Safety Assessment of Panthenol, Pantothenic Acid, and Derivatives as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	November 10, 2017
Panel Meeting Date:	December 4-5, 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 Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Laura N. Scott, Scientific Writer/Analyst and Monice Fiume, Senior Director.

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

Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume MMF
Senior Director
Date: November 10, 2017
Subject: Safety Assessment of Panthenol, Pantothenic Acid, and Derivatives as Used in Cosmetics

Enclosed is the Draft Final Report of the Safety Assessment of Panthenol, Pantothenic Acid, and Derivatives as Used in Cosmetics (identified as *pants122017rep* in the pdf document). At the September 11-12th, 2017 meeting, the Panel issued a tentative report with the conclusion that these 7 ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment. The Panel also noted that these ingredients may contain residual amines as impurities; and, thus cautioned that these ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

No news data have been received since the Tentative Report was issued. Council comments on the Tentative Report were received and have been addressed. Panel edits from the September 2017 meeting were also addressed.

The following are included in this report package:

pants122017flow: report flowchart
pants122017hist: report history
pants122017prof: data profile
pants122017strat: search strategy
pants122017min_current: transcripts of the April and Sept 2017 proceedings
pants122017min_orig review: minutes from the original deliberations of Panthenol and Pantothenic Acid
pants122017min_RR: minutes from the re-review deliberations of Panthenol and Pantothenic Acid
pants122017rep: draft final report
pants122017prev_1: original Final Report of Panthenol Pantothenic Acid (1987)
pants122017prev_2: re-review summary of Panthenol and Pantothenic Acid (published in 2006)
pants122017FDA: 2017 VCRP data
pants122017pcpc: PCPC comments on the tentative report

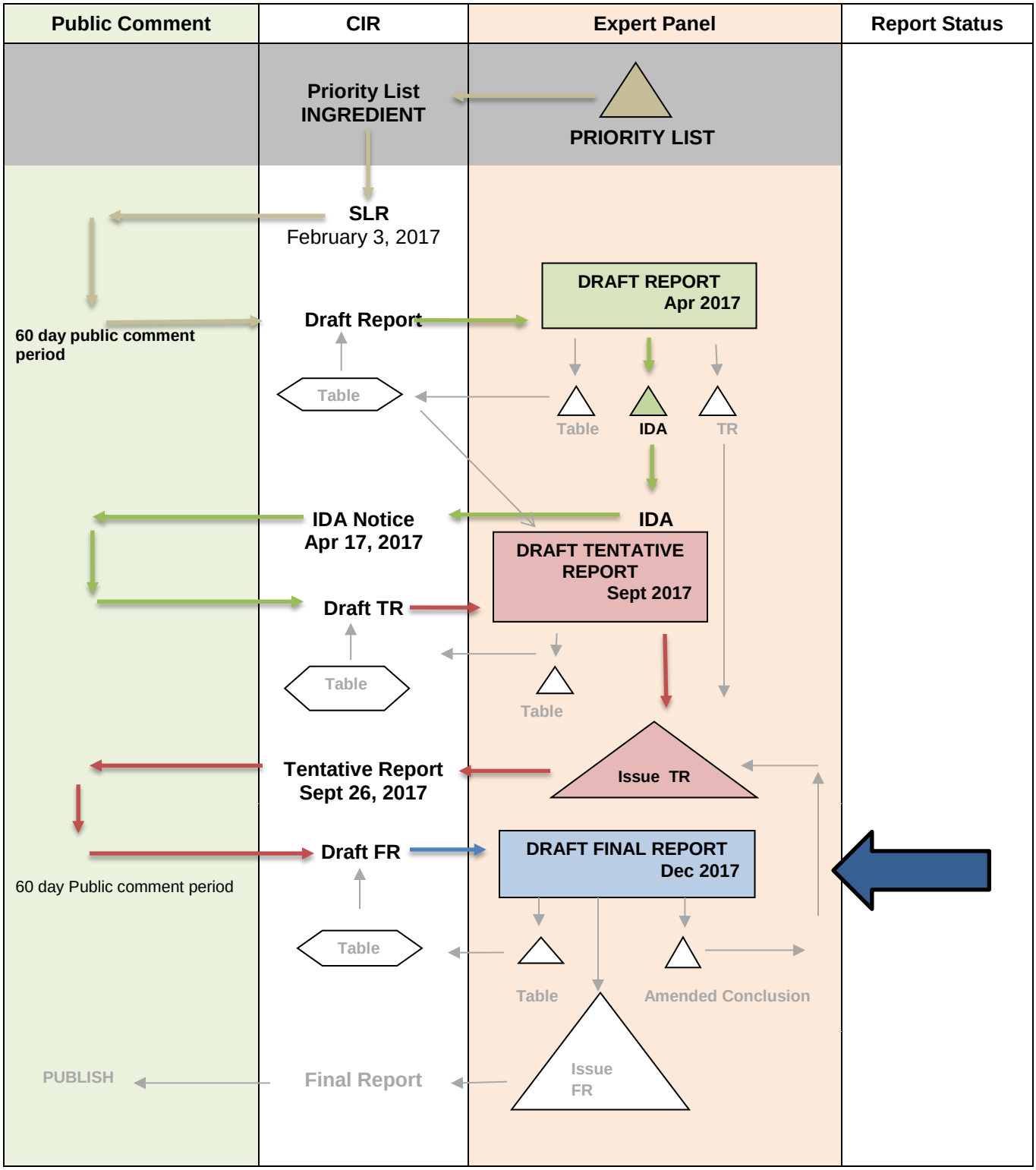
The Panel should be prepared to provide any additional rationale to be described in the Discussion, to verify the Abstract, Discussion, and Conclusion, and issue a Final Report.

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

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY __ Panthenol, Pantothenic Acid, and Derivatives

MEETING ___Dec 2017



Report History-Panthenol, Pantothenic Acid and Derivatives

February 3, 2017-The Panthenol, Pantothenic Acid, and Derivatives Scientific Literature Review was posted online at www.cir-safety.org for public comment.

April 10-11, 2017-The Panel issued an Insufficient Data Announcement for The Panthenol, Pantothenic Acid and Derivatives Safety Assessment presented at this meeting.

September 11-12, 2017-The Panel issued a Tentative Report with the conclusion that these 7 ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

September 26, 2017-The Panthenol, Pantothenic Acid, and Derivatives Tentative Report was posted online at www.cir-safety.org for public comment.

Panthenol, Pantothenic Acid, and Derivatives Data Profile – Monice Fiume (for Laura Scott) – Dec 2017

			Dermal Penetration			Nail Penetration	Penetration Enhancement	ADME				Acute Toxicity					Short-Term Toxicity	Sub-Chronic Toxicity		Chronic Toxicity	DART	Genotoxicity	Irritation		Sensitization		Photoirritation-Sensitization	Ocular Irritation			Clinical Studies-Case Reports	
	Reported to be Used in Cosmetics?	Safety Data Available?	In Vitro-Animal	In Vitro-Human	In Vivo-Human	In Vitro-Human	In Vitro-Animal	Animal-Dermal	Animal-Oral	Animal-IV	Human-Oral	Animal-Dermal	Animal-Oral	Animal-Inhalation	Animal-IV	Animal-Subcutaneous	Animal-Dermal	Animal-Oral	Animal-Dermal	Animal-Oral	Animal-Oral	In Vivo-Oral	In Vitro	Animal	Human	Animal	Human	In Vivo-Animal	In Vitro-Animal	In Vivo-Animal	In Vivo-Human	Dermal	Oral
New Data Added to Current Safety Assessment																																
Panthenol	Y	Y		X		X			X																	X	X					X	
D-Panthenol	Y	Y	X		X		X	X				X	X	X									X	X		X	X	X		X		X	X
DL-Panthenol	Y	Y																			X		X	X		X				X		X	
Pantothenic Acid	Y	Y							X									X															X
Panthenyl Ethyl Ether	Y	Y															X							X			X						
D-Panthenyl Ethyl Ether	N	Y						X																								X	
DL-Panthenyl Ethyl Ether	N	Y										X	X									X	X	X		X				X			
Panthenyl Ethyl Ether Acetate	N	N																															
Panthenyl Triacetate	Y	Y			X								X																				
D-Panthenyl Triacetate	N	Y						X															X		X				X				
Calcium Pantothenate	Y	Y							X	X	X							X			X	X											
D-Calcium Pantothenate	N	Y											X	X						X	X	X											
Sodium Pantothenate	N	Y							X	X													X										
D-Sodium Pantothenate	N	Y																					X										
Data From 1987 Final Report on the Safety Assessment of Panthenol and Pantothenic Acid																																	
Panthenol	Y	Y							X		X		X						X	X	X			X	X		X			X	X		
D-Panthenol	N	Y							X				X		X					X				X						X			
DL-Panthenol	N	Y																						X						X			
Pantothenic Acid	N*	Y							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. *Pantothenic Acid was not reported to be used in cosmetics in the 1987 Final Report on the Safety Assessment of Panthenol and Pantothenic Acid, however it was reported to be in use in the re-review summary report published in 2006.

Panthenol, Pantothenic Acid, and Derivatives-Search Strategy Info

Ingredient	Cas No.	Prev Rev	in Use	Info base *	NTIS	FDA/ CFR	NTP	TOXNET	WHO	ECHA	IUCLID	EPA/ HPVIS	OECD/ SIDS	EU	NICNAS	Web
Panthenol# (also called Pantothenol and Dexpanthenol)	□**81-13-0 (D-form); 16485-10-2 (DL-form)**	Yes	Yes	X	-	X	-	X	-	X	-	-	-	X	** (no data listed)	X
Pantothenic Acid#	**79-83-4**	Yes	Yes	X	-	X	-	X	X	-	-	-	-	X	** (no data listed)	X
Panthenyl Ethyl Ether	**667-83-4**	No	Yes	X	-	-	-	X	-	-	-	-	-	X	** (no data listed)	X
Panthenyl Ethyl Ether Acetate	**476170-37-3; 119516-54-0**	No	No	X	-	-	-	X	-	-	-	-	-	X	-	X
Panthenyl Triacetate	**94089-18-6; 98133-47-2**	No	Yes	X	-	-	-	X	-	-	-	-	-	X	** (no data listed)	X
Calcium Pantothenate	**137-08-6**	No	Yes	X	X	X	X	X	X	-	-	-	-	X	** (no data listed)	X
Sodium Pantothenate	**867-81-2**	No	No	X	X	X	-	X	X	X	-	-	-	X	** (no data listed)	X

#Ingredient was searched from ~2000 to present; □Not all ingredients had CAS#'s associated with specific stereochemistry; X indicates data were available; - indicates no relevant data were available; **w*INCI: Online *International Cosmetic Ingredient Dictionary and Handbook*; **Secondary Notification Conditions Do Not Apply

PubMed:

9-7-2016 Searched: (((((("Panthenyl Ethyl Ether"[All Fields] OR "667-83-4"[All Fields]) OR (("panthenyl ethyl ether"[Supplementary Concept] OR "panthenyl ethyl ether"[All Fields]) AND Acetate[All Fields])) OR (Panthenyl[All Fields] AND Triacetate[All Fields])) OR "Calcium Pantothenate"[All Fields]) OR "137-08-6"[All Fields]) OR "Sodium Pantothenate"[All Fields]

There were 171 hits and 6 potentially useful that were not found in SciFinder. The other CAS#s not listed in the search fields above were not located by PubMed.

9-8-2016 Searched: ("Calcium Pantothenate"[All Fields] OR 137-08-6[All Fields]) AND ("metabolism"[Subheading] OR "metabolism"[All Fields] OR "metabolism"[MeSH Terms] OR "metabolism"[All Fields] OR "metabolic networks and pathways"[MeSH Terms] OR ("metabolic"[All Fields] AND "networks"[All Fields] AND "pathways"[All Fields]) OR "metabolic networks and pathways"[All Fields]) *(33 hits/ 0 useful that were not already found using other search terms above)*

9-8-2016 Searched: ("Calcium Pantothenate"[All Fields] OR 137-08-6[All Fields]) AND ("reproduction"[MeSH Terms] OR "reproduction"[All Fields]) *(2 hits/ 0 useful that were not already found using other search terms above)*

9-8-2016 Searched: ("Calcium Pantothenate"[All Fields] OR 137-08-6[All Fields]) AND carcinogenicity[All Fields] *(0 hits)*

9-8-2016 Searched: ("Calcium Pantothenate"[All Fields] OR 137-08-6[All Fields]) AND irritation[All Fields] *(0 hits)*

Email alert for potential future articles matching the search terms above was setup (9-7-2016 and 9-8-2016).

10-18-2016 Searched: ((((panthenol[All Fields] OR ("dexpanthenol"[Supplementary Concept] OR "dexpanthenol"[All Fields] OR "pantothenol"[All Fields])) OR 81-13-0[All Fields]) OR ("pantothenic acid"[MeSH Terms] OR ("pantothenic"[All Fields] AND "acid"[All Fields]) OR "pantothenic acid"[All Fields])) OR 79-83-4[All Fields]) AND ("toxicity"[Subheading] OR "toxicity"[All Fields]) *(72 hits/ 3 potentially useful)*- Email alert for potential future articles matching the search terms above was setup

10-18-2016 Searched: ((((panthenol[All Fields] OR ("dexpanthenol"[Supplementary Concept] OR "dexpanthenol"[All Fields] OR "pantothenol"[All Fields])) OR 81-13-0[All Fields]) OR ("pantothenic acid"[MeSH Terms] OR ("pantothenic"[All Fields] AND "acid"[All Fields]) OR "pantothenic acid"[All Fields])) OR 79-83-4[All Fields]) AND ("skin"[MeSH Terms] OR "skin"[All Fields]) *(106 hits/ 14 potentially useful)*- Email alert for potential future articles matching the search terms above was setup

10-19-2016 Searched: ((((panthenol[All Fields] OR ("dexpanthenol"[Supplementary Concept] OR "dexpanthenol"[All Fields] OR "pantothenol"[All Fields])) OR 81-13-0[All Fields]) OR ("pantothenic acid"[MeSH Terms] OR ("pantothenic"[All Fields] AND "acid"[All Fields]) OR "pantothenic acid"[All Fields])) OR 79-83-4[All Fields]) AND carcinogenicity[All Fields] *(0 hits)*

10-19-2016 Searched: ((((panthenol[All Fields] OR ("dexpanthenol"[Supplementary Concept] OR "dexpanthenol"[All Fields] OR "pantothenol"[All Fields])) OR 81-13-0[All Fields]) OR ("pantothenic acid"[MeSH Terms] OR ("pantothenic"[All Fields] AND "acid"[All Fields]) OR "pantothenic acid"[All Fields])) OR 79-83-4[All Fields]) AND ("reproduction"[MeSH Terms] OR "reproduction"[All Fields]) *(17 hits/2 potentially useful)*- Email alert for potential future articles matching the search terms above was setup

10-19-2016 Searched: ((((panthenol[All Fields] OR ("dexpanthenol"[Supplementary Concept] OR "dexpanthenol"[All Fields] OR "pantothenol"[All Fields])) OR 81-13-0[All Fields]) OR ("pantothenic acid"[MeSH Terms] OR ("pantothenic"[All Fields] AND "acid"[All Fields]) OR "pantothenic acid"[All Fields])) OR 79-83-4[All Fields]) AND ("metabolism"[Subheading] OR "metabolism"[All Fields] OR "metabolism"[MeSH Terms] OR "metabolism"[All Fields] OR "metabolic networks and pathways"[MeSH Terms] OR ("metabolic"[All Fields] AND "networks"[All Fields] AND "pathways"[All Fields]) OR "metabolic networks and pathways"[All Fields]) AND ("2000/01/01"[PDAT] : "2016/12/31"[PDAT]) *(389 hits/1 potentially useful)*- Email alert for potential future articles matching the search terms above was setup

SciFinder:

9-6-2016 Searched: CAS# 667-83-4 *(10 hits/ 1 potentially useful)*; Panthenyl Ethyl Ether (1 potentially useful hit, but it was also found searching for 667-83-4); CAS# 476170-37-3 *(0 hits)*; CAS# 119516-54-0 *(0 hits)*; Panthenyl Ethyl Ether Acetate *(0 hits)*; CAS# 94089-18-6 *(5 hits/ ~4 potentially useful)*; CAS# 98133-47-2 *(0 hits)*; Panthenyl Triacetate *(6 hits/ 6 potentially useful, but 3 of these 6 were also found searching for 94089-18-6)*.

9-7-2016 Searched: CAS# 137-08-6 > 1000 hits so filters were added to search term as follows: CAS# 137-08-6 and skin *(32 hits)*, CAS# 137-08-6 and toxicity *(65 hits)*, Calcium Pantothenate >900 hits so qualifier was added to search term as follows: Calcium Pantothenate and toxicity *(78 hits)*. The hits from all 3 of these searches with qualifiers were combined to eliminate duplicate hits *(total of 100 hits after duplicates removed/ ~14 potentially useful)*.

9-7-2016 Searched: CAS# 867-81-2 *(84 hits)*; Sodium Pantothenate *(97 hits)*. *The hits from these two searches were combined for a total of 97 hits/ ~8 potentially useful.*

All of the above SciFinder hits were combined into one group for a total of ~29 potentially relevant hits (after duplicates were removed).

9-8-2016 Searched: Calcium Pantothenate and Reproduction *(40 hits/ 1 potentially useful)*; Calcium Pantothenate Metabolism *(73 hits/ ~7 potentially useful)*; Calcium Pantothenate and Irritation *(3 hits/ 3 useful, but were found already using other search terms above)*; Calcium Pantothenate and Carcinogenicity *(14 hits/ 1 potentially useful, but it was found already using other search terms above)*

"Keep Me Posted" (started 9-6-2016, 9-7-2016, and 9-8-2016) was only setup for the ingredients above that had hits; the ingredients with no SciFinder hits could not be setup for "Keep Me Posted".

10-11-2016 Searched: Panthenol and 81-13-0 and 16485-10-2 from 2000 to present *(247 hits/28 potentially useful)*; "Keep Me Posted" was started 10-11-2016 using the search criteria used for Panthenol

10-18-2016 Searched: Pantothenic Acid and 79-83-4 from 2000 to present *(82 hits/13 potentially useful)*; "Keep Me Posted" was started 10-18-2016 using the search criteria for Pantothenic Acid

ECHA

9-12-2016 Searched: 667-83-4 and 1 hit appeared for "(+)-N-(3-ethoxypropyl)-2,4-dihydroxy-3,3-dimethylbutyramide" (another name for Panthenyl Ethyl Ether) https://echa.europa.eu/substance-information/-/substanceinfo/100.010.519

This ingredient is pre-registered on the ECHA website, but no registration dossier exists. The information that was available indicates that no hazards have been classified for this ingredient.

9-12-2016 Searched: 94089-18-6 and 1 hit appeared for "4-[(3-acetoxypropyl)amino]-2,2-dimethyl-4-oxobutane-1,3-diyl diacetate" (another name for Panthenyl Triacetate) https://echa.europa.eu/substance-information/-/substanceinfo/100.092.792

This ingredient is pre-registered on the ECHA website, but no registration dossier exists. The information that was available indicates that no hazards have been classified for this ingredient.

9-12-2016 Searched: 137-08-6 and 1 hit appeared for Calcium pantothenate, D-form https://echa.europa.eu/substance-information/-/substanceinfo/100.004.799

This ingredient is pre-registered on the ECHA website, but no registration dossier exists. The information that was available indicates that no hazards have been classified for this ingredient.

9-12-2016 Searched: 867-81-2 and 1 hit appeared for Sodium D-pantothenate https://echa.europa.eu/substance-information/-/substanceinfo/100.011.608

This ingredient is pre-registered on the ECHA website, but no registration dossier exists. The information that was available indicates that "According to the classification provided by companies to ECHA in CLP notifications this substance causes serious eye irritation, causes skin irritation and may cause respiratory irritation."

10-20-2016 Searched: panthenol and 2 hits appeared for Panthenol, DL-form https://echa.europa.eu/registration-dossier/-/registered-dossier/12624 and Dexpanthenol https://echa.europa.eu/registration-dossier/-/registered-dossier/14227 ; a registration dossier does exist

10-20-2016 Searched: pantothenic acid and 1 hit appeared for D-Pantothenic Acid https://echa.europa.eu/substance-information/-/substanceinfo/100.001.118

This ingredient is pre-registered on ECHA website, but no registration dossier exists. The information that was available indicates that no hazards have been classified for this ingredient.

FDA

9-13-2016 Searched: Caclium Pantothenate and Sodium Pantothenate at http://www.fda.gov/ and www.ecfr.gov resulting in the hits below.

21CFR172.330 (*Calcium Pantothenate, Pantothenic Acid*): Part 172-Food Additives Permitted For Direct Addition To Food For Human Consumption; Subpart D-Special Dietary and Nutritional Additives; Section 172.330 Calcium pantothenate, calcium chloride double salt. The food additive calcium chloride double salt of calcium pantothenate may be safely used in foods for special dietary uses in accordance with good manufacturing practice and under the following prescribed conditions: (a) The food additive is of the *d* (dextrorotatory) or the *dl* (racemic) form. (b) To assure safe use of the additive, the label and labeling of the food additive container, or that of any intermediate premixes prepared therefrom, shall bear, in addition to the other information required by the Act, the following: (1) The name of the additive "calcium chloride double salt of *d*- calcium pantothenate" or "calcium chloride double salt of *dl*- calcium pantothenate", whichever is appropriate. (2) A statement of the appropriate concentration of the additive, expressed as pantothenic acid.

21CFR184.1212 *(Calcium Pantothenate)*: Part 184-Direct Food Substances Affirmed As Generally Recognized As Safe; Subpart B-Listing of Specific Substances Affirmed as **GRAS**; Section 184.1212 Caclium pantothenate. (a) Calcium pantothenate ($(C_9H_{16}NO_5)_2Ca$, CAS Reg. No. of the *D*-isomer, 137-08-6) is a salt of pantothenic acid, one of the vitamins of the B complex. Only the *D*-isomer of pantothenic acid has vitamin activity, although both the *D*-isomer and the *DL*-racemic mixture of calcium pantothenate are used in food. Commercial calcium pantothenate is prepared synthetically from isobutyraldehyde and formaldehyde via 1,1-dimethyl-2-hydroxy-propionaldehyde and pantolactone. (b) Calcium pantothenate meets the specifications of the Food Chemicals Codex, 3d Ed. (1981), p. 56, which is incorporated by reference. Copies are available from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418, or available for inspection at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to:*http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.* (c) In accordance with §184.1(b)(1), the ingredient is used in food with no limitation other than current good manufacturing practice. The affirmation of this ingredient as generally recognized as safe (GRAS) as a direct human food ingredient is based upon the following current good manufacturing practice conditions of use: (1) The ingredient is used as a nutrient supplement as defined in §170.3(o)(20) of this chapter. (2) The ingredient is used in foods at levels not to exceed current good manufacturing practice. Calcium pantothenate may be used in infant formula in accordance with section 412(g) of the Federal Food, Drug, and Cosmetic Act (the act) or with regulations promulgated under section 412(a)(2) of the Act. (d) Prior sanctions for this ingredient different from the uses established in this section do not exist or have been waived.

21CFR310.545 *(Calcium Pantothenate)*: Part 310-New Drugs; Subchapter D-Drugs for Human Use; Subpart E-Requirements for Specific New Drugs or Devices; (a) A number of active ingredients have been present in OTC drug products for various uses, as described below. However, based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified use: …(12) Laxative drug products-(iv)(A) Stimulant laxatives-Approved as of May 7, 1991. Calcium pantothenate; (20) Weight control drug products. Calcium pantothenate. (24) Orally administered menstrual drug products-(i) Approved as of November 10, 1993. Calcium pantothenate.

21CFR582.5212 *(Calcium Pantothenate)*: Chapter 1; Subchapter E-Animal Drugs, Feeds, and Related Products; Part 582-Substances Gernerally Recognized as Safe; Subpart F-Nutrient and/or Dietary Supplements; (a) Product. Calcium pantothenate. (b) Conditions of use. This substance is generally recognized as safe when used in accordance with good manufacturing or feeding practice.

21CFR582.5772 ***(Sodium Pantothenate)***: Chapter 1; Subchapter E-Animal Drugs, Feeds, and Related Products; Part 582-Substances Generally Recognized as Safe; Subpart F-Nutrient and/or Dietary Supplements; (a) Product. (b) Conditions of use. This substance is generally recognized as safe when used in accordance with good manufacturing or feeding practice.

10-26-2016 Searched: "Panthenol" at www.ecfr.gov, resulting in the hits below.

21CFR330.12 ***(Panthenol)***: Chapter 1, Subchapter D, Part 330, Subpart B-Administrative Procedures Part 330.12 "Status of over-the-counter (OTC) drugs previously reviewed under the Drug Efficacy Study (DESI)"; (b) On and after April 20, 1972, a number of notices were published in the Federal Register concerning previously unpublished OTC drug reviewed by the National Academy of Sciences-National Research Council Drug Efficacy Study Group. Only the evaluations and comments of the panels were published, with no conclusions of the Commissioner of Food and Drugs. Those publications were for the purpose of giving interested persons the benefit of the Academy's opinions. For those products, and also for OTC drug products previously published with the Commissioner's conclusions (except for the products listed in paragraphs (b) (1) and (2) of this section, all requests for data, revised labeling, requests for new drug applications, abbreviated new drug applications, updating supplements, data to support less than effective claims, if any, etc., are deferred, and such OTC drug products are instead subject to the OTC drug review in their appropriate classes pursuant to the procedures established in this subpart. (2) Deferral of requirements is not appropriate when an announcement has been published and has been followed by a final order classifying a drug either as lacking substantial evidence of effectiveness or as not shown to be safe. These products will be removed from the market, if they have not already been removed. Regulatory action will also be undertaken against identical, similar and related products (21CFR310.6). Deferral of requirements is not appropriate for the following (the referenced document may also pertain to prescription drugs); (xiv) Those parts of the publication entitled "Certain Mouthwash and Gargle Preparations" (DESI 2855) pertaining to Tyrolaris Mouthwash, containing tyrothricin, panthenol, and alcohol, for which an order revoking provision for certification was published in the Federal Register of February 2, 1967 (32 FR 1172) prior to the drug efficacy study implementation.

21CFR310.545 ***(Panthenol, Dexpanthenol, Pantothenic Acid)***: Chapter 1, Subchapter D, Part 310, Subpart E-Requirements for Specific New Drugs or Devices Part 310.545 "Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses"; (a) A number of active ingredients have been present in OTC drug products for various uses, as described below. However, based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses: (10) External analgesic drug products-(vi) Insect bite and sting drug products…Panthenol (vii) Poison ivy, poison oak, and poison sumac drug products…Dexpanthenol, Panthenol; (18) Skin protectant drug products (vi) Poison ivy, poison oak, and poison sumac drug products-(A) Ingredients-Approved as of November 10, 1993…Panthenol; (20) Weight control drug products…Pantothenic Acid

21CFR310.527 ***(Dexpanthenol)***: Chapter 1, Subchapter D, Part 310, Subpart E-Requirements for Specific New Drugs or Devices Part 310.527 "Drug products containing active ingredients offered over-the-counter (OTC) for external use as hair growers or for hair loss prevention."; (a) Amino acids, aminobenzoic acid, ascorbic acid, benzoic acid, biotin and all other B-vitamins, dexpanthenol, estradiol and other topical

hormones…have been marketed as ingredients in OTC drug products for external use as hair growers or for hair loss prevention. There is a lack of adequate data to establish general recognition of the safety and effectiveness of these or any other ingredients intended for OTC external use as a hair grower or for hair loss prevention. Based on evidence currently available, all labeling claims for OTC hair grower and hair loss prevention drug products for external use are either false, misleading, or unsupported by scientific data. Therefore, any OTC drug product for external use containing an ingredient offered for use as a hair grower or for hair loss prevention cannot be considered generally recognized as safe and effective for its intended use.

10-27-2016 Searched "Pantothenyl Alcohol" at www.ecfr.gov, resulting in the hits below.

21CFR582.5580 ***(D-Pantothenyl alcohol)***: Chapter 1, Subchapter E-Animal Drugs, Feeds, and Related Products, Part 582-Substances Generally Recognized as Safe, Subpart F-Nutrients and/or Dietary Supplements Part 582.5580 "D-Pantothenyl alcohol."; Conditions of use. This substance is generally recognized as safe when used in accordance with good manufacturing or feeding practice.

21CFR172.480 ***(Pantothenyl Alcohol)***: Chapter 1, Subchapter B, Part 172, Subpart E-Anticaking Agents Part 172.480 "Silicon dioxide."; The food additive silicon dioxide may be safely used in food in accordance with the following conditions: (d) It is used or intended for use as an adsorbent for *dl-a*-tocopheryl acetate and pantothenyl alcohol in tableted foods for special dietary use, in an amount not greater than that required to accomplish the intended physical or technical effect.

10-27-2016 Searched "Pantothenic Acid" at www.ecfr.gov. There are numerous CFR citations for Pantothenic Acid (http://www.ecfr.gov/cgi-bin/searchECFR?ob=r&idno=&q1=pantothenic+acid&r=&SID=15e6d735a2dfe04fdeead8853c0846af&mc=true). They are mentioned briefly below and summarized in a Table in the Safety Assessment.

21CFR172.335 ***(D-Pantothenamide, as a food additive source of Pantothenic Acid)***
21CFR104.47 ***(Pantothenic Acid, minimum levels in frozen "heat and serve" dinner)***
21CFR107.100 ***(Pantothenic Acid, nutrient specifications in infant formulas)***
21CFR104.20 ***(Pantothenic Acid, nutritional requirements in foods)***
21CFR107.10 ***(Pantothenic Acid, nutrient information, labeling of infant formulas)***
21CFR101.36 ***(Pantothenic Acid, nutritional labeling of dietary supplements)***
21CFR101.9 ***(Pantothenic Acid, nutrition labeling of food)***

9CFR317.309 ***(Pantothenic Acid, nutrition label content)***: Part 317-Labeling, Marking Devices, and Containers
9CFR381.409 ***(Pantothenic Acid, nutrition label content)***: Part 381-Poultry Products Inspection Regulations

WEBSITES

9-12-2016 Searched: "Panthenyl Ethyl Ether", "Panthenyl Ethyl Ether Acetate", "Panthenyl Triacetate", "Calcium Pantothenate", "Sodium Pantothenate" and there were no restrictions placed on any of the 5 ingredients by the European Union (COSING; http://ec.europa.eu/growth/tools-databases/cosing/); On 11-8-2016 "Panthenol" and "Pantothenic Acid" were searched in the COSING database and found to have no restrictions from the European Union.

9-12-2016 Searched using ingredient names and CAS#s above on IARC website; no relevant information for the ingredients was found.

9-13-2016 Searched: CAS#s and names above on the IFRA website at http://www.ifraorg.org/en-us/standards-library and on the FEMA website at http://www.femaflavor.org/search/apachesolr_search; No data for the ingredients was found.

9-13-2016 Searched for ingredients by CAS# and names above at http://www.accessdata.fda.gov/scripts/cder/iig/; there were no uses as inactive ingredients in FDA approved drugs

9-14-2016 Searched for ingredients by CAS# and names above at https://java.epa.gov/oppt_chemical_search and https://java.epa.gov/chemview; there were no relevant hits.

9-19-2016 Searched for ingredient by CAS# and names above at http://dailymed.nlm.nih.gov/dailymed/ ; Calcium Pantothenate appears on prescription medication labels for numerous multi-vitamins as a source for vitamin B5 and in homeopathic products to treat fibromyalgia that have not been evaluated by FDA for safety and efficacy

9-20-2016 Searched for ingredient by CAS# and names above at https://pubchem.ncbi.nlm.nih.gov/ ; information was available for Panthenyl Ethyl Ether, Panthenyl Ethyl Ether Acetate, Panthenyl Triacetate, Calcium Pantothenate, and Sodium Pantothenate

10-24-2016 Searched for Panthenol and Pantothenic Acid, but found no relevant results for cosmetic use on the following websites:

http://www.ifraorg.org/en-us/standards-library/#.WA5Xf-ArKUn

http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/

http://monographs.iarc.fr/

https://www.femaflavor.org/

http://www.rifm.org/rifm-science-database.php#.WA5cueArKUk

10-24-2016 Searched for Panthenol and Pantothenic Acid at http://www.usp.org/food-ingredients and found Safety Data Sheets for Panthenol (and Dexpanthenol)

10-24-2016 Searched Panthenol and Pantothenic Acid (at COSING; http://ec.europa.eu/growth/tools-databases/cosing/) and there were no restrictions placed on either ingredient by the European Union

10-24-2016 Searched Panthenol and Pantothenic Acid (at https://pubchem.ncbi.nlm.nih.gov) and there was some potentially useful toxicity data

10-27-2016 Searched for Panthenol, Pantothenol, Pantothenyl Alcohol, Dexpanthenol, and Pantothenic Acid at http://www.accessdata.fda.gov/scripts/cder/iig/; there were no uses as inactive ingredients in FDA approved drugs

PANTHENOL, PANTOTHENIC ACID, AND DERIVATIVES

SEPTEMBER 2017 PANEL MEETING MINUTES

DR. MARKS' TEAM

DR. MARKS: Let's move on to panthenol, pantothenic acid and its derivatives. At the April meeting this year the panelists issued an insufficient data notice. We wanted method of manufacturing, as again on Laura's August 18 memo you can read that method of manufacturing for three ingredients, some purities data, and insensitization data, specifically for panthenol at a concentration of greater than or equal to five percent.

And we did receive data. So we're at the point now of moving on to a tentative report. And the question will be can we now say we have all these ingredients are safe, the sensitization data was okay, HRIPT and local lymph node assay would support the safety of panthenol. Method of manufacturing, impurities, we received information depending on the ingredient in each one of those requests, not for all of them.

But what do you feel, Ron, Ron, and Tom? Eight safe now, insufficient for the panthenyl ethyl ether acetate for method of manufacturing and impurities? Where are we? And do you like the sensitization? And then it was also brought up I think in the annotated notes that we should have the N Nitrosation boilerplate included in this report.

So, all the ingredients safe, seven out of the eight?

DR. SHANK: I say yes, safe as used.

DR. MARKS: Mm hmm.

DR. SHANK: And then I have with the usual caveat for ethyl ether acetate. I have to figure out what I meant by that.

DR. MARKS: Ron Hill? Tom?

DR. SLAGA: I say it's all sufficient now.

DR. MARKS: Okay.

DR. HILL: No. So I think we're well the ethyl ether acetate is not in use if I understand correctly, so we're not going to get any data on that one.

DR. SHANK: Okay. So that was the caveat.

DR. HILL: Or least we don't have any report of use. We don't have any report of use. I still feel we don't have what we need on the ethyl ether itself because the only chronic or subchronic studies with that guy are oral dosing of the ether at relatively low levels and rodents, which are aggressive phase two metabolizers and efficient at (inaudible) first pass. And so I don't feel like I have enough data. I would think that 1000 milligrams per kilograms per day should be a high enough dose to swamp all those systems and let plenty in, but I'm not I don't have data to that effect. And there was something else related to that, there's an irritation test with ethyl ether that shows some effects at.125 percent that seem fairly clear, including desquamation and fissuring. And, in fact, they couldn't complete the test as planned, but the uses reported are up to 2 percent in leave ons. So there's at least a couple of places where they show those fissuring or irritation effects at low concentrations around.125 percent of that ethyl ether. And the desquamation and fissuring is pretty clear; that's in one of the tables somewhere down. And, actually, it shows up in three of the tables, tables 8 and 11, page 103 and 109. This is the ethyl ether, not the ethyl ether acetate, which is not in use, but the ethyl ether.

DR. MARKS: I have irritation.

DR. HILL: Irritation.

DR. MARKS: And 100 percent was okay and 100 percent insensitization.

DR. HILL: Where? At the ethyl ether? I don't thinks o

DR. MARKS: Panthenyl ethyl ether. So that was from my review before.

DR. HILL: Where? Where?

DR. MARKS: Let me go take a look

DR. HILL: Because I don't think so.

DR. MARKS: Page 61. But that was from a

DR. EISENMANN: I think short term it's non irritating at 100 percent.

DR. HILL: Yes, short term.

DR. MARKS: Yes.

DR. HILL: Just like single dose, one quick dermal slug.

DR. MARKS: Yes. Insensitization at 100 percent was not an issue, so I didn't have a problem with it.

DR. HILL: But they did a what was it was it a week study at.125 percent?

DR. EISENMANN: I don't know what the point what it was. .125 percent?

DR. HILL: Yes.

DR. EISENMANN: You could probably put that concentration in something and it would be non irritating. It really depends on what else is in it.

DR. HILL: But they couldn't do the study because they

DR. EISENMANN: But I don't know what the vehicle was. All I'm saying is you could say formulated to be non irritating to get around that issue.

DR. MARKS: I don't think that's necessary actually.

DR. EISENMANN: Okay, well, but the

DR. HILL: And how do you write off these fissuring effects that occurred when you gave it chronically over 28 days and you couldn't dose them half the time during that study because they desquamated and they fissured?

DR. MARKS: What page is that?

DR. HILL: You see it in table 8 and table 11.

DR. MARKS: What page?

DR. HILL: I'm sorry, 103 and 109.

DR. MARKS: How about the sensitization, because if

DR. HILL: No, the sensitization was never going to be a problem. I was never worried about that for this guy.

DR. MARKS: Well, you didn't see irritation with the sensitization, so that would be repeat exposure.

DR. HILL: It was just sensitize I don't know. That's what concerned me as were the sensitization studies valid

DR. MARKS: Yeah.

DR. HILL: because if it's doing this and I agree with carol, I don't know why they wouldn't have seen it in the sensitization studies if they were seeing it in these chronic dosing, but I I just had the concern and I still have the concern because we still didn't get the in vitro biology on this to show us for sure. Because this stuff would be so much more cellularly penetrable than panthenol.

DR. EISENMANN: So it's in a hair conditioner?

DR. HILL: Yeah.

DR. EISENMANN: So we put on a leave on hair conditioner

DR. HILL: Okay.

DR. EISENMANN: I mean you put it on (inaudible) and that's part of the reason why it probably comes out that way.

DR. HILL: So if we didn't have the.125 percent panthenyl ethyl ether in there you think it would still be irritating and fissuring and all that?

DR. EISENMANN: Yes.

DR. HILL: Okay. Then it's just a bogus study and maybe it doesn't even need to be in there at all.

DR. MARKS: Yes, there's several non sensitizing. And I was reassured because in a sensitizing study you get repeat applications. And then with a single application there wasn't.

Let's get back. So, you can bring that up tomorrow, Ron Hill. That was not when we looked at it in the last meeting in April, that was not brought up as an issue. The only issue was the sensitization data, which I brought up for that panthenol, and we have that now.

Ron Shank, was the ethyl ether acetate the reason you brought that up? Because we don't have method of manufacturing, nor do we have impurities for that compound.

DR. HILL: It's not in use, or not reported to be in use.

DR. MARKS: So can we do safe if we don't have those and it's not in use? And if it were in use it would be used in the concentration of the others?

DR. SHANK: Others, yes.

DR. MARKS: So we could do safe on it?

DR. SHANK: That's what I have, yes.

DR. MARKS: Okay. Good. And okay. So tomorrow I'm going to propose a tentative report with a conclusion that these eight ingredients are safe as used.

DR. HILL: I have one more thing.

DR. MARKS: And, Ron Hill, you can obviously bring up the irritation issue tomorrow. I don't feel we need to put in formulate to be non irritating, but we'll see what the discussion tomorrow is.

DR. HILL: Okay. Can we look at page 73 for a minute?

DR. MARKS: Mm hmm, sure.

DR. HILL: I'm getting there, sorry. I had a note to go there.

DR. MARKS: Is this the in vitro under animal you're looking at? There was a

DR. HILL: My note says it seems like we're seeing deleterious effects of panthenol at levels below 1 percent so I'm trying to find exactly the spot on page 73 in rabbits and rats both. Must be the wrong page. Okay, here it is. And it's actually on page 74 sorry under subchronic tox. Three month subchronic tox study, dermal exposure in rabbits this is from the previous report. Rabbits exhibited slight they were at.2 percent panthenol or.5 percent panthenol,.5 percent in rabbits and.2 in rats. Rabbits exhibited slight to moderate erythema, edema, and cutaneous desquamation. Rats displayed minimal hyperkeratosis, but no systemic (inaudible).

The question is, we're seeing these effects at.5 percent,.2 percent. I don't know if they're significant or not, but we have leave on doses up to 5 percent I think with this guy 5 percent in humans. And we don't have the panthenol concentration data for 2017 in the table. Is that still out for survey?

DR. EISENMANN: I just surveyed the INCI name and the INCI name is panthenol.

DR. HILL: Panthenol? So you don't know? We don't know?

DR. EISENMANN: Right.

DR. HILL: Well, if it's racemic and you say 5 percent panthenol then it's 2.5 percent active. This still goes back to the ethyl ether I'm concerned about because if ethyl ether is a pro drug for the panthenol, which it is according to the in vivo studies where they looked at urine, then it's probably a good one.

DR. MARKS: So, getting again tomorrow, I'll be moving that a tentative report be issued, with a conclusion safe for all ingredients. And then under the discussion N Nitrosation boilerplate be added. Does that sound good?

DR. SHANK: Yes.

DR. MARKS: Okay?

DR. SLAGA: Sounds good.

DR. BERGFELD: Will that be in the conclusion or the summary?

DR. MARKS: What's that?

DR. BERGFELD: (Inaudible).

DR. MARKS: Oh, that wouldn't be in the conclusion, that would be in the discussion.

DR. HELDRETH: In this particular case it's for N Nitrosation of an impurity.

DR. BERGFELD: Right.

DR. MARKS: Thank you. Thank you. So discussion, yeah. Okay.

DR. BELSITO'S TEAM

DR. BELSITO: Okay, panthenol. Okay, so the sensitization and irritation data were very equivocal. The LLNA was done on a commercial product which is not appropriate. An LLNA should not be done on a mixture of products, then it's issue we're dealing with, with botanicals doing LLNA's of botanicals. So, the LLNA that exists, to me it's meaningless.

And, I just thought we could get away with saying that it's safe as used when formulated to be non sensitizing and non irritant. And then, the question was in April, we got insufficient for method of manufacturer. For three ingredients, we got two. We didn't get it for the panthenol, ethyl, ether, acetate, but we did get it for panthenol, ethyl, ether, so can we surmise the data from this info on apparent compound and clear it, or is it still insufficient?

DR. LIEBLER: So, I said

DR. BELSITO: And it's the same thing with impurities.

DR. LIEBLER: I thought we were fine now for method of manufacturing impurities. Those data needs have met directly. And then the supplementary request from the panel was for chronic toxicity data on panthenol, ethyl, ether, and I just felt this is unnecessary given the favorable overall safety profile.

The panel is largely in agreement, and only Ron Hill asked for this, and even he waffled somewhat on his request. I think he asked about it after we took the vote in fact.

DR. BELSITO: You know, it's just that the sensitization data is still really quirky on this. I can't make I would predict that it should be non sensitized, but you know, when you look at the data, that's not what you see.

DR. HELDRETH: Page 192?

DR. BELSITO: Well that was new data that was submitted, Right?

DR. HELDRETH: Yeah.

DR. SNYDER: On page 286 more sensitization data. Anything on sensitization dose of 5 percent. (inaudible) of five.

DR. BELSITO: Yeah, but the local data was on a commercial product.

DR. SNYDER: Was it also then that

DR. BELSITO: I mean because, if you go back and look at the data we have for sensitization, you're pulling five percent above irritating in the old studies we had.

And then, in another old study,.5, 3 out of 206 subjects during induction and challenge.

On another study with 200 none, less most there were done. Non sensitizing at.1 and.5. Weak sensitization

potential, with slight to well defined irritation potential and the Beuler Test I said, it's difficult to read weeks into sensitization when you have irritation, so I don't know what to make of that. A local (inaudible) I didn't think was valid. Photosensitization is not going to absorb, it's not a photo absorber.

You know, the new studies we had we're clear right. I just don't I mean I don't believe it's an irritant. Ethanol is typically used as a balm for irritated skin as far as a barrier cream, barrier repair cream.

DR. LIEBLER: Well in that older report we did have in asterisks, it says, skill irritation and sensitization studies of cosmetic products, at concentrations up to.5 percent indicated, they were at most mild irritants but did not induce other sensitization.

DR. BELSITO: Right, and you don't even know that it was panthenol that caused the irritation.

DR. LIEBLER: It's just a mixture study and it gives you an equivocal result, and the other ingredients aren't defined. You could just say, you don't know what to attribute this affect to. We don't know if we can attribute it to the panthenol. I'd be curious to hear what Jim's take on this is. He's reporting on this tomorrow.

DR. BELSITO: I could go with a formulated, non irritating and non sensitizing, but in my experience and do we even have one case report? Are there any at all?

DR. LIEBLER: Quite a bit of data.

DR. KLAASSEN: Yeah.

DR. BELSITO: So, we've got a lot of data.

DR. KLAASSEN: I think we just go with it. I don't see a problem.

DR. BELSITO: Clinical studies. Dermatitis clinically patch tested at 50 percent DL Panthenol solution. Five questionable, (inaudible) out of 192 subjects. Fifty percent. Can we granulize (inaudible) by trial. Treated with.5 ethanol,.5 there were six subjects in the treatment group and two in the control.

I mean that's it. And then, patch test studies, 137 positive allergic reactions, so it was said to be a positive allergic in greater than 96,000 people; 23 of 33.01 positive reaction. Seven of them having atopy.

DR. SNYDER: (inaudible) of 13.

DR. BELSITO: And they were all stasis dermatitis. Then I think it's almost like lanolin, you know, if it gets through the barrier, and paraben you know, Alex Fisher was big about talking about the paraben paradox and in (inaudible) maximization text paraben was thought to be a horrible sensitizer, in humans it's not.

In fact, it sounded funny because when those GPMT's came out of the sedimines, some of the companies yanked parabens as a preservative and then put things in like methylisothiazolinone and other preservatives that caused more of an issue. Now, they're back to parabens, Eucerins, and Lubriderms of the world.

I can go either way, Jim is reporting, if he wants to say that when formulated it would be non irritating, non sensitizing, I'm fine. Just safe as used, I'm fine with that to.

DR. LIEBLER: Same.

DR. HELDRETH: Okay, so by non sensitizing which may be based on a QRA, because otherwise this would be a

(inaudible) type? Because we only say it's just (inaudible) non sensitizing or botanicals when it's a discreet chemical whether we say it may be based on QRA.

DR. BELSITO: I would ask them that, because I don't think we need to nitpick it and just say, safe as used.

DR. HELDRETH: Okay.

DR. BELSITO: I don't really have an issue with it. The sensitization data that we're seeing is really quirky. You can't use the LLNA because it's in formulation, that's not appropriate. LLNA in formulation should be the ingredient in acetone or a discreet vehicle, not a multi use vehicle. So, the LLNA study is bogus.

The sensitization studies are all over the place. They just don't make sense to me, I don't believe you know, the number of case reports out there, the data is not really well described. It seems to be maybe it's an issue with patients with damaged skin. Significantly damaged skin, and I think at best, this is like a paraben or a lanolin and you know, I mean, lanolin causes issues in some patients, but I think it's safe as used.

FULL PANEL – DAY 2

DR. MARKS: So we have a draft tentative report before us. At the April meeting, the panel issued an insufficient data announcement. We have received data since that time and our team felt that we could move forward and the motion is a tentative report with a conclusion of "safe for all ingredients."

DR. BERGFELD: Is there a second?

DR. BELSITO: Yes.

DR. BERGFELD: Are there comments or discussion items?

DR. MARKS: Yeah, the only thing we would add is the end, "N nitrosation boilerplate" in the discussion.

DR. BERGFELD: Okay. Ron Hill?

DR. HILL: Yeah. I wish to note that I'm still not comfortable with the body of data for the ethyl ether. I mean, not the ethyl ether acetate because that's not in use and we don't have data, but I'm not comfortable with the ethyl ether body of data yet. So, I'm voting against only because I don't think we have adequate assurance for the ethyl ether.

DR. BERGFELD: Ron Shank, any comment about the ethyl ether?

DR. SHANK: No.

DR. BERGFELD: Dan?

DR. LIEBLER: No.

DR. KLAASSEN: I guess I would like to ask, why don't you feel comfortable about the ethyl ether?

DR. HILL: Well, I closed the document, figured we'd moved past out.

DR. BELSITO: While you're opening that up, there was quirky data about enhancement of dermal penetration. Did you want that in the discussion?

DR. MARKS: It certainly could

DR. BELSITO: (Inaudible) enhancement.

DR. HILL: Yeah. I was concerned with the basis for my concern backing up a step is that the cell penetrability of that particular molecule is expected to be a lot higher than even panthenol itself and definitely higher than pantothenic acid, and since pantothenic acid is the vitamin that are transporters and other compensatory mechanisms that control the traffic of that that would not apply to the diethyl ether. And while there are some oral dosing studies that showed, I think what they did was with a back calculation, that showed 70 percent conversion when dosed orally to rodents that were getting mostly conversion to the pantothenic acid, I think we might be missing things that could be going on in the skin in particular with that ethyl ether giving it additional penetrability and the possibility of it being (inaudible) after getting into cells. And so, either in the liver or in the skin itself.

So I just felt like I was looking for a little more in vitro data to show with either a lack of biological activity or something in the consistent range with pantothenic itself or panthenol. And there are some flags with the panthenol if you look. There's some effects in the skin.

The other thing is, although I think it was written off, is that we have this dermal fissuring where they couldn't complete the 28 day chronic studies in the way that they'd planned it. And while Carol asserted, and I agree with her based on her expertise, that that was related to the formulation and not the compound itself, it sure would be nice to know that for sure.

So we're seeing effects on the skin, what I consider to be deleterious effects in the skin. I got a list here somewhere with that agent that suggests we might not know enough about that compound in terms of its bioactivity. And so that's the basis of my discomfort. I mean, the will of the group is going to prevail here, but I just feel the need to put that out there.

DR. BERGFELD: Any comments with respect Ron Hill's presentation or interpretation?

MR. GREMILLION: I have I didn't

DR. BERGFELD: Yes.

MR. GREMILLION: From the consumer's perspective, I mean we I would just like to point out, you know, that companies can continue to use this product and, I mean, these aren't having an insufficient data conclusion won't prevent these companies from using this product and going and doing the in vitro testing that would address these concerns. So we would support erring on the side of caution.

DR. BERGFELD: All right. Do you want to comment on that?

DR. LIEBLER: So the panthenol ether and the panthenol ether acetate, you know, are freely metabolically interconvertible, and I think the overall favorable safety profile of this family of compounds, in my view, doesn't support Ron's concern about the panthenol ethyl ether, particularly the idea that this is going to have some significantly different ability to penetrate cells or be absorbed.

So my comfort with all of these is based on the overall favorable safety profile of the whole family and the fact that this ethyl ether and the ethyl ether acetate, which is an ingredient that Ron is not objecting to, are so similar and metabolically interconvertible that I don't see a distinction that needs to be made.

MR. GREMILLION: It was the ethyl ether that was done on the rabbits that the rabbit study in a fissuring out approach that it was applied to the rabbits and something happened to the rabbit's skin where they couldn't complete the study to study of the effects on the skin on the rabbits. And there's some question about why that whether that was related to the

DR. LIEBLER: I think our dermatology colleagues are best qualified to

MR. GREMILLION: Yes.

DR. LIEBLER: address the issues with those types of studies.

MR. GREMILLION: I mean, there is the issue of more in vitro testing and then there's that rabbit study, and I guess, I mean, it just seems like from my kind of lay perspective, there's a fair amount of uncertainty. And I understand what you're saying about the read across, but it seems like, in this sense, where it would be reasonable to err on the side of caution.

DR. HILL: Also, that.125 percent were seeing desquamation and fissuring. And again, that might be because of the vehicle that was used. But it would sure be nice to know that it was in fact because of the vehicle that was used. Because, again, I have concerns that this we had an ethyl ether. So that's not like an acetate that's cleaved off by esterases. There will be specific people (inaudible) that have to do that cleavage, and then the I guess, it's sub chronic it's a 28 day tox. The doses should be high enough to swamp out the systems that something would have been picked up there, so I while I

DR. LIEBLER: But the ethyl ether acetate has the same ethyl

DR. HILL: I'm not

DR. LIEBLER: ether piece on it and an acetate on the other end. If anything, that is going to be even more readily absorbed.

DR. HILL: Yeah. We don't have data on that one at all.

DR. LIEBLER: You're not objecting to that.

DR. HILL: We don't have any data on that one, at all.

DR. LIEBLER: So I just, I don't think, I don't accept the logic that this a problem.

DR. HILL: Again for me, it's just absence of information and a comfort level that isn't there because we don't have certain key pieces of information. That's the deal.

DR. BERGFELD: Any comments by other panel members? Curt?

DR. KLAASSEN: No.

DR. BERGFELD: Paul?

DR. SNYDER: No.

DR. BERGFELD: Tom?

DR. SLAGA: No.

DR. BERGFELD: Ron Shank?

DR. SHANK: No.

DR. BERGFELD: Okay. All right. So Dr. Marks will you restate the motion so we can move ahead? Just restate it so we can vote on it.

DR. MARKS: Let me get up here and safe for all ingredients, tentative report.

DR. BERGFELD: Okay. And it was seconded?

DR. BELSITO: Yeah.

DR. BERGFELD: So I'm going to call the vote. All those in favor, please indicate by raising your hands. Abstaining. Negative.

One negative.

DR. HILL: For that one ingredient.

DR. BERGFELD: For what and it'll come out on the minutes why you voted against it.

(The motion passed 7 to 1; Dr. Hill votes against.)

APRIL 2017 PANEL MEETING MINUTES

DR. MARKS' TEAM

DR. MARKS: Okay. Let me see. Next one. Panthenol. Pantothenic Acid and derivatives. Roy, you're up again and Pantothenic Acid is Vitamin B5. Let me go pull that up. So this is a draft report. It's billed as the first review, but that's not exactly true. There's seven ingredients and Panthenol and Pantothenic Acid had a safe conclusion in 1987 and re-affirmed in 2004. So, Tom, Ron, and Ron, do you like these seven ingredients?

DR. SHANK: Yes

DR. MARKS: Okay. Needs? What needs do we have?

DR. SHANK: I don't have any toxicology needs.

DR. SLAGA: Same here. I think we have sufficient data to support it.

DR. MARKS: Yeah. I'm probably going to raise old history here. I thought we needed sensitization data on panthenol. And the reason was 5%. That's what it's being used now, 5%. There are over 7,000 uses, so lots of uses. The original report was only tested at 0.5%. So I'm not sure how we got a safety for 5% on sensitization. I don't know how that gap, when I read the original report I wasn't convinced that we could go ten times greater and say it doesn't sensitize. The wave two data we received had a 5% open epicutaneous test on guinea pigs. And it was a weak sensitizer but, so it said it was a sensitizer in that but I didn't think an open epicutaneous test was adequate. So I actually would propose and insufficient data announcement. And there's gotta be some sensitization test with 5% panthenol. But, that was my take on that one. And the only other thing is I had, this is in terms of the final conclusion, but to clarify the multiple panthenols and the VCRP data using concentration data. But at any rate.

DR. SHANK: It's for panthenol, you're saying?

DR. MARKS: Yeah. Panthenols.

DR. SHANK: Because on page 33, clinical studies

DR. MARKS: 33

DR. SHANK: Human subjects in a dermatitis clinic. Patch tested. 50%.

DR. MARKS: Yeah. And the problem with that, that only detects sensitization, it doesn't detect the potential. That's why I'd like to see an HRIPT or a guinea pig max.

DR. SHANK: Okay.

DR. HILL: I have a long list.

DR. MARKS: Okay. It's a long list of needs?

DR. HILL: Yes

DR. MARKS: So I'm gonna second maybe an insufficient data announcement. We'll see how Don responds to the sensitivity need, even though it was approved before. Okay. Your needs?

DR. HILL: Pantothenic Acid method of manufacture. What we have listed seems highly unlikely to be a commercial production procedure. There's a reference in tox-net source. So I wondered if we could pull out primary information, determine if it's actually relevant to commercial production. Seems to me this probably comes from biological sources of some sort. But I'm not sure. Let's see.

DR. MARKS: So that was for Pantothenic Acid. Ron Shank? Tom? Were you concerned with method of manufacture for Vitamin B5?

DR. HILL: That doesn't affect my assessment of safety actually in this case. I just think we should have it.

DR. MARKS: Okay. So that won't change the conclusion?

DR. HILL: Not on that one. Not on that one.

DR. MARKS: Okay. So I'm not sure I, maybe you can comment some more. That to me, is sort of editorial.

DR. HILL: That probably is an editorial request. So I don't know if that's a need or not actually. The point is, having a method of manufacture is what else might show up as impurities in your product. That's the whole point of the method of manufacture. If it's biological sources, then that's something we should know, for multiple reasons. On the D- Panthenol, we've got purities, but do we have an antimeric, another words, chiral purity? That's actually important to know. Let's see, similarly when the purity is cited for D- Pantothenate, does the purity indicated indicate, or include chiral purity or just chemical purity? Let's see. So, my bigger concerns actually relate to these panthenol ethyl ether, which is up to 2% in foundations. So that's a leave-on that would presumably we used regularly. What information do we have on the ethyl ether as far as dermal penetrability and chronic tox? Especially dermal. We know that there's activity there because page of the, page 31, there's some information about affects on skin healing at 3% concentration. So that induces a cell-proliferative routine which is, I mean, skin healing. We don't have method of manufacture at all for the diethyl ether. Or impurities info, unless it's other there somewhere in an original paper. And, okay, on the search strategy, this is not a need, we're getting D and DL. Are we getting D, the DL, which is the racemic mixture, or scelemic mixture as it might be, and any work that might have been done with the L on every single one of these compounds. And, let's see. I also noted that N,3-athoxyl propyl 2,4-dihydroxy 3,3- dimethyl butherimide, which is an ECHA study. How do we say that one? ECHA. What do most people say? ECHA?

DR. JONAS: ECHA

DR. HILL: ECHA. All right. Which is an ECHA study. Specifically D. So you can't read across the information from D to DL. You can inform, but it's not the same. Okay, this is just editorial there. Okay. This might be it. Oh, do we need the nitrosamines boilerplate due to the possible presence of residual amenes [amines]? I've got PDF pages 24 to 25. So what was that? Pages 24 to 25. Oh, okay. Top of page 25. It talks about three amino propyonic acid as a 0.5% impurity. That's pretty low. In decalcium [d-Calcium] pantothenate.

DR. MARKS: Ron, I'm probably going to ask you to summarize these tomorrow as far as which ones you think are critical needs. If we end up doing an insufficient data announcement. I think it's going to be important. And I'll ask you to summarize it tomorrow. The ones you really feel need to be included in the announcement.

DR. HILL: I think I wouldn't raise, I mean chiral identity, whenever you're using data to do a toxicological study, if you do a study with a racemate, so we've got a mixture of D and DL, except for the occasional pathological thing, where we've got two different anetemers [enantiomers] doing sort of opposite things, then usually we can talk about that one, and antemer is an impurity. But if you do something up to 5% with the racemate, then you've only got 2.5% of the active. So that's always something to keep in mind. And also that we can read across a study from DL to inform D or L, but you can't use a study from D to inform DL. You're not getting the right piece of information. So that's just something. There are a number of places in here where we don't have stereochemistry specified. If it's an older study it might not even be known. But in this day and age, when we've got an ingredient, at least, when it says purity, and we're saying it's D this, or L that, what about chiral purity? Because if it's 99% chemically pure, but it's only 70% chiral purity, we need to know that at least.

MS. SCOTT: It wasn't always specified.

DR. HILL: I know. I'm sure that's true.

DR. MARKS: So that kind of, for me, goes back to Table 3, page 41. Where it's the same as the previous ingredient we talked about. We had, in that current frequency and concentration of use, we have Panthenol

DR. HILL: They are small

DR. MARKS: listed twice at the top with numbers and concentration. And then we have the D form and then we have the DL form. But when we list the ingredients, we only list one. Panthenol. So, do we, for me, again, I find it hard to say, okay, there's only one ingredient, but then we've got a use table of four ingredients.

MS. SCOTT: In the VCRP they are reported separately, so that's why they're here.

DR. HILL: I don't understand the top, the first one and the second one at the top left. The first one is not starred, the second one has the double stars, and then we have Panthenol D. I certainly know that one. So it appears three times. Why is that?

MS. SCOTT: So Panthenol on the left at the top is from the two previous reports.

DR. HILL: Okay.

MS. SCOTT: And I don't know exactly how it's listed other than Panthenol.

DR. HILL: Okay.

MS. SCOTT: And then the second Panthenol with two the stars, from 2017, was listed as D Panthenol and as DL Panthenol in the VCRP. And often times in the sources it's listed various combinations of those. So that's why in the report you might see it not ideally the way it could be helpful, but it's listed in different ways.

DR. HILL: Yeah, again, if we didn't know that this has vitamin activity, and that's why I'm raising the questions about the ethyl ether. Because for the ethyl ether, and definitely also for the triacetate, we've got cell penetrability and quite a bit of it. As compared to Panthenol itself even. And definitely as compared to Pantothenic Acid. But, again, then stereochemistry comes into play as an issue. And you will not always have that information. And that's definitely true for older studies. And I'm partly saying this because I know there are dictionary people listening. So I'm putting it on the record for that. Because in the future that's an issue that has to be, there's a lot of places in the dictionary we don't have a specification for historical reasons.

DR. MARKS: Okay. I had the sensitization data. Ron, you mentioned a lot, you can tomorrow morning, Ron Hill, go ahead. Again, I assume I'm going to be seconded an insufficient data announcement. But we'll see tomorrow what comes up. Any other comments? Tom? Or Ron Shank?

DR. SHANK: Not from me.

DR. HILL: I will try to get that listing as concise as possible.

DR. MARKS: Yeah, that sounds good. Thanks, Ron Hill. Okay. We'll see where that goes tomorrow. Thanks Laura. Okay.

DR. BELSITO'S TEAM

DR. BELSITO: Okay. Do we have the critical people here? Okay. We're going to be resuming. It's 10:30. With Panthenol. So this is the first time we're looking at seven ingredients, five of which are derivatives of ethyl ether and acetyl esthers, or simple swabs of pantothenic acid or panthenol. Panthenol and pantothenic acid were previously reviewed and found to be safe, but were brought back in because they really formed a structure of a report that we're going to be looking at. And so the usual question is, what do we think of the data? Well, let's look at the report. I guess the first thing I had a question on, not being a chemist, is typically we haven't mixed ethers with esthers. Are you okay with that grouping, Dan?

DR. LIEBLER: Yeah, I'm okay with it. That's fine. It makes plenty of sense. I would say, by the way, under the chemistry section, I would please add a structure for the panthenyl ether since that's the most --

DR. BELSITO: Okay.

DR. LIEBLER: I think it's the most --

DR. BELSITO: Frequently --

DR. LIEBLER: -- used.

DR. BELSITO: -- used, yeah.

DR. LIEBLER: Yeah.

DR. HELDRETH: Okay.

DR. LIEBLER: And so it's a little bit distinct, but it's certainly appropriate structure.

SPEAKER: Just add it to figure one?

DR. BELSITO: Yup.

SPEAKER: Okay.

SPEAKER: Just to comment on terminology on page 24, your use of NLT and MT, I know it means not less than and not more than, but don't we just typically just use the symbols, less than or equal to?

SPEAKER: Yeah.

MS. SCOTT: Oh, okay, sure.

DR. BELSITO: Yeah.

MS. SCOTT: Yeah, we could do that. I think that's how it was stated in the reference I found, but, yeah, sure. Yeah.

DR. SNYDER: Under uses, Laura, your memo says 382 uses, but the document says 369. I didn't count them up, but you might just want to verify which one is right.

MS. SCOTT: Okay.

DR. KLAASSEN: That's plus or minus 5%.

MS. SCOTT: I think it's 382 You're talking about for panthenyl ethyl --

DR. SNYDER: Yeah.

MS. SCOTT: -- ether?

DR. SNYDER: Yeah.

MS. SCOTT: Yeah, it should be 382.

DR. BELSITO: On what page, Paul? The correction needs to be in the table or the --

DR. SNYDER: Well, I think the memo's wrong, so I think the -- her documents, what she just -- you said 362?

MS. SCOTT: Three eighty-two.

DR. SNYDER: Because under the, on the first page there, you say, introduction, you say, 362.

MS. SCOTT: Okay. That may be because I updated the CRP data with 2017 and that might not have gotten updated --

DR. SNYDER: Okay.

MS. SCOTT: -- there, but thank you for pointing that out.

DR. BELSITO: So the document is correct.

DR. SNYDER: No, the document is incorrect. Hyper continuous of panthenyl ethyl ether, 362 uses.

MS. SCOTT: Let me just look at the use table

(inaudible) --

DR. BELSITO: Okay, no it says 382 in the document.

DR. SNYDER: Mine says 362.

DR. BELSITO: It says use.

DR. HELDRETH: Yeah, it says it in the table, it says 382 in the documents, but in the intro it says 362.

DR. BELSITO: Oh, in the introduction.

DR. HELDRETH: Narrative, yeah.

DR. BELSITO: Okay.

MS. SCOTT: So then just the intro needs updating.

SPEAKER: Yes.

MS. SCOTT: Yeah, (inaudible).

DR. BELSITO: So, we know that there's some question, very questionable evidence about panthenol being penetration enhancer. And we now know that panthenyl ethyl ether is the most frequently used, but there's no data on enhancement. And mean that the data for panthenol is very questionable, but is this something we're okay with and just going and saying, you know, it's a penetration enhancer. Be careful what you formulate it with? How do we want to deal with that very questionable data on panthenol? What did you think of that data on panthenol? Do you think it's a penetration enhancer?

DR. LIEBLER: I'm not sure that you can necessarily reach that conclusion because the mixtures applied are not just panthenol and progesterone. It's this PMA matrix or the -- and trimethyl citrate. See, you make these matrix mixes up. The polymer matrix that contained 20% D-Panthenol. And then the progesterone which is, I assume, the molecule of this penetration you want to evaluate this mixture. And I honestly don't think you can include from this --

SPEAKER: A whopping one -- oh, I (inaudible).

DR. LIEBLER: Oh, it says, no difference with or without. for the PMA formulation, there was no difference in permeation of progesterone with or without panthenol. There's a slight increase in permeation in the PBA formulation with six and 20% compared to panthenol.

DR. BELSITO: Right. That's why I thought it --

DR. LIEBLER: You know?

DR. BELSITO: -- was, like, really --

DR. LIEBLER: Depending on what they mean by slight, what the measurement variation was for the experiment, and whether they did replicates, I don't know what to conclude. I didn't look at the paper.

MS. SCOTT: Okay.

DR. LIEBLER: So --

DR. BELSITO: So my question is, do we -- what do we do with that in terms of discussion in penetration enhancement?

DR. SNYDER: D-Panthenol versus panthenyl ether

(inaudible) --

SPEAKER: I think --

DR. SNYDER: -- methyl ether.

DR. BELSITO: Yeah, I mean, if panthenol may have that, may, have that effect with panthenyl ether, which is used more frequently, have a similar or potentially greater effect based upon its chemical structure and that -- I think that was my question.

DR. LIEBLER: So, I think it could. I think it's reasonable to say that the structure of the ethyl ether would still be similar now because you've got this kind of, you know, what's it about, 10 or 12 carbons, and then you've got three alcohols on it, only one of which is (inaudible), right? And so, I mean, it could act very similarly to panthenol. So if there's any significant penetration in the intimate, it could be significant. The problem is this experiment is not a simple penetration enhance experiment because you've got this kind of matrix, which is the major --

SPEAKER: Delivery.

DR. LIEBLER: -- delivery vehicle and, you know, the matrix is creating a situation where it's really hard to compare the different experiments very well and conclude. Even if you do just plus or minus panthenol, I don't think you can infer from this what the effect of panthenol would be on some other cosmetic product that contained panthenol possibly affecting the absorption of other molecules. I just don't think you can really draw a conclusion. So, you know, if we have these data in the paper, or in the report, I think, at most, we could simply say, in the discussion, you know, that any of these molecules might be expected to exert similar effects, although the effect was marginal, appeared to be marginal or modest, any of these --

DR. SNYDER: And not directly attributable to the chemical.

DR. LIEBLER: Yeah. Nevertheless, you know, we could basically -- our penetration enhancement boilerplate is based on molecules that are documented clearly to produce penetration enhance, right? So I'm just trying to think of how -- because I don't think this rises to that level.

JAY ANSELL: Yeah, and then, we're not even talking about -- well, now we're talking about a structurally similar material may have an affect similar to a material that we don't know is of interest. So it seems as kind of a stretch to me.

DR. SNYDER: So would it be more appropriate to put it under other tests instead of a penetration enhancement test?

DR. LIEBLER: Well, it is a penetration enhancement study. It's just not a particularly --

SPEAKER: Classical --

DR. LIEBLER: -- well-designed or easily interpreted result. So, I guess, maybe rather than roll out the full penetration enhancement boilerplate, because I don't think it's necessarily just (inaudible) data, it's just -- I think you can simply say the panel considered it and felt that the data were equivocal not necessarily ostensible to the other compounds.

DR. SNYDER: Handle the discussion.

DR. LIEBLER: Yeah.

DR. BELSITO: Okay, so the discussion, the effect was marginal, not necessarily due to the molecule itself and what was that last point, Dan?

DR. LIEBLER: And may not extend to the other molecules, to the other ingredients. And while we're on this again, this isn't one of these things where you got that -- you don't need a structure progesterone there.

DR. BELSITO: So this report was reopened really because of panthenyl ethyl ether and the other addons. And we have only acute studies for the ethyl ether. Does this bother anyone?

DR. LIEBLER: Well, I think we should have more data on the ethyl ether. We don't even have a method of manufacture and impurities on it. And it's the most used. So that's a big gap for me.

DR. BELSITO: So we want method of manufacture and impurities?

DR. LIEBLER: Right.

DR. KLAASSEN: Biology, most likely, will be the same.

DR. LIEBLER: I think it would be pretty similar. I don't think the ethyl ether will participate in any of the biochemistry that the pantothenic panthenol, pantothenic acid does because that ethyl ether is probably not going to be easily metabolized. I mean, it could be metabolized. It could be oxidized off over an (inaudible) ethylation, but there are other -- you know, the other hydroxyls on there are more likely to be, you know, conjugated and excreted. I know I think that biochemistry with this molecule would be somewhat different.

DR. BELSITO: So basically for the ethyl ether at this point, just manufacturing and impurities. We're not asking for additional tox data?

DR. SNYDER: As well, you know, we asked for absorption if we don't have -- we (inaudible) genotox on the ether, ethyl ether.

DR. BELSITO: We have aims [Ames] at 99.2% and we have a mammalian, yes, at 99.2. So we have that. That's from wave two.

DR. SNYDER: The courtesy study is not a courtesy study. That's an invitro -- that's not a classical carcinogenicity study. We need to move that probably to other studies.

DR. BELSITO: What page are you on?

MS. SCOTT: Can you please repeat that?

DR. SNYDER: It's right underneath that section of the genotox, under carcinogenicity. It's a 3T3 transformation assay. So we don't have carcinogenicity --

MS. SCOTT: Okay.

DR. SNYDER: -- data.

DR. BELSITO: So this needs to be moved where, Paul?

DR. SNYDER: I put it under other relevant studies.

MS. SCOTT: Okay.

DR. SNYDER: And you can just put a subtitle, transformation or something. You have cytotoxicity and metabolism, so just put it under a different (inaudible).

MS. SCOTT: Okay.

DR. KLAASSEN: I had a question. You know, in some of these reports, we have new data in italics and other reports we have lines on the side. Some of them we have a shaded -- is this all being evolved into everybody's going to be doing it the same eventually?

MS. SCOTT: So, the --

DR. HELDRETH: This one is different because this is not a rereview. It's not a matter of a 15-year clock expired on the two previously reviewed ingredients. We started looking at these ingredients because of the high frequency of use of the panthenyl ethyl ether came up on our priorities previously. So this is, in essence, a new report, but two of the ingredients that we brought into it have been previously reused, so that's why you're not seeing italicized paragraphs here, which is the standard format for doing a rereview.

DR. BELSITO: Developmental and reproductive toxicity, we have no data on the ethyl ether. Are we okay with that?

DR. SNYDER: Well, no, because it depends upon the absorb (inaudible) right?

DR. BELSITO: So we are asking --

DR. SNYDER: We're asking for method manufacture, impurities, and absorption?

DR. LIEBLER: I agree. I think we do need that. I mean, the thing is, the ethyl ether is different enough from the others. You know, the acetates can be hydrolyzed off and you go back to pantothenyl, but the ethyl ether won't really bio-transform like that, or at least not nearly 100%.

DR. BELSITO: So absorption or (inaudible).

DR. LIEBLER: So I really think it's different enough and its use concentration is comparable to the pantothenic acid molecules.

DR. BELSITO: Absorption and or absorption or 28?

DR. LIEBLER: Well, if absorbed.

DR. SNYDER: Well, if absorbed.

DR. LIEBLER: Then that triggers the 28 day --

DR. SNYDER: And repro.

DR. LIEBLER: Repro, yeah.

MS. SCOTT: So did you say there was not reproduction data for -- what was the concern?

DR. BELSITO: For the panthenol.

SPEAKER: The pantothenyl ethyl --

SPEAKER: (Inaudible.)

SPEAKER: -- ether.

SPEAKER: Basically --

MS. SCOTT: There's one study in in invivo oral on page 58 of the PDF in the table nine.

SPEAKER: (Inaudible.)

DR. SNYDER: The DL pantothenyl ether, no L greater than 1000.

SPEAKER: Yeah.

DR. BELSITO: Whoever did the ones with the tabs where you could do control click to get to the tables, that was neat. It let me split my screen and go down. So it was table nine, Laura?

MS. SCOTT: Oh, yes, page 58 PDF.

DR. SNYDER: Yeah, so we just need to back that off to just (inaudible) manufacturings in a period.

DR. BELSITO: So we don't need the absorption?

DR. LIEBLER: We got invivo oral and it's --

DR. BELSITO: Clean.

DR. LIEBLER: -- clean there.

DR. BELSITO: Okay.

DR. LIEBLER: So, oral repro, that is.

DR. BELSITO: So then we just need manufacturing impurities, not absorption?

DR. LIEBLER: Yep. I'm okay with that.

DR. BELSITO: So, in the discussion we have respiratory boilerplates, penetration, possible penetration enhancement. And we, our conclusion at this point is insufficient for method of manufacturer and impurities on the ethyl ether. Is that correct?

DR. LIEBLER: Yeah, and the triacetates, the pantothenyl triacetates.

MS. SCOTT: So all the derivatives, all five?

DR. LIEBLER: Yeah, I don't --

MS. SCOTT: Basically?

DR. LIEBLER: -- I don't think we have anything on them.

MS. SCOTT: Okay.

DR. LIEBLER: So the pantothenyl ethyl ether, the acetate and the triacetate.

DR. SNYDER: Is it relevant that they keep referring to the DL (inaudible)? Is that --

DR. LIEBLER: It depends on how it's defined. There's a chiral center in the molecule, so you could have stereoisomers (inaudible).

DR. SNYDER: But everything we have is on the DL it appears.

DR. LIEBLER: Yeah, the DL either racemic material, the biologically active pantothenic acid is, I believe,

(inaudible).

DR. BELSITO: Okay. So what I have so far is the discussion respiratory boilerplate, possible penetration or enhancement, and our conclusion at this point is insufficient method of manufacturer of ethyl ether and triacetate.

DR. LIEBLER: Right.

DR. BELSITO: Okay.

DR. LIEBLER: And looking at the Beth's memo, at the end of the report, I was just struck by the counsel has no suppliers listed for the panthenyl ethyl ether acetate, and sodium pantothenate. Okay, the panthenyl ethyl ether acetate, that doesn't have that many uses, right? I misread that. I think I must have -- for the panthenyl ethyl ether, which has over 300 uses, never mind. I just caught that.

MS. SCOTT: So there are no data needs for the alcohol acid or the salts, right?

DR. LIEBLER: Yeah, I think those are probably fine.

MS. SCOTT: Okay.

DR. LIEBLER: I didn't hear anybody say anything about that. I did have one other comment on the page 28 under the ADME section. There's a big paragraph in the middle under invivo animal, which is a mixture of, sort of, ADME stuff and then toxicity. About half of the first paragraph, the second half of the first paragraph's almost all toxicity.

MS. SCOTT: Okay.

DR. LIEBLER: It should probably go in a tox section instead. And then the -- let's see, second, third, fourth paragraph in its entirety on radiation and partial

(inaudible). That goes elsewhere, too.

MS. SCOTT: In (inaudible).

DR. LIEBLER: That goes elsewhere, also.

MS. SCOTT: Oh, okay.

DR. LIEBLER: But that fourth, the one on --

MS. SCOTT: Fourth. Okay.

DR. LIEBLER: -- partial hepatectomy and radiation and calcium pantothenate, that's not ADME, so that goes somewhere else.

MS. SCOTT: Do you have a suggestion where?

DR. SNYDER: That other category and --

DR. LIEBLER: Yeah, probably other.

MS. SCOTT: In irrelevant studies?

DR. LIEBLER: Right, yeah.

MS. SCOTT: Okay.

DR. BELSITO: It won't take me too long to capture all that you have (inaudible) in your --

SPEAKER: Yeah.

DR. BELSITO: And that's not really something we need to discuss (inaudible).

SPEAKER: There's more (inaudible).

SPEAKER: (Inaudible.)

SPEAKER: (Inaudible.)

SPEAKER: Related to this (inaudible).

SPEAKER: I had mentioned it to Laura and we'll get

(inaudible).

SPEAKER: Okay.

DR. SNYDER: So what about this contact dermatitis issue?

DR. BELSITO: Where are you, Paul?

DR. SNYDER: Under the case report or something there's contact dermatitis was noted.

DR. BELSITO: Yeah, again, I'm -- case reports don't bother me unless there're hundreds like methylisothiazolinone known and there's a reason why. I mean, to in a child caused by 75% deep panthenol facial-wide, you know, there're very few reports in this ingredient is pretty widely used. I had a question on table six in the toxic cosmetic studies, the study with D-Panthenol and panthenyl triacetate, you said the -- about this 70% conversion, I didn't see that as part of the study. (Inaudible.)

MS. SCOTT: Can you tell me again which study is table six?

DR. BELSITO: Table six, the -- under invivo animal dermal.

MS. SCOTT: Okay.

DR. BELSITO: So it was rubbed into the shaved neck skin and analyzed for pantothenic acid content. And then you say, 70% conversion to panthenyl ether to pantothenic acid, but the study was on the triacetate. Is that just a typo? Do you see what I'm seeing? It says the D-Panthenol and D- Panthenyl triacetate, and then you say the panthenyl ether -- ethyl ether to pantothenic acid, there was a 70% conversion. But it -- that wasn't one of the molecules studies. It was the panthenyl triacetate.

MS. SCOTT: Oh, oh, okay. I see what you're saying, okay.

DR. BELSITO: So I didn't know whether the ether was studied or the --

MS. SCOTT: Okay.

DR. BELSITO: -- triacetate was studied, and --

MS. SCOTT: It was --

DR. BELSITO: -- which was converted.

MS. SCOTT: It was the triacetate from what I recall. I'm not sure I have the ethyl ether. That might be just a typo. I'll have to check on that one.

DR. BELSITO: Yeah, just --

DR. LIEBLER: It looks like it, because that just would be hard to believe they gave you that much metabolism, that type, that molecule. But the acetate, sure. That makes perfect sense.

MS. SCOTT: Okay. Yeah, I'll correct that.

DR. LIEBLER: So I'll bet you it's a --

MS. SCOTT: (Inaudible.)

DR. LIEBLER: -- (inaudible).

MS. SCOTT: Double (inaudible), thank you for finding that.

KAPAL DEWA: Dr. Belsito, (inaudible) do you see any need (inaudible) study here?

DR. BELSITO: I didn't.

SPEAKER: (Inaudible) phototoxic --

SPEAKER: Phototox? Oh, no, these molecules won't absorb --

KAPAL DEWAL: Okay, thank you.

SPEAKER: -- like --

DR. BELSITO: Yeah, and then I just had a few typos, but nothing else. So we're going insufficient method of manufacturing impurities of the ethyl ether and the triacetate at the (inaudible).

DR. LIEBLER: Actually, it would be acetate and the triacetate. There are two different acetates.

DR. BELSITO: Oh, okay. So insufficient.

MS. SCOTT: So the panthenyl ethyl ether acetate?

DR. LIEBLER: The ethyl ether acetate and the triacetate --

MS. SCOTT: And the triacetate.

DR. LIEBLER: -- correct.

MS. SCOTT: And --

DR. LIEBLER: As well as the ethyl --

MS. SCOTT: Ethyl ether.

DR. LIEBLER: -- ether.

MS. SCOTT: Okay.

DR. LIEBLER: Yeah. So three.

MS. SCOTT: Three, got you.

DR. LIEBLER: Okay. I'm going to save again. Okay.,

FULL PANEL

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

DR. BELSITO: Okay. So, this is the first time that we're looking at this report of seven ingredients. Five of which are derivatives. Those would be the ethyl ether. The acidal ester. Simple salt forms of panthetenic acid.

DR. BERGFELD: Mm-hmm.

DR. BELSITO: And it's alcohol analog panthenol. We have previously reviewed panthenol and panthetenic acid in 1987. And re-reviewed them in 2004. However, they will perform -- they will behave as a structural background for looking at this entire group. So they're being brought into this re-review. Not because they're due for re-review. But they're needed to really assess what's going on with the other materials in this. And, after looking at all of the data, we thought that as a group, that several of them were sufficient. But insufficiencies from method of manufacture and impurities of the ethyl ether, the ethyl ether acetate and the triacetate. Otherwise, we were okay with the safety of the other remaining ingredients.

DR. BERGFELD: And your proposal then is, to go safe with the exception of those three?

DR. BELSITO: Correct.

DR. BERGFELD: And you need methods of manufacturing?

DR. BELSITO: And impurities.

DR. BERGFELD: Impurities. Is there a second? Or a comment?

DR. MARKS: Yeah. There's a comment. And essentially the same. Since this is a first review, and I am

(not exactly) since as Don mentioned, two of the ingredients were reviewed before with a safe conclusion. Our team felt we could move with an insufficient data announcement for the two things you mentioned. I also felt we needed sensitization data on panthenol. And this gets back to your comment, we've approved ingredients before where, the sensitivity testing didn't support the concentration. You look at the original report. First of all, now we have uses over 7,000. The original report tested only 0.5 percent. We now have uses up to five percent. So, over 10 times the use, or 10 times the use concentration. Wave 2 contained the five percent open epicutaneous test on guinea pigs. But I didn't think that was an adequate to confirm the safety of five percent use concentration. And actually, in that guinea pig test, epicutaneous test, it was concluded it was a weak sensitizer. So I'd include in the insufficient data announcement, I'd like sensitization data on panthenol at five percent. Either at guinea pig max. Or an HRIPT.

DR. BELSITO: I'm fine with that.

DR. BERGFELD: That okay? So, as your second?

DR. MARKS: And do you like the insufficient data Don?

DR. BELSITO: I'm fine, you know, I mean --.

DR. HILL: I had a couple of more things.

DR. BELSITO: It's the first time, I mean, so I don't think --

DR. BERGFELD: Okay.

DR. BELSITO: -- we need to go final on a first time.

DR. BERGFELD: Right.

DR. BELSITO: So, insufficient is fine.

DR. BERGFELD: Ron Hill.

DR. HILL: Yeah. We talked about it yesterday, and you indicated you had opened it up for me to add.

DR. MARKS: Yes. I have Ron Hill comments here.

DR. HILL: (Laughter) Thank you.

DR. MARKS: So thank you for Ron for jumping in.

DR. HILL: This is probably not needs, but it relates to chemical identity in the sense that we have purities quoted for D-panthenol. And the D-panthenol derived ingredients. But, I wanted to know if those are chiropurities included in the purity? Or if that's just chemical purities? So that applies to D-panthenol, D-pantothenate and all of these ingredients where we've got quote purities. The other thing relates to that panthenol ethyl ether. So, we've got pantothenic acid and panthenol we've got from personal communication. Maybe other information. But, what I saw was the reference to the personal communication that it's 100 percent converted in the skin to pantothenic acid. Well and good. But the ethyl ether, we predict that to be substantially more cellularly penetrable. The only add-me [ADME] for that ethyl ether that we had in the whole report, is buried in one table, I believe Table 6. I have a page number here. And it's reference 51. And the reference 51 refers to testing of D- panthenol triacetate. And so, at least in the title, it doesn't talk about the ethyl ether. So, I wanted to verify if we have another source of that information, it's in the same personal communication. Not sure, but that's dated February 2017. And the concern I had is, that we know that pantothenic acid, we have data that shows that it invokes wound healing. And that's good. When you have a vitamin like that of panthenol, that's presumably 100 percent converted, then vitamin traffic, and it would be controlled by transporters, binding proteins and so forth. Including access to inside of cells. And it's clearly triggering a regime of wound healing. And perhaps cell proliferation to close that wound. And then we have a study on humans that deals with blistered skin, where the skin is getting healed. So, if you've got a molecule and like the ethyl ether, we have no chronic tox data whatsoever, except two weeks in the DART studies on that molecule. It's really bothersome, if we have, because it's used in a foundation up to two percent. So, I mean, foundation, that's presumably a very limited area of skin on a face, because it's foundation. But, I just -- I'm bothered by the lack of chronic tox here on a compounded. It could get -- wouldn't be dependent on things like transporters to get inside of cells.

DR. BERGFELD: So you're requesting what?

DR. HILL: I would like to see something. And it could be cellular in vitro. Whatever. Because this ingredients been out there a while now. And there's six hundred and some uses, if I read that correct.

DR. BERGFELD: So, you're requesting chronic toxicology?

DR. HILL: It could be at the cellular level. Something to give us further indication of the potential dangers of this compound or lack thereof. Actually, we're looking for some assurance of safety.

DR. BERGFELD: Any other comments?

DR. HILL: On the chronic conditions.

DR. BERGFELD: Dan. Or Paul.

DR. SNYDER: Well, the DL pethyl ether was tested in a repro tox study with NAOEL of 1,000 milligrams.

DR. HILL: Yeah, but that's at two weeks exposure. And I, I mean, I was very assured by that. But two weeks is very different than 90 days. Or six months. I think right now we could toss this out for thinking about it, if we don't want to make it an insufficiency. But I just, I'm concerned that we don't have any kind of chronic tox on this.

DR. BERGFELD: Well, it's going to go out as an insufficient data announcement, so you could make a request for specific data.

DR. HILL: Because we're seeing a pronounced activity with the triacetate, which is another situation where that's enhancing cellular penetrability. And getting it around the transport of the vitamin, pantothenate, into cells.

DR. BERGFELD: Paul?

DR. SNYDER: Both pantothenate and the ethyl ether were done in repro studies and they were negative up to 1,000 and 2,000, respectively. So, I'm not that concerned about toxicity.

DR. BERGFELD: Dan?

DR. LIEBLER: I agree with that. I mean, we did discuss this very issue. I was, you know, two things. One is, that this is a pretty simple derivative of a common nutrient. The second is, 1,000 mgs in a repro study.

DR. HILL: But that was dosed orally. It was dosed orally and you know there's going to be a very high first past metabolism removal of that ether. And we don't even have any add-me [ADME] data on this (inaudible).

DR. LIEBLER: Well, actually you don't know there's going to high first pass data.

DR. HILL: No. That's the point. We don't know.

DR. LIEBLER: You know, but I mean, you know, there are examples of high first pass chemicals, like lidocaine. But, you know, in a way, they're often the exception rather than the rule.

DR. HILL: And the high first pass would be a good thing in this case of oral dosing.

DR. LIEBLER: I actually -- we agree to disagree. It's an insufficient. We'll get what we can get.

DR. BERGFELD: Yes.

DR. LIEBLER: The one point you mentioned at the very beginning of your comments Ron. I think we came to -- that mention of the ethyl ether in the table, I think that's probably incorrect.

MS. SCOTT: It's actually not a typo. I did check it.

DR. LIEBLER: Oh really.

MS. SCOTT: It was buried in a submission from the Council. There's one statement, which is reflected in the table. And the reference is listed there, but I don't have that. So, it's actually in the build. We can take a quick look if you'd like.

DR. LIEBLER: Well, we can come back to it next time.

MS. SCOTT: Okay.

DR. LIEBLER: But it was the issue of the 100 percent --

MS. SCOTT: Right.

DR. LIEBLER: -- metabolism of the ether to the alcohol. And that struck me as pretty unlikely.

DR. HILL: It's 45 percent. 45 percent, isn't it? It's Table 6. Yes. It's like 45 percent.

DR. LIEBLER: Okay. Good.

DR. BERGFELD: Curt? Any comment?

DR. KLAASSEN: No. I don't have anything else to add.

DR. BERGFELD: Ron? Tom?

DR. SHANK: No. I don't think so.

DR. BERGFELD: Okay. So we have basically, an insufficient data announcement that we have concurrence of the whole panel. And, I wonder, Jim, if you can go through --. No, it's Belsito's. Don, can you go through what we're going to ask for now?

DR. BELSITO: Since I'm already on hops, let me go back again. (Laughter)

DR. MARKS: I'm glad you asked Don, because I was on hops too. It was method and manufacture and impurities.

DR. BELSITO: Yeah. So we had method and manufacturing and impurities for three specific ingredients. And those were ethyl ether, ethyl ether acetate and triacetate.

DR. BERGFELD: And is there a request for some chronic tox?

DR. BELSITO: And then --.

DR. MARKS: Then it was the HR for sensitization.

DR. BELSITO: HRIPT and concentration of use five percent for panthenol.

DR. BERGFELD: Okay.

DR. MARKS: Right.

DR. BERGFELD: All right.

DR. HILL: I would have liked to see the chronic tox of some sort.

DR. BERGFELD: But we can put that in as a request, if there's any chronic tox data out there.

DR. HILL: Without formally having to be insufficient.

DR. BERGFELD: Right.

DR. HILL: Just a request.

DR. BERGFELD: Right. Just a request.

DR. HILL: That would be great.

DR. BERGFELD: Okay. All right. Then we'll move on, because we've agreed to what our needs are for that ingredient. Moving onto hops, since you've both been on that one (Laugher). Jim Marks.

MINUTES OF THE TWENTY-EIGHTH MEETING OF THE EXPERT PANEL

April 21-22, 1986
Key Bridge Marriott Hotel
Rosslyn, Virginia

Expert Panel Members

Karl H. Beyer, Jr., M.D., Ph.D., Chairman
Wilma F. Bergfeld, M.D.
William O. Berndt, Ph.D.
William W. Carlton, D.V.M., Ph.D.
Dietrich K. Hoffmann, Ph.D.
Arnold L. Schroeter, M.D.
Ronald C. Shank, Ph.D.

Liaison Representatives

Consumer
Ms. Mary Ellen Fise, Esq.

Industry
Gerald N. McEwen, Jr., Ph.D.

FDA Contact Person
Heinz J. Eiermann

CIR Staff

Robert L. Elder, Sc.D., Director/
Scientific Coordinator

Elizabeth M. Santos, Scientific Analyst

Adopted _____
(Date)

_____
Karl H. Beyer, Jr., M.D., Ph.D.
Chairman

the report. She stated that the Bergfeld team was recommending a conclusion of safe with a limit of 2 percent in products applied to the skin or used in the eye area due to limited testing above 2 percent and notable ocular irritation.

Dr. Hoffmann noted that Diisopropanolamine and Triisopropanolamine can be easily nitrosated to N-nitrosobis (2-hydroxypropyl)amine, a powerful carcinogen in mice, rats, hamsters, rabbits, and guinea pigs. Therefore, it was recommended that the nitrosating agent qualifier be included in the conclusion.

Dr. McEwen suggested using the terminology "rinse-off" to signify brief, discontinuous use of a product (in this case permanent hair waves). However, it was noted the Panel had previously used this term only in reference to shampoos, while the highest concentration use (> 5 to 10 percent) of the isopropanolamines was in permanent hair waves, which remain on the head and hair for 20 to 30 minutes before being rinsed off.

There was also some discussion as to the actual concentration of free isopropanolamine in a product. Mr. Eiermann indicated that most of the isopropanolamine reacts in formulation, leaving very little free isopropanolamine. He stated that any concentration greater than 1 percent would not be free isopropanolamine.

Dr. McEwen noted that the 2 percent concentration (upon which the Panel was setting its limit) was the pure ingredient tested under occlusive patch test conditions, and not a test of product use.

Dr. Bergfeld then recommended a conclusion of safe as used in cosmetics with the inclusion of the qualifier "not to be used in products containing N-nitrosating agents". She also requested that the discussion point out that these compounds had only been tested at concentrations up to 2 percent and that higher concentrations could pose possible problems.

Dr. Schroeter requested that the summary of the report be corrected to say that a small degree of allergic contact dermatitis was observed.

This report was then unanimously approved with the conclusion as proposed.

The Tentative Final Report will shortly be announced for a 90-day public comment period.

Panthenol

Dr. Schroeter reported that the data informally requested had been supplied and that his team now considered the document to be adequate. His team's

questions and considerations were noted in the discussion which he read to the Panel. These included 1) clinical testing at low concentrations only; however, no significant irritation or sensitization were indicated in product formulation testing and no case reports were recorded, and 2) a recognition that no mutagenicity or carcinogenicity data were available; however, because of the nature of these compounds (vitamin and reduced form of vitamin), the high requirement for normal metabolism, and their low concentration use in cosmetics, the normal requirement would far exceed the amount absorbed and precludes the likelihood of genotoxicity. Dr. Schroeter then recommended a standard conclusion of safe as used in cosmetics.

Dr. Bergfeld commented on the fact that the clinical testing was conducted with concentrations of 0.1 to 0.5 percent while the FDA data showed concentrations of use up to 5 percent. Dr. Schroeter responded that this had been addressed in the discussion.

Dr. Bergfeld also commented that the new data received, with one exception, were redundant and did not need to be included in the document. This exception was the paragraph marked for insertion on page 22 and titled "Skin Irritation". She requested that the title be changed to "Comedogenicity" and the paragraph included in the report.

Dr. Hoffmann dissented with the opinion that mutagenicity and carcinogenicity data were not needed. He stated that the Panel had never before approved an ingredient without these data. He also noted that they were dealing with the alcohol (Panthenol) rather than the vitamin (Pantothenic acid). He also questioned the statement in the discussion regarding "poor cutaneous absorption".

Dr. Berndt stated that their team had not ignored the fact that no genotoxicity data were available. They had considered the impurity data and the fact that it's a vitamin and had assessed the data available; they did not feel pressured to request mutagenicity data.

It was noted that Panthenol was a reduced form of the vitamin and that this was stated in the text. Many groups had looked at both the acid and the alcohol.

Dr. Hoffmann agreed that they were dealing with a natural product and therefore he was more inclined to let the report pass; however, he still felt that a technical product (starting with a lactone) was under consideration and that mutagenicity data should be requested.

It was agreed that the last paragraph of the discussion should be revised to more clearly reflect the data.

There was some discussion as to whether the Panel has a checklist of data required, regardless of the ingredient. The general consensus was that the Panel did not have a checklist.

Dr. Schroeter recommended a standard conclusion of "safe as used in cosmetics". This motion was passed with a tally of four in favor and two opposed (Drs. Hoffmann and Bergfeld).

The Tentative Final Report will shortly be announced for a 90-day public comment period.

Dr. McEwen requested a moment to introduce Dr. Richard Bednarz, CTFA's new Vice President-Science. He had taken the position vacated by Dr. Norman Estrin.

2,3-Naphthalenediol

Dr. Bergfeld reported on the status of this report. At the team meeting in January, her team had concluded that this report was insufficient with respect to dermal irritation in animals, photosensitization in animals, 90-day subchronic dermal study in animals, and impurity data. Industry had subsequently responded and agreed to conduct the necessary tests; however they had proposed to do an in vitro phototoxicity test. Dr. Bergfeld stated that her team did not have the expertise to judge this test. She indicated this was a new procedure and was not well established, therefore her team was requesting the opinion of the Schroeter team.

Dr. Shank said that he had no experience with this particular test and that he could comment only as a toxicologist. He stated that this test is where the Ames test was sometime ago in that not enough compounds have been tested comparatively to establish the validity of the test. He noted that the test also did not compensate for differences between the metabolism of a microbial system and that of humans. He concluded that it would be a little premature to accept this test now, although he would like to encourage in vitro testing.

There followed a general discussion of the validity and acceptability of this in vitro test. The consensus was that in vitro testing should be encouraged, but as this test was still in the early stages of development, it could not be accepted in place of standard testing. The possibilty of asking for the in vitro test in addition to the UV spectrum was mentioned.

December 2nd-3rd, 2004-Minutes from 93rd Meeting of the Expert Panel

Panthenol and Pantothenic Acid

Dr. Marks stated that a CIR Final Report with the following conclusion was published in 1987: Based on the available data, Panthenol and Pantothenic Acid are safe as presently used in cosmetics.

Dr. Marks said that after reviewing case studies in the new data, his Team had expressed concern over sensitization reactions to Panthenol and Pantothenic Acid. However, he noted that his Team concluded that these chemicals are rare sensitizers based on the published literature and his experience as a dermatologist. Dr. Marks noted that this determination was made in spite of the human RIPT data on products containing 0.5% Panthenol in the published CIR Final Report. He acknowledged that his Team had also considered that this test concentration of Panthenol (0.5%) is lower than the current maximum use concentration (6%) that is reported in the re-review document.

Dr. Marks added that after reviewing the available new data, his Team concluded that the CIR Final Report on Panthenol and Pantothenic Acid should not be reopened.

Dr. Belsito said that the absence of clinical reports of irritation and sensitization, particularly, given the increased use frequency of Panthenol since the Final Report was published, adds a level of comfort that skin sensitization data on Panthenol at concentrations greater than 0.5% are not needed.

Dr. Bergfeld noted that the comments made by Drs. Belsito and Marks will be incorporated into the discussion section of the Annual Review.

The Panel unanimously concluded that the Final Report on Panthenol and Pantothenic Acid should not be reopened.

Safety Assessment of Panthenol, Pantothenic Acid, and Derivatives as Used in Cosmetics

Status: Draft Final Report for Panel Review
Release Date: November 10, 2017
Panel Meeting Date: December 4-5, 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 Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Laura N. Scott, Scientific Writer/Analyst and Monice Fiume, Senior Director.

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

ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel assessed the safety of Panthenol, Pantothenic Acid, and 5 derivatives as used in cosmetics. These ingredients named in this report are reported to function in cosmetics as hair conditioning agents, and Panthenol also is reported to function as a skin-conditioning agent-humectant and a solvent. The Panel reviewed relevant data for these ingredients, and concluded that these 7 ingredients are safe in cosmetics in the present practices of use concentration described in this safety assessment.

INTRODUCTION

This assessment reviews the safety of Panthenol, Pantothenic Acid and 5 derivatives as used in cosmetic formulations.

Panthenol	Panthenyl Triacetate
Pantothenic Acid	Calcium Pantothenate
Panthenyl Ethyl Ether	Sodium Pantothenate
Panthenyl Ethyl Ether Acetate	

The ingredients reviewed in this safety assessment are reported to function in cosmetics as hair conditioning agents (Table 1), according to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI *Dictionary*).[1] Panthenol is also reported to function as a skin conditioning agent – humectant and as a solvent.

Although this safety assessment includes two ingredients that have been reviewed previously (i.e., Panthenol and Pantothenic Acid), this report is not a re-review. This report was initiated because of the high frequency of use of Panthenyl Ethyl Ether (382 uses) in cosmetic formulations, as reported by the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP).[2] Pantothenic Acid, the water-soluble vitamin B_5,[3] and its alcohol analogue, Panthenol, are closely related to the five derivatives above and, therefore, are included in this safety assessment. In 1987, the Panel reviewed Panthenol and Pantothenic Acid and concluded that these ingredients are safe for use in cosmetics.[4] In accordance with CIR Procedures these ingredients were re-reviewed after 15 years, and the Panel reaffirmed the original conclusion.[5]

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.

Relevant data from the previous reports have been summarized and are included (*italicized text*) at the beginning of the appropriate sections of this safety assessment, but are not included in the tables or summary section. The original safety assessments and re-review summary are available at http://www.cir-safety.org/ingredients. A current search of published literature revealed new data for Panthenol and Pantothenic Acid, which is summarized in this safety assessment (un-italicized text) as appropriate including in tables and the summary section. Additionally, updated frequency of use and concentration of use data for Panthenol and Pantothenic Acid are included in this safety assessment.

Some of the data included in this safety assessment were found on the European Chemicals Agency (ECHA) website.[6,7] In this safety assessment, ECHA is cited as the reference for summaries of information from industry obtained from the ECHA website. Also referenced in this safety assessment are summary data found in reports made publically available by the Food and Drug Administration (FDA)[8-15] and the National Technical Information Service (NTIS).[16]

CHEMISTRY

Definition and Structure

The derivative ingredients in this report are related to Panthenol and Pantothenic Acid, sharing the same structural core. Each ingredient is an ethyl ether, acetyl ester, or simple salt of either Panthenol or Pantothenic Acid (Figure 1). The dextrorotatory (D-) forms and dextrorotatory, levorotatory (D,L-) forms of the ingredients are referred to in this safety assessment when that information was provided. Vitamin activity of Pantothenic Acid is limited to the D- form.[17] However, the panthenyl cosmetic ingredients are defined somewhat vaguely, without indication of stereochemistry. Unfortunately, much of the available literature is just as vague. Stereochemistry is specified when that information was available for the ingredients in this safety assessment.

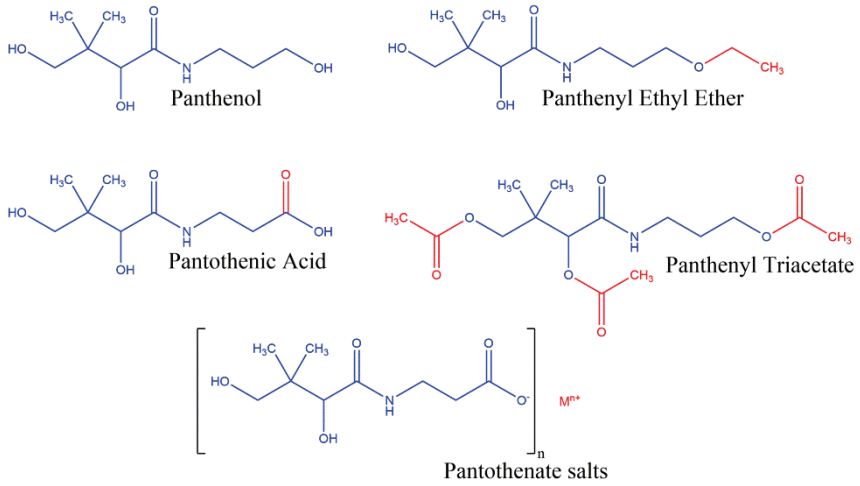


Figure 1. Panthenol, Pantothenic Acid, and derivatives.

Physical and Chemical Properties

Panthenol is a white, crystalline powder (racemic mixture of D- and L- forms) with a molecular weight of 205 g/mol and a melting point of 63°C.[6,18] D-Panthenol and DL-Panthenyl Ethyl Ether may also be colorless to slightly yellow, clear, viscous liquids that can crystalize during storage.[19,20] Pantothenic Acid is a hygroscopic oil with a molecular weight of 219 g/mol and a boiling point of 551 °C.[17,21] Calcium Pantothenate and Sodium Pantothenate, salts of Pantothenic Acid, are highly hygroscopic, water-soluble, crystalline solids with melting points between 170 and 200 °C, and formula weights of 476 g/mol and 241 g/mol, respectively (Table 2).[17,22-24] The remaining ingredients in this report are liquids with boiling points greater than 400 °C, and molecular weights ranging from 233 to 331 g/mol.[25-27]

Calcium Pantothenate is more stable than the unstable forms of free Pantothenic Acid and Sodium Pantothenate.[28] Pantothenic Acid has been reported to be stable to heat in neutral or slightly acidic environments, but less stable under alkaline conditions.[29] D-Panthenol has been reported to be more stable than Pantothenic Acid at pH 3 to 6.[19]

Calcium Pantothenate

When used as a nutritional additive in animal feed, D-Calcium Pantothenate was reported to have a "dusting potential" (mass of the particles per m^3 drawn from a rotating drum containing the test material)[30] of 1.1 g/m^3 and the particle size fraction < 50 µm was measured to be 7% by laser diffraction.[28] In another study, the dusting potential was more variable based on batches of D-Calcium Pantothenate produced from different manufacturers. The particle size fraction < 50 µm ranged from 10% (dusting potential of 12.6 g/kg) to 67%.[31]

Method of Manufacture

Panthenol

D-Panthenol may be produced by a condensation reaction of D-pantolactone with 3-aminopropanol in the presence of methanol and dichloromethane.[31] A condensation reaction of D-pantolactone with aminopropanol is used to synthetically prepare D-Panthenol.[32]

(*R,S*)-Pantolactone (DL-lactone) and aminopropanol are combined at an elevated temperature and then diluted with 1.5% citric acid, after the reaction, to yield DL-Panthenol (minimum 50% (*R,S*)-Panthenol in aqueous solution stabilized with citric acid).[33,34]

Pantothenic Acid

Pantothenic Acid can be synthesized via saponification of sodium β-alaninate with sodium hydroxide, followed by reaction with L-pantolactone.[35]

Panthenyl Ethyl Ether

A condensation reaction of D- and DL-pantolactone with 3-ethoxy-1-propanamine is used to synthetically prepare DL-Panthenyl Ethyl Ether (62.5% D-form, 37.5% L-form).[36]

Panthenyl Triacetate

D-Panthenyl Triacetate is produced by the esterification of D-Panthenol with acetic anhydride, sodium acetate and dimethylamino-pyridine, followed by neutralization with sodium bicarbonate and a water wash.[37]

Calcium Pantothenate

D-Calcium Pantothenate may be produced via amidation of pantolactone with saponified β-alanine.[35] Saponification of β-alanine with calcium hydroxide or calcium oxide, eliminates the need for ion exchange after the amidation. Residual solvents are then removed and the aqueous solution dried.

Sodium Pantothenate

Sodium Pantothenate may be prepared by reacting (*R*)-pantolactone and sodium beta-alaninate in ethanol or methanol.[38]

Impurities

Panthenol

According to the *Food Chemicals Codex (FCC)*, food grade specifications limit lead impurities in DL-Panthenol to ≤ 2 mg/kg (2 ppm).[18] Aminopropanol may be present in DL-Panthenol at ≤ 0.1%. The acceptance criteria recited in the FCC for Panthenol are ≥ 99.0% and ≤ 102%.

When used as a nutritional additive in animal feed D-Panthenol was reported to be 99.5% ± 0.15% pure (drying loss 0.3%-0.4%)[28] and in another animal feed study was reported to be 100.1% ± 0.1% pure in an anhydrous product (0.02% - 0.06% water).[31] The residual solvent impurities from 5 batches tested were methanol and dichloromethane.[28,31] Other impurities were 3-amino-propionic acid (< 0.5%), lead (< 20 mg/kg), and sulfated ash (< 0.1%).

A manufacturer reported specifications from a D-Panthenol (≥ 98.0% on anhydrous material) assay as follows: ≤ 1.0% water, ≤ 0.1% sulfated ash (residue on ignition), ≤ 10 ppm heavy metals, ≤ 1.0 ppm lead, ≤ 0.5% 3-aminopropanol, ≤ 50 ppm dichloro-methane, ≤ 200 ppm methanol, ≤ 0.5% pantoic acid, and ≤ 1.0% D-pantolactone.[19] Potential microbial contamination was below the level of concern in this assay (total aerobic microbial count and total combined yeasts/molds ≤ 100 colony forming units (CFU)/g or ml).

Specifications reported from a DL-Panthenol (≥ 53% (*R,S*)-Panthenol in aqueous solution stabilized with citric acid, pH 5.5 - 7.0) assay included: ≤ 0.5% sulfated ash (residue on ignition), ≤ 10 ppm heavy metals, ≤ 2.0% DL-lactone, ≤ 1.0% aminopropanol, ≤ 50 ppm dichloromethane, and ≤ 500 ppm methanol.[34] Potential microbial contamination was below the level of concern (total aerobic microbial count and total combined yeasts/molds ≤ 100 CFU/g or ml).

Panthenyl Ethyl Ether

Reported specifications from a DL-Panthenyl Ethyl Ether (≥ 98.0% on anhydrous material, slight excess of (*R*)- over *(S*)-isomer) assay were as follows: ≤ 0.5% water, ≤ 0.1% sulfated ash (residue on ignition), ≤ 10 ppm heavy metals, ≤ 1.0% 3-ethoxypropyl-amine, ≤ 50 ppm dichloromethane, and ≤ 500 ppm methanol.[20] Potential microbial contamination was below the level of concern (total aerobic microbial count and total combined yeasts/molds ≤ 100 CFU/g or ml).

Panthenyl Triacetate

A certificate of analysis indicated that a sample of D-Panthenyl Triacetate contained < 1.8 mg/kg antimony; < 0.8 mg/kg selenium; < 0.4 mg/kg copper; < 0.2 mg/kg nickel and silver; 0.08-0.1 mg/kg cobalt, iron, and zinc; < 0.07 mg/kg chromium; < 0.03 mg/kg lead; < 0.02 mg/kg barium; < 0.005 mg/kg arsenic and mercury; and < 0.004 mg/kg cadmium.[39] The production of D-Panthenyl Triacetate was reported to yield an average (3 lots tested) of 95.90% purity (mean pH 7.03); average content of impurities stated were 0.3% Panthenyl Diacetate, 0.14% Panthenyl Acetate, 1.51% acetaminopropanol, 2.15% pantolactone, 0.25% water, and < 0.1% acetic acid.[40]

Calcium Pantothenate

The FCC specifies that D-Calcium Pantothenate or a racemic mixture of DL-Calcium Pantothenate should have ≤ 2 mg/kg (2 ppm) lead.[18] The FCC acceptance criteria for alkaloid impurities include no turbidity present within 1 minute of dissolving 200 mg of D- or DL-Calcium Pantothenate in 5 ml of water and adding 1 ml of 2.7 N hydrochloric acid and 2 drops of mercuric-potassium iodide. The calcium content should be ≥ 8.2% and ≤ 8.6% (dried basis), and loss on drying should be ≤ 5.0%. For either D- or DL-Calcium Pantothenate (calcium chloride) double salt, arsenic impurities should be ≤ 3 mg/kg (3 ppm) and lead impurities ≤ 2 mg/kg (2 ppm); loss on drying should be ≤ 5%; calcium content should be ≥ 12.4% and ≤ 13.6% (dried basis); chloride content should be 10.5% to 12.1% (dried basis). The FCC acceptance criteria for Calcium Pantothenate were stated to be ≥ 97.0% and ≤ 103.0%.

D-Calcium Pantothenate, when used as a nutritional additive in animal feed, was reported to be 99.6% ± 0.05% pure (drying loss 1.6%-2.1%),[28] and, in another animal feed study was reported to be 100.3% ± 1.3% pure (drying loss 1.1%-2.8%).[31] Impurities reported (5 batches tested) were the residual organic solvents methanol and ethyl acetate and the following: 3-aminopropionic acid (< 0.5%), chloride (< 200 mg/kg), and lead (< 20 mg/kg).[28,31]

Natural Occurrence

Pantothenic Acid

Jelly from queen bees, rice bran, molasses, and liver are all sources of Pantothenic Acid.[17] Additional sources are meat, whole grains, legumes, eggs, milk, fruits, and vegetables.[41]

USE

Cosmetic

The Panel evaluates 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 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 indicate that of the ingredients reported in this safety assessment, Panthenol, D-Panthenol, DL-Panthenol, and Panthenyl Ethyl Ether have the highest number of reported uses at 5766, 518, 477, and 382 respectively (Table 3).[2] Panthenol, D-Panthenol, and DL-Panthenol were reported separately in the VCRP, therefore they are reported separately in Table 3. Concentration of use survey data was collected for Panthenyl Ethyl Ether, Panthenyl Ethyl Ether Acetate, Panthenyl Triacetate, Calcium Pantothenate, and Sodium Pantothenate in 2015 [42] and for Panthenol and Pantothenic Acid in 2016 [43] (Table 3). These data indicate that the highest maximum reported concentrations of use were for Panthenol (5.3% in body and hand products; 5% in skin cleansing products and hair conditioners),[43] Panthenyl Ethyl Ether (2% in foundation),[42] and Panthenyl Triacetate (2% in lipstick and other make-up preparations).[42] The concentrations of use (2004) and frequency of use (2002) for Panthenol and Pantothenic Acid from the re-review summary are included in Table 3 for comparison.[5] The highest maximum concentrations of use for Panthenol and Pantothenic Acid are not substantially different in 2016[43] as compared to values reported in 2004.[5] The category for which Panthenol had no reported uses in 2004[5], but had uses reported in 2016, was in baby products (5% in baby shampoos and 2.5% in baby lotions, oils, and creams).[43] The frequency of use for Panthenol increased from 1538 in 2002[5] to 5766 uses reported by the VCRP in 2017 (Table 3).[2] Frequency of use for Pantothenic Acid increased from the 3 uses in 2002[5] to 78 uses reported in 2017.[2]

There are no frequency of use or concentration of use reported for Panthenyl Ethyl Ether Acetate and Sodium Pantothenate.[2,42]

The ingredients in this safety assessment are reported to be used in cosmetic sprays, including hair sprays, body and hand sprays, and fragrances, and could possibly be incidentally inhaled. For example, Panthenol, Panthenyl Ethyl Ether and Calcium Pantothenate are reportedly used in aerosol and pump hair sprays at concentrations up to 0.6%, 0.5%, and 0.19%, respectively.[42,43] Panthenol and Panthenyl Ethyl Ether are used in body and hand sprays at concentrations up to 5% and 0.5%, respectively.[42,43] Panthenol is used in colognes up to 0.5% and in deodorant sprays up to 0.1%.[43] 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.[44-47] 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.[44,46] 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.[46] 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.

Panthenol, Panthenyl Triacetate, and Calcium Pantothenate are reportedly used in face powders at concentrations up to 0.5%, 0.003%, and 0.01%, respectively, and could possibly be inhaled.[42,43] VCRP data indicate that Panthenol and Pantothenic Acid are reportedly used in face powders and Panthenol is used in powders.[2] 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.[48-50]

Panthenol (3% in eye lotions), Pantothenic Acid (0.001% in eye shadows), and Panthenyl Ethyl Ether (0.84% in eye shadows) are reported to be used in cosmetic formulations indicative of potential eye exposure.[42,43] Panthenol (2.5% in other personal cleanliness products; 2% in lipstick) and Panthenyl Triacetate (2% in lipstick) are reported to be used in formulations with possible mucous membrane exposure and/or ingestion.[42,43]

Panthenol, Pantothenic Acid, and the five derivatives included in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union.[51]

Non-Cosmetic

The uses of Panthenol, Pantothenic Acid, Calcium Pantothenate, and Sodium Pantothenate, as specified in the Code of Federal Regulations (CFR) Title 21 and Title 9, are largely as nutritional food additives (Table 4). Generally recognized as safe (GRAS) status was established for Panthenol, Calcium Pantothenate, and Sodium Pantothenate with the use of good manufacturing and feeding practices in animals (21CFR582.5212, 21CFR582.5580, 21CFR582.5772). Calcium Pantothenate is GRAS as a direct food additive (nutritive) intended for human consumption and is also used in infant formulas (21CFR184.1212). The reference

daily intake for Pantothenic Acid for adults and children at least 4 years of age is 5 mg/day, for infants through 12 months 1.8 mg/day, for children 1 to 3 years 2 mg/day, and for lactating women 7 mg/day (21CFR101.9). In food, both the D- and DL-mixtures of Calcium Pantothenate are used. Calcium Pantothenate is authorized by the Alcohol and Tobacco Tax and Trade Bureau to be used in the fermentation of apple wine.[10,11]

There was inadequate safety data to establish generally-recognized-as-safe-and-effective status in various over-the-counter (OTC) drug products for Panthenol, Pantothenic Acid, and Calcium Pantothenate (21CFR310.527, 21CFR310.545).

Panthenol

D-Panthenol (1.5 to 15 mg/ml) is listed as an ingredient in FDA-approved prescription drug products for use as injectable vitamins.[52] D-Panthenol (concentration not specified) is listed as an ingredient in a contact lens multipurpose cleaning solution which was cleared for use under a 510 (k) premarket notification by the FDA based on equivalence to a "legally marketed predicate device".[15] Panthenol is listed as an ingredient that may have chemical activity in a wound dressing.[8] The FDA cleared a 510 (k) premarket notification for a medical device intended for wound healing (prescription and OTC uses), which listed Panthenol (concentration not specified) as a skin conditioning ingredient in a topical formulation.[14]

Calcium Pantothenate

The FDA permitted a 510 (k) premarket notification for a medical device marketed for human oocyte in vitro fertilization, which listed Calcium Pantothenate (concentration not specified) as an ingredient.[13]

TOXICOKINETIC STUDIES

Panthenyl Triacetate

Panthenyl Triacetate has been reported to convert to Panthenol and Pantothenic Acid upon dermal application to human skin.[53,54] Panthenyl Triacetate has also been reported to penetrate underarm skin.[54]

Provided below are summaries of dermal and nail penetration experiments that are presented in detail in Table 5.

Dermal Penetration

In Vitro

Animal

The cutaneous penetration of D-Panthenol (10% in a hydrophilic gel formulation) through the skin of pigs was examined, with and without sonophoresis, in a diffusion cell experiment.[55] The penetration of D-Panthenol into pig skin was enhanced by the use of an ultrasound technique. A steady increase in D-Panthenol concentration was observed in receptor cell fluid from 2 to 120 minutes, with a plateau reached by 180 minutes (903 µg/ml without ultrasound and 1069 µg/ml with ultrasound).

D-Panthenol (concentration not specified) was evaluated in various surfactants (Tween®85, SDS, and Span®80), ranging in concentration from 0.5% to 5%, for 180 minutes in a Franz diffusion cell experiment using porcine abdominal skin.[56] The study authors concluded that 1% surfactant yielded the optimum results in the skin penetration of D-Panthenol for this test and that the nature of the enhancer affected the cutaneous barrier impairment.

Human

The dermal penetration of ^{14}C-Panthenol (20 mg/ml in ethanol, 0.05 mCi/ml) through human abdominal skin samples was evaluated in a Franz (static) diffusion cell experiment.[57] Skin samples were either not stripped or stripped 5x or 10x prior to the application of 10 µl test substance. The receptor solution (0.01 mol/l phosphate buffered saline with 5% polyethylene glycol (v/v)) was collected up to 60 minutes post-application, and then all skin samples were stripped 20x before analysis. In the skin samples not stripped prior to test substance application, the amount of applied radioactivity detected after 60 minutes was 84% in the stratum corneum, 6% in the epidermis, and 4% in the dermis; radioactivity in the receptor fluid was negligible (< 0.03%). For the 5x stripped samples, the radioactivity detected 15 minutes post-application was 81%, 8.7%, and 6% in the stratum corneum, epidermis, and dermis, respectively; radioactivity in the receptor fluid was negligible (< 0.1%). For the 10x stripped samples, the radioactivity detected 15 minutes post-application was 72%, 18%, and 6.3% in the stratum corneum, epidermis, and dermis, respectively; radioactivity in the receptor fluid was negligible (< 0.04%).

In Vivo

Human

D-Panthenol (3% in water-based gel), Panthenyl Triacetate (3% in water-based gel), or a water-based gel control were applied to volar forearms of human subjects; measurements of the ingredients to a skin depth of 25 µm were taken using confocal Raman infrared microspectroscopy at 1, 5, and 24 hours following application.[53] At all time points, D-Panthenol and Panthenyl Triacetate were detected in the upper layers of the stratum corneum, exceeding baseline levels (see Table 5 for levels detected); D-Panthenol was detected to a lesser extent (slightly above baseline level at all time points) and Panthenyl Triacetate was virtually undetected (at all time points and baseline level) at depths of 25 µm. D-Panthenol was detected in the stratum corneum upper layers

(exceeding baseline) down to 25 µm (above baseline level) 24 hours after Panthenyl Triacetate application. The researchers stated that Panthenyl Triacetate was converted to D-Panthenol by deacetylation in the deeper layers of skin. Another experiment very similar to that described above produced comparable results, indicating that Panthenyl Triacetate is converted to D-Panthenol in the deeper stratum corneum layers.[58]

Nail Penetration

In Vitro

Human

An experiment examined the penetration of 1-[^{14}C]-Panthenol through human fingernails.[59] Nail incubation was conducted by inserting the nail plate into one-chamber of a diffusion cell with the dorsal nail surface exposed to air and the ventral side touching a cotton ball containing saline for moisture. Fifteen microliters of 2% [^{14}C]-Panthenol (0.07-0.08 µCi) in either a 98% nail formulation (containing ethanol, acrylates copolymer, and phytantriol) or water, was applied to the dorsal nail daily for 1 week. Results showed that, by day 7, the applied radioactivity from the formulation was 2 times higher in the interior nail plate and 3 times higher in the cotton ball compared to the radioactivity in the applied aqueous solutions. The radioactivity was 34% lower in the dorsal nail by day 7 when the formulation was used, compared to the aqueous solution. The researchers speculated that solvent evaporation of the formulation may have concentrated the [^{14}C]-Panthenol on the dorsal nail, and that diffusion of the test substance may have been enhanced by a formulation-induced increase in nail hydration and increased thermodynamic activity of [^{14}C]-Panthenol in the formulation.

Penetration Enhancement

In Vitro

Animal

The effect of D-Panthenol on the penetration of progesterone in rat skin was examined in a Franz-type diffusion cell (0.95 cm^2 diffusion area) experiment.[60] The test formulations consisted of 0% (control), 6%, or 20% D-Panthenol, progesterone (0.8 g), triethylcitrate (2.6 to 3 g), and either PMA (polyethacrylate-methacrylate matrix with 2% hydroxypropylmethylcellulose gel), PVA (polyvinyl alcohol matrix with water), or PVP (polyvinyl pyrrolidone matrix with 2% hydroxypropylmethylcellulose gel and water). The polymer matrix test formulations were applied to the stratum corneum in the diffusion cell. The receptor fluid (propylene glycol:water, 40:60, w/w) was collected at intervals up to 24 hours post-application and assayed for progesterone. For the PMA formulation, there was no difference in permeation of progesterone with or without the addition of D-Panthenol. There was a slight increase in progesterone permeation for the PVA formulation with 6% and 20% D-Panthenol compared to the control. The PVP matrix formulations with 6% and 20% D-Panthenol increased progesterone permeation 4.5-fold and 2.5-fold, respectively, compared to the PMA matrix and to formulations without D-Panthenol.

Additional experiments evaluating the release of progesterone from the polymer formulations were conducted. The polymer matrix formulations (200 µm total thickness) described above were placed in a diffusion cell without rat skin. The receptor cell conditions and fluid analysis were as described above. The PMA formulations (6% and 20% D-Panthenol) showed a 1.1-fold increase in release rate of progesterone compared to formulations without D-Panthenol. D-Panthenol had no effect on the release rate of progesterone from the PVA matrix system. In the PVP matrix system, the 6% and 20% D-Panthenol formulations increased the release rate of progesterone 1.3-fold and 4.3-fold, respectively, compared to controls.

Absorption, Distribution, Metabolism, Excretion (ADME)

Panthenol can be oxidized in the skin to Pantothenic Acid.[4] The reactions in which Pantothenic Acid plays a role are the synthesis and metabolism of steroid hormones, sterols, and fatty acids, the synthesis of acetylcholine and porphyrins, and carbohydrate metabolism. A toxicokinetics study in rats fed 20 mg/kg/day D-Panthenol for 24 or 45 days or up to 6 months showed an increase of the Pantothenate content in the heart (by 20%) and in the kidney (by 43%) after 6 months. In another rat study, single doses (administered orally) of 1.0 mg Panthenol resulted in 0.8 mg detected in excreted urine. Pantothenic Acid absorption in humans occurs in the small intestines. Panthenol is oxidized to Pantothenic Acid in human cells. Human subjects who consumed 100 mg Panthenol showed urinary excretion of Pantothenic Acid to be 10- to 50-fold higher than normal values within 4-hours post-administration.

D-Panthenol can be absorbed into the skin and converted to Pantothenic Acid.[61]

D-Panthenol

D-Panthenol, a synthetic pro-vitamin, is oxidized in the body to Pantothenic Acid, the only biologically active form of this B vitamin.[28]

Pantothenic Acid

Pantothenic Acid naturally occurs in all animal and plant tissues.[17] As a vitamin in the B complex, it is vital for coenzyme A synthesis in mammalian cells. The Pantothenic Acid Reference Daily Intake (RDI) for essential human nutrition is 5 to 10 mg (Table 4).

Absorption, distribution, metabolism, and excretion studies are summarized below; details are presented in Table 6.

Animal

A dermal exposure experiment in rats treated with D-Panthenol (20 mg in 50% ethanol), D-Panthenyl Ethyl Ether (22.8 mg in 50% ethanol), or a control (50% ethanol only) resulted in 100% and 70% conversion of D-Panthenol and D-Panthenyl Ethyl Ether, respectively, to Pantothenic Acid as determined by urine analysis up to 114 hours post-application.[62] Study researchers noted that D-Panthenyl Ethyl Ether exhibited a gradual, more delayed conversion as compared to D-Panthenol, resulting in a vitamin depot effect. In a similar experiment, rats were dermally exposed to D-Panthenol (20 mg in ethanol), D-Panthenyl Triacetate (20 mg in ethanol), or a control (ethanol only); analysis of the urine samples collected for 114 hours post-application showed 100% and 45% conversion of D-Panthenol and D-Panthenyl Triacetate, respectively, to Pantothenic Acid.[63]

Single doses of either Pantothenic Acid (4 mg) or Calcium Pantothenate (4 mg) were orally administered to rats; 64% of Pantothenic Acid was detected in the urine 24 hours after Pantothenic Acid administration and ~25% of Pantothenic Acid was found in the urine 24 hours following Calcium Pantothenate dosing.[12] In another experiment, rats were dosed daily in the diet with 0, 4, 8, or 16 mg/kg Calcium Pantothenate for 28 days.[64] In the control group (vitamin deficient group), Pantothenic Acid content of the liver and adrenal glands and urinary excretion were statistically significantly lower than all the treated groups. A dose-dependent increase in urinary Pantothenic Acid content corresponding to Calcium Pantothenate intake was observed. A study was conducted in rats fed 0 (vitamin deficient group), 0.0016%, 1%, or 3% Calcium Pantothenate daily in the diet for 29 days.[65] Notable results included an increase in liver Pantothenic Acid levels and a decrease in urinary excretion of vitamins B_1 and B_6 metabolites with increasing Calcium Pantothenate doses, and an adverse effect on nicotinamide metabolism in the vitamin deficient group and in the animals exposed to 1% and 3% concentrations. Rats were orally dosed with 1, 2, 5, or 10 mg/kg Calcium Pantothenate or Panthenol; 24 hour urine and feces samples were collected and analyzed.[9] Results showed that 85% (from 5 mg/kg dosage) and 173% (from 10 mg/kg dosage) more Pantothenic Acid was detected in urine after Panthenol administration than following Calcium Pantothenate dosing. Pantothenate was excreted in greater amounts after Panthenol exposure (60% of dose) than after Calcium Pantothenate exposure (23%-33% of dose). In rats orally exposed to 23 mg/kg Calcium Pantothenate daily in the diet for 5-6 months a 32% increase in Pantothenic Acid content in the heart and a 25% decrease in Pantothenic Acid content in the liver were observed.[9,12] Radiolabelled Sodium Pantothenate (location and identity of label was not specified) was orally administered to dogs (0.8 mg/kg) and rats (1.6 mg/kg) and urine was analyzed.[12] In dogs, 0.5% of the dosed radioactivity was excreted as unchanged Pantothenate in the urine 24 hours post-dosing and 40% was excreted as the β-glucuronide within 7 days. In rats, no glucuronide was detected and 27% of the radioactivity was excreted as Pantothenate in the urine within 7 days of administration.

Human

Human subjects were orally dosed with 100 mg of Calcium Pantothenate (no additional details were provided) and by 4 hours post-administration ~20% of the dose was excreted as Pantothenate in the urine.[12] Following oral administration (dosage not specified) in human subjects, Pantothenic Acid was absorbed from the gastrointestinal tract; urinary excretion of unchanged Pantothenic Acid was approximately 70% and in feces about 30%.[41]

TOXICOLOGICAL STUDIES

Human subjects received 10-20 g/day Pantothenic Acid orally for an unspecified period of time; water retention and occasional diarrhea were noted.[4]

Acute Toxicity

In acute studies, there were no deaths in mice orally dosed with 10 g/kg D-Panthenol, in another test an oral LD_{50} of 15 g/kg D-Panthenol in mice was reported; all mice died after oral dosing with 20 g/kg D-Panthenol; no toxicity was observed in rats orally administered 26 ml/kg of a product containing 0.5% Panthenol; and slight thinning of the body of male rats was noted after oral dosing with 7 ml/kg of a cream containing 0.5% Panthenol.[4] *In mice and rats, LD_{50}s of 2.5 g/kg and 3.5 g/kg, respectively, were reported following subcutaneous exposure to Pantothenic Acid. After intravenous administration of D-Panthenol the LD_{50}s were reported to be 7 g/kg and > 10 g/kg in mice and 4 g/kg in rabbits.*

Provided below is a summary of the acute toxicity studies; details are presented in Table 7.

Dermal

In a 24-hour occlusive patch test, 3 ml/kg D-Panthenol was applied to shaved rat skin in a single treatment in accordance with OECD TG 402 (Acute Dermal Toxicity).[66] No deaths occurred, gross pathology was unremarkable, and no skin reactions were

observed; LD_{50} > 3 ml/kg/day was reported. Rats were dermally exposed to a single semi-occlusive application of 2 g/kg (no vehicle) DL-Panthenyl Ethyl Ether for 24 hours using good laboratory practice (GLP) and in accordance with the Organization for Economic Cooperation and Development Test Guideline (OECD TG) 402.[6] The LD_{50} was reported to be > 2 g/kg.

Oral

In separate experiments, rats were orally exposed to single dosages of 10 g/kg D-Panthenol,[7] 2 g/kg DL-Panthenyl Ethyl Ether[6], or up to 10 ml/kg Panthenyl Triacetate[67] in accordance with OECD TG 401 (Acute Oral Toxicity). The LD_{50} of D-Panthenol was reported to be > 10 g/kg; on the first study day an impaired general state was noted, however there were no deaths and gross pathology exam revealed no findings.[7] The LD_{50} of DL-Panthenyl Ethyl Ether was reported to be > 2 g/kg and the LD_{50} of Panthenyl Triacetate was reported to be > 10 ml/kg; there were no deaths or clinical signs noted and necropsy was unremarkable for both ingredients.[6,67] In other tests of animals orally exposed to single doses of D-Calcium Pantothenate, no toxicity was reported in dogs and a monkey and the LD_{50} was reported to be 10 g/kg and > 10 g/kg in mice and rats, respectively.[12]

Inhalation

A single dose inhalation study in rats exposed to 5.2 mg/l D-Calcium Pantothenate dust particulates (mass median aerodynamic diameters ≤ 3.6 µm) in air for 4 hours, in accordance with OECD TG 403, revealed increased respiration and piloerection from 3 hours to 7 days after exposure, which were both reversed by day 8.[31] No mortalities were reported.

Short-Term Toxicity

Summaries of the short-term, subchronic, and chronic toxicity studies are presented below and details are presented in Table 8.

Dermal

Panthenyl Ethyl Ether (0.125%) in a leave-on hair conditioner was applied (restraint collars used for 7 hours after administration of test substance; further details not provided) to the shaved skin of New Zealand White rabbits for 5 days/week for 28 days.[68] No mortality was reported; diarrhea and soft stools were observed in 1 treated female rabbit periodically throughout the study.

Oral

Rats were administered 0 or 0.03% Pantothenic Acid daily in their drinking water for 9 weeks; the only statistically significant finding was a ~2-fold increase in basal plasma corticosterone levels in the Pantothenic Acid group, compared to the control group.[69] In another experiment, rats were dosed daily in the diet with 0, 4, 8, or 16 mg/kg Calcium Pantothenate for 28 days.[64] In the control group (vitamin deficient group), body weight gain and total food intake were statistically significantly lower than in all the treated groups. A study was conducted in rats fed 0 (vitamin deficient group), 0.0016%, 1%, or 3% Calcium Pantothenate daily in the diet for 29 days.[65] Notable results included a decrease in body weight gain and food intake in the vitamin deficient group, an increase in brain and testis weights in the vitamin deficient group, an increase in lung and spleen weights in the animals exposed to 3%, and diarrhea at 3% concentration. A no-observed-adverse-effect-level (NOAEL) of 1% and a lowest-observed-adverse-effect-level (LOAEL) of 3% Calcium Pantothenate were reported. The same researchers performed a test of 5% Calcium Pantothenate in the diet; 4 of the 5 rats died within 2 days from severe diarrhea.

Subchronic Toxicity

In 3-month subchronic toxicity studies there were no deaths reported from dermal exposure in rabbits (6 mg/cm^2 of 0.5% Panthenol) and rats (227 to 680 mg/kg of 0.2% Panthenol).[4] The rabbits exhibited slight to moderate erythema, edema, and cutaneous desquamation. The rats displayed minimal hyperkeratosis in the subcutis and skin, but no systemic toxicity was observed. There were no toxicological effects reported in rats orally administered up to 200 mg/day D- and DL-Panthenol and in dogs orally dosed with up to 500 mg/day D-Panthenol. Slight renal toxicity (100 mg/kg Panthenol) and more substantial renal toxicity (400 mg/kg Panthenol) were observed in rats orally exposed to Panthenol in a 13-week study.

Oral

A NOAEL of 200 mg/kg/day was reported for rats dosed daily in drinking water, available *ad libitum*, with 20, 50, or 200 mg/kg bw/day DL-Panthenol for 3 months (OECD TG 408).[6] When rats were dosed daily in diet to D-Calcium Pantothenate (up to 200 mg/kg/day) for 3 months, adrenal gland weights were greater in males (24% increase in 50 mg/kg/day group) and lower in females (17% decrease in 200 mg/kg/day group) of treated animals compared to controls.[12] A slight hyperemia of the spleen in some animals dosed with 200 mg/kg/day was also noted.

Chronic Toxicity

In rats orally administered 2 mg/day Panthenol for 6 months there were no histopathological changes.[4]

Oral

D-Calcium Pantothenate was administered to dogs (~5 mg/kg), monkeys (up to 400 mg/kg), and rats (up to 2000 mg/kg) in the diet daily for 6 months and no toxicities were reported.[12] Calcium Pantothenate (~20 mg/kg) was administered to mice daily in drinking water for their life span. A statistically significant increase in mean life span of treated animals (653 days) compared to untreated controls (550 days) was observed.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Two different groups of female albino rats were supplemented with the same vitamin mixture and either 100 µg or 1 mg Calcium Pantothenate after giving birth to their first litter (stock diet for all female rats during first pregnancies) and through the birth of young from their second pregnancies (gestation period not provided).[4] The young born from both the first and second pregnancies were normal. No teratogenicity or fetotoxicity were reported.

Provided below is a summary of DART studies that are presented in detail in Table 9.

DL-Panthenyl Ethyl Ether (up to 1000 mg/kg/day) was administered by gavage to pregnant rats 1x/day on days 6 through 19 of gestation using GLP and in accordance with OECD TG 421; the maternal and developmental NOAELs were reported to be ≥ 1000 mg/kg/day.[6]

In different experiments examining the effects of orally administered Calcium Pantothenate (up to 2000 mg/kg) on pregnant rats (details on gestation were not provided) no toxicity, teratogenicity, or fetotoxicity was reported; Calcium Pantothenate was found to cross the placenta.[12]

GENOTOXICITY

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

In Vitro

DL-Panthenol and DL-Panthenyl Ethyl Ether were found to be non-mutagenic in Ames tests using *Salmonella typhimurium* and in WP2 assays using *Escherichia coli* (both tests were performed with and without activation) at concentrations up to 5000-10,000 µg/plate.[7,16,66] D-Panthenol (up to 2080 µg/ml) was non-mutagenic in a mammalian cell gene mutation assay using Chinese hamster V79/HPRT (hypoxanthine phosphoribosyl transferase) cells (with and without activation) and was non-clastogenic in a mammalian chromosomal aberration test performed in human lymphocytes (with and without activation).[66] DL-Panthenyl Ethyl Ether (up to 2400 µg/ml) was negative for genotoxicity (cytotoxicity was reported at concentrations of 300 µg/ml and above) in a mammalian cell gene mutation assay, conducted both with and without metabolic activation, using Chinese hamster lung fibroblasts.[6] In a mammalian chromosomal aberration test performed in human peripheral lymphocytes, with and without metabolic activation, DL-Panthenyl Ethyl Ether (up to 5000 µg/ml) was non-clastogenic.[66] D-Panthenyl Triacetate was non-mutagenic in an Ames test using *S. typhimurium*, with and without metabolic activation, up to 5000 µg/plate.[70] In a microbial plate suspension assay, performed with and without metabolic activation, D-Sodium Pantothenate (concentrations not specified) was determined to be non-mutagenic when tested in *Saccharomyces cerevisiae* and *S. typhimurium*.[12] Sodium Pantothenate (up to 10,000 µg/plate) was non-mutagenic in an Ames test in *S. typhimurium*, conducted with and without metabolic activation.[71]

CARCINOGENICITY

There were no carcinogenicity studies identified in the literature for the ingredients presented in this report, and unpublished data were not submitted.

OTHER RELEVANT STUDIES

Data summaries included therapeutic uses of D-Panthenol for radiation protection in rats and as an anti-inflammatory for UV-induced erythema in guinea pigs.[61] Additionally, the use of D-Panthenol was investigated for in vitro cytotoxicity prevention and for skin wound healing in animals. Studies indicated that D-Panthenol was used in skin wound healing and corneal wound healing in human subjects.

Transformation

Calcium Pantothenate

Calcium Pantothenate was evaluated in experiments performed with the BALB/c-3T3 cell neoplastic transformation system, known to produce a tumor-promoting response to phorbol esters.[72] As part of the protocol for the transformation assay, 0.1 µg/ml of 3-methylcholanthrene (carcinogen) was used to initiate the 1-13 cell line of BALB/c-3T3 cells; controls without 3-methyl-cholanthrene were also used in the experiment.[72] The culture plates were treated with fresh medium (no carcinogen present) 72 hours following treatment with 3-methylcholanthrene. On day 7 and twice weekly for 28 days, Calcium Pantothenate (50 µg/ml initiated concentration; 500 µg/ml uninitiated concentration) or control medium were added to dishes treated with 3-methyl-cholanthrene (0.1 µg/ml) and to dishes not treated with the carcinogen. After 4 weeks, 3-methylcholanthrene was removed from the plates. The plates were scanned for Type III foci after staining with Giemsa. Results indicated that Calcium Pantothenate had a promoting effect on Type III transformed foci; a repeat experiment showed this effect to be marginal.

Cytotoxicity

Panthenyl Triacetate

The Skin^2 ZK 1200 Model was used in a study evaluating the cytotoxic potential of D-Panthenyl Triacetate.[73] D-Panthenyl Triacetate was applied (neat) to tissue samples; both untreated controls and positive controls were used. The researchers determined that there was no concern for D-Panthenyl Triacetate to potentially cause irritation or cytotoxicity.

Effect on Metabolism

Panthenol and Panthenyl Triacetate

The epidermis of human abdominal skin samples was treated with 2% D-Panthenol, 2% Panthenyl Triacetate, or placebo cream and incubated for 6 or 24 hours.[53] Skin samples were analyzed for metabolism markers. D-Panthenol and Panthenyl Triacetate were found to stimulate the citric acid cycle, mevalonate pathway, and cholesterol sulfate synthesis. D-Panthenol increased measures of lipid transport. The researchers concluded that Panthenyl Triacetate dermal treatment inhibited lipid transport and stimulated glycolysis.

Effect on Human Skin Fibroblasts

Calcium Pantothenate, Panthenol, and Pantothenic Acid

RNA from proliferating human dermal fibroblasts was incubated with Calcium Pantothenate (20 µg/ml) or without Calcium Pantothenate for 8-12 hours in a 2% fetal calf serum medium, then exon array analysis and quantitative polymerase chain reaction were performed.[74] Results indicated that Calcium Pantothenate caused substantial upregulation of mRNA encoding 7 genes in dermal fibroblasts. Human skin fibroblasts were incubated in a medium with Panthenol (up to 20 mM), Pantothenic Acid (up to 1000 µM), or in a control medium for 24 hours and analyzed for protein. Heme oxygenase-1 protein inductions were observed in cells treated with Panthenol and Pantothenic Acid. Human skin fibroblasts were treated with Panthenol (up to 20 mM) for 24 hours and assayed using chemiluminescence to determine the formation of reactive oxygen species; results showed that Panthenol inhibited the formation of reactive oxygen species.

Wound Healing

In Vitro

Calcium Pantothenate

In vitro experiments performed in human dermal fibroblast monolayers showed that 20 µg/ml of Calcium Pantothenate accelerated wound healing compared to controls when applied to artificially induced monolayer scrape wounds for 24 hours at 37 °C.[74] By 20 hours, 80% closure of the wound was observed in treated samples compared to 21% in controls. Further experiments indicated that cell migration also aided in wound closure. Cell culture experiments evaluating cell proliferation, in which 20 or 40 µg/ml of Calcium Pantothenate were incubated with human dermal fibroblasts for up to 16 h, resulted in higher cell counts in treated (effect was more pronounced with 20 than 40 µg/ml) compared to untreated control samples.

Human

D-Panthenol and D-Panthenyl Triacetate

In a double-blind, wound-healing study, suction blisters were formed on the volar forearms of human subjects (n = 40) using a vacuum and then treated (occlusively) with different emulsions containing 3% D-Panthenol, 3% Panthenyl Triacetate, a placebo emulsion, or saline control for up to 72 hours.[53] Transepidermal water loss (TEWL) was statistically significantly decreased by 8.7% after 72 hours with the Panthenyl Triacetate treatment compared to the saline control; TEWL after placebo or D-Panthenol treatments was not statistically different from TEWL after saline exposure at 72 hours. Two different studies (n = 20 to 25 human subjects in each study) examined the effect of 5% D-Panthenol in volar forearm skin, irritated by sodium lauryl sulfate.[75,76] In one study, the skin irritation was induced with sodium lauryl sulfate prior to D-Panthenol treatment,[75] and in the other study, skin irritation was induced during the 26-day course of D-Panthenol treatment.[76] Results from both studies indicated that D-Panthenol reduced irritation and edema compared to placebos.

Therapeutic Effect

D-Panthenol

The therapeutic effect of D-Panthenol (5%) in a hydrogel formulation was evalauted in guinea pig skin by applying the formulation for 1hour after 20 minutes of UV exposure to shaved skin (2 cm^2).[77] The D-Panthenol hydrogel formulation was reapplied at various time points up to 48 hours; inflammation was evaluated at those time points. Results showed that D-Panthenol had a statistically significant inhibitory effect on inflammation compared to controls.

Radioprotective Effect

Calcium Pantothenate

Calcium Pantothenate (180 mg/day administered in the diet for 42 days) had radioprotective effects in the skin of partially hepatectomized rats that were exposed to irradiation (Sr^{90}-Y^{90} beta radiation, 3.6 repetitions/second for 2.48 min), and it facilitated

normal metabolic function of hepatocytes.[78] Hepatectomized and irradiated animals that had not been treated with Calcium Pantothenate exhibited both skin changes and hepatocyte dysfunction.

DERMAL IRRITATION AND SENSITIZATION STUDIES

In rabbit skin treated with 100% D- and DL-Panthenol and covered with an occlusive patch for 4 hours, slight erythema was observed, however it cleared within 24-48 hours following patch removal.[4] There were no signs of irritation to abraded and intact rabbit skin treated with 2% D- and DL-Panthenol. Rabbits were treated in different experiments with 0.5% Panthenol for 4 to 14 days yielding the following results: erythema 24 hours after patch removal; erythema and edema 48 hours post-application that lasted for 7 days; moderate to severe erythema and mild edema persisting for 7 days; and no dermal irritation after 14 days of treatment. Panthenol (0.5%) was non-comedogenic in rabbit skin.

A product containing 0.5% Panthenol was applied to the skin of human subjects for 4 days, in a cumulative irritation test (procedures were not provided); results indicated that the test substance was non-irritating.[4] In a different study, a lotion containing 0.5% Panthenol was applied (occlusively) to the backs of 10 subjects. After 23 hours the patch was removed and skin washed prior to evaluation. This process was repeated for 21 days. Eight subjects exhibited minimal erythema during the test; study researchers determined that the test substance was mildly irritating.

Panthenol, in various products, was applied to the skin of human subjects and occlusively covered for 24-48 hours during the induction and challenge phases of different experiments.[4] In one test, erythema and papules were observed in 3 out of 200 subjects during induction and challenge phases (0.5% Panthenol). Erythema and edema were seen in 3 out of 206 subjects during the induction and challenge phases (0.5% Panthenol) of another test. Erythema was reported in 1 out of 238 subjects during the induction phase (0.5% Panthenol) of an experiment. There were no signs of irritation or sensitization in another study with 200 subjects (0.5% Panthenol) or in a smaller test with 25 subjects (0.5% Panthenol). In other experiments, products containing 0.1% to 0.5% Panthenol were applied to the skin of human subjects and occlusively covered for 24-72 hours during induction and challenge phases; the test substance was non-sensitizing.

A summary of dermal irritation and sensitization studies is provided below; details are presented in Table 11.

Irritation

Animal

An irritation test in rabbits revealed that 0.5 g of 5% (w/w) D-Panthenol in a cream formulation was non-irritating when applied semi-occlusively to shaved skin for 4 hours using GLP and in accordance with OECD TG 404 (Acute Dermal Irritation/ Corrosion).[6,7] In several dermal irritation experiments (occlusive and/or semi-occlusive for 4 hours) in rabbit skin, D-Panthenol and DL-Panthenyl Ethyl Ether (concentrations not provided) were non-irritating.[66] D-Panthenol was reported to be a mild skin irritant and D-Calcium Pantothenate was reported to be non-irritating to rabbit skin in a European Food and Safety Authority (EFSA) article; no further details were provided.[31] Panthenyl Ethyl Ether (0.125%; leave-on hair conditioner formulation) was applied to shaved rabbit skin for 5 days/week for 28 days (restraining collars used during 7 h/day exposures; abrading days 1-6 and 10-12).[68] Instances of slight-to-moderate erythema, edema, atonia, desquamation, and fissuring were reported in most treated animals by the end of the first week; except for slight erythema and desquamation that continued throughout the study, the other irritation effects resolved by day 13. Mild acanthosis and trace chronic dermatitis were observed in the Panthenyl Ethyl Ether treated animals; controls exhibited no signs of irritation. Overall, in animals, the ingredients were non-to-mildly irritating.

Human

D-Panthenyl Triacetate (10% in polyglycol P-4000) caused no skin reactions in a closed epicutaneous patch test for 24 hours in human subjects.[79]

Sensitization

Animal

A Buehler test was performed on the shaved flank skin of guinea pigs in accordance with OECD TG 406 (Skin Sensitization) to evaluate the sensitization potential of DL-Panthenol.[7] During the epicutaneous induction phase, undiluted DL-Panthenol was applied occlusively for 6-hour exposure periods on days 0, 7, and 14; in the epicutaneous challenge phase, undiluted DL-Panthenol was applied occlusively for a 6-hour exposure period on day 28. DL-Panthenol was non-irritating and non-sensitizing. D-Panthenol in a lotion formulation was evaluated in a guinea pig maximization test in accordance with OECD TG 406.[66] Intradermal injections on day 1 and topical application (2.5% D-Panthenol) under occlusive conditions on day 8 were performed during the induction phase; the challenge phase (2.5% D-Panthenol) was conducted under occlusive conditions 2 weeks following topical induction. D-Panthenol was non-sensitizing in this test. Two open epicutaneous tests (induction phase 4 weeks, challenge on days 30 and 44) were performed in guinea pigs to evaluate 5% D-Panthenol in an ointment (0.1 ml induction; 0.025 ml challenge); results were non-sensitizing in one test and weak sensitization potential with slight, to well defined, irritation potential in the other test. A guinea pig maximization test evaluating 5% Panthenol in a test solution (induction) and dilutions up to 30% of the 5% Panthenol test solution (challenge), showed that the formulation was non-sensitizing.[80] However, primary skin irritation reactions were noted in 3 guinea pigs 24 hours following a rechallenge using the test solution containing 5% Panthenol (no details

were provided as to whether any reactions at this concentration were observed during induction). DL-Panthenyl Ethyl Ether was examined in a guinea pig maximization test conducted using GLP in accordance with OECD TG 406.[6] The induction phase consisted of intradermal injections (5%-10% DL-Panthenyl Ethyl Ether) on day 1 and epicutaneous application (100% DL-Panthenyl Ethyl Ether secured with patch) on day 8. The challenge phase (25%, 50%, or 100% DL-Panthenyl Ethyl Ether with semi-occlusive patch) occurred on day 22. Results showed that DL-Panthenyl Ethyl Ether was non-sensitizing at challenge and slightly irritating to the skin during epicutaneous induction. In a local lymph node assay (LLNA), a crème product and a spray product (i.e. not in a pure, defined vehicle) each containing 5% Panthenol were non-sensitizing in mice.[81] Generally, Panthenol and DL-Panthenyl Ethyl Ether were non-sensitizing in animals with instances of mild irritation noted.

Human

D-Panthenol (5% in a hydrogel formulation or 5% in liquid drops) was evaluated in epidermal patch tests in healthy human subjects and in those with allergic dermatoses and found to be non-sensitizing (no further details provided).[77] In a human-repeat-insult-patch-test (HRIPT), 5% D-Panthenol in a cosmetic baby product was reported to be non-sensitizing and non-irritating.[82] A test gel containing 3% Panthenol (concentration used during induction and challenge) was evaluated for 24 hours under occlusion, 3 times/week, for 4 weeks (induction) in human subjects.[83] There was approximately 1 week between induction and challenge; the test gel was non-sensitizing, however 1 instance of mild erythema was reported during induction. In a very similar experiment, 6% Panthenol in a test gel was non-sensitizing in human subjects, but mild erythema, attributed by the study researchers to be an irritation reaction, was noted in 1 subject at 4 days post-challenge; there were rare occurrences of mild erythema during induction.[84] Panthenol (5% concentration used during induction and challenge) in a leave-on product was evaluated in a HRIPT under occlusion for 24 hours (9 patches applied during 3-week induction followed by 2 weeks rest prior to challenge); results were non-sensitizing with 1 subject of 113 showing low level erythema during the challenge phase.[85] Panthenyl Ethyl Ether (0.005%) was evaluated in a very similar HRIPT and found to be non-sensitizing; out of 106 subjects, mild-to-definite erythema was observed in 48 subjects during induction and 5 subjects at challenge.[86] Overall, in humans, Panthenol and Panthenyl Ethyl Ether were non-sensitizing and non-to-mildly irritating.

Photoirritation / Photosensitization

The structures of these ingredients lack conjugated unsaturations, or other chromophore core moieties. Accordingly, there is no reason to suspect that these would be positive for photoirritation or photosensitization.

Animal

D-Panthenol

In an EFSA article, D-Panthenol was reported not to cause photoallergenic reactions in guinea pig skin (no further details provided).[31]

OCULAR IRRITATION

Rabbits treated with 100% D- and DL-Panthenol displayed slight conjunctival redness and chemosis, but the effects resolved within 3 weeks following treatment.[4] Slight conjunctival redness was observed in rabbits that were administered 0.5% and 2% Panthenol, however in most cases it cleared by 24-72 hours after treatment. A test evaluating 0.1% Panthenol in both rinsed and unrinsed rabbit eyes revealed no signs of ocular irritation. For 3 weeks, 23 subjects were exposed to 0.1% Panthenol in 2 mascaras (study procedures were not provided). No eye irritation caused by the test substance was observed.

A summary of ocular irritation studies is provided below; details are presented in Table 12.

In Vitro

An in vitro test was performed using GLP in accordance with OECD TG 437 (Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants).[87] D-Panthenyl Triacetate (undiluted, > 95% purity) was applied (0.75 ml) to the corneas surface. The study researchers determined that D-Panthenyl Triacetate was a non-eye irritant based on the lack of opacity or cornea permeability indicated by the experimental results.

Animal

In several experiments, single applications of D-Panthenol or DL-Panthenyl Ethyl Ether (either undiluted, 5% in a formulation, or concentration not specified) were instilled into the conjunctival sac of one rabbit eye (no rinsing) in accordance with OECD TG 405 (Acute Eye Irritation/ Corrosion).[6,7,66] D-Panthenol was found to be non to-slightly irritating in these studies; corneal redness/irritation was observed, but resolved by 48 hours in most cases. DL-Panthenyl Ethyl Ether was non-irritating. Calcium Pantothenate (10% solution) was non-irritating to rabbit eyes after 0.5 ml were instilled into the conjunctival sac (no further details provided).[12]

CLINICAL STUDIES

Panthenol

Human subjects in a dermatitis clinic were patch tested with a standard diagnostic series that included a 50% DL-Panthenol solution tested at 5% in petrolatum(effective test concentration, 2.5% DL-Panthenol).[88] Their reactions to DL-Panthenol were reported to be 5 (+/-), 1 (+), and 1(++) out of 192 subjects. In a 10-week, randomized, double-blind trial, 207 women with epidermal hyperpigmented facial spots were treated 2x/day with a lotion containing 0.5% Panthenol, 4% niacinamide, 0.5% tocopheryl acetate, sunscreen, glycerol, and other unspecified ingredients or a control lotion (no further details provided).[89] There were 6 subjects in the treatment group and 2 in the control group reporting a mild, transient burning sensation; 1 subject in the treatment group reported dry skin and increased acne. TEWL decreased in treatment and control groups; hyperpigmentation spots were statistically significantly reduced in treatment groups as compared to controls.

Retrospective and Multicenter Studies

Panthenol

A European Union report cited data from the Information Network of Departments of Dermatology from 2000 to 2009, documenting 137 positive allergic reactions from a large population (> 96,000 patients) to D-Panthenol (no further details provided).[90] D-Panthenol was classified by the study researchers to be a "rare" allergen.

In a different study, a total of 3301 patients were patch tested for D-Panthenol (5% pet.) from 1990 to 2016.[91] The patch tests were designed based on a pharmaceutical or cosmetic series or according to the use of D-Panthenol in products the patients were using. The European Society of Contact Dermatitis guideline was followed when readings were performed on days 2, 4, and after. Some patients were sensitized based on prescription or cosmetic products they used containing D-Panthenol. There were 23 of 3301 patients (0.7%) who had positive reactions to D-Panthenol, mainly on the face and hands and sometimes on the trunk, legs, and feet. Seven of the patients were noted to have a history of atopy.

Another retrospective study, conducted from 2010 to 2015, included patients who developed cosmetic dermatitis (iatrogenic dermatitis not included) as a result of using cosmetic products.[92] Panthenol was identified as an individual allergen from a cosmetic product (type not defined). It was reported that of the 311 patients patch tested for Panthenol (concentration not specified), 3 (0.96%) exhibited positive reactions. Patch tests were conducted under occlusion for 2 days and test sites read on days 2, 4, and sometimes 7 in accordance with the European Society of Contact Dermatitis guidelines.

Case Reports

Patients with stasis dermatitis and multiple allergies experienced contact allergy to D-Panthenol.[61] A lymphocyte transformation test with dexpanthenol-modified microsomes was conducted after a patient experienced contact dermatitis from using a cream containing D-Panthenol. The patient showed positive reactions to D-Panthenol (1%) and the D-Panthenol cream in a patch test while controls were negative to both. The authors speculated that the allergic reaction was T-cell dependent coupled with the antigen's microsomal-dependent metabolism. In a 33 year old woman presenting with chronic facial dermatitis, an allergic reaction to D-Panthenol was confirmed through a patch test with D-Panthenol (5% pet). Her condition improved after she discontinued using a cream containing D-Panthenol and she began consuming a diet low in vitamin B_5. A 21 year old patient exhibited symptoms of facial erythema caused by a sunscreen containing D-Panthenol (validated by a patch test with 5% D-Panthenol). A woman with itchy eczema of the face had a positive reaction to 5% D-Panthenol in a patch test, confirming that her lotion containing 0.5% Panthenol caused her symptoms; patch tested controls were negative. There were 7 additional case reports of contact dermatitis in men, women, and a child, caused by D-Panthenol (validated by patch testing) in products they were using.

Below is a synopsis of case reports that are described in detail in Table 13.

The case reports involving human dermal exposure to Panthenol in lotions or creams include allergic contact dermatitis in a child, caused by the use of a 75% D-Panthenol facial wipe and a 30% D-Panthenol formulation (confirmed by patch testing);[93] episodes of severe erythema and facial edema in a woman, caused by using a hydrating lotion containing 0.5% D-Panthenol (confirmed by patch testing);[94] and allergic contact dermatitis caused by a 5% D-Panthenol topical cream (confirmed by patch testing) used to treat stasis dermatitis in one patient and to treat radiotherapy effects in another.[96] Case reports involving exposure to Panthenol or Panthenyl Ethyl Ether in hair products include facial edema, erythema, and pruritus (on trunk) in a woman caused by using a conditioner containing Panthenol, and pruritus and edema at the hairline of the same woman after using a hair-coloring product containing Panthenol (positive reactions to Panthenol were confirmed in a skin prick test),[95] and relapsing facial dermatitis in a woman caused by hair lotion containing 30% D-Panthenyl Ethyl Ether (positive reactions to D-Panthenyl Ethyl Ether confirmed by patch testing).[97]

Included are 2 case reports related to oral exposure. One describes a woman who experienced an anaphylactic reaction attributable to 3.33 mg D-Panthenol in a vitamin B complex (allergic reaction confirmed in a friction test).[98] The woman recalled that she had a previous reaction to a sun cream containing D-Panthenol, which caused pruritus and urticaria. In the other report, a woman with alopecia took trimetazidine (for 6 years), vitamin H (biotin, 10 mg/day for 2 months), and Pantothenic Acid (300 mg/day for 2 months) and developed eosinophilic pleuropericarditis.[99] The condition was reversible upon discontinuing administration of

vitamin H and Pantothenic Acid. Once study researchers had eliminated other causes, they thought the vitamin H and Pantothenic Acid treatment were associated with the adverse reaction.

SUMMARY

The 7 ingredients included in this safety assessment reportedly function in cosmetics as hair conditioning agents. VCRP data obtained from the FDA in 2017 indicate that the highest reported use frequencies are for Panthenol (5766 uses), D-Panthenol (518 uses), DL-Panthenol (477 uses), and Panthenyl Ethyl Ether (382 uses). The highest maximum use concentrations in leave-on products are for Panthenol (5.3% in body and hand products), Panthenyl Ethyl Ether (2% in foundation) and Panthenyl Triacetate (2% in lipstick and other make-up preparations). Frequency of use reported to the VCRP increased for both Panthenol and Pantothenic Acid in 2017, compared to 2002. Highest maximum concentration of use data received in the 2016 Council industry survey was not substantially different for Panthenol and Pantothenic Acid as compared to 2004.

Non-cosmetic uses of Panthenol, Pantothenic Acid, Calcium Pantothenate, and Sodium Pantothenate include nutritional food additives. Panthenol, Calcium Pantothenate, and Sodium Pantothenate are GRAS when used in animal feeds. Calcium Pantothenate is GRAS as a direct food additive for human consumption and is also used in infant formulas.

D-Panthenol was listed on the product label in a new drug application for a prescription vitamin mixture. 510 (k) premarket notifications for medical devices were permitted by the FDA for a contact lens multipurpose cleaning solution containing D-Panthenol, a wound healing topical formulation containing Panthenol as a skin conditioning ingredient, and a human oocyte in vitro fertilization device containing Calcium Pantothenate.

An in vitro diffusion cell experiment evaluated the penetration of D-Panthenol (10% in a hydrophilic gel formulation) through the skin of pigs. A steady increase in D-Panthenol concentration was observed in receptor cell fluid 2 to 120 minutes after the gel was applied, which plateaued by 180 minutes (903 µg/ml to 1069 µg/ml). In a different diffusion cell experiment in porcine skin, D-Panthenol (concentration not specified) was evaluated in various surfactants (0.5% to 5%) for 180 minutes. The study authors concluded that the skin penetration of D-Panthenol was optimized in this test using 1% surfactant and the nature of the enhancer effected the cutaneous barrier impairment.

In human skin, the dermal penetration of ^{14}C-Panthenol (20 mg/ml in ethanol) was evaluated in a Franz (static) diffusion cell experiment. Skin samples were either not stripped or stripped up to 10 times before the addition of test substance. The receptor solution (0.01 mol/l phosphate buffered saline with 5%, polyethylene glycol (v/v)) was collected for up to 60 minutes post-application. The amount of applied radioactivity measured (after 60 min) in the stratum corneum of skin that was not stripped before application was 84%; 6% and 4% were found in the epidermis and dermis, respectively. For the samples stripped 10 times before application of the test material, the applied radioactivity detected (after 15 min) in the stratum corneum was 72%; 18% and 6.3% were found in the epidermis and dermis, respectively. The receptor fluid for all samples contained negligible amounts of the radioactivity applied.

The penetration of 1-^{14}C-Panthenol through human fingernails was examined in a nail plate diffusion experiment in vitro. Results indicated that the radioactivity of the formulation base (2% ^{14}C-Panthenol in a 98% nail formulation) was 2 times higher in the interior nail plate and 3 times higher in the cotton ball compared to the radioactivity in the applied aqueous solution (2% ^{14}C-Panthenol in water) after application to the dorsal side of the nail daily for 1 week.

The in vivo dermal penetration of D-Panthenol (3% in water-based gel), Panthenyl Triacetate (3% in water-based gel), or a water-based gel control was evaluated on the volar forearms of human subjects; measurements of the ingredients to a skin depth of 25 µm were taken using confocal Raman infrared microspectroscopy up to 24 hours following application. D-Panthenol and Panthenyl Triacetate were detected in the stratum corneum. D-Panthenol levels were detected in the stratum corneum 24 hours after the application of Panthenyl Triacetate.

The effect of D-Panthenol on the penetration of progesterone in rat skin was examined in vitro using a Franz-type diffusion cell. The following test formulations were applied to the stratum corneum in the diffusion cell: D-Panthenol (0%, 6%, or 20%), progesterone (0.8 g), and triethylcitrate (2.6 to 3 g), in 1 of 3 polymer matrices. Receptor cell fluid (40:60, propylene glycol: water) was collected at intervals up to 24 hours post-application. In the PVP (polyvinyl pyrrolidone matrix) treatment with D-Panthenol (6% and 20%), progesterone permeation increased by 2.5-fold to 4.5-fold compared to other polymer matrix systems and to formulations without D-Panthenol.

A dermal exposure experiment in rats treated with D-Panthenol (20 mg in 50% ethanol), D-Panthenyl Ethyl Ether (22.8 mg in 50% ethanol), or a control (50% ethanol only) resulted in 100% and 70% conversion of D-Panthenol and D-Panthenyl Ethyl Ether, respectively, to Pantothenic Acid as detected via urine analysis. A similar test in rats dermally exposed to D-Panthenol (20 mg in ethanol) or D-Panthenyl Triacetate (20 mg in ethanol) showed 100% and 45% conversion, respectively, to Pantothenic Acid as measured in urine up to 114 hour post-application.

In vivo oral exposure toxicokinetics studies in animals resulted in the following observations: a dose-dependent increase in Pantothenic Acid content in the urine with increasing Calcium Pantothenate dosages (up to 16 mg/kg daily in rat diet for 28 days); by 24 hours post-dosing in rats, 85% (5 mg/kg dosage) and 173% (10 mg/kg dosage) more Pantothenic Acid was excreted in urine

following Panthenol administration than after Calcium Pantothenate dosing; after radioactive Sodium Pantothenate (location of label not specified) administration in rats (1.6 mg/kg), 27% of radioactivity was detected as urinary Pantothenate by 7 days post-dosing; in dogs, radioactive Sodium Pantothenate (0.8 mg/kg) was found in urine at 24 hours post-dosing to be 0.5% of the administered radioactivity and by 7 days 40% of the radioactivity was excreted in urine as the β-glucuronide. In rats dosed daily in the diet for 29 days with up to 3% Calcium Pantothenate, the results indicated the following: a decrease in urinary excretion of vitamins B_1 and B_6 metabolites; an increase in liver Pantothenic Acid levels with increasing Calcium Pantothenate doses; diarrhea (3% concentration); an adverse effect on nicotinamide metabolism (0%, 1%, and 3% concentrations); and a 1% NOAEL and a 3% LOAEL. An additional test with 5% Calcium Pantothenate (oral administration) caused death in 4 of 5 rats because of severe diarrhea. In rats orally exposed to 23 mg/kg Calcium Pantothenate daily in the diet for 5-6 months a 32% increase in Pantothenic Acid content in the heart and a 25% decrease in Pantothenic Acid content in the liver were observed. In humans, ~20% of a 100 mg Calcium Pantothenate oral dose was excreted in the urine within 4 hours post-administration. In the body, D-Panthenol is oxidized to Pantothenic Acid.

In acute dermal exposure experiments an LD_{50} > 3 ml/kg D-Panthenol and an LD_{50} > 2 g/kg DL-Panthenyl Ethyl Ether in rats were reported. In acute, oral exposure experiments in rats administered single dosages, an LD_{50} > 10 g/kg D-Panthenol, an LD_{50} > 2 g/kg DL-Panthenyl Ethyl Ether, and an LD_{50} > 10 ml/kg Panthenyl Triacetate were reported. D-Calcium Pantothenate administered in single, oral dosages, resulted in an LD_{50} of 10 g/kg and an LD_{50} > 10 g/kg for mice and rats, respectively. An acute inhalation study in rats administered a single exposure of 5.2 mg/l D-Calcium Pantothenate dust particulates (mass median aerodynamic diameters ≤ 3.6 µm) for 4 hours, caused increased respiration from 3 hours to 7 days post-exposure and piloerection, which both resolved by day 8.

In a short-term, dermal exposure study, Panthenyl Ethyl Ether (0.125%) in a leave-on hair conditioner was applied (further details regarding application not provided) to the shaved skin of New Zealand White rabbits for 5 days/week for 28 days. No mortality was reported; diarrhea and soft stools were observed in 1 treated female rabbit periodically throughout the study. In an oral exposure study in rats, the only statistically significant finding was a ~2-fold increase in basal plasma corticosterone levels in the Pantothenic Acid treated group (0.03% in the diet for 9 weeks) as compared to the control group.

A NOAEL of 200 mg/kg/day for DL-Panthenol was reported in dosed daily in drinking water, available *ad libitum*, for 3 months. In a dietary study, observations in rats exposed to D-Calcium Pantothenate (up to 200 mg/kg/day) for 3 months were increased (24%) adrenal gland weights in males (50 mg/kg/day) and decreased (17%) adrenal weight in females (200 mg/kg/day) of treated animals compared to controls. A slight hyperemia of the spleen in some animals (200 mg/kg/day) was also noted.

No toxicities were reported when D-Calcium Pantothenate was administered to dogs (~5 mg/kg), monkeys (up to 400 mg/kg), and rats (up to 2000 mg/kg) daily in the diet for 6 months. A statistically significant increase in mean life span of mice with daily, oral exposure to 20 mg/kg Calcium Pantothenate (653 days) compared to untreated controls (550 days) was noted in a chronic study.

A maternal and developmental NOAEL ≥ 1000 mg/kg/day for DL-Panthenyl Ethyl Ether was reported in rats that were orally dosed on days 6 through 19 of gestation. In different experiments, results indicated that orally administered Calcium Pantothenate (up to 2000 mg/kg) crossed the placenta of rats, however no toxicity, teratogenicity, or fetotoxicity was reported.

At concentrations up to 5000-10,000 µg/plate, DL-Panthenol and DL-Panthenyl Ethyl Ether were non-mutagenic in Ames tests using *S. typhimurium* and in WP2 assays evaluating *E. coli*. D-Panthenol (up to 2080 µg/ml) was non-mutagenic in a mammalian cell gene mutation assay performed in Chinese hamster V79/ HPRT cells and non-clastogenic in a mammalian chromosomal aberration test conducted in human lymphocytes. DL-Panthenyl Ethyl Ether (up to 2400 µg/ml) was negative for genotoxicity in a mammalian cell gene mutation assay conducted in Chinese hamster lung fibroblasts. In a mammalian chromosomal aberration test performed in human peripheral lymphocytes, DL-Panthenyl Ethyl Ether (up to 5000 µg/ml) was non-clastogenic. D-Panthenyl Triacetate (up to 5000 µg/ml) was non-mutagenic in an Ames test using *S. typhimurium*. D-Sodium Pantothenate (concentrations not provided) was non-mutagenic in a microbial plate suspension assay evaluating *S. cerevisiae* and *S. typhimurium*. In an Ames test examining *S. typhimurium*, Sodium Pantothenate (up to 10,000 µg/plate) was non-mutagenic.

Other relevant studies included a BALB/c-3T3 cell neoplastic transformation system to which Calcium Pantothenate (50-500 µg/ml) was added several times in a 28-day period to a culture medium either with or without 3-methylcholanthrene (known carcinogen). Results showed that Calcium Pantothenate induced Type III transformed foci, however these effects were considered marginal upon repeat experimentation. D-Panthenyl Triacetate (applied neat to tissue samples) was non-cytotoxic in an in vitro test. Another in vitro test in the epidermis of human abdominal skin samples showed that D-Panthenol (2%) and Panthenyl Triacetate (2%) stimulated the citric acid cycle, mevalonate pathway, and cholesterol sulfate synthesis. Lipid transport was negatively regulated by Panthenyl Triacetate and positively regulated by D-Panthenol. An in vitro test in proliferating human dermal fibroblasts, incubated with Calcium Pantothenate (20 µg/ml) or without for 8-12 hour in 2% fetal calf serum medium, showed that Calcium Pantothenate caused substantial upregulation of mRNA encoding 7 genes in dermal fibroblasts. Panthenol (up to 20 mM for 24 hours) inhibited the formation of reactive oxygen species in human skin fibroblast cells. In wound-healing studies, Calcium Pantothenate (20 µg/ml) was shown to accelerate wound healing in human dermal fibroblast monolayers in vitro. D-Panthenyl Triacetate (3%) reduced TEWL in human subjects with suction blisters. D-Panthenol (5%) was shown to reduce irritation and erythema in human subjects whose skin was irritated by sodium lauryl sulfate. In vivo tests in guinea pigs showed that D-Panthenol (5%) applied to skin after UV exposure, inhibited inflammation compared to controls. In a test on rats having

undergone a partial hepatectomy and irradiation, Calcium Pantothenate (180 mg/day administered in the diet for 42 days) was shown to have radioprotective effects in the skin and facilitated normal metabolic function of hepatocytes.

D-Panthenol (5%, w/w) was non-irritating to rabbit skin when applied semi-occlusively for 4 hours. In other dermal irritation experiments, occlusive and/or semi-occlusive for 4 hours, both D-Panthenol and DL-Panthenyl Ethyl Ether (concentrations not provided) were non-irritating to rabbit skin. Panthenyl Ethyl Ether (0.125%) was slightly-to-moderately irritating with erythema, edema, atonia, desquamation, and fissuring reported in most treated rabbits by the end of the first week. Except for erythema and desquamation, the effects resolved by day 13; mild acanthosis and trace chronic dermatitis were observed in treated rabbits. D-Panthenyl Triacetate (10% in polyglycol P-4000) caused no skin reactions in human subjects during a closed epicutaneous patch test for 24 hours. DL-Panthenol (undiluted) was non-irritating and non-sensitizing to guinea pig skin in a Buehler test. D-Panthenol (2.5% in a lotion) was non-sensitizing in a guinea pig maximization test. Two open epicutaneous tests in guinea pigs examined 5% D-Panthenol in an ointment (0.1 ml induction; 0.025 ml challenge); results were non-sensitizing in one test and weak sensitization potential with slight-to-well-defined irritation potential in the other test. A guinea pig maximization test evaluating 5% Panthenol in a test solution (induction) and dilutions of that formulation up to 30% (challenge), indicated that the solution was non-sensitizing. However, primary skin irritation reactions were observed in 3 guinea pigs 24 hours following a rechallenge using the 5% Panthenol test solution (no details were provided as to whether any reactions at this concentration were observed during induction). A guinea pig maximization test was conducted to evaluate DL-Panthenyl Ethyl Ether. During the induction phase, DL-Panthenyl Ethyl Ether (100% secured with a patch) was slightly irritating to guinea pig skin, and was determined to be non-sensitizing in the challenge phase (up to 100% DL-Panthenyl Ethyl Ether, semi-occlusive). A crème product and a spray product, each containing 5% Panthenol, were non-sensitizing to mice in an LLNA test.

D-Panthenol (5%) was found to be non-sensitizing in human subjects during an epidermal patch test. An HRIPT revealed that 5% Panthenol in a cosmetic baby product was non-sensitizing and non-irritating. A test gel containing 3% Panthenol (same concentration at induction and challenge) was evaluated for 24 hours under occlusion, 3 times/ week, for 4 weeks (induction) in human subjects; the test gel was non-sensitizing with one instance of mild erythema reported during induction. In another similar experiment, 6% Panthenol in a test gel was non-sensitizing in human subjects, however an irritation reaction (mild erythema) was noted in 1 subject at 4 days post-challenge; there were rare occurrences of mild erythema during induction. Panthenol (5% concentration used during induction and challenge) in a leave-on product was non-sensitizing in a HRIPT performed under occlusion for 24 hours (9 patches used during a 3-week induction with 2 weeks rest prior to challenge); at challenge, 1 subject of 113 exhibited low level erythema. In a very similarly conducted HRIPT, Panthenyl Ethyl Ether (0.005%) was non-sensitizing with reports of mild-to-definite erythema observed in 48 of 106 subjects during induction and 5 of 106 subjects at challenge.

An in vitro test performed using GLP in accordance with OECD TG 437 (Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants) indicated that D-Panthenyl Triacetate (undiluted, > 95% purity) was a non-eye irritant based on the lack of opacity or cornea permeability observed.

In rabbit eyes, D-Panthenol (undiluted, 5% in a formulation, or concentration not specified) was considered to be non-to-slightly irritating in several tests. Slight, but reversible corneal irritation and conjunctival redness were observed. DL-Panthenyl Ethyl Ether (concentration not specified) and Calcium Pantothenate (10% solution) were non-irritating in rabbit eyes.

In clinical studies, positive reactions to a 50% DL-Panthenol solution tested at 5% in petrolatum were reported in 2 of 192 (1.04%) human subjects patch tested in a dermatitis clinic. In human subjects treated twice daily for 10 weeks with a lotion containing 0.5% Panthenol or a control lotion, 6 treated subjects and 2 control subjects experienced a mild, transient burning sensation and 1 treated subject experienced dry skin and worsening of acne. Hyperpigmentation spots were statistically significantly reduced in treatment groups as compared to controls. A multicenter study noted 137 positive allergic reactions in > 96,000 patients to D-Panthenol (no concentrations provided), classified by the study researchers to be a “rare” allergen. In another study, 23 of 3301 (0.7%) patients had positive reactions to D-Panthenol (5%) in patch tests conducted from 1990 to 2016. Some patients were sensitized based on prescription or cosmetic products they used containing D-Panthenol; a history of atopy was noted in 7 of the 23 patients showing reactions. A retrospective study conducted from 2010 to 2015 showed that 3 of 311 patients (0.96%) patch tested with Panthenol (concentration not specified) exhibited positive responses.

The case reports associated with dermal exposure to Panthenol or Panthenyl Ethyl Ether include allergic contact dermatitis in a child (75% D-Panthenol facial wipe and a 30% D-Panthenol formulation); episodes of severe erythema and facial edema in a woman (0.5% D-Panthenol in a lotion); facial edema, erythema, and pruritus in a woman (hair conditioner and a hair coloring product containing Panthenol); allergic contact dermatitis (5% D-Panthenol in a topical cream) when used to treat stasis dermatitis or radiotherapy effects; and relapsing facial dermatitis in a woman (hair lotion containing 30% D-Panthenyl Ethyl Ether).

Case reports related to oral exposure involve a woman who had an anaphylactic reaction attributable to 3.33 mg D-Panthenol in a vitamin B complex product and another woman who took trimetazidine (for 6 years), vitamin H (biotin, 10 mg/day for 2 months), and Pantothenic Acid (300 mg/day for 2 months) for alopecia and developed eosinophilic pleuropericarditis.

DISCUSSION

The Panel reviewed this safety assessment of Panthenol, Pantothenic Acid and derivatives, and determined that these 7 ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment. The Panel also noted that these ingredients may contain residual amines as impurities; and, thus cautioned that these ingredients should not be used in cosmetic products in which *N*-nitroso compounds may be formed.

Previously, the Panel issued an Insufficient Data Announcement (IDA) with the following data needs:

- Method of manufacturing for Panthenyl Ethyl Ether, Panthenyl Ethyl Ether Acetate, and Panthenyl Triacetate
- Impurities data for Panthenyl Ethyl Ether, Panthenyl Ethyl Ether Acetate, and Panthenyl Triacetate
- Sensitization data, specifically an HRIPT or guinea pig maximization test for Panthenol at a concentration ≥ 5%.

Some data were received, and those data addressed the majority of the needs outlined above. Therefore, the Panel determined that based on the data submitted in response to this IDA, in combination with the overall weight of evidence presented in this report, these insufficiencies have been met or otherwise deemed moot.

The Panel recognized that D-Panthenol showed a marginal effect of penetration enhancement on the penetration of progesterone through the skin; this effect may not have been directly attributable to the ingredient itself and does not necessarily extend to the other ingredients presented in this safety assessment.

Panthenol, Panthenyl Ethyl Ether, Panthenyl Ethyl Ether Acetate, and Panthenyl Triacetate can be metabolized to Pantothenic Acid, an essential nutrient. The Panel recognized that exposures from absorbed amounts of these compounds is below what would be typical from dietary intake, thereby underscoring the safety of the ingredients. The safety profile is consistent with that of a common dietary constituent and an essential nutrient. Also, the data indicate that Panthenol and it ethers and esters are metabolically interconvertible, which support the favorable safety profile of the group.

The Panel considered other data available to characterize the potential for Panthenol, Pantothenic Acid, and derivatives to cause systemic toxicity, irritation, sensitization, reproductive and developmental toxicity, and genotoxicity. They noted the low potential for systemic toxicity at high doses in several dermal, oral, and inhalation acute exposure studies, in short-term dermal and oral exposure studies, and in subchronic oral exposure studies. In 6-month oral exposure studies in multiple animal species, no toxicity was reported. The ingredients were non-toxic in developmental and reproductive toxicity studies. Although no carcinogenicity studies were located in the literature for the ingredients presented in this report, many in vitro studies evaluating genotoxicity were available. Multiple Ames tests and mammalian cell gene mutation assays were non-mutagenic and chromosomal aberration tests were non-clastogenic.

The Panel noted that there was minimal potential for the ingredients to cause sensitization and irritation. In dermal exposure studies conducted in animals, Panthenol and Panthenyl Ethyl Ether were non-to-mildly irritating and non-sensitizing. In human subjects, Panthenyl Triacetate was non-irritating and Panthenol was non-to-mildly irritating and non-sensitizing in dermal exposure studies. An in vitro ocular irritation study showed Panthenyl Triacetate to be a non-irritant; in ocular irritation studies conducted in rabbits, Panthenyl Ethyl Ether and Calcium Pantothenate were non-irritating and Panthenol was non-to-slightly irritating. However, based on their collective clinical experience, the Panel did not expect these ingredients to be sensitizers or irritants.

The Panel discussed the issue of incidental inhalation exposure from hair sprays, body and hand sprays, fragrances, deodorant sprays, and face powders. These ingredients are reportedly used at concentrations up to 5% in cosmetic products that may be aerosolized and up to 0.5% in other products that may become airborne. The limited data available from animal inhalation studies, including acute exposure data, suggest little potential for respiratory effects at relevant doses. Although particles appear to have reached the lungs in these animal studies, the sizes of the particles used were either clearly within the respirable range (i.e., ≤ 10 μm) or were not reported. The Panel believes that the sizes of a substantial majority of the particles of these ingredients, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles of formulation. Thus, the adverse effects reported using high doses of respirable particles in the inhalation studies do not indicate risks posed by use in cosmetics. The Panel noted that 95%-99% of droplets/particles 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 Panel concluded that the following 7 ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Panthenol
Pantothenic Acid
Panthenyl Ethyl Ether
Panthenyl Ethyl Ether Acetate*
Panthenyl Triacetate
Calcium Pantothenate
Sodium Pantothenate*

**Not reported to be in current use. Were the ingredients in this group not currently in 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.[1;CIR Staff]

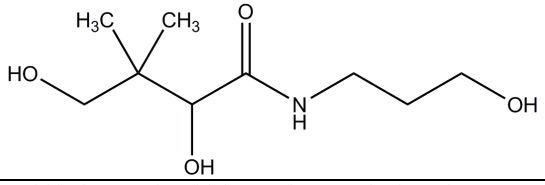
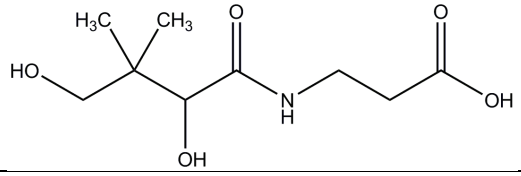
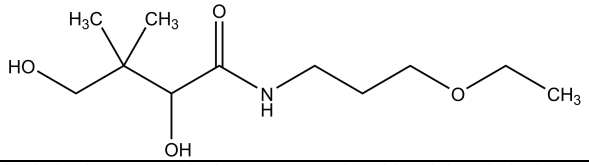
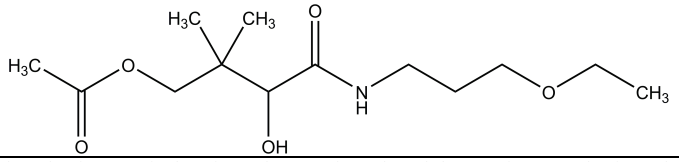
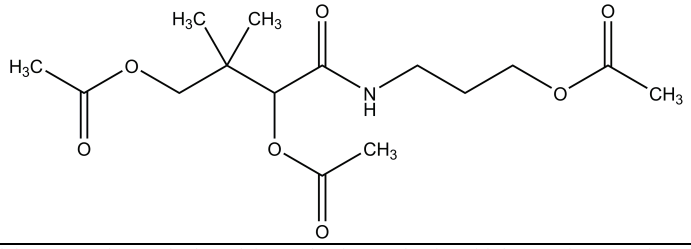
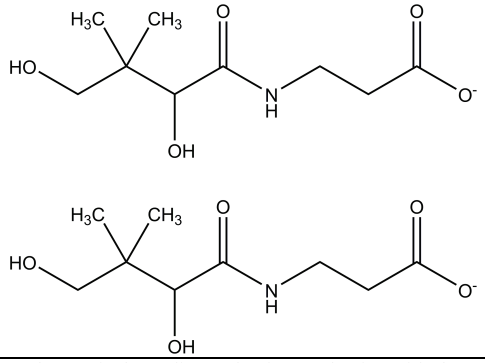
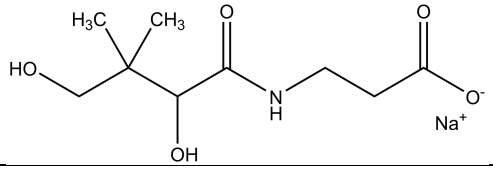
Ingredient CAS No.	Definition & Structure	Function
Panthenol 81-13-0 (D-) 16485-10-2 (D,L-)	Panthenol is the alcohol that conforms to the formula: 	Hair Conditioning Agents; Skin-Conditioning Agents-Humectant; Solvents
Pantothenic Acid 79-83-4	Pantothenic Acid is the organic acid that conforms to the formula: 	Hair Conditioning Agents
Panthenyl Ethyl Ether 667-83-4	Panthenyl Ethyl Ether is the ethyl ether of Panthenol. It conforms to the formula: 	Hair Conditioning Agents
Panthenyl Ethyl Ether Acetate [476170-37-3 119516-54-0 D-]	Panthenyl Ethyl Ether Acetate is the ester of acetic acid and the ethyl ether of Panthenol. It conforms to the formula: 	Hair Conditioning Agents
Panthenyl Triacetate 94089-18-6 98133-47-2	Panthenyl Triacetate is the triacetyl ester of Panthenol that conforms to the formula: 	Hair Conditioning Agents
Calcium Pantothenate 137-08-6 (D-)	Calcium Pantothenate is the calcium salt of pantothenic acid that conforms to the formula: 	Hair Conditioning Agents
Sodium Pantothenate 867-81-2	Sodium Pantothenate is the sodium salt of Pantothenic Acid [that conforms to the structure:] 	Hair Conditioning Agents

Table 2. Physical and Chemical Properties

Property	Value	Reference
Panthenol		
Physical Form	Crystalline powder; racemic mixture of D (active) and L (inactive); D-form may also be a viscous liquid that crystallizes during storage, hygroscopic and sensitive to heat at 70 °C (may cause racemization)	18,19
Color	White (D,L-form, powder); colorless to slightly yellow (D-form, liquid)	18,19
Molecular Weight (g/mol)	205.25 (D,L-form)	18
Density (g/ml) @ 20 °C and 760 mmHg	1.166 ± 0.06 est. (D-form)	21
Vapor pressure mmHg @ 25 °C	2.21 x 10^{-11} est. (D-form)	21
Melting Point (°C)	63.3 (D,L-form)	6
Boiling Point (°C) @ 760 mmHg	483.6 ± 45.0 est. (D-form)	21
Water Solubility	Freely soluble (D,L-form)	18
Other Solubility	Freely soluble in alcohol and propylene glycol; soluble in chloroform and ether; slightly soluble in glycerin (D,L-form); insoluble in fats and oils (D-form)	18,19
Log P @ 25 °C	-0.989 ± 0.602 est. (D-form)	21
pKa @ 25 °C	13.03 ± 0.20; -0.88 ± 0.70 est. (D-form)	21
Pantothenic Acid		
Physical Form	Viscous oil; extremely hygroscopic; destroyed by acids, bases, heat	17
Molecular Weight (g/mol)	219.24	17
Density g/ml @ 20 °C and 760 mmHg	1.266 ± 0.06 est.	21
Boiling Point (°C) @ 760 mmHg	551.5 ± 50 est.	21
Water Solubility	Freely soluble	17
Other Solubility	Freely soluble in ethyl acetate, dioxane, glacial acetic acid; moderately soluble in ether and amyl alcohol; insoluble in benzene and chloroform	17
Log P @ 25 °C	-0.856 ± 0.605 est.	21
pKa @ 25 °C	4.30 ± 0.10; -1.00 ± 0.70 est.	21
Panthenyl Ethyl Ether		
Physical Form	Viscous liquid (D,L-form) that may crystalizes during storage; slightly hygroscopic; hydrolysis may occur in presence of strong acids or alkalis	20
Color	Clear, colorless to slightly yellow	20
Molecular Weight (g/mol)	233.308	25
Density (g/ml) @ 20 °C and 760 mmHg	1.070 ± 0.06 est.	21
Vapor Pressure mmHg @ 25 °C	9.7 x 10^{-10} est.	21
Boiling Point (°C) @ 760 mmHg	443.8 ± 45.0 est.	21
Water Solubility	Miscible	20
Other Solubility	Miscible with alcohol, propylene glycol, glycerin, and corn oil; insoluble in fats and mineral oils	20
Log P @ 25 °C	0.354 ± 0.619 est.	21
pKa @ 25 °C	13.04 ± 0.20; -0.86 ± 0.70 est.	21
Panthenyl Ethyl Ether Acetate		
Molecular Weight (g/mol)	275.345	26
Density (g/ml) @ 20 °C and 760 mmHg	1.072 ± 0.06 est.	21
Vapor Pressure mmHg @ 25 °C	9.4 x 10^{-9} est.	21
Boiling Point (°C) @ 760 mmHg	418.5 ± 45.0 est.	21
Water Solubility (g/l) @ 25 °C & pH 6.7	49 (Soluble) est. (in unbuffered water)	21
Log P @ 25 °C	1.058 ± 0.553 est.	21
pKa @ 25 °C	12.99 ± 0.20; -0.87 ± 0.70 est.	21
Panthenyl Triacetate		
Molecular Weight (g/mol)	331.365	27
Density (g/ml) @ 20 °C and 760 mmHg	1.131 ± 0.06 est.	21
Vapor Pressure mmHg @ 25 °C	4.47 x 10^{-9} est.	21
Boiling Point (°C) @ 760 mmHg	471.9 ± 45.0 est.	21
Water Solubility (g/l) @ 25 °C & pH 7	4.3 (Slightly soluble) est. (in unbuffered water)	21
Log P @ 25 °C	0.837 ± 0.471 est.	21
pKa @ 25 °C	14.19 ± 0.46; -1.01 ± 0.70 est.	21
Calcium Pantothenate		
Physical Form	White powder; moderately hygroscopic	17,41
Formula Weight (g/mol)	476.54	17
Melting Point (°C)	195 - 196 (decomposition)	22
Water Solubility	Soluble	17
Other Solubility	Soluble in glycerol; Slightly soluble in alcohol and acetone	17
Log Kow	-1.69 est.	100
Sodium Pantothenate		
Physical Form	Very hygroscopic crystals (only stored in sealed ampuls)	17
Formula Weight (g/mol)	241.219	23
Melting Point (°C)	171 - 178	24

Table 3. Frequency and concentration of use of Panthenol, Pantothenic Acid, and Derivatives[2,5,42,43]

	# of Uses	*Max Conc Use (%)*	*# of Uses*	*Max Conc Use (%)*	*# of Uses*	*Max Conc Use (%)*
	Panthenol**		**Panthenol*****		**Panthenol, D-*****	
	2002	**2004**	**2017**	**2016**	**2017**	**2016**
Totals*	**1538**	**0.00005-6**	**5766**	**0.0000053-5.3**	**518**	**NR**
Duration of Use						
Leave-On	*867*	*0.001-6*	*3543*	*0.0001-5.3*	*339*	NR
Rinse-Off	*656*	*0.00005-6*	*2178*	*0.000045-5*	*177*	NR
Diluted for (Bath) Use	*15*	*0.01-2*	*45*	*0.0000053-1.2*	*2*	NR
Exposure Type						
Eye Area	100	0.001-2	636	0.0075-3	49	NR
Incidental Ingestion	6	0.01-2	50	0.001-2	18	NR
Incidental Inhalation-Spray	spray: 110 possible: 341[a]; 61[b]	spray: 0.003-5 possible: 0.01-5[a]; 0.001-6[b]	spray: 213 possible: 1414[a]; 711[b]	spray: 0.005-5 possible: 0.0005-1.5[a]; 0.01-0.5[b]	spray: 7 possible: 98[a]; 59[b]	NR
Incidental Inhalation-Powder	powder: 7 possible: 61[b]	powder: 0.02-1 possible: 0.001-6[b]	powder: 21 possible: 711[b]; 5[c]	powder: 0.5 possible: 0.01-0.5[b]; 0.001-5[c]	possible: 59[b]	NR
Dermal Contact	503	0.001-6	3196	0.0000053-5.3	266	NR
Deodorant (underarm)	3[a]	0.05-0.5[a]	11[a]	spray: 0.0001-0.1 not spray: 0.013-0.53	NR	NR
Hair - Non-Coloring	857	0.01-6	1874	0.0005-5	164	NR
Hair-Coloring	62	0.00005-1	219	0.000045-0.6	10	NR
Nail	40	0.03-1	63	0.0005-2.9	29	NR
Mucous Membrane	44	0.01-4	601	0.0000053-2.5	49	NR
Baby Products	3	NR	22	0.04-5	1	NR

	Panthenol, DL-***		**Pantothenic Acid****		**Pantothenic Acid**	
	2017	**2016**	**2002**	**2004**	**2017**	**2016**
Totals*	**477**	**NR**	**3**	**0.00001-0.01**	**78**	**0.0001-0.0034**
Duration of Use						
Leave-On	*356*	NR	*3*	*0.001-0.01*	*65*	*0.0001-0.0034*
Rinse-Off	*118*	NR	*NR*	*0.00001*	*13*	*0.001*
Diluted for (Bath) Use	*3*	NR	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	34	NR	1	0.001-0.01	10	0.0001-0.001
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	spray: 3; possible:147[a];116[b]	NR	possible: 1[a]	possible: 0.003[a]	possible: 24[a]; 9[b]	NR
Incidental Inhalation-Powder	possible: 116[b]	NR	NR	powder: 0.001	powder: 2 possible: 9[b]	possible: 0.0005-0.0034[c]
Dermal Contact	336	NR	3	0.00001-0.003	62	0.0001-0.0034
Deodorant (underarm)	1[a]	NR	NR	NR	NR	NR
Hair - Non-Coloring	123	NR	NR	NR	15	NR
Hair-Coloring	2	NR	NR	NR	NR	NR
Nail	1	NR	NR	NR	1	NR
Mucous Membrane	17	NR	NR	NR	1	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Panthenyl Ethyl Ether		**Panthenyl Triacetate**		**Calcium Pantothenate**	
	2017	**2015**	**2017**	**2015**	**2017**	**2015**
Totals*	**382**	**0.001-2**	**99**	**0.003-2**	**265**	**0.0000005-0.5**
Duration of Use						
Leave-On	*150*	*0.001-2*	*87*	*0.003-2*	*227*	*0.0000005-0.5*
Rinse-Off	*232*	*0.005-0.5*	*12*	*0.003-0.1*	*37*	*0.0001-0.2*
Diluted for (Bath) Use	*NR*	*0.15*	*NR*	*NR*	*1*	*NR*
Exposure Type						
Eye Area	14	0.05-0.84	2	0.2	19	0.0000005-0.1
Incidental Ingestion	3	0.034-0.4	36	2	NR	0.019
Incidental Inhalation-Spray	spray: 8 possible: 104[a]; 9[b]	spray: 0.09-0.5 possible: 0.09-0.5[a]	possible: 15[a]; 16[b]	possible: 0.95[a]	spray: 1 possible: 56[a]; 57[b]	spray: 0.0018-0.19 possible: 0.05-0.08[a]
Incidental Inhalation-Powder	possible: 9[b]	possible: 0.01-1[c]	powder: 3 possible: 16[b]	powder: 0.003 possible: 0.003-0.17[c]	possible: 57[b]	powder: 0.01 possible: 0.0001-0.5[c]
Dermal Contact	44	0.01-2	57	0.003-2	151	0.0000005-0.5
Deodorant (underarm)	NR	NR	NR	0.96	NR	NR
Hair - Non-Coloring	329	0.001-0.5	3	NR	42	0.0001-0.19
Hair-Coloring	2	NR	NR	NR	4	NR
Nail	NR	NR	3	1	66	0.001-0.4
Mucous Membrane	15	0.034-0.4	37	2	1	0.019
Baby Products	NR	NR	NR	NR	1	NR

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

**Panthenol and Pantothenic Acid data (from the re-review report published in 2006) presented here for comparison to recent data.

*** Frequency of use data from the VCRP were reported separately for the different forms of Panthenol, therefore they are reported separately in this table

NR – no reported use

[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

Table 4. Appearance of Ingredients in Code of Federal Regulations

Ingredient	Non-Cosmetic Use	References*
Panthenol	-Silicon dioxide is used as a direct food additive intended as an absorbent for pantothenyl alcohol (i.e. Panthenol) in tableted dietary use foods -For D-Panthenol: inadequate data for GRAS establishment in OTC drug products for use as a hair grower or for hair loss prevention -For panthenol and D-Panthenol: inadequate data for GRAS establishment in OTC drug products for uses as an analgesic for insect bites and stings, poison ivy, poison oak, and poison sumac; uses as skin protectant drug products for poison ivy, poison oak, and poison sumac -"'Certain Mouthwash and Gargle Preparations'…pertaining to Tyrolaris Mouthwash, containing tyrothricin, panthenol, and alcohol, for which an order revoking provision for certification was published in the Federal Register of February 2, 1967…prior to the drug efficacy study implementation." -For D-pantothenyl alcohol (i.e. D-panthenol): GRAS with good manufacturing or feeding practice in animals	21CFR172.480; 21CFR310.527; 21CFR310.545; 21CFR330.12; 21CFR582.5580
Pantothenic Acid	- RDI is established for pantothenic acid to be 10 mg for essential human nutrition and food should be labeled as appropriate -Nutritional labeling of dietary supplements should contain pantothenic acid as applicable -Essential nutritional values for pantothenic acid in food based on RDI is 5 mg (adults and children ≥ 4 years), 1.8 mg (infants through 12 months), 2 mg (children 1-3 years), 7 mg (pregnant and lactating women) and food should be labeled as appropriate -Nutritional value of pantothenic acid is 0.5 mg/ 100 calories (assuming a 2000 calorie/day diet) in fortified foods -Minimum level nutrient (pantothenic acid) in frozen heat and serve dinners is 1.1 mg for total dinner meal -Infant formula labels should contain Pantothenic acid in mg units -Minimum level nutrient (pantothenic acid) in infant formula is 300 µg/ 100 kilocalories of formula (no maximum level specified) -Direct food additive -For D-pantothenamide (as a source of pantothenic acid activity) is safe in dietary food use (not in excess of what is necessary to produce intended effect) -Inadequate data for GRAS establishment in OTC weight control drug products	9CFR317.309 and 9CFR381.409; 21CFR101.36; 21CFR101.9; 21CFR104.20; 21CFR104.47; 21CFR107.10; 21CFR107.100; 21CFR172.330; 21CFR172.335; 21CFR310.545
Calcium Pantothenate	-Direct food additive (D- or D,L-forms) -Direct food additive (nutritional supplement) affirmed as GRAS (may also be used in infant formula) when used with good manufacturing practice -Inadequate data for GRAS establishment in OTC laxative drug products, weight control drug products, and oral menstrual drug products -GRAS when used with good manufacturing or feeding practice in animals	21CFR172.330; 21CFR184.1212; 21CFR310.545; 21CFR582.5212
Sodium Pantothenate	-GRAS when used with good manufacturing or feeding practice in animals	21CFR582.5772

*References listed in the order of corresponding data, reported in Non-Cosmetic Use column

Table 5. Dermal and Nail Penetration Studies

Test Substance(s)	Species	Sample Type or Test Population-Sex	Concentration (Vehicle)	Exposure Route	Procedure	Results	Reference
DERMAL PENETRATION							
IN VITRO							
Animal							
D-Panthenol	Pig (hybrid Landrace with Large White)	Skin samples, n = 6 samples/animal/group, number of animals used not specified	Hydrophilic gel formulation containing 10% D-Panthenol, 1% carboxyvinyl acid, 5% propylene glycol, 0.5% imidazonidinyl urea, 0.1% methylparaben, water, triethanolamine	N/A	Cutaneous penetration was examined with and without ultrasound (technique called phonophoresis or sonophoresis); 8 cm^2 skin area containing gel formulation was evaluated in a diffusion cell experiment; receptor cell fluid (distilled water) was in contact with dermis; receptor cell fluid was collected at 2, 60, 120, 180, and 240 min and samples were assayed (alkaline hydrolysis followed by neutralization and absorbance measured at 406 nm) for D-Panthenol content	D-Panthenol was shown to penetrate pig skin both with and without ultrasound; effect was enhanced with ultrasound at all time-points tested (statistically significant increase in penetration at 2, 60, and 240 min); a steady increase in D-Panthenol concentration in receptor cell fluid was observed from 2 min (330 µg/ml without ultrasound, 480 µg/ml with ultrasound) to 120 min (890 µg/ml without ultrasound, 1189 µg/ml with ultrasound); D-Panthenol in receptor cell fluid reached a plateau by 180 min (903 µg/ml without ultrasound, 1069 µg/ml with ultrasound)	[55]
D-Panthenol	Pig	Abdominal skin samples	D-Panthenol (concentration not specified in abstract) in different mixtures containing surfactants (Tween®85, SDS, and Span®80) at 0.5%, 1%, 2%, and 5%	N/A	Test substance applied to skin mounted on Franz diffusion cells; permeation experiment lasted 180 min; permeation of test substance analyzed by HPLC	Surfactants enhanced permeation of D-Panthenol; 1% surfactant yielded best results; study authors concluded that nature of enhancer effected cutaneous barrier impairment	[56]

Table 5. Dermal and Nail Penetration Studies

Test Substance(s)	Species	Sample Type or Test Population-Sex	Concentration (Vehicle)	Exposure Route	Procedure	Results	Reference
				Human			
^{14}C-Panthenol (>95% radiochemical purity)	Human	n = 5 abdominal skin samples from adult cadavers, thickness was 400 µm (circular cut samples were used)	20 mg/ml ^{14}C-Panthenol (0.05 mCi/ml), ethanol vehicle	N/A	Franz (static) diffusion cell experiments were performed; 30 min prior to application of test substance, skin samples were either not stripped or stripped 5x or 10x, then equilibrated at room temperature in diffusion cell; following equilibration, 10 µl of test substance was applied to skin samples in donor chamber; receptor solution was 0.01 mol/l PBS with 5%, v/v, polyethylene glycol; receptor fluid was collected 15 or 60 min after test substance was applied and then all skin samples were stripped 20x (stratum corneum was separated from epidermis); protein content, TEWL, and applied radioactivity were measured in 20x tape-stripping samples; following tape-stripping, the epidermis and dermis in skin samples were separated using heat; epidermis and dermis were digested overnight and analyzed for radioactivity	*Skin samples not tape-stripped before test substance application*: diffusion coefficients were reported to be 6.4 nmol/s (15 min) and 2.2 nmol/s (60 min); amount of applied radioactivity detected in stratum corneum was 84% (at 15 and 60 min), in epidermis was 9% (15 min) and 6% (60 min), and in dermis was 3% (15 min) and 4% (60 min); receptor fluid (both 15 and 60 min samplings) contained negligible amounts of applied radioactivity (< 0.03%) *Skin samples tape-stripped 5x before test substance application*: (15 min data reported here, 60 min data not provided) diffusion coefficient < 2 nmol/s, applied radioactivity detected in stratum corneum was 81%, in epidermis 8.7%, and 6% in dermis; receptor fluid contained negligible amounts of applied radioactivity (< 0.1%) *Skin samples tape-stripped 10x before test substance application*: (15 min reported here, 60 min data not provided) diffusion coefficient < 2 nmol/s, radioactivity detected in stratum corneum was 72% of applied amount, in epidermis was 18%, and in dermis was 6.3%; receptor fluid contained negligible amounts of applied radioactivity (< 0.04%) *Skin samples after tape-stripped 20X*: general exponential decline of protein with increasing number of tape strips; TEWL increased in the deeper layers of stratum corneum	[57]

Table 5. Dermal and Nail Penetration Studies

Test Substance(s)	Species	Sample Type or Test Population-Sex	Concentration (Vehicle)	Exposure Route	Procedure	Results	Reference
IN VIVO							
Human							
D-Panthenol; Panthenyl Triacetate	Human	n = 3/treatment group	3% Panthenyl Triacetate in water-based gel 3% D-Panthenol in water-based gel Water-based gel control	Dermal	Subjects applied 2 mg/cm^2 of gel to volar forearm; at 1 h, 5 h, and 24 h measurements (10x per treatment area) were taken down to a 25 µm skin depth using confocal Raman micro-spectroscopy (skin was not wiped prior to measurement); baseline measurements serving as controls were taken before the addition of test substance	Panthenyl Triacetate was distinguished from D-Panthenol in Raman spectroscopy by a peak shift at 1722 cm^{-1} representing acetylated groups of Panthenyl Triacetate; by 24 h D-Panthenol was detected in upper portion of stratum corneum (20 mg/g keratin) and at 25 µm depth (> 10 mg/g keratin at all time points) while baseline levels in upper stratum corneum were 10 mg/g keratin and < 10 mg/g keratin at 25 µm; by 24 h Panthenyl Triacetate was detected in upper portion of stratum corneum (< 20 mg/g keratin), but was negligible at 25 µm at all time points and for comparison baseline levels in upper stratum corneum were ~10-15 mg/g keratin and negligible at 25 µm; after Panthenyl Triacetate was applied, levels of D-Panthenol were monitored and found to be ~13 mg/g keratin at 24 h in upper stratum corneum and 10-15 mg/g keratin at all time points at 25 µm depth while baseline levels in upper stratum corneum were 10 mg/g keratin and ~10-12 mg/g keratin; study researchers stated that Panthenyl Triacetate is converted to D-Panthenol through de-acetylation in deeper layers of skin by 24 h	53,58

Table 5. Dermal and Nail Penetration Studies

Test Substance(s)	Species	Sample Type or Test Population-Sex	Concentration (Vehicle)	Exposure Route	Procedure	Results	Reference
NAIL PENETRATION							
IN VITRO							
Human							
1-^{14}C-Panthenol (99% radiochemical purity, 50 mCi/ mmol); non-radiolabeled portion was DL-Panthenol	Human	<u>*Penetration Study*</u>: cadaver fingernail plates were used (washed with saline and re-hydrated for 3 h on a cloth containing saline) <u>*Kinetic Study*</u>: same type of samples used as above; n=3/ 7 groups	<u>*Penetration Study*</u>: 2% ^{14}C-Panthenol (0.07 µCi) in 98% nail formulation base (base contained ethanol, acrylates copolymer, and phytantriol) 2% ^{14}C-Panthenol (0.08 µCi) in water <u>*Kinetic Study*</u>: 2% ^{14}C-Panthenol (0.11 µCi) in 98% nail formulation base (same composition as above)	N/A	<u>*Penetration Study*</u>: Nail incubation performed by inserting nail plate into one-chamber diffusion cell; dorsal (top) nail surface exposed to air and ventral (interior) side touching a cotton ball containing saline for moisture; incubation was conducted 24 h before and remained until 24 h after application of test substance; 15 µl of test substance in either the nail formulation base or in water were applied to dorsal portion of nail plate 1x/day for 7 days (nail plates were washed with ethanol, soap, and water before application of test substance) After test substance application and incubation phases were complete, powder nail samples (0.3 to 0.4 mm deep and 7.9 mm diameter) were taken from the interior portion of the nail without contacting the dorsal nail surface to which the test substance was applied Recovery of applied radioactivity was determined by assaying washing liquids from nail plate and diffusion cell components <u>*Kinetic Study*</u>: 15 µl of test substance was applied to nail 1x/day for 7 days as described above; 24 h following each application of test substance, samples were collected to determine daily penetration rates and flux	<u>*Penetration Study*</u>: Radioactivity from the nail formulation base was 2x higher in the interior nail plate than the radioactivity from the aqueous solution by day 7; radioactivity from the nail formulation base was 3x higher in cotton ball than the radioactivity from the aqueous solution by 7 days; radioactivity from the nail formulation base was 34% lower in dorsal nail than the radioactivity from the aqueous solution by 7 days; study researchers postulated that greater nail penetration of test substance in the formulation base compared to the test substance in the aqueous solution may be explained by solvent evaporation from the formulation base, which could concentrate the ^{14}C-Panthenol on the dorsal nail surface; thus diffusion of test substance in the formulation base was potentially enhanced by increased nail hydration and increased thermodynamic activity of ^{14}C-Panthenol Generally, over time, test substance concentrations increased linearly and were highest in the dorsal layer, followed by interior layer, and lastly by cotton ball Applied radioactivity recovered from the formulations tested was 93-104%, indicating no loss of test substance in diffusion cell system <u>*Kinetic Study*</u>: Steady-state flux of test substance through nail was reached within 24 h; no statistical differences in measured ^{14}C-Panthenol in formulation base between 7th day of kinetic study and after 7 days of penetration study	[59]

HPLC = High Performance Liquid Chromatography; PBS = Phosphate Buffered Saline; TEWL = Transepidermal Water Loss

Table 6. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
IN VIVO						
ANIMAL						
Dermal						

D-Panthenol; D-Panthenyl Ethyl Ether	Rat/ Wistar	n = 10 (D-Panthenol group);
		n = 9 (D-Panthenyl Ethyl Ether group);
		n = 4 (control group)
			20 mg D-Panthenol in 0.2 ml 50% ethanol solution
			22.8 mg D-Panthenyl Ethyl Ether in 0.2 ml 50% ethanol solution
			0.2 ml 50% ethanol solution (control)
				Test substance or control rubbed into shaved neck skin of animal; urine analyzed for Pantothenic Acid content from time 0 to 18 h, and then in 24-h intervals after that up to 114 h, using a microbiological determination (with *Lactobacillus arabinosus*) specific for Pantothenic Acid; Panthenol and Panthenyl Ethyl Ether have no growth effect on *L. arabinosus*	Average Pantothenic Acid in urine reported as follows:
					D-Panthenol group 8.35 mg (0-18 h), 1.97 mg (19-42 h), 0.59 mg (43-66 h), 0.46 mg (67-90 h), and 0.34 mg (91-114 h);
					D-Panthenyl Ethyl Ether group 2.4 mg (0-18 h), 3.01 mg (19-42 h), 1.34 mg (43-66 h), 0.73 mg (67-90 h), and 0.77 mg (91-114 h);
					Controls group 0.08 mg (0-18 h), 0.07 mg (19-42 h), 0.10 mg (43-66 h), and negligible after that
					Study researchers stated that mean vitamin efficiency measured as conversion to Pantothenic Acid was 100% for D-Panthenol and 70% for D-Panthenyl Ethyl Ether; conversion of D-Panthenyl Ethyl Ether to Pantothenic Acid more gradual and delayed compared to D-Panthenol conversion to Pantothenic Acid; study researchers noted that D-Panthenyl Ethyl Ether exhibited a vitamin depot effect compared to D-Panthenol
						[62]

D-Panthenol; D-Panthenyl Triacetate	Rat	n = 6/group	20 mg D-Panthenol in 0.2 ml absolute ethanol 20 mg D-Panthenyl Triaceate in 0.2 ml absolute ethanol 0.2 ml absolute ethanol (control)	Test substance or control was rubbed into shaved neck skin of animal; urine analyzed for Pantothenic Acid content 66 and 114 h post-application using a microbiological determination (with *L. arabinosus*)	Average precipitated Pantothenic Acid in urine reported as follows: from 0 to 66 h: 0.25 mg (control), 16.28 mg (D-Panthenol), and 3.69 mg (D-Panthenyl Triacetate) from 66 to 114 h: 0.16 mg (control), 1.07 mg (D-Panthenol), and 1.19 mg (D-Panthenyl Triacetate) Study researchers stated that mean vitamin efficiency measured as conversion to Pantothenic Acid was 100% for D-Panthenol and 45% for D-Panthenyl Triacetate	[63]
Oral						
Pantothenic Acid; Calcium Pantothenate	Rat	n = not specified	4 mg Pantothenic Acid; 1 or 4 mg Calcium Pantothenate; undosed animals were used as controls	Single doses of either Pantothenic Acid or Calcium Pantothenate were administered; Pantothenic Acid excretion of test and control animals was measured	64% (2.57 mg) Pantothenic Acid was excreted in urine after Pantothenic Acid administration; 0.32 mg Pantothenic Acid excreted in urine 24 h after 1 mg Calcium Pantothenate administration; 0.98 mg (~25%) Pantothenic Acid excreted in urine 24 h after 4 mg Calcium Pantothenate administration; 0.12 mg Pantothenic Acid excreted in urine of control rats	[12]

Table 6. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
Calcium Pantothenate	Rat/ Wistar	n= not specified, males	0, 4, 8, or 16 mg/kg Calcium Pantothenate in feed	Animals were dosed in diet (available ad libitum) for 28 days; 24-h urine samples were collected on the last study day; animals were killed at study completion, blood was analyzed and tissue samples were collected and assayed for Pantothenic Acid content	Animals treated without Calcium Pantothenate showed statistically significantly lower Pantothenic Acid content of liver and adrenal glands and urinary excretion compared to all groups treated with Calcium Pantothenate; contents of Pantothenic Acid in liver and adrenal glands were equally maintained with 4 mg/kg and 16 mg/kg in the diet; concentration-dependent increase in urinary Pantothenic Acid content corresponding to Calcium Pantothenate intake was observed; for toxicological results reported from this study see Table 8	[64]
Calcium Pantothenate	Rat/ Wistar	n = not specified, males	4 mg/kg Calcium Pantothenate in a 5% fat diet or 5.5 mg/kg Calcium Pantothenate in a 30% fat diet Some rats were also fed diet with 16 mg/kg Calcium Pantothenate (5% fat) or 22 mg/kg Calcium Pantothenate (30% fat)	Animals were dosed in diet (available ad libitum) for 28 days; fecal samples were collected (no further details were provided); 24-h urine samples were collected on the last study day; animals were killed at study completion, blood was analyzed and tissue samples were collected and assayed for Pantothenic Acid content	Body weight gain and total food intake were statistically significantly lower with 30% fat diet (5.5 mg/kg Calcium Pantothenate) compared to 5% fat diet (4 mg/kg Calcium Pantothenate); Pantothenic Acid content in urine, plasma, liver, and adrenal glands were statistically significantly lower with 30% fat diet (5.5 mg/kg) compared to 5% fat diet (4 mg/kg); 30% fat diet (22 mg/kg Calcium Pantothenate) did not affect body weight gain or other measurements of Pantothenic Acid nutritional status; there were no differences between 5% or 30% fat diet in Pantothenic Acid content of fecal samples	[64]
Calcium Pantothenate	Rat/ Wistar	n = 5 males/ group	Group 1: 0% test substance Group 2: 0.0016% test substance Group 3: 1% test substance Group 4: 3% test substance	Animals were dosed as indicated in diet for 29 days; food was available ad libitum; 24-h urine samples were collected on day 29; free Pantothenic Acid content in urine was measured; animals were killed at completion of experiment and organs/tissues removed and weighed	Urinary excretion of Pantothenic Acid in Groups 1 and 2 was negligible and in Groups 3 and 4 was ~15 and ~30 nmol/g, respectively; Pantothenic Acid levels in liver increased with increasing Calcium Pantothenate doses; Coenzyme A content in liver in Groups 2-4 was similar (saturated) and more than double that of Group 1; urinary excretion of ascorbic acid was similar for Groups 1-4; urinary excretion of vitamin B_1 and vitamin B_6 metabolites decreased with increasing administration of Calcium Pantothenate, while no dose-related trend was observed for vitamin B_2; nicotinamide metabolism was adversely affected by insufficient (Group 1) or excessive (Groups 3 and 4) Pantothenic Acid doses; for toxicological results from this study see Table 8	[65]

Table 6. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
Calcium Pantothenate and Panthenol	Rat/ Sprague-Dawley	n = 10 to 20/ dose group	1 to 2, 5, 10 mg/kg Calcium Pantothenate or Panthenol	Food was available ad libitum; animals were dosed as indicated; 24 h post-dosing urine and feces samples were collected and analyzed	85% and 173% (for 5 and 10 mg/kg dosages, respectively) more Pantothenic Acid was detected in urine after Panthenol administration than after Calcium Pantothenate administration; Pantothenate was excreted in higher amounts from Panthenol (60% of dose) than Calcium Pantothenate (23%-33% of dose) 24 h post-dosing	[9]
Calcium Pantothenate	Dog	n = not specified	4 mg/kg	Animals were dosed as indicated (non-fasting); urine was collected for 24 h post-dosing; feces collected (time not specified)	1.7% of administered dose was excreted in urine; 14% to 27% of administered dose was excreted in feces	[9]
Calcium Pantothenate	Rat/ Wistar	n = 5 males/ group	Control group: 2 ml of water Test group: 10.28 mg Calcium Pantothenate/kg bw (21.6 µmoles/2 ml water/kg bw Calcium Pantothenate or 43.2 µmoles/kg bw Pantothenic Acid equivalent)	Animals were dosed as indicated by stomach tube; blood was collected prior to dosing and at time intervals up to 24-h post-dosing from tail vein and assayed for free and total Pantothenic Acid; urine was collected prior to dosing and at 24-h time points (up to 72 h) following dosing, then analyzed for free and total Pantothenic Acid	*Pantothenic Acid equivalent content from blood:* at time zero was 2.58 and 2.87 nmoles/ml for free and total, respectively; in the controls by 24 h was 2.61 and 2.65 nmoles/ml for free and total, respectively; in test group peaked at 2 h for free (2.82 nmoles/ml) and at 7.5 h for total (3.45 nmoles/ml); all total values in test group were statistically significantly higher than controls except at 24 h time point *Pantothenic Acid equivalent content from urine:* by 24 h, peak amounts were reached in test group (~2-3 µmoles/ml for free and total); 18% of administered dose in test group was detected in urine by 24 h post-dosing	[101]
Calcium Pantothenate	Rat	n = not specified	0 or 2.3 mg (23 mg/kg)	Animals were dosed daily by gastric cannula (24 or 45 days) or daily in the diet (5-6 months); controls were used (no further details provided)	24 or 45 days results: slight increase in Pantothenic Acid content in kidneys compared to controls; Pantothenic Acid content in liver was not substantially different than controls 5-6 months results: 32% increase in Pantothenic Acid content in heart compared to controls; Pantothenic Acid content in kidney and spleen was not substantially different than controls; 25% decrease in Pantothenic Acid content in liver compared to controls	[9,12]
Sodium Pantothenate (location and identity of label not specified)	Dog	n = not specified	7 mg (0.8 mg/kg)	Animals were dosed and urine analyzed	0.5% of radioactive dose was excreted as unchanged Pantothenate in urine 24 h after administration; 40% of radioactive dose was excreted as β-glucuronide in urine 7 days after administration	[12]
Sodium Pantothenate (location and identity of label not specified)	Rat	n = 2	330 µg (1.6 mg/kg)	Animals were dosed and urine analyzed	27% of radioactive dose was excreted as Pantothenate in urine 7 days after administration (no glucuronide detected)	[12]

Table 6. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
Sodium Pantothen[^{14}C]ate (3.6 mCi/mmol)	Dog/ Beagle	n = 2/single doses n = 1/ repeated dose	6.68 or 1.67 mg (100 or 25 µCi) test substance in a gelatin capsule with 1 ml of water	Animals were administered either a single dose capsule (6.68 or 1.67 mg) or were repeatedly dosed with capsule (1.67 mg) 4x in 2 days; food and water were available ad libitum; urine was collected at multiple time points up to 8 h post-dosing and daily after that for 7 days; daily feces samples were collected; blood samples were collected for up to 2 days post-dosing; equilibrium dialysis was used to determine binding affinity of test substance (6.68 mg) to plasma proteins	Radioactivity detected in urine (mainly as β-glucuronide metabolite) during 7 days post-dosing was 22%-39% (6.68 mg group), 28%-35% (1.67 mg group), and 23% (total for 4x 1.67 mg group) of administered dose; radioactivity recovered in feces (as unchanged test substance) during 7 days was 17%-26% (6.68 mg group), 14%-16% (1.67 mg group), and 15% (total for 4x 1.67 mg group) of administered dose; plasma concentrations of [^{14}C] (6.68 mg group) peaked at 2-2.5 h post-dosing (half-life 15-17 h); plasma concentrations of unchanged Pantothen[^{14}C]ate peaked 2-2.5 h post-dosing (half-life 3 h) and were determined to be 55 ng/ml; ^{14}C β-glucuronide metabolite plasma concentrations were highest 10-12 h post-dosing (half-life 15-17 h); plasma concentrations of unchanged Sodium Pantothen[^{14}C]ate (4x 1.67 mg group) peaked from 19-31 ng/ml as measured after each of 4 individual doses; [^{14}C] was not found to be bound to plasma proteins; renal clearance following dosing (6.68 mg group) was 2 ml/min (unchanged Panthen[^{14}C]ate) and 25.4 ml/min ([^{14}C] metabolite)	[102]
Intravenous						
Calcium Pantothenate	Rat/ Wistar	n = 3 males/ group for urine and liver analysis and n=5 males/group for blood analysis	Group 1: 10.28 mg Calcium Pantothenate/ml saline/kg bw (21.6 µmoles/kg bw Calcium Pantothenate or 43.2 µmoles/kg bw Pantothenic Acid equivalent) Group 2: 1 ml/kg bw saline (control group)	Animals were administered test substance as indicated by injection through femoral vein; blood was collected for up to 5 h from tail vein and assayed for free and total Pantothenic Acid; urine was collected prior to and at 24-h following administration, then analyzed for free and total Pantothenic Acid; 1 g of liver was removed 24-h post-administration and assayed for free and total Pantothenic Acid	*Pantothenic Acid equivalent content in blood:* in Group 1 free and total levels at 10 min were ~30 nmoles/ml and by 5 h were < 5 nmoles/ml; basal levels (Group 2) were subtracted from above results in treated animals *Pantothenic Acid equivalent content in urine:* by 24 h in Group 1 free and total were 11.2 and 13.1 µmoles, respectively; by 24 h Group 1 showed 87% and 99% of administered dose of free and total, respectively; by 24 h Group 2 (control) showed 2.2 and 2.9 µmoles of free and total, respectively *Pantothenic Acid equivalent content in liver:* in Group 1 free and total were 16.5 and 371 nmoles/g wet liver, respectively; by 24 h Group 2 (control) showed free and total to be 15.6 and 316 nmoles/g wet liver, respectively	[101]

Table 6. Toxicokinetics Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
Sodium Pantothen[^{14}C]ate (3.6 mCi/mmole)	Dog/ Beagle	n = 2	6.68 mg (100 µCi) test substance (aqueous solution)	Animals were administered a single dose intravenously into saphenous vein; food and water were available ad libitum; urine was collected at multiple time points up to 8 h post-dosing and daily thereafter for 7 days; daily feces samples were collected; blood samples were collected for up to 2 days post-dosing	Radioactivity detected in urine (mainly as β-glucuronide metabolite) during 7 days post-dosing was 34%-44% of administered dose; radioactivity recovered in feces (as unchanged test substance) during 7 days was 7%-9% of administered dose; plasma concentrations of [^{14}C] declined rapidly in 12 h post-administration (half-life 15-17 h); plasma concentrations of unchanged Pantothen[^{14}C]ate declined rapidly in 2 h post-administration (half-life 2.5 h); Pantothen[^{14}C]ate clearance rate in plasma for each animal was 135 and 276 ml/min; [^{14}C] metabolite was measured in plasma beginning ~1 h post-administration; ^{14}C β-glucuronide metabolite plasma concentrations were highest 10-12 h post-dosing (half-life 15-17 h); renal clearance following administration was 2.1 to 6.5 ml/min (unchanged Pantothen[^{14}C]ate) and 36.7 to 37.4 ml/min ([^{14}C] metabolite)	[102]
HUMAN						
Oral						
Calcium Pantothenate	Human	n = not specified	100 mg	Dose administered and urine analyzed	~20% of dose excreted as Pantothenate in urine within 4 h after administration	[12]
Calcium Pantothenate	Human	n = 10	50 mg in 200 ml water	Dose administered and urine analyzed; urine samples collected prior to dosing (4 h period) and 4 h post-dosing	Pantothenic Acid measured in urine prior to dosing was 1 ± 0.15 mg; Pantothenic Acid measured in urine post-dosing was 6 ± 0.48 mg	[9]

LOAEL = Lowest Observed Adverse Effect Level; NOAEL = No Observed Adverse Effect Level; PCR = Polymerase Chain Reaction

Table 7. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population- Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
ANIMAL						
Dermal						
D-Panthenol	Rat/ SPF albino	n = 5/sex/group	3 ml pure test substance (undiluted)/ kg	Test substance applied to 4 x 4 cm^2 shaved skin area and occlusively covered for 24 h in accordance with OECD TG 402 (distilled water control used); occlusive patch removed after 24 h and skin washed and dried; animals observed up to 2 weeks	LC_{50} > 3 ml/kg; no deaths; gross pathology unremarkable at necropsy; health and behavior of treated animals no different than controls; researchers speculated that slightly slower healing of scarification marks in 30% of treated animals could be attributed to greasiness of test substance and humidity under occlusion	[66]
DL-Panthenyl Ethyl Ether	Rat/ Wistar	n = 5/sex	2 g/kg (no vehicle)	Single treatment applied to 25 cm^2 (males) or 18 cm^2 (females) skin (semi-occlusive) for 24 hours using GLP in accordance with OECD TG 402 (Acute Dermal Toxicity); 24 hours post-application patch was removed and skin washed with water; animals were observed for 14 days post-application; necropsy performed	LD_{50} > 2 g/kg was reported; no deaths; no clinical signs; scabs in 1 male were observed on days 5 thru 9; 3 females had low body weight gain during week 2; no treatment-related abnormalities seen during necropsy	[6]
Oral						
D-Panthenol	Rat	n = 5-10/ sex/group	10 g/kg (46.4%-50%, w/v, test substance in distilled water vehicle)	Single dosage administered by gavage in accordance with OECD TG 401 (Acute Oral Toxicity); animals were observed for 14 days post-dosing; necropsy performed	LD_{50} > 10 g/kg reported; no deaths ; first day of study impaired general state observed at 10 g/kg (no further details provided); gross pathology revealed no findings	[7]
DL-Panthenyl Ethyl Ether	Rat/ Wistar	n = 5/sex	2 g/kg (water vehicle)	Single dosage administered by gavage in accordance with OECD TG 401; animals were observed for 14 days post-dosing; necropsy performed	LD_{50} > 2 g/kg was reported; no deaths or clinical signs observed; no abnormalities revealed during necropsy	[6]
Panthenyl Triacetate	Rat/ Wistar (Winkelmann Paderborn)	n = 5/sex/group	5 ml/kg or 10 ml/kg	Single dosage administered by gavage in accordance with OECD TG 401; animals were observed for 14 days post-dosing; necropsy performed	LD_{50} > 10 ml/kg; no deaths; no effect on weight gain; gross pathology was not effected by test substance	[67]
D-Calcium Pantothenate	Mouse	n = not specified	10 g/kg	Single dosage administered	LD_{50} of 10 g/kg reported	[12]
D-Calcium Pantothenate	Rat	n = not specified	10 g/kg	Single dosage administered	LD_{50} of > 10 g/kg reported; no signs of toxicity	[12]
D-Calcium Pantothenate	Dog	n = 5	1 g/kg	Single dosage administered	No signs of toxicity	[12]
D-Calcium Pantothenate	Monkey	n = 1	1 g/kg	Single dosage administered	No signs of toxicity	[12]
Inhalation						
D-Panthenol	Rat	n = 6/sex	Test substance (vapor) was delivered in saturated atmosphere at 20 °C	Single dose administered (whole body exposure) for 7-h exposure duration in accordance with OECD TG 403; animals were observed for 14 days; necropsy performed	Endpoint of study was LC_{50}; no concentration estimation could be determined because of low saturation vapor pressure; no deaths; no signs of toxicity; gross pathology showed no abnormalities	[7]

Table 7. Acute Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
D-Calcium Pantothenate	Rat/Wistar	n = not specified	5.2 mg/l dust particulate delivery (max concentration achievable); mass median aerodynamic diameters ≤ 3.6 µm	Single dose administered to head and nose region only (4-h exposure duration) in accordance with OECD TG 403; animals were observed for 14 days	No mortality; from 3 hours duration to day 7 increased respiration rate, abdominal or noisy respiration, and piloerection were noted, but cleared by day 8 and were considered by study researchers to be reversible; no abnormalities observed by day 14	[31]

GLP = Good Laboratory Practice; LC_{50} = Lethal Concentration at which 50% of population dies; OECD TG = Organization for Economic Co-operation and Development Test Guideline

Table 8. Short-Term, Subchronic, and Chronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
SHORT-TERM (< 3 MONTHS EXPOSURE)							
ANIMAL							
Dermal							
Panthenyl Ethyl Ether; 0.125% in leave-on hair conditioner	Rabbit/ New Zealand White	n = 5/sex/group	Neat	28 days	Test substance (2 ml/kg) applied 5 days/week for 28 days to shaved skin (skin abraded in test and control groups on days 1-6 and 10-12, but discontinued on remaining study days for both groups because of fissuring in test group); no further details provided regarding application of test substance; negative controls treated with deionized water; exposure time 7 h/day while animals wore restraining collars; animals killed at study termination ; necropsy and gross and microscopic pathologies performed	No deaths reported; diarrhea (day 14) and soft stool observed sporadically throughout study in 1 treated female; no statistically significant changes in body weights for treated compared to control males and females, however, body weights of treated females 24%-31% lower than controls; hematological values, gross pathology and organ weights unaffected by treatment; microscopic findings typical of spontaneous lesions found in normal rabbits of type used in study; dermal effects of treatment are summarized in Table 11	[68]
Oral							
Pantothenic Acid	Rat/ Wistar Imamichi	n = 21/group, males	0 or 0.03%	9 weeks	Animals were dosed daily in drinking water (food available ad libitum); animals were killed at the end of 9 weeks, adrenal glands removed and assayed for corticosterone and progesterone	No statistically significant difference in body weights or weights of adrenal glands in treated compared to control animals; in treatment group a statistically significant increase (~2 fold) in the basal plasma corticosterone levels as compared to control group was reported; basal plasma progesterone levels in treatment group were slightly higher than controls, but not statistically significant	[69]

Table 8. Short-Term, Subchronic, and Chronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
Calcium Pantothenate	Rat/ Wistar	n = not specified, males	0, 4, 8, or 16 mg/kg Calcium Pantothenate in feed	28 days	Animals were dosed in diet (available ad libitum) for 28 days; 24-h urine samples were collected on the last study day; animals were killed at study completion, blood was analyzed and tissue samples were collected and assayed for Pantothenic Acid content	Body weight gain and total food intake were consistent with 4, 8, or 16 mg/kg, but with 0 mg/kg Calcium Pantothenate these parameters were less than optimum and statistically significantly lower than all treated groups; for toxicokinetics data from this study see Table 6	[69]
Calcium Pantothenate	Rat/ Wistar	n = 5 males/ group	Group 1: 0% test substance Group 2: 0.0016% test substance Group 3: 1% test substance Group 4: 3% test substance	29 days	Animals were dosed as indicated in diet for 29 days; food was available ad libitum; 24-h urine samples were collected on day 29; free Pantothenic Acid content in urine was measured; animals were killed at completion of experiment and organs/tissues removed and weighed	Body weight gain and food intake were lower in Groups 1 (after day 7) and 4 (during first 5 days) compared to Group 2; body weight gain (by day 7) and food intake (by day 20) in Group 4 were similar to Group 2; no adverse effects on body weight gain or food intake were noted for Group 3; weights of brain and testis were higher in Group 1 compared to Groups 2-4; Groups 2 and 3 showed similar organ weights; weights of lung and spleen were higher in Group 4 compared to Group 2; in Group 4 diarrhea was reported; NOAEL of 1% and LOAEL of 3% were reported; study researchers speculated that 10 mg/kg/day of Calcium Pantothenate would be a "tolerable upper intake level"; study researchers mentioned conducting experiment in rats administered 5% Calcium Pantothenate in diet–4 of 5 rats died in 2 days from severe diarrhea; for toxicokinetics results from this study see Table 6	[64]
SUBCHRONIC (≥ 3 MONTHS TO < 6 MONTHS EXPOSURE)							
ANIMAL							
Oral							
DL-Panthenol	Rat/ CR	n = 6/sex/dose	0, 20, 50, 200 mg/kg/day (water vehicle)	90 days	Animals dosed daily in drinking water available *ad libitum*; experiment performed in accordance with OECD TG 408 (Repeated Dose 90-Day Oral Toxicity in Rodents); control animals receiving no test substance were used	NOAEL of 200 mg/kg/day was reported; mortalities observed (1 male at 200 mg/kg/day, 2 males at 50 mg/kg/day, 1 male at 20 mg/kg/day; 4/10 control males, 1/14 control females) were considered to be not treatment-related by study researchers (no further details provided as to cause of death); mild eosinophilia observed in treatment animals, but were considered insignificant; liver weights were decreased in males (20 and 200 mg/kg/day) compared to controls, but this was not significant	[6]

Table 8. Short-Term, Subchronic, and Chronic Toxicity Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
D-Calcium Pantothenate	Rat/ CB	n = 6/sex/group	20, 50, 200 mg/kg/day	90 days	Animals dosed daily in diet; controls were used (no further details provided)	Growth, mortality, hematological results, histopathological findings, vital organ weights were unaffected by treatment; mild eosinophilia observed in some treated animals, but study investigators could not confirm it was related to treatment; adrenal gland weights were higher in males (24% increase in 50 mg/kg/day group) and lower in females (17% decrease in 200 mg/kg/day group) of treated animals compared to controls; slight hyperemia of spleen noted in some animals dosed with 200 mg/kg	[6]
CHRONIC (≥ 6 MONTHS EXPOSURE)							
ANIMAL							
Oral							
D-Calcium Pantothenate	Dogs	n = 6	50 mg (~5 mg/kg)	180 days	Animals dosed daily in diet (no further details provided)	No toxicity reported	[12]
D-Calcium Pantothenate	Monkey	n = 4	1 g (250 to 400 mg/kg)	180 days	Animals dosed daily in diet (no further details provided)	No toxicity reported	[12]
D-Calcium Pantothenate	Rat	n = 20	50 or 200 mg (~500 or 2000 mg/kg)	190 days	Animals dosed daily in diet (no further details provided)	No toxicity reported; normal growth; no gross or microscopic organ changes seen in necropsies	[12]
Calcium Pantothenate	Mouse/C-57 black	n = 33 (treated males and females) n = 41 (control animals)	300 µg (~20 mg/kg)	Mean life span 653 days (treated) Mean life span 550 days (controls)	Animals dosed daily in drinking water; untreated controls were used (no further details provided)	Statistically significant increase (~20%) in mean life span of treated animals compared to controls; at 250 days old, body weight of treated animals were slightly higher than controls (no further details provided)	[12]

NOAEL = No-Observed-Adverse-Effect-Level

Table 9. Developmental and Reproductive Toxicity (DART) Studies

Test Substance(s)	Species/ Strain	Test Population- Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
IN VIVO						
Oral						
DL-Panthenyl Ethyl Ether	Rat/ Crl:CD(SD)	n = 6 females/group	0, 500, 750, 1000 mg/kg/day (water vehicle)	Animals were dosed by gavage 1x/day on days 6 through 19 of gestation using GLP and in accordance with OECD TG 421 (Reproduction/ Developmental Toxicity Screening Test); this was a screening study for OECD 414; controls were used	Maternal and developmental NOAEL ≥ 1000 mg/kg/day was reported	[6]
D-Calcium Pantothenate	Rat	n = 20	50 or 200 mg/day (~500 or 2000 mg/kg/day)	Adult animals dosed daily in diet; weaned offspring from the 50 mg treatment group were dosed with 50 mg daily; controls were used (no further details provided)	No toxicity reported; offspring weight increases were the same as controls (no further details provided)	[12]
Calcium Pantothenate	Rat/ Wistar	n = not specified, females	1 mg/day (5 mg/kg/day)	Adult rats were dosed daily in diet as indicated before mating and during gestation (no further details provided)	No teratogenicity or fetotoxicity was reported	[12]
Calcium Pantothenate	Rat	n = not specified, females	Stock diet: equivalent to 450 to 600 µg/ day Pantothenic Acid Synthetic diet: equivalent to 0, 100, or 1000 µg/day Pantothenic Acid	Pregnant rats were dosed with Calcium Pantothenate in diet as indicated (no further details provided)	Study investigators noted that Calcium Pantothenate crosses the placenta as a result of increased Pantothenic Acid concentrations in fetal blood and tissues; offspring from rats fed stock diet had 450 µg/ 100 ml (blood values) of Pantothenic Acid; offspring from rats fed synthetic diet had 295, 500, and 2200 µg/ 100 ml, respectively, of Pantothenic Acid as measured in blood	[12]

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 10. Genotoxicity Studies

Test Substance(s)	Species/ Strain or Sample Type	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
			IN VITRO		
DL-Panthenol	*Salmonella typhimurium*/ TA1535, TA100, TA1537, TA98; *Escherichia coli*/ WP2 uvrA	0, 20, 100, 500, 250, 5000 µg/plate (water vehicle) With and without metabolic activation	Using GLP an Ames test was performed; exposure duration was 48-72 h @ 37 °C in dark; negative, positive and vehicle controls were used A preincubation Ames test was performed similarly as above except that it included a preincubation period of 20 min (@ 37 °C) prior to exposure duration of 48-72 h @ 37 °C in dark	Non-mutagenic	[7]
D-Panthenol	*S. typhimurium*/ TA1535, TA1537, TA1538, TA98, TA100; *Escherichia coli*/ WP2 (uvrA)	33, 100, 333, 1000, 3333, 10,000 µg/plate With and without metabolic activation	Ames test and *E. coli* WP2 assays were performed; negative and positive controls were used	Non-mutagenic	[16]
D-Panthenol (99.2% pure)	Chinese hamster, HPRT locus in V79 cells	130, 260, 520, 1040, 2080 µg/ml (water vehicle) With and without metabolic activation	Mammalian cell gene mutation assay was performed using GLP in accordance with OECD TG 476; cells exposed to treatment for 4 hours (with and without activation) and for 24 hours (without activation); vehicle and positive controls were used	Non-mutagenic	[66]
D-Panthenol (99.2% pure)	Human lymphocytes	679.2, 1188.6, 2080.0 µg/ml (vehicle: culture medium with 10% deionized water) With and without metabolic activation	Mammalian chromosomal aberration test performed using GLP in accordance with OECD TG 473; cells exposed to treatment for 4 hours (with and without activation) and for 22 hours (without activation); vehicle and positive controls used	Non-clastogenic	[66]
DL-Panthenyl Ethyl Ether	Chinese hamster/ lung fibroblasts, HPRT locus in V79 cells	150, 300, 600, 1200, 2400 µg/ml (DMSO vehicle) With and without metabolic activation	Mammalian cell gene mutation assay was conducted using GLP in accordance with OECD 476; cells exposed to treatment for 4 hours in one test and 24 hours in another test; vehicle and positive controls were used	Negative for genotoxicity (non-mutagenic); cytotoxicity was reported in second experiment at 300 µg/ml and above; controls performed as expected	[6]
DL-Panthenyl Ethyl Ether (99.2% pure)	*S. typhimurium*/ TA1535, TA1537, TA1538, TA98, TA100; *Escherichia coli*/ WP2 (uvrA)	50, 100, 500, 1000, 5000 µg/plate With and without metabolic activation	Ames test and *E. coli* WP2 assays were performed using GLP in accordance with OECD TG 471; negative and positive controls were used	Non-mutagenic	[66]
DL-Panthenyl Ethyl Ether (99.2% pure)	Human peripheral lymphocytes	333 to 5000 µg/ml (no further details provided) With and without metabolic activation	Mammalian chromosomal aberration test performed using GLP in accordance with OECD TG 473; cells exposed to treatment for 24 and 48 hours without activation and 3 hours with activation; vehicle (not specified) and positive controls used	Non-clastogenic	[66]

Table 10. Genotoxicity Studies

Test Substance(s)	Species/ Strain or Sample Type	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
D-Panthenyl Triacetate	*S. typhimurium*/ TA97a, TA98, TA100, TA102, TA1535	50, 100, 500, 1000, 5000 µg/plate With and without metabolic activation	Ames test was performed (non-GLP); solvent and positive controls were used	Non-mutagenic; controls performed as expected; there was no cytotoxicity reported	[70]
D-Sodium Pantothenate	*Saccharomyces cerevisiae*/ D4; *S. typhimurium*/ TA1535, TA1537, TA1538, TA98, TA100	Not specified	A microbial plate suspension assay was performed with and without metabolic activation (no further details provided)	Non-mutagenic	[12]
Sodium Pantothenate	*S. typhimurium*; TA97A and TA102	0.1-10 mg/plate With and without metabolic activation	Ames test was performed (preincubation method used)	Non-mutagenic	[71]

GLP = Good Laboratory Practice; HPRT= Hypoxanthine Phosphorybosyl Transferase; non-GLP = non-Good Laboratory Practice; PCR = Polymerase Chain Reaction

Table 11. Dermal Irritation and Sensitization Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
IRRITATION						
Animal						
D-Panthenol; 5% (w/w) in cream formulation	Rabbit/ New Zealand White	n = 3 (1 male, 2 females)	0.5 g applied neat	Test substance applied (semi-occlusive) to shaved skin (6 cm^2) for 4-h exposure duration using GLP in accordance with OECD TG 404 (Acute Dermal Irritation/ Corrosion) and EU Method B.4 (Acute Toxicity: Dermal Irritation/ Corrosion); treatment removed with water 4 hours post-application; animals were observed for 72 hours	Non-irritating; no erythema or edema; no deaths; 1 female showed slight body weight loss	[6,7]
D-Panthenol and DL-Panthenol (cosmetic grade)	Rabbit/ New Zealand White	n = 3/sex	0.5 ml of each test substance (further information on concentration not provided)	Test substance applied under occlusion to shaved skin, intact and abraded, for 4 h; coverings were then removed and skin examined; test site was washed with water and skin examined at 24 and 48 hours	Non-irritating; test substances caused very slight erythema on intact and abraded skin of 1 rabbit, but it resolved within 24 h	[66]
D-Panthenol	Rabbit/ New Zealand White	n = 3 (2 males, 1 female)	0.5 g of perfumed cream formulation (concentration not specified)	Test substance applied (semi-occlusive) to a 6 cm^2 area of shaved, intact skin for 4 h using GLP in accordance with OECD TG 404; 4 h post-application patches removed and skin washed with water; skin examined 1, 24, 48, and 72 h after test substance removal	Non-irritating; mean grade 0.3 erythema noted	[66]

Table 11. Dermal Irritation and Sensitization Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
D-Panthenol	Rabbit/ New Zealand White	n = 3 (1 male, 2 females)	0.5 g of unperfumed cream formulation (concentration not specified)	Test substance applied (semi-occlusive) to a 6 cm^2 area of shaved, intact skin for 4 h using GLP in accordance with OECD TG 404; skin was washed with water after patch removal; skin examined 1, 24, 48, and 72 h after test substance removal	Non-irritating	66
DL-Panthenyl Ethyl Ether (99.2% pure)	Rabbit/ New Zealand White	n = 3 males	0.5 ml of test substance (concentration not specified)	Test substance applied (semi-occlusive) to a 6 cm^2 area of shaved, intact flank skin for 4 h using GLP in accordance with OECD TG 404; a patch free of test substance was applied to shaved contralateral flank as control; skin was washed with water after patch removal r; skin examined 1, 24, 48, and 72 h after test substance removal	Non-irritating; no deaths or signs of toxicity	66
Panthenyl Ethyl Ether; 0.125% in leave-on hair conditioner	Rabbit/ New Zealand White	n = 5/sex/group	Test substance applied neat	Test substance (2 ml/kg) applied 5 days/week for 28 days to shaved skin (skin abraded in test and control groups on days 1-6 and 10-12, but discontinued on remaining study days for both groups because of fissuring in test group); negative controls treated with deionized water; exposure time 7 h/day with restraining collars; animals killed at study termination; necropsy and gross and microscopic pathologies performed	By end of first week, slight-to-moderate erythema , edema, atonia, desquamation, and fissuring was observed in most treated animals; all signs of irritation cleared by day 13 except for slight erythema and desquamation, which lasted throughout the study; on days 17-28 red raised areas noted in 1 treated male; microscopic analysis showed mild acanthosis in all treated males and females; trace chronic dermatitis seen in 2 of 5 treated males and 4 of 5 treated females; no irritation exhibited in controls; toxicological effects summarized in Table 8	68
				Human		
D-Panthenyl Triacetate; 10% in polyglycol P-4000, pH 6.2	Human	n = 54 (16 to 60 years old, males and females, 1/3 of subjects were noted to have sensitive skin)	Test substance applied neat	A closed epicutaneous patch test was performed by applying 0.1 g of test substance into a plaster chamber which was secured to the volar forearm skin for 24 h; chamber was removed after 24 h and skin assessed for reactions; a repeat assessment of skin was conducted at 48 h to detect any additional reactions	No skin reactions observed	79

Table 11. Dermal Irritation and Sensitization Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
SENSITIZATION						
Animal						
DL-Panthenol	Guinea Pig/ Pirbright-Hartley	Range-Finding Study: n = 4 Main Study: n = 20 (test group) and 10 (controls) Positive Control Study: n = 20 (test group) and 10 (controls)	Range-Finding Study: 25%, 50%, and 75% in distilled water, and undiluted Main Study: Undiluted Positive Control Study: alpha-hexylcinnamaldehyde techn. 85%	Buehler Test performed in accordance with OECD TG 406 (Skin Sensitization) and EU Method B.6 (Skin Sensitization); range-finding study performed on shaved flank skin (occlusive) for 2 exposures (6 h duration, 1 per week); skin examined 6 and 30 hours post-application *Induction*: 0.5 ml of test substance was applied (epicutaneous, occlusive) to anterior left flank for 6-h exposure duration on days 0, 7, and 14; skin was examined 24 hours after patch removal *Challenge*: 0.5 ml of test substance was applied (epicutaneously, occlusive) to right flank for 6-h exposure duration on day 28; skin was examined 24- and 48-h after patch removal Positive Control Study: Conducted using GLP and testing guidelines indicated above	Range-Finding Study: Non-irritating at all concentrations Main Study: Non-irritating (induction); non-sensitizing (challenge) Positive Control Study: Results were as expected	[7]
D-Panthenol; 2.5% in lotion	Guinea Pig/Albino	Preliminary Study: n = 2 for intradermal injection, n = 4 for topical application Main Study: n = 10/sex in treatment group; n = 5/sex in control group	Preliminary Study Intradermal injection: 0.5, 1, 3, 5% test lotion in saline Topical application: 25, 50, 70, 100% test lotion in saline Main Study-Induction Intradermal injection: Freund's complete adjuvant 50:50 with saline, 5% test lotion in saline, and 5% test lotion in saline emulsified with 50:50 Freund's complete adjuvant and saline Topical application: 100% test lotion Main Study-Challenge Topical application: 100% test lotion	Guinea pig maximization test was conducted in accordance with OECD TG 406 (Skin Sensitization) *Preliminary range-finding study*: intradermal injection into shaved flank skin; skin was examined 24 h post-injection; topical application of test lotion to shaved flank skin under occlusive conditions for 24 h; patch removed 24 h post-application and skin examined then and again 24 and 48 h following patch removal *Main Study-Induction*: 3 pairs intradermal injections to shaved dorsal skin performed with Freund's complete adjuvant and/or test lotion as indicated (controls treated without test lotion); 1 week later, topical application performed on shaved skin at injection sites and occlusive patches 4x4 cm^2 secured in place for 24 h (controls were similarly treated without test lotion); patches removed 24 h post-application and skin examined *Main Study-Challenge*: 2 weeks following topical induction, challenge application to skin conducted under occlusive conditions for 24 h then patches removed and skin examined (controls had vehicle only); 2 weeks after first challenge re-challenge was similarly performed (controls treated with test lotion same as test group to limit false positives)	Non-Sensitizing	[66]

Table 11. Dermal Irritation and Sensitization Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
D-Panthenol; 5% in test ointment	Guinea Pig/ Himalayan White Spotted	Induction: n = 20 in test group; n = 10 controls	Induction: 0.1 ml of test ointment Challenge: 0.025 ml of test ointment	An open epicutaneous test performed as indicated below Induction: test ointment applied to same 8 cm^2 shaved flank skin area 1x/day for 5 days/week for 4 weeks; skin examined daily; untreated controls used Challenge: on days 30 and 44, challenge applications applied to 2 cm^2 skin area in treated and control animals; skin examined 24 and 48 h post-application	Non-sensitizing; no signs of irritation observed	[66]
D-Panthenol; 5% in test ointment	Guinea Pig/ Himalayan White Spotted	Induction: n = 20 in test group; n = 10 controls	Induction: 0.1 ml of test ointment Challenge: 0.025 ml of test ointment	An open epicutaneous test using same procedure as described above	slight to well-defined primary irritant potential; weak sensitizing potential after single application slight skin reactions observed; with repeated applications slight-to-well-defined inflammatory skin reactions noted; following challenge phase a substantial difference noted in frequency of skin reactions in treated animals compared to controls	[66]
Panthenol; 5% in a test solution	Guinea Pig/ Albino	n = 20 females in test group; n = 10 females in control group	Induction: test substance applied epicutaneously; intradermal administration of 5% ethanolic dilution of test substance Challenge: 5%, 10%, and 30% ethanolic dilutions of test substance	Guinea Pig Maximization Test (per Magnusson and Kligman) performed using GLP in accordance with OECD TG 406 (1981) Rechallenge performed in test group animals using 5% Panthenol in test solution (number of animals included and use of control animals in rechallenge not specified)	Non-sensitizing; no skin reactions at 24 and 48 h post-challenge in test group; primary skin irritation reactions of short duration to 5% Panthenol in test solution observed in 3 animals at 24 h reading during rechallenge; no details provided as to whether 5% Panthenol in a test solution caused any reactions during induction	[80]

Table 11. Dermal Irritation and Sensitization Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
DL-Panthenyl Ethyl Ether	Guinea Pig/ Himalayan albino	Prelim Study: n = 5 females Experimental group (induction and challenge): n = 10 females Negative control group (induction and challenge): n = 5 females	*Induction*: intradermal injection (5%-10% test substance); epicutaneous application (100% test substance) *Challenge*: epicutaneous (25%, 50%, or 100% test substance in distilled water, w/w)	Guinea pig maximization test was conducted using GLP in accordance with OECD TG 406; positive controls were used; a preliminary range-finding study was performed (no further details provided) *Induction (negative controls treated similarly to experimental animals except without test substance)*: On day 1, animals were intradermally injected (3 pairs of injections) in shaved scapular area (0.1 ml/site) with 50:50 Freund's Complete Adjuvant: water, 5% test substance in physiological saline (w/w), and 10% test substance in 50:50 mix of Freund's Complete Adjuvant On day 7, animals were rubbed (in shaved scapular region) with 10% sodium-dodecyl-sulfate in petroleum to increase sensitization potential On day 8, 0.5 ml of 100% test substance were applied to shaved area between sites of injection, which was secured in place with a patch (dry patch used for controls); 48 hours post-application patch was removed, test substance wiped from skin, and skin evaluated *Challenge (negative controls and experimental animals treated the same)*: On day 22, test substance (0.05 ml) was applied to shaved flank skin and secured in place with a patch (semi-occlusive); 24 hours post-application the patch was removed and test substance wiped from skin; skin evaluated at 24 and 48 hours post-application	Non-sensitizing; most experimental animals showed slight skin irritation to test substance during epicutaneous induction; positive controls performed as expected	[6]
Panthenol; 5% in a crème product or 5% in a spray product	Mouse/ HsdWin: NMRI	n = 6 females/ group	Spray and crème test substances applied neat; same concentrations used in induction and challenge phases	LLNA/IMDS performed using GLP in accordance with OECD TG 406 (1992) and 429 (2010); test substances applied epicutaneously as follows (50 µl applied to flank during induction and 25 µl to ear during challenge, where applicable): Group 1-acetone/olive oil, 4:1, to flank (days 1-3) and to ears (days 15-17); Group 2-acetone/olive oil 4:1 to flank (days 1-3) and spray to ears (days 15-17); Group 3-spray to flank (days 1-3) and to ears (days 15-17); Group 4-acetone/olive oil, 4:1, to flank (days 1-3) and crème to ears (days 15-17); Group 5-crème to flank (days 1-3) and to ears (days 15-17)	Non-sensitizing (no induction of treatment-specific memory cells observed); study authors stated that cell counts and ear weights in treated animals, compared to controls, did not reach positive levels defined for mouse strain	[81]

Table 11. Dermal Irritation and Sensitization Studies

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
			Human			
D-Panthenol	Human	n = 23 patients with allergic dermatoses; n = 7 healthy subjects (13 female and 17 male)	Test formulation containing 5% D-Panthenol in a hydrogel preparation also containing 2.5% hydroxyethylcellulose, 0.4% sorbitol, 0.066% methylparaben, 0.033% propylparaben, 0.185% disodium phosphate, 0.38% potassium dihydrogen phosphate, and 91% distilled water Another test formulation contained 5% D-Panthenol in liquid drops containing sorbitol and preservatives in water	Epidermal patch tests were performed on subjects to evaluate hydrogel formulation and liquid drops (no further details provided)	Patch tests were negative for allergic dermatoses patients and healthy subjects	[77]
D-Panthenol; 5% in a cosmetic baby product	Human	n = 100	Test substance applied neat	HRIPT performed under occlusion in accordance with Marzulli-Maibach Method	Non-sensitizing, non-irritating	[82]
Panthenol; 5% in a leave-on product	Human	n = 113	Test substance applied neat (equivalent to 2.5 mg/cm^2 test substance)	Test substance applied to 2 cm^2 skin area under occlusion for 24 h in HRIPT; 9 patches applied during 3-week induction period followed by 2 weeks rest prior to challenge (at previously untreated skin site); challenge readings occurred at 24, 48, 72, and 96 h	Non-sensitizing; no reactions observed during induction; 1 subject exhibited low level reaction (erythema) during challenge	[85]
Panthenol; 3% in test gel	Human	n = 106	Test substance applied neat	Test gel applied to upper portion of arm and secured under occlusion for 24 h, then subject removed patch and washed skin (no other products applied to test skin sites during the testing period); induction phase lasted 4 weeks (~3 treatments/week); approximately 1 week between induction and challenge; same procedure for test gel application followed for challenge as during induction; skin examined for reactions on days 2 and 4 post-challenge	Non-sensitizing; 1 instance of mild erythema reported during induction	[83]
Panthenol; 6% in test gel	Human	n = 99	Test substance applied neat	Same procedure as described above	Non-sensitizing; mild erythema noted at test sites in 1 subject 4 days post-challenge, but study researchers indicated reaction caused by irritation; instances of mild erythema observed rarely during induction	[84]
Panthenyl Ethyl Ether; 0.25% in a rinse-off shampoo product	Human	n = 106	Rinse-off shampoo product diluted to 2% in distilled water; concentration of Panthenyl Ethyl Ether in this dilution product was 0.005%, equivalent to 0.0000025 mg/cm^2 Panthenyl Ethyl Ether applied to skin in HRIPT	Test substance applied to 2 cm^2 skin area under occlusion for 24 h in HRIPT; 9 patches applied during 3-week induction period followed by 2 weeks rest prior to challenge (at previously untreated skin site); challenge readings occurred at 24, 48, 72, and 96 h	Non-sensitizing; low level reactions (minimal-to-definite erythema, no edema) observed in 48 subjects during induction; 5 subjects exhibited low level reactions (minimal-to-definite erythema, no edema) during challenge	[86]

EU = European Union; GLP = Good Laboratory Practice; HRIPT = Human Repeat Insult Patch Test; LLNA/IMDS = Local Lymph Node Assay/ Integrated Model for the Differentiation of Skin reactions; non-GLP = non-Good Laboratory Practice; OECD TG = Organization for Economic Co-operation and Development Test Guideline

Table 12. Ocular Irritation

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
			IN VITRO			
D-Panthenyl Triacetate (> 95% pure)	Bovine	Corneas	Undiluted	Ocular irritation test performed using GLP in accordance with OECD TG 437 (Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants)	Non-irritating based on lack of opacity and absence of cornea permeability; controls performed as expected	[87]
			IN VIVO			
D-Panthenol	Rabbit/ Vienna White	n = 2	Undiluted	A single, 50 µl application of test substance instilled into conjunctival sac of one eye (no rinsing) in accordance with OECD TG 405(Acute Eye Irritation/ Corrosion); other eye served as saline-treated control; animals observed for 8 days after treatment	Non-irritating; slight corneal irritation noted in both treated eyes, but resolved within 2 days	[6,7]
D-Panthenol; 5% (w/w) in cream	Rabbit/ New Zealand White	n = 3	Test substance applied neat	A single, 0.1 g application of test substance instilled into conjunctival sac of one eye (no rinsing) in accordance with OECD TG 405; other untreated eye served as control; animals observed for 72 h	Non-irritating; slight conjunctival redness (primary irritation scored 0.25 on a 0 to 3 scale) observed in all treated eyes, but resolved within 24 h	[6]
D-Panthenol and DL-Panthenol (cosmetic grade)	Rabbit/ New Zealand White	n = 3/group	Undiluted	A single, 0.1 ml application of D-Panthenol instilled into conjunctival sac of one eye while other eye was similarly treated with DL-Panthenol; eyes of 3 animals washed 5 min post-application (group 1) and remaining eyes washed 24 h after application (group 2); eyes examined 1, 24, 48, and 72 h and up to 21 days post-application; use of controls not specified	Non-irritating; all eyes treated with D-Panthenol or DL-Panthenol showed slight conjunctival redness, which reversed in most animals by 7 days and all animals by 21 days; slight corneal opacity observed in eyes treated with D-Panthenol or DL-Panthenol, but resolved by 21 days (no further details provided)	[66]
D-Panthenol; 5% in nose ointment	Rabbit/ New Zealand White	n = 6	Test substance applied neat	A single, 0.1 ml application of test substance instilled into conjunctival sac of one eye (no rinsing) using GLP in accordance with OECD TG 405; untreated eye used as control; eyes examined 1, 24, 48, and 72 h and up to 14 days post-application	Non-irritating; mild-to-moderate conjunctival redness observed in treated eyes (Draize scores of 1.3 and 0.3 after 1 and 24 h, respectively), which reversed by 48 h	[66]
D-Panthenol	Rabbit/ New Zealand White	n = 3 (2 males, 1 female)	D-Panthenol in a perfumed cream (concentration not specified)	A single, 0.1 g application of test substance instilled into conjunctival sac of one eye (no rinsing) using GLP in accordance with OECD TG 405; untreated eye used as control; eyes examined 1, 24, 48, and 72 h post-application	Very slight irritation potential (Draize primary score 0.58); all treated eyes showed conjunctival redness (grade 1) at 1 and 24 h; chemosis (grade 1) noted in one treated eye at 1 h; conjunctival effects resolved by 48 h	[66]
D-Panthenol	Rabbit/ New Zealand White	n = 3 (1 male, 2 females)	D-Panthenol in an unperfumed cream (concentration not specified)	A single, 0.1 g application of test substance instilled into conjunctival sac of one eye (no rinsing) using GLP in accordance with OECD TG 405; untreated eye used as control; eyes examined 1, 24, 48, and 72 h post-application	Non-irritating; all treated eyes showed slight conjunctival redness that resolved by 24 h	[66]
DL-Panthenyl Ethyl Ether (99.2% pure)	Rabbit/ New Zealand White	n = 3 males	DL-Panthenyl as a viscous liquid (concentration not specified)	A single, 0.1 ml application of test substance instilled into conjunctival sac of one eye (no rinsing) using GLP in accordance with OECD TG 405; untreated eye used as control; eyes examined 1, 24, 48, and 72 h and up to 14 days post-application	Non-irritating; 2 treated eyes showed iridic irritation (Draize scale, grade 1) at 1 h that resolved by 24 h; all treated eyes exhibited redness (grade 2), swelling (grade 1-2), and discharge (grade 1-2) that reversed in 2 animals by 7 days and in third animal by 14 days; study researchers attributed clinical effects to physical properties of viscous test substance rather than toxicity	[66]

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

Table 13. Case Reports

Test Substance(s)	Subjects	Product	Patient History/Procedure	Observations/Results	Reference
			DERMAL		
D-Panthenol	n = 1 (child, 11 years old), 12 control patients	75% D-Panthenol in a facial wipe 30% D-Panthenol as a facial wipe constituent	A child used a 75% D-Panthenol facial wipe to remove make-up from her face, which resulted in eczema 1 day later; a follow-up patch test (using a baseline series, facial series, and the facial wipe with 75% or 30% D-Panthenol) on her back (with Finn Chambers® on Scanpor® tape) was performed; control patients were also tested for D-Panthenol in the 30% facial wipe formulation	The child had a positive allergic contact dermatitis reaction (on days 2 and 4) to the 75% D-Panthenol facial wipe and to 30% D-Panthenol formulation (controls patch testing was negative for 30% D-Panthenol)	[93]
D-Panthenol	n = 1 (child, 8 years old)	Cream formulation containing test substance	2 days following application of a facial moisturizing cream, pustular irritant contact dermatitis was reported on face and neck of child; routine biochemistry of blood was performed; skin biopsy of affected skin was performed	No fever or systemic symptoms were reported; blood biochemistry was normal; topical corticosteroids were applied to child's affected skin; after lesions healed, patch testing (European Standard Series including D-Panthenol) was conducted, but found to be negative	[103]
D-Panthenol	n = 1 (55 year old woman, healthy, taking no medications, history of hay fever)	Hydrating lotion containing 2.5% cocamidopropyl PG dimonium chloride phosphate (aqueous) and 0.5% D-Panthenol (aqueous), any other ingredients were not specified	A hydrating lotion was applied to face/neck region; 3 episodes (each lasting 4 days) of severe erythema and face, eyelids, and neck edema were reported; patient responded to treatment with oral corticosteroids; patch tests (European standard series; supplementary, cosmetic, and hairdressing series) were conducted; additional patch tests using the subject's hydrating lotion and individual ingredients in lotion were performed	Study researchers noted that the cause of the allergic reaction was unclear (subject attributed it to perfumes); patch testing results showed a weak 1+ reaction to subject's hydrating lotion on days 2 and 4; additional patch testing exhibited a 2+ reaction to 2.5% cocamidopropyl PG dimonium chloride phosphate and 1+ reaction to 0.5% D-Panthenol on day 4; follow-up patch testing of the hydrating lotion on the subject's arm revealed a stronger 1+ reaction (no vesicles, but more papules) on days 2 and 4	[94]
Panthenol	n = 1 (53 year old woman)	Amount of Panthenol in conditioner not specified	Patient had history of allergic contact dermatitis from Myroxylon Pereirae, nickel, and benzoyl peroxide; 1 min after using conditioner containing Panthenol, patient reported facial edema, erythema, pruritus (on trunk); symptoms improved an hour after washing off conditioner; patient recalled experiencing pruritus at hairline when using hair coloring products containing Panthenol at hair dresser; skin allergy testing on volar forearm was performed for 30 min and skin prick testing conducted (for both tests 30% Panthenol and 1:5 mix of conditioner/water were used); positive and negative controls were used for skin prick test	Skin allergy testing on patient's forearm was negative; 2 to 5 min following skin prick test patient showed positive reactions including pruritus, erythema, and wheals; skin test reading (after 20 min) were Panthenol (3+) and conditioner/water mix (1+) based on Kanerva et al. rating system; negative control performed as expected; by 30 min post-pricking, Panthenol showed same reaction as positive histamine control; patient stopped using conditioner with Panthenol; within 1 month following prick testing, patient's hair dresser used Panthenol-containing hair coloring on her again and patient exhibited pruritus and edema at hairline, but no other urticarial responses were reported; study researchers speculated that contact urticaria may be the result of a Crotein Q-type allergic reaction because Panthenol is a coenzyme derived from β-alanine	[95]
D-Panthenol	n = 2	Topical cream containing 5% Panthenol	Use of cream caused allergic contact dermatitis in 2 patients; cream also caused eczema in patient 1 (cream used on lower extremities for treatment of stasis dermatitis); patient 2 used cream on face for treatment of radiotherapy (for basal cell carcinoma) effects; both patients discontinued use of cream and were treated with topical steroids and/or oral antihistamines; both patients were patch tested with Finn Chambers® and Scanpor® tape (International Contact Dermatitis Research Group criteria used) to evaluate Portuguese baseline series and ingredients in Panthenol-containing cream	On days 2 and 4 of patch testing, patient 1 and 2 exhibited positive reactions to topical cream ingredients, and especially to D-Panthenol; the study researchers' opinion was that use of D-Panthenol in topical formulations will lead to increases in allergic contact dermatitis and possibly systemic reactions	[96]

Table 13. Case Reports

Test Substance(s)	Subjects	Product	Patient History/Procedure	Observations/Results	Reference
D-Panthenyl Ethyl Ether	n = 1 (44 year old woman), 10 control subjects	Hair lotion contained ethanol, castor oil, 10% lactic acid, 30% D-Panthenyl Ethyl Ether, 2 dyes, 1 UV absorber, 14 perfume ingredients	A woman applied hair lotion and experienced relapsing hair lotion dermatitis of the face (on temples, ears, and neck); patch tests using the hair lotion and with another series (including a fragrance mixture) were performed on the woman; control subjects were also patch tested	Patch testing for the woman was strongly positive for 30% D-Panthenyl Ethyl Ether and mildly positive for 10% lactic acid; patch testing results for controls were negative for D-Panthenyl Ethyl Ether	[97]
			ORAL		
D-Panthenol	n = 1 (30 year old female)	B vitamin complex tablets containing 3.33 mg of D-Panthenol	Anaphylactic symptoms (facial edema, dyspnea, dizziness, faintness) developed 20 min after patient consumed breakfast (including consuming B vitamin complex); for a few weeks before this incident patient experienced swollen eyelids, coated tongue, and itching (lips, face) after eating B vitamin complex at breakfast; a few weeks following anaphylactic reaction, skin scratch allergy testing (using B vitamin complex tablets dissolved on the skin in a drop of 0.9% sodium chloride) was conducted on patient (5 mm arm skin area); potential food allergies were evaluated using a skin prick test and scratch tests of food extracts and preservatives; patient had no prior history of pollinosis or atopic dermatitis	Patient's B complex vitamin tablets showed positive allergic reaction during skin testing; patient also had systemic allergic reaction (tightness in throat, facial edema, breathlessness) 15 min following scratch testing; additional scratch testing was conducted during emergency conditions and showed that vitamins B1, B2, B6, B12, and folic acid were negative compared to 10 mg/ml histamine hydrochloride (positive control); D-Panthenol (5% in Vaseline used as test substance) was found to be the source of allergen by a friction test, which resulted in pruritus and erythema on skin, lip pruritus, coated tongue; patient recalled that previously a sun cream containing D-Panthenol caused pruritus and urticaria;	[98]
Pantothenic Acid	n = 1 (76 year old woman, Caucasian)	300 mg/d Pantothenic Acid (vitamin B_5), 10 mg/d vitamin H (biotin), and trimetazidine	A woman took trimetazidine (6 years), and vitamin H (2 months) and Pantothenic Acid (2 months) to treat alopecia and developed eosinophilic pleuropericarditis	Study researchers speculated the cause of the condition to be related to the vitamin H and Pantothenic Acid treatment, after other causes were eliminated; the condition was reversible following discontinuation of vitamin H and Pantothenic Acid	[99]

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6

Final Report on the Safety Assessment of Panthenol and Pantothenic Acid

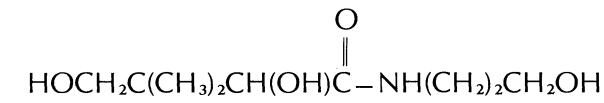
Panthenol is the alcohol analogue of Pantothenic Acid (vitamin B_3). The LD_{50} for D-Panthenol administered orally to mice was 15 g/kg. No toxicological effects were associated with the subchronic and/or chronic oral administration of Panthenol to rats. Minimal cutaneous hyperkeratosis was noted in rats in a subchronic dermal study of creams containing 0.2% Panthenol. In ocular irritation studies involving rabbits, concentrations up to 2% produced, at most, slight conjunctival redness and chemosis. Panthenol (100%) and products containing Panthenol (0.5% and 2%) administered to rabbits during skin irritation studies caused reactions ranging from no skin irritation to moderate-to-severe erythema and well-defined edema. Neither teratogenic nor fetotoxic effects were noted in the offspring when rats were fed calcium pantothenate prior to mating and throughout gestation. Skin irritation and sensitization studies of cosmetic products at concentrations up to 0.5% indicated that they were, at most, mild irritants but did not induce allergic sensitization. No test substance-related observations of eye irritation were reported for 23 subjects receiving instillations of products containing 0.1% Panthenol. Mutagenicity and carcinogenicity data were not available for the safety assessment of Panthenol. It is noted that the level of this ingredient required by humans exceeds the amount that could be absorbed from the low concentrations used in cosmetic products. The human metabolic requirement would preclude the likelihood of genotoxicity. It is concluded that Panthenol and Pantothenic Acid are safe as presently used in cosmetics.

CHEMISTRY

Panthenol is the alcohol analogue of Pantothenic Acid (vitamin B_3), both having equivalent biological activity.[1] The oxidation of Panthenol to Pantothenic Acid occurs in the skin.[2]

Definition and Structure

Panthenol conforms to the formula[5]:



Synonyms for Panthenol are dexpanthenol, pantothenyl alcohol, and pantenyl alcohol.[3-6] D-Panthenol and DL-Panthenol occur in cosmetic products.[5] D-Panthenol is a viscous hygroscopic liquid, whereas DL-Panthenol is a creamy white, crystalline powder.[6,7] Both are freely soluble in water and alcohol, and their solutions are alkaline to litmus.[7] Panthenol absorbs maximally in the 202–206 nm region of the spectrum.[8] Additional properties of Panthenol are shown in Table 1.

Pantothenic Acid is a viscous hygroscopic oil and is available commercially as the D-isomer calcium salt or the DL-racemate.[9,11] The ingredient is stable in neutral solution and is destroyed by heat at either alkaline or acid pH.[11] Panthenol has the advantage of being more stable than Pantothenic Acid at pH 3–5 in solutions.[9] Additional properties of Pantothenic Acid are included in Table 1.

Methods of Production

Panthenol is prepared by the combination of 3-amino-1-propanolamine with the lactone of 2,4-dihydroxy-3,3-dimethyl butyric acid.[4] Similarly, Pantothenic Acid is prepared by the direct condensation of 3-aminopropanoic acid with the lactone of 2,4-dihydroxy-3,3-dimethyl butyric acid.[10]

TABLE 1. Properties of Panthenol and Pantothenic Acid

	D-Panthenol	*DL-Panthenol*	*Pantothenic acid*
Molecular weight	205.25[a]	205.25[a]	219.23[b]
Form	Hygroscopic oil[c]	Crystalline powder[a]	Viscous oil[b]
Boiling point	Decomposes at 118–120°C[c]		Decomposes at 195–196°C[d]
Melting point		64.5°–68.5°C[a]	
Density	1.2[c]		
Refractive index	1.497[c]		
Solubility	Freely soluble in water and alcohol; slightly soluble in ether[e]	Freely soluble in water and alcohol; soluble in chloroform and ether[a]	Soluble in water, ether and benzene[c]
Residue on ignition	Not more than 0.1%[a]	Not more than 0.1%[a]	

[a]Food Chemicals Codex[7]
[b]Windholz[10]
[c]Weast[12]
[d]Altman and Dittmer[13]
[e]Osol[4]

Analytical Methods

Pantothenic Acid and Panthenol may be identified via gas chromatography[11] and paper and thin-layer chromatography.[14]

Impurities

D-Panthenol contains not less than 98.0% D-Panthenol (calculated on the anhydrous basis). DL-Panthenol contains not less than 99.0% DL-Panthenol (calculated on the dried basis).[7] The following impurities have been reported for the D and DL forms of Panthenol[7]:

	D-Panthenol	*DL-Panthenol*
Aminopropanol	1.0% maximum	0.1% maximum
Arsenic (as As)	3.0 ppm maximum	3.0 ppm maximum
Heavy metals (as Pb)	10.0 ppm maximum	10.0 ppm maximum
Water	1.0% maximum	

USE

Purpose in Cosmetics

Panthenol is used in cosmetic products as an emollient and hair conditioner.[15]

The cosmetic formulation listing, which is made available by the Food and Drug Administration (FDA),[16] is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations.[17] Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration. The product formulation listing for Panthenol appears in Table 2. For most of the products listed, the concentration range for Panthenol is >0.1–1%.

Surfaces to which Applied

Cosmetic products containing Panthenol are applied to the skin and hair and may come in contact with the eyes and the oral and nasal mucosae.

TABLE 2. Product Formulation Data (FDA, 1981)

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)			
			>10–25	>1–5	>0.1–1	≤0.1
Eyeliner	396	5	–	–	5	–
Eye shadow	2582	23	–	–	23	–
Eye makeup remover	81	2	–	–	2	–
Mascara	397	10	–	1	9	–
Other eye makeup preparations	230	2	–	–	1	–
Colognes and toilet waters	1120	1	–	–	1	–
Hair conditioners	478	33	–	2	25	6
Hair sprays (aerosol fixatives)	265	17	–	–	3	14
Permanent waves	474	2	–	–	2	–
Hair rinses (noncoloring)	158	1	–	–	1	–
Hair shampoos (noncoloring)	909	25	–	1	19	5
Tonics, dressings, and other hair grooming aids	290	11	–	–	10	1
Wave sets	180	31	–	3	27	1
Other hair preparations (noncoloring)	177	6	–	–	2	4
Blushers (all types)	819	3	1	–	2	–
Face powders	555	1	–	–	1	–
Makeup foundations	740	8	–	–	2	6
Lipstick	3319	27	–	3	16	8
Makeup bases	831	1	–	–	–	1
Rouges	211	1	–	–	1	–
Other makeup preparations (not eye)	530	2	–	–	2	–
Cuticle softeners	32	1	–	–	1	–
Nail creams and lotions	25	1	–	–	1	–
Deodorants (underarm)	239	1	–	–	1	–
Aftershave lotions	282	3	–	–	2	1
Preshave lotions (all types)	29	1	–	–	1	–
Other shaving preparation products	29	1	–	–	1	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	5	–	–	5	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	8	–	–	5	3
Moisturizing skin care preparations	747	22	–	1	15	6
Night skin care preparations	219	14	–	–	14	–
Paste masks (mud packs)	171	1	–	–	–	1

TABLE 2. (Continued)

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)			
			>10–25	>1–5	>0.1–1	≤0.1
Skin fresheners	260	2	–	–	2	–
Other skin care preparations	349	5	–	–	4	1
Suntan gels, creams, and liquids	164	5	–	–	5	–
Other suntan preparations	28	2	–	–	2	–
1981 TOTALS		284	1	11	213	59

Frequency and Duration of Application

Product formulations containing Panthenol may be applied on a monthly basis or as often as several times daily. Many of the products may be expected to remain in contact with the skin for as briefly as 15–30 minutes or for several hours and may be used repeatedly over a period of several years.

Noncosmetic Use

The Select Committee on Generally Recognized as Safe (GRAS) Substances (1978) concluded that there were no reasonable grounds for suspecting any hazards associated with using Panthenol as a food ingredient.[18] The conclusion was based on data from the following types of studies: metabolic studies,[1,19–23] acute studies,[24–26] subchronic studies,[24,26] chronic study,[24] intravenous feeding study,[27] and clinical studies.[28–35] D-Panthenol is generally recognized as being safe when used as a dietary supplement in accordance with good manufacturing practices.[17]

Panthenol is included in the 1984 listing of over-the-counter (OTC) drugs published by the Food and Drug Administration.[36]

Pantothenic Acid exists in all living cells and tissues, and, as a component of coenzyme A, it is involved in the following processes: energy release from carbohydrates, synthesis of acetylcholine and porphyrins, and the synthesis and degradation of fatty acids, sterols, and steroid hormones.[3,37] Foods that usually comprise American diets provide an intake of approximately 7 mg of Pantothenic Acid per day, with a range of 5 to 20 mg per day.[11]

BIOLOGICAL PROPERTIES

Absorption, Metabolism, and Excretion

The following mammalian studies describe the absorption of Pantothenic Acid and the metabolism and excretion of its alcohol analogue, Panthenol.

The concentrations of Pantothenic Acid in food and digesta samples from

sheep fitted with duodenal and ileal re-entrant cannulas were determined via a microbiological assay using *Lactobacillus planarum.*[38] The sheep received a variety of diets. In the duodenum, free Pantothenic Acid was significantly related to the dietary intake of free Pantothenic Acid. The apparent absorption of total Pantothenic Acid was significantly related to the dose, suggesting a passive absorption mechanism.

Following daily doses of 2 mg (20 mg/kg) of D-Panthenol fed to rats for 24 or 45 days or 5–6 months, the total Panthenol content of the liver, kidney, heart, and spleen was measured. At the end of a 6-month feeding period, there was a 20% increase in heart Pantothenate. The content of Pantothenate in the liver and spleen was not increased over controls in any of the groups. There was a large increase in the kidneys, 43%, in the group fed D-Panthenol for 6 months.[24]

The enzymatic oxidation of Panthenol to Pantothenic Acid has been demonstrated in rat liver extract.[1] Panthenol (20 μmol) was administered via peritoneal injection to rats. Approximately 40% of the administered Panthenol was excreted as Pantothenic Acid in the 24-h urine.

Panthenol, incubated in a medium consisting of rat liver extract, NAD, and methylene blue at pH 9.6 was converted partly (approx. 20%) to Pantothenic Acid within 20 minutes.[1]

Results from the oral administration of single doses (1.0 mg each) of Panthenol to rats (weight range: 100–300 g) indicated that 0.80 mg was excreted in the urine.[20] Further, following the intraperitoneal administration of single doses of up to 4 mg of Panthenol, as much as 80% of the doses given was excreted in the urine in 24 h.

The absorption of Pantothenic Acid occurs in the small intestine of humans.[39] Also, in human cells, the oxidation of Panthenol to Pantothenic Acid is known to occur.[40] Gounelle and Richet[41] determined that the ingestion of 100 mg of Panthenol increased urinary concentrations of Pantothenic Acid 10- to 50-fold above normal during a 4-h period after administration.

TOXICOLOGY

Acute Oral Toxicity

The oral administration of D-Panthenol (10 g/kg) to six mice resulted in no deaths; an oral dose of 20 g/kg resulted in 100% mortality[26] (Table 3).

Acute oral toxicity studies were conducted with fasted rats (both sexes) of the Harlan Wistar strain (Table 3). In one study, 10 rats (weight range: 105–130 g) were given a single oral dose (26 ml/kg) of a product containing 0.5% Panthenol. No signs of toxicity were noted during a 7-day period after administration.[42] In the other study, 10 rats (average weight: 113.5 ± 1.3 g) were given a single oral dose (7 ml/kg) of a cream containing 0.5% Panthenol. Slight body thinness was noted in the five male animals after 2 days of testing. No signs of toxicity were observed in females during the 7-day observation period.[43]

TABLE 3. Oral Toxicity of Panthenol

Type of study	*Animals tested*	*Test substance*	*Methodology*	*Results*	*Reference*
Acute oral toxicity	Mice (no. and strain not stated)	100% D-Panthenol	– – –	LD_{50} of 15 g/kg	44
Acute oral toxicity	6 mice (strain not stated)	100% D-Panthenol	Single oral dose of 10 g/kg	No reported deaths	26
Acute oral toxicity	6 mice (strain not stated)	100% D-Panthenol	Single oral dose of 20 g/kg	All animals died	26
Acute oral toxicity	10 Harlan Wistar rats	0.5% Panthenol product	Single oral dose of 26 ml/kg. 7-day observation period	No signs of toxicity	42
Acute oral toxicity	10 Harlan Wistar rats	0.5% Panthenol cream product	Single oral dose of 7 ml/kg. 7-day observation period	Slight body thinness (5 males). No signs of toxicity (5 females)	43
Subchronic oral toxicity	Rats (no. and strain not stated) and dogs (no. not stated)	100% D-Panthenol	Rats: 20 mg/day for 3 months. Dogs: 500 mg/day for 3 months	No histopathological changes	24
Subchronic oral toxicity	12 CB strain rats	100% D-Panthenol	Doses of 20, 50, or 200 mg/day for 90 days	No test substance-related toxicological effects	26
Subchronic oral toxicity	12 CR strain rats	100% D- and DL-Panthenol	Doses of 20, 50, or 200 mg/day for 90 days	No toxicological effects	44
Subchronic oral toxicity	20 Sprague-Dawley weanling rats	100% Panthenol	Doses of 100 mg/kg (10 rats) and 400 mg/kg (10 rats) daily for 13 weeks	No apparent gross lesions. Slight renal toxicity (100 mg/kg group), more marked renal toxicity (400 mg/kg group)	44
Chronic oral toxicity	24 rats (strain not stated)	100% Panthenol	2 mg/day for 6 months	No histopathological changes	24

Subchronic Oral Toxicity

Daily oral doses of 20 mg of Panthenol administered to rats and 500 mg/day to dogs for 3 months produced no toxic effects or histopathological changes[24] (Table 3).

Doses of 20, 50, or 200 mg/kg per day of D-Panthenol in drinking water were fed to young CB strain rats for 90 days[26] (Table 3). Each experimental and control group consisted of six male and six female animals with an average weight of approximately 100 g. There were no major differences in growth, mortality, hematological findings, and final weights of vital organs between experimental and control groups. However, mild eosinophilia was present in some of the animals. The authors questioned the administration of D-Panthenol as a possible cause of the eosinophilia. No toxicological effects were noted in a similar study (Table 3) in which rats (12, CR strain) received doses of 20, 50, or 200 mg/kg of D- and DL-Panthenol for a 90-day period.[44]

In another study, Panthenol was administered in drinking water to Sprague-Dawley weanling female rats[44] (Table 3). One group (10 rats) received 100 mg/kg and the other group (10 rats) received 400 mg/kg; both doses were administered daily for a 13-week period. Growth retardation was noted for the group receiving the 400 mg/kg dose. This was attributed to a reduction in fluid intake. Autopsies revealed no apparent gross lesions. Microscopic examinations revealed a slight toxic reaction in the kidneys of rats in the 100 mg/kg group and a more marked reaction in the kidneys of rats in the 400 mg/kg group.. Other microscopic observations included slight changes in the lungs and liver.

Chronic Oral Toxicity

Oral doses of Panthenol were administered to 24 rats for 6 months; 2 mg of Panthenol was given daily[24] (Table 3). No histopathological changes were reported.

Subcutaneous and Intravenous Toxicity

Subcutaneous LD_{50}s for Pantothenic Acid that have been reported for mice and rats are 2.5 g/kg and 3.5 g/kg, respectively[45] (Table 4).

The intravenous administration of D-Panthenol to mice and rabbits has resulted in LD_{50} values of 7 g/kg and 4 g/kg, respectively[24] (Table 4). The number of animals studied was not indicated.

In another study, 27 mice each received an intravenous injection of D-Panthenol, with doses ranging from 4 to 10 g/kg. The LD_{50} was not achieved at the highest dose tested. Also, no deaths were reported for nine dogs that received intravenous injections ranging from 2 to 10 g/kg[26] (Table 4).

Subchronic Dermal Toxicity

A cream containing 0.5% Panthenol was applied at a dosage of 6 mg/cm^2 to the shaved flank skin (10% of total body surface area) of 10 New Zealand albino rabbits daily for 90 days (Table 4). The animals (5 males, 5 females) were 12–14 weeks old and weighed 2.39 ± 0.06 kg (males) and 2.40 ± 0.04 kg (females). The

TABLE 4. Dermal and Intravenous Toxicity of Panthenol and Pantothenic Acid

Type of study	*Animals tested*	*Test substance*	*Methodology*	*Results*	*Reference*
Subcutaneous toxicity	Mice and rats (no. and strain not stated)	100% Pantothenic Acid	– – –	LD_{50}s of 2.5 g/kg (mice) and 3.5 g/kg (rats)	38
Intravenous toxicity	Mice and rabbits (no. and strain not stated)	100% D-Panthenol	– – –	LD_{50}s of 7 g/kg (mice) and 4 g/kg (rabbits)	24
Intravenous toxicity	27 mice (strain not stated	100% D-Panthenol	Doses of 4–10 g/kg	$LD_{50} > 10$ g/kg	26
Subchronic dermal toxicity	10 New Zealand albino rabbits	0.5% Panthenol cream	Dose of 6 mg/cm² applied to skin of flank daily for 90 days	All animals had slight to moderate erythema, edema, and cutaneous desquamation. No test substance-related deaths	46
Subchronic dermal toxicity	10 New Zealand white rabbits	0.5% Panthenol cream	Dose of 5.5 mg/cm² applied to back daily for 90 days	Well-defined to moderate erythema and slight edema noted in all animals. No test substance-related deaths or systemic toxic effects	47
Subchronic dermal toxicity	45 Sprague-Dawley rats (3 groups of 15)	0.2% Panthenol creams (3 products)	Doses of 680, 420, and 227 mg/kg applied to the back daily for 13 consecutive weeks	Minimal hyperkeratosis of skin and subcutis in rats from all treatment groups. No deaths or systemic toxic effects	48

untreated control group consisted of 5 male and 5 female rabbits with shaved flanks. All treated animals had slight to moderate cutaneous erythema and edema, beginning during the first week of treatment and persisting until termination of the study. Slight to moderate desquamation was also observed in all treated animals. Fine cutaneous fissures were observed in 4 animals during the third week of treatment, and 1 animal had epidermal fissures and bleeding on days 46–48. During the 12th week of treatment, dermal papillae were observed in 2 animals. There was no evidence of dermal irritation in untreated control animals. No test substance-related deaths were reported.[46]

Another cream containing 0.5% Panthenol was applied daily at a dosage of 5.5 mg/cm^2 to the backs (8.4% of total body surface area) of 10 New Zealand white rabbits for 90 days (Table 4). The animals (5 males, 5 females) were approximately 12–16 weeks old and weighed 3.26 ± 0.07 kg (males) and 3.36 ± 0.08 kg (females). The untreated control group consisted of 7 males and 7 females. Persistent, moderate erythema and slight edema were noted in all treated animals. Slight desquamation occurred intermittently throughout the treatment period. Papular erythema was observed in 6 untreated control rabbits after 6–7 weeks of testing but was not noted in treated rabbits. No test substance-related deaths or systemic toxic effects were reported.[47]

Three creams containing 0.2% Panthenol were administered once daily for 13 consecutive weeks (5 days/week) to three respective groups of 15 female Sprague-Dawley rats (doses of 680, 420, and 227 mg/kg, respectively) (Table 4). Applications were made to the anterior dorsal shaved skin (10–15% of total body surface area) of animals ranging in weight from 161 to 222 g. Sporadic and transient observations of skin irritation were noted in the three groups during the treatment period. Microscopic examinations revealed minimal cutaneous hyperkeratosis in some rats (number not specified) from all treatment groups. All animals survived the 13-week treatment period. The three cosmetic products did not cause systemic toxic effects.[48] Identical results were reported in another study (same protocol) involving a product containing 0.2% Panthenol.[49]

Ocular Irritation

The ocular irritation potential of DL-Panthenol was determined with six New Zealand white rabbits (Table 5). One-tenth milliliter of the test substance (powder form) was instilled into one eye (conjunctival sac) of each animal. The eyes of three rabbits were washed 5 minutes after instillation and those of the remaining three rabbits were washed 24 h after instillation. Ocular irritation was scored at 1 hour and 1, 2, 3, 7, and 14 days after treatment. Slight conjunctival redness (six animals) and chemosis (one animal) were first noted at 1 h posttreatment. Diffuse areas of corneal opacity were first noted in one animal at day 3 posttreatment. All ocular reactions had cleared by day 21. In a second experiment employing the same procedure (Table 5), 0.1 ml of DL-Panthenol (viscous form) was instilled into the eyes of six New Zealand white rabbits. Diffuse areas of corneal opacity (two animals) and slight conjunctival redness (six animals) and chemosis (four animals) were first noted at 1 h posttreatment. All ocular reactions had cleared by day 21.[50]

TABLE 5. Ocular Irritation of Panthenol

	Animals tested	*Test substance*	*Methodology*	*Results*	*Reference*
Ocular irritation	6 New Zealand white rabbits	100% D- and DL-Panthenol	0.1 ml of both substances instilled into eye. Eyes rinsed 5 minutes (3 animals) and 24 h (3 animals) after instillation	Slight conjunctival redness and chemosis had cleared by day 21 posttreatment	50
Ocular irritation	3 rabbits (strain not stated)	2% aqueous solutions of D- and DL-Panthenol	0.1 ml of both solutions instilled into eye	Very slight conjunctival redness had cleared within 72 h posttreatment	50
Ocular irritation	6 rabbits (strain not stated)	0.5% Panthenol product	0.1 ml of product instilled into eye	Slight conjunctival redness cleared within 24 h posttreatment	42
Ocular irritation	6 New Zealand albino rabbits	0.5% Panthenol cream	0.1 ml of product instilled into eye	Slight conjunctival redness had cleared by 24 h posttreatment	43
Ocular irritation	Rabbits (no. and strain not stated)	0.5% Panthenol in 2 mascaras	0.1 ml of both products instilled into eye	Slight conjunctivitis had cleared within 3 days posttreatment	51
Ocular irritation	6 New Zealand albino rabbits	Mascara containing 0.5% Panthenol	0.1 ml of product instilled into eye daily for 14 days	Slight conjunctival redness observed during first week but not during second week of treatment	52
Ocular irritation	6 New Zealand white rabbits	Mascara containing 0.5% Panthenol	0.1 ml of product instilled into eye	Slight conjunctivitis had cleared by 1–2 days posttreatment	53
Ocular irritation	9 albino rabbits	0.5% Panthenol lotion	0.1 ml of product instilled into eye. Eyes of 3 animals rinsed 30 seconds postinstillation	Slight conjunctival redness and chemosis (unrinsed eyes). No signs of ocular irritation (rinsed eyes)	54
Ocular irritation	6 rabbits (strain not stated)	0.5% Panthenol product	Product (amount not stated) instilled into eye	Test substance "practically nonirritating" to eye	55
Ocular irritation	9 albino rabbits	Mascara containing 0.1% Panthenol	0.1 ml of product instilled into eye. Eyes of 5 animals rinsed	No signs of ocular irritation in rinsed or unrinsed eyes	56

The ocular irritation potential of 2% aqueous solutions of DL-Panthenol and D-Panthenol was evaluated in rabbits (strain not specified) (Table 5). One-tenth milliliter of each solution was instilled into one eye of three animals, and untreated eyes served as controls. Observations for signs of irritation were made immediately after instillation and at 1, 2, 4, 24, 48, and 72 h thereafter. Very slight conjunctival redness was observed in all animals of both treatment groups immediately after instillation. Ocular reactions were not noted during the remainder of the observation period. It was concluded that DL-Panthenol and D-Panthenol aqueous solutions were nonirritating to the eyes of rabbits.[42]

One-tenth milliliter of a product containing 0.5% Panthenol was instilled into the eyes of six rabbits (Table 5). Observations for signs of irritation were made each day after instillation for a total of 7 days. Slight conjunctival redness was noted 1 h after instillation (number of animals not stated), having cleared within 24h. There were no signs of corneal or iridial irritation.[42]

The ocular irritation potential of a cream containing 0.5% Panthenol was evaluated in six New Zealand albino rabbits (average weight: 3.45 ± 0.13 kg). One-tenth milliliter of the test substance was instilled into one eye of each animal, and ocular irritation was scored at 1 h and days 1, 2, 3, and 7 posttreatment (Table 5). Slight conjunctivitis was noted within 1 h posttreatment, having cleared after 24 h. There were no signs of corneal or iridial irritation.[43]

One-tenth milliliter of two mascara products (1 and 2) containing 0.5% Panthenol was instilled into the eyes of rabbits (number and strain not specified) (Table 5). Slight conjunctivitis was observed 1 h after the administration of both products and had cleared within 2 and 3 days, products 1 and 2, respectively.[51]

Another mascara containing 0.5% Panthenol was instilled into the eyes of six New Zealand white rabbits (Table 5). Each animal was treated once with 0.1 ml of the formulation. Ocular reactions were scored at 1 h and days 1, 2, 3, and 7 posttreatment. Slight conjunctivitis was noted 1 h after treatment and had cleared by 1–2 days. There was no evidence of irritation to the cornea or iris.[53]

An ocular irritation study of a mascara containing 0.5% Panthenol was conducted with six New Zealand albino rabbits (Table 5). Each animal received 14 daily instillations of the test substance (0.1 ml each), and ocular reactions were graded 24 h after each treatment. Slight conjunctival redness was observed intermittently during the first week (number of animals not stated) but not during the second week. Signs of corneal or iridial irritation were not observed.[52]

The ocular irritation potential of a lotion containing 0.5% Panthenol was determined with nine albino rabbits (Table 5). One-tenth milliliter of the test substance was instilled into the conjunctival sac of each animal. The treated eyes of three rabbits were rinsed with deionized water 30 seconds after instillation. Grading of ocular reactions occurred at 1, 2, 3, 4, and 7 days posttreatment. No signs of ocular irritation were observed in the three animals with rinsed eyes. For unrinsed eyes (six animals), the following observations were made: slight conjunctival redness (two animals), slight conjunctival chemosis (one animal), and no signs of ocular irritation (three animals). Slight conjunctival redness and chemosis were not regarded as positive reactions. It was concluded that the test substance did not cause irritation in rinsed and unrinsed eyes.[54]

A skin care preparation containing 0.5% Panthenol was instilled into the eyes of six rabbits (strain not stated) (Table 5). Ocular irritation was scored on days 1, 2, 4, and 7 posttreatment. Two animals had total scores of 2 and 4, re-

spectively (max = 20) for conjunctival reactions (redness, chemosis, and discharge) 1 day after treatment; reactions had cleared by day 2. It was concluded that the test substance was practically nonirritating.[55]

The ocular irritation potential of a mascara containing 0.1% Panthenol was determined with nine albino rabbits (Table 5). One-tenth milliliter of the test substance was instilled into the right eye of each animal: three animals (eyes rinsed 10 seconds posttreatment), two animals (eyes rinsed 20 seconds posttreatment), and four animals (eyes not rinsed. Ocular irritation was scored on days 1, 2, 3, 4, and 7 posttreatment. None of the animals had signs of ocular irritation.[56]

Skin Irritation

The skin irritation potential of D- and DL-Panthenol was determined with three New Zealand white rabbits (Table 6). Five-tenths milliliter of each test substance was applied to both abraded and intact skin (clipped free of hair) of the

TABLE 6. Skin Irritation of Panthenol

Animals tested	*Test substance*	*Methodology*	*Results*	*Reference*
3 New Zealand white rabbits	100% D- and DL-Panthenol	0.5 ml of both substances applied to abraded and intact skin via occlusive patches. Patches remained for 4 h	Slight erythema observed in 1 rabbit, having cleared by 24 h after patch removal	50
3 New Zealand white rabbits	100% Panthenol	0.5 ml of substance applied to abraded and intact skin via occlusive patches. Patches remained for 4 h	Very slight erythema at 24 and 48 h after patch removal	50
3 rabbits (strain not stated)	2% aqueous solutions of D- and DL-Panthenol	Both solutions (volumes not stated) applied to abraded and intact skin	No signs of skin irritation	50
9 rabbits (strain not stated)	0.5% Panthenol product	Product applied (volume not stated) to skin via occlusive patches	One animal showed erythema 24 h after patch removal	57
3 albino rabbits	0.5% Panthenol product	0.5 ml of product applied to shaved skin 1 application/day for 4 days	Well-defined erythema and edema observed within 48 h posttreatment, persisting for 7 days	42
6 New Zealand albino rabbits	0.5% Panthenol cream	Product applied (volume not stated) to shaved skin (3 rabbits) and shaved and abraded skin (3 rabbits) once a day for 4 days	Moderate to severe erythema and slight edema persisted throughout 7-day observation period	43
6 New Zealand albino rabbits	Mascara containing 0.5% Panthenol	0.5 ml of product applied to clipped skin daily for 14 days	No evidence of dermal irritation	52

back via occlusive patches. Patch removals occurred after a 4 h contact period, and skin reactions were immediately evaluated. The test sites were then washed to prevent further exposure, and evaluations were made again at 24 and 48 h. Slight erythema was noted in one rabbit (abraded and intact skin) immediately after removal of patches containing D-Panthenol and those containing DL-Panthenol, having cleared by 24 h.[50] In another experiment (same protocol), liquid Panthenol (0.5 ml) was applied to abraded and intact skin (clipped free of hair) of three New Zealand white rabbits via occlusive patches (Table 6). One rabbit had very slight erythema at 24 and 48 h after patch removal.[50]

The skin irritation potential of 2% aqueous solutions of DL-Panthenol and D-Panthenol was evaluated with three rabbits (strain not indicated) (Table 6). Each solution was applied to abraded and intact skin. Observations for signs of irritation occurred at 24 and 72 h postadministration. The test substance did not induce skin irritation.[50]

A skin care preparation containing 0.5% Panthenol was applied to the skins of nine rabbits (strain not stated) via occlusive patches (Table 6). One rabbit had erythema 24 h after patch removal. It was concluded that the test substance was "practically nonirritating."[57]

Five-tenths milliliter of a product containing 0.5% Panthenol was applied to the shaved backs of three albino rabbits (one application/day for 4 days) (Table 6). Within 48 h posttreatment, well-defined erythema and edema were observed and persisted for 7 days, after which dehydration and desquamation were noted. The irritation index was 3.1 (scale: 1–8).[42]

A cream containing 0.5% Panthenol was applied to the backs of six New Zealand albino rabbits (mean weight: 5.01 ±0.1 kg) once a day for a period of 4 days (Table 6). The backs of three rabbits were shaved, and the backs of the remaining three were shaved and abraded prior to treatment. Erythema, ranging from slight to well-defined, was observed in all animals 24–48 h after the first treatment. After 72 h, moderate to severe erythema and slight edema were observed (number of animals not specified). Slight cutaneous desquamation was also noted during the treatment period (time not indicated). Skin irritation persisted throughout the 7-day observation period, and the irritation index reported was 2.88 (scale: 1–8).[43]

A mascara containing 0.5% Panthenol was applied to the clipped skin of the backs of six New Zealand albino rabbits (Table 6). The test substance (0.5 ml) was applied daily for a period of 14 days. Observations for signs of dermal irritation occurred daily during the 2-week period. There was no evidence of dermal irritation or systemic toxicity during the test period. However, a black stain was noted at the application sites.[52]

Comedogenic Potential

The comedogenic potential of a moisturing lotion containing 0.5% Panthenol was evaluated using three rabbits (strain not stated). The product was applied (amount not stated) once daily to the external ear canals for a 2-week period. Whole mount examinations of the tissue specimens were performed according to the method of Kligman and Kwong.[58] The product was classified as being noncomedogenic.[59]

Teratogenicity

Female albino rats (28 days old) were selected from an inbred colony of the Wistar strain. The animals were maintained on a stock diet consisting of mixed grains and dried whole milk until birth of the first litters. Eighteen females that produced normal first litters were divided into two groups and transferred to different diets. One group of nine received a vitamin mixture plus 100 μg of calcium pantothenate. The other group received the same vitamin mixture plus 1 mg of calcium pantothenate. The animals were fed during a period encompassing the termination of the first pregnancies and birth of the second litters. The gestation period was not specified. Histological sections of the liver, duodenum, adrenals, and tibias of the young produced during second pregnancies were prepared and examined. No structural differences were encountered for the four types of tissues examined, which could be attributed to differences in dietary treatment of the females.[60,61]

CLINICAL ASSESSMENT OF SAFETY

Oral Toxicity

Minimal toxic effects have been associated with the administration of Pantothenic Acid to humans. Occasional diarrhea at doses of 10–20 g/day have been reported[62] (Table 7).

Ocular Irritation

The ocular irritation potential of two mascaras containing 0.1% Panthenol was evaluated with 23 female subjects (age range: 21–52) during a 3-week period (Table 7). The experimental procedure was not stated. There were no observations of eye irritation that were considered to be test substance-related[63] (Table 7).

Skin Irritation

A skin care preparation containing 0.5% Panthenol was applied to 18 subjects during a 4-day cumulative skin irritation study. The experimental procedure was not stated (Table 7). Seventeen subjects had no signs of skin irritation, and one had an equivocal reaction to the product. The authors concluded that the product was "essentially nonirritating" to the skin.[64]

A lotion containing 0.5% Panthenol was applied daily to the backs of 10 female subjects (age range: 18–>60) via closed patches for 21 consecutive days (Table 7). Each patch contained 0.3 ml of the test substance and remained in contact with the skin for 23 h. Each test site was bathed immediately after patch removal and evaluated for signs of irritation 1 h later. Seven subjects had minimal erythema (barely perceptible), and one subject had minimal to definite erythema during the treatment period. The authors concluded that the lotion was a mild irritant.[65]

TABLE 7. Clinical Assessment of Safety

Type of study	*No. of subjects*	*Test substance*	*Methodology*	*Results*	*Reference*
Oral toxicity	– – –	100% Pantothenic Acid	Doses of 10–20 g/day	Occasional diarrhea and water retention	62
Ocular irritation	23	Two mascaras containing 0.1% Panthenol	Instillations of products occurred during a 3-week period	No observations of eye irritation that were test substance-related	63
Skin irritation	18	0.5% Panthenol product	Product applied to skin during a 4-day period	17 subjects had no signs of skin irritation. 1 subject had an equivocal skin reaction	64
Skin irritation	10	0.5% Panthenol lotion	0.3 ml of product applied to skin via closed patch daily for 21 consecutive days. Patches remained for 23 h	7 subjects had minimal erythema and 1 subject had minimal to definite erythema during treatment period	65
Skin irritation and sensitization	200	0.5% Panthenol product	Applications were made via occlusive patches. Patches remained for 24 h during induction and for 48 h during challenge phase	2 subjects had erythema and papules during induction, and 1 subject during challenge phase	66
Skin irritation and sensitization	206	Mascara containing 0.5% Panthenol	0.1 g of product applied via occlusive patch. Patches remained for 24 h during induction phase and for 48 h during challenge phase	3 subjects had erythema and edema during either the induction or challenge phase	67
Skin irritation and sensitization	200	0.5% Panthenol cream	Product (volume not stated) applied to skin and sites covered with occlusive dressing. Patches remained for 48 h during induction and challenge phases	None of the subjects had signs of skin irritation or sensitization	68

Skin irritation and sensitization	238	0.5% Panthenol cream	Product (volume not stated) applied via occlusive patches. Patches remained for 24 h during induction phase and for 48 h during challenge phase	1 subject had erythema during induction phase	69
Skin irritation and sensitization	25	0.5% Panthenol lotion	0.3 g of product applied via occlusive patch. Patches remained for 24 h during induction phase and for 48 h during challenge phase	None of the subjects had signs of skin irritation or sensitization	70
Skin sensitization	99	0.5% Panthenol product	0.1 ml of product applied via occlusive patch. Patches remained for 24 h during induction and challenge phases	Product did not have potential for inducing allergic sensitization	71
Skin sensitization	86	0.2% Panthenol product	0.1 ml of product applied via occlusive patch. Patches remained for 24 h during induction and challenge phases	Product did not have potential for inducing allergic sensitization	72
Skin sensitization	200	0.2% Panthenol product	0.1 ml of product applied via occlusive patch. Patches remained for 24 h during induction and challenge phases	Product did not have potential for inducing allergic sensitization	73
Skin sensitization	107	0.2% Panthenol product	0.1 ml of product applied via occlusive patch. Patches remained for 24 h during induction and challenge phases	Product did not have potential for inducing allergic sensitization	74
Skin sensitization	208	Mascara containing 0.1% Panthenol	0.1 ml or 0.1 g of product applied via occlusive patch. Patches remained from 48–72 h during induction and challenge phases	No evidence of allergic contact sensitization in any of the subjects	75

Skin Irritation and Sensitization

A product containing 0.5% Panthenol was applied to the backs of 200 male and female subjects (age range: 18–65) via occlusive patches. Patches were removed after a 24-h contact period during the induction phase, and test sites were washed with distilled water (Table 7). The sites were then graded for signs of irritation. Insult patches were applied every Monday, Wednesday, and Friday for 3½ weeks (total of 10 insults). Ten to fourteen days after grading of the tenth insult, subjects were tested again (first challenge) via the same procedure, the exception being that patches remained for 48 h. The second challenge (same procedure) began 7–10 days after grading of the tenth 48-h insult; patches remained for 48 h. Test sites were graded 48 and 72 after patch application. Two subjects had erythema and papules during the induction phase, and one subject had these reactions at 72 h after patch application during the second challenge. The product was neither a strong irritant nor a strong contact sensitizer.[65]

Two-hundred six male and female subjects participated in a skin irritation and sensitization study of a mascara containing 0.5% Panthenol (Table 7). Occlusive patches containing approximately 0.1 g of the test substance were applied to the subjects' backs during a 6-week test period (total of 10 applications). Induction patches were applied on Monday, Wednesday, and Friday during the first 3 weeks (induction phase), remaining for 24 h. The grading of skin reactions occurred prior to the second through the tenth applications. Challenge patches were applied to new test sites on Monday of week 6, remaining for 48 h. Grading of sites occurred at 48 and 72 after application. Skin reactions were observed at the application sites in three subjects. One subject had erythema and edema during the induction phase. Another had erythema and edema during the induction phase and challenge phase (48- and 72-h readings). In the remaining subject, erythema and edema were observed during the induction phase and, erythema, edema, and vesiculation, during the challenge phase (48- and 72-h readings).[67]

The skin irritation and sensitization potential of a cream containing 0.5% Panthenol was evaluated with 200 subjects (Table 7). Applications were made to the subjects' backs, and sites were covered with an occlusive dressing. Sites were washed after a 48- contact period and then graded for signs of irritation. This procedure was conducted every Monday, Wednesday, and Friday for 3½ weeks (total of 10 induction insults). Forty-eight hours after the tenth insult, sites were again graded; grading was followed by a 10–14 day nontreatment period. The test procedure was then repeated (challenge phase), and sites were 48 h after the tenth insult. Signs of irritation were not noted in any of the subjects. It was concluded that the product was not an allergic sensitizer or primary irritant.[68]

A cream containing 0.5% Panthenol was applied to the backs of 238 female subjects (age range: 18–65) via occlusive patches during a 2-week period (Table 7). Applications were made on Mondays, Wednesdays, and Fridays, and patches remained for 24 h. Skin reactions were graded prior to the second through the ninth applications and at the time of the tenth and final application (Monday of week 4). Subjects were again graded 48 h after application of the tenth induction patch. Challenge patches were applied to new test sites on Monday of week 6, remaining for 48 h. Sites were graded at 48 and 72 h after application. One subject had erythema after application of the sixth induction patch. It was con-

cluded that the test substance was not a primary irritant or an allergic contact sensitizer.[69]

The irritation and sensitization potential of a lotion containing 0.5% Panthenol were determined with 25 adult subjects (Table 7). An occlusive patch containing 0.3 g of the test substance was applied to the forearm of each subject for a total of five applications. Patches remained for a period of 48 h. After a 10-day nontreatment period, challenge patches were applied and remained for 48 h. Challenge sites were pretreated for 1 h with a 10% aqueous solution of sodium lauryl sulfate. Grading of skin reactions occurred immediately after challenge patch removal and 24 h thereafter. Signs of irritation were not observed during the induction phase, and there were no instances of contact sensitization.[70]

Skin Sensitization

One-tenth milliliter of a skin care preparation containing 0.5% Panthenol was applied via occlusive patches to 99 subjects every Monday, Wednesday, and Friday for 3 consecutive weeks (induction phase) (Table 7). Patches were applied to the right (5 patches). and left (5 patches) of the dorsal midline of each subject, remaining 24 h. Challenge applications were made during week 6; one patch was applied to a new site in each subject, remaining for 24 h. Skin reactions were graded 24 and 48 h after patch removal. Six subjects had a barely perceptible erythema during the induction phase. No reactions were noted during the challenge phase. It was concluded that the test substance did not have any potential for inducing allergic sensitization.[71]

In two similar studies (same protocol as above), products containing 0.2% Panthenol were applied to the backs of 86 and 100 subjects, respectively (Table 7). In the first study (86 subjects), skin reactions were observed at the application sites of 41 subjects. Twenty-nine of the subjects had barely perceptible erythema during the induction phase. Eleven subjects had barely perceptible to mild erythema during the induction phase. Four of the eleven subjects also had reactions ranging from barely perceptible to mild erythema at 24 and 48 h after challenge patch removal. One subject had mild to moderate erythema during the induction phase. In the second study (100 subjects), skin reactions were observed at the application sites of 56 subjects. Twenty-seven and three of the subjects had barely perceptible and mild erythema, respectively, during the induction phase. The remaining 26 subjects showed barely perceptible to mild erythema during induction. During the challenge phase, 9 subjects had reactions ranging from barely perceptible to mild erythema at 24 h after patch removal; 1 subject had moderate erythema. Two subjects had a barely perceptible erythema at 48 h after patch removal. It was concluded in both studies that the products did not have any potential for inducing allergic sensitization.[72,73] In two other studies (same protocol), two different products containing 0.2% Panthenol were applied to 86 and 107 subjects, respectively (Table 7). Skin reactions were not observed in any of the 86 subjects. One of the 107 subjects had barely perceptible to mild erythema during induction and barely perceptible erythema 24 h after challenge patch removal. It was concluded that the two products did not have any potential for inducing allergic sensitization.[74,76]

A mascara containing 0.1% Panthenol was applied to the backs or upper-

arms of 208 subjects (>18 years old) via occlusive patches during a 6-week study (Table 7). Applications were made three times per week during the first 3 weeks (induction phase). Each patch contained 0.2 ml or 0.2 g of the test substance and remained for 48–72 h. Challenge patches were applied 2 weeks after termination of the induction phase and also remained for 48–72 h. There was no evidence of allergic contact sensitization in any of the subjects.[75]

SUMMARY

Panthenol (D- and DL -forms are available) is the alcohol analogue of Pantothenic Acid (vitamin B_3). They have equivalent biological activity, and the oxidation of Panthenol to Pantothenic Acid is known to occur in human cells. Panthenol is present in approximately 284 cosmetic products in concentrations ranging from ≤0.1 to 5%

The LD_{50} for D-Panthenol (100%) administered orally to mice was 15 g/kg. In two other acute oral studies of D-Panthenol (six mice/study), doses of 10 and 20 g/kg resulted in no deaths and the death of all animals, respectively. Acute oral studies (10 rats/study) of products containing 0.5% Panthenol resulted in no signs of toxicity with one product (dose = 26 ml/kg) and slight body thinness in five male rats (dose = 7 ml/kg) with another product.

No toxicological effects were associated with the subchronic (90 days) oral administration of D- and DL-Panthenol (100%) in studies conducted with rats. Chronic oral toxicity studies of Panthenol (100%) resulted in no toxicological effects in rats receiving 2 mg/day for 6 months and renal toxicity in rats receiving doses of 100 and 400 mg/kg daily for 13 weeks.

Subcutaneous LD_{50}s for Pantothenic Acid administered to mice and rats were 2.5 and 3.5 g/kg, respectively. The intravenous administration of D-Panthenol to mice and rabbits resulted in LD_{50} values of 7 and 4 g/kg, respectively. An intravenous LD_{50} of >10 g/kg was reported in another study involving mice.

The subchronic (90 days) dermal administration of creams containing 0.5% Panthenol induced erythema and edema in rabbits. Minimal cutaneous hyperkeratosis was noted in rats in a subchronic (13 weeks) dermal study of creams containing 0.2% Panthenol.

In ocular irritation studies involving rabbits, the administration of Panthenol (100%) and products or solutions containing Panthenol (0.1, 0.5, and 2%) resulted in reactions ranging from no signs of ocular irritation to slight conjunctival redness and chemosis.

Panthenol (100%) and products or solutions containing Panthenol (0.5 and 2%) administered to rabbits during skin irritation studies caused reactions ranging from no skin irritation to moderate-to-severe erythema and well-defined edema.

Neither teratogenic nor fetotoxic effects were noted in the offspring when rats were fed calcium pantothenate before mating and throughout gestation.

Pantothenic Acid has been reported to induce minimal toxic effects when administered to humans. Occasional diarrhea has been reported with doses of 10–20 g/day.

No test substance-related observations of eye irritation were reported for 23 subjects receiving instillations of products containing 0.1% Panthenol.

Skin irritation and sensitization studies of products containing 0.1, 0.2, and 0.5% Panthenol indicated that they were, at most, mild irritants and that they did not have any potential for inducing allergic sensitization.

DISCUSSION

The Expert Panel recognizes that only product formulations containing low concentrations of Panthenol were tested in human sensitization and irritation studies. These formulations did not induce sensitization or significant skin irritation. Additionally, significant skin irritation was not observed when 100% Panthenol was applied to New Zealand white rabbits. Photosensitization data were not available. However, an absorption spectrum of Panthenol indicated maximum absorbance in the 202–206 nm range.

Mutagenicity and carcinogenicity data were not available for the safety assessment of Panthenol, which is the alcohol form of the vitamin Panthothenic Acid (vitamin B_3). Because of its low concentrations of use in cosmetics and the requirement for normal metabolism, the required human levels of this ingredient exceed the amount that could be absorbed. The human metabolic requirement would preclude the likelihood of genotoxicity.

CONCLUSION

Based on the available data, Panthenol and Pantothenic Acid are safe as presently used in cosmetics.

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Annual Review of Cosmetic Ingredient Safety Assessments—2004/2005[1]

The Cosmetic Ingredient Review (CIR) program Expert Panel has assessed the safety of almost 1300 cosmetic ingredients since its inception in 1976 These safety assessments were published in the *Journal of Environmental Pathology and Toxicology* in 1980, the *Journal of the American College of Toxicology*, from 1982 to 1996, and since then in the *International Journal of Toxicology*

Because information relevant to the safety of ingredients may have become available since early safety assessments were published, the CIR Expert Panel has initiated a re-review process If new information is thought to be available or if a long period of time has passed, the CIR Expert Panel may initiate a search for relevant new data

In some cases, newly available data are largely redundant with the data available in the original safety assessment In other cases, there are new safety data If the CIR Expert Panel decides to not reopen a safety assessment, this finding is summarized and announced publicly To assure that the scientific community is aware of any new information and the decision to not reopen, this *Annual Review of Cosmetic Ingredient Safety Assessments* is prepared

A reference list is provided that updates the available published literature and includes any unpublished data made available since the original safety assessment The re-review also captures information on the industry's current practices of ingredient use, updating the data available in the earlier report Although this material provides the opinion of the CIR Expert Panel regarding the new data described, it does not constitute a full safety review

The ingredients the CIR Expert Panel reconsidered in 2004/2005, and decided not to reopen are

Benzethonium Chloride and Methylbenzethonium Chloride
2-Bromo-2-Nitropropane-1,3-Diol
Butylated Hydroxyanisole (BHA)
Butylene Glycol, Hexylene Glycol, Ethoxydiglycol, and Dipropylene Glycol
Cetearyl Octanoate (Ceteraryl Ethylhexanoate)
Cholesterol
Chloroxylenol
Diisopropanolamine, Isopropanolamine, Triisopropanolamine, and Mixed Isopropanolamines
Dioctyl Adipate and Diisopropyl Adipate
Formaldehyde
Hydrolyzed Collagen
p-Hydroxyanisole
Isostearyl Neopentanoate
2-Nitro-*p*-Phenylenediamine and 4-Nitro-*o*-Phenylenediamine
Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid, Stearic Acid
Panthenol and Pantothenic Acid
p-Phenylenediamine
Phenyl Trimethicone
Propylene Carbonate
Propyl Gallate
Polyvinylpyrrolidone/Vinyl Acetate Copolymer
Safflower Oil
Sodium Borate and Boric Acid
Sodium Dehydroacetate and Dehydroacetic Acid
Sodium Lauryl Sulfoacetate
Sodium Sesquicarbonate, Sodium Bicarbonate, and Sodium Carbonate
Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol
Toluene
Toluenesulfonamide/Formaldehyde Resin
Tragacanth Gum
Vinyl Acetate/Crotonic Acid Copolymer
Zinc Phenolsulfonate

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[1]Reviewed by the Cosmetic Ingredient Review Expert Panel Address correspondence to Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036, USA

ABRIDGED

PANTHENOL AND PANTOTHENIC ACID

A safety assessment of Panthenol and Pantothenic Acid was published in 1987 with the conclusion that these ingredients are safe as presently used in cosmetics (Elder 1987) Studies published since the last assessment, along with updated information concerning frequency of use and use concentrations, were considered by the CIR Expert Panel The Panel determined to not reopen the safety assessment

The safety assessment applies to Panthenol in both the D and the DL form

The available use and concentration information is provided in Table 15 The most recent information now constitutes the present use of these ingredients

Panthenol reported usage increased from 284 in 1981 to 1538 in 2002, based on industry voluntary reports provided to FDA (Elder 1987, FDA 2002) An industry survey in 2004 indicated that use concentrations range from 0 00005% to 6%, which is lower than the maximum use concentration range reported in 1981 (Elder 1987)

Pantothenic Acid was not reportedly used in cosmetics in 1981 (Elder 1987), but industry voluntary reports provided to FDA in 2002 included three uses in eye makeup and skin care products (FDA 2002) An industry survey in 2004 indicated that use concentrations range from 0 00001% to 0 01% in those product categories and in makeup and shaving preparations (categories in which no uses were reported to FDA)

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[16]Available for review Director, Cosmetic Ingredient Review, 1101 17th Street, NW Suite 412, Washington, DC 20036-4702, USA

TABLE 15

Historical and current cosmetic product uses and concentrations for Panthenol and Pantothenic Acid

Product category	1981 uses (Elder 1987)	2002 uses (FDA 2002)	1981 concentrations (Elder 1987) %	2004 concentrations (CTFA 2004) %
		Panthenol		
Baby care				
Lotions, oils, powders, and creams	—	3	—	—
Bath				
Oils, tablets and salts	—	—	—	2
Soaps and detergents	—	15	—	0 05–4
Bubble baths	—	3	—	0 01–2
Capsules	—	1	—	—
Other bath	—	11	—	0 3–2
Eye makeup				
Eyebrow pencils	—	3	—	0 01–2
Eyeliners	5	—	>0 1–1	0 01–0 05
Eye shadow	23	—	>0 1–1	0.5–1
Eye lotions	—	5	—	0 01–0 6
Eye makeup remover	2	8	>0 1–1	0 001–1
Mascara	10	70	>0 1–5	0 1–2
Other eye makeup	2	14	>0 1–1	0 3–0 5
Fragrances				
Colognes and toilet waters	1	5	>0 1–1	0 003–0 1
Perfumes	—	—	—	1
Powders	—	3	—	—
Other fragrances	—	11	—	1
Noncoloring hair care				
Conditioners	33	264	≤0 1–5	0 09–6
Sprays/aerosol fixatives	17	82	≤0 1–1	0 01–5
Straighteners	—	1	—	—
Permanent waves	2	6	>0 1–1	5
Rinses	1	6	>0 1–1	0 1–0 5
Shampoos	25	206	≤0 1–5	0 01–5
Tonics, dressings, etc	11	187	≤0 1–1	0 01–5
Wave sets	31	12	≤0 1–5	0 9–1
Other noncoloring hair care	6	93	≤0 1–1	0 01–1*
Hair coloring				
Dyes and colors	—	52	—	0 01–0 1
Tints	—	1	—	—
Color sprays	—	2	—	—
Bleaches	—	1	—	0 5
Other hair coloring	—	6	—	0 00005–1
Makeup				
Blushers	3	2	>0 1–1 >10–25	0 2–1
Face powders	1	1	>0 1–1	0 02–1
Foundations	8	45	≤0 1–1	0 2–1
Lipsticks	27	6	≤0 1–5	0 01–2
Makeup bases	1	8	≤0 1	0 5
Rouges	1	—	>0 1–1	—
Other makeup	2	4	>0 1–1	<1–6

TABLE 15

Historical and current cosmetic product uses and concentrations for Panthenol and Pantothenic Acid *(Continued)*

Product category	1981 uses (Elder 1987)	2002 uses (FDA 2002)	1981 concentrations (Elder 1987) %	2004 concentrations (CTFA 2004) %
Nail care				
Basecoats and undercoats	—	9	—	0.03–0.2
Cuticle softeners	1	4	>0.1–1	0.1–0.2
Creams and lotions	1	1	>0.1–1	0.05–0.5
Polishes and enamels	—	10	—	0.2–1
Polish and enamel removers	—	5	—	0.03–0.5
Other nail care	—	11	—	0.1–0.2
Personal hygiene				
Underarm deodorants	1	3	>0.1–1	0.05–0.5
Douches	—	—	—	0.1–0.8
Other personal hygiene	—	8	—	0.1
Shaving				
Aftershave lotions	3	14	≤0.1–1	0.03–3
Preshave lotions	1	—	>0.1–1	—
Shaving cream	—	1	—	0.1–0.3
Other shaving	1	2	>0.1–1	0.4–1
Skin care				
Cleansing creams, lotions, etc	5	38	>0.1–1	0.05–3
Depilatories	—	—	—	1
Face and neck skin care	8**	29	≤0.1–1**	0.001–6
Body and hand skin care		32		0.1–5
Body and hand sprays	—	—	—	2
Foot powders and sprays	—	—	—	0.5
Moisturizers	22	98	≤0.1–5	0.1–3
Night skin care	14	29	>0.1–1	0.08–2
Paste masks/mud packs	1	24	≤0.1	0.1–5
Skin fresheners	2	15	>0.1–1	0.01–3
Other skin care	5	46	≤0.1–1	0.1–5
Suntan				
Suntan gels, creams, liquids, and sprays	5	10	>0.1–1	0.1–2
Indoor tanning	—	2	—	0.1–2
Other suntan	2	10	>0.1–1	0.5
Total uses/ranges for Panthenol	**284**	**1538**	**≤0.1–25**	**0.00005–6**
	Pantothenic Acid			
Eye makeup				
Mascara	—	—	—	0.001–0.01
Other eye makeup	—	1	—	—
Makeup				
Face powders	—	—	—	0.001
Foundations	—	—	—	0.002
Shaving				
Aftershave lotions	—	—	—	0.001
Shaving cream	—	—	—	0.00001
Skin Care				
Moisturizers	—	1	—	0.003
Other skin care	—	1	—	0.001
Total uses/ranges for Pantothenic Acid	**—**	**3**	**—**	**0.00001–0.01**

*Includes two non-aerosol hair sprays

**These categories were combined originally, but are now separate

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VCRP data for Panthenol, Pantothenic Acid and Derivatives-2017

62507760	PANTHENOL	01A - Baby Shampoos	3
62507760	PANTHENOL	01B - Baby Lotions, Oils, Powders, and Creams	5
62507760	PANTHENOL	01C - Other Baby Products	14
62507760	PANTHENOL	02B - Bubble Baths	32
62507760	PANTHENOL	02D - Other Bath Preparations	13
62507760	PANTHENOL	03A - Eyebrow Pencil	9
62507760	PANTHENOL	03B - Eyeliner	19
62507760	PANTHENOL	03C - Eye Shadow	25
62507760	PANTHENOL	03D - Eye Lotion	102
62507760	PANTHENOL	03E - Eye Makeup Remover	37
62507760	PANTHENOL	03F - Mascara	359
62507760	PANTHENOL	03G - Other Eye Makeup Preparations	85
62507760	PANTHENOL	04A - Cologne and Toilet waters	10
62507760	PANTHENOL	04C - Powders (dusting and talcum, excluding aftershave talc)	1
62507760	PANTHENOL	04E - Other Fragrance Preparation	30
62507760	PANTHENOL	05A - Hair Conditioner	503
62507760	PANTHENOL	05B - Hair Spray (aerosol fixatives)	173
62507760	PANTHENOL	05C - Hair Straighteners	5
62507760	PANTHENOL	05D - Permanent Waves	5
62507760	PANTHENOL	05E - Rinses (non-coloring)	8
62507760	PANTHENOL	05F - Shampoos (non-coloring)	519
62507760	PANTHENOL	05G - Tonics, Dressings, and Other Hair Grooming Aids	472
62507760	PANTHENOL	05H - Wave Sets	38
62507760	PANTHENOL	05I - Other Hair Preparations	148
62507760	PANTHENOL	06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	172
62507760	PANTHENOL	06B - Hair Tints	1
62507760	PANTHENOL	06C - Hair Rinses (coloring)	22
62507760	PANTHENOL	06D - Hair Shampoos (coloring)	14
62507760	PANTHENOL	06F - Hair Lighteners with Color	1
62507760	PANTHENOL	06G - Hair Bleaches	1
62507760	PANTHENOL	06H - Other Hair Coloring Preparation	8
62507760	PANTHENOL	07A - Blushers (all types)	19
62507760	PANTHENOL	07B - Face Powders	20
62507760	PANTHENOL	07C - Foundations	54
62507760	PANTHENOL	07D - Leg and Body Paints	3
62507760	PANTHENOL	07E - Lipstick	45
62507760	PANTHENOL	07F - Makeup Bases	16
62507760	PANTHENOL	07G - Rouges	2
62507760	PANTHENOL	07H - Makeup Fixatives	3
62507760	PANTHENOL	07I - Other Makeup Preparations	24
62507760	PANTHENOL	08A - Basecoats and Undercoats	5
62507760	PANTHENOL	08B - Cuticle Softeners	8
62507760	PANTHENOL	08C - Nail Creams and Lotions	1
62507760	PANTHENOL	08E - Nail Polish and Enamel	34
62507760	PANTHENOL	08F - Nail Polish and Enamel Removers	8
62507760	PANTHENOL	08G - Other Manicuring Preparations	7
62507760	PANTHENOL	09A - Dentifrices	3

VCRP data for Panthenol, Pantothenic Acid and Derivatives-2017

62507760	PANTHENOL	09C - Other Oral Hygiene Products	2
62507760	PANTHENOL	10A - Bath Soaps and Detergents	213
62507760	PANTHENOL	10B - Deodorants (underarm)	11
62507760	PANTHENOL	10C - Douches	5
62507760	PANTHENOL	10E - Other Personal Cleanliness Products	288
62507760	PANTHENOL	11A - Aftershave Lotion	69
62507760	PANTHENOL	11D - Preshave Lotions (all types)	1
62507760	PANTHENOL	11E - Shaving Cream	16
62507760	PANTHENOL	11F - Shaving Soap	8
62507760	PANTHENOL	11G - Other Shaving Preparation Products	19
62507760	PANTHENOL	12A - Cleansing	229
62507760	PANTHENOL	12C - Face and Neck (exc shave)	352
62507760	PANTHENOL	12D - Body and Hand (exc shave)	357
62507760	PANTHENOL	12E - Foot Powders and Sprays	2
62507760	PANTHENOL	12F - Moisturizing	726
62507760	PANTHENOL	12G - Night	94
62507760	PANTHENOL	12H - Paste Masks (mud packs)	49
62507760	PANTHENOL	12I - Skin Fresheners	52
62507760	PANTHENOL	12J - Other Skin Care Preps	117
62507760	PANTHENOL	13A - Suntan Gels, Creams, and Liquids	14
62507760	PANTHENOL	13B - Indoor Tanning Preparations	44
62507760	PANTHENOL	13C - Other Suntan Preparations	12
81130	PANTHENOL, D-	01A - Baby Shampoos	1
81130	PANTHENOL, D-	02D - Other Bath Preparations	2
81130	PANTHENOL, D-	03A - Eyebrow Pencil	1
81130	PANTHENOL, D-	03D - Eye Lotion	7
81130	PANTHENOL, D-	03E - Eye Makeup Remover	3
81130	PANTHENOL, D-	03F - Mascara	31
81130	PANTHENOL, D-	03G - Other Eye Makeup Preparations	7
81130	PANTHENOL, D-	05A - Hair Conditioner	45
81130	PANTHENOL, D-	05B - Hair Spray (aerosol fixatives)	7
81130	PANTHENOL, D-	05C - Hair Straighteners	2
81130	PANTHENOL, D-	05F - Shampoos (non-coloring)	56
81130	PANTHENOL, D-	05G - Tonics, Dressings, and Other Hair Grooming Aids	19
81130	PANTHENOL, D-	05H - Wave Sets	1
81130	PANTHENOL, D-	05I - Other Hair Preparations	33
81130	PANTHENOL, D-	06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	4
81130	PANTHENOL, D-	06D - Hair Shampoos (coloring)	4
81130	PANTHENOL, D-	06H - Other Hair Coloring Preparation	2
81130	PANTHENOL, D-	07A - Blushers (all types)	7
81130	PANTHENOL, D-	07C - Foundations	2
81130	PANTHENOL, D-	07E - Lipstick	18
81130	PANTHENOL, D-	07F - Makeup Bases	1
81130	PANTHENOL, D-	07I - Other Makeup Preparations	7
81130	PANTHENOL, D-	08A - Basecoats and Undercoats	3
81130	PANTHENOL, D-	08B - Cuticle Softeners	5

VCRP data for Panthenol, Pantothenic Acid and Derivatives-2017

81130	PANTHENOL, D-	08C - Nail Creams and Lotions	1
81130	PANTHENOL, D-	08E - Nail Polish and Enamel	5
81130	PANTHENOL, D-	08F - Nail Polish and Enamel Removers	5
81130	PANTHENOL, D-	08G - Other Manicuring Preparations	10
81130	PANTHENOL, D-	10A - Bath Soaps and Detergents	16
81130	PANTHENOL, D-	10E - Other Personal Cleanliness Products	13
81130	PANTHENOL, D-	11A - Aftershave Lotion	11
81130	PANTHENOL, D-	11G - Other Shaving Preparation Products	1
81130	PANTHENOL, D-	12A - Cleansing	17
81130	PANTHENOL, D-	12C - Face and Neck (exc shave)	35
81130	PANTHENOL, D-	12D - Body and Hand (exc shave)	23
81130	PANTHENOL, D-	12E - Foot Powders and Sprays	1
81130	PANTHENOL, D-	12F - Moisturizing	61
81130	PANTHENOL, D-	12G - Night	8
81130	PANTHENOL, D-	12H - Paste Masks (mud packs)	7
81130	PANTHENOL, D-	12I - Skin Fresheners	5
81130	PANTHENOL, D-	12J - Other Skin Care Preps	26
81130	PANTHENOL, D-	13B - Indoor Tanning Preparations	3
81130	PANTHENOL, D-	13C - Other Suntan Preparations	2
16485102	PANTHENOL, DL-	02B - Bubble Baths	2
16485102	PANTHENOL, DL-	02D - Other Bath Preparations	1
16485102	PANTHENOL, DL-	03B - Eyeliner	1
16485102	PANTHENOL, DL-	03C - Eye Shadow	1
16485102	PANTHENOL, DL-	03D - Eye Lotion	8
16485102	PANTHENOL, DL-	03E - Eye Makeup Remover	3
16485102	PANTHENOL, DL-	03F - Mascara	15
16485102	PANTHENOL, DL-	03G - Other Eye Makeup Preparations	6
16485102	PANTHENOL, DL-	04E - Other Fragrance Preparation	2
16485102	PANTHENOL, DL-	05A - Hair Conditioner	31
16485102	PANTHENOL, DL-	05B - Hair Spray (aerosol fixatives)	1
16485102	PANTHENOL, DL-	05C - Hair Straighteners	1
16485102	PANTHENOL, DL-	05E - Rinses (non-coloring)	3
16485102	PANTHENOL, DL-	05F - Shampoos (non-coloring)	33
16485102	PANTHENOL, DL-	05G - Tonics, Dressings, and Other Hair Grooming Aids	24
16485102	PANTHENOL, DL-	05H - Wave Sets	2
16485102	PANTHENOL, DL-	05I - Other Hair Preparations	28
16485102	PANTHENOL, DL-	06B - Hair Tints	1
16485102	PANTHENOL, DL-	06H - Other Hair Coloring Preparation	1
16485102	PANTHENOL, DL-	07C - Foundations	12
16485102	PANTHENOL, DL-	07I - Other Makeup Preparations	7
16485102	PANTHENOL, DL-	08A - Basecoats and Undercoats	1
16485102	PANTHENOL, DL-	10A - Bath Soaps and Detergents	9
16485102	PANTHENOL, DL-	10B - Deodorants (underarm)	1
16485102	PANTHENOL, DL-	10E - Other Personal Cleanliness Products	5
16485102	PANTHENOL, DL-	11A - Aftershave Lotion	6
16485102	PANTHENOL, DL-	12A - Cleansing	13

VCRP data for Panthenol, Pantothenic Acid and Derivatives-2017

16485102	PANTHENOL, DL-	12C - Face and Neck (exc shave)	62
16485102	PANTHENOL, DL-	12D - Body and Hand (exc shave)	54
16485102	PANTHENOL, DL-	12F - Moisturizing	108
16485102	PANTHENOL, DL-	12G - Night	10
16485102	PANTHENOL, DL-	12H - Paste Masks (mud packs)	16
16485102	PANTHENOL, DL-	12I - Skin Fresheners	3
16485102	PANTHENOL, DL-	12J - Other Skin Care Preps	4
16485102	PANTHENOL, DL-	13B - Indoor Tanning Preparations	2
79834	PANTOTHENIC ACID	03C - Eye Shadow	8
79834	PANTOTHENIC ACID	03D - Eye Lotion	1
79834	PANTOTHENIC ACID	03G - Other Eye Makeup Preparations	1
79834	PANTOTHENIC ACID	05A - Hair Conditioner	9
79834	PANTOTHENIC ACID	05C - Hair Straighteners	1
79834	PANTOTHENIC ACID	05I - Other Hair Preparations	5
79834	PANTOTHENIC ACID	07A - Blushers (all types)	6
79834	PANTOTHENIC ACID	07B - Face Powders	2
79834	PANTOTHENIC ACID	07I - Other Makeup Preparations	1
79834	PANTOTHENIC ACID	08G - Other Manicuring Preparations	1
79834	PANTOTHENIC ACID	10A - Bath Soaps and Detergents	1
79834	PANTOTHENIC ACID	11A - Aftershave Lotion	1
79834	PANTOTHENIC ACID	11E - Shaving Cream	1
79834	PANTOTHENIC ACID	12A - Cleansing	1
79834	PANTOTHENIC ACID	12C - Face and Neck (exc shave)	8
79834	PANTOTHENIC ACID	12D - Body and Hand (exc shave)	1
79834	PANTOTHENIC ACID	12F - Moisturizing	24
79834	PANTOTHENIC ACID	12J - Other Skin Care Preps	6
667834	PANTHENYL ETHYL ETHER	03B - Eyeliner	3
667834	PANTHENYL ETHYL ETHER	03C - Eye Shadow	2
667834	PANTHENYL ETHYL ETHER	03D - Eye Lotion	2
667834	PANTHENYL ETHYL ETHER	03F - Mascara	4
667834	PANTHENYL ETHYL ETHER	03G - Other Eye Makeup Preparations	3
667834	PANTHENYL ETHYL ETHER	05A - Hair Conditioner	115
667834	PANTHENYL ETHYL ETHER	05B - Hair Spray (aerosol fixatives)	8
667834	PANTHENYL ETHYL ETHER	05F - Shampoos (non-coloring)	101
667834	PANTHENYL ETHYL ETHER	05G - Tonics, Dressings, and Other Hair Grooming Aids	97
667834	PANTHENYL ETHYL ETHER	05H - Wave Sets	2
667834	PANTHENYL ETHYL ETHER	05I - Other Hair Preparations	6
667834	PANTHENYL ETHYL ETHER	06C - Hair Rinses (coloring)	1
667834	PANTHENYL ETHYL ETHER	06D - Hair Shampoos (coloring)	1
667834	PANTHENYL ETHYL ETHER	07C - Foundations	2
667834	PANTHENYL ETHYL ETHER	07E - Lipstick	3
667834	PANTHENYL ETHYL ETHER	07G - Rouges	1
667834	PANTHENYL ETHYL ETHER	10A - Bath Soaps and Detergents	9
667834	PANTHENYL ETHYL ETHER	10E - Other Personal Cleanliness Products	3
667834	PANTHENYL ETHYL ETHER	12C - Face and Neck (exc shave)	8

VCRP data for Panthenol, Pantothenic Acid and Derivatives-2017

667834	PANTHENYL ETHYL ETHER	12D - Body and Hand (exc shave)	1
667834	PANTHENYL ETHYL ETHER	12F - Moisturizing	6
667834	PANTHENYL ETHYL ETHER	12G - Night	1
667834	PANTHENYL ETHYL ETHER	12J - Other Skin Care Preps	3
98133472	PANTHENYL TRIACETATE	03D - Eye Lotion	1
98133472	PANTHENYL TRIACETATE	03G - Other Eye Makeup Preparations	1
98133472	PANTHENYL TRIACETATE	05A - Hair Conditioner	2
98133472	PANTHENYL TRIACETATE	05F - Shampoos (non-coloring)	1
98133472	PANTHENYL TRIACETATE	07B - Face Powders	3
98133472	PANTHENYL TRIACETATE	07C - Foundations	1
98133472	PANTHENYL TRIACETATE	07E - Lipstick	36
98133472	PANTHENYL TRIACETATE	07F - Makeup Bases	3
98133472	PANTHENYL TRIACETATE	07I - Other Makeup Preparations	3
98133472	PANTHENYL TRIACETATE	08A - Basecoats and Undercoats	2
98133472	PANTHENYL TRIACETATE	08B - Cuticle Softeners	1
98133472	PANTHENYL TRIACETATE	10A - Bath Soaps and Detergents	1
98133472	PANTHENYL TRIACETATE	12A - Cleansing	8
98133472	PANTHENYL TRIACETATE	12C - Face and Neck (exc shave)	16
98133472	PANTHENYL TRIACETATE	12F - Moisturizing	9
98133472	PANTHENYL TRIACETATE	12G - Night	1
98133472	PANTHENYL TRIACETATE	12I - Skin Fresheners	2
98133472	PANTHENYL TRIACETATE	12J - Other Skin Care Preps	5
98133472	PANTHENYL TRIACETATE	13A - Suntan Gels, Creams, and Liquids	2
98133472	PANTHENYL TRIACETATE	13C - Other Suntan Preparations	1
137086	CALCIUM PANTOTHENATE	01C - Other Baby Products	1
137086	CALCIUM PANTOTHENATE	02B - Bubble Baths	1
137086	CALCIUM PANTOTHENATE	03D - Eye Lotion	10
137086	CALCIUM PANTOTHENATE	03E - Eye Makeup Remover	1
137086	CALCIUM PANTOTHENATE	03F - Mascara	2
137086	CALCIUM PANTOTHENATE	03G - Other Eye Makeup Preparations	6
137086	CALCIUM PANTOTHENATE	05A - Hair Conditioner	10
137086	CALCIUM PANTOTHENATE	05B - Hair Spray (aerosol fixatives)	1
137086	CALCIUM PANTOTHENATE	05E - Rinses (non-coloring)	1
137086	CALCIUM PANTOTHENATE	05F - Shampoos (non-coloring)	12
137086	CALCIUM PANTOTHENATE	05G - Tonics, Dressings, and Other Hair Grooming Aids	8
137086	CALCIUM PANTOTHENATE	05I - Other Hair Preparations	10
137086	CALCIUM PANTOTHENATE	06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	4
137086	CALCIUM PANTOTHENATE	07C - Foundations	6
137086	CALCIUM PANTOTHENATE	07I - Other Makeup Preparations	5
137086	CALCIUM PANTOTHENATE	08A - Basecoats and Undercoats	11
137086	CALCIUM PANTOTHENATE	08B - Cuticle Softeners	1
137086	CALCIUM PANTOTHENATE	08C - Nail Creams and Lotions	2
137086	CALCIUM PANTOTHENATE	08D - Nail Extenders	1
137086	CALCIUM PANTOTHENATE	08E - Nail Polish and Enamel	32
137086	CALCIUM PANTOTHENATE	08G - Other Manicuring Preparations	19

VCRP data for Panthenol, Pantothenic Acid and Derivatives-2017

137086	CALCIUM PANTOTHENATE	11A - Aftershave Lotion	1
137086	CALCIUM PANTOTHENATE	11G - Other Shaving Preparation Products	1
137086	CALCIUM PANTOTHENATE	12A - Cleansing	7
137086	CALCIUM PANTOTHENATE	12C - Face and Neck (exc shave)	41
137086	CALCIUM PANTOTHENATE	12D - Body and Hand (exc shave)	16
137086	CALCIUM PANTOTHENATE	12F - Moisturizing	33
137086	CALCIUM PANTOTHENATE	12G - Night	11
137086	CALCIUM PANTOTHENATE	12H - Paste Masks (mud packs)	1
137086	CALCIUM PANTOTHENATE	12I - Skin Fresheners	1
137086	CALCIUM PANTOTHENATE	12J - Other Skin Care Preps	6
137086	CALCIUM PANTOTHENATE	13B - Indoor Tanning Preparations	2
137086	CALCIUM PANTOTHENATE	13C - Other Suntan Preparations	1

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Memorandum

TO: Bart Heldret, P.h.D., Executive Director
COSMETIC INGREDIENT REVIEW (CIR)

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

DATE: October 18, 2017

SUBJECT: Tentative Report: Safety Assessment of Panthenol, Pantothenic Acid, and Derivatives as Used in Cosmetics

Introduction - As Pantothenic Acid is included in the first sentence, it does not need to be included in the list of ingredients.

Cosmetic Use - Please correct: "are reportedly used fragrance preparations."

Acute, Summary - If kg in ">3 ml/kg/day" represents body weight, "LC_{50}" should be "LD_{50}".

Acute - It is not clear where the LD_{50} of 2 g/kg for DL-Panthenyl Ethyl Ether comes from as it is stated in Table 7 (and later in the text of the Acute section) as >2 g/kg.

Only one monkey was tested so the "s" needs to be deleted.

Subchronic - Rather than saying the rats were dosed "orally" please be more specific, e.g., gavage, diet, drinking water.

Other Relevant Studies, previous report summary - Please provide some indication of the concentrations/doses tested.

Cytotoxicity, Summary - The study in the Skin^2 ZK 1200 Model should be moved to the *in vitro* skin irritation section.

Therapeutic Effect - This is not a relevant subheading for a CIR report that is concerned about safety. How was the inflammatory response measured in the study described in reference 77?

Irritation, Summary - It should be made clear that the 0.125% Panthenyl Ethyl Ether study was of a leave-on hair conditioner, and according to Table 8, the skin of the rabbits was abraded on days 1-6 and 10-12.

Sensitization - How much Panthenol was in the lotion evaluated in a guinea pig maximization test?

Summary - Was there only one 510(k) premarket notification for three different devices?

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The Summary says that mice were exposed to "~20% Calcium Pantothenoate (653 days)". This would be an extremely high water or food concentration. Earlier in the report it says the mice were exposed in Calcium Pantothenate in drinking water at a concentration that resulted in a dose of ~20 mg/kg (presumably this is a daily dose).

Discussion - As time passes, and when the report is published, the April 10th-11th date will not be relevant.

Table 2 - Please correct "Feely"

Table 3 - Please delete "Current" as some of the information in the report is not current and the information will not be current by the time the report is published. The dates in the heading row indicates when the information was collected.

Table 5, *in vitro*, animal - It is not clear why reference 56 was not obtained. Additional details are likely to be found in the complete paper.

Table 5, *in vivo,* human - The two studies on D-Panthenol and Panthenyl Triacetate appear to be the same study from two different sources.

Table 6 - The study on Calcium Pantothenate in rats (reference 78) is not an ADME study. It does not belong in Table 6. This study is appropriately presented in the Radioprotective Effect section.