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

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All interested persons are provided 60 days from the above date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Director, Dr. Lillian J. Gill.

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INTRODUCTION

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

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

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

In 1987, The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed Panthenol and Pantothenic Acid and concluded that they were safe for use in cosmetics.[2] In accordance with CIR Procedures, these ingredients were re-reviewed in 2006 and the Panel determined to not reopen the safety assessment, thereby reaffirming the safety of Panthenol and Pantothenic Acid.[3] Relevant data from the 1987 and 2004 reports have been summarized and are included (*italicized text*) at the beginning of the appropriate sections of this safety assessment. The safety assessments from 1987 and 2004 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). Additionally, updated frequency of use data for Panthenol and Pantothenic Acid are included and updated concentration of use data will be included in this safety assessment when those data become available. Pantothenic Acid, the water-soluble vitamin B_5,[4] and its alcohol analogue, Panthenol, are closely related to the five derivatives above and, therefore, are included in this safety assessment; this report is not a re-review. The high frequency of use of Panthenyl Ethyl Ether (362 uses) in cosmetic formulations, as reported by the Food and Drug Administration's (FDA) Voluntary Cosmetic Registration Program (VCRP),[5] is the reason for reviewing this group of ingredients.

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). Calcium Pantothenate is more chemically stable than the unstable forms of free Pantothenic Acid and Sodium Pantothenate.[17] The dextrorotatory (D-) forms and dextrorotatory, levorotatory (DL-) 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.[18]

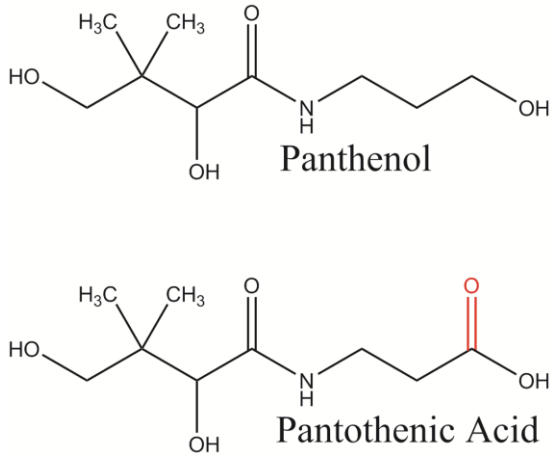


Figure 1. Panthenol and Pantothenic Acid, the core structures of the ingredients in this report.

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.[6,19] Pantothenic Acid is a hygroscopic oil with a molecular weight of 219 g/mol and a boiling point of 551 °C.[18,20] Calcium Pantothenate and Sodium Pantothenate, salts of Pantothenic Acid, are highly hygroscopic, water soluble, crystalline solids with melting points between 170 and 200 degrees Celsius, and formula weights of 476 g/mol and 241 g/mol, respectively (Table 2).[18,21-23] The remaining ingredients in this report are liquids with boiling points greater than 400 degrees Celsius, and molecular weights ranging from 233 to 331 g/mol.[24-26]

Method of Manufacture

Panthenol

D-Panthenol is reported to be produced by a condensation reaction of D-pantolactone with 3-aminopropanol in the presence of methanol and dichloromethane.[27]

Pantothenic Acid

Pantothenic Acid is synthesized in the presence of adenosine triphosphate by an enzyme-catalyzed condensation reaction of pantoic acid and beta-alanine.[28]

Calcium Pantothenate

Calcium Pantothenate is synthesized for commercial use from isobutyraldehyde and formaldehyde by 1,1-dimethyl-2-hydroxy-propionaldehyde and pantolactone (21CFR184.1212). A method used in industry to produce D-Calcium Pantothenate involves reacting calcium hydroxide or calcium oxide, in the presence of methanol, with D-pantolactone and β-alanine. Residual solvents are then removed and the aqueous solution dried.[27]

Sodium Pantothenate

Sodium Pantothenate is prepared by reacting R-pantolactone and sodium beta-alaninate in ethanol or methanol.[28]

Impurities

Panthenol

According to the *Food Chemicals Codex (FCC)*, food grade specifications limit lead impurities in DL-Panthenol to not-more-than (NMT) 2 mg/kg (2 ppm) based on the lead-limit test performed by the flame atomic absorption spectrophotometric method.[19] Aminopropanol may be present in DL-Panthenol at NMT 0.1% as determined by titration (10 g sample aminopropanol dissolved in 25 ml of water titrated with 0.1 N sulfuric acid). Sulfated ash residue on ignition of DL-Panthenol should contain NMT 0.1%.

D-Panthenol, when used as a nutritional additive in animal feed, was reported to be 99.5% ± 0.15% pure (drying loss 0.3%-0.4%)[17] and in another study 100.1% ± 0.1% pure for the anhydrous product (0.02%-0.06% water).[27] The residual solvent impurities from 5 batches tested were methanol and dichloromethane.[17,27] Other reported impurities were 3-aminopropionic acid (< 0.5%), lead (< 20 mg/kg), and sulphated ash (< 0.1%).

Calcium Pantothenate

The FCC specifies that D-Calcium Pantothenate or a racemic mixture of DL-Calcium Pantothenate should have NMT 2 mg/kg (2 ppm) lead as determined by the lead-limit test (flame atomic absorption spectrophotometric method). 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.[19] The calcium content should be not-less-than (NLT) 8.2% and NMT 8.6% (dried basis), and loss on drying should be NMT 5.0%. For either D- or DL-Calcium Pantothenate (calcium chloride) double salt, arsenic impurities should be NMT 3 mg/kg (3 ppm) in an arsenic-limit test and lead impurities NMT 2 mg/kg (2 ppm) in a lead-limit test; loss on drying should be NMT 5%; calcium content should be NLT 12.4% and NMT 13.6% (dried basis); chloride content should be 10.5% to 12.1% (dried basis).

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%)[17] and in another study 100.3% ± 1.3% pure (drying loss 1.1%-2.8%).[27] 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).[17,27] The "dusting potential" (mass of the particles per m^3 drawn from a rotating drum containing the test material)[29] of D-Calcium Pantothenate was reported to be 1.1 g/m^3 and the particle size fraction < 50 µm was measured to be 7% by laser diffraction.[17] 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%.[27] The dusting potential is the mass of the particles per m3 that is drawn from a rotating drum containing the test material

Natural Occurrence

Pantothenic Acid

Pantothenic Acid naturally occurs in all animal and plant tissues.[18] As a vitamin in the B complex, it is vital for coenzyme A synthesis in mammalian cells. Jelly from queen bees, rice bran, molasses, and liver are all sources of Pantothenic Acid.[18] Additional sources are meat, whole grains, legumes, eggs, milk, fruits, and vegetables.[30]

USE

Cosmetic

The CIR Expert Panel evaluates the safety of the cosmetic ingredients included in this assessment based in part 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 2016 indicated that of the ingredients reported in this safety assessment, Panthenol, D-Panthenol, and Panthenyl Ethyl Ether had the highest number of reported uses at 5475, 502, and 362, respectively (Table 3).[5] 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 in 2015-2017 (Table 3) 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),[31] Panthenyl Ethyl Ether (2% in foundation),[32] and Panthenyl Triacetate (2% in lipstick and other make-up preparations).[32] 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.[3] The highest maximum concentrations of use for Panthenol and Pantothenic Acid are not substantially different in 2017[31] as compared to values reported in 2004.[3] In 2017, maximum concentrations of use were reported for Panthenol in baby products (5% in baby shampoos and 2.5% in baby lotions, oils, and creams);[31] there were no reported concentrations of use for Panthenol in baby products in 2004.[3] The frequency of use for Panthenol increased from 1538 in 2002[3] to 5475 uses reported by the VCRP in 2016 in all categories represented in Table 3.[5] Frequency of use for Pantothenic Acid increased from the 3 uses in 2002[3] to 58 uses (48 of which are leave-on use) reported in 2016.[5]

There are no frequency of use or concentration of use reported for Panthenyl Ethyl Ether Acetate and Sodium Pantothenate.[5,32]

The ingredients in this safety assessment were reported to be used in cosmetic sprays, including hair sprays, body and hand sprays, and fragrances, and could possibly be inhaled. For example, Panthenol, Panthenyl Ethyl Ether and Calcium Pantothenate were reportedly used in aerosol and pump hair sprays at concentrations up to 0.6%, 0.5%, and 0.19%, respectively.[31,32] Panthenol and Panthenyl Ethyl Ether were used in body and hand sprays at concentrations up to 5% and 0.5%, respectively.[31,32] According to the VCRP, Panthenol and DL-Panthenol were reportedly used in fragrance preparation.[5] Panthenol was used in colognes up to 0.5% and in deodorant sprays up to 0.1%.[31] 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.[33-36] 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.[33,35] 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.[35] 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 were reportedly used in face powders at concentrations up to 0.5%, 0.003%, and 0.01%, respectively, and could possibly be inhaled.[31,32] The VCRP indicated that Pantothenic Acid was reportedly used in face powders.[5] 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.[37-39]

Panthenol (3% in eye lotions), Pantothenic Acid (0.001% in eye shadows), and Panthenyl Ethyl Ether (0.84% in eye shadows) were reported to be used in cosmetic formulations indicative of potential eye exposure.[31,32] Panthenol (2.5% in other personal cleanliness products; 2% in lipstick) and Panthenyl Triacetate (2% in lipstick) were reported to be used in formulations with possible mucous membrane exposure and/or ingestion.[31,32] The VCRP data indicated that Calcium Pantothenate was reported to be used in the FDA product category of "other baby products" (no concentrations of use were reported).[5]

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.[40]

Non-Cosmetic

The non-cosmetic uses of Panthenol, Pantothenic Acid, Calcium Pantothenate, and Sodium Pantothenate (Table 4), as specified in the CFR Title 21 and Title 9, are largely as nutritional food additives. 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). 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 GRAS status in various over-the-counter (OTC) drug products for Panthenol, Pantothenic Acid, and Calcium Pantothenate (21CFR310.527, 21CFR310.545).

Panthenol

Panthenol and D-Panthenol were found on numerous drug product labels.[41,42] For example, D-Panthenol (15 mg/5 ml) was listed on a new drug application prescription product label for an intravenous vitamin mixture, to be administered to adults and children over age 11, in the treatment of vitamin deficiency.[42] Additionally, several OTC drug product labels listed 0.2% D-Panthenol for topical scalp use in hair loss prevention, 0.2 % D-Panthenol for topical use in hair dying, and 0.5% Panthenol for topical use as a skin protectant; however, these products have not been evaluated by the FDA. D-Panthenol (1.5 to 15 mg/ml), is listed as an ingredient in FDA approved prescription drug products for use as injectable vitamins.[43] 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 (concentration not specified) is listed as an ingredient (not active) in OTC suncreens[44] and 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] A British patent lists D-Panthenol (0.25% wt.) as an ingredient in an oral formulation used to treat inflammatory gum disease.[45]

Pantothenic Acid

Pantothenic Acid is listed on many drug product labels for various uses, such as, OTC homeopathic remedies intended to treat respiratory, gastrointestinal, and urinary issues, as well as, fatigue, dry skin, and nail problems.[46] However, these claims have not been substantiated by the FDA. A prescription drug product label included Pantothenic Acid (8 mg), intended for use in a prenatal vitamin, but its safety and efficacy have not been approved by the FDA.

Calcium Pantothenate

Calcium Pantothenate (10 mg) was found on the label of a prescription drug product intended to be used to improve the nutrition of renal dialysis patients; this product has not been approved by the FDA.[46] 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

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.[47] The gel formulation was applied to an 8 cm^2 skin area in the diffusion cell; the receptor cell fluid (water), in contact with the dermis, was collected periodically between 2 and 240 minutes after application of the formulation. The penetration of D-Panthenol into pig skin was enhanced by the use of the 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).

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.[48] 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%, v/v, polyethylene glycol) was collected up to 60 minutes post-application, and then skin samples were stripped 20x. In the skin samples not stripped prior to test substance application, the amount of applied radioactivity detected was 84% in the stratum corneum, 6% in the epidermis, and 4% in the dermis. For the 5x and 10x stripped samples the applied radioactivity detected was 81% and 72% in the stratum corneum, was 8.7% and 18% in the epidermis, and was 6% and 6.3% in the dermis, respectively.

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 microspectroscopy at 1, 5, and 24 hours following application.[49] At all time points, D-Panthenol and Panthenyl Triacetate were

detected in the upper layers of the stratum corneum; D-Panthenol was detected to a lesser extent and Panthenyl Triacetate was not detected at depths of 25 µm. D-Panthenol levels were detected in the stratum corneum upper layers down to 25 µm 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.

Panthenyl Triacetate has been reported to penetrate underarm skin and has been used to help treat skin issues associated with underarm shaving.[50]

Nail Penetration

In Vitro

Human

An experiment examined the penetration of 1-^{14}C-Panthenol through human fingernails.[51] 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. The test substance, 15 µl 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 1x/day for 1 week. Results showed that by day 7 the radioactivity from the formulation was 2x higher in the interior nail plate and 3x higher in the cotton ball compared to the radioactivity from the 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 in 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 increased nail hydration and thermodynamic activity of ^{14}C-Panthenol.

Penetration Enhancement

In Vitro

Animal

D-Panthenol

D-Panthenol was evaluated for its ability to enhance the penetration of metronidazole in pig ear skin (~0.5 mm thickness, dermatomed) in a flow-through diffusion cell experiment.[52] Metronidazole (concentration not specified) was prepared in phosphate buffered saline and added to a formulation containing either D-Panthenol (concentration not specified) or transcutol (5% wt). The formulation (2 ml) was applied to 1.6 cm diameter skin membrane samples in diffusion cells with a 32 °C circulating water bath. The membranes were hydrated in the diffusion cell for 1 hour before applying the formulation. The receptor cell fluid (1.5 ml/h flow rate) was collected every 2 hours for 24 hours post-application. The results showed that the receptor solution contained 0.31% metronidazole and 0.45% transcutol (percent of donor solution total amount). D-Panthenol was below the limit of detection in the receptor fluid, indicating slow diffusion through the membrane. The membrane was not evaluated to identify formulation components that may have diffused into the skin samples. The researchers concluded that D-Panthenol and transcutol increased the penetration of metronidazole through the skin.

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.[53] 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 (polyvinylalcohol matrix with water), or PVP (polyvinyl pyrrolidon matrix with 2% hydroxypropylmethylcellulose gel and water). The polymer matrix test formulations were applied to the stratum corneum in the diffusion cell. The dermis of excised, shaved rat skin faced the receptor cell, containing propylene glycol: water (40:60, w/w) at 32 °C. The receptor fluid 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 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 also 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

Panthenol can be oxidized in the skin to Pantothenic Acid.[2] 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. The Pantothenate content increased 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.[54]

D-Panthenol

D-Panthenol, a synthetic pro-vitamin, is oxidized in the body to Pantothenic Acid, the only biologically active form of the B vitamin.[17]

Panthenyl Triacetate

Panthenyl Triacetate has been reported to convert to Panthenol and Pantothenic Acid upon dermal application to human skin.[49,50]

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

In Vitro

Human

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.[49] 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 participated in glycolysis.

In Vivo

Animal

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.[55] In another experiment, rats were dosed daily in the diet with 0, 4, 8, or 16 mg/kg Calcium Pantothenate for 28 days.[56] In the control group (vitamin deficient group), body weight gain, total food intake, and 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.[57] Notable results included a decrease in body weight gain and food intake in the controls, an increase in brain and testis weights in the controls, an increase in lung and spleen weights in the animals exposed to 3% concentration, 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 (reflecting an adverse effect on nicotinamide metabolism) in the controls and the animals exposed to 1% and 3% concentrations, 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 an additional test with 5% Calcium Pantothenate in the diet; 4 of the 5 rats died within 2 days from severe diarrhea.

Rats were orally dosed with 1, 2, 5, or 10 mg/kg Calcium Pantothenate or Panthenol, then 24 hour urine and feces samples were collected and analyzed.[58] 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.[59]

In a test on rats having undergone a partial hepatectomy and irradiation (Sr^{90}-Y^{90} applied at 3.6 rep/sec, beta rays, for 2.48 min), 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 as compared to the hepatectomized and irradiated animals that had not been treated with Calcium Pantothenate and experienced skin changes from irradiation and hepatocyte disfunction.[60]

Radioactive Sodium Pantothenate (location of label was not specified) was orally administered to dogs (0.8 mg/kg) and rats (1.6 mg/kg) and urine was analyzed.[61] 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.[62]

Following oral administration (dosage not specified), Pantothenic Acid was absorbed from the gastrointestinal tract; urinary excretion of unchanged Pantothenic Acid was approximately 70% and in feces about 30%.[30]

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.[2]

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.[2] *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 in mice and rabbits, LD_{50}s of > 10 g/kg and 4 g/kg, respectively, were reported.*

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

Rats were dermally exposed to a single application of 2 g/kg (no vehicle) DL-Panthenyl Ethyl Ether semi-occlusively for 24 hours using good laboratory practice (GLP) and in accordance with the Organization for Economic Cooperation and Development Test Guideline (OECD TG) 402 (Acute Dermal Toxicity).[6] There were no deaths or clinical signs noted; the only observations were scabs in one male on days 5 through 9 and low body weight gain in 3 females during week 2. The LD_{50} was reported to be > 2 g/kg.

In two separate experiments, rats were orally exposed to single dosages of 10 g/kg D-Panthenol[7] or 2 g/kg DL-Panthenyl Ethyl Ether[6] 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 pathology was normal.[7] The LD_{50} of DL-Panthenyl Ethyl Ether was reported to be > 2 g/kg; there were no deaths or clinical signs noted and necropsy was unremarkable.[6] In other tests of animals orally exposed to single doses of D-Calcium Pantothenate, no toxicity was reported in dogs and monkeys and the LD_{50} was reported to be 10 g/kg and > 10 g/kg in mice and rats, respectively.[63]

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 from 3 hours to 7 days after exposure and piloerection, which were both reversed by day 8.[27] No mortalities were reported.

Short-Term Toxicity

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

Animal

Rats were administered 0 or 0.03% Pantothenic Acid daily in their drinking water for 9 weeks; the only statistically significant finding was an ~2-fold increase in basal plasma corticosterone levels in the Pantothenic Acid group, compared to the control group.[64]

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).[2] *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.*

Summaries of the subchronic toxicity studies are presented below and details are presented in Table 8.

Animal

A NOAEL of 200 mg/kg/day was reported in rats orally dosed with up to 200 mg/kg/day DL-Panthenol for 3 months (OECD TG 408).[6] When rats were orally exposed to D-Calcium Pantothenate (up to 200 mg/kg/day) in the diet 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.[2]

A summary of the chronic toxicity studies are presented below and details are presented in Table 8.

Animal

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.[63] Calcium Pantothenate (~20 mg/kg) was administered daily in drinking water to mice for their life span.[65] 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).[2] *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.

In Vitro

D-Pantothenate (salt form not specified) was evaluated to determine its effect on the development of hamster embryos.[66] Embryos from pregnant females were removed 10 hours after egg activation and placed in various media containing 1 µmol/l to 1 mmol/l D-Pantothenate or a control medium without D-Pantothenate. Embryos were incubated at 37.5 °C for 72 hours, then some were fixed and stained and cell numbers were calculated while others were implanted into female hamsters to evaluate post-implantation viability. By 72 hours, 68%-73% of cells developed into blastocysts from embryos cultured in D-Pantothenate medium compared to 37%-41% in controls; the difference was statistically significant. None of the concentrations of D-Pantothenate tested inhibited blastocyst formation. The mean number of live fetuses produced from the embryos incubated in the medium containing D-Pantothenate (24 fetuses/ 100 1-cell embryos) was statistically significantly greater than the mean number produced from the embryos incubated in the control medium (11 fetuses/ 100 1-cell embryos).

In Vivo

Rats were dosed with 0% or 0.0016% Pantothenic Acid daily in the diet for 7 weeks.[67] The researchers stated that Pantothenic Acid is necessary for the testicular and adrenal function in rats, based on the results of the study, including a statistically significant increase in testis weight (relative to body weight) and a statistically significant decrease in sperm motility, testosterone, and corticosterone plasma concentrations in untreated animals compared to treated ones.

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 NOAEL was 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 were reported; Calcium Pantothenate was found to cross the placenta. [63,68,69]

GENOTOXICITY

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

In Vitro

DL-Panthenol was 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] 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 using Chinese hamster lung fibroblasts.[6] This experiment was conducted using GLP in accordance with OECD 476, both with and without metabolic activation. Cells from human dermal fibroblasts were exposed to Calcium Pantothenate (0 or 20 µg/ml for 8-12 hour incubation), then exon array analysis and quantitative polymerase chain reaction were performed on RNA from the cells.[70] 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. 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

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 was used to initiate the 1-13 cell line of BALB/c-3T3; controls without 3-methylcholanthrene were also used in the experiment. The culture plates were treated with fresh medium (no carcinogen present) 72 hours following treatment with 3-methylcholanthrene. On day 7 and 2x/week 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-methylcholanthrene (0.1 µg/ml) and to dishes not treated with the carcinogen. After 4 weeks, the 3-methylcholanthrene carcinogen was removed from the plates. The plates were

scanned for Type III foci after staining with Giemsa. Results indicated that Calcium Pantothenate produced a promoting effect of Type III transformed foci; a repeat experiment showed these observations to be marginal.

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.[54] Additionally, the use of D-Panthenol was implicated in in vitro cytotoxicity prevention and for skin wound healing in animals.

In Vitro

Human

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 scratch wounds for 24 hours at 37 °C.[70] 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.

In Vivo

Animal

An in vivo test in guinea pig skin (inflammation induced by UV radiation) examined the therapeutic effect of D-Panthenol (5%).[73] Results showed that D-Panthenol had a statistically significant inhibitory effect on inflammation compared to controls.

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.[2] 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.[2] 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.

Half a percent of 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.[2] In one test, erythema and papules were observed in 3 out of 200 subjects during induction and challenge phases. Erythema and edema were seen in 3 out of 206 subjects during the induction and challenge phases of another test. Erythema was reported in 1 out of 238 subjects during the induction phase of an experiment. There were no signs of irritation or sensitization in another study with 200 subjects or in a smaller test with 25 subjects. 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

In Vivo

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] 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.[27]

Sensitization

In Vivo

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. 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 and slightly irritating to the skin during epicutaneous induction.

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).[73]

Photoirritation / Photosensitization

In Vivo

Animal

In an EFSA article, D-Panthenol was reported not to cause photoallergenic reactions in guinea pig skin (no further details provided).[27]

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.[2] 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.

In Vivo

Animal

D-Panthenol

A single, 50 µl application of undiluted D-Panthenol was instilled into the conjunctival sac (no rinsing) of 2 Vienna White rabbits in accordance with OECD TG 405 (Acute Eye Irritation/ Corrosion).[6,7] The other eye was used as a saline-treated control and animals were observed for 8 days following treatment. D-Panthenol was found to be non-irritating (slight corneal irritation was noted, but was reversible after 2 days). In a different experiment, a single application of 0.1 g of a cream formulation containing 5% (w/w) D-Panthenol was instilled into the conjunctival sac (no rinsing) of 3 New Zealand White rabbits in accordance with OECD TG 405 and observed for 72 hours.[6] The other untreated eye served as the control. A slight conjunctival redness (scored 0.25 on a 0 to 3 scale) was observed in all animals, which was resolved within 24 hours; D-Panthenol was considered to be non-irritating.

Calcium Pantothenate

Calcium Pantothenate (10% solution) was non-irritating to rabbit eyes after 0.5 ml were instilled into the conjunctival sac (no further details provided).[74]

CLINICAL STUDIES

Clinical studies indicated that D-Panthenol was used in skin wound healing and corneal wound healing in human subjects.[54]

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

In a double-blind, wound-healing study, suction blisters were formed on human subjects 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.[49] Transepidermal water loss (TEWL) was 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 examined the effect of 5% D-Panthenol in human skin, irritated by sodium lauryl sulfate; results indicated that D-Panthenol reduced irritation and edema.[75,76]

Human subjects in a dermatitis clinic were patch tested using a standard diagnostic series that included a 50% DL-Panthenol solution.[77] Positive reactions to DL-Panthenol were reported in 2 of 192 (1%) 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).[78] 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.

Case Reports

Patients with stasis dermatitis and multiple allergies experienced contact allergy to D-Panthenol.[54] A lymphocyte transformation test with dexpanthenol 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 presented in detail in Table 13.

The case reports involving human dermal exposure to Panthenol or Panthenyl Ethyl Ether 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);[79] 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);[80] 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);[81] 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;[82] 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).[83]

There 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).[84] 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. [85] 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.

EPIDEMIOLOGY STUDIES

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 of > 96,000 patients to D-Panthenol (no further details provided).[86] D-Panthenol was classified by the study researchers to be a "rare" allergen.

SUMMARY

The 7 ingredients included in this safety assessment reportedly function in cosmetics as hair and skin conditioning agents.

VCRP data obtained from the FDA in 2016 indicated that the highest reported uses are for Panthenol (5475uses), D-Panthenol (502 uses), and Panthenyl Ethyl Ether (362 uses). The highest maximum use concentration in leave-on products were 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 2016, compared to 2002. Highest maximum concentration of use data received in the 2017 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. A 510 (k) premarket notification for a medical device was 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 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 10x before the addition of test substance. The receptor solution (0.01 mol/l phosphate buffered saline with 5%, v/v, polyethylene glycol) was collected for up to 60 minutes post-application. The amount of applied radioactivity measured in the stratum corneum of skin that was not stripped before application was 84%; 6% and 4% was found in the epidermis and dermis, respectively. For the samples stripped 10x before application of the test material, the applied radioactivity detected in the stratum corneum was 72%; 18% and 6.3% was 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 applied radioactivity of the formulation base (2% ^{14}C-Panthenol in a 98% nail formulation) was 2x higher in the interior nail plate and 3x higher in the cotton ball compared to the aqueous samples (2% ^{14}C-Panthenol in water) after application to the dorsal side of the nail 1x/day 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 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.

An in vitro penetration enhancement experiment was conducted to evaluate the ability of D-Panthenol (concentration not specified) to increase the penetration of metronidazole in pig ear skin in a diffusion cell. The results indicated that the receptor solution (collected up to 24 hours post-application) contained 0.31% metronidazole and 0.45% transcutol (of donor solution total amount). D-Panthenol exhibited slow diffusion through the membrane. The study researchers stated that the skin penetration of metronidazole was enhanced by D-Panthenol and transcutol.

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 pyrrolidon 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.

An 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.

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, the biologically active form of the ingredient.

In an acute, dermal exposure experiment (semi-occlusive for 24 hours) an LD_{50} > 2 g/kg DL-Panthenyl Ethyl Ether in rats was reported. In acute, oral exposure experiments in rats administered single dosages, an LD_{50} > 10 g/kg D-Panthenol and an LD_{50} > 2 g/kg DL-Panthenyl Ethyl Ether 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, 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 rats orally exposed for 3 months. Observations in rats orally 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% Calcium Pantothenate (653 days) compared to untreated controls (550 days) was noted in a chronic study.

An in vitro experiment conducted on hamster embryos that were cultured in D-Pantothenate (1 µmol/l to 1 mmol/l) containing medium showed that, by 72 hours, 68%-73% of cells developed into blastocysts compared to 37%-41% of control cells (without D-Pantothenate). Additionally, the number of live fetuses (24 fetuses/ 100 1-cell embryos) produced from embryos cultured in medium with D-Pantothenate was statistically significantly greater than the number of live fetuses (11 fetuses/ 100 1-cell embryos) from embryos cultured in medium without D-Pantothenate.

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 were reported.

At concentrations up to 5000-10,000 µg/plate, DL-Panthenol was non-mutagenic in Ames tests using *S. typhimurium* and in WP2 assays using *E. coli* (both tests with and without metabolic activation). DL-Panthenyl Ethyl Ether (up to 2400 µg/ml) was negative for genotoxicity (with and without metabolic activation) in a mammalian cell gene mutation assay conducted in Chinese hamster lung fibroblasts. In an vitro test in human dermal fibroblasts exposed to Calcium Pantothenate (0 or 20 µg/ml for 8-12 hour incubation), Calcium Pantothenate caused substantial upregulation of mRNA encoding 7 genes in dermal fibroblasts. A separate in vitro experiment in human skin fibroblasts (incubated for 24 hours in a medium containing up to 20 mM Panthenol or up to 1000 µM Pantothenic Acid) indicated that heme oxygenase-1 protein inductions occurred in cells treated with Panthenol and Pantothenic Acid. Panthenol (up to 20 mM for 24 hours) inhibited the formation of reactive oxygen species in human skin fibroblast cells. D-Sodium Pantothenate (concentrations not provided) was non-mutagenic in a microbial plate suspension assay (with and without metabolic activation) evaluating *S. cerevisiae* and *S. typhimurium*. In an Ames test examining *S. typhimurium* (with and without metabolic activation), Sodium Pantothenate (up to 10,000 µg/plate) was non-mutagenic.

In a BALB/c-3T3 cell neoplastic transformation system, 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.

In other relevant studies, Calcium Pantothenate (20 µg/ml) was shown to accelerate wound healing in human dermal fibroblast monolayers in vitro; in vivo tests in guinea pig skin showed that D-Panthenol (5%) effectively inhibited inflammation.

D-Panthenol (5%, w/w) was non-irritating to rabbit skin when applied semi-occlusively for 4 hours. DL-Panthenol (undiluted) was non-irritating and non-sensitizing to guinea pig skin in a Buehler test. 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). D-Panthenol (5%) was found to be non-sensitizing in human subjects during an epidermal patch test.

In rabbit eyes, D-Panthenol (undiluted or 5% in a cream formulation) was considered to be non-irritating in two different tests, although slight, but reversible corneal irritation and conjunctival redness were observed. Calcium Pantothenate (10% solution) was non-irritating to rabbit eyes.

In a clinical study, D-Panthenyl Triacetate (3%) reduced TEWL in a wound healing study in human subjects with suction blisters. D-Panthenol (5%) was shown to reduce irritation and erythema in human skin irritated by sodium lauryl sulfate. Positive reactions to 50% DL-Panthenol were reported in 2 of 192 human subjects patch tested in a dermatitis clinic. In human subjects treated 2x/day 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.

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.

An epidemiological 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.

INFORMATION SOUGHT

The CIR is seeking any data relevant to the determination of safety of Panthenol, Pantothenic Acid, Panthenyl Ethyl Ether, Panthenyl Ethyl Ether Acetate, Panthenyl Triacetate, Calcium Pantothenate, and Sodium Pantothenate as used in cosmetics.

TABLES

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

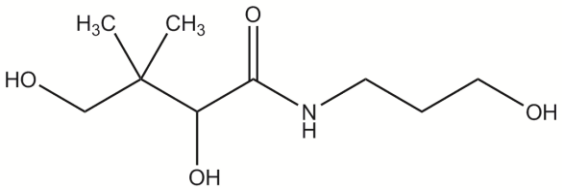
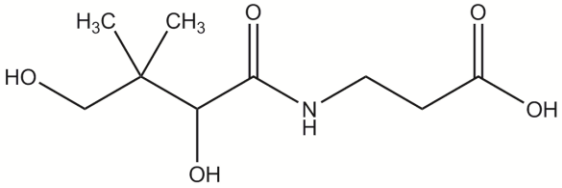
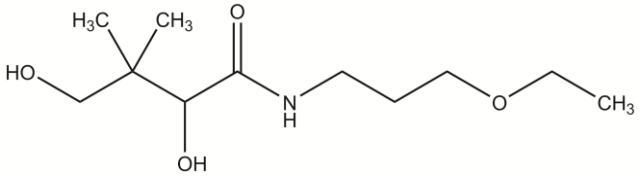
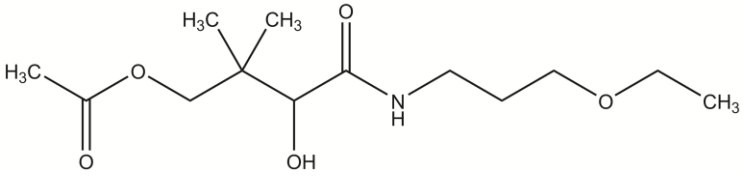
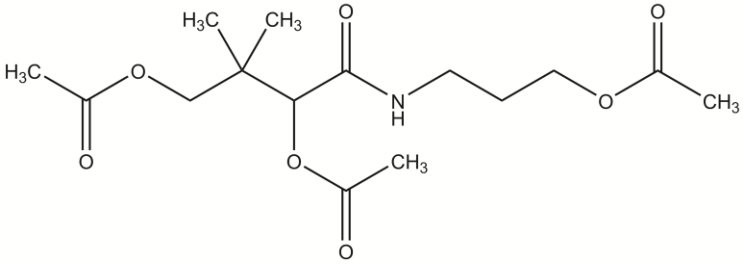
Ingredient CAS No.	Definition & Structure	Function
Panthenol 81-13-0 (D-) 16485-10-2	Panthenol is the alcohol that conforms to the formula: 	Hair Conditioning Agents; Skin-Conditioning Agents-Humectant; Solvents
Pantothenic Acid 79-83-4	Pantothenic Acid is the organic acid that conforms to the formula: 	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 (*R*)]	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

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

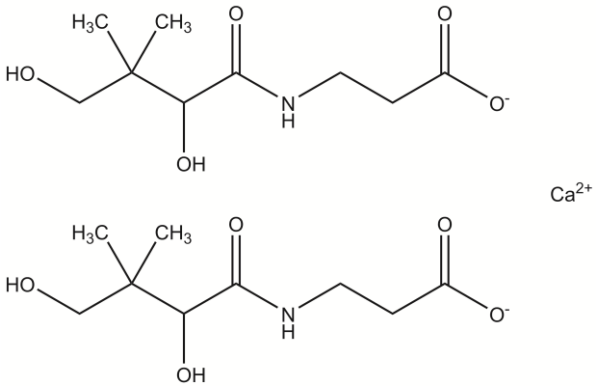
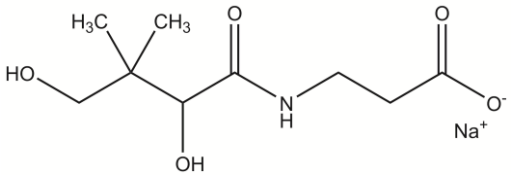
Ingredient CAS No.	Definition & Structure	Function
Calcium Pantothenate 137-08-6 (D-)	Calcium Pantothenate is the calcium salt of pantothenic acid that conforms to the formula:  	Hair Conditioning Agents
Sodium Pantothenate 867-81-2	Sodium Pantothenate is the sodium salt of Pantothenic Acid [that conforms to the structure:]  	Hair Conditioning Agents

Table 2. Physical and Chemical Properties

Property	Value	Reference
Panthenol		
Physical Form	Crystalline powder; racemic mixture of dextrorotatory (active) and levorotatory (inactive)	19
Color	White (DL-form)	19
Molecular Weight (g/mol)	205.25 (DL-form)	19
Density (g/ml) @ 20 °C and 760 mmHg	1.166±0.06 calculated (D-form)	20
Vapor pressure mmHg @ 25 °C	2.21 x 10^{-11} calculated (D-form)	20
Melting Point (°C)	63.3 °C (DL-form)	6
Boiling Point (°C) @ 760 mmHg	483.6±45.0 calculated (D-form)	20
Water Solubility	Feely soluble (DL-form)	19
Other Solubility	Freely soluble in alcohol and propylene glycol; soluble in chloroform and ether; slightly soluble in glycerin (DL-form)	19
Log P @ 25 °C	-0.989±0.602 calculated (D-form)	20
pKa @ 25 °C	13.03±0.20; -0.88±0.70 calculated (D-form)	20
Pantothenic Acid		
Physical Form	Viscous oil; extremely hygroscopic; destroyed by acids, bases, heat	18
Molecular Weight (g/mol)	219.24	18
Density g/ml @ 20 °C and 760 mmHg	1.266±0.06 calculated	20
Boiling Point (°C) @ 760 mmHg	551.5±50 calculated	20
Water Solubility	Freely soluble	18
Other Solubility	Freely soluble in ethyl acetate, dioxane, glacial acetic acid; moderately soluble in ether and amyl alcohol; insoluble in benzene and chloroform	18
Log P @ 25 °C	-0.856±0.605 calculated	20
pKa @ 25 °C	4.30±0.10; -1.00±0.70 calculated	20
Panthenyl Ethyl Ether		
Molecular Weight (g/mol)	233.308	24
Density (g/ml) @ 20 °C and 760 mmHg	1.070±0.06 calculated	20
Vapor Pressure mmHg @ 25 °C	9.7 x 10^{-10} calculated	20
Boiling Point (°C) @ 760 mmHg	443.8±45.0 calculated	20
Log P @ 25 °C	0.354±0.619 calculated	20
pKa @ 25 °C	13.04±0.20; -0.86±0.70 calculated	20
Panthenyl Ethyl Ether Acetate		
Molecular Weight (g/mol)	275.345	25
Density (g/ml) @ 20 °C and 760 mmHg	1.072±0.06 calculated	20
Vapor Pressure mmHg @ 25 °C	9.4 x 10^{-9} calculated	20
Boiling Point (°C) @ 760 mmHg	418.5±45.0 calculated	20
Water Solubility (g/l) @ 25 °C & pH 6.7 (in unbuffered water)	49 (Soluble) calculated	20
Log P @ 25 °C	1.058±0.553 calculated	20
pKa @ 25 °C	12.99±0.20; -0.87±0.70 calculated	20
Panthenyl Triacetate		
Molecular Weight (g/mol)	331.365	26
Density (g/ml) @ 20 °C and 760 mmHg	1.131±0.06 calculated	20
Vapor Pressure mmHg @ 25 °C	4.47 x 10^{-9} calculated	20
Boiling Point (°C) @ 760 mmHg	471.9±45.0 calculated	20
Water Solubility (g/l) @ 25 °C & pH 7 (in unbuffered water)	4.3 (Slightly soluble) calculated	20
Log P @ 25 °C	0.837±0.471 calculated	20
pKa @ 25 °C	14.19±0.46; -1.01±0.70 calculated	20
Calcium Pantothenate		
Physical Form	White powder; moderately hygroscopic	18,30
Formula Weight (g/mol)	476.54	18
Melting Point (°C)	195-196 (decomposition) experimental	21
Water Solubility	Soluble	18
Other Solubility	Soluble in glycerol; Slightly soluble in alcohol and acetone	18
Log Kow	-1.69 calculated	87
Sodium Pantothenate		
Physical Form	Very hygroscopic crystals (only stored in sealed ampuls)	18
Formula Weight (g/mol)	241.219	22
Melting Point (°C)	171-178 experimental	23

Table 3. Current frequency and concentration of use of Panthenol, Pantothenic Acid, and Derivatives[3,5,31,32]

	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)
	2002-2004 Panthenol		**2016-2017 Panthenol****		**2016 Panthenol, D-****	
Totals*	**1538**	**0.00005-6**	**5475**	**0.000005-5.3**	**502**	**NR**
Duration of Use						
Leave-On	*867*	*0.001-6*	*3286*	*0.0001-5.3*	*330*	NR
Rinse-Off	*656*	*0.00005-6*	*2144*	*0.00005-5*	*170*	NR
Diluted for (Bath) Use	*15*	*0.01-2*	*45*	*0.000005-1.2*	*2*	NR
Exposure Type						
Eye Area	100	0.001-2	583	0.0075-3	46	NR
Incidental Ingestion	6	0.01-2	43	0.001-2	17	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: 208 possible: 1368[a]; 603[b]	spray: 0.005-5 possible: 0.0005-1.5[a]; 0.01-0.5[b]	spray: 7 possible: 94[a]; 59[b]	NR
Incidental Inhalation-Powder	powder: 7 possible: 61[b]	powder: 0.02-1 possible: 0.001-6[b]	powder: 19 possible: 603[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	2880	0.000005-5.3	253	NR
Deodorant (underarm)	3[a]	0.05-0.5[a]	9[a]	spray: 0.0001-0.1 not spray: 0.013-0.53	NR	NR
Hair - Non-Coloring	857	0.01-6	1914	0.0005-5	161	NR
Hair-Coloring	62	0.00005-1	226	0.00005-0.6	10	NR
Nail	40	0.03-1	63	0.0005-2.9	29	NR
Mucous Membrane	44	0.01-4	578	0.000005-2.5	46	NR
Baby Products	3	NR	22	0.04-5	1	NR
	2016 Panthenol, DL-**		**2002-2004 Pantothenic Acid**		**2016-2017 Pantothenic Acid**	
Totals*	**73**	**NR**	**3**	**0.00001-0.01**	**58**	**0.0001-0.0034**
Duration of Use						
Leave-On	*51*	NR	*3*	*0.001-0.01*	*48*	*0.0001-0.0034*
Rinse-Off	*21*	NR	*NR*	*0.00001*	*10*	*0.001*
Diluted for (Bath) Use	*1*	NR	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	6	NR	1	0.001-0.01	3	0.0001-0.001
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	spray: 3 possible: 9[a]; 20[b]	NR	possible: 1[a]	possible: 0.003[a]	possible: 20[a]; 8[b]	NR
Incidental Inhalation-Powder	possible: 20[b]	NR	NR	powder: 0.001	powder: 2 possible: 8[b]	possible: 0.0005-0.0034[c]
Dermal Contact	38	NR	3	0.00001-0.003	44	0.0001-0.0034
Deodorant (underarm)	1[a]	NR	NR	NR	NR	NR
Hair - Non-Coloring	30	NR	NR	NR	13	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	1	NR	NR	NR	1	NR
Mucous Membrane	4	NR	NR	NR	1	NR
Baby Products	NR	NR	NR	NR	NR	NR
	2016 Panthenyl Ethyl Ether		**2016 Panthenyl Triacetate**		**2016 Calcium Pantothenate**	
Totals*	**362**	**0.001-2**	**67**	**0.003-2**	**197**	**0.0000005-0.5**
Duration of Use						
Leave-On	*133*	*0.001-2*	*56*	*0.003-2*	*164*	*0.0000005-0.5*
Rinse-Off	*229*	*0.005-0.5*	*11*	*0.003-0.1*	*32*	*0.0001-0.2*
Diluted for (Bath) Use	*NR*	*0.15*	*NR*	*NR*	*1*	*NR*
Exposure Type						
Eye Area	13	0.05-0.84	2	0.2	9	0.0000005-0.1
Incidental Ingestion	2	0.034-0.4	13	2	1	0.019
Incidental Inhalation-Spray	spray: 6 possible: 91[a]; 9[b]	spray: 0.09-0.5 possible: 0.09-0.5[a]	possible: 12[a]; 12[b]	possible: 0.95[a]	spray: 1 possible: 25[a]; 37[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: 12[b]	powder: 0.003 possible: 0.003-0.17[c]	possible: 37[b]	powder: 0.01 possible: 0.0001-0.5[c]
Dermal Contact	43	0.01-2	48	0.003-2	80	0.0000005-0.5
Deodorant (underarm)	NR	NR	NR	0.96	NR	NR
Hair - Non-Coloring	309	0.001-0.5	3	NR	46	0.0001-0.19
Hair-Coloring	4	NR	NR	NR	4	NR
Nail	NR	NR	3	1	64	0.001-0.4
Mucous Membrane	14	0.034-0.4	14	2	2	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
** 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. Non-Cosmetic Uses

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	-Reference Daily Intake (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)	[47]

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 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 *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 *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 *Skin samples after tape-stripped 20X after test substance application*: general exponential decline of protein with increasing number of tape strips; TEWL increased in the deeper layers of stratum corneum	[48]

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 microspectroscopy	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); 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; 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; study researchers stated that Panthenyl Triacetate is converted to D-Panthenol through de-acetylation in deeper layers of skin by 24 h	[49]
NAIL PENETRATION							
IN VITRO							
Human							

Table 5. Dermal and Nail Penetration Studies

Test Substance(s)	Species	Sample Type or Test Population-Sex	Concentration (Vehicle)	Exposure Route	Procedure	Results	Reference
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-Panethnol 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-Panethnol in formulation base between 7th day of kinetic study and after 7 days of penetration study	[51]

PBS=Phosphate Buffered Saline; TEWL=Transepidermal Water Loss

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

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
IN VITRO						
HUMAN						
Dermal						
D-Panthenol; Panthenyl Triacetate	Human	Abdominal skin (from plastic surgery), n=12 skin samples (5 cm^2, adipose tissue removed)	2% D-Panthenol cream 2% Panthenyl Triacetate cream Placebo cream	Skin samples were added to Dulbecco's Modified Eagle's medium with 10% fetal calf serum in 6-well plates @ 37 °C; after medium was exchanged for new medium, epidermis was treated as indicated and incubated for 6 or 24 h (untreated skin samples used as controls); following both incubation periods, 3 punched samples were removed from skin, phosphate buffered saline wash applied, and epidermal portion separated and frozen until mRNA extraction; mRNA was analyzed by quantitative PCR for 27 skin metabolism markers	Panthenyl Triacetate and D-Panthenol stimulated 11 and 7, respectively, metabolism markers in human skin; markers were associated with citric acid cycle, mevalonate pathway, glycolysis, and lipid synthesis; results indicated Panthenyl Triacetate advanced citric acid cycle, glycolysis, and mevalonate pathway and was involved in regulation of lipid metabolism, increasing synthesis of cholesterol sulfate as related to keratinocyte differentiation, and inhibiting transport of lipids; D-Panthenol was also found to advance citric acid cycle, mevalonate pathway, cholesterol sulfate synthesis, but was not implicated in glycolysis; D-Panthenol positively impacted lipid transport	[49]
IN VIVO						
ANIMAL						
Oral						
Pantothenic Acid; Calcium Pantothenate	Rat	n=?	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	[55]

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

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
Calcium Pantothenate	Rat/ Wistar	n=?, 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	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; 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	[56]
Calcium Pantothenate	Rat/ Wistar	n=?, 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	[56]

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

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
Calcium Pantothenate	Rat/ Wistar	n=?	Groups 2 & 4; each animal received ~180 mg/day Calcium Pantothenate as a powder incorporated into standard pellet diet	Animals were dosed daily in diet as indicated below: Group 1-rats administered standard diet without test substance Group 2-rats administered test substance in diet for 42 days Group 3-rats administered standard diet without test substance; partial hepatectomy (day 34 of experiment) and irradiation performed (7 days following hepatectomy) on 2 cm^2 femoral skin area (hair removed); a device applied irradiation for 2.48 min with Sr^{90}-Y^{90} at 3.6 rep/sec beta rays; 72 h following irradiation animals were killed; Group 4-rats administered test substance in diet for 42 days; partial hepatectomy (day 34 of experiment) and irradiation performed as mentioned above (7 days following hepatectomy) on 2 cm^2 femoral skin area (hair removed); 72 h following irradiation animals were killed Skin and liver samples were collected from animals in Groups 1 thru 4, prepared, and examined in an electron microscope	Group 1: *Epidermis results*-stratum corneum (5-7 layers) at epidermis surface consisted of degenerated epidermis cells; disappearance of intercellular cohesion, dilation of intercellular space, variable electron density were observed; stratum granulosum contained keratohyalin granules; stratum spinosum contained desmosomes; *Liver results*-study researchers indicated that results were consistent with normal hepatocytes Group 2: *Epidermis results*-study researchers stated that Calcium Pantothenate facilitated desmosomes level transfer of keratinosomes toward stratum corneum (keratinization); granular layer contained small granules of keratohyalin; study researchers stated that Calcium Pantothenate induced metabolic activity of cells in stratum spinosum; less dilation of intercellular space; *Liver results*-study researchers noted that Calcium Pantothenate was metabolized well and no ultrastructural hepatocyte changes were observed Group 3: *Epidermis results*-extremely thin stratum corneum; dense cytoplasm observed in granular layer (few granules of keratohyalin transferred to stratum corneum); skin appeared pigmented; dilation of intercellular space in stratum spinosum (2-3 cell rows) and increase in collagen noted; study researchers stated that these observations are typical of irradiated skin; *Liver results*-ultrastructural changes indicated liver dysfunction Group 4: *Epidermis results*-stratum corneum contained 4-5 layers; study researchers stated that Calcium Pantothenate had a radioprotective effect; high electron density in layers 1-2 (study researchers stated that Calcium Pantothenate facilitated keratinization); stratum spinosum noted to have electron-dense cytoplasm; *Liver results*-study researchers stated that metabolic function of hepatocytes was comparable to that of control animals	[60]

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

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
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	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; 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; 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	[57]
Calcium Pantothenate or 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	[58]
Calcium Pantothenate	Dog	n=?	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	[88]

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

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
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	[89]
Calcium Pantothenate	Rat	n=?	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 and was no 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	[9,59]
Sodium Pantothenate	Dog	n=?	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	[61]
Sodium Pantothenate	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)	[61]

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

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
Sodium Pantothen[^{14}C]ate (3.6 mCi/mmole)	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)	[90]
			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	[89]

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

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
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)	[90]
HUMAN						
Oral						
Calcium Pantothenate	Human	n=?	100 mg	Dose administered and urine analyzed	~20% of dose excreted as Pantothenate in urine within 4 h after administration	[62]
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						
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} > 2000 mg/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 dose administered by gavage using GLP 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); pathology showed no abnormalities	[7]
DL-Panthenyl Ethyl Ether	Rat/ Wistar	n=5/sex	2 g/kg (water vehicle)	Single dose 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]
D-Calcium Pantothenate	Mouse	n=?	10 g/kg	Single dose administered	LD_{50} of 10 g/kg reported	[63]
D-Calcium Pantothenate	Rat	n=?	10 g/kg	Single dose administered	LD_{50} of > 10 g/kg reported; no signs of toxicity	[63]
D-Calcium Pantothenate	Dog	n=5	1 g/kg	Single dose administered	No signs of toxicity	[63]
D-Calcium Pantothenate	Monkey	n=1	1 g/kg	Single dose administered	No signs of toxicity	[63]
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]
D-Calcium Pantothenate	Rat/Wistar	n=?	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	[27]

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							
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	[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]
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	[12]
CHRONIC (≥ 6 MONTHS EXPOSURE)							
ANIMAL							
Oral							

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	Dogs	n=6	50 mg (~5 mg/kg)	180 days	Animals dosed daily in diet (no further details provided)	No toxicity reported	[63]
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	[63]
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	[63]
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)	[65]

NOAEL=No-Observed-Adverse-Effect-Level

Table 9. Developmental and Reproductive Toxicity (DART) Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
IN VITRO						
D-Pantothenate (salt form was not specified)	Hamster	Embryos from at least 4 females were used to determine embryo cell count in vitro; n=18 females for embryo transfer into pseudopregnant females	Hamster embryo culture medium-6 (HECM-6) used as control (no vitamins) HECM-6 containing various combinations of vitamins used as test medium, some including D-Pantothenate (3 µmol/l) HECM-6 containing 0, 1, 3, 10, 30 µmol/l or 1 mmol/l D-Pantothenate used as test medium	Females were administered pregnant mare's serum gonadotrophin on day 1 (post-estrus discharge); 3 days later females were mated with fertile males; at 10 h post-egg activation the 1-cell embryos were removed and placed under a mineral overlay containing 50 µl of control culture medium or a test medium (controlled pooling performed) and incubated for 72 h @ 37.5°C; at 48 and 72 h post-egg activation, embryos were evaluated for development to 8-cell stage, morula, and blastocyst phases; some embryos were fixed and stained to calculate cell numbers; blastocysts from control medium were inserted into one uterine horn of pseudopregnant females (females mated to vasectomized males) and blastocysts from medium containing D-Pantothenate and were transferred into remaining uterine horn of same female (embryos cannot travel between uterine horns) to evaluate post-implantation viability; females were inspected for fetuses 11 days after embryo transfer (gestation day 14)	By 72 h, 68%-73% of cells developed into blastocysts from embryos cultured in D-Pantothenate only medium compared to 37%-41% in controls (difference was statistically significant); medium with D-Pantothenate alone showed statistically significant increases in blastocyst formation as compared to control or some mediums with other vitamin combinations (both with and without D-Pantothenate); there was no difference between mediums (including control) in most cases when mean cell number of embryos were compared; experiment with varying D-Pantothenate concentrations (1 µmol/l-1 mmol/l), 3 µmol/l yielded highest amount of blastocysts (70%), which was statistically significant as compared to control (37%), however not statistically significant comparted to other concentrations; none of these varying D-Pantothenate concentrations inhibited formation of blastocysts; live fetuses produced from medium containing D-Pantothenate (24 fetuses/100 1-cell embryos) was statistically significantly greater than those produced from control medium (11 fetuses/ 100 1-cell embryos); study researchers stated that D-Pantothenate produced a stimulatory effect on development of embryos (preimplantation) compared to control and various single vitamins, except for thiamine	[66]

Table 9. Developmental and Reproductive Toxicity (DART) Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population- Sex	Concentration or Dosage (Vehicle)	Procedure	Results	Reference
IN VIVO						
Oral						
Pantothenic Acid	Rat/ Wistar-Imamichi	n=15 males/group (3 weeks old)	Group 1 received 20% casein diet without test substance (untreated) Group 2 received 20% casein diet containing 0.0016% test substance (treated)	Animals were dosed in the diet, provided ad libitum, for 7 weeks; animals were killed at completion of study; blood samples were collected for hormonal analysis; organs were weighed; sperm-motility was evaluated	Untreated animals had a statistically significantly lower increase in body weight compared to treated animals; liver, kidney, pituitary, testis, epididymis, seminal vesicle, and prostate weights of untreated animals were statistically significantly lower than those of treated animals; when organ weights were reported relative to body weight, the testis weight was statistically significantly higher in untreated animals compared to treated, but there was no statistically significant difference in other relative organ weights between untreated and treated animals; sperm motility parameters were statistically significantly lower in untreated animals compared to treated; testosterone and corticosterone plasma concentrations were statistically significantly lower in untreated compared to treated animals; LH and FSH plasma concentrations were not significantly different in untreated compared to treated animals; study researchers stated that Pantothenic Acid is necessary for the testicular and adrenal function of rats	[67]
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)	[63]
Calcium Pantothenate	Rat/ Wistar	n=?, 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	[68,69]
Calcium Pantothenate	Rat	n=?, 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	[68,69]

FSH=Follicle-Stimulating Hormone; GLP=good laboratory practice; LH=Luteinizing Hormone; 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	*Salmonella 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]
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]
Calcium Pantothenate; Panthenol and Pantothenic Acid	Human dermal fibroblasts (multiple donors)	*Exon Expression Array Experiments with RNA and tRNA*: 0 or 20 µg/ml Calcium Pantothenate *Heme Oxygenase-1 Protein Analysis*: 5, 10, 20 mM Panthenol and 10, 30, 100, 300, 500, 1000 µM Pantothenic Acid *Reactive Oxygen Species Analysis*: 5, 10, 20 mM Panthenol	*Exon Expression Array Experiments with RNA and tRNA*: RNA from dermal fibroblasts was isolated and quantified by photometric measurement; 2 µg total RNA was incubated with or without Calcium Pantothenate as indicated, for 8-12 h in 2% fetal calf serum medium and analyzed using exon expression arrays; tRNA was isolated from proliferating dermal fibroblasts incubated with or without Calcium Pantothenate and harvested after 12 h, human exon array analysis was conducted and quantitative PCR performed *Heme Oxygenase-1 Protein Analysis*: human skin fibroblast cells were incubated for 24 h in control medium or Panthenol or Pantothenic Acid medium, then cells were washed, extracted and protein analyzed *Reactive Oxygen Species Analysis*: human skin fibroblast cells were treated with Panthenol for 24 h (negative controls were used) and assayed using chemiluminescence to determine formation of reactive oxygen species	Substantial upregulation of mRNA coding 7 genes in dermal fibroblasts incubated with Calcium Pantothenate (20 µg/ml) compared to untreated cells was noted; heme oxygenase-1 protein inductions in human skin fibroblasts were observed in cells treated with Panthenol and Pantothenic Acid; inhibition of formation of reactive oxygen species were observed in cells treated with Panthenol	[70]

Table 10. Genotoxicity Studies

Test Substance(s)	Species/ Strain or Sample Type	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
D-Sodium Pantothenate	*Saccharomyces cerevisiae*/ D4; *Salmonella 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	*Salmonella Typhimurium*; TA97A and TA102	0.1-10 mg/plate With and without metabolic activation	Ames test was performed (preincubation method used)	Non-mutagenic	[91]

GLP=Good Laboratory Practice; PCR=Polymerase Chain Reaction

Table 11. Dermal Irritation and Sensitization Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
IRRITATION						
Animal						
D-Panthenol	Rabbit/ New Zealand White	n=3 (1 male, 2 females)	0.5 g of 5% (w/w) test substance in cream formulation	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]
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]

Table 11. Dermal Irritation and Sensitization Studies

Test Substance(s)	Species/ Strain	Sample Type or Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
DL-Panthenyl Ethyl Ether	Guinea Pig/ Himalayan albino	Prelim Study: 5 females Experimental group (induction and challenge): 10 females Negative control group (induction and challenge): 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 (Skin Sensitization); 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 Freunds Complete Adjuvant: water, 5% test substance in physiological saline (w/w), and 10% test substance in 50:50 mix of Freunds 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]
			Human			
D-Panthenol	Human	n=23 patients with allergic dermatoses; n=7 healthy subjects (subjects were 18 to 67 years old; 13 female and 17 male)	Test formulation containing 5% D-Panthenol in a hydrogel formulation 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	[73]

EU=European Union; GLP=Good Laboratory Practice; HRIPT=Human Repeat Insult Patch Test; non-GLP=non-Good Laboratory Practice; OECD TG= Organization for Economic Co-operation and Development Test Guideline

Table 12. Clinical Studies

Test Substances(s)	Test Population	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
HUMAN					
DERMAL					
Wound Healing					
D-Panthenol; D-Panthenyl Triacetate	n=40 males and females (40-60 years old)	Emulsion containing 3% D-Panthenyl Triacetate and another emulsion containing 3% D-Panthenol Controls used were a placebo emulsion or saline	No skin care products were used on volar forearms of subjects 3 days prior to beginning double-blind wound healing study; 2-3 suction blisters (5 mm diameter) per forearm were formed using a vacuum; TEWL was measured 30 min, 48 h, and 72 h after blisters formed; 100 µl emulsion treatments were occlusively applied, immediately following blister formation, for 30 min, 48 h, and 72 h; some areas were left untreated to serve as controls	37 subjects completed study; TEWL increased substantially 30 min after blisters formed; by 30 min treatments had not impacted TEWL compared to saline; by 48 h there was a statistically significant difference of treatments on TEWL compared to saline (no further details provided); TEWL was statistically significantly decreased (8.7%) after 72 h by D-Panthenyl Triacetate treatment as compared to the saline control; placebo or D-Panthenol treatments were not statistically significantly different from saline by 72 h	[49]
D-Panthenol	n=25 (healthy, Caucasian, 18-45 years old)	Test formulation containing 5% D-Panthenol; Placebo test formulation free from D-Panthenol	Randomized, double-blind, placebo-controlled test was performed; test formulations were applied to inner forearm skin (16 cm^2, one arm was treated with test substance and the other received placebo) 2x/day for 26 days; on days 15-22 an irritant, sodium lauryl sulfate (2%), was applied 2x/day to both arms	21 subjects completed study (3 excluded for non-compliance and 1 had a severe adverse event not related to the study); 6 subjects experienced dermatitis (erythema, papulovesicules, itching) on days 19-26 on both arms at sites of sodium lauryl sulfate application; 5 of those 6 subjects showed more severe irritation symptoms at placebo site as compared to D-Panthenol site; no other symptoms were reported	[76]
D-Panthenol	n=20 (12 women, 8 men, 18-55 years old)	Test cream containing 5% D-Panthenol; Placebo cream free from D-Panthenol	An irritant, sodium lauryl sulfate (5%) was applied at two sites on each volar forearm and occlusively covered for 24 hours; after covering was removed, skin was wiped and rinsed clean; untreated sites were used as controls; 4 hours after covering was removed skin was examined and test cream or placebo were applied to forearms (2 mg/cm^2; one arm received test cream and other placebo) 2x/day for 7 days; untreated sites on each forearm used as controls; no other products were used on forearms during study; TEWL, stratum corneum hydration, skin roughness and redness were evaluated on day 0 (prior to treatment) and on treatment days 2, 3, 5, and 7 (4 hours following 2nd application that day)	Test cream statistically significantly decreased TEWL on days 3 and 5 compared to placebo cream and untreated sites; stratum corneum hydration was statistically significantly increased with test cream as compared to placebo at all evaluated time-points; statistically significant decrease in erythema on days 2, 3, and 5 with test cream as compared to placebo or untreated sites	[75]
Other					
DL-Panthenol	n=192	50% solution, 5% pet	Patients at a dermatitis clinic were patch tested (standard diagnostic series) with ingredients compatible to those on the labels of personal care products they were already using	2 patients (1% of test population) were reported to have positive reactions to DL-Panthenol	[77]

Table 12. Clinical Studies

Test Substances(s)	Test Population	Concentration/ Dosage (Vehicle)	Procedure	Results	Reference
Panthenol	n=207 Healthy Indian women (30-60 years old) with epidermal hyperpigmented spots on face completed study; 39 subjects withdrew for reasons unrelated to treatment	Treatment lotion contained 4% niacinamide, 0.5% Panthenol, 0.5% tocopheryl acetate, sunscreen, glycerol, and additional unspecified ingredients also found in control lotion; Control lotion was used (no further details provided)	Acclimation period of 2 weeks prior to study (all subjects used same facial wash and control lotion during that time); test substance or control applied 2x/day (after washing face) for 10 weeks in a randomized, double-blind trial; the facial products subjects were allowed to use during the study included lipstick, eye makeup, and non-medicated facial powder, however they were instructed not to be exposed to indoor tanning or excessive sunlight; during study skin was evaluated for changes in texture and color; TEWL was measured	6 subjects in treatment group and 2 in control group reported mild, transient burning sensation; 1 subject in treatment group reported dry skin and worsening of acne; TEWL decreased in treatment and control groups (during week 8 the treatment group showed statistically significant reduction in TEWL compared to controls); statistically significant reduction in hyperpigmentation spots including melanin-containing spots were reported in treatment group compared to baseline levels and controls	[78]

TEWL=Transepidermal Water Loss

Table 13. Case Reports

Test Substance(s)	Patient(s), Control Human 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)	[79]
D-Panthenol	n=1 (child, 8 years old)	Cream formulation containing the 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	[92]

Table 13. Case Reports

Test Substance(s)	Patient(s), Control Human Subjects	Product	Patient History/Procedure	Observations/Results	Reference
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	[80]
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 truck); 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 pruritis, 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	[81]
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	[82]
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	[83]

Table 13. Case Reports

Test Substance(s)	Patient(s), Control Human Subjects	Product	Patient History/Procedure	Observations/Results	Reference
			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;	[84]
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	[85]

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