Safety Assessment of Hexa/Penta-Hydric Alcohols as Used in Cosmetics

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date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a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

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INTRODUCTION

This scientific literature review is the initial step in preparing a safety assessment of the following 3 hexa/penta-hydric alcohols as used in cosmetic formulations:

Mannitol
Sorbitol
Xylitol

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook (*wINCI; *Dictionary),* Mannitol, Sorbitol and Xylitol are structurally similar to one another and all three are reported to function as humectants, skin-conditioning agents, or flavoring ingredients.[1] (Table 1)

The United States (US.). Food and Drug Administration (FDA) has determined that Mannitol is generally recognized as safe (GRAS) as a nutrient and/or dietary supplement when used in accordance with good manufacturing or feeding practice [21CFR582.5470]. Additionally, Sorbitol is used as a direct food substance that is GRAS [21CFR184.1835], and Xylitol is commonly used as a sweetener [21CFR172.395]. Because these hexa/penta-hydric alcohols are GRAS substances, the systemic toxicity potential of these ingredients will not be the focus of this safety assessment. Although such information may be included, the primary focus of this safety assessment is the review of safety based on topical exposures.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated.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 CIR typically evaluates, is provided 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.

CHEMISTRY

Definition and Structure

Mannitol, Sorbitol, and Xylitol are organic compounds that are typically derived from a sugar by reduction.[2] These ingredients occur naturally, however, they are most commonly obtained industrially by the hydrogenation of sugars. The definitions and structures of the ingredients included in this review are provided in Table 1. The ingredients in this group are all sugar alcohols and are in that way, structurally similar. Mannitol and Sorbitol are differentiated solely by the relative orientation of their hydroxyl groups, while Xylitol differs in chain length (Figure 1).

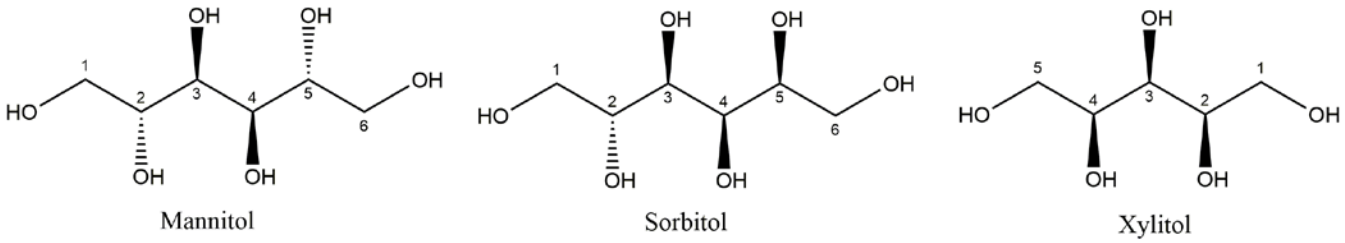


Figure 1. Hexa/Penta-Hydric Alcohols

Physical and Chemical Properties

Mannitol, Sorbitol, and Xylitol are white, water-soluble powders or granules (Table 2). [3-5] 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 processing of Mannitol, Sorbitol, and Xylitol; it is unknown if these methods apply to cosmetic ingredient manufacture.

Traditional synthesis of Mannitol and Sorbitol involves the high-pressure hydrogenation of fructose/galactose mixtures in an aqueous solution.[2] 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.[6] 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.[2] The xylose is hydrogenated at 80 - 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.[2] 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 can be formed from two fructose and one glucose molecule. Examples of homofermatative LABs include *Streptococcus mutants* and *Lactobacillus leichmanii*. These homofermentive bacteria produce minimal amounts of Mannitol from glucose most often when bacteria are defective in lactate dehydrogenase activity.[7] Heterofermentive 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 strands have the ability to create large amounts of Xylitol.[2] 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.[2] 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

According to the *Food Chemicals Codex*, the inorganic impurities of these three sugar alcohols include lead and nickel.[8] According to specifications, these impurities are not allowed to exceed 1 mg/kg when formulated for use in food. According to the Joint FAO/WHO Expert Committee on Food Additives (JEFCA), these hexa/penta-hydric alcohols should not be composed of more than 0.1% sulphated ash, 100 mg/kg sulfates, 2 mg/kg nickel, or 1 mg/kg lead.[9-11]

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 tree.[12]

Sorbitol

Sorbitol occurs naturally in mountain ash berries and other plants that are part of the Rosaceae family.[13]

Xylitol

Xylitol is found in many plants, including oats, berries, beets, sugar cane, cornhusks, and birch.[14]

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 2018 VCRP data, Sorbitol has the highest frequency of use, with a total of 1849 formulations.[15] Sorbitol is most commonly used in moisturizing products (261 formulations), bath soaps and detergents (205 formulations), and cleansing products (161 formulations). Xylitol is reported to have 346 uses, 213 of which are leave-on formulations. Mannitol has a frequency of use of 325 formulations, 96 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. 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.[15,16] Additionally, Sorbitol is used in hair sprays and could be incidentally inhaled; concentrations of these formulations have not been reported. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10 µm, with propellant sprays yielding a greater fraction of droplets/particles < 10 µm compared with pump sprays.[17,18] 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.[19,20] Mannitol and Sorbitol were reportedly used in face powders at concentrations up to 0.2 and 3.6%, respectively, and could be incidentally inhaled.[16] 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.[21-23]

The three hexa/penta-hydric alcohols named in the report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[24]

Non-Cosmetic

Mannitol

In the US, Mannitol is GRAS as a nutrient and/or dietary supplement when used in accordance with good manufacturing or feeding practice. [21CFR582.5470] Mannitol 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. [21CFR180.25] 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. [21CFR180.25] Mannitol is currently a food additive permitted in food or in contact with food on an interim basis pending additional study. This ingredient is known to reduce the crystallization of sugars, therefore increasing its shelf life.[2]

When labeling food that could result in a daily consumption of 20 grams of Mannitol, the food must bear the statement "Excess consumption may have a laxative effect." [21CFR180.25]

In medicine, Mannitol can be used as an osmotic diuretic used to prevent and treat acute renal failure and promote the removal of toxic substances from the body.[25] 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

Sorbitol is a direct food substance that is GRAS when used in accordance with good manufacturing or feeding practice. [21CFR682.5835] In addition, Sorbitol is 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 may be used in mouthwash and toothpaste, bacterial culture media, and transparent gels.[2,25] 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.

Xylitol

Xylitol is commonly used as a sweetener.[2] 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 a GRAS food additive permitted for direct addition to food for human consumption. 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. [21CFR172.395]

TOXICOKINETIC STUDIES

Dermal Penetration

Mannitol

The skin permeability of [^{14}C]-Mannitol in Wistar-derived Alderley Park (AP) and Sprague-Dawley (SD) rats was studied.[26] 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 ºC 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 was 3.23 (± 0.17) x 10^{-4} cm/hr (n = 178) for the AP rat samples, and 2.89 (± 0.17) x 10^{-4} cm/hr (n = 150) for the SD rat samples. The mean K_p values obtained for epidermal membranes was 2.30 (± 0.27) x 10^{-4}cm/hr (n = 30) and 0.89 (± 0.15) x 10^{-4} cm/hr (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.[27] (The method of oral administration was not specified.) Approximately 50% of the radioactivity was recovered in the expired [^{14}C]-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}C]-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.

Sorbitol

Rats were fed Sorbitol at a concentration of 16% in the diet for 3 months.[28] No other study details were provided. High calcium absorption and retention, along with heavy citric acid excretion and thickening of the skeleton, was observed.

Inhalation

Mannitol

Sprague-Dawley rats (5/sex) were used in a 7-day inhalation study.[29] Rats were exposed to 5 or 9 mg of Mannitol/L of air for 120 to 240 minutes/day. Rats were killed after treatment. The amount of Mannitol delivered to the lungs was determined by measuring the amount of Mannitol in the bronchoalveolar fluid (BALF). In the low dose group, the mean Mannitol concentration in the BALF was 36.7 µg/mL in males and 43.6 in females µg/mL. In the high dose group, mean Mannitol concentrations in the BALF were 42 and 33.4 µg/mL in males and females, respectively.

Human

Oral

Mannitol

Ten subjects fasted overnight and were given 28 to 100g of [U-^{14}C]-Mannitol orally as a 5% aqueous solution.[27] Within this dose range, approximately 20% of the administrated dose was excreted unchanged in the urine. In the first two hours following ingestion, the radioactivity in the blood rose. Radioactivity remained at a plateau for 2 to 4 hours. Expired $^{14}CO_2$ increased for 8 hours 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 hours after ingestion. In a different study, 18 healthy male volunteers were given an oral dose of 500 mg Mannitol in 50 mL water.[30] The mean bioavailability of the orally ingested Mannitol was 0.625. No other details regarding this study were provided.

Xylitol

Five healthy subjects were used to study the absorption of Xylitol.[31] 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 hours in a series of samples. Blood samples were collected at 60 and 120 minutes, and urine samples were collected from 0 to 12 hours and from 12 to 24 hours after ingestion. Xylitol was nearly completely absorbed in most subjects (72 to 92%). Plasma samples at one and two hours after the test meal showed no Xylitol. Urine analysis showed negligible amounts of Xylitol at 0 - 12 or 12 - 24 hours after ingestion.

Inhalation

Mannitol

Eighteen healthy male volunteers received a 635 mg dose of Mannitol via inhalation.[30] The mean bioavailability of the inhaled dose was 0.591. No other details regarding this study were provided.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

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

Animal

Three acute oral toxicity studies were performed with Mannitol. The LD_{50}s of Mannitol were reported to be 5 g/kg bw (mice), 13.5 g/kg bw (rats), and 17.3 g/kg bw (rats).[27,32 30] 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).[28] Numerous studies regarding the acute oral toxicity of Xylitol were found. The lowest LD_{50}s in mice, rats, and rabbits were reported to be 12.5 g/kg bw, 14.1 g/kg bw, and 25 g/kg bw, respectively. The vehicles used in these acute oral toxicity studies were not provided.

Various inhalation studies were performed on animals and humans. In one study, rats (number of animals not specified) were given up to .098 g/kg of Mannitol via inhalation for 1 hour.[30] No other details regarding study methods were reported. In males given the highest dose, reduction of body weight gain was observed. 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 minutes. No adverse effects were reported.[33]

Short-Term Studies

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

Dermal

A 30-day dermal study was performed on 4 groups of 5 female albino rabbits.[34] Sorbitol (30% in equal parts of water and propylene glycol) was applied to an area of 10 cm x10 cm on the right flank of the animal. A fixed dose of 0.5 mL was massaged into the skin until no longer visible. 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 provided for the hexa/penta-hydric alcohols. No adverse effects were reported when B6C3F1 mice (groups of 5/sex) were fed diets containing 0.6, 1.25, 2.5, 5, or 10% Mannitol for 14 days.[32] 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 days. No animals died the duration of the study, and all groups had similar increases in body weight. Females fed diets containing 10% Mannitol gained less weight than females dosed with a lower concentration. No gross lesions were observed. No evidence of hepatotoxicity was observed when Sprague-Dawley rats (20 rats/sex/dose) were given Xylitol via gavage for 14 days. 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.[35]

In a study involving Sorbitol, two adult mongrel dogs (male and female) were given Sorbitol (90% w/vol in aqueous solution) at doses of 0.675 and 1.35 g/kg bw. [28] Doses were given three times daily for three days. At the highest dose, the stomach appeared hyperemic.

Inhalation

An inhalation study was performed using Sprague-Dawley rats for 7 days (5/sex/dose).[29] When given 5 or 9 mg of Mannitol/L of air, no effects were reported. In a similar study, CD-1 rats (10/sex/dose) were given 0, 0.9, 2.5, or 6.0 mg/kg Mannitol via a nose-only apparatus for two weeks. No significant treatment related effects were observed. When Beagle dogs (3/sex/group) were dosed for 2 weeks 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.

Beagle dogs (3/sex/group) were given either saline or aerosolized Xylitol (4 mg/L) for 15, 30, or 60 minutes.[36] 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. Additionally, there was no exposure-related change in organ weight, gross pathology lesions, or microscopic lesions.

Subchronic Toxicity Studies

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 weeks. 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 different study, F344 rats (groups of 10/sex) were given diets containing 0, 0.3, 0.6, 1.25, or 5%

Mannitol for 13 weeks. Mean body weight gains of the high-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.

Rats (16/group) were given 0, 10, or 20 g/kg/d of Xylitol in the diet for 13 weeks. Diarrhea and slight weight gain was observed at the highest dose level.[37] Transient diarrhea and soft stools were also observed in a study using monkeys given 1, 3, or 5 g/kg/d Xylitol for 13 weeks (number of animals was not reported). No other adverse effects were reported.

Chronic Toxicity Studies

Female Sprague-Dawley rats were given Mannitol in doses of 0, 1, 5, or 10% for 27 months.[27] The number of rats used in the study was not stated. The mortality of the rats receiving 10% Mannitol was 68%. No other Mannitol-induced effects were reported. A study using Beagle dogs (4/sex/group) was performed for 26 weeks using 0, 43, or 179 mg/kg/d Mannitol, via inhalation. Coughing occurred throughout and after 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.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Mannitol

Pregnant mice, rats, and hamsters were given oral doses of Mannitol.[27] Method of administration was not specified. Rats and mice were given 1.6 g/kg for 10 days, and hamsters were given 1.2 g/kg for 5 days. No other details regarding these studies were provided. No maternal or fetotoxic symptoms were observed.

Sorbitol

A reproductive study on 30 rats extended over four generations using 10 or 15% Sorbitol in the diet for 17 months did not reveal any abnormalities.[28] 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.[38] After 14 weeks 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 twelve male and 24 females of the F_{1b} litter were then mated. Likewise the resulting F_{2b} 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 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.

When 1600 mg/kg/bw of Sorbitol was administered to pregnant rabbits for 13 days (days of gestation not stated), no effects on maternal or fetal survival were observed.[39] 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

When rats were given a diet containing 20% Xylitol for 4 months, reproduction, lactation, and pup growth was normal.[37] No other details regarding this study were provided. In a different study, rabbits were given Xylitol in concentrations of 0, 2, 5, 10, or 20%, on days 7 – 19 of gestation. 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 TA 98, TA 100, TA 1535, and TA 1537), mouse lymphoma $TK^{+/-}$ assay, or in a sister chromatid exchange assay in Chinese Hamster Ovary (CHO) cells.[40] Mannitol was not clastogenic in a mouse bone marrow micronucleus test in which doses of 3000 mg/kg/d Mannitol was administered for 3 days.[30] Mannitol was non-mutagenic in a host-mediated assay in mice using *Salmonella typhimurium* G46 and TA1530 and Saccharomyces

cerevisiae strain D3, in a cytogenic assay in rat bone marrow, and in human W1-38 cells at concentrations of 2, 20, and 200 mcg/mL.[41]

Xylitol

An Ames test was performed on Xylitol using *S. typhimurium* strains TA 100 and TA 98 (up to 500 mg/plate).[37] No detectable mutagenic activity was reported. A sister chromatid exchange was performed on Xylitol using diploid human fibroblastic cells (HE 2144) and pseudodiploid Chinese hamster cell line (Don-6) at concentrations of up to 76.1 mg/mL. No induction of sister chromatid exchange was observed in either test system.

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 weeks.[12,32] An increased incidence of the dilation of the gastric fundal gland was observed in dosed female rats compare 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 weeks.[42] 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 weeks.[27] No other details regarding this study were provided. In another study, female Fischer rats (100/sex/group) were given 0, 1, 5, or 10% Mannitol in the diet for 30 months. 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 weeks.[37] 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 (species not stated) in the diet at concentrations of 0, 2, 10, or 20%.[37] 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 (species 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 phaeochromocytomas 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 Damage

The protective effect of Mannitol on corneal damage caused by benzalkonium chloride (BAC) (a preservative in timolol maleate eye drops) was studied using rat debrided corneal epithelium.[43] 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 hours, 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.[44] 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.

DERMAL IRRITATION AND SENSITIZATION

Irritation

Xylitol

Xylitol (5 or 10%) was incorporated in gel or cream through a 60% mixture in ultra-pure water, and administered to New Zealand albino rabbits (3/sex/group).[45] 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 hours 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 not irritative.

Sensitization

Sensitization studies on the hexa/penta-hydric alcohols were not discovered in the published literature, and unpublished data were not submitted.

Phototoxicity

Xylitol

Xylitol (10%) was incorporated into either cream or gel, and applied to the skin of male Dunkin-Hartley albino guinea pigs.[45] Four animals were used per formulation containing Xylitol, as well as the positive control, and 2 animals were used as negative controls. 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 minutes). Test sites were graded at 1, 24, 48, and 72 hours 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, while all controls presented expected reactions. It was determined that Xylitol has moderate phototoxic potential at this UVA dose.

OCULAR IRRITATION STUDIES

Ocular irritation studies on the hexa/penta-hydric alcohols were not discovered in the published literature, and unpublished data were not submitted.

CLINICAL STUDIES

Case Reports

A 68-year old long-term renal transplant recipient was receiving cyclosporine therapy along with intravenous Mannitol.[46] The total amount of Mannitol given over the course of 4 days was 236 g. After 4 days of Mannitol administration, elevated blood urea nitrogen levels (BUN) and serum creatine levels were reported. Glomerulosclerosis, patchy intestinal fibrosis and moderate tubular atrophy were also noted. Mannitol administration was discontinued on day 4. On day 7, improved renal perfusion along with decreased serum creatinine levels were reported.

Metabolism

Mannitol

Six adults and three adolescents with cystic fibrosis inhaled dry powder Mannitol (400 mg) twice daily for 7 days.[30] 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 hours, respectively. In adolescents, the mean half-lives on day 1 and 7, were 7.29 and 6.52 hours, respectively.

Sorbitol

The metabolism of Sorbitol was studied in 6 normal and 8 diabetic adults.[47] 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 hours. For some subjects, urine was collected for 24 hours, and feces for 3 days. 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/100mL 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 hours. No Sorbitol was detected in the urine after 24 hours. 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.[28] No other details regarding this study were provided.

Respiratory

In a study involving humans, 10 subjects were exposed to 1 (22 – 29 minute exposure time), 5(15 – 33 minute exposure time), or 10 mL (30 – 49 minute exposure time) of 5% Xylitol (vehicle not provided).[33] Fifty-percent 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.

SUMMARY

The safety of three hexa/penta-hydric alcohols as used in cosmetics is reviewed in this scientific literature review. According to the *Dictionary*, Mannitol, Sorbitol, and Xylitol are all reported to function as humectants, skin-conditioning agents, and flavoring agents.

According to 2018 VCRP data, Sorbitol is reported to be used in 1849 formulations, 1102 of which are leave-on products and 731 are rinse-off. Mannitol and Xylitol are reported to be used in 325 and 346 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 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/hr (n = 30) and 0.89 (± 0.15) x 10^{-4} cm/hr (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}C]-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. High calcium retention, heavy citric acid excretion, and thickening of the skeleton were observed when rats were fed Sorbitol (16%) for 3 months. SD rats were exposed to 5 or 9 mg of Mannitol/L of air for 7 days. In the high dose group, mean Mannitol concentrations in BALF were 42 and 33.4 µg/mL in males and females, respectively.

Radioactivity plateaued 2 to 4 hours after ten 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 0.625 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 0.591. In normal and diabetic subjects, less than 3% of an administrated oral dose of 35 g Sorbitol was excreted in the urine. Plasma samples taken one and two hours after the ingestion of Xylitol and glucose in water from 5 subjects revealed no Xylitol. Urinalysis showed negligible amounts of Xylitol at 0 - 12 or 12 - 24 hours after dose.

The lowest LD_{50}s reported for Mannitol, Sorbitol, and Xylitol were 5 g/kg bw (mice), 15.9 g/kg bw (female rats), and 12.5 g/kg bw (mice), 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 hour. When 6 mice were exposed to aerosolized Xylitol (5%) in water for 150 minutes, no adverse effects were observed. Fifty-percent of subjects reported a stuffy nose when given 10 mL of 5% Xylitol via inhalation.

Moderate acanthosis with cellular vacuolization and a thinning out of collagen fibers of the superficial portions of the dermis was observed when albino rabbits were dosed dermally with Sorbitol (30%) for 30 days. No adverse effects were reported when B6C3F1 mice were given up to 10% Mannitol for 14 days. Increases in body weights were noted when F344/N rats were given up to 10% Mannitol for 14 days. The stomachs of two adult mongrel dogs appeared hyperaemic after 3 doses/day of 1.35 g/kg bw Sorbitol (90%) was given for 3 days. 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 weeks. 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 weeks via inhalation.

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 weeks. 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 was noted when rats were given 20 g/kg/d of Xylitol in the diet for 13 weeks. Similar symptoms were reported in monkeys given 1, 3, or 5 g/kg/d Xylitol for 13 weeks. Female Sprague-Dawley rats given 10%

Mannitol for 27 months displayed a 68% death rate. No other Mannitol-induced effects were reported. Minimal laryngeal ulceration and sinus histiocytosis in the mediastinal lymph node were observed when Beagle dogs (4/sex/group) were given 179 mg/kg/d Mannitol.

No maternal or fetotoxic symptoms were observed when mice and hamsters were given oral doses of Mannitol (1.6 g/kg for 10 days in mice; 1.2 g/kg for 5 days in hamsters). Reduced weight gain, cecal enlargement, and significant rises in serum calcium were observed in a four-generation reproductive study using mice. No adverse effects were reported when pregnant rabbits were given 1600 mg/kg/bw of Sorbitol for 13 days. Reproduction, lactation, and pup growth were normal in rats given a diet containing 20% Xylitol for 4 months. Similarly, no adverse effects were reported with rabbits were given Xylitol in concentrations of up to 20% on gestation days 7 - 19.

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, host-mediated assay, and a cytogenic assay. Mannitol was not clastogenic in a mouse bone marrow micronucleus test. Similarly, Xylitol was not mutagenic in an Ames test or a sister chromatid exchange assay.

Rats and mice were given a diet containing D-Mannitol (98 – 100% pure (25or 50 g/kg)) for 103 weeks. 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 weeks. 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 weeks. 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 months. Unilateral and bilateral hyperplasia of the adrenal medulla was increased significantly in Sprague-Dawley rats given 20% Sorbitol in the diet for 78 weeks. 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 phaeochromocytomas 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 rabbits. The same test substance 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.

A long-term renal transplant recipient received Mannitol over the course of 4 days. The total amount of Mannitol given was 236 g. Elevated blood urea nitrogen levels, serum creatinine levels, glomerulosclerosis, patchy intestinal fibrosis, and moderate tubular atrophy were noted after 4 days or Mannitol treatment. Three days after the discontinuation of Mannitol treatment, improved renal perfusion and decreased serum creatinine levels were observed.

In adult cystic fibrosis patients, the reported mean half-lives of inhaled dry powder Mannitol, twice daily, for 7 days, was 5.42 hours 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/100mL occurred after Sorbitol administration. Thirty-eight bronchiectasis patients were given spray dried Mannitol (420 mg), twice a day, for 2 weeks, via inhalation. Adverse effects were reported in 71.1% of subjects given Mannitol, and in 69.4% control subjects. A similar study was performed in 48 subjects given up to 400 mg Mannitol for 2 weeks. Headache, aggravated condition, pyrexia, and pharyngolaryngeal pain was among the adverse effects reported. When 10 subjects were exposed to 1, 5, or 10 mL of 5% Xylitol, adverse effects such as a stuffy nose, cough, chest tightness, and phlegm production were noted.

INFORMATION SOUGHT

The CIR is seeking the following information on Mannitol, Sorbitol, and Xylitol for use in the resulting safety assessment:

1. method of manufacture of these ingredients
2. irritation and sensitization data at concentrations of use
3. any additional available information that will inform this safety assessment

TABLES

Table 1. Definitions, Idealized structures, and functions of the ingredients in this safety assessment[48, CIR staff]

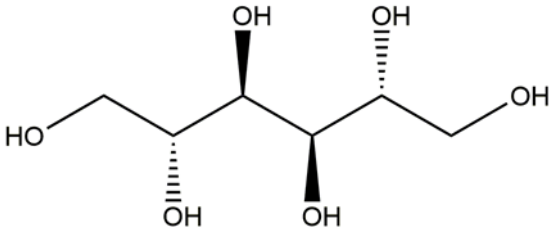
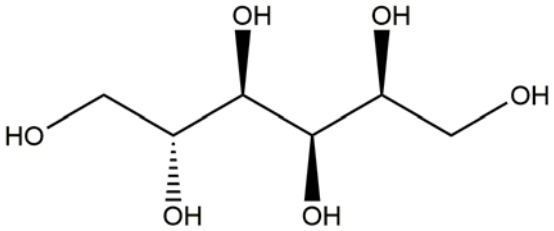
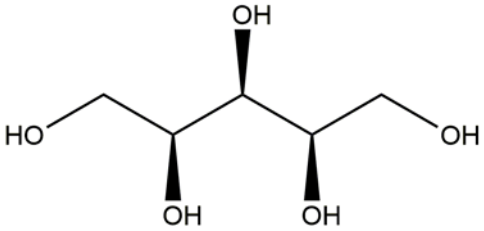
Ingredient CAS No.	Definition & Structure	Function(s)
Mannitol 69-65-8 87-78-5	Mannitol is the hexahydric alcohol that conforms to the formula: 	Binders; Flavoring Agents; Humectants; Skin-Conditioning Agents- Humectant
Sorbitol 50-70-4	Sorbitol is the hexahydric alcohol that conforms to the formula: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

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

Property	Value	Reference
Mannitol		
Physical Form	crystalline powder or free-flowing granules	4
Color	white	4
Odor	odorless	4
Molecular Weight (g/mol)	182.172	4
Density/Specific Gravity (@ 20 ºC)	1.52	4
Melting Point (ºC)	168	4
Boiling Point (ºC)	290 - 295	4
Water Solubility (g/L @ 25 ºC)	216	4
log K_{ow}	-3.10	4
Disassociation constants (pKa) (@ 25 ºC)	13.50	4
Sorbitol		
Physical Form	crystalline powder, granules	5
Color	white	5
Molecular Weight (g/mol)	182.172	5
Density/Specific Gravity (@ 20 ºC)	1.489	5
Vapor Pressure (mmHg@ 25 ºC)	9.9×10^{-9}	5
Melting Point (ºC)	111	5
Boiling Point (ºC)	295	5
Water Solubility (g/L @ 25 ºC)	2750	5
log K_{ow}	-2.20	5
Disassociation constants (pKa) (@ 25 ºC)	13.6	5
Xylitol		
Physical Form	crystalline powder	3
Color	white	3
Molecular weight (g/mol)	152.146	3
Vapor Pressure (mmHg @ 25 ºC)	2.47×10^{-3}	3

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

Property	Value	Reference
Melting Point (ºC)	93.5	[3]
Boiling Point (ºC)	216	[3]
Water Solubility (g/L @ 20 ºC)	642	[3]
log K_{ow}	-2.56	[3]

Table 3. Frequency and Concentration of Use

	# of Uses[15]	Max Conc of Use (%)[16]	# of Uses[15]	Max Conc of Use (%)[16]	# of Uses[15]	Max Conc of Use (%)[16]
	MANNITOL		SORBITOL		XYLITOL	
Totals*	325	0.000063 – 60.5	1849	0.00007 – 70	346	0.013 – 14
Duration of Use						
Leave-On	277	0.000063 – 60.5	1102	0.0005 – 20	213	0.013 – 2
Rinse-Off	47	0.023 – 20	731	0.00007 – 70	132	0.05 – 14
Diluted for (Bath) Use	1	NR	16	0.02 – 2.5	1	NR
Exposure Type						
Eye Area	34	0.00008 – 0.1	141	0.00044 – 4.9	16	NR
Incidental Ingestion	4	0.4 – 4.1	85	1.1 – 70	85	0.06 – 14
Incidental Inhalation-Spray	105[a]; 73[b]	0.9[b]	6; 310[a]; 429[b]	1.8 – 3.5[a]; 0.0012 – 32[b]	1; 72[a]; 71[b]	0.15[b]
Incidental Inhalation-Powder	7; 105[a]	0.2; 0.1 – 2.3[c]	2; 310[a]; 4[c]	2.3 – 3.6; 1.8 – 3.50[a]; 0.006 – 20[c]	72[a]; 2[c]	0.042 – 2[c]
Dermal Contact	299	0.000063 – 60.5	1458	0.00044 – 31.9	237	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	10	0.023 – 12.5	274	0.00007 – 10.9	23	0.15 – 0.24
Hair-Coloring	1	NR	11	0.006 – 5	NR	0.05
Nail	10	0.015 – 0.03	5	3.5 – 7	NR	NR
Mucous Membrane	12	0.051 – 4.1	317	0.02 – 70	93	0.06 - 14
Baby Products	NR	NR	9	1.4 – 14	7	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[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
NR – no reported use

Table 4. Acute toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/Results (g/kg/bw)	Reference
			ORAL			
Mannitol	Mice	5/sex/group	water	0.3, 0.6, 1.2, 2.5 or 5 g/kg via gavage	5	[32]
Mannitol	Mice	NR	NR	NR	22	[30]
Mannitol	Rats	NR	NR	NR	13.5	[30]
Mannitol	Rats	NR	NR	NR	17.3	[27]
Sorbitol	Mouse (male)	NR	NR	NR	23.2	[28]
Sorbitol	Mouse (female)	NR	NR	NR	25.7	[28]
Sorbitol	Rat (male)	NR	NR	NR	17.5	[28]
Sorbitol	Rat (female)	NR	NR	NR	15.9	[28]
Xylitol	Mouse	NR	NR	NR	25.7	[37]
Xylitol	Mouse	NR	NR	NR	12.5	[37]
Xylitol	Mouse	NR	NR	NR	22	[37]
Xylitol	Rat	NR	NR	NR	14.1	[37]
Xylitol	Rat	NR	NR	NR	17.3	[37]
Xylitol	Rabbit	NR	NR	NR	25	[37]

Table 4. Acute toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/Results (g/kg/bw)	Reference
INHALATION						
Mannitol	Rats	NR	NR	≤ 98 mg/kg.d	No deaths, reduction of bdoy 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)	[30]
Xylitol	Mice	6	Water	Mice were exposed to aerosolized Xylitol (5%) for 150 minutes in an exposure chamber	Well tolerated by mice with no significant effects on the airway physiology or composition of airway inflammatory cells	[33]
Xylitol	Human	10	NR	Subjects received 1, 5, and 10 mL of 5% Xylitol	Five subjects reported a stuffy nose after treatment of the 10 mL dose, cough was reported by 2 subjects, chest tightness was reported by 2 subjects, and phlegm production was reported by 3 subjects. All reported symptoms were resolved by day 5.	[33]

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 treatment 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.	34
				ORAL		
Mannitol	$B6C3F_1$ 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.	28
Mannitol	$B6C3F_1$ Mice (10/sex)	13 weeks	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.	28
Mannitol	$B6C3F_1$ Mice (50/sex)	13 weeks	Feed	0, 2.5, or 5.0%	Treated female mice and control female mice displayed similar mean body weights, however, mean body weights of treated males were 5-10% greater than control males. Survival and food consumption rates were similar in all groups. Lymphocytic leukemia was observed with a positive trend in female mice ($P < 0.05$). Lymphocytic lymphoma occurred with a negative trend ($P < 0.01$). Subcutaneous tissue sarcomas in male mice and malignant mammary gland tumors were observed in female mice were observed with a negative trend ($P < 0.05$).	12
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	28
Mannitol	F344/N Rats (10/sex)	13 weeks	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.	28
Mannitol	Fischer 344 Rats (50/sex)	13 weeks	Feed	0, 2.5, 5.0%	Mean body weights in control males versus treated males were similar. The weights of females remained 3-10% lower than the controls throughout the study. Survival and food consumption was similar in all groups, however, females given 5% D-Mannitol displayed a significantly increased survival rate ($P < 0.05$). The incidence of tumors was similar in all groups. In females, dilation of the fundal gland was apparent in the stomach, with an incidence of 6/50 for controls and 23/50 for each of the D-Mannitol groups.	12
Mannitol	Wistar-derived SPF albino Rats	94 weeks	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.	27
Mannitol	Female Sprague Dawley Rats	27 months	NR	0, 1, 5, 10%	The mortality rate of the rats receiving 10% Mannitol was 68%. No other Mannitol-induced effects were reported. The mortality rate of control rats was not stated.	27
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 hyperaemic.	28
Xylitol	Sprague-Dawley Rats (20 rats/sex/dose)	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 measures were within normal limits.	35
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

Table 5. Repeated Dose Toxicity Studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Results	Reference
Xylitol	16 Rats/group	13 weeks	Feed	5, 10, 20 g/kg/d	The test substance was considered to be tolerated well. Slightly reduced weight gains and transient diarrhea were observed at the highest dose levels.	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	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. Dogs in the 20% Xylitol group had slightly heavier livers than in other groups. No degenerative changes were reported.	37
Xylitol	Monkeys (# of animals not provided)	13 weeks (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.	37
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. Dogs in the 20% Xylitol group had slightly heavier livers than in other groups. No degenerative changes were reported.	37
INHALATION						
Mannitol	Sprague-Dawley Rats (5/sex/dose)	7 days	Air	5 or 9 mg of Mannitol/L of air	No treatment-related effects were reported.	29
Mannitol	CD-1 Rats (10/sex/dose)	2 week	Air	0, 0.9, 2.5 and 6.9 mg/kg	No significant treatment related effects were observed. An NOAEL of 6.9 mg/kg/d was determined.	29
Mannitol	Beagle Dogs (3/sex/group)	2 week	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 submandicular 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 was seen in 1/3 high dose female animals.	29
Mannitol	Beagle Dogs (4/sex/dose)	26 weeks	Air	0, 43, 178 mg/kg/d (0, 0.20, 8.7 mg/L)	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.	29

Table 6. Carcinogenicity studies

Ingredient	Animal (#/group)	Vehicle	Procedure	Results	Reference
Mannitol (98-100%)	50 F344/N rats/sex and 50 B6C3F1 mice/sex	Diet	A diet containing D-Mannitol was given to animals for 103 weeks.	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 observed in increased in dosed female rats compared to that of the controls. Retinopathy and cataracts was 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.	[12,12,32]
Mannitol (10%)	50 Wistar rats/group/sex	Diet	Animals were given diets containing 10% Mannitol for 104-107 weeks.	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 effected by treatment. In male and female rats, pelvic nephrocalcinosis, which in females was directly associated with pelvic hyperplasia, was noted.	[42]
Mannitol (0, 1, 5, or 10%)	Wistar-derived SPF albino rats (# of rats not stated)	Diet	Animals were fed a diet containing 0, 1, 5, or 10% Mannitol for 94 weeks.	A low incidence of benign thyomas was observed.	[27]
Mannitol (0, 1, 5, or 10%)	Female Fischer rats (100 animals/group)	Diet	Rats were given 0, 1, 5, or 10% Mannitol in the diet for 30 months.	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.	[27]
Sorbitol (0 or 20%)	75 Sprague-Dawley rats/sex/dose	Diet	Animals were given Sorbitol in the diet for 78 weeks.	Unilateral and bilateral hyperplasia of the adrenal medulla was increased significantly for males and females receiving Sorbitol.	[37]
Xylitol (0, 2, 10, or 20%)	100 mice/sex (species not stated)	Diet	Mice were fed a diet containing 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.	[37]
Xylitol (0, 2, 5, 10, or 20%)	75 rats/sex (species not stated)	Diet	Rats were fed a diet containing Xylitol for the majority of the animals' lifespan.	Unilateral or bilateral phaeochromocytomas were observed in a proportion of rats from all groups, including controls. A statistically significant increase in the number of phaeochromocytomas 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.	[37]

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