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

Status:	Draft Report for Panel Review
Release Date:	March 15, 2019
Panel Meeting Date:	April 8-9, 2019

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth. Ph.D. This safety assessment was prepared by Priya Cherian, Scientific Analyst/Writer.

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Memorandum

To: CIR Expert Panel Members and Liaisons

From: Priya Cherian
Scientific Writer/Analyst

Date: March 15, 2019

Subject: Draft Report on Hexa/Penta-Hydric Alcohols

Enclosed is a draft report on the hexa/penta-hydric alcohols, i.e., Mannitol, Sorbitol, and Xylitol, as used in cosmetics. Outside of cosmetics, these ingredients are commonly used in foods. A Scientific Literature Review (SLR) was announced on January 25, 2019.

The attached report (*hexpen042019DR*) includes the following:

1) Use concentration data received from Council (*hexpen042019data1* and *hexpen042019data2*)
2) Comments on the SLR (*hexpen042019pcpc*) that were received from the Council and have been addressed
3) Report history (*hexpen042019hist*)
4) Flow chart (*hexpen042019flow*)
5) Literature search strategy (*hexpen042019strat*)
6) Ingredient data profile (*hexpen042019prof*)
7) FDA VCRP data (*hexpen042019fda*)

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

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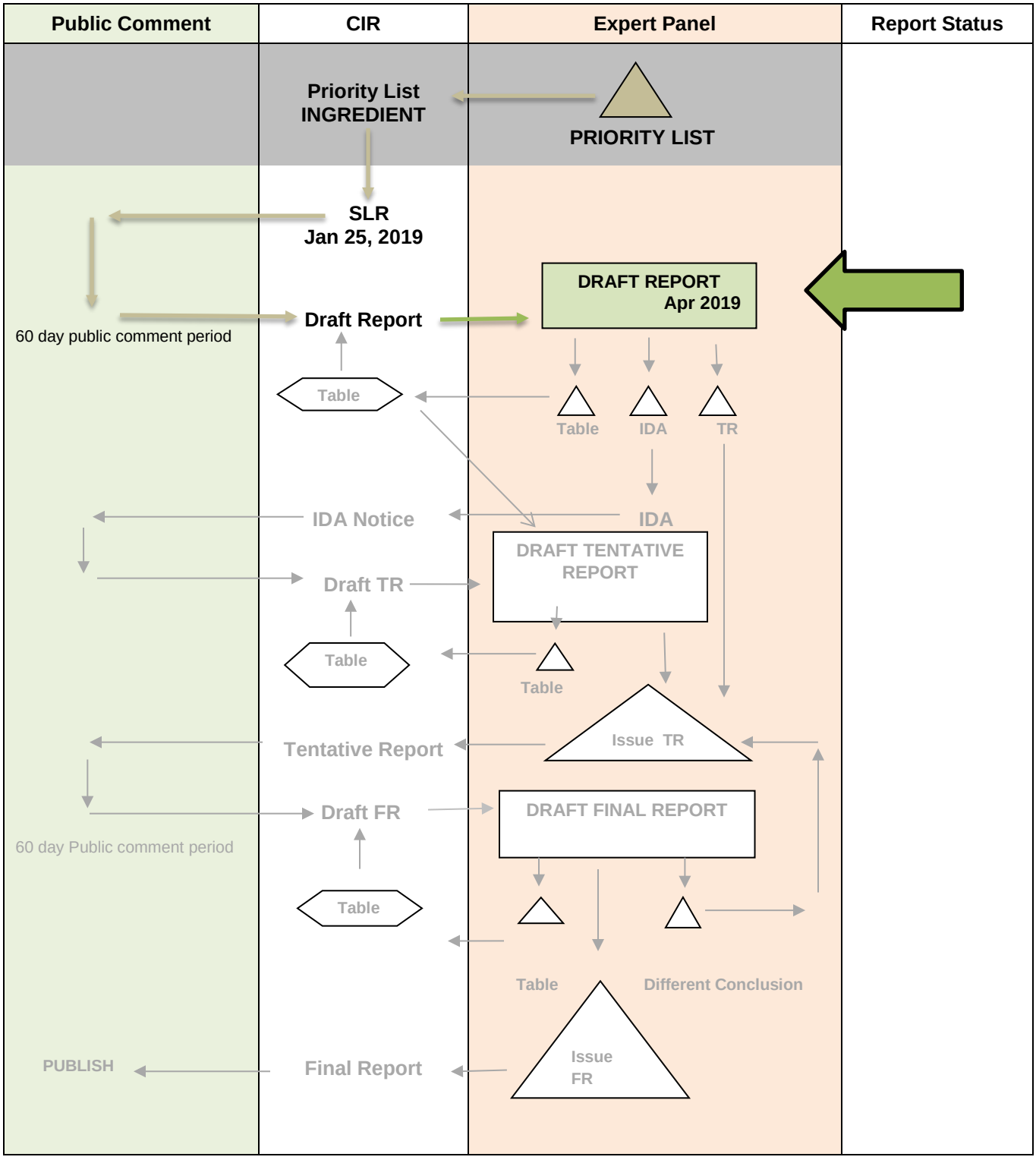
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Hexa/Penta-Hydric Alcohols

MEETING April 2019



CIR History of Hexa/Penta-Hydric Alcohols (Mannitol, Sorbitol, and Xylitol)

January 2019

-A Scientific Literature Review (SLR) on the hexa/penta-hydric alcohols was issued on January 25, 2019.

February 2019

-Comments and unpublished data were received from the Council after announcement of the SLR.
-the draft report was revised to address Council comments, and FDA VCRP data were updated for 2019

April 2019

-The Panel reviews the Draft Report

Hexa/Penta-Hydric Alcohols Data Profile* – April 2019 – Writer, Priya Cherian																													
				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Mannitol	X	X	X	X	X	X		X	X		X	X		X	X			X										X	X
Sorbitol	X	X	X	X		X		X		X	X			X				X										X	
Xylitol	X	X	X	X		X		X	X		X	X		X	X			X		X					X			X	

* "X" indicates that data were available in a category for the ingredient

[Hexa/Penta-Hydric Alcohols – April 2019 – Priya Cherian]

Ingredient	CAS #	InfoB	SciFin	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Mannitol	69-65-8	x	x	x	x	x	x	x							x	x	x			x
Sorbitol	50-70-4	x	x	x	x	x	x	x							x	x	x			x
Xylitol	87-99-0	x	x	x	x	x	x	x							x	x	x			x

Search Strategy

[*document search strategy used for SciFinder, PubMed, and Toxnet*]

Mannitol cosmetics (0/56) – PubMed
Mannitol toxicity (20/1052) – PubMed
Mannitol dermal (1/40) – PubMed
Mannitol cosmetic (1/76) – Pubmed
Mannitol metabolism
Mannitol cancer
69-65-8 (1/2) – pubmed
Mannitol toxicity (4/20) – Scifinder
Mannitol dermal (0/1) – Scifinder
Mannitol cosmetic (0/108) – Scifinder
69-65-8 (0/3)-SciFinder
Sorbitol Cosmetic (2/59)-pubmed
Sorbitol toxicity (5/1147)-pubmed
50-70-4 (0/1)-pubmed
Sorbitol dermal (0/38)-pubmed
Sorbitol metabolism (10/489)-pubmed
Sorbitol Cancer (0/1555)-pubmed
50-70-4 (0)-scifinder
Sorbitol Cosmetics (0/17)-scifinder
Sorbitol toxicity (1/9)-scifinder
Xylitol cosmetics (2/97) – pubmed
Xylitol toxicity (15/103)-pubmed
Xylitol metabolism-pubmed
Xylitol dermal (1/1) – pubmed
Xylitol toxicity (5/33)- scifinder
87-99-0

All terms also searched in google

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Toxnet (https://toxnet.nlm.nih.gov/); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)
- Scifinder (https://scifinder.cas.org/scifinder)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org
- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

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INTRODUCTION

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

The United States (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 hexa/penta-hydric alcohols are affirmed GRAS substances and/or direct food additives, the systemic toxicity potential of these ingredients 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 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.

Much of the data included in this safety assessment was found from the National Toxicology Program (NTP), European Chemicals Agency (ECHA) and World Health Organization (WHO) websites.[2-6] Please note that these websites provide summaries of information from other studies, and it is those summary data that are reported in this safety assessment when NTP or WHO is cited.

CHEMISTRY

Definition and Structure

Mannitol, Sorbitol, and Xylitol are organic compounds that are typically derived from a sugar by reduction.[7] These ingredients occur naturally, however, they are most commonly obtained industrially by the hydrogenation of sugars. The ingredients in this group are all 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).

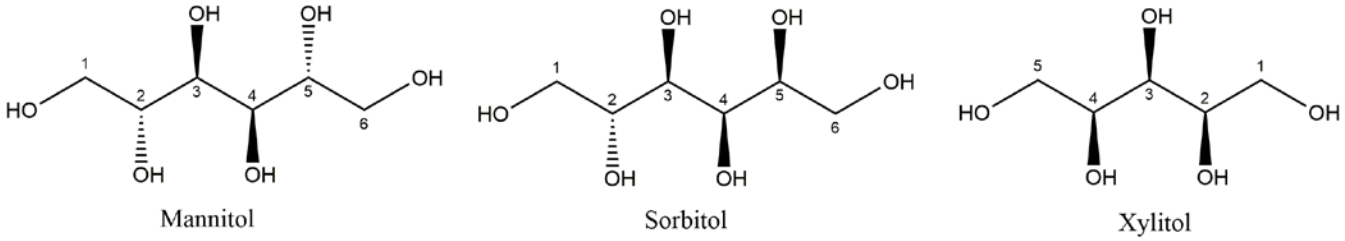


Figure 1. Hexa/Penta-Hydric Alcohols

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 processing 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 - 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 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 create 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

According to the *Food Chemicals Codex*, the inorganic impurities of these three sugar alcohols include lead and nickel.[13] 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% sulfated ash, 100 mg/kg sulfates, 2 mg/kg nickel, or 1 mg/kg lead.[14-16]

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.[17]

Sorbitol

Sorbitol occurs naturally in mountain ash berries and other plants that are part of the Rosaceae family.[18]

Xylitol

Xylitol is found in many plants, including oats, berries, beets, sugar cane, cornhusks, and birch.[19]

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 1976 formulations.[20] 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.[21] 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.[20,21] 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.[22,23] 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.[24,25] Mannitol and Sorbitol were reportedly used in face powders at concentrations up to 0.2 and 3.6%, respectively, and could be incidentally inhaled.[21] 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.[26-28]

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.[29]

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 removal of toxic substances from the body.[30] 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 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.[7,30] 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 in Wistar-derived Alderley Park (AP) and Sprague-Dawley (SD) rats was studied.[31] 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/h (n = 178) for the AP rat samples, and 2.89 (± 0.17) x 10^{-4} cm/h (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/h (n = 30) and 0.89 (± 0.15) x 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.[3] (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.[32] The substance is partially metabolized and the remains are excreted in the urine. There is evidence that intestinal flor 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.[3] Within this dose range, approximately 20% of the given dose was excreted unchanged in the urine. In the first two hours following ingestion, the radioactivity in the blood increased. 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.

Sorbitol

Sorbitol administered orally to humans is absorbed and metabolized rapidly through normal glycolytic pathways.[33] The substance is ultimately metabolized into carbon dioxide and water. When 35 grams 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.[6] 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.[34] 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.

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.[35] 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 hours was approximately 55% for the inhalation and oral doses, and 87% for the intravenous dose.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

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

Animal

Oral

Several acute oral toxicity studies were performed with Mannitol. The lowest 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.[35,36] 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).[4] 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, > 4 g/kg bw, and 25 g/kg bw, respectively. The vehicles used in these acute oral toxicity studies were not provided.

Inhalation

Inhalation studies were performed on animals. In one study, rats (number of animals not specified) were given up to 98 mg/kg of Mannitol via inhalation for 1 hour.[35] 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.[37]

Human

Inhalation

In a study involving humans, 10 subjects were exposed to 1 (2 - 10 minute exposure time), 5 (15 – 33 minute exposure time), or 10 mL (30 – 49 minute exposure time) of 5% Xylitol.[37] Xylitol was prepared by adding 5 g of crystal sugar to ever 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 microns with a GSD of 1.71 microns. 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. 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-day dermal study was performed on 4 groups of 5 female albino rabbits.[38] Sorbitol (30% in equal parts of water and propylene glycol) was applied to an area of 10 cm x 10 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 available 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.[2] 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.[39]

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. [4] 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).[40] 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 6.9 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 (control) or aerosolized Xylitol formulated with water (4 mg/L) for 15, 30, or 60 minutes.[41] 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

Oral

Groups of 10 B6C3F$_1$/N mice/sex were fed diets containing 0, 0.3, 0.6, 1.2, 2.5, or 5.0% Mannitol for 13 weeks.[2] 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. 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 9.6% lower compared to 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. Rats (number of animals was not provided) were given Xylitol (0.5 or 1.73 g/kg) via gavage for 90 days.[42] No change was recorded at the 0.5 g/kg dose level. At the 1.73 g/kg dose level, reduced sleep and activity of rats was observed. Diarrhea and slight weight gain was observed at the highest dose level.[6] 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).[43] No other adverse effects were reported.

Chronic Toxicity Studies

Oral

Female Sprague-Dawley rats were given Mannitol in doses of 0, 1, 5, or 10% for 27 months.[3] 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. Fifteen male Wistar rats were given Sorbitol in the diet at concentrations of 10 or 15% for 17 months.[4] No negative effects on weight gain, reproduction, or histopathological appearances of the main organs were observed. Beagle dogs (8/sex/dose) were given 0, 2, 5, 10, or 20% Xylitol in their diet for 2 years. 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. Dogs in this group also displayed slightly heavier livers.

Inhalation

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.

Mannitol given to dogs (number of animals was noted stated) via inhalation at up to 834 mg/kg/d for 26 weeks caused coughing during and immediately after dosing.[35] 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.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Mannitol

Pregnant mice, rats, and hamsters were given oral doses of Mannitol.[3] 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.[4] 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.[44] 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 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 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 and route of administration not stated), no effects on maternal or fetal survival were observed.[45] 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 NMRI mice.[14] Groups of 12 females and 3 males were placed in a group and 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. [6] 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. Caecal 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 Xylitol in concentrations of 0, 2, 5, 10, or 20% 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 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 (doses not stated).[36] 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, and in human W1-38 cells at concentrations of 2, 20, and 200 mcg/mL.[46] It is not stated whether or not metabolic activation was used in these studies. 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, TA 100, and in *Escherichia coli* WP2 (uvrA), with and without metabolic activation.[47] 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).[48,49] Negative results were also obtained when Sorbitol (5 mg/plate) was used in chromosomal aberration assays using Chinese hamster ovary cells and Chinese hamster lung fibroblasts without metabolic activation. Sorbitol was negative for mutagenicity in host mediated assays of mutagenicity in mice using *Salmonella* strains G46 and TA1530, and *Saccharomyces cerevisiae* strain D3 as indicator strains. The doses and use of metabolic activation was not stated in this study.

Xylitol

An Ames test was performed on Xylitol using *S. typhimurium* strains TA 100 and TA 98 (up to 500 mg/plate; unknown if metabolic activation was used).[50] No detectable mutagenic activity was reported. A different Ames test was performed using *S. typhimurium* strains TA 1535, 1537, and 1538, with and without metabolic activation.[6] Cells were exposed to up 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* 1538 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 cell line (Don-6) at concentrations of up to 76.1 mg/mL.[42] 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 days intraperitoneally.[35] 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.[2] 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.[49] 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 guidelines (OECD TG) 474.[6] 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 4000 erythrocytes per animal were checked for micronuclei. No significant increase of micronuclei containing erythrocytes were 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 weeks.[2,17] 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.[51] 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.[3] 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 months.[3] 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 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.[4] 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%.[52] 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 Healing Promotion

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.[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 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.[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 Fluid (BALF)

Sprague-Dawley rats (5/sex) were used in a 7-day inhalation study.[40] 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 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 weeks) and dogs (26 weeks).[40] 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 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 non-irritating.

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 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 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

In Vitro

Isolated bovine corneas were incubated with mannitol powder (20 %) or imidazole (positive control) at 32º C for 4 hours.[40] 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

Three New Zealand white rabbits were administered 78 mg (0.1 mL in volume) of Mannitol in one eye and observed for irritation for 72 hours post administration.[40] 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

Case Reports

A 68-year old long-term renal transplant recipient was receiving cyclosporine therapy along with intravenous Mannitol.[56] 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.[35] 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.[57] 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.[4] No other details regarding this study were provided.

SUMMARY

The safety of three hexa/penta-hydric alcohols as used in cosmetics is reviewed in this assessment. According to the *Dictionary*, Mannitol, Sorbitol, and Xylitol 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 1976 formulations, 269 of which are used in moisturizing products and 217 in 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}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.

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 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 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 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 hour. When 6 mice were exposed to aerosolized Xylitol (5%) in water for 150 minutes, no adverse effects were observed. Fifty percent Humans administered 10 mL of 5% Xylitol in water for 30-49 minutes reported a stuffy nose. Cough, chest tightness, and phlegm production was also reported.

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 B6C3F_1 mice were given up to 10% Mannitol for 14 days. Female F344/N rats fed diets containing 10% Mannitol for 14 days 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 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. In a different study, Beagle dogs were given aerosolized Xylitol (4 mg/L) for up to 60 minutes for 14 days. 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 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 were 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. Reduced sleep activity was reported in rats given 1.73 g/kg Xylitol via gavage for 90 days.

In Female Sprague-Dawley rats given Mannitol in concentrations of up to 10% for 27 months, the mortality rate was reported to be 68% (in highest dosed rats). No negative effects, excluding slight diarrhea, was observed in male Wistar rats given Sorbitol (10 or 15%) in the diet for 17 months. 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 years.

Beagle dogs were given 0, 43, or 179 mg/kg d Mannitol via inhalation for 26 weeks. 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 weeks via inhalation. 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.

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). 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. Reduced weight gain, cecal enlargement, and significant rises in serum calcium were observed in a three-generation reproductive study using rats. 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. 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 mcg/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 days). 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 also yielded negative results. A chromosomal aberration assay performed 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 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 rabbit skin. 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.

TABLES

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

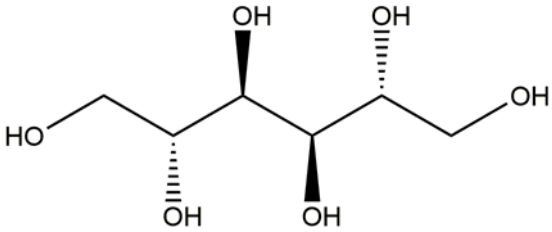
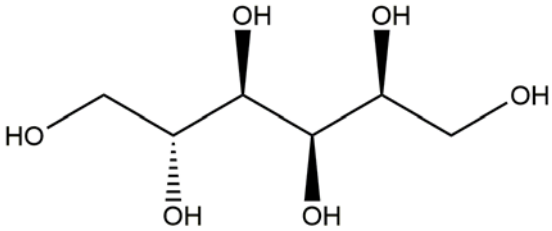
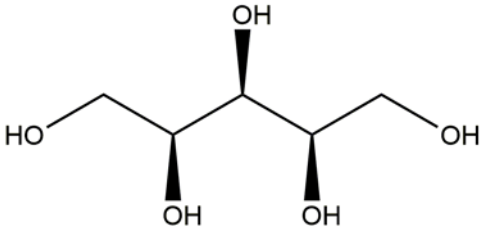
Ingredient CAS No.	Definition & Structure	Function(s)
Mannitol 69-65-8 87-78-5	Mannitol is the hexahydric alcohol that conforms to the formula: 	Binders; Flavoring Agents; Humectants; Skin-Conditioning Agents- Humectant
Sorbitol 50-70-4	Sorbitol is the hexahydric alcohol that conforms to the formula: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

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

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

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

Property	Value	Reference
Melting Point (ºC)	93.5	[8]
Boiling Point (ºC)	216	[8]
Water Solubility (g/L @ 20 ºC)	642	[8]
log K_{ow}	-2.56	[8]

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

	# of Uses[20]	Max Conc of Use (%)[21]	# of Uses[20]	Max Conc of Use (%)[21]	# of Uses[20]	Max Conc of Use (%)[21]
	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

*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	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	[2]
Mannitol	Mice	NR	NR	NR	22 g/kg/bw	[35]
Mannitol	Rats	NR	NR	NR	13.5 g/kg/bw	[35]
Mannitol	Rats	10/group	NR	NR	17.3 g/kg/bw	[3]
Sorbitol	Mouse (male)	NR	NR	NR	23.2 g/kg/bw	[4]
Sorbitol	Mouse (female)	NR	NR	NR	25.7 g/kg/bw	[4]
Sorbitol	Rat (male)	NR	NR	NR	17.5 g/kg/bw	[4]
Sorbitol	Rat (female)	NR	NR	NR	15.9 g/kg/bw	[4]
Xylitol	Mouse	NR	NR	NR	25.7 g/kg/bw	[42]
Xylitol	Mouse	NR	NR	NR	12.5 g/kg/bw	[42]
Xylitol	Mouse	NR	NR	NR	22 g/kg/bw	[42]
Xylitol	Rat	10/group	5% gum acacia solution	up to 4 g/kg/bw; gavage	> 4 g/kg/bw	[6]
Xylitol	Rat	NR	NR	NR	14.1 g/kg/bw	[42]
Xylitol	Rat	NR	NR	NR	17.3 g/kg/bw	[42]
Xylitol	Rabbit	NR	NR	NR	25 g/kg/bw	[42]

Table 4. Acute toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/Results	Reference
			INHALATION			
Mannitol	Rats	10/group	NR	≤ 98 mg/kg/d	No deaths, 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.	[35]
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	[37]
Xylitol	Humans	10	Water	Xylitol was prepared by adding 5 g of crystal sugar to ever 100 mL of sterile water. Subjects were exposed to aerosolized saline as a control. Subjects were exposed to 1 (2 - 10 minute exposure time), 5 (15 – 33 minute exposure time), or 10 mL (30 – 49 minute exposure time) of 5% Xylitol. The mass median aerodynamic diameter of the aerosol was 1.63 microns with a GSD of 1.71 microns.	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. No effects regarding electrolytes, lung function, osmolarity, or bronchoalveolar lavage were observed.	[37]

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.	38
			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.	2
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.	2
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	2
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.	2
Mannitol	Wistar-derived SPF albino Rats (# of animals not provided)	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.	3
Mannitol	Female Sprague Dawley Rats (# of animals not provided)	27 months	Feed	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. The authors of the study did not attribute deaths to Mannitol exposure.	3
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.	4
Sorbitol	Wistar Rats (15 males)	17 months	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.	4
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.	39
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.	42

Table 5. Repeated Dose Toxicity Studies

Ingredient	Animals/Group	Study Duration	Vehicle	Dose/Concentration	Results	Reference
Xylitol	8 CD rats/sex/group	13 weeks	Feed	0, 5, 10, 20 g/kg/d	At study completion, mean body weights of male and female rats fed the Xylitol-containing compound 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.	6,42
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.	42
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.	58
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.	59
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.	40
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.	40
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.	40
Mannitol	Beagle Dogs (4/sex/dose)	26 weeks	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.	40
Mannitol	Dogs (number of animals and strain not reported)	26 weeks	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.	35
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.	41

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 weeks 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 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.	[2,17]
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 weeks 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.	[51]
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 weeks.	A low incidence of benign thymomas was observed.	[3]
Mannitol	Female Wistar rats (100/group)	Diet	Animals were fed a diet containing 0, 1, 5, or 10% Mannitol for 30 months.	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.	[3]
Mannitol	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.	[3]
Sorbitol	75 Sprague-Dawley rats/sex/dose	Diet	Animals were given Sorbitol (0 or 20%) in the diet for 78 weeks.	Unilateral and bilateral hyperplasia of the adrenal medulla was increased significantly for males and females receiving Sorbitol.	[4]

Ingredient	Animal (#/group)	Vehicle	Procedure	Results	Reference
Xylitol	100 mice/sex (strain 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.	[60]
Xylitol	75 rats/sex (strain 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.	[61]

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2019 FDA Frequency of Use Data

Xylitol: 472 total

01A - Baby Shampoos	XYLITOL	1
01B - Baby Lotions, Oils, Powders, and Creams	XYLITOL	2
01C - Other Baby Products	XYLITOL	4
02A - Bath Oils, Tablets, and Salts	XYLITOL	1
03D - Eye Lotion	XYLITOL	11
03E - Eye Makeup Remover	XYLITOL	8
03F - Mascara	XYLITOL	1
03G - Other Eye Makeup Preparations	XYLITOL	7
04E - Other Fragrance Preparation	XYLITOL	1
05A - Hair Conditioner	XYLITOL	4
05C - Hair Straighteners	XYLITOL	2
05F - Shampoos (non-coloring)	XYLITOL	14
05G - Tonics, Dressings, and Other Hair Grooming Aids	XYLITOL	2
05I - Other Hair Preparations	XYLITOL	5
07C - Foundations	XYLITOL	8
07F - Makeup Bases	XYLITOL	3
07I - Other Makeup Preparations	XYLITOL	6
09A - Dentifrices	XYLITOL	52
09B - Mouthwashes and Breath Fresheners	XYLITOL	22
09C - Other Oral Hygiene Products	XYLITOL	39
10A - Bath Soaps and Detergents	XYLITOL	6
10B - Deodorants (underarm)	XYLITOL	27
10E - Other Personal Cleanliness Products	XYLITOL	8
11A - Aftershave Lotion	XYLITOL	1
11E - Shaving Cream	XYLITOL	1

12A - Cleansing	XYLITOL	21
12C - Face and Neck (exc shave)	XYLITOL	82
12D - Body and Hand (exc shave)	XYLITOL	21
12F - Moisturizing	XYLITOL	76
12G - Night	XYLITOL	6
12H - Paste Masks (mud packs)	XYLITOL	3
12I - Skin Fresheners	XYLITOL	1
12J - Other Skin Care Preps	XYLITOL	24
13B - Indoor Tanning Preparations	XYLITOL	1
13C - Other Suntan Preparations	XYLITOL	1

Mannitol: 404 total

02A - Bath Oils, Tablets, and Salts	MANNITOL	1
03B - Eyeliner	MANNITOL	1
03C - Eye Shadow	MANNITOL	8
03D - Eye Lotion	MANNITOL	8
03E - Eye Makeup Remover	MANNITOL	8
03F - Mascara	MANNITOL	1
03G - Other Eye Makeup Preparations	MANNITOL	20
05A - Hair Conditioner	MANNITOL	1
05E - Rinses (non-coloring)	MANNITOL	1
05F - Shampoos (non-coloring)	MANNITOL	6
05I - Other Hair Preparations	MANNITOL	3
06G - Hair Bleaches	MANNITOL	1
07A - Blushers (all types)	MANNITOL	6
07B - Face Powders	MANNITOL	6
07C - Foundations	MANNITOL	12
07F - Makeup Bases	MANNITOL	3
07I - Other Makeup Preparations	MANNITOL	2

08A - Basecoats and Undercoats	MANNITOL	1
08B - Cuticle Softeners	MANNITOL	1
08E - Nail Polish and Enamel	MANNITOL	11
08G - Other Manicuring Preparations	MANNITOL	1
09A - Dentifrices	MANNITOL	5
10A - Bath Soaps and Detergents	MANNITOL	11
10B - Deodorants (underarm)	MANNITOL	3
11A - Aftershave Lotion	MANNITOL	1
11G - Other Shaving Preparation Products	MANNITOL	1
12A - Cleansing	MANNITOL	22
12C - Face and Neck (exc shave)	MANNITOL	104
12D - Body and Hand (exc shave)	MANNITOL	12
12E - Foot Powders and Sprays	MANNITOL	1
12F - Moisturizing	MANNITOL	81
12G - Night	MANNITOL	11
12H - Paste Masks (mud packs)	MANNITOL	10
12I - Skin Fresheners	MANNITOL	6
12J - Other Skin Care Preps	MANNITOL	31
13B - Indoor Tanning Preparations	MANNITOL	1
13C - Other Suntan Preparations	MANNITOL	2

Sorbitol: 1976 total

01B - Baby Lotions, Oils, Powders, and Creams	SORBITOL	4
01C - Other Baby Products	SORBITOL	5
02A - Bath Oils, Tablets, and Salts	SORBITOL	9
02B - Bubble Baths	SORBITOL	6
02D - Other Bath Preparations	SORBITOL	1
03A - Eyebrow Pencil	SORBITOL	1
03B - Eyeliner	SORBITOL	25

03C - Eye Shadow	SORBITOL	8
03D - Eye Lotion	SORBITOL	42
03E - Eye Makeup Remover	SORBITOL	4
03F - Mascara	SORBITOL	14
03G - Other Eye Makeup Preparations	SORBITOL	45
04A - Cologne and Toilet waters	SORBITOL	1
04B - Perfumes	SORBITOL	1
04E - Other Fragrance Preparation	SORBITOL	1
05A - Hair Conditioner	SORBITOL	53
05B - Hair Spray (aerosol fixatives)	SORBITOL	5
05C - Hair Straighteners	SORBITOL	13
05E - Rinses (non-coloring)	SORBITOL	2
05F - Shampoos (non-coloring)	SORBITOL	70
05G - Tonics, Dressings, and Other Hair Grooming Aids	SORBITOL	94
05H - Wave Sets	SORBITOL	7
05I - Other Hair Preparations	SORBITOL	65
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	SORBITOL	4
06C - Hair Rinses (coloring)	SORBITOL	1
06D - Hair Shampoos (coloring)	SORBITOL	1
06G - Hair Bleaches	SORBITOL	1
06H - Other Hair Coloring Preparation	SORBITOL	4
07B - Face Powders	SORBITOL	2
07C - Foundations	SORBITOL	30
07D - Leg and Body Paints	SORBITOL	1
07E - Lipstick	SORBITOL	3
07F - Makeup Bases	SORBITOL	5
07G - Rouges	SORBITOL	1
07H - Makeup Fixatives	SORBITOL	1
07I - Other Makeup Preparations	SORBITOL	25
08B - Cuticle Softeners	SORBITOL	3

08C - Nail Creams and Lotions	SORBITOL	1
08G - Other Manicuring Preparations	SORBITOL	1
09A - Dentifrices	SORBITOL	65
09B - Mouthwashes and Breath Fresheners	SORBITOL	15
09C - Other Oral Hygiene Products	SORBITOL	22
10A - Bath Soaps and Detergents	SORBITOL	205
10B - Deodorants (underarm)	SORBITOL	3
10E - Other Personal Cleanliness Products	SORBITOL	11
11A - Aftershave Lotion	SORBITOL	15
11D - Preshave Lotions (all types)	SORBITOL	1
11E - Shaving Cream	SORBITOL	23
11F - Shaving Soap	SORBITOL	8
11G - Other Shaving Preparation Products	SORBITOL	42
12A - Cleansing	SORBITOL	175
12B - Depilatories	SORBITOL	5
12C - Face and Neck (exc shave)	SORBITOL	217
12D - Body and Hand (exc shave)	SORBITOL	122
12E - Foot Powders and Sprays	SORBITOL	4
12F - Moisturizing	SORBITOL	269
12G - Night	SORBITOL	44
12H - Paste Masks (mud packs)	SORBITOL	51
12I - Skin Fresheners	SORBITOL	14
12J - Other Skin Care Preps	SORBITOL	87
13A - Suntan Gels, Creams, and Liquids	SORBITOL	4
13B - Indoor Tanning Preparations	SORBITOL	13
13C - Other Suntan Preparations	SORBITOL	1

Concentration of Use by FDA Product Category – Hexa/Penta-Hydric Alcohols

Sorbitol
Mannitol
Xylitol

Ingredient	Product Category	Maximum Concentration of Use
Sorbitol	Baby lotions, oils and creams Not powder	 1.4-14%
Sorbitol	Bath capsules	2.5%
Sorbitol	Other bath preparations	0.02%
Sorbitol	Eyebrow pencils	1.8%
Sorbitol	Eyeliners	0.2-1.1%
Sorbitol	Eye shadows	0.0033-0.07%
Sorbitol	Eye lotions	0.008-4.9%
Sorbitol	Eye makeup removers	0.00044%
Sorbitol	Mascara	0.0027-1.1%
Sorbitol	Other eye makeup preparations	0.12-0.7%
Sorbitol	Hair conditioners	0.00007-4%
Sorbitol	Hair sprays Aerosol Pump spray	 0.0012-1.4% 0.2-0.96%
Sorbitol	Hair straighteners	0.0011-0.64%
Sorbitol	Permanent waves	7%
Sorbitol	Rinses (noncoloring)	0.00007%
Sorbitol	Shampoos (noncoloring)	0.00028-2.8%
Sorbitol	Tonics, dressings and other hair grooming aids	0.011-10.9%
Sorbitol	Hair dyes and colors	0.006-5%
Sorbitol	Hair bleaches	0.4%
Sorbitol	Other hair coloring preparations	0.35%
Sorbitol	Blushers	2.1%
Sorbitol	Face powders	2.3-3.6%
Sorbitol	Foundations	0.1-3.5%
Sorbitol	Lipstick	1.1-4.5%
Sorbitol	Cuticle softeners	7%
Sorbitol	Nail creams and lotions	3.5%
Sorbitol	Dentifrices	13.3-70%
Sorbitol	Mouthwashes and breath fresheners (liquids and sprays)	2.8-32%
Sorbitol	Bath soap and detergents	0.5-16.7%
Sorbitol	Deodorants Not spray	 0.0005-1.1%
Sorbitol	Aftershave lotions	0.7%
Sorbitol	Preshave lotions	1.9%
Sorbitol	Shaving cream	0.69-5.6%
Sorbitol	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.00055—31.9%

Sorbitol	Depilatories	0.065-0.7%
Sorbitol	Face and neck products Not spray	 0.006-20%
Sorbitol	Body and hand products Not spray Spray	 0.006-20% 0.0038%
Sorbitol	Foot powders and sprays	1.8-3.5%
Sorbitol	Moisturizing products Not spray	 0.003-2%
Sorbitol	Night products Not spray	 0.006-0.7%
Sorbitol	Paste masks and mud packs	0.7-4.1%
Sorbitol	Skin fresheners	0.7%
Sorbitol	Other skin care preparations	0.35-3.5%
Sorbitol	Suntan products Not spray	 1.3-2.1%
Sorbitol	Other suntan preparations	0.35-3.5%
Mannitol	Eyeliners	0.00008%
Mannitol	Eye lotions	0.1%
Mannitol	Shampoos (noncoloring)	0.023%
Mannitol	Other hair preparations (noncoloring)	0.046-12.5%
Mannitol	Face powders	0.2%
Mannitol	Foundations	0.1%
Mannitol	Lipstick	0.4%
Mannitol	Nail polish and enamel	0.015-0.03%
Mannitol	Dentifrices	4.1%
Mannitol	Mouthwashes and breath fresheners (liquids and sprays)	0.9%
Mannitol	Bath soaps and detergents	0.051-0.51%
Mannitol	Deodorants Aerosol	 0.12%
Mannitol	Shaving cream	0.046-0.21%
Mannitol	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.29-20%
Mannitol	Face and neck products Not spray	 0.1-2.3%
Mannitol	Body and hand products Not spray	 0.4-2%
Mannitol	Night products Not spray	 0.000063%
Mannitol	Other skin care preparations	1.2-60.5%
Xylitol	Shampoos (noncoloring)	0.24%
Xylitol	Tonics, dressings and other hair grooming aids	0.15%
Xylitol	Hair dyes and colors	0.05%
Xylitol	Lipstick	0.06%
Xylitol	Dentifrices	5-14%
Xylitol	Mouthwashes and breath fresheners (liquids and sprays)	5%
Xylitol	Deodorants	

	Not spray Aerosol	0.09% 0.013%
Xylitol	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.09-0.12%
Xylitol	Face and neck products Not spray	 0.12-2%
Xylitol	Body and hand products Not spray	 0.042-0.5%
Xylitol	Moisturizing products Not spray	 0.35-0.5%
Xylitol	Paste masks and mud packs	0.5%
Xylitol	Other skin care preparations	1%

Information collected in 2017

Table prepared December 14, 2017

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: December 14, 2017

SUBJECT: Concentration of Use by FDA Product Category: Hexa/Penta-Hydric Alconols

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: February 15, 2019

SUBJECT: Scientific Literature Review: Safety Assessment of Hexa/Penta-Hydric Alcohols (release date January 25, 2019)

The Council respectfully submits the following comments on the scientific literature review, Safety Assessment of Hexa/Penta-Hydric Alcohols as Used in Cosmetics.

Key Issues

Introduction - As much of the information included in the report is cited to secondary references, it would be helpful to describe the secondary references used in the Introduction.

Introduction - The statement that the focus of the safety assessment is topical exposure should be deleted from the Introduction as most of the information in the report concerns oral and inhalation exposure. As these ingredients are used in oral products, e.g., dentifrices, the oral exposure information is correctly included in the report.

Much of the information in the report on Xylitol is cited to reference 37 which is a 1982 thesis. Is this an appropriate reference for a CIR report? For a number of studies, this thesis cites the WHO food additive series document on Xylitol (making the thesis a tertiary reference for some studies). Although this reference is cited in the CIR report, the original work included in the thesis (chapter 2 and beyond) is not in the CIR report.

Although the WHO food additive series documents on Mannitol and Sorbitol are cited in the CIR report, the WHO food additive series document on Xylitol is not included in the CIR report. It is at http://www.inchem.org/documents/jecfa/jecmono/v12je22.htm and should be added to the CIR report.

Acute, Summary, Table 4 - It is not correct to state that there was an oral LD_{50} of 5 g/kg bw for Mannitol in mice. This value is cited to the NTP report (reference 32) in Table 4. Please check this reference. The NTP report indicates that there were no deaths and no compound related effects observed in mice or rats at any of the doses tested. No LD_{50} value is stated. The NTP single dose oral gavage study in rats (0.3, 0.6, 1.2, 2.5 or 5 g/kg) is not included in the CIR report.

Clinical, Respiratory, Table 4, Summary - The human inhalation exposure study to Xylitol should be presented in the acute section rather than the clinical section (if it is left in the

clinical section, this section should also refer to Table 4 where the study is presented). This is one example of a study where important information from the study is omitted from the CIR report. In addition to stating the negative effects that were noted, the endpoints examined with no effects should also be stated. The human inhalation study of Xylitol also looked at electrolytes, osmolarity, lung function (spirometry [FEV1]) and bronchoalveolar lavage and found no effects. It should also be made clear that the subjects were exposed to saline as a control and that the particle MMAD was 1.63 μm with a GSD of 1.71 μm. The duration of exposure for the low dose is misstated in the text. It was 22-49 minutes for exposure to 10 mL saline and 2-10 minutes for 1 mL Xylitol. It is not correct to state that the vehicle was not report. The study states: "Xylitol was prepared by adding 5 gm of crystal sugar to every 100 ml of sterile water." The solution was then sterilized before use.

A brief description of this study is in the Summary twice; once with the acute studies and once with the clinical studies.

Additional Considerations

Method of Manufacture - The is no special manufacturing process used to make Mannitol, Sorbitol and Xylitol for cosmetics relative to making these ingredients for other purposes. Please delete: "it is unknown if these methods apply to cosmetic ingredient manufacture".

Please correct "yeast strands" to "yeast strains"

Dermal Penetration - The title of reference 26 suggests that they looked at dermal penetration in skin of rats of different ages. Did they find an effect of age?

ADME, Human, Oral, Mannitol - Please correct "administrated"

Acute - The paragraph on inhalation exposure says that there were studies in humans, but no human studies are described. Please state the dose in the inhalation study in rats as 98 mg/kg (as stated in Table 4) rather than .098 g/kg (if g are used, it should be stated as 0.098 g/kg).

Short-term, Oral - Who "provided" the multiple short-term studies?

Short-term, Inhalation - The hours/day, days/week of exposure should be stated.

Subchronic - Please provide a reference for the monkey study.

DART, Sorbitol - In the description of the three-generation study of Sorbitol in rats it states: "F_{2b} rats were killed, and the F_{2b} litter was mated". Consistent with the other generations, it is likely that the F_{2a} offspring were killed and offspring from the F_{2b} litters were mated.

DART, Xylitol - Please provide a reference for the rabbit study. Was this a dietary study?

Genotoxicity, In Vitro, Summary - Please include the dose/concentrations tested and whether or not the assays were completed with and without metabolic activation (the results both with and without metabolic activation should be stated).

Carcinogenicity, Xylitol, Table 6 - It is not correct to say that the "species" was not stated as the report (and Table 6) says the studies were in mice and rats (it should be "strain").

Corneal Damage - As the study looked at the healing rate, not damage, the subtitle should be revised.

Clinical, Metabolism - These studies should be moved to the ADME section.

Reference 28 cites the study of Sorbitol in normal and diabetic subjects to Adcock and Gray (1957). This is reference 47 in the SLR. Perhaps more details about this study can be found in the primary reference (47) rather than the secondary reference (28).

Summary - The Summary should also mention the food use of these ingredients.

Please provide units for 0.591.

Please state the days during gestation the rabbits were treated

Table 4 - Based on how reference 30 presents the inhalation study of Mannitol in rats, it is clear that the rats were exposed for 1 hour with a 14 day observation period and that there were 10 rats per group (likely 5 males and 5 females). This additional information should be added to Table 4

Table 5, Dermal - Please revise: "Microscopic treatment after 10 days of treatment..." (it is likely that they examined the skin microscopically rather than treated it).

Table 5, Oral, Mannitol - Reference 28 is the WHO Food Additive Series report on Sorbitol. It is not clear why Mannitol studies in mice are cited to this report on Sorbitol (they appear to be the NTP 14 day and 13 week studies). Rather than 13 weeks, the NTP studies in mice and rats (50 animals/sex/dose) at 0, 2.5% and 5% were 103 weeks in duration.

It should be made clear that the 27 month study was a dietary study and that the WHO monograph (reference 27) concluded that there were no effects of Mannitol on the rats in this study. The deaths were not actually attributed to Mannitol, 68% was the percentage of deaths at 27 months when they ended the study.

Table 5, Oral, Sorbitol - It is not clear why the following study in reference 28 is not included in Table 5 (and elsewhere in the CIR report): " Fifteen weanling male Wistar rats given sorbitol at levels of 10% or 15% in the diet for 17 months showed no evidence of deleterious effect on weight gain, reproduction, lactation or histopathological appearances of the main organs. The only difference with the controls was slight diarrhoea and, consequently, a retardation in growth, with rapid return to the normal."

Table 5, Oral, Xylitol - The results column (reference 35) states: "Serum levels of all parameters measures were within normal limits." Please state what was measured. Did this study just look at endpoints related to the liver?

The 2-year feed study in dogs (cited to reference 37) is presented in Table 5 twice (the wording is exactly the same in both places).

Table 5, Inhalation - The hours/day, days/week and particle sizes should be stated. Please include the references for these studies.

Table 6, Mannitol - The dietary concentrations used in the NTP bioassay in rats and mice is not stated. This is the only study in which the purity of the compound tested is given in the Ingredient column. It would be clearer if the dietary concentration was stated in the

Procedure column for all studies in this table. The references for this study are stated as "12, 12, 32".

It should be made clear that the study in which rats were fed diets containing 10% Mannitol for 104-107 weeks was a control group for a study on erythritol (reference 42).

Were the number of benign "thyomas" (needs to be corrected to "thymomas") significantly greater in treated rats (reference 27)?

Table 6, Sorbitol - Was this study on Sorbitol really included in reference 37 (the thesis on Mannitol)?