positive responses were also noted with 2-HEMA sensitizer/ 2-HEMA challenge; the results for Hexanediol sensitizer/ Hexanediol challenge were negative	[96]

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
1,10-Decanediol (supplier reported > 98% pure); Propylene Glycol	Guinea Pig	n=?	Test substance: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Propylene Glycol; Test substance used at 100% (induction) and 25% (challenge)	Buehler test was performed; test substance was occlusively applied to shaved skin for an induction period of at least 6 h on days 1, 9, and 15 (negative controls were used); challenge phase occurred on day 28 for 6 h; skin was examined 24 and 48 h post-challenge	Non-sensitizer; no erythema observed during challenge	[88]
1,10-Decanediol (supplier reported > 98% pure); Butylene Glycol	Guinea Pig	n=20 treated males; 10 controls used	Test substance: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Butylene Glycol; Induction concentration not specified; test substance used at 25% during challenge	A Buehler test was performed; treated (shaved skin) was observed for 11 days following induction (negative controls used); challenge phase occurred on day 28; skin was examined 24 and 48 h post-challenge	Non-sensitizer; no erythema or clinical signs indicating sensitization reaction	[88]
Methylpropanediol	Guinea Pig, Himalayan	n=20 test animals, n=10 controls	Intradermal Induction: 10% test substance in saline; 50:50 Freund's Complete Adjuvant (FCA)/distilled water; and 20% test substance emulsified in FCA Epidermal Induction: 100% test substance Challenge: 0, 25, 50, or 100% test substance in distilled water	Guinea pig maximization test was conducted in accordance with OECD Guidelines for Testing Chemicals Induction Phases: 0.1 ml intradermal injections were performed at the indicated concentrations; on the 6th day following intradermal inductions a treatment of 10% sodium-dodecyl-sulfate in petrolatum was applied; on the 7th day, 0.5 ml of the test substance (100%) was applied to injection sites and covered with a patch for 48 h Challenge: 2 weeks following the epidermal induction phase the test material was applied at the indicated concentrations and covered with a patch for up to 48 h	Mild sensitization potential was reported; 24 h after the patch from the challenge treatment was removed positive responses were noted in 1 animal with 25% and 1 animal with 50% challenge concentrations, but not at 100%; by 48 h after the patch was removed following challenge, 1 animal with 25%, 3 animals with 50%, and 1 animal with 100% challenge concentrations showed positive reactions; controls performed as expected	[19]

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
Butyl Ethyl Propanediol	Guinea Pig, Dunkin-Hartley	Males, n=10 test animals, n=5 controls	Intradermal Induction: 2.5% (v/v) Topical Induction: 100% Topical Challenge: 100% and 50% (v/v) (vehicle=Alembicol D)	A guinea pig maximization test was performed (GLP) in accordance with EU Method B.6 (Skin Sensitization) Intradermal Induction: 3 pairs of injections as follows: 2 injections of 0.1 ml Freund's adjuvant diluted with water (1:1); 2 injections of 0.1 ml test substance in Alembicol D; 2 injections of 0.1 ml test substance in 50:50 of Freund's adjuvant/Alembicol D Epicutaneous Induction: 6 days following intradermal induction; shaved skin (same site as injection) was pretreated with 0.5 ml 10% sodium lauryl sulfate in petroleum (w/w); after 24 h a patch soaked with 0.4 ml of test substance was applied to same skin area and occlusively covered for 48 h Challenge: 0.2 ml of test substance was applied to anterior site and 50% test substance (diluted in Alembicol D) was applied to posterior site; both sites were occlusively covered for 24 h; then patches were removed and skin was examined at 24, 48, and 72 h post-application	Non-sensitizing; no reaction were observed	16
Isopentyldiol	Guinea Pig, Dunkin-Hartley	n=20 test animals, n=10 controls	*Main Study:* Intradermal Induction: 10% in distilled water Topical Induction: 100% undiluted Challenge: 50% in distilled water	Guinea pig maximization test was performed in accordance with OECD TG 406 (Skin Sensitization-Magnusson & Kligman) Preliminary study was conducted using an intradermal concentration of 10% test substance in distilled water and a topical induction concentration of 50% test substance in distilled water; these were the maximum non-irritating concentrations Induction Phases: test substance was applied at indicated concentrations (volumes were not specified) Challenge: test substance was applied at indicated concentration (volumes were not specified); skin was examined 24 and 48 h post-challenge application; positive and negative controls were used	Induction Phases: moderate and confluent erythema was reported 24 h post-application at intradermal injection sites and topical application sites; controls showed slight or discrete erythema Challenge: Non-sensitizing; no reactions in test group or negative controls; positive controls performed as expected	18
				Human		
Propanediol	Human	n=100	Both induction and challenge phase concentrations were 5%, 25%, 50%; controls used water vehicle only	For the induction phase 0.1 ml of test solution was applied to pad (1 inch), covered with clear adhesive, and pressed onto left arm; this patch was removed 24 h post-application to examine skin (skin examined again at 48 h post-application); at 48 h post-application a new patch was applied to the same site and the procedure above repeated for 9 applications total; a 2 week rest period was allowed prior to challenge; application of test solution for challenge was the same as for the induction phase; to a previously untreated site on the other arm, a duplicate challenge treatment was applied; after 24 h the challenge patches were removed and skin examined immediately and again 48 h after patch removal (72 h post-application)	Propanediol was non-sensitizing	97

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
Propanediol; 1,2-Propanediol*	Human	n=200	Both induction and challenge phase concentrations were 25% (pH 4), 50% (pH 7), and 75% (pH 9), vehicle=water	For the induction phase 0.1 ml of test solution was applied to pad (1 inch), covered with clear adhesive, and pressed onto the upper back; this patch was removed 24 h post-application to examine skin (skin examined again at 48 h post-application); at 48 h post-application a new patch was applied to the same site and the procedure above repeated for 9 applications total; a 2 week rest period was allowed prior to challenge; application of test solution for challenge was the same as for the induction phase; to a previously untreated site on the back, a duplicate challenge treatment was applied; after 24 h the challenge patches were removed and skin examined immediately and again 48 h after patch removal (72 h post-application)	Propanediol and 1,2-Propanediol were non-sensitizing	[97]
1,4-Butanediol	Human	n=200	Unknown	Sensitization test was performed (no further details provided)	Non-sensitizing	[21]
1,5-Pentanediol	Human	n=20 (males)	5% in a scalp wash formulation	Scalp wash was used ≥ 2 times/day for 4 weeks (no other products were used on hair during this time); scalp skin was assessed periodically throughout study; after 4 weeks, test substance was applied (single application) to inner forearms and occlusively covered with a patch; 24 h post-application, the patch was removed and skin was immediately assessed and assessed again 48 and 72 h after patch removal	Non-irritating, non-sensitizing	[48]
1,5-Pentanediol	Human	n=30	25% in a topical formulation	Single application of test substance to inner forearms and occlusively covered with a patch; 24 h post-application, the patch was removed and skin was immediately assessed and assessed again 48 and 72 h after patch removal; this patch test was repeated 1 week later and at week 6	Non-irritating, non-sensitizing	[48]
Methylpropanediol	Human	n=104	Unknown	4 patch tests were conducted; they included 9 induction applications (occlusive and semi-occlusive); no further details provided	Non-sensitizing	[35]

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
Methylpropanediol	Human	n=110 (male and female)	Both induction and challenge phase concentrations were 50% aqueous dilution	0.2 ml of test substance was applied to 0.75 x 0.75 $in^2$and secured between the scapulae; test substance applied 3 times/week for 10 applications total; patches removed 24 h after application and skin examined 48 h and 72 h after initial application; 2 weeks following the 10th application a challenge patch was applied to the initial site and a new site on forearm; patch was removed after 24 h and examined immediately and again 48 h post-application If a subject showed a reaction on challenge the subject was re-challenged 7 days later with 100% and 50% aqueous dilution of test substance (occlusive and semi-occlusive conditions were used)	At the 9th and 10th days during induction "mild dermal responses" were observed in 3 subjects indicating irritation or a potential allergic reaction; another subject exhibited skin reactions on days 2-19 of inductions indicating a potential atopic reaction; at challenge 5 subjects showed "mild dermal responses" 24 h and 48 h post-application that lasted until 72 h post-application; 2 subjects had skin reactions at the forearm site; the re-challenge in 4 subjects showed mild, well-defined delayed reactions at 48 h post-application (occlusive, semi-occlusive showed less reaction); subjects re-challenged with propylene glycol or butylene glycol (occlusive) showed mild-to-well-defined reactions at 24 h post-application; it is unclear as to whether irritation, allergy, or an unrecognizable atopic condition were the cause of the above reactions; Methylpropanediol was not considered to be a strong irritant or potent sensitizer	[35,79]
Methylpropanediol	Human	n=230 (healthy adults) enrolled and 205 completed study; 16 were "lost due to follow-up" (no further details specified); 9 withdrew voluntarily	21.2% in facial serum (used during induction and challenge phases)	*Induction:* 0.2 ml test substance was applied to a 2 x 2 cm^2 area of skin on the left or right infrascapular location of the back or to upper arm under occlusive conditions for 24 h; patch was removed 24 h post-application and skin assessed at 48, 72 or 96 h post-application depending on the occurrence of weekends/holidays; following assessment, test substance was applied again to same skin area under occlusive conditions and assessed as described above; this process was repeated until 9 applications of test substance were administered *Rest:* Subjects received no treatment during the 10-15 days after completion of induction and prior to challenge phase *Challenge:* at week 6, 0.2 ml test substance was applied to 2 x 2 cm^2 skin site not previously exposed to test substance during induction; same procedures for patch removal and skin assessment were followed as in induction phase; if evidence of potential sensitization was noted, a rechallenge was conducted; during rechallenge, test substance was applied to skin (previously unexposed to test substance) using occlusive and semi-occlusive patches to distinguish between irritation and sensitization reactions	Study researchers stated that test substance was non-sensitizing and the irritation responses were considered acceptable *Induction:* 41 subjects exhibited definite erythema with no edema, 3 of those subjects also showed damage to epidermis (a protocol deviation occurred for the 1st subject resulting in an inadvertent discontinued use of test substance, 2nd subject declined to complete patch tests for the remainder of study, 3rd subject showed no further reactions for remainder of induction phase when test substance was applied to a new site under semi-occlusive conditions during 6th induction, but subject declined to participate at challenge); on another day, 31 subjects showed definite erythema with no edema, and 7 of those subjects showed damage to epidermis; those 7 subjects did not experience any additional reactions after test substance was applied to a new site under semi-occlusive conditions	[98]

Table 12. Dermal Irritation, Sensitization, and Photoirritation/ Photosensitization Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
PHOTOIRRITATION/ PHOTOSENSITIZATION						
Animal						
1,10-Decanediol (supplier reported > 98% pure); Butylene Glycol	Guinea Pig, albino	n=10/group	Test substance: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Butylene Glycol	1 ml of test substance was applied with or without UVA irradiation; UVA irradiation was applied for 20 min with 310 nm light source located 5 cm away from treatment area; treatment areas were examined 1, 6, and 24 h following irradiation; no further details were provided	Non-Phototoxic; no dermal reactions in treated or control animals	[88]
Isopentyldiol	Guinea Pig, Dunkin-Hartley	n=10 test animals, n=10 controls	Undiluted	To the shaved back of each animal 0.025 ml of test substance and a positive control (8-methoxysporalen or 8-MOP) were applied epicutaneously to test animals; animals were exposed to 20 J/cm^2 of UVA radiation (320-400 nm); when exposure of UVA radiation reached 2.5 J/cm^2 the positive control site was concealed with lightproof tape; control animals were not exposed to UVA radiation; skin of all animals examined 24, 48, and 72 h post-application	Isopentyldiol was a not a photoirritant; positive control performed as expected	[18]
Isopentyldiol	Guinea Pig, Dunkin-Hartley	n=10 test animals, n=10 controls, n=10 positive controls	Undiluted (used on test animals during induction and challenge); distilled water (controls); 0.1% tetrachlorosalicylani-lide in petrolatum (positive controls)	Induction: to the shaved and chemically depilated back of each test animal, 0.025 ml of test substance was epicutaneously applied; animals were exposed to 485 mJ/cm^2 of UVA radiation and 185 mJ/cm^2 of UVB radiation for 10 min; this procedure was repeated 5x every 48 h for a total of 6 applications in 2 weeks (animals were shaved/depilated as needed); control and positive control animals were similarly treated except with distilled water and tetrachlorosalicylanilide, respectively; skin was examined 24, 48, and 72 h post-application Challenge: 12 days after induction phase was complete, test substance was applied epicutaneously (open) to the backs (shaved/depilated) of test and control animals following the same procedures used in the induction phase; 30 min post-application test and control animals were exposed to 10 J/cm^2 of UVA radiation, then test substance was applied to a nearby skin site of the test and control animals and no radiation exposure applied to those sites; skin of all animals was examined 24, 48, and 72 h post-application of test substance, distilled water, or positive control substance	Isopentyldiol was non-photosensitizing; 1 animal was killed before challenge because of probable pneumonia; no skin reactions post-application of treatment during induction or challenge phases; positive controls performed as expected	[18]
Human						
1,5-Pentanediol	Human	n=30	5% in a topical formulation	Test substance was applied (single application) to inner forearms; test sites on skin were then exposed to UV-A light (30 J/cm^2) and UV-B light (0.05 J/cm^2); test skin sites were covered with occlusive patch for 24 h and then patch was removed; skin was assessed immediately after patch removal and again at 48, 72, and 96 h post-application	Non-phototoxic and non-photosensitizer; study authors stated that 1,5-Pentanediol does not absorb in long-wave ultra-violet range	[48,70]

2-HEMA=2-hydroxyethyl methacrylate; EU=European Union; FCA=Freund's Complete Adjuvant; GLP=Good Laboratory Practice; HRIPT=Human Repeat Insult Patch Test; ICDRG=International Contact Dermatitis Research Group; non-GLP=non-Good Laboratory Practice; OECD TG= Organization for Economic Co-operation and Development Test Guideline; **Dictionary* name is Propylene Glycol

Table 13. Ocular Irritation Studies

Test Substance	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
			IN VITRO			
1,10-Decanediol (supplier reported > 98% pure); Butylene Glycol	Chicken/ Leghorn (Lohmann)	Chorioallantoic membrane, n=4 eggs	Test substance: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Butylene Glycol; 100% test substance used in experiment	Shell and shell membrane were removed to reveal chorioallantoic membrane from fertilized hen's eggs after 10 days of incubation; 0.3 ml of test substance was applied to this membrane for 20 sec, then membrane was rinsed with 0.9% NaCl (5 ml); membrane was observed for 5 min and scored for signs of potential irritancy (i.e., hyperemy, hemorrhage, coagulation)	Mean score (6.5) of 4 eggs indicated moderate irritation	[88]
1,10-Decanediol (supplier reported > 98% pure); Butylene Glycol	Human	Corneal epithelium	Test substance: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Butylene Glycol	30 µl of test substance was applied to top of reconstructed human corneal epitheliums for 1 and 24 h (controls were used)	Non-irritating; based on the quantitative 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay, viability compared to control was 76% (after 1 h) and 86% (after 24 h)	[88]
			ANIMAL			
Propanediol	Rabbit, New Zealand White	n=6	Undiluted	Procedures followed were in accordance with OECD TG 405 (Acute Eye Irritation/ Corrosion); 0.1 ml of test substance was applied to the everted lower lid of one eye (remaining eye was the control), upper and lower lid were held together for 1 second, no eye washing occurred; eyes were examined 24, 48, and 72 h and 7 days post-application	Slight conjunctivae redness was observed in 4 of 6 rabbits, but had cleared by 48 h post-application; results were considered to be non-irritating	[11]
Propanediol	Rabbit	n=4	Undiluted	Procedures followed (non-GLP) were in accordance with Federal Register 28 (110), 1963 para 191.12 Test for eye irritants; 0.2 ml of test substance was instilled into the conjunctival sac of one eye (remaining eye served as control); 2 treated eyes were rinsed and 2 treated eyes were unrinsed; eyes were examined 30 min and 1, 2, 3, and 7 days post-application	Transient, mild conjunctival reddening/swelling was reported in 3 rabbits, 2 of the eyes had been rinsed and 1 was not rinsed, however all symptoms had resolved by 48 h post-application	[11]
1,4-Butanediol	Rabbit, New Zealand White	n=4	Undiluted	A single application (0.1 ml) of test substance was instilled into the conjunctival sac of the right eye (left eyes were used as controls); eyes were examined at 1, 24, 48 and 72 h post-application	Slightly irritating; all rabbits showed small discharge and slight redness of conjunctives at 1 h post-application, however these symptoms lessened by 48 h post-application	[86]
1,4-Butanediol	Rabbit	Not specified	Not specified	Test substance was instilled into the conjunctival sac of rabbit eyes (no further details provided)	Slight conjunctival irritation without corneal damage was reported	[40]
2,3-Butanediol	Rabbit, Vienna White	n=6	Undiluted	This non-GLP study evaluated the effect of the test substance on rabbit eyes (no mention of controls used); the eyes were observed for 72 h post-application (no further details specified)	Non-irritating	[15]
1,5-Pentanediol	Rabbit	Unknown	Unknown	Test substance was instilled into the conjunctival sac (no further details specified)	On a scale of 1 (very small area of necrosis) to 10 (a severe burn) 1,5-Pentanediol application resulted in a rating of 2, suggesting mild irritation	[83]
1,5-Pentanediol	Rabbit	Not specified	Not specified	Not specified	Mildly irritating	[36]

Table 13. Ocular Irritation Studies

Test Substance	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
1,5-Pentanediol	Rabbit, Vienna White	n=2 male, 4 female	Undiluted	Procedures followed (non-GLP) were in accordance with OECD TG 405 (Acute Eye Irritation/ Corrosion); 0.1 ml test substance was instilled into the conjunctival sac of one eye (remaining eye served as control); eye were unwashed; examination of eyes occurred 24 to 72 h post-application and for up to 8 days post-application	Results were considered to be non-irritating; average eye ratings were: slight irritation, fully reversible by 72 h for cornea, iris, conjunctivae, chemosis	[13]
Hexanediol	Rabbit	Unknown	Concentration unknown, a suitable vehicle was used	Test substance was instilled into the conjunctival sac (no further details specified)	On a scale of 1 (very small area of necrosis) to 10 (a severe burn) 1,5-Pentanediol application resulted in a rating of 3, suggesting it is mildly irritating	[83,84]
Hexanediol	Rabbit, Vienna White	n=2	Undiluted	Non-GLP study; 50 mg of test substance was instilled into the conjunctival sac of the eye (the other eye was talcum-treated and served as control); eyes were at 1, 3, 24, 48, 72 h post-application and at 5 days post-application; eyes were washed with Lutrol® and Lutrol®/water (1:1) mixture 20 h post-application	Results were considered to be non-irritating; average eye ratings were: cornea=slightly irritating, fully reversible by 72 h; chemosis=slightly irritating, fully reversible by 48 h; conjunctivae=slightly irritating, fully reversible by 72 h; discharge was noted in 1 eye 1 h post-dosing	[14]
1,10-Decanediol (supplier reported > 98% pure); Propylene Glycol	Rabbit	n=?	Test substance: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Propylene Glycol; 100% test substance used in experiment	Study authors stated that a modified Kay and Calendra method was used; 0.1 ml of test substance was instilled into the conjunctival sac of the right eye and left for 24 h (unwashed); eyes were examined at 24, 48, 72, 96, and 120 h post-instillation	Slightly irritating; transient, reversible irritation was observed during study	[88]
Methylpropanediol	Rabbit, New Zealand White	n=6	Unknown	Procedures followed were in accordance with OECD Guidelines for Testing Chemicals; 0.1 ml was instilled into the conjunctival sac of one eye of each rabbit; eyes were observed up to 72 h post-application	Non-irritating	[19]
Methylpropanediol	Rabbit	Not specified	Not specified	Not specified	Non-irritating	[35]
Butyl Ethyl Propanediol	Rabbit	Unknown	Not specified	Test substance was instilled into rabbit eye, but the method used was not described	Results indicate severe eye injury	[85]
Butyl Ethyl Propanediol	Rabbit, New Zealand White	n=3	Undiluted	Procedures followed were in accordance with GLP and European Union Method B.5 (Acute Toxicity: Eye Irritation/ Corrosion); 0.1 ml of warm liquid test substance was applied to the lower everted lid of one eye of each rabbit (other eye served as control); eyes were not washed; eyes examined at 1 h and at 1, 2, 3, 4, 7, and 14 days post-application	Irritating; all 3 rabbits showed corneal opacification and diffuse crimson conjunctiva coloration with swelling and partial eyelid eversion or eyelids half-closed, 1 rabbit exhibited iridial inflammation; eyes returned to normal 7 to 14 days post-application; no toxic signs in rabbits during observation period	[16]
Isopentyldiol	Rabbit, New Zealand White	n=6	Not specified	Procedures followed were in accordance with OECD TG 405 (Acute Eye Irritation/ Corrosion); eyes were examined at 1, 24, 48, and 72 h and up to 7 days post-application	Non-irritating	[18]

GLP=Good Laboratory Practice; OECD TG= Organization for Economic Co-operation and Development Test Guideline

Table 14. Case Reports

Test Substances(s)	Patients	Concentration/ Dosage (Vehicle)	Investigation and Method (when available)	Observations/Results	Reference
			Dermal		
1,5-Pentanediol	n=1 (39 yr old male); n=10 controls for each of Test 2 and Test 3	Test 2: 0.5%, 5%, and 10% 1,5-Pentanediol (in water); 0.1%, 1%, and 10% resveratrol (in 70% ethanol); 10 controls were patch tested with the doses of test substances above Test 3: 0.1%, 1%, and 5% resveratrol (in petrolatum); 10 more control subjects were patch tested with same doses of resveratrol in Test 3	A patient was prescribed a resveratrol-containing cream (also contained 1,5-Pentanediol, concentration not specified) for recurrent scaling erythematous dermatitis; dermatitis intensified after 2 weeks of cream application; after use of cream was discontinued eczema eventually cleared Patient underwent patch testing (Test 1: propylene glycol and the resveratrol cream unchanged were applied) 4 months later an additional patch test (Test 2) was performed on the patient and controls using the ingredients in the resveratrol cream A final patch test (Test 3) was performed on the patient and controls using resveratrol diluted in petrolatum	Test 1 on patient: the resveratrol cream produced +/++ reactions by days 2 and 3 Test 2 on patient and controls: patient had strong reaction to 1,5-Pentanediol (++ with 5% and 10% doses and +/++ with 0.5% dose); patient had slight reactions to resveratrol showing erythema on days 2 and 3 with all dose levels; 9 of 10 controls were negative and 1 control subject developed slight erythema with all doses levels of 1,5-Pentanediol and resveratrol (this control subject had not been previously exposed to resveratrol and had no prior reactions to cosmetics, but did report hyperirritable skin type) Test 3 on patient and controls: patient reacted to 5% resveratrol only (+ by days 2 and 3); controls were negative Final conclusion: patient was diagnosed with allergic contact dermatitis from resveratrol containing cream attributed to sensitization to 1,5-Pentanediol and potential co-sensitization to resveratrol	[101]
1,5-Pentanediol	n=1 (56 yr old female), 3 control subjects	5% in water	A patient used a toleriane cream for a month and developed facial dermatitis with edema of eyelids; patch testing using European standard series, Belgian cosmetic pharmaceutical series, and toleriane cream was performed; patient had a positive reaction to toleriane cream but not to other series tested; 2 months later patch testing was conducted with ingredients in cream, but had no reaction; patient began using another lotion and developed facial dermatitis; patch testing was conducted with cream and lotion which both produced positive responses; propylene glycol ingredient in lotion caused a positive reaction; patient was retested with toleriane cream because it contained 1,5-Pentanediol	Patient was negative to 1,5-Pentanediol in patch test, but exhibited a positive reaction to 1,5-Pentanediol in repeated open application test (3 control subjects were negative)	[102]

Table 14. Case Reports

Test Substances(s)	Patients	Concentration/ Dosage (Vehicle)	Investigation and Method (when available)	Observations/Results	Reference
Hexanediol; ethylene glycol	n=1 (32 yr old female)	Test compounds used were experimental dentin primers (by wt %): 62.5% Ethylene Glycol; 45% Hexanediol; 35% Hydroxyethyl methacrylate	A dentist worked with ethylene glycol dentin primer for a year, which required repeated dermal contact with the compound; this dermal contact resulted in 2 months of symptoms including cracked fingertip skin, reddening desquamation, desiccation and inflammatory dolorific sclerosis; she was diagnosed with (irritant) contact dermatitis; a patch test was performed on the dentist with the test compounds indicated; test compounds were soaked into a cotton patch and occlusively applied to healthy brachial skin for 48 h; 48 h post-application the patches were removed and skin was examined immediately, 24, and 48 h after patch removal	Slight erythema was noted with ethylene glycol 48 h after patch removal; study researchers noted that dental professionals sensitized to hydroxyethyl methacrylate should take precautions if using Hexanediol in a dentin primer (no further patch test results specified); other supporting tests in animals were conducted in conjunction with this case report (results presented in Table 12)	[96]
			Oral		
1,4-Butanediol	Report of n >100	Unknown	US FDA reported more than 100 people were ill and 3 died as a result of taking unregulated 'party drugs', also sold as dietary supplements to induce sleep, containing 1,4-Butanediol	Side effects reported by FDA were dangerously low respiratory rates, unconsciousness, vomiting, seizures, and death; effects were amplified when consumed with alcohol or depressant drugs	[37]
1,4-Butanediol	n ≥ 8 (14 months to 10 yrs old)	Approximately 14% of extractable 1,4-Butanediol by weight	Children developed vomiting, ataxia, self-limited coma after swallowing small, colored plastic beads (sold in toy craft kits); in biological samples collected from some of the children GHB was found; in 2007 a voluntary recall of the beads was issued by the US Consumer Product Safety Commission; investigation determined that 1,4-Butanediol had been substituted for the more expensive 1,5-Pentanediol (used in glues) in the plastic beads; 1,4-Butanediol converts to GHB in the body	Small, plastic toy beads were found to have 14% 1,4-Butanediol and no 1,5-Pentanediol or GHB; clinical signs reported were consistent with ingestion of several dozen of the plastic toy beads containing 1,4-Butanediol (approximately 9-12 mg of 1,4-Butanediol per bead)	[103]
1,4-Butanediol	n=8 patients (22 to 51 yrs old)	Non-fatal cases of 1,4-Butanediol ingestion were 1 to 14 g; Fatalities occurred at doses between 5.4 to 20 g	Patients having toxic effects from oral ingestion of 1,4-Butanediol were identified (from emergency room department visits and/or from public health officials and family members); analysis of 1,4-Butanediol and/or GHB in urine, serum, or blood was performed and/or hospital records or autopsy reports were examined	Patients ingested 1,4-Butanediol for recreational use, enhancement during body building, or for the treatment of depression or insomnia; evidence of addiction and withdrawal were seen in some cases; clinical signs included vomiting, urinary and fecal incontinence, agitation, combativeness, labile level of consciousness, respiratory depression, and death; in 6 patients (2 of whom died) no additional toxicants were detected; the 2 other patients reported that they did not ingest other toxicants; GHB was detected in blood, serum, and urine at levels exceeding normal concentrations; 1,4-Butanediol was not detected in non-fatal cases potentially because ingested doses were smaller, conversion to GHB in the body is rapid, and there were limits on detection of the assay used	[104]
1,4-Butanediol	n=1 male (44 yrs old)	Unknown	A man was taken to the emergency room with signs of intoxication, agitation, loss of consciousness, vomiting, and myoclonic jerking (heart rate 40 and respiration rate 8); negative blood ethanol; man was awake and alert after 3 h	Man reported ingesting nine yohimbine tablets and pine needle oil; 3 oz spray bottle reported to contain 'pine needle oil' was determined to contain 1,4-Butanediol	[12]

Table 14. Case Reports

Test Substances(s)	Patients	Concentration/ Dosage (Vehicle)	Investigation and Method (when available)	Observations/Results	Reference
1,4-Butanediol	n=1	Unknown	A patient ingested an illicit product called 'liquid ecstasy'; blood, urine, and gastric content were analyzed for 1,4-Butanediol and GHB by immunoassay and GC-MS; identification of the 'liquid ecstasy' substance was determined by GC-MS	The 'liquid ecstasy' substance was found to contain 1,4-Butanediol; in the patient 1,4-Butanediol was found at 82 µg/ml (in blood), 401 µg/ml (in urine), and 7.4 µg/ml (in gastric content); GHB was found at 103 µg/ml (in blood) and 430 µg/ml (in urine); other drugs detected were methylenedioxymethylamphetamine (0.23 µg/ml in blood) and its metabolite methylenedioxyphenylamphetamine (0.1 µg/ml in blood); benzoylecgonine (0.1 µg/ml in urine)	[12]
			Other Exposure Routes		
1,4-Butanediol	n=7	15 or 30 g (0.21 or 0.43 g/kg, assumed body weight of 70 kg)	Single dose rectally administered (no further details specified)	Clinical signs observed 10 to 20 min post-administration included coma, miosis and areflexia (sustained for 1 to 16 h); 2 deaths within 72 h post-administration (both found to have renal disorder); 5 remaining patients were given analeptic and recovered	[12]
1,4-Butanediol	Unknown	30 mg/kg (intravenous) or 15 to 22 mg/kg/h (by infusion) for 38 to 68 h (initial dose 30 mg/kg)	Dose administered intravenously (no further details provided)	Clinical signs after dosing included sleep, restlessness, clonic spasms of muscles of the extremities	[21]

GC-MS=Gas Chromatography-Mass Spectrometry; GHB=Gamma-Hydroxybutyric Acid

REFERENCES

1. Nikitakis J and Lange B. International Cosmetic Ingredient Dictionary and Handbook. 15 *ed*. Washington, D.C.: Personal Care Products Council, 2015.

2. Johnson W, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler D, Marks JG, Shank RC, Slaga TJ, Snyder PW, and Andersen FA. Safety Assessment of 1,2-Glycols as Uses in Cosmetics. *International Journal of Toxicology*. 2012;31(Supplement 2):147S-168S. www.cir-safety.org.

3. Fiume MM, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler D, Marks JG, Shank RC, Slaga TJ, Snyder PW, and Andersen FA. Safety Assessment of Propylene Glycol, Tripropylene Glycol, and PPGs as Used in Cosmetics. *International Journal of Toxicology*. 2012;31(Supplement 2):245S-260S. www.cir-safety.org.

4. Andersen FA and Cosmetic Ingredient Review. Final Report on the Safety Assessment of Propylene Glycol and Polypropylene Glycols. *Journal of the American College of Toxicology*. 1994;13(6):437-491. www.cir-safety.org.

5. Andersen FA and Cosmetic Ingredient Review. Final Report on the Safety Assessment of Ethyl Hexanediol. *Journal of the American College of Toxicology*. 1994;13(6):418-436. www.cir-safety.org.

6. Andersen FA. Annual Review of Cosmetic Ingredient Safety Assessments: 2007-2010. *International Journal of Toxicology*. 2011;30(Supplement 2):73S-127S. www.cir-safety.org.

7. CIR and Elder (ed). Final Report on the Safety Assessment of Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol. *Journal of the American College of Toxicology*. 1985;4(5):223-248. www.cir-safety.org.

8. Cosmetic Ingredient Review (CIR). Annual Review of Cosmetic Ingredient Safety Assessments-2004/2005. *International Journal of Toxicology*. 2006;25(Supplement 2):1-89. www.cir-safety.org.

9. Andersen FA (ed). Final Report on the Safety Assessment of Maleic Acid. *International Journal of Toxicology*. 2007;26(Supplement 2):125-130.

10. Fiume MM, Heldreth B, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler D, Marks Jr JG, Shank RC, Slaga TJ, Snyder PW, and Andersen FA. Final Report of the Cosmetic Ingredient Review Expert Panel on the Safety Assessment of Dicarboxylic Acids, Salts, and Esters. *International Journal of Toxicology*. 2012;31(Supplement I):5S-76S.

11. European Chemical Agency (ECHA). Propanediol (CAS#504-63-2); Propane-1,3-diol. http://echa.europa.eu/registration-dossier/-/registered-dossier/2099. Last Updated 2015. Date Accessed 3-16-2016.

12. European Chemical Agency (ECHA). 1,4-Butanediol (CAS#110-63-4); Butane-1,4-diol. http://echa.europa.eu/registration-dossier/-/registered-dossier/15496. Last Updated 2016. Date Accessed 3-16-2016.

13. European Chemical Agency (ECHA). 1,5-Pentanediol (CAS#111-29-5); Pentane-1,5-diol. http://echa.europa.eu/registration-dossier/-/registered-dossier/14818. Last Updated 2016. Date Accessed 3-16-2016.

14. European Chemical Agency (ECHA). 1,6-Hexanediol (CAS#629-11-8); Hexane-1,6-diol. http://echa.europa.eu/registration-dossier/-/registered-dossier/15109. Last Updated 2016. Date Accessed 3-16-2016.

15. European Chemical Agency (ECHA). 2,3-Butanediol (CAS#513-85-9); Butane-2,3-diol. http://echa.europa.eu/registration-dossier/-/registered-dossier/10060. Last Updated 2015. Date Accessed 3-16-2016.

16. European Chemical Agency (ECHA). Butyl Ethyl Propanediol (CAS#115-84-4); 2-Butyl-2-Ethylpropanediol. http://echa.europa.eu/registration-dossier/-/registered-dossier/12725. Last Updated 2015. Date Accessed 3-16-2016.

17. National Industrial Chemicals Notification And Assessment Scheme (NICNAS). Human Health Tier II Assessment For 1,4-Butanediol CAS Number: 110-63-4. http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=188#cas-A_110-63-4. Last Updated 2016. Date Accessed 3-22-2016.

18. National Industrial Chemicals Notification And Assessment Scheme (NICNAS). Full Public Report: Isoprene Glycol (Isopentyldiol). 2010. http://www.nicnas.gov.au/. Date Accessed 12-10-2015. Report No. STD/1352. pp. 1-27. CAS #2568-33-4.

19. National Industrial Chemicals Notification And Assessment Scheme (NICNAS). Full Public Report: 2-Methyl-1,3-Propanediol. 1996. http://www.nicnas.gov.au/. Date Accessed 3-16-2016. Report No. NA/279. CAS#2163-42-0.

20. World Health Organization (WHO). 1,4-Butanediol (1,4-BD) Pre-Review Report from Expert Committee on Drug Dependence (35th Meeting). 2012. www.who.org. Date Accessed 3-17-2016.pp. 1-31.

21. Organization for Economic Co-Operation and Development Screening Information Data Sets (OECD SIDS). 1,4-Butanediol (CAS# 110-63-4)-SIDS Initial Assessment Report for 10th SIDS Initial Assessment Meeting (SIAM). United Nations Environment Programme (UNEP) Publications. 2000. www.inchem.org. Date Accessed 3-17-2016.pp. 1-60.

22. National Toxicology Program (NTP). National Toxicology Program Report Series No. 406: Toxicology and Carcinogenesis Studies of Gamma-Butyrolactone (Cas No. 96-48-0) In F344/N Rats and B6C3F1 Mice (Gavage Studies); US Department of Health and Human Services, Public Health Service, National Institute of Health. 1992. http://ntp.niehs.nih.gov/. Date Accessed 5-31-2016. Report No. 406. pp. 1-232.

23. Irwin RD. NTP Summary Report on the Metabolism, Disposition, and Toxicity of 1,4-Butanediol (CAS No. 110-63-4). 1996. pp. 1-28, A1. MEDLINE AN 2002077930(Journal; Article; (JOURNAL ARTICLE); General Review; (REVIEW)).

24. Food and Drug Administration (FDA). Xyrem (sodium oxybate) Information. http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm332408.htm. Last Updated 2015. Date Accessed 4-29-2016.

25. Food and Drug Administration (FDA). Medicantion Guide for Xyrem (sodium oxybate) oral solution CIII [pamphlet]. 2015.

26. Industry Submission to FDA. GRAS Exemption Claim: 1,3-Propanediol. 2009. http://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm269352.pdf. Date Accessed 3-22-2016.pp. 1-713. This report contains unpublished data for 1,3-Propanediol.

27. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database.* 1-12-2017.

28. Food and Drug Administration (FDA). Federal Register Rules and Regulations 21 CFR Part 177 (Docket No. 98F-1019) Indirect Food Additives: Polymers; Vol. 65, No. 90, page 26744-26745 (May 9, 2000). 2000. https://www.gpo.gov/fdsys/pkg/FR-2000-05-09/pdf/00-11478.pdf. Date Accessed 3-24-2016. 1,4-Butanediol is used in polyurethane resins, exposure to 1,4-Butanediol 90 micrograms/person/day.

29. Food and Drug Administration (FDA). FDA Talk Paper (1999): FDA Warns about GBL-Related Products. http://www3.scienceblog.com/community/older/archives/M/1/fda0562.htm. Last Updated 2004. Date Accessed 3-23-2016.

30. Food and Drug Administration (FDA). FDA Approved Drugs: XYREM (sodium oxybate); NDA 021196. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Last Updated 2016. Date Accessed 4-29-2016.

31. Industry Submission to FDA. 510(k) Summary for Hydrogel wound dressing containing Pentylene Glycol (Jul 23, 2008). www.fda.gov. Last Updated 2008. Date Accessed 3-23-2016.

32. Environmental Protection Agency (EPA). Federal Register Rules and Regulations 40 CFR Part 180: 2-Methyl-1,3-Propanediol; Exemption From the Requirement of a Tolerance; Vol. 77, No. 148, pages 45495-45498 (August 1, 2012). 2012. www.regulations.gov. Date Accessed 3-24-2016.

33. Environmental Protection Agency (EPA). Federal Register Rules and Regulations 40 CFR Part 180: 2-Methyl-1,3-Propanediol; Exemption From the Requirement of a Tolerance; Vol. 75, No. 161, pages 51388-51392 (August 20, 2010). 2010. www.regulations.gov. Date Accessed 5-2-2016.

34. Environmental Protection Agency (EPA). Decision Document for Petition Number 2E6484; 2-methyl-1,3-propanediol [CAS Reg. No. 2163-42-0], requesting the establishment of an inert ingredient exemption from the requirement of a tolerance. 2010. www.regulations.gov. Date Accessed 5-2-2016.pp. 1-10.

35. Industry Submission to United States Environmental Protection Agency (EPA). High Production Volume (HPV) Chemical Challenge Program for 2-Methyl-1,3-Propanediol (CAS RN 2163-42-0). 2004. Date Accessed 3-29-2016. Report No. 201-15559A. pp. 1-16.

36. United States Department of Commerce-National Technical Information Service (NTIS). Second Draft-Information Profiles on Potential Occupational Hazards: Glycols; Prepared by Center for Chemical Hazard Assessment Syracuse Research Corporation for NIOSH (National Institute for Occupational Safety and Health). 1982. Report No. NTIS Doc# PB89-215776. pp. 1-214.

37. United States Department of Commerce-National Technical Information Service (NTIS). 2010. DuPont Submission of Data for 1,4-Butanediol (CAS# 110-63-4; NTIS Document# 8EHQ-10-17815) in Accordance with EPA Guidance Under Toxic Substances Control Act. Dupont Data Submission.

38. United States Department of Commerce-National Technical Information Service (NTIS). 2011. DuPont Submission of Data for 1,3-Propanediol (CAS# 504-63-2; NTIS Document# 8EHQ-11-18251) in Accordance with EPA Guidance Under Toxic Substances Control Act. Dupont Data Submission.

39. United States Department of Commerce-National Technical Information Service (NTIS). 1992. BASF Corporation Submission of Data for 1,6-Hexanediol (CAS# 629-11-8; NTIS Document# 8EHQ-0592-4394) to EPA in Accordance with Toxic Substance Control Act 8 (e) Compliance Audit Program. From BASF Corp. Acute and Subacute oral tox data for 1,6-Hexanediol in rabbits; Data in German, Cover Letter Summary in English.

40. Miller LM. Investigation of Selected Potential Environmental Contaminants: Ethylene Glycol, Propylene Glycols and Butylene Glycols. Report Prepared for Office of Toxic Substances U.S. EPA (made available to public through National Technical Information Service). 1979. Date Accessed 12-15-2015. Report No. PB80109119. pp. 1-272.

41. Spencer PS and Schaumburg HH. Neurotoxic Properties of Certain Aliphatic Hexacarbons. *Proc.Roy.Soc.Med.* 1977;70(1):37-39.

42. Spencer PS, Bischoff MC, and Schaumburg HH. On the Specific Molecular Configuration of Neurotoxic Aliphatic Hexacarbon Compounds Causing Central-Peripheral Distal Axonopathy. *Toxicology and Applied Pharmacology*. 1978;44:17-28.

43. United States Pharmacopeia (USP). Food Chemicals Codex. 8th *ed*. Baltimore: United Book Press, Inc., 2012.

44. Anonymous. 2016. 1,3-Propanediol and skin penetration enhancement: A literature review. Unpublished data submitted by Personal Care Products Council.

45. The Merck Index. 15th *ed*. The Royal Society of Chemistry (RSC Publishing), 2013.

46. Sahler J. Scientists Develop Plastic-Producing Bacteria. http://inhabitat.com/scientists-develop-plastic-producing-bacteria/. Last Updated 2008. Date Accessed 9-22-2016.

47. DuPont Tate and Lyle BioProducts. Propanediol (CAS# 504-63-2) Product Description from Manufacturer. http://www.duponttateandlyle.com/zemea_cosmetic_ingredients. Last Updated 2016. Date Accessed 2-6-2017.

48. Faergemann, J. 2016. Pentane-1,5-diol: Safety of pentane-1,5-diol in topical formulations. Unpublished data submitted by Personal Care Products Council.

49. United Nations Environmental Programme (UNEP). Organization for Economic Co-Operation and Development Screening Information Data Sets (OECD SIDS). Hexamethylene Glycol (CAS# 629-11-8). SIDS Initial Assessment Report. 1995. www.inchem.org. Date Accessed 2-6-2017.pp. 1-14.

50. Lyondellbasell. 2-Methyl-1,3-Propanediol Product Description from Manufacturer. https://www.lyondellbasell.com/en/chemicals/p/MPDIOL-GLYCOL/c7a027bf-16f1-41d5-b571-57df3b04be16. Last Updated 2016. Date Accessed 2-6-2017.

51. Personal Care Products Council. 11-2-2016. Purity Information Alkane Diols. Unpublished data submitted by Personal Care Products Council.

52. Anadon A, Binderup M, Bursch W, Castle L, Crebelli R, Engel KH, Franz R, Gontard N, Haertle T, Husoy T, Jany KD, Leclercq C, Lhuguenot JC, Mennes W, Milana MR, Pfaff K, Svensson K, Toldra F, Waring R, Wolfle D, Sundh UB, Beltoft V, Carere A, Frandsen H, Gurtler R, Hill F, Larsen JC, Lund P, Mulder G, Norby K, Pascal G, Pratt I, Speijers G, Wallin H, and Nielsen KR. Scientific opinion on flavouring group evaluation 11, revision 2 (FGE.11Rev2): aliphatic dialcohols, diketones, and hydroxyketones from chemical groups 8 and 10. *EFSA Journal*. 2011;9(2):1170, 52 http://www.efsa.europa.eu/en/efsajournal/doc/1170.pdf.

53. Personal Care Products Council. 2-16-2016. Concentration of Use by FDA Product Category: Alkane Diols. Unpublished data submitted by Personal Care Products Council.

54. Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicology Letters*. 2011;205(2):97-104. PM:21669261.

55. Rothe H. 2011. Special aspects of cosmetic spray safety evaluation. Unpublished information presented to the 26 September CIR Expert Panel. Washington, D.C.

56. Bremmer HJ, Prud'homme de Lodder LCH, and van Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. Date Accessed 8-24-2011. Report No. RIVM 320104001/2006. pp. 1-77.

57. Johnsen MA. The Influence of Particle Size. *Spray Technology and Marketing*. 2004. 14:(11): pp.24-27.

58. CIR Science and Support Committee of the Personal Care Products Council (CIR SSC). 2015. (Nov 3rd) Cosmetic Powder Exposure. Unpublished data submitted by the Personal Care Products Council.

59. Aylott RI, Byrne GA, Middleton J, and Roberts ME. Normal use levels of respirable cosmetic talc: preliminary study. *Int J Cosmet Sci.* 1979;1(3):177-186. PM:19467066.

60. Russell RS, Merz RD, Sherman WT, and Siverston JN. The determination of respirable particles in talcum powder. *Food Cosmet Toxicol.* 1979;17(2):117-122. PM:478394.

61. European Commission. CosIng database; following Cosmetic Regulation No. 1223/2009. http://ec.europa.eu/growth/tools-databases/cosing/. Last Updated 2016. Date Accessed 4-7-2016.

62. Drug Enforcement Agency (DEA). Gamma Hydroxybutyric Acid Bulletin from DEA Office of Diversion Control *Drug & Chemical Evaluation Section*. http://www.deadiversion.usdoj.gov/drug_chem_info/ghb.pdf. Last Updated 2013. Date Accessed 3-22-2016.

63. Schep LJ, Knudsen K, Slaughter RJ, Vale JA, and Megarbane B. The Clinical Toxicology of Gamma-Hydroxybutyrate, Gamma-Butyrolactone and 1,4-Butanediol. *Clinical Toxicology*. 2012;50(6):458-470.

64. FDA. FDA Executive Summary. Classification of Wound Dressings Combined with Drugs (Prepared for the Meeting of the General and Plastic Surgery Devices Advisory Panel). 2016. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/GeneralandPlasticSurgeryDevicesPanel/UCM518494.pdf. Date Accessed 10-3-2016.

65. United States National Library of Medicine. PRUMYX-Prescription Medical Device Label. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=75125. Last Updated 2016. Date Accessed 10-3-2016.

66. United States National Library of Medicine. LOUTREX-Prescription Medical Device Label. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=120465. Last Updated 2016. Date Accessed 10-3-2016.

67. United States National Library of Medicine and TOXNET (Toxicology Data Network). TOXNET: ChemIDplus. UNII: 50C1307PZG; Pentylene glycol. https://chem.sis.nlm.nih.gov/chemidplus/unii/50C1307PZG. Last Updated 2016. Date Accessed 10-3-2016.

68. FDA. FDA Substance Registration System-Unique Ingredient Identifier. Pentylene glycol. https://fdasis.nlm.nih.gov/srs/unii/50c1307pzg. Last Updated 2016. Date Accessed 10-3-2016.

69. Sundberg J and Faergemann J. A Comparison of Pentane-1,5-diol to Other Diols for Use in Dermatology. *Expert Opinion on Investigational Drugs*. 2008;17(4):601-610.

70. Faergemann, J. Letter to Carol Eisenmann concerning the CIR Safety Assessment of Alkane Diols as Used in Cosmetics with additional information on 1,5-Pentanediol. 2016. Unpublished data submitted by Personal Care Products Council.

71. Mollgaard B and Hoelgaard A. Permeation of estradiol through the skin-effect of vehicles. *International Journal of Pharmaceutics*. 1983;15:185-197.

72. Faergemann J, Wahlstrand B, Hedner T, Johnsson J, Neubert RHH, Nystroem L, and Maibach HI. Pentane-1,5-diol as a percutaneous absorption enhancer. *Archives of Dermatological Research*. 2005;297(6):261-265.

73. Evenbratt H and Faergemann J. Effect of Pentane-1,5-diol and Propane-1,2-diol on Percutaneous Absorption of Terbinafine. *Acta Derm Venereol*. 2009;89:126-129.

74. Poldrugo F, Barker S, Basa M, Mallardi F, and Snead OC. Ethanol Potentiates the Toxic Effects of 1,4-Butanediol. *Alcoholism: Clinical and Experimental Research*. 1985;9(6):493-497.

75. Otsuka M, Mine T, Ohuchi K, and Ohmori S. A Detoxication Route for Acetaldehyde: Metabolism of Diacetyl, Acetoin, and 2,3-Butanediol in Liver Homogenate and Perfused Liver of Rats. *Journal of Biochemistry*. 1996;119(2):246-251.

76. Summerfield FW and Tappel AL. Cross-Linking of DNA in Liver and Testes of Rats Fed 1,3-Propanediol. *Chem Biol Interactions*. 1984;50(1):87-96.

77. Gessner PK, Parke DV, and Williams RT. Studies in Detoxication. The Metabolism of Glycols. *Biochemistry*. 1960;74(80):1-5.

78. Snead OC, Poldrugo F, and Barker SJ. Presence of 1,4-Butanediol in Neuronal and Extraneuronal Tissue. *Soc Neurosci (Abstract only)*. 1986;12:285

79. National Institute of Health U.S.National Library of Medicine, Toxnet. Hazardous Substances Data Bank: 2-Methyl-1,3-Propanediol, CASRN: 2163-42-0. https://toxnet.nlm.nih.gov. Last Updated 2012. Date Accessed 8-3-2016.

80. Thai D, Dyer JE, Jacob P, and Haller CA. Clinical Pharmacology of 1,4-Butanediol and Gamma-hydroxybutyrate After Oral 1,4-Butanediol Administration to Healthy Volunteers. *Clinical Pharmacology & Therapeutics*. 2007;81(2):178-184.

81. Brenneisen R, Elsohly MA, Murphy TP, Passarelli J, Russmann S, Salamone SJ, and Watson DE. Pharmacokinetics and Excretion of Gamma-Hydroxybutyrate (GHB) in Healthy Subjects. *Journal of Analytical Toxicology*. 2004;28(November/December):625-630.

82. Scott R, Frame S, Ross P, Loveless S, and Kennedy G. Inhalation Toxicity of 1,3-Propanediol in the Rat. *Inhalation Toxicology*. 2005;17(9):487-493.

83. Smyth HF, Carpenter CP, Weil CS, Pozzani UC, and Striegel JA. Range-Finding Toxicity Data: List VI. *American Industrial Hygiene Association Journal*. 1962;23:95-107.

84. Carpenter CP, Weil CS, and Smyth HF. Range-Finding Toxicity Data: List VIII. *Toxicology and Applied Pharmacology*. 1974;28(2):313-319.

85. Deichmann WB and Gerarde HW. Toxicology of Drugs and Chemicals. Academic Press, Inc., 1969.

86. Jedrychowski RA, Stetkiewicz J, and Stetkiewicz I. Acute toxicity of 1,4-Butanediol in laboratory animals. *Polish journal of occupational medicine*. 1990;3(4):415-420.

87. Rowe VK and Wolf MA. Glycols. Chapter: 50. Clayton GD and Clayton FE. In: *Patty's Industrial Hygiene and Toxicology*. 3 ed. New York: John Wiley & Sons; 1982:3817-3908.

88. Anonymous. 2016. Summary information on trade name materials containing 1,10-Decanediol. Unpublished data submitted by Personal Care Products Council.

89. Kinney LA, Burgess BA, Stula EF, and Kennedy GL Jr. Inhalation toxicology of 1,4-Butanediol. *Inhalation Toxicology*. 1991;3(4):379-388.

90. Jedrychowski RA, Gorny R, Stetkiewicz J, and Stetkiewicz I. Subacute oral toxicity of 1,4-Butanediol in rats. *Polish journal of occupational medicine*. 1990;3(4):421-428.

91. Gingell R, Kirkpatrick JB, and Steup DR. Subchronic toxicity study of 1,3-Propanediol administered orally to rats. *International Journal of Toxicology*. 2000;19(1):27-32.

92. Little A. Water Quality Criteria Data Book Volume 1. Organic Chemical Pollution of Freshwater. Prepared for EPA Water Quality Office. 1970. Date Accessed 2-13-2017. Report No. 18010DPV12/70.

93. Price CJ, Marr MC, Myers CB, Heindel JJ, and Schwetz BA. Developmental Toxicity Evaluation of 1,4-Butanediol (BUTE) in Swiss Mice. *Teratology Society Abstracts*. 1993. 47:(5): pp.433-433.

94. Zeiger E, Anderson B, Haworth S, Lawlor T, and Mortelmans K. Salmonella Mutagenicity Tests: V. Results from the Testing of 311 Chemicals. *Environmental and Molecular Mutagenesis*. 1992. 19:(21): pp.2-141.

95. Irwin RD. A Review of Evidence Leading to the Prediction that 1,4-Butanediol is Not a Carcinogen. *Journal of Applied Toxicology*. 2006;26(1):72-80.

96. Kurihara A, Manabe A, Katsuno K, Itoh K, Hisamitsu H, Wakumoto S, and Yoshida T. Evaluation of skin irritation and sensitization of two diol solutions used as experimental dentin primers in humans and guinea pigs. *Dental materials journal*. 1996;15(2):226-232.

97. Belcher LA, Muska CF, and DeSalvo JW. Evaluating 1,3-Propanediol for Potential Skin Effects. *Cosmetics & Toiletries*. 2010;125(5):81-84.

98. TKL Research Inc. 2010. Repeated insult patch test of a facial serum containing 21.2% Methylpropanediol. Unpublished data submitted by Personal Care Products Council.

99. Sandstrom Falk MH, Sarnhult T, Hedner T, and Faergemann J. Treatment of Atopic Dermatitis with 1% Hydrocortisone and 25% Pentane-1,5-diol: Effect on *Staphylococcus aureus*. *Acta Derm Venereol*. 2006;86:1-2.

100. Busch R, Graubaum HJ, Gruenwald J, and Faergemann J. Therapeutic Effect of 1,5-Pentanediol for Herpes Simplex Labialis: a Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Adv Ther*. 2009;26(7):719-727.

101. Gallo R, Viglizzo G, Vecchio F, and Parodi A. Allergic contact dermatitis from Pentylene Glycol in an emollient cream, with possible co-sensitization to resveratrol. *Contact Dermatitis*. 2003;48(3):176-177.

102. Kerre S. Allergic contact dermatitis to pentylene glycol in a cosmetic cream. *Contact Dermatitis*. 2008;58:122-123.

103. Suchard JR, Nizkorodov SA, and Wilkinson S. 1,4-Butanediol Content of Aqua Dots Children's Craft Toy Beads. *Journal of Medical Toxicology*. 2009;5(3):120-124.

104. Zvosec DL, Smith SW, McMutcheon JR, Spillane J, Hall BJ, and Peacock EA. Adverse Events, Including Death, Associated with the Use of 1,4-Butanediol. *New England Journal of Medicine*. 2001;344:87-94.

105. American Chemical Society (ACS). SciFinder. https://scifinder.cas.org. Last Updated 2016. Date Accessed 3-29-2016.

106. Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2016 ACD/Labs). 2016.

107. Montgomery JA, David F, Garneau M, and Brunengraber H. Metabolism of 2,3-Butanediol Stereoisomers in the Perfused Rat Liver. *The Journal of Biological Chemistry*. 1993;268(27):20185-20190.

108. National Institute of Health US National Library of Medicine Toxicology Data Network (TOXNET). ChemIDplus database search results for 1,5-Pentanediol (CAS #111-29-5). https://chem.nlm.nih.gov/chemidplus/name/1%2C5-pentanediol. Last Updated 2016. Date Accessed 2-8-2017.

VCRP Data for Alkane Diols-2017

504632	Propanediol	01A - Baby Shampoos	2
504632	Propanediol	01B - Baby Lotions, Oils, Powders, and Creams	4
504632	Propanediol	01C - Other Baby Products	1
504632	Propanediol	03B - Eyeliner	2
504632	Propanediol	03C - Eye Shadow	2
504632	Propanediol	03D - Eye Lotion	14
504632	Propanediol	03E - Eye Makeup Remover	3
504632	Propanediol	03F - Mascara	6
504632	Propanediol	03G - Other Eye Makeup Preparations	16
504632	Propanediol	04A - Cologne and Toilet waters	1
504632	Propanediol	04E - Other Fragrance Preparation	11
504632	Propanediol	05A - Hair Conditioner	8
504632	Propanediol	05B - Hair Spray (aerosol fixatives)	1
504632	Propanediol	05C - Hair Straighteners	3
504632	Propanediol	05F - Shampoos (non-coloring)	11
504632	Propanediol	05G - Tonics, Dressings, and Other Hair Grooming Aids	17
504632	Propanediol	05H - Wave Sets	1
504632	Propanediol	05I - Other Hair Preparations	13
504632	Propanediol	06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	3
504632	Propanediol	06D - Hair Shampoos (coloring)	1
504632	Propanediol	06E - Hair Color Sprays (aerosol)	5
504632	Propanediol	07C - Foundations	8
504632	Propanediol	07D - Leg and Body Paints	1
504632	Propanediol	07F - Makeup Bases	5
504632	Propanediol	07I - Other Makeup Preparations	4
504632	Propanediol	09C - Other Oral Hygiene Products	1
504632	Propanediol	10A - Bath Soaps and Detergents	555
504632	Propanediol	10B - Deodorants (underarm)	11
504632	Propanediol	10E - Other Personal Cleanliness Products	6
504632	Propanediol	11A - Aftershave Lotion	4
504632	Propanediol	11G - Other Shaving Preparation Products	1
504632	Propanediol	12A - Cleansing	41
504632	Propanediol	12C - Face and Neck (exc shave)	127
504632	Propanediol	12D - Body and Hand (exc shave)	17
504632	Propanediol	12E - Foot Powders and Sprays	1
504632	Propanediol	12F - Moisturizing	124
504632	Propanediol	12G - Night	21
504632	Propanediol	12H - Paste Masks (mud packs)	49
504632	Propanediol	12I - Skin Fresheners	4
504632	Propanediol	12J - Other Skin Care Preps	28
504632	Propanediol	13A - Suntan Gels, Creams, and Liquids	1
504632	Propanediol	13B - Indoor Tanning Preparations	3
504632	Propanediol	13C - Other Suntan Preparations	1

VCRP Data for Alkane Diols-2017

110634	1,4-Butanediol	03G - Other Eye Makeup Preparations	1
110634	1,4-Butanediol	12F - Moisturizing	1
110634	1,4-Butanediol	12I - Skin Fresheners	1
110634	1,4-Butanediol	13B - Indoor Tanning Preparations	1
629118	1,6-Hexanediol	08G - Other Manicuring Preparations	1
629414	Octanediol	12I - Skin Fresheners	3
112470	1,10-Decanediol	12A - Cleansing	1
112470	1,10-Decanediol	12C - Face and Neck (exc shave)	1
112470	1,10-Decanediol	12D - Body and Hand (exc shave)	1
112470	1,10-Decanediol	12F - Moisturizing	9
112470	1,10-Decanediol	12G - Night	3
2163420	Methylpropanediol	02D - Other Bath Preparations	2
2163420	Methylpropanediol	03A - Eyebrow Pencil	1
2163420	Methylpropanediol	03B - Eyeliner	5
2163420	Methylpropanediol	03C - Eye Shadow	10
2163420	Methylpropanediol	03D - Eye Lotion	14
2163420	Methylpropanediol	03E - Eye Makeup Remover	2
2163420	Methylpropanediol	03F - Mascara	11
2163420	Methylpropanediol	03G - Other Eye Makeup Preparations	4
2163420	Methylpropanediol	04A - Cologne and Toilet waters	2
2163420	Methylpropanediol	05A - Hair Conditioner	5
2163420	Methylpropanediol	05B - Hair Spray (aerosol fixatives)	4
2163420	Methylpropanediol	05E - Rinses (non-coloring)	1
2163420	Methylpropanediol	05F - Shampoos (non-coloring)	1
2163420	Methylpropanediol	05G - Tonics, Dressings, and Other Hair Grooming Aids	3
2163420	Methylpropanediol	05H - Wave Sets	1
2163420	Methylpropanediol	06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	5
2163420	Methylpropanediol	06D - Hair Shampoos (coloring)	1
2163420	Methylpropanediol	06H - Other Hair Coloring Preparation	2
2163420	Methylpropanediol	07A - Blushers (all types)	1
2163420	Methylpropanediol	07C - Foundations	18
2163420	Methylpropanediol	07E - Lipstick	2
2163420	Methylpropanediol	07F - Makeup Bases	4
2163420	Methylpropanediol	07H - Makeup Fixatives	1
2163420	Methylpropanediol	07I - Other Makeup Preparations	3
2163420	Methylpropanediol	08B - Cuticle Softeners	1
2163420	Methylpropanediol	10A - Bath Soaps and Detergents	101
2163420	Methylpropanediol	10E - Other Personal Cleanliness Products	19

VCRP Data for Alkane Diols-2017

2163420	Methylpropanediol	11A - Aftershave Lotion	5
2163420	Methylpropanediol	11E - Shaving Cream	1
2163420	Methylpropanediol	11G - Other Shaving Preparation Products	1
2163420	Methylpropanediol	12A - Cleansing	35
2163420	Methylpropanediol	12C - Face and Neck (exc shave)	58
2163420	Methylpropanediol	12D - Body and Hand (exc shave)	82
2163420	Methylpropanediol	12F - Moisturizing	78
2163420	Methylpropanediol	12G - Night	10
2163420	Methylpropanediol	12H - Paste Masks (mud packs)	28
2163420	Methylpropanediol	12I - Skin Fresheners	4
2163420	Methylpropanediol	12J - Other Skin Care Preps	10
2163420	Methylpropanediol	13A - Suntan Gels, Creams, and Liquids	1
2163420	Methylpropanediol	13B - Indoor Tanning Preparations	4
2568334	Isopentyldiol	03A - Eyebrow Pencil	2
2568334	Isopentyldiol	03B - Eyeliner	2
2568334	Isopentyldiol	03C - Eye Shadow	7
2568334	Isopentyldiol	03D - Eye Lotion	9
2568334	Isopentyldiol	03F - Mascara	1
2568334	Isopentyldiol	03G - Other Eye Makeup Preparations	4
2568334	Isopentyldiol	04E - Other Fragrance Preparation	4
2568334	Isopentyldiol	05I - Other Hair Preparations	1
2568334	Isopentyldiol	07A - Blushers (all types)	8
2568334	Isopentyldiol	07B - Face Powders	3
2568334	Isopentyldiol	07C - Foundations	1
2568334	Isopentyldiol	07I - Other Makeup Preparations	5
2568334	Isopentyldiol	12A - Cleansing	3
2568334	Isopentyldiol	12C - Face and Neck (exc shave)	9
2568334	Isopentyldiol	12D - Body and Hand (exc shave)	1
2568334	Isopentyldiol	12F - Moisturizing	58
2568334	Isopentyldiol	12J - Other Skin Care Preps	1
2568334	Isopentyldiol	13B - Indoor Tanning Preparations	15
2568334	Isopentyldiol	13C - Other Suntan Preparations	1

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: September 19, 2016

SUBJECT: 1,10-Decanediol

Anonymous. 2016. Summary information on trade name materials containing 1,10-Decanediol.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

September 2016

Summary Information on Trade Name Materials Containing 1,10-Decanediol

A supplier reports that 1,10-Decanediol (>98% pure) is sold to the cosmetics industry as part of trade name mixtures. The concentration of 1,10-Decanediol in these mixtures is 1.2%. Safety studies (summarized below) have been completed on two trade name mixtures containing 1,10-Decanediol, one mixture also contains Butylene Glycol (1,3 [previously reviewed by CIR]) and the other mixture also contains Propylene Glycol (1,2 [previously reviewed by CIR]).

Studies of 1,10-Decanediol Trade Name Mixture Containing Butylene Glycol

Acute Oral

The acute oral toxicity of the 1,10-Decanediol trade name mixture containing Butylene Glycol, was studied using 10 male mice (IFFA CREDO OF 1). The test substance was administered at a maximal oral dose of 20 ml/kg, and dosing was followed by an 8-day observation period. Gross necropsy was performed on day 8. There was no evidence of test substance-related clinical signs in the study, and the behavior of animals was considered normal. Gross necropsy did not reveal any evidence of modification of the main organs. Particularly, there were no signs of necrosis or ulceration of the digestive tract.

Skin Irritation and Sensitization

In vitro – irritation

The skin irritation potential of the 1,10-Decanediol trade name mixture containing Butylene Glycol was evaluated by application on the top of reconstructed human epidermis (RhE): application time 15 min; quantity used 10 µl; tested concentration 100%. The assessment criteria were: (1) % of viability compared to the untreated control and (2) IL1-α released concentration, after 15 min active ingredient application and 42 h culture. Average results of assessment criteria: (1) % viability compared to the untreated control was 92% and (2) IL1- α concentration released was less than 5 pg/mL. The 1,10-Decanediol trade name mixture containing Butylene Glycol was not an irritant.

Beuhler test – sensitization

The skin sensitization potential of the 1,10-Decanediol trade name mixture containing Butylene Glycol was evaluated in a Beuhler test using 20 male guinea pigs. The animals were shaved 24 hours prior to the topical application of the 1,10-Decanediol trade name mixture containing Butylene Glycol. The inductions were then observed for in an 11-day resting period. In parallel, a control group of 10 male guinea pigs was subject to the same treatment except no 1,10-Decanediol trade name mixture containing Butylene Glycol. At 28-day, 25% (0.3 mL) 1,10-Decanediol trade name mixture containing Butylene Glycol was applied. Reactions/erythema were scored at 24 hours and 48 hours post-application. No clinical sign/erythema, a characteristic of a sensitizing effect, was observed during the study. The 1,10-Decanediol trade name mixture containing Butylene Glycol did not induce sensitization.

Human – irritation

The 1,10-Decanediol trade name mixture containing Butylene Glycol was applied under an occlusive patch to the inside upper arm of 10 subjects for 48 hours. The skin reaction was observed 1h, 24h and 48h after patch removal and the clinical examination was conducted by the laboratory assistant (0: No itching ;1: Slight itching; 2: Moderate itching; 3: Intense itching; 4: Burning sensations). Throughout the test, more erythema was observed at the placebo treated site. On the active ingredient treated site, mild erythema which occurred 1h after patch removal was observed in two subjects. No other observations were noted during the clinical examination, and the volunteers reported no adverse effects. Therefore, it can be concluded that throughout the test, the 1,10-Decanediol trade name mixture containing Butylene Glycol was very well tolerated on the skin.

Ocular Irritation

In vitro

The potential ocular irritancy of the 1,10-Decanediol trade name mixture containing Butylene Glycol was evaluated by measuring its ability to induce toxicity in the chorioallantoic membrane of a chicken. After 10 days of incubation, fertilized hen's eggs, Leghorn strain (Lohmann), the shell and shell membrane were gently removed in order to uncover the underlying chorioallantoic membrane (CAM). 1,10-Decanediol trade name mixture containing Butylene Glycol (0.3 ml) was applied onto the CAM of 4 eggs. After a contact of 20 seconds, the membrane was rinsed with 5 ml of 0.9% NaCl. Potential irritancy phenomena (hyperemy, hemorrhage, coagulation) were observed and scored for 5 minutes. The mean score of 4 eggs was 6.5 (moderately irritating) with 1,10-Decanediol trade name mixture containing Butylene Glycol or 0 (practically non-irritating) with 1,10-Decanediol trade name mixture containing Butylene Glycol.

The ocular irritancy of 1,10-Decanediol trade name mixture containing Butylene Glycol was evaluated by application on the top of reconstructed human corneal epitheliums: 30µl on the top of epitheliums for 1h and 24h. The % viability compared to the untreated control after 1h and 24h of application was 76% at 1 hr and 86% at 24 hr based on the quantitative 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. 1,10-Decanediol trade name mixture containing Butylene Glycol was a non-irritant.

The irritation potential of 1,10-Decanediol trade name mixture containing Butylene Glycol was evaluated by cytotoxicity by diffusion in agarose gel (Agarose Overlay Test). The total score of the average diameters (cm) was 1.075. 1,10-Decanediol trade name mixture containing Butylene Glycol displayed low cytotoxicity.

Phototoxicity

The phototoxicity of 1,10-Decanediol trade name mixture containing Butylene Glycol was studied using albino guinea pigs. The animals (10 per group) received an application of the test substance (1 ml) with or without UVA irradiation (20 min of UVA with a 310 nm light source placed 5 cm away from the treated zones). Test sites were examined at 1 h, 6 h, and 24 h post-irradiation. There was no evidence

of dermal reactions in irradiated or non-irradiated animals, and the test substance was classified as non-phototoxic.

Genotoxicity

In vitro

1,10-Decanediol trade name mixture containing Butylene Glycol was evaluated for mutation in five tester strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA 1537 and TA 1538). This assay was performed at concentrations of 10, 50, 100, 1000, and 5000 µg/plate both in the absence and presence of an S9 exogenous metabolic activation system. Revertant frequencies in 1,10-Decanediol trade name mixture containing Butylene Glycol treated plates were similar to vehicle control values. All positive and vehicle control data were within acceptable ranges. Based on the results of this study, 1,10-Decanediol trade name mixture containing Butylene Glycol was found to be non-mutagenic and non-cytogenic under the test conditions.

Studies of 1,10-Decanediol Trade Name Mixture Containing Propylene Glycol

Acute Toxicity

The acute oral toxicity of the 1,10-Decanediol trade name mixture containing Propylene Glycol was evaluated using mice. The test article was administered at a maximal oral dose of 20 mL/kg, followed by an 8-day observation period. Gross necropsy was performed on study day 8. There was no evidence of test article-related clinical signs, behavior, or gross pathology. Based on the results of the study, the LD_{50} was greater than 20 mL/kg.

Skin Irritation and Sensitization

Irritation – Rabbits

The dermal irritation potential of 1,10-Decanediol trade name mixture containing Propylene Glycol was evaluated in a primary irritation test using rabbits. The test article was occlusively applied to the animals (0.5 mL of 100%) and kept in place for 24-hours. The test article application site was evaluated for irritation at 25-, 48-, and 72-hours post administration. Transient dermal irritation (erythema) was observed at the 48-hour observation time point, but resolved by the 72-hour observation time point. Based on the results of the study, 1,10-Decanediol trade name mixture containing Propylene Glycol was determined to be a non-irritant.

Buehler test – sensitization

The skin sensitization potential of 1,10-Decanediol trade name mixture containing Propylene Glycol was evaluated in a Buehler test using guinea pigs. The animals were shaved 24 hours prior to the topical application of the test article. The test article (100%) was impregnated on to a compress and applied on the animals for at least 6-hours per induction period (days 1, 9 and 15). In parallel, a control group of animals was subjected to the same treatment except the application of the test article. At day 28, the animals were challenged with the test article at 25% for 6-hours. Dermal reactions were scored at 24- and 48-hours post challenge phase. No clinical signs of erythema was observed during the challenge

phase of the study. Therefore, 1,10-Decanediol trade name mixture containing Propylene Glycol was concluded not to be a dermal sensitizer under the condition of this study.

Ocular Irritation

The ocular irritation potential of 1,10-Decanediol trade name mixture containing Propylene Glycol was evaluated in an modified Kay and Calendra method for ocular irritation in rabbits. The test article (0.1 mL of 100%) was dosed to the inner side of the right eyelid and left unwashed for 24-hours. The animals were evaluated at 24-, 48-, 72-, 96- and 120-hours after administration. Transient ocular irritation effects were observed throughout the study, but were considered to be reversible. Based on the results of the study, 1,10-Decanediol trade name mixture containing Propylene Glycol was determined to be a slight irritant.

Genotoxicity

In vitro

The mutagenic potential of 1,10-Decanediol trade name mixture containing Propylene Glycol was evaluated in the Ames assay using Salmonella typhimurium strains TA 98, 100 and 1537 with and without metabolic activation. The test article was tested up to 10,000 µg/plate in each of the strains. The test article did not demonstrate any signs of cytotoxicity at the maximal concentration tested, and also did not demonstrate any revertants with and without metabolic activation. Based on the results of the study, 1,10-Decanediol trade name mixture containing Propylene Glycol was not considered to be a mutagen.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: November 2, 2016

SUBJECT: Purity Information Alkane Diols

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

Alkane Diols Purity Information

Ingredient	Purity/Impurities	Reference
Methylpropanediol	"high" (0.1-1.5% 2-methyl-1,3-pentanediol)	NICNAS NA/279 (link from On-Line CIR report reference 56)
Methylpropanediol	98% 2% 2-methyl-1,3-pentanediol	Lyondell sales specifications at https://www.lyondellbasell.com/en/chemicals/p/MPDIOL-GLYCOL/c7a027bf-16f1-41d5-b571-57df3b04be16
Propanediol	99.8% pure	Dupont website http://www.duponttateandlyle.com/sites/default/files/Zemea%28r%29%20Propanediol%20Product%20Data%20Sheet.pdf
Isopentyldiol	97% impurities not known	NICNAS STD/1352 CIR report reference 64
Isopentyldiol	>99%	Anonymous. 2016. Purity information Isopentyldiol (attached)
1,4-Butanediol	98% pure impurities not stated	OECD SIDS screening data set CIR report reference 66
Hexanediol	>96% pure impurities not stated	OECD SIDS screening data set http://www.inchem.org/documents/sids/sids/629118.pdf

November 2016

A supplier reports that the purity of the Isopentyldiol supplied to the cosmetics industry is greater than 99%.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: November 8, 2016

SUBJECT: 1,5-Pentanediol

Faergemann J. 2016. Pentane-1,5-diol: Safety of pentane-1,5-diol in topical formulations.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

November, 2016

Pentane-1,5-diol
CAS No. 111-29-5

Pentane-1,5-diol

Safety of pentane-1,5-diol in topical formulations

Jan Faergemann MD, PhD
Professor in the Department of Dermatology
Sahlgrenska University Hospital
Gothenburg, Sweden

1. TABLE OF CONTENTS

1. TABLE OF CONTENTS 2
2. INTRODUCTION 3
3. PHYSICAL, CHEMICAL PROPERTIES 4
3.1 Chemical formula 4
3.2 Physical properties 4
3.3 Current technical use and potential new areas of application 6
4. TOXICOLOGY 7
4.1 Pharmacokinetics and product metabolism in animals 7
4.2 Acute toxicity 7
4.2.1 Chronic toxicity 8
4.2.2 Genotoxicity 8
4.2.3 Skin and eye irritation tests 8
4.2.4 Photo toxicity tests 8
4.2.5 Reproductive toxicity 8
5. SKIN PENETRATION
5.1 *in vitro* percutaneous absorption 8
5.1.1 Tiratricol release 8
5.1.2 Percutaneous absorption of mometasone furoate (Elocon) 9
5.1.3 Percutaneous absorption of hydrocortisone 9
6. EFFECTS IN HUMANS 10
6.1 Pharmacokinetics and product metabolism in humans 10
6.2 Clinical Safety and Efficacy 10
6.2.1 Safety and tolerability in healthy volunteers 10
7. CONCLUSION 12
8. REFERENCES 15
APPENDIX 1: 17

2. INTRODUCTION

Pentane-1,5-diol ($C_5H_{12}O_2$) belongs to the group of aliphatic diols or glycols. Some aliphatic diols are frequently used in pharmaceutical formulations as solvents, absorptions enhancers, as ingredients in cosmetic products and as antimicrobial agents. It has been shown *in vitro* that the anti-mycotic activity of diols or glycols was increased with increasing length of the carbon chain (1).

So far propane-1,2-diol is the only diol widely used in clinical dermatology. It has been found to be efficient against dandruff where *Malassezia* species (formerly *Pityrosporum orbiculare*) play an important role. Propane-1,2-diol is used in the treatment of patients with pityriasis versicolor, *Malassezia* (*Pityrosporum*) folliculitis and seborrhoeic dermatitis (2). Propane-1,2-diol has been shown to be active against influenza A virus *in vitro*.

It is suggested that pentane-1,5-diol (PD) is a more effective diol, causing less adverse events such as skin and eye irritation.

PD is a colourless, viscous, oily liquid with a slightly bitter taste. Unlike hexylene glycol, 1,2-pentane diol and other diols, all characterised by bad odour, PD is odourless. PD is miscible with water, methanol, ethanol, acetone, ethyl acetate and ether. It's solubility in benzene, trichlorethylene, methylene chloride, petroleum ether and heptane is limited (3). PD has earlier been used in a variety of non-medical applications, e.g. as plasticizer in cellulose products and adhesives, as ingredient in dental composites, in brake fluid compositions, and as a preservative for grain (4, 5). However, today it is used in several cosmetics, pharmaceuticals and medical device products. Compared to propane-1,2-diol, PD was superior in enhancement of the absorption of terbinafine (6), tiratricol release from Essex cream (7) and hydrocortisone (7).

PD can be easily mixed with various substances for topical treatment, such as corticosteroids, other hormones or hormone analogues, anti-microbial drugs (antiviral, antibacterial, antifungal) and local anaesthetics. Apart from its own activity as anti-microbial agent, PD acts as an excipient enhancing the solubility and percutaneous absorption and increasing the efficacy of the active ingredient(s) of such combined formulations.

In vivo metabolic experiments have shown that PD is metabolised to glutaric acid and further to carbon dioxide (rabbit) involving the alcohol dehydrogenase system (mouse) (8-9).

In a cutaneous absorption study in human healthy volunteers PD was metabolized to glutaric acid and eliminated through urine. No toxic effects were found (10).

In animal experiments skin and eye irritation tests with PD were negative (11). PD has low oral toxicity compared to other diols. Ames test results (Salmonella typhimurium reverse mutation assay) were negative, hence there is no indication for mutagenicity caused by PD (12). PD has a documented low toxicity in animal models of oral, topical (skin), intravenous and inhalation routes of administration (8-9, 11-13). The absence of genotoxicity *in vitro* indicates a very low carcinogenic potential of PD *in vivo*. No studies are yet available on chronic toxicity (repeat dose) or reproductive toxicity of PD. However, long term exposure data in medical reports available from workers chronically exposed for PD for many years, do not indicate increased morbidity or mortality among those workers (11).

PD does not absorb electromagnetic waves in the long-wave UV range, and is not expected to act as a photo-sensitizer or to cause photo-toxic/photo-allergic skin reactions (14).

The exact anti-microbial mechanism of action of PD is unknown, but might, similar to propane-1,2-diol, involve extracting water out of bacterial and fungi cells, which eventually leads to their collapse. The probability of developing bacterial resistance to this mechanism is considered highly unlikely (15).

PD was found to be safe and well tolerated when tested by healthy volunteers. Assessments included photo patch tests, patch tests after single as well as repeated application, and sensitization test acc. to Magnusson. There was no evidence of primary skin irritation, allergic hypersensitivity or photo-sensitivity seen in any of the participating healthy volunteers (14, 16-18).

PD has been present in products contributing to the successful treatment results seen in open as well as double-blind, randomized, controlled clinical trials when it was added as an ingredient to various formulations for the treatment of herpes simplex labialis (18), atopic dermatitis (20) and male pattern baldness (21).

PD has now been used in a new topical formulation worldwide in more than 1 000 000 units and no negative effects have been reported.

3. PHYSICAL, CHEMICAL PROPERTIES

3.1 Chemical formula

IUPAC name:	Pentane-1,5-diol
Synonyms:	1,5-pentanediol, pentamethylene glycol, pentylene glycol
Chemical formula:	$C_5H_{12}O_2$
Structure formula:	
Molecular weight:	104.15
CAS Number:	111-29-5

3.2 Physical properties

(PD) is a viscous oily, odourless liquid with a slightly bitter taste. Freezing point is -18°C, boiling point is 238-240°C and flash point is 125°C. Specific gravity is 0.9925. PD is miscible with water, methanol, ethanol, acetone, ethyl acetate and ether. Its solubility in benzene, trichlor ethylene, methylene chloride, petroleum ether and heptane is limited (3, 9).

3.2.1 Impurities

To ensure that the Pentan-1,5-diol is of constant quality, whereas the focus is laid on the by products, a gas chromatographic/mass spectrometry (GC/MS) determination of the content of these by products is carried out. For this purpose, a test method for the determination of related substances was developed (22).

Aim of this test method development was to identify the impurity profile of Penatn-1,5-diol. During the development, almost all impurities have been identified except two: the impurities at RRT 1.08 (relative retention time; Pentane-1,5-diol = 1.00) and RRT 1.33 could be identified as linear diols by means of the mass spectra. As the amount of the impurity at RRT 1.33 was below the disregard limit of 0.05% in all three investigated batches, no further clearing the structure of the substance was carried out.

Through an interpretation of the fragmentation pattern, the impurity at RRT 1.08 could be described as linear hexanediol. According to the mass spectrum, a cyclic compound can be definitely excluded. It is very likely that the substance is 1,3-Hexanediol or 1,4-Hexandiol which is commercially not available. Therefore, a confirmation of this hypothesis was not possible. The specification of these unknown impurities was set to no more than 0.5%.

Cyclic derivates of hexandiol were present in one investigated batch. As the toxicity of such cyclic compounds is likely to be more relevant than it is the case for the linear compounds, the specification was set to "not detectable".

The toxicological properties of the linear diols investigated is comparable to the toxicity of Pentan-1,5-diol, the respective MSDS of the detected 1,5-hexandiol and 1,6-hexandiol were available. Therefore, a limit of 3.0% diols (known!) is justified. Appendix 1 to this report shows the internal specification of 1,5-Pentanediol and an example of an external certificate of analysis according to the developed GC/MS test method.

Validation of Test methods - Summary of Results

The validation of test procedures was performed according to the *„Allgemeine Verwaltungsvorschriftenzur Anwendung der Arzneimittelprüfrichtlinien"* issued May 5, 1995. The test carried out and the statistic definitions correspond to the *„Note for Guidance"* of the *CPMP Working Party on Quality of Medicinal Products: „VALIDATION OF ANALYTICAL METHODS" (CPMP/ICH/281/95 & CPMP/ICH/381/95)* and *DIN 55 350 Part 13.*

The acceptance criteria given are concordant with *"Method Validation in Pharmaceutical Analysis: A Guide to Best Practice"* by Joachim Ermer, John H. McB. Miller (Editors), Wiley, February 2005, ISBN: 3-527-31255-2.

All chromatograms used for validation are contained in the *Appendix* of the validation report (22).

The GC/MS methodology used for the determination of the potential impurities *1,4-butanediol, 1,4-pentanediol, 1,2-hexanediol, 1,5-hexanediol, 1,6-hexanediol, 1,2-cis-cyclohexanediol, 1,2-transcyclohexanediol,1,3-cis-cyclohexanediol, 1,3-trans cyclohexanediol, 1,4-cis-cyclohexanediol* and *1,4-trans-cyclohexanediol* in *1,5-pentanediol* is according to the accumulated data:

- specific, i.e. the determination of the potential impurities, is not mutually influenced by the drug substance *1,5-pentanediol*, the *derivatisation reagent* and the *solvent* (Rs > 1.0).

- precise in terms of the analytical procedure, i.e. the *mean values (MV)* of the *intra* and *inter Assay Precision* of six individual test solutions prepared from *1,5-pentanediol, Batch No. 35466547GO* and evaluated for the known impurities *1,5-hexanediol, 1,6-hexanediol, 1,3-ciscyclohexanediol* and *1,4-cis-cyclohexanediol* found in this batch were 100.35, 100.85, 100.51 and 99.96 % with *coefficients of variation (CV)* of *0.79 / 0.56 %, 1.22 / 0.61 %, 0.47 / 0.87 %* and *0.49 / 0.49 %.* This is well within the acceptance range of 95.0 - 105.0 % and NMT 1.0.

- linear, i.e. the *coefficients of correlation (r)* for the drug substance *1,5-pentanediol* as reference for unknown impurities and the known impurities in the range 0.05 - 3.00 % of the nominal concentration of *1,5-pentanediol* in the test solution for n = 7 are all *r = 1.0000.* This is well within the acceptance criterion of NLT 0.9900.

- accurate, i.e. the mean *recovery rates (RC)* for the known potential impurities *1,4-butanediol, 1,4-pentanediol, 1,2-hexanediol, 1,5-hexanediol, 1,6-hexanediol, 1,2-cis-cyclohexanediol, 1,2-trans-cyclohexanediol, 1,3-cis-cyclohexanediol, 1,3-trans-cyclohexanediol, 1,4-cis-cyclohexanediol* and *1,4-trans-cyclohexanediol* spiked on the drug substance *1,5-pentanediol, Batch No. 35466547GO* in the range 0.20 - 0.60% of the nominal concentration in the test solution were all in the range *RC = 99.27 - 99.89 %* with *relative standard deviations (RSD)* of *0.26 - 0.69 % (3 levels, 3 replicates).* This is well within the acceptance criteria of 95.0 - 105.0 % and NMT 2.0.

- robust, i.e. minor changes of the oven temperature ramp, the carrier gas flow and the temperature of the injection system did not affect the assay determination of the ingredient in the test solution.

3.3 Current technical use and potential new areas of application

PD was earlier predominantly used in a variety of non- pharmaceutical applications, e.g. as plasticizer in cellulose products and adhesives, as ingredient in dental composites, in brake fluid compositions, and as a preservative for grain (4, 5). However, today it is used in several cosmetic products as well as in medical device products in a large number of individuals. The interesting properties of the substance, however, render it a highly suitable candidate also as enhancer/ excipient in various applications for topical treatment.

PD has a similar water binding capacity as urea and is thus capable of increasing the skin moisturizing effect of various cosmetic and pharmaceutical formulations (16).

PD acts as an excipient enhancing the solubility and percutaneous absorption, and thereby the efficacy of the active ingredient(s) of a given formulation. Compared to propane-1,2-diol, PD was found to be a superior absorption enhancer of the percutaneous absorption of terbinafine (6), tiratricol release (7) and hydrocortisone (7). Combined formulations can easily be prepared mixing PD with various active ingredients for topical treatment, such as corticosteroids, other hormones or hormone analogues, anti-microbial drugs and local anaesthetics and to improve cosmetic formulations.

4. Toxicology

4.1 Pharmacokinetics and product metabolism in animals

Metabolic reactions *in vivo* have been investigated for more than 20 diols including PD (8). Experiments were performed in chinchilla rabbits with a weight between 2 to 3 kg. Diet and water intake were controlled. The test substances were diluted in water and given by gavages. Urine samples were taken 1 to 2 days after the animals have been given the test substances. The samples were analysed for metabolites of the test substances.

The metabolism for PD was studied in 4 rabbits. The animals were given 8.5 g of oral PD. There was no presence of any unchanged PD in the urine. However, small amounts of glutaric acid as a metabolic producer were found in the urine when the rabbits were given PD. Glutaric acid was quickly metabolised to carbon dioxide (8).

Alkyldiols, including PD, were compared to ethanol as antidotes in ethylene glycol toxicity. Mouse liver alcohol dehydrogenase oxidized ethanol and alkyldiols, including PD. PD had higher affinity to mouse liver alcohol dehydrogenase than ethylene glycol (13).

4.2 Acute toxicity

In the National Library of Medicine the following toxicity data for PD are found in Chem ID plus (11-12):

LD50	species	route	dose
	guinea pig	oral	4,600 mg/kg
	mouse	intraperitoneal	2,250 mg/kg
		oral	6,300 mg/kg
	rabbit	oral	6,300 mg/kg
		skin	>20 mL/kg
	rat	oral	2,000 mg/kg

Further details of toxicity studies:

Acute oral toxicity for rats was tested in 5 Carworth-Wistar male rats with a weight of 90 to 120 g. The oral administrated dose was logarithmically increased with a factor of 2. The substance tested was given concentrated and diluted in water, oil or agar. The mortality was investigated during a 14 days period and expressed as LD_{50}. LD_{50} for oral PD was 5.89 g/kg body weight.

Penetration of rabbit skin was investigated with a cuff model. Four male rabbits with a weight between 2.5 to 3.5 kg were used. On the back part of their body the hair was totally shaved away. The test substance was then applied on the skin and the skin was occluded with plastic film for 24 hrs. The rabbits were immobilised during the test period. After the test period the animals were observed during 14 days to study mortality. In rabbits LD_{50} for

PD after topical administration was more than 20 mL/kg which was the highest dose that was tested.

In another acute toxicity protocol a group of 6 rats were receiving concentrated vapour inhalation of PD for 8 hrs. None of the rats died.

4.2.1 Chronic toxicity

No studies are yet available on chronic toxicity (repeat dose) or reproductive toxicity of PD. However, long term exposure data in medical reports available from workers chronically exposed for PD for many years, do not indicate increased morbidity or mortality among those workers (11).

4.2.2 Genotoxicity

Results from a GLP performed Ames test (Salmonella Thyphimurium Reverse Mutation Assay) are negative (BASF 40M0153/924092) (12). Hence, there are no indications of any mutagenic toxicity for PD. No direct carcinogenicity tests have been performed *in vivo*. The absence of genotoxicity *in vitro* indicates a very low carcinogenic potential of PD *in vivo*.

4.2.3 Skin and eye irritation tests

Primary irritation tests were performed on shaved skin of 5 albino rabbits. The skin was exposed to the test substance for 24 hrs and the effect was assessed using a 1 to 10 scale where 1 means no irritation and 10 maximum irritation. PD had a score of 1 which means that no skin irritation was seen (12). PD was also installed in the eye (conjunctiva) of 5 albino rabbits. PD induced only a very mild eye irritation with an assessment score of 2 on the scale 1-10 (12).

4.2.4 Photo toxicity tests

Pentane-1,5-diol does not absorb electromagnetic waves in the long-wave UV range, and is not expected to act as a photo-sensitizer nor to cause photo-toxic/photo-allergic skin reactions (14).

4.2.5 Reproductive toxicity

No studies are yet available.

5. SKIN PENETRATION

5.1 *in vitro* percutaneous absorption

The percutaneous absorption of active ingredients in cream formulations containing either PD or propane-1,2-diol has been compared using the diffusion cell model (6-7, 16). These *in vitro* experiments showed that PD enhanced the percutaneous absorption of the active ingredients mometasone furoate (7, 16), hydrocortisone (7, 16), triiodothyroacetic acid (7, 16) or terbinafine (6).

5.1.1 Tiratricol release

Triac, a thyroid hormone analogue, was added to Essex cream (Schering-Plough) containing either 10% propylene glycol (propane-1,2-diol) or 10% PD. Using a multi-membrane system the absorption of Triac was 25% higher with PD compared to propylene glycol (7, 16).

5.1.2 Percutaneous absorption of mometasone furoate (Elocon)

In a further study a cream containing 0.1% mometasone furoate and 25% PD (Elocon novum) was prepared according to GLP by Apoteket AB, Stockholm, Sweden. The cream was prepared by dissolving mometasone furoate in PD and then mixing with Essex cream (Merck) the normal way a cream formulation is prepared (16). This cream was compared with the commercial available 0.1 % mometasone furoate (Elocon) cream containing 12 % hexylene glycol. The percutaneous absorption of the two creams was compared *in vitro* using fresh human skin and the diffusion cell technology. The creams were then placed on top of the skin piece (stratum corneum site up). Samples from the receptor site of the skin piece were taken at 30 minutes intervals for 48 hrs. The mometasone furoate concentration in the receptor fluid was analysed with HPLC. After 48 hrs the amount of cream left on top of the skin piece was measured. There were no significant difference between Elocon and Elocon Novum cream in the amount of mometasone furoate that was absorbed through the skin and into the skin. However, there was a significant difference in the amount of cream that was still present on the skin at the end of the experiment; 29 mg for Elocon cream and 12.4 mg for Elocon Novum cream. This difference may explain the greasiness of Elocon cream which is currently a great disadvantage with Elocon (hexylene glycol based) and that was not present at all in Elocon Novum (PD based). It was also noted that the Elocon cream has a musty odour which was not the case with the Elocon Novum cream.

5.1.3 Percutaneous absorption of hydrocortisone

In another experiment the percutaneous absorption was investigated *in vitro* of hydrocortisone 1% in Essex cream in combination with either propane-1,2-diol or PD. In this model human breast skin was used (7, 16). The skin pieces were 250 µm and transferred to a diffusion cell. The test cream was applied on the stratum corneum site of the skin and the receptor fluid contained 30% ethanol and 70% PBS. Both the absorption of hydrocortisone through the skin and the absorption into the skin were measured. The absorption through the skin was increased 12 times with propylene glycol and 4.4 times with PD. However, the amount of hydrocortisone detected in the skin was 50% higher with PD compared to propylene glycol. The results are very interesting because they indicate that PD will increase the absorption of hydrocortisone into the skin. However, propylene glycol may also increase the penetration of hydrocortisone through the skin giving a risk for systemic side effects. This penetration was much lower with PD.

5.1.4 Percutaneous absorption of terbinafine

A hydrogel containing 1 % terbinafine alone or in combination with 5 % or 20 % of either PD or propane-1,2-diol was prepared (6). Fresh human skin was used through the entire study, which was placed in a continuous flow diffusion cell with the test gels on top of the skin. Samples were collected from the receptor fluid and analysed with HPLC. The amount of gel left on the skin after completion of each test was weighed and the amount of drug in the skin was also analysed. The results showed that addition of both diols (propane-1,2-diol and PD) to the gel increased the percutaneous absorption of the drug. The most efficient absorption enhancer in this comparison was 5 % of pentane-1,5-diol.

6. EFFECTS IN HUMANS

6.1 Pharmacokinetics and product metabolism in humans

Investigations on the water binding capacity and of enhancement of drug absorption have been performed *in vitro* using human fresh skin. (16). In rabbit PD is metabolized to glutaric acid and further to carbon dioxide (8), and it has been shown in mouse that the alcohol dehydrogenase system is involved (13). It is reasonable to assume the same system is utilized in humans. The cutaneous absorption, metabolism and excretion of PD have been performed in a study in 12 healthy volunteers (see section 6.3).

6.2 Clinical Safety and Efficacy

Results from both pre-clinical and clinical assessments with PD carried out so far indicate that the substance is safe and well tolerated.

By comparison propane-1,2-diol is also widely used in clinical dermatology, which has been classified by the FDA as "safe for use in food, cosmetics and medicines". It has been reported to induce eczematous skin reactions of toxic, and, more rarely, an allergic nature (23-24). Several reports on patients developing contact dermatitis following use of propane-1,2-diol are available (23-25).

In animal experiments skin and eye irritation tests with PD were negative (9). PD has low oral toxicity compared to other diols. Ames test results (*Salmonella typhimurium* reverse mutation assay) were negative; hence there is no indication for mutagenicity caused by PD (12). PD has a documented low toxicity in animal models of oral, topical (skin), intravenous and inhalation routes of administration (8-9, 11-12). The absence of genotoxicity *in vitro* indicates a very low carcinogenic potential of PD *in vivo*

No studies are yet available on chronic toxicity (repeat dose) or reproductive toxicity of PD. However, long term exposure data in medical reports available from workers chronically exposed for PD for many years, do not indicate increased morbidity or mortality among those workers (12).

6.2.1 Safety and tolerability in healthy volunteers

PD was found to be safe and well tolerated when tested by healthy volunteers. Assessments included photo patch tests, patch tests after single as well as repeated application, and sensitization test acc. to Magnusson (14, 17-18).

Patch tests with single application were carried out on 30 healthy volunteers with no known history of allergic hypersensitivity and no visible skin diseases. The patch tests involved topical application of the test substance RECAPEEN containing the active ingredient PD (5%), on the skin of the inner side of the forearms and subsequent assessments, after penetration of the test substance into stratum corneum, of its putative provocation of a local immune response (14, 17). PD was applied on a patch of filter paper, placed on an occlusive, impermeable sheet and fixed on the skin with Leucotest®. After 24 hrs. the test patch package was removed and the test area on the forearms was assessed by a dermatologist immediately after, 48 and 72 hrs after removal of the test patch. The assessments were carried out under standardized light conditions. There was no evidence of primary skin irritation, allergic hypersensitivity or photo-sensitivity seen in any of the participating healthy volunteers (14, 17).

In parallel with the single application patch test described above, the test substance was applied contralaterally to the inside of the lower arm and the test skin area exposed to a predefined dose of UV-A light (30 J/sq.cm) and UV-B light (0.05 J/sq.cm) (14). The irradiation source was a Waldmann UV800 irradiation unit fitted 1:1 with UV-A and UV-B tubes (Philips TL20W/09N and Sylvania F75 20WUV6). The test skin area is then covered by an occlusive, water and light impermeable sheet, and was subsequently assessed by a dermatologist after 24, 48 and 72 hrs and again a further 3 days after removal of the test patch. It could be concluded that PD does not absorb electromagnetic waves in the long-wave UV range, does not appear to act as a photo-sensitizer, and did not cause photo-toxic/photo-allergic skin reactions or hyperpigmentation in healthy volunteers (14).

Patch tests with repeated application were carried out on 20 healthy male subjects with no pathological skin/scalp findings. The tests involved scalp wash using the test substance RECAPEEN, containing the active ingredient PD (5 %), at least twice daily over a period of four weeks. No other hair care products were to be used during the test period. The skin of the scalp was examined at regular intervals by a dermatologist. It was assumed that if the test substance caused any sensitization of the skin area involved, that should result in clinically relevant detectable skin reactions. At the end of the four-week test period a single application patch test was carried out and assessed as described above. The dermatological assessments could conclude that test substance containing PD was well tolerated over the four-week test period as well as during/after the subsequent patch test. No skin reactions, no symptoms of skin irritation nor hyper sensitization were seen (14, 17)

A sensitization test according to Magnusson was carried out on 30 healthy volunteers with no known history of allergic hypersensitivity and no visible skin diseases. The patch test involved the test substance NOQ, containing the active ingredient PD in 25 %, and was carried out as described above (18) and repeated one week later, and again at week 6, i.e. after four weeks. The results concluded that there was no evidence of primary skin irritation or allergic hypersensitivity, and the patch tests of all 30 test subjects were negative after 24, 48 and 72 hrs (18).

6.3 Cutaneous absorption of topical applied PD

A cutaneous absorption study of topical applied PD to the skin of healthy human volunteers has been performed at the Clinical Trial Unit, R&D Centre, Skåne University Hospital. A 25 % PD gel was applied twice, 12 hours apart, on the back of 12 volunteers (10).

EFFICACY RESULTS

At the time of the last sample there was still measurable concentration of PD in plasma indicating a medium long elimination time and due to the design of the study deposition characteristics of PD could not be defined.

PD is eliminated by biotransformation to glutaric acid and excreted unchanged into urine.

At the time of the last serum concentration at 24h post first treatment the samples showed various levels of glutaric acid in serum and no individual had reached zero. An increasing level over time is found both in serum and urine in different individuals also for glutaric acid levels.

Glutaric acid in urine was detected in all subjects also before treatment. The data suggest that the risk of accumulation of PD at therapeutic dose is low. PD 25% gel used as a topical application was safe and well tolerated (10).

6.4 Reported cases of adverse reactions

So far two isolated case reports from Italy on contact sensitization following use of cosmetic creams with pentylene glycol being one of the ingredients, were found in the literature (26-27). The problem is that although pentylene glycol from a strict chemical point of view is pentane-1,5-diol it is often instead 1,2-pentane diol that is used. Although very few safety data are available for 1,2-pentane diol this diol is used in several cosmetic products world vide. As the contents of the cosmetic creams include other ingredients as well, and because of the very small number of cases (1 case in each of the two case reports) it is not possible to estimate the overall risk based on data from these two isolated reports.

Case report 1 (26):

A 39-year-old man in Italy with scaling erythematous dermatitis was using an emollient cream (Resvelife, Nuova ICT, Italy), containing resveratrol as active ingredient and pentane-1,5-diol (could be 1,2-pentane diol as well) as an excipients, developed an exudative and itchy dermatitis which slowly cleared when the cream was discontinued. Using patch testes it was shown that the patient reacted strongly against pentane diol and less strongly against resveratrol, though it was considered to have a low risk of allergic and irritant skin reactions. Resveratrol (3,5,4′-trans-trihydroxystilbene) is a phenolic phytoalexin produced in red grape skins and in various other plants. It is concluded that there was contact sensitization to pentane diol with a possible co-sensitization to resveratrol. It is not possible to estimate the risk of contact sensitization on the basis of one case-report.

Case report 2 (27):

A 56-year-old female consulted her doctor because of facial dermatitis with swelling of the eyelids over the last week. This patient was non-atopic and had no dermatological history/history of contact allergy. She had used toleriane riche cream (La Roche Posay Laboratories, La Roche Posay, France) for 1 month. She did not use any other products. Patch testing resulted in a 2+ reaction to the toleriane riche cream. Two months later the patient was tested with the ingredients of the cream, with negative result in the single application patch test. Meanwhile patient started using L. Widmer body lotion, which also provoked facial dermatitis. Upon a retest using the Repeated Open Application Test ROAT) both toleriane riche cream and L. Widmer body lotion resulted in a 3+ reaction after 2 days. The similar properties shared by pentylene glycol and propylene glycol are discussed, as well as their possible role as allergens and the possibility of cross-reaction to both substances. The importance of ROAT as a tool in detecting the causative allergen is also discussed.

At present the possibility that the two case reports (26-27) in fact refer to pentane-1,2-diol rather than PD cannot be ruled out. Hitherto several attempts to contact the manufacturers in order to clarify which the actual ingredients were that were used in the above products have failed.

7. CONCLUSION

Pentane-1,5-diol ($C_5H_{12}O_2$) belongs to the group of aliphatic diols or glycols, known to be used as solvents, anti-freezing agents and vehicles in pharmaceutical and cosmetic preparations (3-5, 7, 16, 20, 21,28). Some aliphatic diols have an anti-microbial effect (1, 2,

15, 16, 20, 21, 28). It is suggested that PD is a more effective anti-microbial agent with superior antibacterial activity over propane-1,2-diol (1, 16). Unlike hexylene glycol, 1,2-pentane diol and other diols, all characterised by bad odour, PD is odourless (16). Compared to propane-1,2-diol, PD was superior in enhancement of the absorption of terbinafine, tiratricol release from Essex cream and hydrocortisone (6-7).

In animal models of oral, topical (skin), intravenous and inhalation toxicity PD has shown a very low toxicity and absence of symptoms of skin and eye irritation (8-9, 11-14, 16). Genotoxic screening tests are negative for PD (11-12). The absence of genotoxicity *in vitro* indicates a very low carcinogenic potential of PD *in vivo*. PD does not absorb electromagnetic waves in the long-wave UV range, and is not expected to act as a photo-sensitizer nor to any cause photo-toxic/photo-allergic skin reactions (14).

A comprehensive impurity study was performed on 1,5-pentanediol to identify all other diols present using GS/MS (22). The 1,5-pentanediol was over 98% in purity with only 0.28% unknown substances. These unknown substances were not diols. The data clearly show that there was no 2,5-hexanediol present as an impurity. (Appendix 1)

PD has shown high activity against both multi-resistant and sensitive bacteria and against herpes virus and fungi (1-2, 15). It is a good preservative in various topical formulations and acts as an effective vehicle, capable of increasing the solubility and percutaneous absorption of other pharmaceutical substances (4, 6-7, 16). PD was shown to be superior in enhancing the absorption of terbinafine compared to e.g. propane-1,2-diol (6).

Several substances for topical use can be easily mixed with PD (6-7, 16). In that way PD will increase their activity and the usefulness of the formulation.

PD was found to be safe and well tolerated when tested by healthy volunteers. There was no evidence of any primary skin irritation, allergic hypersensitivity or photo-sensitivity seen in any of the participating healthy volunteers (11, 12, 14, 17, 18). The cutaneous absorption of PD was investigated in 12 healthy volunteers in a study performed in Lund, Sweden. PD was metabolized to glutaric acid and water. The data suggest that the risk of accumulation of PD at therapeutic dose is low and that PD 25% gel used as a topical application was safe and well tolerated.The therapeutic efficacy and clinical safety of PD was successfully tested in randomised, controlled, double-blind clinical trials as an ingredient in formulations for the topical treatment of herpes simplex I, atopic dermatitis and hair loss (19-21).

To date more than 300 patients with the diagnosis of herpes labialis, atopic dermatitis, or hair loss have been treated in clinical trials investigating the efficacy and safety of PD. In these studies patients have been exposed to various concentrations of PD (5-50%) and treatment durations up to 6 months. No adverse events specifically attributable to PD were reported in any of these studies. In a product launched worldwide over 1 000 000 units have already been sold and no adverse events have been reported. Except for a slight burning sensation in the skin after application reported in the atopic dermatitis study with 64 patients enrolled, two cases in the Hydrocortisone/PD group and two in the Hydrocortisone group, no adverse events specifically associated with PD have been reported in any of the clinical studies (20). Given the fact that all patients, in both groups, received study treatments containing 1% hydrocortisone, and that equal numbers, 2 patients in each group, reported burning sensation, it is not possible to draw any conclusions whether or not this adverse event could be attributed specifically to PD.

Since 2010 products for hair care, nail care, lip care and skin care (5-25% PD) have been on sale and accumulated over 1.5 million units in sales with no reported side effects.

So far two isolated case reports from Italy on contact sensitization following use of cosmetic creams with PD being one of the ingredients, were the only adverse events reported (26-27). As the contents of the cosmetic creams include other ingredients as well, and because of the very small number of cases (1 case in each of the two case reports) it is not possible to estimate the overall risk based on data from these two isolated case reports. At present the possibility that the two case reports in fact refer to pentane-1,2-diol rather than pentane-1,5-diol cannot be ruled out. Hitherto attempts to contact the manufacturers in order to clarify which the actual ingredients were that were used in the above products have failed.

8. REFERENCES

1. Faergemann J, Fredriksson T. The antimycotic activity in vitro of five diols. Sabouraudia 1980;18:287-293
2. Faergemann J. Pityrosporum yeasts – what's new? Mycoses 1997;40(Suppl 1):29-32
3. Rowe VK, Wolf MA. Glycols; Table 50.1 Physical and chemical properties of common glycols (diols). In: Clayton GD and Clayton FE (eds). Patty's Industrial Hygiene and Toxicology (3rd ed.), John Wiley & Sons, New York. 1982;3818-3819
4. Frankenfeld JW et al. Preservation of grain with aliphatic 1,3-diols and their esters. J Agric Food Chem 1975;23:418-425
5. Frankenfeld JW, Miller SA. High energy food supplements comprising linear aliphatic 1,3 diols. US patent 3791241, 1974, Feb 12, pp. 0-10
6. Evenbratt H, Faergemann J. The effect of pentane-1,5-diol and propane-1,2-diol on the percutaneous absorption of terbinafine. Acta Dermato-Venereologica 2009;89:126-129
7. Faergemann J, Wahlstrand B, Hedner T, Johnsson J, Neubert RHH, Nyström L, Maibach I H. Pentane-1,5-Diol as a percutaneous absorption enhancer. Arch Dermatol Res (2005); 297: 261-265
8. 10. Gessner PK et al. Studies in detoxification; 80. The metabolism of glycols. Bioch. 1960;74:1-5
9. Smyth HF et al. Range finding toxicity data: List VI. Ind Hyg Assoc J. 1962;23:95-9
10. An open bioavailability single center study in healthy subjects to evaluate the pharmacokinetic profile od Pentane-1,5-diol after topical application. Clinical Study Report. 2013. EudraCT No: 201-002084-97. Report on file.
11. National Library of Medicine. ChemID plus Advanced Full Record. http://chem.sis.nlm.nih.gov/chemidplus.
12. IUCLID Dataset, European Commission 18 FEB 2000, European Chemicals Bureau substance ID 111-29-5.
13. Holman Jr. NW et al. Alkyldiol antidotes to ethylene glycol toxicity in mice. Toxicol Appl Pharmacol 1979;49:385-392
14. Dermatest®. Dermatological Report on a Human Photo-Patch Test. Test on Primary Skin Irritation and Allergic Hypersensitivity and Photo-Sensitivity on Human Subjects. Münster (Germany) 29 April 2005. RECAPEEN
15. Faergemann J, Hedner T, Larsson P. The in vitro Activity of Pentane-1,5-diol against Aerobic Bacteria. A New Antimicrobial Agent for Topical Usage? Acta Derm Venereol 2005;85:203-205.
16. Sundberg JJ, Faergemann J. A comparison of pentane-1,5-diol to other diols for use in dermatology. Expert Opinion in Investigational Drugs 2008;17:601-610
17. Dermatest®. Dermatological Expertise on a Four-Week Clinical Dermatological Application Test with Subsequent Patch Testing in Accordance with International Guidelines. Münster (Germany) 23 May 2005. RECAPEEN

18. Dermatest®. Specialist Dermatologicacl Report on a Sensitization Test According to Magnussen (Repetitive Epicutaneous Test) for Primary Irriation and detection of Sensitization in Humans based on Three Applications within 6 Weeks. Münster (Germany) 4 August 2006. NOQ

19. Busch R, Graubaum H-J, Gruenwald J, Faergemann J. Therapeutic Effect of 1,5-pentanediol for Herpes Simplex Labialis: a Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Adv Ther 2009; 26(7):719-727

20. Sandström MH, Särnhult T, Hedner T, Faergemann J. Treatment of atopic dermatitis with 1% hydrocortisone and 25% pentane-1,5-diol: Effect on staphylococcus aureus. Acta Derm Venereol 2006;86:1-2.

21. Faergemann J, Hedner T. The effect of A100 gel, on hair growth and hair quality: An explanatory study. Journal of Cosmetics, Dermatological Sciences and Applications 2016;6:19-23

22. Validation of the Determination of Related Substances in 1,5-Pentanediol by GC/MS according to Ph.Eur. 2.2.28. 2007. Report on file

23. Swensson Å. Nordiska Expertgruppen för gränsvärdesdokumentation 44. Propylene glycol. Arbete och hälsa, vetenskaplig skriftserie. 1983;27:1-38

24. Andersen KE, Storrs FJ. Skin irritation caused by propylene glycols. Hautarzt 1982;33:12-14

25. Heine G, Schnuch A, Uter W, Worn M. Frequency of contact allergy in German children and adolescents patch tested between 1992 and 2002:results from the Information Network of Departments of Dermatology and the German Contact Dermatitis Research Group. Contact Dermatitis 2004;51:111-117

26. Gallo R et al. Allergic contact dermatitis from pentylene glycol in an emollient cream, with possible co-sensitization to resveratrol. Case Report. Contact Dermatitis 2003:48:176-177

27. Kerre Stefan. Allergic contact dermatitis to pentylene glycol in a cosmetic cream. Case Report. Contact Dermatitis 2008:58:122-123

28. Karami N, Alsterhol M, Faergemann J. The in vitro activity of chlorhexidine and pentane-1,5-diol and their combination on Candida albicans, Staphylococcus aureus and Propionibacterium acnes. Acta Derm Venereol 2009;89:514-547

APPENDIX 1:

Internal specification:

SPECIFICATION STARTING MATERIAL Page 1 (1)

PRODUCT: 1,5-Pentanediol
Article no.: 800128
Document no.: SSM1004 **Version: 04**
Date: 2015-03-19

Reanalyse date: 2 years from sampling date (date sent to laboratory)

Parameter	Specification	Method
Appearance	Clear, colourless, slightly viscous liquid	Visual inspection
ID: Refractive index	1.447 – 1.451	Ph. Eur 2.2.6
Colour*	colourless, ≤ B_9	Ph. Eur 2.2.2
Water (Karl Fischer)*	NMT 0.2 %	Ph. Eur 2.5.12
Assay*	NLT 97.0 %	Ph. Eur 2.2.28
Related substances*		Ph. Eur 2.2.28
- Other diols	NMT 3.0 %	
- Unknown substances	NMT 0.5 %	
- Cyclic diols	Not detectable	

Certificate of Analysis

CERTIFICATE OF ANALYSIS

Customer:

Test substance: **1,5-Pentanediol, Bulkware 100 ml**

Batch No.: 0009195737 **Retest date:** --/----

Test date: 21 October 2014 *Lab code: 22595/2141028-004*

Test Parameters	Test Method	Test Results	Specification
Appearance	visual test	conforms	clear, colourless, slightly viscous liquid
Colour	Ph.Eur. 2.2.2	colourless, < B_9	colourless, ≤ B_9
Water (Karl-Fischer)	Ph.Eur. 2.5.12	0.02 %	≤ 0.2 %
Assay 1,5-pentanediol	Ph.Eur. 2.2.28	98.1 %	≥ 97.0 %
Related substances[1)]	Ph.Eur. 2.2.28		
• 1,4-Butanediol		< 0.05 %	for information
• 1,4-Pentanediol		< 0.05 %	for information
• 1,2-Hexanediol		< 0.05 %	for information
• 1,5-Hexanediol		1.02 %	for information
• 1,6-Hexanediol		0.56 %	for information
• 1,2-cis-Cyclohexanediol		< 0.05 %	for information
• 1,2-trans-Cyclohexanediol		< 0.05 %	for information
• 1,3-cis-Cyclohexanediol		< 0.05 %	for information
• 1,3-trans-Cyclohexanediol		< 0.05 %	for information
• 1,4-cis-Cyclohexanediol		< 0.05 % (0.01 %)	for information
• 1,4-trans-Cyclohexanediol		< 0.05 %	for information
• Unknown impurities		0.27 % (RRT 1.068[2)]) 0.01 % (RRT 1.287[2)])	≤ 0.5 %
• Total other diols		1.58 %	≤ 3.0 %
• Total cyclic diols		< 0.05 % (0.01 %)	≤ 0.05 %
• Total unknown impurities		0.28 %	≤ 0.5 %

[1)] disregard limit 0.05 %
[2)] according to mass spectra linear diols

The batch meets the requirements of the quality specification SSM1004.03 with regard to the parameters under examination

Aschau, 12 November 2014

AN:C.DATUM: 2014-11-19

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: November 11, 2016

SUBJECT: Propanediol

Anonymous. 2016. 1,3-Propanediol and skin penetration enhancement: A literature review.

Anonymous. 2016. Propanediol: Method of manufacture and composition.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

November 8, 2016

1,3-Propanediol and Skin Penetration Enhancement: A Literature Review

Summary:

The literature was reviewed for information related to the skin penetration enhancement properties of propylene glycol (PG), 1,3-propanediol (PDO), and ethanol. The results of this review along with a structure activity relationship comparison between PG and PDO, suggests that the skin penetration enhancement properties of PDO are similar to that of PG and ethanol. Since PDO is of very low toxicity, is expected to act similarly to a substance (ethanol) that has a safe history of use as a skin penetration enhancer, and the formulations containing PDO consist of low toxicity components, this skin penetration enhancing property of PDO will not increase the risk from using formulations containing PDO.

Background:

The property of skin (dermal) penetration enhancement refers to the ability of a substance to enhance the penetration of another substance (permeant) through the skin, when they are applied together in a solution on the skin (topical application). There are various mechanisms by which skin penetration enhancers work and some work predominately by one mechanism, while others may use multiple mechanisms. Skin penetration enhancement does not necessarily correlate with skin penetration/ permeation of the enhancer alone. That is, an enhancer can slowly or poorly penetrate the skin but affect the skin in a way that it still enhances the penetration of other substances. Skin penetration is also dependent on the physical chemical properties of the substance intended to be enhanced or transported, and well recognized skin penetration enhancers may enhance the penetration of some substances better than others. The most widely used application of skin penetration enhancers is transdermal delivery of drugs/therapeutics to treat medical conditions. Physical treatments to skin such as hydration, UV-irradiation, and temperature may also enhance the penetration of materials through the skin.

The three basic layers of the skin include the stratum corneum (SC), epidermis, and dermis with sweat ducts and hair follicles passing through all three layers. The SC is the most effective barrier among these three layers and mechanisms for enhancement target the SC. The SC consists of flattened elongated cells "glued" together in a lipid and protein-bridge matrix that varies in thickness and barrier properties with health, age, race, and hydration (Buck, 2004). Mechanisms by which enhancers affect skin permeability include 1) disruption of the intercellular lipid structure, 2) interaction with intracellular proteins of the SC, and 3) improvement of partitioning of a drug, co-enhancer, or co-solvent into the SC (Barry, 1991; Benson, 2005).

Alcohols (e.g., ethanol) have been shown to increase permeability by disordering or "fluidizing" the lipid structure of the SC. Some alcohols may also extract lipids, forming aqueous channels within the SC that increase permeability. However, many enhancers that act on lipid bilayers also cause skin irritation and have limited use as enhancers for this reason. Ethanol and PG behave similarly and increase permeant (e.g., many drugs) partitioning into and solubility within the SC. Ethanol was one of the first enhancers incorporated into transdermal systems and showed a shifting of the solubility of the skin closer to that of the permeant. Synergistic skin penetration enhancement effects have been shown between PG and other agents such as azone, oleic acid, terpenes, N-methylpyrrolidone, and urea analogues, where PG and the other agents act by different but complementary mechanisms. Propylene glycol may act to increase the concentration of both the permeant and the co-enhancer in the SC. Ethanol has also been used as a co-solvent in many applications. Some substances such as DMSO, use multiple mechanisms by disturbing intercellular organization, extracting SC lipids, interacting with SC cells, and facilitating lipid drug partitioning (Benson 2005).

Results:

The potential for skin penetration enhancement of PDO is based on two pieces of scientific literature and an expert structure activity relationship assessment (Dr. Grace Tier, 2009).

One study directly comparing the skin penetration enhancement of a hydrophobic substance by PG and PDO was identified. This paper was published in 1983 by Mollgaard and Hoelgaard where excised human abdominal skin was exposed to a variety of substances with the hydrophobic permeant estradiol, to determine relative enhancement of estradiol through the skin. In this paper propylene glycol, PDO, and glycerol were three of the 21 substances tested. Seven other glycols were also tested and compared for their enhancement properties. The authors reported steady-state flux (ug cm^{-2} h^{-1}) and lag time (hours) for estradiol of 0.12, 0.11, and 0.037 ug cm^{-2} h^{-1} and 18, 39, and 26 hours in the presence of PG, PDO, and glycerol, respectively. PG and PDO enhanced estradiol permeation in the skin to similar degrees at steady state, while the lag time for steady state to occur for estradiol in the presence of PDO was about two times longer than that for PG. This suggests for hydrophobic substances, that PDO and PG will similarly enhance skin penetration. Also noted in the paper was that steady-state flux decreased with increasing number of carbons in the glycols tested (ethylene glycol > propanediol > butanediol > pentanediol).

Another paper was published in 2008 by Liang and Yang where cadaver skin was exposed to oleic acid, PDO, azone, or glycerol as enhancers, with diphenhydramine hydrochloride (DH) to determine relative skin penetration enhancement properties. This paper was published in Zhongguo Yaofang 19(31):2414-2416, was written in Chinese, and only a cryptic abstract was available describing the results. In the absence of further detail, only limited conclusions were drawn. Penetration enhancement of DH was in the following order: oleic acid > 1,3-propanediol > azone > glycerol. Since azone is a well known skin penetration enhancer, this suggests that 1,3-propanediol will have skin penetration enhancing properties.

An expert structure activity relationship (SAR) modeler explored the feasibility of developing a QSAR model for a subset of polyols with regard to skin penetration enhancement. Sufficient literature was available to develop relationships but not to construct a model; however, it was concluded that there is likely no significant difference between PG and PDO with respect to skin penetration enhancement given their Log P values and size (Tier, 2009). The branching of PG relative to the linear structure of PDO is not expected to result in a significant difference in skin penetration enhancement.

Discussion/Conclusions:

The toxicity of PDO is well characterized. It is of low acute oral, dermal, and inhalation toxicity. PDO is not considered to be a skin irritant or sensitizer. It is considered to be a slow skin penetrator. PDO is low in repeat-dose oral toxicity and it is not a genetic or developmental toxin. It has low toxicity to aquatic organisms and will not persist or bioaccumulate in the environment. PDO has received Generally Recognized As Safe (GRAS) status from an expert panel of scientists indicating its safe use as a food additive under relatively broad GRAS conditions of use (US EPA HPVIS, 2009; Wood, 2009). Overall, the toxicity for PG (OECD SIDS, 2001) and PDO appear similar with the exception of skin reactions. In a 200-person human skin patch test PG produced significant irritation, while PDO produced no clinically significant irritation (Eisenberg, 2007).

The data suggest that the skin penetration enhancement properties of PDO are likely similar to that of PG. Although a direct comparison between ethanol and PDO skin penetration enhancement was not identified, it is well recognized that PG and ethanol act similarly; therefore, PDO and ethanol would be expected to act similarly. Since PDO is of very low toxicity, is expected to act similarly to a substance (ethanol) that has a safe history of use as a skin penetration enhancer, and the formulations containing PDO consist of low toxicity components, this skin penetration enhancing property of PDO will not increase the risk from using formulations containing PDO.

References

Barry BW (1991) Lipid-Protein-Partitioning Theory of Skin Penetration Enhancement. *J Controlled Release* 15:237-248.

Benson, HAE (2005) Transdermal Drug Delivery: Penetration Enhancement Techniques. *Current Drug Delivery* 2:23-33.

Buck P (2004) Skin Barrier Function: Effect of Age, Race and Inflammatory Disease. *Int. J. Aromatherapy* 14:70-76.

Eisenberg RR (2007) H-27814 and H-27815: Exclusive Repeated Insult Patch Test Study in Human Volunteers. Consumer Product Testing Co.

Liang Y and Yang X (2008) Effect of Four Penetration Enhancers on Percutaneous Absorption of Diphenhydramine Hydrochloride. *Zhongguo Yaofang*, 19(31):2414-2416.

Mollgaard B and Hoelgaard A (1983) Permeation of Estradiol Through the Skin – Effect of Vehicles. *Intl. J. Pharmaceutics*, 15:185-197.

OECD SIDS SIAR (2001) SIDS Initial Assessment Report for 1,2-Dihydroxypropane (CAS # 57-55-6), UNEP Publications.

Tier G (2009) Assessment of Skin Penetration Enhancement – Brief Update March 6, 2009. (1,3-propanediol CAS # 504-63-2)

US EPA HPVIS (2009) Website for robust summaries of 1,3-propanediol toxicity study information. http://iaspub.epa.gov/oppthpv/quicksearch.display?pChem=25301188

Wood D (2009 Propanediol GRAS Status, April 1, 2009 Customer Letter.

November 11, 2016

Propanediol Method of manufacture: Fermentation of glucose followed by distillation.

Impurity profile: Propanediol production batches average greater than 99.98% purity. No other component is greater than 0.10%. The largest other component is water, and there are no known monomer, amine, or heavy metal impurities present.

COMPOSITIONAL INFORMATION

Chemical Name	INCI Name	CAS #	EINECS #	Quantity
1,3 Propanediol	Propanediol	504-63-2	207-997-3	≥ 99.8 %*

*Batches average 99.98. No other component greater than 0.10%.

Harmonized Tariff #: 2905-39-90-00

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: January 23, 2017

SUBJECT: Methylpropanediol

TKL Research, Inc. 2010. Repeated insult patch test of a facial serum containing 21.2% Methylpropanediol.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

TKL RESEARCH

REPEATED INSULT PATCH TEST

Facial serum containing 21.2% Methylpropanediol

TKL STUDY NO. DS100810/100910-2

[redacted] **STUDY NO. DT036656**

CONDUCTED FOR:

[redacted]

Attention: [redacted]

DATE OF ISSUE:

April2, 2010

TABLE OF CONTENTS

SIGNATURES 1
STATEMENT OF QUALITY CONTROL 1
TITLE OF STUDY 2
SPONSOR 2
STUDY MATERIAL 2
DATE STUDY INITIATED 2
DATE STUDY COMPLETED 2
DATE OF ISSUE 2
INVESTIGATIVE PERSONNEL 2
CLINICAL SITES 2
SUMMARY 3
1.0 OBJECTIVE 4
2.0 RATIONALE 4
3.0 STUDY DESIGN 4
3.1 STUDY POPULATION 4
3.1.1 Inclusion Criteria 4
3.1.2 Exclusion Criteria 4
3.1.3 Informed Consent 5
3.2 DESCRIPTION OF STUDY 5
3.2.1 Outline of Study Procedures 5
3.2.2 Study Flow Chart 6
3.2.3 Definitions Used for Grading Responses 7
3.2.4 Evaluation of Responses 7
4.0 NATURE OF STUDY MATERIAL 8
4.1 STUDY MATERIAL SPECIFICATIONS 8
4.2 STORAGE, HANDLING, AND DOCUMENTATION OF STUDY MATERIAL 8
4.3 APPLICATION OF STUDY MATERIAL 8
4.4 DESCRIPTION OF PATCH CONDITIONS 8
5.0 INTERPRETATION 8
6.0 DOCUMENTATION AND RETENTION OF DATA 9
7.0 RESULTS AND DISCUSSION 9
8.0 CONCLUSION 10
9.0 REFERENCES 10

APPENDICES

I SUMMARY TABLES
II DATA LISTINGS
III INFORMED CONSENT DOCUMENTS

SIGNATURES

This study was conducted in compliance with the requirements of the protocol and TKL's Standard Operating Procedures, and in the spirit of GCP ICH Topic E6.[1] The report accurately reflects the raw data for this study.

Jonathan S. Dosik, MD
Dermatologist
Principal Investigator

4/2/10
Date

Kathleen Georgelan
Kathleen Georgelan
Director, Dermatologic Safety Testing

Date

Michelle Medina
Clinical Research Coordinator

4/2/10
Date

STATEMENT OF QUALITY CONTROL

The Quality Control Unit of the Dermatological Safety Department conducted a 100% review of all study-related documents. The protocol was reviewed prior to the start of the study, and the medical screening forms and informed consent documents were reviewed in-process of the study. The regulatory binder and study data were reviewed post-study to ensure accuracy. The study report was reviewed and accurately reflects the data for this study.

[1] ICH Topic E6 "Note for guidance on Good Clinical Practices (CPMP/ICH/135/95)" – ICH Harmonised Tripartite Guideline for Good Clinical Practices having reached Step 5 of the ICH Process at the ICH Steering Committee meeting on 1 May 1996.

TITLE OF STUDY

Repeated Insult Patch Test

SPONSOR

[redacted]

STUDY MATERIAL

Methylpropanediol 21.2%

Facial Serum

DATE STUDY INITIATED

January 29, 2010

DATE STUDY COMPLETED

March 11, 2010

DATE OF ISSUE

April 2, 2010

INVESTIGATIVE PERSONNEL

Jonathan S. Dosik, MD - Dermatologist
Principal Investigator

Kathleen Georgeian
Director, Dermatologic Safety Testing

Michelle Medina
Clinical Research Coordinator

CLINICAL SITES

TKL RESEARCH, INC.
4 Forest Avenue
Paramus, NJ 07652

TKL RESEARCH, INC.
1 Palmer Terrace
Carlstadt, NJ 07072

SUMMARY

One (1) study material, Formula No. Methylpropanediol 21.2% Facial Serum, was evaluated neat to determine its ability to sensitize the skin of volunteer subjects with normal skin using a semi-occlusive repeated insult patch study. Two hundred five (205) subjects completed the study.

Due to inclement weather, TKL Research Inc. was closed on February 10, 2010. Subjects came in on February 11, 2010 for the February 10, 2010 visit. On February 26, 2010 only the subjects who required a makeup reading came in due to inclement weather.

On DS100810, 38 subjects had definite erythema, no edema (+), and 3 subjects experienced definite erythema, no edema with damage to the epidermis (+D) during Induction.

One (1) subject experienced definite erythema, no edema with damage to the epidermis (+D) at the 2nd Induction reading. This product was inadvertently discontinued rather than switched to a new site under semi-occlusive conditions, a protocol deviation.

One (1) subject experienced definite erythema, no edema with damage to the epidermis (+D) at the 3rd Induction reading and refused to be patched with the product for the remainder of the study. Another subject experienced definite erythema, no edema with damage to the epidermis (+D) at the 6th Induction reading, had their patch switched to a new site under semi-occlusive conditions, and experienced no reaction for the remainder of Induction. However, the subject refused to be patched at Challenge.

On DS100910, 22 subjects had definite erythema, no edema (+), and 7 subjects experienced definite erythema, no edema with damage to the epidermis (+D) during Induction. The 7 subjects each had their patch switched to a new site under semi-occlusive conditions and experienced no reactions for the remainder of the study.

Under the conditions employed in this study, Formula No. Methylpropanediol 21.2% Facial Serum was irritation acceptable and showed no evidence of sensitization.

1.0 OBJECTIVE

The objective of this study was to determine the ability of the study material to cause sensitization by repeated topical applications to the skin of humans under controlled patch study conditions.

2.0 RATIONALE

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions. The method herein employed is generally accepted for such a purpose.

Repeated insult patch evaluation is a modified predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure. Results are interpreted according to interpretive criteria based upon published works, as well as the clinical experience of TKL Research, Inc. These interpretive criteria are periodically reviewed and amended as new information becomes available.

3.0 STUDY DESIGN

3.1 STUDY POPULATION

A sufficient number of subjects were enrolled to provide 200 completed subjects. In the absence of any sensitization reactions in this sample size (200 evaluable subjects), a 95% upper confidence bound on the population rate of sensitization would be 1.5%.

3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. were males or females, 18 to 70 years of age, in general good health;
2. were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events;
3. were of any skin type or race, providing the skin pigmentation would allow discernment of erythema;
4. had completed a medical screening procedure; and
5. had read, understood, and signed an informed consent agreement.

3.1.2 Exclusion Criteria

Individuals excluded from participation in the study were those who:

1. had any visible skin disease at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluation;

2. were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;
3. had psoriasis and/or active atopic dermatitis/eczema;
4. were females who were pregnant, planning to become pregnant during the study, or breast-feeding;
5. had a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated; and/or
6. were participating in another study or had been recruited to participate in another study concurrently.

3.1.3 Informed Consent

A properly executed informed consent document was obtained from each subject prior to entering the study. The signed informed consent document is maintained in the study file. In addition, the subject was provided with a copy of the informed consent document (see Appendix III).

3.2 DESCRIPTION OF STUDY

3.2.1 Outline of Study Procedures

Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. Prior to study entry, the subjects were screened to assure that they met the inclusion/exclusion criteria. Informed consent was obtained. Each subject was provided with a schedule of the study activities. All subjects were told to avoid wetting the patches and were asked not to engage in activities that caused excessive perspiration. They were instructed to notify the staff if they experienced any discomfort beyond mild itching or observed any adverse changes at the patch sites, while on the study or within 2 weeks of completing the study.

The Induction Phase consisted of 9 applications of the study material and subsequent evaluations of the patch sites. Prior to application of the patches, the sites were outlined with a skin marker, eg, gentian violet. The subjects were required to remove the patches approximately 24 hours after application. They returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patches applied on Friday were removed by subjects after 24 hours. The sites were evaluated on the following Monday, ie, 72 hours after patch application.[2] Following the ninth evaluation, the subjects were dismissed for a rest period of approximately 10-15 days.

Subjects who were absent once during the induction phase received a make-up (MU) patch at the last induction visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as N9G (no ninth grading).

[2] A Monday or Friday holiday could result in evaluation at 96 hours after patch application.

The Challenge Phase was initiated during the sixth week of the study. Identical patches were applied to sites previously unexposed to the study material. The patches were removed by subjects after 24 hours and the sites graded after additional 24-hour and 48-hour periods (ie, 48 and 72 hours after application). Rechallenge was performed whenever there was evidence of possible sensitization.

To be considered a completed case, a subject must have had 9 applications and no fewer than 8 subsequent readings during induction, and a single application and 2 readings during challenge. Only completed cases were used to assess sensitization.

3.2.2 Study Flow Chart

WEEK 1

DAY	ACTIVITIES
1*	Staff obtained informed consent, reviewed completed medical screening form, applied patches
2	Subject removed patches
3	Staff graded sites, applied patches
4	Subject removed patches
5	Staff graded sites, applied patches
6	Subject removed patches

WEEK 2

DAY	ACTIVITIES
1	Staff graded sites, applied patches
2-6	Same as Week 1

WEEK 3

DAY	ACTIVITIES
1-6	Same as Week 2

WEEK 4

DAY	ACTIVITIES
1	Staff graded sites; applied make-up (MU) induction patches, if required
2	Subject removed MU patches
3	Staff graded MU induction sites at MU visit
2-7	Rest period

WEEK 5

DAY	ACTIVITIES
1-7	Rest period

* Study flow starting with Week 1, Day 1, was altered when enrollment occurred on Wednesday or Friday. Study flow could be altered if a holiday occurred during the study.

WEEK 6

DAY	ACTIVITIES
1	Staff applied patches
2	Subject removed patches
3	Staff graded sites
4	Staff graded sites

3.2.3 Definitions Used for Grading Responses

The symbols found in the scoring scales below were used to express the response observed at the time of examination:

SYMBOL		REACTION
-	=	No reaction
?	=	Minimal or doubtful response, slightly different from surrounding normal skin
+	=	Definite erythema, no edema
++	=	Definite erythema, definite edema
+++	=	Definite erythema, definite edema and vesiculation

SPECIAL NOTATIONS

E	=	Marked/severe erythema
S	=	Spreading of reaction beyond patch site (ie, reaction where material did not contact skin)
p	=	Papular response > 50%
pv	=	Papulovesicular response > 50%
D	=	Damage to epidermis: oozing, crusting and/or superficial erosions
I	=	Itching
X	=	Subject absent
PD	=	Patch dislodged
NA	=	Not applied
NP	=	Not patched (due to reaction achieved)
N9G	=	No ninth grading

3.2.4 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting TKL's strict certification requirements to standardize the assignment of response grades.

4.0 NATURE OF STUDY MATERIAL

4.1 STUDY MATERIAL SPECIFICATIONS

Identification	:	Methylpropanediol 21.2%	Facial Serum
Amount Applied	:	0.2 mL	
Special Instructions	:	Volatilized for 30 minutes prior to patch application.	

4.2 STORAGE, HANDLING, AND DOCUMENTATION OF STUDY MATERIAL

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by TKL. On the basis of information provided by the sponsor, the study material was considered reasonably safe for evaluation on human subjects. A sample of the study material was reserved and will be stored for a period of 6 months. All study material was kept in a locked product storage room accessible to clinical staff members only. At the conclusion of the clinical study, the remaining study material was discarded or returned to the sponsor and the disposition documented in the logbook.

4.3 APPLICATION OF STUDY MATERIAL

All study material was supplied by the sponsor. Material was applied in an amount proportionate to the patch type or as requested by the sponsor, generally 0.2 mL or g or an amount sufficient to cover the 2 cm x 2 cm patch. The patches were applied to the infrascapular area of the back, either to the right or left of the midline, or to the upper arm.

4.4 DESCRIPTION OF PATCH CONDITIONS

Material evaluated under occlusive patch conditions is applied to a 2 cm x 2 cm Webril pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patches are secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions is applied to a 2 cm x 2 cm Webril pad. The pads are affixed to the skin with hypoallergenic tape (Micropore).

5.0 INTERPRETATION

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the challenge phase of a Repeated Insult Patch Test (RIPT) than that seen during induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours. Removal of the offending agent results in gradual improvement of the epidermal damage. The

reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the challenge phase is generally similar to that seen during induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to rechallenge the subjects who have demonstrated sensitization-like reactions to confirm that these reactions are, indeed, associated with the product. Our preferred rechallenge procedure involves the application of the product to naïve sites, under both occlusive and semi-occlusive patch conditions. Use of the semi-occlusive patch condition helps to differentiate irritant and sensitization reactions. Generally speaking, if a product is a sensitizer it will produce a similar reaction under both occlusion and semi-occlusion. Whereas, if the product has caused an irritant reaction, the reactions will be less pronounced under the semi-occlusive condition.

6.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) were designed to identify each subject by subject number and initials, and to record demographics, examination results, adverse events, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. Storage was maintained either at a TKL facility in a secured room accessible only to TKL employees, or at an offsite location which provided a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation will be available for the sponsor's review on the premises of TKL.

7.0 RESULTS AND DISCUSSION

Two hundred thirty (230) subjects between the ages of 18 and 70 were enrolled and 205 subjects completed the study (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II).

The following table summarizes subject enrollment and disposition.

Number enrolled:		230
Number discontinued:		25
Lost to follow-up:	16	
Voluntary withdrawal:	9	
Number completed:		205

Source: Table 1, Appendix I

There was 1 non-product-related adverse event (AE) reported on DS100810. See Data Listing 4, Appendix II for details.

Due to inclement weather, TKL Research Inc. was closed on February 10, 2010. Subjects came in on February 11, 2010 for the February 10, 2010 visit. On February 26, 2010 only the subjects who required a makeup reading came in due to inclement weather.

On DS100810, 38 subjects had definite erythema, no edema (+), and 3 subjects (Nos. 40, 62, and 64) experienced definite erythema, no edema with damage to the epidermis (+D) during Induction.

Subject No. 040 experienced definite erythema, no edema with damage to the epidermis (+D) at the 2nd Induction reading. This product was inadvertently discontinued rather than switched to a new site under semi-occlusive conditions, a protocol deviation.

Subject Nos. 062 and 064 experienced definite erythema, no edema with damage to the epidermis (+D) at the 3rd Induction reading and 6th Induction reading respectively. Subject No. 062 refused to be patched with the product for the remainder of the study. Subject No. 064 had their patch switched to a new site under semi-occlusive conditions at the 6th Induction reading and experienced no reaction for the remainder of Induction. However, the subject however refused to be patched at Challenge.

On DS100910, 22 subjects had definite erythema, no edema (+), and 7 subjects (Nos. 018, 023, 039, 067, 084, 086, and 108) experienced definite erythema, no edema with damage to the epidermis (+D) during Induction. The 7 subjects each had their patch switched to a new site under semi-occlusive conditions and experienced no reactions for the remainder of the study.

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades and residual readings are provided in Data Listings 3 and 3A, Appendix II.

8.0 CONCLUSION

Under the conditions employed in this study, Formula No. Methylpropanediol 21.2% Facial Serum was acceptable irritation and showed no evidence of sensitization.

9.0 REFERENCES

Schwartz L, Peck SM. The patch test in contact dermatitis. Publ Health Pep 1944; 59:2.

Draize JH, Woodward G, Calvary HO. Methods for the study of irritation and toxicology of substances applied topically to the skin and mucous membranes. J Pharmacol Exp Ther 1944; 82: 377-390.

Lanman BM, Elvers WB, Howard CS. The role of human patch testing in a product development program. Joint Conf Cosmet Sci Toilet Goods Assoc 1968; 135-145

Marzulli FN, Maibach HI. Contact allergy: predictive testing in man. Contact Dermatitis 1976; 2:1.

Zhai H, Maibach HI. Dermatotoxicology. 6th ed. New York:Hemisphere, 1996.

Stotts J. Planning, conduct and interpretation of human predictive sensitization patch tests. In:Drill VA, Lazar P, eds. Current Concepts in Cutaneous Toxicity. New York: Academic Press, 1980: 41-53.

Griffith JF. Predictive and diagnostic testing for contact sensitization. Toxicol Appl Pharmacol, Suppl 1969; 3:90.

Gerberick GF, Robinson MK, Stotts J. An approach to allergic contact sensitization risk assessment of new chemicals and product ingredients. American Journal of Contact Dermatitis 1993; 4(4): 205-211.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Jonas, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: September 21, 2016

SUBJECT: Draft Report: Safety Assessment of Alkane Diols as Used In Cosmetics (draft prepared for the September 26-27, 2016 CIR Expert Panel Meeting)

Key Issues

The Chemistry section correctly indicates that 2,3-Butanediol is a vicinal diol. The placement of 2,3-Butanediol after Methylpropanediol in the list of ingredients in the Introduction and Table 1 indicate that 2,3-Butanediol is branched. Branching refers to the carbon chain. 2,3-Butanediol is not branched.

The Chemistry section correctly states that "Variations in the regiochemistry of small alkane diols may lead to significant differences in toxicity." The differences in toxicity among the ingredients in this report is not made clear. For example, referring to acute oral studies, the Summary states: "Clinical signs in the affected animals included ataxia, paresis, dyspnea, and exsiccosis in these studies. Necropsy and histological examinations revealed bloody stomach ulcerations, abnormal bladder contents, congestive hyperemia, and changes in the liver and kidneys in the affected animals." Based on the information in Table 8, ataxia was observed with Propanediol, dyspnea with 1,4-Butanediol and 2,3-Butanediol, exsicoosis with 1,4-Butanediol and 1,5-Pentanediol, bloody stomach ulceration and abnormal bladder contents with 1,5-Pentanediol and changes in the liver and kidneys with 1,4-Butanediol. No signs were observed in the limit dose (5 g/kg) study of Isopentyldiol.

A second example is the description of the sensitization results. The last sentence of the sensitization section states "Sensitization results were mixed with no-to-mild sensitization potential and some positive skin reactions observed during induction." Based on the information in Table 12, only Methylpropanediol was reported to have mild sensitization potential, and the reactions were not dose related. [Note: the Sensitization section incorrectly states that the study with Hexanediol induction and Hexanediol challenge showed a positive reaction. Table 12 states "the results for Hexanediol

sensitizer/Hexanediol challenge were negative".]

Table 9 - The ECHA dossier indicated that the 15 week oral (gavage or diet) study of Propanediol in rats was considered unreliable. This study was from a 1941 publication and it was not completed by any specific Guideline. In all places in the report where this study is mentioned, it should be stated that it was considered unreliable.

Additional Considerations

Cosmetic Use - The inhalation paragraph notes use in powder products, but no specific information about use in powder products is stated.

ADME, *In Vitro* - Please state the species from which the liver alcohol dehydrogenase was obtained.

Acute - Rather than stating all the LD_{50} values (or LC_{50}) first followed by a description of the effects, it would be helpful to discuss the effects observed for each ingredient.

Acute, Oral - Table 8 states that the LD_{50} for the Propanediol of 70% purity was 17 g/kg, not >17 g/kg as stated in the text.

Subchronic, Oral - Please name the organs with increased weights in male rats treated with Hexanediol at 1000 mg/kg/day.

Carcinogenicity - The only carcinogenicity study is on gamma-butyrolactone. The CIR Expert Panel has indicated that when a substance is being used for read-across, the substance on which the study was completed should be used as the sub-heading.

Sensitization, Summary - Table 12 indicates that induction with Hexanediol followed with challenge with Hexanediol was negative. This is not correctly stated in either the Sensitization section or the Summary.

Case Reports, Summary - Rather than stating that 1,4-Butanediol at varying doses caused death and adverse effects in children and adults, it would be better to state some specific information about doses. For example, one report (reference 78) stated that following 1,4-Butanediol ingestion by adults, non-fatal cases occurred at doses of 1-14 g and fatalities occurred at 5.4-20 g.

Table 4 - The use information from the Council included a body and hand product containing 0.5% Hexanediol. Although the total and leave-on row includes a 0.5% concentration, 0.5% is not found elsewhere, e.g., in the dermal exposure row, in the table.

Table 6 - It would be helpful to indicate that 1,2-propylene glycol has the INCI name Propylene Glycol

In the results column for reference 39, it is not clear why it states "control not used" as the results also state that absorption was increased "compared to control".

Table 7 - The doses used in the rabbit study described in reference 43 are not clear. The dose column states: "1.0-1.5 g/kg test substances in water is specified in the reference with the total g administered listed in the Procedure column". The Procedure column the states (one example) 16 g total Propanediol fed to 4 rabbits. What was the frequency of dosing?

What were the concentrations of 1,4-Butanediol in treated rats (references 40, 45)?

Please correct C^{14} (reference 44).

The last 1,4-Butanediol study (reference 40) does not describe any ADME results. This study does not belong in Table 7.

Table 8, Dermal, 1,4-Butanediol, Reference 57 - Please correct "monomuclear"

Table 8, Dermal, Butyl Ethyl Propanediol - RTECS available on the Council's database reports a dermal LD_{50} in rabbits of 3810 mg/kg (citing Deichmann 1969). As Butyl Ethyl Propanediol is a solid, units of mg/kg seem more appropriate than ml/kg as stated in Table 8.

Table 8, Oral, Propanediol, reference 38 - The units in the dose column are ml/kg, while mg/kg (10.8 mg/kg) is used in the Results column.

Table 8, Inhalation, 1,4-Butanediol - Please check the acute inhalation study in reference 55 and reference 61. Both describe a study report dated 1991. The exposure concentration stated in reference 66 is actually 5.1 g/m^3 (not 5100 mg/L as stated in Table 8). Since there are 1000 liters in a cubic meter, and 1000 milligrams in a gram, 5.1 g/m^3 equals 5.1 mg/L, the exposure concentration stated for reference 55. The two inhalation studies of 1,4-Butanediol in Wistar rats are the same study found in two sources.

Table 10, Hexanediol, reference 61 - In OECD 421 studies (Reproduction/Developmental Toxicity Screening Test) the females are allowed give birth and a majority of the offspring are examined 13 days after delivery. Therefore, it is not correct to state that "fetuses" were examined, as the offspring are no longer considered fetuses after being born.

Table 10, Methylpropanediol, reference 46 - If the animals were dosed during gestation, it does not make sense to state that the sex was not specified. Female rabbits were treated.