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Final Report on the Safety Assessment of Panthenol and Pantothenic Acid

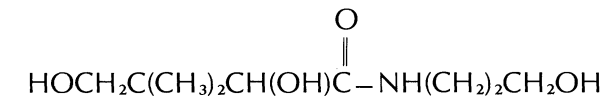
Panthenol is the alcohol analogue of Pantothenic Acid (vitamin B_3). The LD_{50} for D-Panthenol administered orally to mice was 15 g/kg. No toxicological effects were associated with the subchronic and/or chronic oral administration of Panthenol to rats. Minimal cutaneous hyperkeratosis was noted in 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]:



$$HOCH_2C(CH_3)_2CH(OH)\overset{\overset{O}{\|}}{C}-NH(CH_2)_2CH_2OH$$

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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