# Safety Assessment of Alkane Diols as Used in Cosmetics

Status: Draft Final Report for Panel Review

Release Date: August 18, 2017

Panel Meeting Date: September 11-12, 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 Interim Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Laura N. Scott, Scientific Writer/Analyst.



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**Memorandum**

To: CIR Expert Panel Members and Liaisons
From: Laura N. Scott
Senior Scientific Writer
Date: August 18, 2017
Subject: Draft Final Report of the Safety Assessment of Alkane Diols as Used in Cosmetics

Enclosed is the Draft Final Report of the Safety Assessment of Alkane Diols as Used in Cosmetics (identified as *ADIOLS092017rep* in the pdf document). At the April 2017 Meeting, the Panel issued a Tentative Report with a Safe Conclusion for 9 of the alkane diols and an Insufficient Data Conclusion for concentration of use for 1,4-Butanediol; that report was posted on the CIR website for public comment on April 27th, 2017.

The CIR report history (*ADIOLS092017hist*), Process Flow Chart (*ADIOLS092017flow*), Literature Search Strategy (*ADIOLS092017strat*), 2017 VCRP data (*ADIOLS092017FDA*), Ingredient Data Profile (*ADIOLS092017prof*), and Minutes from the April 2017 and September 2016 Meetings (*ADIOLS092017min*) are enclosed for the Panel's review. Council comments on the Draft Tentative Report from the April 2017 Meeting (*ADIOLS092017pcpc_1*) and the Tentative Report *(ADIOLS092017pcpc_2)* were received and have been addressed.

A neurotoxicity study referring to 2,5-hexanedione has been added (|bracketed| in text) to the safety assessment since the April 2017 Meeting. Panel edits from the April 2017 Meeting were addressed; the Abstract and Discussion were updated and the Conclusion was added to the report.

Additional clarification from the Panel is needed regarding the following:

A. A comment from the Council *(ADIOLS092017pcpc_2)* refers to addressing the toxicity of diacetyl in the safety assessment [this reference was provided as a review article in this issue: B. Starek-Swiechowicz, A. Starek, Rocz Panstw Zakl High 2014; 65(2): 87-92; http://wydawnictwa.pzh.gov.pl/roczniki_pzh/annals-of-the-national-institute-of-hygiene-articles?year=0&author=Author%E2%80%99s++name&keywords=Key+word+or+phrase&title=Diacetyl+Exposure+As+A+Pneumotoxic+Factor%3A+A+Review&search]. This article is not included in the safety assessment, but is noted in this memo for informational purposes. The ADME studies currently in the safety assessment show that 2,3-Butanediol is metabolized in small amounts to diacetyl (aka 2,3-butanedione) after oral administration in rats. If appropriate, the Panel should provide relevant language to add to the report/Discussion. There are no current uses or concentrations reported in the VCRP and the Industry survey for 2,3-Butanediol; uses in the report for the other alkane diols range from 0.006% to 39.9%.

   Additionally, there is a draft report on 2,3-butanedione available through NTP (https://ntp.niehs.nih.gov/ntp/about_ntp/trpanel/2017/july/tr593_peerdraft.pdf) with a conclusion that

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indicates there is evidence of carcinogenicity in 2-year inhalation studies in rats exposed to 2,3-butanedione (squamous cell papilloma and squamous cell carcinoma of the nose). Does the Panel think this data is relevant to cosmetic use and, if so, should it be included in the report? If appropriate, the Panel should provide language and rationale to add to the report/Discussion.

B. Does the Panel agree with the rationale in the Discussion describing the determination of safe use of Octanediol in cosmetics in the absence of toxicological data in the report? This issue was raised in a Council comment (*ADIOLS092017pcpc_2).* The expectation that Octanediol would be used in product categories and at concentrations comparable to others in this group implies that Octanediol could be used at maximum concentrations between 0.006%-39.9%. Is the Panel comfortable with this potential range for this ingredient? It is reportedly used in skin fresheners, but no concentrations of use are available. Does the Panel feel it is appropriate to add a footnote to the conclusion to this effect?

C. Based on deliberations from previous Panel meetings, the following sentence appeared in the Discussion of the Tentative Report posted online April $27^{th}$, 2017, "The Panel discussed that alkane diols have a high potential to be dermally absorbed, especially considering their low molecular weights." Further explanation is needed in support of this point (i.e. should there be any mention of dermal absorption in relation to chain length of the alkane diols?). The Panel should provide language and rationale to add to the Discussion regarding dermal absorption.

D. The Panel should provide language and rationale to be used in the Discussion addressing the absence of carcinogenicity data in the report; there are genotoxicity data for many of the alkane diols.

E. If appropriate, the Panel should provide language and rationale for the Discussion concerning the systemic toxicity observed following exposure to alkane diols in acute and repeated dose animal studies. For example, systemic toxicity was reported following acute dermal exposure to 1,4-Butanediol (2 or 5 g/kg) and Methylpropanediol (2 g/kg); toxic effects were noted after acute oral exposure to high doses (1 to 25 g/kg) of Propanediol, 1,4-Butanediol, 2,3-Butanediol, 1,5-Pentanediol, Hexanediol, Methylpropanediol, and Butyl Ethyl Propanediol; animal mortality was observed in subchronic studies following oral exposures to high doses of Propanediol and Butyl Ethyl Propanediol.

F. If appropriate, language and rationale for the Discussion about the in vivo genotoxicity study indicating that Propanediol is converted to malondialdehyde, subsequently causing damage to rat DNA (liver and testicular homogenates were tested). Propanediol is used up to 39.9% in non-spray deodorants.

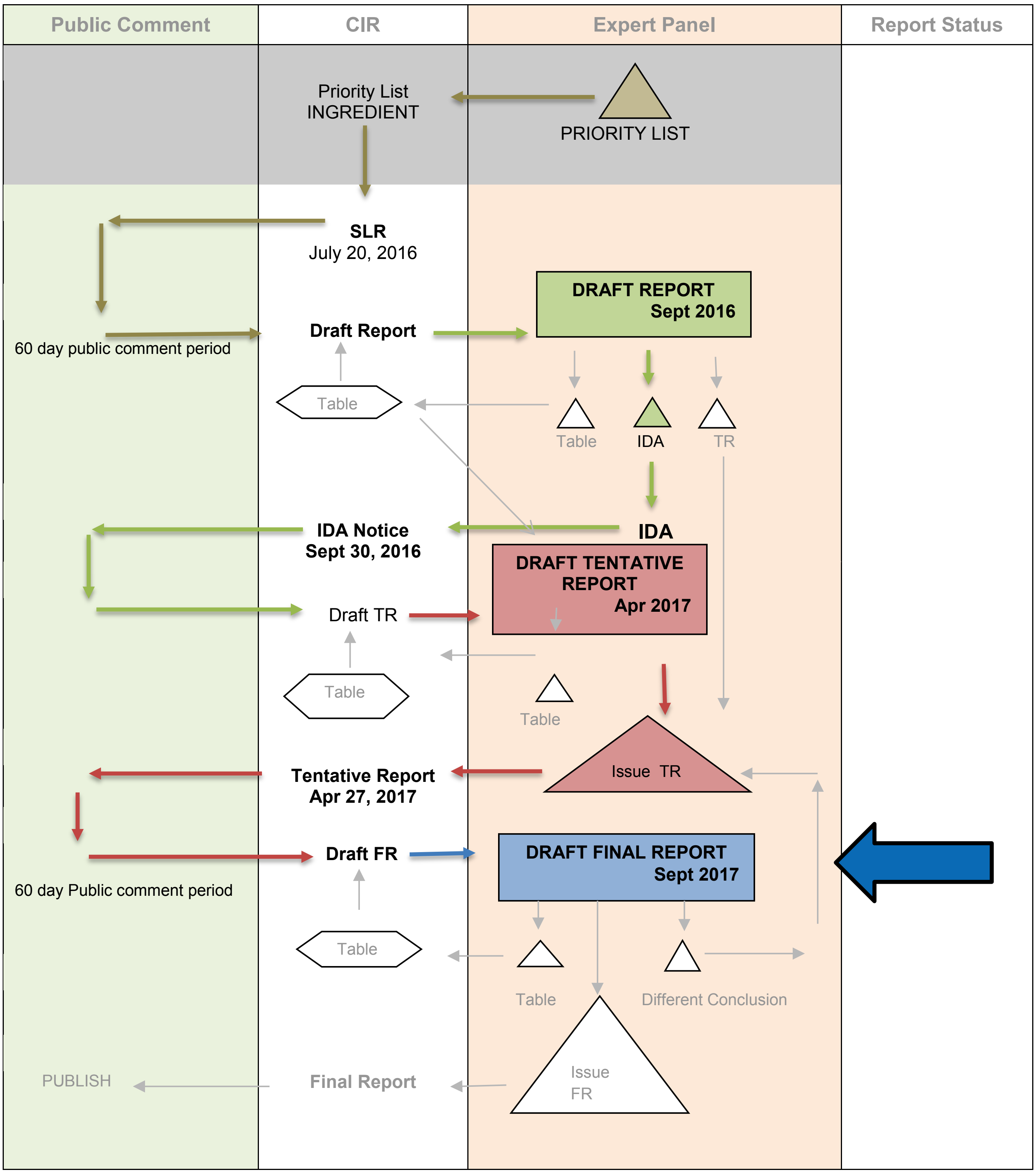
G. If appropriate, language and rationale for the Discussion mentioning dermal and ocular irritation studies. In the skin of animals and human subjects the alkane diols were non-to-mildly irritating. Most of the alkane diols were non-to-slightly irritating to rabbit eyes, while Butyl Ethyl Propanediol was irritating, but reversible within 14 days. If irritation is not a concern, please indicate whether a statement is needed in the Discussion specifying why there is no concern.

If the data included in this report adequately address the safety of the alkane diols, the Panel should be prepared to provide any additional rationale to be described in the Discussion, to verify the Discussion and Conclusion, and issue a Final Report.

# SAFETY ASSESSMENT FLOW CHART

**INGREDIENT/FAMILY** ____Alkane Diols_______________________________________________

**MEETING** ______Sept 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.

**April 10th-11th, 2017**-The Panel issued a Safe Conclusion for 9 Alkane Diols and an Insufficient Data Conclusion for concentration of use for 1,4-Butanediol at this meeting.

**April 27th, 2017**-The Alkane Diols Tentative Report was posted at www.cir-safety.org for public comment.

**Alkane Diols Data Profile for September 11-12, 2017. Writer – Laura Scott**

| | | | | 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 | | Occular Irr. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Used in Cosmetics? | Safety Data Available? | *In Vitro*-Dermal Penetration | 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 |
| 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 | | | | | 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.

# 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***.

**APRIL 2017 PANEL MEETING MINUTES**
**ALKANE DIOLS (Day 1)**
**DR. MARKS' TEAM**

DR. MARKS: Okay. Science and support. Okay. Next ingredient is the alkane diols. And Laura is here. Yeah, this is really actually interesting. Okay. We received a memo from Laura with a draft tentative report of the safety assessment of alkane diols. As you recall, in the September 26, 27th meeting last year, the panel issued an Insufficient Data Announcement for all the alkane diols. And was method of manufacturing for all ingredients, impurities for all ingredients, penetration enhancement all ingredients, neurotoxicity for the Isopentydiol, and the concentration of use 1,4-Butanediol. We received a lot of data. And so, Ron and Tom, do we have any further needs? Or can we proceed forward with an actual tentative report? And my review, will be to see what your reaction was, was that we could go safe for eight, insufficient for the Isopentydiol, since we didn't receive any neurotoxicity data. And also insufficient for the 1,4- Butanediol because we don't have concentration of use. And as you recall it's metabolized for GHB, aka the Date Rape Drug. And it's a penetration enhancer. And I'd even say, if we had the concentration of use, do we need the serum concentration from topical application. I guess if it were so small, then it would be below the concentration, the serum concentration to have a neurologic affect. But, any rate, Tom, Ron and Ron, did you feel we could go forward with a tentative report? And is it safe for eight of these ingredients? Or am I missing needs in here?

DR. SHANK: I still have the need for the purity of the Hexanediol. They didn't answer that.

DR. MARKS: Hexanediol

DR. SHANK: Yes. We asked for the impurity data on that.

DR. MARKS: On all of them

DR. SHANK: Because there's a neurotoxin

DR. EISENMANN: Is that just in the 1,6-Hexanediol you're talking about?

DR. SHANK: Pardon me?

DR. EISENMANN: Part of the 1,6-Hexanediol you're talking about?

DR. SHANK: Yes

DR. EISENMANN: Okay

DR. SHANK: And the other one we had, the Isopentyl, the diol, we have an oral toxicity study that showed no adverse clinical signs or hysta-pathological [histopathological] signs. If it has neurotoxicity properties, that would have been detected in the orals. I would think. Would have been detected in the oral study.

DR. MARKS: So that's for the Iso

DR. SHANK: Isopentydiol

DR. MARKS: Yeah. And you had brought up that issue last time.

DR. SHANK: Yeah. I was the one who threw that out.

DR. MARKS: Okay

DR. EISENMANN: The other thing about the Isopentydiol is that in the NICNAS review, they approved it up to 10% in cosmetics. And they used, that was the concentration that was requested, and they also supported it with read across from butanediol, hexanediol, and isoamyl alcohol. There are sub-chronic studies on those three ingredients. Isoamylate only differs, doesn't have the additional hydroxyl group with the, on one end. So it's the same, except it's missing a hydroxyl.

DR. SHANK: I had a question. Is it legal to add a controlled substance to a cosmetic? Butanediol.

DR. EISENMANN: I don't think you could buy it. I'm not sure whether it's legal or not, but I don't think you could buy it to add.

DR. JONAS: You'd have to have a DEA license to purchase it.

DR. SHANK: To purchase the ingredient.

DR. JONAS: Yes

DR. SHANK: But you could put it into a cosmetic product.

DR. JONAS: It'd be a really dumb move.

(laughter)

DR. SHANK: It's a legal question, not a toxicology question.

DR. SADRIEH: I think if it's regulated by DEA as a controlled substance, I don't think you can put it in the cosmetic.

DR. SHANK: Isn't one form butanediol a DEA- controlled substance?

MS. SCOTT: For oral administration. I don't know about dermal.

DR. HLIL: Yeah, because it generates, it's a pre- cursor for GHB.

DR. MARKS: Right

DR. HLL: Same as gammo butyl electo, which I think you can still purchase. But a little more difficult than you could a few years back.

DR. MARKS: So, I'm going to be moving tomorrow for our team issuing a tentative report. It's still the same number, eight. But the 1,4-Butanediol we need the concentration of use. And we need the impurity data for hexanediol. Is that correct?

DR. SHANK: Yes.

DR. SLAGA: And the rest are fine.

DR. MARKS: The rest are fine.

DR. HILL: I have a few issues. So I'm still puzzling, is propanediol for sure only 1,3-Propanediol? Because one of the methods of manufacture that's listed suggests that it's 1,2.

DR. EISENMANN: We do have a representative

DR. COLOMBO: So I'm Pete Colombo with Dupont Tate and Lyle Bioproducts. We're a manufacturer of 1,3-Propanediol. The inci name is propanediol, or 1,2-Propanediol, which is Propanyl glycol. That is propanyl glycol is the inci name.

DR. HILL: Okay. So I guess the question from me is there a gremlin in that report? Because I can find the method of manufacture here, I've got a page number. Sorry to go back and forth. Due to an AWOL laptop.

DR. EISENMANN: It's a fermentation process is the method of manufacture.

DR. HILL: I'm talking about the lithium aluminum hydrid production that's mentioned in the report.

DR. EISENMANN: It may be mentioned but the main method of manufacture of the material used is fermentation.

DR. HILL: Right. I got that. So, that's why I'm wondering if that one should actually be stricken from the report because propanediol can be prepared by reducing ethyl glycetate with lithium aluminum hydrid. I believe that would give a 1,2-Propanediol. That's what's in here and there's a reference.

DR. COLOMBO: Yeah, I'm not familiar

DR. HLIL: My guess is that might not belong in here. So it might be the problem is with that statement and not, but we don't have any language in here, anywhere in the report that says that it is in fact explicitly and always 1,3- Propanediol. I mean 1,2 is just propylene glycol but.

DR. COLOMBO: Isn't it by the INCI name though?

DR. EISENMANN: That's the definition of that INCI name.

DR. HILL: Is it?

DR. COLOMBO: So we have propanediol, I believe it's INCI name exclusive to 1,3.

DR. HILL: It should be. I'm just making sure. It's got structure in there that's 1,3.

DR. EISENMANN: Yes

DR. HILL: And that structure is in the INCI, right? Okay. So I think my original question for this ingredient was related to impurities, which I was fishing around to see if 1,2 was an impurity in there or an aldehyde. So we have a pretty good purity profile though. But the question in my mind was is it all 1,3? Because if you say propanediol and you haven't specified that for sure, but I guess I'm clear now on that. That's all. Unless there's something that you want to add.

DR. MARKS: Ron Shank, let me clarify again. The impurity for hexanediol was your concern your about neurotoxins, or neurotoxicity. Did I hear you correctly?

DR. SHANK: A potential impurity could be 2,5- Hexanediome or diol. That can be metabolized to a neurotoxin. I just looked up, I should have done this before, hexanediol is used in leave-ons up to 0.5%. In some place in here it says the impurity, hexanediol is more than 96% pure.

DR. HILL: That's page 51, at the top.

DR. SHANK: Page 51. That being the case, there's not going to be enough there to be a toxicological issue.

DR. MARKS: Okay. Good.

DR. SHANK: I withdraw my request for impurity data.

DR. MARKS: Okay.

DR. BERGFELD: But you're not withdrawing your request for the neurotox data? Or are you?

DR. SHANK: Yes. Because of the oral study.

DR. BERGFELD: Okay.

DR. SHANK: Which would have picked that up.

DR. BERGFELD: Okay.

DR. MARKS: So, if I'm following the score card correctly, tomorrow I'm gonna move that a tentative report be issued. Safe for nine ingredients.

DR. HILL: I had one more.

DR. MARKS: Oh. Okay. Let me summarize at this point. Insufficient for one ingredient, that's the 1,4-butadiol up to this point. Okay. Ron Hill, we'll see if we change the scorecard again after your comments.

DR. HILL: I was just wondering if everybody's comfortable with reading across to 1,8-octanediol given that we have no data on it at all. I mean we do have data for 1,10 and 1,6.

DR. MARKS: I think we must have gotten a wave two, did we? Oh no, that's the one below, that's the 1,10. Decadenediol. For sensitization. That was all okay.

DR. HILL: I guess part of what I'm asking is, I mean that's in a, what is the concentration of use maximally on that one? 1,8-diol.

DR. EISENMANN: No reported concentrations

DR. HILL: No reported concentrations

DR. MARKS: Right.

DR. HILL: For me, that's an insufficiency.

DR. MARKS: Is there uses?

DR. HILL: It says there is.

DR. MARKS: Yeah, I didn't

DR. HILL: There's no toxicity data. It's enough difference in length. I think in terms of possible, theoretical at least, possibility, Dr. Liebler will shoot me down, but I will think of it anyway, aldehyde at both ends and cross-linking something, so then length matters. And also, yes, it's a diol, but that's getting lypathitic enough where absorbity into the skin will be much better than some of these shorter ones, or the very longer ones.

DR. SHANK: Is it used?

MS. SCOTT: The 2017 VCRP says it's used in skin fresheners. And that's all we have.

DR. HILL: So skin fresheners, that's not exactly leave-on but

DR. JONAS: Skin fresheners are typically leave-on. They are sometimes used instead of a toner. But it would be, after you wash you would then take a cotton ball and put a skin freshener. Yeah, so you would still have a leave-on residue.

DR. HILL: So just a residue?

DR. JONAS: Yeah

DR. HILL: That's where the concentration for me would be a little important. And maybe if it's just being used in a swab, maybe that's what the issue is with trying to even put a concentration to that. I mean, how would you give a concentration for something that's? I mean, it is, a concentration in the product, and then you're swabbing it on, but you know.

DR. MARKS: Ron and Tom, do you feel we can read across for that? Or, should be put insufficient since there's no data on it?

DR. SHANK: I did read across.

DR. SLAGA: That's what I did, a read across. But Ron brings up a good point. Would have a little different absorption probably. I could go with insufficient there.

DR. MARKS: Okay. As I said, the score card keeps changing. We'll see what tomorrow, with Belsito. But I'm gonna say safe for eight ingredients, insufficient for two. Those two are two ingredients, those two are what I began with. It seems like we delete and add and we still come up with the same number. 1,4-butadiane [1,4-Butanediol] again for concentration of use. And The octanediol we have no data at all on that and we want to see something. Does that sound good, team?

DR. HILL: The other thing is, who's our writer on this one, sorry?

DR. MARKS: It's Laura over here.

DR. HILL: I knew she's here. Sorry. I'm about to go grab a little more caffeine. Okay. My answer to the questions raised, you had a series of five questions that you raised in the memo, and my answer was yes to all of them. Except the fifth one, dealing with the Chinese translation. I think it's yes for all the other four.

MS. SCOTT: And not to use the Chinese translation?

DR. HILL: I didn't see that that added anything so crucial. And unless the whole article is being translated, I don't like just abstracting unless there's no choice and it's important. And I don't see that that's the case here. The other thing that I had is a question, which is why we only have metabolism information for 1,4-Butanediol and basically nothing else. It's hard for me to believe that there isn't more information out there on the biotransformation of this group of substances. I mean, I know we know more about hexanediol because that's been studied to death, but, maybe it's. That's really an editorial question is, have you caught everything in terms of biotransformation by the way that we searched or whatever. I like structure-based searches when looking for certain kinds of information. And that goes to my assertion about the 1,8-Diol for example. And there may not be anything on there out there. But again, if these things have toxicity, other than these goofy things like the neurotoxicity of this one, I think metabolism to aldehydes on either end with cross linking is the most likely source of things that I would worry about.

DR. MARKS: Okay. Any other comments? We'll certainly have opportunities tomorrow and I'm sure there's gonna be a discussion around these as to, I think the 1,4-butanediol is a pretty straight forward one. It's the other nine ingredients. Okay. So again, I will move tomorrow a tentative report, safe for eight ingredients, insufficient for two ingredients, the 1,4-Butanediol for concentration of use and the octanediol because we have no tox data and we felt uncomfortable about reading across with that particular ingredient. And we'll see what Dan's, Dan Liebler says tomorrow also.

DR. HILL: However, I will stand my ground on that one.

DR. MARKS: Yeah, that's fine. I wouldn't expect otherwise, Ron Hill.

DR. HILL: No, I listen to Dan and I have backed off in a number of cases. And anybody else who, I'm always ready to be proven wrong, no problem.

## APRIL 2017 PANEL MEETING MINUTES
## ALKANE DIOLS (Day 1)
## DR. BELSITO'S TEAM

DR. LIEBLER: Alkanediol.

DR. BELSITO: So, alkanediols. So, in September 2016, you issued an insufficient data announcement for these

ingredients, and we got a lot of data looking at manufacture impurities, skin penetration enhancement were included in the report; and under concentration of use data, we got for the 1,4 butanediol -- oh, no, we didn't get the 1,4 butanediol -- and we also didn't get Ron Shank's request for neurotoxicity on isopentylediol. But, like I said, we got lots of data, so let's try and open the documents and see what we thought because we weren't as concerned. We were, basically, asking, you know, for the 1,4 butanediol and that was it, which is where we were at. It was the Mark's team added everything else. So, the neurotoxin is the 2,5 hexanediol.

DR. LIEBLER: Right.

DR. BELSITO: And on page 50 of the PDF, it says that 1,5 pentanediol can have 2,5 hexanediol. So, do we limit; what do we do with that?

DR. LIEBLER: The 1,5 pentanediol can have --

DR. BELSITO: It says that gas -- bottom of the PDF, page 50 -- other diol impurities including were below -- oh, I'm sorry -- were below the limit of detachment [detection?] ; okay, sorry, got rid of that.

DR. LIEBLER: Yeah; so we're okay. I did not understand the reason that they were asking for neurotox data on the isopentylediol; so, I couldn't find anything in the discussion.

DR. BELSITO: I didn't either; it's in their group. He just asked for it.

DR. LIEBLER: It just slipped through in our joint panel meeting, it's just been a slip-through as a data request, and we didn't flag it; but I didn't understand what the basis for that would be.

DR. BELSITO: Laura, do you remember?

MS. SCOTT: No.

DR. BELSITO: Ron Shank was the one who requested it -- neurotox data for the isopentylediol. I think at that point, we just said, well, we're going insufficient, so you add in anything else you want, we really don't care -- is, basically, as I recall the discussion.

DR. LIEBLER: It would not occur to me as something we would need neurotox data on; and, maybe, Ron's thinking of something that didn't occur to me, but I just can't think of what it would be, and if anyone said what was the issue. So, that's one that might go away tomorrow if we just talk about it for a minute because I don't think that's really a need; and then there is the issue of the --

DR. SNYDER: Penetration enhancement.

DR. LIEBLER: -- documentation that the hexanediol does not contain 2,5 hexanediol, and the data at the very top of PDF 51 that says, hexanediol has been reported to be greater than 96 percent pure, impurities not specified. Well, that's the problem. It doesn't say whether or not it contains any hexanediol; and, if it did, you know, somewhere in that 4 percent that's, you know, not the 1,6 hexanediol, then we could have an issue. So, I think that data need is still not addressed.

DR. BELSITO: So, we need to know whether it's --

DR. LIEBLER: Composition.

DR. BELSITO: -- it's the 2,5 is the problem.

DR. SNYDER: 2,5 is the problem, right.

DR. BELSITO: So, we need to know if there's 2,5 in the hexanediol.

DR. SNYDER: Like a 1,6.

DR. LIEBLER: Right. So, we didn't get that, and we don't have anything on method of manufacture on the hexanediol, either; and that was another request.

DR. BELSITO: So, we need method of manufacture for hexanediol?

DR. LIEBLER: Right; and the 2,5 impurity.

DR. SNYDER: So, based on the five, insufficiency needs of the method of manufacture, impurities, penetration enhancement, neurotoxicity, and concentration use of the 1,4 butanediol, we have only received penetration enhancement, is that right?

MS. SCOTT: We also received some impurities data, but not enough.

DR. SNYDER: Okay.

DR. LIEBLER: Not too specifically, but I will look at what everybody's talking about.

DR. BELSITO: So, the manufacturing is missing for hexanediol, octanediol, butylether, propanediol, and isopentylediol. Impurities are missing for 2,3 butanediol, hexanediol, octanediol, 1,10 decanediol, methopropanediol, and butylether propanediol. The neurotox data for isopentylediol we didn't get; and we still don't have a use concentration for 1,4 butanediol.

DR. SNYDER: Okay.

DR. BELSITO: So, that's what is missing from what we requested last meeting. So, from what I'm hearing is that we, however, at the last meeting only asked for the concentration of use of 1,4 butanediol. So, this is missing, based upon what the Mark's team asked for. So, the question is -- and what I'm hearing from you, Dan, is -- in terms of impurities, you really want to know hexanediol --

DR. LIEBLER: Yeah.

DR. BELSITO: -- what else is in there and how it's manufactured? You don't care that we're also missing it for 2,3 butane, octane, and all the others?

DR. LIEBER: No. Remember that, yes, going into the full panel meeting last time, I didn't really have a concern about hexanediol. Its single use -- it's a low use concentration -- any 2,5 that might be in there will be present in a very little amount; and, so, I really wasn't concerned about that. I mean, if I were a manufacturer, I wouldn't bother to go anywhere near hexanediol because of the possible impurities issue and the bad optics associated with it, but, particularly, when there's all these other solvents that are just as good, basically; but having said that, I'm only responding to my assessment of whether Ron's, you know, data request that the panel approved has been met -- and it has not been met.

DR. BELSITO: Okay; that's what I was responding to in making those notes.

DR. HELDRETH: A quick look at the minutes for Dr. Shank's request on isopentylediol; and his request, specifically, was because a neurotoxicity, because it can be metabolized to a diketone similar to 2,4 hexanediol. That was his rationale.

DR. LIEBLER: Not similar enough.

DR. HELDRETH: Okay.

DR. LIEBLER: I mean, if you count the carbon's distant, yes; but the problem is that bio activation story is exquisitely sensitive to everything else in the molecule, if you are saying -- you would have these methyl groups all over the place too; and I just don't --

DR. HELDRETH: That doesn't form a nice ring

(inaudible).

DR. LIEBLER: Right.

DR. BELSITO: Okay; then just one of the questions that I had in terms of the concentration of use of the 1,4 butanediol, it's my understanding that, you know, our concerning was it's potential to being metabolized to JHB [GHB]. We do have a four month inhalation study on 1,4 butanediol where it's negative at 2.5 mg/kg; so does that, based upon -- I mean, because we've always said globally, okay, you know, there's no reported concentration here, but this is -- then we would expect it to fall within the range of concentrations of everything else that is being used in this report.

If we don't get concentration of use for 1,4 butanediol, can we use that it was a four month inhalation study to support that lack of data? And, again, I'm not good at converting respiratory studies to just dermal absorption and other issues.

DR. LIEBLER: I think it was the butanediol as a dermal absorption, or as a potential dermal absorption metabolism and a CNS-affect issue.

DR. BELSITO: Right.

DR LIEBLER: So, I don't think we can really infer from the respiratory pulmonary to that, first of all.

DR. BELSITO: Okay.

DR. LIEBLER: And, second, the use concentration for the nearest neighbor chemical is propanediol, and that's up to

percent.

DR. BELSITO: Right; I understand.

DR. LIEBLER: So, you, potentially, have an awful lot of butanediol even though that respiratory study didn't.

DR. BELSITO: Okay; so, it doesn't help clear it?

DR. LIEBLER: No, I don't think so.

DR. BELSITO: Okay. Just wanted to make sure we weren't missing some data that would help us out. Okay.

DR. SNYDER: So, where does this aldehyde come in -- this reproductive toxin, aldehyde -- where does that come in as far as an impurity or --

DR. LIEBLER: Could you point me to the page we're talking about?

DR. SNYDER: Malondialdehyde genotoxic?

DR. LIEBLER: Oh, from propanediol. So, malondialdehyde is right. It's actually formed indigenously from oxidation of blood bits, and it can form DNA adducts.

DR. SNYDER: So, whatever impurity issue for any of the other ingredients that we don't have impurity data on?

DR. LIEBLER: No; it'll be only for the propane because it's a three carbon --

DR. SNYDER: Okay; thank you.

DR. BELSITO: Okay; still insufficient, the question is what the final insufficiency needs will be based upon; our discussions with the team. I've outlined what is missing from the Mark's request; basically, what we're asking for is method of manufacture and impurities for the hexanediol --

DR. LIEBLER: Right.

DR. BELSITO: -- and the use concentration for the 1,4.

DR. LIEBLER: Yeah, I think that the latter is the most important.

DR. BELSITO: Use concentration for the 1,4?

DR. LIEBLER: Yeah.

DR. SNYDER: What about the 1,6, does not contain the (inaudible)?

DR. LIEBLER: It's not used; so we're never going to get an answer.

MS. SCOTT: Well, it's not -- I think there were frequency of uses, not concentration, in the VCRP.

DR. SNYDER: Right.

MS. SCOTT: Okay.

DR. LIEBLER: So, they're reporting concentrations?

DR. BELSITO: No; it's reported to be used, but we don't know the concentration. That was the issue.

DR. LIEBLER: I mean, it would make no sense to use this in a property, so --

DR. ANSELL: So, we don't believe those four cases were (inaudible)?

DR. LIEBLER: Well, I mean, it remains insufficient, and that's maybe where it ends up, so.

DR. BELSITO: Okay; so, I've got the Mark's thing; so, for us it's manufacturing and impurities for hexanediol, and the use concentration for 1,4, correct?

DR. HELDRETH: Correct.

DR. LIEBLER: And I would probably argue the point about the need for the neurotoxin on the isopentylediol.

DR. BELSITO: You think we do need it?

DR. LIEBLER: I would argue --

DR. BELSITO: So, I'm eliminating that from our needs.

DR. LIEBLER: Okay.

DR. BELSITO: So, I've got two tables, what we're missing from the Mark's team and what we think we need.

DR. LIEBLER: Right; yeah.

DR. BELSITO: Anything else on these alkanediols?

MS. SCOTT: Two quick questions?

DR. LIEBLER: Sure.

MS. SCOTT: So, the memo, e, basically, point e, there is some data submitted indicating a translated abstract. It was a Chinese paper, but we can only get an English translation of the abstract; and it talks briefly about the ability of propanediol to increase in vitro skin penetration, so as a potential penetration enhancer; my question is would you want this information included in the report? It was submitted through the council from industry. Is this something you would like in the report, or is this not reliable enough? So, it was data 4 in the panel build.

DR. BELSITO: Yeah.

DR. LIEBLER: But I thought we got a literature review on penetration enhancement. Didn't you do a review of it?

MS. SCOTT: We have other data.

DR. LIEBLER: Right.

MS. SCOTT: So, my question is just do we include this data, an addition or --

DR. LIEBLER: Sure.

MS. SCOTT: Is it okay, basically?

DR. LIEBLER: Yeah.

MS. SCOTT: Okay.

DR. LIEBLER: And I do have -- on the penetration -- you did remind me that one point to make is I don't think we need to add the structures of chemicals whose penetration was enhanced in some of these studies.

MS. SCOTT: Okay.

DR. LIEBLER: It's just unnecessary.

MS. SCOTT: Okay. Can you remove those?

DR. LIEBLER: Doesn't really tell us much.

MS. SCOTT: Okay; sure.

DR. KLAASSEN: We have that in a couple of the reports this time.

DR. LIEBLER: Yeah; I agree.

DR. HELDRETH: Since things will often be a penetration enhancement for one type of molecule versus another, is there anything that you would like to see in the penetration enhancement sections that indicate what types of molecules?

DR. LIEBLER: I don't think I've never seen penetration enhancement data presented to the panel that has been sufficiently broad to allow you to kind of get at the issue of what types, you know. It's they try it with this compound, you have no idea why they did it, and it could have been lots of different compounds this penetration might be enhanced by these -- I wouldn't be surprised if that's true. So, that's why pointing out individual structures -- it kind of suggests there's something special here when, you know, you have one of these structures highlighted; and there's probably nothing special about this phenomenon. These are solvents.

DR. HELDRETH: That's too much focus?

DR. LIEBLER: Right.

DR. HELDRETH: That's my point (inaudible).

DR. KLAASSEN: In some of these studies, you know, they're looking at a testosterone-type compound or an estrogen-type compound; and probably why some of these studies were done was to see if they could enhance the absorption of testosterone across the skin.

DR. SNYDER: Through formulation.

DR. KLAASSEN: Yeah; as a formulation process.

DR. SNYDER: Thank you.

DR. BELSITO: Anything else?

MS. SCOTT: One more quick question.

DR. BELSITO: Sure.

MS. SCOTT: The carcinogenicity section, PDF page 58 --

DR. BELSITO: Yeah.

MS. SCOTT: -- there's one study, which is basically read-across -- it's 1,4 butandiol is what it is supposed to be -- read-across for -- gamma butylrolactone is metabolized in the body to GHB, similarly to 1,4 butanediol; and my question just is, is it appropriate to have this study? It's the only carcinogenetic study I could find through an NTP report; and is it appropriate to keep it in?

DR. BELSITO: Not my purview.

DR. HELDRETH: That's chemistry.

DR. LIEBLER: Yeah; this is a study of the GHB as opposed to the butandiol.

MS. SCOTT: Right.

DR. LIEBLER: No.

MS. SCOTT: Not appropriate.

DR. LIEBLER: No.

MS. SCOTT: Okay.

DR. LIEBLER: I don't think so. I mean, I don't think you can infer that much. It's true that the butandiol is metabolized in part to GHB, but that's not good for (inaudible).

DR. ANSELL: It should be the step up, not the step down.

DR. LIEBLER: Yeah; right.

DR. ANSELL: 1,4 were the first (inaudible) metabolize then.

DR. LIEBLER: You're not going to say putting in GHB is going to generate some pool of 1,4 that you can infer from the carcinogenicity, so.

MS. SCOTT: Okay.

DR. LIEBLER: It doesn't help us.

MS. SCOTT: Okay.

DR. BELSITO: So, that's the in vitro?

DR. LIEBLER: In vivo, oral.

DR. BELSITO: In vivo, oral; so, that entire section?

DR. LIEBLER: Right. So, we end up not having carcinogenicity data?

MS. SCOTT: Yes.

DR. BELSITO: But we have sufficient genotox data; you okay with that?

DR. LIEBLER: Yes.

DR. KLAASSEN: Kind of surprising there isn't any carcinogenicity on any of those chemicals, but if there isn't, there isn't, I guess. You would've thought someone would have found it.

DR. LIEBLER: I agree.

DR. BELSITO: Okay; anything else? Okay. It's 10:20; do we need a 10 minute bio break and then resume at 10:30?

**APRIL 2017 PANEL MEETING MINUTES**
**ALKANE DIOLS (Day 2)**

DR. BERGFELD: Good. Any other points of discussion or comments? Then I'll move the question. All those in favor of a safe conclusion, indicate by raising your hand. Unanimous. Then moving on to the next ingredient in this group, Dr. Marks, the alkanediols.

DR. MARKS: At the September meeting last year, the expert panel issued an insufficient data announcement for these alkanediols. We needed method of manufacturing, impurities, penetration enhancement, neurotoxicity, concentration of use. Which is outlined in Laura Scott's March 17th memo. We did receive a significant amount of data. After reviewing that, our team felt we could move on with a tentative report. So, I'll make a motion that eight of these ingredients are safe. Two of them, our team felt would be insufficient. The one for butanediol, we still do not have the concentration of use. And as you recall, that's metabolized at GHB, a.k.a., the Date Rape

Drug. And it's also a penetration enhancer. So, be insufficient for concentration of use of that ingredient. And the octanediol, we have no toxicologic data. And we were uncomfortable reading across with that ingredient. So the motion is a tentative report, safe for eight. Insufficient for the two ingredients that I mentioned.

DR. BERGFELD: Comment by the Belsito team.

DR. BELSITO: Yeah, if you changed octanediol to hexanediol, we might agree. We thought we still need manufacturing impurities for the hexanediol, because it says that it could contain 2-5, which we know is a neurotoxin. We did not have issues with the octanediol, but I'll refer to my colleagues to comment on that.

DR. LIEBLER: Was octanediol mentioned last time as a problem?

DR. BELSITO: It was mentioned from method of manufacturer. We had asked for hexanediol, octanediol --

DR. LIEBLER: Oh.

DR. BELSITO: -- butyl ethyl propanediol, and isopentyldiol. And we've got none of those.

DR. LIEBLER: Yeah. The hexanediol was the one, obviously, that was on our radar. And I felt that they still hadn't come through with the impurities. They came through with, you know, 97 percent pure or something like that. But that didn't answer the crucial question about any 2-5 contamination. With the octanediol, I'd like to hear what the thought is behind the concern about that one.

DR. BERGFELD: Ron Hill.

DR. HILL: Now, that one is lipophylic enough to be dermally penetrable. And I didn't feel -- well, we don't have any chronic tox data in particular on that agent. And so, considering that it would be likely dermally penetrable, almost certainly, based on physical chemical properties, that we don't have any data on it. Our only chronic toxin in this whole group is the 1-4 butanediol. And we don't know concentration of use. Although, we do have information about how it was tested. My concern is, always with the long chain alcohol. And in this particular case, the diol, there's always a possibility of metabolizing at each end to aldehyde. In which case, you can get cross-linking reactions. And I just feel like the absence of data, in this case, is not a full assurance. And I didn't feel like the read-across was good. Because, even though we have the 1-10 in there, we don't really have chronic tox data of any kind on that one either. Hexane is really smallish. And so, with the idea that we could cross- link between two aldehyde groups, those kinds of reactions are known. And having no data, whatsoever, on that agent, and I just felt like it's insufficient and somebody could bring forth data to give us greater assurance.

DR. BERGFELD: Ron Shank.

DR. SHANK: Regarding the hexanediol, we're told that the purity is great than 95 percent.

DR. LIEBLER: Right.

DR. SHANK: And the maximum use concentration is 0.5 percent in leave on's.

DR. LIEBLER: Mm-hmm.

DR. SHANK: So, I don't think there would be enough potential neurotoxin involved. Except with limited use.

DR. LIEBLER: I agree with you. I agree with you. I think --.

DR. SNYDER: That's a nail use also.

DR. SHANK: Pardon me?

DR. SNYDER: That leave on is a nail use.

DR. SHANK: So --.

DR. SNYDER: So what I'm saying -- so, I wasn't concerned about it from the beginning. It was brought up previously --

DR. SHANK: By me. Yeah. (Laughter)

DR. SNYDER: -- by you. So, I was looking to see things your way.

DR. SHANK: Thank you. (Laughter)

DR. SNYDER: And I'm still looking to see things your way.

DR. SHANK: Thank you.

DR. SNYDER: So.

DR. SLAGA: You're not wrong to go that way.

DR. HILL: And I concur on that too. And I have pretty good neuro credentials, so.

DR. LIEBLER: But we -- actually, I mean, in the acute dermal, we have data on several of these diols, not the octane. I'm not concerned about the read-across, so I respect Ron's point of view. But I don't share a concern about that. So.

DR. BERGFELD: Tom. Did you want to make a comment?

DR. SLAGA: Well, I agree with Ron. I think that if the additional chemistry in getting through the skin, I think we need a little data to satisfy.

DR. HILL: It may be that the dermal penetration data would show that there isn't a problem. But we don't have it.

DR. SLAGA: Yeah. Yeah right.

DR. BELSITO: For it, we're talking octane not --.

DR. LIEBLER: 1-8. 1-8.

DR. SLAGA: Only that. Yeah.

DR. BERGFELD: Do you want to restate your conclusion then Jim, and then --?

DR. MARKS: Yes. So, it sounds like after the discussion, we're getting closer. I move that a tentative report be issued. Eight of the ingredients would be safe. Insufficient for two ingredients. If I got the gist of our discussion, the 1-4 butanediol concentration at use, both teams agree with that. We haven't received that. And then, we had the discussion about the octanediol, and there was concern on their team about no toxicologic data whatsoever. So, we would still put that insufficient. And it sounds like the hexanediol impurities is a non-issue now, because if there are impurities, the concentration in the final product would be so low, that we aren't worried about a toxicologic effect. So, actually, my initial motion is still -- it's the same.

DR. BERGFELD: Same? The explanation was helpful. Do you concur with the second?

DR. BELSITO: I just, you know, I'm not a neurotoxicologist, so I don't know at what level 2-5 begins to cause neurologic problems. So, it's hard for me to say that, I mean, there are some things that are (inaudible) cause issues. So, can someone please tell me what the dose response is for neurotoxicity?

DR. BERGFELD: Maybe Curt could comment?

DR. KLAASSEN: I don't know exactly what dose causes that. I would like to, however, talk about, you know, while there is, in regard to the octanediol that was brought up. You know, there's been a lot of work on the 2-5 hexanediol being a neurotoxicant. And they have done studies with a number of other structure activity relationship here. And it is just this one chemical that so far has ever been shown to produce a neurotoxicity. So, you know, this does not follow any SAR.

DR. HILL: Let me be clear. I'm not worried about neurotox for the 1-8. Or other toxicologies that we might not --

DR. KLAASSEN: Yeah.

DR. HILL: -- be capturing. We don't have concentration of use. So, I want to be clear about that point.

DR. KLAASSEN: Okay. I misunderstood what you were getting at.

DR. HILL: Because I remember the neuro effect for that is specific to that particular structure --

DR. KLAASSEN: Right. Right.

DR. HILL: -- in a very specific way. So there's no reason to expect that kind of problem with the 1-8. That's not what I'm concerned about. There are other things that I don't know that have been captured. And we don't have concentration of use. And we don't have chronic tox on any of these, except the 1-4. And 1-4 is a different size molecule for multiple reasons. So.

DR. LIEBLER: So if we go back to, I realize you're not strictly concerned about neurotoxicity here. But, really the, sort of the genesis of the concern about these short chain hydrocarbons comes from the hexane story. And, even though, I mean, I agree with Curt. You know, we don't -- couldn't recite to you the dose per se. What it is is it was -- it first came out as a clear occupational exposure toxicology story, for people who were working with solvents that contained high proportions of hexane. And were exposed to hexane breathing over extended period of times, developed this peripheral neuropathy. And that, after a lot of investigation, what turned out to be a story of metabolism of hexane by, you know, hydroxylation at the 2 and 5 positions, followed by oxidation to the ketone, followed by, what I would call, sort of a biochemical bad luck reaction with lysine's on neurofilaments that just happened to have the right spacing in distance. So, and Curt's right about the extensive studies of structure activity to try and figure out if this is a risk for other solvents. And you can't make this work with, you know, 1-6. Or you can't make it work with other hydrocarbons. You can't make it work if you've got methyl groups on the intervening chain, because it distorts the structure. So, I mean, it's a very, you know, as I say, biochemical bad luck.

DR. HILL: But that work was focused on neurotoxicity.

DR. LIEBLER: It was but it actually was a high dose toxicology problem. With octanediol, we admittedly, we have no concentration of use. We've got three uses. No concentration of use.

DR. HILL: So I'm worrying about things like DNA cross-linking at that length.

DR. LIEBLER: Yeah.

DR. HILL: And I don't think that's just a hypothetical concern, because those chemistries are known.

DR. LIEBLER: Those chemistries are known. And sometimes, they do contribute -- rarely they contribute to toxicity. Serious toxicities or cancer. But, the idea of, you know, straight chain hydrocarbons being carcinogens because they're oxidized, you know, to carbinols and shift [Schiff] based formation, etcetera. I mean, there's nothing like that in the literature.

DR. HILL: It's not a straight chain hydrocarbon. If it was, if it was just octane, I wouldn't have this concern.

DR. LIEBLER: Well, no, no. I mean.

DR. HILL: Because we've already got the first oxidation step at both ends. But if you look at the kinds of roots and metabolism. So, typically, if you have just octanol or octane, that's oxidized octanol, then the faster reactions will be conversion of that alcohol to aldehyde carboxylic acid conjugation elimination. It's gone. This is a unique compound, and it seems like we have zero toxicology on it, unless I'm missing something, and it will be dermally penetrable, so if you did the -- if for example, it was used at five percent in a foundation, where somebody's using it on a fairly large surface area, every day, I just feel like we have no data. There may be no problem. I doubt there's a problem. I don't have any strong gut feel there's a problem. But in this particular case, I'm bothered by it. And there are uses it seems. But we aren't being given the concentration to even work from.

DR. LIEBLER: Yeah. So I look at octanediol as a -- essentially a metabolite of octane. A possible metabolite of octane. And this is why -- well, I mean, and it's certainly precedent. Because we already know the other hydrocarbons do undergo those hydroxylation reactions. And that's how the hexane story happened. So, I think that, you know, we don't have any in the toxicology literature, there is really nothing that points to this problem. This is a kind of metabolism related toxicity problem with these hydrocarbons. Aside from hexane, the main toxicity story with hydrocarbons, is acute very high dosage exposure in the kind of, you know, seeing as to the pressure you get. So, for that reason, I don't deny that the chemistry could happen. But I do feel that there's no evidence on literature to say, it's toxicologically significant. And I think this is kind of the toxicology version of the argument I often hear Jim and Don make about, you know, in our experience, we have never seen sensitization to such and such. Or this or that or the other.

And I feel like that's kind of what I -- having been familiar with the tox literature for a long time, this is just not a red flag area for me. And I don't know if Curt shares this opinion. But, that's the reason I'm not as concerned about the points you've made Don. And Ron, I'm not saying that they're not potentially real, but I don't think their toxicologically significant.

DR. HILL: Given the nature of the compound, I would just like to know that it's not used at 80 percent in some foundation. And we, I mean, if it's one percent. If it's even five percent, I agree. But we don't have it and I don't understand why something is in use when at least we have indication that it's in use. We don't have a concentration. I know it's VCRP. I know we survey and usually the industry's pretty good. But I think that's ridiculous in this case.

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

DR. SNYDER: No comment.

DR. LIEBLER: Curt, do you have an additional comment?

DR. KLAASSEN: I don't think so.

DR. BERGFELD: Okay. Don?

DR. BELSITO: Well, yeah. I mean, I think if we're going to dismiss the hexane dial before I would be comfortable signing off on that, I would like a little bit more information on dose response for 2-5, in terms of neurotoxicity. Because you're going to ask me to sign off on something where I agree it will be used in low amounts. But, I don't know the dose response for neurotoxicity with that. And, as I said before, sometimes low amounts of things can cause bad problems.

DR. BERGFELD: Jim.

DR. KLAASSEN: I'd just like to say that that data is available. I mean, we can pull out the papers. It's actually the people at Kodak that did these studies about 25 years ago. So, they're probably done well. And how this thing with hexane really came out in the first place, was the people that made shoes in Italy in their garages, and they used various glues that contained hexane. And they got neurotoxicity. And it was eventually figured out what it was. And it was a scientist at Kodak that did it. So, there is good science there. And we can figure out very easily what the dose is.

DR. SHANK: I think the dose response data that's available is on hexane and the dione. But not on the diol.

DR. KLAASSEN: That's true.

DR. SHANK: So, I'm not sure that's going to help you.

DR. HILL: Yeah but they -- once you get to the ketone stage, there's a pretty free and rapid metabolic interchange between ketone and secondary alcohol. So, I mean, essentially having the data for, you're right, but essentially having the data for that dione should pretty much give us the answer.

DR. BELSITO: The (inaudible) of magnitude about what we're seeing from potential exposure in cosmetics are to be comfortable. I just don't have any idea what order of magnitude we're talking about. And it's not in this document. And I would feel uncomfortable signing off on something that I know absolutely nothing about four percent of the material.

DR. SNYDER: I just did a quick Google search, and there's a paper here where they show an NOAEL, the hexanediol, and at 20 milligrams per kilogram in rats.

DR. BELSITO: So.

DR. SHANK: So, just the diol then?

DR. SNYDER: Yes.

DR. LIEBLER: Yeah. But just to clarify, this is the active metabolite, if you will, the direct -- reacts directly. So, this should be the most potent.

DR. BELSITO: Right.

DR. LIEBLER: So the diol is going to be another order of magnitude less potent most likely.

DR. BELSITO: So incorporating that information into the neurotoxicity section, would make me comfortable not knowing the other four percent of hexanediol.

DR. HILL: Is that oral dosing though in rats?

DR. LIEBLER: Subcutaneous.

DR. HILL: Sub -- okay great. Okay.

DR. BERGFELD: So go ahead. Where are we standing now Jim?

DR. MARKS: Well, I wanted to --.

DR. BELSITO: We've gotten rid of hexanediol,

(Laughter) which show we'd all agree on butanediol. And I'm -- it's not my expertise to argue about octanediol.

DR. MARKS: Well, I actually like Dan's reference to expert opinion. A collective intelligence in experience. So, for Ron Shank and Tom, I know Ron Hill, you still have concerns. But, because of the lack of toxicologic. That and the concentration of use. But I think Dan, in my mind, is persuasive that his collective knowledge and experiences, that we should not be concerned about the toxicology of octanediol.

DR. SLAGA: I agree. I didn't have any concerns that it would cause the pathological effect. It's just, when Ron brought up the argument that it possibly would penetrate. And we didn't have any, you know, concentration use. Once it gets in, I don't think it's going to do anything.

DR. MARKS: Ron Shank.

DR. SHANK: I don't have a concern.

DR. MARKS: So, I'll change my motion for the tentative report. That it's safe for nine ingredients. And the only ingredient which is insufficient, is the 1-4 butanediol. And we need the concentration of use.

DR. BERGFELD: Is there a second?

DR. BELSITO: Second.

DR. BERGFELD: Any further discussion?

DR. BELSITO: We'd be (inaudible).

DR. BERGFELD: Call for the vote then. All those in favor, raise your hand.

DR. HILL: (Raises hand)

DR. BERGFELD: Opposed? One opposed. Thank you very much. The next ingredient then, after this vigorous discussion, will be Dr. Belsito with panthenol.

**SEPTEMBER 2016 PANEL MEETING MINUTES**
**ALKANE DIOLS (Day 1)**
**DR. MARKS' TEAM**

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 [decane?] 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.

**SEPTEMBER 2016 PANEL MEETING MINTUES**
**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.

**SEPTEMBER 2016 PANEL MEETING MINUTES**
**ALKANE DIOLS (Day 2)**

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

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## 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 issued an insufficient data conclusion for the concentration of use in cosmetics for 1,4-Butanediol. The Panel concluded that the remaining 9 alkane diols are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

## INTRODUCTION

This assessment reviews the safety of the 10 alkane diols listed below (with systematic nomenclature in parenthesis when different from the ingredient name) as used in cosmetic formulations. 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 (2-butyl-2-ethyl-1,3-propanediol)
Isopentyldiol (3-methyl-1,3-butanediol)

The alkane diols reviewed in this safety assessment have various reported functions in cosmetics (Table 1), as indicated in the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI *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. Please see the original reports for further details (www.cir-safety.org/ingredients).

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; http://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

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] and in reports made publically available by the Food and Drug Administration (FDA),[22-28] the Environmental Protection Agency (EPA),[29-32] and the National Technical Information Service (NTIS).[33-37]

## 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).

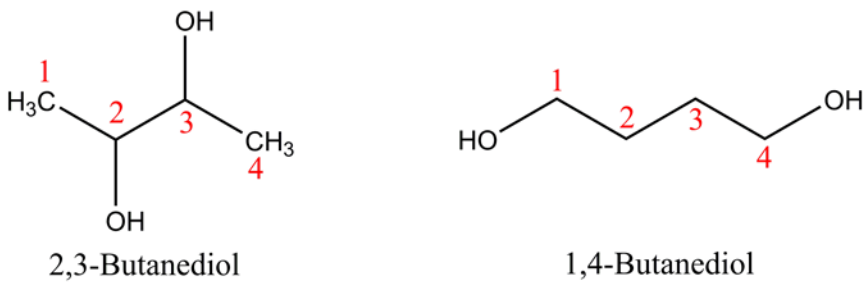



Figure 1. 2,3-Butanediol and 1,4-Butanediol

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.[38,39] 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. Some are soluble in alcohol (Table 3). All of the terminal diols are soluble or somewhat soluble in water, except for the longest chain ingredient, 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 by fermentation from corn-derived glucose using a biocatalyst (non-pathogenic strain of *Escherichia coli* K-12).[40] Propanediol can also be manufactured by heating γ,γ-dihydroxydipropyl ether with hydrobromic acid, followed by hydrolysis with sodium hydroxide. It is also reported to be obtained from plants that produce glycerol.[37]

*1,4-Butanediol*

Some industrial chemical companies manufacture 1,4-Butanediol using cupric acetylide catalysts in the condensation reaction of acetylene with formaldehyde.[37] 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 via vapor phase hydrogenation of their corresponding esters and anhydrides. *E. coli* can be genetically engineered to metabolize sugar to 1,4-Butanediol.[41]

*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*) to produce 2,3-Butanediol.[37] Fermentation of potatoes or wheat mash also yields 2,3-Butanediol. Mixtures of gases containing isobutylene and *n*-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*.[42]

*1,5-Pentanediol*

1,5-Pentanediol can be prepared in the presence of copper chromite via hydrogenolysis of tetrahydrofurfuryl alcohol.[42]

*1,10-Decanediol*

1,10-Decanediol may be prepared by reducing diethyl or dimethyl sebacate with sodium metal in ethyl alcohol. It may also be prepared by catalytic hydrogenation of sebacic esters.[42]

*Methylpropanediol*

On an industrial scale, carbon monoxide and hydrogen can be used to hydroformylate allyl alcohol to the intermediate, hydroxy-methylpropionaldehyde, which is then hydrogenated to yield Methylpropanediol.[32]

## Impurities

*Propanediol*

The following Food Chemicals Codex acceptance criteria apply for Propanediol in relation to food preparation: cobalt (≤ 1.0 mg/kg or 1 ppm); lead (≤ 1.0 mg/kg or 1 ppm); nickel (≤ 1.0 mg/kg or 1 ppm).[40] The purity of Propanediol should be ≥ 99.9% and water content should be ≤ 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.[43] Propanediol was reported to be ≥ 99.98% pure; 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 of 1,4-Butanediol because they are sometimes used as starting materials in the manufacture of this ingredient, as mentioned above.[20] 1,4-Butanediol has been reported to be 98% pure (impurities were not specified).[21]

*1,5-Pentanediol*

1,5-Pentanediol was found to be 98.1% pure by gas chromatographic/mass-spectrometry analysis; a total of 0.28% unknown impurities (not diols, as stated by the study authors) were reported.[45] 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).[46]

*Methylpropanediol*

Methylpropanediol has been reported to be 98% pure (maximum 2% impurities; maximum 0.1% water content, maximum 0.05% carbonyl content) by a manufacturer.[47]

*Isopentyldiol*

Isopentyldiol has been reported to be 97% pure with 3% of impurities (no further details provided).[18] Isopentyldiol is > 99% pure as reported by a cosmetics raw material supplier.[48]

### 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 raspberries, up to 850 mg/kg in vinegar, 1.9 mg/kg in sherry, and up to 2900 mg/kg in various types of wine."[49]

## USE

### Cosmetic

The 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[50] indicated that some of the alkane diols are being used in cosmetic formulations (Table 4). Among the ingredients reported to be most frequently used are Propanediol (1138 reported uses), Methylpropanediol (541 reported uses), and Isopentyldiol (135 reported uses). Results from a concentration of use survey conducted in 2015[51] (Table 4) indicated that the ingredients with some of the highest maximum reported concentrations of use were 39.9% Propanediol (in non-spray deodorants), 21.2% Methylpropanediol (in non-spray body and hand products), and 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.[50] Conversely, there was an instance in which no uses were reported in the VCRP, but use concentrations were provided in the industry survey; 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% in tonics, dressings and other hair grooming aids.[51] It should be presumed that there is at least one use in this category.

There are no frequency of use, or concentration of use, data reported for 2,3-Butanediol and 1,5-Pentanediol.[50,51]

Alkane diols were reported to be used in cosmetic sprays, including perfumes, hair sprays, and deodorants, and could potentially be incidentally inhaled. For example, Propanediol was reportedly used in aerosol and pump hair sprays at concentrations up to 0.12% and 1.5%, respectively, and it was used in face and neck sprays at concentrations up to 3%.[51] 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.[52-55] 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.[52,54] 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.[54] 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%[51] 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.[56-58]

Alkane diols were reported to be used in cosmetic formulations indicative of potential eye exposure (e.g., Propanediol is used at up to 10% in eye makeup removers) and possible mucous membrane exposure and ingestion (e.g., Propanediol at 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.[59] In a NICNAS report, Isopentyldiol was determined not to be an unacceptable risk to public health in cosmetic products up to 10% (the highest use concentration reported in the NICNAS document).[18]

### Non-Cosmetic

The non-cosmetic uses of the alkane diols (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.[60] GHB, occurring endogenously in mammals, is a neurotransmitter with a high affinity for pre- and postsynaptic neuron GHB-receptors.[61] 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.[26] 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 reportedly 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.[61] In 1997, the FDA re-issued a warning for GHB used recreationally and in body building because it caused serious adverse health effects.[26] As of 2000, the Drug Enforcement Agency (DEA) reported GHB to be a Schedule I Controlled Substance and 1,4-Butanediol and gamma-butyrolactone to be controlled substance analogs if they are intended for human consumption pursuant to 21 U.S.C §§802(32)(A) and 813.[60] Sodium oxybate (the sodium salt form of GHB) is an FDA-approved prescription drug product (schedule III controlled substance)[60] used to treat attacks of muscle weakness and daytime sleepiness in narcolepsy patients.[22,23,27] 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 cleared by the FDA (Section 510(k)).[28,62] Sources did not specify 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.[45,63,64] Additionally, 1,5-Pentanediol has reported uses in products for hair loss, cold sores, nail problems, dry and scaly feet, and eczema; it can be used as a moisturizing substance and solvent.[64]

## 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 $1.50 \times 10^{-5}$ 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 in human skin was evaluated in an in vitro experiment using a Franz diffusion cell.[65] 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 estradiol in 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.

Penetration enhancement tests in vitro showed 1,5-Pentanediol to be a penetration enhancer for certain pharmaceutical drugs.[66,67] Test cream formulations containing 0.1% tri-iodothyroacetic acid (TRIAC; a thyroid hormone analog) 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.[66]

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.[66] In a separate experiment, test cream formulations containing 1% hydrocortisone and either 1,5-Pentanediol (25%) or 1,2-Propanediol (25%) were evaluated using human breast skin.

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.[66] 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 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.

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, in a hydrogel formulation.[67] 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.

## Absorption, Distribution, Metabolism, Excretion

Absorption, distribution, metabolism, and excretion studies are summarized below; 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.[68] 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.[69] Methylpropanediol was a substrate for rat liver alcohol dehydrogenase.[32]

### *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.[70] 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.[71]

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).[68] 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).[72] 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.[73]

Experiments in rats orally administered 1 M diacetyl, acetoin or 2,3-Butanediol showed that these compounds interconvert.[69] 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).[31,32,74]

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.[69]

***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).[64] 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).[75] 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.[72] 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.[76] 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.[61] This metabolism has been reported to occur in rat brain and liver.[73] Ethanol, a competitive substrate for alcohol dehydrogenase, can inhibit 1,4-Butanediol metabolism.[61,68] 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.[61] 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,[77] > 20 ml/kg in rabbits for 1,5-Pentanediol,[78] > 10 g/kg in rabbits for Hexanediol,[78,79] and > 2 g/kg in rabbits for Butyl Ethyl Propanediol.[80] 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.[81] 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).[82] Clinical signs reported in rabbits 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 approximate lethal dosage (ALD) of 17 g/kg (70% purity) and > 25 g/kg (99.8% purity) and an $LD_{50}$ of 14.9 ml/kg were reported in rats dosed with Propanediol; clinical effects noted were sluggishness, sedation, ataxia, irregular respiration, unconsciousness followed by the death of some of the animals.[11,35] Various animal studies reported an $LD_{50}$ between 1.2 and 2.5 g/kg for 1,4-Butanediol.[12,21,34,37,72,81] 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.[81] 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.[12,34,81] For the following alkane diols, $LD_{50}$s were reported as: > 5 g/kg in rats[15] and 9 g/kg[49] in mice for 2,3-Butanediol, 10 g/kg 1,5-Pentanediol in rats,[13] 3 g/kg Hexanediol in rats,[14] > 0.20 ml/kg 1,10-Decanediol (1.2% in a 20 ml/kg trade name mixture also containing unspecified amounts of Propylene Glycol) in mice,[83] > 5 g/kg Methylpropanediol in rats,[19] 2.9 g/kg[16] and 5 g/kg[80] Butyl Ethyl Propanediol in rats, and > 5 g/kg Isopentyldiol in mice.[18] Clinical signs reported in rats 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 dosed with Hexanediol[14] or Butyl Ethyl Propanediol[16] and mice dosed with 1,10-Decanediol[83] or Isopentyldiol[18] showed no abnormalities. 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.[77] 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.[84] 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),[78] Hexanediol (concentrated vapor),[78,79] or an $LC_{50}$ > 5.1 g/l was reported for inhalation of Methylpropanediol (duration of inhalation not specified).[32]

## 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.[85] 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 no-observed-adverse-effect-level (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)[36] 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.[36] 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 abnormalities of the liver (in males at 1000 mg/kg/day) and kidney (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.[77] 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 slight, red nasal discharge at all levels tested (0.2, 1.1, 5.2 mg/l), lower body weights (at 5.2 mg/l only), and abnormal blood chemistry parameters (at 5.2 mg/l only); a no-observed-adverse-effect-concentration (NOAEC) of 1.1 mg/l was reported.[84]

## 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;[86] 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, and urinary (at 150 and 1000 mg/kg/day) and kidney abnormalities (at ≥ 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 lowest-observed-adverse-effect-level, 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 histopathological exam revealed pulmonary emphysema, mild lung edema, treatment-related inflammatory changes of single alveolar cell and weak hyperplasia of alveolar septum.[21]

## Chronic Toxicity

**Oral**

*1,4-Butanediol*

Experimental details for one chronic toxicity study found in the literature were limited.[21,87] 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.

**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)[86] 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.[88] For male and female rats 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).[31,32] 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),[89] 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 (1.2% in a trade name mixture also containing unspecified amounts of Propylene Glycol or Butylene Glycol) was non-mutagenic in an Ames test (up to ~ 120 µg/plate 1,10-Decanediol).[83] 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.[70] 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 oral dose of 2150 mg/kg)[11] and for Butyl Ethyl Propanediol (single oral dosage up to 1250 mg/kg).[16]

## CARCINOGENICITY STUDIES

Carcinogenicity studies data on alkane diols were not found in the published literature, and unpublished data were not submitted.

## OTHER RELEVANT STUDIES

### Cytotoxicity

*1,10-Decanediol*

An Agarose Overlay Test was performed by evaluating the diffusion in an agarose gel of a trade name 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.[83]

### Neurotoxicity

*1,4-Butanediol*

Central nervous system effects have been reported for exposures to 1,4-Butanediol.[72] 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).

*Hexanediol (2,5-hexanedione, a potential impurity of hexane)*

Experiments were conducted in female Wistar rats (n=12 to 19/group) to determine the effects of 2,5-hexanedione (a known neurotoxin and can be an impurity in hexane); testing examined open field behavior, step-down inhibitory avoidance, and shuttle avoidance.[90] In the first experiment, rats were subcutaneously injected with 200 mg/kg/day 2,5-hexanedione (97% pure) in a vehicle comprised of 120 mM NaCl and 10 mM phosphate buffer (pH 7.2) or with vehicle only, 4 to 5 hours prior to the behavioral testing. Animals were trained in the behavioral exercises 24 hours prior to the testing session. Food and water were available ad libitum. The animals treated for 25 or 50 days were subjected to open-field behavioral testing on days 15 or 30, step-down inhibitory avoidance testing on days 20 or 40, and avoidance test on days 25 and 50, respectively. Results indicated that the 200 mg/kg/day treatment caused a statistically significant reduction in body weight, 10% (by 25 days) to 15% (by 61 days), compared to controls. General motor activity of rats treated for 15 and 30 days was impaired with 200 mg/kg/day treatment. The treatment was shown to cause diminished activity in the open field testing, however habituation was not impacted. Shuttle avoidance was substantially impaired with the 200 mg/kg/day treatment in both the 25 and 50 day groups; inhibitory avoidance was unaltered by treatment, implying that memory was not affected for this test.

In a second experiment by the same researchers, animals were treated for 50 days with vehicle only or 20 mg/kg/day 2,5-hexanedione subcutaneous injections using the same vehicle as above.[90] These animals underwent open-field behavioral testing on day 30, step-down inhibitory avoidance testing on day 40, and avoidance testing on day 50. Results showed that none of the behavioral tasks tested were impacted by the 20 mg/kg/day treatment.

## 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 trade name 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.[83]

#### *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;[81] 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[78] 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;[14,78,79,91] 1,10-Decanediol (1.2% in a trade name mixture also containing an unspecified amount of Propylene Glycol) was non-irritating to rabbit skin in a 24 h occlusive patch test;[83] Methylpropanediol (concentration not specified) was non-irritating to animal skin;[19,19,32] 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 in 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 (undiluted) was non-irritating after a single application of test substance (no further details provided);[92] 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;[45] 1,10-Decanediol (1.2% in a trade name 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;[83] Methylpropanediol (100%, 50% aqueous dilution) was non-irritating to subjects with sensitive skin in a 14-day cumulative irritation study;[32,74]Isopentyldiol (concentration not specified) was slightly irritating in a 48-hour Finn chamber skin test.[18] Generally, the alkane diols evaluated were non-to-slightly irritating in 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 in guinea pigs. Propanediol (2.5% intradermal and 100% epicutaneous concentrations applied at induction, 50% epicutaneous and semi-occlusive at challenge) was non-sensitizing;[11] 1,4-Butanediol (10% intradermal and 30% topical concentrations applied at induction and challenge) was non-sensitizing.[81] 2,3-Butanediol (5% intradermal and 50% epicutaneous concentrations applied at induction, 25% at challenge) was non-sensitizing, 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 in one test.[14] In another test, strong erythema was reported 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.[91] 1,10-Decanediol (1.2% in a trade name mixture containing an unspecified amount of Propylene Glycol or Butylene Glycol) was non-sensitizing in a Buehler test (1.2% 1,10-Decanediol in trade name mixture used at induction and 0.3% 1,10-Decanediol in trade name mixture used at challenge).[83] Methylpropanediol showed mild sensitization potential (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.[16] Isopentyldiol (10% intradermal and 100% topical concentrations applied at induction, 50% at challenge) was non-sensitizing. However, during intradermal injection at induction and topical induction, moderate and confluent erythema were observed.[18] The alkane diols showed non-to-mildly sensitization potential and some positive skin irritation reactions were observed during induction.

***Human***

Clinical 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) with mild erythema reported in 4 subjects of 207 during induction (75% only) after the 1st of 9 applications;[92] 1,4-Butanediol (concentration not specified) was non-sensitizing;[21] 1,5-Pentanediol (5% and 25% in different tests) was non-sensitizing;[45] Methylpropanediol (concentration not specified) was non-sensitizing in one test;[32] 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 condition.[32,74] 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.[93] The alkane diols evaluated were non-sensitizing in human skin.

### Photoirritation /Photosensitization

***Animal***

1,10-Decanediol (1.2% in a trade name mixture also containing an unspecified amount of Butylene Glycol) was non-phototoxic in guinea pig skin.[83] 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 UVA/ UVB exposure to the treated skin; study authors stated that it does not absorb in the long-wave ultraviolet range (i.e. UVA).[45,64]

## 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 trade name 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.[83] 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. No-to-slight irritation (resolved within 48 hours post-application) was reported for undiluted Propanediol.[11] Undiluted 1,4-Butanediol was slightly irritating.[37,81] Undiluted 2,3-Butane-diol was non-irritating to rabbit eyes.[15] No-to-mild irritation was observed for undiluted 1,5-Pentanediol[13,33,78] and undiluted Hexanediol.[14,78,79] 1,10-Decanediol (1.2% in a trade name mixture also containing an unspecified amount of Propylene Glycol) was slightly irritating.[83] Methylpropanediol (concentration not specified) was non-irritating to rabbit eyes.[19,32] Butyl Ethyl Propanediol (concentration not specified) resulted in severe eye injury in one test.[80] 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] Generally, the alkane diols were non-to-mildly irritating, with the exception that Butyl Ethyl Propanediol was irritating.

## CLINICAL STUDIES

*1,5-Pentanediol*

A controlled, double-blind comparative study was conducted to evaluate the treatment of atopic dermatitis with hydrocortisone and 1,5-Pentanediol.[94] 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.[95] 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,[96,97] 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,[91] and adverse effects reported in adults (including death) and poisoning in children from oral exposure to 1,4-Butanediol (varying doses).[12,21,34,98,99]

## RISK ASSESSMENT

### Occupational Standards

*1,4-Butanediol*

In Germany, the occupational limit value for 1,4-Butanediol is 50 $ml/m^3$ (ppm) or 200 $mg/m^3$.[100]

## 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.

1,4-Butanediol, Hexanediol, and Methylpropanediol 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, > 0.20 ml/kg 1,10-Decanediol (1.2% in a 20 ml/kg trade name 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 of 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 (duration of inhalation not specified) 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 in females and 50 mg/kd/day in males (28 days), and 1000 mg/kg/day Propanediol and Methylpropanediol (14 days) or Hexanediol and Butyl Ethyl Propanediol (28 days). The 28-day experiment in rats evaluating the toxicity of 1,4-Butanediol revealed liver abnormalities in treated animals. The 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). The

28-day experiment evaluating oral exposure to Butyl Ethyl Propanediol in rats resulted in abnormalities in the liver (in males at 1000 mg/kg/day) and kidney (in males at 150 or 1000 mg/kg/day). Rabbits orally exposed to Hexanediol (up to 2000 mg/kg for 25 doses, duration unknown) exhibited thrombosis and treatment-related effects (unspecified) on 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 slight red nasal discharge (at levels 0.2, 1.1, and 5.2 mg/l), lower body weights (at 5.2 mg/l only), and abnormal blood chemistry parameters (at 5.2 mg/l only); a 1.1 mg/l NOAEC was reported.

The NOAELs reported in subchronic oral exposure studies were 15 mg/kg/day and 150 mg/kg/day Butyl Ethyl Propanediol (90 days) in male and female rats, respectively. In 90-day studies, a NOAEL of 600 mg/kg/day was reported for Methylpropanediol and NOAELs of 1000 mg/kg/day were reported for Propanediol and Hexanediol (in females; 400 mg/kg/day NOAEL in males) in oral exposure studies in rats. An evaluation of oral exposure to 5 or 10 ml/kg Propanediol for 15 weeks in rats resulted in 100% mortality (5 deaths) at 10 ml/kg and 2 deaths at 5 ml/kg. In the male rats dosed with Hexanediol, mentioned above, a treatment-related decrease (in males at 1000 mg/kg/day) in mean body weights and a statistically significant increase in organ weights (in males at 400 and 1000 mg/kg/day) were observed. The rats dosed with Methylpropanediol showed decreased liver enzymes and inorganic phosphate (at 1000 mg/kg/day). In rats dosed with Butyl Ethyl Propanediol, there were 4 treatment-related deaths (males at 150 or 1000 mg/kg/day), abnormal respiration 1 to 2 hours post-dosing (after which animals returned to normal), and urinary (at 150 and 1000 mg/kg/day) and kidney abnormalities (at ≥ 15 mg/kg/day) reported.

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 a histopathological exam revealed 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 an oral exposure 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 orally 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 in oral exposure studies for maternal and developmental effects in animals. In another oral exposure study, 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.

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 (1.2% in a trade name mixture also containing unspecified amounts of Propylene Glycol or Butylene Glycol) was negative in an Ames test (up to ~120 µg/plate 1,10-Decanediol). 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).

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 provided). Neurotoxicity was evaluated in behavioral tests in rats subcutaneously injected for 50 days with vehicle only or 20 mg/kg/day 2,5-hexanedione. Results showed that none of the behavioral tasks tested were impacted by the 20 mg/kg/day treatment. In other similar behavioral tests in rats subcutaneously injected with 200 mg/kg/day 2,5-hexanedione for up to 50 days, substantial behavioral impairment was observed.

1,10-Decanediol (1.2% in a trade name 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 trade name 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. The alkane diols were non-to-mildly irritating to the skin of animals.

A single, dermal application of undiluted Propanediol was non-irritating in human subjects (no further details). 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 trade name 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. Generally, the alkane diols were non-to-slightly irritating in human skin.

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 trade name mixture containing an unspecified amount of Propylene Glycol or Butylene Glycol) in a Buehler test (1.2% 1,10-Decanediol in trade name mixture used at induction and 0.3% 1,10-Decanediol in trade name mixture used 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). The alkane diols were non-to-mildly sensitizing in animals.

Propanediol (5% to 75% concentrations applied at induction and challenge) was non-sensitizing in human subjects; mild erythema was reported in 4 subjects during induction (75% only) after the 1$^{st}$ of 9 applications. 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. Overall, the alkane diols were non-sensitizing to human subjects.

1,10-Decanediol (1.2% in a trade name 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 UVA/ UVB 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 trade name 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 trade name 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; recommendations 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

At the April 2017 CIR Expert Panel Meeting, the Panel concluded that the available data are insufficient to make a determination that 1,4-Butanediol is safe under the intended conditions of use in cosmetic formulations, specifying a need for concentration of use data. No concentration of use data for 1,4-Butanediol have been submitted. There are frequencies of use reported in the 2017 VCRP for 1,4-Butanediol in FDA product categories for other eye makeup preparations, moisturizing, skin fresheners, and indoor tanning preparations. Neurotoxicity effects have been observed with oral administration of 1,4-Butanediol, which converts to GHB in animals and humans.

Although no neurotoxicity data for Isopentyldiol was found in the literature, the Panel determined that the acute oral toxicity data in mice showed no adverse clinical or histopathological changes and, therefore, no specific neurotoxicity data was needed.

The Panel also concluded that there was no safety concern for the known neurotoxin, 2,5-hexanediol, being present as a possible impurity of Hexanediol. The Panel arrived at this conclusion after considering the low maximum concentration of Hexanediol reported to be used at 0.5% in leave-on dermal contact cosmetics, a > 96% purity reported for Hexanediol, and research showing no adverse behavioral effects in rats subcutaneously exposed to 20 mg/kg/day 2,5-hexanedione (the relatively more toxic ketone form of 2,5-hexanediol) for 50 days.

Although there were no toxicology data found in the literature or submitted to CIR for Octanediol, the Panel did not have toxicological concerns with this ingredient. Octanediol is reportedly used in skin fresheners (no concentration of use data was available). The collective knowledge base and experience of the Panel confirmed a lack of evidence in the literature for this ingredient, essentially a metabolite of octane, to produce toxic effects in the body.

The Panel discussed that alkane diols have a high potential to be dermally absorbed, especially considering their low molecular weights.

The 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.

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

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.

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. The occupational exposure limit for 1,4-Butanediol in Germany is 200 $mg/m^3$. Propanediol (up to 3%) and Isopentyldiol (up to 5%) are reportedly used 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.

## CONCLUSION

The CIR Expert Panel concluded that the following 9 ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment:

Propanediol (1,3-Propanediol)
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 Panel also concluded that the available data are insufficient to make a determination that 1,4-Butanediol is safe under the intended conditions of use in cosmetic formulations.

**Not reported to be in current use or no maximum concentration of use reported. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

# TABLES

**Table 1. Definitions, structures, and functions of the ingredients in this safety assessment.** [101;CIR Staff]

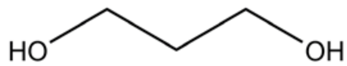
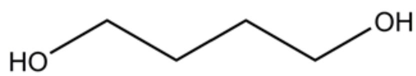
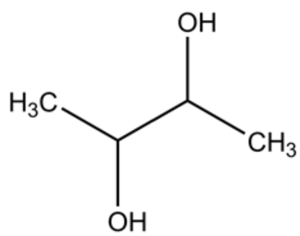
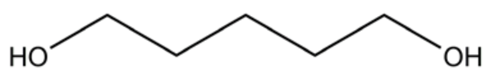
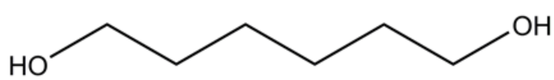
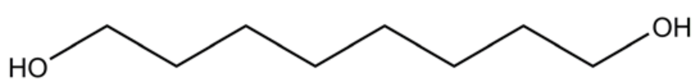
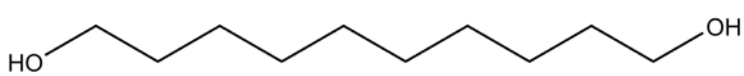
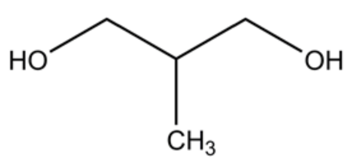
| Ingredient Name & CAS No. | Definition & Structure | Function |
|---|---|---|
| Propanediol<br><br>26264-14-2<br><br>504-63-2 | Propanediol is the organic compound that conforms to the formula:<br> | Solvent; Viscosity Decreasing Agent |
| 1,4-Butanediol<br><br>110-63-4 | 1,4-Butanediol is the organic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

**Table 1. Definitions, structures, and functions of the ingredients in this safety assessment.** [101;CIR Staff]

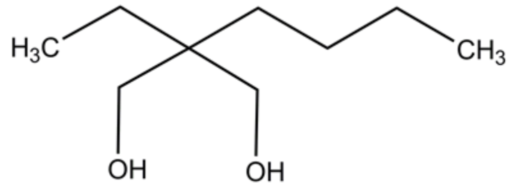
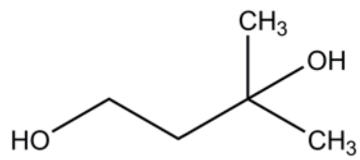
| Ingredient Name & CAS No. | Definition & Structure | Function |
|---|---|---|
| Butyl Ethyl Propanediol<br><br>115-84-4 | Butyl Ethyl Propanediol is the organic compound that conforms to the formula:<br> | Skin-Conditioning Agent; Humectant |
| Isopentyldiol<br><br>2568-33-4 | Isopentyldiol is the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

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

| Ingredient | Conclusion (year issued)* | Reference |
|---|---|---|
| **1,2-ALKANE DIOLS (aliphatic diols)** | | |
| Propylene Glycol (i.e., 1,2-propanediol) | Safe as used when formulated to be non-irritating (2012) | 3,4 |
| 1,2-Butanediol | Safe as used (2012) | 2 |
| Pentylene Glycol (i.e., 1,2-pentanediol) | Safe as used (2012) | 2 |
| 1,2-Hexanediol | Safe as used (2012) | 2 |
| Ethyl Hexanediol (i.e., 2-ethyl-1,3-hexanediol) | Safe as used (1994); reaffirmed in 2011 | 5,6 |
| Caprylyl Glycol (i.e., 1,2-octanediol) | Safe as used (2012) | 2 |
| Decylene Glycol (i.e., 1,2-decanediol) | Safe as used (2012) | 2,3 |
| **OTHER ALIPHATIC DIOLS** | | |
| Butylene Glycol (i.e., 1,3-butanediol) | Safe as used (1985); reaffirmed in 2006 | 7,8 |
| Hexylene Glycol (i.e., 2-methyl-2,4-pentanediol) | Safe as used (1985); reaffirmed in 2006 | 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) | 9 |
| Succinic Acid (sometimes used in the synthesis of 1,4-Butanediol) | Safe as used (2012) | 10 |

*Please see the original reports for further details (www.cir-saftey.org/ingredients).

**Table 3. Physical and Chemical Properties**

| Property | Value | Reference |
|---|---|---|
| **Propanediol** | | |
| Physical Form | Hygroscopic liquid; viscid (sticky) liquid | 40,42 |
| Color | Colorless; Colorless to pale yellow | 40,42 |
| Odor | Mild, sweet | 40,42 |
| Molecular Weight (g/mol) | 76.10 | 42 |
| Density (g/ml) | 1.0597 | 42 |
| Melting Point (°C) | 146-147 | 102 |
| Boiling Point (°C) | 210-212 | 42 |
| Water Solubility | Slightly soluble | 40 |
| Other Solubility | Soluble in alcohols and acetone; miscible with many polar solvents | 40 |
| Log P @ 25 °C | -1.093±0.458 calculated | 103 |
| pKa @ 25 °C | 14.46±0.10 calculated | 103 |

**Table 3. Physical and Chemical Properties**

| Property | Value | Reference |
|---|---|---|
| **1,4-Butanediol** | | |
| Physical Form | Viscous liquid | 42 |
| Color | Colorless | 42 |
| Molecular Weight (g/mol) | 90.12 | 42 |
| Density g/ml @ 20 °C | 1.069 | 102 |
| Melting Point (°C) | 19-19.5 | 42 |
| Boiling Point (°C) | 230 | 42 |
| Water Solubility | Soluble | 42 |
| Other Solubility | Soluble in DMSO, acetone, 95% ethanol | 42 |
| Log P @ 25 °C | -0.767±0.187 calculated | 103 |
| pKa @ 25 °C | 14.73±0.10 calculated | 103 |
| **2,3-Butanediol** | | |
| Physical Form | Hygroscopic crystals (*meso*-form) | 42 |
| Molecular Weight (g/mol) | 90.12 | 42 |
| Density (g/ml) @ 25 °C | 0.9873 | 102 |
| Melting Point °C (meso-Form) | 34.4 | 42 |
| Boiling Point (°C) | 181.7 | 42 |
| Water Solubility (pH 6.90) (g/l) in unbuffered @ 25 °C | 245 calculated | 103 |
| Other Solubility | Moderately soluble in diisopropyl ether | 42 |
| Log P @ 25 °C | -0.655±0.221 calculated | 103 |
| pKa @ 25 °C | 14.67±0.20 calculated | 103 |
| **1,5-Pentanediol** | | |
| Physical Form | Viscous, oily liquid; bitter taste | 42 |
| Odor | Odorless | 64 |
| Molecular Weight (g/mol) | 104.15 | 42 |
| Density (g/ml) | 0.9941 | 42 |
| Melting Point (°C) | -18 | 42 |
| Boiling Point (°C) | 239 | 42 |
| Water Solubility | Miscible with water | 42 |
| 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 | 42 |
| Log P @ 25 °C | -0.559±0.185 calculated | 103 |
| pKa @ 25 °C | 14.83±0.10 calculated | 103 |
| **Hexanediol** | | |
| Physical Form | Crystals | 42 |
| Molecular Weight (g/mol) | 118.18 | 42 |
| Density (g/ml) @ 0°C | 0.967 | 102 |
| Melting Point (°C) | 42.8 | 42 |
| Boiling Point (°C) @ 760 mmHg | 208 | 102 |
| Water Solubility | Soluble | 42 |
| Other Solubility | Soluble in alcohol; Sparingly soluble in hot ether | 42 |
| Log P @ 25 °C | -0.049±0.185 calculated | 103 |
| pKa @ 25 °C | 14.87±0.10 calculated | 103 |
| **Octanediol** | | |
| Molecular Weight (g/mol) | 146.23 calculated | 103 |
| Density (g/ml) | 0.939±0.06 calculated | 103 |
| Melting Point (°C) | 61-62 | 102 |
| Boiling Point (°C) | 140-150 | 102 |
| Water Solubility (pH 7.00) (g/l) in unbuffered water @ 25 °C | 4.8 calculated | 103 |
| Log P @ 25 °C | 0.970±0.186 calculated | 103 |
| pKa @ 25 °C | 14.89±0.10 calculated | 103 |
| **1,10-Decanediol** | | |
| Physical Form | Needles from water or diluted alcohol | 42 |
| Molecular Weight (g/mol) | 174.28 | 42 |
| Density (g/ml) @ 20 °C, 760 mmHg | 0.923±0.06 calculated | 103 |
| Melting Point (°C) | 74 | 42 |
| Boiling Point (°C) | 71.5 | 102 |
| Water Solubility | Almost insoluble | 42 |
| Other Solubility | Freely soluble in alcohol, warm ether; almost insoluble in petroleum ether | 42 |
| Log P @ 25 °C | 1.989±0.186 calculated | 103 |
| pKa @ 25 °C | 14.89±0.10 calculated | 103 |

**Table 3. Physical and Chemical Properties**

| Property | Value | Reference |
|---|---|---|
| **Methylpropanediol** | | |
| Physical Form | Viscous liquid | 32 |
| Molecular Weight (g/mol) | 90.12 calculated | 103 |
| Density (g/ml) @ 20 °C | 1.020 | 102 |
| Vapor Pressure (mmHg) @ 25 °C | 0.021 | 32 |
| Melting Point (°C) | -91 | 102 |
| Boiling Point (°C) | 195 | 102 |
| Water Solubility (pH 6.88) (g/l) in unbuffered water @ 25 °C | 215 calculated | 103 |
| Log P @ 25 °C | -0.740±0.462 calculated | 103 |
| pKa @ 25 °C | 14.51±0.10 calculated | 103 |
| **Butyl Ethyl Propanediol** | | |
| Molecular Weight (g/mol) | 160.25 calculated | 103 |
| Density (g/ml) @ 20 °C, 760 mmHg | 0.930±0.06 calculated | 103 |
| Melting Point (°C) | 41.4-41.9 | 102 |
| Boiling Point (°C) | 262 | 102 |
| Water Solubility ( pH 7.00) (g/l) in unbuffered @ 25 °C | 1.9 calculated | 103 |
| Log P @ 25 °C | 1.709±0.470 calculated | 103 |
| pKa @ 25 °C | 14.54±0.10 calculated | 103 |
| **Isopentyldiol** | | |
| Molecular Weight (g/mol) | 104.15 calculated | 103 |
| Density (g/ml) @ 20 °C | 0.9867 | 102 |
| Boiling Point (°C) @ 760 mmHg | 202 | 102 |
| Water Solubility (pH 6.96) (g/l) in unbuffered @ 25 °C | 122 calculated | 103 |
| Log P @ 25 °C | -0.329±0.470 calculated | 103 |
| pKa @ 25 °C | 14.90±0.29 calculated | 103 |

**Table 4. Current frequency and concentration of use of alkane diols[50,51]**

| | *# of Uses* | *Max Conc Use (%)* | *# of Uses* | *Max Conc Use (%)* | *# of Uses* | *Max Conc Use (%)* |
|---|---|---|---|---|---|---|
| | **Propanediol** | | **1,4-Butanediol** | | **Hexanediol** | |
| **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<br>possible: 171[a]; 145[b] | spray: 0.0001-3<br>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** | |
| **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<br>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** | |
|---|---|---|---|---|
| **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<br>possible: 74[a]; 10[b] | spray: 3-5<br>possible: 2-5[a] |
| Incidental Inhalation-Powder | NR | NR | powder: 3<br>possible: 10[b] | powder: 0.33<br>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. US Permitted 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<br>– Indirect food additive used as a component of adhesives<br>– 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<br>– 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<br>– Indirect food additive used as a reactant in the formation of polyester elastomers, which are used as basic components of food contact surfaces<br>– Indirect food additive used as a reactant to modify polyethylene phthalate polymers used as components of plastics in contact with food<br>– Indirect food additive used as a reactant in the formation of poly (tetramethylene terephthalate), which is used as a component in food contact surfaces<br>– Indirect food additive used as a reactant in the formation of polyurethane resins, which are used as components of food contact surfaces<br>– 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.<br>– 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; [25] |
| Hexanediol | – Indirect food additive used as a component of adhesives<br>– 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<br>– 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<br>– 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;[29,30] |

**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 of estradiol in Propanediol, 1,4-Butanediol, and 1,5-Pentanediol was 0.11, 0.017, and 0.005 µg/$cm^2$·h, respectively | 65 |
| 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:<br>0.1% TRIAC (a thyroid hormone analog) + 10% 1,5-Pentanediol or<br>0.1% TRIAC + 6% 1,2-Propanediol or<br>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<br>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<br>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 | 66 |

**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<br><br>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) | 66 |
| 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<br><br>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 | 66 |

**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% PEG-40 Hydrogenated Castor Oil and water, pH 6) containing:<br>1% terbinafine only (control);<br>1% terbinafine + 5% or 20% 1,5-Pentanediol;<br>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<br><br>Control: 8% terbinafine absorbed into skin, 0.35% in receptor fluid, 11 µg gel not absorbed<br><br>20% 1,2-Propanediol + 1% terbinafine: 21% terbinafine absorbed into skin, 2% in receptor fluid, 19 µg gel not absorbed<br><br>20% 1,5-Pentanediol + 1% terbinafine: 11% terbinafine absorbed into skin, 3% in receptor fluid, 76 µg gel not absorbed<br><br>5% 1,2-Propanediol + 1% terbinafine: 19% terbinafine absorbed into skin, 2.5% in receptor fluid, 34 µg gel not absorbed<br><br>5% 1,5-Pentanediol + 1% terbinafine: 52% terbinafine absorbed into skin, 3% in receptor fluid, 14 µg gel not absorbed | 67 |

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 | 68 |

**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) | 69 |
| 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) | 32 |
| | | | | ***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<br><br>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) | 70 |
| 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):<br><br>16 g total Propanediol fed to 4 rabbits;<br><br>9 g total 1,4-Butanediol fed to 4 rabbits;<br><br>1.2-1.5 g total 2,3-Butanediol fed to rabbits and 2 g total 2,3-Butanediol fed to 4 rabbits;<br><br>8.5 g total 1,5-Pentanediol fed to 4 rabbits;<br><br>2.8 g total Hexanediol fed to 1 rabbit;<br><br>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<br><br>1,4-Butanediol: 0.81 g (7% of dose) of succinic acid was isolated<br><br>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<br><br>1,5-Pentanediol: phenacyl glutarate (0.5% of dose) was isolated from the urine<br><br>Hexanediol: unchanged diol was not isolated from urine, from the carboxylic acid fraction of urine adipic acid was isolated | 71 |

**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<br><br>4 mmol/kg 1,4-Butanediol<br><br>2 mmol/kg 1,5-Pentanediol<br><br>2 mmol/kg Hexanediol<br><br>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;<br><br>1,4-Butanediol glucuronic acid conjugation was 0-2% of dose, urinary metabolite identified was succinic acid;<br><br>2,3-Butanediol glucuronic acid conjugation was 20%-26% of dose, glucuronide of the glycol (triacetyl methyl ester) was the urinary metabolite identified;<br><br>1,5-Pentanediol had no glucuronic acid conjugation reported, urinary metabolite identified was glutaric acid (glutaric acid is metabolized to $CO_2$ in body);<br><br>Hexanediol glucuronic acid conjugation was 4%-9% of dose, urinary metabolite identified was adipic acid | 71 |
| 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 | 68,73 |

**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 | 72 |
| 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 | 68 |
| 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 | 68 |

**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 | 69 |
| 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) | 31,32,74 |
| ***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<br><br>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<br><br>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 | 69 |

**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<br>Exp. 1, n=6 livers/substrate<br>Exp. 2, n=2<br>Exp. 3, n=1 | Exp. 1:<br>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);<br>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<br>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<br>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)<br>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<br>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<br>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<br>Controls did not show any detectable 2,3-Butanediol (<1 µM) after the start of the perfusion | 104 |
| **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 | 45,64 |
| ***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 | 75 |
| 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 | 76 |

**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) | 72 |

$C_{max}$=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 provided | $LD_{50}$> 20 g/kg | 77 |
| 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 | 81 |

**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 | 78 |
| 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 | 78,79 |
| 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 | 32 |
| 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 | 80 |

**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)<br><br>Authors' speculated that the variable mortality was potentially related to gastrointestinal absorption variability<br><br>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<br><br>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 | 35 |
| Propanediol | Rat | <u>Preliminary Test</u>: n=1/sex/group<br><br><u>Definitive Test</u>: n=4/sex | <u>Preliminary Test</u>: 0.63, 1.25, 2.5, 5, 10 ml/kg<br><br><u>Definitive Test</u>: 10 ml/kg | <u>Preliminary Test</u>: Single dose administered by gavage; animals observed through 9 days post-dosing (no further details provided)<br><br><u>Definitive Test</u>: Single dose administered by gavage (no further details provided) | <u>Preliminary Test</u>: 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<br><br><u>Definitive Test</u>: $LD_{50}$ of 10 ml/kg (or 10.5 g/kg) | 24 |

**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 | 68 |
| 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) | 68 |
| 1,4-Butanediol | Rat, Wistar Imp: DAK | n=4/sex/dose group;<br>n=5/sex/dose group | 1.5 to 2.5 g/kg at increasing doses;<br>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<br>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<br>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 | 81 |

**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 | 34 |
| 1,4-Butanediol | Rat, albino | n=25/sex | Not specified | Not specified | $LD_{50}$ of 1.55 g/kg | 72 |
| 1,4-Butanediol | Rat | Not specified | Not specified | Not specified | $LD_{50}$ of 1.78 g/kg | 37 |
| 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 | 21,37 |
| 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 | 21,37 |
| 1,4-Butanediol | Mouse | Not specified | Not specified | Not specified | $LD_{50}$ of 2.2 g/kg (24 h post-dosing) | 37 |
| 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 | 21,37 |
| 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 | 21,37 |
| 2,3-Butanediol | Mouse | Not specified | Not specified | Oral administration, details were not provided | $LD_{50}$ of 9 g/kg | 49 |

**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 | 78 |
| 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) | 105 |
| 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) | 105 |
| 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) | 105 |
| 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 | 78,79 |
| 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 mixture: 1.2% 1,10-Decanediol in a trade name mixture containing unspecified amount of Propylene Glycol; 20 ml/kg test mixture was used | Single dose was administered; animals were observed for 8 days post-exposure and then necropsies were performed | $LD_{50}$ > 0.20 ml/kg (1.2% of a 20 ml/kg test mixture); clinical signs, behavior, and gross pathology were unaffected by test substance | 83 |
| 1,10-Decanediol (supplier reported > 98% pure); Butylene Glycol | Mice, IFFA CREDO of 1 | n=10 males | Test mixture: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Butylene Glycol; 20 ml/kg of test mixture 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 | 83 |
| 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 | 32 |
| 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 | 80 |
| 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 | 77 |
| 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 | 84 |
| 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 | [78] |
| 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 | [78,79] |
| 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 | [32] |

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 |
| 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 | 85 |

**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, 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 |
| 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<br>Hexanediol: weight gain and clinical signs were unaffected; histology results revealed no changes in tissues compared to controls | 39 |
| 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) | 36 |
| 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 |

**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, 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 |
| | | | | ***Inhalation*** | | | |
| Propanediol | 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 | 77 |
| 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 | 84 |

**Table 9. Short-Term and Subchronic Toxicity Studies**

| Test Substance(s) | Species/ Strain | Test Population-Sex | Concentration/ Dosage (Vehicle) | Exposure Duration | Procedure | Results | Reference |
|---|---|---|---|---|---|---|---|
| **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) | 86 |
| Propanediol | Rat | n=5/group (7 groups total) | 5% or 12% in diet; 5 ml/kg or 10 ml/kg (by gavage); control diet; control diet + 10 ml water by gavage; control diet + 10 ml 1,2-Propanediol* by 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 (by gavage); 2 rats died (5 ml/kg group administered by gavage); reduced growth weights were noted in groups dosed in diet with 5% and 12% Propanediol and in rats dosed with 5 ml/kg Propanediol by gavage | 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 |
|---|---|---|---|---|---|---|---|
| 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 | [86] |
| 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) | [88] |
| 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 | 31 |

**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) | 32 |
| 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 | 31 |
| 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);<br>500, 2500, 5000 µg/ml (18 h, with activation);<br>375, 1250, 2500 µg/ml (18 h, without activation);<br>1250 µg/ml (28 h, without activation);<br>2500, 3750, 5000 µg/ml (18 h, with activation);<br>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;<br>*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 | 89 |
| 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 mixture: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Propylene Glycol;<br><br>Test mixture was evaluated up to 10,000 µg/plate (~120 µg/plate 1,10-Decanediol) | Ames test was performed with and without metabolic activation | Non-mutagenic; no cytotoxicity observed | 83 |
| 1,10-Decanediol (supplier reported > 98% pure); Butylene Glycol | *Salmonella typhimurium* | TA98, TA100, TA1535, TA1537, TA1538 | Test mixture: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Butylene Glycol;<br><br>Test mixture was evaluated at 10, 50, 100, 1,000, 5,000 µg/plate (up to ~60 µg/plate 1,10-Decanediol) | 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 | 83 |
| 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);<br>10 to 5000 µg/plate (24 and 48 h, without metabolic activation)<br>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);<br>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);<br>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;<br>*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.<br>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 | 70 |
| 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<br>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 mixture: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Butylene Glycol | 10 µl of test mixture 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 | 83 |
| | | | ***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<br><br>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 | 81 |
| 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 | 21,37 |
| 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) | 78 |
| 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 | 78,79 |
| 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<br>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<br>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 | 91 |
| 1,10-Decanediol (supplier reported > 98% pure); Propylene Glycol | Rabbit | n=? | Test mixture: 1.2% 1,10-Decanediol in trade name mixture containing unspecified amount of Propylene Glycol | 0.5 ml of test mixture 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 | 83 |
| 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 | 32 |
| 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 | 80 |
| 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<br>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<br>On days 15, 18, and 27 slight erythema and/or edema was observed in 4 animals, but by the following day irritation had resolved<br>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 | 92 |
| 1,4-Butanediol | Human | n=200 | Unknown | A patch test was performed (no further details provided) | Non-irritating | 21 |
| 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 | 45 |
| 1,10-Decanediol (supplier reported > 98% pure); Butylene Glycol | Human | n=10 | Test mixture: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Butylene Glycol | Test mixture 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 mixture 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 | 83 |
| 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 | 31,32,74 |
| 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 | Isopentyldiol 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 |

**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 |
|---|---|---|---|---|---|---|
| **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)<br>Induction Phase 1: 0.05 ml of test substance was intradermally injected (1st injection)<br>Induction Phase 2: 0.01 ml of test substance was intradermally injected (2nd through 10th injections)<br>Challenge: 0.05 ml of test substance was intradermally injected skin examined 24 h post-challenge<br>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 |
| 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)<br>Challenge: 50% (epicutaneous and semi-occlusive)<br>vehicle=water | A guinea pig maximization test was performed (non-GLP) in accordance with OECD TG 406 (Skin Sensitization)<br>Preliminary Test: conducted to find the concentrations for intradermal and topical challenge<br>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<br>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<br>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 | 81 |

**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<br><br>Epicutaneous Induction: 50% test substance in distilled water<br><br>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<br><br>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<br><br>Epicutaneous Induction: no further details were provided explaining this induction other than concentration<br><br>Challenge: no further details were provided explaining challenge other than concentration | Non-sensitizing<br><br>The following reactions were reported:<br><br>-All animals injected with only Freund's adjuvant/ 0.9% aqueous sodium chloride showed erythema and swelling at injection sites<br><br>-Animals injected with only 0.9% aqueous sodium chloride had no skin reactions<br><br>-Test group animals injected with 5% test substance in Freund's adjuvant/ 0.9% aqueous sodium chloride showed erythema and swelling at injection sites<br><br>-Test group animals injected with 5% test substance in 0.9% aqueous sodium chloride showed moderate and confluent erythema and swelling<br><br>-Test group animals epicutaneously exposed to 50% test substance during induction showed incrustation and confluent erythema with swelling<br><br>-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<br><br>Epicutaneous Induction: 50% Hexanediol in double distilled water<br><br>Challenge: 25% Hexanediol in double distilled water | 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)<br><br>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)<br><br>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<br><br>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<br><br>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):<br><br>2-HEMA sensitizer/ Ethylene Glycol challenge (n=5)<br>2-HEMA sensitizer/ Hexanediol challenge (n=5)<br>Ethylene Glycol sensitizer/ Ethylene Glycol challenge (n=2)<br>Hexanediol sensitizer/ Hexanediol challenge (n=2)<br>2-HEMA sensitizer/ 2-HEMA challenge (n=5)<br><br>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<br><br>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 | 91 |

**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 mixture: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Propylene Glycol;<br>Test mixture used (1.2% 1,10-Decanediol) at induction and 25% dilution of test mixture used at challenge (0.3% 1,10-Decanediol) | Buehler test was performed; test mixture 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 | 83 |
| 1,10-Decanediol (supplier reported > 98% pure); Butylene Glycol | Guinea Pig | n=20 treated males; 10 controls used | Test mixture: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Butylene Glycol;<br>Induction concentration not specified; test mixture used at 25% dilution during challenge (0.3% 1,10-Decanediol) | 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 | 83 |
| 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<br>Epidermal Induction: 100% test substance<br>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<br>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<br>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)<br>Topical Induction: 100%<br>Topical Challenge: 100% and 50% (v/v)<br>(vehicle=triglycerides of coconut oil) | A guinea pig maximization test was performed (GLP) in accordance with EU Method B.6 (Skin Sensitization)<br><br>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 triglycerides of coconut oil; 2 injections of 0.1 ml test substance in 50:50 of Freund's adjuvant/triglycerides of coconut oil<br><br>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<br><br>Challenge: 0.2 ml of test substance was applied to anterior site and 50% test substance (diluted in triglycerides of coconut oil) 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:*<br>Intradermal Induction: 10% in distilled water<br>Topical Induction: 100% undiluted<br>Challenge: 50% in distilled water | Guinea pig maximization test was performed in accordance with OECD TG 406 (Skin Sensitization-Magnusson & Kligman)<br><br>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<br><br>Induction Phases: test substance was applied at indicated concentrations (volumes were not specified)<br><br>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<br><br>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; no skin reactions or irritation at any concentration levels nor with controls were observed | 92 |

**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=207 | 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); non-sensitizing<br><br>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%; non-sensitizing | 92 |
| 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 | 45 |
| 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 | 45 |
| 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 | 32 |

**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 $10^{th}$ 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<br><br>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 $9^{th}$ and $10^{th}$ 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 | 31,32,74 |
| 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<br><br>*Rest:* Subjects received no treatment during the 10-15 days after completion of induction and prior to challenge phase<br><br>*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<br><br>*Induction:* 41 subjects exhibited definite erythema with no edema, 3 of those subjects also showed damage to epidermis (a protocol deviation occurred for the $1^{st}$ subject resulting in an inadvertent discontinued use of test substance, $2^{nd}$ subject declined to complete patch tests for the remainder of study, $3^{rd}$ subject showed no further reactions for remainder of induction phase when test substance was applied to a new site under semi-occlusive conditions during $6^{th}$ 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 | 93 |

**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 mixture: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Butylene Glycol | 1 ml of test mixture 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 | 83 |
| 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<br><br>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 | 45,64 |

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 mixture: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Butylene Glycol | 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 mixture 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 | 83 |
| 1,10-Decanediol (supplier reported > 98% pure); Butylene Glycol | Human | Corneal epithelium | Test mixture: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Butylene Glycol | 30 µl of test mixture 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) | 83 |
| | | | ***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 | 81 |
| 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 | 37 |
| 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 | 78 |
| 1,5-Pentanediol | Rabbit | Not specified | Not specified | Not specified | Mildly irritating | 33 |
| 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 |

**Table 13. Ocular Irritation Studies**

| Test Substance | Species/ Strain | Sample Type or Test Population-Sex | Concentration (Vehicle) | Procedure | Results | Reference |
|---|---|---|---|---|---|---|
| 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 | 78,79 |
| 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 mixture: 1.2% 1,10-Decanediol in a trade name mixture also containing unspecified amount of Propylene Glycol | Study authors stated that a modified Kay and Calendra method was used; 0.1 ml of test mixture 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 | 83 |
| 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 | 32 |
| 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 | 80 |
| 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<br><br>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<br><br>Patient underwent patch testing (Test 1: propylene glycol and the resveratrol cream unchanged were applied)<br><br>4 months later an additional patch test (Test 2) was performed on the patient and controls using the ingredients in the resveratrol cream<br><br>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<br><br>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)<br><br>Test 3 on patient and controls: patient reacted to 5% resveratrol only (+ by days 2 and 3); controls were negative<br><br>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 | 96 |
| 1,5-Pentanediol | n=1 (56 yr old female), 3 control subjects | 5% in water | A patient used a cream for a month and developed facial dermatitis with edema of eyelids; patch testing using European standard series, Belgian cosmetic pharmaceutical series, and patient's cream was performed; patient had a positive reaction to 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 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) | 97 |

**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) | 91 |
| | | | ***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 | 34 |
| 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) | 98 |
| 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 | 99 |
| 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 (eds). Web-Based Ingredient Dictionary (wINCI). http://webdictionary.personalcarecouncil.org/jsp/Home.jsp. Washington, D.C. Last Updated 2017. Date Accessed 8-9-2017.

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. 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.

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

24. 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.

25. 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.

26. 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.

27. 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.

28. 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.

29. 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.

30. 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.

31. 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.

32. 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.

33. 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.

34. 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.

35. 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.

36. 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.

37. 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.

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

39. 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.

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

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

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

43. 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.

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

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

46. 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.

47. 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.

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

49. 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.

50. U.S. Food and Drug Administration Center for Food Safety & Applied Nutrition (CFSAN). Voluntary Cosmetic Registration Program – Frequency of Use of Cosmetic Ingredients. College Park, MD, 2017. Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 2017; received February 2017).

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

52. 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.

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

54. 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.

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

56. 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.

57. 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.

58. 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.

59. 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.

60. 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.

61. 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.

62. 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.

63. 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.

64. 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.

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

66. 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.

67. 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.

68. 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.

69. 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.

70. 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.

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

72. 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)).

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

74. National Institute of Health US National Library of Medicine Toxicology Data Network (TOXNET). Hazardous Substances Data Bank: 2-Methyl-1,3-Propanediol, CASRN: 2163-42-0. http://toxnet.nlm.nih.gov. Last Updated 2012. Date Accessed 8-3-2016.

75. 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.

76. 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.

77. 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.

78. 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.

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

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

81. 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.

82. 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.

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

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

85. 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.

86. 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.

87. 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.

88. 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.

89. 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.

90. Pereira ME, Huang CI, and Izquierdo I. Effects of chronic treatment with 2,5-hexanedione on several behavioral measures in rats. *Psychobiology*. 1992;20(2):133-138.

91. 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.

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

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

94. 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.

95. 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.

96. 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.

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

98. 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.

99. 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.

100. German Federal Institute for Occupational Safety and Health. Technical Rules for Hazardous Substances-Occupational Exposure Limits, TRGS 900 (GMBI 2016 S. 886-889, no. 45). 4-11-2016. http://jr.chemwatch.net/galleria/LEGSREGS/40-5-1-73-49-4-AA-20161129.pdf. Date Accessed 4-27-2017.

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

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

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

104. 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.

105. 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). http://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:** April 4, 2017

**SUBJECT:** Draft Report: Safety Assessment of Alkane Diols as Used In Cosmetics (draft prepared for the April 10-11, 2017 CIR Expert Panel Meeting)

Key Issue

In the Cosmetic Use Section (or risk assessment section) it should also be noted that NICNAS concluded that: "the notified chemical [Isopentyldiol also called 3-methyl-1,3-butanediol] is not considered to pose an unreasonable risk to public health at concentrations up to 10% in cosmetic products." Somewhere in the report, it should also be stated that NICNAS used read-across (especially for subchronic oral toxicity) from 1,3-butanediol (INCI: Butylene Glycol, CIR: S), 2-methyl-2,4-pentanediol (INCI: Hexylene Glycol, CIR: S) and 3-methyl-1-butanol (INCI: Isoamyl Alcohol not yet CIR reviewed) to support the safety of Isopentyldiol. The 90-day oral rat study on 3-methyl-1-butanol is in the published study:

Schilling, K., Kayser, M., Deckardt, K., Küttler, K., Klimish, H-J. (1997) Subchronic toxicity studies of 3-methyl-1-butanol and 2-methyl-1-propanol in rats. Hum. & Exp. Tox. 16:722-726.

Additional Considerations

Introduction - As other names have been added to ingredients without numbers in their INCI names, it would also be helpful to add other names to Butyl Ethyl Propanediol, e.g., 2-butyl-2-ethyl-1,3-propanediol, and Isopentyldiol, e.g., 1,1-dimethyl-1,3-propanediol, 3-methyl-1,3-butanediol. This would also be consistent with Table 2 where other names have been provided for other diols already reviewed by CIR.

The NTP bioassay on gamma-butyrolactone (reference 22) should not be included among the reviews.

Acute, Oral - It is not helpful to list $LD_{50}$ values as being in "rats and/or mice", please state the species for each value. It should be stated that the concentration of 1,10-Decanediol in the tested trade name mixtures was 1.2%. Therefore, approximately 0.20 ml/kg of the 20 ml/kg trade name mixtures was 1,10-Decanediol.

Subchronic, Inhalation - What type of "pulmonary abnormalities" were observed, e.g., microscopic changes, functional changes?

Developmental and Reproductive Toxicity Studies - What species was dosed with up to 800 mg/kg/day 1,4-Butanediol?

Genotoxicity - It should be stated that the tested trade name mixtures contained 1.2% 1,10-Decanediol. Therefore, the tested doses, 10,000 µg/plate of the mixture, were about 120 µg/plate of 1,10-Decanediol.

Ocular Irritation - It is not helpful and misleading to say that the results of the ocular irritation studies were "mixed". Please be more specific. With the exception of Butyl Ethyl Propanediol which was irritating, all other tested compounds were only mildly to non-irritating.

Occupational Standards - Rather than citing occupational standards from European countries to a reference from Australia, it would be helpful to find the original sources or a summary of European occupational standards.

Discussion - Does the CIR Expert Panel really want to limit the discussion about impurities to the ingredients that may be derived from plants (note: 1,4-Butanediol may also be derived from plants)? It is not necessary for an ingredient to be derived from plants to have potential impurity issues.

Table 5 - As all of the "uses" in Table 5 are from the CFR, a more specific title for this table (such as US Permitted Non-Cosmetic Uses) would be helpful.

Personal Care Products Council
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**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:** May 16, 2017

**SUBJECT:** Comments Tentative Report: Safety Assessment of Alkane Diols as Used In Cosmetics

Key Issue

References summarized in Table 7 indicate that in rats (reference 71), but not rabbits (reference 73), 2,3-Butanediol is metabolized to diacetyl (2,3-butanedione). Somewhere in the report the potential toxicity of diacetyl should be discussed. Diacetyl has been used as an artificial butter flavoring in microwave popcorn and has been associated with bronchiolitis obliterans in exposed workers. One example of a review of this issue (full text available on the internet):

Starek-Świechowica, Starek A. 2014. Diacetyl exposure as a pneumotoxic factor: a review. Rocz Panstw Zakl High 65(2): 87-92.

Although there are no safety data on Octanediol in the report, the CIR Expert Panel included Octanediol among the ingredients considered safe in the described practices of use and concentration. It would be helpful if the Discussion included a description of how the CIR Expert Panel reached a safe conclusion for Octanediol. There are no use concentrations reported for Octanediol. Therefore, "the expectation is that they [Octanediol] would be used in product categories and concentrations comparable to others in this group." Maximum use concentrations among the ingredients in the report vary from a high of 39.9% for Propanediol to a low of 0.006% for 1,10-Decanediol. Should this wide range of use concentrations apply to Octanediol?

Additional Considerations

Introduction, Reference 22 - The NTP bioassay on gamma-butyrolactone is no longer presented in the report. Therefore, it does not seem necessary to include the NTP in the Introduction, or include the bioassay in the reference section (reference 22).

Method of Manufacture, Propanediol - Rather than saying that "Propanediol may be prepared" by fermentation, it should be stated that Propanediol is prepared by fermentation. This was

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confirmed by a representative of a major manufacturer at the April 2017 CIR Expert Panel meeting. The first sentence of this subsection is saying the same thing twice. It states: "Propanediol may be [is] prepared from corn-derived glucose using a biocatalyst (non-pathogenic strain of *Escherichia coli* K-12)[this is a description of a fermentation process]; it is also prepared by glucose fermentation with subsequent distillation."

Impurities, Isopentyldiol - The NICAS report (reference 18) on Isopentyldiol included a heading "Impurities/Residual Monomers (>1% by weight)". Since Isopentyldiol is not a polymer, "Residual Monomers" should not have been included in this heading. Please delete "and residual monomers" from the Impurities section.

Cosmetic Use - Please indicate that the 10% concentration of Isopentyldiol found acceptable in the NICNAS assessment was the highest reported use concentration.

Penetration Enhancement - The description of the estradiol penetration study (reference 67) needs to be corrected. It currently states: "The study-state flux of Propanediol, 1,4-Butanediol and 1,5-Pentanediol was determined to be..." The values presented are actually the steady-state flux of estradiol in the various alkane diols, not the flux of the alkane diols themselves as currently stated.

Short-Term, Inhalation - It is not clear that the effects described for the 1,4-Butanediol study (reference 85) were only observed at the high concentration. It should also be stated that the 1.1 mg/L exposure concentration was a NOEAC.

Neurotoxicity - Please correct the subheading "Hexandeiol"

Occupational Standards - It does not make sense to state: "In Germany, the international occupational limit..." If it is an international standard, it should apply to more than just Germany.

Summary - It is misleading to state that the "alkane diols are indirect food additives". Only three alkane diols are listed as indirect food additives in Table 5.

Please include the duration for the inhalation $LC_{50}$ of >5.1 g/L for Methylpropanediol.

Please be sure effects observed are associated with the compound. The compound(s) associated with the following sentences is not clear. "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." "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."

The Occupational Standard section only gives one occupational exposure limit for 1,4-Butanediol, 200 $mg/m^3$, while the Summary states that the occupational exposure limits range from 100 to 800 $mg/m^3$. The information in the Summary should agree with the information presented earlier in the report.

Table 2 - It would be helpful to include the maximum reported use concentrations in this table.

Table 6 - Rather than trade name, Chremophor RH40 (which should be spelled Cremophor), please use the INCI name, PEG-40 Hydrogenated Castor Oil (or other chemical name).

Table 9, Subchronic, Oral, Propanediol, reference 11 - The results based on route of administration (gavage, dietary, drinking water) are not clear.

Table 12, Irritation and Sensitization, Human - It is not clear why two HRIPTs on Propanediol (both from reference 93) are presented in both the irritation and sensitization section. The other HRIPTs are only presented in the sensitization section.

Table 12, Sensitization, Animal, reference 14 - Please use "double distilled water" rather than "aqua bidest."

Table 12, Sensitization, Animal, Reference 16 - Rather than the trade name "Alembicol D"please use triglycerides of coconut oil or fractionated coconut oil.

Table 14, reference 98 - It is not necessary to use the trade name "toleriane" when describing this case report.

Reference 18 - Why is the following at the end of this reference: "1,4-Butanediol is used in polyurethane resins, exposure to 1,4-Butanediol is 90 micrograms/person/day."