
Safety Assessment of Saccharide Humectants as Used in Cosmetics

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All interested persons are provided 60 days from the above date (March 24, 2020) to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a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 Executive Director, Dr. Bart Heldreth.

The 2020 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst.

INTRODUCTION

The safety of the following 7 saccharide humectants, as used in cosmetics, is reviewed in this Cosmetic Ingredient Review (CIR) safety assessment

Anhydrogalactose
Anhydroglucitol

Anhydroxylitol
Arabinose

Psicose
Saccharide Hydrolysate

Saccharide Isomerate

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (WINCI; *Dictionary*), all 7 saccharide humectants are reported to function as skin-conditioning agents – humectant in cosmetics (See Table 1).¹ Anhydrogalactose is also reported to function as an antioxidant, and Anhydroglucitol also functions as an oral care agent.

Because Saccharide Hydrolysate contains glucose and fructose, and saccharides/saccharide mixtures are being reviewed in this report, it is important to note that the CIR Expert Panel (Panel) has evaluated the safety of glucose and fructose (monosaccharides), as well as other monosaccharides and disaccharides. In 2019, the Panel published a report with a conclusion stating that the monosaccharides, disaccharides, and related ingredients are safe in the present practices of use and concentration in cosmetics described in the safety assessment.²

This safety assessment includes relevant published and unpublished data for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A list of the typical search engines and websites used, sources explored, and endpoints that CIR evaluates is available on the CIR website (<https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites>; <https://www.cir-safety.org/supplementaldoc/cir-report-format-outline>). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Of the 5 discrete saccharides that are reviewed in this safety assessment, Anhydrogalactose is supplied as the L-stereoisomer; while the other 4 (Anhydroglucitol, Anhydroxylitol, Arabinose, and Psicose) are each defined as the D-stereoisomers. For any one of the monosaccharides reviewed in this report, available relevant data on a different stereoisomer may be included, as these data may have some value in the safety assessment of isomer(s) under review. In such instances, the *Dictionary* name (including capitalization) will not be used (e.g., L-arabinose). Since Saccharide Hydrolysate and Saccharide Isomerate are defined as products by various processes, various stereochemistries are possible.

CHEMISTRY

Definition and Structure

All of the ingredients in this report are hygroscopic, saccharides or saccharide derivatives. Such ingredients are commonly used for their moisturizing (humectant) properties. For example, Anhydroglucitol (CAS No. 154-58-5), a pyranoid polyol, is similar in structure to that of glucose, except for a methylene group at the C1 position (Figure 1).^{1,3,4} Psicose (CAS No. 23140-52-5) has been defined as a C-3 epimer of D-fructose (Figure 2).^{1,5}

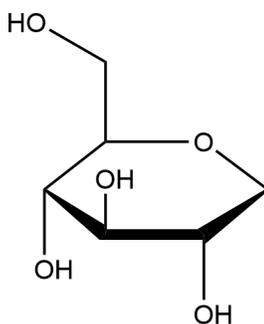


Figure 1. Anhydroglucitol

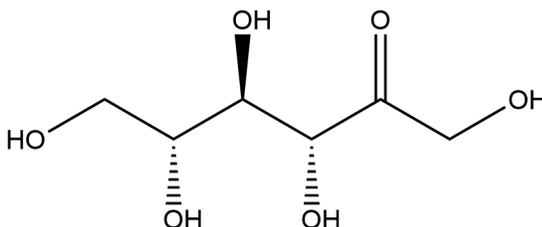


Figure 2. Psicose

The definitions, structures, and CAS Nos. of all the saccharide humectants included in this safety assessment are presented in Table 1.¹

Physical and Chemical Properties

Physical and chemical properties of saccharide humectants are presented in Table 2.⁶⁻¹² Anhydrogalactose, Anhydroxylitol, Psicose, and Saccharide Hydrolysate are water-soluble.

Method of Manufacture

Methods of manufacture specific to cosmetics were neither found in the publicly available literature, nor were such methods submitted as unpublished data. However, these ingredients are chemical entities known and utilized in other industries, and, general methods, not specific to the cosmetics industry, are thus known. Such are described below.

Anhydrogalactose

Anhydrogalactose may be prepared by enzymatic saccharification of agar, using a combination of agarolytic enzymes.¹³ According to another source, the following 3 steps are required for production of high purity Anhydrogalactose from agarose: acid pre-hydrolysis of agarose, enzymatic saccharification, and purification of Anhydrogalactose.¹⁴

Anhydroglucitol

A single-enzyme process for the production of Anhydroglucitol has been designed.¹⁵ The process involves the acid pre-hydrolysis of agarose into agarobiose and the enzymatic hydrolysis of agarobiose into Anhydroglucitol and galactose.

Psicose

It has been reported that Psicose is easily generated by heating sugar preparations.¹⁶ Details relating to this process were not provided. According to another source, Psicose has been produced from fructose using the enzyme tagatose 3-epimerase.¹⁷

Composition and Impurities

Composition and impurities data specific to cosmetics were neither found in the publicly available literature, nor were such methods submitted as unpublished data. However, these ingredients are chemical entities known and utilized in other industries, and, general composition/impurities profiles, not specific to the cosmetics industry, are thus known. Such are described below.

Saccharide Hydrolysate

According to the *Food Chemicals Codex* description, invert sugar is marketed as invert sugar syrup and contains dextrose (glucose), fructose, and sucrose in various amounts, as represented by the manufacturer.⁹ In accordance with the *Food Chemicals Codex*, the acceptance criteria for invert sugar are that it contains not less than 90% and not more than 110% of the labeled amount of sucrose and of invert sugar. Other acceptance criteria for invert sugar in the *Food Chemicals Codex* relate to lead content (not more 0.1 mg/kg) and sulfated ash content (not more than 0.2%).

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2019 VCRP data, Saccharide Isomerate is reported to be used in 455 cosmetic products (406 leave-on products and 49 rinse-off products).¹⁸ Of the saccharide humectants reviewed in this safety assessment, this is the greatest reported use frequency. The results of a concentration of use survey conducted by the Council in 2018 indicate that Saccharide Hydrolysate is being used at maximum use concentrations up to 4.6% in rinse off products (skin cleansing products), and that Saccharide Isomerate is being used at maximum use concentrations up to 2.8% in leave-on products (face and neck skin care preparations, not spray).¹⁹ These are the highest use concentrations in rinse-off and leave-on products reported for the saccharide humectants that are reviewed in this safety assessment. Further use data are presented in Table 3.

According to VCRP and Council survey data, the following 3 ingredients are not currently in use in cosmetic products: Anhydrogalactose, Arabinose, and Psicose.

Cosmetic products containing saccharide humectants may be applied to the skin, or, incidentally, may come in contact with the eyes (e.g., Saccharide Isomerate at concentrations up to 1% in eye shadows). Anhydroglucitol (at concentrations up to 0.17% in bubble baths) is used in products that come in contact with mucous membranes. Anhydroxylitol and Saccharide Isomerate are also used in products that come in contact with mucous membranes. However, use concentration data on these

ingredients in cosmetics are not included in the Council's survey. Products containing saccharide humectants may be applied as frequently as several times per day, and may come in contact with the skin for variable periods following application. Daily or occasional use may extend over many years.

Anhydroxylitol is reported to be used in products (other fragrance preparations) that are sprayed.¹⁸ 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.²⁰⁻²³ 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.^{20,21}

The saccharide humectants reviewed in this safety assessment are not included on the European Union's list of substances that are restricted or list of substances that are prohibited in cosmetic products.²⁴

Non-Cosmetic

Anhydroglucitol

The use of Anhydroglucitol to monitor new classes of therapies for managing post-meal glucose in patients with diabetes has been reported.²⁵ The use of Anhydroglucitol is included in the International Diabetes Federation guideline for management of post-meal glucose as an emerging technology to measure postprandial glucose levels.

Arabinose

The stereoisomer, L-arabinose, is used in the bacterial mutagenesis test system that is known as the *Salmonella*/arabinose-resistant (Ara^r) assay system.²⁶ In the Ara^r assay system, L-arabinose is added to molten soft agar.

Psicose

Psicose (rarely found in nature) is a sugar substitute that has 70% of the sweetness of sucrose, but almost zero calories.⁵

Saccharide Hydrolysate

Saccharide Hydrolysate is a direct food substance affirmed generally recognized as safe (GRAS) by the US FDA [21 CFR 184.1859]. This ingredient is used in food with no limitation other than current good manufacturing practice.

According to one source, the indications for use of invert sugar in an obstetrics and gynecology center in the US have been limited to diabetic women during the intrapartum period.²⁷

TOXICOKINETIC STUDIES

Dermal Penetration

Anhydroxylitol

A National Industrial Chemicals Notification and Assessment Scheme (NICNAS) public report on Anhydroxylitol is available.⁶ According to NICNAS, based on the low molecular weight of Anhydroxylitol (134 Da), there is potential for dermal absorption and passage across the gastrointestinal tract. However, this may be limited by its high water-solubility (674 g/L), and low partition coefficient (log P_{ow} = -2).

Absorption, Distribution, Metabolism, and Excretion

Animal

Oral

Anhydroglucitol

The fate of anhydroglucitol (D or L not stated) in white laboratory rats after dosing was studied.²⁸ In short-term experiments, anhydroglucitol (2 to 7 mg, in saline) was administered orally to 5 rats as follows: 2 mg (1 rat), 5 mg (3 rats), and 7 mg (1 rat). The concentration of anhydroglucitol in the serum of 11 untreated rats was 47 ± 24 (standard deviation) µmol/L, and no anhydroglucitol was found in the urine. These control data suggest that anhydroglucitol is efficiently reabsorbed by rat kidney tubuli. In the 5 test rats, the serum anhydroglucitol concentration increased rapidly after oral dosing. The peak concentration in the serum was observed at 1 h post-dosing, suggesting that anhydroglucitol was readily absorbed by the gut. Of the 5 mg dose that was administered, 1.4 to 1.6 mg was recovered in the urine in 48 h. There was no urinary excretion of anhydroglucitol after 48 h.

In another experiment involving 12 white laboratory rats, Anhydroglucitol (7 mg, 0.14 mmol/kg body weight) was administered orally (in drinking water) daily for 7 weeks.²⁸ Six rats served as controls. Blood and urine samples were collected (schedule for collection of samples not stated). In test animals, a high serum Anhydroglucitol concentration (62 to 126 µmol/L) was maintained in the 12 rats. The concentration of Anhydroglucitol in the serum of the 6 control rats (not dosed with Anhydroglucitol) ranged from 24 to 62 µmol/L. Data from this study relating to toxicity are included in the Short-Term Oral Toxicity section of this report.

Psicose

U-[¹⁴C]- Psicose (2 µCi) was administered by stomach tube to rats (number and strain not stated).²⁹ Of the exhaled [¹⁴C]-carbon dioxide, 26% was exhaled within 7 h and 80% was inhaled within 24 h. Much of the radioactivity was rapidly excreted in

the urine, whereby 95% of the excreted radioactivity was recovered within the first 7 h. Of the excreted radioactivity recovered, at least 70% was U-[¹⁴C]-Psicose. The remaining 30% of the radioactivity in the urine was associated with unidentified products of metabolism. The authors noted that rapid excretion of orally administered U-[¹⁴C]-Psicose is suggestive of easy passage through the wall of the small intestine. It then enters the blood and is eliminated through the kidneys. The authors also stated that the increased metabolism to [¹⁴C]-carbon dioxide and the finding that 39% of the radioactivity is retained by the carcass for 72 h after oral feeding suggests that a large portion of the U-[¹⁴C]-Psicose is metabolized by intestinal microorganisms. It was noted that some of these metabolites are absorbed into the metabolic system of the rat.

The intestinal absorption, organ distribution, and urinary excretion of [¹⁴C]-Psicose was studied using 30 male Wistar rats.³⁰ All of the rats were fasted for 24 h. Approximately 0.6 mL of [¹⁴C]-Psicose solution (30 mg, 120 kilobecquerels (kBq)) was administered at an oral dose of 100 mg/kg. The rats were killed at 10, 30, 60, and 120 min post-administration. [¹⁴C]-Psicose entered the blood after oral dosing, and the maximum blood concentration ($48.5 \pm 15.6 \mu\text{g/g}$) was observed at 1 h. Urinary excretion was 20% within 1 h and 33% within 2 h. Accumulation of the test substance was detected in the liver. Other organs (lung, thymus, spleen, heart, brain, skin, and muscle) showed lower radioactivity, whereas the kidney showed higher radioactivity. At 7 days after oral dosing, the remaining amounts of the test substance in the whole body were < 1%. After reviewing the results of this experiment, the authors concluded that [¹⁴C]-Psicose was absorbed well after oral dosing and eliminated rapidly.

Parenteral

Anhydroglucitol

The distribution of Anhydroglucitol was evaluated using normal and diabetic rats, and perfused rat bodies.³ The 3 non-diabetic male Sprague-Dawley used were identified as having very low, very high, and medium concentrations of plasma Anhydroglucitol. The variable plasma concentrations were, perhaps, due to less controlled feeding conditions. Another group of 3 rats was rendered diabetic by intravenous (i.v.) streptozocin injection. Animals of both groups were thoroughly depleted of blood, after which various organs and tissues were immediately removed. The perfusion experiment involved 2 male Sprague-Dawley rats (controls). An isotonic solution containing heparin was used as the perfusion solution, which was infused through a cannula inserted into the pulmonary trunk through the right ventricle. At the end of perfusion, several organs were removed. The plasma of control rats contained 3 to 12 $\mu\text{g/mL}$ of Anhydroglucitol. In the 3 normal rats, Anhydroglucitol was distributed throughout the rat bodies. Low, but highly variable, concentrations were present in lipid-rich tissues, such as adipose tissue and the testis. The liver and kidney contained much higher concentrations, though they were less than the corresponding plasma concentrations. The authors noted that these observations are indicative of Anhydroglucitol distribution that was dependent on the concentration equilibrium between the circulation and the intra- and inter-cellular water spaces. The concentration of Anhydroglucitol in the brain appeared to have been less dependent on the concentration in the plasma. Other results are summarized below.

In all 3 diabetic rats, the Anhydroglucitol concentration in plasma was < 0.5 $\mu\text{g/mL}$. The diabetic kidney, liver, and some other organs and tissues contained little Anhydroglucitol, and the same was true for the brain. Anhydroglucitol depletion during perfusion was demonstrated in several organs, except for the spleen. The plasma of the 2 rats perfused for 100 min and 300 min contained 8.8 $\mu\text{g/mL}$ and 9.0 $\mu\text{g/mL}$ of Anhydroglucitol, respectively. Anhydroglucitol was almost completely depleted from the lung, liver, and kidney of the rat perfused for 300 min. In the other rat (100-min perfusion), it was completely depleted only from the lung. Also, in this rat (100-min perfusion), the concentrations of Anhydroglucitol in the liver and kidney were considerably lower than what would have been expected based on its concentration in the plasma. The spleens of both perfused rats contained 5.1 $\mu\text{g/g}$ and 4.4 $\mu\text{g/g}$ of Anhydroglucitol. The authors noted that these 2 values were as high as could have been expected for the spleen of an untreated rat with a plasma Anhydroglucitol concentration similar to that of the 2 rats. The authors noted that the observations made in this study indicated that Anhydroglucitol from the circulation readily diffused into the inter- and intra-cellular water spaces. They also suggested that the plasma membranes of cells in the organs were permeable to Anhydroglucitol.

Psicose

The intestinal absorption, organ distribution, and urinary excretion of [¹⁴C]-Psicose was studied using 30 male Wistar rats.³⁰ All of the rats were fasted for 24 h. Approximately 0.6 mL of [¹⁴C]-Psicose solution (30 mg, 120 kBq) was administered i.v. at a dose of 100 mg/kg. The rats were killed at 10, 30, 60, and 120 min post-administration. After i.v. dosing, the concentration of [¹⁴C]-Psicose in the blood decreased (half-life = 57 min). Also, excretion in the urine was up to ~ 50% within 1 h. High counts of radioactivity were detected in the liver and kidney. An experiment involving mice, summarized below, is also included in this study.

After fasting for 24 h, 10 male C3H mice were injected i.v. with [¹⁴C]-Psicose (20 KBq in saline, dose of 100 mg/kg).³⁰ At 30 min post-injection, the animals were perfused and whole-body frozen sections from the sagittal plane were prepared. Autoradiography results indicated high signals of [¹⁴C]-Psicose in the liver, kidney, and bladder, but no accumulation in the brain. After reviewing the results of rat and mouse i.v. dosing experiments in this study, the authors concluded that [¹⁴C]-Psicose was absorbed and eliminated rapidly.

U-[¹⁴C]-Psicose (15 mg; 1.5 μCi in 0.5 mL of saline) was injected i.v. in a series of fasted rats (number and strain not stated).²⁹ Urine and exhaled [¹⁴C]-carbon dioxide were collected for 6 h. During this period, 97% to 98% of the radioactivity was excreted in the urine, where it was associated with U-[¹⁴C]-Psicose. Liver glycogen contained 1% of the radioactivity, and only 0.6% of the radioactivity was exhaled as [¹⁴C]-carbon dioxide. The authors noted that these results indicate that i.v.-administered U-[¹⁴C]-Psicose is rapidly removed by the kidney and is metabolized to only a small degree.

Human

Anhydroglucitol

Anhydroglucitol is present in human blood, and the average plasma concentration is in the vicinity of 20 µg/mL.⁴ A remarkable decrease in plasma Anhydroglucitol is observed in diabetes mellitus.

The origin and disposal of Anhydroglucitol, a major polyol in the human body, was studied using 36 normal subjects (20 men and 16 women).³¹ The amount of urinary Anhydroglucitol was measured 3 times in each subject. The mean Anhydroglucitol supplement through foods was estimated to be ~4.38 mg per day. The mean Anhydroglucitol excretion in the urine was ~4.76 mg per day. An Anhydroglucitol balance study was performed using a subgroup (6 men and 2 women) of the 36 normal subjects. Total dietary calorie intake was fixed to 35 kcal/real body weight (kg) of individual subjects. Fasting plasma Anhydroglucitol and 24-h urinary Anhydroglucitol were monitored over 3 consecutive days, and their mean values were calculated. In another subgroup (6 men and 3 women), the subjects were observed for urinary Anhydroglucitol excretion after a breakfast meal. The subjects fasted for 14 h before urination. The study results implied that urinary excretion of Anhydroglucitol occurred soon after food ingestion, and that the amount excreted in the urine was closely correlated with daily supplement through foods. The fundamental kinetics of Anhydroglucitol were recognized as follows: Anhydroglucitol in the body originates mainly from foods, is well absorbed in the intestine, and is little degraded and metabolized in the body.

Psicose

In a study involving 26 human subjects (16 males and 10 females) on a normal diet (composition not stated), 24-h urine samples were collected.³² All subjects were healthy and undergoing normal physical activity. Individual sugars (psicose; D- or L- not stated) included in the urine were determined using gas chromatography, accounting for over 90% of the total neutral sugars. Psicose was the most common neutral sugar that was found in human urine. The excretion of total neutral sugars in the urine ranged from 0.1 to 4.1 mmol/24 h, based on 28 urine samples from 26 subjects. The excretion of psicose in the urine ranged from 0.1 to 2.7 mmol/24 h. The authors stated that there is uncertainty regarding the source of psicose in the urine. They noted that psicose was absent from the urine of 6 patients who were maintained on total parenteral nutrition (method of feeding that bypasses the gastrointestinal tract), suggesting an exogenous origin of the sugar.

Psicose is present in human urine in amounts of 15 to 30 mg/L, presumably from a dietary source because it disappears from the urine of subjects who have fasted for 48 h.²⁹

Oral

Arabinose

After an overnight fast, 40 normal volunteers drank an isosmotic solution containing raffinose (8 g), lactose (20 g), and L-arabinose (2 g) in 250 mL of water.³³ The median 5-h urinary sugar excretion was 0.26% of ingested raffinose, 0.05% of ingested lactose, and 17.5% of ingested L-arabinose.

Parenteral

Arabinose

The metabolic stability of L-arabinose was investigated using 5 normal subjects.³³ A sterile, pyrogen-free solution containing 500 mg of L-arabinose in 5 ml of water was injected intravenously into each subject. Within 5 h, 63.3 ± 4.1% (mean + standard deviation) of administered L-arabinose was excreted in the urine. Within 12 h, 73.1 ± 4.5% was excreted in the urine.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Anhydroxylitol

The dried extract of a trade name mixture containing 25% to 35% Anhydroxylitol was evaluated for acute dermal toxicity in rats (number not stated), according to Organization for Economic Cooperation and Development (OECD) Test Guideline (TG) 402.⁶ Doses up to 2 g/kg were tested. No mortalities, abnormal clinical signs, body weight changes, or gross pathological changes were observed in this study. The LD₅₀ was > 2 g/kg.

Oral

Anhydroxylitol

The acute oral toxicity of the dried extract of a trade mixture containing 25% to 35% Anhydroxylitol was evaluated in rats (number not stated), according to OECD TG 401.⁶ Doses up to 2 g/kg were tested. No mortalities, abnormal clinical signs, body weight changes, or gross pathological changes were observed in this study. The LD₅₀ was > 2 g/kg.

Arabinose

In an acute oral toxicity study on Arabinose, the LD₅₀ was calculated to be 12.1 g/kg in male rats and 11.6 g/kg in female rats.³⁴ This data summary is from an English language translation of a publication abstract written in Japanese. Details relating to the number of animals used, test protocol, and study results are not included in the abstract.

Psicose

The acute oral toxicity of 50% aqueous Psicose was evaluated using 5 groups of 8 male Wistar rats.³⁵ The groups received single oral doses ranging from 8 g/kg to 20 g/kg. A stainless feeding tube attached to a 20 mL syringe was used for dosing. A 14-day observation period was initiated after test substance administration. Necropsy was performed on animals that died. Animal deaths were reported as follows: 3 rats (14 g/kg dose group), 3 rats (17 g/kg dose group), and 8 rats (20 g/kg dose group). The animals died within 2 days after dosing. The calculated LD₅₀ values were 16.3 g/kg (using the Behrens-Karber method) and 15.8 g/kg (using the Litchfield-Wilcoxon method). All of the rats experienced diarrhea at 1 h to 24 h after dosing. The condition of high-dose animals (17 g/kg and 20 g/kg doses) was described as quite weak. There was no evidence of abnormalities in surviving rats after 3 days. At necropsy, bleeding was observed in the mucous layers of the stomach or small intestine in rats of the 17 g/kg or 20 g/kg dose groups.

Each of 6 beagle dogs received a single oral dose (by plastic syringe) of Psicose (1 g/kg and 4 g/kg) and a placebo (water, 100 ml).³⁶ The test substance was administered in 100 ml of water. The control, 1 g/kg of Psicose and 4 g/kg of Psicose were administered on 3 different study days. All dogs were active and had a good appetite throughout the study. The 4 g/kg dose caused vomiting in 1 dog and transient diarrhea in the remaining 5 dogs. Two dogs had transient nausea within 1 h after receiving the 1 g/kg dose. The blood glucose was slightly decreased, without an increase in the plasma insulin concentration, at 2 h after dosing with the test substance. A mild, dose-dependent increase ($P < 0.05$) in plasma alkaline phosphatase activities was also observed between 12 h and 48 h after dosing. Histological examination of the liver or other tissues was not performed in this study. Furthermore, the plasma inorganic phosphorus concentration in dogs dosed with 4 g/kg was slightly higher ($P < 0.05$) at 8-h post-dosing when compared to control dogs. Though no possible causes of inorganic phosphorus alteration were observed in this study, the authors stated that dosing with Psicose may mildly exaggerate the diurnal pattern of plasma inorganic phosphorus concentration in dogs. The authors concluded that these data indicate that Psicose did not induce severe toxicity in dogs.

Short-Term Toxicity Studies

Oral

Anhydroglucitol

In an experiment involving 12 white laboratory rats, anhydroglucitol (D- or L- isomer was not stated; 7 mg, 0.14 mmol/kg body weight) was administered orally (in drinking water) daily for 7 weeks.²⁸ Six rats served as controls. No apparent toxic signs were observed in test animals after dosing. Body weight gain (5.2 g/rat/week) in test animals was similar to that reported for control rats (4.6 g/rat/week). (Results relating to the distribution and excretion of anhydroglucitol after oral dosing are included in the section on Toxicokinetic Studies.)

Anhydroxylitol

A 28-day oral toxicity study on a tradename mixture comprising ~ 25% Anhydroxylitol (and unstated quantities of xylitol and xylitylglucoside) was performed using groups of at least 10 rats (5 males and 5 females per group), according to OECD TG 407.⁶ The test substance was administered at doses of 0 (vehicle was negative control (water)), 15, 150, and 1000 mg/kg/day. Study results indicated no treatment-related changes in the following: mortality, clinical observations, behavioral assessment, functional performance, sensory reactivity, body weight, food consumption, hematology, blood chemistry, organ weights. Additionally, no treatment-related changes were observed at necropsy of animals in the highest dose group. However, minimal focal myocarditis was observed in 2 males and 1 female of the highest dose group. Histopathological examination was not performed on animals of the other 2 dose groups. The authors noted that the lesions observed in this study are typical of findings that are expected in animals of this type, strain, and age. They also noted that the incidence of these lesions is typical of that observed in rats in this type of study. However, no historical data supporting this statement were provided. Given the uncertainty relating to the cause of myocarditis in animals of the highest dose group and the limited histopathology data, the authors noted that it was not possible to clearly establish a no-observed-adverse-effect-level (NOAEL) for the test substance in this study.

Arabinose

In a short-term toxicity test, rats were given feed containing 5% Arabinose.³⁴ The rats developed diarrhea. This data summary is from an English translation of an abstract from a publication that is written in Japanese. Details relating to the number of animals used, test protocol, study duration, and study results are not included in the abstract.

Psicose

Six Sprague-Dawley rats were fed a normal diet and consumed 2% Psicose-supplemented water for 14 days.³⁷ A control group (6 rats) was fed a normal diet and consumed water without Psicose. At the end of the experiment, the animals were killed and body, testes, and liver weights were determined. There was no difference in mean testes weight (2.0 ± 0.2 g) between treated and control rats. The mean body weight of treated rats (232 ± 12 g) was higher when compared to the control group (214 ± 14 g).

Mean liver weight values were 12.7 ± 0.7 g (treated rats) and 12.7 ± 0.7 g (controls). These 2 groups (treated and controls) were among the groups included in a study evaluating the protective effect of Psicose on di-(2-ethylhexyl) phthalate-induced testicular injury in the rat.

Groups of 7 male Wistar rats were fed diets containing 10%, 20%, 30%, and 40% Psicose for 34 days.³⁵ Butylated hydroxytoluene was (0.01 g/kg diet) was added to all diets as an antioxidant. The control group was fed the diet without Psicose. After day 34, the rats were fasted for 3 h and then killed. One rat fed 30% and 5 rats fed 40% Psicose died during the experimental period. Body weight gain, food intake, and food efficiency were more extensively suppressed after feeding with the higher % Psicose diets (i.e., 30% and 40% diets). A statistically significant difference in body weight gain was observed between the 0, 10%, 20%, and 30% dietary groups ($P < 0.05$). The rats fed the 20%, 30%, and 40% diets experienced diarrhea during the first 8 days. The weights of the heart and spleen were smaller ($P < 0.05$) in rats fed the higher Psicose concentration diets. Liver and kidney weights were heavier ($P < 0.05$) in rats fed the 10% diet than in rats fed the 0 and 30% diets. Cecal enlargement was observed in rats fed 10% to 40% diets. Epididymal, perirenal, and mesenteric adipose tissue weights were statistically significantly smaller ($P < 0.05$) in rats fed the higher Psicose concentration diets. Other results indicated that serum glucose and triacylglycerol concentrations were significantly lower ($P < 0.05$) in the 30% dietary group than in the other groups. Furthermore, liver triacylglycerol content was higher in the 10% dietary group than in the 0% group. Many of the effects observed were assumed to be secondary to a decrease in food consumption or the consumption of large amounts of a non-nutritive, poorly absorbed, osmotically active substance. It was also noted that it is not clear whether or not the cause of Psicose-induced liver enlargement was due to liver glycogen disposition. The authors concluded that the feeding of diets extremely high in Psicose appears to be harmful to the intestinal tract.

In another study, Psicose (0.2 g/kg) was fed to 5 beagle dogs daily for 12 weeks.³⁸ The control group (5 dogs) was fed a placebo (not stated) according to the same procedure. During the course of the experiment, plasma triglyceride concentrations increased in the control group, whereas they remained low in the group fed Psicose. At week 2 and thereafter, plasma total cholesterol concentrations in the test group were statistically significantly lower ($P < 0.05$) when compared to the control group. Platelet count levels in the test group were statistically significantly lower at both week 0 and week 12 ($P < 0.05$). Dosing with the test substance had no influence on body weight. With the exception of a change in lipid levels (lipid lowering effect), dosing with Psicose did not cause clinical signs or changes in biochemical parameters (plasma alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, urea nitrogen, creatinine, total protein, albumin, total cholesterol, triglyceride, total calcium, inorganic phosphorus, sodium, potassium, and chloride concentrations). Also, there was no cumulative effect of test substance dosing on glucose metabolism, and there were not statistically significant differences in the following between test and control groups: liver enzymes, renal function markers, and electrolytes. The mild increase in plasma alkaline phosphatase was not considered suggestive of Psicose toxicity. The authors concluded that dosing with Psicose did not cause any harmful effects in dogs.

Chronic Toxicity Studies

Oral

Psicose

The chronic oral toxicity of Psicose was evaluated using groups of 18 male Wistar rats.³⁹ The test group had free access to a commercial rodent diet containing 3% Psicose, and the control group to diet containing 3% sucrose, for 12 or 18 months. The rats actually ingested 1.28 g/kg/day Psicose and 1.22 g/kg/day sucrose. After 12 months of feeding, 8 rats from each group were fasted prior to collection of blood for hematological analysis. The remaining rats (10 per group) were killed at the end of 18 months, and various organs were weighed. Parts of the liver and kidney were preserved for histopathological examination. At 12 months, final body weights and weight gains in the 3% Psicose dietary group were comparable to those in the 3% sucrose control group. At 18 months, final body weights and weight gains in the 3% Psicose dietary group were significantly lower when compared to the 3% sucrose control group. Liver and kidney weights were found to be statistically significantly heavier in the 3% Psicose group at 12 months, when compared to the control group. However, there were no differences in weight when this comparison involved other tissues. At 18 months, liver and kidney weights were also statistically significantly heavier in the test group when compared to the control group. Higher weights were also reported for the brains, lungs, and pancreas in test animals. On the other hand, relative intraabdominal adipose tissue weights lighter at 18 months were statistically significantly lighter in the 3% Psicose group, when compared to the control group.

At 12 months, mean corpuscular hemoglobin was statistically significantly lower in the test group when compared to the control group. Hemoglobin and mean corpuscular volume at 18 months were statistically significantly greater in the test group than in the control group. Serum chemistry analysis results for rats fed 3% Psicose in the diet for 12 months did not indicate any differences between test and control animals. Age-related, naturally-occurring lesions were observed in the liver and kidneys at 12 months; however, no abnormalities due to test substance ingestion were observed. Histopathological examination of the liver at 18 months revealed fatty degeneration and hepatocellular fibrosis in the group fed 3% Psicose in the diet, but not in the control group. These findings appeared to be slight and local. The mean value for pathological lesions (liver) in the test group was statistically significantly higher ($p < 0.0498$; i.e., slight difference) when compared to the control group. At 12 months, there was no difference in histopathological observations (in liver and kidneys) between test and control groups. In the kidneys at 18 months, the total value for pathological lesions did not differ between test and control groups. The authors concluded that this study found the

effects of long-term dietary administration of 3% Psicose to rats to be increased liver and kidney weights, with no gross pathological findings correlated with this hypertrophy. They also concluded that the hematological and chemical values were not suggestive of overt Psicose toxicity; and that, overall, no adverse effects were seen after feeding with 3% Psicose in the diet.³⁹

Subcutaneous

Arabinose

Chronic subcutaneous toxicity data are presented in a carcinogenicity study on L-arabinose involving 60 rats of the Bethesda black strain (30 males, 30 females) and 60 C57BL mice (30 males, 30 females).⁴⁰ Details relating to the experimental procedure and results relating to tumor formation are summarized in the section on Carcinogenicity Studies. A 25% aqueous solution of L-arabinose (2 ml [in rats] and 0.5 ml [in mice]) was injected subcutaneously into the nape of the neck for periods up to 2 years. The rats tolerated the test substance injections without any untoward effects. However, the mice developed symptoms of shock, and some died (number not stated). Also, in mice, white necrotic masses were identified in the subcutaneous tissue of the nape of the neck. There was no histologic evidence of an injurious effect of the injected test substance on any internal organ, especially the liver and kidneys, in mice or rats. However, nephrotic changes of varying degrees were observed in many animals (number not stated), including controls. Rather extensive amyloidosis of the liver, spleen, and kidneys occurred frequently in mice.

Risk Assessment - Dermal

Anhydroxylitol

A risk assessment was performed by NICNAS.⁶ Data on typical use patterns of cosmetic product categories in which Anhydroxylitol may be used were obtained from a 2010 Scientific Committee on Cosmetic Safety (SCCS) published document.⁴¹ The use patterns involved the following 8 product types: body lotion, face cream, eyeliner, lipstick, makeup remover, shower gel, shampoo, and hair conditioner. Systemic exposure was based on a trade mixture containing 30% Anhydroxylitol at a use concentration of 5% (equivalent to 1.5% Anhydroxylitol) in each product. In the absence of dermal absorption data, the default dermal absorption of 100% was assumed for calculation purposes.^{42,43} An adult body weight of 60 kg was also assumed for calculation purposes. The worst-case scenario estimation using these assumptions is for a person who is a simultaneous user of all 8 products, each containing 1.5% Anhydroxylitol (from trade mixture at concentration of 5%). This would result in a systemic dose of 8.550 mg/kg/day of the trade mixture.

The repeated dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the trade mixture containing 30% Anhydroxylitol at a use concentration of 5% (equivalent to 1.5% Anhydroxylitol) using the worst-case exposure scenario (from the use of multiple products) of 8.550 mg/kg/day and the NOAEL of 1000 mg/kg/day for xylitol (from 2-year dietary studies). An MoE value of ≥ 100 was considered acceptable to account for intra- and inter-species differences. Using the NOAEL of 1000 mg/kg/day, an MoE of 117 was estimated for cosmetic products containing up to 5% of the trade mixture (equivalent to 1.5% Anhydroxylitol). Thus, based on the available information, it was concluded that the risk to the public associated with use of Anhydroxylitol up to a concentration of 1.5% in cosmetic products is not considered to be unreasonable.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental and reproductive toxicity studies of saccharide humectants were neither found in the published literature, nor were these data submitted.

GENOTOXICITY

In Vitro

Anhydroxylitol

The genotoxicity of the dried extract of a trade mixture containing 25% to 35% Anhydroxylitol was evaluated in a bacterial reverse mutation assay, according to OECD TG 471.⁶ The test substance was classified as non-mutagenic in this assay. The same test substance was evaluated for genotoxicity in a chromosome aberration assay using human peripheral blood lymphocytes, according to OECD TG 473. Results were also classified as negative in this assay. (Further details were not provided for these studies.)

In Vivo

Anhydroxylitol

The micronucleus test was used to evaluate the genotoxicity of the dried extract of a trade mixture containing 25% to 35% Anhydroxylitol, according to OECD TG 474.⁶ Mice received a dose of ≤ 2000 mg/kg/day for 2 days. (Further details, including route of administration, were not provided.) The test substance was classified as non-genotoxic in this assay. However, the authors stated that it is not clear that the test substance was systemically absorbed and reached the bone marrow in this in vivo assay.

CARCINOGENICITY STUDIES

Subcutaneous

Arabinose

The carcinogenicity of L-arabinose was evaluated using 60 rats of the Bethesda black strain (30 males, 30 females) and 60 C57BL mice (30 males, 30 females).⁴⁰ (Results relating to chronic subcutaneous toxicity are included in that section of this report.) A 25% aqueous solution of L-arabinose (2 ml [in rats] and 0.5 ml [in mice]) was injected subcutaneously into the nape of the neck twice per week for periods up to 2 years. Control animals (60 rats and 60 mice) were injected with water. In rats, the number of tumors observed after dosing with the test substance ranged from 1 tumor (at 0 to 6 months) to 32 tumors (at 22 to 24 months). The tumor types observed in rats at 22 to 24 months included urinary bladder papilloma, lymphangiosarcoma of the subcutis, adenofibroma of the breast, and carcinoma of the uterus. In mice, the number of tumors observed after dosing with the test substance ranged from 4 tumors (at 13 to 15 months, tumors first observed) to 40 tumors (at 0 to 6 months). Additional tumors were not observed in mice from month 16 to the end of the study. The tumor types observed in mice were not identified. Injection site tumors were not observed in rats or mice dosed with the test substance. The great majority of the benign and malignant tumors found in test and control rats and mice were at sites remote from the nape of the neck. Furthermore, the numbers and sites of these neoplasms were found to be similar when results for test and control animals (mice and rats) were compared. Therefore, the authors noted that it is unlikely that the development of most of the tumors was related to test substance administration.

ANTI-CARCINOGENICITY STUDIES

The effect of Psicose on cell proliferation was evaluated in the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, using the following cancer cell lines: HeLa (human cervical cancer), HepG2 (human hepatocarcinoma), HuH-7 (human hepatocarcinoma), and immortalized cell line HaCaT (human skin keratinocytes).⁴⁴ The assay was initiated when the cells were in the logarithmic growth phase. The following concentrations of Psicose were added to the medium: 1 mM, 5 mM, 10 mM, 20 mM, and 50 mM. After exposure to the test substance for 24 h, 48 h, and 72 h, MTT was added and the plates were incubated for 4 h. Psicose did not have an antiproliferative effect on the cell lines at any of the concentrations tested.

OTHER RELEVANT STUDIES

Cytotoxicity

Anhydrogalactose

In the MTT assay, Anhydrogalactose was not cytotoxic to melanin-producing murine B16 melanoma cells or human epidermal melanocytes at concentrations of 12.5, 25, and 50 µg/mL during the 2-h incubation period.⁷ The MTT assay was also used to evaluate the cytotoxicity of Anhydrogalactose and D-anhydrogalactose using B16F10 mouse melanoma cells and RAW264.7 cells (mouse macrophages).¹⁴ The cells were treated for 24 h with concentrations up to 100 µg/mL (B16F10 cells) and up to 200 µg/mL (RAW264.7 cells). There was no statistically significant inhibition of growth of either cell type at the concentrations of Anhydrogalactose and D-anhydrogalactose tested.

Anti-Melanogenic Activity

Anhydrogalactose

A study was performed to determine whether Anhydrogalactose exerts anti-melanogenic activity in murine B16F10 melanoma cells and human epidermal melanocytes.⁷ The effect on melanogenesis at non-cytotoxic concentrations was determined by measuring α -melanocyte stimulating hormone (α -MSH)-induced intracellular and extracellular melanin levels in the 2 cell types. The cells were pretreated with Anhydrogalactose (50 µg/mL) for 1 h prior to exposure to α -MSH (100 nM). Melanin content was assayed 3 days later. Anhydrogalactose markedly inhibited melanin secretion.

The skin-whitening activity of Anhydrogalactose (95.6% pure) was evaluated using B16F10 mouse melanoma cells.¹⁴ The melanoma cells were induced for melanin production by treatment with α -MSH, and were cultured for 1 h with Anhydrogalactose and D-anhydrogalactose at concentrations up to 100 µg/mL. Arbutin served as the positive control. The extracellular melanin concentration of melanoma cells treated with 100 µg/mL Anhydrogalactose was statistically significantly lower than that of cells treated with the same concentration of arbutin or D-anhydrogalactose. Particularly, the extracellular melanin concentration of melanoma cells treated with 100 µg/mL Anhydrogalactose was only 23.9% of melanoma cells treated with 100 nM α -MSH. The authors noted that these study results suggested that treatment with Anhydrogalactose strongly suppressed melanin production in B1610 melanoma cells.

Anti-Inflammatory Activity

Anhydrogalactose

Nitrite levels in the culture media of RAW264.7 mouse macrophages (stimulated by lipopolysaccharide [LPS] to produce nitrite) were measured in an experiment investigating the possible anti-inflammatory activity of Anhydrogalactose (95.6% pure).¹⁴ Cellular nitrite levels increase considerably under inflammatory conditions. The macrophages were incubated for 24 h with Anhydrogalactose and D-anhydrogalactose at concentrations up to 200 µg/mL. Statistically significant ($P < 0.05$) suppression of nitrite production was observed at concentrations of 100 µg/mL and 200 µg/mL Anhydrogalactose. Nitrite levels in the culture

media of cells treated with 100 µg/mL and 200 µg/mL Anhydrogalactose were 64.5% and 38.8% of those in LPS-treated controls. Anhydrogalactose also had a nitrite-suppressing effect, only at a concentration of 200 µg/mL. However, the effect of the D-anhydrogalactose was statistically significantly lower when compared to the Anhydrogalactose. The authors noted that Anhydrogalactose had statistically significant anti-inflammatory activity.

Antimicrobial Activity

Anhydrogalactose

The inhibitory activity of Anhydrogalactose against *Streptococcus mutans* ATCC 25175 growth was evaluated in the spot assay by monitoring the bacterial cell mass concentration and counting the colonies formed on the growth medium.⁴⁵ Bacterial cells were diluted to 10, 10², 10³, 10⁴, and 10⁵-fold, and each diluted cell suspension was spotted on the growth medium. The bacteria were cultured for 30 h on growth medium supplemented with 10 g/L (w/v) Anhydrogalactose. Growth inhibitory activity of Anhydrogalactose was compared to that of xylitol (10 g/L). Spot assay results indicated that the numbers of *S. mutans* colonies were lower in the presence of Anhydrogalactose than in the presence of xylitol or in growth medium without sugar. When Anhydrogalactose (10 g/L) was present in the growth medium, *S. mutans* colonies were not formed, that is, when plates were seeded with bacterial inocula of either 10⁴ or 10⁵ dilution. In contrast, *S. mutans* colonies were formed on a minimal agar plate inoculated with bacterial dilutions of either 10⁴ or 10⁵, when 10 g/L xylitol was supplied as the sole carbon source.

Effect of Epidermal Barrier Recovery

Psicose

The effect of topical application of aqueous Psicose on epidermal permeability barrier recovery rate after barrier disruption (by tape stripping) was evaluated using male hairless mice of the HR-1 strain (number not stated).⁴⁶ Permeability barrier function was evaluated by measurement of transepidermal water loss. Skin on both flanks was treated by repeated tape stripping until the transepidermal water loss reached 7 to 10 mg/cm²/h. Immediately after tape stripping, 100 µm of a 0.1 M aqueous solution of Psicose was applied to the skin. Transepidermal water loss was then measured at the same sites at 1 h, 2h, 6 h, and 24 h later. Barrier recovery results were expressed as % recovery because of the day-to-day variations in the extent of barrier disruption. Psicose accelerated barrier recovery of tape-stripped skin. This effect on barrier recovery rate appeared within 1 h. The authors stated that Psicose may influence phase transition of the lipid bilayers of lamellar bodies and cell membrane, which is a crucial step in epidermal permeability barrier homeostasis.

DERMAL IRRITATION AND SENSITIZATION

Irritation

Animal

Anhydroxylitol

The skin irritation potential of the dried extract of a trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside) was evaluated in 3 New Zealand White albino rabbits, according to OECD TG 404.⁶ Test substance application to the skin, using a semi-occlusive patch, was followed by a 72-h observation period. The dose per cm² was not stated. There was no evidence of erythema or edema in any animal during the observation period. The test substance was classified as non-irritating to the skin of rabbits.

Sensitization

Animal

Anhydroxylitol

The skin sensitization potential of the dried extract of a trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside) was evaluated in the maximization test, according to OECD TG 406.⁶ The number of guinea pigs used was not stated; however, a minimum of 10 test animals and 5 controls is in keeping with this protocol. The undiluted test substance was applied during induction. However, the challenge concentration was 50% (effective concentration = 17.5%). The test substance was classified as a non-sensitizer in guinea pigs.

OCULAR IRRITATION STUDIES

Animal

Anhydroxylitol

The ocular irritation potential of the dried extract of a trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside) was evaluated in 3 New Zealand White albino rabbits, according to OECD TG 405.⁶ Instillation of the test substance was followed by a 72-h observation period. Slight conjunctival irritation (redness and chemosis) was observed, but had fully resolved by the end of the observation period. The conjunctival irritation was first observed at 1 h post-instillation. The test substance was classified as slightly irritating to the eyes of rabbits.

CLINICAL STUDIES

Case Reports

Arabinose (L-arabinose was studied)

A pediatric patient presented with large amounts of L-arabinose and L-arabitol (Arabinose metabolite) in the urine.⁴² The sugar L-arabinose mainly originated from the fruit formula in the child's diet. Highly elevated levels of L-arabitol were also found in the plasma and cerebrospinal fluid. The authors stated that the accumulation of L-arabinose and L-arabitol suggested a disturbance in L-arabinose metabolism at the level of L-arabitol degradation. Therefore, they presumed that the enzyme L-arabitol dehydrogenase was deficient in the pediatric patient.

Psicose and Saccharide Hydrolysate

A male patient had urticarial attacks over a period of 6 months after eating foods such as hamburgers, spaghetti, and cakes, and after consuming certain drinks.^{16,47} When the patient was given a refreshing drink (type not stated), urticarial lesions developed within 2 h. The ingredients of the drink were then given separately, with a week between each test. Two ingredients of the drink, invert sugar (also known as Saccharide Hydrolysate) and high-fructose corn syrup (containing mostly glucose and 0.07% Psicose), induced urticarial lesions. High-fructose corn syrup caused the stronger reaction, and a skin test on this ingredient (3 mg) yielded a positive reaction. Psicose was partly purified using thin layer chromatography, and yielded a positive skin reaction when applied at a dose of 21.8 µg. The authors concluded that Psicose was responsible for the urticarial attacks in the male patient.

Other Clinical Reports

Psicose

The safety of long-term ingestion of Psicose was studied using 17 normal subjects (males and females).⁴⁸ A randomized, double-blind, placebo-controlled crossover experiment of single ingestion was performed. The subjects consumed Psicose (5 g) with meals 3 times per day for 12 continuous weeks. Physical examinations, blood examinations, and urine analyses were performed. There was no evidence of abnormal effects or clinical problems.

SUMMARY

The safety of 7 saccharide humectants as used in cosmetics is reviewed in this CIR safety assessment. According to the *Dictionary*, all 7 saccharide humectants are reported to function as skin-conditioning agents – humectant in cosmetics. Anhydrogalactose is also reported to function as an antioxidant, and Anhydroglucitol functions as an oral care agent.

In the *Food Chemicals Codex* description, invert sugar (Saccharide Hydrolysate) is marketed as invert sugar syrup and contains dextrose (glucose), fructose, and sucrose in various amounts, as represented by the manufacturer. In accordance with the *Food Chemicals Codex*, the acceptance criteria for invert sugar are that it contains not less than 90% and not more than 110% of the labeled amount of sucrose and of invert sugar. Other acceptance criteria for invert sugar in the *Food Chemicals Codex* relate to lead content (not more 0.1 mg/kg) and sulfated ash content (not more than 0.2%).

According to 2019 VCRP data, Saccharide Isomerate is reported to be used in 455 cosmetic products (406 leave-on products and 49 rinse-off products). Of the saccharide humectants reviewed in this safety assessment, this is the greatest reported use frequency. The results of a concentration of use survey conducted by the Council in 2018 indicate that Saccharide Hydrolysate is being used at maximum use concentrations up to 4.6% in rinse off products (skin cleansing products), and that Saccharide Isomerate is being used at maximum use concentrations up to 2.8% in leave-on products (face and neck skin care preparations, not spray). These are the highest use concentrations in rinse-off and leave-on products reported for the saccharide humectants that are reviewed in this safety assessment.

Psicose is a sugar substitute that has 70% of the sweetness of sucrose, but almost zero calories. The cosmetic ingredient Saccharide Hydrolysate contains fructose and glucose, and Saccharide Hydrolysate is also a direct food substance affirmed as GRAS by the US FDA.

Anhydroglucitol (7 mg, 0.14 mmol/kg body weight) was administered orally (in drinking water) to rats daily for 7 weeks. A high serum Anhydroglucitol concentration (62 to 126 µmol/L) was maintained in the animals tested.

The intestinal absorption, organ distribution, and urinary excretion of [¹⁴C]-Psicose was studied using male rats and male mice. [¹⁴C]-Psicose was absorbed well after oral dosing and eliminated rapidly after both oral and i.v. administration. In another oral dosing study, U-[¹⁴C]-Psicose (2 µCi) was administered by stomach tube to rats. Much of the radioactivity was rapidly excreted in the urine, whereby 95% of the excreted radioactivity was recovered within the first 7 h.

Anhydroglucitol is present in human blood, and the normal average plasma concentration is in the vicinity of 20 µg/mL. The origin and disposal of Anhydroglucitol, was studied using normal subjects. It was concluded that Anhydroglucitol in the body originates mainly from foods, is well absorbed in the intestine, and is little degraded and metabolized in the body. According to NICNAS, based on the low molecular weight of Anhydroxylitol (134 Da), there is potential for dermal absorption and passage across the gastrointestinal tract. However, this may be limited by its high water-solubility (674 g/L), and low partition coefficient (log P_{ow} = -2).

After an overnight fast, normal volunteers drank an isosmotic solution containing raffinose (8 g), lactose (20 g), and L-arabinose (2 g) in 250 mL of water. The median 5-h urinary excretion was 17.5% of ingested L-arabinose. In a study involving human subjects on a normal diet, 24-h urine samples were collected. The excretion of Psicose (most common neutral sugar found in human urine) ranged from 0.1 to 2.7 mmol/24 h. Results from another study involving human subjects indicate that Psicose is present in human urine in amounts of 15 to 30 mg/L. The diet is presumed to be the source of Psicose because it disappears from the urine of subjects who have fasted for 48 h.

In an acute dermal toxicity study involving rats (number not stated), an LD₅₀ of > 2 g/kg was reported for a trade name mixture containing 25% to 35% Anhydroxylitol. No mortalities or gross pathological changes were observed.

An oral LD₅₀ of > 2 g/kg was also reported for the same trade name mixture containing 25% to 35% Anhydroxylitol in a study involving rats (number not stated). No mortalities or gross pathological changes were observed. LD₅₀ values of 12.1 g/kg and 11.6 g/kg were reported for male and female rats (number not stated), respectively, in an acute oral toxicity study on Arabinose. In an acute oral toxicity study on 50% aqueous Psicose involving groups of 8 male Wistar rats, calculated LD₅₀ values (2 different methods used) of 15.8 g/kg and 16.3 g/kg were reported. Bleeding in the mucous layers of the stomach or small intestine (17 g/kg or 20 g/kg dose groups) was observed at necropsy. Single oral doses of 1 g/kg and 4 g/kg administered to 6 Beagle dogs did not induce severe toxicity in dogs. A dose-dependent increase (P < 0.05) in plasma alkaline phosphatase activity was reported. However, histological examination of the liver or other tissues was not performed.

A 28-day oral toxicity study on a tradename mixture comprising ~25% Anhydroxylitol (and unstated quantities of xylitol and xylitylglucoside) was performed using groups of least 10 rats. Doses up to 1000 mg/kg/day were tested. Minimal focal myocarditis was observed in 3 animals of the highest dose group; due to uncertainty relating to the cause of myocarditis and limited histopathology data, the authors noted that it was not possible to clearly establish NOAEL for the test substance in this study. No apparent toxicity signs were observed after anhydroxyglucitol (D or L form not stated) was administered orally (in drinking water) to 12 white rats daily for 7 weeks. Rats (number not stated) given feed containing 5% Arabinose in a short-term oral toxicity test developed diarrhea.

The short-term oral toxicity of Psicose was evaluated using groups of 7 male Wistar rats.³⁵ The groups were fed diets containing 10%, 20%, 30%, and 40% Psicose for 34 days. Liver and kidney weights were heavier (P < 0.05) in rats fed the 10% diet than in rats fed the 0 and 30% diets. It was also noted that it is not clear whether or not the cause of Psicose-induced liver enlargement was due to liver glycogen disposition. Many of the effects observed were assumed to be secondary to a decrease in food consumption or the consumption of large amounts of a non-nutritive, poorly absorbed, osmotically active substance. However, it was noted that Psicose appears to be harmful to the intestinal tract. In another short-term study, Psicose (0.2 g/kg) was fed to 5 beagle dogs daily for 12 weeks. Dosing with Psicose did not cause any harmful effects in dogs. The mild increase in plasma alkaline phosphatase was not considered suggestive of Psicose toxicity.

A group of 18 male Wistar rats had free access to a commercial rodent diet containing 3% Psicose for 12 or 18 months. The hematological and chemical values were not suggestive of overt Psicose toxicity and, overall, no adverse effects were seen after feeding with 3% Psicose in the diet. The effects of long-term 3% Psicose administration in the diet to rats were found to be increased liver and kidney weights, with no gross pathological findings correlated with this hypertrophy in a carcinogenicity study on L-arabinose involving 60 rats of the Bethesda black strain (30 males, 30 females) and 60 C57BL mice (30 males, 30 females), there was no histologic evidence of an injurious effect of the injected test substance on any internal organ, especially the liver and kidneys, in mice or rats. However, extensive amyloidosis of the liver, spleen, and kidneys occurred frequently in mice.

In a risk assessment for dermal exposure that was performed by NICNAS, the repeated dose toxicity potential was estimated by calculation of the MoE of the trade mixture containing 30% Anhydroxylitol at a use concentration of 5% (equivalent to 1.5% Anhydroxylitol). An MoE of 117 was estimated.

Six Sprague-Dawley rats were fed a normal diet and consumed 2% Psicose-supplemented water for 14 days. There was no difference in mean testes weight (2.0 ± 0.2 g) between treated and control rats.

The genotoxicity of the dried extract of a trade mixture containing 25% to 35% Anhydroxylitol was evaluated in a bacterial reverse mutation assay. Results were classified as negative in this assay. The same test material was non-genotoxic in a chromosome aberration assay using human peripheral blood lymphocytes. The micronucleus test was used to evaluate the genotoxicity of the same test substance. Mice received a dose of ≤ 2000 mg/kg/day (route of administration not specified) for 2 days, and results were negative. However, it is not clear that the test substance was systemically absorbed and reached the bone marrow in this in vivo assay.

The carcinogenicity of L-arabinose was evaluated using 60 rats of the Bethesda black strain (30 males, 30 females) and 60 C57BL mice (30 males, 30 females). A 25% aqueous solution of Arabinose (2 ml [in rats] and 0.5 ml [in mice]) was injected subcutaneously into the nape of the neck twice per week for periods up to 2 years. In rats, the number of tumors observed after dosing with the test substance ranged from 1 tumor (at 0 to 6 months) to 32 tumors (at 22 to 24 months). In mice, the number of tumors observed after dosing with the test substance ranged from 4 tumors (at 13 to 15 months, tumors first observed) to 40 tumors (at 0 to 6 months). The great majority of the benign and malignant tumors found in test and control rats and mice were at sites remote from the nape of the neck. It was concluded that it is unlikely that development of most of the tumors was related to test substance administration.

In the in vitro MTT cell proliferation assay involving various cancer cell lines, Psicose did not have an antiproliferative effect over the range of concentrations tested (1 mM to 50 mM). The following results relate to use of the MTT assay to evaluate the cytotoxicity of Anhydrogalactose and D-anhydrogalactose in various cell types. Anhydrogalactose was not cytotoxic to melanin-producing murine B16 melanoma cells or human epidermal melanocytes at concentrations of 12.5, 25, and 50 µg/mL. Anhydrogalactose and D-anhydrogalactose at concentrations up to 100 µg/mL (B16F10 cells) and up to 200 µg/mL (RAW264.7 cells) did not cause statistically significant growth inhibition.

Anhydrogalactose markedly inhibited melanin secretion at a concentration of 50 µg/mL in murine B16F10 melanoma cells and human epidermal melanocytes. The cells were pretreated with the test substance for 1 h prior to exposure to α -MSH. In a similar assay, Anhydrogalactose strongly suppressed melanin production in B1610 mouse melanoma cells. The extracellular melanin concentration of melanoma cells treated with 100 µg/mL Anhydrogalactose was statistically significantly lower than that of cells treated with the same concentration of arbutin (positive control) or D-anhydrogalactose.

The anti-inflammatory activity of Anhydrogalactose and D-anhydrogalactose was evaluated at concentrations of 100 µg/mL and 200 µg/mL using RAW264.7 mouse macrophages. Cellular nitrite levels, which increase considerably under inflammatory conditions, were monitored. Anhydrogalactose had statistically significant anti-inflammatory activity at both concentrations. The stereoisomer D-anhydrogalactose had a nitrite-suppressing effect, only at a concentration of 200 µg/mL; however, the effect of D-anhydrogalactose was statistically significantly lower when compared to Anhydrogalactose.

In an antimicrobial assay, *S. mutans* colonies were not formed when Anhydrogalactose (10 g/L) was present in the growth medium.

The effect of topical application of aqueous Psicose (0.1 M aqueous solution) on epidermal permeability barrier recovery rate after barrier disruption (by tape stripping) was evaluated using male hairless mice of the HR-1 strain (number not stated). The test substance accelerated barrier recovery.

The dried extract of a trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside) was classified as non-irritating to the skin of 3 New Zealand White albino rabbits. The same test substance was evaluated in the maximization test using a minimum of 10 guinea pigs in the test group. At a challenge concentration of 50% (effective concentration = 17.5%), the test substance did not induce skin sensitization.

In an ocular irritation test (3 New Zealand White albino rabbits) on the dried extract of a trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside), slight ocular irritation was observed.

In a case report, a pediatric patient presented with large amounts of L-arabinose and L-arabitol (an Arabinose metabolite) in the urine. The stereoisomer L-arabinose mainly originated from the fruit formula in the child's diet. It was presumed that the enzyme L-arabitol dehydrogenase was deficient in the child patient. A male patient had urticarial attacks over a period of 6 months after consuming certain drinks. Two ingredients of the drink, Saccharide Hydrolysate and high-fructose corn syrup (contained mostly glucose and 0.07% Psicose), induced urticarial lesions. Psicose yielded a positive skin reaction when applied at a dose of 21.8 µg.

INFORMATION SOUGHT

- Dermal penetration data; if absorption occurs, additional data, such as 28-day dermal toxicity data and developmental and reproductive toxicity data, may be needed
- Dermal irritation and sensitization data

TABLES

Table 1. Definitions, structures, and functions^{1, CIR Staff}

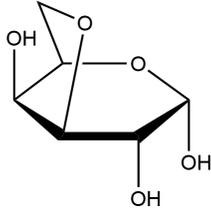
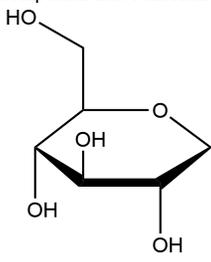
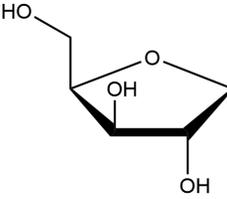
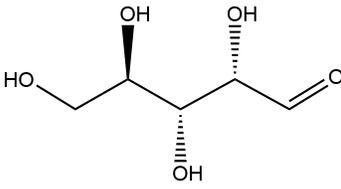
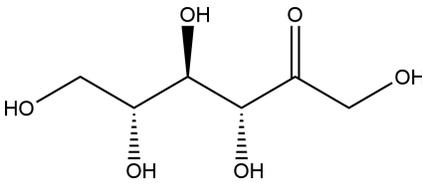
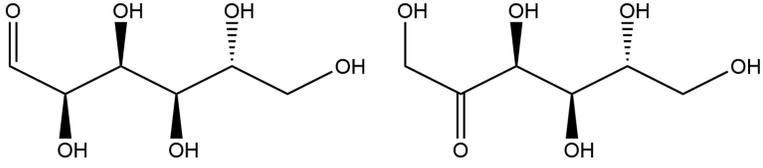
Ingredient CAS No.	Definition	Function(s)
Anhydrogalactose 28251-55-0	Anhydrogalactose is the organic compound that conforms to the formula: 	Antioxidants; Humectants; Skin-Conditioning Agents - Humectant
Anhydroglucitol 154-58-5	Anhydroglucitol is the organic compound that conforms to the formula: 	Humectants; Oral Care Agents; Skin-Conditioning Agents - Humectant
Anhydroxylitol 53448-53-6	Anhydroxylitol is the organic compound that conforms to the formula: 	Skin-Conditioning Agents - Humectant
Arabinose 10323-20-3	Arabinose is the organic compound that conforms to the formula: 	Skin-Conditioning Agents - Humectant
Psicose 23140-52-5	Psicose is the monosaccharide that conforms to the formula: 	Skin-Conditioning Agents - Humectant
Saccharide Hydrolysate 8013-17-0	Saccharide Hydrolysate is an invert sugar derived by the hydrolysis of sucrose by acid, enzyme, or other method of hydrolysis. It is characterized by a content of fructose and glucose. 	Skin Protectants; Skin- Conditioning Agents - Humectant
Saccharide Isomerate 100843-69-4	Saccharide Isomerate is a carbohydrate complex formed from a base catalyzed rearrangement of a mixture of saccharides.	Skin-Conditioning Agents - Humectant

Table 2. Physical and Chemical Properties

Property	Value/Results	Reference
Anhydrogalactose		
Molecular weight (g/mol)	162.14	10
log K_{ow}	-2.01 (estimated)	12
Anhydroglucitol		
Molecular weight (g/mol)	164.16	10
log K_{ow}	-2.17 (estimated)	12
Anhydroxylitol		
Molecular weight (g/mol)	134.13	10
log K_{ow}	-1.72 (estimated)	12
Anhydroxylitol ~35% in dried extract of tradename mixture (comprising in part, xylitol and xylitylglucoside)		
Form (of tradename mixture)	Clear, light yellow liquid	6
Density (g/mL at 20°C)	1.435	6
Melting point (°C)	< 50	6
Boiling point (°C at 760 mmHg)	315	6
Vapor pressure mmHg at 25°C)	2.7×10^{-6}	6
Water solubility (g/L at 20°C)	674	6
Partition coefficient (log P_{ow})	-2	6
Arabinose		
Molecular weight (g/mol)	150.13	10
log K_{ow}	-1.98 (estimated)	12
Psicose		
Form	White crystalline solid	8
Molecular weight (g/mol)	180.156	8
Melting point (°C)	96	8
Solubility (% w/w at 25°C and 50 °C)	74 at 25°C; 83 at 50°C	8
log K_{ow}	-1.46 (estimated)	12
Saccharide Hydrolysate		
Form	Hygroscopic liquid	9
Molecular weight (average; g/mol)	180.16	11
Solubility	Very soluble in water, glycerin, and in glycols; very sparingly soluble in acetone and in ethanol	9
log K_{ow}	-1.46; -2.43 (estimated)	12

Table 3. Frequency (2019) and Concentration (2018) of Use According to Duration and Type of Exposure.^{18,19}

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Anhydroglucitol		Anhydroxylylitol		Saccharide Hydrolysate	
Totals*/Conc. Range	NR	0.17-1	151	0.0028-0.88	30	0.002-4.6
Duration of Use						
<i>Leave-On</i>	<i>NR</i>	<i>0.33-1</i>	<i>125</i>	<i>0.28-0.88</i>	<i>28</i>	<i>0.002</i>
<i>Rinse off</i>	<i>NR</i>	<i>0.28</i>	<i>26</i>	<i>0.0028</i>	<i>2</i>	<i>4.6</i>
<i>Diluted for (bath) Use</i>	<i>NR</i>	<i>0.17</i>	<i>NR</i>	<i>NR</i>	<i>NR</i>	<i>NR</i>
Exposure Type						
Eye Area	NR	0.28-0.83	7	NR	3	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	NR	NR	1;6 ^a ;41 ^b	0.88 ^a	10 ^a ; 4 ^b	NR
Incidental Inhalation- Powders	NR	0.9 ^c	41 ^b ;54 ^c	0.88 ^c	4 ^b ;7 ^c	0.002 ^c
Dermal Contact	NR	0.17-1	140	0.0028-0.88	30	0.002-4.6
Deodorant (underarm)	NR	NR	1 ^a	NR	NR	NR
Hair - Non-Coloring	NR	NR	7	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	0.17	11	NR	NR	NR
Baby Products	NR	NR	1	NR	5	NR
Saccharide Isomerate						
	# of Uses	Conc. (%)				
Totals/Conc. Range	455	0.001-2.8				
Duration of Use						
<i>Leave-On</i>	<i>406</i>	<i>0.001-2.8</i>				
<i>Rinse off</i>	<i>49</i>	<i>0.01-0.7</i>				
<i>Diluted for (bath) Use</i>	<i>NR</i>	<i>NR</i>				
Exposure Type						
Eye Area	32	1				
Incidental Ingestion	NR	NR				
Incidental Inhalation- Sprays	162 ^a ;3 ^b	0.01 ^a				
Incidental Inhalation- Powders	3 ^b ;131 ^c	0.02-2.8 ^c				
Dermal Contact	430	0.001-2.8				
Deodorant (underarm)	NR	NR				
Hair - Non-Coloring	14	0.27				
Hair-Coloring	NR	NR				
Nail	11	0.03				
Mucous Membrane	8	NR				
Baby Products	2	NR				

NR = Not Reported

* 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.

^aIt is possible that these products may be sprays, but it is not specified whether the reported uses are sprays^bNot specified these products are sprays or powders, but it is possible the use can be as a spray or powder, therefore the information is captured in both categories^cIt is possible that these products may be powders, but it is not specified whether the reported uses are powders

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