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Safety Assessment of Anhydrogalactose, Anhydroglucitol, Anhydroxylitol, Arabinose, Psicose, Saccharide Hydrolysate, and Saccharide Isomerate as Used in Cosmetics

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Abstract

The Expert Panel for Cosmetic Ingredient Safety (Panel) reviewed the safety of 7 saccharides/saccharide derivatives as used in cosmetic products; all of these ingredients are reported to function as skin-conditioning agents—humectant in cosmetics. The Panel reviewed data relevant to the safety of these ingredients in cosmetic formulations and concluded that Anhydrogalactose, Anhydroglucitol, Anhydroxylitol, Arabinose, Psicose, Saccharide Hydrolysate, and Saccharide Isomerate are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Keywords

Cosmetic Ingredient Review, Expert Panel for Cosmetic Ingredient Safety, Safety, Cosmetics, Anhydrogalactose, Anhydroglucitol, Anhydroxylitol, Arabinose, Psicose, Saccharide Hydrolysate, Saccharide Isomerate

Introduction

The safety of the following 7 ingredients, as used in cosmetics, is reviewed in this safety assessment: Anhydrogalactose, Anhydroglucitol, Anhydroxylitol, Arabinose, Psicose, Saccharide Hydrolysate, and Saccharide Isomerate.

According to the *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*), all 7 ingredients are reported to function as skin-conditioning agents—humectant in cosmetics (see Table 1).[1] Other reported functions include antioxidant, humectant, skin protectant, and oral care agent.

Because Saccharide Hydrolysate, also known as invert sugar, contains glucose and fructose, and saccharides/saccharide mixtures are being reviewed in this report, it is important to note that the Expert Panel for Cosmetic Ingredient Safety (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 report is available on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/ingredients).

This safety assessment includes relevant published and unpublished data for each endpoint that is evaluated.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 search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically 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

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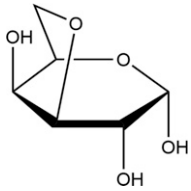
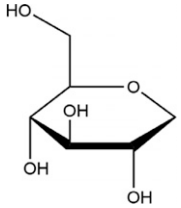
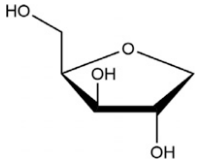
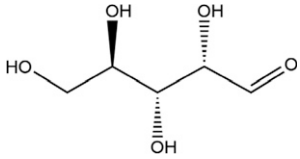
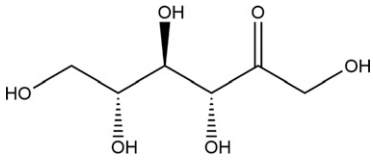
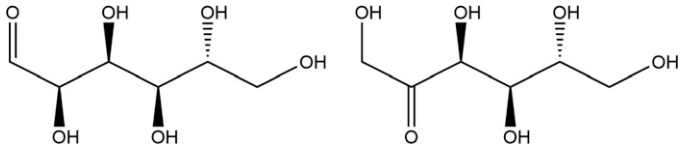
Table 1. Definitions, Structures, and Reported functions[1,CIR Staff].

Ingredient CAS No.	Definition	Function(s)
Anhydrogalactose 28251-55-0	Anhydrogalactose is the organic compound that conforms to the structure: 	Antioxidants; humectants; skin-conditioning agents - humectant
Anhydroglucitol 154-58-5	Anhydroglucitol is the organic compound that conforms to the structure: 	Humectants; oral care agents; skin-conditioning agents - humectant
Anhydroxylitol 53448-53-6	Anhydroxylitol is the organic compound that conforms to the structure: 	Skin-conditioning agents - humectant
Arabinose 10323-20-3	Arabinose is the organic compound that conforms to the structure: 	Skin-conditioning agents - humectant
Psicose 23140-52-5	Psicose is the monosaccharide that conforms to the structure: 	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

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,

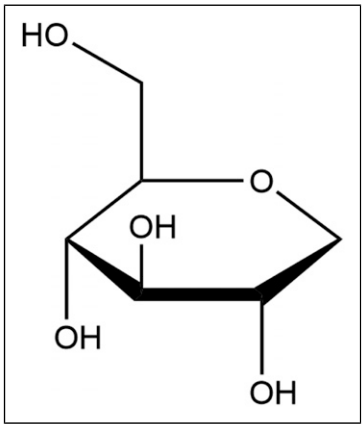


Figure 1. Anhydroglucitol.

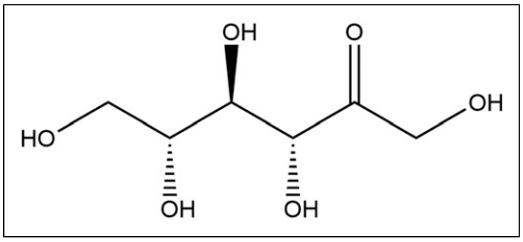


Figure 2. Psicose.

various stereochemistries (and connectivities) are possible.

An Australian Industrial Chemicals Scheme (formerly National Industrial Chemicals Notification and Assessment Scheme (NICNAS)) public report on Anhydroxylitol is available.[3] Data summaries from that report are included in this safety assessment.

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 an unsubstituted methylene group at the C1 position (i.e., no hydroxyl group; Figure 1).[1,4,5] Psicose (CAS No. 23140-52-5) has been defined as a C-3 epimer of D-fructose (Figure 2).[1,6]

The definitions, structures, and CAS nos. of all the saccharide ingredients included in this safety assessment are presented in Table 1.[1]

Chemical Properties

Properties of the ingredients reviewed in this report are presented in Table 2.[3,7-14] Anhydrogalactose, Anhydroxylitol, Psicose, and Saccharide Hydrolysate are water-soluble. Anhydroxylitol has a molecular weight of 134.13 Da.[10] The available data indicate that Saccharide Isomerate with different molecular weights (MWs) is being marketed. The weight range for the lower MW Saccharide Isomerate is 120-400 Da.[15] The reported values for higher MW Saccharide Isomerate are 15,000 Da, 20,000 Da, and >1.4 MDa.[13] Throughout the report text, the molecular weight of the Saccharide Isomerate being tested will be identified in parentheses.

Method of Manufacture

Anhydrogalactose. Anhydrogalactose may be prepared by enzymatic saccharification of agar, using a combination of agarolytic enzymes.[16] 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.[17]

Anhydroglucitol. A single-enzyme process for the production of Anhydroglucitol has been designed.[18] The process involves the acid pre-hydrolysis of agarose into agarobiose and the enzymatic hydrolysis of agarobiose into Anhydroglucitol and galactose.

Anhydroxylitol. Anhydroxylitol results from the dehydration of xylitol under acidic conditions.[19] Glucose has been identified as a by-product in the reaction medium.

Arabinose. Arabinose is produced by catalytic decarboxylation of D-gluconic acid, sodium salt.[20] Additional processes used to prepare the final product include ultrafiltration, chromatography, crystallization, grinding, and drying.

Psicose. It has been reported that Psicose is easily generated by heating sugar preparations.[21] Details relating to this process were not provided. According to another source, Psicose has been produced from fructose using the enzyme tagatose 3-epimerase.[22]

Saccharide Isomerate. According to a supplier of this ingredient, Saccharide Isomerate (plant-derived; MW = 120-400 Da) is formed by a base catalyzed isomerization of plant-derived D-glucose of kernel corn and is similar to that of the carbohydrate complex found in human skin.[15] The product of this process is a mixture of mono and disaccharides, mainly glucose and fructose.

The method of manufacture for 3 other trade name materials (MW >1.4 MDa) from an anonymous source is described as catalyzed rearrangement of a mixture of saccharides/purification.[13] The method of manufacture for 1 of the 3 trade name materials mixed with water (MW of 20,000 Da) and a fourth trade name material mixed with water (MW of 15,000 Da) from the same source is described as catalyzed rearrangement of a mixture of

Table 2. Chemical Properties.

Property	Value/Results	Reference
Anhydrogalactose		
Molecular weight (Da)	162.1	10
log K_{ow}	−2.0 (estimated)	12
Anhydroglucitol		
Molecular weight (Da)	164.1	10
log K_{ow}	−2.2 (estimated)	12
Anhydroxylitol		
Molecular weight (Da)	134.1	10
log K_{ow}	−1.7 (estimated)	12
Anhydroxylitol ~35% in dried extract of trade name mixture (also comprising in part xylitol and xylitylglucoside)		
Form (of trade name mixture)	Clear, light yellow liquid	3
Density (g/ml at 20°C)	1.44	3
Melting point (°C)	<50	3
Boiling point (°C at 760 mmHg)	315	3
Vapor pressure (mmHg at 25°C)	2.7×10^{-6}	3
Water solubility (g/l at 20°C)	674	3
Partition coefficient (log P_{ow})	−2	3
Arabinose		
Molecular weight (Da)	150.1	10
log K_{ow}	−2.0 (estimated)	12
Log P	−2.2	14
Psicose		
Form	White crystalline solid	8
Molecular weight (Da)	180.2	8
Melting point (°C)	96	8
Solubility (% w/w at 25°C; 50°C)	74; 83	8
log K_{ow}	−1.5 (estimated)	12
Saccharide Hydrolysate		
Form	Hygroscopic liquid	9
Molecular weight (average; Da)	180.2	11
Solubility	Very soluble in water, glycerin, and in glycols; very sparingly soluble in acetone and in ethanol	9
log K_{ow}	−1.5; −2.4 (estimated)	12
Saccharide Isomerate		
Molecular weight (MDa)	>1.4 (eq dextran)	13
Molecular weight (Da)	20,000	13
Molecular weight (Da)	15,000	13
Molecular weight (Da)	120-400	15

saccharides/purification and hydrothermolysis accelerated with carbon dioxide supercritical.

Composition and Impurities

Anhydroxylitol. According to a chemical supplier, a trade name mixture that contains Anhydroxylitol has the following composition: xylitylglucoside (35%-50%), Anhydroxylitol (24%-34%), xylitol (5%-15%), water (15%-17%), and glucose (0%-5%).[19]

Saccharide Hydrolysate. According to the *Food Chemicals Codex* description, Saccharide Hydrolysate 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 Saccharide Hydrolysate are that it contains not less than 90% and not more than 110% of the labeled amount of sucrose and of Saccharide Hydrolysate. Other acceptance criteria for Saccharide Hydrolysate in the *Food Chemicals Codex* relate to lead content (not more 0.1 mg/kg) and sulfated ash content (not more than 0.2%).

Saccharide Isomerate. As stated earlier in the report text, the available data indicate that Saccharide Isomerate with different MWs is being marketed. The weight range for the lower MW Saccharide Isomerate is 120-400 Da.[15] The reported values for higher MW Saccharide Isomerate are 15,000 Da, 20,000 Da, and >1.4 MDa. According to a chemical supplier, Saccharide Isomerate (MW = 120-400 Da) is a mixture of mono and

Table 3. Frequency (2021) and Concentration (2018) of Use According to Duration and Type of Exposure.[23,24]

	# of Uses	Max Conc. of Use (%)	# of Uses	Max Conc. of Use (%)	# of Uses	Max Conc. of Use (%)	# of Uses	Conc. (%)
	Anhydroglucitol		Anhydroxylitol		Saccharide Hydrolysate		Saccharide Isomerate	
Totals*/Conc. Range	**NR**	**0.17-1**	**153**	**0.0028-0.88**	**33**	**0.002-4.6**	**352**	**0.001-2.8**
Duration of use								
Leave-on	*NR*	*0.33-1*	*123*	*0.28-0.88*	*32*	*0.002*	*302*	*0.001-2.8*
Rinse off	*NR*	*0.28*	*30*	*0.0028*	*1*	*4.6*	*50*	*0.01-0.7*
Diluted for (bath) use	*NR*	*0.17*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure type								
Eye area	NR	0.28-0.83	5	NR	2	NR	13	1
Incidental ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental inhalation—sprays	NR	NR	1;10[b];46[c]	0.88[b]	10[b]; 6[c]	NR	55[b];46[c]	0.01[b]
Incidental inhalation—powders	NR	0.9[a]	46[c]	0.88[a]	6[c];10[a]	0.002[a]	46[c]	0.02-2.8[a]
Dermal contact	NR	0.17-1	146	0.0028-0.88	33	0.002-4.6	328	0.001-2.8
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair—non-coloring	NR	NR	6	NR	NR	NR	14	0.27
Hair—coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	9	0.03
Mucous membrane	NR	0.17	11	NR	NR	NR	7	NR
Baby products	NR	NR	1	NR	5	NR	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.
[a]It is possible that these products may be powders, but it is not specified whether the reported uses are powders.
[b]It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.
[c]Not 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.

disaccharides (mainly glucose and fructose) and also contains water, citric acid, and sodium citrate.[15] Regarding the presence of impurities, the supplier confirms that Saccharide Isomerate is produced without using solvents. Therefore, Saccharide Isomerate does not contain residual solvents.

A source provided composition data on Saccharide Isomerate trade name materials.[13] Data on one of the trade name materials (MW >1.4 MDa) indicate an Osidic composition of glucuronic acid-mannose-galactose-galacturonic acid-*N*-acetylglucosamine. Data on another trade name material (MW >1.4 MDa), and the same trade name material mixed with water (MW of 20,000 Da), indicate an Osidic composition of rhamnose-glucose-galactose-galacturonic acid-*N*-acetylglucosamine. A third trade name material (MW of 15,000 Da) has an Osidic composition of galacturonic acid-*N*-acetylglucosamine. A fourth trade name material (MW >1.4 MDa) has an Osidic composition of galactose-*N*-acetyl glucosamine-*N*-acetylglucuronic acid (GuINAcA)/3-acetylated *N*-acetylglucuronic acid (3OAc-GuINAcA).

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 2021 VCRP data, Saccharide Isomerate is reported to be used in 352 cosmetic products (302 leave-on products and 50 rinse-off products).[23] Of the saccharide ingredients 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 used at maximum use concentrations up to 4.6% in rinse-off products (skin cleansing products) and that Saccharide Isomerate is used at maximum use concentrations up to 2.8% in leave-on products (face and neck skin care preparations, not spray).[24] These are the highest use concentrations in rinse-off and leave-on products reported for the ingredients 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 the ingredients that are being reviewed 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 concentrations were not reported for these 2 ingredients in products of this type in the Council's use concentration survey. Products containing the ingredients that are being reviewed 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; however, there are no reported concentrations of use of this ingredient in products of this type in the Council's use concentration survey.[23] In practice, most 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.[25-28] 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.[25,26]

The ingredients that are being reviewed in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union.[29]

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.[30] 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.[31] 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.[6]

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 Saccharide Hydrolysate in an obstetrics and gynecology center in the US have been limited to diabetic women during the intrapartum period.[32]

Toxicokinetic Studies

Dermal Penetration

Arabinose. The dermal/percutaneous absorption of D-Arabinose is limited by its hydrophilicity (log P = −2.22) and ability to form hydrogen bonds (4 donor groups and 5 acceptor groups).[14]

Anhydroxylitol. According to the Australian Industrial Chemicals Scheme, based on the low-molecular weight of Anhydroxylitol (134 Da), there is potential for dermal absorption and passage across the gastrointestinal tract.[3] However, this may be limited by its high water-solubility (674 g/L) and low partition coefficient (log P_{ow} = −2).

Saccharide Isomerate. A statement from a supplier of Saccharide Isomerate (MW = 120-400 Da) indicates that dermal absorption studies were not performed because, other than containing Saccharide Isomerate, it contains water, citric acid, and sodium citrate.[15] According to another source, Saccharide Isomerate (120-400 Da) is uniquely bound at the corneocytes to the free amino group of lysine found in the keratin of the stratum corneum.[33] This unique binding mechanism to the skin and scalp ensures that the ingredient is not washed off but continues to improve hydration until removed by the natural process of desquamation.

Absorption, Distribution, Metabolism, and Excretion

Animal

Oral

Anhydroglucitol. The fate of Anhydroglucitol (stereochemistry not stated) in white laboratory rats after dosing was studied.[34] Anhydroglucitol (2 to 7 mg, in saline) was administered orally as a single dose 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 tubules. 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.[34] 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-[^{14}C]Psicose (2 μCi) was administered by stomach tube to rats (number and strain not stated).[35] Of the exhaled [^{14}C]carbon dioxide, 26% was exhaled within 7 h and 80% was exhaled 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. Radioactivity in the urine was associated with D-Psicose, as observed by using paper chromatography. Of the excreted radioactivity recovered, at least 70% was U-[^{14}C]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-[^{14}C]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 [^{14}C]carbon dioxide and the finding that 39% of the radioactivity is retained by the carcass for 72 h after oral feeding suggest that a large portion of the U-[^{14}C]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 [^{14}C]Psicose were studied using 30 male Wistar rats.[36] All of the rats were fasted for 24 h. Approximately 0.6 mL of [^{14}C]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. [^{14}C]Psicose entered the blood after oral dosing, and the maximum blood concentration (48.5 ± 15.6 μg/g) was observed at 1 h. Urinary excretion was 20% within 1 h and 33% within 2 h. The values for radioactivity (from administered [^{14}C]Psicose) in the liver were 41.4 ± 28.7, 126.3 ± 45.0, 200 ± 86.3, and 127.5 ± 32.6 μg/g liver tissue at 10, 30, 60, and 120 min, respectively. 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 [^{14}C]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.[4] 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 μg/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 the 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 μg/ml. Amounts of Anhydroglucitol detected in the following organs were as follows: diabetic kidney (1.5 and 2.6 μg/ml), liver (0.8 and 1.6 μg/ml), spleen (1.4 and 1.6 μg/ml), skin (0.5 and 1.1 μg/ml), and brain (<0.5 μg/ml). 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 μg/ml and 9.0 μg/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 μg/g and 4.4 μg/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 perfused rats. The authors noted that the observations made in this study indicated that Anhydroglucitol readily diffused from the circulation 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 [^{14}C]Psicose were studied using 30 male Wistar rats.[36] All of the rats were fasted for 24 h. Approximately 0.6 mL of [^{14}C]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 of [^{14}C]Psicose, radioactivity in the blood decreased (half-life = 57 min). Also, the excretion of radioactivity 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 [^{14}C]Psicose (20 KBq in saline, dose of 100 mg/kg).[36] 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 ^{14}C-labeled-Psicose in the liver, kidney, and bladder, but there was no accumulation in the brain. After reviewing the results of rat and mouse i.v. dosing experiments in this study, the authors concluded that [^{14}C]Psicose was absorbed and eliminated rapidly.

U-[^{14}C]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).[35] Urine and exhaled [^{14}C]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-[^{14}C]Psicose. Liver glycogen contained 1% of the radioactivity, and only 0.6% of the radioactivity was exhaled as [^{14}C]carbon dioxide. The authors noted that these results indicate that i.v.-administered U-[^{14}C]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.[5] 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).[37] 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/d. The mean Anhydroglucitol excretion in the urine was ~4.76 mg/d. 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.[38] All subjects were healthy and undergoing normal physical activity. Individual sugars (Psicose; stereochemistry 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.[35]

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.[39] The median 5-h urinary sugar excretion was 0.26% of ingested oral dose of raffinose, 0.05% of ingested oral dose of lactose, and 17.5% of ingested oral dose of L-arabinose.

Parenteral

Arabinose. The metabolic stability of L-arabinose was investigated using 5 normal subjects.[39] 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

The acute dermal and oral toxicity studies summarized below are presented in Table 4.

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 Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 402.[3] No mortalities or gross pathological changes were observed, and the LD_{50} was >2 g/kg.

The acute oral toxicity of the dried extract of a trade mixture containing 25%–35% Anhydroxylitol was evaluated in rats (number not stated), according to OECD TG 401.[3] No mortalities or gross pathological changes were observed, and the LD_{50} was >2 g/kg. In an acute oral toxicity study on Arabinose, the LD_{50} was calculated to be 12.1 g/kg in male rats and 11.6 g/kg in female rats (number not stated).[40] The acute oral toxicity of 50% aqueous Psicose was evaluated using 5 groups of 8 male Wistar rats.[41] The groups received single oral doses ranging from 8 g/kg to 20 g/kg. 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 calculated LD_{50} values were 16.3 g/kg (using the Behrens-Karber method) and 15.8 g/kg (using the Litchfield-Wilcoxon method). In another study, each of 6 beagle dogs received a single oral dose in water (by using a plastic syringe) of Psicose (1 g/kg and 4 g/kg).[42] Each animal received the control on day 1, the 1 g/kg dose on day 2, and the 4 g/kg dose on day 3. Histological examination of tissues was not performed. A mild, dose-dependent increase ($P < 0.05$) in plasma alkaline phosphatase activities was observed between 12 h and 48 h after dosing. It was concluded that Psicose did not induce severe toxicity in dogs. The acute oral toxicity of undiluted Saccharide Isomerate (MW = 120-400 Da) was evaluated (animal species not stated) in accordance with OECD TG 401.[15] An LD_{50} of >2 g/kg was reported.

Short-Term and Chronic Toxicity Studies

The short-term and chronic toxicity studies summarized below are presented in Table 5.

In an experiment involving 12 white laboratory rats, Anhydroglucitol (stereochemistry not stated; 7 mg, 0.14 mmol/kg body weight) was administered orally (in drinking water) daily for 7 weeks.[34] No apparent toxic signs were observed (results relating to the distribution and excretion of Anhydroglucitol after oral dosing are included in the section on Toxicokinetic Studies.) A 28-day oral toxicity study on a trade name 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.[3] The test substance was administered at doses of 15, 150, and 1000 mg/kg/d. There were no treatment-related necropsy changes or changes in mortality. 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. Diarrhea was a finding reported in a short-term toxicity test in which rats were given feed containing 5% Arabinose.[40] Additional findings were not reported. Six Sprague-Dawley rats were fed a normal diet and consumed 2% Psicose-supplemented water for 14 days.[43] 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 or mean liver weight between treated and control rats. Groups of 7 male Wistar rats were fed diets containing 10, 20, 30, and 40% Psicose for 34 days.[41] One rat fed 30% and 5 rats fed 40% Psicose died during the experimental period. Liver and kidney weights were heavier ($P < 0.05$) in rats fed the 10% diet than in rats fed the 0 and 30% diets. Many of the effects observed in this study were assumed to be secondary to a decrease in food consumption or the consumption of large amounts of a non-nutritive, poorly absorbed substance. It is not clear whether or not the cause of Psicose-induced liver enlargement was due to liver glycogen deposition. 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.[44] During the course of the experiment, plasma triglyceride concentrations increased in the control group, whereas they remained low in the group fed Psicose. 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. There were no statistically significant differences in liver enzymes or renal function markers between test and control groups. The authors concluded that dosing with Psicose did not cause any harmful effects in dogs.

The chronic oral toxicity of Psicose was evaluated using groups of 18 male Wistar rats.[45] 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/d Psicose and 1.22 g/kg/d sucrose. Liver and kidney weights were found to be statistically significantly heavier in the 3% Psicose group at 12 and 18 months, when compared to the control group. Histopathological examination of the liver at 18 months revealed slight fatty degeneration and hepatocellular fibrosis in the group fed 3% Psicose in the diet. 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. These results were not observed at 12 months. 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.

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.[46] The study involved 60 rats of the Bethesda black strain (30 males and 30 females) and 60 C57BL mice (30 males and 30 females). No untoward effects were observed in rats. However, some of the mice (number not stated) developed symptoms of shock and died. The mice also had white necrotic masses in the subcutaneous tissue of the neck. These chronic toxicity data are from a carcinogenicity

Table 4. Acute Toxicity Studies.

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/Results	Reference
Dermal						
Anhydroxylitol (25% to 35%)	Rats	Not stated	Dried extract of trade name mixture	Doses up to 2 g/kg. OECD TG 402.3.	No mortalities, abnormal clinical signs, body weight changes, or gross pathological changes observed. The LD_{50} > 2 g/kg.	[3]
Oral						
Anhydroxylitol (25% to 35%)	Rats	Not stated	Dried extract of trade name mixture	Doses up to 2 g/kg. OECD TG 401.	No mortalities, abnormal clinical signs, body weight changes, or gross pathological changes were observed. The LD_{50} > 2 g/kg	[3]
Arabinose	Rats (male and female; strain not stated)	Not stated	Not stated	Doses administered and study details not stated. Data summary is from English language translation of Japanese publication abstract	LD_{50} (calculated) = 12.1 g/kg (males) and 11.6 g/kg (females)	[40]
Psicose (50%)	Male Wistar rats (5 groups of 8) male Wistar rats.	5 groups (8 rats per group)	Water	Groups received single oral doses ranging from 8 g/kg to 20 g/kg. Stainless feeding tube attached to 20 mL syringe used for dosing. 14-d observation period initiated after test substance administration. Necropsy performed on animals that died. LD_{50} values calculated using Behrens-Karber method and Litchfield-Wilcoxon method.	Animal deaths: 3 rats (14 g/kg dose group), 3 rats (17 g/kg dose group), and 8 rats (20 g/kg dose group). Animals died within 2 days after dosing. All rats experienced diarrhea at 1 h to 24 h after dosing. Condition of high-dose animals (17 g/kg and 20 g/kg doses) described as quite weak. No evidence of abnormalities in surviving rats after 3 days. At necropsy, bleeding observed in mucous layers of stomach or small intestine in rats of 17 g/kg or 20 g/kg dose group. LD_{50} = 16.3 g/kg (Behrens-Karber method) and 15.8 g/kg (Litchfield-Wilcoxon method)	[41]

(continued)

Table 4. (continued)

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/Results	Reference
Psicose	Beagle dogs	6	Water (100 mL)	Single oral dose (in water, by plastic syringe) of Psicose (1 g/kg and 4 g/kg) or a placebo (water, 100 mL). The control, 1 g/kg of Psicose, and 4 g/kg of Psicose administered on 3 different study days. Each animal received the control on day 1, the 1 g/kg dose on day 2, and the 4 g/kg dose on day 3. Mean values in data presented were representative of 6 dogs (for control and 1 g/kg dose) and 5 dogs (for 4 g/kg dose). All dogs were active and had good appetite throughout the study.	4 g/kg dose caused vomiting in 1 dog and transient diarrhea in remaining 5 dogs. Two dogs had transient nausea within 1 h after receiving 1 g/kg dose. Blood glucose slightly decreased, without an increase in the plasma insulin concentration, at 2 h after dosing with the test substance. Mild, dose-dependent increase ($P < 0.05$) in plasma alkaline phosphatase activities observed between 12 h and 48 h after dosing. Histological examination of liver or other tissues not performed. Plasma inorganic phosphorus concentration at 4 g/kg dose slightly higher ($P < 0.05$) at 8-h post-dosing, when compared to control dogs. Though no possible causes of inorganic phosphorus alteration observed, authors stated that dosing with Psicose may mildly exaggerate diurnal pattern of plasma inorganic phosphorus concentration in dogs. Authors concluded that Psicose did not induce severe toxicity in dogs.	[42]

Table 5. Repeated Dose Toxicity Studies.

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	Results	Reference
Short-term toxicity – oral						
Anhydroglucitol	White laboratory rats	12	Water	Anhydroglucitol (stereochemistry not stated; 7 mg, 0.14 mmol/kg body weight) administered orally (daily for 7 wk. 6 rats served as controls.	Body weight gain (5.2 g/rat/wk) in test animals similar to that of control rats (4.6 g/rat/wk). No apparent toxic signs observed in test animals.	34
Anhydroxylitol (~25%)	Rats (strain not stated)	At least 10 (5 males, 5 females)	Trade name mixture (with unstated quantities of xylitol and xylitylglucoside)	28-d oral toxicity study (OECD TG 407). Test substance administered at doses of 0 (vehicle was negative control (water)), 15, 150, and 1000 mg/kg/d.	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 observed at necropsy of animals in highest dose group. However, minimal focal myocarditis observed in 2 males and 1 female of highest dose group. Histopathological examination not performed on animals of other 2 dose groups. The Australian Industrial chemicals Scheme noted that lesions (type and incidence) observed are typical of findings that are expected in animals of this type, strain (not specified), and age. However, no historical data supporting this statement provided. Given the uncertainty relating to cause of myocarditis in animals of highest dose group and limited histopathology data, the Australian Industrial chemicals Scheme noted that was not possible to clearly establish a no-observed-adverse-effect-level (NOAEL) for test substance.	3
Arabinose (5%)	Rats (strain not stated)	Not stated	Feed	Short-term toxicity test (duration not stated). Data summary is from English translation of Japanese publication abstract. Details relating to test protocol and results not included	Rats given feed containing 5% arabinose developed diarrhea.	40
Psicose (2%)	Sprague-Dawley rats	6	Water	Rats fed normal diet and consumed 2% Psicose-supplemented water for 14 d. Control group (6 rats) fed normal diet and consumed water without Psicose. After 14 d, animals killed and body, testes, and liver weights determined	Mean body weight of treated rats (232 ± 12 g) higher when compared to control group (214 ± 14 g). No difference in mean testes weight (2.0 ± 0.2 g) between treated and control rats. Mean liver weight values were 12 .7 ± 0.7 g (treated rats) and 12.7 ± 0.7 g (controls).	43

(continued)

Table 5. (continued)

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	Results	Reference
Psicose (10%, 20%, 30%, and 40%)	Male Wistar rats	7	Diet	Groups of 7 rats fed diets for 34 d. Butylated hydroxytoluene (0.01 g/kg diet) added to all diets as antioxidant. Control group fed t diet without Psicose. After day 34, rats fasted for 3 h and then killed.	One rat fed 30% and 5 rats fed 40% Psicose died during experimental period. Body weight gain, food intake, and food efficiency more extensively suppressed after feeding with higher % Psicose diets (i.e., 30% and 40% diets). Statistically significant difference in body weight gain observed between 0, 10%, 20%, and 30% dietary groups ($P < 0.05$). Rats fed 20%, 30%, and 40% diets experienced diarrhea during first 8 d. Weights of heart and spleen smaller ($P < 0.05$) in rats fed higher Psicose concentration diets. Liver and kidney weights heavier ($P < 0.05$) in rats fed 10% diet than in rats fed the 0 and 30% diets. Cecal enlargement observed in rats fed 10% to 40% diets. Epididymal, perirenal, and mesenteric adipose tissue weights statistically significantly smaller ($P < 0.05$) in rats fed higher Psicose concentration diets. Other results indicated that serum glucose and triacylglycerol concentrations significantly lower ($P < 0.05$) in 30% dietary group than in other groups. Liver triacylglycerol content higher in 10% dietary group than in 0% group. Many effects observed assumed to be secondary to decrease in food consumption or consumption of large amounts of a non-nutritive, poorly absorbed, osmotically active substance. Not clear as to whether or not cause of Psicose-induced liver enlargement due to liver glycogen deposition. Authors concluded that feeding of diets extremely high in Psicose appears to be harmful to intestinal tract.	[41]
Psicose	Beagle dogs	5	Not stated	Psicose (0.2 g/kg) was fed to animals daily for 12 wk. Control group (5 dogs) fed placebo (not stated) according to same procedure.	During course of experiment, plasma triglyceride concentrations increased in control group, but remained low in group fed Psicose. At week 2 and thereafter, plasma total cholesterol concentrations in test group statistically significantly lower ($P < 0.05$) when compared to control group. Platelet count levels in test group statistically significantly lower at week 0 and week 12 ($P < 0.05$). Psicose dosing had no influence on body weight. Except for change in lipid levels (lipid lowering effect), Psicose dosing 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 chlorine concentrations). Also, no cumulative effect of Psicose dosing on glucose metabolism, and no statistically significant differences in the following between test and control groups: Liver enzymes, renal function markers, and electrolytes. Mild increase in plasma alkaline phosphatase not considered suggestive of Psicose toxicity. Authors concluded that dosing with Psicose did not cause harmful effects in dogs.	[44]

(continued)

Table 5. (continued)

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	Results	Reference
Chronic toxicity – oral						
Psicose (3%)	Male Wistar rats	18	Commercial rodent diet	Test animals had free access to diet for 12 or 18 mo. Rats actually ingested 1.28 g/kg/d Psicose and 1.22 g/kg/d sucrose. After 12 months of feeding, 8 rats from each group fasted prior to collection of blood for hematological analysis. Remaining rats (10 per group) killed at the end of 18 mo, and various organs weighed. Parts of liver and kidney preserved for histopathological examination.	Liver and kidney weights statistically significantly heavier in 3% Psicose group at 12 months and 18 months when compared to control group. At 18 months, liver and kidney weights also statistically significantly heavier in test group when compared to control group. Higher weights also reported for brains, lungs, and pancreas in test animals. At 12 mo, mean corpuscular hemoglobin statistically significantly lower in test group when compared to control group. Hemoglobin and mean corpuscular volume at 18 months statistically significantly greater in test group than in control group. Histopathological examination of liver at 18 months revealed fatty degeneration and hepatocellular fibrosis in group fed 3% Psicose in diet, but not in control group. These findings appeared to be slight and local. Mean value for pathological lesions (liver) in test group statistically significantly higher ($P < 0.0498$; i.e., slight difference) when compared to control group. At 12 mo, no difference in histopathological observations (in liver and kidneys) between test and control groups. In kidneys at 18 mo, no difference in total value for pathological lesions between test and control groups. Authors concluded that study found 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 hematological and chemical values not suggestive of overt Psicose toxicity, and that, overall, no adverse effects seen after feeding with 3% Psicose in the diet.	[45]
Chronic toxicity – parenteral						
l-Arabinose (25%)	Bethesda black rats and C57BL mice	60 (30 males, 30 females) per strain tested	Water	Chronic subcutaneous toxicity data from carcinogenicity study on l-arabinose. Aqueous solution of l-arabinose (2 mL [in rats] and 0.5 mL [in mice]) injected subcutaneously into nape of neck for periods up to 2 yr.	Rats tolerated test substance injections without any untoward effects. However, mice developed symptoms of shock, and some died (number not stated). Also, in mice, white necrotic masses identified in the subcutaneous tissue of nape of neck.	[46]

study on L-arabinose. Protocol details and results relating to tumor formation are presented in the section on Carcinogenicity Studies.

Developmental and Reproductive Toxicity Studies

Developmental and reproductive toxicity studies of the ingredients that are being reviewed were neither found in the published literature nor were these data submitted.

Genotoxicity

The in vitro and in vivo genotoxicity studies summarized below are presented in Table 6.

In the Ames test (according to OECD TG 471), the dried extract of a trade mixture containing 25 to 35% Anhydroxylitol was classified as non-mutagenic.[3] The same test substance was also classified as non-mutagenic in a chromosome aberration assay (according to OECD TG 473) using human peripheral blood lymphocytes (further details were not provided for these studies). Undiluted Saccharide Isomerate (MW = 120-400 Da) was evaluated for genotoxicity in the Ames test (according to OECD TG 471).[15] The test substance was classified as non-genotoxic. The genotoxicity of a Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-*N*-acetylglucosamine) was evaluated using the Ames test (OECD TG 471), with and without metabolic activation.[13] Test substance concentrations ranged from 0.5 to 1.5% (at doses ranging from 0.06 to 5 µl/plate). Results were classified as negative. A Saccharide Isomerate and water trade name material (MW of 20,000 Da; Osidic composition: rhamnose-glucose-galactose-galacturonic acid-*N*-acetylglucosamine) was evaluated in the Ames test (according to OECD TG 471) using 5 *Salmonella typhimurium* strains.[13] The test substance (doses up 5000 µg/plate) was neither mutagenic nor pro-mutagenic with or without metabolic activation. In the same assay, a Saccharide Isomerate and water trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-*N*-acetylglucosamine) was also classified as neither mutagenic nor pro-mutagenic. Similarly, a Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: galactose-*N*-acetylglucuronic acid (GuINAcA)/3-acetylated *N*-acetylglucuronic acid (3OAc-GuINAcA)) had the same classification in this assay (further details were not provided for these studies). Undiluted Saccharide Isomerate (MW = 120-400 Da) was also classified as non-genotoxic in the micronucleus test (according to OECD TG 487).[15]

The micronucleus test (according to OECD TG 474) was used to evaluate the genotoxicity of the dried extract of a trade mixture containing 25 to 35% Anhydroxylitol.[3] Mice received a dose of ≤2000 mg/kg/d for 2 days. The test substance was classified as non-genotoxic. However, according to the Australian Industrial Chemicals Scheme, it is not clear that the test substance was systemically absorbed and reached the bone marrow (further details were not provided for this study).

Carcinogenicity Studies

Subcutaneous

Arabinose. The carcinogenicity of L-arabinose was evaluated using 60 rats of the Bethesda black strain (30 males and 30 females) and 60 C57BL mice (30 males and 30 females)[46] (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, a total of 11 tumors was observed after dosing with the test substance. The tumor types observed (mostly at 22 to 24 months) in rats included urinary bladder papilloma, lymphangiosarcoma of the subcutis, adenofibroma of the breast, and carcinoma of the uterus. In mice, no tumors were observed. Injection site tumors were not observed in rats. The great majority of the benign and malignant tumors found in test and control rats 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 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

Psicose

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: human cervical cancer (HeLa), human hepatocarcinoma (HepG2), human hepatocarcinoma (HuH-7), and immortalized human skin keratinocytes (HaCaT).[47] The assay was initiated when the cells were in the logarithmic growth phase. The following concentrations of Psicose were added to the medium: 1, 5, 10, 20, and 50 mM. After exposure to the test substance for 24, 48, and 72 h, MTT was added and the plates were incubated for 4 h. Psicose did not have an anti-proliferative 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

Table 6. Genotoxicity Studies.

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
In Vitro						
Anhydroxylitol	25% to 35% (doses not stated)	Trade mixture	Ames test (OECD TG 471). Bacterial reverse mutation assay (strains not stated)	Details relating to test protocol not included	Non-genotoxic	3
Anhydroxylitol	25% to 35% (doses not stated)	Trade mixture	Chromosome aberration assay (OECD TG 473), using human peripheral blood lymphocytes	Details relating to test protocol not included	Non-genotoxic	3
Saccharide Isomerate (MW = 120-400 Da)	Undiluted (doses not stated)	Not stated	Ames test (OECD TG 471). Bacterial strains not stated	Details relating to test protocol not included	Non-genotoxic	15
Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-N-acetylglucosamine)	0.5% to 1.5% (at doses ranging from 0.06 to 5 μl/plate)	Not stated	Ames test (OECD TG 471), with and without metabolic activation. Bacterial strains not stated	Dosing with and without metabolic activation. Additional protocol details not stated	No point mutations or frame-shifts in the genome of the bacterial strains tested, with or without metabolic activation. Non-genotoxic	13
Saccharide Isomerate and water trade name material (MW of 20,000 Da; Osidic composition: rhamnose-glucose-galactose-galacturonic acid-N-acetylglucosamine)	Doses up to 5000 μg/plate	Not stated	Ames test (OECD TG 471). Five *Salmonella typhimurium* strains (not stated)	Dosing with and without metabolic activation. Additional protocol details not stated	Neither mutagenic nor pro-mutagenic	13
Saccharide Isomerate and water trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-N-acetylglucosamine)	0.5% to 1.5% (at doses ranging from 0.06 to 5 μl/plate)	Not stated	Ames test (OECD TG 471). Five *Salmonella typhimurium* strains (not stated)	Dosing with and without metabolic activation. Additional protocol details not stated	Neither mutagenic nor pro-mutagenic	13
Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: galactose-N-acetylglucuronic acid (GulNAcA)/3-acetylated N-acetylglucuronic acid (3OAc-GulNAcA))	Doses up to 5000 μg/plate		Ames test (OECD TG 471). Five *Salmonella typhimurium* strains (not stated)	Dosing with and without metabolic activation. Additional protocol details not stated	Neither mutagenic nor pro-mutagenic	13
Saccharide Isomerate (MW = 120-400 Da)	Undiluted (doses not stated)	Not stated	Micronucleus test (OECD TG 487). Cell type not stated	Details relating to test protocol not included	Non-genotoxic	15
In Vivo						
Dried extract of a trade mixture containing Anhydroxylitol (25% to 35%)	Mice received ≤2000 mg/kg/d for 2 d		Micronucleus test (OECD TG 474), using mouse bone marrow erythrocytes	Protocol details not included	Classified as non-genotoxic. However, the Australian Industrial Chemicals Scheme stated that it is not clear that the test substance was systemically absorbed and reached the bone marrow in this in vivo assay	3

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 or D-anhydrogalactose using B16F10 mouse melanoma cells and RAW264.7 cells (mouse macrophages).[17] 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 or 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 L-Anhydrogalactose (95.6% pure) was evaluated using B16F10 mouse melanoma cells.[17] The melanoma cells were induced for melanin production by treatment with α-MSH and were cultured for 1 h with L-Anhydrogalactose and D-anhydrogalactose at concentrations up to 100 µg/ml. Arbutin (up to 100 µg/ml) served as the positive control. The extracellular melanin concentration of melanoma cells treated with 100 µg/ml L-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).[17] 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%, respectively, 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 a 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.[48] Bacterial cells were diluted to 10, 10^2, 10^3, 10^4, and 10^5-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 10^4 or 10^5 dilution. In contrast, *S. mutans* colonies were formed on a minimal agar plate inoculated with bacterial dilutions of either 10^4 or 10^5, 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).[49] Use of a control in this study was not indicated. 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/cm^2/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, 2, 6, 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

The dermal irritation and sensitization studies summarized below are presented in Table 7.

Table 7. Dermal Irritation and Sensitization Studies.

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Animal					
Irritation					
Trade mixture containing Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside)	~35% Anhydroxylitol	3 New Zealand White albino rabbits	Skin irritation test (OECD TG 404).[3] Test substance applied (dose per cm^2 was not stated) to skin for 4 h using a semi-occlusive patch. Application followed by a 72-h observation period	No evidence of erythema or edema during observation period. Test substance classified as non-irritating to skin	3
Saccharide Isomerate (MW = 120-400 Da)	20% (v/v)	Species and number of animals not stated	Skin irritation test (OECD TG 404). Details relating to test protocol not included	Test substance classified as non-irritating and non-corrosive to skin	15
Saccharide Isomerate (MW = 120-400 Da)	20% (v/v)	Guinea pigs (number and species not stated)	Repeated application test. Details relating to test protocol not included	No evidence of skin irritation or corrosion	15
Sensitization					
Dried extract of a trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside)	Induction: Undiluted; challenge: 50% (actual concentration = 17.5%). Intradermal injection concentrations not stated	Guinea pigs (number and strain not stated)	Maximization test (OECD TG 406). Details relating to test protocol not included	Non-sensitizer	3
Saccharide Isomerate (MW = 120-400 Da)	20% (v/v). Intradermal injection concentrations not stated	Number of animals and species not stated	Maximization test (OECD TG 406). Details relating to test protocol not included	Non-sensitizer	15
Human					
Irritation					
Saccharide Isomerate (MW = 120-400 Da)	20% (v/v)	Number of subjects not stated	Occlusive patch test. Details relating to test protocol not included	Test substance classified as non-irritating and non-corrosive to the skin	15
Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-N-acetylglucosamine)	0.5% to 1.5%	10	24-h occlusive patch test. Details relating to test protocol not included	Test substance classified as a non-irritant	13
Saccharide Isomerate and water trade name material (MW of 20,000 Da; Osidic composition: rhamnose-glucose-galactose-galacturonic acid-N-acetylglucosamine)	0.5% to 1.5%	11	48-h occlusive patch test. Details relating to test protocol not included	Test substance classified as a non-irritant	13

(continued)

Table 7. (continued)

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Saccharide Isomerate and water trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-N-acetylglucosamine)	0.5% to 1.5%.	10	24-h occlusive patch test. Details relating to test protocol not included	Test substance classified as a non-irritant	[13]
Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: galactose-N-acetylglucuronic acid (GulNAcA)/3-acetylated N-acetylglucuronic acid (3OAc-GulNAcA))	0.5% to 1.5%	11	48-h occlusive patch test. Details relating to test protocol not included	Test substance classified as a non-irritant	[13]
Sensitization					
Eye cream containing Saccharide Isomerate	2.75% (dose per area not stated)	213 subjects	HRIPT. Product, under an occlusive patch, applied to upper back (between the scapulae and waist, lateral to midline). The. Applications made 3 times per week (Mondays, Wednesdays, and Fridays) for a total of 9 applications. Reactions scored 48 h after patch application on Mondays and Wednesdays, and at 72 h post-application on Fridays. After a 2-week non-treatment period, challenge patches applied to original and new sites on back. Challenge reactions scored at 48 h, 72 h, and 96 h	Non-irritant and non-sensitizer	[50]
Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-N-acetylglucosamine)	0.5% to 1.5%	100 subjects	Marzulli-Maibach HRIPT. Induction phase involved three, 48-h applications per week. Additional details relating to test protocol not included	Non-irritant and non-sensitizer	[13]
Saccharide Isomerate and water trade name material (MW of 20,000 Da; Osidic composition: rhamnose-glucose-galactose-galacturonic acid-N-acetylglucosamine)	0.5% to 1.5%	102 subjects	Marzulli-Maibach HRIPT. 3-week induction phase involved repeated occlusive patch applications. Additional details relating to test protocol not included	Non-irritant and non-sensitizer	[13]

(continued)

Table 7. (continued)

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Saccharide Isomerate and water trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-N-acetylglucosamine)	0.9% (at induction)	109 subjects	Marzulli-Maibach HRIPT. During induction, applications repeated at same test site over period of 3 consecutive weeks. Additional details relating to test protocol not included	No irritation or allergenicity	[13]
Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: galactose-N-acetylglucuronic acid (GulNAcA)/3-acetylated N-acetylglucuronic acid (3OAc-GulNAcA))	0.5% to 1.5%	52 subjects (26 with sensitive skin)	Marzulli-Maibach HRIPT. During induction, applications of the test substance were repeated at same test site over period of 3 consecutive weeks. Additional details relating to test protocol not included	No significant reaction of contact allergy observed	[13]

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.[3] The test substance (dose per cm^2 not stated) was applied to the skin for 4 h, and there was no evidence of skin irritation. The skin irritation potential of 20% (v/v) Saccharide Isomerate (MW = 120-400 Da) was evaluated (animal species not stated) according to OECD TG 404.[15] Details relating to the test protocol are not included. The test substance was classified as non-irritating and non-corrosive to the skin. Saccharide Isomerate (20% v/v; MW = 120-400 Da) was also evaluated for skin irritation potential in a repeated application test involving guinea pigs (strain not stated).[15] There was no evidence of skin irritation or corrosion.

An occlusive patch test was used to evaluate the skin irritation potential of Saccharide Isomerate (20% v/v; MW = 120-400 Da) in human subjects (number not stated).[15] Details relating to the test protocol are not included. The test substance was non-irritating and non-corrosive to the skin. The skin irritation potential of a Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-*N*-acetylglucosamine) was evaluated using 10 subjects.[13] In the 24-h occlusive patch test, the material was applied at concentrations of 0.5 to 1.5%. Skin irritation was not observed. A Saccharide Isomerate and water trade name material (MW of 20,000 Da; Osidic composition: rhamnose-glucose-galactose-galacturonic acid-*N*-acetylglucosamine) was evaluated for skin irritation potential in a study involving 11 subjects.[13] In the 48-h occlusive patch test, the material was applied at concentrations of 0.5 to 1.5%. There was no evidence of skin irritation. Another study involved evaluation of the skin irritation potential of a Saccharide Isomerate and water trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-*N*-acetylglucosamine) using 10 subjects.[13] The material (0.5 to 1.5%) was applied to the skin for 24 h in an occlusive patch test. Skin irritation was not observed. A Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: galactose-*N*-acetylglucuronic acid (GuINAcA)/3-acetylated *N*-acetylglucuronic acid (3OAc-GuINAcA)) was evaluated for skin irritation potential in a study involving 11 subjects.[13] In the 48-h occlusive patch test, the material was applied at concentrations of 0.5 to 1.5%. There was no evidence of skin irritation.

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.[3] A minimum of 10 test and 5 control guinea pigs is specified in this protocol. The undiluted test substance was applied during induction, and the challenge concentration was 50% (actual concentration = 17.5%). Skin sensitization was not observed. A skin sensitization study (maximization test) on 20% (v/v) Saccharide Isomerate (MW = 120-400 Da) was performed in accordance with OECD TG 406.[15] Skin sensitization was not observed (further details were not provided for this study).

A human repeated insult patch test (HRIPT) involving 213 subjects was used to evaluate the skin irritation and sensitization potential of an eye cream containing 2.75% Saccharide Isomerate (MW not stated).[50] Occlusive patches were used; the dose per area was not stated. Neither skin irritation nor sensitization was observed. The skin sensitization potential of a Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-*N*-acetylglucosamine) was evaluated in an HRIPT involving 100 subjects.[13]

Table 8. Ocular Irritation Studies.

Test Article	Concentration/ Dose	Test Population	Procedure	Results	Reference
Animal					
Dried extract of trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside)	Not stated	3 New Zealand White albino rabbits	Ocular irritation test (OECD TG 405). Instillation followed by 72-h observation period	Slight conjunctival irritation (redness and chemosis) observed but had fully resolved by the end of observation period. Conjunctival irritation first observed at 1-h post-instillation. Test substance classified as slightly irritating to eyes	[3]
Saccharide Isomerate (MW = 120-400 Da)	20% (v/v)	Number of animals and species not stated	Ocular irritation test (OECD TG 405). Details relating to study protocol not included	Practically non-irritating to eyes	[15]
Human					
Eye cream containing 2.75% Saccharide Isomerate	Not stated	56 female subjects: (19 contact lens wearers, 19 non-contact lens wearers, and 18 sensitive eye, non-contact lens wearers); 53 completed study	Protocol for product use in study not stated	Trace increases in palpebral conjunctival irritation observed in 3 subjects (unrelated to use of eye cream). No reports of subjective irritation. Increases in lacrimation, eyelid inflammation, or bulbar conjunctival inflammation not observed. Absence of changes in visual acuity and corneal tissue integrity noted. Eye cream did not have potential for causing ocular irritation	[51]

Test concentrations ranged from 0.5 to 1.5%. The test substance was non-irritating and non-sensitizing. An HRIPT was performed to evaluate the skin sensitization potential of a Saccharide Isomerate and water trade name material (MW of 20,000 Da; Osidic composition: rhamnose-glucose-galactose-galacturonic acid-*N*-acetylglucosamine) in 102 subjects.[13] The same test concentrations were applied. The material was a non-irritant and a non-sensitizer. The skin sensitization potential of a Saccharide Isomerate and water trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-*N*-acetyl-glucosamine) was evaluated in another HRIPT involving 109 subjects.[13] The induction concentration is 0.9%, but the challenge concentration is not stated. There was no evidence of skin irritation or allergenicity. An HRIPT was performed to evaluate the skin sensitization potential of a Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: galactose-*N*-acetylglucuronic acid (GuINAcA)/3-acetylated *N*-acetylglucuronic acid (3OAc-GuINAcA)) in 52 subjects (26 with sensitive skin).[13] Induction concentrations ranged from 0.5% to 1.5%. The challenge concentration is not stated. No significant reaction of contact allergy was observed.

Photosensitization/Phototoxicity

In Vitro

Saccharide Isomerate. The phototoxicity of a Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: galactose-*N*-acetylglucuronic acid (GuINAcA)/3-acetylated *N*-acetylglucuronic acid (3OAc-GuINAcA)) was evaluated in an in vitro assay (OECD TG 432), with and without long-wavelength ultraviolet light (UVA).[13] The test substance (which contained 0.5 to 1.5% Saccharide Isomerate) was evaluated for cytotoxicity at test substance concentrations up to 1000 µg/ml (8 concentrations total in range (not stated)). Details relating to the test protocol are not included in the study summary. The test substance was classified as non-phototoxic over the range of concentrations tested.

Animal

Saccharide Isomerate. The photosensitization/phototoxicity potential of Saccharide Isomerate (20% v/v; MW = 120-400 Da) was evaluated using guinea pigs (number and strain

not stated).[15] Details relating to the test protocol are not included in this study summary. Neither photosensitization nor phototoxicity was observed in this study.

Ocular Irritation Studies

The ocular irritation studies summarized below are presented in Table 8.

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.[3] Transient conjunctival irritation was observed, and the test substance was classified as slightly irritating to the eyes.

Saccharide Isomerate (20% v/v; MW = 120-400 Da) was evaluated for ocular irritation potential in accordance with OECD TG 405.[15] The animal species tested (rabbit is preferred, according to OECD TG 405) and details relating to the study protocol are not included in the study summary. The test substance was classified practically non-irritating to the eyes (Further details were not provided for this study).

The ocular irritation potential of an eye cream containing 2.75% Saccharide Isomerate (MW not stated) was evaluated using 53 female subjects.[51] Trace increases in palpebral conjunctival irritation observed in 3 subjects were said to have been unrelated to use of the eye cream. It was concluded that the eye cream did not have the potential for causing ocular irritation.

Clinical Studies

Case Reports

Arabinose (L-arabinose). A pediatric patient presented with large amounts of L-arabinose and L-arabitol (Arabinose metabolite) in the urine.[52] 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.[21,53] 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, 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).[54] A randomized, double-blind, placebo-controlled crossover experiment 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.

Risk Assessment

Dermal

Anhydroxylitol. A risk assessment was performed by the Australian Industrial Chemicals Scheme.[3] 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) Notes of Guidance, 7th revision.[55] 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.[52,56] 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/d 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/d and the NOAEL of 1000 mg/kg/d 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/d, 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 use of Anhydroxylitol up to a concentration of 1.5% in cosmetic products is not considered to pose an unreasonable risk to public health.

Summary

The safety of 7 saccharides/saccharide derivatives, as used in cosmetics, is reviewed in this safety assessment. The available data indicate that Anhydroxylitol has a molecular weight of 134.13 Da. Saccharide Isomerate with different molecular weights (MWs) is being marketed. The weight range for the lower MW Saccharide Isomerate is 120-400 Da. The reported values for higher MW Saccharide Isomerate are 15,000 Da, 20,000 Da, and >1.4 MDa.

According to the *Dictionary*, all 7 ingredients reviewed in this safety assessment are reported to function as skin-conditioning agents—humectant in cosmetics. Other reported functions include antioxidant, humectant, skin protectant, and oral care agent.

In the *Food Chemicals Codex* description, 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 Saccharide Hydrolysate are that it contains not less than 90% and not more than 110% of the labeled amount of sucrose and of Saccharide Hydrolysate. Other acceptance criteria for Saccharide Hydrolysate 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 2021 VCRP data, Saccharide Isomerate is reported to be used in 352 cosmetic products (302 leave-on products and 50 rinse-off products). Of the ingredients 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 ingredients that are being reviewed in this safety assessment.

Psicose is a sugar substitute that has 70% of the sweetness of sucrose, but it has 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.

According to one source, Saccharide Isomerate (MW not stated) is uniquely bound at the corneocytes to the free amino group of lysine found in the keratin of the stratum corneum. This unique binding mechanism to the skin and scalp ensures that the ingredient is not washed off but remains until removed by the natural process of desquamation.

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). Anhydroglucitol was readily absorbed by the gut, and there was no urinary excretion of Anhydroglucitol after 48 h. In another study, Anhydroglucitol (7 mg, 0.14 mmol/kg body weight) was administered orally (in drinking water) to rats daily for 7 wk. 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 [^{14}C]Psicose were studied using male rats and male mice. [^{14}C]Psicose was absorbed well after oral dosing and eliminated rapidly after both oral and i.v. administration. In another oral dosing study, U-[^{14}C]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 the Australian Industrial Chemicals Scheme, 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 LD_{50} 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 LD_{50} 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. LD_{50} 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 LD_{50} values (2 different methods used) of 15.8 and 16.3 g/kg were reported. Bleeding in the mucous layers of the stomach or small intestine (17 or 20 g/kg dose groups) was observed at necropsy. Single oral doses of 1 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. An acute oral LD_{50} of >2 g/kg was reported for undiluted Saccharide Isomerate (MW = 120-400 Da) in a study in which the species tested is not stated.

A 28-day oral toxicity study on a trade name mixture comprising ~25% Anhydroxylitol (and unstated quantities of xylitol and xylitylglucoside) was performed using groups of at least 10 rats. Doses up to 1000 mg/kg/d 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 Australian Industrial Chemicals Scheme noted that it was not possible to clearly establish an NOAEL for the test substance in this study. No apparent toxicity signs were observed after Anhydroglucitol (stereochemistry 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.

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 between treated and control rats. The short-term oral toxicity of Psicose was evaluated using groups of 7 male Wistar rats. 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 deposition. 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 and 30 females) and 60 C57BL mice (30 males and 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.

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. Undiluted Saccharide Isomerate (MW = 120-400 Da) was classified as non-genotoxic in both the Ames test and the micronucleus test in vitro. Ames test results for the following Saccharide Isomerate trade name materials were also negative, with and without metabolic activation: Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-*N*-acetylglucosamine) at 0.5 to 1.5% (at doses ranging from 0.06 to 5 µl/plate); Saccharide Isomerate and water trade name material (MW of 20,000 Da; Osidic composition: rhamnose-glucose-galactose-galacturonic acid-*N*-acetylglucosamine) at doses up to 5000 µg/plate; Saccharide Isomerate and water trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-*N*-acetylglucosamine) at doses up to 5000 µg/plate; and Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: galactose-*N*-acetylglucuronic acid (GuINAcA)/3-acetylated *N*-acetylglucuronic acid (3OAc-GuINAcA)) at doses up to 5000 µg/plate.

The micronucleus test was used to evaluate the genotoxicity of the dried extract of a trade mixture containing 25 to 35% Anhydroxylitol. Mice received a dose of ≤2000 mg/kg/d (route of administration not specified) for 2 d 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 and 30 females) and 60 C57BL mice (30 males and 30 females). 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. In rats, a total of 11 tumors was observed. Tumors were not observed in mice. The great majority of the benign and malignant tumors found in test and control rats were at sites remote from the nape of the neck. It was concluded that it is unlikely that the 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 anti-proliferative effect over the range of concentrations tested (1 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 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, when applied for 4 h using a semi-occlusive patch. 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% (actual concentration = 17.5%), the test substance did not induce skin sensitization.

Saccharide Isomerate 20% (v/v; MW = 120-400 Da) was evaluated for skin irritation potential (animal species not stated) and was classified as non-irritating and non-corrosive. Saccharide Isomerate (20% v/v; MW = 120-400 Da) was also evaluated for skin irritation potential in a repeated application test involving guinea pigs. Results were negative for skin irritation or corrosion.

In an occlusive patch test involving human subjects (number not stated), Saccharide Isomerate (20% v/v; MW = 120-400 Da) was non-irritating and non-corrosive to the skin. A Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-*N*-acetylglucosamine) was applied for 24 h to the skin of 10 subjects in an occlusive patch test. Test concentrations ranging from 0.5 to 1.5% did not induce skin irritation. In a 48-h occlusive patch test involving 11 subjects, a Saccharide Isomerate and water trade name material (MW of 20,000 Da; Osidic composition: rhamnose-glucose-galactose-galacturonic acid-*N*-acetylglucosamine) results were negative for skin irritation potential at concentrations of 0.5 to 1.5%. The same concentrations of a Saccharide Isomerate and water trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-*N*-acetylglucosamine) did not cause skin irritation in a 24-h occlusive patch test involving 10 subjects. A Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: galactose-*N*-acetylglucuronic acid (GuINAcA)/3-acetylated *N*-acetylglucuronic acid (3OAc-GuINAcA)) was evaluated for skin irritation potential in a 48-h occlusive patch test involving 11 subjects. There was no evidence of skin irritation at concentrations ranging from 0.5 to 1.5%.

Skin sensitization was not observed in a maximization test (animals) on 20% (v/v) Saccharide Isomerate (MW = 120-400 Da). An HRIPT involving 213 subjects was used to evaluate the skin irritation and sensitization potential of an eye cream containing 2.75% Saccharide Isomerate (MW not stated). The product did not have dermal irritation or sensitization potential in this study. The skin sensitization potential of a Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: glucuronic acid-mannose-galactose-galacturonic acid-*N*-acetylglucosamine) was evaluated in an HRIPT involving 100 subjects. The material was non-irritating and non-sensitizing at test concentrations of 0.5 to 1.5%. In an HRIPT involving 102 subjects, a Saccharide Isomerate and water trade name material (MW of 20,000 Da; Osidic composition: rhamnose-glucose-galactose-galacturonic acid-*N*-acetylglucosamine) was also non-irritating and non-sensitizing at the same test concentrations. The skin sensitization potential of a Saccharide Isomerate and water trade name material (MW of 15,000 Da; Osidic composition: galacturonic acid-*N*-acetylglucosamine) was evaluated in another HRIPT involving 109 subjects. The induction concentration is 0.9%, but the challenge concentration is unknown. Neither skin irritation nor allergenicity was noted. An HRIPT (100 subjects) evaluating the skin sensitization potential of a Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: galactose-*N*-acetylglucuronic acid (GuINAcA)/3-acetylated *N*-acetylglucuronic acid (3OAc-GuINAcA)) involved induction concentrations of 0.5 to 1.5% (challenge concentration unknown). There was no significant reaction of contact allergy.

Results were negative in a study evaluating the photosensitization/phototoxicity potential of Saccharide Isomerate (20% v/v; MW = 120-400 Da) in guinea pigs (number not stated). The phototoxicity of a Saccharide Isomerate and water trade name material (MW >1.4 MDa; Osidic composition: galactose-*N*-acetylglucuronic acid (GuINAcA)/3-acetylated *N*-acetylglucuronic acid (3OAc-GuINAcA)) was

evaluated in an in vitro assay. The test substance (contained 0.5 to 1.5% Saccharide Isomerate) was evaluated for cytotoxicity at concentrations up to 1000 µg/ml in the presence of UVA. Results were negative.

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. The ocular irritation potential of an eye cream containing 2.75% Saccharide Isomerate (MW not stated) was evaluated using 53 female subjects. The eye cream did not have the potential for causing ocular irritation. Saccharide Isomerate (20% v/v; MW = 120-400 Da) was practically non-irritating to the eyes (number of animals and species not stated) in an ocular irritation study.

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 (containing mostly glucose and 0.07% Psicose), induced urticarial lesions. Psicose yielded a positive skin reaction when applied at a dose of 21.8 µg.

In a risk assessment for dermal exposure to 8 product types that was performed by the Australian Industrial Chemicals Scheme, 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.

Discussion

This assessment reviews the safety of 7 saccharides/saccharide derivatives as used in cosmetic formulations. The Panel concluded that the data included in this review are sufficient for determining the safety of these ingredients as reportedly used in cosmetics. All of the ingredients reviewed in this safety assessment are hygroscopic saccharides or saccharide derivatives. The Panel noted data on Saccharide Isomerate with varying molecular weights (lower MW range: 120 to 400 Da; higher MW of 15,000 Da, 20,000 Da, or >1.4 MDa). The lower-molecular weight Saccharide Isomerate consists primarily of glucose and fructose. In the absence of 28-day dermal toxicity data and developmental and reproductive toxicity data, the Panel noted that any concerns relating to these toxicity endpoints are mitigated based on the predominance of these 2 constituents. Furthermore, the Panel agreed that any concerns relating to this endpoint are also mitigated for the higher-molecular weight Saccharide Isomerate, as it would not be expected to be percutaneously absorbed. Thus, the absence of safety concerns relating to Saccharide Isomerate can be expanded to be inclusive of all of the saccharide/saccharide derivatives that are evaluated in this safety assessment.

Anti-melanogenic activity of Anhydrogalactose in B16F10 melanoma cells and human epidermal melanocytes was observed in in vitro experiments. However, the Panel noted that the high exposure concentrations (much higher than would be observed from cosmetic use) in these in vitro studies was not predictive of in vivo effects following exposure via cosmetic use. Furthermore, the Panel agreed that skin lightening is not a cosmetic effect and that manufacturers should be diligent about ensuring that this effect would not be caused by cosmetic products.

The issue of incidental inhalation exposure from the use of Anhydroxylitol in cosmetic products (fragrance preparations) was discussed by the Panel. The Panel noted that in aerosol products, most droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredient is used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at https://www.cir-safety.org/cir-findings.

Finally, the Panel expressed concern about heavy metals that may be present in any of the ingredients that are being reviewed in this safety assessment. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

Conclusion

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 7 ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment:

Anhydrogalactose*
Anhydroglucitol
Anhydroxylitol
Arabinose*
Psicose*
Saccharide Hydrolysate
Saccharide Isomerate

*Not reported to be in current use. 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 this group.

Author's Note

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