Article

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

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Abstract

The Cosmetic Ingredient Review Expert Panel (Panel) assessed the safety of 25 monosaccharides, disaccharides, and related ingredients and concluded these are safe in the present practices of use and concentration described in the safety assessment. Many of these ingredients are common dietary sugars, dietary sugar replacements, or very closely related analogs and salts; 7 of the ingredients are listed by the Food and Drug Administration as generally recognized as safe food substances. 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 assessment, 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.

Keywords

monosaccharides, disaccharides, safety, cosmetics

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

The monosaccharides, disaccharides, and related ingredients have a number of reported functions in cosmetics, with the most common use as a skin-conditioning agent (Table 1).[1] Other commonly reported functions are use as a humectant or as a flavoring agent.

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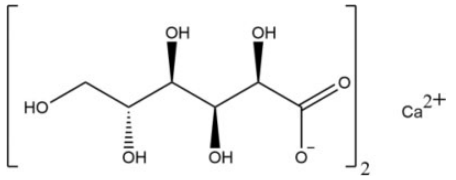
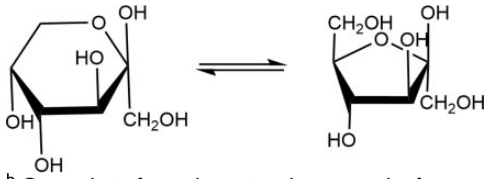
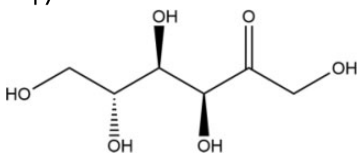
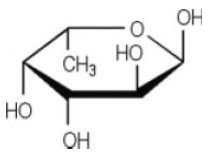
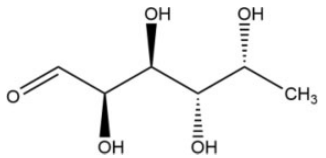
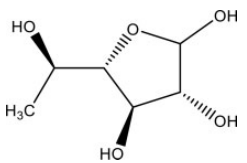
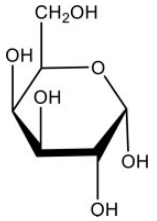
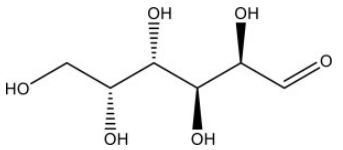
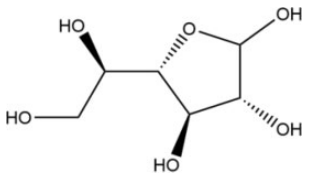
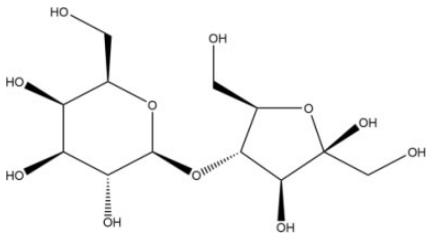
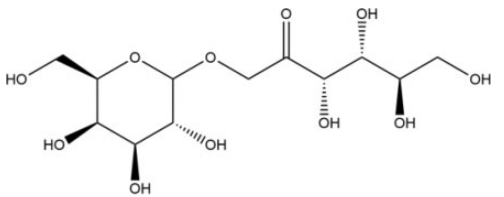
Table 1. Definitions, Structures, and Reported Functions.[a,b]

Ingredient (CAS No.)	Definition[a]	Structure[b]	Reported function(s)
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 2 cyclized forms in equilibrium, namely fructopyranose and fructofuranose.*	 [b] 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).*	  [b] **open chain form**  [b] **furanose form**	Skin-conditioning agent—miscellaneous

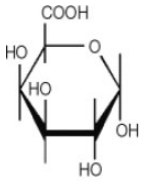
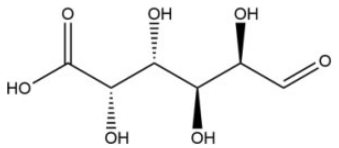
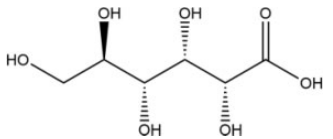
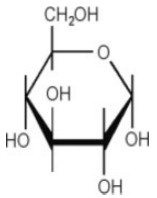
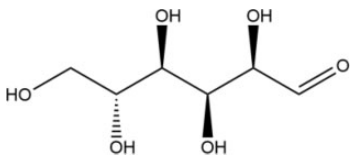
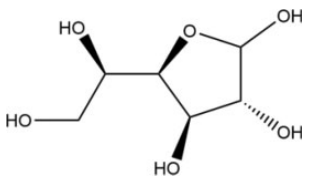
(continued)

Table 1. (continued)

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

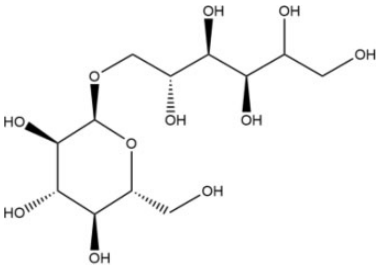
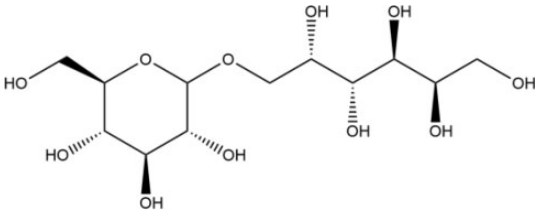
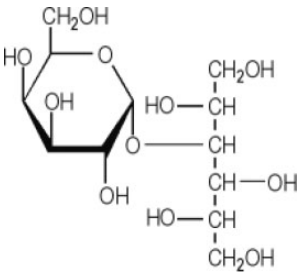
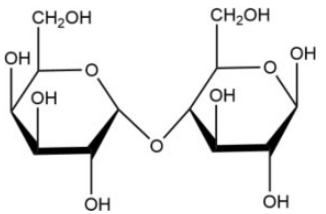
(continued)

Table 1. (continued)

Ingredient (CAS No.)	Definition[a]	Structure[b]	Reported function(s)
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*	  [b] **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	  [b] **open chain form**  [b] **furanose form**	Flavoring agent; humectants; skin-conditioning agent-humectant; skin-conditioning agent – miscellaneous

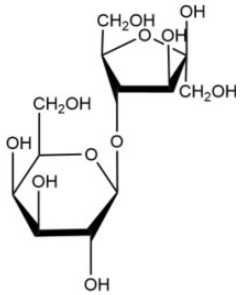
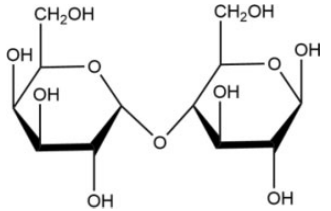
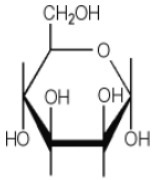
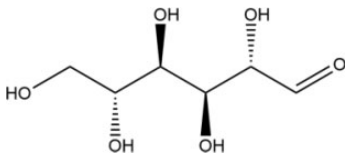
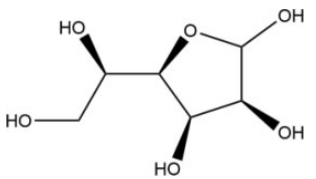
(continued)

Table 1. (continued)

Ingredient (CAS No.)	Definition[a]	Structure[b]	Reported function(s)
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	[b] **one example of an isomalt form** 	Anticaking agent; bulking agent; flavoring agent
Kefiran, 86753-15-3	A disaccharide consisting of glucose and galactose	[b] **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

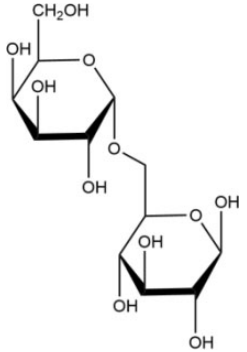
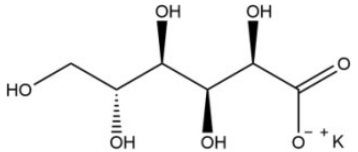
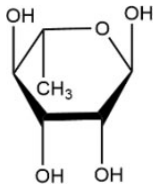
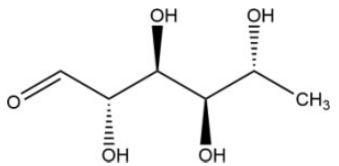
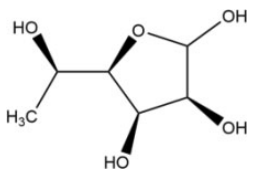
(continued)

Table 1. (continued)

Ingredient (CAS No.)	Definition[a]	Structure[b]	Reported function(s)
Lactulose, 4618-18-2	The disaccharide that conforms to the formula provided; *lactulose is the disaccharide (β1 → 3) galactopyranosyl-fructofuranose*		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*	  [b] **open chain form**  [b] **furanose form**	Humectant; skin-conditioning agent—humectant

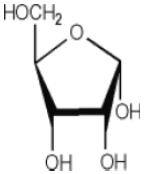
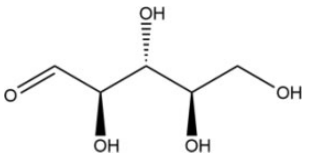
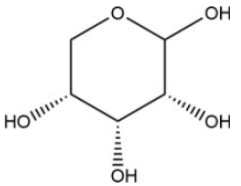
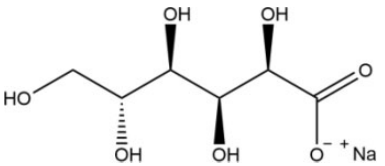
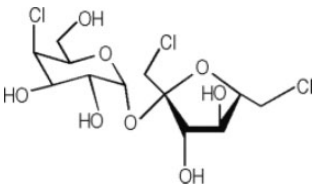
(continued)

Table 1. (continued)

Ingredient (CAS No.)	Definition[a]	Structure[b]	Reported function(s)
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)*	  [b] **open chain form**  [b] **furanose form**	Flavoring agent; fragrance ingredient

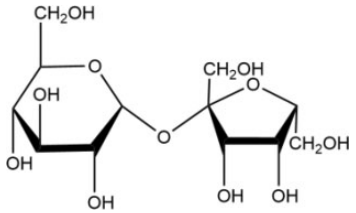
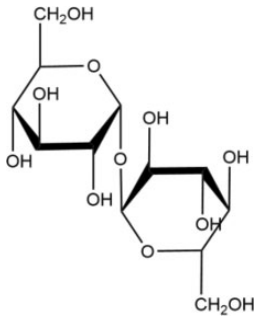
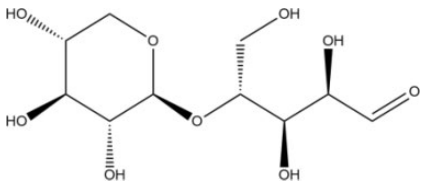
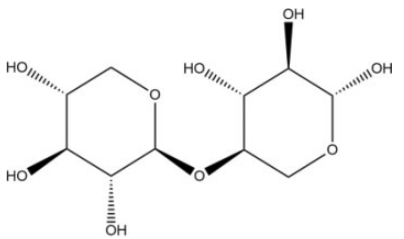
(continued)

Table 1. (continued)

Ingredient (CAS No.)	Definition[a]	Structure[b]	Reported function(s)
Ribose, 50-69-1	The sugar that conforms to the formula provided; *ribose is an aldopentose*	  [b] **open chain form**  [b] **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

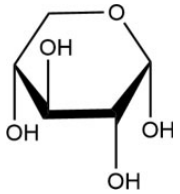
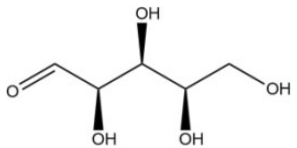
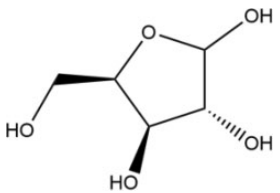
(continued)

Table 1. (continued)

Ingredient (CAS No.)	Definition[a]	Structure[b]	Reported function(s)
Sucrose, 57-50-1	The disaccharide that conforms to the formula provided; *sucrose is the disaccharide α(1 → 4) glucosyl-fructose*		Flavoring agent; humectant
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	 b  b	Skin-conditioning agent—humectant

(continued)

Table 1. (continued)

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

[a]The italicized text represents additions made by CIR staff.
[b]Structures preceded with ([b]) have been added by CIR staff.

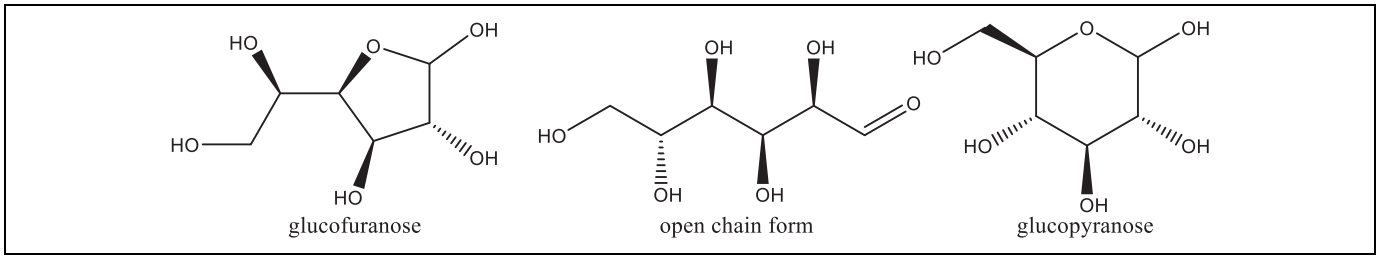


Figure 1. Structural forms of D-glucose (stereoisomer found in natural sources) that exist in equilibrium.

Most of these ingredients included in this safety assessment are common dietary sugars, dietary sugar replacements, or very closely related analogs and salts. Several are listed by the Food and Drug Administration (FDA) as generally recognized as safe (GRAS) food additives[2] or direct food additives and/or are listed in the *Food Chemicals Codex*[3] as used in foods; for these ingredients, the focus of this assessment will be on dermal effects, primarily dermal irritation and sensitization. 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, Authorization and Restriction of Chemicals (REACH),[4] which "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."[5]

For those ingredients that are not identified as common dietary substances, that is, 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.[6] A disaccharide is a carbohydrate that yields 2 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 2 possible stereochemical configurations (Figure 1). The resulting stereoisomers are called anomers, and the stereocenter is referred to as the anomeric carbon. 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 monosaccharides 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, with many having multiple known crystalline forms (Table 2).[3,7-29]

Natural Occurrence and Methods of Manufacture

The manufacture of the majority of these monosaccharides, disaccharides, and related ingredients is accomplished by extraction from plant sources (Table 3). For instance, the sugar industry processes sugar cane and sugar beets to obtain sucrose.[30] Sugar cane contains 70% water, 14% fiber, 13.3% saccharose (about 10%-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 (75% water and 17% sugar) 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, and so on), 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 is as a skin conditioning agent; many are also reported to function as flavoring agents (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). The VCRP data obtained from the FDA in 2014[31] 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[32]

Table 2. Chemical and Physical Properties.

Property	Description	Reference
Calcium gluconate		
Physical characteristics	odorless, white, crystalline granules or powder	7
Molecular weight	430.4	8
Melting point	120°C	9
Solubility	soluble in water; insoluble in ethanol	7
Density	0.30-0.65 g/cm^3 (bulk density)	9
log P_{ow}	−7.51 (estimated)	9
Fructose		
Physical characteristics	D-: orthorhombic, bisphenoidal prisms from alcohol	10
	DL-: needles from methanol	11
	white crystals or powder	
Molecular weight	180.16	10
Particle size distribution	crystalline fructose: 170 to 450 μm	12
	powdered fructose: 25 to 40 μm	
Melting point	D-: decomposes at 103°C to 105°C	10
	DL-: 129-130°C	
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	3,10
Specific optical rotation (α^{20}_D)	D-: shows mutarotation; −132° to −92°	10
Density	1.59 kg/m^3 (20°C)	13
pK_a	D-: 12.06 (18°C)	10
Specific gravity (d^{16}_4)	DL-: 1.665	10
Fucose		
Physical characteristics	D-, α-Form: needles from alcohol; sweet taste	10
	L-, α-Form: minute needles from absolute alcohol	
Molecular weight	164.16	10
Melting point	D-, α-Form: 144°C	10
	L-, α-Form: 140°C	
Solubility	D-, α-Form: soluble in water; moderately soluble in alcohol	10
	L-, α-Form: soluble in water and alcohol	
Specific optical rotation (α^{19}_D)	D-, α-Form: shows mutarotation; +127.0° (7 minutes) → +89.4° (31 minutes) → +77.2° (71 minutes) → +76.0° (final value 146 minutes)	10
Specific optical rotation (α^{20}_D)	L-, α-form: shows mutarotation, −124.1° (10 minutes) → −108.0° (20 minutes) → −91.5° (36 minutes) → −78.6° (70 minutes) → −75.6° (final value, 24 hours)	10
Galactose		
Physical characteristics	α-Form: prisms from water or ethanol	10
	β-Form: crystals	
	Monohydrate: prisms from water	
Molecular weight	180.16	10
Melting point	α-Form: 167°C	10
	β-Form: 167°C	
	Monohydrate: 118°C to 120°C	
Solubility	α-Form: freely soluble in hot water; soluble in pyridine; slightly soluble in alcohol	10
Specific optical rotation (α_D)	α-Form: +150.7° → +80.2° (water)	10
	β-Form: +52.8° → +80.2° (water)	14
	D-, α-Form: (α^{20}_D): +78.0° to 81.5°	
Galactosyl fructose		
Molecular weight	342.30 (predicted)	15
Boiling point	780.1°C ± 60°C (at 760 Torr; predicted)	15
log P	−2.810 ± 0.846 (at 25°C; predicted)	15
Galacturonic acid		
Physical characteristics	α-Form: monohydrate, needles	10
Molecular weight	194.14	10
Melting point	α-Form: 159°C	10
	β-Form: 166°C	
Solubility	α-Form: soluble in water; slightly soluble in hot alcohol; practically insoluble in ether	10
Specific optical rotation	α-Form, (α^{20}_D): +98.0° → +50.9° (water)	10
	β-Form, (α_D): +27° → +55.6° (water)	

(continued)

Table 2. (continued)

Property	Description	Reference
Gluconic acid		
Physical characteristics	Crystals; mild acid taste	16
	White crystalline powder	17
	Anhydrous: commercial form is a 50% aqueous solution, which is a colorless to brownish liquid.	9,17
Molecular weight	196.16	16
Melting point	131°C	16
Solubility	Freely soluble in water; slightly soluble in alcohol; insoluble in ether and most other organic solvents	16
Stability	In aqueous solutions, the acid is partially transformed into an equilibrium mixture with γ- and δ-gluconolactones	16 17
	Reacts with strong oxidants	17
	On combustion, forms carbon monoxide	
Specific optical rotation (α^{20}_{D})	−16.7°	16
Density	1.23 g/cm^3	17
log P_{ow}	−1.87 (estimated)	17
pK_a	12.06 (18°C)	16
Glucose		
Physical characteristics	α-Form monohydrate: crystals from water	10
	α-Form anhydrous: crystals from hot ethanol or water	18
	β-Form: crystals from hot water and ethanol, from diluted acetic acid, or from pyridine	
	White D-glucose: powder with sweet taste	
Molecular weight	180.16	10
Melting point	α-Form monohydrate: 83°C	10
	α-Form anhydrous: 146°C	
	β-Form: 148-155°C	
Solubility	α-Form anhydrous: soluble in hot glacial acetic acid, pyridine, aniline; very sparingly soluble in absolute alcohol, ether, acetone	10
log P_{ow}	D-Glucose: −3.3	18
Specific optical rotation	α-Form monohydrate, (α^{20}_{D}): +102.0° → +47.9°C (water)	10
	α-Form anhydrous, (α^{20}_{D}): +112.2° → +52.7°C (water)	
	β-Form, (α^{20}_{D}): +18.7° → +52.7° (water)	
Stability	D-Glucose reacts violently with strong oxidants	18
Isomalt		
Physical characteristics	White crystalline, odorless, slightly hydroscopic substance	3,19
Molecular weight	380.32	3
Boiling point	788.5°C ± 60°C (at 760 Torr; predicted)	15
Solubility	Soluble in water; very slightly soluble in ethanol	3,19
log P	−2.810 ± 0.846 (at 25°C; predicted)	15
pK_a	12.89 ± 0.70 (25°C) (predicted)	15
Lactitol		
Physical characteristics	crystals from absolute ethanol; strongly hygroscopic	10
	monohydrate: white, sweet, odorless crystalline solid; non-hygroscopic	
	dihydrate: white, sweet, odorless crystalline powder	
Molecular weight	344.31 (anhydrous); 362.37 (monohydrate)	3,10
Melting point	146°C	10
	monohydrate: 94-97°C	
	dihydrate: 75°C (food-grade)	
Partition coefficient	<−3 (20°C)	20
Solubility	soluble in water, dimethyl sulfoxide, *N, N*-dimethylformamide; slightly soluble in ethanol, ether	10
Specific optical rotation	(α^{23}_{D}): +14°	10
	monohydrate, (α^{22}_{D}): +12.3°	
	dihydrate, (α^{25}_{D}): +13.5 – 15.0°	
Lactose		
Physical characteristics	α-Lactose monohydrate: monoclinic sphenoidal crystals from water; faintly sweet taste; readily absorbs odors	10
Molecular weight	342.30	10
Particle size distribution	Varies by grade	12
Melting point	α-Lactose monohydrate: 201°C to 202°C	10
Solubility	α-Lactose monohydrate: practically insoluble in alcohol; insoluble in chloroform, ether	10

(continued)

Table 2. (continued)

Property	Description	Reference
Specific optical rotation	α-Lactose monohydrate, (α^{20}_D): shows mutarotation; +92.6° → +83.5° (10 minutes.) → +69° (50 minutes) → +52.3° (22 hours)	10
	β-Lactose, (α^{25}_D): +34° (3 minutes) → +39° (6 minutes) → +46° (1 hour) → +52.3° (22 hours)	
K_a (16.5°C)	α-Lactose monohydrate: 6.0×10^{-13}	10
Lactulose		
Physical characteristics	Hexagonal clustered plates from methanol	10
Molecular weight	342.30 (anhydrous); 360.32 (monohydrate)	3,10
Melting point	168°C to 171°C	10
Solubility	Freely soluble in water	21
Specific optical rotation (α^{22}_D)	Shows mutarotation; constant value after 24 h, −51.5°	10
Maltose		
Physical characteristics	Monohydrate: crystals from water or diluted alcohol	10
Molecular weight	342.30	10
Melting point	Monohydrate: 102°C to 103°C	10
Solubility	α-Lactose monohydrate: practically insoluble in alcohol; insoluble in chloroform, ether	10
pH	Anhydrous: 3.7-4.7; monohydrate: 4.5-5.5	14
Specific optical rotation (α^{20}_D)	Monohydrate: shows mutarotation; +111.7° → 2+130.4°	10
pK_a (21°C)	Monohydrate: 12.05	10
Mannose		
Physical characteristics	α-Form: crystals from methanol	10
	β-Form: orthorhombic, bisphenoidal needles from alcohol or acetic acid; sweet taste with bitter aftertaste	
Molecular weight	180.16	10
Melting point	α-Form: 133°C	10
	β-Form: decomposes at 132°C	
Specific optical rotation	α-Form, (α_D): +29.3° → +14.2° (water)	10
	β-Form, (α^{20}_D): −17.0° → +14.2° (water)	
Melibiose		
Physical characteristics	Dihydrate: monoclinic crystals from water of diluted alcohol	10
Molecular weight	342.30	10
Dihydrate	α-form: 84°C to 85°C	10
Specific optical rotation (α^{20}_D)	Dihydrate: +111.7° → +129.5°	10
Potassium gluconate		
Physical characteristics	Yellowish-white crystals; mild, slightly saline, taste	16
Molecular weight	234.25 (anhydrous); 252.26 (monohydrate)	3,16
Melting point	Decomposes at 180°C	16
Solubility	Freely soluble in water and glycerin; practically insoluble in alcohol, ether, benzene, and chloroform	3,16
log P_{ow}	−5.99 (estimated)	9
pH	7.5 to 8.5 (aqueous solution)	16
Stability	Stable in air	16
Specific optical rotation (α^{20}_D)	−16.7°	16
Density	0.80 g/cm^3 (20°C; bulk density)	9
Rhamnose		
Physical characteristics	α-Form: monohydrate, holohedric rods from water; hemihedric monoclinic columns from alcohol; very sweet taste	10
	β-Form: needles; hygroscopic	
Molecular weight	164.16	10
Melting point	α-Form: 82°C to 92°C; sublimes at 105°C and 2 mm Hg	10
	β-Form: 122°C to 126°C	
Specific optical rotation	α-Form, (α^{20}_D): shows mutarotation; −7.7° → +8.9°	10
	β-Form, (α^{20}_D): −17.0° → +31.5°	
Specific gravity (d^{20}_4)	1.4708	10
Stability	α-Form: loses water of crystallization upon heating, and partially changes to the β-modification	10
	β-Form: changes into crystals of the α-modification upon exposure to moist air	
Ribose		
Physical characteristics	Plates from absolute alcohol	10
Molecular weight	150.13	10
Melting point	87°C	10

(continued)

Table 2. (continued)

Property	Description	Reference
Solubility	Soluble in water, slightly soluble in alcohol	10
Specific optical rotation (α^{20}_D)	Final, shows complex mutarotation; −25°	10
Sodium gluconate		
Physical characteristics	White crystals	22
	White to tan, granular to fine, crystalline powder	3
	Technical grade may have a pleasant odor	16
Molecular weight	218.14	16
Melting point	170°C to 175°C; decomposes at 196°C to 198°C	22
Solubility	Soluble in water; sparingly soluble in alcohol; insoluble in ether	16
log P_{ow}	−5.99 (estimated)	22
Density	1.8 g/cm^3	22
Sucralose		
Physical characteristics	Anhydrous crystalline form: orthorhombic needle-like crystals; intensely sweet taste	10
Molecular weight	397.63	10
Particle size distribution	90% <12 μm	12
Solubility	Soluble in water	23
Octanol/water partition coefficient	−0.51 ($\log_{10}$ P)	12
Specific optical rotation (α_D)	+68.2°	10
	(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	10
	Hard, white, odorless crystals, lumps, or powder; may have a characteristic caramel odor when heated	24
Molecular weight	342.30	10
Melting point	Decomposes at 160°C to 186°C	10
Solubility	Moderately soluble in glycerol, pyridine; practically insoluble in dehydrated alcohol	10
log P_{ow}	−3.67	25
Specific optical rotation	(α^{20}_D): +65.9° to +66.7°	3
	(α^{25}_D): +66.47 to +66.49°	y
pK_a	12.62	10
Specific gravity (d^{25}_4)	1.587	10
Stability	Stable in air	10
	Hydrolyzed to glucose and fructose by diluted acids and by invertase	
Trehalose		
Physical characteristics	Orthorhombic, bisphenoidal crystals for diluted alcohol; sweet taste	10
	Typically found in the dihydrate form; characterized by low hygroscopicity	26,27
Molecular weight	342.30	10
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	27
Solubility	Very soluble in water, formamide, and dimethyl sulfoxide; soluble hot alcohol; slightly soluble to insoluble in ether	3,10
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 trehalase	28
Specific optical rotation (α^{20}_D)	+178°	10
Xylobiose		
Molecular weight	282.24 (predicted)	15
Boiling point	604 ± 55°C (at 760 Torr; predicted)	15
log P	−2.900 ± 0.852 (at 25°C; predicted)	15
pK_a	12.40 ± 0.20 (25°C; predicted)	15
Xylose		
Physical characteristics	Monoclinic needles or prisms; very sweet taste	10
	white, odorless, crystal or crystalline powder with a sweet taste	29
Molecular weight	150.13	10
Melting point	144°C to 145°C	10
Solubility	Soluble in glycerol, pyridine, hot alcohol	10
Specific optical rotation (α^{20}_D)	Shows mutarotation; +92° → +18.6° (16 hours)	10
pK_a (18°C)	12.14	10
Specific gravity (d^{20}_4)	1.525	10

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	10
	- Prepared by adding absolute alcohol to the syrup obtained from the acid hydrolysis of inulin; prepared from dextrose; prepared from sucrose by enzymatic conversion	3,13
	- Obtained from glucose in corn syrup by the use of glucose isomerase	
Fucose	D-: obtained from glucosides found in various species of Convolvulaceae	10
	L-: occurs in seaweed—*Ascophyllum nodosum*, *(Fucus nodosus*), *Fucus vesiculosu*., *F. serratus*, *F. virsoides*, *Fucaceae*—and in gum tragacanth	48
	L-: a common component of many N- and O-linked glycans and glycolipids produced by mammals	
Galactose	- Constituent of many oligo- and polysaccharides in pectins, gums, and mucilages; isolation in the processing of the red algae, *Porphyra umbilicalis*	10
	- A product of lactose metabolism	14
Galacturonic acid	Obtained by hydrolysis of pectin where it is present as polygalacturonic acid	10
Gluconic acid	- Prepared by oxidation of glucose; produced commercially using *Aspergillus niger, A. fumaricus, Aerobacter aceti, Penicillium chrysogenum,* or other *Penicillia*	16,50
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	21CFR184.1857
	- 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	10
	- Normal human blood contains 0.08-0.1%	
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	12
Lactitol	Prepared by the hydrogenation of lactose	10
Lactose	- Present in the milk of mammals: human, 6.7%: cow, 4.5%	10
	- By-product of the cheese industry, produced from whey	
	- β-Lactose: obtained by crystallizing concentrated solutions of α-lactose above 93.5°C	
Lactulose	- Synthetic disaccharide composed of galactose and fructose	10
	- Can be produced from agricultural by-products and from lactose	64
Maltose	Obtained in 80% yield by enzymatic (diastase) degradation of starch	10
Mannose	α-Form prepared by treating ivory nut shavings with H_2SO_4	10
Melibiose	Prepared from raffinose by fermentation with top yeast, which removes the fructose	10
Potassium gluconate	Prepared by the reaction of potassium hydroxide or carbonate with gluconic acid	45
Rhamnose	- Occurs free in poison sumac; combined in the form of glycosides of many plants; isolated from the walls of gram-negative bacteria	10
	α-Form: obtained by crystallization from water or ethyl alcohol	
	β-Form: prepared by heating α-rhamnose monohydrate on a steam bath	
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	10
Sucralose	- Chlorinated derivative of sucrose	10
	- Synthesized by selective chlorination of sucrose at 3 of the primary hydroxyl groups	55
	- Can be synthetized by the reaction of sucrose (or an acetate) with thionyl chloride	12
Sucrose	- Obtained from sugar cane and sugar beet: sugar cane (*Saccharum officinarum*) contains 10% to 15% sucrose, sugar beet (*Beta vulgaris*) contains 10% to 17% sucrose	10
	- Sucrose is obtained by crystallization from sugar cane or sugar beet juice that has been extracted by pressing or diffusion, then clarified and evaporated	21CFR184.1854
	- Most abundant carbohydrate in the sap of land plants	49
Trehalose	- Found in fungi, bacteria, yeasts, and insects; isolated from the ergot of rye; isolated from yeast	10
	- Produced from starch using the enzymes maltooligosyl-trehalose synthase and maltooligosyl-trehalose trehalohydrolase	27
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	10
	- Produced industrially by hydrolysis of extracts from cotton seed shells, press residue of sugarcane and beech tree chips	29

Table 4. Purity Specifications.

Ingredient	Purity specifications
Fructose	Food use: NMT 0.018% chloride; NMT 0.1 mg/kg lead; NMT 0.5% glucose; NMT 0.1% hydroxymethylfurfural, 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[14]
Galactose	USP: NMT 1.0% water; NMT 0.1% residue on ignition[14]
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[19];—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[14]
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% to 5.5% water, monohydrate, or 10.5%, dihydrate; NMT 0.5% water, anhydrate; NMT 0.5% residue on ignition[14]
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% to 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[14]
Maltose	USP: water: NMT 1.5%, anhydrous, 4.5% to 5.5%, monohydrate; NMT 5 μg/g heavy metals; NMT 0.05% residue on ignition[14]
Potassium gluconate	Food use: NMT 1% calculated as D-glucose;[84] NMT 2 mg/kg lead;[3,84] NMT 1.0% reducing substances; NMT 3.0% (anhydrous) and 6.0% to 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% to 7.5%, monohydrate [14]
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[14]
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[14]
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[14]
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[14]

Abbreviations: NMT, not more than; USP, United States Pharmacopeia.

indicate that 22 of the 25 ingredients included in this safety assessment are used in cosmetic formulations.

According to the VCRP data, sucrose has the greatest number of reported uses, 738, followed by trehalose with 474 uses and glucose with 425 uses (Table 5).[31] A concentration of use survey conducted by the Council found that the use of these monosaccharides and disaccharides varies widely by ingredient and use type.[32] Glucose has the highest reported use concentration in a leave-on product; it is reported to be used at 91% in "other" noncoloring hair preparations. 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 (ie, in other skin care preparations) and 65% in rinse-off products (ie, in other personal cleanliness products). However, most of the ingredients are used at <1% in leave-on products. The 3 ingredients not reported to be used are galactose, galacturonic acid, and lactulose (Table 6).

Voluntary Cosmetic Registration Program 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 used are 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 (eg, 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 (eg, 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 to pump sprays.[33,34] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[35,36] All of the ingredients included in this safety assessment are listed in the European Union inventory of cosmetic ingredients.[37]

Noncosmetic

Several of the ingredients have specific GRAS food 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,

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

	# of uses[31]	Max. conc. of use (%)[32]	# of uses[31]	Max. conc. of use (%)[32]	# of uses[31]	Max. conc. of use (%)[32]
	Calcium Gluconate		Fructose		Fucose	
Totals[a]	68	0.0000075-1	172	0.0001-20	3	NR
Duration of use						
Leave-on	50	0.0000075-1	144	0.0002-2	3	NR
Rinse off	18	0.0000075-0.1	28	0.0001-20	NR	NR
Diluted for (bath) use	NR	NR	NR	NR	NR	NR
Exposure type						
Eye area	4	0.0000075-.05	10	0.002-0.075	1	NR
Incidental ingestion	NR	0.00006-0.5	1	NR	NR	NR
Incidental inhalation—spray	21[b]; 13[c]	Spray: 0.0006-0.1 0.0000075-0.01[b]	1; 62[b]; 50[c]	0.23; aerosol: 0.0002 0.08-2[b]	2[c]	NR
Incidental inhalation—powder	2; 13[c]	0.2	50[c]	0.002	2[c]	NR
Dermal contact	61	0.0000075-1	153	0.0003-20	3	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—noncoloring	7	0.008-0.1	18	0.0001-0.1	NR	NR
Hair—coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	4	0.00006-0.5	4	0.0015-0.002	NR	NR
Baby products	NR	NR	NR	NR	NR	NR
	Galactosyl Fructose		Gluconic Acid		Glucose	
Totals[a]	1	NR	2	0.0001-0.18	425	0.00003-97.8
Duration of use						
Leave-on	1	NR	2	0.0001-0.18	276	0.0001-91
Rinse off	NR	NR	NR	NR	140	0.00003-97.8
Diluted for (bath) use	NR	NR	NR	NR	9	19
Exposure type						
Eye area	NR	NR	NR	NR	28	0.0001-0.48
Incidental ingestion	NR	NR	NR	NR	1	0.059-97.8 (97.8 is an ingested breath freshener)
Incidental inhalation—spray	1[c]	NR	2[b]	NR	1; 38[b]; 101[c]	0.24; spray: 1 0.0045-2.9[b]
Incidental inhalation—powder	1[c]	NR	NR	NR	3[d]; 101[c]	NR
Dermal contact	1	NR	2	0.001-0.18	319	0.0001-84
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—noncoloring	NR	NR	NR	NR	36	0.00003-91
Hair—coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	1	0.0004
Mucous membrane	NR	NR	4	NR	29	0.00063-97.8 (97.8 is an ingested breath freshener)
Baby products	NR	NR	NR	NR	4	NR
	Isomalt		Kefiran		Lactitol	
Totals[a]	12	0.19-7.77	2	0.1	9	0.15-0.2
Duration of use						
Leave-on	11	0.19	2	0.1	NR	NR
Rinse off	1	7.77	NR	NR	9	0.15-0.2
Diluted for (bath) use	NR	NR	NR	NR	NR	NR
Exposure type						
Eye area	2	NR	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation—spray	2[b]; 5[c]	NR	2[c]	NR	NR	NR

(continued)

Table 5. (continued)

	# of uses[31]	Max. conc. of use (%)[32]	# of uses[31]	Max. conc. of use (%)[32]	# of uses[31]	Max. conc. of use (%)[32]
	Calcium Gluconate		Fructose		Fucose	
Incidental inhalation—powder	5[c]	NR	2[c]	NR	NR	NR
Dermal contact	10	0.19	2	0.1	4	0.15-0.2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—noncoloring	NR	NR	NR	NR	5	NR
Hair—coloring	NR	7.77	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	NR	NR	1	0.2
Baby products	NR	NR	NR	NR	NR	NR
	Lactose		Maltose		Mannose	
Totals[a]	77	0.0005-9.4	3	0.3-0.5	5	5
Duration of use						
Leave-on	28	0.0005-6	3	0.3-0.5	5	5
Rinse off	48	0.038-9.4	NR	0.5	NR	NR
Diluted for (bath) use	1	8	NR	NR	NR	NR
Exposure type						
Eye area	8	NR	1	NR	1	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation—spray	4[b]; 10[c]	0.0005[b]; 6[c]	NR	NR	4[b]	NR
Incidental inhalation—powder	10[c]	6[c]	NR	NR	NR	NR
Dermal contact	70	0.001-6	1	0.3-0.5	5	5
Deodorant (underarm)	NR	Aerosol: 0.038 Not spray: 0.075-0.25	NR	NR	NR	NR
Hair—noncoloring	3	0.0005-9.4	NR	NR	NR	NR
Hair—coloring	NR	NR	NR	NR	NR	NR
Nail	3	0.3	1	NR	NR	NR
Mucous membrane	33	0.038-8 diluted use product:	NR	NR	NR	NR
Baby products	1	NR	NR	NR	NR	NR
	Melibiose		Potassium Gluconate		Rhamnose	
Totals[a]	2	0.1-0.25	8	0.002-0.1	7	5-10
Duration of use						
Leave-on	2	0.1-0.25	7	0.002-0.1	7	5-10
Rinse off	NR	NR	1	NR	NR	NR
Diluted for (bath) use	NR	NR	NR	NR	NR	NR
Exposure type						
Eye area	1	0.1	1	NR	1	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation—spray	NR	NR	1[b]; 3[c]	0.05[b]	4[b]	NR
Incidental inhalation—powder	NR	NR	3[c]	NR	NR	NR
Dermal contact	2	0.1-0.25	7	0.002-0.1	7	5-10
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—noncoloring	NR	NR	1	0.05	NR	NR
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

(continued)

Table 5. (continued)

	# of uses[31]	Max. conc. of use (%)[32]	# of uses[31]	Max. conc. of use (%)[32]	# of uses[31]	Max. conc. of use (%)[32]
	Calcium Gluconate		Fructose		Fucose	
	Ribose		Sodium Gluconate		Sucralose	
Totals[a]	13	0.05	168	0.0000075-12	84	0.012-1.2
Duration of use						
Leave-on	11	0.05	78	0.0000075-12	39	0.2-0.6
Rinse off	2	NR	90	0.0000075-0.8	45	0.012-1.2
Diluted for (bath) use	NR	NR	NR	NR	NR	NR
Exposure type						
Eye area	NR	NR	5	0.0000075-0.2	1	NR
Incidental ingestion	NR	NR	NR	0.00006-0.75	68	0.012-1.2
Incidental inhalation—spray	7[b]; 2[c]	NR	29[b]; 27[c]	Spray: 0.0006 0.0000075-0.6[b]	3[b]	0.012-0.95[b]
Incidental inhalation—powder	2[c]	NR	27[c]	NR	NR	NR
Dermal contact	13	0.05	104	0.0000075-5	16	0.5-0.6
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—noncoloring	NR	NR	61	0.2-12	NR	NR
Hair—coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	19	0.00006-0.8	68	0.012-1.2
Baby products	NR	NR	1	NR	NR	NR
	Sucrose		Trehalose		Xylobiose	
Totals[a]	738	0.001-65	474	0.0001-2	2	0.0075-0.15
Duration of use						
Leave-on	423	0.001-58	356	0.00055-2	2	0.075-0.15
Rinse off	303	0.001-65	118	0.0001-1	NR	0.0075-0.05
Diluted for (bath) use	12	1-52	NR	NR	NR	NR
Exposure type						
Eye area	57	0.0035-2	47	0.02-1.1	NR	NR
Incidental ingestion	4	9-45	3	0.005-0.1	NR	NR
Incidental inhalation—spray	4; 157[b]; 84[c]	0.002; spray: 1; 0.002-2[b]	4; 163[b]; 88[c]	0.002-1[b]	1[b]; 1[c]	0.091[b]
Incidental inhalation—powder	4; 84[c]	NR	1; 88[c]; 1[d]	0.12	1[c]	NR
Dermal contact	672	0.001-65	376	0.00055-2	2	0.0075-0.15
Deodorant (underarm)	NR	Aerosol: 0.004 not spray: 0.005-0.009	NR	NR	NR	NR
Hair—noncoloring	53	0.001-10.5	91	0.0001-1	NR	0.091
Hair—coloring	5	NR	NR	NR	NR	NR
Nail	2	13.6	1	1	NR	NR
Mucous membrane	205	0.001-65	11	0.005-0.1	NR	0.0075
Baby products	1	NR	1	NR	NR	NR
	Xylose					
Totals[a]	75	0.1-1				
Duration of use						
Leave-on	68	0.1-0.11				
Rinse off	7	0.1-1				
Diluted for (bath) use	NR	NR				
Exposure type						
Eye area	1	NR				
Incidental ingestion	NR	NR				
Incidental inhalation—spray	4; 10[b]; 13[c]	pump spray: 0.11				

(continued)

Table 5. (continued)

	# of uses[31]	Max. conc. of use (%)[32]	# of uses[31]	Max. conc. of use (%)[32]	# of uses[31]	Max. conc. of use (%)[32]
	Calcium Gluconate		Fructose		Fucose	
Incidental inhalation—powder	13[c]	NR				
Dermal contact	28	NR				
Deodorant (underarm)	NR	NR				
Hair—noncoloring	47	0.1-0.11				
Hair—coloring	NR	1				
Nail	NR	NR				
Mucous membrane	NR	NR				
Baby products	NR	NR				

Abbreviations: NR, not reported.
[a]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.
[b]Includes products that can be sprays, but it is not known whether the reported uses are sprays.
[c]Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories.
[d]Includes products that can be powders, but it is not known whether the reported uses are powders.

Table 6. Ingredients Not Reported to be Used.

Galactose
Galacturonic acid
Lactulose

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.[38]
- 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.[39] A general list of noncosmetic uses, including food uses that are not affirmed as GRAS or those that are inactive ingredients in approved drugs, are listed in Table 7.[3,9,10,12,26,39-41] Table 8 provides a listing of those ingredients that are nutritive and nonnutritive sweeteners.[3,14,42,43]

In Europe, the following are listed in REACH Annex IV: fructose, galactose, glucose, lactose, sodium gluconate, and sucrose.[4] 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 (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[44] and potassium gluconate[45,46] are rapidly absorbed in the small intestine (Table 9).[9,12,23,27,38,44-61] In contrast, isomalt is absorbed only to a limited extent,[12] and lactitol,[12] lactulose,[52] and sucralose[23,55,57] are not absorbed in the gut. Trehalose can be metabolized by trehalase in the gut to produce glucose, which can then be

Table 7. Examples of Noncosmetic 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	9
	- 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	14
	- 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	40 12
Galactose	- Listed in the USP/NF	14
	- Inactive ingredient for approved drugs; used in oral and rectal products	40
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	9
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	14
	- Approved as an inactive ingredient for approved drugs; used in oral products	40
Isomalt	- Listed in the *Foods Chemicals Codex* as a texturizer, formulation aid, surface finishing agent, stabilizer, thickener	3 14
	- Listed in the USP/NF	40
	- Inactive ingredient for approved drugs; used in oral products	12
	- Can function as a coating agent, granulation aid, medicated confectionary base, sweetening agent, or tablet and capsule diluent in pharmaceuticals; a noncariogenic excipient used in tablets or capsules, coatings, sachets, and effervescent tablets; often used in buccal applications	
Lactitol	- Listed in the *Foods Chemicals Codex* as a humectant, stabilizer	3
	- Listed in the USP/NF	14
	- Inactive ingredient for approved drugs; used in oral products (the monohydrate)	40
	- Can function as a sweetening agent, tablet and capsule diluent, and therapeutic agent in pharmaceuticals; used as a noncariogenic replacement for sucrose, a diluent in solid dosage forms, and therapeutically in the treatment of encephalopathy and as a laxative	12
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)	10 3
	- Listed in the *Foods Chemicals Codex* as a processing aid, humectant (anhydrous form), texturizer	40
	- Inactive ingredient for approved drugs; used in transdermal, oral, sublingual, buccal, inhalation, subcutaneous, vaginal, intravenous, intramuscular, and rectal drugs	12
	- 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 IV injections	
	- 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 in 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	14
	- An approved drug used to treat constipation; used in oral and rectal products	39
Maltose	-Listed in the Everything Added to Food in the United States (EAFUS) inventory	41
	- Listed in the USP/NF	14
	- Inactive ingredient for approved drugs; used in oral drugs (the anhydrous form)	40
	- Can function as a sweetening agent and tablet excipient in pharmaceuticals	12
Mannose	Inactive ingredient for approved drugs; used in oral drugs (D-mannose)	40

(continued)

Table 7. (continued)

Ingredient	Use	Reference
Potassium Gluconate	- Listed in the *Foods Chemicals Codex* as a sequestrant	3
	- Listed in the USP/NF	14
Rhamnose	Listed in the EAFUS inventory	41
Ribose	Listed in the EAFUS inventory	41
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	14
	- Inactive ingredient for approved drugs; used in oral products	40
Sucralose	- Listed in the *Foods Chemicals Codex* as a flavor enhancer	3
	- Listed in the USP/NF	14
	- Inactive ingredient for approved drugs; used in oral, sublingual, and buccal drugs	40
	- Can function as a sweetening agent in pharmaceuticals	12
Sucrose	- As the starting material in the fermentative production of ethanol, butanol, glycerol, citric acid, and levulinic acid	10
	- 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	40
	- 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	12
Trehalose	- Llisted in the *Foods Chemicals Codex* as a humectant, stabilizer, thickener, texturizer	3
	- Used as an excipient in a few monoclonal antibody products	26
	- 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	12
Xylose	- Listed in the EAFUS inventory	41
	- Listed in the USP/NF	14

Abbreviation: IV, intravenous.

Table 8. Nutritive and Nonnutritive Sweeteners and Food Additives.

Nutritive[3,14,42,85]	Nonnutritive[3,43]
Fructose	Lactitol
Galactose	Sucralose
Glucose	Xylose
Isomalt	
Lactose	
Maltose	
Potassium gluconate	
Sodium gluconate	
Sucrose	
Trehalose	

readily absorbed. Some of these ingredients (eg, 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.[9] 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.[62] Unlabeled glucose, 0.01 mol/L, was first used on both sides of the skin to saturate the sorptive capacity of the cell system. A concentration of 3.3×10^{-6} mol/L D-[1,3-^{14}C]-glucose, supplied as a sterile aqueous solution containing 3% alcohol, was placed in the donor cell. After 6 hours, the permeability coefficient of glucose was 9.5×10^{-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).[63] The hair on the right hind leg of 4 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

Table 9. Summary Metabolism Data.

Ingredient (GRAS foods are noted)	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	47
Fucose	L-Fucose is a common component of many N- and O-linked glycans and glycolipids produced by mammalian cells	48
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	12, 49
	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	
Galactose	Actively absorbed from the gut; converted in the liver through the Leloir pathway to yield glucose-6-phosphate	85-87
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	9,38,50
Glucose (GRAS)	Rapidly absorbed from the small intestine, principally by an active mechanism	44
Potassium gluconate (GRAS)	Important intermediate in carbohydrate metabolism	9
	Readily absorbed in the intestine, the potassium ion ionizes almost immediately to potassium and gluconic acid; with parental administration, a significant portion (60%-85%) is excreted unchanged in the urine	45,46
Ribose	Rapidly and extensively metabolized; converted into glucose via the pentose phosphate pathway in the liver and other tissues	88
Sodium gluconate (GRAS)	Important intermediate in carbohydrate metabolism	9
Sucrose	Known to be a relatively efficient source of energy; rapidly metabolizable for utilization and storage	51, 12
	Hydrolyzed in the small intestine by sucrose to yield dextrose and fructose, which are then absorbed	49, 12
	There is evidence that sucrose can be absorbed unchanged to a small extent, particularly at a high dietary level; nearly all ingested sucrose is absorbed as glucose and fructose, its metabolism is essentially that of these 2 monosaccharides	
	Excreted unchanged in the urine when administered intravenously	
Metabolized in the small intestines		
Lactose	Broken down in the gut by lactase to produce glucose and galactose	85
Maltose	Broken down in the gut by maltase to yield two glucose molecules	85
Trehalose	Rapidly metabolized in the gut to glucose by trehalase	12
	Metabolism is essentially identical to that of other disaccharides that are consumed as part of the human diet	27,53
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)	12
Lactitol	Not absorbed in the small intestine; broken down by microflora in the large intestine (non-nutritive)	12
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	52, 21
	Reaches the large intestine essentially unchanged, where it is metabolized by bacteria with the formation of low molecular weight acids	
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	54

(continued)

Table 9. (continued)

Ingredient (GRAS foods are noted)	Metabolism data	Reference
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 2 minor metabolites were detected following oral dosing in the mouse, rat, and man, and only 1 urinary metabolite was found in the rabbit and the dog	23,55-59,89 60
	Not metabolized or used for energy in mammalian systems	
Limited absorption/not metabolized		
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	61

Abreviation: GRAS, generally recognized as safe.

imaged using OCT for 8 minutes prior to application of the glucose and then for 2 hours 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 $(4.41 \pm 0.28) \times 10^{-6}$ cm/s.

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 monosaccharides and disaccharides. Examples of these reviews include the "Evaluation of the Health Aspects of Sucrose as a Food Ingredient"[49] and "Evaluation of the Health Aspects of Sodium, Potassium Magnesium, and Zinc Gluconates as Food Ingredients."[50] 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 food substances, direct food additives, or identified in the *Food Chemicals Codex* as used in foods. The focus of the safe use of those monosaccharides 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, that is, 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.[20]

Oral

Lactulose. The oral LD_{50} of lactulose is 48.8 mL/kg in mice and >30 mL/kg in rats.[21]

Repeated Dose Toxicity

Oral

Lactulose. Groups of 8 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/d, respectively) of a 50% lactulose syrup for 21 weeks.[64] 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/d of the test material; diarrhea subsides with 3 to 5 hours 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% aqueous solution of gluconic acid was evaluated in vitro in enucleated rabbit eyes.[9] The test material was applied to 4 eyes and observed over a period of 4 hours 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 nonirritant. A neutral red uptake assay was performed in human keratinocytes, and the cytotoxicity of undiluted isomalt to the cells was measured after 24-hour exposure.[65] Two experiments were performed. Undiluted isomalt was classified as a nonirritant in this in vitro test.

A red blood cell (RBC) lysis and denaturation assay, comprised of 2 range-finding and denaturation assays and 2 lysis assays, was performed in calf RBCs.[66] Concentrations of ≤100 000 mg/L isomalt were tested. Isomalt did not induce hemolysis or protein denaturation and was classified as a nonirritant. 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 in which isomalt was tested undiluted according to the end point assessment and at concentrations of 10% and 50% (w/w) in water according to the reaction-time method.[67] Each aspect of the experiment was performed twice. According to the European Cosmetic Toiletry and Perfumery Association (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 nonirritant using the reaction-time method.

In vivo—nonhuman

Gluconic acid. A 50% aqueous solution of gluconic acid was not irritating to rabbit eyes.[9] A 50% solution of gluconic acid (pH 1.8; 0.1 mL) was instilled into the conjunctival sac of 1 eye in 9 New Zealand white rabbits; the contralateral eye served as an untreated control. The eyes of 3 animals were rinsed after 2 seconds, and of another 3 animals after 4 seconds; the eyes of the remaining 3 animals were not rinsed. The eyes were examined for irritation 1, 24, 48, and 72 hours and 7 days after instillation. Slight redness and conjunctival swelling were observed initially; however, no signs of irritation were observed after 72 hours.

Lactitol. Lactitol was not irritating to rabbit eyes.[20] The study was performed according to the Organization for Economic Co-operation and Development Test Guideline 405.[68] 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-week safety-in use ophthalmological evaluation.[69] Thirty-one participants participated in the study.

Reproductive and Developmental Toxicity

According to the package insert for the prescription drug lactulose in studies of mice, rats, and rabbits, doses of lactulose solution up to 6 or 12 mL/kg/d produced no deleterious effects on breeding, conception, or parturition.[21] (Details were not provided.)

Genotoxicity

The genotoxicity of a number of the monosaccharides and disaccharides has been evaluated in in vitro and in vivo studies. The results of these studies are overwhelmingly negative (Table 10[9,20,27,53,70-75]).

Carcinogenicity

According to the package insert for the prescription drug lactulose, administration of lactulose solution in the diet of mice for 18 months at concentrations of 3% and 10% (v/w) did not produce any evidence of carcinogenicity.[21] (Details were not provided.)

Irritation and Sensitization

Dermal Irritation/Sensitization

Dermal irritation and sensitization studies are summarized in Table 11. In nonhuman studies, a 50% aqueous solution of gluconic acid was not a dermal irritant[9] and lactitol was not an irritant or sensitizer in rabbits.[20] In human repeated insult patch tests (HRIPTs), formulations containing 10% rhamnose,[76] up to 8% glucose,[77,78] 5% mannose,[79] 2.48% lactose,[69] and <1% isomalt,[80] kefiran,[69] lactitol,[69] sucralose,[81] and xylobiose[82] were not irritants or sensitizers. A formulation containing 10% rhamnose did induce a significant irritation reaction in 1 participant,[76] and irritation was observed in 16% of the participants during induction in an HRIPT of a rinse-off hair product containing 29% sucrose (tested as a 50% dilution); no sensitization reactions were reported for this product.[83]

Occupational Exposure Limits

Sucrose

The National Institute for Occupational Safety and Health recommended exposure limit for sucrose is a time-weighted average (TWA) of 10 mg/m^3 (total exposure) and TWA of 5 mg/m^3 (respiratory exposure).[25] The Occupational Safety and Health Administration 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 threshold limit value 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 food substances, direct food additives, or common dietary sugars, dietary sugar replacements, or very closely related analogs; for these ingredients, the primary focus of this review was on local effect, such as dermal irritation and sensitization. For the ingredients that are not identified as dietary substances, oral toxicity data were also searched.

The monosaccharides, disaccharides, and related 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, 22 of the 25 ingredients reviewed in this assessment are reported to be in use. Sucrose has the greatest number of reported uses, 738, 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 vary widely by ingredient and type of use; most of the

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	70
Calcium gluconate	7.5, 15, and 30 μg/mL	With and without metabolic activation	*Saccharomyces cerevisiae* strain D4	Negative	70
Lactitol	Not provided	Reverse mutation assay; details not provided	*S. typhimurium* (stains not specified)	Negative	20
Lactitol	Not provided	Mammalian gene mutation assay; details not provided	Human lymphocytes	Negative	20
Sodium gluconate	0.006, 0.012, and 0.024 μg/mL	Ames test, with and without metabolic activation; appropriate positive and negative controls were used	*S. typhimurium* strains TA1535, TA1537, TA1538	Negative	71
Sodium gluconate	12.5, 25, and 50 μg/mL	Ames test, with and without metabolic activation; appropriate positive and negative controls were used	*S. cerevisiae* strain D4	Negative	71
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	72
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	72
Sucralose	$\leq$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	72
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	72
Sucrose	156-5000 μg/mL	Mouse lymphoma assay, with and without metabolic activation; appropriate controls were used	L5178Y mouse lymphoma cells	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	1311-5000 μg/mL	Mouse lymphoma assay, with and without metabolic activation; appropriate controls were used	L5178Y mouse lymphoma cells	Negative	75
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	27
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	27
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	9

(continued)

Table 10. (continued)

Test article	Concentration/vehicle	Procedure	Test system	Results	Reference
Sodium gluconate	0, 1.25, or 2.5 g/kg in physiological saline	Chromosomal aberration assay; mice were dosed orally with 1 mL, 1×/d 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	9
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 hours after the final dose	Rat bone marrow cells; male and female Sprague-Dawley rats, 5/group	Negative; no mortality	72
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 hours; 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	72
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 hours after dosing	Female CD-1 Swiss mice; 5/sex/group	Negative	72
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	27
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	53

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 (eg, glucose) are sources of energy and others (eg, sucralose) are not. Also, absorption is not the same for each of these ingredients; some are absorbed in the intestines (eg, glucose and potassium gluconate), whereas others are not absorbed in the gut (eg, lactitol and sucralose).

In an in vitro study, 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 an in vivo study with Rhesus monkeys, using OCT, the mean permeability rate of 20% glucose was calculated to be $(4.41 \pm 0.28) \times 10^{-6}$ cm/s.

Lactulose fed to rats at concentrations of up to 5.0% of 50% lactulose syrup for 21 weeks did not result in toxicity. Mild diarrhea was reported for animals fed >2.2 g/kg bw/d of the test material; diarrhea subsides with 3 to 5 hours of feeding. Doses of up to 12 mL/kg/d of lactulose solution produced no deleterious effects on breeding, conception, or parturition in mice, rats, or rabbits. No evidence of carcinogenicity was observed in mice with dosing of up to 10% lactulose solution in the diet for 18 months.

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 nonirritant. Gluconic acid, as a 50% aqueous 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-week safety-in use ophthalmological evaluation

In nonhuman studies, a 50% aqueous solution of gluconic acid was not a dermal irritant and lactitol was not an irritant or sensitizer in rabbits. In HRIPTs, formulations containing 10% rhamnose, 8% glucose, 5% mannose, 2.48% lactose, and <1% isomalt, kefiran, lactitol, sucralose, and xylobiose were not irritants or sensitizers. A formulation containing 10% rhamnose did induce a significant irritation reaction in 1 participant, and irritation was observed in 16% of the participants during induction in an HRIPT of a product containing 29% sucrose (that was a rinse-off hair product tested as a 50% dilution); no sensitization reactions were reported for this product.

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.

Table 11. Irritation and Sensitization Studies.

Test article	Concentration/Dose	Test population	Procedure	Results	Reference
Nonhuman					
Gluconic acid	50% aqueous solution 0.5 mL	6 rabbits/group	- 1 sq. in. occlusive patch was applied for 4 hours - Test sites of 1 group was abraded - Test sites were scored after 24, 48, and 72 hours	- Slight erythema observed during the initial observation; it is not clear if this is only for abraded skin - No signs of irritation at 72 hours	9
Lactitol	Not specified	Rabbits; no./group not specified	- Study was performed according to the OECD Guidelines 404 and 406, respectively.[90,91] (No other details were provided.)	- Not an irritant or sensitizer	20
Human					
Hair styling cream containing 0.08% glucose	Applied neat	100 participants	HRIPT *Induction*: the test material was applied neat under semi-occlusive patches; 9 applications were made over a 3-week period; the first patch was applied for 48 hours, and the remainder for 24 hours *Challenge*: the patch was applied after a 2-week nontreatment period to a previously untreated site; the test sites were scored 48 and 96 hours after application.	Not an irritant or a sensitizer	78
A leave-on hairproduct containing 8% glucose	Applied neat 0.2 mL	208 participants	HRIPT; 24 hours, 2 cm^2, semi-occlusive patches were used	Not a sensitizer 1% of participants had a "+" reaction during induction	77
Mixture containing isomalt	Final applied concentration of isomalt is 0.94% 20 μL	49 participants	- Single insult patch test; test material was applied to the ventral forearm using Finn Chambers, and the test site was scored 15 minutes, 24, and 48 hours 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	80
Face and neck product containing 0.1% kefiran	Applied neat	100 participants	HRIPT using semi-occlusive patches	Not an irritant or sensitizer	69
Paste mask and mud pack containing 0.15% lactitol	Applied neat	28 participants	4-Week in-use dermal study with open applications	Not an irritant	69
Paste mask and mud pack containing 0.15% lactitol	Applied neat	110 participants	HRIPT using semi-occlusive patches	Not an irritant or sensitizer	69
Face and neck product containing 2.48% lactose	Applied neat	114 participants	HRIPT using occlusive patches	Not an irritant or sensitizer	69
Leave-on facial product containing 5% mannose	Applied neat	103 participants	HRIPT with 48 to 72 hours occlusive induction patches and a 48-hour challenge patch - Distilled water was used as a negative control.	Not an irritant or a sensitizer	79

(continued)

Table 11. (continued)

Test article	Concentration/Dose	Test population	Procedure	Results	Reference
Leave-on formulation containing 10% rhamnose	Applied neat	106 participants	HRIPT using 48 to 72 hours 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 participant	76
Lip balm formulation containing 0.6% sucralose	Applied neat	50 participants	Modified Draize HRIPT; similar to that described previously, with the exceptions that all the induction patches were applied for 24 hours, the challenge patch was applied for 24 hours, and the challenge sites scored 24 and 48 hours after application	Not an irritant or sensitizer	81
Rinse-off hair product containing 29% sucrose	Diluted to 50% in distilled water 0.02 mL over 50 mm^2	102 participants	HRIPT using 48 to 72 hours occlusive patches for induction, and a 48-hour patch at challenge	- Not an irritant or sensitizer - Mean irritation index of <0.25; 16% of the participants presented with score ≥ 2 reactions during induction	83
Eye cream formulation containing 0.1% xylobiose	Applied neat	56 participants	HRIPT using 24-hour occlusive patches	Not an irritant or sensitizer	82

Abbreviations: HRIPT, human repeated insult patch test; OECD, Organization for Economic Co-operation and Development.

Discussion

The Cosmetic Ingredient Review Expert Panel (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 food substances 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 inventory, and/or listed as an inactive ingredient in oral drugs. Moreover, the leave-on use concentrations of these ingredients are typically <1%. Therefore, the Panel stated that although oral toxicity data are very limited and reproductive toxicity data are mostly absent, the systemic toxicity of these ingredients was not a concern because of the low concentrations of use and their limited systemic exposure from dermal application.

The Panel commented that sucrose is used at high concentrations in some products that come in contact with mucous membranes (ie, 65% in personal cleanliness products). The Panel noted that sucrose is a GRAS food substance, 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 following current good manufacturing practice. However, if an ingredient that does not have GRAS food additive status was used at concentrations such as these with similar exposure types, the Panel would most likely want data substantiating the safety of that use, such as metabolism after oral administration.

The Panel discussed an HRIPT of a hair product that contained 29% sucrose, diluted to 50%, which reported irritation during induction. The Panel concluded that the irritation reported was likely attributable to a surfactant effect and was not due to sucrose itself. 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 <1% (eg, glucose is used at 1% in a spray body and hand preparation). In the absence of inhalation data, the Panel noted that 95% to 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.

Authors' Note

Unpublished sources cited in this report are available from the Executive Director, Cosmetic Ingredient Review, Suite 1200, 1620L Street, NW, Washington, DC 20036, USA.

Author Contributions

Monice M. Fiume contributed to conception and design, contributed to acquisition, analysis, and interpretation, drafted manuscript, and critically revised manuscript; Wilma F. Bergfeld, Donald V. Belsito, Ronald A. Hill, Curtis D. Klaassen, Daniel C. Liebler, James G. Marks, Ronald C. Shank, Thomas J. Slaga, Paul W. Snyder, and Lillian J. Gill contributed to conception and design, contributed to analysis and interpretation, and critically revised manuscript; Bart Heldreth contributed to analysis and interpretation and critically revised manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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