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

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (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This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated.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 dextrorotary (D-), levorotary (L-), and racemic (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.

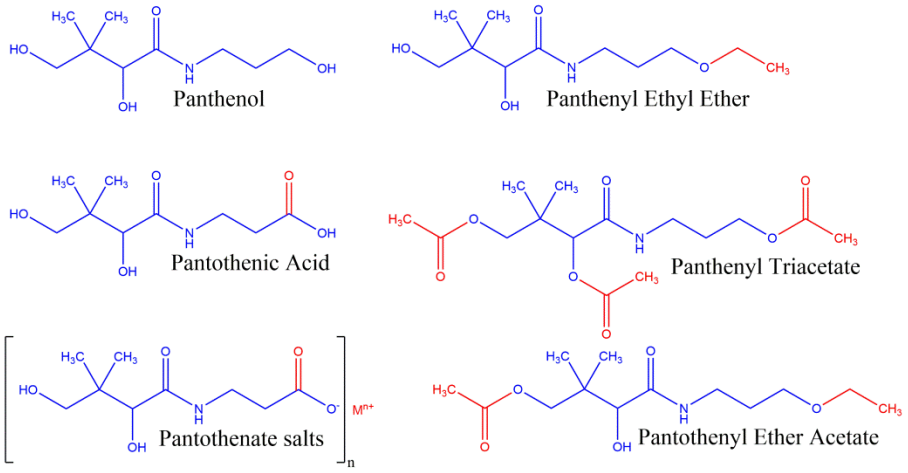


Figure 1. Panthenol, Pantothenic Acid, and derivatives.

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 chemically stable than free Pantothenic Acid and Sodium Pantothenate, which are chemically unstable.[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 afected 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, potentially *N*-nitrosatable, amines as impurities; and, thus cautioned that these ingredients should not be used in cosmetic products in which *N*-nitroso compounds may be formed.

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 quantities of these ingredients are below what would be typical from dietary intake, thereby underscoring the systemic 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 converted to Panthenol and Pantothenic Acid, 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 acute dermal, oral, and inhalation 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. Negative results were obtained of multiple Ames tests and mammalian cell gene mutation assays and in chromosomal aberration tests.

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. 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, and the overall favorable safety profile of the ingredients in this family, 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]

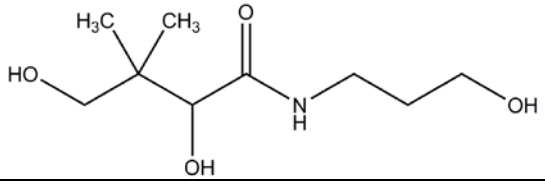
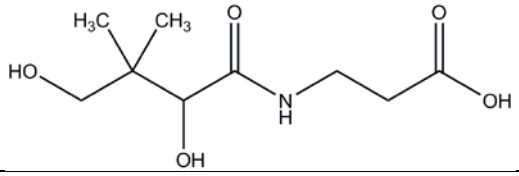
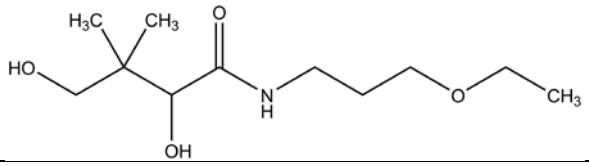
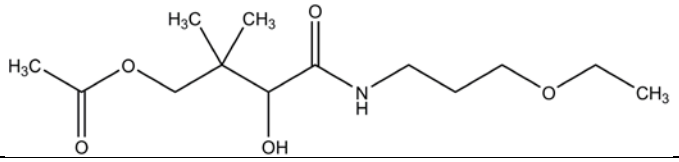
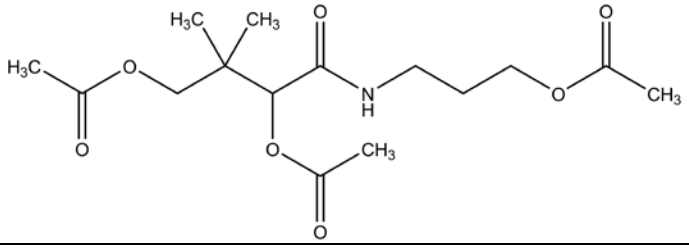
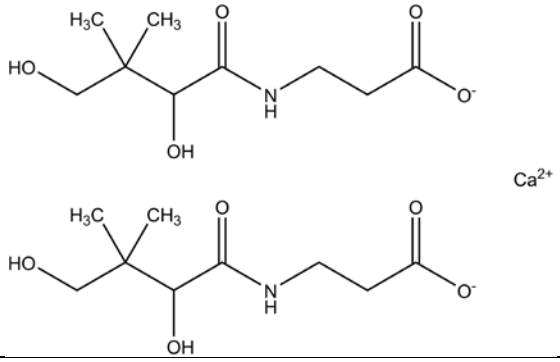
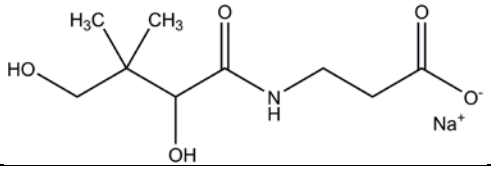
Ingredient CAS No.	Definition & Structure	Function
Panthenol 81-13-0 (D-) 16485-10-2 (D,L-)	Panthenol is the alcohol that conforms to the formula: 	Hair Conditioning Agents; Skin-Conditioning Agents-Humectant; Solvents
Pantothenic Acid 79-83-4	Pantothenic Acid is the organic acid that conforms to the 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	*Penetration Study*: cadaver fingernail plates were used (washed with saline and re-hydrated for 3 h on a cloth containing saline) *Kinetic Study*: same type of samples used as above; n=3/ 7 groups	*Penetration Study*: 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 *Kinetic Study*: 2% ^{14}C-Panthenol (0.11 µCi) in 98% nail formulation base (same composition as above)	N/A	*Penetration Study*: 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 *Kinetic Study*: 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	*Penetration Study*: 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 *Kinetic Study*: 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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