International Journal of Toxicology
29(Supplement 2) 84S-97S

DOI: 10.1177/1091581810362805
http://ijt.sagepub.com

Final Report of the Safety Assessment of Allantoin and Its Related Complexes

Lillian C. Becker[1], Wilma F. Bergfeld, MD, FACP[2], Donald V. Belsito, MD[2], Curtis D. Klaassen, PhD[2], James G. Marks, Jr MD[2], Ronald C. Shank, PhD[2], Thomas J. Slaga, PhD[2], Paul W. Snyder, DVM, PhD[2], and F. Alan Andersen, PhD[3]

Abstract

Allantoin is a heterocyclic organic compound. Allantoin ascorbate, allantoin biotin, allantoin galacturonic acid, allantoin glycyrrhetinic acid, allantoin panthenol, and allantoin polygalacturonic acid are complexes of allantoin. All of the ingredients in this review act as skin-conditioning agents. Allantoin was reported to be used in 1376 cosmetic products at concentrations up to 2%. There are data gaps regarding use and concentration of the remaining allantoin complexes. Ascorbic acid, biotin, glycyrrhetinic acid, and panthenol have been determined by the CIR Expert Panel to be safe. Galacturonic acid and polygalacturonic acid have not been reviewed by the CIR Expert Panel, and substantial data on these chemicals were not available. The safety test data in this safety assessment and in previous safety assessments were considered sufficient to support the safety of allantoin and the allantoin complexes in product categories and at concentrations reviewed in this safety assessment.

Keywords

safety, cosmetics, allantoin

This is a safety assessment of the cosmetic ingredient allantoin and the related complexes allantoin ascorbate, allantoin biotin, allantoin galacturonic acid, allantoin glycyrrhetinic acid, allantoin panthenol, and allantoin polygalacturonic acid.

There was a paucity of data in the literature on the related allantoin complexes. The safety of ascorbic acid, biotin, glycyrrhetinic acid, and panthenol, however, has already been assessed by the Cosmetic Ingredient Review (CIR) Expert Panel. These previously reviewed cosmetic ingredients are summarized in Table 1.

Galacturonic acid and polygalacturonic acid have not been reviewed by the CIR Expert Panel. A search of the literature revealed no safety test data relevant to these 2 compounds. Galacturonic acid is a sugar that is, in the form of polygalacturonic acid, a major component of pectin. The US Food and Drug Administration (FDA)[6] has designated pectin as generally recognized as safe (GRAS) as a food additive.

Data in the safety assessments of allantoin and the related complexes and further data about pectin allow conclusions to be drawn about the safety of allantoin ascorbate, allantoin biotin, allantoin glycyrrhetinic acid, allantoin panthenol, allantoin galacturonic acid, and allantoin polygalacturonic acid.

Chemistry

Definition and Structure

According to the *International Cosmetic Ingredient Dictionary and Handbook*,[7] allantoin (CAS No. 97-59-6) is a heterocyclic organic compound that conforms to the formula in Figure 1A. Its source in cosmetics is synthetic. Allantoin is also known as (2,5-dioxo-4-imidazolidinyl)urea; glyoxyldiureid; glyoxyldiureide; glyoxylic diureide; urea, (2,5-dioxo-4-imidazolidinyl); and 5-ureidohydantoin[7] and 6-ureidohydantoin.[8] Other names are alantan; alloxantin; ureidohydantoin; hemocane; paxyl; allantol; cordianine; hydantoin, 5-ureido-; and 2,5-dioxo-4-imidazolidinyl-urea.[9]

Allantoin ascorbate (CAS No. 57448-83-6) is the organic compound that conforms to the formula in Figure 1B. Its chemical classes are heterocyclic compounds and organic salts. It is also known as L-ascorbic acid, compounded with (2,5-dioxo-4-imidazolidinyl)urea.[7]

Allantoin biotin (CAS No. 4492-73-3) is the organic compound that conforms to the formula in Figure 1C. Its chemical classes are heterocyclic compounds and organic salts. It is also known as 1H-thieno(3,4-)imidazole-4-pentanoic acid,

[1] Cosmetic Ingredient Review Scientific Analyst/Writer
[2] Cosmetic Ingredient Review Expert Panel Members
[3] Cosmetic Ingredient Review Director

Corresponding Author:
Lillian C. Becker, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036, USA.
Email: cirinfo@cir-safety.org

Table 1. Previously Reviewed Ingredients Complexed to Allantoin

Ingredient	Uses	Use Concentration, %	Conclusion
Ascorbic acid[a]	431	<0.01-10	Safe as used in cosmetic products.
Biotin[b]	75	≤0.6	Safe as used in cosmetic formulations.
Glycyrrhetinic acid[c]	65	2	Safe for use in cosmetic formulations in the practices of use and concentration as described in this safety assessment.
Panthenol[d,e]	284	≤0.1-5	Safe as presently used in cosmetics.

[a] Andersen 2005.[1]
[b] Andersen 2001.[2]
[c] Andersen 2007.[3]
[d] Elder 1987.[4]
[e] Andersen 2006.[5]

hexahydro-2-oxo-, compd. with (2,5-dioxo-4-imidazolidinyl) urea (1:1).[7]

Allantoin galacturonic acid (CAS No. 5119-24-4) is the complex of allantoin and galacturonic acid that conforms to the formula in Figure 1D. Its chemical classes are heterocyclic compounds and organic salts. It is also known as allantoin α-D-galacturonic acid; allantoin, monogalactopyranuronat; and galactopyranuronic acid, compd. with allantoin (1:1).[7]

Allantoin glycyrrhetinic acid (CAS No. 4572-09-2) is a complex of allantoin and glycyrrhetinic acid and has the empirical formula: C30H46O4 · C4H6N4O3. Its chemical classes are heterocyclic compounds and organic salts. It is also known as olean-12-en-29-oic acid, 3β-hydroxy-11-oxo-, compd. with allantoin (1:1).[7]

Allantoin panthenol (no CAS No.) is a complex between allantoin and panthenol. Its chemical classes are alcohols, amides, and heterocyclic compounds. A technical name is allantoin DL-pantothenyl alcohol.[7]

Allantoin polygalacturonic acid (CAS No. 29659-38-9) is a complex of allantoin and polygalacturonic acid. Its chemical classes are heterocyclic compounds and organic salts. Allantoin polygalacturonic acid has the empirical formula (C6H10O7)x · xC4H6N4O3.[7]

Physical and Chemical Properties

Allantoin is a white powder[8,9] that is odorless and tasteless[10,11] and does not stain.[12] Allantoin is an amphoteric substance.[13]

Chemical properties of allantoin are listed in Table 2.

Akema Fine Chemicals[11] stated that allantoin exists in solution as a tautomeric mixture of ketonic and enolic forms in equilibrium. With 1 chiral center, the 2 enantiomeric forms R and S are a 50:50 mixture that is optically inactive. Optically active forms can be obtained by extraction procedures.

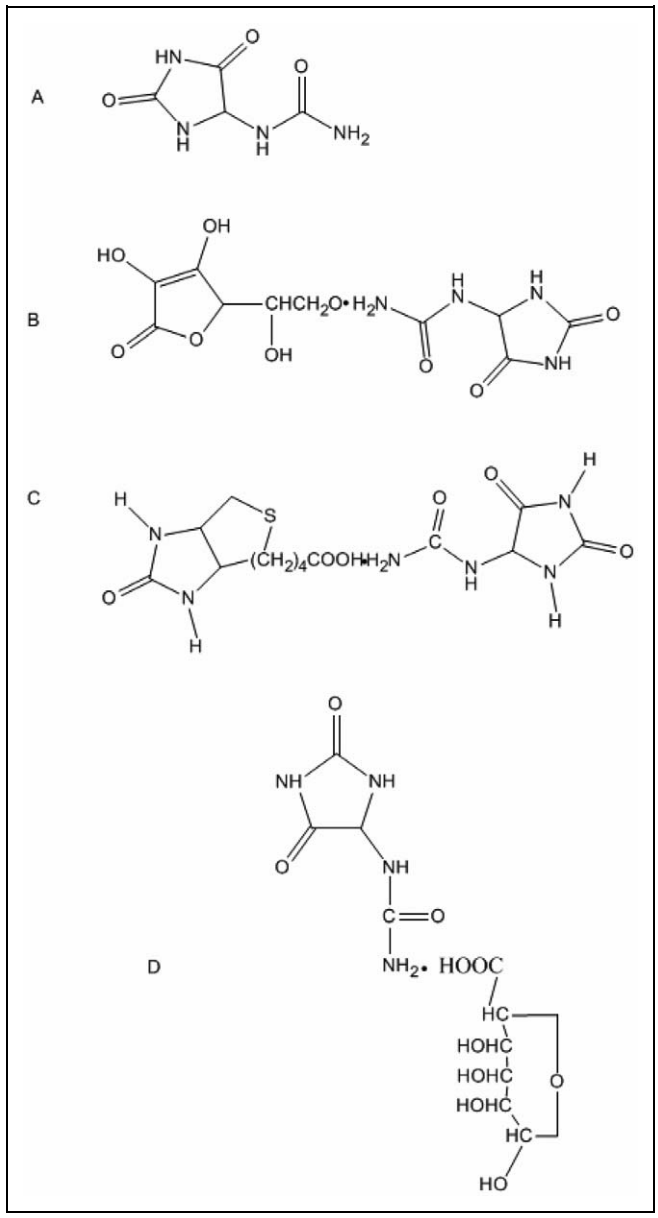

Figure 1. (A) Allantoin, (B) allantoin ascorbate, (C) allantoin biotin, and (D) allantoin galacturonic acid.[7]

Allantoin is soluble in hot water; slightly soluble in cold water, glycerin, and propylene glycol; very slightly soluble in alcohol; and practically insoluble in apolar solvents (ie, mineral oil, dimethylisosorbide, ether, and chloroform).[11]

Allantoin ascorbate is a white-yellowish powder that is water soluble.[17]

Allantoin α-D-galacturonic acid is soluble at 3% to 5%. It contains ~41.6% ± 4.0% allantoin and ~58.4% ± 4.0% α-D-galacturonic acid.[18]

Allantoin glycyrrhetinic acid, as described in a product data sheet by Active Ingredients Ltd,[19] is the combination of allantoin and glycyrrhetinic acid in molar ratios of 1:1, 1:2, or 1:3. The product specification states that allantoin, measured as nitrogen, is 30% ± 2% and glycyrrhetinic acid is 70% ±

Table 2. Chemical Properties of Allantoin

Property		Reference
Molecular weight	158.12	Sheker et al[8]
Melting point, °C	234.6-235.2	Buzard et al[14]
	225-230	Akema Fine Chemicals[11]
	230	Chemical LAND21[9]
	239	ChemIDplus Lite[15]
Solubility	1 g per 190 mL of distilled water	Sheker et al[8]
	5260 mg/L of water	ChemIDplus Lite[15]
	0.5% at 25°C in water (freely dissolves in alkalis)	Chemical LAND21[9]
pH	4-6 (0.5% solution)	Chemical LAND21[9]
Stability range	pH 4-9	Mecca[16]
Vapor pressure	4.32E-09 mm Hg	ChemIDplus Lite[15]

2% of the complex. It is a yellowish-white powder with a mild, characteristic odor. Allantoin glycyrrhetinic acid is soluble in propylene glycol, dimethylisosorbide, and alcohol; it is practically soluble in water and mineral oil.

In a product data sheet, Akema Fine Chemicals[17] states that allantoin glycyrrhetinic acid is a white-yellowish powder that is alcohol soluble but not water soluble. It has a working temperature of up to 80°C.

Allantoin panthenol, as described in a product data sheet by Akema Fine Chemicals,[17] is a white powder that is water soluble.

Allantoin polygalacturonic acid, as described in a product data sheet by Akema Fine Chemicals,[17] is a white-yellowish powder. It forms a clear thin gel in sodium citrate solution.

Stability

Allantoin degrades when dissolved in distilled water. At 0.13% allantoin (0.6556 g per 500 mL), 6.3% was lost after 620 days; at 0.45% (1.1396 g per 250 mL), 1.5% was lost after 415 days; at 0.24% (2.421 g per 1000 mL), 6.4% was lost after 24 days. At 0.13% allantoin in tap water, 6.4% was lost after 24 days. When 2 samples of allantoin (25 mL) were mixed with 23.94 mL of potassium hydroxide (KOH) and let stand for a month, there was a 90.2% loss and a 91.1% loss. When 2 samples of allantoin (25 mL) were incubated in KOH (20 mL) for 24 hours (at "body temperature"), there was a 43.4% loss of allantoin.[20]

Kaliszan and Halkiewicz[21] used infrared (IR) analysis to look for deterioration in stored allantoin. After 3 months, the samples differed at ~ 720 cm^{-1} in the position of V amide band of the hydrogen-bonded secondary amides and in the formation of the III amide band at 1275 cm^{-1}. The samples also differed at the region of N-H rocking vibrations (666-800 cm^{-1}).

Allantoin is unstable in alkaline conditions and hydrolyzes to urea and glyoxylic acid, possibly via allantoic acid.[22] However, it is stable in ordinary conditions.[9] It should be stored at room temperature away from sunlight.[12]

Sznitowska and Janicki[23] measured the release of allantoin from various ointments using a modified Mutimer apparatus. At 150 minutes, more than 80% of the allantoin from the oil/water ointment (15% wt/wt oily phase and 84% wt/wt aqueous ethanol phase) was released with a solubility of 1.12 g/cm^3. At 300 minutes, $\sim 50\%$ of the allantoin from the water/oil ointment (73% wt/wt oily phase and 26% wt/wt aqueous ethanol phase) was released with a solubility of 0.78 g/cm^3. At 300 minutes, $\sim 50\%$ of the oil/water ointment (no wt/wt oily phase and 94% wt/wt aqueous ethanol phase) was released with a solubility of 0.97 g/cm^3.

Allantoin glycyrrhetinic acid has a shelf life of 5 years in the original packaging.[19]

UV Absorption

Lukasiak et al[24] reported that the absorption of allantoin in aqueous solution is most stable at a pH range of 10.5 to 11.5 at λmax = 225 nm.

Methods of Manufacture

Allantoin can be extracted from blow-fly larvae[25] and maize silk.[26]

According to Hartman et al,[27] allantoin is prepared from the heated combination of uric acid and sodium hydroxide with the addition of potassium permanganate to the cooled flask. The solution is filtered to remove manganese dioxide, and acetic acid is added. After standing for several hours, allantoin crystallizes and can be filtered. To further purify the filtrate, the allantoin is dissolved in boiling water, treated with Norite, and then rapidly filtered again.

Akema Fine Chemicals[28] reported that it manufactures allantoin by chemical means and does not use any animal sources.

Akema Fine Chemicals[11] also reported that allantoin is synthetically obtained by oxidation of uric acid with permanganate, heating of dichloroacetic acid and urea, and a condensation process between glyoxylic acid and urea.

The *International Cosmetic Ingredient Dictionary and Handbook* stated that allantoin has a synthetic source for use in cosmetics.[7]

Analytical Methods

Analytical methods for measuring allantoin under different circumstances and conditions are listed in Table 3.

Impurities

Allantoin. Kahn and Nolan[41] reported that [4,514C]allantoin was 96.0% pure by thin-layer chromatography (TLC) and 96.3% pure by high-performance liquid chromatography (HPLC).

Wang et al[42] gave the purity of allantoin powder from Jiangsu Huanghai Pharmaceutical Factory as 99.6%.

Table 3. Methods for the Analysis of Allantoin

Analytical Method	Application	Reference
Potentiometric titration in a mixed solvent system	Measure the amount of allantoin in a cream formulation	Weber and Higgins[29]
IR analysis	Measure deterioration in stored allantoin	Kaliszan and Halkiewicz[21]
RP-HPLC	Determine allantoin in human body fluids	Tiemeyer and Giesecke[30]
HPLC	Determine allantoin in human body fluids or cosmetic products	Grootveld and Halliwell,[31] Kawase et al[32]
Chromatographic assay	Determine allantoin and uric acid in plasma ultrafiltrate simultaneously	Lux et al[33]
Direct spectrophotometry	Determine presence of allantoin	Chen et al[34]
Alkalimetric titration with pH indicator	Determine presence of allantoin	Chen et al[34]
TLC and LC	Determine presence of allantoin	Chen et al,[34] Berthemy et al[35]
Modified HPLC	Measure allantoin and urate simultaneously	Benzie et al[36]
HPLC	Simultaneously determine the levels of hypoxanthine, uric acid, and allantoin in small (4 μL) microdialysis samples	Marklund et al[37]
GC-MS	Determine presence of serum allantoin.	Pavitt et al[38]
RP-HPLC	Analyze allantoin extracted from maize	Maksimović et al[26]
Enzymatic assay	Measure serum allantoin in experimental animals	Muratsubaki et al[39]
TLC	Identify allantoin	United States Pharmacopeia[40]

GC-MS, gas chromatography–mass spectrometry; IR, infrared; LC, liquid chromatography; RP-HPLC, reversed-phase high-performance liquid chromatography; TLC, thin-layer chromatography.

Impurities have been reported to include sulfated ash (0.1%-0.2%), sulfate (200 ppm), chloride (50 ppm), heavy metals (10 ppm), lead (<20 ppm), iron (10 ppm), arsenic (3 ppm), urea (0.5%), glyoxylic acid (0.5%), and glycoluril (<0.2%).[9,11,19]

Natural Occurrence in Plants and Food

Allantoin is found naturally in the leaf buds of *Platanus orientalis* (oriental plane tree), *Acer pseudoplatanus* (sycamore), and *Acer campestre* (hedge maple) and in the bark of *Aesculus hippocastanum* (horse chestnut) and *A pseudoplatanus*. Allantoin is also found in the embryos of wheat separated in the milling process and in beet juice.[43] Allantoin has been found in trace amounts in other plants and in foods.[11,26,44]

Use

Cosmetic

According to the *International Cosmetic Ingredient Dictionary and Handbook*,[7] allantoin functions as a skin-conditioning agent - miscellaneous and a skin protectant. Allantoin ascorbate, allantoin biotin, allantoin galacturonic acid, allantoin glycyrrhetinic acid, allantoin panthenol, and allantoin polygalacturonic acid also act as skin-conditioning agents - miscellaneous.[7]

According to information supplied to the FDA by industry as part of the Voluntary Cosmetic Ingredient Reporting Program (VCRP), allantoin is used in a total of 1376 cosmetic products.[45] A survey of current use concentrations conducted by the Cosmetic, Toiletry, and Fragrance Association (CTFA) reported that allantoin is used at concentrations ranging from 0.0001% to 2%.[46] Allantoin ascorbate was reported by industry to be used at concentrations of 0.001% and 0.05% for allantoin biotin and allantoin galacturonic acid. Table 4 summarizes the available cosmetic use data on frequency of use and concentrations of use of allantoin and allantoin complexes.

Allantoin glycyrrhetinic acid was reported to be used in 6 cosmetic products, allantoin panthenol in 2 cosmetic products, and allantoin polygalacturonic acid in 2 cosmetic products[47]; concentrations of use were not reported to CTFA.

The Ministry of Health, Labor and Welfare[48] of Japan lists allantoin as an acceptable medicinal ingredient to be used in cosmetics.

Allantoin is used in 11 sprays and fixatives. The potential adverse effects of inhaled aerosols depend on the specific chemical species, the concentration, the duration of the exposure, and the site of deposition within the respiratory system.[49] In general, the smaller the particle, the farther into the respiratory tree the particle will deposit and the greater the impact on the respiratory system.[50]

Anhydrous hair spray particle diameters of 60 to 80 μm have been reported, and pump hair sprays have particle diameters of 80 μm or larger.[51] The mean particle diameter is around 38 μm in a typical aerosol spray.[52] In practice, aerosols should have at least 99% of particle diameters in the 10- to 110-μm range. This means that most aerosol particles are deposited in the nasopharyngeal region and are not respirable.

Noncosmetic

Allantoin is FDA approved for use as a skin protectant at 0.5% to 2.0%.[53] It is considered safe for use as an oral wound healing

Table 4. Frequency of Use and Concentration of Allantoin, Allantoin Ascorbate, Allantoin Glycyrrhetinic Acid, Allantoin Panthenol, and Allantoin Polygalacturonic Acid

Product Category (no. of products in each category)[45]	Frequency of Use[45]	Concentration of Use, %[46]
Allantoin		
Baby products		
Lotions, oils, powders, and creams (67)	6	0.05-2
Other (64)	3	—
Bath products		
Oils, tablets, and salts (207)	3	—
Soaps and detergents (594)	28	0.1-0.2
Bubble baths (256)	2	0.3
Other (276)	3	0.0001-0.1
Eye makeup		
Eyebrow pencils (124)	—	0.1
Eyeliners (639)	3	0.2
Eye shadow (1061)	2	—
Eye lotions (32)	12	0.1-0.2
Eye makeup remover (114)	15	0.0005-0.1
Mascara (308)	4	—
Other (229)	17	0.001-0.2[a]
Fragrance products		
Powders (324)	4	—
Other (187)	20	—
Noncoloring hair care products		
Conditioners (5)	34	0.001-0.1
Sprays/aerosol fixatives (294)	11	—
Straighteners (61)	1	—
Permanent waves (169)	4	—
Rinses (46)	1	—
Shampoos (1022)	31	0.1
Tonics, dressings, etc (623)	24	0.0001-0.1
Other (464)	4	0.3[b]
Makeup		
Blushers (459)	8	—
Face powders (447)	13	2
Foundations (530)	10	0.02-0.5
Lipsticks (1681)	51	0.01-0.8
Makeup bases (273)	6	0.02
Rouges (115)	1	—
Other (304)	17	0.5
Nail care products		
Cuticle softeners (20)	1	0.1
Creams and lotions (13)	1	—
Other (58)	1	0.005-0.1
Oral hygiene products		
Dentifrices (54)	5	0.1-0.2
Mouthwashes and breath fresheners (57)	—	0.1-0.2
Personal hygiene products		
Underarm deodorants (281)	10	0.001-0.1
Douches (8)	1	—
Other (390)	25	0.001-0.1
Shaving products		
Aftershave lotions (260)	110	0.05-0.5
Shaving cream (135)	9	0.01-0.5
Other (64)	10	0.001-0.2
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1009)	92	0.001-0.2
Face and neck creams, lotions, powders, and sprays (546)	102	0.002-0.4
Body and hand creams, lotions, powders, and sprays (992)	146	0.002-0.4
Foot powders and sprays (43)	2	—
Moisturizers (1200)	241	0.005-0.5

(continued)

Table 4 (continued)

Product Category (no. of products in each category)[45]	Frequency of Use[45]	Concentration of Use, %[46]
Night creams, lotions, powders, and sprays (229)	55	0.1-0.2
Paste masks/mud packs (312)	35	0.001-0.1
Skin fresheners (212)	39	0.1-0.2
Other (915)	116	0.005-0.2[c]
Suntan products		
Suntan gels, creams, liquids, and sprays (138)	19	0.2-0.5
Indoor tanning preparations (74)	5	0.1
Other (41)	13	0.002
Total uses/ranges for allantoin	1376	0.0001-2
Allantoin ascorbate		
Personal hygiene products		
Underarm deodorants (281)	—	0.001
Shaving products		
Aftershave lotions (260)	—	0.05
Total uses/ranges for allantoin ascorbate	—	0.001-0.05
Allantoin glycyrrhetinic acid		
Shaving products		
Shaving cream (135)	2	—
Skin care products		
Skin cleansing creams, lotions, liquids, and pads (1009)	1	—
Moisturizers (1200)	2	—
Night creams, lotions, powders, and sprays (229)	1	—
Total uses/ranges for allantoin glycyrrhetinic acid	6	—
Allantoin panthenol		
Skin care products		
Face and neck creams, lotions, powders, and sprays (546)	1	—
Moisturizers (1200)	1	
Total uses/ranges for allantoin panthenol	2	—
Allantoin polygalacturonic acid		
Shaving products		
Aftershave lotions (260)	1	—
Skin care products		
Body and hand creams, lotions, powder and sprays (992)	1	—
Total uses/ranges for allantoin polygalacturonic acid	2	—

Dashes indicate not reported.
[a] 0.2% in an eye pencil and an eye cream.
[b] 0.3% in a hair-straightening balm.
[c] 0.2% in skin wipes and skin toner.

agent, but there are inadequate data to establish the effectiveness.[45] Allantoin for a variety of other skin uses has been described.[25,54-57]

The safety and effectiveness of allantoin for use in dandruff/seborrheic dermatitis psoriasis drug products have not been established.[58]

Use of allantoin ascorbate, allantoin polygalacturonic acid, allantoin glycyrrhetinic acid, and allantoin polygalacturonic acid in various skin treatments has been described by manufacturers.[18,19,59]

General Biology

Most mammals process purines to allantoin, as shown in Figure 2. However, higher apes and humans do not possess urate oxidase, the final step in the process; thus, purines in humans become uric acid, which is excreted in urine.[60]

The oxidation of uric acid by cytochrome c produced allantoin. This may be a possible source of allantoin in human tissues and may be of significance in patients with Reye's syndrome, in whom elevated uric acid has been demonstrated.[61]

Animals and Humans

Allantoin is found in blood or serum in humans in the range of 7.2 to 48.2 μmol/L.[31,33,36,62-65]

Absorption, Distribution, Metabolism, and Excretion

Sznitowska and Janicki[66] applied allantoin (1%) in 3 different vehicles to the inner forearm of volunteers (n = 6) to test skin penetration. The vehicles were a hydrophilic gel (5% wt/wt aqueous solution of methyl cellulose with added glycerol and propylene glycol), an oil/water cream (sodium lauryl sulfate and cetostearyl alcohol), and a water/oil ointment (cetyl

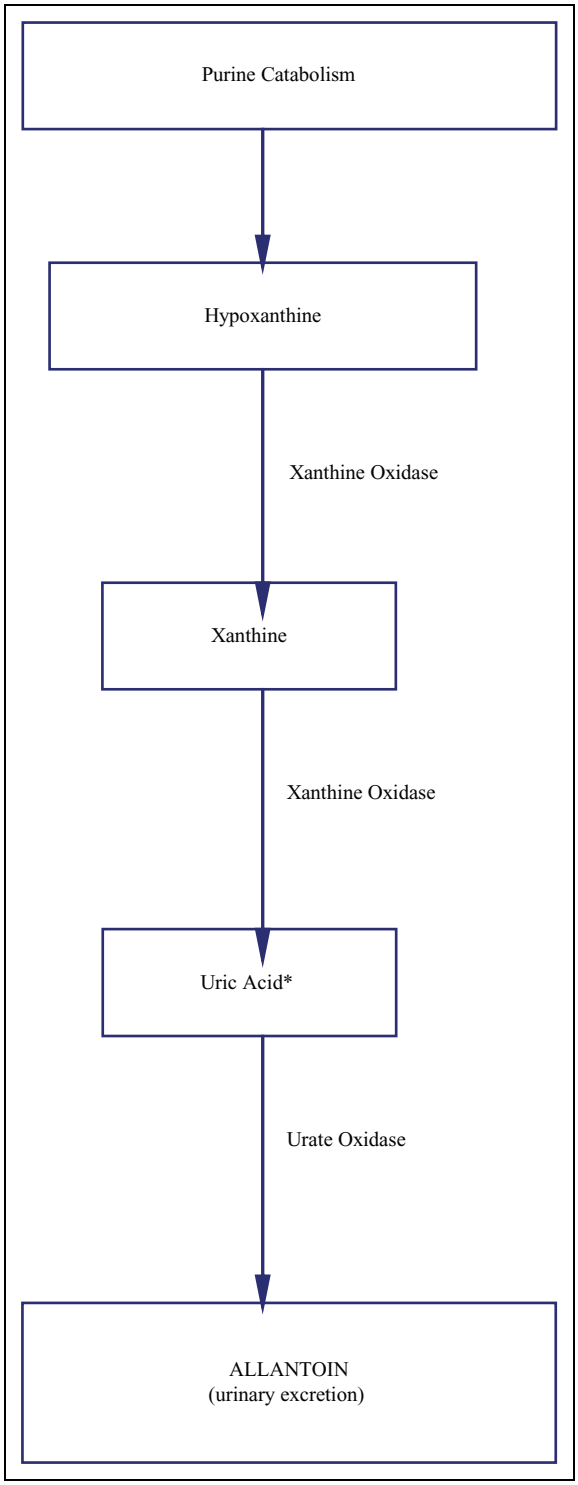

Figure 2. Mechanism of purine catabolism to allantoin in most animals. *Normal end point in higher apes and humans.[60]

alcohol and cholesterol). Two applications of each vehicle were made, 1 removed after 3 hours and the other after 6 hours. The remaining allantoin in the removed portion was measured and subtracted from the original amount to determine the absorption of allantoin. Allantoin penetration with the hydrophilic gel at 3 and 6 hours was 5.00% ± 1.25% and 6.9% ± 1.4%, respectively; with the oil/water cream 13.0% ± 1.8% and 15.4% ± 2.7%, respectively; and with the water/oil ointment 12.5% ± 2.1% and 20.0% ± 2.3%, respectively.

Allantoin (600 mg) was administered by stomach tube to dogs.[67] Elimination was complete in ~4 hours. Urine allantoin peaked at ~260 mg per 100 mL in less than 30 minutes and declined rapidly. Blood allantoin peaked at ~90 mg per 100 mL in less than 1 hour and declined steadily. Recovery was 674 mg (112%).

Friedman and Byers[68] performed clearance studies on male albino rats (n = 20; 1 was used twice) and male dogs (n = 4; 9 runs were done) following intravenous (IV) administration of allantoin. The renal clearance of endogenous allantoin in rats was 33.7 mL/h per 100 g (range, 25.8-41.7 mL/h per 100 g). The mean plasma allantoin concentration was 1.76 mg% (range, 1.20-2.23 mg%) during clearance. The renal clearance of endogenous allantoin in dogs was 85.5 mL/min/m^2 (range, 1.46-7.55 mL/g per 100 g). The mean plasma allantoin concentration was 0.66 mg% (range, 0.40-1.03 mg%).

Wallenburg and van Kreel[69] tested the transference of allantoin from the fetus to the dam in a pregnant rhesus monkey (*Macaca mulatta*). The dam was anesthetized. After fasting, a lower midline laparotomy was performed and the uterus exposed and delivered from the abdominal cavity. A fetal leg was delivered through a small incision and dissected for the application of catheters to the fetal femoral artery and vein. The fetal groin was sutured and returned to the amniotic cavity after draining the urinary bladder. The uterus was returned to the abdominal cavity and the incision partially closed. The maternal aorta, through a femoral artery, and the vena cava, through a saphenous vein, were catheterized. [^{14}C]Allantoin was infused into the fetal femoral artery (10 mL/g of body weight for 30 minutes and then 3 mL/h). Samples were collected from the fetal femoral artery (0.4 mL) and from the maternal aorta (1.0 mL) at 15-minute intervals and stored in heparinized vials. After centrifugation, fetal red cells were suspended in an equal volume of dilute heparin-normal saline and reinjected into the fetal circulation. The fetus was delivered by Cesarean section and killed, and the urinary bladder was emptied.

The total fetal clearance of allantoin was 3.8 mL/min/kg; renal clearance of allantoin was 0.09 mL/min/kg and of creatinine 0.29 mL/min/kg. The total clearance of allantoin was similar to that of uric acid clearance. Unlabeled uric acid in the fetal plasma was 60 μmol/L at the beginning of the experiment and rose 2- to 3-fold; steady concentration levels were never observed. Maternal renal uric acid and creatinine clearances were 3.2 ± 0.6 and 3.0 ± 0.5 mL/min/kg, respectively, and maternal plasma unlabeled uric acid remained stable at a low level (1.54 ± 0.30 μmol/L). Less than 5% of the available uric acid metabolized to allantoin. The authors stated that it is unlikely that fetal uric acid contributes to the maternal uric acid load in pre-eclamptic pregnancies.[69]

Animal Toxicology

No short-term or subchronic toxicity data were available. Chronic toxicity data are presented in the Carcinogenicity section.

Oral Acute Toxicity

In a toxicology assessment,[70] an acute oral toxicity test on Wistar rats (n = 10, 5 males and 5 females) was performed. The rats were orally administered a single dose of allantoin (5000 mg/kg) and observed for 14 days. No clinical signs were observed during the observation period. No mortality occurred. No abnormalities were noted at necropsy.

Akema Fine Chemicals[11] reported the oral median lethal dose (LD_{50}) of allantoin in rats to be more than 5000 mg/kg and considered allantoin to be slightly toxic.

Acute Dermal Toxicity

Akema Fine Chemicals[11] reported the LD_{50} of allantoin on the intact and abraded skin of rabbits (n = 10) to be 5000 mg/kg or higher.

Ocular Irritation

Centre International de Toxicoligie[71] performed a primary ocular irritancy test of allantoin (100 mg) on 1 eye of New Zealand rabbits (n = 6). The other eye served as the control. The eyes were examined 1, 24, 72, and 96 hours after instillation. No ocular reactions were observed. The authors concluded that allantoin was not irritating to eyes. Akema Fine Chemicals[11] reported that no eye irritation was observed in a Draize test on rabbits without washout (details not provided).

Phototoxicity

No phototoxicity or photosensitization data were available.

Reproductive and Developmental Toxicity

No reproductive or developmental toxicity data were available.

Genotoxicity

Allantoin was not mutagenic to *Salmonella typhimurium* strains TA1535, TA1538, TA98, and TA100, with or without S9 up to 1000 μg.[72]

Gus'kov et al[73] measured the frequency of rifampicin-resistant mutants in the *Escherichia coli* SOS-*lux* test to measure the mutagenicity of allantoin. Allantoin (1 mL) was added to the test plates 1.5 hours before hydrogen peroxide (10^{-7} and 10^{-6} M) was added to plates containing *E coli* (PT-1 strain transformed with plasmid pPls-1 carrying the *Lux* operon controlled by an SOS-responder). Water was the control. Allantoin decreased the mutant frequency at both hydrogen peroxide concentrations ($P < .05$). In further testing, allantoin did not affect the induction of the SOS response when added simultaneously with the hydrogen peroxide. When allantoin was added 1.5 hours before and after hydrogen peroxide, the mutations decreased ($P < .001$ and .01, respectively).

Akema Fine Chemicals[11] reported that allantoin was not mutagenic in an Ames test.

Dermal Irritation

Akema Fine Chemicals[11] reported that allantoin (0.5% in water) was not a primary skin irritant when applied to the intact and abraded skin of rabbits (details not provided).

Shiseido Research Center[74] applied allantoin (10% in water) to the clipped and shaved flanks of guinea pigs (n = 3) daily for 3 days. The skin was evaluated 24 hours after each application. The cumulative irritation score index was 0.2. The authors concluded that allantoin is classified as a "none to weak irritant" and is safe for use as a cosmetic ingredient.

The authors treated the germinated roots of *Allium cepa* L. (onion) with hydrogen peroxide after treating them with allantoin (10^{-6} to 10^{-5} M). After 18 hours, the seedlings were fixed and examined for aberrant cells, and chromosomal aberrations were quantified and compared with untreated seedlings. The treated seedlings decreased the level of Fe^{2+}-induced chromosomal aberrants ($P < .001$). The level of chromosomal aberrations decreased after 42 hours ($P < .01$). The authors stated that allantoin is neither cytotoxic nor cytostatic while exerting antimutagenic effects at concentrations corresponding to physiological values (ie, blood plasma 6.5×10^{-6}).[75]

Carcinogenicity

Lijinsky[76] fed F344 rats (males and females) rat chow with and without 0.2% allantoin with or without 0.2% sodium nitrite ad libitum for 106 weeks (n = 20). The rats were necropsied and all gross lesions and major organs and tissues were examined histologically. Controls (n = 24) were fed untreated chow and tap water.

The approximate total doses of allantoin were calculated to be 42 g per male rat and 28 g per female rat. Most of the rats were alive at the end of the 2-year treatment; there was no difference in the life spans of the rats in any group. The incidence of nonneoplastic lesions of the organs did not differ between treated and control rats. There was no difference in the incidence of tumors between groups. There was an increase in papillomas of the forestomach in male rats fed allantoin plus nitrite compared with controls ($P < .047$). The incidence of pituitary tumors was lower in females, but not males, fed allantoin without nitrite than in the untreated or nitrite-treated controls (P not provided).[76]

Clinical Assessment of Safety

Absorption, Distribution, Metabolism, and Excretion

Young et al[67] administered allantoin to male subjects orally, intravenously, and subcutaneously. Almost all of the allantoin administered by IV and subcutaneous injection was recovered by urinary excretion within 2 days; less was recovered

following oral administration. The authors suggest that allantoin goes through decomposition in the intestine prior to absorption.

Friedman et al[77] measured the clearance of orally administered allantoin in 5 men and 1 woman. The volunteers were administered 10 g of allantoin. The average plasma clearance of allantoin at 3.0, 3.5, and 4.0 hours after ingestion was 5.9, 5.9, and 6.2 mg per 100 mL, respectively, and the average renal clearance of allantoin was 123, 123, and 123 mL/min, respectively. No adverse effects were observed as a result of allantoin ingestion.[77]

Freidman et al[78] repeated the above experiment on healthy volunteers (n = 9; 1 female, 8 males) and patients with hypertension (n = 8; 3 female, 5 male), coarctation (n = 1 male), or nephritis (n = 2; 1 female, 1 male). The procedure was repeated with inulin (10 g in saline intravenously). The authors concluded that allantoin clearance was a measure of glomerular filtration rate; allantoin is absorbed by the gastrointestinal tract at a stable rate. There were no signs of toxicity following ingestion of allantoin.[78]

Dermal Irritation and Sensitization

Mecca[79] reported a personal communication from R.W. Gould that allantoin was not a primary skin sensitizer in a Schwartz patch test on 200 people. Allantoin was nontoxic, nonirritating, and nonallergenic. Allantoin was not a primary skin irritant or primary sensitizer in a repeated-insult test of 12 people.

Akema Fine Chemicals[11] reported no irritation and no sensitization using allantoin on healthy volunteers (n = 200; details not provided).

Tronnier[80] performed a skin irritation test on volunteers (n = 50; 31 females, 19 males; 18-72 years old). Eleven of the subjects had allergies and 7 had sensitive skin. A plaster of allantoin (2-5 mg/cm^2) was applied to the backs of the volunteers. The test plaster was removed after 24 hours. The test area was observed at removal of the plaster and after 72 hours. There were no signs of irritation.

Consumer Product Testing Co[81] performed a repeated-insult patch test of a product containing allantoin (0.095%) on human subjects (n = 105; age 16-78 years). The product (~0.2 mL) was applied to the upper back under an absorbent pad 3 times a week for 9 applications. The pad was left in place for 24 hours. After ~2 weeks' rest, a challenge pad was applied to a naive site and read 24 and 72 hours after application. There were scattered, transient, barely perceptible to moderate responses with occasional dryness and/or edema noted throughout the test period. No evidence of induced allergic contact sensitization was observed. The authors concluded that the results did not indicate a clinically significant potential for dermal irritation or allergic contact sensitization.

The Personal Care Products Council[82] submitted summaries of tests of products containing allantoin. In a 21-day cumulative irritation study, baby talc containing allantoin (0.5%) was repeatedly applied, under occlusion, to volunteers with self-perceived sensitive skin (n = 33). No skin irritation was detected with a normalized score of 0.00 out of 630. In a second test of the same product, with volunteers with self-perceived sensitive skin (n = 35), no skin irritation was detected with a normalized score of 8.9 out of 630.

In a repeated-insult patch test of baby talc containing allantoin (0.5%), the product was applied to volunteers with normal skin (n = 214). There were no reactions to 212 volunteers during induction (2 volunteers with a minimal or doubtful response). There were no reactions during the challenge phase.

This study was repeated with volunteers with normal skin (n = 213). During the induction phase, there were no reactions for 211 volunteers (2 volunteers with minimal or doubtful responses). There were no reactions during the challenge phase.

This study was repeated with volunteers with normal skin (n = 206). During the induction phase, there were no reactions in all volunteers. There were no reactions during the challenge phase.[82]

Other Dermal Tests

Mecca[83] stated that when allantoin is used in shampoos, not all of the allantoin is washed away, but rather some is left on the scalp and in the hair.

Henning[84] tested the effects of allantoin on stratum corneum renewal by applying a cream containing allantoin (0.5%) twice a day to untreated skin on forearms (number of subjects not stated). Another area was treated with a placebo and another was untreated. A suspension of dansyl chloride in petrolatum was applied to the forearm skin, and the level of fluorescence was assessed every second day under UV light. The time taken for dansyl chloride to disappear provided a measure of stratum corneum renewal time. Untreated skin had a renewal time of ~23 days, placebo ~21 days, and allantoin-treated skin ~19 days. No adverse effects were reported.

In a second experiment, irritation on the volar skin of forearms (number of subjects not stated) was induced by sodium dodecyl sulfate–tape stripping and UV radiation. Redness was measured with a chromatometer before irritation and after 2 hours and 1, 3, and 5 days. The skin was untreated, treated with a placebo (~2 mg/cm^2), or treated with the cream containing allantoin (0.5%; ~2 mg/cm^2). Before irritation, redness was measured at ~8.4. Allantoin-treated skin had lower redness scores at all observation times (no statistics were reported). No adverse effects were reported.

In a third experiment, transepidermal water loss (TEWL) was measured before treatment with sodium dodecyl sulfate, after treatment, and then after treatment as in the above experiments (number of subjects not stated). TEWL was closer to normalized in the allantoin-containing cream-treated group on day 5 than in the other 2 groups.[84]

Vinson and Proch[85] tested the use of an allantoin-based protectant as a moisture barrier in 12 subjects. The product containing allantoin (concentration not provided) was applied to 1-inch-square areas of the forearm and then covered with a bandage treated with a saline solution that simulated the density and ionic strength of urine and contained a dye solution. No reactions were reported from the allantoin barrier product at

4 or 8 hours. The allantoin barrier product began to lose its effectiveness in both groups after 1 hour.

Skin Disease Treatment

Topical agents containing allantoin and other ingredients were tested for effectiveness in treatment of diaper rash in infants. No adverse effects were reported in the studies.[86,87] Studies of topical agents containing allantoin and refined coal tar extract in treating psoriasis or other skin conditions reported no adverse effects.[88-92]

In another study, 22 patients were treated with an ointment containing allantoin, coal tar extract, and other ingredients.[93] One adverse side effect (acute dermatitis) was reported.

Almeyda and Wood[94] compared an allantoin (2%)–coal tar (5%) cream-based treatment to a fluorinated steroid preparation for the treatment of psoriasis on 33 patients (17 male, 16 female; age 16-74 years). The former was applied to the left arm and the latter to the right arm 2 or 3 times a day after an initial evaluation. The progress was evaluated after 2 and 4 weeks. Two patients dropped out because of deteriorating conditions. The allantoin–coal tar preparation performed better in 8 cases, worse in 13 cases, and equally well in 7 cases, and it failed equally in 7 cases. Six patients dropped out after the 2-week evaluation, 1 because of worsening of the condition with the allantoin–coal tar preparation that included a secondary infection. No other adverse effects were reported.

Wound Treatment

Creams, gels, and ointments containing allantoin (alone or in combination with other ingredients) have been tested for wound healing and treatment of other skin conditions.[56,94-97] No adverse effects attributed to allantoin were reported.

Galacturonic acid and polygalacturonic acid. No relevant safety test data were found on galacturonic acid and polygalacturonic acid. Galacturonic acid, in the form of polygalacturonic acid, is a major component of the polysaccharides that form pectin. Pectin is a group of polysaccharides rich in galacturonic acid. Galacturonic acid is present in the following major structural features that form the backbone of polysaccharide domains that are thought to be found in all pectin species: homogalacturonan, rhamnogalacturonan-I, and rhamnogalacturonan-II.[98,99]

Homogalacturonan is a homopolymer of (1-4)-α-D-galacturonic acid residues that may be methylesterfied and acetylated. Rhamnogalacturonan-I has a repeating backbone of (1-2)-α-L-rhamnose-(1-4)-α-D-galacturonic acid. Rhamnogalacturonan-II has a homogalacturonan backbone with oligosaccharide side chains, as in Figure 3.[98,99] The FDA has deemed pectin as GRAS when used as a direct human food additive.[47]

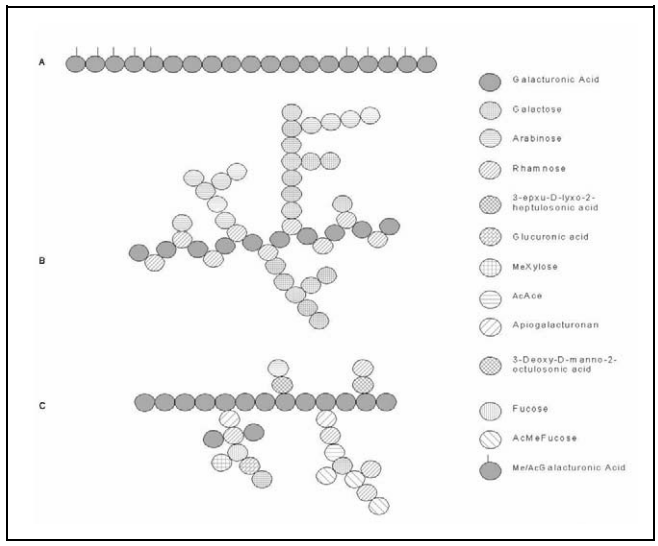

Figure 3. The structure of pectin. Galacturonic acid is the major component of all three types of polylsaccharide: A) homogalacturonan, B) rhamnogalacturonan I, C) rhamnogalactrunan.

Summary

This safety assessment includes the cosmetic ingredient allantoin and its related complexes: allantoin ascorbate, allantoin biotin, allantoin galacturonic acid, allantoin glycyrrhetinic acid, allantoin panthenol, and allantoin polygalacturonic acid. The safety of ascorbic acid, biotin, glycyrrhetinic acid, and panthenol has already been assessed by the CIR Expert Panel, and these agents were found to be safe. Galacturonic acid and polygalacturonic acid have not been reviewed by the CIR Expert Panel. Galacturonic acid is a sugar that is a component of pectin.

Polygalacturonic acid is the polysaccharide of the acid. Pectin was deemed GRAS as a direct human food additive by FDA.

Allantoin is a heterocyclic organic compound that may be prepared by several methods, including uric acid oxidation in the presence of permanganate. The other ingredients in this assessment are organic salts of this compound, except for allantoin panthenol, which is an alcohol/heterocyclic compound complex. Multiple analytical methods for allantoin are reported, including HPLC. Impurities include sulphated ash, sulphate, chloride, lead, arsenic, urea, and glycoluril.

All of the ingredients in this review act as skin-conditioning agents - miscellaneous.

Allantoin was reported to be used in 1376 cosmetic products at concentrations ranging from 0.0001% to 2%. Allantoin ascorbate was reported to be used at concentrations of 0.001% and 0.05%. Allantoin glycyrrhetinic acid was reported to be used in 6 cosmetic products, allantoin panthenol in 2 cosmetic products, and allantoin polygalacturonic acid in 2 cosmetic products. There were no reported uses for allantoin biotin or allantoin galacturonic acid. Allantoin, allantoin glycyrrhetinic acid, allantoin panthenol, and allantoin polygalacturonic acid were reportedly used in hair sprays. Noncosmetic uses included wound treatment and skin protectant.

Allantoin is found in plants and foods. Mammals process purines to allantoin with the exception of higher apes and humans because of their lack of urate oxidase. Only small amounts of allantoin are produced by oxidation of uric acid by cytochrome c and other oxidation pathways.

There was 98% recovery of allantoin in urine in dogs 5 hours after intravenous administration. When allantoin was administered orally, elimination was complete at 4 hours. Recovery averaged 66% when allantoin was administered in feed. No urinary allantoin was recovered from rabbits with allantoin in the diet. In sheep, most of the intravenously administered allantoin was excreted in the urine; degradation in the gut occurred post ruminally.

Acute oral toxicity of allantoin was greater than 5000 mg/kg in rats. Acute dermal toxicity of allantoin was equal to 5000 mg/kg in rabbits with intact and abraded skin.

Allantoin was nonirritating when instilled into the eyes of rabbits. Allantoin at 0.5% is not a dermal irritant to the intact or abraded skin of rabbits.

Allantoin was not mutagenic in an Ames test.

When fed to rats at 28 g per female and 42 g per male over 2 years, allantoin did not increase the instances of neoplastic lesions and tumors compared with controls. Allantoin with nitrite increased the incidence of papillomas of the forestomach in males and reduced the incidence of pituitary tumors in females without nitrite. There was no difference in life spans between rats fed allantoin and controls.

In a fasting blood clinical test, serum allantoin levels were 10.8 ± 1.7 μmol/L for women and 13.4 ± 1.6 μmol/L for men. Individual urinary recovery of orally administered allantoin to human males was 18.6% in 24 hours and 33.8% in 72 hours. Intravenously administered allantoin recovery in the urine was 98% in 72 hours and 94.5% and 88.8% in 12 hours. Subcutaneously administered allantoin recovery in the urine was 81.2% in 6 hours and 73.2% in 24 hours.

Allantoin (1%) penetration of human skin after 3- and 6-hour exposures was $5.00\% \pm 1.25\%$ and $6.9\% \pm 1.4\%$ in a hydrophilic gel, $13.0\% \pm 1.8\%$ and $15.4\% \pm 2.7\%$ for an oil/water cream, and $12.5\% \pm 2.1\%$ and $20.0\% \pm 2.3\%$ for a water/oil ointment, respectively.

Allantoin was found to be clinically nonirritating and nonsensitizing in multiple tests at various concentrations in various vehicles up to 0.5%.

Allantoin-containing medications were tested for effectiveness and were successful in treating and preventing diaper rash in infants. No adverse effects were reported for the babies or the persons applying the medication. Medications containing allantoin (2%)–coal tar successfully treated patients with psoriasis with no adverse effects. Allantoin-containing treatments, up to 4%, successfully treated psoriasis patients; 1 of 22 patients using an allantoin–coal tar lotion developed acute dermatitis after 1 week. Application of a coal tar lotion with allantoin (2%) 1 to 4 times daily for 6 months resulted in no adverse effects. A treatment containing allantoin (0.35%) in 40 patients with seborrheic dermatitis reported 1 adverse event. There were no adverse effects in the treatment of skin conditions with allantoin up to 2%.

Discussion

The CIR Expert Panel noted that none of the sensitization and irritation safety test studies were conducted at the 2% level, which is reported to be used in cosmetics. However, the therapeutic use studies were conducted at 2% to 4% on damaged skin with no adverse effects. These clinical data were considered to support the safety of allantoin in cosmetics.

The panel noted that allantoin is a natural metabolic product for which no reproductive/developmental toxicity has been suggested.

The ingredients in the complexes were found to be safe in previous safety assessments. Pectin is a GRAS substance that is mostly made up of galacturonic and polygalacturonic acid. These allantoin complexes, as well as allantoin polygalacturonic acid and allantoin galacturonic acid, were not expected to be toxic.

The potential adverse effects of inhaled aerosols depend on the specific chemical species, the concentration and the duration of the exposure, and their site of deposition within the respiratory system. The reported mean diameter of particles in hair sprays is 38 μm, with other reported diameters of 60 to 80 μm. Because the aerodynamic diameters of respirable particles are less than 10 μm, most aerosol particles found in hair sprays are not respirable. In the absence of inhalation toxicity data, the panel determined that allantoin and its related complexes can be used safely in hair sprays, because the ingredient particle size is not respirable.

The CIR Expert Panel recognizes that there are data gaps regarding use and concentration of these ingredients. However, the overall information available on the types of products in which these ingredients are used and at what concentrations indicates a pattern of use, which was considered by the Expert Panel in assessing safety.

Conclusion

The CIR Expert Panel concluded that allantoin and its related complexes, allantoin ascorbate, allantoin biotin, allantoin galacturonic acid, allantoin glycyrrhetinic acid, allantoin panthenol, and allantoin polygalacturonic acid, are safe as cosmetic ingredients in the practices of use and concentrations as described in this safety assessment. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group.

Authors' Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1101 17th Street, Suite 412, Washington, DC 20036, USA.

Declaration of Conflicting Interests

No potential conflict of interest relevant to this article was reported. F. Alan Andersen, PhD, and Lillian C. Becker are employed by the Cosmetic Ingredient Review.

Funding

The articles in this supplement were sponsored by the Cosmetic Ingredient Review. The Cosmetic Ingredient Review Program is financially supported by the Personal Care Products Council.

References

1. Andersen FA. Final report on the safety assessment of l-asorbic acid, calcium ascorbate, magnesium ascorbate, magnesium ascorbyl phosphate, sodium ascorbate, and sodium ascorbyl phosphate as used in cosmetics. *Int J Toxicol*. 2005;24:51-111.
2. Andersen FA. Final report on the safety assessment of biotin. *Int J Toxicol*. 2001;20:1-12.
3. Andersen FA. Final report on the safety assessment of glycyrrhetinic acid, potassium glycyrrhetinate, disodium succinoyl glycyrrhetinate, glyceryl glycyrrhetinate, glycyrrhetinyl stearate, stearyl glycyrrhetinate, glycyrrhizic acid, ammonium glycyrrhizate, dipotassium glycyrrhizate, disodium glycyrrhizate, trisodium glycyrrhizate, methyl glycyrrhizate, and potassium glycyrrhizinate. *Int J Toxicol*. 2007;26:79-112.
4. Elder RL. Final report on the safety assessment of panthenol and pantothetic acid. *J Am Coll Toxicol*. 1987;6:139-162.
5. Andersen FA. Annual review of cosmetic ingredient safety assessments—2004/2005. *Int J Toxicol*. 2006;25:1-89.
6. Health and Human Services. Direct food substances affirmed as generally recognized as safe. *Code Fed Regul*. 2006;184:(1588).
7. Gottschalck TE, Bailey JE. *International Cosmetic Ingredient Dictionary and Handbook*. 12th ed. Washington, DC: CTFA; 2008.
8. Sheker KM, Black HJ, Lach JL. Silver allantoinate for the topical treatment of burns. *Am J Hosp Pharm*. 1972;29:852-855.
9. ChemicalLAND21. Allantoin. 2007. http://chemicalland21.com/lifescience/phar/ALLANTOIN.htm. Accessed January 1, 2007.
10. Fisher AA. A non-sensitizing topical medicament therapeutic effects of the addition of 5 percent allantoin to Vaseline. *Cutis*. 1981;27:230-231, 234, 329.
11. Akema Fine Chemicals. Allantoin: a safe and effective skin protectant; 2006. Unpublished data.
12. Lesser MA. Allantoin. *Drug Cosmetic Ind*. 1938;42:451-453, 456, 469.
13. Schali C, Roch-Ramel F. Renal handling of [14C] allantoin in the rabbit. *J Pharmacol Exp Ther*. 1980;213:168-172.
14. Buzard JA, Bishop C, Talbott JH. The conversion of uric acid to allantoin in the normal and gouty human. *J Biol Chem*. 1954;211:559-611.
15. ChemIDplus Lite. Allantoin. 2007. http://chem.sis.nlm.nih.gov/chemidplus/jsp/common/ChemFull.jsp?calledFrom=lite. Accessed January 1, 2007.
16. Mecca SB. Allantoin in cosmetic formulations. *Proceedings of the Scientific Section of the Toilet Goods Association*. 1955;23:8-13.
17. Akema Fine Chemicals. Akema Fine Chemicals overview. 2007. http://www.akema.it/pdf/COMPANY_BROCHURE.pdf. Accessed December 1, 2007.
18. Mecca SB. Allantoin and its derivatives. *Cosmet Toilet*. 1978;93:39-41.
19. Active Ingredients Ltd. Glyceratoin. 2004. http://www.activeingredient.plus.com/glyceratoin.pdf.
20. Givens MH. Brief notes concerning allantoin. *J Biol Chem*. 1912;18:417-424.
21. Kaliszan R, Halkiewicz J. IR analysis of crystalline samples of some urea derivatives. *Pol J Pharmacol Pharm*. 1975;27:579-587.
22. Zaidi ZR, Sena FJ, Basilio CP. Stability assay of allantoin in lotions and creams by high-pressure liquid chromatography. *J Pharm Sci*. 1982;77:997-999.
23. Sznitowska M, Janicki S. In vitro study of allantoin release from various ointment formulations. *Pharmazie*. 1987;42:62-63.
24. Lukasiak J, Jamrogiewicz Z, Sznitowska M. Some remarks on the UV spectrophotometric determination of allantoin. *Pharmazie*. 1987;42:200-201.
25. Livingston SK, Prince LH. The treatment of chronic osteomylitis. *JAMA*. 1932;98:1143-1149.
26. Maksimovic Z, Malenovic A, Jancic B, Kovacevic N. Quantification of allantoin in various Zea mays L. hybrids by RP-HPLC with UV detection. *Pharmazie*. 2004;59:524-527.
27. Hartman WW, Moffett EW, Dickey JB. Allantoin. *Org Syntheses, Coll*. 1943;2:21.
28. Akema Fine Chemicals. Allantoin CTFA; 2005. http://www.akema.it/allantoin.htm. Accessed January 1, 2007.
29. Weber DJ, Higgins JW. Potentiometric titration of allantoin in cream formulation. *J Pharm Sci*. 1970;59:1819-1821.
30. Tiemeyer W, Giesecke D. Quantitative determination of allantoin in biological fluids by reversed-phase high-pressure liquid chromatography. *Anal Biochem*. 1982;123:11-13.
31. Grootveld M, Halliwell B. Measure of allantoin and uric acid in human body fluids. *Biochem*. 1987;243:803-808.
32. Kawase J, Ueno H, Tsuji K. Determination of allantoin and chlorohydroxy-aluminum allantoinate in cosmetic and pharmaceutical products by high-performance liquid chromotography. *J Chromatog*. 1982;253:237-242.
33. Lux O, Naidoo D, Salonikas C. Improved HPLC method for the simultaneous measurement of allantoin and uric acid in plasma. *Ann Clin Biochem*. 1992;29:674-675.
34. Chen XB, Matsuzewski W, Kowalczyk J. Determination of allantoin in biological, cosmetic, and pharmaceutical samples. *J AOAC Int*. 1996;79:628-635.
35. Berthemy A, Newton J, Wu D, Buhrman D. Quantitative determination of extremely polar compound allantoin in human urine by LC-MS/MS based on the separation on a polymeric amino column. *J Pharm Biomed Anal*. 1999;19:429-434.
36. Benzie IFF, Chung WY, Tomlinson B. Simultaneous measurement of allantoin and urate in plasma: analytical evaluation and potential clinical application in oxidant antioxidant balance studies. *Clin Chem*. 1999;45:901-904.
37. Marklund N, Östman B, Nalmo L, Persson L, Hillered L. Hypoxanthine, uric acid and allantoin as indicators of in vivo radical reactions: description of a HPLC method and human brain microdialysis data. *Acta Neurochir*. 2000;142:1142.
38. Pavitt DV, De Fonseka S, Al-Khalaf N, Cam JM, Reaveley DA. Assay of serum allantoin in humans by gas chromatography—mass spectrometry. *Clin Chim Acta*. 2002;318:63-70.

39. Muratsubaki H, Satake K, Enomoto K. Enzymatic assay of allantoin in serum using allantoinase and allantoate amidohydrolase. *Anal Biochem*. 2006;359:161-166.
40. United States Pharmacopia. Allantoin. 2005:1323-1324.
41. Kahn LP, Nolan JV. Kinetics of allantoin metabolism in sheep. *Br J Nutr*. 2000;84:629-634.
42. Wang X-C, Gui C-Q, Zheng Q-S. Combined therapy of allantoin metronidazole, dexamethasone on the prevention of intra-abdominal adhesion in dogs and in its quantitative analysis. *World J Gastroenterol*. 2003;9:568-565.
43. Ackroyd H. On the presence of allantoin in certain foods. *Biochem J*. 1911;5:400-406.
44. Zhang L, Liu Y, Chen G. Simultaneous determination of allantoin, choline, and l-arginine in Rhizoma Dioscoreae by capillary electrophoresis. *J Chromatog A*. 2004;1043:317-321.
45. Food and Drug Administration. Frequency of use of cosmetic ingredients. *FDA Database*. 2007.
46. Cosmetic, Toiletry and Fragrance Association. Concentration of use allantoin and related ingredients; 2007. Unpublished data.
47. Food and Drug Administration. Frequency of use of cosmetic ingredients. *FDA Database*. 2006.
48. Ministry of Health, Labor and Welfare. *Unofficial Translation of MHLW Notification No 0524001 Regarding the Handling of Medicinal Ingredients That May Be Incorporated in Cosmetics*. Tokyo, Japan: Pharmaceutical and Medical Safety Bureau, Inspection and Guidance Division; 2007.
49. Willeke K, Baron PA. *Industrial Hygiene: Aerosol Measurement: Principles Techniques and Applications*. New York, NY: Wiley; 1993.
50. Lehman-McKeeman LD. Absorption of Toxicants by the Lungs. In: *Casarret and Doull's Toxicology: The Basic Science of Poisons*. Klassen CD, ed. New York: McGraw-Hill; 2008: 140-142.
51. Bower D. Unpublished information on hair spray particle sizes provided at the September 9, 1999 CIR Expert Panel meeting; 1999.
52. Johnsen MA. The influence of particle size. *Spray Technology and Marketing*. November 2004:24-27.
53. Health and Human Services. Skin protectant active ingredients. *Code Fed Regul*. 2007;347:(10).
54. Robinson W. Stimulation of healing in non-healing wounds. *J Bone Joint Surg*. 1935;17:267-262.
55. Morris GE. Pedicuosis corporis and leg ulcers. *N Engl J Med*. 1945;22:180.
56. Margraf HW, Covey TH. A trial of silver-zinc allantoinate in the treatment of leg ulcers. *Arch Surg*. 1977;112:699-704.
57. Koerber KA, Spangler HA, O'Donnell C, Moffses GH. Sulfallantoin in industrial medicine. *Industrial Med*. 1942;11:475-476.
58. Health and Human Services. Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses. *Code Fed Regul*. 2007;310:(545).
59. Akema Fine Chemicals. Allantoin and derivatives. 2007. http://www.iper.net/akema/ALLANTOIN%20AND%20DERIVATIVES%20.htm. Accessed December 1, 2007.
60. Goldman SC, Holcenberg JS, Finklestein JZ, et al. A randomized comparison between rasburicase and allopuinol in children with lymphoma or leukemia at high risk for tumor lysis. *Blood*. 2001;97:2998-3003.
61. Martens Me, Storey BT, Lee CP. Generation of allantoin from the oxidation of urate by cytochrome *c* and its possible role in Reye's syndrome. *Arch Biochem Biophys*. 1987;252:91-96.
62. Lagendijk J, Ubbink JB, Vermaak WJ. The determination of allantoin, a possible indicator of oxidant status, in human plasma. *J Chromatog Sci*. 1995;33:186-193.
63. Hellsten Y, Tullston PIC, Richter EA, Bangsbo J. Oxidation of urate in human skeletal muscle during exercise. *Free Rad Biol Med*. 1997;22:169-174.
64. Kock R, Delvoux B, Sigmund M, Greiling H. A comparative study of the concentrations of hypoxanthine, zanthine, uric acid and allantoin in the peripheral blood of normals and patients with acute myocardial infarction and other ischaemic diseases. *Eur J Clin Chem Clin Biochem*. 1994;32:837-842.
65. Naidoo D, Lux O. The effect of vitamin C and E supplementation on lipid and urate oxidation products in plasma. *Nutr Res*. 1998; 18:953-961.
66. Sznitowska M, Janicki S. The effect of vehicle on allantoin penetration into human skin from an ointment for improving scar elasticity. *Pharmazie*. 1988;43:H3.
67. Young EG, Wentworth HP, Hawkins WW. The absorption and excretion of allantoin in mammals. *J Pharmacol Exp Ther*. 1944;81:1-9.
68. Friedman M, Byers SO. Clearance of allantoin in the rat and dog as a measure of glomerular filtration rates. *Am J Physiol*. 1947; 151:192-197.
69. Wallenburg HCS, van Kreel BK. Transfer and dynamics of uric acid in the pregnant rhesus monkey, I: transplacental and renal uric acid clearances. *Eur J Obstet Gynecol Reprod Biol*. 1978;8: 211-217.
70. HF 0041—Evaluation de toxicite aigue chez le rat par voie orale. Study no. 1757 TAR. November 22, 1985. Allantoin compilation of toxicity studies. Clariant GmBH.
71. Allantoin (HF-0041)—Eye irritation study in the rabbit. Study no. 5420 TAR. September 28, 1989. Allantoin compilation of toxicity studies. Clariant GmbH.
72. Andrews AW, Lijinsky W, Snyder SW. Mutagenicity of amine drugs and their products of nitrosation. *Mutat Res*. 1984;135: 105-108.
73. Gus'kov EP, Kletskii ME, Korniendo IV, et al. Allantoin as a free-radical scavenger. *Dokl Biochem*. Biophys. 2002;383:105-107.
74. Shiseido Research Center. Safety data of allantoin; 2008. Unpublished data.
75. Gus'kov EP, Prokof'ev VN, Kletskii ME, et al. Allantoin as a vitamin. *Dokl Biochem Biophys*. 2004;398:320-324.
76. Lijinsky W. Induction of tumours in rats by feeding nitrosatable amines together with sodium nitrite. *Food Chem Toxicol*. 1984; 22:715-720.
77. Friedman M, Byers SO, Abraham PM. Allantoin clearance as a measure of glomerular filtration in man. *Proc Soc Exp Biol Med*. 1947;66:522-523.
78. Friedman M, Byers SO, Abraham PM. Renal clearance of allantoin as a measure of glomerular filtration rate. *Am J Physiol*. 1948;155:278-281.

79. Mecca SB. Allantoin and the newer aluminum allantoinates. *Proc Sci Sec Toilet Goods Assoc*. 1959;(31):1-6.
80. Tronnier H. April 18, 1996. Epikutantest zur Prüfung der hautirritierenden Wirkung kosmetischer Produkte am Menschen—Allantoin. Institute für experimentelle Dermatologie, Uninversität Witten-Herdeck. Forschngsaufrag 57/4/96. Cited in Clariant GmbH. 2003 Allantoin compilation of toxicity studies. Unpublished data.
81. Consumer Product Testing Co. Exclusive repeated insult patch test. 2007. Unpublished data.
82. Personal Care Products Council. Summaries of products containing allantoin for the CIR review of allantoin and related ingredients. 2008. Unpublished data.
83. Mecca SB. The function and applicability of the allantoins. *Proc Sci Sec Toilet Goods Assoc*. 1963;39:7-15.
84. Henning T. Evaluation of the efficacy of allantoin. *Eur Cosmet*. 2001;2:20-22.
85. Vinson J, Proch J. Inhibition of moisture penetration to the skin by a novel incontinence barrier product. *J Wound Ostomy Continence Nurs*. 1998;25:256-260.
86. Kahan H, Schwartzman J, Sawicky HH. A new topical remedy for the prevention and management of napkin dermatitis (diaper rash). *Arch Pediatr*. 1956;73:12-29.
87. Kaessler HW. Dermatitis of the diaper area: a new remedy for an old affliction. *Arch Pediatr*. 1957;74:47-50.
88. Bleiberg J, Saltzman JA. Experience with a new preparation in the local treatment of psoriasis. *Clin Med*. 1958;5:485-488.
89. Clyman SG. Clinical experience with a new preparation for psoriasis: a paired comparative study. *Ann NY Acad Sci*. 1958;73: 1032-1037.
90. Welsh AL, Ede M. Therapeutic effectiveness of tar-allantoin lotion (Alphosyl ®) in selected dermatoses. *Ohio Med*. 1959; 55:805-807.
91. Meister B. Treatment with tar and allantoin cream. *Skin*. 1962;1: 55-56.
92. Allenby CF, Munro-Ashman EJE, Wells RS, Barr A. Outpatient treatment of psoriasis a double-blind trial of ointments. *Lancet*. 1966;15:124-125.
93. Herdenstam CG. Allantoin in the treatment of psoriasis: a double blind study. *Acta Derm Venereol*. 1959;39:216-214.
94. Almeyda J, Wood H. Treatment of psoriasis: comparative study using allantoin coal tar extract combined with hydrocortisone and betamethasone valerate. *Br J Clin Prac*. 1979;33: 106-108.
95. Willital GH, Heine H. Efficacy of Contracubex® Gel in the treatment of fresh scars after thoracic surgery in children and adolescents. *Int J Clin Pharm Res*. 1994;14:193-202.
96. Garnick JJ, Singh B, Winkley G. Effectiveness of a medicament containing silicon dioxide, aloe, and allantoin on aphthous stomatitis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1998;86:550-556.
97. Wadhams PS, Griffith J, Nikravesh P, Chodosh D. Efficacy of a surfactant, allantoin, and benzalkonium chloride solution for onychomycosis. *J Am Podiatr Med Assoc*. 1999;89:124-130.
98. Willats WGT, McCarney L, Mackie W, Knox JP. Pectin: cell biology and prospects for functional analysis. *Plant Mol Biol*. 2001;47:9-27.
99. Bacic A. Breaking an impasse in pectin biosynthesis. *Proc Natl Acad Sci U S A*. 2006;103:5639-5640.