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Safety Assessment of Mannitol, Sorbitol, and Xylitol as Used in Cosmetics

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Abstract

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Mannitol, Sorbitol, and Xylitol as used in cosmetics. These ingredients are reported to function as humectants, skin-conditioning agents, or flavoring agents. The Panel considered the available data and concluded that these sugar alcohol ingredients are safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Keywords

Cosmetics, Ingredients, Safety, Mannitol, Sorbitol, Xylitol, Expert Panel for Cosmetic Ingredient Safety, Cosmetic Ingredient Review

Introduction

This is a safety assessment of Mannitol, Sorbitol, and Xylitol as used in cosmetic formulations. These 3 ingredients are all simple sugar alcohols and are in that way, structurally similar to one another; therefore, they are being reviewed together in this assessment. Each has several functions listed in the web-based *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*), but all three are reported to function as humectants, skin-conditioning agents, or flavoring agents (Table 1).[1]

The US Food and Drug Administration (FDA) has affirmed that Sorbitol is a direct food substance that is generally recognized as safe (GRAS) for human consumption [21CFR184.1835], and Xylitol is approved for use as a direct food additive [21CFR172.395]. Additionally, Mannitol is GRAS as a nutrient and/or dietary supplement for animals when used in accordance with good manufacturing or feeding practice [21CFR582.5470]. Because these ingredients are affirmed GRAS substances and/or direct food additives, systemic toxicity via the oral route will not be the focus of this safety assessment. Although oral exposure data are included in this report, the primary focus of this safety assessment is topical exposure and local effects.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the Cosmetic Ingredient Review (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.

Much of the data included in this safety assessment was found on the US FDA, European Chemicals Agency (ECHA), and World Health Organization (WHO) websites.[2–6] Data summaries are available on the respective websites, and when deemed appropriate, information from the summaries has been included in this report.

Chemistry

Definition and Structure

Mannitol, Sorbitol, and Xylitol are organic compounds that are typically derived from a sugar by reduction.[7] These

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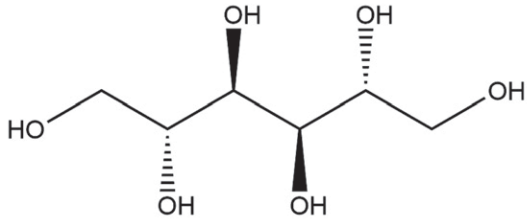
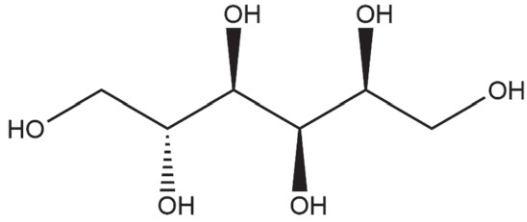
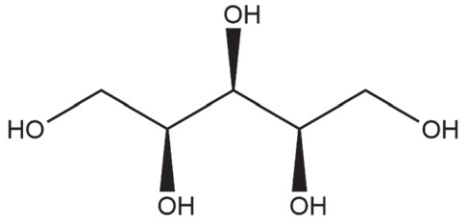
Table 1. Definitions, Idealized Structures, and Functions of the Ingredients in This Safety Assessment.[1, CIR staff]

Ingredient CAS No.	Definition & Structure	Function(s)
Mannitol 69-65-8 87-78-5	Mannitol is the hexahydric alcohol that conforms to the formula: 	Binders; Flavoring Agents; Humectants; Skin-Conditioning Agents- Humectant
Sorbitol 50-70-4	Sorbitol is the hexahydric alcohol that conforms to the formula: 	Flavoring Agents, Fragrance Ingredients, Humectants; Skin-Conditioning Agents- Humectant
Xylitol 87-99-0	Xylitol is the pentahydric alcohol that conforms to the formula: 	Deodorant Agents; Flavoring Agents; Humectants; Skin-Conditioning Agents- Humectant

ingredients occur naturally; however, they are most commonly obtained industrially by the hydrogenation of sugars. The ingredients in this group are all simple sugar alcohols and are in that way, structurally similar. The definitions of the ingredients included in this review, as given in the *Dictionary*, are provided in Table 1. Mannitol and Sorbitol are differentiated solely by the relative orientation of their hydroxyl groups, while Xylitol differs in chain length (Figure 1).

Physical and Chemical Properties

Mannitol, Sorbitol, and Xylitol are white, water-soluble powders or granules (Table 2).[8–10] Although Mannitol and Sorbitol are stereoisomers, the two sugar alcohols differ in melting points and water solubility.

Method of Manufacture

The methods below are general to the production and purification of Mannitol, Sorbitol, and Xylitol; no methods specific to cosmetic ingredient manufacture were found in the literature or submitted as unpublished data.

Traditional synthesis of Mannitol and Sorbitol involves the high-pressure hydrogenation of fructose/galactose mixtures in an aqueous solution.[7] When using this method, Raney nickel is used as a catalyst. Alpha-fructose is converted to Mannitol, and beta-fructose and glucose are converted to Sorbitol. The hydrogenation of a 50:50 fructose/galactose mixture generally results in a 25:75 mixture of Mannitol and Sorbitol. Sorbitol itself can also be produced via similar glucose hydrogenation methods.[11] Glucose from wet milling plants is used as the feedstock for the Sorbitol production. The glucose solution is hydrogenated inside of a batch reactor using a nickel or ruthenium catalyst. After the reaction, the catalyst is recovered by filtering the product slurry. The Sorbitol solution is then purified via ion exchange chromatography and filtration through activated charcoal.

Xylitol can be produced synthetically by first extracting xylose from hemicellulose by acid-catalyzed hydrolysis.[7] The xylose is hydrogenated at 80°C–140°C and hydrogen pressures up to 50 atm, in the presence of Raney nickel. The Xylitol solution that is formed undergoes purification via chromatography, followed by concentration and crystallization of the product.

Biosynthetic mechanisms have also been described to produce both Mannitol and Xylitol. Mannitol is produced naturally by many organisms such as bacteria, yeast, fungi, algae, and lichens.[7] Lactic acid bacteria (LAB) have the ability to convert fructose molecules into Mannitol molecules. For example, three fructose molecules can be converted into two Mannitol molecules and one molecule each of lactic acid, acetic acid, and carbon dioxide. The same yield

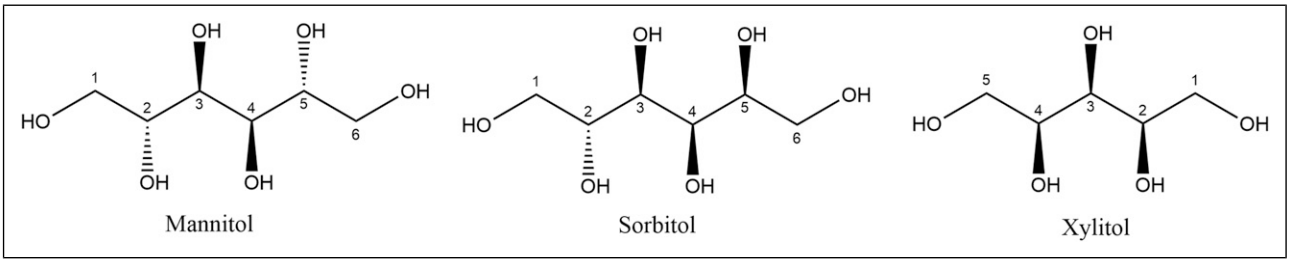


Figure 1. Mannitol, Sorbitol, and Xylitol.

Table 2. Chemical Properties of Mannitol, Sorbitol, and Xylitol.

Property	Value	Reference
Mannitol		
Physical Form	crystalline powder or free-flowing granules	8
Color	white	8
Odor	odorless	8
Molecular Weight (g/mol)	182.172	8
Specific Gravity (@ 20°C)	1.52	8
Melting Point (°C)	168	8
Boiling Point (°C)	290 - 295	8
Water Solubility (g/l @ 25°C)	216	8
log K_{ow}	−3.10	8
Disassociation constants (pKa @ 25°C)	13.50	8
Sorbitol		
Physical Form	crystalline powder, granules	9
Color	white	9
Molecular Weight (g/mol)	182.172	9
Specific Gravity (@ 20°C)	1.489	9
Vapor Pressure (mmHg@ 25°C)	9.9×10^{-9}	9
Melting Point (°C)	111	9
Boiling Point (°C)	295	9
Water Solubility (g/l @ 25°C)	2750	9
log K_{ow}	−2.20	9
Disassociation constants (pKa @ 25°C)	13.6	9
Xylitol		
Physical Form	crystalline powder	10
Color	white	10
Molecular weight (g/mol)	152.146	10
Vapor Pressure (mmHg @ 25°C)	2.47×10^{-3}	10
Melting Point (°C)	93.5	10
Boiling Point (°C)	216	10
Water Solubility (g/l @ 20°C)	642	10
log K_{ow}	−2.56	10

can be formed from two fructose and one glucose molecule. Examples of homofermentative LABs include *Streptococcus mutants* and *Lactobacillus leichmanii*. These homofermentative bacteria produce minimal amounts of Mannitol from glucose most often when bacteria are defective in lactate dehydrogenase activity.[12] Heterofermentative LAB, however, produce Mannitol in larger quantities, using fructose as an electron acceptor and reducing it to Mannitol using the enzyme mannitol-2-dehydrogenase. In addition, the yeast *Zygosaccharomyces rouxii* ferments sugars or sugar alcohols such as glucose, sucrose, fructose, or sorbitol, leading to the production of Mannitol. [21CFR180.25]

In addition, certain yeast strains have the ability to yield large amounts of Xylitol.[7] The genus *Candida* are known to be the best Xylitol producers. In a study, *Candida guilliermondii* and *Candida tropicalis* produced 77.2 g Xylitol from 104 g xylose via high cell densities and a defined medium under aerobic conditions.

Natural extraction is also a method in which Mannitol can be obtained, as Mannitol is found in numerous plants.[7] Traditionally, Mannitol is extracted by a process called Soxhlet extraction. This method involves using ethanol, water, and methanol to steam and hydrolyze the crude material. The resulting Mannitol is then recrystallized from the extract. Natural extraction can also occur via the use of supercritical and subcritical fluids. The super-/sub-critical fluid is pumped through the crude material to extract Mannitol. Then the fluid is simply evaporated to reveal a pure product.

Impurities

Specifications for these sugar alcohols, as used in foods, are given in the *Food Chemicals Codex*.[13] According to specifications, the amount of lead and nickel are not allowed to exceed 1 mg/kg when formulated for use in food. In addition, Xylitol must not exceed 1% of other polyols. According to the Joint FAO/WHO Expert Committee on Food Additives (JECFA), these ingredients should not be comprise more than 0.1% sulfated ash, 100 mg/kg sulfates, 2 mg/kg nickel, or 1 mg/kg lead.[2,4,5]

Natural Occurrence

Mannitol. Mannitol can be found in marine algae, in vegetables such as pumpkins, celery and strawberries, and in the exudate of shrubs and trees, such as the manna ash and olive trees.[14]

Sorbitol. Sorbitol occurs naturally in mountain ash berries and other plants that are part of the Rosaceae family.[15]

Xylitol. Xylitol is found in many plants, including oats, berries, beets, sugar cane, cornhusks, and birch.[16]

Use

Cosmetic

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

According to 2019 VCRP data, Sorbitol has the highest frequency of use, with a total of 1,976 formulations.[17] Sorbitol is most commonly used in moisturizing products (269 formulations), face and neck products (217 formulations), and bath soaps and detergents (205 formulations). Xylitol is reported to have 472 uses, 290 of which are leave-on formulations. Mannitol has a frequency of use of 404 formulations, 104 of which are face and neck products. The results of the concentration of use survey conducted by the Council indicate Sorbitol also has the highest concentration of use; it is used at up to 70% in dentifrices.[18] The highest concentration of use reported for products resulting in leave-on dermal exposure is 60.5% Mannitol in other skin care preparations. Further use data are described in Table 3.

Incidental ingestion and mucous membrane exposure can occur via the use of dentifrices containing Mannitol, Sorbitol, or Xylitol at concentrations up to 4.1, 70, and 14%, respectively.[17,18] Additionally, Sorbitol is used in hair sprays and could be incidentally inhaled; concentrations of these formulations have not been reported. In practice, most of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles <10 μm compared with pump sprays.[19,20] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract, and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[21,22] Mannitol and Sorbitol were reportedly used in face powders at concentrations up to 0.2 and 3.6%, respectively, and could be incidentally inhaled.[18] Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the air.[23–25]

Mannitol, Sorbitol, and Xylitol are not restricted from use in any way under the rules governing cosmetic products in the European Union.[26]

Non-Cosmetic

Mannitol. In the US, Mannitol is a food additive permitted in food or in contact with food on an interim basis pending additional study. [21CFR180.25] Levels may not exceed 98% in pressed mints and 5% in all other hard candy and cough drops, 31% in chewing gum, 40% in soft candy, 8% in confections and frostings, 15% in non-standardized jams and jellies, and at levels less than 2.5% in all other foods. Mannitol is also used as an indirect food additive in substances for use as components of coatings. [21CFR175.300] In addition, Mannitol can be used as a nutritive sweetener, anticaking agent, lubricant and release agent, flavoring agent, stabilizer, thickener, surface-finishing agent, and texturizer. When it is reasonable that daily consumption could result in ingestion of 20 grams of Mannitol, the food must bear the statement, "excess consumption may have a laxative effect." Mannitol is GRAS for animals as a nutrient and/or dietary supplement when used in accordance with good manufacturing or feeding practice. [21CFR582.5470] Mannitol is known to reduce the crystallization of sugars, therefore increasing its shelf life.[7]

In medicine, Mannitol can be used as an osmotic diuretic used to prevent and treat acute renal failure and promote the

Table 3. Frequency (2019) and Concentration (2018) of Use.

	# of Uses[17]	Max Conc of Use (%)[18]	# of Uses[17]	Max Conc of Use (%)[18]	# of Uses[17]	Max Conc of Use (%)[18]
	Mannitol		Sorbitol		Xylitol	
Totals*	404	0.000063 – 60.5	1976	0.00007 – 70	472	0.013 – 14
Duration of Use						
Leave-On	337	0.000063 – 60.5	1177	0.0005 – 20	290	0.013 – 2
Rinse-Off	66	0.023 – 20	783	0.00007 – 70	181	0.05 – 14
Diluted for (Bath) Use	1	NR	16	0.02 – 2.5	1	NR
Exposure Type						
Eye Area	46	0.00008 – 0.1	139	0.00044 – 4.9	27	NR
Incidental Ingestion	5	0.4 – 4.1	105	1.1 – 70	113	0.06 – 14
Incidental Inhalation-Spray	117[a]; 101[b]	0.9[b]	8; 343[a]; 454[b]	1.8 – 3.5[a]; 0.0012 – 32[b]	1; 103[a]; 109[b]	0.15[b]
Incidental Inhalation-Powder	6; 117[a]	0.2; 0.1 – 2.3[c]	2; 343[a]; 4[c]	2.3 – 3.6; 1.8 – 3.50[a]; 0.006 – 20[c]	103[a]; 2[c]	0.042 – 2[c]
Dermal Contact	372	0.000063 – 60.5	1532	0.00044 – 31.9	330	0.013 – 2
Deodorant (underarm)	3[b]	0.12	3[b]	0.0005 – 1.1	27[b]	0.09; 0.013[b]
Hair - Non-Coloring	11	0.023 – 12.5	309	0.00007 – 10.9	28	0.15 – 0.24
Hair-Coloring	1	NR	11	0.006 – 5	NR	0.05
Nail	14	0.015 – 0.03	5	3.5 – 7	NR	NR
Mucous Membrane	17	0.051 – 4.1	337	0.02 – 70	128	0.06 - 14
Baby Products	NR	NR	9	1.4 – 14	7	NR

NR – no reported use.
*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]Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories.
[b]It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[c]It is possible these products are powders, but it is not specified whether the reported uses are powders.

removal of toxic substances from the body.[27] Mannitol is also used during surgery to prevent kidney failure by altering the osmolarity of the glomerular filtrate, flush dye, and reduce cerebral edema. Mannitol can be inhaled to improve the hydration and surface properties of sputum in cystic fibrosis patients. In addition, it is used in the pharmaceutical formulation of chewable tablets and granulated powders.

Sorbitol. In the US, Sorbitol is a GRAS direct food additive used an anti-caking agent, free-flow agent, curing and pickling agent, drying agent, emulsifier, emulsifier salt, firming agent, humectant, nutritive sweetener, sequestrant, stabilizer, thickener, surface-finishing agent, and texturizer. [21CFR184.1835] When used in foods, levels of Sorbitol may not exceed 99% in hard candy and cough drops, 75% in chewing gum, 98% in soft candy, 30% in non-standardized jams and jellies, 30% in baked goods and baking mixes, 17% in frozen dairy desserts, and 12% in all other foods. Sorbitol is approved as an indirect food additive in substances for use as components of coatings [21CFR175.300], and it is GRAS as a substance migrating to food from paper and paperboard products used in food packaging. [21CFR182.90]

Sorbitol may be used in mouthwash and toothpaste, bacterial culture media, and transparent gels.[7,27] Sorbitol may also be used as a cryoprotectant additive in the manufacture of surimi and as a laxative when taken orally or as an enema.

In addition, Sorbitol is a direct food substance that is GRAS for animals when used in accordance with good manufacturing or feeding practice. [21CFR582.5835]

Xylitol. Xylitol is commonly used as a sweetener.[7] Xylitol contains 33% fewer calories and is absorbed at a slower pace than table sugar, allowing it to be a sweetener alternative for those with diabetes. In the US, Xylitol is permitted for direct addition to food for human consumption. [21CFR172.395] This ingredient may be safely used in foods for special dietary uses, provided the amount used is not greater than that required to produce its intended effect.

Toxicokinetics Studies

Dermal Penetration

Mannitol. The skin permeability of [^{14}C]Mannitol was studied in Wistar-derived Alderley Park (AP) and Sprague-Dawley (SD) rats.[28] Both whole-skin and epidermal membranes were used. The whole-skin membranes were removed from the dorsal region of the animal, and the epidermal membranes were obtained using a chemical separation technique. Membranes were mounted on static glass diffusion cells with an exposure area of 2.54 cm^2. Samples were placed in a 30°C water bath. Physiological saline (0.9%) was used as the receptor fluid. The overall mean permeability coefficient

(K_p) values (± standard error (SE)) for whole-skin membranes were 3.23 (±0.17) × 10^{-4} cm/h (n = 178) for the AP rat samples and 2.89 (±0.17) × 10^{-4} cm/h (n = 150) for the SD rat samples. The mean K_p values obtained for epidermal membranes were 2.30 (±0.27) × 10^{-4} cm/h (n = 30) and 0.89 (±0.15) × 10^{-4} cm/h (n = 22) for the AP and SD rat samples, respectively.

Absorption, Distribution, Metabolism, and Excretion (ADME)

Animal

Oral

Mannitol. [^{14}C]-d-Mannitol was given orally to non-fasted rats at a dose of 240 mg/kg.[29] (The method of oral administration was not specified.) Approximately 50% of the radioactivity was recovered in the expired $^{14}CO_2$. No other details regarding this study were reported. In a similar study, the same test substance was given to fasted and non-fasted rats in a dose of 500 mg/kg bw. Method of administration was not stated. Fasted rats oxidized 40% of the dose to $^{14}CO_2$, and non-fasted rats oxidized 68%. In non-fasted rats, 9.75% was stored in the carcass, 1.28% in the liver, and 6.32% was excreted in the urine.

Human

Oral

Mannitol. Mannitol is absorbed from the gastrointestinal tract of man [and animals], and it is not expected to accumulate.[30] The substance is partially metabolized and the remains are excreted in the urine. There is evidence that intestinal flora may convert Mannitol into more readily utilized substances. This transformation may influence the actual amount of Mannitol absorbed and metabolized by the liver.

Ten subjects fasted overnight and were given 28 to 100 g of [U-^{14}C]Mannitol orally as a 5% aqueous solution.[29] Within this dose range, approximately 20% of the given dose was excreted unchanged in the urine. In the first 2 h following ingestion, the radioactivity in the blood increased. Radioactivity remained at a plateau for 2 to 4 h. Expired $^{14}CO_2$ increased for 8 h after ingestion. Oral doses of 40 g or more caused frequent bowel movements, diarrhea, and excretion in the stool of a higher percentage of the dose. Only minimal amounts of radioactivity occurred in the urine and stools 48 h after ingestion.

Sorbitol. Sorbitol administered orally to humans is absorbed and metabolized rapidly through normal glycolytic pathways.[31] The substance is ultimately metabolized into carbon dioxide and water. When 35 g of Sorbitol were given to diabetic and healthy adults, less than 3% of the Sorbitol was excreted in the urine, and an immeasurably small amount was found in the blood.

Xylitol. Xylitol is slowly absorbed from the digestive tract, and 25%–50% is absorbed in the small intestine.[32] Upon entering the hepatic metabolic system, it is further metabolized into fructose-6-phosphate, triose-phosphate, and ribose-5-phosphate.

Five healthy subjects were used to study the absorption of Xylitol.[33] Each subject was intubated with a mercury-weighted polyvinyl tube, passed until the distal orifice was 250 to 300 cm from the teeth. Test substances were given as either 5 or 10 g of Xylitol plus an equal amount of glucose in 200 ml water, or 15 or 30 g of Xylitol plus an equal amount of glucose in 600 ml of water. The test substance also contained polyethylene glycol (PEG) as a nonabsorbable reference marker. After ingestion, ileal fluid was aspirated for 3 to 4 h in a series of samples. Blood samples were collected at 60 and 120 min, and urine samples were collected from 0 to 12 h and from 12 to 24 h after ingestion. Xylitol was nearly completely absorbed in most subjects (72 to 92%). Plasma samples at 1 and 2 h after the test meal showed no Xylitol. Urine analysis showed negligible amounts of Xylitol at 0–12 or 12–24 h after ingestion.

Oral, Inhalation, and Parenteral

Mannitol. The effect of route of administration on bioavailability was compared in a study in which 18 healthy male volunteers were given an oral, inhaled, or intravenous dose of Mannitol.[34] Oral doses consisted of 500 mg Mannitol in 50 ml water and intravenous doses were given as 500 mg of Mannitol in a 10% intravenous solution. The study used a low resistance inhaler provided with 635 mg aerosolized Mannitol. The mean bioavailability of the orally ingested and inhaled Mannitol was 63% and 59%, respectively. Mean urinary excretion over a period of 24 h was approximately 55% for the inhalation and oral doses, and 87% for the intravenous dose.

Toxicological Studies

Acute Toxicity Studies

The acute toxicity studies in animals summarized below are described in Table 4.

Animal

Oral. Several acute oral toxicity studies were performed. When Mannitol was given to rats and mice at doses of up to 5 g/kg bw, all animals survived.[35] Oral LD_{50}s of up to 22 g/kg bw and 17.3 g/kg bw were reported for mice and rats given Mannitol, respectively.[29,34] Sorbitol acute oral toxicity studies resulted in LD_{50}s of 23.2 g/kg bw (male mice), 25.7 g/kg bw (female mice), 17.5 g/kg bw (male rats), and 15.9 g/kg bw (female rats).[36] For Xylitol, the lowest LD_{50}s in mice, rats, and rabbits were reported to be 12.5 g/kg bw, >4 g/kg bw, and 25 g/kg bw, respectively.[32,37] The vehicles used in these acute oral toxicity studies were not provided.

Inhalation. Inhalation studies were performed on animals. In one study, rats (10/group) were given up to 98 mg/kg of

Table 4. Acute Toxicity Studies.

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/ Protocol	LD_{50}/Results	Reference
ORAL						
Mannitol	Mice	5/sex/group	distilled water	0.3, 0.6, 1.2, 2.5, or 5 g/kg via gavage	>5 g/kg/bw	35
Mannitol	Mice	NR	NR	NR	22 g/kg/bw	34
Mannitol	Rats	5/sex/group	distilled water	0.3, 0.6, 1.2, 2.5, or 5 g/kg via gavage	>5 g/kg/bw	35
Mannitol	Rats	NR	NR	NR	13.5 g/kg/bw	34
Mannitol	Rats	10/group	NR	NR	17.3 g/kg/bw	29
Sorbitol	Mouse (male)	NR	NR	NR	23.2 g/kg/bw	36
Sorbitol	Mouse (female)	NR	NR	NR	25.7 g/kg/bw	36
Sorbitol	Rat (male)	NR	NR	NR	17.5 g/kg/bw	36
Sorbitol	Rat (female)	NR	NR	NR	15.9 g/kg/bw	36
Xylitol	Mouse	NR	NR	NR	25.7 g/kg/bw	37
Xylitol	Mouse	NR	NR	NR	12.5 g/kg/bw	37
Xylitol	Mouse	NR	NR	NR	22 g/kg/bw	37
Xylitol	Rat	10/group	5% gum acacia solution	up to 4 g/kg/bw; gavage	>4 g/kg/bw	32
Xylitol	Rat	NR	NR	NR	14.1 g/kg/bw	37
Xylitol	Rat	NR	NR	NR	17.3 g/kg/bw	37
Xylitol	Rabbit	NR	NR	NR	25 g/kg/bw	37
INHALATION						
Mannitol	Rats	10/group	NR	≤98 mg/kg; observation for 14 days after 1 h exposure	No deaths. Over the 14-day observation period, there was a reduction of body weight gain (42% lower than controls, 24% lung/bronchi weight decrease, arterial mural mineralization in the lung/bronchi (4/10), inflammatory cells in nasal turbinates (4/10), loss of cilia in trachea (6/10). These effects were seen at 98 mg/kg/d.	34
Xylitol	Mice	6	Water	Mice were exposed to aerosolized Xylitol (5%) for 150 min in an exposure chamber	Well tolerated by mice with no significant effects on the airway physiology or composition of airway inflammatory cells	38

Mannitol via inhalation for 1 h.[34] No other details regarding study methods were reported. Over the 14-d observation period, a reduction of body weight gain was observed in males. Decreases in lung/bronchi weight, as well as effects on the respiratory tract, were observed in both male and females. In a different study, six mice were exposed to aerosolized Xylitol (5%) in water for 150 min. No adverse effects were reported.[38]

Human

Inhalation. In a study involving humans, 10 subjects were exposed to 1 (2–10 min exposure time), 5 (15–33 min exposure time), or 10 ml (30–49 min exposure time) of 5% Xylitol.[38] Xylitol was prepared by adding 5 g of crystal sugar to 100 ml of sterile water. Subjects were exposed to aerosolized saline as a control. The mass median aerodynamic diameter of the aerosol was 1.63 µm with a geometric standard deviation (GSD) of 1.71 µm. 50% of the subjects reported a stuffy nose after administration of the highest dose level. Cough, chest tightness, and phlegm production was among the other symptoms reported by subjects. No effects regarding electrolytes, lung function, osmolarity, or bronchoalveolar lavage were observed.

Short-Term Studies

Details of the short-term, subchronic, and chronic toxicity studies summarized below are provided in Table 5.

Dermal. A 30-d dermal study was performed on 4 groups of 5 female albino rabbits.[39] Sorbitol (30% in equal parts of water and propylene glycol; 0.5 ml) was applied to an area of 10 cm × 10 cm on the right flank of the animal. No macroscopic changes were noted. Microscopic examination after 10 days of treatment revealed moderate acanthosis with cellular vacuolization and a thinning out of collagen fibers of the superficial portions of the dermis.

Oral. Multiple short-term studies were available for this ingredient group. No adverse effects were reported when B6C3F1 mice (groups of 5/sex) were fed diets containing up to 10% Mannitol for 14 d.[35] Studies using rats were also performed. Groups of 5 F344/N rats/sex were fed diets containing 0.6, 1.25, 2.5, 5, or 10% Mannitol for 14 d. No deaths were reported, and all groups had similar increases in body weight. In a study involving Sorbitol, two adult mongrel dogs (one male and one female) were given Sorbitol (90% w/vol in aqueous solution) at doses of 0.675 and 1.35 g/kg bw.[36] Doses were given three times daily for 3 d. At the highest dose, the stomach appeared hyperemic. No evidence of hepatotoxicity was observed when Sprague-Dawley rats (20 rats/sex/dose) were given Xylitol via gavage for 14 d.[40] Rats were dosed with 0, 2.5, or 5 g/kg/d, or with a dose of 1.25 g/kg/d, followed by 10 g/kg/d.

Inhalation. An inhalation study was performed using Sprague-Dawley rats for 7 d (5/sex/dose).[6] When 5 or 9 mg of Mannitol/l of air was administered for 120–240 min/d, no effects were reported. In a similar study, CD-1 rats (10/sex/dose) were given 0, 0.9, 2.5, or 6.9 mg/kg/d Mannitol via a nose-only apparatus for 2 wk. No significant treatment related effects were observed. When Beagle dogs (3/sex/group) were dosed for 2 wk with up to 197 mg/kg/d Mannitol, spongy and froth-filled lungs, lung congestion/ hemorrhage, and pigment in the submandicular lymph node was observed. At all dose levels (25, 100, and 197 mg/kg/d Mannitol), peribronchiolar infiltration and foamy alveolar macrophages were apparent. In a similar study, Beagle dogs (3/sex/group) were given either saline (control) or aerosolized Xylitol formulated with water (4 mg/l) for 15, 30, or 60 min.[42] Animals were dosed for 14 consecutive days. All animals survived to their scheduled sacrifice and no statistically significant difference among exposed and control groups were observed in body weights or food consumption. No other signs of toxicity were observed.

Subchronic Toxicity Studies

Oral. Groups of 10 B6C3F1/N mice/sex were fed diets containing 0, 0.3, 0.6, 1.2, 2.5, or 5.0% Mannitol for 13 wk.[35] Mean body weight gains were higher than controls in all dose groups except for males given 5.0% Mannitol. No other adverse effects were observed. In a similar study, F344 rats (groups of 10/sex) were given diets containing 0, 0.3, 0.6, 1.25, or 5% Mannitol for 13 wk. Mean body weight gains of the high-dose group males were 9.6% lower compared to controls. Mean body weight gains in all other groups were similar to the control group. No compound-related clinical signs were observed. Rats (16/group) were given 0, 10, or 20 g/kg/d of Xylitol in the diet for 13 wk.[32,37] Slightly reduced weight gains and transient diarrhea was observed at the highest dose level. Rats (number of animals was not provided) were given Xylitol (0.5 or 1.73 g/kg) via gavage for 90 d.[37] No effects were observed at the 0.5 g/kg dose level, however, reduced sleep and activity of animals was recorded after treatment with 1.73 g/kg. Diarrhea and slight weight gain was observed in a different study involving rats (number of animals not provided) given Xylitol at up to 1.73 g/kg via gavage for 90 d.[32] Transient diarrhea and soft stools were also observed in a study using monkeys given 1, 3, or 5 g/kg/d Xylitol for 13 wk (number of animals was not reported).[41] No other adverse effects were reported.

Chronic Toxicity Studies

Oral. Female Sprague-Dawley rats were given Mannitol at concentrations of 0, 1, 5, or 10% for 27 mo in the diet.[29] The number of rats used in the study was not stated. The mortality of the rats receiving 10% Mannitol was 68%. No other effects were reported in the Mannitol exposure groups. Although the mortality rate in the control group was not provided, the authors of the study did not attribute deaths to Mannitol exposure. Fifteen male Wistar rats were given Sorbitol in the diet at concentrations of 10 or 15% for 17 mo.[36] No negative effects on weight gain, reproduction, or histopathological appearances of the main organs were observed. In a different study, Beagle dogs (8/sex/dose) were given 0, 2, 5, 10, or 20% Xylitol in their diet for 2 yr.[41] Biochemical investigations yielded results within the usual biological range, however, during the first year, a slightly elevated serum alkaline phosphatase and serum protein value was observed in the highest dose group.

Inhalation. A study using Beagle dogs (4/sex/group) was performed for 26 wk using 0, 43, or 197 mg/kg/d Mannitol, via inhalation.[6] Animals were exposed to the test substance for 120 min/d. Coughing occurred throughout and after the study in the high-dose group, and during the first week in the mid-dose group. Minimal laryngeal ulceration and sinus histiocytosis in the mediastinal lymph node were observed in the high-dose group. No other treatment related effects were noted. In a different study, Mannitol given to dogs (number of animals was noted stated) via inhalation at up to 834 mg/kg/d for 26 wk caused coughing during and immediately after dosing.[34] Coughing primarily occurred early in the treatment phase, and then reduced down to a minimum. Salivation and

Table 5. Repeated Dose Toxicity Studies.

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Results	Reference
			DERMAL			
Sorbitol	4 groups of 5 female albino rabbits	30 days	water and propylene glycol	30%; a dose of 0.5 ml was applied to shaved skin and covered with an occlusive patch	No macroscopic changes were noted. Microscopic evaluation after 10 days of treatment displayed moderate acanthosis with cellular vacuolization and a thinning out of collagen fibers of the superficial portions of the dermis.	[39]
			ORAL			
Mannitol	B6C3F1 Mice (5/sex)	14 days	Feed	0.6, 1.25, 2.5, 5 or 10%	All animals survived the study and no compound-related effects were observed.	[35]
Mannitol	B6C3F1 Mice (10/sex)	13 wks	Feed	0, 0.3, 0.6, 1.2, 2.5 or 5%	Mean body weight gain was higher than controls in all dose groups except for males given 5.0% Mannitol. All animals survived the duration of the study and no compound-related effects were observed.	[35]
Mannitol	F344/N Rats (5/sex)	14 days	Feed	0.6, 1.25, 2.5, 5, 10%	Necropsies were performed on all animals. No animals died, and all groups had similar increases in body weight. Females fed diets containing 10% Mannitol gained less weight than females fed a lower concentration. Two out of 5 of the male rats given 10% Mannitol had diarrhea on days 4 to 6. No gross lesions were observed	[35]
Mannitol	F344/N Rats (10/sex)	13 wks	Feed	0, 0.3, 0.6, 1.25, 5%	Mean body weight gains of the top-dose group males were depressed by 9.6% relative to the controls. Mean body weight gains in all other groups were similar to the control group. All animals survived the study and no compound-related clinical signs were observed.	[35]
Mannitol	Wistar-derived SPF albino Rats (# of animals not provided)	94 wks	Feed	0, 1, 5, 10%	Body weights were generally decreased by 5-7% in the medium and high dose male rats. A low incidence of benign thymomas was present in female rats (2 thymic tumors in female controls, 6 in each of the 1 and 5% Mannitol group, and 10 in the 10% Mannitol group). No significant difference in thymomas between treated and control groups were observed in male rats.	[29]
Mannitol	Female Sprague Dawley Rats (# of animals not provided)	27 mos	Feed	0, 1, 5, 10%	The mortality rate of the rats receiving 10% Mannitol was 68%. No other effects were reported in the Mannitol exposure groups. The mortality rate of control rats was not stated. The authors of the study did not attribute deaths to Mannitol exposure.	[29]

(continued)

Table 5. (continued)

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Results	Reference
Sorbitol	Mongrel Dogs (1 male, 1 female)	3 days	Water	0.675, 1.35 g/kg bw (90% w/vol); doses given via stomach tube	At the highest dose, the stomach appeared hyperemic.	[36]
Sorbitol	Wistar Rats (15 males)	17 mos	Diet	10 or 15%	No evidence of deleterious effect on weight gain, reproduction, or histopathological appearances of the main organs. Slight diarrhea was apparent in treated animals.	[36]
Xylitol	Sprague-Dawley Rats (20 rats/sex/dose)	2, 5, or 14 days (gavage)	NR	0, 1.25 then 10 g/kg/d, 2.5 g/kg/d only, or 5 g/kg/d only	No evidence of hepatotoxicity was reported. Serum levels of all parameters measured (glucose, bilirubin, free fatty acids, total lipids, triglycerides, cholesterol, alkaline phosphatases, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, glucose 6-phosphate dehydrogenase) were within normal limits.	[40]
Xylitol	Rats (# of animals not provided)	NR	Feed	10 or 30%	No effect on weight gain, fertility, or histology of the liver, kidneys, or heart.	[37]
Xylitol	8 CD rats/sex/group	13 wks	Feed	0, 5, 10, 20 g/kg/d	At study completion, mean body weights of male and female rats fed Xylitol at 20 g/kg/d and 10 g/kg/d were significantly less than control groups. A slight increase in brain, liver, kidney, heart, spleen, and testes weight was observed in the same groups when expressed as a percent body weight. The test substance was considered to be tolerated well. Slightly reduced weight gains and transient diarrhea were observed at the highest dose levels.	[32,37]
Xylitol	Rats (# of animals not provided)	90 days (gavage)	NR	0.5 or 1.73 g/kg	Reduced sleep and activity of rats was recorded after treatment with 1.73 g/kg. At the 0.5 g/kg dose level, no changes were recorded.	[37]
Xylitol	Monkeys (# of animals not provided)	13 wks (gavage)	NR	1, 3, 5 g/kg/d	Transient diarrhea and soft stools were initially present in the high dose group. No effects relating to behavior, appetite, body weight, organ weight, gross pathology, or microscopic pathology were observed.	[41]
Xylitol	Beagle Dogs (8/sex/dose)	2 years	Feed	0, 2, 5, 10, 20%	Treated animals gained weight more rapidly than controls. Urinary, hematological, and biochemical investigations yielded results within the usual biological range. However, during the first year of treatment, a slightly elevated serum alkaline phosphatase and serum protein values was observed in the 20% Xylitol group. No degenerative changes were reported.	[41]

(continued)

Table 5. (continued)

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Results	Reference
				INHALATION		
Mannitol	Sprague-Dawley Rats (5/sex/dose)	7 days	Air	5 or 9 mg of Mannitol/L of air (exposure of 120-240 minutes/day)	The estimated achieved dose of Mannitol was 573 and 979 mg/kg/d for the low dose and high dose groups, respectively. No treatment-related effects were reported.	[6]
Mannitol	CD-1 Rats (10/sex/dose)	2 wks	Air	0, 0.9, 2.5, and 6.9 mg/kg/d	No significant treatment related effects were observed. An NOAEL of 6.9 mg/kg/d was determined.	[6]
Mannitol	Beagle Dogs (3/sex/group)	2 wks	Air	0, 25, 100, 197 mg/kg/d	Coughing occurred during and after dosing in all treated groups. Spongy (4/6) and froth-filled lung (3/6) were reported in the animals dosed with 197 mg/kg of Mannitol. Lung congestion/hemorrhage was apparent in 2/6 high-dose animals, and pigment in the submandibular lymph node was seen in 3/6 high-dose animals. Peribronchiolar infiltration and foamy alveolar macrophages was observed in all dosed animals. Inflammatory foci and focal hyperplasia were seen in 1/3 high dose female animals.	[6]
Mannitol	Beagle Dogs (4/sex/dose)	26 wks	Air	0, 43, 178 mg/kg/d (0, 0.20, 8.7 mg/L) (120 minutes exposure/day)	Coughing occurred during and after dosing in the high dose group, but only in the first week in the low dose group. Minimal laryngeal ulceration and sinus histiocytosis in the mediastinal lymph node were observed in the high-dose group. No other treatment related effects were noted.	[6]
Mannitol	Dogs (number of animals and strain not reported)	26 wks	Air	up to 834 mg/kg/d	Coughing primarily occurred early in the treatment phase, and then reduced down to a minimum. Salivation and emesis were also observed. Enlargements of the mandibular lymph nodes were observed in 2 out of the 4 treated animals. One out of four treated females given 716 mg/kg Mannitol per day displayed erythrophagocytosis or lymphadenitis, however, this effect was not present in male dogs.	[34]
Xylitol	Beagle Dogs (3/sex/group)	14 days	Water	4 mg/L of either saline (control) or aerosolized Xylitol for 15, 30, or 60 minutes/day	All animals survived to their scheduled sacrifice and no statistically significant difference among exposed and control groups were observed in body weights or food consumption. Additionally, there was no exposure-related change in organ weight, gross pathology lesions, or microscopic lesions.	[42]

emesis were also observed. Enlargements of the mandibular lymph nodes were observed in 2 out of the 4 treated animals. One out of 4 treated females given 716 mg/kg/d Mannitol displayed erythrophagocytosis or lymphadenitis, however, this effect was not present in male dogs.

Developmental and Reproductive Toxicity Studies

Mannitol

Pregnant mice, rats, and hamsters were given oral doses of Mannitol.[29] Method of administration was not specified. Rats and mice were given 1.6 g/kg for 10 d, and hamsters were given 1.2 g/kg for 5 d. No maternal or fetotoxic symptoms were observed. No other details regarding these studies were provided.

Sorbitol

A reproductive study on 30 rats extended over four generations using 10 or 15% Sorbitol in the diet for 17 mo did not reveal any abnormalities.[36] No other details regarding this study were provided.

In a three-generation study, groups of 12 male and 24 female Charles River CD (SD) BR rats were fed a diet containing 0, 2.5, 5, or 10% Sorbitol.[43] After 14 wk of exposure to Sorbitol via diet, rats were mated, and gave rise to litters F_{1a} and F_{1b}. F_{1a} rats were weaned and killed, while 12 male and 24 females of the F_{1b} litter were then mated. Likewise, the resulting F_{2a} rats were killed, and the F_{2b} litter was mated, giving rise to litters F_{3a} and F_{3b}. No clinical signs of toxicity were observed to treatment in the F_0, F_{1b}, or F_{2b} rats. Reduced weight gain was recorded in response to Sorbitol in both sexes at the 10% level. This effect was more prominent in females, and in the F_0 generation than in the F_{1a} or F_{2b} generation. Cecal enlargement was consistently observed during necropsy of all treated rats. Significant increases in serum calcium were observed in F_0 males and females exposed to 10% Sorbitol, and in F_{1b} males exposed to either 5 or 10% Sorbitol. Variations in triiodothyronine (T_3), thyroid stimulating hormone (TSH), and gonadal weights were observed, but were considered to have no toxicological significance due to a lack of consistency. No adverse effects were observed after microscopic evaluation of lesions of the gonads and other selected tissues.

Administration of 1600 mg/kg/bw of Sorbitol to pregnant rabbits for 13 d (days of gestation and route of administration not stated) had no effects on maternal or fetal survival.[44] The number of abnormalities seen in either soft or skeletal tissues of the test groups was similar to controls. No other details regarding this study were provided.

Xylitol

A three-generation study was conducted in NMRI mice.[2] Twelve females and three males were given 20% Xylitol. No abnormalities of condition or behavior were observed in the successive generation. Gross examination revealed no abnormalities attributable to Xylitol treatment. CD rats (20/sex/group) were given 2, 5, 10, or 20% Xylitol in the diet in a three-generation study.[32] A control group received 20% rice starch, and a comparison group received 20% sucrose. At the low diet levels, food intake was comparable with controls in all generations. At the 10 and 20% level, food intake was slightly lowered. No treatment related effects were noted regarding mating performance or pregnancy rate. Cecal enlargement was noted at terminal necropsy of F_{2b} parents of both sexes in all Xylitol-treated groups. At the 20% level, lower values for viable litter size at birth were noted. There was no indication of a treatment effect on occurrence of terata. No histopathological abnormalities were noted. In a different study, female rabbits (20/group) were given 0, 2, 5, 10, or 20% Xylitol in the diet on days 7–19 of gestation. Male rabbits were left untreated. No reproductive, teratogenic, or embryotoxic effects were observed.

Genotoxicity

In Vitro

Mannitol. According to studies conducted by the US National Toxicology Program (NTP), Mannitol was non-mutagenic in a bacterial reverse mutation assay (*Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537; 10 mg/plate), mouse lymphoma $TK^{+/-}$ assay, or in a sister chromatid exchange assay in Chinese hamster ovary (CHO) cells (doses not stated).[45,46] Mannitol was non-mutagenic in a host-mediated assay using *S. typhimurium* G46 and TA1530 and *Saccharomyces cerevisiae* strain D3, in a cytogenic assay in rat bone marrow, or in human W1-38 cells at concentrations of 2, 20, and 200 μg/ml.[47] In a different study, the mutagenic potential of Mannitol (0.3–10,000 μg/plate) was studied in an Ames test using *S typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100, and in *Escherichia coli* WP2 (uvrA), with and without metabolic activation.[48] The test substance was considered to be non-mutagenic.

Sorbitol. An Ames test performed on Sorbitol using *S typhimurium* strains TA92, TA1535, TA100, TA1537, TA94, and TA98 yielded negative results (with metabolic activation; doses not stated).[49,50] Negative results were also obtained when Sorbitol (5 mg/plate) was used in chromosomal aberration assays using CHO cells and Chinese hamster lung fibroblasts without metabolic activation. Sorbitol was not genotoxic in host-mediated assays of mutagenicity in mice using *Salmonella* strains G46 and TA1530, and *Saccharomyces cerevisiae* strain D3 as indicator strains. The doses used were not stated in this study.

Xylitol. An Ames test was performed on Xylitol using *S. typhimurium* strains TA100 and TA98 (up to 500 mg/plate; unknown if metabolic activation was used).[51] No detectable mutagenic activity was reported. A different Ames test was

performed using *S. typhimurium* strains TA1535, TA1537, and TA1538, with and without metabolic activation.[32] Cells were exposed to 0, 15.6, 31.25, 62.5, or 125 mg/plate. A two-fold increase in the revertants above background could be observed with *S. typhimurium* TA1538 at the highest concentration level. However, this result could not be reproduced, and the positive control, methylcholanthrene, resulted in a 15-fold increase of the revertant colonies above background. All other strains yielded negative results. A sister chromatid exchange was performed on Xylitol using diploid human fibroblastic cells (HE 2144) and pseudodiploid Chinese hamster lung fibroblast cell line (Don-6) at concentrations of up to 76.1 mg/ml.[37] No induction of sister chromatid exchange was observed in either test system. It is unknown whether or not metabolic activation was used in these studies.

In Vivo

Mannitol. Mannitol was not clastogenic in a mouse bone marrow micronucleus test in which doses of 3000 mg/kg/d Mannitol was administered for 3 d intraperitoneally.[34] Results of a dominant lethal assay in rats at doses of 20, 200, 2000, and 5000 mg/kg of d-Mannitol by gavage were negative.[35] A chromosomal aberration study in rat bone marrow also yielded negative results (doses not stated). No other details regarding these studies were given.

Sorbitol. A chromosomal aberration assay performed in mouse bone marrow yielded negative results.[50] No other details regarding this study were provided.

Xylitol. A mammalian erythrocyte micronucleus test was performed using SPF mice (3/sex/group) according to Organization for Economic Co-operation and Development test guideline (OECD TG) 474.[32] Xylitol was dissolved in phosphate-buffered saline and given to animals via gavage. The doses given were 0, 1820, 3280, and 5333 mg/kg/bw. Smears of the bone marrow of both femora were prepared, and 4,000 erythrocytes per animal were checked for micronuclei. No significant increase of micronuclei containing erythrocytes was observed in the bone marrow of the treated mice.

Carcinogenicity Studies

Details of the carcinogenicity studies summarized below are provided in Table 6.

Mannitol

A diet containing d-Mannitol (98%–100% pure (25 or 50 g/kg)) was given to groups of 50 F344/N rats/sex and 50 B6C3F1 mice of each sex for 103 wk.[14,35] An increased incidence of the dilation of the gastric fundal gland was observed in dosed female rats compared to that of controls. Mild nephrosis characterized by focal vacuolization of the renal tubular epithelium was seen in increased incidence in dosed mice of each sex. The test substance was considered to be non-carcinogenic.

In a different study, 10% Mannitol was given to 50 Wistar rats/group/sex via diet for 104–107 wk.[52] In both sexes, pelvic nephrocalcinosis, which in females was directly associated with pelvic hyperplasia, was noted. No significant increase in tumor incidence was noted. A low incidence of benign thymomas was observed when Wistar-derived SPF albino rats were given 1, 5, or 10% Mannitol in the diet for 94 wk.[29] No other details regarding this study were provided.

Female Wistar rats (100/group) were given diets containing 0, 1, 5, or 10% Mannitol for 30 mo.[29] A slightly increased incidence of tissue masses in the cervix and/or uterus was noted in the treated groups compared to control animals. Evaluation of mortality, behavior, organ and body weights, and subcutaneous tissue masses were similar to controls. In a similar study, female Fischer rats (100/sex/group) were given 0, 1, 5, or 10% Mannitol in the diet for 30 mo. A slight increase in the incidences of tissue masses in the anogenital area, cervix, and uterus were noted in the high-dosed group. Focal medullary hyperplasia and medullary pheochromocytoma was higher in the high-dose group compared to the control group, however, no clear dose response was seen.

Sorbitol

Sprague-Dawley rats (75/sex/group) were given 0 or 20% Sorbitol in the diet for 78 wk.[36] Unilateral and bilateral hyperplasia of the adrenal medulla was increased significantly in dosed animals of both sexes.

Xylitol

Xylitol was fed to 100 mice/sex (strain not stated) in the diet at concentrations of 0, 2, 10, or 20%.[41] Animals were treated for their entire life span. An increased incidence of crystalline calculi was noted in the urinary bladder in male mice treated with 10 or 20% Xylitol. A small number of tumors were found in the transitional epithelium in high-dosed males. All treated animals showed fewer renal tumors than control animals. In a different study, Xylitol was given in the diet to 75 rats/sex (strain not stated), at the same concentrations as above. Rats were fed this diet for the majority of their lifespan. A statistically significant increase in the number of pheochromocytomas was observed in male rats treated with 20% Xylitol ($P < 0.05$) compared to the controls. The total number of tumor-bearing rats was similar between treated and control groups.

Other Relevant Studies

Corneal Healing Promotion

The protective effect of Mannitol on corneal damage caused by benzalkonium chloride (BAC) (a preservative in timolol

Table 6. Carcinogenicity Studies.

Ingredient	Animal (#/group)	Vehicle	Procedure	Results	Reference
Mannitol	50 F344/N rats/sex and 50 B6C3F1 mice/sex	Diet	A diet containing d-Mannitol was given to animals for 103 wks at concentrations of 0, 2.5, or 5%.	Survival and mean body weights of dosed and control male rats and of dosed and control mice of both sexes were similar. High-dose female rats had a statistically significant higher ($P < 0.05$) survival rate than low-dose female rats; however, neither the survival of the low-dose group nor that of the high-dose group was significantly different than that of the controls. Mean body weight gain of treated rats was depressed (<10%) compared to that of the controls. Dilation of the gastric fundal gland was increased in dosed female rats compared to that of the controls. Retinopathy and cataracts were apparent in high-dose male rats and low- and high-dose female rats. Mild nephrosis characterized by focal vacuolization of the renal tubular epithelium was seen in increased incidence in dosed mice of each sex. The test substance was considered to be non-carcinogenic.	[14,35]
Mannitol	50 Wistar rats/group/sex	Diet	In a study examining the toxic potential of erythritol, a control group of animals given diets containing 10% Mannitol for 104 - 107 wks was used.	No significant increase in tumor incidence noted. Treatments were well-tolerated without diarrhea or other side effects. Body weights were significantly below control levels. Survival of the animals was not adversely affected by treatment. In male and female rats, pelvic nephrocalcinosis, which in females was directly associated with pelvic hyperplasia, was noted.	[52]
Mannitol	Wistar-derived SPF albino rats (# of rats not stated)	Diet	Animals were fed a diet containing 0, 1, 5, or 10% Mannitol for 94 wks.	A low incidence of benign thymomas was observed.	[29]
Mannitol	Female Wistar rats (100/group)	Diet	Animals were fed a diet containing 0, 1, 5, or 10% Mannitol for 30 mos.	Slightly increased incidences of tissues masses in the cervix and/or uterus was noted in the treated groups compared to the control. This was considered of no biological importance because of their low overall incidence. Histopathological evaluations of the thymus did not reveal any abnormalities. Overall body weight gain differences between the control and treated groups were slight, and not statistically significant. Evaluation of mortality, behavior, food consumption, urinary chemistry, organ and body weights, and subcutaneous tissue masses were similar to controls.	[29]

(continued)

Table 6. (continued)

Ingredient	Animal (#/group)	Vehicle	Procedure	Results	Reference
Mannitol	Female Fischer rats (100 animals/group)	Diet	Rats were given 0, 1, 5, or 10% Mannitol in the diet for 30 mos.	Slightly increased incidences of tissue masses in the anogenital area, cervix and uterus were noted in the high dosed group compared to the control group. The incidence of uterine masses was well within the expected spontaneous incidence rate for this strain of rats. Focal medullary hyperplasia and medullary pheochromocytoma was higher in the high-dose group compared to the control group, however, no clear dose response was seen. The mean body weights of rats receiving 5 or 10% Mannitol were slightly lower than control rats.	[29]
Sorbitol	75 Sprague-Dawley rats/ sex/dose	Diet	Animals were given Sorbitol (0 or 20%) in the diet for 78 wks.	Unilateral and bilateral hyperplasia of the adrenal medulla was increased significantly for males and females receiving Sorbitol.	[36]
Xylitol	100 mice/sex (strain not stated)	Diet	Mice were fed a diet containing up to 20% Xylitol for their entire life-span.	An increased incidence of crystalline calculi in the urinary bladder was apparent in male mice treated with 10 and 20% Xylitol. A small number of tumors, both benign and malignant, were found in the transitional epithelium in high-dose male mice. All Xylitol-treated animals showed fewer renal tumors than control animals. Hepatocellular tumors were observed in both sexes in all experimental groups, but were more frequent in males; However, male mice treated with Xylitol showed a lower incidence of hepatocellular tumor than control mice. Male mice in the highest Xylitol dosage group displayed an increase in centrilobular degenerative changes in the liver compared to the control group.	[41]
Xylitol	75 rats/sex (strain not stated)	Diet	Rats were fed a diet containing up to 20% Xylitol for the majority of the animals' lifespan.	Unilateral or bilateral pheochromocytomas were observed in a proportion of rats from all groups, including controls. A statistically significant increase in the number of pheochromocytomas was observed in male rats treated with 20% Xylitol ($p < 0.05$) compared to the controls. The total number of tumor-bearing rats was similar between treated and control groups.	[41]

maleate eye drops) was studied using rat debrided corneal epithelium.[53] After corneal epithelium abrasion, eye drops were instilled into rat eyes five times a day. The corneal healing rate and cell viability were higher following treatment with a solution consisting of 0.005% BAC and 0.5% Mannitol than after treatment with BAC alone. After 36 h, corneal wounds of rat eyes instilled with 0.02% BAC solution were 75% healed, while those instilled with 0.02% BAC solution plus 0.5% Mannitol were 90.1% healed. The healing rate constant (k_H) for rat eyes instilled with commercially available timolol maleate eye drops containing 0.5% mannitol was significantly higher than that for eyes instilled with timolol eyedrops alone.

Anti-Inflammatory/Anti-Irritant Effects

The ability of Xylitol to alleviate irritation and inflammation of sodium lauryl sulfate (SLS)-induced acute dermal irritation was studied in 23 male SKH-1 hairless mice per group.[54] The dorsal region skin was exposed to either 5% SLS alone, or a combination of 5% SLS with 8.26% or 16.52% Xylitol. At both concentrations, Xylitol was able to prevent the irritant-induced red blood cell velocity (RBCV) elevation in the dermal capillaries. A decreased lymphocyte number was observed in the epidermis when animals treated with Xylitol and SLS, compared to SLS alone. The addition of Xylitol also effectively decreased myeloperoxidase (MPO) activity in the skin.

Deposition in Bronchoalveolar Lavage Fluid

Sprague-Dawley rats (5/sex) were used in a 7-d inhalation study.[6] Rats were exposed to 5 or 9 mg of Mannitol/l of air for 120 to 240 min/d. Rats were killed after treatment. The amount of Mannitol delivered to the lungs was determined by measuring the amount of Mannitol in the bronchoalveolar lavage fluid (BALF). In the low dose group, the mean Mannitol concentration in the BALF was 36.7 μg/ml in males and 43.6 μg/ml in females. In the high dose group, mean Mannitol concentrations in the BALF were 42 and 33.4 μg/ml in males and females, respectively.

Inhalation studies were performed in rats (13 wk) and dogs (26 wk).[6] In rats, the mean Mannitol level in BALF was 0, 3.8, and 3.2 μg/ml in the control, 12.4 mg/kg/d dosed group, and 21 mg/kg/d dosed group, respectively. In dogs, the BALF Mannitol concentrations were below the level of quantification for both the low (43 mg/kg/d) and high doses (179 mg/kg/d).

Dermal Irritation and Sensitization

Irritation

Xylitol. Xylitol was incorporated at 5% and 10% in both gel and cream formulations through a 60% mixture in ultra-pure water, and administered to New Zealand albino rabbits (3/sex/group).[55] The test substance (0.5 g) was placed on a 2 cm^2 gauze pad and applied to each abraded and intact skin dosing site, and held in place for 4 h with occlusive tape. After patch removal, the degree of erythema and edema was evaluated according to the Draize method. All the tested formulations were classified as non-irritating.

Sensitization

Animal

Mannitol. A Magnusson–Kligman guinea pig maximization test was performed on Pirbright white guinea pigs (number of animals not stated).[56] The test substance was a trade name mixture containing 15% Mannitol and 15% disodium adenosine triphosphate. A 0.5% aqueous dilution of the test substance was used for the intracutaneous induction, and a 10% aqueous dilution of the test substance was used for the epicutaneous induction and challenge. No signs of irritation and skin reactions indicative of an immune response were seen at the readings 24 and 48 h after removal of the challenge patch.

Human

Mannitol. A human repeated insult patch test (HRIPT) was performed on 50 volunteers using a trade name material consisting of 15% Mannitol and 15% disodium adenosine triphosphate.[56] A 10% aqueous dilution of the trade name material was applied to the backs of subjects under an occlusive patch for a total of 9 applications within a 3-wk period. After a rest period of 2 wk, a challenge patch was applied to a previously unexposed area. Readings were taken 24, 48, and 96 h after removal of patches. No skin reactions were noted in any subject during the induction or challenge phase.

Xylitol. An HRIPT involving a product containing 0.115% Xylitol was performed using 119 subjects.[57] During induction, the product was applied neat, under an occlusive patch, for 48–72 h. The amount of material used for testing was not specified. This procedure was repeated for a total of 9 induction applications. The ninth application was followed by a 2-wk rest period, after which, the challenge phase was initiated. A challenge patch was applied to a new test site, and reactions were scored at 48 h and 96 h after patch application. Three individuals displayed low-level reactions (mild erythema) during the induction phase, and one individual displayed a low-level reaction in the challenge phase. The authors concluded that there was no evidence of sensitization to the product tested in this study.

An HRIPT was performed on 110 subjects using a body lotion containing 3% Xylitol.[58] Subjects were given a questionnaire. Based on the responses, 100% of the subjects had self-perceived sensitive skin. During the induction phase, the lotion (0.15 ml) was applied on an occlusive patch, and placed on the skin for 24 h. Subjects returned to the facility at 48-h intervals to have sites evaluated and identical patches applied to the same sites. Following the ninth application, the volunteers were dismissed for a rest period of approximately 10–15 d. For the challenge phase, a patch was applied to a site previously unexposed to the study material, and removed after 24 h. Sites were graded after additional 24-h and 48-h periods. There was no evidence of sensitization to the test material.

Phototoxicity/Photosensitization

Animal

Xylitol. Xylitol (10%) was incorporated into a cream and a gel, and applied to the skin of male Dunkin–Hartley albino guinea pigs.[55] Four animals were used per formulation containing Xylitol, as well as the positive control, and groups of 2 animals were used as negative controls for both the cream and the gel vehicles. Each animal had 4 application sites of approximately 1.5 cm^2 to which aliquots (0.5 g/site) of the test substance or positive control (8-methoxypsoralen (8-MOP)) was applied in duplicate. Sunscreen was placed on the right side of the back to protect from irradiation, while the other side was left uncovered. After application, animals were exposed to long-wave ultraviolet (UVA) light (200 J/cm^2 for 15 min). Test sites were graded at 1, 24, 48, and 72 h after exposure using a Draize scoring system. In animals exposed to 10% Xylitol via cream or gel, 3 out of 4 animals displayed a positive reaction. Phototoxicity was observed in all animals treated with 8-MOP, but no phototoxicity was observed in the gel or cream vehicle control groups. The authors concluded that Xylitol has moderate phototoxic potential at this UVA

dose. However, the chemical structure for Xylitol contains no UV-active chromophore (i.e., UV light absorption, and thus phototoxicity, is not possible for Xylitol). In addition, the study authors indicated that the irradiation used in this study is 100 times higher than the dose that a person could be exposed to on a summer day at noon.

Human

Mannitol. A phototoxicity study was conducted with a trade name mixture consisting of 15% Mannitol and 15% disodium adenosine triphosphate in 10 volunteers.[56] A 10% aqueous solution of the trade name mixture (0.2 ml) was applied under an occlusive patch to two different areas of the forearm, one irradiated and one non-irradiated. After a 24-h exposure, one site was irradiated with UVA light (320–400 nm) for 15 min. Skin reactions were scored immediately after light exposure as well as 24 and 48 h later. No reactions were noted on either the irradiated or non-irradiated test material contact site in any subject.

A photosensitization test was performed on 34 subjects with a trade name mixture consisting of 15% Mannitol and 15% disodium adenosine triphosphate.[56] For 3 wk, six 24-h induction patches were applied containing a 2% aqueous solution of the trade name mixture. Applications were performed in duplicate; one site was subsequently irradiated with UV light (260–400 nm) for 15 min each session. After 2 wk, a challenge patch was applied at virgin sites with and without irradiation. At the challenge phase, no skin reactions were exhibited at either the irradiated site or the non-irradiated site.

Ocular Irritation Studies

In Vitro

Mannitol. Isolated bovine corneas were incubated with Mannitol powder (20%) or imidazole (positive control) at 32°C for 4 h.[6] Opacity was determined by light transmission through the cornea, and permeability was measured by the rate of sodium fluorescein crossing the cornea with a spectrophotometer. A composite score was derived for each cornea based on the opacity and permeability readings. A score below 25 was considered to be non-irritating. The composite scores of Mannitol and imidazole were 0.2 and 142.4, respectively. The test substance was not considered to be an eye irritant.

Animal

Mannitol. Three New Zealand white rabbits were administered 78 mg (0.1 ml) of Mannitol in one eye and observed for irritation for 72 h post administration.[6] Parameters evaluated included corneal capacity, iridial lesions, and conjunctival redness/chemosis. No abnormalities among these parameters were found. The test substance was considered to be non-irritating.

Clinical Studies

Metabolism

Mannitol. Six adults and three adolescents with cystic fibrosis inhaled dry powder Mannitol (400 mg) twice daily for 7 d.[34] On days 1 and 7, administration only occurred in the morning. The reported mean half lives in adults on day 1 and 7 were 6.10 and 5.42 h, respectively. In adolescents, the mean half-lives on day 1 and 7 were 7.29 and 6.52 h, respectively.

Sorbitol. The metabolism of Sorbitol was studied in 6 normal and 8 diabetic adults.[59] Diabetic patients controlled their diabetes symptoms through diet alone. All subjects fasted overnights, emptied their bladders, and had blood collected from the earlobes for glucose and Sorbitol estimations. Dissolved Sorbitol (35 g in 300 ml) was taken orally. Blood draws occurred in half-hour intervals for 2.5 h. For some subjects, urine was collected for 24 h, and feces for 3 d. In normal subjects, Sorbitol did not have a significant effect on blood sugar levels. However, in all diabetic patients, significant increases in blood-sugar concentrations ranging from 9 to 49 mg/100 ml occurred after Sorbitol administration. Neither group had attained measurable levels of Sorbitol in the blood for a prolonged period of time. Excretion of Sorbitol in the urine of all subjects varied between 0.07–0.91 g. The majority of excretion occurred during the first 5 h. No Sorbitol was detected in the urine after 24 h. No unchanged Sorbitol could be detected in the feces of three subjects, and only 10% or less of the administered dose was found in the feces of patients whose gastrointestinal tract had been sterilized by the adequate administration of antibiotics. When 35 g of Sorbitol was given to normal subjects and diabetic patients, less than 3% of the administrated oral dose was excreted in the urine.[36] No other details regarding this study were provided.

Summary

The safety of Mannitol, Sorbitol, and Xylitol as used in cosmetics is reviewed in this assessment. According to the *Dictionary*, these ingredients are all reported to function as humectants, skin-conditioning agents, and flavoring agents. These ingredients have a wide non-cosmetic use in food products. Sorbitol is a direct food substance that is generally recognized as safe (GRAS) for human consumption, and Xylitol is approved for use as a direct food additive [21CFR172.395]. Additionally, Mannitol is GRAS as a nutrient and/or dietary supplement for animals.

According to 2019 VCRP data, Sorbitol is reported to be used in 1,976 formulations, 269 of which are moisturizing products and 217 are face and neck products. Mannitol and Xylitol are reported to be used in 404 and 472 formulations, respectively. The results of the concentration of use survey conducted by the Council, indicated Sorbitol also has the highest concentration of use; it is used at up to 70% in

dentifrices. The highest concentration of use reported for products resulting in leave-on dermal exposure is 60.5% Mannitol in other skin care preparations.

The skin permeability of [^{14}C]Mannitol in Wistar-derived AP rats and SD rats, was studied. The mean K_p values obtained for epidermal membranes were 2.30 (±0.27) x 10^{-4} cm/h (n = 30) and 0.89 (±0.15) x 10^{-4} cm/h (n = 22) for the AP and SD rat samples, respectively. In an oral ADME study, [^{14}C]-d-Mannitol was given to rats. Approximately 50% of the radioactivity was recovered in the expired $^{14}CO_2$. A similar study was performed in rats given 500 mg/kg bw [^{14}C]-d-Mannitol. Non-fasted rats oxidized 68% of the given dose; 9.75% was stored in the carcass, 1.28% in the liver, and 6.32% was excreted in the urine.

Radioactivity plateaued 2 to 4 h after 10 fasted subjects were given 28 to 100 g of [U-^{14}C]Mannitol orally as a 5% aqueous solution. The mean bioavailability of orally ingested Mannitol was 63% when 18 males were given a dose of 500 mg Mannitol in 50 ml water. The mean bioavailability of Mannitol in 18 males given 635 mg Mannitol via inhalation was 59%. In normal and diabetic subjects, less than 3% of an oral dose of 35 g Sorbitol was excreted in the urine. Plasma samples taken 1 and 2 h after the ingestion of Xylitol and glucose in water from 5 subjects revealed no Xylitol. Urinalysis showed negligible amounts of Xylitol at 0–12 and 12–24 h after dose.

The lowest acute oral LD_{50}s of Mannitol were reported to be greater than 5 g/kg bw in mice and 13.5 g/kg bw in rats. Sorbitol acute oral toxicity studies resulted in LD_{50}s of 23.2 g/kg bw (male mice), 25.7 g/kg bw (female mice), 17.5 g/kg bw (male rats), and 15.9 g/kg bw (female rats). The lowest LD_{50}s in mice, rats, and rabbits were reported to be 12.5 g/kg bw, >4 g/kg bw, and 25 g/kg bw, respectively. Decreases in lung/bronchi weight and a reduction of body weight gain were observed when rats were exposed to 98 mg/kg of Mannitol via inhalation for 1 h. When 6 mice were exposed to aerosolized Xylitol (5%) in water for 150 min, no adverse effects were observed. Fifty percent of humans administered 10 ml of 5% Xylitol in water for 30–49 min reported a stuffy nose. Cough, chest tightness, and phlegm production were also reported.

Moderate acanthosis with cellular vacuolization and a thinning out of collagen fibers of the superficial portions of the dermis were observed when albino rabbits were dosed dermally with Sorbitol (30%) for 30 d.

No adverse effects were reported when B6C3F1 mice were given up to 10% Mannitol for 14 d. Female F344/N rats fed diets containing 10% Mannitol for 14 d displayed a lower weight gain than females given lower doses of Mannitol and control females. No other adverse effects were reported in this study. No evidence of hepatotoxicity was observed when Sprague-Dawley rats were given up to 10 g/kg/d Xylitol via gavage for 14 d. The stomachs of two adult mongrel dogs appeared hyperemic after 3 doses/d of 1.35 g/kg bw Sorbitol (90%) was given for 3 d.

In an inhalation study, SD rats were exposed to 5 or 9 mg of Mannitol/l of air. No adverse effects were reported. Similarly, no adverse effects were reported when CD-1 rats were given up to 6 mg/kg Mannitol for 2 wk. Froth-filled lungs, lung congestion/hemorrhage, and pigment in the submandibular lymph node was observed in beagle dogs given 197 mg/kg/d Mannitol for 2 wk via inhalation. In a different study, Beagle dogs were given aerosolized Xylitol (4 mg/l) for up to 60 min for 14 d. No exposure-related adverse effects were reported.

Mean body weights were increased compared to controls when B6C3F1/N mice were given diets containing 0.3, 0.6, 1.2, and 5% (females) Mannitol for 13 wk. However, increased mean body weight was not observed in males given 5% Mannitol. In a similar study, F344 rats given 5% Mannitol displayed a 9.6% depression in weight gain compared to control rats. Diarrhea and slight weight gain were noted when rats were given 20 g/kg/d of Xylitol in the diet for 13 wk. Similar symptoms were reported in monkeys given 1, 3, or 5 g/kg/d Xylitol for 13 wk. Reduced sleep activity was reported in rats given 1.73 g/kg Xylitol via gavage for 90 d.

In Female Sprague-Dawley rats given Mannitol in concentrations of up to 10% for 27 mo in the diet, the mortality rate was reported to be 68% (in highest dosed rats). The authors of the study did not attribute deaths to Mannitol exposure. No negative effects, excluding slight diarrhea, was observed in male Wistar rats given Sorbitol (10 or 15%) in the diet for 17 mo. A slightly elevated serum alkaline phosphatase and serum protein value (compared to controls) was noted in Beagle dogs given 20% Xylitol in the diet for 2 yr.

Beagle dogs were given 0, 43, or 179 mg/kg d Mannitol via inhalation for 26 wk. Minimal laryngeal ulceration and sinus histiocytosis in the mediastinal lymph node were observed in the high-dose group. In a different study, Mannitol was given to dogs at doses of up to 834 mg/kg/d for 26 wk via inhalation. Enlargements of the mandibular lymph nodes were observed in 2 out of the 4 treated animals. One out of 4 treated females given 716 mg/kg/d Mannitol displayed erythrophagocytosis or lymphadenitis.

No maternal or fetotoxic symptoms were observed when mice and hamsters were given oral doses of Mannitol (1.6 g/kg for 10 d in mice; 1.2 g/kg for 5 d in hamsters). A reproductive study on 30 rats extended over four generations using 10 or 15% Sorbitol in the diet for 17 mo did not reveal any abnormalities. Reduced weight gain, cecal enlargement, and significant rises in serum calcium were observed in a three-generation reproductive study using rats treated with 5 or 10% Sorbitol. No adverse effects were reported when pregnant rabbits were given 1600 mg/kg/bw of Sorbitol for 13 d. Reproduction, lactation, and pup growth were normal in rats given a diet containing 20% Xylitol for 4 mo. Similarly, no adverse effects were reported with rabbits given Xylitol in concentrations of up to 20% on gestation days 7–19. No test substance related abnormalities were noted in a three-generation study involving NMRI mice given 20% Xylitol in the diet.

Mannitol was non-mutagenic in a bacterial reverse mutation assay, mouse lymphoma $TK^{+/-}$ assay, a sex-linked recessive lethal mutation test, sister chromatid exchange assay (concentrations not stated). Mannitol was non-mutagenic in cytogenic assays at concentrations of 2, 20, and 200 μg/ml. Additionally, Mannitol was considered to be non-mutagenic when used in an Ames test at up to 10,000 μg/plate. An Ames test performed on Sorbitol using *S typhimurium* yielded negative results (concentrations not stated). Negative results were also obtained in chromosomal aberration assays (5 mg/plate) and host mediated assays. Ames tests performed on Xylitol at up to 500 mg/plate yielded negative results. A sister chromatid exchange assay performed on Xylitol at up to 7.1 mg/ml resulted in negative results.

Mannitol was not clastogenic in a mouse bone marrow micronucleus tests (3000 mg/kg/d Mannitol for 3 d). Results of a dominant lethal assay in rats at doses of up to 5000 mg/kg of d-Mannitol by gavage were negative. A chromosomal aberration study in rat bone marrow testing the mutagenic potential of Mannitol also yielded negative results. A chromosomal aberration assay performed on Sorbitol in mouse bone marrow yielded negative results. Similarly, a mammalian erythrocyte micronucleus test performed on Xylitol (up to 5333 mg/kg/bw) using SPF mice, resulted in negative results.

Rats and mice were given a diet containing d-Mannitol (98%–100% pure (25 or 50 g/kg)) for 103 wk. The test substance was considered to be non-carcinogenic. Pelvic nephrocalcinosis was observed in Wistar rats given 10% Mannitol in the diet for 104–107 wks. A low incidence of benign thymomas was observed when Wistar-derived SPF albino rats were given 1, 5, or 10% Mannitol in the diet for 94 wk. A slight increase in the incidences of tissue masses in the anogenital area, cervix, and uterus were noted when female Fischer rats were given 10% Mannitol in the diet for 30 mo. Unilateral and bilateral hyperplasia of the adrenal medulla was increased significantly in Sprague-Dawley rats given 20% Sorbitol in the diet for 78 wk. A small number of tumors were found in the transitional epithelium of male mice treated with 20% Xylitol. Animals treated with 2, 10, or 20% Mannitol showed fewer renal tumors than control mice. A statistically significant increase in the number of pheochromocytomas was observed in male rats treated with 20% Xylitol for their entire life span, however, the total number of tumor-bearing rats was similar between treated and control groups.

The protective effect of Mannitol was assessed using rat debrided corneal epithelium. Eye drops containing a BAC solution alone had a 75% healing rate, while eye drops containing a BAC solution with 0.5% Mannitol displayed a 90.1% healing rate. The ability of Xylitol to alleviate irritation and inflammation was studied in SKH-1 hairless mice. A decreased lymphocyte number was observed in the epidermis when animals treated with Xylitol and SLS, compared to SLS alone. The addition of Xylitol also effectively decreased MPO activity in the skin.

Xylitol (5 or 10%) incorporated into a gel or cream was non-irritating to New Zealand rabbit skin. A trade name material consisting of 15% Mannitol and 15% disodium adenosine triphosphate was used in a Magnusson–Kligman maximization test (0.5 % aqueous dilution (injection induction) and 10% aqueous dilution (dermal induction and challenge)) and HRIPT (10% aqueous dilution). No signs of sensitization were observed in either study. No evidence of sensitization was observed when an HRIPT was performed on 119 subjects using a product containing 0.115% Xylitol, however, mild erythema was observed in the challenge phase. No sensitization was reported when an HRIPT was performed on 110 subjects using a lotion containing 3% Xylitol.

A human phototoxicity and photosensitization study was performed with a trade name mixture consisting of 15% Mannitol and 15% disodium adenosine triphosphate. The test substances were applied at 10% and 2% aqueous dilutions in the phototoxicity and photosensitization studies, respectively. No skin reactions were noted in either study.

A test substance consisting of Xylitol (5 or 10%) incorporated into a gel or cream was applied to Dunkin–Hartley albino guinea pigs in a phototoxicity assay. In animals exposed to 10% Xylitol via cream or gel, 3 out of 4 animals displayed a positive reaction, while all controls presented a negative reaction. It was determined that Xylitol has moderate phototoxic potential.

In adult cystic fibrosis patients, the reported mean half-lives of inhaled dry powder Mannitol, twice daily, for 7 d, was 5.42 h on day 7. Both normal and diabetic adults were given 35 g Sorbitol orally. In patients without diabetes, Sorbitol did not have a significant effect on blood sugar levels. However, in all diabetic subjects, significant increases in blood-sugar concentrations ranging from 9 to 49 mg/100 ml occurred after Sorbitol administration.

Discussion

The 3 ingredients in this report are sugar alcohols, each of which is commonly ingested in food products. The Panel noted a lack of adverse clinical reports after ingestion of foods containing these ingredients at high concentrations, and concluded that both systemic toxicity data and irritation data at use concentration were unnecessary to determine safety for this ingredient group.

A negative Magnusson–Kligman guinea pig maximization test performed using a test substance containing 15% Mannitol mitigated the need for sensitization data at maximum use concentrations, as this method of testing stresses the system and utilizes intradermal injections, which bypass the stratum corneum. Because the dermal barrier is eliminated in this method of testing, it may be assumed that other sensitization studies performed using these ingredients would also yield negative results. The Panel further supported this claim by clarifying that these ingredients have a long history of use, including in foods,

and there are no clinical reports of adverse effects following the handling or ingestion of these ingredients.

The Panel noted a positive phototoxicity study for Xylitol-containing formulations, which the authors therein incorrectly attributed to Xylitol. However, it is clear that Xylitol lacks a UV light-absorbing chromophore, and cannot directly trigger phototoxicity. In addition, levels of irradiation used in this phototoxicity study were far greater than typical exposure. Two additional negative phototoxicity results with Mannitol (which also lacks a chromophore) support this interpretation. The Panel felt that the available data do not indicate a risk of phototoxicity with these ingredients.

The Panel discussed the issue of incidental inhalation exposure from formulations that may be aerosolized (e.g., in hair sprays; concentration not reported). 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 ingredients are 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.

Conclusion

The Expert Panel for Cosmetic Ingredient Safety concluded that Mannitol, Sorbitol, and Xylitol are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

Author's Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 555 13th Street, NW, Suite 300W, Washington, DC 20004, USA.

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