Safety Assessment of Monosaccharides, Disaccharides, and Related Ingredients as Used in Cosmetics

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date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a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

The 2013 Cosmetic Ingredient Review Expert Panel members are: Chairman, 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 Director is Lillian J. Gill, D.P.A. This safety assessment was prepared by Monice M. Fiume, Senior Scientific Analyst/Writer and Bart Heldreth, Ph.D., Chemist.

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ABSTRACT

The Expert Panel assessed the safety of 25 monosaccharides, disaccharides, and related ingredients, and concluded these ingredients are safe as used in cosmetics. Many of these ingredients are common dietary sugars, dietary sugar replacements, or very closely related analogs and salts; seven of the ingredients are GRAS ingredients. The most commonly reported cosmetic function is as a skin conditioning agent; other commonly-reported functions are use as a humectant or as a flavoring agent. The Panel reviewed the animal and clinical data included in this review. The Panel also acknowledged that the oral safety of many of these ingredients has been well established, and found it appropriate to extrapolate the existing information to conclude on the safety of all the monosaccharides, disaccharides, and related ingredients.

INTRODUCTION

This report addresses the safety of the following 25 monosaccharides, disaccharides, and related ingredients as used in cosmetic formulations:

Calcium Gluconate[#]
Fructose[#]
Fucose
Galactose
Galactosyl Fructose
Galacturonic Acid
Gluconic Acid
Glucose[#]
Isomalt[##]
Kefiran
Lactitol[##]
Lactose[##]
Lactulose
Maltose
Mannose
Melibiose
Potassium Gluconate[#]
Rhamnose
Ribose
Sodium Gluconate[#]
Sucralose[#]
Sucrose[#]
Trehalose[##]
Xylobiose
Xylose

[#]generally recognized as safe (GRAS) food additive or approved direct food additive
[##]listed in the Food Chemical Codex

These ingredients have a number of reported functions in cosmetics, and the most common is use as a skin conditioning agent.[1] Other commonly-reported functions are use as a humectant or as a flavoring agent.

Most of these ingredients are common dietary sugars, dietary sugar replacements, or very closely related analogs and salts, and several are listed by the Food and Drug Administration (FDA) as GRAS food additives or direct food additives, and/or are listed in the *Food Chemicals Codex* as used in foods. A few are inactive ingredients in drugs.[2-6]

For those ingredients identified as common dietary substances, systemic toxicity is not a concern. This approach is supported by the fact that some of these ingredients, namely fructose, galactose, glucose, lactose, sodium gluconate, and sucrose, are listed in Annex IV of the European Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).[7] Annex IV "sets out substances that are exempted from the registration, evaluation and downstream user provisions of REACH as sufficient information is known about these substances that they are considered to cause minimum risk because of their intrinsic properties."[8]

For those ingredients that are GRAS ingredients, direct food additives, or identified in the *Food Chemicals Codex* as used in foods, the focus of this assessment will be on dermal effects, primarily dermal irritation and sensitization. For those ingredients that are not identified as common dietary substances, i.e., fucose, galactosyl fructose, galacturonic acid, kefiran, lactulose, mannose, melibiose, and xylobiose, a search for oral toxicity data was performed; very limited published data were found.

CHEMISTRY

Definition

A monosaccharide is a carbohydrate that cannot be decomposed to a simpler carbohydrate by hydrolysis, and is often called a simple sugar.[9] A disaccharide is a carbohydrate that yields two monosaccharides upon hydrolysis. Many of these ingredients exist in equilibrium between an open chain form and one or more ring forms resulting in a hemiacetal or hemiketal linkage involving the aldehyde (aldose) or ketone (ketose) moiety of the open chain form, with two possible stereochemical configurations. The resulting stereoisomers are called anomers and the stereocenter is referred to as the anomeric carbon.

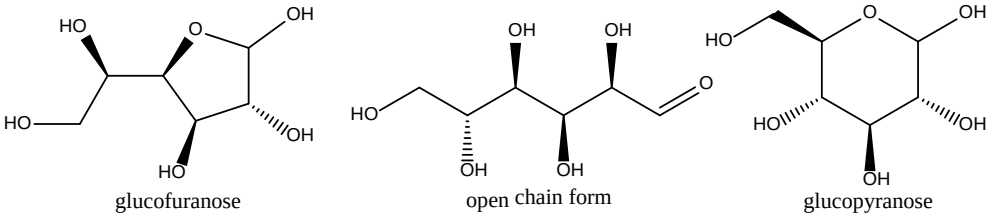


Figure 1. Structural forms of D-glucose (stereoisomer found in natural sources) that exist in equilibrium.

The definition and structure of each ingredient included in this report is provided in Table 1.

Chemical and Physical Properties

Due to the high degree of substitution with hydroxyl groups, the mono- and disaccharides are very hydrophilic and readily dissolve in aqueous solvent systems. These sugars have molecular weights ranging from 142 to 391 daltons, and are solids at room-temperature, many having multiple known crystalline forms (Table 2)

Natural Occurrence and Methods of Manufacture

The manufacture of the majority of these monosaccharides and disaccharides is accomplished by extraction from plant sources (Table 3). For instance, the sugar industry processes sugar cane and sugar beets to obtain sucrose.[10] Sugar cane contains 70% water; 14% fiber; 13.3% saccharose (about 10 to 15% sucrose), and 2.7% soluble impurities. Sugar cane is extracted with water, clarified to remove mud, evaporated to prepare syrup, crystallized to separate the liquor, and centrifuged to separate molasses from the crystals. Sugar crystals are then dried and may be further refined before bagging for shipment. Sugar beet (water, 75%; sugar, 17%) processing differs in the washing, preparation, and extraction. After washing, the beet is sliced and extracted with water. Sugar refining involves removal of impurities and decolorization. The steps generally followed include affination (mingling and centrifugation), melting, clarification, decolorization (with activated carbon, ion exchange resins, etc.), evaporation, crystallization, and finishing.

Constituents/Impurities

Purity and composition specifications are available for the food and pharmaceutical uses of many of these ingredients (Table 4).

USE

Cosmetic

The ingredients included in this safety assessment have a variety of functions in cosmetics. The most common function as skin conditioning agents; many also are reported to function as flavoring agents. A listing of all the reported functions for each ingredient is provided in Table 1.

The FDA collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). VCRP data obtained from the FDA and data received in response to a survey of the maximum reported use concentration by category conducted by the Personal Care Products Council (Council) in 2013 indicate that 19 of the 24 ingredients included in this safety assessment are used in cosmetic formulations.[11]

According to the VCRP data, sucrose has the greatest number of reported uses, 695, followed by trehalose with 449 uses and glucose with 357 uses.[11] A concentration of use survey conducted by the Council, found that the use of these mono- and disaccharides varies widely by ingredient and use-type.[12] Glucose has the highest reported use concentration in a leave-on product; it is reported to be used at 91% in "other" hair coloring products. It is also used at 97.8% in an ingestible oral hygiene product. Sucrose has the next highest reported use concentration; it is used at up to 58% in leave-on formulations and 65% in rinse-off products. However, most of the ingredients are used at less than 1% in leave-on products.

Frequency and concentration of use data categorized by exposure and duration of use are provided in Table 5. The five ingredients not reported to be used are listed in Table 6.

VCRP data indicate that glucose, lactose, sodium gluconate, sucrose, and trehalose are used in baby products; however concentration of use data for baby products were not reported by industry. Some of the ingredients are used in products that could be incidentally, or are purposely, ingested (e.g., 97.8% glucose in an ingestible oral hygiene product), and some are used near the eye area or mucous membranes (e.g., 2% sucrose in eye lotion and 65% in personal cleanliness products, respectively). Additionally, some of these ingredients are used in cosmetic sprays and powders that could possibly be inhaled (e.g., glucose is used at 1% in a spray body and hand preparation). 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.[13,14] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[15,16]

All of the ingredients included in this safety assessment are listed in the European Union inventory of cosmetic ingredients.[17] Additionally, the following ingredients are listed in REACH Annex IV: fructose; galactose; glucose; lactose; sodium gluconate; sucrose.[7]

Non-Cosmetic

Several of the ingredients have specific GRAS and direct food additive uses:

- Calcium gluconate: GRAS designation; a direct food additive that meets the specifications of the *Foods Chemical Codex*; it is used as a firming agent, formulation aid, sequestrant, and texturizer at levels not to exceed current good manufacturing practices (GMP); GMP result in a maximum level, as served, of 1.75% for baked goods; 0.4% for dairy product analogs; 4.5% for gelatins and puddings; and 0.01% for sugar substitutes (21CFR184.1199)
- Fructose: a direct food additive; in high fructose corn syrup (containing approximately 42 or 55% fructose); high fructose corn syrup must conform to the identity and specifications listed in the monograph entitled "High-Fructose Corn Syrup" in the *Food Chemicals Codex*, with no limitation other than current GMP (21CFR184.1866)
- Glucose: GRAS direct food additive (D-glucose) meeting the specifications of the *Foods Chemical Codex*; it is used in foods with no limitation other than current GMP (21CFR184.1857)
- Potassium gluconate: GRAS designation; does not have a CFR citation.[2] The Select Committee on GRAS Substances (SCOGS) concluded there is no evidence in the available information on potassium gluconate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or might reasonably be expected in the future.[18]
- Sodium gluconate: GRAS designation; as a sequestrant in food, with no limitation other than current GMP (21CFR182.6757)
- Sucralose: direct food additive as a multipurpose additive that meets the specifications of the *Foods Chemical Codex*; it is used as a sweetener in foods generally, in accordance with current GMP in an amount not to exceed that reasonably required to accomplish the intended effect (21CFR172.831)
- Sucrose: GRAS designation; a direct food additive that must be of a purity suitable for its intended use, with no limitation other than current GMP (21CFR184.1854)

Lactulose is an approved drug used to treat constipation.[19] A general list of non-cosmetic uses, including food uses that are not affirmed as GRAS or those that are inactive ingredients in approved drugs, are listed in Table 7. Table 8 provides a listing of those ingredients that are nutritive and non-nutritive sweeteners.

In Europe, the following are listed in REACH Annex IV: fructose; galactose; glucose; lactose; sodium gluconate; sucrose.[7] Substances included in Annex IV are exempted from registration (as well as downstream user requirements and evaluation) for all their possible uses irrespective of the tonnage in which they are manufactured or imported (currently or in the future).

TOXICOKINETICS

Although many of the ingredients included in this safety assessment are food ingredients, they are not all processed by the body in the same manner (e.g., see Tables 8 and 9). Some are nutrients, which are absorbed intact in the small intestines and then metabolized in the body to serve as sources of energy, and others are not (Table 8). For example, glucose[20] and potassium gluconate,[21,22] are rapidly absorbed in the small intestine (Table 9). In contrast, isomalt is absorbed only to a limited extent,[4] and lactitol,[4] lactulose,[23] and sucralose,[24-26] are not absorbed in the gut. Trehalose can be metabolized by trehalase in the gut to produce glucose, which can then be readily absorbed. Some of these ingredients (e.g., gluconic acid, potassium gluconate, and sodium gluconate) are important intermediates in carbohydrate metabolism; gluconic acid is a normal metabolic product of glucose oxidation, and the amounts produced endogenously are much greater than what is consumed.[27] Because the absorption, distribution, metabolism, and elimination of most of the ingredients included in this safety assessment have been reviewed to evaluate their use as common dietary substances, only summary information is provided in this report.

Dermal Penetration

In Vitro

Glucose

The permeability coefficient for glucose was determined *in vitro* using full thickness mouse skin and the dermis of nude mice.[28] Unlabeled glucose, 0.01 M, was first used on both sides of the skin to saturate the sorptive capacity of the cell

system. A concentration of 3.3 x 10^{-6} M D-[1,3-^{14}C]glucose, supplied as a sterile aq. solution containing 3% alcohol, was placed in the donor cell. After 6 h, the permeability coefficient of glucose was 9.5 x 10^{-5} cm/h through full-thickness skin and 0.29 cm/h through the dermis. The permeation rate continued to increase as a function of time; the researchers stated that physical and chemical deterioration of the barrier phase seemed to be responsible for the increase in permeation.

In Vivo

Glucose

The transdermal penetration of glucose through Rhesus monkey skin was measured using optical coherence tomography (OCT).[29] The hair on the right hind leg of four anesthetized monkeys was shaved, a probe holder was taped to the shaved skin, and 0.2 ml of 20% concentrated glucose in distilled water was applied topically through the hole in the probe holder during the course of imaging. The skin was imaged using OCT for 8 min prior to application of the glucose, and then for 2 h after application. The diffusion process was monitored in a 140 µm thick region 210 µm below the dermis region. The mean permeability rate of 20% glucose was calculated to be (4.41 ± 0.28) x 10^{-6} cm/sec.

TOXICOLOGICAL STUDIES

Most of the ingredients included in this assessment are found in foods, and the daily exposure from that food use would result in a much larger systemic dose than that resulting from use in cosmetic products. Numerous studies and reviews have been published about the safety of dietary exposure to mono- and disaccharides. Also, many of the ingredients included in this report are used as inactive ingredients in approved drugs that are administered via numerous routes. Consequently, systemic toxicity is not addressed further in this report for those ingredients that are GRAS ingredients, direct food additives, or identified in the *Food Chemicals Codex* as used in foods. The focus of the safe use of those mono- and disaccharides as cosmetic ingredients is on the potential for irritation and sensitization. When available, dermal toxicity, ocular irritation, and genotoxicity studies are included.

For the ingredients that are not identified as common dietary substances, i.e., the monosaccharides fucose, galacturonic acid, and mannose and the disaccharides galactosyl fructose, kefiran, lactulose, melibiose, and xylobiose, a search for oral toxicity data was performed. However, very little published data were found.

Single Dose (Acute) Toxicity

Dermal

Lactitol

The dermal LD_{50} of lactitol in rabbits is >4500 mg/kg bw.[30]

Repeated Dose Toxicity

Oral

Lactulose

Groups of eight male albino rats were fed a diet containing 0.0, 0.5, 1.0, 2.0, or 5.0% (equivalent to 0.0, 1.1, 2.2, 4.0, and 11.3 g/kg bw/day, respectively) of a 50% lactulose syrup for 21 weeks.[31] None of the animals died during the study, and no signs of general toxicity were observed. Mild diarrhea was reported for animals fed >2.2 g/kg bw/day of the test material; diarrhea subsides with 3-5 h of feeding. Feed consumption was not statistically significantly affected at any dose level. The organ weights were similar for treated and control animals. A statistically significant increase in cecal weights in the 2 and 5% groups was considered an adaptive reaction. No toxicologically-significant changes in hematology, clinical chemistry, or urinalysis parameters were reported.

Ocular Irritation

In Vitro

Gluconic Acid

The ocular irritation potential of a 50% aq. solution of gluconic acid was evaluated *in vitro* in enucleated rabbit eyes.[27] The test material was applied to four eyes and observed over a period of 4 h following application. Slight corneal swelling and slight permeability of the superficial epithelial cells were not considered to be of any toxicological significance.

Isomalt

A battery of *in vitro* tests were performed to determine the ocular irritation potential of isomalt; based on the overall results of each test included in the battery, isomalt was classified as a non-irritant. A neutral red uptake (NRU) assay was performed in human keratinocytes, and the cytotoxicity of undiluted isomalt to the cells was measured after 24-h exposure.[32] Two experiments were performed. Undiluted isomalt was classified as a non-irritant in this *in vitro* test.

A red blood cell lysis and denaturation (RBC) assay, comprised of two range-finding and denaturation assays and two lysis assays, was performed in calf red blood cells.[33] Concentrations of ≤100,000 mg/l isomalt were tested. Isomalt did not induce hemolysis or protein denaturation, and was classified as a non-irritant. Based on the lack of induction of hemolysis, the predicted *in vivo* ocular irritation potential corresponded to a modified maximum average score of 0.

The third test in the battery was the hen's egg test on the chorioallantoic membrane (HET-CAM) in which isomalt was tested undiluted according to the endpoint assessment and at concentrations of 10 and 50% (w/w) in water according to the reaction-time method.[34] Each aspect of the experiment was performed twice. According to COLIPA (now, Cosmetics Europe) classifications, undiluted isomalt was classified as a slight irritant when tested undiluted in the endpoint assessment; the 10% and 50% concentrations were classified as non-irritant using the reaction-time method.

In Vivo – Non-Human

Gluconic Acid

A 50% aq. solution of gluconic acid was not irritating to rabbit eyes.[27] A 50% solution of gluconic acid (pH 1.8; 0.1 ml) was instilled into the conjunctival sac of one eye in nine New Zealand white rabbits; the contralateral eye served as an untreated control. The eyes of three animals were rinsed after 2 sec, and of another three animals after 4 sec; the eyes of the remaining three animals were not rinsed. The eyes were examined for irritation 1, 24, 48, and 72 h and 7 days after instillation. Slight redness and conjunctival swelling were observed initially; however, no signs of irritation were observed after 72 h.

Lactitol

Lactitol was not irritating to rabbit eyes.[30] The study was performed according to the Organisation for Economic Co-operation and Development (OECD) Guideline 405.[35] No other details were provided.

In Vivo – Human

Lactose

A face and neck formulation containing 2.48% lactose did not produce irritation or hypersensitivity in a 4-wk safety-in use ophthalmological evaluation.[36] Thirty-one subjects participated in the study.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Pertinent reproductive and developmental toxicity studies were not found in the published literature, and unpublished data were not submitted.

GENOTOXICITY

The genotoxicity of a number of the mono- and disaccharides has been evaluated in *in vitro* and *in vivo* studies. The results of these studies are overwhelmingly negative (Table 10).

CARCINOGENICITY

Pertinent carcinogenicity studies were not found in the published literature, and unpublished data not were submitted.

IRRITATION AND SENSITIZATION

Dermal Irritation/Sensitization

Dermal irritation and sensitization studies are summarized in Table 11. In non-human studies, a 50% aq. solution of gluconic acid was not a dermal irritant and lactitol was not an irritant or sensitizer in rabbits. In human repeated insult patch tests (HRIPTs), formulations containing 29% sucrose (diluted to 50%), 10% rhamnose, 8% glucose, 5% mannose, 2.48% lactose, and less than 1% isomalt, kefiran, lactitol, sucralose, and xylobiose were not irritants or sensitizers. A formulation containing 10% rhamnose did induce a significant irritation reaction in one subject, and irritation was observed during induction in a HRIPT of 29% sucrose.

OCCUPATIONAL EXPOSURE LIMITS

Sucrose

The National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL) for sucrose is a time-weighted average (TWA) of 10 mg/m^3 (total exposure) and TWA of 5 mg/m^3 (respiratory exposure).[37] The Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) is a TWA of 15 mg/m^3 (total) and TWA of 5 mg/m^3 (respiratory). The American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) is 10 mg/m^3 as TWA; it is in category A4, not classifiable as a human carcinogen.

SUMMARY

This report addresses the safety of 25 monosaccharides, disaccharides, and related ingredients as used in cosmetics. Many of these ingredients are GRAS ingredients, direct food additives, or common dietary sugars, dietary sugar replacements, or very closely related analogs; for these ingredients, the focus of this review was on dermal irritation and sensitization. For the ingredients that are not identified as dietary substances, a search for oral toxicity data was performed.

These ingredients are reported to have a number of functions in cosmetics, and the most common function is as a skin conditioning agent; use as a humectant or flavoring agent was also common. According to VCRP data obtained from the FDA and concentration of use data obtained by the Council, 20 of the 25 ingredients reviewed in this assessment are reported to be in use. Sucrose has the greatest number of reported uses, 695, and glucose has the highest reported use concentration, 97.8% in an ingested breath freshener and 91% in "other" hair coloring products. The number of uses and maximum concentration of use varies widely by ingredient and type of use; most of the ingredients are used in leave-on products at less than 1%. Non-cosmetic uses include food use and use as inactive ingredients in approved drugs.

Although many of the ingredients included in this safety assessment are food ingredients, they are not all processed by the body in the same manner; some (e.g, glucose) are sources of energy and others (e.g., sucralose) are not. Also, absorption is not the same for each of these ingredients; some are absorbed in the small intestine, while others are not absorbed in the gut.

In vitro, the permeability coefficient of glucose was 9.5×10^{-5} cm/h through full thickness nude mouse skin and 0.29 cm/h through the dermis (only) of nude mouse skin. *In vivo* in Rhesus monkeys, using OCT, the mean permeability rate of 20% glucose was calculated to be $(4.41 \pm 0.28) \times 10^{-6}$ cm/sec.

Lactulose fed to rats at concentrations of up to 5.0% of 50% lactulose syrup for 21 weeks did not result in toxicity.

A battery of *in vitro* tests were performed to determine the ocular irritation potential of isomalt; based on the results, isomalt was classified as a non-irritant. Gluconic acid, as a 50% aq. solution, and lactitol, concentration not specified, were not irritating to rabbit eyes. A face and neck formulation containing 2.48% lactose did not produce irritation or hypersensitivity in a 4-wk safety-in use ophthalmological evaluation

In non-human studies, a 50% aq. solution of gluconic acid was not a dermal irritant and lactitol was not an irritant or sensitizer in rabbits. In human repeated insult patch tests (HRIPTs), formulations containing 29% sucrose (diluted to 50%), 10% rhamnose, 8% glucose, 5% mannose, 2.48% lactose, and less than 1% isomalt, kefiran, lactitol, sucralose, and xylobiose were not irritants or sensitizers. The formulation containing 10% rhamnose did induce a significant irritation reaction in one subject, and irritation was observed during induction in a HRIPT of 29% sucrose.

Lactitol, sodium gluconate, sucralose, sucrose and trehalose were not genotoxic *in vitro*. Additionally, the genotoxic potential of sodium gluconate, sucralose, and trehalose was evaluated *in vivo*; again negative results were obtained.

DISCUSSION

The Panel reviewed this safety assessment of monosaccharides, disaccharides, and related ingredients. Most of these ingredients are common dietary sugars, dietary sugar replacements, or very closely related analogs and salts. Several are GRAS food additives, direct food additives, listed in the *Food Chemicals Codex* as used in foods, and/or listed in REACH Annex IV. Because the oral safety of these ingredients has been well-documented, systemic toxicity is not a concern of the Panel.

Some of the ingredients, however, are not GRAS ingredients or direct food additives; even so, these ingredients are either listed in the *Food Chemicals Codex* as having a function in foods, listed in the Everything Added to Foods in the United States (EAFUS) inventory, and/or listed as an inactive ingredient in oral drugs. Moreover, the leave-on use concentrations of these ingredients are typically less than 1%. Therefore, the Panel stated that although oral toxicity data are very limited and reproductive toxicity data are absent, the systemic toxicity of these ingredients was not a concern because of the low concentrations of use and that these are large molecules with little chance of penetrating the skin.

The Panel commented that sucrose is used at high concentrations in some products that come in contact with mucous membranes (i.e., 65% in personal cleanliness products). The Panel noted that sucrose is a GRAS ingredient, and therefore, the Panel was not concerned about this reported use. Additionally, the Panel observed that glucose is reported to be used at 97.8% in an ingestible oral hygiene product, but recognized that glucose is a GRAS direct food additive with no limitations other than current good manufacturing practice.

The Panel discussed a human repeated insult patch test of a hair product that contained 29% sucrose, diluted to 50%, that reported irritation observed during induction. The Panel concluded that the irritation reported was likely attributable to a surfactant effect, and was not due to sucrose. Furthermore, the Panel acknowledged that sucrose and glucose are used in cosmetics at relatively high concentrations, and that data from irritation and sensitization studies at maximum use concentrations of these ingredients are lacking; however, based on the clinical experience of the Panel, there is little concern that these ingredients are irritants or sensitizers.

Because some of the ingredients included in this safety assessment can be used in products that may be aerosolized, the Panel discussed the issue of incidental inhalation exposure. Most of the use concentrations of the ingredients used in cosmetic products that may be aerosolized are less than 1% (e.g., glucose is used at 1% in a spray body and hand preparation). In the absence of inhalation data, the Panel noted these ingredients are generally large molecules, and that there is little concern for system toxicity of these ingredients. Additionally, the Panel also noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. The Panel acknowledged that the potential for

inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs, but because of the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects.

Finally, because many of these ingredients are obtained from plant sources, the Expert Panel expressed concern regarding pesticide residues and heavy metals that may be present. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulation.

CONCLUSION

The CIR Expert Panel concluded that the following 25 monosaccharides, disaccharides, and related ingredients are safe in the present practices of use and concentration in cosmetics described in this safety assessment:

calcium gluconate
fructose
fucose*
galactose*
galactosyl fructose*
galacturonic acid*
gluconic acid
glucose
isomalt
kefiran
lactitol
lactose
lactulose*
maltose
mannose
melibiose
potassium gluconate
rhamnose
ribose
sodium gluconate
sucralose
sucrose
trehalose
xylobiose
xylose

**Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.*

TABLES

Table 1. Definitions, Structures, and Reported Functions

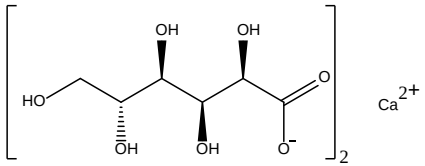
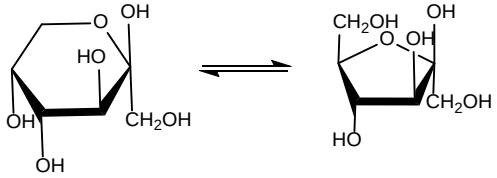
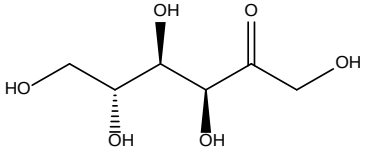
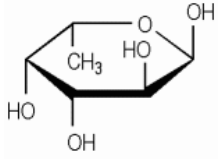
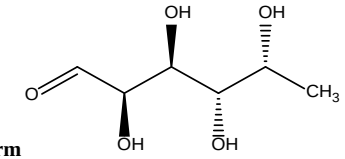
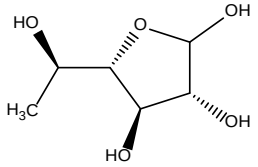
Ingredient (CAS No.)	Definition[1]*	Structure[1]***	Reported Function(s)[1]
Calcium Gluconate 299-28-5	the calcium salt of gluconic acid		chelating agent; skin-conditioning agent - miscellaneous
Fructose 30237-26-4 57-48-7 (D-)	a sugar which occurs in fruit and honey; *fructose exists in solution primarily as two cyclized forms in equilibrium,namely fructopyranose and fructofuranose.*	 ***** open chain form that exists between the furanose and pyranose forms** 	flavoring agent; humectants skin-conditioning agent - humectant
Fucose 2438-80-4 (L-) 3615-37-0 (D-)	the organic compound that conforms to the formula provided; *fucose is a deoxyhexose that is present in a wide variety of organisms; unlike most sugars, fucose occurs in nature as the L-form and lacks a hydroxyl group on the carbon at the 6-position (C-6).*	  ***** open chain form**  ***** furanose form**	skin-conditioning agent - miscellaneous

Table 1. Definitions, Structures, and Reported Functions

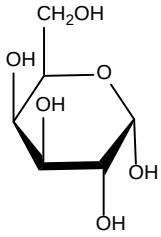
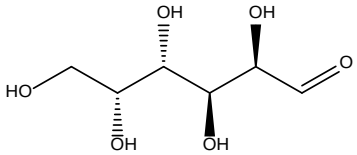
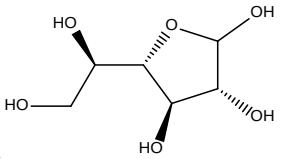
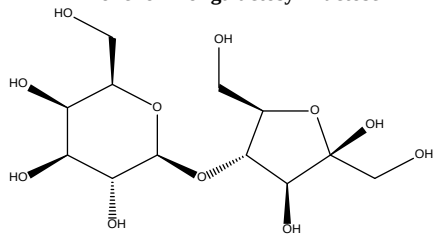
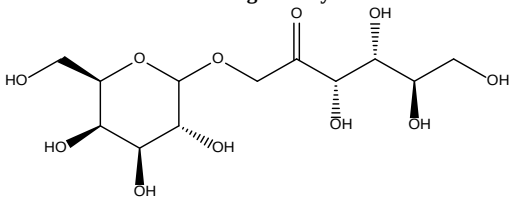
Ingredient (CAS No.)	Definition[1]*	Structure[1]***	Reported Function(s)[1]
Galactose 59-23-4	the sugar that conforms to the formula provided; g*alactose is the C4 epimer of glucose*	 ***** open chain form**   ***** furanose form**	skin-conditioning agent - miscellaneous
Galactosyl Fructose 110312-93-1	a disaccharide consisting of galactose and fructose	***** one form of galactosyl fructose**  ***** one form of galactosyl fructose** 	skin-conditioning agent - humectant

Table 1. Definitions, Structures, and Reported Functions

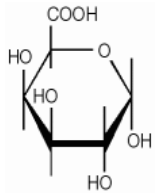
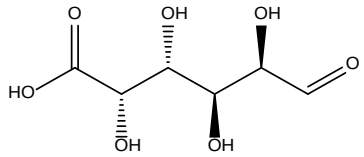
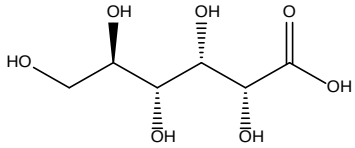
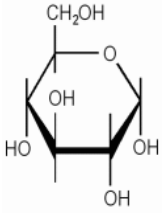
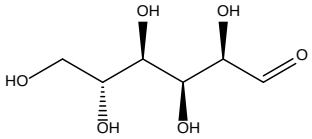
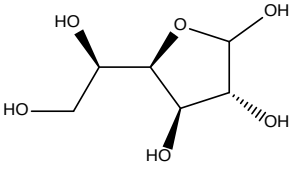
Ingredient (CAS No.)	Definition[1]*	Structure[1]***	Reported Function(s)[1]
Galacturonic Acid 14982-50-4 (DL-) 552-12-5 (D-) 685-73-4 (D-)	the organic compound that conforms to the formula provided; *galacturonic acid is the c-6 oxidation product of galactose*	  *** open chain form	chelating agent; skin-conditioning agent - humectant; pH adjuster
Gluconic Acid 133-42-6; 526-95-4	the organic compound that conforms to the formula provided; *gluconic acid is the C1 oxidation product of glucose*		chelating agent; fragrance ingredient
Glucose 50-99-7 (D-) 58367-01-4 (DL-) 5996-10-1 (DL-) 8029-43-4	a sugar that is generally obtained by the hydrolysis of starch	  *** open chain form  *** furanose form	flavoring agent; humectants; skin-conditioning agent-humectant; skin-conditioning agent – miscellaneous

Table 1. Definitions, Structures, and Reported Functions

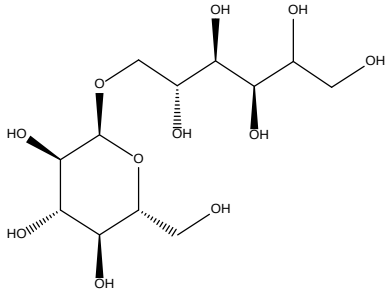
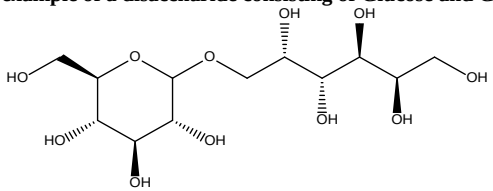
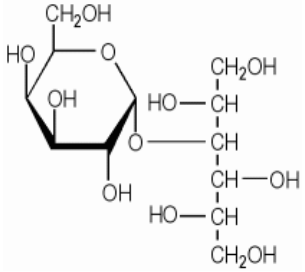
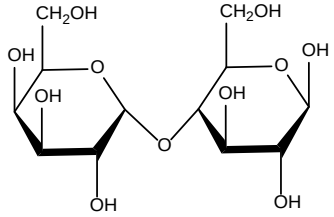
Ingredient (CAS No.)	Definition[1]*	Structure[1]***	Reported Function(s)[1]
Isomalt 64519-82-0	a mixture of polysaccharides produced by the enzymatic rearrangement of sucrose; it consists chiefly of 1-O-α-D-glucopyranosyl-D-mannitol dihydrate and 6-O-α-D-glucopyranosyl-d-sorbitol	***** one example of an isomalt form** 	anticaking agent; bulking agent; flavoring agent
Kefiran 86753-15-3	a disaccharide consisting of glucose and galactose	***** one example of a disaccharide consisting of Glucose and Galactose** 	skin-conditioning agent - humectant
Lactitol 585-86-4	a disaccharide polyol obtained by the controlled hydrogenation of lactose		flavoring agent; humectant; skin-conditioning agent - humectant
Lactose 63-42-3	the disaccharide that conforms to the formula provided; *lactose is the disaccharide (β1→4) galactosyl-glucose*		skin-conditioning agent - humectant

Table 1. Definitions, Structures, and Reported Functions

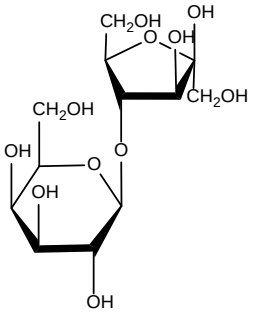
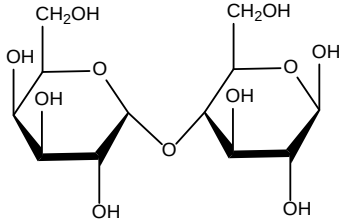
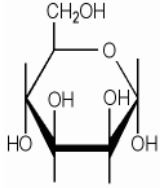
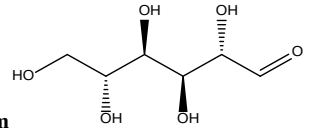
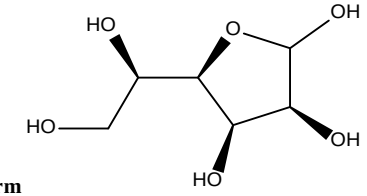
Ingredient (CAS No.)	Definition[1]*	Structure[1]***	Reported Function(s)[1]
Lactulose 4618-18-2	the disaccharide that conforms to the formula provided; *lactulose is the disaccharide (β1 →3) galactopyranosyl-fructo-furanose*		skin-conditioning agent - humectant
Maltose 16984-36-4; 69-79-4	the sugar that conforms to the formula provided; *maltose is the disaccharide α(1 →4) glucosyl-glucose*		flavoring agent; humectant; skin-conditioning agent - humectant
Mannose 3458-28-4	the sugar that conforms to the formula provided; *mannose is the C2 epimer of glucose*	 ***** open chain form**   ***** furanose form**	humectant; skin-conditioning agent - humectant

Table 1. Definitions, Structures, and Reported Functions

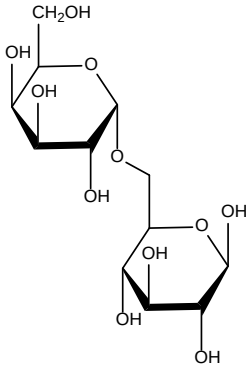
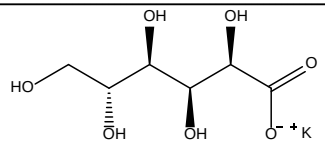
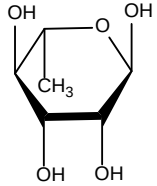
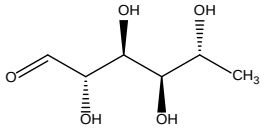
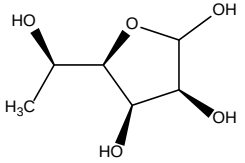
Ingredient (CAS No.)	Definition[1]*	Structure[1]***	Reported Function(s)[1]
Melibiose 5340-95-4; 585-99-9	the carbohydrate that conforms to the formula provided; *melibiose is the disaccharide α(1→6) galactosyl-glucose*		skin-conditioning agent – humectant
Potassium Gluconate 299-27-4	the potassium salt of gluconic acid		chelating agent; skin-protectant
Rhamnose 10030-85-0 3615-41-6 (L-)	the organic compound that conforms to the formula provided; *unlike most naturally abundant sugars, rhamnose occurs in nature as the L form and lacks a hydroxyl group on the carbon at the 6-position* (*C6*)	  ***** open chain form**  ***** furanose form**	flavoring agent; fragrance ingredient

Table 1. Definitions, Structures, and Reported Functions

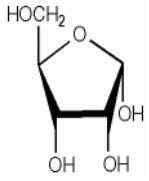
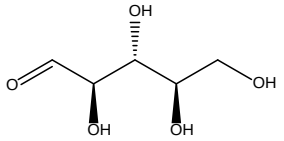
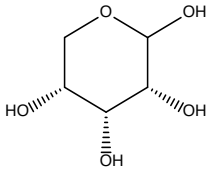
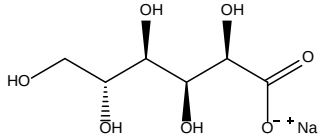
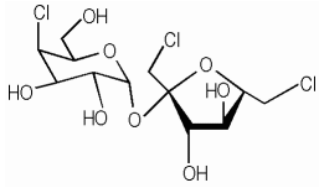
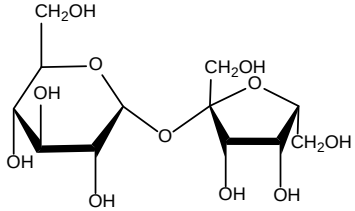
Ingredient (CAS No.)	Definition[1]*	Structure[1]***	Reported Function(s)[1]
Ribose 50-69-1	the sugar that conforms to the formula provided; *ribose is an aldopentose*	 ***** open chain form**   ***** pyranose form**	humectant; skin-conditioning agent - humectant
Sodium Gluconate 14906-97-9 527-07-1	the sodium salt of gluconic acid		chelating agent; skin-conditioning agent - miscellaneous
Sucralose 56038-13-2	the organic compound that conforms to the formula provided; *sucralose is a selectively tri-chlorinated analog of sucrose (1,6-fructo- and 4-galacto-chlorinated)*		flavoring agent
Sucrose 57-50-1	the disaccharide that conforms to the formula provided; *sucrose is the disaccharide α(1→4) glucosyl-fructose*		flavoring agent; humectant

Table 1. Definitions, Structures, and Reported Functions

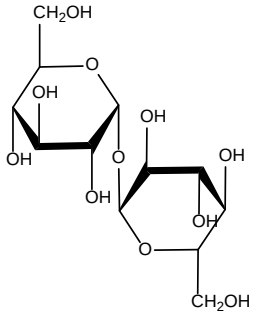
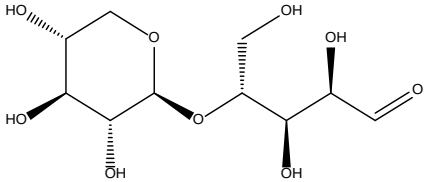
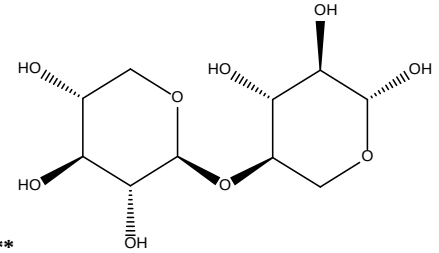
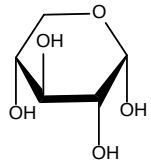
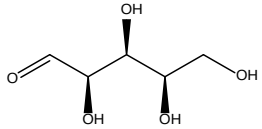
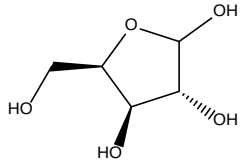
Ingredient (CAS No.)	Definition[1]*	Structure[1]***	Reported Function(s)[1]
Trehalose 99-20-7; 6138-23-4	the disaccharide that conforms to the formula provided; *trehalose is the disaccharide α(1 →1) glucosyl-glucose*		flavoring agent; humectant
Xylobiose 6860-47-5	a disaccharide consisting of two xylose units with β-1 to β-4 linkage	 ***  ***	skin-conditioning agent - humectant

Table 1. Definitions, Structures, and Reported Functions

Ingredient (CAS No.)	Definition[1]*	Structure[1]***	Reported Function(s)[1]
Xylose 58-86-6	the sugar that conforms to the formula provided; *xylose is an aldopentose*	 ***** open chain form**  ***** furanose form** 	flavoring agent; fragrance ingredient; humectant; skin-conditioning agent - humectant

*The italicized text represents additions made by CIR staff.
Structures preceded with asterisks (***) have been added by CIR staff

Table 2. Chemical and Physical Properties

Property	Description	Reference
	Calcium Gluconate	
physical characteristics	odorless, white, crystalline granules or powder	38
molecular weight	430.4	39
melting point	120°C	27
solubility	soluble in water; insoluble in ethanol	38
density	0.30-0.65 g/cm³ (bulk density)	27
log P_{ow}	-7.51 (estimated)	27
	Fructose	
physical characteristics	D-: orthorhombic, bisphenoidal prisms from alcohol DL-: needles from methanol white crystals or powder	40 41
molecular weight	180.16	40
particle size distribution	crystalline fructose: 170-450 µm powdered fructose: 25-40 µm	4
melting point	D-: decomposes at 103-105°C DL-: 129-130°C	40
solubility	D-: freely soluble in water; slightly soluble in cold and freely soluble in hot acetone; soluble in methanol, ethanol, pyridine, ethylamine, and methylamine; insoluble in ether	3,40
specific optical rotation (α^{20}_D)	D-: shows mutarotation; -132° to -92°	40
density	1.59 kg/m^3 (20°C)	42
pK_a	D-: 12.06 (18°C)	40
specific gravity (d^{16}_4)	DL-: 1.665	40
	Fucose	
physical characteristics	D-, α-form: needles from alcohol; sweet taste L-, α-form: minute needles from absolute alcohol	40
molecular weight	164.16	40
melting point	D-, α-form: 144°C L-, α-form: 140°C	40
solubility	D-, α-form: soluble in water; moderately soluble in alcohol L-, α-form: soluble in water and alcohol	40
specific optical rotation (α^{19}_D)	D-, α-form: shows mutarotation; +127.0° (7 min) ⟶ +89.4° (31 min) ⟶ +77.2° (71 min) ⟶ +76.0° (final value 146 min)	40
specific optical rotation (α^{20}_D)	L-, α-form: shows mutarotation, -124.1° (10 min) ⟶ -108.0° (20 min) ⟶ -91.5° (36 min) ⟶ -78.6° (70 min) ⟶ -75.6° (final value, 24 hrs)	40
	Galactose	
physical characteristics	α-form: prisms from water or ethanol β-form: crystals monohydrate: prisms from water	40
molecular weight	180.16	40
melting point	α-form: 167°C β-form: 167°C monohydrate: 118-120°C	40
solubility	α-form: freely soluble in hot water; soluble in pyridine; slightly soluble in alcohol	40
specific optical rotation (α_D)	α-form: +150.7° ⟶ +80.2° (water) β-form: +52.8° ⟶ +80.2° (water) D-, α-form: (α^{20}_D): +78.0° to 81.5°	40 6
	Galactosyl Fructose	
molecular weight	342.30 (predicted)	43
boiling point	780.1 ± 60°C (at 760 Torr; predicted)	43
log P	-2.810 ± 0.846 (at 25°C; predicted)	43
	Galacturonic Acid	
physical characteristics	α-form: monohydrate, needles	40
molecular weight	194.14	40
melting point	α-form: 159°C β-form: 166°C	40
solubility	α-form: soluble in water; slightly soluble in hot alcohol; practically insoluble in ether	40
specific optical rotation	α-form, (α^{20}_D): +98.0° ⟶ +50.9° (water) β-form, (α_D): +27° ⟶ +55.6° (water)	40
	Gluconic Acid	
physical characteristics	crystals; mild acid taste white crystalline powder anhydrous: commercial form is a 50% aq. solution, which is a colorless to brownish liquid.	44 45 27,45
molecular weight	196.16	44

Table 2. Chemical and Physical Properties

Property	Description	Reference
melting point	131°C	44
solubility	freely soluble in water; slightly soluble in alcohol; insoluble in ether and most other organic solvents	44
stability	in aq. solutions, the acid is partially transformed into an equilibrium mixture with γ - and δ-gluconolactones	44
	reacts with strong oxidants	45
	on combustion, forms carbon monoxide	45
specific optical rotation (α^{20}_D)	-16.7°	44
density	1.23 g/cm^3	45
log P_{ow}	-1.87 (estimated)	45
pK_a	12.06 (18°C)	44
	Glucose	
physical characteristics	α-form monohydrate: crystals from water α-form anhydrous: crystals from hot ethanol or water β-form: crystals from hot water and ethanol, from diluted acetic acid, or from pyridine	40
	white D-glucose: powder with sweet taste	46
molecular weight	180.16	40
melting point	α-form monohydrate: 83°C α-form anhydrous: 146°C β-form: 148-155°C	40
solubility	α-form anhydrous: soluble in hot glacial acetic acid, pyridine, aniline; very sparingly soluble in absolute alcohol, ether, acetone	40
log P_{ow}	D-glucose: -3.3	46
specific optical rotation	α-form monohydrate, (α^{20}_D): +102.0° ⟶ +47.9°C (water) α-form anhydrous, (α^{20}_D): +112.2° ⟶ +52.7°C (water) β-form, (α^{20}_D): +18.7° ⟶ +52.7° (water)	40
stability	D-glucose reacts violently with strong oxidants	46
	Isomalt	
physical characteristics	white crystalline, odorless, slightly hydroscopic substance	3,47
molecular weight	380.32	3
boiling point	788.5 ± 60°C (at 760 Torr; predicted)	43
solubility	soluble in water; very slightly soluble in ethanol	3,47
log P	-2.810 ± 0.846 (at 25°C; predicted)	43
pK_a	12.89 ± 0.70 (25°C) (predicted)	43
	Lactitol	
physical characteristics	crystals from absolute ethanol; strongly hygroscopic monohydrate: white, sweet, odorless crystalline solid; non-hygroscopic dihydrate: white, sweet, odorless crystalline powder	40
molecular weight	344.31 (anhydrous); 362.37 (monohydrate)	3,40
melting point	146°C monohydrate: 94-97°C dihydrate: 75°C (food-grade)	40
partition coefficient	< -3 (20°C)	30
solubility	soluble in water, dimethyl sulfoxide, *N*,*N*-dimethylformamide; slightly soluble in ethanol, ether	40
specific optical rotation	(α^{23}_D): +14° monohydrate, (α^{22}_D): +12.3° dihydrate, (α^{25}_D): +13.5 – 15.0°	40
	Lactose	
physical characteristics	α-lactose monohydrate: monoclinic sphenoidal crystals from water; faintly sweet taste; readily absorbs odors	40
molecular weight	342.30	40
particle size distribution	varies by grade	4
melting point	α-lactose monohydrate: 201-202°C	40
solubility	α-lactose monohydrate: practically insoluble in alcohol; insoluble in chloroform, ether	40
specific optical rotation	α-lactose monohydrate, (α^{20}_D): shows mutarotation; +92.6° ⟶+83.5° (10 min.) ⟶+69° (50 min) ⟶+52.3° (22 h) β-lactose, (α^{25}_D): +34° (3 min) ⟶+39° (6 min) ⟶+46° (1 hr) ⟶+52.3° (22 h)	40
K_a (16.5°C)	α-lactose monohydrate: 6.0 x 10^{-13}	40
	Lactulose	
physical characteristics	hexagonal clustered plates from methanol	40
molecular weight	342.30 (anhydrous); 360.32 (monohydrate)	3,40
melting point	168-171°C	40
specific optical rotation (α^{22}_D)	shows mutarotation; constant value after 24 h, -51.5°	40

Table 2. Chemical and Physical Properties

Property	Description	Reference
	Maltose	
physical characteristics	monohydrate: crystals from water or diluted alcohol	40
molecular weight	342.30	40
melting point	monohydrate: 102-103°C	40
solubility	α-lactose monohydrate: practically insoluble in alcohol; insoluble in chloroform, ether	40
pH	anhydrous: 3.7-4.7; monohydrate: 4.5-5.5	6
specific optical rotation (α^{20}_D)	monohydrate: shows mutarotation; +111.7° ⟶ +130.4°	40
pK_a (21°C)	monohydrate: 12.05	40
	Mannose	
physical characteristics	α-form: crystals from methanol β-form: orthorhombic, bisphenoidal needles from alcohol or acetic acid; sweet taste with bitter aftertaste	40
molecular weight	180.16	40
melting point	α-form: 133°C β-form: decomposes at 132°C	40
specific optical rotation	α-form, (α_D): +29.3° ⟶ +14.2° (water) β-form, (α^{20}_D): -17.0° ⟶ +14.2° (water)	40
	Melibiose	
physical characteristics	dihydrate: monoclinic crystals from water of diluted alcohol	40
molecular weight	342.30	40
dihydrate	α-form: 84-85°C	40
specific optical rotation (α^{20}_D)	dihydrate:: +111.7° ⟶ +129.5°	40
	Potassium Gluconate	
physical characteristics	yellowish-white crystals; mild, slightly saline, taste	44
molecular weight	234.25 (anhydrous); 252.26 (monohydrate)	3,44
melting point	decomposes at 180°C	44
solubility	freely soluble in water and glycerin; practically insoluble in alcohol, ether, benzene, and chloroform	3,44
log P_{ow}	-5.99 (estimated)	27
pH	7.5-8.5 (aq. solution)	44
stability	stable in air	44
specific optical rotation (α^{20}_D)	-16.7°	44
density	0.80 g/cm^3 (20°C; bulk density)	27
	Rhamnose	
physical characteristics	α-form: monohydrate, holohedric rods from water; hemihedric monoclinic columns from alcohol; very sweet taste β-form: needles; hygroscopic	40
molecular weight	164.16	40
melting point	α-form: 82-92°C; sublimes at 105°C and 2 mm Hg β-form: 122-126°C	40
specific optical rotation	α-form, (α^{20}D): shows mutarotation; -7.7° ⟶ +8.9° β-form, (α^{20}_D): -17.0° ⟶ +31.5°	40
specific gravity (d^{20}_4)	1.4708	40
stability	α-form: loses water of crystallization upon heating, and partially changes to the β-modification β-form: changes into crystals of the α-modification upon exposure to moist air	40
	Ribose	
physical characteristics	plates from absolute alcohol	40
molecular weight	150.13	40
melting point	87°C	40
solubility	soluble in water, slightly soluble in alcohol	40
specific optical rotation (α^{20}_D)	final, shows complex mutarotation; -25°	40
	Sodium Gluconate	
physical characteristics	white crystals white to tan, granular to fine, crystalline powder technical grade may have a pleasant odor	48 3 44
molecular weight	218.14	44
melting point	170-175°C; decomposes at 196-198°C	48
solubility	soluble in water; sparingly soluble in alcohol; insoluble in ether	44
log P_{ow}	-5.99 (estimated)	48
density	1.8 g/cm^3	48
	Sucralose	
physical characteristics	anhydrous crystalline form: orthorhombic needle-like crystals; intensely sweet taste	40
molecular weight	397.63	40

Table 2. Chemical and Physical Properties

Property	Description	Reference
particle size distribution	90% <12 µm	4
solubility	soluble in water	24
octanol/water partition coefficient	-0.51 ($\log_{10}$ P)	4
specific optical rotation (α_D)	+68.2°	40
	(α^{20}_D): +84.0° to +87.5°, calculated on the anhydrous basis	3
	Sucrose	
physical characteristics	monoclinic sphenoidal crystals, crystalline masses, blocks, or powder; sweet taste	40
	hard, white, odorless crystals, lumps, or powder; may have a characteristic caramel odor when heated	49
molecular weight	342.30	40
melting point	decomposes at 160-186°C	40
solubility	moderately soluble in glycerol, pyridine; practically insoluble in dehydrated alcohol	40
log P_{ow}	-3.67	37
specific optical rotation	(α^{20}_D): +65.9° to +66.7°	3
	(α^{25}_D): +66.47 to +66.49°	40
pK_a	12.62	40
specific gravity (d^{25}_4)	1.587	40
stability	stable in air	40
	hydrolyzed to glucose and fructose by diluted acids and by invertase	
	Trehalose	
physical characteristics	orthorhombic, bisphenoidal crystals for diluted alcohol; sweet taste	40
	typically found in the dihydrate form; characterized by low hygroscopicity	50,51
molecular weight	342.30	40
melting point	the dihydrate melts at 97°C; additional heat drives off the water of crystallization until it resolidifies at 130°C; the anhydrous then melts at 210°C	51
solubility	very soluble in water, formamide, and dimethyl sulfoxide; soluble hot alcohol; slightly soluble to insoluble in ether	3,40
stability	very stable and chemically unreactive; does not dissociate into two reducing monosaccharidic constituents unless exposed to extreme hydrolytic conditions or to the actions of trehalose	52
specific optical rotation (α^{20}_D)	+178°	40
	Xylobiose	
molecular weight	282.24 (predicted)	43
boiling point	604 ± 55°C (at 760 Torr; predicted)	43
log P	-2.900 ± 0.852 (at 25°C; predicted)	43
pK_a	12.40 ± 0.20 (25°C) (predicted)	43
	Xylose	
physical characteristics	monoclinic needles or prisms; very sweet taste	40
	white, odorless, crystal or crystalline powder with a sweet taste	53
molecular weight	150.13	40
melting point	144-145°C	40
solubility	soluble in glycerol, pyridine, hot alcohol	40
specific optical rotation (α^{20}_D)	shows mutarotation; +92° → +18.6° (16 hrs)	40
pK_a (18°C)	12.14	40
specific gravity (d^{20}_4)	1.525	40

Table 3. Natural Occurrence and /or Methods of Preparation

Ingredient	Natural Occurrence and/or Method of Preparation	Reference
Fructose	- occurs in many fruits and in honey	40
	- prepared by adding absolute alcohol to the syrup obtained from the acid hydrolysis of inulin; prepared from dextrose; prepared from sucrose by enzymatic conversion	
	- obtained from glucose in corn syrup by the use of glucose isomerase	3,42
Fucose	D-: obtained from glucosides found in various species of Convolvulaceae	40
	L-: occurs in seaweed - *Ascophyllum nodosum* (L.), *(Fucus nodosus* L.), *Fucus vesiculosus* L., *F. serratus, F. virsoides*, *Fucaceae* - and in gum tragacanth	
	L-: a common component of many N- and O-linked glycans and glycolipids produced by mammals	54
Galactose	- constituent of many oligo- and polysaccharides in pectins, gums, and mucilages; isolation in the processing of the red algae, *Porphyra umbilicalis*	40
	- a product of lactose metabolism	6
Galacturonic Acid	obtained by hydrolysis of pectin where it is present as polygalacturonic acid	40
Gluconic Acid	- prepared by oxidation of glucose; produced commercially using *Aspergillus niger, A. fumaricus, Aerobacter aceti, Penicillium chrysogenum,* or other *Penicillia*	44,55

Table 3. Natural Occurrence and /or Methods of Preparation

Ingredient	Natural Occurrence and/or Method of Preparation	Reference
Glucose	- produced by the complete hydrolysis of corn starch with safe and suitable acids or enzymes, followed by refinement and crystallization from the resulting hydrolysate - occurs naturally and in the free state in fruits and other parts of plants; combined in glucosides, in disaccharides and oligosaccharides, in the cellulose and starch of polysaccharides, and in glycogen; manufactured on a large scale from starch; below 50°C, α-D-glucose hydrate is the stable crystalline form, above 50°C, the anhydrous form is obtained, and at higher temperatures, β-D-glucose is formed - normal human blood contains 0.08-0.1%	21CFR184.1857 40
Isomalt	produced from food-grade sucrose in a two-stage process: beet sugar is converted by enzymatic transglucosidation into isomaltulose, which undergoes catalytical hydrogenation to produce isomalt	4
Lactitol	prepared by the hydrogenation of lactose	40
Lactose	- present in the milk of mammals: human, 6.7%: cow, 4.5% - by-product of the cheese industry, produced from whey - β-lactose: obtained by crystallizing concentrated solutions of α-lactose above 93.5°C	40
Lactulose	- synthetic disaccharide composed of galactose and fructose - can be produced from agricultural by-products and from lactose	40 31
Maltose	obtained in 80% yield by enzymatic (diastase) degradation of starch	40
Mannose	α-form prepared by treating ivory nut shavings with H_2SO_4	40
Melibiose	prepared from raffinose by fermentation with top yeast, which removes the fructose	40
Potassium Gluconate	prepared by the reaction of potassium hydroxide or carbonate with gluconic acid	21
Rhamnose	- occurs free in poison sumac; combined in the form of glycosides of many plants; isolated from the walls of gram-negative bacteria α-form: obtained by crystallization from water or ethyl alcohol β-form: prepared by heating α-rhamnose monohydrate on a steam bath	40
Ribose	prepared by hydrolysis of yeast-nucleic acid; obtained from glucose, nucleosides, D-erythrose, and L-glutamic acid; obtained by the reduction of D-ribonic acid	40
Sucralose	- chlorinated derivative of sucrose - synthesized by selective chlorination of sucrose at three of the primary hydroxyl groups - can be synthetized by the reaction of sucrose (or an acetate) with thionyl chloride	40 25 4
Sucrose	- obtained from sugar cane and sugar beet: sugar cane (*Saccharum officinarum* L.) contains 10-15% sucrose, sugar beet (*Beta valgaris* L., Chenopodiaceae) contains 10-17% sucrose - sucrose is obtained by crystallization from sugar cane or sugar beet juice that has been extracted by pressing or diffusion, then clarified and evaporated - most abundant carbohydrate in the sap of land plants	40 21CFR184.1854 56
Trehalose	- found in fungi, bacteria, yeasts, and insects; isolated from the ergot of rye; isolated from yeast - produced from starch using the enzymes maltooligosyl-trehalose synthase and maltooligosyl-trehalose trehalohydrolase	40 51
Xylose	- widely distributed in plant materials, especially wood (maple, cherry), in straw, and in hulls; not found in the free state – is found in the form of xylan, a polysaccharide consisting of D-xylose units occurring in association with cellulose; also occurs as part of glycosides; can be isolated from corn cobs - produced industrially by hydrolysis of extracts from cotton seed shells, press residue of sugarcane and beech tree chips	40 53

Table 4. Purity specifications

Ingredient	Purity Specifications
Fructose	food use: not more than (NMT) 0.018% chloride; NMT 0.1 mg/kg lead; NMT 0.5% glucose; NMT 0.1% hydroxy-methylfurfural, calculated on the dried ash and free-ash basis; NMT 0.5% loss on drying; NMT 0.5% residue on ignition (sulfated ash)[3] USP: NMT 1 ppm arsenic;; NMT 5 ppm heavy metals: NMT 0.5% loss on drying; NMT 0.5% residue on ignition[6]
Galactose	USP: NMT 1.0% water; NMT 0.1% residue on ignition[6]
Isomalt	food use: NMT 7% water; NMT 0.05% sulfated ash; NMT 3% D-mannitol; NMT 6% D-sorbitol; NMT 0.3% reducing sugars; NMT 2 mg/kg nickel; NMT 1 mg/kg lead[47]; - NMT 1 mg/kg lead; NMT 2 mg/kg nickel; NMT 3% mannitol and NMT 6% sorbitol; NMT 0.3% cuprous oxide (as glucose); NMT 7.0% water; NMT 0.05% residue on ignition (sulfated ash)[3] USP: NMT 7% water; NMT 1 µg/g nickel; NMT 10 µg/g heavy metals; NMT 0.3% reducing sugars[6]
Lactitol	food use: NMT 1 mg/kg lead; NMT 1 mg/kg nickel; NMT 4.0% other hydrogenated saccharides (polyols); NMT 5% water; NMT 0.3% cuprous oxide residue; NMT 0.1% residue on ignition (sulfated ash)[3] USP: 4.5-5.5% water, monohydrate, or 10.5%, dihydrate; NMT 0.5% water, anhydrate; NMT 0.5% residue on ignition[6]
Lactose	food use: NMT 0.5 mg/kg arsenic; NMT 0.5 mg/kg lead; NMT 0.3% residue on ignition (sulfated ash)[3]; loss on drying: not less than 4.5% and NMT 5.5%, monohydrate and spray-dried mixture; NMT 1.0%, anhydrous[3] USP: water: NMT 1.0%, anhydrous, 4.5-6.5%, monohydrate; heavy metals: 5 µg/g, anhydrous and monohydrate; loss on drying: NMT 0.5%, anhydrous and monohydrate; residue on ignition: NMT 0.1%, anhydrous and monohydrate[6]
Maltose	USP: water: NMT 1.5%, anhydrous, 4.5-5.5%, monohydrate; NMT 5 µg/g heavy metals; NMT 0.05% residue on ignition[6]

Table 4. Purity specifications

Ingredient	Purity Specifications
Potassium Gluconate	food use: NMT 1% calculated as D-glucose;[57] NMT 2 mg/kg lead;[3,57] NMT 1.0% reducing substances; NMT 3.0% (anhydrous) and 6.0-7.5% (monohydrate) loss on drying[3] USP: NMT 0.002% heavy metals; NMT 1.0% reducing substances; loss on drying: NMT 3.0%, anhydrous, and 6.0-7.5%, monohydrate [6]
Sodium Gluconate	food use: NMT 2 mg/kg lead; NMT 0.5% reducing substances, calculated as D-glucose [3] USP: NMT 0.001% lead; NMT 0.002% heavy metals; NMT 0.5% reducing substances[6]
Sucralose	food use: NMT 1 mg/kg lead; NMT 2.0% water; NMT 0.1% methanol; NMT 0.7% residue on ignition (sulfated ash)[3] USP: NMT 2.0% water; NMT 0.001% heavy metals; NMT 0.7% residue on ignition[6]
Sucrose	food use: NMT 1 mg/kg arsenic; NMT 0.1 mg/kg lead; NMT 0.1% invert sugars; NMT 0.15% residue on ignition (sulfated ash); NMT 0.1% loss on drying[3] USP: NMT 5 ppm heavy metals; NMT 0.05% residue on ignition[6]
Trehalose	food use: NMT 0.1 mg/kg lead; NMT 11.0% water; NMT 0.05% residue on ignition (sulfated ash)[3]
Xylose	USP: NMT 5 ppm iron; NMT 0.001% heavy metals; NMT 0.1% loss on drying; NMT 0.5% residue on ignition[6]

Table 5. Frequency and concentration of use according to duration and type of exposure

	# of Uses[11]	*Max. Conc. of Use (%)*[12]	*# of Uses*[11]	*Max. Conc. of Use (%)*[12]	*# of Uses*[11]	*Max. Conc. of Use (%)*[12]
	Calcium Gluconate		**Fructose**		**Gluconic Acid**	
Totals*	**58**	**0.0000075-1**	**153**	**0.0001-20**	**6**	**0.0001-0.18**
Duration of Use						
Leave-On	*47*	*0.0000075-1*	*130*	*0.0002-2*	*2*	*0.0001-0.18*
Rinse Off	*11*	*0.0000075-0.1*	*23*	*0.0001-20*	*4*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	3	0.0000075-.05	10	0.002-0.075	NR	NR
Incidental Ingestion	NR	0.00006-0.5	1	NR	NR	NR
Incidental Inhalation-Spray	5[a]	spray: 0.0006-0.1 0.0000075[a]	aerosol: 1 1[a]	aerosol: 0.0002 0.08-2[a]	NR	NR
Incidental Inhalation-Powder	2	0.2	NR	powder: 0.002 0.033-0.68[b]	NR	NR
Dermal Contact	53	0.0000075-1	136	0.0003-20	6	0.001-0.18
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	5	0.008-0.1	16	0.0001-0.1	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	.00006-0.5	3	0.0015-0.002	4	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Glucose		**Isomalt**		**Kefiran**	
Totals*	**357**	**0.00003-97.8**	**7**	**0.19-7.77**	**NR**	**0.1**
Duration of Use						
Leave-On	*266*	*0.0001-91*	*6*	*0.19*	*NR*	*0.1*
Rinse Off	*83*	*0.00003-97.8*	*1*	*7.77*	*NR*	*NR*
Diluted for (Bath) Use	*8*	*19*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	27	0.0001-0.48	2	NR	NR	NR
Incidental Ingestion	1	0.059-97.8 (97.8 is an ingested breath freshener)	NR	NR	NR	NR
Incidental Inhalation-Spray	15[a]	spray: 1 0.0045-2.9[a]	NR	NR	NR	NR
Incidental Inhalation-Powder	2	0.0003-1[b]	NR	NR	NR	NR
Dermal Contact	319	0.0001-84	7	0.19	NR	0.1
Deodorant (underarm)	NR		NR	NR	NR	NR
Hair - Non-Coloring	36	0.00003-91	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	7.77	NR	NR
Nail	1	0.0004	NR	NR	NR	NR
Mucous Membrane	29	0.00063-97.8 (97.8 is an ingested breath freshener)	NR	NR	NR	NR
Baby Products	4	NR	NR	NR	NR	NR

Table 5. Frequency and concentration of use according to duration and type of exposure

	# of Uses[11]	Max. Conc. of Use (%)[12]	# of Uses[11]	Max. Conc. of Use (%)[12]	# of Uses[11]	Max. Conc. of Use (%)[12]
	Lactitol		**Lactose**		**Maltose**	
Totals*	**8**	**0.15-0.2**	**68**	**0.0005-9.4**	**2**	**0.3-0.5**
Duration of Use						
Leave-On	*NR*	*NR*	*24*	*0.0005-6*	*1*	*0.3-0.5*
Rinse Off	*8*	*0.15-0.2*	*43*	*0.038-9.4*	*1*	*0.5*
Diluted for (Bath) Use	*NR*	*NR*	*1*	*8*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	8	NR	NR	NR
Incidental Ingestion	NR	NR	1	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	6[c]	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	6[c]	NR	NR
Dermal Contact	3	0.15-0.2	61	0.001-6	1	0.3-0.5
Deodorant (underarm)	NR	NR	NR	aerosol: 0.038 not spray: 0.075-0.25	NR	NR
Hair - Non-Coloring	5	NR	3	0.0005-9.4	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	3	0.3	1	NR
Mucous Membrane	NR	0.2	23	0.038-8 diluted use product:	NR	NR
Baby Products	NR	NR	1	NR	NR	NR

	Mannose		**Melibiose**		**Potassium Gluconate**	
Totals*	**3**	**5**	**2**	**0.1-0.25**	**10**	**0.002-0.1**
Duration of Use						
Leave-On	*3*	*5*	*2*	*0.1-0.25*	*8*	*0.002-0.1*
Rinse Off	*NR*	*NR*	*NR*	*NR*	*2*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	1	NR	1	0.1	1	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	0.05[a]
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	0.1[b]
Dermal Contact	3	5	2	0.1-0.25	9	0.002-0.1
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	1	0.05
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Rhamnose		**Ribose**		**Sodium Gluconate**	
Totals*	**5**	**5-10**	**11**	**0.05**	**154**	**0.0000075-12**
Duration of Use						
Leave-On	*5*	*5-10*	*9*	*0.05*	*73*	*0.0000075-12*
Rinse Off	*NR*	*NR*	*2*	*NR*	*81*	*0.0000075-0.8*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	6	0.0000075-0.2
Incidental Ingestion	NR	NR	NR	NR	NR	0.00006-0.75
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	spray: 0.0006 0.0000075-0.6[a]
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	0.2[b]
Dermal Contact	5	5-10	11	0.05	94	0.0000075-5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	57	0.2-12
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	12	0.00006-0.8
Baby Products	NR	NR	NR	NR	1	NR

Table 5. Frequency and concentration of use according to duration and type of exposure

	# of Uses[11]	*Max. Conc. of Use (%)*[12]	*# of Uses*[11]	*Max. Conc. of Use (%)*[12]	*# of Uses*[11]	*Max. Conc. of Use (%)*[12]
	Sucralose		**Sucrose**		**Trehalose**	
Totals*	**89**	**0.012-1.2**	**695**	**0.001-65**	**449**	**0.0001—2**
Duration of Use						
Leave-On	*45*	*0.2-0.6*	*402*	*0.001-58*	*336*	*0.00055-2*
Rinse Off	*44*	*0.012-1.2*	*278*	*0.001-65*	*113*	*0.0001-1*
Diluted for (Bath) Use	*NR*	*NR*	*15*	*1-52*	*NR*	*NR*
Exposure Type						
Eye Area	1	NR	54	0.0035-2	45	0.02-1.1
Incidental Ingestion	73	0.012-1.2	4	9-45	3	0.005-0.1
Incidental Inhalation-Spray	NR	0.012-0.95[a]	16[a] spray: 2	spray: 1 0.002-2[a]	6[a] spray: 2	0.002-1[a]
Incidental Inhalation-Powder	NR	NR	4	0.001-5.5[b]	6	0.12 0.00055-2[b]
Dermal Contact	16	0.5-0.6	621	0.001-65	355	0.00055-2
Deodorant (underarm)	NR	NR	NR	aerosol: 0.004 not spray: 0.005-0.009	NR	NR
Hair - Non-Coloring	NR	NR	51	0.001-10.5	87	0.0001-1
Hair-Coloring	NR	NR	13	NR	NR	NR
Nail	NR	NR	2	13.6	1	1
Mucous Membrane	74	0.012-1.2	172	0.001-65	11	0.005-0.1
Baby Products	NR	NR	1	NR	1	NR

	Xylobiose		**Xylose**			
Totals*	**3**	**0.0075-0.15**	**59**	**0.1-1**		
Duration of Use						
Leave-On	*3*	*0.075-0.15*	*54*	*0.1-0.11*		
Rinse Off	*NR*	*0.0075-0.05*	*5*	*0.1-1*		
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*		
Exposure Type						
Eye Area	NR	NR	2	NR		
Incidental Ingestion	NR	NR	NR	NR		
Incidental Inhalation-Spray	NR	NR	1	pump spray: 0.11		
Incidental Inhalation-Powder	NR	0.075[2]	NR	NR		
Dermal Contact	3	0.0075-0.15	27	NR		
Deodorant (underarm)	NR	NR	NR	NR		
Hair - Non-Coloring	NR	0.091	30	0.1-0.11		
Hair-Coloring	NR	NR	NR	1		
Nail	NR	NR	NR	NR		
Mucous Membrane	NR	0.0075	NR	NR		
Baby Products	NR	NR	NR	NR		

* Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types my not equal the sum of total uses
[a] Includes products that can be sprays, but it is not known whether the reported uses are sprays
[b] Includes products that can be powders, but it is not known whether the reported uses are powders
[c]Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation
NR – not reported

Table 6. Ingredients Not Reported to be Used
Fucose
Galactose
Galactosyl Fructose
Galacturonic Acid
Lactulose

Table 7. Examples of non-cosmetic uses

Ingredient	Use	Reference
Calcium Gluconate	- a direct food additive used as a firming agent, formulation aid, sequestrant, and texturizer	21CFR184.1199
	- used as mineral supplements in pharmaceutical injection solutions	[27]
	- GRAS in animal feed	21CFR582.1199; 21CFR582.6199
Fructose	- listed in the *United States Pharmacopeia* (USP)*/National Formulary* (NF)	[3]
	- inactive ingredient for approved drugs; used in oral, intravenous, and rectal drugs	[6]
	- can function as a dissolution enhancer, flavoring agent, sweetening agent, and tablet diluent in pharmaceuticals, is used tablets, syrups, and solutions as a flavoring and sweetening agent	[5] [4]
Galactose	- listed in the USP/NF	[6]
	- inactive ingredient for approved drugs; used in oral and rectal products	[5]
Gluconic Acid	industrial cleaning; metal surface treatment; textile bleach stabilizer; aluminum processing ; chelating agent in dispersive cements, cleaning products, pharmaceuticals, and food stuff; sequestering agent in dispersive building materials	[27]
Glucose	- in sweeteners and table syrups, with specifications defined in the CFR	21CFR168.110, 111, 120, 121
	- in a glucose/glycine/electrolyte in animal drugs, feeds, and related products	21CFR520.550
	- listed in the USP/NF as a liquid	[6]
	- approved as an inactive ingredient for approved drugs; used in oral products	[5]
Isomalt	- listed in the *Foods Chemicals Codex* as a texturizer, formulation aid, surface finishing agent, stabilizer, thickener	[3]
	- listed in the USP/NF	[6]
	- inactive ingredient for approved drugs; used in oral products	[5]
	- can function as a coating agent, granulation aid, medicated confectionary base, sweetening agent, or tablet and capsule diluent in pharmaceuticals; a non-cariogenic excipient used in tablets or capsules, coatings, sachets, and effervescent tablets; often used in buccal applications	[4]
Lactitol	- listed in the *Foods Chemicals Codex* as a humectant, stabilizer	[3]
	- listed in the USP/NF	[6]
	- inactive ingredient for approved drugs; used in oral products (the monohydrate)	[5]
	- can function as a sweetening agent, tablet and capsule diluent, and therapeutic agent in pharmaceuticals; used as a non-cariogenic replacement for sucrose, a diluent in solid dosage forms, and therapeutically in the treatment of encephalopathy and as a laxative	[4]
Lactose	- in sweeteners and table syrups, with specifications defined in the CFR	21CFR168.122
	- used as a nutrient in the preparation of modified milk and food for infants and convalescents (predominantly the α-form, but also the β-form)	[40]
	- listed in the *Foods Chemicals Codex* as a processing aid, humectant (anhydrous form), texturizer	[3]
	- inactive ingredient for approved drugs; used in transdermal, oral, sublingual, buccal, inhalation, subcutaneous, vaginal, intravenous, intramuscular, and rectal drugs	[5]
	- in pharmaceuticals, lactose, anhydrous can function as a directly compressible tablet excipient, dry powder inhaler carrier, lyophilization aid, tablet and capsule diluent, tablet and capsule filler; widely used in direct compression tableting applications and as a tablet and capsule filler and binder, and it can be used in i.v. injections	[4]
	- lactose, monohydrate can function as a dry powder inhaler carrier, lyophilization aid, tablet binder, tablet and capsule diluent, tablet and capsule filler; is widely used as a filler and diluent in tablets and capsules	
	- lactose, inhalation can function as a diluent and as a dry powder inhaler carrier; it is widely used as a carrier, diluent, and flow aid in dry powder formulations, and when of suitable particle size, it can be used to prepare soft pellets of dry powder inhaler formulations	
	- lactose, spray-dried can function as a directly compressible tablet excipient, tablet and capsule diluent, tablet and capsule filler; widely used as a binder, filler-binder, and flow aid in direct compression tableting	
Lactulose	- listed in the USP/NF as a concentrate	[6]
	- an approved drug used to treat constipation; used in oral and rectal products	[19]
Maltose	-listed in the Everything Added to Food in the United States (EAFUS) inventory	[58]
	- listed in the USP/NF	[6]
	- inactive ingredient for approved drugs; used in oral drugs (the anhydrous form)	[5]
	- can function as a sweetening agent and tablet excipient in pharmaceuticals	[4]
Mannose	inactive ingredient for approved drugs; used in oral drugs (D-mannose)	[5]
Potassium Gluconate	- listed in the *Foods Chemicals Codex* as a sequestrant	[3]
	- listed in the USP/NF	[6]
Rhamnose	listed in the EAFUS inventory	[58]
Ribose	listed in the EAFUS inventory	[58]
Sodium Gluconate	- GRAS as a sequestrant in animal drugs, feeds, and related products, with no limitation other than current GMP	21CFR582.6757
	- listed in the *Foods Chemicals Codex* as sequestrant	[3]
	- listed in the USP/NF	[6]
	- inactive ingredient for approved drugs; used in oral products	[5]
Sucralose	- listed in the *Foods Chemicals Codex* as a flavor enhancer	[3]
	- listed in the USP/NF	[6]
	- inactive ingredient for approved drugs; used in oral, sublingual, and buccal drugs	[5]
	- can function as a sweetening agent in pharmaceuticals	[4]

Table 7. Examples of non-cosmetic uses

Ingredient	Use	Reference
Sucrose	- as the starting material in the fermentative production of ethanol, butanol, glycerol, citric acid, and levulinic acid	40
	- listed in the *Foods Chemicals Codex* as a formulation and texturizing aid	3
	- inactive ingredient for approved drugs; used in topical, oral, sublingual, buccal, subcutaneous, intravenous, and rectal drugs	5
	- functions as a confectionary base, coating agent, granulation aid, suspending agent, sweetening agent, tablet binder, tablet and capsule diluent, tablet filler, therapeutic agent, and viscosity increasing agent in pharmaceuticals; widely used in oral formulations	4
Trehalose	- listed in the *Foods Chemicals Codex* as a humectant, stabilizer, thickener, texturizer	3
	- used as an excipient in a few monoclonal antibody products	50
	- can function as a color adjuvant, flavor enhancer, freeze-drying agent, humectant, stabilizing agent, sweetening agent, table diluent, and thickening agent in pharmaceuticals; used for the lyoprotection of therapeutic proteins	4
Xylose	- listed in the EAFUS inventory	58
	- listed in the USP/NF	6

Table 8. Nutritive and non-nutritive sweeteners and food additives

Nutritive[3,6,59]	Non-Nutritive[3,60]
fructose	lactitiol
glucose	sucralose
isomalt	xylose
lactose	
maltose	
potassium gluconate	
sodium gluconate	
sucrose	
trehalose	

Table 9. Summary metabolism data

Ingredient	Metabolism Data	Reference
	Absorbed and Metabolized (Nutritive)	
Calcium Gluconate (GRAS)	calcium and the gluconate anion are common constituents of food and are metabolized by the normal metabolic processes in man	61
Fucose	L-fucose is a common component of many *N*- and *O*-linked glycans and glycolipids produced by mammalian cells	54
Fructose (GRAS)	- metabolism of fructose occurs mainly in the liver; it is converted partially to dextrose and to lactic and pyruvic acid; further metabolism occurs by a variety of metabolic pathways	4
	- serum fructose levels were higher in adult humans fed sucrose than when fed a mixture of glucose and fructose; release of fructose by hydrolysis of sucrose within the brush border may facilitate absorption of fructose; also the furanose ring structure of fructose as released may be more readily absorbed than the equilibrium mixture of pyranose and furanose forms attained after being in solution for some time	56
Gluconic Acid	a normal metabolic product of glucose oxidation, is an important intermediate in carbohydrate metabolism in mammals; contributes to the synthesis of nicotinamide-adenine dinucleotide phosphate (NADPH), and it leads to the formation of ribose-5-phosphate; the amount produced endogenously is many times greater than the largest amounts likely to be consumed from food; the daily production of gluconate from endogenous sources is about 450 mg/kg for a 60 kg person	18,27,55
Glucose (GRAS)	rapidly absorbed from the small intestine, principally by an active mechanism	20
Potassium Gluconate (GRAS)	- important intermediate in carbohydrate metabolism	27
	- readily absorbed in the intestine, the potassium ion ionize almost immediately to potassium and gluconic acid; with parental administration, a significant portion (60-85%) is excreted unchanged in the urine	21,22
Sodium Gluconate (GRAS)	important intermediate in carbohydrate metabolism	27
Sucrose	- known to be a relatively efficient source of energy; rapidly metabolizable for utilization and storage	62
	- hydrolyzed in the small intestine by sucrose to yield dextrose and fructose, which are then absorbed	4
	- there is evidence that sucrose can be absorbed unchanged to a small extent, particularly at high dietary level; nearly all ingested sucrose is absorbed as glucose and fructose, its metabolism is essentially that of these two monosaccharides	56
	- excreted unchanged in the urine when administered intravenously	4
	Metabolized in the small intestines	
Trehalose	- rapidly metabolized in the gut to glucose by trehalase	4
	- metabolism is essentially identical to that of other disaccharides that are consumed as part of the human diet	51,63

Table 9. Summary metabolism data

Ingredient	Metabolism Data	Reference
	Not Absorbed (or Limited Absorption)	
Isomalt	hydrolysis and absorption in the small intestine is limited because the glycoside linkage between the mannitol or sorbitol moiety and the glucose moiety is very stable; the majority of isomalt is fermented in the large intestine (nutritive)	4
Lactitol	not absorbed in the small intestine; broken down by microflora in the large intestine (non-nutritive)	4
Lactulose	-not readily absorbed from the intestine in humans; not hydrolyzed by intestinal disaccharidases; <1% of a 5 g dose given orally was recovered in the urine - completely degraded in in the large intestine to short chain fatty acids, H_2, and CO_2	23 64
Mannose	little disposition of glycogen in the liver following oral ingestion; transport across the liver is approximately 1/10 that of glucose, suggesting diffusion; significant amounts excreted in the urine following oral administration; no significant reabsorption by the kidney	65
Sucralose (GRAS)	- highly water-soluble, not lipophilic, and does not bioaccumulate; the major portion of an oral dose of sucralose is unabsorbed and excreted unchanged in the feces of rats, mice, rabbits, dog, and man; only two minor metabolites were detected following oral dosing in the mouse, rat, and man, and only one urinary metabolite was found in the rabbit and the dog - not metabolized or used for energy in mammalian systems	24-26,66-69 70
Xylose	- D-xylose is passively absorbed in rats; in rats and man, oral absorption was incomplete (about 70% absorbed) and xylose was eliminated primarily unchanged in the urine	71

Table 10. Genotoxicity studies

Test Article	Concentration/Vehicle	Procedure	Test System	Results	Reference
		IN VITRO			
Calcium Gluconate	12.5, 25 and 50 µg/ml	Ames test; with and without metabolic activation	*Salmonella typhimurium* strains TA1535, TA1537, TA1538	negative	[27]
Calcium Gluconate	7.5, 15 and 30 µg/ml	with and without metabolic activation	*Saccharomyces cerevisiae* strain D4	negative	
Lactitol	not provided	reverse mutation assay; details not provided	*S. typhimurium* (stains not specified)	negative	[30]
Lactitol	not provided	mammalian gene mutation assay; details not provided	human lymphocytes	negative	[30]
Sodium Gluconate	0.0006, 0.0012, and 0.0024%	Ames test, with and without metabolic activation; appropriate positive and negative controls were used	*S. typhimurium* strains TA1535, TA1537, TA1538	negative	[72]
Sodium Gluconate	1.25, 2.5, and 5.0 %	Ames test, with and without metabolic activation; appropriate positive and negative controls were used	*Saccharomyces cerevisiae* strain D4	negative	[72]
Sucralose	0.16-10 mg/plate; distilled water was the vehicle	Ames test, with and without metabolic activation; appropriate positive and negative controls were used	*S. typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100	negative	[73]
Sucralose	0.16-10 mg/plate; distilled water was the vehicle	DNA damage test; appropriate positive and negative controls were used	*Escherichia coli* strains W3110 and P3478	negative	[73]
Sucralose	≤10 mg/ml; distilled water was the vehicle	mouse lymphoma assay, with and without metabolic activation; appropriate positive and negative controls were used	L5178Y TK +/- mouse lymphoma cells	originally classified as equivocal results; redefined as negative using revised criteria	[73]
Sucralose	8, 40, and 200 µg/ml; distilled water was the vehicle	human peripheral lymphocyte assay, without metabolic activation; appropriate positive and negative controls were used	human lymphocytes	negative	[73]
Sucrose	156-5000 µg/ml	mouse lymphoma assay, with and without metabolic activation; appropriate controls were used	L5178Y mouse lymphoma cells	negative	[74]
Sucrose	156-5000 µg/ml	mouse lymphoma assay, with and without metabolic activation; appropriate controls were used	L5178Y mouse lymphoma cells	negative	[75]
Sucrose	1311-5000 µg/ml	mouse lymphoma assay, with and without metabolic activation; appropriate controls were used	L5178Y mouse lymphoma cells	negative	[76]
Trehalose	312.5-5000 µg/plate	Ames test, with and without metabolic activation; appropriate controls were used	*S. typhimurium* strains TA1535, TA1537, TA98, and TA100; *E. coli* strain WP2 uvrA	negative	[51]
Trehalose	to 312, 1250, or 5000 µg/ml	chromosomal aberration assay, with and without metabolic activation; appropriate controls were used	Chinese hamster ovary cells	negative	[51]
		IN VIVO			
Sodium Gluconate	0, 2.5, 5, or 10 g/kg in physiological saline	chromosomal aberration assay; mice were given a single oral 1 ml dose	mouse bone marrow cells; C57BL male mice, 3/group	not clastogenic; all animals of the 5 and 10 g/kg groups died	[27]
Sodium Gluconate	0, 1.25,or 2.5 g/kg in physiological saline	chromosomal aberration assay; mice were dosed orally with 1 ml, 1x/day for 4 days	mouse bone marrow cells; C57BL male mice, 2 (control and low dose) or 3 (high dose)/group	not clastogenic; 1 animal of each test group died	[27]
Sucralose	0.5, 1, and 2 g/kg bw in distilled water	chromosomal aberration assay; rats were dosed by gavage daily for 5 days; aberrations were evaluated 6 h after the final dose	rat bone marrow cells; male and female Sprague-Dawley rats, 5/group	negative; no mortality	[73]
Sucralose	2 or 10 g/kg bw in distilled water	micronucleus test; 5 male and 5 female CD-1 COBS Swiss mice were dosed twice by gavage in 24 h; micronuclei were evaluated after 6 h, the study was preliminary and was not Good Laboratory Practices (GLP)-compliant	male and female CD-1 COBS Swiss mice; 5/sex/group	negative	[73]
Sucralose	1 or 5 g/kg bw in distilled water	micronucleus test; mice were given a single dose by gavage, and micronuclei were evaluated 24, 48,or 72 h after dosing	female CD-1 Swiss mice; 5/sex/group	negative	[73]
Trehalose	1250, 2500, or 5000 mg/kg	micronucleus test; mice were dosed intraperitoneally and then killed 1 or 2 days after dosing; cyclophosphamide was used as the positive control.	male and female mice; 5/group	negative	[51]

Table 10. Genotoxicity studies

Test Article	Concentration/Vehicle	Procedure	Test System	Results	Reference
Trehalose	1.25, 2.5, and 5 g/kg in distilled water	micronucleus test; mice were dosed by gavage for 3 days and killed on day 4	male mice; 10/group	negative; no mortality	[63]

Table 11. Irritation and Sensitization Studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			NON-HUMAN		
Gluconic Acid	50% aq. solution 0.5 ml	6 rabbits/group	- 1 sq. in. occlusive patch was applied for 4 h - tests sites of one group was abraded - tests sites were scored after 24, 48, and 72 h	- slight erythema observed during the initial observation; it is not clear if this is only for abraded skin - no signs of irritation at 72 h	[27]
Lactitol	not specified	rabbits; no./group not specified	- study was performed according to the OECD Guidelines 404 and 406, respectively.[77,78] (No other details were provided)	- not an irritant or sensitizer	[30]
			HUMAN		
hair styling cream containing **0.08% glucose**	applied neat	100 subjects	HRIPT induction: the test material was applied neat under semi-occlusive patches; 9 applications were made over a 3-wk period; the first patch was applied for 48 h, and the remainder for 24 h challenge: the patch was applied after a 2-wk non-treatment period to a previously untreated site; the test sites were scored 48 and 96 h after application.	not an irritant or a sensitizer	.[79]
a leave-in hair product containing **8% glucose**	applied neat 0.2 ml	208 subjects	HRIPT; 24-h, 2 cm^2, semi-occlusive patches were used	not a sensitizer 1% of subjects had a "+" reaction during induction	[80]
mixture containing **isomalt**	final applied concentration of isomalt is 0.94% 20 µl	49 subjects	- single insult patch test; test material was applied to the ventral forearm using Finn Chambers, and the test site was scored 15 min, 24 h, and 48 h after patch removal - SDS (not defined) was used as a positive control - water was the negative control	not an irritant; no reactions to the test formulation were observed	[81]
face and neck product containing **0.1% kefiran**	applied neat	100 subjects	HRIPT using semi-occlusive patches	not an irritant or sensitizer	[36]
paste mask and mud pack containing **0.15% lactitol**	applied neat	28 subjects	4-wk in-use dermal study with open applications	not an irritant	[36]
paste mask and mud pack containing **0.15% lactitol**	applied neat	110 subjects	HRIPT using semi-occlusive patches	not an irritant or sensitizer	[36]
face and neck product containing **2.48% lactose**	applied neat	114 subjects	HRIPT using occlusive patches	not an irritant or sensitizer	[36]

Table 11. Irritation and Sensitization Studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
leave-on facial product containing **5% mannose**	applied neat	103 subjects	HRIPT with 48-72 h occlusive induction patches and a 48-h challenge patch - distilled water was used as a negative control.	not an irritant or a sensitizer	[82]
leave-on formulation containing **10% rhamnose**	applied neat	106 subjects	HRIPT using 48-72 h occlusive patches - distilled water was used as a negative control.	- not a sensitizer - irritation reaction consisting of severe to mild erythema, bulla, coloration, fissuring, and scabbing was observed in one subject	[83]
lip balm formulation containing **0.6% sucralose**	applied neat	50 subjects	modified Draize HRIPT; similar to that described previously, with the exceptions that all the induction patches were applied for 24 h, the challenge patch was applied for 24 h, and the challenge sites scored 24 and 48 h after application	not an irritant or sensitizer	[84]
rinse-off hair product containing **29% sucrose**	diluted to 50% in distilled water 0.02 ml over 50 mm^2	102 subjects	HRIPT using 48-72 h occlusive patches for induction, and a 48-h patch at challenge	- not an irritant or sensitizer - mean irritation index of <0.25; 16% of the subjects presented with score ≥2 reactions during induction	[85]
eye cream formulation containing **0.1% xylobiose**	applied neat	56 subjects	HRIPT using 24-h occlusive patches	not an irritant or sensitizer	[86]

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