Toxicological profile for

Sugars (high fructose corn syrup)

This ingredient has been assessed to determine potential human health effects for the consumer. It was considered not to increase the inherent toxicity of the product and thus is acceptable under conditions of intended use.

1. Name of substance and physico-chemical properties

1.1. IUPAC systematic name

(3R,4S,5S,6R)-6-(hydroxymethyl)oxane-2,3,4,5-tetrol;hydrate (CAS RN 8029-43-4) (PubChem)

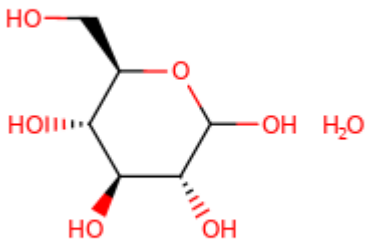
1.2. Synonyms

High levulose corn syrup; Corn syrup, high fructose; Syrup, corn, high fructose (CAS RN 977042-84-4); Corn sugar syrup; Corn syrup; Syrups, corn; EINECS 232-436-4; Glucose syrup; Hydrolyzed starch syrups; UNII-9G5L16BK6N; Syrups, hydrolyzed starch (CAS RN 8029-43-4) (ChemIDplus)

1.3. Molecular formula

Unspecified (CAS RN 8029-43-4) (ChemIDplus).

1.4. Structural Formula



(CAS RN 8029-43-4) (ChemIDplus)

1.5. Molecular weight (g/mol)

198.17 (CAS RN 8029-43-4) (ChemIDplus).

1.6. CAS registration number

8029-43-4; 977042-84-4; 8052-08-2

1.7. Properties

1.7.1. Melting point

(°C): <25 (CAS RN 8029-43-4) (EPISuite, 2017)

1.7.2. Boiling point

(°C): 380.68 (estimated) (CAS RN 8029-43-4) (EPISuite, 2017)

1.7.3. Solubility

Highly soluble: 1.2e+006 mg/L at 30°C (CAS RN 8029-43-4) (EPISuite, 2017); 5e+005 mg/L at 20°C (CAS RN 8029-43-4) (EPISuite, 2017)

1.7.4. pKa

No data available to us at this time.

1.7.5. Flashpoint

(°C): No data available to us at this time.

1.7.6. Flammability limits (vol/vol%)

Not flammable; not explosive (EC, undated)

1.7.7. (Auto)ignition temperature

(°C): “Not flammable” (CAS RN 8029-43-4) (PubChem)

1.7.8. Decomposition temperature

(°C): No data available to us at this time.

1.7.9. Stability

No data available to us at this time.

1.7.10. Vapor pressure

8.02E-14 mm Hg at 25°C (CAS RN 8029-43-4) (EPISuite, 2017)

1.7.11. log Kow

-3.24 (CAS RN 8029-43-4) (EPISuite, 2017)

2. General information

2.1. Exposure

Cosmetics	No evidence
Food	Yes (Ash, 1995)
Environment	No evidence
Pharmaceuticals	No evidence
Tobacco products	In burnt part

Syrups, hydrolyzed starch (CAS RN 8029-43-4) are listed as fragrance ingredients by IFRA.

Hydrolyzed corn starch (CAS RN 8029-43-4) is used as a humectant, binding agent, viscosity controlling agent and skin conditioning agent in cosmetics in the EU (CosIng).

Hydrolyzed corn starch (CAS RN 8029-43-4) is listed as an ingredient in personal care, inside the home, pesticide and pet care products by the CPID.

“OBJECTIVE: Excess fructose consumption is hypothesized to be associated with risk for metabolic disease. Actual fructose consumption levels are difficult to estimate because of the unlabeled quantity of fructose in beverages. The aims of this study were threefold: 1) re-examine the fructose content in previously tested beverages using two additional assay methods capable of detecting other sugars, especially maltose, 2) compare data across all methods to determine the actual free fructose-to-glucose ratio in beverages made either with or without high-fructose corn syrup (HFCS), and 3) expand the analysis to determine

fructose content in commonly consumed juice products. METHODS: Sugar-sweetened beverages (SSBs) and fruit juice drinks that were either made with or without HFCS were analyzed in separate, independent laboratories via three different methods to determine sugar profiles. RESULTS: For SSBs, the three independent laboratory methods showed consistent and reproducible results. In SSBs made with HFCS, fructose constituted 60.6% ± 2.7% of sugar content. In juices sweetened with HFCS, fructose accounted for 52.1% ± 5.9% of sugar content, although in some juices made from 100% fruit, fructose concentration reached 65.35 g/L accounting for 67% of sugars. CONCLUSION: Our results provide evidence of higher than expected amounts of free fructose in some beverages. Popular beverages made with HFCS have a fructose-to-glucose ratio of approximately 60:40, and thus contain 50% more fructose than glucose. Some pure fruit juices have twice as much fructose as glucose. These findings suggest that beverages made with HFCS and some juices have a sugar profile very different than sucrose, in which amounts of fructose and glucose are equivalent. Current dietary analyses may underestimate actual fructose consumption." As taken from Walker RW et al. 2014. Nutrition 30(7-8), 928-35. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/24985013

"National food supply data and dietary surveys are essential to estimate nutrient intakes and monitor trends, yet there are few published studies estimating added sugars consumption. The purpose of this report was to estimate and trend added sugars intakes and their contribution to total energy intake among Canadians by, first, using Canadian Community Health Survey (CCHS) nutrition survey data of intakes of sugars in foods and beverages, and second, using Statistics Canada availability data and adjusting these for wastage to estimate intakes. Added sugars intakes were estimated from CCHS data by categorizing the sugars content of food groups as either added or naturally occurring. Added sugars accounted for approximately half of total sugars consumed. Annual availability data were obtained from Statistics Canada CANSIM database. Estimates for added sugars were obtained by summing the availability of "sugars and syrups" with availability of "soft drinks" (proxy for high fructose corn syrup) and adjusting for waste. Analysis of both survey and availability data suggests that added sugars average 11%-13% of total energy intake. Availability data indicate that added sugars intakes have been stable or modestly declining as a percent of total energy over the past three decades. Although these are best estimates based on available data, this analysis may encourage the development of better databases to help inform public policy recommendations." As taken from Brisbois TD et al. 2014. Nutrients 6(5), 1899-912. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/24815507

"OBJECTIVE: The obesigenic and related health effects of caloric sweeteners are subjects of much current research. Consumers can properly adjust their diets to conform to nutritional recommendations only if the sugars composition of foods and beverages is accurately measured and reported, a matter of recent concern. We tested the hypothesis that high-fructose corn syrup (HFCS) used in commercial carbonated beverages conforms to commonly assumed fructose percentages and industry technical specifications, and fulfills beverage product label regulations and Food Chemicals Codex-stipulated standards. DESIGN: A high-pressure liquid chromatography method was developed and verified for analysis of sugars in carbonated beverages sweetened with HFCS-55. The method was used to measure percent fructose in three carbonated beverage categories. Method verification was demonstrated by acceptable linearity ($R(2)>0.99$), accuracy (94-104% recovery) and precision ($RSD<2\%$). RESULT: Fructose comprised 55.58% of total sugars (95% confidence interval 55.51-55.65%), based on 160 total measurements by 2

independent laboratories of 80 randomly selected carbonated beverages sweetened with HFCS-55. The difference in fructose measurements between laboratories was significant but small (0.1%), and lacked relevance. Differences in fructose by product category or by product age were not statistically significant. Total sugars content of carbonated beverages showed close agreement within product categories (95% confidence interval=0.01-0.54%). CONCLUSIONS: Using verified analytical methodology for HFCS-sweetened carbonated beverages, this study confirmed the hypothesis that fructose as a percentage of total sugars is in close agreement with published specifications in industry technical data sheets, published literature values and governmental standards and requirements. Furthermore, total sugars content of commercial beverages is consistent with common industry practices for canned and bottled products and met the US Federal requirements for nutritional labeling and nutrient claims. Prior concerns about composition were likely owing to use of improper and unverified methodology." As taken from White JS et al. 2015. Int. J. Obes. (Lond.) 39(1), 176-82. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/24798032

"Artificial food colors (AFCs) are used to color many beverages, foods, and sweets in the United States and throughout the world. In the United States, the Food and Drug Administration (FDA) limits the AFCs allowed in the diet to 9 different colors. The FDA certifies each batch of manufactured AFCs to guarantee purity and safety. The amount certified has risen from 12 mg/capita/d in 1950 to 62 mg/capita/d in 2010. Previously, we reported the amounts of AFCs in commonly consumed beverages. In this article, the amounts of AFCs in commonly consumed foods and sweets are reported. In addition, the amount of sugars in each product is included. Amounts of AFCs reported here along with the beverage data show that many children could be consuming far more dyes than previously thought. Clinical guidance is given to help caregivers avoid AFCs and reduce the amount of sugars in children's diets." As taken from Stevens LJ et al. 2015. Clin. Pediatr. (Phila.) 54(4), 309-21. PubMed, 2016 available at: http://www.ncbi.nlm.nih.gov/pubmed/24764054

National Occupational Exposure Survey (1981 - 1983)

Estimated Numbers of Employees Potentially Exposed to corn syrup (CAS RN 8029-43-4) by Occupation*

Code	Occupation Description (1980)	Total # Employees (Male & Female)	Total # Female Employees
086	VETERINARIANS	1,472	294
095	REGISTERED NURSES	15,146	14,575
096	PHARMACISTS	2,224	1,221
185	DESIGNERS	575	246

203	CLINICAL LABORATORY TECHNOLOGISTS AND TECHNICIANS	255	221
223	BIOLOGICAL TECHNICIANS	3,052	872
235	TECHNICIANS, N.E.C.	665	
356	MAIL CLERKS, EXC. POSTAL SERVICE	1,682	146
364	TRAFFIC, SHIPPING, AND RECEIVING CLERKS	885	52
368	WEIGHERS, MEASURERS, AND CHECKERS	119	
389	ADMINISTRATIVE SUPPORT OCCUPATIONS, N.E.C.	52	
435	WAITERS AND WAITRESSES	1,438	1,233
436	COOKS, EXCEPT SHORT ORDER	856	
444	MISCELLANEOUS FOOD PREPARATION OCCUPATIONS	876	803
446	HEALTH AIDES, EXCEPT NURSING	1,285	784
447	NURSING AIDES, ORDERLIES, AND ATTENDANTS	2,608	2,608
453	JANITORS AND CLEANERS	5,274	
469	PERSONAL SERVICE OCCUPATIONS, N.E.C.	758	237
487	ANIMAL CARETAKERS, EXCEPT FARM	589	589
518	INDUSTRIAL MACHINERY REPAIRERS	262	
547	SPECIFIED MECHANICS AND REPAIRERS, N.E.C.	524	

549	NOT SPECIFIED MECHANICS AND REPAIRERS	646	
558	SUPERVISORS, N.E.C.	150	
563	BRICKMASONS AND STONEMASONS	7,330	
567	CARPENTERS	1,408	
575	ELECTRICIANS	87	
579	PAINTERS, CONSTRUCTION AND MAINTENANCE	46	
583	PAPERHANGERS	387	
588	CONCRETE AND TERRAZZO FINISHERS	1,004	
599	CONSTRUCTION TRADES, N.E.C.	344	
633	SUPERVISORS, PRODUCTION OCCUPATIONS	2,129	
637	MACHINISTS	1,130	
679	BOOKBINDERS	6,338	2,883
687	BAKERS	2,836	368
688	FOOD BATCHMAKERS	1,986	364
719	MOLDING AND CASTING MACHINE OPERATORS	109	18
723	METAL PLATING MACHINE OPERATORS	2,081	1,392
734	PRINTING MACHINE OPERATORS	753	
735	PHOTOENGRAVERS AND LITHOGRAPHERS	536	215

736	TYPESETTERS AND COMPOSITORS	2,607	
737	MISCELLANEOUS PRINTING MACHINE OPERATORS	4,401	2,400
749	MISCELLANEOUS TEXTILE MACHINE OPERATORS	231	71
753	CEMENTING AND GLUING MACHINE OPERATORS	285	285
754	PACKAGING AND FILLING MACHINE OPERATORS	3,660	1,247
755	EXTRUDING AND FORMING MACHINE OPERATORS	572	68
756	MIXING AND BLENDING MACHINE OPERATORS	8,630	237
757	SEPARATING, FILTERING, AND CLARIFYING MACHINE OPERATORS	206	
759	PAINTING AND PAINT SPRAYING MACHINE OPERATORS	1,360	322
766	FURNACE, KILN, AND OVEN OPERATORS, EXC. FOOD	4,737	861
768	CRUSHING AND GRINDING MACHINE OPERATORS	701	64
774	PHOTOGRAPHIC PROCESS MACHINE OPERATORS	35	6
777	MISCELLANEOUS MACHINE OPERATORS, N.E.C.	3,708	1,427
779	MACHINE OPERATORS, NOT SPECIFIED	779	270
785	ASSEMBLERS	1,945	1,373

795	MISCELLANEOUS HAND WORKING OCCUPATIONS	266	
796	PRODUCTION INSPECTORS, CHECKERS, AND EXAMINERS	4,245	2,773
797	PRODUCTION TESTERS	68	68
804	TRUCK DRIVERS, HEAVY	19,488	
856	INDUSTRIAL TRUCK AND TRACTOR EQUIPMENT OPERATORS	85	
859	MISCELLANEOUS MATERIAL MOVING EQUIPMENT OPERATORS	2,139	729
869	CONSTRUCTION LABORERS	6,605	453
878	MACHINE FEEDERS AND OFFBEARERS	2,793	
883	FREIGHT, STOCK, AND MATERIAL MOVERS, HAND, N.E.C.	276	
887	VEHICLE WASHERS AND EQUIPMENT CLEANERS	113	
888	HAND PACKERS AND PACKAGERS	5,099	3,111
889	LABORERS, EXCEPT CONSTRUCTION	5,477	718
TOTAL		150,409	45,604

*(1) The estimates for each occupation apply across the surveyed industries in which the agent was observed. Not all industries were surveyed, and not all agents were observed in all surveyed industries. (2) When using the estimates, standard errors associated with estimates should be considered. (3) Potential exposures to a chemical agent are categorized as actual (i.e., the surveyor observed the use of the specific agent) or tradename (i.e., the surveyor observed the use of a tradename product known to contain the specific agent). The estimates presented in the table combine both categories.

As taken from NIOSH, available at https://web.archive.org/web/20111028104200/http://www.cdc.gov/noes/noes2/80589occ.html .

2.2. Combustion products

This ingredient High Fructose Corn Syrup was investigated in a pyrolysis study. Results are given in JTI Study Report (s).

Compound	Two stage heating		One stage heating	
	Abundance	Area%	Abundance	Area%
furfural	39027650	24.53	362534193	24.75
2,3-dihydro-3,5-dihydroxy-6-methyl-4H-pyran-4-one	16374209	1.03	17027099	1.16
1,4:3,6-dianhydro-alpha-D-glucopyranose	19941009	1.25	14203118	0.97
5-hydroxymethylfurfural	644398220	40.50	544894421	39.49
unknown	36006319	2.26	62346551	4.26
levoglucosan	222502641	13.99	195543669	13.35
1,6-anhydro-beta-D-glucofuranose	90474343	5.69	59920613	4.09
5,5'-oxy-dimethylene-bis(2-furaldehyde)	27338832	1.72	28367292	1.94
Total ion chromatogram	1589466977	100	1462231546	100

This ingredient (corn syrup) was investigated in a pyrolysis study. Results are given in JTI Study Report(s).

Compound	Two stage heating	One stage heating

	Abundance	Area %	Abundance	Area %
unknown	6562563	0.98	13958818	1.53
furfural	18920964	2.82	30980067	3.41
unknown	15343207	2.29	34889101	3.83
1,4:3,6-dianhydro-alpha-D-glucopyranose	9704885	1.45	28966665	3.18
5-hydroxymethylfurfural	40270933	6.01	58282893	6.41
unknown	4943488	0.74	10839360	1.19
unknown	16738412	2.50	35459550	3.90
Unknown (mixture)	5286501	0.79	15028443	1.65
unknown	624337	0.09	15145779	1.66
levoglucosan	545660102	81.46	610288641	67.08
1,6-anhydro-beta-D-glucofuranose	trace	trace	20389034	2.24
Total ion chromatogram	669850358	100	910224732	100

This ingredient was investigated in a pyrolysis study. Results are given in Baker R and Bishop L. (2005). The pyrolysis of non-volatile tobacco ingredients using a system that stimulates cigarette combustion conditions. J. Anal. Appl. Pyrolysis 74, 145–170. (CAS 68131-37-3)

Ingredient Name & CAS Number	Max. cig. appln. Level (ppm)	Purity of Sample (%)	Composition of pyrolysate (Compound, %)	Max. level in smoke (µg)

Corn Syrup 68131-37-3	17000	na	**Furfural (45.3)** Hydroxymethylfurfural (44.0) Methyl benzenediol (1.6) Dihydrodihydroxymethylpyranone (1.2) Furfuryl alcohol (0.7) **Phenol (0.4)**	3850 3850 140 100 60 30

2.3. Ingredient(s) from which it originates

Corn syrup is obtained by partial hydrolysis of corn starch by the action of acids or enzymes. Depending on the degree of hydrolysis it contains in addition to glucose, maltose and higher saccharides

High fructose corn syrup is prepared from high dextrose-equivalent corn starch hydrolysate by partial enzymatic conversion of glucose (dextrose) to fructose using an insoluble glucose isomerase enzyme preparation.

As taken from FDA, 2020a,b.

Sucrose and HFCS are similar in their composition. Sucrose contains 50% fructose and 50% glucose. There are two major forms of HFCS in common usage within the food industry. HFCS-55 contains 55% fructose, 42% glucose and 3% other carbohydrates which are readily hydrolysable polymers of glucose. HFCS-55 is the form of HFCS commonly used in soft drinks and other sugar sweetened beverages in the United States. HFCS-42 contains 42% fructose and 53% glucose as well as 5% polymers which are hydrolysable to glucose. [4]This is the common form of fructose used in solid foods and other applications. (Klurfeld et al, 2013)

3. Status in legislation and other official guidance

States approving use in tobacco	Unknown
Food	EU/ US Unknown
ADI	No formal ADI identified. In the US, corn syrup and high fructose corn syrup are Generally Recognized As Safe (GRAS) for use in food, with no limitation other than current good manufacturing practice (FDA, 2020a,b).
Codex Alim.	Not listed
C of E no.	Not listed
FEMA no.	Not identified
TLV (ACGIH)	Not listed
Cosmetics (UK)	Not listed in Schedule 1

US FDA - 21 CFR 184 – Direct Food Substances Affirmed as Generally Recognized as Safe (GRAS):

“**§ 184.1866 High fructose corn syrup.**

(a) High fructose corn syrup, a sweet, nutritive saccharide mixture containing either approximately 42 or 55 percent fructose, is prepared as a clear aqueous solution from high dextrose-equivalent corn starch hydrolysate by partial enzymatic conversion of glucose (dextrose) to fructose using an insoluble glucose isomerase enzyme preparation described in 184.1372. The product containing more than 50 percent fructose (dry weight) is prepared through concentration of the fructose portion of the mixture containing less than 50 percent fructose.

(b) The ingredient shall conform to the identity and specifications listed in the monograph entitled "High-Fructose Corn Syrup" in the Food Chemicals Codex, 4th ed. (1996), pp. 191-192, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Office of Food Additive Safety (HFS-200), Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740, 240-402-1200, or may be examined at the Food and Drug Administration's Main Library, 10903 New Hampshire Ave., Bldg. 2, Third Floor, Silver Spring, MD 20993, 301-796-2039, or at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to: http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.

(c) In accordance with 184.1(b)(1), the ingredient is used in food with no limitation other than current good manufacturing practice.

[61 FR 43450, Aug. 23, 1996, as amended at 78 FR 14667, Mar. 7, 2013; 81 FR 5596, Feb. 3, 2016] ”

“§184.1865 Corn syrup.

(a) Corn syrup, commonly called "glucose sirup" or "glucose syrup," is obtained by partial hydrolysis of corn starch with safe and suitable acids or enzymes. It may also occur in the dehydrated form (dried glucose sirup). Depending on the degree of hydrolysis, corn syrup may contain, in addition to glucose, maltose and higher saccharides.

(b) The ingredient meets the specifications as defined and determined in 168.120(b) or 168.121(a) of this chapter, as appropriate.

(c) In accordance with 184.1(b)(1), the ingredient is used in food with no limitation other than current good manufacturing practice.

(d) Prior sanctions for this ingredient different from the uses established in this section do not exist or have been waived.

[53 FR 44876, Nov. 7, 1988, as amended at 73 FR 8608, Feb. 14, 2008] ”

As taken from FDA, 2020a,b.

High fructose corn syrup (CAS RN 977042-84-4) is included on the FDA’s inventory of “Substances Added to Food (formerly EAFUS) as a nutritive sweetener, is generally recognised as safe (GRAS) under 21 CFR section 184.1866 (direct food substances) and is also included under 21 CFR sections 131.111 - acidified milk; 131.112 - cultured milk; 131.170 - eggnog; 131.200 - yogurt; 131.203 - lowfat yogurt; 131.206 - nonfat yogurt.

As taken from FDA, 2020a,b.

Syrups, hydrolyzed starch (CAS RN 8029-43-4) are pre-registered under REACH (“envisaged registration deadline 30 November 2010”) (ECHA a).

CAS RNs 8052-08-2 and 977042-84-4 are neither registered nor pre-registered under REACH (ECHA b).

“Syrups, hydrolyzed starch” (CAS RN 8029-43-4) are not classified for packaging and labelling under Regulation (EC) No. 1272/2008. CAS RNs 8052-08-2 and 977042-84-4 are not included in ECHA’s C&L inventory (ECHA, 2020).

Corn sugar syrup (CAS RN 8029-43-4) is included on the list of Safer Chemical Ingredients (US EPA, 2019).

Hydrolyzed starch syrups (CAS RN 8029-43-4) are listed in the US EPA Toxic Substances Control Act (TSCA) inventory, and also in the US EPA 2020 CDR Partial Exempt and 2020 CDR Full Exempt lists (Chemical Data Reporting Rule). The CDR regulation requires companies that manufacture (including import) certain chemicals at certain volumes in the U.S. to report to EPA every four years through its CDR.

The TSCA inventory, and 2020 CDR Partial Exempt and 2020 CDR Full Exempt lists are available at https://iaspub.epa.gov/sor_internet/registry/substreg/searchandretrieve/searchbylist/search.do

“EFSA will provide scientific advice on the daily intake of added sugar in food by early 2020. The Authority aims to establish a science-based cut-off value for daily exposure to added sugars from all sources which is not associated with adverse health effects. The work will be carried out following a request from Denmark, Finland, Iceland, Norway and Sweden.

Added sugars from all sources comprise sucrose, fructose, glucose, starch hydrolysates such as glucose syrup, high-fructose syrup, and other sugar preparations consumed as such or added during food preparation and manufacturing.

The adverse health effects under consideration will include body weight, glucose intolerance and insulin sensitivity, type-2-diabetes, cardiovascular risk factors, as well as dental caries. In its assessment, EFSA will look at the general healthy population, including children, adolescents, adults and the elderly.

The advice will guide Member States when establishing recommendations for the consumption of added sugars and in planning food-based dietary guidelines.”

As taken from EFSA, 2017

Syrups, hydrolyzed starch (CAS RN 8029-43-4) are included on the New Zealand Inventory of Chemicals and may be used as a single component chemical under an appropriate group standard (NZ EPA, 2006).

Corn syrup (CAS RN 8029-43-4) is “not considered to pose an unreasonable risk to the health of workers and public health on the basis of the Tier I IMAP assessment” and has been “identified as low concern to human health by application of expert validated rules” (NICNAS, 2018).

Corn syrup (CAS RN 8029-43-4) and high fructose corn syrup (no CAS RN) are included on the US FDA’s list of inactive ingredients for approved drug products. They are permitted for use as ingredients in various products at the following maximum potencies per unit dose:

Inactive Ingredient	**Route**	**Dosage Form**	**CAS Number**	**UNII**	**Maximum Potency per unit dose**
CORN SYRUP	BUCCAL	TROCHE	8029434	9G5L16BK6N	NA

CORN SYRUP	ORAL	CAPSULE, EXTENDED RELEASE	8029434	9G5L16BK6N	28.5mg
CORN SYRUP	ORAL	ELIXIR	8029434	9G5L16BK6N	400mg/ 1.00 ml
CORN SYRUP	ORAL	SOLUTION	8029434	9G5L16BK6N	750mg/ 5.00 ml
CORN SYRUP	ORAL	SUSPENSION	8029434	9G5L16BK6N	2500mg/ 5.00 ml
CORN SYRUP	ORAL	SUSPENSION, EXTENDED RELEASE	8029434	9G5L16BK6N	1500mg/ 5.00 ml
CORN SYRUP	ORAL	SYRUP	8029434	9G5L16BK6N	600mg
CORN SYRUP	ORAL	TABLET	8029434	9G5L16BK6N	14.07mg
CORN SYRUP	ORAL	TABLET, COATED	8029434	9G5L16BK6N	17mg
CORN SYRUP	ORAL	TROCHE	8029434	9G5L16BK6N	NA
HIGH FRUCTOSE CORN SYRUP	ORAL	LIQUID		XY6UN3QB6S	17mg/ 1.00 ml
HIGH FRUCTOSE CORN SYRUP	ORAL	SOLUTION		XY6UN3QB6S	1250mg/ 5.00 ml
HIGH FRUCTOSE CORN SYRUP	ORAL	SUSPENSION		XY6UN3QB6S	300mg/ 1.00 ml
HIGH FRUCTOSE CORN SYRUP	ORAL	SUSPENSION, EXTENDED RELEASE		XY6UN3QB6S	1500mg/ 5.00 ml

As taken from FDA, 2020c

4. Metabolism/Pharmacokinetics

4.1. Metabolism/metabolites

Straight talk about high-fructose corn syrup: what it is and what it ain't (Abstract). High-fructose corn syrup (HFCS) is a fructose-glucose liquid sweetener alternative to sucrose (common table sugar) first introduced to the food and beverage industry in the 1970s. It is not meaningfully different in composition or metabolism from other fructose-glucose sweeteners like sucrose, honey, and fruit juice concentrates. HFCS was widely embraced by food formulators, and its use grew between the mid-1970s and mid-1990s, principally as a replacement for sucrose. This was primarily because of its sweetness comparable with that of sucrose, improved stability and functionality, and ease of use. Although HFCS use today is nearly equivalent to sucrose use in the United States, we live in a decidedly sucrose-sweetened world: >90% of the nutritive sweetener used worldwide is sucrose. Here I review the history, composition, availability, and characteristics of HFCS in a factual manner to clarify common misunderstandings that have been a source of confusion to health professionals and the general public alike. In particular, I evaluate the strength of the popular hypothesis that HFCS is uniquely responsible for obesity. Although examples of pure fructose causing metabolic upset at high concentrations abound, especially when fed as the sole carbohydrate source, there is no evidence that the common fructose-glucose sweeteners do the same. Thus, studies using extreme carbohydrate diets may be useful for probing biochemical pathways, but they have no relevance to the human diet or to current consumption. I conclude that the HFCS-obesity hypothesis is supported neither in the United States nor worldwide (White JS, 2008).

The effect of various types of dry starch syrup on the rate of glucose utilization in lipid, carbohydrate, and protein components of rat liver (Abstract).

Effect of a diet, containing dextran maltose and dry starch syrup, on some patterns of liver tissue metabolism were studied in young Wistar rats within 30 days. The animals of Control Group 1 were kept on a diet containing corn starch as a source of carbohydrates; in Group 2 the starch was replaced by the dry starch syrup enriched with disaccharides and especially with maltose; the dry starch syrup added into the Group 3 diet containing mainly oligosaccharides and polymers with high levels of glucose residues. The label mixtures of 6-3N- and 6-14C-glucose as well as of 6-3H- and I-14C-glucose were administered into the animals on the day of death. Analysis of the findings has shown that the products of starch hydrolysis may the specific parameters of glucose metabolism. Incorporation of the label into liver tissue lipids was similar to the control values in the group of animals kept on a diet enriched with maltose as compared with group 3. The glycolytic pathway of glucose utilization was more activated than the pentosephosphate pathway after substituting starch for dry starch syrup as shown by differences in the rates of carbon incorporation at positions 1 and 6 of a glucose molecule. [Article in Russian] (Antonova ZhV et al., 1994).

“Both controversy and confusion exist concerning fructose, sucrose, and high-fructose corn syrup (HFCS) with respect to their metabolism and health effects. These concerns have often been fueled by speculation based on limited data or animal studies. In retrospect, recent controversies arose when a scientific commentary was published suggesting a possible unique link between HFCS consumption and obesity. Since then, a broad scientific consensus has emerged that there are no metabolic or endocrine response differences between HFCS and sucrose related to obesity or any other adverse health outcome. This equivalence is not surprising given that both of these sugars contain approximately equal amounts of fructose and glucose, contain the same number of calories, possess the same level of sweetness, and are absorbed identically through the gastrointestinal tract. Research comparing pure fructose with pure glucose, although interesting from a scientific point of view, has limited application to human nutrition given that neither is consumed to an appreciable degree in isolation in the human diet. Whether there is a link between fructose, HFCS, or sucrose and increased risk of heart disease, metabolic syndrome, or fatty infiltration of the liver or muscle remains in dispute with different studies using different methodologies arriving at different conclusions. Further randomized clinical trials are needed to resolve many of these issues. The purpose of this review is to summarize current knowledge about the metabolism, endocrine responses, and potential health effects of sucrose, HFCS, and fructose.” As taken from Rippe JM & Angelopoulos TJ. 2013. Adv. Nutr. 4(2), 236-45. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/23493540?dopt=AbstractPlus

“Fructose in the form of sucrose and high fructose corn syrup is absorbed by the intestinal transporter and mainly metabolized in the small intestine. However, excess intake of fructose overwhelms the absorptive capacity of the small intestine, leading to fructose malabsorption. Carbohydrate response element-binding protein (ChREBP) is a basic helix-loop-helix leucine zipper transcription factor that plays a key role in glycolytic and lipogenic gene expression in response to carbohydrate consumption. While ChREBP was initially identified as a glucose-responsive factor in the liver, recent evidence suggests that ChREBP is essential for fructose induced lipogenesis and gluconeogenesis in the small intestine as well as in the liver. We recently identified that the loss of ChREBP leads to fructose intolerance via insufficient induction of genes involved in fructose transport and metabolism in the intestine. As fructose consumption is increasing and closely associated with metabolic and gastrointestinal diseases, a comprehensive understanding of cellular fructose sensing and metabolism via ChREBP may uncover new therapeutic opportunities. In this mini review, we briefly summarize recent progress in intestinal fructose metabolism, regulation and function of ChREBP by fructose, and delineate the potential mechanisms by which excessive fructose consumption may lead to irritable bowel syndrome.” As taken from Lee HJ and Cha JY. 2018. BMB Rep. 51(9), 429-436. PubMed, 2019 available at: https://www.ncbi.nlm.nih.gov/pubmed/30158026

“Glucose/fructose in beverages/foods containing high-fructose corn syrup (HFCS) are metabolized to glyceraldehyde (GA) in the liver. We previously reported that GA-derived advanced glycation end-products (toxic AGEs, TAGE) are generated and may induce the onset/progression of non-alcoholic fatty liver disease (NAFLD). We revealed that the generation of TAGE in the liver and serum TAGE levels were higher in NAFLD patients than in healthy humans. Although we propose the intracellular generation of TAGE in the normal liver, there is currently no evidence to support this, and the levels of TAGE produced have not yet been measured. In the present study, male Wister/ST rats that drank normal water

or 10% HFCS 55 (HFCS beverage) were maintained for 13 weeks, and serum TAGE levels and intracellular TAGE levels in the liver were analyzed. Rats in the HFCS group drank 127.4 mL of the HFCS beverage each day. Serum TAGE levels and intracellular TAGE levels in the liver both increased in the HFCS group. A positive correlation was observed between intracellular TAGE levels in the liver and serum TAGE levels. On the other hand, in male Wister/ST rats that drank Lactobacillus beverage for 12 weeks-a commercial drink that contains glucose, fructose, and sucrose- no increases were observed in intracellular TAGE or serum TAGE levels. Intracellular TAGE were generated in the normal rat liver, and their production was promoted by HFCS, which may increase the risk of NAFLD." As taken from Takata T et al. 2019. Nutrients 11(7), 1612. PubMed, 2020 available at https://pubmed.ncbi.nlm.nih.gov/31315223/

4.2. Absorption, distribution and excretion

Effects of sucromalt on postprandial responses in human subjects (Abstract). To compare postprandial responses elicited by sucromalt, a nutritive sweetener produced by treating a blend of sucrose and corn syrup with an enzyme from Leuconostoc mesenteroides, with those after 42% of high-fructose corn syrup (HFCS), and to see if the reduced responses after sucromalt could be accounted for by carbohydrate malabsorption.

SUBJECT AND METHODS: Three experiments were performed in separate groups of normal subjects studied after overnight fasts using double-blind, randomized, cross-over designs. HFCS was used as the control because it contained a similar amount of fructose as sucromalt. Experiment 1 (n = 10): plasma glucose and insulin were measured after 50 g sucromalt and 50 g HFCS. Experiment 2 (n = 10): metabolic profiles were measured after 80 g HFCS, 80 g sucromalt or 56 g fructose/glucose blend plus 24 g inulin. Experiment 3 (n = 20): the glycaemic indices of sucromalt and HFCS were determined.

RESULTS: Mean glucose and insulin responses after sucromalt were 66 and 62%, respectively, of those after HFCS ($P<0.05$). The inulin treatment, used to mimic the effects of carbohydrate malabsorption, elicited higher breath hydrogen (H2), lower glucose and insulin responses, and a significantly earlier rise in serum free fatty acids (FFA) than those of HFCS (all $P<0.05$). Sucromalt elicited no rise in breath H2, and delayed falls in glucose and insulin, and a delayed rebound of FFA compared to HFCS (all $P<0.05$).

CONCLUSIONS: The reduced glucose and insulin responses elicited by sucromalt are not explained by malabsorption and are more likely related to differences in either rate of digestion and absorption or postabsorptive handling by body. As taken from Grysman A et al. Eur J Clin Nutr. 2008 Dec; 62(12):1364-71. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/17717534

A critical examination of the evidence relating high fructose corn syrup and weight gain (Abstract). The use of high fructose corn syrup (HFCS) has increased over the past several decades in the United States while overweight and obesity rates have risen

dramatically. Some scientists hypothesize that HFCS consumption has uniquely contributed to the increasing mean body mass index (BMI) of the U.S. population. The Center for Food, Nutrition, and Agriculture Policy convened an expert panel to discuss the published scientific literature examining the relationship between consumption of HFCS or "soft drinks" (proxy for HFCS) and weight gain. The authors conducted original analysis to address certain gaps in the literature. Evidence from ecological studies linking HFCS consumption with rising BMI rates is unreliable. Evidence from epidemiologic studies and randomized controlled trials is inconclusive. Studies analyzing the differences between HFCS and sucrose consumption and their contributions to weight gain do not exist. HFCS and sucrose have similar monosaccharide compositions and sweetness values. The fructose:glucose (F:G) ratio in the U.S. food supply has not appreciably changed since the introduction of HFCS in the 1960s. It is unclear why HFCS would affect satiety or absorption and metabolism of fructose any differently than would sucrose. Based on the currently available evidence, the expert panel concluded that HFCS does not appear to contribute to overweight and obesity any differently than do other energy sources. Research recommendations were made to improve our understanding of the association of HFCS and weight gain. As taken from Forshee RA et al. Crit Rev Food Sci Nutr. 2007; 47(6):561-82. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/17653981

Fructose intake at current levels in the United States may cause gastrointestinal distress in normal adults (Abstract). Fructose intake has increased considerably in the United States, primarily as a result of increased consumption of high-fructose corn syrup, fruits and juices, and crystalline fructose. The purpose was to determine how often fructose, in amounts commonly consumed, would result in malabsorption and/or symptoms in healthy persons.

DESIGN: Fructose absorption was measured using 3-hour breath hydrogen tests and symptom scores were used to rate subjective responses for gas, borborygmus, abdominal pain, and loose stools.

SUBJECTS/SETTING: The study included 15 normal, free-living volunteers from a medical center community and was performed in a gastrointestinal specialty clinic.

INTERVENTION: Subjects consumed 25- and 50-g doses of crystalline fructose with water after an overnight fast on separate test days.

MAIN OUTCOME MEASURES: Mean peak breath hydrogen, time of peak, area under the curve (AUC) for breath hydrogen and gastrointestinal symptoms were measured during a 3-hour period after subjects consumed both 25- and 50-g doses of fructose.

STATISTICAL ANALYSES: Differences in mean breath hydrogen, AUC, and symptom scores between doses were analyzed using paired t tests. Correlations among peak breath hydrogen, AUC, and symptoms were also evaluated. RESULTS: More than half of the 15 adults tested showed evidence of fructose malabsorption after 25 g fructose and greater than two thirds showed malabsorption after 50 g fructose. AUC, representing overall breath hydrogen response, was significantly greater after the 50-g dose. Overall symptom scores were significantly greater than baseline after each dose, but scores were only marginally

greater after 50 g than 25 g. Peak hydrogen levels and AUC were highly correlated, but neither was significantly related to symptoms.

CONCLUSIONS: Fructose, in amounts commonly consumed, may result in mild gastrointestinal distress in normal people. Additional study is warranted to evaluate the response to fructose-glucose mixtures (as in high-fructose corn syrup) and fructose taken with food in both normal people and those with gastrointestinal dysfunction. Because breath hydrogen peaks occurred at 90 to 114 minutes and were highly correlated with 180-minute breath hydrogen AUC, the use of peak hydrogen measures may be considered to shorten the duration of the exam. As taken from Beyer PL et al. J Am Diet Assoc. 2005 Oct;105 (10):1559-66. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/16183355

Plasma glucose and insulin after fructose a high-fructose corn syrup meals in subjects with non-insulin-dependent diabetes mellitus (Abstract). The impact on plasma glucose of 35 g of fructose or an equicaloric amount (43.75 g) of high-fructose corn syrup (HFCS) (as part of a 400-calorie meal) was measured in six patients with non-insulin-dependent diabetes mellitus (NIDDM). Blood samples were collected periodically at all points for all patients for 3 h for plasma glucose (PG) and insulin (IRI) determinations. The mean peak PG increment was higher after the HFCS meal (66.5 mg/dl) than after the fructose meals (45.5 mg/dl). When increase in the mean plasma glucose concentration (delta PG) after the fructose meals were compared with the delta PG after the HFCS meals, there was statistical significance at 15 min (P less than 0.02) and 30 min (P less than 0.05). The total areas under the 3-h curves of mean delta PG showed a highly significant (P less than 0.001) difference between the fructose meal (5601 planimetry U) compared with the HFCS meal (8023 planimetry U). Mean changes in IRI after meals with either sweetener were comparable. These findings suggest that fructose is superior to HFCS as a sweetening agent in patients with NIDDM. As taken from Akgün S, Ertel NH. Diabetes Care. 1981 Jul-Aug; 4(4):464-7. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/7049631?dopt=AbstractPlus

The effects of sucrose, fructose, and high-fructose corn syrup meals on plasma glucose and insulin in non-insulin-dependent diabetic subjects (Abstract). We have previously shown that fructose and sorbitol given with a standard meal cause less increment in plasma glucose than sucrose and high fructose corn syrup (HFCS) in patients with NIDDM. However, there was no direct comparison of sucrose with HFCS. Sixteen men and one woman aged 54-67) with NIDDM were given either 35 g sucrose, 35 g fructose, or 43.75 g HFCS containing 35 g carbohydrate as part of a 400-calorie test meal. Blood samples were obtained at frequent intervals up to 3 h and were analyzed for glucose and insulin. As compared with a fructose meal, the mean increment in plasma glucose (delta PG) after a sucrose meal was significantly higher at 45 min and after an HFCS meal it was significantly higher at 30 and 45 min, but sucrose and HFCS meals did not differ. When delta PGs were compared in nine patients with basal PG greater than 140 mg/dl and in eight patients with basal PG less than 140 mg/dl, differences in delta PG after sucrose and HFCS versus fructose meals became more significant but still did not differ from each other. The integrated total areas under the delta PG curves after sucrose, HFCS, and fructose

meals were not statistically different. However, the areas under the curves up to 90 min after sucrose and HFCS meals, which did not differ, were greater than the fructose meal. The mean delta IRI after sucrose meals was markedly elevated at 45, 60, and 75 min (P less than 0.05) and after HFCS meals at 45 min as compared with fructose meals. As taken from Akgün S, Ertel NH. Diabetes Care. 1985 May-Jun; 8(3):279-83. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/3891268?dopt=AbstractPlus

Effects of high-fructose (90%) corn syrup on plasma glucose, insulin, and C-peptide in non-insulin-dependent diabetes mellitus and normal subjects (Abstract). Interest in sweetening agents is encouraging manufacturers and researchers to find a safe substance to maintain the life quality of diabetics. The popularity of sweetened food items has increased recently in Taiwan. The glycemic index of fructose has been reported to be 20%, much lower than most carbohydrate foods. A high-fructose corn syrup (HFCS) has come onto the market of sweetening agents and has been proposed as a low-cost substitute for fructose in dietetic management of diabetes. The aim of this study was to compare the glycemic effects of HFCS and glucose to see if there is a place for high-fructose corn syrup in diabetic management. In 8 normal and 21 non-insulin dependent diabetes mellitus (NIDDM) subjects, we performed oral tolerance tests. After an overnight fast, the subjects were given either 75g of glucose or an equivalent amount of HFCS containing 75g of carbohydrate. Blood was sampled before and at 30, 60, 90, 120 and 180 minutes after the glucose load. Blood glucose was analyzed by the glucose oxidase method using YSI 23 A (Yellow-Springs Intrument). The insulin and C-peptide were measured by RIA kits from Daiichi. The area under the curves (AUC) was calculated for plasma glucose, immunoreactive insulin (IRI) and immunoreactive C-peptide (IRCP). The results showed that the glycemic effect of HFCS was 73% of glucose. The AUC of IRI after HFCS was 56% of that of glucose. The AUC of IRCP after HFCS was 57% of that of glucose. The high glycemic index of HFCS in our study does not support the use of HFCS as a substitute for fructose. As taken from Hung CT. Taiwan Yi Xue Hui Za Zhi. 1989 Sep; 88(9):883-5. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/2695593?dopt=AbstractPlus

Moreover, sucrose and HFCS are absorbed identically in the human GI tract. HFCS consists of free fructose and free glucose when consumed (Kulber et al, 2013)

“Adsorption-desorption properties of different sweeteners in the oral cavity were evaluated using high performance liquid chromatography-based methodology. Three low calorie artificial sweeteners (aspartame, acesulfame potassium and sucralose), one steviol glycoside (rebaudioside A), and high fructose corn syrup (HFCS) were examined and compared with sucrose at pH 3 and 7 in a model beverage matrix. Results indicated that HFCS had the highest adsorption in the oral cavity, followed by rebaudioside A and the artificial sweeteners. The physicochemical interaction between sweeteners and salivary proteins did not affect the adsorption properties significantly as validated from a series of characterization techniques.” As taken from Bülbül G et al. 2019. Food Chem. 271, 577-580. PubMed, 2019 available at: https://www.ncbi.nlm.nih.gov/pubmed/30236718

“Objective: Evaluate and quantify the effects of mucosal corn syrup and 50% dextrose application on blood glucose concentrations in healthy dogs, to assess the effectiveness of a widely used practice for treatment of hypoglycemia. Design: Randomized controlled trial. Setting: University teaching hospital. Animals: Twelve client-owned dogs that were healthy, >1 year of age, weighing >5 kg, and had normal physical exam and biochemical profiles. Interventions: Dogs were fasted overnight for a minimum of 12 hours. Once normal physical exam and biochemical profile were confirmed, an IV catheter was placed in a peripheral vein for serial blood sampling. Each dog served as their own control and received each of 3 treatments, the orders of which were randomized for each dog. Treatments included mucosal application of commercially available corn syrup (Karo light syrup), water (control), and 50% dextrose solution, each at a dose of 1 mL/kg of body weight. Blood glucose was measured using a point-of-care glucometer. Samples were taken immediately prior to each treatment and at 5-, 10-, 15-, 20-, 30-, and 60-minute intervals. Results: All treatments were well tolerated and no adverse events were observed. A statistically significant increase in blood glucose was observed at the 15-, 20-, 30-, and 60-minute time points in the corn syrup and 50% dextrose groups as compared with the control. Conclusions: A significant effect on the blood glucose concentrations of the treated animals was not observed until 15 minutes after application of concentrated glucose solutions. These findings suggest that, in more severely hypoglycemic patients, parenteral glucose administration may be necessary.” As taken from Holt RL et al. 2019. J. Vet. Emerg. Crit. Care (San Antonio) 29(6), 630-634. PubMed, 2020 available at https://pubmed.ncbi.nlm.nih.gov/31625689/

4.3. Interactions

“BACKGROUND: Although high-fructose corn syrup(HFCS) as a kind of sugar has been widely used in manufactured foods recently, there is little information available regarding its cariogenicity. The aim of this study was to evaluate the cariogenic potential of HFCS. METHODS: Streptococcus mutans UA159 was inoculated into HFCS media and cultivated. The pH of each culture was measured to assess acidogenicity. Spectrophotometric turbidity was measured to determine the percentage of adherence. Confocal laser scanning microscopy and SYTO-9 staining were employed to observe biofilm formation. Sucrose media was used as a positive control. RESULTS: The ΔpH in HFCS media was significantly larger than that in sucrose media and the pH in HFCS media decreased faster ($P<0.05$). The percentage of adherence of S. mutans in HFCS media was significantly lower than that in sucrose media ($P<0.05$). The biofilm formed in sucrose media was significantly thicker than that in HFCS media ($P<0.05$). CONCLUSIONS: The results of this study suggest that the cariogenicity of S. mutans in the presence of HFCS may differ compared to its cariogenicity in the presence of sucrose. Further in vivo studies need to be undertaken to resolve this uncertainty.” As taken from Ma R et al. 2013a. Aust. Dent J. 58(2), 213-8. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/23713642

“The aim of this study was to evaluate the role of α-lipoic acid (α-LA) on oxidative damage and inflammation that occur in endothelium of aorta and heart while constant consumption of high-fructose corn syrup (HFCS). The rats were randomly divided into three groups with each group containing eight rats. The groups include HFCS, HFCS + α-LA treatment, and

control. HFCS was given to the rats at a ratio of 30% of F30 corn syrup in drinking water for 10 weeks. α-LA treatment was given to the rats at a dose of 100 mg/kg/day orally for the last 6 weeks. At the end of the experiment, the rats were killed by cervical dislocation. The blood samples were collected for biochemical studies, and the aortic and cardiac tissues were collected for evaluation of oxidant-antioxidant system, tissue bath, and pathological examination. HFCS had increased the levels of malondialdehyde, creatine kinase MB, lactate dehydrogenase, and uric acid and showed significant structural changes in the heart of the rats by histopathology. Those changes were improved by α-LA treatment as it was found in this treatment group. Immunohistochemical expressions of tumor necrosis factor α and inducible nitric oxide synthase were increased in HFCS group, and these receptor levels were decreased by α-LA treatment. All the tissue bath studies supported these findings. Chronic consumption of HFCS caused several problems like cardiac and endothelial injury of aorta by hyperuricemia and induced oxidative stress and inflammation. α-LA treatment reduced uric acid levels, oxidative stress, and corrected vascular responses. α-LA can be added to cardiac drugs due to its cardiovascular protective effects against the cardiovascular diseases." As taken from Saygin M et al. 2016. Hum. Exp. Toxicol. 35(2), 194-204. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/25825413

"A popular concept is that the significant global progression in prevalence and intensification of elevated blood pressure (BP) levels is due in part to dietary indiscretions. Excess intake of several food sources causing overweight/obesity plays an important role in BP perturbations. However, certain nutrients are involved in ways other than via body fat accumulation, particularly table salt (sodium chloride) and popular refined carbohydrates like dietary sugars (sucrose, fructose, high fructose corn syrup). In nondiabetics and diabetics, several functions of salt and sugar influence BP and metabolism. For example, salt intake is linked to volume expansion, insulin resistance, and hypertension, while sugar intake is associated with enhanced salt sensitivity via urinary sodium retention, insulin resistance, and hypertension. The key postulate evaluated here is that when two popular nutrients-salt and dietary sugars-are consumed together in adequate amounts, their respective individual BP effects are significantly amplified. In previous laboratory studies, a sugar challenge did not increase BP in the face of marked sodium depletion, and combining sugar and salt challenges caused a synergistic BP elevation. Among examples of amplification on the clinical side, the greatest increases in BP following sugar challenges were seen in diabetic subjects having the highest sodium excretion. Interplay between table salt and common dietary sugars in BP regulation is a reasonable postulate and should be carefully considered when developing optimal prevention and treatment regimens to ameliorate the worldwide crisis arising from harmful elevated BP levels." As taken from Preuss HG et al. 2017. J. Am. Coll. Nutr. 36(8), 677-684. PubMed, 2018 available at https://www.ncbi.nlm.nih.gov/pubmed/28960144

"Little is known about the pathogenesis of high fructose corn syrup (HFCS) induced hepatic toxicity. We investigated hepatic lesions induced by chronic HFCS consumption and the protective effects of alpha-lipoic acid (ALA) on liver pathology. We used 24 rats allocated randomly into three groups of eight. The HFCS group was given in drinking water for 10 weeks. The ALA + HFCS group was given the same dose of HFCS and ALA also was administered during the last 6 weeks of the experiment. The control group was untreated. The rats were euthanized at the end of 10 weeks and 24 h after the last ALA administration. A significant increase was observed in the serum aspartate aminotransferase (AST) level of the HFCS group compared to controls. Tissue malondialdehyde (MDA) levels also

increased significantly and catalase (CAT) activity decreased significantly in the HFCS group. Caspase-3 expression increased significantly in the HFCS group compared to controls. In the ALA treated group, the levels of MDA, CAT and caspase-3 returned to near control levels. HFCS caused hepatic toxicity by increasing oxidative stress and apoptosis. ALA administration ameliorated the pathological changes." As taken from Topsakal S et al. 2019. Biotech. Histochem. 11, 1-6. PubMed, 2019 available at: https://www.ncbi.nlm.nih.gov/pubmed/30632398

"Contrave® is an adjunct pharmacotherapy for obesity that contains bupropion (BUP) and naltrexone (NTX). To further explore the psychopharmacology of this drug combination, male Sprague-Dawley rats were implanted with subcutaneous osmotic mini-pumps releasing: 40 mg/kg/day BUP, 4 mg/kg/day NTX, or 40 + 4 mg/kg/day BUP and NTX (BN). During 12 days of exposure, the animals were tested on operant intraoral self-administration (IOSA) of high fruc tose corn syrup (HFCS) on continuous (FR1) and progressive ratio (PR) schedules, on home cage drinking of HFCS, and on HFCS taste reactivity. Locomotion activity was also assessed. At the conclusion of the study, mRNA expression of genes involved in reward processing, appetite and mood were quantified. It was found that BN produced effects that could largely be ascribed to either BUP or NTX independently. More specifically, BN-induced reductions of HFCS IOSA on a FR1 schedule and home cage drinking, as well as alterations of MOR and POMC mRNA in the nucleus accumbens core and hypothalamus respectively, were attributable to NTX; while alterations of hippocampal BDNF mRNA was attributable to BUP. But, there was also some evidence of drug synergy: only BN caused persistent reductions of HFCS IOSA and drinking; BN produced the least gain of body weight; and only BN-treated rats displayed altered D2R mRNA in the caudate-putamen. Taken together, these observations support the use of BUP + NTX as a mean to alter consumption of sugars and reducing their impact on brain systems involved in reward, appetite and mood." As taken from Levy A et al. 2018. Neuropharmacology 135, 547-554. PubMed, 2019 available at: https://www.ncbi.nlm.nih.gov/pubmed/29408463

5. Toxicity

5.1. Single dose toxicity

"There was no death observed after oral administration of BCS in Sprague-Dawley-strain rats. Lethal dose (LD)50, value was estimated to be more than 10 g/kg body weight".

"Fifty adults were divided into five groups often (five of each sex) and orally administered BCS at 0.2, 0.3, 0.4. 0.5 and 0.6 g/kg body weight as indigestible portion. Although no diarrhea was observed in females, BCS at 0.6 g/kg as indigestible portion caused diarrhea in two out of five males. The maximum non-effective dose of indigestible portion of BCS

was estimated to be 0.5 g/kg in males and more than 0.6 g/kg in females." (Kishimoto Y, 2001).

5.2. Repeated dose toxicity

Adverse effects from chronic inhalation or ingestion are not known (EC, undated).

Effect of drinking soda sweetened with aspartame or high-fructose corn syrup on food intake and body weight (Abstract). To examine whether artificial sweeteners aid in the control of long-term food intake and body weight, we gave free-living, normal-weight subjects 1150 g soda sweetened with aspartame (APM) or high-fructose corn syrup (HFCS) per day. Relative to when no soda was given, drinking APM-sweetened soda for 3 wk significantly reduced calorie intake of both females (n = 9) and males (n = 21) and decreased the body weight of males but not of females. However, drinking HFCS-sweetened soda for 3 wk significantly increased the calorie intake and body weight of both sexes. Ingesting either type of soda reduced intake of sugar from the diet without affecting intake of other nutrients. Drinking large volumes of APM-sweetened soda, in contrast to drinking HFCS-sweetened soda, reduces sugar intake and thus may facilitate the control of calorie intake and body weight. As taken from Tordoff MG, Alleva AM. Am J Clin Nutr. 1990 Jun; 51(6):963-9. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/2349932?dopt=AbstractPlus

Dietary modulation of parathion-induced neurotoxicity in adult and juvenile rats (Abstract). Previous studies indicated that dietary glucose (15% in drinking water) could markedly exacerbate the toxicity of parathion in adult rats. The present study evaluated the effect of consumption of the commonly used sweetener, high fructose corn syrup (HFCS), on parathion toxicity in adult and juvenile rats. Animals were given free access to either water or 15% HFCS in drinking water for a total of 10 days and challenged with parathion (6 or 18 mg/kg, s.c., for juveniles or adults, respectively) on the 4th day. Signs of cholinergic toxicity, body weight and chow/fluid intake were recorded daily. Acetylcholinesterase (AChE) activity and immunoreactivity (AChE-IR) in frontal cortex and diaphragm were measured at 2, 4, and 7 days after parathion. As HFCS was associated with significant reduction in chow intake, adult rats were also pair-fed to evaluate the effect of similar reduced chow intake alone on parathion toxicity. The results indicated that the cholinergic toxicity of parathion was significantly increased by HFCS feeding in both age groups. The excess sugar consumption, however, did not significantly affect parathion-induced AChE inhibition in either tissue or either age group. Enzyme immunoreactivity in frontal cortex was generally not affected in either age group while diaphragm AChE-IR was significantly reduced by parathion and HFCS alone in adult animals at 2 and 4 days timepoints, and more so by the combination of sugar feeding and parathion exposure in both age groups. Food restriction alone did not exacerbate parathion toxicity. While the mechanism(s) remains unclear, we conclude that voluntary consumption of the common sweetener HFCS can markedly amplify parathion acute toxicity in both juvenile and adult rats. As taken from Liu J, Karanth S, Pope C. Toxicology. 2005 Jun 1; 210(2-3):135-45. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/15840427

Comparison of breath testing with fructose and high fructose corn syrups in health and IBS (Abstract). Although incomplete fructose absorption has been implicated to cause gastrointestinal symptoms, foods containing high fructose corn syrup (HFCS) contain glucose. Glucose increases fructose absorption in healthy subjects. Our hypothesis was that fructose intolerance is less prevalent after HFCS consumption compared to fructose alone in healthy subjects and irritable bowel syndrome (IBS). Breath hydrogen levels and gastrointestinal symptoms were assessed after 40 g of fructose (12% solution) prepared either in water or as HFCS, administered in double-blind randomized order on 2 days in 20 healthy subjects and 30 patients with IBS. Gastrointestinal symptoms were recorded on 100-mm Visual Analogue Scales. Breath hydrogen excretion was more frequently abnormal (P<0.01) after fructose (68%) than HFCS (26%) in controls and patients. Fructose intolerance (i.e. abnormal breath test and symptoms) was more prevalent after fructose than HFCS in healthy subjects (25% vs. 0%, P = 0.002) and patients (40% vs. 7%, P = 0.062). Scores for several symptoms (e.g. bloating r = 0.35) were correlated (P < or = 0.01) to peak breath hydrogen excretion after fructose but not HFCS; in the fructose group, this association did not differ between healthy subjects and patients. Symptoms were not significantly different after fructose compared to HFCS. Fructose intolerance is more prevalent with fructose alone than with HFCS in health and in IBS. The prevalence of fructose intolerance is not significantly different between health and IBS. Current methods for identifying fructose intolerance should be modified to more closely reproduce fructose ingestion in daily life. As taken from Skoog SM et al. Neurogastroenterol Motil. 2008 May; 20(5):505-11. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/18221251

Effects of sucromalt on postprandial responses in human subjects (Abstract). The rise in prevalence of obesity, diabetes, metabolic syndrome, and fatty liver disease has been linked to increased consumption of fructose-containing foods or beverages. Our aim was to compare the effects of moderate consumption of fructose-containing and non-caloric sweetened beverages on feeding behavior, metabolic and serum lipid profiles, and hepatic histology and serum liver enzymes, in rats. Behavioral tests determined preferred (12.5-15%) concentrations of solutions of agave, fructose**,** high fructose corn syrup (HFCS), a combination of HFCS and Hoodia (a putative appetite suppressant), or the non-caloric sweetener Stevia (n=5/gp). HFCS intake was highest, in preference and self-administration tests. Groups (n=10/gp) were then assigned to one of the sweetened beverages or water as the sole source of liquid at night (3 nights/wk, 10wks). Although within the normal range, serum cholesterol was higher in the fructose and HFCS groups, and serum triglycerides were higher in the Agave, HFCS, and HFCS/Hoodia groups (vs. water-controls, P<0.05). Liver histology was normal in all groups with no evidence of steatosis, inflammation, or fibrosis; however serum alanine aminotransferase was higher in the fructose and HFCS groups (vs. water-controls, P<0.05). Serum inflammatory marker levels were comparable among Stevia, agave, fructose, HFCS, and water-consuming groups, however levels of IL-6 were significantly lower in association with the ingestion of Hoodia. There were no differences in terminal body weights, or glucose tolerance assessed by 120-min IVGTTs performed at the end of the 10-week regimen. We conclude that even moderate consumption of fructose-containing liquids may lead to the onset of unfavorable changes in the plasma lipid profile and one marker of liver health, independent of significant effects of sweetener consumption on body weight. As taken from Figlewicz DP et al. Physiol Behav . 2009 Dec 7; 98(5):618-24. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/19815021

The type of caloric sweetener added to water influences weight gain, fat mass, and reproduction in growing Sprague-Dawley female rats (Abstract). Caloric sweetened beverages have been suggested to be a major dietary contributor to weight gain, particularly among adolescents. Dietary recommendations are for moderating intakes of added sugars; however, the question remains whether certain types of sugars should be limited. The objective of this study was to determine the effect of drinking different caloric sweetened beverages on the development of adiposity, metabolic, and endocrine disorders Young (age 28 days) female Sprague-Dawley rats (n = 8-9 rats/group) were randomly assigned to drink either deionized distilled water (ddH2O) or ddH2O sweetened with 13% (w/v) glucose, sucrose, fructose or high fructose corn syrup 55 (HFCS-55) for 8 weeks. Rats drinking caloric sweetened solutions failed to completely compensate for liquid calories ingested by reducing their consumption of solid food. This resulted in greater total energy intake compared to the ddH2O control; however, there was no significant difference in total energy intake between rats drinking sucrose, fructose or HFCS-55. Of the different caloric sweeteners, only rats drinking HFCS-55 had greater ($P<0.05$) final body weights and fat mass compared to the rats drinking ddH2O or glucose solution. This may have occurred because drinking HFCS-55 solution promoted a faster body weight gain. Adiposity induced by caloric sweetened water was not accompanied by metabolic disorders indicated by the absence of dyslipidemia and no differences in fasting serum glucose, insulin or C-peptide among the treatment groups. However, rats drinking HFCS-55 showed lengthened estrous cycles due to prolonged estrus. Based on this study, the type of caloric sweetener added to beverages should be considered when making dietary recommendation for reducing excess body weight and related health risk. As taken from Light HR et al. Exp Biol Med (Maywood). 2009 Jun; 234(6):651-61. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/19359658

Fructose consumption: recent results and their potential implications (Abstract). In addition to acquiring a better understanding of foods that may have intrinsic health benefits, increasing our knowledge of dietary components that may adversely impact health and wellness, and the levels of consumption at which these adverse effects may occur, should also be an important priority for the Foods for Health initiative. This review discusses the evidence that additional research is needed to determine the adverse effects of consuming added sugars containing fructose. Current guidelines recommend limiting sugar consumption in order to prevent weight gain and promote nutritional adequacy. However, recent data suggest that fructose consumption in human results in increased visceral adiposity, lipid dysregulation, and decreased insulin sensitivity, all of which have been associated with increased risk for cardiovascular disease and type 2 diabetes. A proposed model for the differential effects of fructose and glucose is presented. The only published study to directly compare the effects of fructose with those of commonly consumed dietary sweeteners, high fructose corn syrup and sucrose, indicates that high fructose corn syrup and sucrose increase postprandial triglycerides comparably to pure fructose. Dose-response studies investigating the metabolic effects of prolonged consumption of fructose by itself, and in combination with glucose, on lipid metabolism and insulin sensitivity in both normal weight and overweight/obese subjects are needed. As taken from Stanhope KL & Havel PJ. Ann N Y Acad Sci. 2010, Mar; 1190:15-24. PubMed, 2012 available at http://www.ncbi.nlm.nih.gov/pubmed/20388133?dopt=AbstractPlus

“**Sugar-sweetened soda consumption, hyperuricemia, and kidney disease (Abstract).** The metabolism of high-fructose corn syrup used to sweeten soda drinks may lead to

elevations in uric acid levels. Here we determined whether soda drinking is associated with hyperuricemia and, as a potential consequence, reduced kidney function. At baseline, 15,745 patients in the Atherosclerosis Risk in Communities Study completed a dietary questionnaire and had measurements of their serum creatinine and uric acid. After 3 and 9 years of follow-up, multivariate odds ratios from logistic regressions for binary outcome of hyperuricemia and chronic kidney disease (eGFR less than 60 ml/min per 1.73 m(2)) were evaluated. Compared to participants who drank less, consumption of over one soda per day was associated with increased odds of prevalent hyperuricemia and chronic kidney disease. The odds ratio for chronic kidney disease significantly increased to 2.59 among participants who drank more than one soda per day and had a serum uric acid level over 9.0 mg/dl. In longitudinal analyses, however, drinking more than one soda per day was not associated with hyperuricemia or chronic kidney disease. Neither preexistent hyperuricemia nor development of hyperuricemia modified the lack of association between soda drinking and incident chronic kidney disease. Thus our study shows that high consumption of sugar-sweetened soda was associated with prevalent but not incident hyperuricemia and chronic kidney disease." As taken from Bomback AS et al. Kidney Int. 2010, Apr; 77(7):609-16. PubMed, 2012 available at http://www.ncbi.nlm.nih.gov/pubmed/20032963?dopt=AbstractPlus

"Background and Objectives: High fructose corn syrup (HFCS) is the most commonly used sweetener in the United States. Some studies show that HFCS consumption correlates with obesity and insulin resistance, while other studies are in disagreement. Owing to conflicting and insufficient scientific evidence, the safety of HFCS consumption remains controversial. Subjects/Methods: We investigated the metabolic consequences of mice fed a (a) regular diet, (b) 'Western' high-fat diet or (c) regular diet supplemented with 8% HFCS in drinking water (to mimic soft drinks) for 10 months. Adipose tissue macrophages (ATMs) have emerged as a major pathogenic factor for obesity and insulin resistance. ATMs consist of proinflammatory F4/80(+)CD11c(+) macrophages and anti-inflammatory F4/80(+)CD11c(-) macrophages. In this study, we assessed the effects of HFCS on ATMs in intra-abdominal fat. Results: We found that HFCS feeding in mice induced more severe adipose inflammation and insulin resistance than even the higher-calorie-containing 'Western' high-fat diet, and these HFCS-induced deleterious effects were independent of calorie intake or body fat content. We showed that similar to 'Western' high-fat diet, HFCS triggered a robust increase of both proinflammatory ATMs and anti-inflammatory ATMs in intra-abdominal fat. Remarkably, however, the anti-inflammatory ATMs were much less abundant in HFCS-fed mice than in high-fat-fed mice. Furthermore, we showed that deletion of the ghrelin receptor (growth hormone secretagogue receptor, GHS-R) ameliorates HFCS-induced adipose inflammation and insulin resistance. HFCS-fed GHS-R-null mice exhibit decreased proinflammatory ATMs in intra-abdominal fat, reduced adipose inflammation and attenuated liver steatosis. Conclusion: Our studies demonstrate that HFCS has detrimental effects on metabolism, suggesting that dietary guidelines on HFCS consumption for Americans may need to be revisited. GHS-R deletion mitigates the effects of HFCS on adipose inflammation and insulin resistance, suggesting that GHS-R antagonists may represent a novel therapy for insulin resistance." As taken from Ma X et al. 2013b. Nutr. Diabetes 3, e99. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/24366371

"The consumption of high-fructose corn syrup (HFCS) beverages has increased since the 1970s. At the same time, childhood obesity is on the rise, causing children to be at risk of heart disease, diabetes and other diseases. Healthcare providers have attributed childhood

obesity to the consumption of HFCS in the form of beverages. This article will look at the available research and determine if there is scientific evidence underlying the idea that sweetened soft drinks, especially those containing HFCS, could cause or contribute to childhood obesity. A thorough literature search was performed using the ISI Web of Sciences, PubMed and Scopus databases within the years 2006-2012. The search generated 19 results. The articles were screened, and six were deemed eligible: four systematic reviews and two meta-analyses. Two systematic reviews found that there is no relationship between consumption of HFCS beverages and obesity in children. The other two systematic reviews found possible links between HFCS and childhood obesity. The meta-analysis articles found that consumption of HFCS beverages can contribute to childhood obesity, and limitation of sweetened beverages may help decrease obesity in children. Available research studies demonstrate inconclusive scientific evidence definitively linking HFCS to obesity in children." As taken from Morgan RE. 2013. Pediatr. Obes. 8(4), 249-54. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/23630060

"The overall aim of this study was to evaluate, from a global and ecological perspective, the relationships between availability of high fructose corn syrup (HFCS) and prevalence of type 2 diabetes. Using published resources, country-level estimates (n =43 countries) were obtained for: total sugar, HFCS and total calorie availability, obesity, two separate prevalence estimates for diabetes, prevalence estimate for impaired glucose tolerance and fasting plasma glucose. Pearson's correlations and partial correlations were conducted in order to explore associations between dietary availability and obesity and diabetes prevalence. Diabetes prevalence was 20% higher in countries with higher availability of HFCS compared to countries with low availability, and these differences were retained or strengthened after adjusting for country-level estimates of body mass index (BMI), population and gross domestic product (adjusted diabetes prevalence=8.0 vs. 6.7%, p=0.03; fasting plasma glucose=5.34 vs. 5.22 mmol/L, p=0.03) despite similarities in obesity and total sugar and calorie availability. These results suggest that countries with higher availability of HFCS have a higher prevalence of type 2 diabetes independent of obesity." As taken from Goran MI et al. 2013. Glob. Public Health 8(1), 55-64. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/23181629

"Intake of high-fructose corn syrup (HFCS) has been suggested to contribute to the increased prevalence of obesity, whereas a number of studies and organizations have reported metabolic equivalence between HFCS and sucrose. We hypothesized that HFCS and sucrose would have similar effects on energy-regulating hormones and metabolic substrates at normal levels of human consumption and that these values would not change over a 10-week, free-living period at these consumption levels. This was a randomized, prospective, double-blind, parallel group study in which 138 adult men and women consumed 10 weeks of low-fat milk sweetened with either HFCS or sucrose at levels of the 25th, 50th, and 90th percentile population consumption of fructose (the equivalent of 40, 90, or 150 g of sugar per day in a 2000-kcal diet). Before and after the 10-week intervention, 24-hour blood samples were collected. The area under the curve (AUC) for glucose, insulin, leptin, active ghrelin, triglyceride, and uric acid was measured. There were no group differences at baseline or posttesting for all outcomes (interaction, $P > .05$). The AUC response of glucose, active ghrelin, and uric acid did not change between baseline and posttesting ($P > .05$), whereas the AUC response of insulin ($P < .05$), leptin ($P < .001$), and triglyceride ($P < .01$) increased over the course of the intervention when the 6 groups were averaged. We conclude that there are no differences in the metabolic effects of HFCS and sucrose when compared at low, medium, and high levels of consumption." As taken from

Yu Z et al. 2013. Nutr. Res. 33(12), 1043-52. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/24267044

“BACKGROUND: The metabolic effect of fructose in sugar-sweetened beverages (SSB) has been linked to de novo lipogenesis and uric acid (UA) production. OBJECTIVES: This study investigated the biological effects of SSB consumption on serum lipid profiles and retinol-binding protein 4 (RBP4) among Taiwanese adolescents. METHODS: We evaluated the anthropometric parameters and biochemical outcomes of 200 representative adolescents (98 boys and 102 girls) who were randomly selected from a large-scale cross-sectional study. Data were analyzed using multiple regression models adjusted for covariates. RESULTS: Increased SSB consumption was associated with increased waist and hip circumferences, body mass index (BMI) values and serum UA, triglyceride (TG) and RBP4 levels. Adolescents who consumed >500 ml/day of beverages half-to-heavily sweetened with high-fructose corn syrup(HFCS) exhibited TG and RBP4 levels 22.7 mg/dl and 13.92 ng/ml higher than non-drinkers, respectively. HFCS drinkers with hyperuricemia had higher TG levels than HFCS drinkers with normal UA levels (98.6 vs. 81.6 mg/dl). The intake of HFCS-rich SSBs and high value of BMI (≥24) interactively reinforced RBP4 levels among overweight/obese adolescents. Circulating RBP4 levels were significantly correlated with weight-related outcomes and TG and UA concentration among HFCS drinkers (r=0.253 to 0.404), but not among non-drinkers. CONCLUSIONS: High-quantity HFCS-rich beverage consumption is associated with higher TG and RBP4 levels. Hyperuricemia is likely to intensify the influence of HFCS-rich SSB intake on elevated TG levels, and in overweight and obese adolescents, high BMI may modify the action of fructose on higher circulating levels of RBP4.” As taken from Chan TF et al. 2014. PLoS One 9(1), e82004. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/24475021

“BACKGROUND: There is lack of consensus in the lay literature to support consumption of table sugar as a preferred sweetener when compared to high fructose corn syrup (HFCS). AIMS: The purpose of this study was to search the literature for evidence to determine the health effects of consumption of table sugar (sucrose) and HFCS on blood glucose, lipid levels, obesity, and appetite as well as to make recommendations for patient and family teaching of those at risk for developing negative health outcomes, including coronary heart disease. METHODS: Nursing and health-related databases, including CINAHL, PubMed, Cochrane Central Registry of Controlled Trials, and Health and Wellness were searched for research articles, which were compared and evaluated for purpose, sample size, procedure, findings, and level of evidence. FINDINGS: Five studies that met inclusion criteria were evaluated. No difference was found in changes in blood glucose levels, lipid levels, or appetite between table sugar consumption and HFCS consumption. When only fructose was consumed, lipid levels were significantly increased. LINKING EVIDENCE TO ACTION: The evidence suggests that fructose, found in both table sugar and HFCS, has a negative effect on health outcomes. Clinicians should teach patients and families that all sugar consumption should be closely monitored and kept below the 40 g/day recommended by the World Health Organization.” As taken from Sobel LL & Dalby E. 2014. Worldviews Evid. Based Nurs. 11(2), 126-32. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/24612636?dopt=AbstractPlus

“KEY POINTS: Fructose-containing sugars, including sucrose and high fructose corn syrup (HFCS), have been implicated in the epidemics of obesity and type 2 diabetes. Few studies have evaluated the impact of perinatal exposure to these sugars on metabolic and

physiological outcomes in the offspring. Using a rat model, offspring exposed to a maternal sucrose or HFCS diet during the prenatal and/or suckling periods were found to have altered adiposity and liver fat content and composition at weaning. Plasma levels of free fatty acids remained elevated in young adulthood, but consumption of a control diet following weaning appeared to ameliorate most other effects of perinatal exposure to a maternal high-sugar diet. Guidelines for maternal nutrition should advise limiting consumption of fructose-containing sugars, and it is particularly important that these recommendations include maternal nutrition during lactation. ABSTRACT: Perinatal exposure to excess maternal intake of added sugars, including fructose and sucrose, is associated with an increased risk of obesity and type 2 diabetes in adult life. However, it is unknown to what extent the type of sugar and the timing of exposure affect these outcomes. The aim of this study was to determine the impact of exposure to maternal consumption of a 10% (w/v) beverage containing sucrose or high fructose corn syrup-55 (HFCS-55) during the prenatal and/or suckling periods on offspring at 3 and 12 weeks, utilising a cross-fostering approach in a rodent model. Perinatal sucrose exposure decreased plasma glucose concentrations in offspring at 3 weeks, but did not alter glucose tolerance. Increased adiposity was observed in 3-week-old offspring exposed to sucrose or HFCS-55 during suckling, with increased hepatic fat content in HFCS-55-exposed offspring. In terms of specific fatty acids, hepatic monounsaturated (omega-7 and -9) fatty acid content was elevated at weaning, and was most pronounced in sucrose offspring exposed during both the prenatal and suckling periods, and HFCS-55 offspring exposed during suckling only. By 12 weeks, the effects on adiposity and hepatic lipid composition were largely normalised. However, exposure to either sucrose or HFCS-55 during the prenatal period only was associated with elevated plasma free fatty acids at weaning, and this effect persisted until 12 weeks. This study suggests that the type of sugar and the timing of exposure (prenatal or suckling periods) are both important for determining the impact on metabolic health outcomes in the offspring." As taken from Toop CR et al. 2017. J. Physiol. 595(13), 4379-4398. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/28447343

"BACKGROUND: Sugar-sweetened beverage (SSB) consumption and low-grade chronic inflammation are both independently associated with type 2 diabetes and cardiovascular disease. Fructose, a major component of SSBs, may acutely trigger inflammation, which may be one link between SSB consumption and cardiometabolic disease. OBJECTIVE: We sought to determine whether beverages sweetened with fructose, high-fructose corn syrup (HFCS), and glucose differentially influence systemic inflammation [fasting plasma C-reactive protein and interleukin-6 (IL-6) as primary endpoints] acutely and before major changes in body weight. Secondary endpoints included adipose tissue inflammation, intestinal permeability, and plasma fetuin-A as potential mechanistic links between fructose intake and low-grade inflammation. DESIGN: We conducted a randomized, controlled, double-blind, crossover design dietary intervention (the Diet and Systemic Inflammation Study) in 24 normal-weight to obese adults without fructose malabsorption. Participants drank 4 servings/d of fructose-, glucose-, or HFCS-sweetened beverages accounting for 25% of estimated calorie requirements while consuming a standardized diet ad libitum for three 8-d periods. RESULTS: Subjects consumed 116% of their estimated calorie requirement while drinking the beverages with no difference in total energy intake or body weight between groups as reported previously. Fasting plasma concentrations of C-reactive protein and IL-6 did not differ significantly at the end of the 3 diet periods. We did not detect a consistent differential effect of the diets on measures of adipose tissue inflammation except for adiponectin gene expression in adipose tissue ($P = 0.005$), which was lowest

after the glucose phase. We also did not detect consistent evidence of a differential impact of these sugars on measures of intestinal permeability (lactulose:mannitol test, plasma zonulin, and plasma lipopolysaccharide-binding protein). CONCLUSION: Excessive amounts of fructose, HFCS, and glucose from SSBs consumed over 8 d did not differentially affect low-grade chronic systemic inflammation in normal-weight to obese adults." As taken from Kuzma JN et al. 2016. Am. J. Clin. Nutr. 104(2), 306-14. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/27357093

Type of Test	Route of Exposure or Administration	Species/Test System	Dose Data	Toxic Effects	Reference
TDLo - Lowest published toxic dose	Oral	Rodent - rat	2030 gm/kg/10W (continuous)	Vascular - contraction (isolated tissues) Vascular - other changes Biochemical - Metabolism (Intermediary) - lipids including transport	FCTOD7 Food and Chemical Toxicology. (Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, NY 10523) V.20- 1982- Volume(issue)/page/year: 50,2135,2012
TDLo - Lowest published toxic dose	Oral	Rodent - rat	2296 gm/kg/10W (continuous)	Vascular - BP elevation not characterized in autonomic section Vascular - other changes Endocrine - other changes	FCTOD7 Food and Chemical Toxicology. (Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, NY 10523) V.20- 1982- Volume(issue)/page/year: 50,2135,2012

As taken from RTECS, 2013.

5.3. Reproduction toxicity

Effects of feeding sows fat or fructose during late gestation and lactation (Abstract). The effects of dietary fat or fructose supplementation during late gestation and lactation on sow milk production and composition and on progeny were examined. On d 88 of gestation, 24 sows were allotted by parity to three dietary treatments (eight sows/treatment). Treatments were 1) a 12.5% crude protein, corn-soybean meal control, 2) the control + 10% added fat or 3) the control + 23% high fructose corn syrup. All treatments were fed to supply

1.82 kg/d of the control diet from d 89 of gestation to parturition with sows in treatments 2 or 3 receiving .18 kg of additional fat or .53 kg of additional high fructose corn syrup, respectively. Feed was gradually increased from d 1 to 7 of lactation to 4.54 kg/d of the control diet (plus .45 kg of added fat and 1.33 kg of added fructose for treatments 2 and 3) and remained at these levels for the remainder of the 21 d lactation period. All treatments were iso-nitrogenous; treatments 2 and 3 were iso-caloric. Litter birth weights, number of pigs born alive, weaning weights and piglet survival rate were not affected by sow treatment. Stillbirths were less (P less than .05) for sows fed fat. Lipid content of milk 24 h post-farrowing was greater (P less than .05) from sows fed fat compared with sows fed fructose. Milk production estimates indicated that multiparous sows fed fat produced more (P less .05) milk than sows fed the control diet. On d 112 of gestation and d 15 of lactation, serial blood samples were drawn to monitor sow response to a glucose challenge (1 g/kg body weight). As taken from Coffey MT et al. J Anim Sci. 1987 Nov; 65(5):1249-56. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/3320005

"**Effect of dietary monosodium glutamate on HFCS-induced hepatic steatosis: expression profiles in the liver and visceral fat (Abstract).** It has previously been shown that patients with nonalcoholic fatty liver disease (NAFLD) exhibit alterations in both hepatic and adipose tissue metabolism, and the dietary factors that contribute to the pathogenesis of NAFLD are likely to be multifactorial. Using C57BL/6J mice, we examined whether chronic exposure to low-dose dietary monosodium glutamate (MSG), high-fructose corn syrup (HFCS), or a combination of the two, vs. control would affect metabolism and hepatic and visceral fat gene expression in adult male progeny. A maternal diet containing 20% HFCS and/or dietary MSG (97.2 +/- 6.3 mg/kg body weight (bw), provided in the drinking water) was offered ad libitum from 3 weeks before mating, and continued throughout gestation and weaning until the progeny reached 32 weeks of age. Liver and abdominal fat gene expression was compared with control animals fed isocaloric standard chow under identical conditions. HFCS induced hepatic steatosis and increased the expression of genes involved in carbohydrate and lipid metabolism. Conversely, dietary MSG elevated serum free fatty acids (FFAs), triglycerides (TGs), high-density lipoprotein-cholesterol (HDL-C), and insulin, together with the expression of hepatic genes involved in lipid metabolism and bile synthesis. The HFCS+MSG combination elevated hepatic TGs, serum FFAs, and TG levels. In visceral white adipose tissue, both MSG and HFCS diets increased the expression of transcription factor Srebf2 and decreased expression of Ppargc1a, while downregulating the expression of mitochondrial respiratory chain components. MSG increased the expression of several genes implicated in adipocytes differentiation. We hypothesize that HFCS may promote hepatic steatosis, whereas dietary MSG induces dyslipidemia and markers of insulin resistance." As taken from Collison KS et al. Obesity (Silver Spring). 2010, Jun; 18(6):1122-34. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/20111022?dopt=AbstractPlus

"Fructose is an increasingly common constituent of the Westernized diet due to cost and production efficiencies. Although an integral component of our pre-industrial revolution diet, over the past two decades human and animal studies have highlighted that excessive fructose intake appears to be associated with adverse metabolic effects. Excessive intake of fructose is the combined result of increased total energy consumption and increased portion sizes of foods, which often incorporate the fructose-containing sugars sucrose and high-fructose corn-syrup (HFCS). The adverse metabolic effects following excessive fructose consumption have become a hot topic in mainstream media and there is now

rigorous scientific debate regarding periods of exposure, dosage levels, interactive effects with other sugars and fats and mechanisms underlying the actions of fructose. There is still a degree of controversy regarding the extent to which sugars such as sucrose and HFCS have contributed to the current epidemic of obesity and diabetes. Furthermore, an increasing number of infants are being exposed to sugar-sweetened food and beverages before birth and during early postnatal life, highlighting the importance of determining the long-term effects of this perinatal exposure on the developing offspring. There are limited human observational and controlled studies identifying associations of excessive sweetened food and beverage consumption with poor pregnancy outcomes. Animal research has demonstrated an increased incidence of gestational diabetes as well as altered maternal, fetal and offspring metabolic function, although the long-term effects and the mechanism underlying these perturbations are ill defined. This review aims to understand the role of early life fructose exposure in modifying postnatal risk of disease in the offspring, focusing on fructose intake during pregnancy and in early postnatal life." As taken from Regnault TR et al. 2013. Clin. Exp. Pharmacol. Physiol. 40(11), 824-37. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/24033459?dopt=AbstractPlus

"The consumption of artificially sweetened processed foods, particularly high in fructose or high fructose corn syrup, has increased significantly in the past few decades. As such, interest into the long term outcomes of consuming high levels of fructose has increased significantly, particularly when the exposure is early in life. Epidemiological and experimental evidence has linked fructose consumption to the metabolic syndrome and associated comorbidities-implicating fructose as a potential factor in the obesity epidemic. Yet, despite the widespread consumption of fructose-containing foods and beverages and the rising incidence of maternal obesity, little attention has been paid to the possible adverse effects of maternal fructose consumption on the developing fetus and long term effects on offspring. In this paper we review studies investigating the effects of fructose intake on metabolic outcomes in both mother and offspring using human and experimental studies." As taken from Sloboda DM et al. 2014. J. Obes. 2014, 203474. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/24864200?dopt=AbstractPlus

"Maternal obesity and the use of assisted reproductive technologies (ART) are two suboptimal developmental environments that can lead to offspring obesity and cardiovascular disease. We hypothesized that these environments independently and synergistically adversely affect the offspring's weight and cardiovascular performance at ~7 weeks of age. Mice were fed either 24% fat and 17.5% high-fructose (HF) corn syrup or maintenance chow (5% fat; low-fat, no-fructose (LF)). Dams were subdivided into no ART and ART groups. ART embryos were cultured in Whitten's medium and transferred into pseudopregnant recipients consuming the same diet as the donor. Offspring were fed the same diet as the mother. Body weights (BW) were measured weekly and mean arterial pressure (MAP) was collected through carotid artery catheterization at killing (55±0.5 days old). Expression of genes involved in cardiovascular remodeling was measured in thoracic aorta using qRT-PCR, and levels of reactive oxygen species (ROS) were measured intracellularly and extracellularly in mesenteric resistance arteries. ART resulted in increased BW at weaning. This effect decreased over time and diet was the predominant determinant of BW by killing. Males had greater MAP than females ($P=0.002$) and HF consumption was associated with greater MAP regardless of sex ($P<0.05$). Gene expression was affected by sex ($P<0.05$) and diet ($P<0.1$). Lastly, the use of ART resulted in offspring with increased intracellular ROS ($P=0.05$). In summary, exposure to an

obesogenic diet pre- and/or post-natally affects weight, MAP, and gene expression while ART increases oxidative stress in mesenteric resistance arteries of juvenile offspring, no synergistic effects were observed." As taken from Schenewerk AL et al. 2014. Reproduction 147(1), 111-23. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/24163396?dopt=AbstractPlus

"Excess consumption of added sugars, including sucrose and high fructose corn syrup (HFCS-55), have been implicated in the global epidemics of obesity and type 2 diabetes. This study aimed to investigate and compare the impact of maternal consumption of sucrose or HFCS-55 during pregnancy and lactation on the metabolic health of the dam and her offspring at birth. Female Albino Wistar rats were given access to chow and water, in addition to a sucrose or HFCS-55 beverage (10% w/v) before, and during pregnancy and lactation. Maternal glucose tolerance was determined throughout the study, and a postmortem was conducted on dams following lactation, and on offspring within 24 h of birth. Sucrose and HFCS-55 consumption resulted in increased total energy intake compared with controls, however the increase from sucrose consumption was accompanied by a compensatory decrease in chow consumption. There was no effect of sucrose or HFCS-55 consumption on body weight, however sucrose consumption resulted in increased adiposity and elevated total plasma cholesterol in the dam, while HFCS-55 consumption resulted in increased plasma insulin and decreased plasma non-esterified fatty acids (NEFA). Maternal HFCS-55 consumption was associated with decreased relative liver weight and plasma NEFA in the offspring at birth. There was no effect of either treatment on pup weight at birth. These findings suggest that both sucrose and HFCS-55 consumption during pregnancy and lactation have the potential to impact negatively on maternal metabolic health, which may have adverse consequences for the long-term health of the offspring." As taken from Toop CR et al. 2015. J. Dev. Orig. Health Dis. 6(1), 38-46. PubMed 2016, available at http://www.ncbi.nlm.nih.gov/pubmed/25523154

"Uterine adenogenesis, a unique post-natal event in mammals, is vulnerable to endocrine disruption by estrogens and progestins resulting in infertility or reduced prolificacy. The absence of uterine glands results in insufficient transport of nutrients into the uterine lumen to support conceptus development. Arginine, a component of histotroph, is substrate for production of nitric oxide, polyamines and agmatine and, with secreted phosphoprotein 1, it affects cytoskeletal organization of trophectoderm. Arginine is critical for development of the conceptus, pregnancy recognition signaling, implantation and placentation. Conceptuses of ungulates and cetaceans convert glucose to fructose which is metabolized via multiple pathways to support growth and development. However, high fructose corn syrup in soft drinks and foods may increase risks for metabolic disorders and increase insulin resistance in adults. Understanding endocrine disrupters and dietary substances, and novel pathways for nutrient metabolism during pregnancy can improve survival and growth, and prevent chronic metabolic diseases in offspring." As taken from Bazer FW et al. 2014. Mol. Cell. Endocrinol. 398(1-2), 53-68. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/25224489

"BACKGROUND: Intake of added sugar has been shown to correlate with many human metabolic diseases, and rodent models have characterized numerous aspects of the resulting disease phenotypes. However, there is a controversy about whether differential health effects occur because of the consumption of either of the two common types of added sugar-high-fructose corn syrup (fructose and glucose monosaccharides; F/G) or table sugar (sucrose, a fructose and glucose disaccharide). OBJECTIVES: We tested the

equivalence of sucrose- vs. F/G-containing diets on mouse (Mus musculus) longevity, reproductive success, and social dominance. METHODS: We fed wild-derived mice, outbred mice descended from wild-caught ancestors, a diet in which 25% of the calories came from either an equal ratio of F/G or an isocaloric amount of sucrose (both diets had 63% of total calories as carbohydrates). Exposure lasted 40 wk, starting at weaning (21 d of age), and then mice (104 females and 56 males) were released into organismal performances assays-seminatural enclosures where mice competed for territories, resources, and mates for 32 wk. Within enclosures all mice consumed the F/G diet. RESULTS: Females initially fed the F/G diet experienced a mortality rate 1.9 times the rate ($P = 0.012$) and produced 26.4% fewer offspring than females initially fed sucrose ($P = 0.001$). This reproductive deficiency was present before mortality differences, suggesting the F/G diet was causing physiologic performance deficits prior to mortality. No differential patterns in survival, reproduction, or social dominance were observed in males, indicating a sex-specific outcome of exposure. CONCLUSION: This study provides experimental evidence that the consumption of human-relevant levels of F/G is more deleterious than an isocaloric amount of sucrose for key organism-level health measures in female mice." As taken from Ruff JS et al. 2015. J. Nutr. 145(3), 434-41. PubMed, 2016 available at http://www.ncbi.nlm.nih.gov/pubmed/25733457

"KEY POINTS: Fructose-containing sugars, including sucrose and high fructose corn syrup (HFCS), have been implicated in the epidemics of obesity and type 2 diabetes. Few studies have evaluated the impact of perinatal exposure to these sugars on metabolic and physiological outcomes in the offspring. Using a rat model, offspring exposed to a maternal sucrose or HFCS diet during the prenatal and/or suckling periods were found to have altered adiposity and liver fat content and composition at weaning. Plasma levels of free fatty acids remained elevated in young adulthood, but consumption of a control diet following weaning appeared to ameliorate most other effects of perinatal exposure to a maternal high-sugar diet. Guidelines for maternal nutrition should advise limiting consumption of fructose-containing sugars, and it is particularly important that these recommendations include maternal nutrition during lactation. ABSTRACT: Perinatal exposure to excess maternal intake of added sugars, including fructose and sucrose, is associated with an increased risk of obesity and type 2 diabetes in adult life. However, it is unknown to what extent the type of sugar and the timing of exposure affect these outcomes. The aim of this study was to determine the impact of exposure to maternal consumption of a 10% (w/v) beverage containing sucrose or high fructose corn syrup-55 (HFCS-55) during the prenatal and/or suckling periods on offspring at 3 and 12 weeks, utilising a cross-fostering approach in a rodent model. Perinatal sucrose exposure decreased plasma glucose concentrations in offspring at 3 weeks, but did not alter glucose tolerance. Increased adiposity was observed in 3-week-old offspring exposed to sucrose or HFCS-55 during suckling, with increased hepatic fat content in HFCS-55-exposed offspring. In terms of specific fatty acids, hepatic monounsaturated (omega-7 and -9) fatty acid content was elevated at weaning, and was most pronounced in sucrose offspring exposed during both the prenatal and suckling periods, and HFCS-55 offspring exposed during suckling only. By 12 weeks, the effects on adiposity and hepatic lipid composition were largely normalised. However, exposure to either sucrose or HFCS-55 during the prenatal period only was associated with elevated plasma free fatty acids at weaning, and this effect persisted until 12 weeks. This study suggests that the type of sugar and the timing of exposure (prenatal or suckling periods) are both important for determining the impact on metabolic health

outcomes in the offspring." As taken from Toop CR et al. 2017. J. Physiol. 595(13), 4379-4398. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/28447343

"High-fructose corn syrup (HFCS) is widely used as sweetener, and its overconsumption is become a major health problem. In the present study, we used adult female rats and applied a 28 days HFCS feeding model to monitor the estrous cycle and changes in tissue weights and histology. Adult female rats were divided into three groups. Animals were fed with ad libitum normal chow and (1) 24 hours tap water (Control group), (2) 12 hours HFCS access during dark period and 12 hours tap water (12H group), and (3) 24 hours HFCS only access (24H group). Total exposure period was 28 days. There is no significant change in body weight between control and HFCS-fed animals. Both absolute and relative weights of ovary in 24H animals were significantly heavier than those in control or 12H animals. The absolute and relative weights of the kidney and liver in 24H groups were significantly heavier than those in control or 12H animals. The estrous cycles of the 24H animals were significantly longer. Histological analyses revealed that 24H ovaries were relatively bigger and possessed more corpus lutea than control ovaries. Uterine sections of 12H and 24H animals showed a well-developed stratum vasculare between inner and outer myometrial layers. The number of endometrial glands were decreased in 12H uteri, and recovered in 24H uteri compared to control. Numbers of convoluted tubule in distal region increased in 12H and 24H kidney samples. Liver specimens of 12H and 24H showed the increased number of fat containing vacuoles. In conclusion, our study demonstrated that HFCS treatment for 28 days could induce (1) changes in length of estrous cycle with extended estrous and diestrous stages, (2) altered ovarian and uterine histology, and (3) liver and renal lipid accumulation. These findings reveal the adverse effects of HFCS drinking on the reproductive function and lipid metabolism of female rats." As taken from Ko EA et al. 2017. Dev. Reprod. 21(2), 151-156. PubMed, 2018 available at https://www.ncbi.nlm.nih.gov/pubmed/28785736

"BACKGROUND: Maternal dietary choices throughout preconception, pregnancy, and lactation irreversibly affect the development of fetal tissues and organs, known as fetal programming. Recommendations tend to emphasize reducing added sugars. However, the impact of maternal dietary free or bound fructose in added sugars on developmental programming of lipogenesis is unknown. METHODS: Virgin Sprague-Dawley rats were randomly divided into five groups. Rats were given feed and plain water (control) or water containing maltodextrin (vehicle), fructose, high-fructose corn syrup (HFCS) containing 55% fructose, sucrose (20% w/v) for 12 weeks before mating and throughout the pregnancy and lactation periods. Body weight, water, and feed intake were measured throughout the study. At the end of the lactation period, blood was drawn to determine the fasting levels of glucose, insulin, triglycerides, and non-esterified fatty acids (NEFA) in blood. Triglycerides and acetyl Co-A Carboxylase-1 (ACC1) levels in livers were analyzed, and insulin resistance was calculated. RESULTS: The energy intake of dams in the HFCS group was higher than in the fructose group, while weight gain was less in the HFCS group than in the fructose group. HFCS resulted in greater insulin resistance in dams, whereas free fructose had a robust effect on the fetal programming of insulin resistance. Free fructose and HFCS in the maternal diet increased blood and liver triglycerides and NEFA content in pups. Furthermore, fructose and HFCS exposure increased phosphorylated ACC1 as compared to maltodextrin and control, indicating greater fatty acid synthesis in pups and dams. CONCLUSION: Different types of added sugar in the maternal diet have different metabolic effects on the developmental programming of lipogenesis. Consequently, high fructose intake via processed foods may increase the risk for chronic diseases, and free fructose

might contribute to developmental programming of chronic diseases more than bound fructose." As taken from Yuruk AA & Nergiz-Unal R. 2017. Lipids Health Dis. 16(1), 226. PubMed, 2018 available at https://www.ncbi.nlm.nih.gov/pubmed/29191195

"RATIONALE: Cross-sectional studies have linked intake of high-fructose corn syrup-sweetened beverages with asthma in schoolchildren. OBJECTIVES: To examine associations of maternal prenatal and early childhood intake of sugar-sweetened beverages and fructose with current asthma in midchildhood (median age, 7.7 yr). METHODS: We assessed maternal pregnancy (first- and second-trimester average) and child (median age, 3.3 yr) intake of sugar-sweetened beverages and total fructose using food frequency questionnaires in 1,068 mother-child pairs from Project Viva, a prospective prebirth cohort. In a multivariable analysis, we examined associations of quartiles of maternal and child sugar-sweetened beverage, juice, and total fructose intake with child current asthma in midchildhood, assessed by questionnaire as ever having doctor-diagnosed asthma plus taking asthma medications or reporting wheezing in the past 12 months. RESULTS: Higher maternal pregnancy sugar-sweetened beverage consumption (mean, 0.6 servings/d; range, 0-5) was associated with younger maternal age, nonwhite race/ethnicity, lower education and income, and higher prepregnancy body mass index. Adjusting for prepregnancy body mass index and other covariates, comparing quartile 4 with quartile 1, higher maternal pregnancy intake of sugar-sweetened beverages (odds ratio, 1.70; 95% confidence interval, 1.08-2.67) and total fructose (odds ratio, 1.58; 95% confidence interval, 0.98-2.53) were associated with greater odds of midchildhood current asthma (prevalence, 19%). Higher early childhood fructose intake (quartile 4 vs. quartile 1) was also associated with midchildhood current asthma in models adjusted for maternal sugar-sweetened beverages (odds ratio, 1.79; 95% confidence interval, 1.07-2.97) and after additional adjustment for midchildhood body mass index z-score (odds ratio, 1.77; 95% confidence interval, 1.06-2.95). CONCLUSIONS: Higher sugar-sweetened beverage and fructose intake during pregnancy and in early childhood was associated with childhood asthma development independent of adiposity." As taken from Wright LS et al. 2018. Ann. Am. Thorac. Soc. 15(2), 217-224. PubMed, 2018 available at https://www.ncbi.nlm.nih.gov/pubmed/29219619

"The influence of HFCS (high fructose corn syrup - free fructose) and sucrose (bound fructose) on fetal appetite signals is unknown. This study aimed to determine the effects of HFCS or sucrose on the peptide-mediated appetite regulation in fetal programming of obesity. Sprague Dawley female rats were administered feed and plain water (control) or water containing maltodextrin (vehicle), sucrose, fructose, or HFCS (20%, w/v) for 12 weeks before mating and throughout pregnancy and lactation (ndams = 31; npups = 207). Maternal chow-feed consumption in the HFCS and sucrose groups and sugar-added drink consumption in the HFCS group were higher compared to the vehicle and control groups ($P < 0.05$). The total body fat accumulated in sucrose, fructose, and HFCS groups in dams and pups was higher than those in the vehicle and control groups ($P < 0.05$). The HFCS groups showed lower plasma leptin levels and higher ghrelin levels. Soluble CD36 levels in plasma and tongue samples were high in HFCS groups of dams and pups ($P < 0.05$). Rather than bound fructose, the free fructose from the maternal diet contributes to the programming of obesity through the disruption of leptin, ghrelin, and CD36 expression involved in appetite regulation." As taken from Kisioglu B and Nergiz-Unal R. 2020. Nutr. Neurosci. 23(3), 210-220. PubMed, 2020 available at: https://pubmed.ncbi.nlm.nih.gov/29961406/

“Perinatal exposure to sucrose or high-fructose corn syrup-55 (HFCS-55) in rats has previously been associated with altered hepatic fat content and composition post-weaning, although the effects on hepatic metabolism are unknown. The current study aimed to determine the sex-specific effects of maternal consumption of sucrose or HFCS-55 on the expression of hepatic lipogenic genes in the offspring. Liver samples were collected from offspring of albino Wistar rats provided with ad libitum access to either water (control), 10% sucrose or 10% HFCS-55 solution during pregnancy and lactation at 3 weeks (control n=16, sucrose n=22, HFCS-55 n=16) and 12 weeks (control n=16, sucrose n=10, HFCS-55 n=16) of age. Hepatic expression of the transcription factors such as carbohydrate response element-binding protein, sterol regulatory element-binding protein-1c and downstream genes was determined by quantitative real-time PCR. Sucrose-exposed offspring had higher hepatic SREBP-1c messenger RNA expression compared with control and HFCS-55 groups at both 3 weeks (P=0.01) and 12 weeks (P=0.03) of age. There were no differences in the expression of other hepatic lipogenic genes between groups at either 3 or 12 weeks. Thus, perinatal exposure to sucrose may be more detrimental to offspring hepatic metabolism compared with HFCS-55, independent of sex, and it will be important to evaluate the longer-term effects of perinatal sucrose exposure in future studies.” As taken from Kaur H et al. 2018. J. Dev. Orig. Health Dis. 9(5), 481-486. PubMed, 2019 available at: https://www.ncbi.nlm.nih.gov/pubmed/29909805

“This study determined the effects of consuming a high-fructose corn syrup (HFCS)-sweetened beverage on breast milk fructose, glucose, and lactose concentrations in lactating women. At six weeks postpartum, lactating mothers (n = 41) were randomized to a crossover study to consume a commercially available HFCS-sweetened beverage or artificially sweetened control beverage. At each session, mothers pumped a complete breast milk expression every hour for six consecutive hours. The baseline fasting concentrations of breast milk fructose, glucose, and lactose were 5.0 ± 1.3 μg/mL, 0.6 ± 0.3 mg/mL, and 6.8 ± 1.6 g/dL, respectively. The changes over time in breast milk sugars were significant only for fructose (treatment × time, $p < 0.01$). Post hoc comparisons showed the HFCS-sweetened beverage vs. control beverage increased breast milk fructose at 120 min (8.8 ± 2.1 vs. 5.3 ± 1.9 μg/mL), 180 min (9.4 ± 1.9 vs. 5.2 ± 2.2 μg/mL), 240 min (7.8 ± 1.7 vs. 5.1 ± 1.9 μg/mL), and 300 min (6.9 ± 1.4 vs. 4.9 ± 1.9 μg/mL) (all $p < 0.05$). The mean incremental area under the curve for breast milk fructose was also different between treatments (14.7 ± 1.2 vs. -2.60 ± 1.2 μg/mL × 360 min, $p < 0.01$). There was no treatment × time interaction for breast milk glucose or lactose. Our data suggest that the consumption of an HFCS-sweetened beverage increased breast milk fructose concentrations, which remained elevated up to five hours post-consumption.” As taken from Berger PK et al. 2018. Nutrients 10(6), pii: E669. PubMed, 2019 available at: https://www.ncbi.nlm.nih.gov/pubmed/29795005

5.4. Mutagenicity

Test system	Test conditions	Endpoint	Activation	Result	References

Salmonella typhimurium, starins TA98, TA100, TA1535 and TA1537	« Branched corn syrup » (BCS) tested at uup to 5mg/plate.				
Escherichia coli WP2uvrA	BCS prepared by heat-treatment of indigestible dextrin with hydrochloric acid. Average molecular weight 500, indigestible portion 45%)	Mutation	With and without S9	-ve Good quality study	Kishimoto et al 2001
-ve: negative					

“Expert judgement, anticipated to be negative” (EC, undated).

5.5. Cytotoxicity

No data available to us at this time.

5.6. Carcinogenicity

“Obesity is increasingly prevalent, strongly associated with nonalcoholic liver disease, and a risk factor for numerous cancers. Here, we describe the liver-related consequences of long-term diet-induced obesity. Mice were exposed to an extended obesity model comprising a diet high in trans-fats and fructose corn syrup concurrent with a sedentary lifestyle. Livers were assessed histologically using the nonalcoholic fatty liver disease (NAFLD) activity score (Kleiner system). Mice in the American Lifestyle-Induced Obesity Syndrome (ALIOS)

model developed features of early nonalcoholic steatohepatitis at 6 months (mean NAFLD activity score = 2.4) and features of more advanced nonalcoholic steatohepatitis at 12 months, including liver inflammation and bridging fibrosis (mean NAFLD activity score = 5.0). Hepatic expression of lipid metabolism and insulin signaling genes were increased in ALIOS mice compared with normal chow-fed mice. Progressive activation of the mouse hepatic stem cell niche in response to ALIOS correlated with steatosis, fibrosis, and inflammation. Hepatocellular neoplasms were observed in 6 of 10 ALIOS mice after 12 months. Tumors displayed cytological atypia, absence of biliary epithelia, loss of reticulin, alteration of normal perivenular glutamine synthetase staining (absent or diffuse), and variable α-fetoprotein expression. Notably, perivascular tumor cells expressed hepatic stem cell markers. These studies indicate an adipogenic lifestyle alone is sufficient for the development of nonalcoholic steatohepatitis, hepatic stem cell activation, and hepatocarcinogenesis in wild-type mice." As taken from Dowman JK et al. 2014. Am. J. Pathol. 184(5), 1550-61. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/24650559?dopt=AbstractPlus

"Sugar intake has dramatically increased during the last few decades. Specifically, there has been a clear trend towards higher consumption of fructose and high fructose corn syrup, which are the most common added sugars in processed food, soft drinks and other sweetened beverages. Although still controversial, this rising trend in simple sugar consumption has been positively associated with weight gain and obesity, insulin resistance and type 2 diabetes mellitus and non-alcoholic fatty liver disease. Interestingly, all of these metabolic alterations have also been related to the development of hepatocellular carcinoma. The purpose of this review is to discuss the evidence coming from epidemiological studies and data from animal models relating the consumption of simple sugars, and specifically fructose, with an increased risk of hepatocellular carcinoma and to gain insight into the putative molecular mechanisms involved." As taken from Laguna et al. 2014. Nutrients 6(12), 5933-54. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/25533006

"OBJECTIVE: A diet high in sugars may promote colorectal carcinogenesis, but it remains uncertain whether high intake of sugars or sucrose confers increased risk of colorectal cancer. The authors investigated the associations of sugars and sucrose intake with colorectal cancer risk in a community-based case-control study in Japan. METHODS: The study subjects comprised 816 incident cases of colorectal cancer and 815 community controls. Consumption frequencies and portion sizes of 148 food and beverage items were ascertained by a computer-assisted interview. The authors used the consumption of 29 food items to estimate sugars and sucrose intake. The odds ratios of colorectal cancer risk according to intake categories were obtained using a logistic regression model with adjustment for potential confounding variables. RESULTS: Overall, intakes of sugars and sucrose were not related to colorectal cancer risk either in men or women. The association between sugars intake and colorectal cancer risk differed by smoking status and alcohol use in men, but not in women. In men, sugars intake tended to be associated with colorectal cancer risk inversely among never-smokers and positively among male ever-smokers (interaction p=0.01). Sugars intake was associated with an increased risk among men with no alcohol consumption, but was unrelated to the risk among male alcohol drinkers (interaction p=0.02). Body mass index did not modify the association with sugars intake in either men or women. CONCLUSION: Sugars intake was associated with increased risk of colorectal cancer among smokers and non-alcohol drinkers in men selectively." As taken

from Wang Z et al. 2014. Scand. J. Gastroenterol. 49(5), 581-8. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/24716480

“Excessive consumption of beverages sweetened with high-fructose corn syrup (HFCS) is associated with obesity and with an increased risk of colorectal cancer. Whether HFCS contributes directly to tumorigenesis is unclear. We investigated the effects of daily oral administration of HFCS in adenomatous polyposis coli (APC) mutant mice, which are predisposed to develop intestinal tumors. The HFCS-treated mice showed a substantial increase in tumor size and tumor grade in the absence of obesity and metabolic syndrome. HFCS increased the concentrations of fructose and glucose in the intestinal lumen and serum, respectively, and the tumors transported both sugars. Within the tumors, fructose was converted to fructose-1-phosphate, leading to activation of glycolysis and increased synthesis of fatty acids that support tumor growth. These mouse studies support the hypothesis that the combination of dietary glucose and fructose, even at a moderate dose, can enhance tumorigenesis.” As taken from Goncalves MD et al. 2019. Science 22, 363(6433), 1345-1349. PubMed, 2019 available at: https://www.ncbi.nlm.nih.gov/pubmed/30898933

“In the past century the western world has found a way to combat most communicative diseases; however, throughout that time the prevalence of obesity, hyperglycemia, and hyperlipidemia have drastically increased. These symptoms characterize metabolic syndrome-a non-communicable disease which has become one of the greatest health hazards of the world. During this same time period the western diet had dramatically changed. Homecooked meals have been replaced by highly-processed, calorically dense foods. This conversion to the current western diet was highlighted by the incorporation of high-fructose corn syrup (HFCS) into sweetened beverages and foods. The consumption of large amounts of dietary sugar, and fructose in particular, has been associated with an altered metabolic state, both systemically and in specific tissues. This altered metabolic state has many profound effects and is associated with many diseases, including diabetes, cardiovascular disease, and even cancer (1). Specific types of cancer, like triple-negative breast cancer (TNBC), are both responsive to dietary factors and exceptionally difficult to treat, illustrating the possibility for preventative care through dietary intervention in at risk populations. To treat these non-communicable diseases, including obesity, diabetes, and cancer, it is imperative to understand systemic and localized metabolic abnormalities that drive its progression. This review will specifically explore the links between increased dietary fructose consumption, development of metabolic disturbances and increased incidence of TNBC.” As taken from Strober JW et al. 2019. Front. Endocrinol. (Lausanne) 10, 367. PubMed, 2020 available at https://pubmed.ncbi.nlm.nih.gov/31244777/

5.7. Irritation/immunotoxicity

Clinical trial: gluten microchallenge with wheat-based starch hydrolysates in coeliac disease patients - a randomized, double-blind, placebo-controlled study to evaluate safety (Abstract).

Wheat-based starch hydrolysates such as glucose syrups, dextrose and maltodextrins are found in more than 50% of European processed food. These products contain low amounts

of residual gluten and it has been questioned whether they are safe for coeliac disease patients.

AIM: To investigate whether coeliac disease patients can safely consume wheat-based starch hydrolysate products. METHODS: This randomized, double-blind, placebo-controlled, prospective follow-up study involved 90 coeliac disease patients in remission randomized to consume glucose syrups, maltodextrins or placebo for 24 weeks. Small bowel mucosal morphology and inflammation, symptoms, coeliac serology and malabsorption laboratory data were evaluated at baseline and at the end of the study.

RESULTS: Daily ingestion of wheat-based starch hydrolysates, glucose syrups and maltodextrins, had no deleterious effect on small-bowel mucosal villous architecture or inflammation in coeliac disease patients when compared to the placebo group. Neither were there any significant differences in gastrointestinal symptoms, serology or malabsorption parameters after 24 weeks.

CONCLUSIONS: Wheat-based starch hydrolysates, glucose syrups and maltodextrins did not have harmful effect on coeliac disease patients. Coeliac patients can thus safely continue to consume these products.

As taken from Kaukinen K et al. Aliment Pharmacol Ther. 2008, Nov 15; 28(10):1240-8. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&list_uids=18710436&dopt=AbstractPlus

"No data, not expected to be sensitizing" (EC, undated).

"Abstract Context: Metabolic syndrome and non-alcoholic fatty liver disease (NAFLD) are the emerging co-morbidities of skin inflammation. Occurrence of skin inflammation such as psoriasis is substantially higher in NAFLD patients than normal. Currently, there are no animal models to study the interaction between these co-morbidities. Objective: The present study seeks to develop a simple mouse model of NAFLD-enhanced skin inflammation and to study the effect of NAFLD on different parameters of skin inflammation. Materials and method: Metabolic syndrome and NAFLD were induced in C57BL/6 mice by feeding high-fat diet (HFD, 60% kcal) and high fructose liquid (HFL, 40% kcal) in drinking water. Skin inflammation was induced by repeated application of oxazolone (1% sensitization and repeated 0.5% challenge) in both normal and NAFLD mice and various parameters of skin inflammation and NAFLD were measured. Results: HFD and HFL diet induced obesity, hyperglycemia, hyperinsulinemia, and histological features of NAFLD in mice. Oxazolone challenge significantly increased ear thickness, ear weight, MPO activity, NF-κB activity, and histological features of skin inflammation in NAFLD mice as compared with normal mice. Overall, induction of oxazolone-induced skin inflammation was more prominent in NAFLD mice than normal mice. Hence, HFD and HFL diet followed by topical oxazolone application develops metabolic syndrome, NAFLD, and enhanced skin inflammation in mice. Discussion and conclusion: This simple model can be utilized to evaluate a therapeutic strategy for the treatment of metabolic syndrome and NAFLD with skin inflammation and also to understand the nexus between these co-morbidities." As taken from Kulkami NM et al. 2015. Pharm. Biol. 53(8), 1110-7. PubMed, 2016 available at: http://www.ncbi.nlm.nih.gov/pubmed/25430922

"It has been postulated that dietary sugar consumption contributes to increased inflammatory processes in humans, and that this may be specific to fructose (alone, in

sucrose or in high-fructose corn syrup (HFCS)). Therefore, we conducted a meta-analysis and systematic literature review to evaluate the relevance of fructose, sucrose, HFCS, and glucose consumption for systemic levels of biomarkers of subclinical inflammation. MEDLINE, EMBASE, and Cochrane libraries were searched for controlled intervention studies that report the effects of dietary sugar intake on (hs)CRP, IL-6, IL-18, IL-1RA, TNF-α, MCP-1, sICAM-1, sE-selectin, or adiponectin. Included studies were conducted on adults or adolescents with ≥20 participants and ≥2 weeks duration. Thirteen studies investigating 1141 participants were included in the meta-analysis. Sufficient studies (≥3) to pool were only available for (hs)CRP. Using a random effects model, pooled effects of the interventions (investigated as mean difference (MD)) revealed no differences in (hs)CRP between fructose intervention and glucose control groups (MD: −0.03 mg/L (95% CI: −0.52, 0.46), I^2 = 44%). Similarly, no differences were observed between HFCS and sucrose interventions (MD: 0.21 mg/L (−0.11, 0.53), I^2 = 0%). The quality of evidence was evaluated using Nutrigrade and was rated low for these two comparisons. The limited evidence available to date does not support the hypothesis that dietary fructose, as found alone or in HFCS, contributes more to subclinical inflammation than other dietary sugars." As taken from Della Corte KW et al. 2018. Nutrients 10(5), pii: E606. PubMed, 2019 available at: https://www.ncbi.nlm.nih.gov/pubmed/29757229

5.8. All other relevant types of toxicity

Total particulate matter (TPM) from heated (tobacco or nicotine) product(s) containing Sugars (High Fructose Corn Syrup) was tested in a battery of *in vitro* and/or *in vivo* test(s). Within the sensitivity and specificity of the bioassay(s) the activity of the TPM was not increased by the addition of Sugars (High Fructose Corn Syrup) when compared to TPM from 3R4F cigarettes. The table below provides tested level(s) and specific endpoint(s).

Endpoint	**Tested level (ppm)**	**Reference**
In vitro genotoxicity	1432	JTI KB Study Report(s)
In vitro cytotoxicity	1432	JTI KB Study Report(s)

"Consumption of high fructose corn syrup (HFCS)-sweetened beverages increases serum urate and risk of incident gout…." As taken from Batt C et al. 2014. Ann. Rheum. Dis. 73(12), 2101-6. PubMed, 2015 available at http://www.ncbi.nlm.nih.gov/pubmed/24026676

"During the past 20 y, there has been much interest in sugars and especially fructose in relation to human health. Over the past decade, considerable scientific debate and controversy have arisen about the potential health effects of sucrose, high-fructose corn syrup (HFCS), and fructose itself. HFCS increasingly has been used as a sweetener in thousands of food products and soft drinks, leading to the development of obesity, diabetes, dyslipidemia, and metabolic syndrome (MetS) in both rodents and humans, which is associated with an increase in body weight. There is a need for detailed research on the mechanism underlying MetS that could lead to a remedy. This review will first systematically present a definition of MetS, its history, prevalence, and comparative diagnostic criteria. We will then consider fructose and its effects on human health, the diet-induced obesity model

(various fat contents), the hypercholesterolemic model, the diabetes model, the hypertensive model, the MetS or insulin resistance model, and biomarkers related to MetS, in light of contemporary data using multiple databases (PubMed, MEDLINE, and OVID).” As taken from Aydin S et al. 2014. Nutrition 30(1), 1-9. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/24290591

“OBJECTIVE: The aim of this study was to review the current corpus of human studies to determine the association of various doses and durations of fructose consumption on metabolic syndrome. METHODS: We searched human studies in PubMed, Scopus, Ovid, ISI Web of Science, Cochrane library, and Google Scholar databases. We searched for the following keywords in each paper: metabolic syndrome x, insulin resistance, blood glucose, blood sugar, fasting blood sugar, triglycerides, lipoproteins, HDL, cholesterol, LDL, blood pressure, mean arterial pressure, systolic blood pressure, diastolic blood pressure, hypertens*, waist circumference, and fructose, sucrose, high-fructose corn syrup, or sugar. RESULTS: Overall, 3102 articles were gathered. We excluded studies on natural fructose content of foods, non-clinical trials, and trials in which fructose was recommended exclusively as sucrose or high-fructose corn syrup. Overall, 3069 articles were excluded. After review by independent reviewers, 15 studies were included in the meta-analysis. Fructose consumption was positively associated with increased fasting blood sugar (FBS; summary mean difference, 0.307; 95% confidence interval [CI], 0.149-0.465; P = 0.002), elevated triglycerides (TG; 0.275; 95% CI, 0.014-0.408; P = 0.002); and elevated systolic blood pressure (SBP; 0.297; 95% CI, 0.144-0.451; P = 0.002). The corresponding figure was inverse for high-density lipoprotein (HDL) cholesterol (-0.267; 95% CI, -0.406 to -0.128; P = 0.001). Significant heterogeneity existed between studies, except for FBS. After excluding studies that led to the highest effect on the heterogeneity test, the association between fructose consumption and TG, SBP, and HDL became non-significant. The results did not show any evidence of publication bias. No missing studies were identified with the trim-and-n¼üll method. CONCLUSION: Fructose consumption from industrialized foods has significant effects on most components of metabolic syndrome.” As taken from Kelishadi R et al. 2014. Nutrition 30(5), 503-10. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/24698343?dopt=AbstractPlus

“The impact of fructose, commonly consumed with sugars by humans, on blood pressure and uric acid has yet to be defined. A total of 267 weight-stable participants drank sugar-sweetened milk every day for 10 weeks as part of their usual, mixed-nutrient diet. Groups 1 and 2 had 9% estimated caloric intake from fructose or glucose, respectively, added to milk. Groups 3 and 4 had 18% of estimated caloric intake from high fructose corn syrup or sucrose, respectively, added to the milk. Blood pressure and uric acid were determined prior to and after the 10-week intervention. There was no effect of sugar type on either blood pressure or uric acid (interaction P>.05), and a significant time effect for blood pressure was noted (P<.05). The authors conclude that 10 weeks of consumption of fructose at the 50th percentile level, whether consumed as pure fructose or with fructose-glucose-containing sugars, does not promote hyperuricemia or increase blood pressure.” As taken from Angelopoulos TJ et al. 2015. J. Clin. Hypertens. (Greenwich) 17(2), 87-94. PubMed 2016, available at: http://www.ncbi.nlm.nih.gov/pubmed/25496265

“High-fructose corn syrup-55 (HFCS-55) has been widely welcomed in recent years as a substitute for sucrose on the basis of its favourable properties and price. The objective of this study was to determine the influence of HFCS-55 on the expression of Streptococcus mutans UA159 virulence genes and on tooth demineralization. Real-time reverse-

transcription PCR (real-time RT-PCR) and microhardness evaluations were performed to examine gene expression and enamel demineralization, respectively, after treatment with HFCS-55 and/or sucrose. Significant up-regulation of glucosyltransferase B (gtfB) by HFCS-55 was found. A mixture of HFCS-55 and sucrose could positively enhance expression of glucan-binding protein (gbp) genes. Regarding acidogenicity, expression of the lactate dehydrogenase (ldh) gene was unaffected by HFCS-55. A notable finding in this study was that 5% HFCS-55 significantly enhanced expression of the intracellular response gene of the two-component VicRK signal transduction system (vicR). Demineralization testing showed that the microhardness of teeth decreased by a greater extent in response to HFCS-55 than in response to sucrose. The results indicate that HFCS-55 can enhance S. mutans biofilm formation indirectly in the presence of sucrose and that HFCS-55 has a more acidogenic potential than does sucrose. Summing up the real-time PCR and demineralization results, HFCS-55 appears to be no less cariogenic than sucrose in vitro - at least, not under the conditions of our experiments." As taken from Sun M et al. 2014. Eur. J. Oral Sci. 122(3), 216-22. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/24813075

"Obesity and high-fructose corn syrup (HFCS)-sweetened beverages are associated with an increased risk of chronic disease, but it is not clear whether obese (Ob) individuals are more susceptible to the detrimental effects of HFCS-sweetened beverages. The purpose of this study was to examine the endocrine and metabolic effects of consuming HFCS-sweetened beverages, and whether weight classification (normal weight (NW) vs. Ob) influences these effects. Ten NW and 10 Ob men and women who habitually consumed ≤355 mL per day of sugar-sweetened beverages were included in this study. Initially, the participants underwent a 4-h mixed-meal test after a 12-h overnight fast to assess insulin sensitivity, pancreatic and gut endocrine responses, insulin secretion and clearance, and glucose, triacylglycerol, and cholesterol responses. Next, the participants consumed their normal diet ad libitum, with 1065 mL per day (117 g·day(-1)) of HFCS-sweetened beverages added for 2 weeks. After the intervention, the participants repeated the mixed-meal test. HFCS-sweetened beverages did not significantly alter body weight, insulin sensitivity, insulin secretion or clearance, or endocrine, glucose, lipid, or cholesterol responses in either NW or Ob individuals. Regardless of previous diet, Ob individuals, compared with NW individuals, had ~28% lower physical activity levels, 6%-9% lower insulin sensitivity, 12%-16% lower fasting high-density-lipoprotein cholesterol concentrations, 84%-144% greater postprandial triacylglycerol concentrations, and 46%-79% greater postprandial insulin concentrations. Greater insulin responses were associated with reduced insulin clearance, and there were no differences in insulin secretion. These findings suggest that weight classification does not influence the short-term endocrine and metabolic effects of HFCS-sweetened beverages." As taken from Heden TD et al. 2014. Appl. Physiol. Nutr. Metab. 39(5), 544-52. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/24766236

"BACKGROUND AND OBJECTIVE: The role of sugars in solutions on subjective appetite and food intake (FI) has received little investigation in children. Therefore, we examined the effect of isocaloric solutions (200 kcal/250 ml) of sugars including sucrose, high-fructose corn syrup-55 (HFCS) or glucose, compared with a non-caloric sucralose control, on subjective appetite and FI in 9- to 14-year-old normal weight (NW) boys. PARTICIPANTS AND METHODS: NW boys (n=15) received each of the test solutions, in random order, 60 min before an ad libitum pizza meal. Subjective appetite was measured at baseline (0 min), and 15, 30, 45 and 60 min. RESULTS: Only glucose (P=0.003), but neither sucrose nor HFCS, reduced FI compared with the sucralose control. This led to a higher cumulative

energy intake, compared with sucralose, after sucrose (P=0.009) and HFCS (P=0.01), but not after glucose. In all treatment sessions, subjective average appetite increased from baseline to 60 min, but change from baseline average appetite was the highest after sucrose (P<0.005). Furthermore, sucrose (r=-0.59, P=0.02) and HFCS (r=-0.56, P=0.03), but not glucose, were inversely associated with test meal FI when the treatment dose (200 kcal) was expressed on a body weight (kg) basis. CONCLUSIONS: Change from baseline subjective average appetite was the highest after sucrose, but only the glucose solution suppressed FI at the test meal 60 min later in NW boys." As taken from Van Engelen M et al. 2014. Eur. J. Clin. Nutr. 68(7), 773-7. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/24667751

"OBJECTIVE: There is a link between joint and gut inflammation of unknown etiology in arthritis. Existing research indicates that regular consumption of high-fructose corn syrup sweetened (HFCS) soft drinks, but not diet soft drinks, may be associated with increased risk of seropositive rheumatoid arthritis (RA) in women, independent of other dietary and lifestyle factors. One unexplored hypothesis for this association is that fructose malabsorption, due to regular consumption of excess free fructose (EFF) and HFCS, contributes to fructose reactivity in the gastrointestinal tract and intestinal in situ formation of enFruAGEs, which once absorbed, travel beyond the intestinal boundaries to other tissues and promote inflammation. In separate studies, the accumulation of advanced glycation end-products has been associated with joint inflammation in RA. Objective of this study was to assess the association between EFF beverages intake and non-age, non-wear and tear-associated arthritis in US young adults. METHODS: In this cross sectional study of 1209 adults aged 20-30y, (Nutrition and Health Examination Surveys 2003-2006) exposure variables were high EFF beverages, including HFCS sweetened soft drinks, and any combination of HFCS sweetened soft drinks, fruit drinks (FD) and apple juice, referred to as tEFF. Analyses of diet soda and diet FD were included for comparison. The outcome was self-reported arthritis. Rao Scott -¦(2) was used for prevalence differences and logistic regression for associations, adjusted for confounders. RESULTS: Young adults consuming any combination of high EFF beverages (tEFF) >5 times/week (but not diet soda) were three times as likely to have arthritis as non/low consumers (odds ratios=3.01; p350 mL/d intake of heavy high-fructose corn syrup-containing SSBs had a 0.52 and 0.30 higher multivariate-adjusted HOMA1-IR and HOMA2-IR, respectively. Waist circumference and serum uric acid were correspondingly found to explain 25.4% and 23.6%, as well as 23.2% and 20.6%, of the increases in the 2 IR markers. Both the elevations of HOMA1-IR and HOMA2-IR for high-fructose corn syrup-rich SSB intake were strengthened among obese adolescents (P for interaction, ≤.033). CONCLUSIONS: Fructose-rich SSB intake is associated with elevated levels of IR, and this relationship may be partially mediated by central adiposity and serum uric acid. Obesity may modify the effect of this type of SSB consumption in intensifying the elevation of IR in adolescents." As taken from Lin WT et al. 2016. J. Pediatr. 171, 90-6. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/26817591

"BACKGROUND: The objective of this study was to compare, in an animal model, the effect of different sugar types (sucrose vs. high-fructose corn syrup 55%) consumed as 10% by weight of the diet (11.6% of daily caloric intake) on the amount of food consumed, body weight, fatty tissue deposits, concentrations of selected lipids, and atherogenic indices of blood plasma. Material and method. The experiment was carried out on 30 5-month-old Wistar male rats, fed three differ- ent diets, containing, amongst other foods, (1) ground unrefined cereal grains, (2) sucrose, (3) high-fructose corn syrup. Results. Weight gains in

animals on sucrose or high-fructose corn syrup diets were higher than those consuming basic feed, but the effect was not associated with perivisceral fat accumulation. It has been found that all the atherogenic indices (Castelli's Risk Index I, Castelli's Risk Index II, Atherogenic Index of Plasma, Atherogenic Coefficient) were statistically significantly higher in animals on a high-fructose corn syrup diet compared to both the control group and those on a sucrose diet. Conclusion. The effect of the 55% high-fructose corn syrup on the tested parameters of lipid metabolism was not equivalent to that of sucrose. Using HFCS-55 instead of sucrose has an adverse effect on blood lipid parameters, while weight gains and peri-organ fat deposits are comparable. Moreover, the obtained results confirm that tested animals were susceptible to the adverse effects of sugars added to their diet, even in small amounts. This emphasises the need to precisely control the amount of added sugars in. METHODS: nd. The objective of this study was to compare, in an animal model, the effect of different sugar types (sucrose vs. high-fructose corn syrup 55%) consumed as 10% by weight of the diet (11.6% of daily caloric intake) on the amount of food consumed, body weight, fatty tissue deposits, concentrations of selected lipids, and atherogenic indices of blood plasma. Material and method. The experiment was carried out on 30 5-month-old Wistar male rats, fed three differ- ent diets, containing, amongst other foods, (1) ground unrefined cereal grains, (2) sucrose, (3) high-fructose corn syrup. RESULTS: Weight gains in animals on sucrose or high-fructose corn syrup diets were higher than those con- suming basic feed, but the effect was not associated with perivisceral fat accumulation. It has been found that all the atherogenic indices (Castelli's Risk Index I, Castelli's Risk Index II, Atherogenic Index of Plasma, Atherogenic Coefficient) were statistically significantly higher in animals on a high-fructose corn syrup diet compared to both the control group and those on a sucrose diet. CONCLUSIONS: The effect of the 55% high-fructose corn syrup on the tested parameters of lipid metabolism was not equivalent to that of sucrose. Using HFCS-55 instead of sucrose has an adverse effect on blood lipid parameters, while weight gains and peri-organ fat deposits are comparable. Moreover, the obtained results confirm that tested animals were susceptible to the adverse effects of sugars added to their diet, even in small amounts. This emphasises the need to precisely control the amount of added sugars in the diet." As taken from Sadowska J and Bruszkowska M. 2017. Acta Sci. Pol. Technol. Aliment. 16(2), 231-240. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/28703963

"High fructose corn syrup (HFCS) is widely used as sweetener in processed foods and soft drinks in the United States, largely substituting sucrose (SUC). The orexigenic hormone ghrelin promotes obesity and insulin resistance; ghrelin responds differently to HFCS and SUC ingestion. Here we investigated the roles of ghrelin in HFCS- and SUC-induced adiposity and insulin resistance. To mimic soft drinks, 10-week-old male wild-type (WT) and ghrelin knockout (Ghrelin-/-) mice were subjected to ad lib. regular chow diet supplemented with either water (RD), 8% HFCS (HFCS), or 10% sucrose (SUC). We found that SUC-feeding induced more robust increases in body weight and body fat than HFCS-feeding. Comparing to SUC-fed mice, HFCS-fed mice showed lower body weight but higher circulating glucose and insulin levels. Interestingly, we also found that ghrelin deletion exacerbates HFCS-induced adiposity and inflammation in adipose tissues, as well as whole-body insulin resistance. Our findings suggest that HFCS and SUC have differential effects on lipid metabolism: while sucrose promotes obesogenesis, HFCS primarily enhances inflammation and insulin resistance, and ghrelin confers protective effects for these metabolic dysfunctions." As taken from Ma X et al. 2017. Int. J. Mol. Sci. 18(6), E1302. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/28629187

“Obesity is caused by a number of factors including heredity, lack of exercise, and poor diet. Diets rich in fats and carbohydrates are the common culprits leading to obesity. Here we studied the effects of these components on proteins involved in drug disposition. Male rats were given a normal diet (lean controls) or one rich in fats, carbohydrates (as high-fructose corn syrup equivalent) or in combination. After 14 weeks, plasma biochemistry, liver and kidney mRNA and protein for selected cytochrome P450 (CYP) and transporters were determined. Significant increases in body and perinephric fat weight were noted in each of the high-calorie diet-fed groups, with increases being higher in those given high-fat diets. Increases in the protein of CYP3A1/2 and CYP2C11 were seen in liver in high-fat-fed rats. No changes were seen for CYP1A1 at the level of mRNA or protein. For transporters, decreases in expressions of Oct1/2 and Mate1 were seen, with no change in Mdr1. The results showed similarity to earlier assessments of genetically prone rats and suggested that diet-induced obesity has the potential to lead to decreases in the clearance of drugs acting as substrates for CYP 3A, 2C11, and organic cation transport.” As taken from Abdussalam A et al. 2017. J. Pharm. Sci. 106(6), 1650-1658. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/28189626

“The objective of the current study was to explore our hypothesis that average consumption of fructose and fructose containing sugars would not increase risk factors for cardiovascular disease (CVD) and the metabolic syndrome (MetS). A randomized, double blind, parallel group study was conducted where 267 individuals with BMI between 23 and 35 kg/m^2 consumed low fat sugar sweetened milk, daily for ten weeks as part of usual weight-maintenance diet. One group consumed 18% of calories from high fructose corn syrup (HFCS), another group consumed 18% of calories from sucrose, a third group consumed 9% of calories from fructose, and the fourth group consumed 9% of calories from glucose. There was a small change in waist circumference (80.9 ± 9.5 vs. 81.5 ± 9.5 cm) in the entire cohort, as well as in total cholesterol (4.6 ± 1.0 vs. 4.7 ± 1.0 mmol/L, $P<0.01$), triglycerides (TGs) (11.5 ± 6.4 vs. 12.6 ± 8.9 mmol/L, $P<0.01$), and systolic (109.2 ± 10.2 vs. 106.1 ± 10.4 mmHg, $P<0.01$) and diastolic blood pressure (69.8 ± 8.7 vs. 68.1 ± 9.7 mmHg, $P<0.01$). The effects of commonly consumed sugars on components of the MetS and CVD risk factors are minimal, mixed and not clinically significant.” As taken from Angelopoulos TJ et al. 2016. Nutrients 8(4), 179. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/27023594

“The impact of sugar consumption on health continues to be a controversial topic. The objective of this review is to discuss the evidence and lack of evidence that allows the controversy to continue, and why resolution of the controversy is important. There are plausible mechanisms and research evidence that supports the suggestion that consumption of excess sugar promotes the development of cardiovascular disease (CVD) and type 2 diabetes (T2DM) both directly and indirectly. The direct pathway involves the unregulated hepatic uptake and metabolism of fructose, leading to liver lipid accumulation, dyslipidemia, decreased insulin sensitivity and increased uric acid levels. The epidemiological data suggest that these direct effects of fructose are pertinent to the consumption of the fructose-containing sugars, sucrose and high fructose corn syrup (HFCS), which are the predominant added sugars. Consumption of added sugar is associated with development and/or prevalence of fatty liver, dyslipidemia, insulin resistance, hyperuricemia, CVD and T2DM, often independent of body weight gain or total energy intake. There are diet intervention studies in which human subjects exhibited increased circulating lipids and decreased insulin sensitivity when consuming high sugar compared with control diets. Most recently, our group has reported that supplementing the

ad libitum diets of young adults with beverages containing 0%, 10%, 17.5% or 25% of daily energy requirement (Ereq) as HFCS increased lipid/lipoprotein risk factors for CVD and uric acid in a dose-response manner. However, un-confounded studies conducted in healthy humans under a controlled, energy-balanced diet protocol that enables determination of the effects of sugar with diets that do not allow for body weight gain are lacking. Furthermore, recent reports conclude that there are no adverse effects of consuming beverages containing up to 30% Ereq sucrose or HFCS, and the conclusions from several meta-analyses suggest that fructose has no specific adverse effects relative to any other carbohydrate. Consumption of excess sugar may also promote the development of CVD and T2DM indirectly by causing increased body weight and fat gain, but this is also a topic of controversy. Mechanistically, it is plausible that fructose consumption causes increased energy intake and reduced energy expenditure due to its failure to stimulate leptin production. Functional magnetic resonance imaging (fMRI) of the brain demonstrates that the brain responds differently to fructose or fructose-containing sugars compared with glucose or aspartame. Some epidemiological studies show that sugar consumption is associated with body weight gain, and there are intervention studies in which consumption of ad libitum high-sugar diets promoted increased body weight gain compared with consumption of ad libitum low- sugar diets. However, there are no studies in which energy intake and weight gain were compared in subjects consuming high or low sugar, blinded, ad libitum diets formulated to ensure both groups consumed a comparable macronutrient distribution and the same amounts of fiber. There is also little data to determine whether the form in which added sugar is consumed, as beverage or as solid food, affects its potential to promote weight gain. It will be very challenging to obtain the funding to conduct the clinical diet studies needed to address these evidence gaps, especially at the levels of added sugar that are commonly consumed. Yet, filling these evidence gaps may be necessary for supporting the policy changes that will help to turn the food environment into one that does not promote the development of obesity and metabolic disease." As taken from Stanhope KL. 2016. Crit. Rev. Clin. Lab. Sci. 53(1), 52-67. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/26376619

"Background: Studies on the effects of high fructose corn syrup (HFCS) on the metabolism are scarce and their results are inconsistent. Objectives: The aim of this research was to examine in an animal model the effect of replacing sucrose with HFCS-55 on the levels of glucose, insulin and leptin, and on the consumption of feed, body weight gain and fat storage. Material and methods: The experiment was carried out on 30 Wistar male rats aged 5 months, fed 3 different diets, containing whole grains (group I), 10% sucrose (group II) and 10% HFCS (group III). Results: It was found that the amount of daily energy intake was similar for all the groups of animals. There was no difference in fasting glucose and insulin level and homeostatic model assessment for insulin resistance (HOMA-IR) index. The higher leptin level was determined in blood plasma of the animal fed a feed with sucrose (group 2) compared to group 1 and group 3 (360 ng/mL vs 263 and 230 ng/mL, respectively). Despite the similar amounts of consumed energy, the animals fed with modified feeds achieved higher weight gain and the effect of HFCS-55 was similar to the effect of sucrose. Conclusions: The obtained results indicate similar metabolic effects of HFCS-55 and sucrose in feed, at the level of 11% dietary energy value, on the energy intake, body weight gain and periorgan adipose tissue accumulation in rats. The results suggest that accusations against HFCS as the major dietary contributor to overweight and obesity are unfounded, and the total elimination of HFCS from the diet seems to be unnecessary. The modified feeds (containing both sucrose and HFCS) produced greater

absolute weight gain and weight gain per kilojoule consumed compared to standard feeds. This may indicate not just a basic thermodynamic consequence of consuming more energy, but a change in the metabolic efficiency when consuming a diet with simple sugars and refined carbohydrates." As taken from Sadowska J et al. 2019. Adv. Clin. Exp. Med. 28(7), 879-884. PubMed, 2020 available at https://pubmed.ncbi.nlm.nih.gov/31237122/

"In modern societies, high fructose intake from sugar-sweetened beverages has contributed to obesity development. In the diet, sucrose and high fructose corn syrup are the main sources of fructose and can be metabolized in the intestine and transported into the systemic circulation. The liver can metabolize around 70% of fructose intake, while the remaining is metabolized by other tissues. Several tissues including adipose tissue express the main fructose transporter GLUT5. In vivo, chronic fructose intake promotes white adipose tissue accumulation through activating adipogenesis. In vitro experiments have also demonstrated that fructose alone induces adipogenesis by several mechanisms, including (1) triglycerides and very-low-density lipoprotein (VLDL) production by fructose metabolism, (2) the stimulation of glucocorticoid activation by increasing 11β-HSD1 activity, and (3) the promotion of reactive oxygen species (ROS) production through uric acid, NOX and XOR expression, mTORC1 signaling and Ang II induction. Moreover, it has been observed that fructose induces adipogenesis through increased ACE2 expression, which promotes high Ang-(1-7) levels, and through the inhibition of the thermogenic program by regulating Sirt1 and UCP1. Finally, microRNAs may also be involved in regulating adipogenesis in high fructose intake conditions. In this paper, we propose further directions for research in fructose participation in adipogenesis." As taken from Hernández-Díazcouder A et al. 2019. Int. J. Mol. Sci. 20(11), 2787. PubMed, 2020 available at https://pubmed.ncbi.nlm.nih.gov/31181590/

"A central theme of Atwater's research was the development and application of methods to understand how human beings and animals adapt to the nutrients they ingest. The research described in this article also deals with adaptation to nutrition focusing on adaptation to overnutrition, adaptation to undernutrition, adaptation to dietary fat, adaptation to dietary protein, adaptation to micronutrients, and adaptation to sugar and high-fructose corn syrup (HFCS). Studies using overfeeding have shown several things. First, overfeeding did not change the thermic response to ingestion of food nor the coupling of oxidative phosphorylation in muscle to energy expended by muscles during work on a bicycle ergometer between 25 and 100 watts. Second, the response to overfeeding was significantly influenced by the quantity of protein in the diet. During carefully controlled studies of underfeeding of people with obesity, the macronutrient composition of the diet did not affect the magnitude of weight loss. However, baseline genetic and metabolic information could provide guidance for selecting among the lower or higher protein diets, and lower or higher fat diets. Adaptation to an increase in dietary fat from 35% to 50% is slow and variable in healthy sedentary men. Adaptation is more rapid and complete when these same men were physically active. This effect of muscular exercise was traced to changes in the metabolism of glucose in muscles where pathways inhibiting glucose metabolism were activated by exercise. Dietary patterns that increased the intake of calcium, magnesium, and potassium effectively lower blood pressure in individuals with high normal blood pressure. Finally, the intake of sugary beverages was related to the onset of the current epidemic of obesity." As taken from Bray GA. 2019. Adv. Nutr. Epub ahead of print. PubMed, 2020 available at https://pubmed.ncbi.nlm.nih.gov/31925422/

6. Functional effects on

6.1. Broncho/pulmonary system

“BACKGROUND: High fructose corn syrup (HFCS) sweetened soft drink intake has been linked with asthma in US high-schoolers. Intake of beverages with excess free fructose (EFF), including apple juice, and HFCS sweetened fruit drinks and soft drinks, has been associated with asthma in children. One hypothesis for this association is that underlying fructose malabsorption and fructose reactivity in the GI may contribute to in situ formation of enFruAGEs. EnFruAGEs may be an overlooked source of advanced glycation end-products (AGE) that contribute to lung disease. AGE/ RAGEs are elevated in COPD lungs. EFF intake has increased in recent decades, and intakes may exceed dosages associated with adult fructose malabsorption in subsets of the population. Intestinal dysfunction has been shown to be elevated in COPD patients. The objective of this study was to investigate the association between HFCS sweetened soft drink intake and chronic bronchitis (CB), a common manifestation of COPD, in adults. METHODS: DESIGN: In this cross sectional analysis, the outcome variable was self-reported existing chronic bronchitis or history of CB. Exposure variable was non-diet soda. Rao Scott -¦(2) was used for prevalence differences and logistic regression for associations, adjusted for age, sex, race-ethnicity, BMI, smoking, exposure to in-home smoking, pre-diabetes, diabetes, SES, total energy and total fruits and beverages consumption. SETTING: Data are from the National Health and Nutrition Examination Survey 2003-2006. SUBJECTS: 2801 adults aged 20-55 y. RESULTS: There was a statistically significant correlation between intake of non-diet soft drinks and greater prevalence and odds of chronic bronchitis ($p < 0.05$). Independent of all covariates, intake of non-diet soda ≥5 times a week (vs. non/low non-diet soda) was associated with nearly twice the likelihood of having chronic bronchitis (OR = 1.80; p = 0.047; 95% CI 1.01-3.20). CONCLUSIONS: HFCS sweetened soft drink intake is correlated with chronic bronchitis in US adults aged 20-55 y, after adjusting for covariates, including smoking. Results support the hypothesis that underlying fructose malabsorption and fructose reactivity in the GI may contribute to chronic bronchitis, perhaps through in situ formation of enFruAGEs, which may contribute to lung disease. Longitudinal and biochemical research is needed to confirm and clarify the mechanisms involved.” As taken from DeChristopher et al. 2015. Nutr. J. 14, 107. PubMed, 2016 available at http://www.ncbi.nlm.nih.gov/pubmed/26474970

“OBJECTIVE: High soft drink consumption has been linked with asthma. Anecdotal evidence links high-fructose corn syrup with asthma. The receptor of advanced glycation end products (RAGE) has emerged as a mediator of asthma. The objectives of the present study were to: (i) assess the correlation between intake of beverages containing excess free fructose (EFF beverages) and asthma in children; and (ii) epidemiologically test the mechanistic hypothesis that intake of high EFF beverages, such as apple juice or beverages sweetened with high-fructose corn syrup, is associated with increased risk of asthma. This hypothesis is based on the possible effect of increases in the in situ intestinal

formation of advanced glycation end products (enFruAGE) with EFF, which may be absorbed and play a role in RAGE-mediated asthma. DESIGN: We examined cross-sectional associations between beverage intake and self-reported current or history of asthma. Exposure variables were EFF beverages, including apple juice (AJ), non-diet soft drinks (ndSD) and fruit drinks (FD). Orange juice (OJ), not an EFF beverage, was included as a comparison. Rao-Scott χ 2 analysis was used for prevalence differences and logistic regression for associations, adjusted for age, sex, race/ethnicity, BMI and total energy intake. SETTING: Data are from the National Health and Nutrition Examination Survey 2003-2006, a nationally representative survey. SUBJECTS: US children (n 1961) aged 2-9 years with complete responses on the dietary frequency questionnaire. RESULTS: Intakes of EFF beverages were significantly associated with asthma in 2-9-year-olds. Adjusted odds of asthma in children consuming EFF beverages ≥5 times/week was more than five times that in children consuming these beverages ≤1 time/month (OR=5·29, P=0·012). Children consuming AJ ≥5 times/week v. ≤1 time/month, adjusted for the other beverages, were more than twice as likely to have asthma (OR=2·43, P=0·035). In contrast, there was a tendency for OJ to be protective. CONCLUSIONS: These results support the hypothesis that intake of high EFF beverages, including AJ and beverages sweetened with high-fructose corn syrup, is associated with asthma in children aged 2-9 years. Results support the mechanistic hypothesis that enFruAGE may be an overlooked contributor to asthma in children. Longitudinal studies are needed to provide evidence of causal association." As taken from DeChristopher LR et al. 2016b. Public Health Nutr. 19(1), 123-30. PubMed, 2016, available at http://www.ncbi.nlm.nih.gov/pubmed/25857343

"Recent research conducted by investigators at the National Center for Chronic Disease Prevention and Health Promotion-a division of the US Centers for Disease Control and Prevention (CDC)-found that 'Regular-Soda Intake, Independent of Weight Status, is Associated with Asthma among US High School Students.' On the basis of their review of prior studies, researchers hypothesized that the association may be due to high intake of sodium benzoate, a commonly used preservative in US soft drinks. But a closer look at these prior research studies suggests that there is no strong scientific evidence that the preservatives in US soft drinks are associated with asthma. Importantly, other recent research suggests that the association may be with the unpaired (excess free) fructose in high fructose corn syrup." As taken from DeChristopher LR et al. 2016c. Nutr. Diabetes 6(11), e234. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/27892935

"There is growing evidence that intakes of high-fructose corn syrup (HFCS), HFCS-sweetened soda, fruit drinks and apple juice - a high-fructose 100 % juice - are associated with asthma, possibly because of the high fructose:glucose ratios and underlying fructose malabsorption, which may contribute to enteral formation of pro-inflammatory advanced glycation end products, which bind receptors that are mediators of asthma. Cox proportional hazards models were used to assess associations between intakes of these beverages and asthma risk, with data from the Framingham Offspring Cohort. Diet soda and orange juice - a 100 % juice with a 1:1 fructose:glucose ratio - were included for comparison. Increasing intake of any combination of HFCS-sweetened soda, fruit drinks and apple juice was significantly associated with progressively higher asthma risk, plateauing at 5-7 times/week v. never/seldom, independent of potential confounders (hazard ratio 1·91, P<0·001). About once a day consumers of HFCS-sweetened soda had a 49 % higher risk (P<0·011), moderate apple juice consumers (2-4 times/week) had a 61 % higher risk (P<0·007) and moderate fruit drink consumers had a 58 % higher risk (P<0·009), as compared with never/seldom consumers. There were no associations with diet soda/orange juice. These

associations are possibly because of the high fructose:glucose ratios, and fructose malabsorption. Recommendations to reduce consumption may be inadequate to address asthma risk, as associations are evident even with moderate intake of these beverages, including apple juice - a 100 % juice. The juice reductions in the US Special Supplemental Nutrition Program for Women, Infants, and Children in 2009, and the plateauing/decreasing asthma prevalence (2010-2013), particularly among non-Hispanic black children, may be related. Further research regarding the consequences of fructose malabsorption is needed." As taken from DeChristopher LR & Tucker KL. 2018. Br. J. Nutr. 119(10), 1157-1167. PubMed, 2019 available at https://www.ncbi.nlm.nih.gov/pubmed/29587887

6.2. Cardiovascular system

Sugar-sweetened beverages and risk of obesity and type 2 diabetes: epidemiologic evidence (Abstract). In recent decades, temporal patterns in SSB intake have shown a close parallel between the upsurge in obesity and rising levels of SSB consumption. SSBs are beverages that contain added caloric sweeteners such as sucrose, high-fructose corn syrup or fruit-juice concentrates, all of which result in similar metabolic effects. They include the full spectrum of soft drinks, carbonated soft drinks, fruitades, fruit drinks, sports drinks, energy and vitamin water drinks, sweetened iced tea, cordial, squashes, and lemonade, which collectively are the largest contributor to added sugar intake in the US. It has long been suspected that SSBs have an etiologic role in the obesity epidemic, however only recently have large epidemiological studies been able to quantify the relationship between SSB consumption and long-term weight gain, type 2 diabetes (T2DM) and cardiovascular disease (CVD) risk. Experimental studies have provided important insight into potential underlying biological mechanisms. It is thought that SSBs contribute to weight gain in part by incomplete compensation for energy at subsequent meals following intake of liquid calories. They may also increase risk of T2DM and CVD as a contributor to a high dietary glycemic load leading to inflammation, insulin resistance and impaired beta-cell function. Additional metabolic effects from the fructose fraction of these beverages may also promote accumulation of visceral adiposity, and increased hepatic de novo lipogenesis, and hypertension due to hyperuricemia. Consumption of SSBs should therefore be replaced by healthy alternatives such as water, to reduce risk of obesity and chronic diseases. As taken from Hu FB and Malik VS. 2010. Physiol. Behav. 100(1), 47-54. PubMed, 2015 available at http://www.ncbi.nlm.nih.gov/pubmed/20138901

Soft drink consumption and obesity: it is all about fructose (Abstract). The purpose of the review is to suggest that fructose, a component of both sucrose (common sugar) and high fructose corn syrup, should be of concern to both healthcare providers and the public. RECENT FINDINGS: Consumption of sugar-sweetened beverages has increased steadily over the past century and with this increase has come more and more reports associating their use with the risk of overweight, diabetes and cardiometabolic disease. In a meta-analysis of the relationship between soft drink consumption and cardiometabolic risk, there was a 24% overall increased risk comparing the top and bottom quantiles of consumption. Several factors might account for this increased risk, including increased carbohydrate load and increased amounts of dietary fructose. Fructose acutely increases thermogenesis,

triglycerides and lipogenesis as well as blood pressure, but has a smaller effect on leptin and insulin release than comparable amounts of glucose. In controlled feeding studies, changes in body weight, fat storage and triglycerides are observed as well as an increase in inflammatory markers. SUMMARY: The present review concludes on the basis of the data assembled here that in the amounts currently consumed, fructose is hazardous to the cardiometabolic health of many children, adolescents and adults. As taken from Bray GA. Curr Opin Lipidol. 2010 Feb; 21(1):51-7. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/19956074

Multiple abnormalities of myocardial insulin signaling in a porcine model of diet-induced obesity (Abstract). Heightened cardiovascular risk among patients with systemic insulin resistance is not fully explained by the extent of atherosclerosis. It is unknown whether myocardial insulin resistance accompanies systemic insulin resistance and contributes to increased cardiovascular risk. This study utilized a porcine model of diet-induced obesity to determine if myocardial insulin resistance develops in parallel with systemic insulin resistance and investigated potential mechanisms for such changes. Micropigs (n = 16) were assigned to control (low fat, no added sugars) or intervention (25% wt/wt coconut oil and 20% high-fructose corn syrup) diet for 7 mo. Intervention diet resulted in obesity, hypertension, and dyslipidemia. Systemic insulin resistance was manifest by elevated fasting glucose and insulin, abnormal response to intravenous glucose tolerance testing, and blunted skeletal muscle phosphatidylinositol-3-kinase (PI 3-kinase) activation and protein kinase B (Akt) phosphorylation in response to insulin. In myocardium, insulin-stimulated glucose uptake, PI 3-kinase activation, and Akt phosphorylation were also blunted in the intervention diet group. These findings were explained by increased myocardial content of p85alpha (regulatory subunit of PI 3-kinase), diminished association of PI 3-kinase with insulin receptor substrate (IRS)-1 in response to insulin, and increased serine-307 phosphorylation of IRS-1. Thus, in a porcine model of diet-induced obesity that recapitulates many characteristics of insulin-resistant patients, myocardial insulin resistance develops along with systemic insulin resistance and is associated with multiple abnormalities of insulin signaling. As taken from Lee J et al. Am J Physiol Heart Circ Physiol. 2010 Feb; 298(2):H310-9. Epub 2009 Nov 6. PubMed available at http://www.ncbi.nlm.nih.gov/pubmed/19897715

“**Consumption of fructose and high fructose corn syrup increase postprandial triglycerides, LDL-cholesterol, and apolipoprotein-B in young men and women (Abstract).** CONTEXT: The American Heart Association Nutrition Committee recommends women and men consume no more than 100 and 150 kcal of added sugar per day, respectively, whereas the Dietary Guidelines for Americans, 2010, suggests a maximal added sugar intake of 25% or less of total energy. OBJECTIVE: To address this discrepancy, we compared the effects of consuming glucose, fructose, or high-fructose corn syrup **(**HFCS) at 25% of energy requirements (E) on risk factors for cardiovascular disease. PARTICIPANTS, DESIGN AND SETTING, AND INTERVENTION: Forty-eight adults (aged 18-40 yr; body mass index 18-35 kg/m(2)) resided at the Clinical Research Center for 3.5 d of baseline testing while consuming energy-balanced diets containing 55% E complex carbohydrate. For 12 outpatient days, they consumed usual ad libitum diets along with three servings per day of glucose, fructose, or HFCS-sweetened beverages (n = 16/group), which provided 25% E requirements. Subjects then consumed energy-balanced diets containing 25% E sugar-sweetened beverages/30% E complex carbohydrate during 3.5 d of inpatient intervention testing. MAIN OUTCOME MEASURES: Twenty-four-hour triglyceride area

under the curve, fasting plasma low-density lipoprotein (LDL), and apolipoprotein B (apoB) concentrations were measured. RESULTS: Twenty-four-hour triglyceride area under the curve was increased compared with baseline during consumption of fructose (+4.7 ± 1.2 mmol/liter × 24 h, P = 0.0032) and HFCS (+1.8 ± 1.4 mmol/liter × 24 h, P = 0.035) but not glucose (-1.9 ± 0.9 mmol/liter × 24 h, P = 0.14). Fasting LDL and apoB concentrations were increased during consumption of fructose (LDL: +0.29 ± 0.082 mmol/liter, P = 0.0023; apoB: +0.093 ± 0.022 g/liter, P = 0.0005) and HFCS (LDL: +0.42 ± 0.11 mmol/liter, P<0.0001; apoB: +0.12 ± 0.031 g/liter, P<0.0001) but not glucose (LDL: +0.012 ± 0.071 mmol/liter, P = 0.86; apoB: +0.0097 ± 0.019 g/liter, P = 0.90). CONCLUSIONS: Consumption of HFCS-sweetened beverages for 2 wk at 25% E increased risk factors for cardiovascular disease comparably with fructose and more than glucose in young adults." As taken from Stanhope KKL et al. J Clin Endocrinol Metab. 2011, Oct; 96(10):E1596-605. PubMed available at http://www.ncbi.nlm.nih.gov/pubmed/21849529?dopt=AbstractPlus

"The possible role of high-fructose corn syrup in the epidemic of obesity in the USA is reviewed. Protective diets include higher consumption of fish, olive oil, grains, fruits and vegetables (Mediterranean diet), as well as probiotic bacteria in yogurt and dairy products. Careful attention should be given to the patient's environment looking for modifiable factors. The effects of clean environmental air and water, adequate diet and appropriate nutrition, healthy teeth, exercise, and refreshing sleep in the prevention of stroke and cardiovascular disease appear to be quite compelling. Although some of these modifiable risk factors lack evidence-based information, judicious clinical sense should be used to counteract the potentially damaging effects of adverse environmental vascular risk factors."

As taken from Bernal-Pacheco O; Román GC. Environmental vascular risk factors: new perspectives for stroke prevention. J Neurol Sci. 2007, Nov 15; 262(1-2):60-70, PubMed, 2010 available at

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=retrieve&db=pubmed&list_uids=17655871&dopt=AbstractPlus

"Excessive fructose intake from high-fructose corn syrup (HFCS) and sucrose has been implicated as a driving force behind the increasing prevalence of obesity and its downstream cardiometabolic complications including hypertension, gout, dyslidpidemia, metabolic syndrome, diabetes, and non-alcoholic fatty liver disease (NAFLD). Most of the evidence to support these relationships draws heavily on ecological studies, animal models, and select human trials of fructose overfeeding. There are a number of biological mechanisms derived from animal models to explain these relationships, including increases in de novo lipogenesis and uric acid-mediated hypertension. Differences between animal and human physiology, along with the supraphysiologic level at which fructose is fed in these models, limit their translation to humans. Although higher level evidence from large prospective cohorts studies has shown significant positive associations comparing the highest with the lowest levels of intake of sugar-sweetened beverages (SSBs), these associations do not hold true at moderate levels of intake or when modeling total sugars and are subject to collinearity effects from related dietary and lifestyle factors. The highest level of evidence from controlled feeding trials has shown a lack of cardiometabolic harm of fructose and SSBs under energy-matched conditions at moderate levels of intake. It is only when fructose-containing sugars or SSBs are consumed at high doses or supplement diets with excess energy that a consistent signal for harm is seen. The available evidence suggests that confounding by excess energy is an important consideration in assessing the

role of fructose-containing sugars and SSBs in the epidemics of hypertension and other cardiometabolic diseases." As taken from Ha V et al. 2013. Curr. Hypertens. Rep. 15(4), 281-97. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/23793849

"Dietary intake of fructose and sucrose can cause development of metabolic and cardiovascular disorders. The consequences of high-fructose corn syrup (HFCS), a commonly consumed form of fructose and glucose, have poorly been examined. Therefore, in this study, we investigated whether HFCS intake (10% and 20% beverages for 12 weeks) impacts vascular reactivity to insulin and endothelin-1 in conjunction with insulin receptor substrate-1(IRS-1), endothelial nitric oxide synthase (eNOS) and inducible NOS (iNOS) mRNA/proteins levels in aorta of rats….HFCS (20%) diet feeding increased plasma triglyceride, VLDL, cholesterol, insulin and glucose levels, but not body weights of rats. Impaired nitric oxide-mediated relaxation to insulin (10(-9) to 3×10(-6) M), and enhanced contraction to endothelin-1 (10^(-11) to 10^(-8) M) were associate with decreased expression of IRS-1 and eNOS mRNA and protein, but increased expression of iNOS, in aortas of rats fed with HFCS….In conclusion, dietary HFCS causes vascular insulin resistance and endothelial dysfunction through attenuating IRS-1 and eNOS expressions as well as increasing iNOS in rats…." As taken from Babacanoglu C et al. 2013. Food Chem. Toxicol. 60, 160-7. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/23872130

"PURPOSE OF REVIEW: The effects of dietary sugar on risk factors and the processes associated with metabolic disease remain a controversial topic, with recent reviews of the available evidence arriving at widely discrepant conclusions. RECENT FINDINGS: There are many recently published epidemiological studies that provide evidence that sugar consumption is associated with metabolic disease. Three recent clinical studies, which investigated the effects of consuming relevant doses of sucrose or high-fructose *corn syrup* along with ad libitum diets, provide evidence that consumption of these sugars increase the risk factors for cardiovascular disease and metabolic syndrome. Mechanistic studies suggest that these effects result from the rapid hepatic metabolism of fructose catalyzed by fructokinase C, which generates substrate for de novo lipogenesis and leads to increased uric acid levels. Recent clinical studies investigating the effects of consuming less sugar, via educational interventions or by substitution of sugar-sweetened beverages for noncalorically sweetened beverages, provide evidence that such strategies have beneficial effects on risk factors for metabolic disease or on BMI in children. SUMMARY: The accumulating epidemiological evidence, direct clinical evidence, and the evidence suggesting plausible mechanisms support a role for sugar in the epidemics of metabolic syndrome, cardiovascular disease, and type 2 diabetes." As taken from Stanhope KL et al. 2013. Curr. Opin. Lipidol. 24(3), 198-206. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/23594708

"BACKGROUND: There is lack of consensus in the lay literature to support consumption of table sugar as a preferred sweetener when compared to high fructose corn syrup (HFCS). AIMS: The purpose of this study was to search the literature for evidence to determine the health effects of consumption of table sugar (sucrose) and HFCS on blood glucose, lipid levels, obesity, and appetite as well as to make recommendations for patient and family teaching of those at risk for developing negative health outcomes, including coronary heart disease. METHODS: Nursing and health-related databases, including CINAHL, PubMed, Cochrane Central Registry of Controlled Trials, and Health and Wellness were searched for

research articles, which were compared and evaluated for purpose, sample size, procedure, findings, and level of evidence. FINDINGS: Five studies that met inclusion criteria were evaluated. No difference was found in changes in blood glucose levels, lipid levels, or appetite between table sugar consumption and HFCS consumption. When only fructose was consumed, lipid levels were significantly increased. LINKING EVIDENCE TO ACTION: The evidence suggests that fructose, found in both table sugar and HFCS, has a negative effect on health outcomes. Clinicians should teach patients and families that all sugar consumption should be closely monitored and kept below the 40 g/day recommended by the World Health Organization." As taken from Sobel LL & Dalby E. 2014. Worldviews Evid. Based Nurs. 11(2), 126-32. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/24612636?dopt=AbstractPlus

"The impact of fructose, commonly consumed with sugars by humans, on blood pressure and uric acid has yet to be defined. A total of 267 weight-stable participants drank sugar-sweetened milk every day for 10 weeks as part of their usual, mixed-nutrient diet. Groups 1 and 2 had 9% estimated caloric intake from fructose or glucose, respectively, added to milk. Groups 3 and 4 had 18% of estimated caloric intake from high fructose corn syrup or sucrose, respectively, added to the milk. Blood pressure and uric acid were determined prior to and after the 10-week intervention. There was no effect of sugar type on either blood pressure or uric acid (interaction P>.05), and a significant time effect for blood pressure was noted (P<.05). The authors conclude that 10 weeks of consumption of fructose at the 50th percentile level, whether consumed as pure fructose or with fructose-glucose-containing sugars, does not promote hyperuricemia or increase blood pressure." As taken from Angelopoulos TJ et al. 2015. J. Clin. Hypertens. (Greenwich) 17(2), 87-94. PubMed 2016, available at: http://www.ncbi.nlm.nih.gov/pubmed/25496265

"BACKGROUND: Nonalcoholic fatty liver disease (NAFLD) is a common liver disease in obese children. Diets high in added fructose (high fructose corn syrup; HFCS) and glycemic index (GI)/glycemic load (GL) are associated with increased risk of NAFLD. Lifestyle modification is the main treatment, but no guidelines regarding specific dietary interventions for childhood NAFLD exist. We hypothesized that reductions in dietary fructose (total, free, and HFCS)/GI/GL over 6 months would result in improvements in body composition and markers of liver dysfunction and cardiometabolic risk in childhood NAFLD. METHODS: Children and adolescents with NAFLD (n = 12) and healthy controls (n = 14) 7-18 years were studied at baseline and 3 and 6 months post-dietary intervention. Plasma markers of liver dysfunction (ALT, AST, γGT), cardiometabolic risk (TG, total cholesterol, LDL-HDL cholesterol, Apo-B100, Apo-B48, Apo-CIII, insulin, homeostasis model of assessment of insulin resistance [HOMA-IR]), inflammation (TNF-α, IL-6, IL-10), anthropometric, and blood pressure (BP) were studied using validated methodologies. RESULTS: Significant reductions in systolic BP (SBP), percentage body fat (BF), and plasma concentrations of ALT (P = .04), Apo-B100 (P <.001), and HOMA-IR were observed in children with NAFLD at 3 and 6 months (P <.05). Dietary reductions in total/free fructose/HFCS and GL were related to reductions in SBP (P = .01), ALT (P = .004), HOMA-IR (P = .03), and percentage BF in children with NAFLD. Reductions in dietary GI were associated with reduced plasma Apo-B100 (P = .02) in both groups. With the exception of Apo-B100, no changes in laboratory variables were observed in the control group. CONCLUSION: Modest reductions in fructose (total/free, HFCS) and GI/GL intake result in improvements of plasma markers of liver dysfunction and cardiometabolic risk in childhood NAFLD." As taken from Mager DR et al. 2015. JPEN J. Parenter. Enteral. Nutr. 39(1), 73-84. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/23976771

“OBJECTIVE: The aim of this study was to review the current corpus of human studies to determine the association of various doses and durations of fructose consumption on metabolic syndrome. METHODS: We searched human studies in PubMed, Scopus, Ovid, ISI Web of Science, Cochrane library, and Google Scholar databases. We searched for the following keywords in each paper: metabolic syndrome x, insulin resistance, blood glucose, blood sugar, fasting blood sugar, triglycerides, lipoproteins, HDL, cholesterol, LDL, blood pressure, mean arterial pressure, systolic blood pressure, diastolic blood pressure, hypertens*, waist circumference, and fructose, sucrose, high-fructose corn syrup, or sugar. RESULTS: Overall, 3102 articles were gathered. We excluded studies on natural fructose content of foods, non-clinical trials, and trials in which fructose was recommended exclusively as sucrose or high-fructose corn syrup. Overall, 3069 articles were excluded. After review by independent reviewers, 15 studies were included in the meta-analysis. Fructose consumption was positively associated with increased fasting blood sugar (FBS; summary mean difference, 0.307; 95% confidence interval [CI], 0.149-0.465; P = 0.002), elevated triglycerides (TG; 0.275; 95% CI, 0.014-0.408; P = 0.002); and elevated systolic blood pressure (SBP; 0.297; 95% CI, 0.144-0.451; P = 0.002). The corresponding figure was inverse for high-density lipoprotein (HDL) cholesterol (-0.267; 95% CI, -0.406 to -0.128; P = 0.001). Significant heterogeneity existed between studies, except for FBS. After excluding studies that led to the highest effect on the heterogeneity test, the association between fructose consumption and TG, SBP, and HDL became non-significant. The results did not show any evidence of publication bias. No missing studies were identified with the trim-and-n¼üll method. CONCLUSION: Fructose consumption from industrialized foods has significant effects on most components of metabolic syndrome.” As taken from Kelishadi R et al. 2014. Nutrition 30(5), 503-10. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/24698343?dopt=AbstractPlus

“OBJECTIVES: Although most controlled feeding trials have failed to show an adverse effect of fructose on blood pressure, concerns continue to be raised regarding the role of fructose in hypertension. To quantify the association between fructose-containing sugar (high-fructose corn syrup, sucrose, and fructose) intake and incident hypertension, a systematic review and meta-analysis of prospective cohort studies was undertaken. METHODS: MEDLINE, EMBASE, CINAHL and the Cochrane Library (through February 5, 2014) were searched for relevant studies. Two independent reviewers reviewed and extracted relevant data. Risk estimates were aggregated comparing the lowest (reference) quintile with highest quintile of intake using inverse variance random effect models and expressed as risk ratios (RR) with 95% confidence intervals (CIs). Interstudy heterogeneity was assessed (Cochran Q statistic) and quantified (I(2) statistic). The Newcastle-Ottawa Scale assessed study quality. Clinicaltrials.gov NCT01608620. RESULTS: Eligibility criteria were met by 3 prospective cohorts (n = 37,375 men and 185,855 women) with 58,162 cases of hypertension observed over 2,502,357 person-years of follow-up. Median fructose intake was 5.7-6.0% total energy in the lowest quintile and 13.9-14.3% total energy in the highest quintile. Fructose intake was not associated with incident hypertension (RR = 1.02, 95% CI, 0.99-1.04), with no evidence of heterogeneity (I(2) = 0%, p = 0.59). Spline curve modeling showed a U-shaped relationship with a negative association at intakes <50th percentile (~10% total energy) and a positive association at higher intakes. CONCLUSIONS: Total fructose intake was not associated with an increased risk of hypertension in 3 large prospective cohorts of U.S. men and women.” As taken from Jayalath VH et al. 2014. J. Am. Coll. Nutr. 33(4), 328-39. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/25144126

“The American Heart Association (AHA) and World Health Organization (WHO) have recommended restricting calories from added sugars at lower levels than the Institute of Medicine (IOM) recommendations, which are incorporated in the Dietary Guidelines for Americans 2010 (DGAs 2010). Sucrose (SUC) and high fructose corn syrup (HFCS) have been singled out for particular concern, because of their fructose content, which has been specifically implicated for its atherogenic potential and possible role in elevating blood pressure through uric acid-mediated endothelial dysfunction. This study explored the effects when these sugars are consumed at typical population levels up to the 90th percentile population consumption level for fructose. Three hundred fifty five overweight or obese individuals aged 20-60 years old were placed on a eucaloric diet for 10 weeks, which incorporated SUC- or HFCS-sweetened, low-fat milk at 8%, 18% or 30% of calories. There was a slight change in body weight in the entire cohort (169.1 ± 30.6 vs. 171.6 ± 31.8 lbs, P<0.01), a decrease in HDL (52.9 ± 12.2 vs. 52.0 ± 13.9 mg/dL, P<0.05) and an increase in triglycerides (104.1 ± 51.8 vs. 114.1 ± 64.7 mg/dL, P<0.001). However, total cholesterol (183.5 ± 42.8 vs. 184.4 mg/dL, P>0.05), LDL (110.3 ± 32.0 vs. 110.5 ± 38.9 mg/dL, P>0.05), SBP (109.4 ± 10.9 vs. 108.3 ± 10.9 mmHg, P>0.05) and DBP (72.1 ± 8.0 vs. 71.3 ± 8.0 mmHg, P>0.05) were all unchanged. In no instance did the amount or type of sugar consumed affect the response to the intervention (interaction P>0.05). These data suggest that: (1) when consumed as part of a normal diet, common fructose-containing sugars do not raise blood pressure, even when consumed at the 90th percentile population consumption level for fructose (five times the upper level recommended by the AHA and three times the upper level recommended by WHO); (2) changes in the lipid profile are mixed, but modest.” As taken from Lowndes J et al. 2014. Nutrients 6(8), 3153-68. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/25111121

“Adropin is a peptide hormone encoded by the Energy Homeostasis Associated (ENHO) gene whose physiological role in humans remains incompletely defined. Here we investigated the impact of dietary interventions that affect systemic glucose and lipid metabolism on plasma adropin concentrations in humans. Consumption of glucose or fructose as 25% of daily energy requirements (E) differentially affected plasma adropin concentrations (P<0.005) irrespective of duration, sex or age. Glucose consumption reduced plasma adropin from 3.55 ± 0.26 to 3.28 ± 0.23 ng/ml (N = 42). Fructose consumption increased plasma adropin from 3.63 ± 0.29 to 3.93 ± 0.34 ng/ml (N = 45). Consumption of high fructose corn syrup (HFCS) as 25% E had no effect (3.43 ± 0.32 versus 3.39 ± 0.24 ng/ml, N = 26). Overall, the effect of glucose, HFCS and fructose on circulating adropin concentrations were similar to those observed on postprandial plasma triglyceride concentrations. Furthermore, increases in plasma adropin levels with fructose intake were most robust in individuals exhibiting hypertriglyceridemia. Individuals with low plasma adropin concentrations also exhibited rapid increases in plasma levels following consumption of breakfasts supplemented with lipids. These are the first results linking plasma adropin levels with dietary sugar intake in humans, with the impact of fructose consumption linked to systemic triglyceride metabolism. In addition, dietary fat intake may also increase circulating adropin concentrations.” As taken from Butler AA et al. 2015. Sci. Rep. 5, 14691. PubMed, 2016 available at http://www.ncbi.nlm.nih.gov/pubmed/26435060

“BACKGROUND: Public health recommendations call for a reduction in added sugars; however, controversy exists over whether all nutritive sweeteners produce similar metabolic effects. OBJECTIVE: The objective was to compare the effects of the chronic consumption of 3 nutritive sweeteners [honey, sucrose, and high-fructose corn syrup containing 55% fructose (HFCS55)] on circulating glucose, insulin, lipids, and inflammatory markers; body

weight; and blood pressure in individuals with normal glucose tolerance (GT) and those with impaired glucose tolerance (IGT). METHODS: In a crossover design, participants consumed daily, in random order, 50 g carbohydrate from assigned sweeteners for 2 wk with a 2- to 4-wk washout period between treatments. Participants included 28 GT and 27 IGT volunteers with a mean age of 38.9 ± 3.6 y and 52.1 ± 2.7 y, respectively, and a body mass index (in kg/m(2)) of 26 ± 0.8 and 31.5 ± 1.0, respectively. Body weight, blood pressure (BP), serum inflammatory markers, lipids, fasting glucose and insulin, and oral-glucose-tolerance tests (OGTTs) were completed pre- and post-treatment. The OGTT incremental areas under the curve (iAUCs) for glucose and insulin were determined and homeostasis model assessment of insulin resistance (HOMA-IR) scores were calculated. RESULTS: Body weight and serum glucose, insulin, inflammatory markers, and total and LDL-cholesterol concentrations were significantly higher in the IGT group than in the GT group at baseline. Glucose, insulin, HOMA-IR, and the OGTT iAUC for glucose or insulin did not differ by treatment, but all responses were significantly higher in the IGT group compared with the GT group. Body weight was unchanged by treatment. Systolic BP was unchanged, whereas diastolic BP was significantly lower in response to sugar intake across all treatments. An increase in high-sensitivity C-reactive protein (hsCRP) was observed in the IGT group in response to all sugars. No treatment effect was observed for interleukin 6. HDL cholesterol did not differ as a result of status or treatment. Triglyceride (TG) concentrations increased significantly from pre- to post-treatment in response to all sugars tested. CONCLUSIONS: Daily intake of 50 g carbohydrate from honey, sucrose, or HFCS55 for 14 d resulted in similar effects on measures of glycemia, lipid metabolism, and inflammation. All 3 increased TG concentrations in both GT and IGT individuals and elevated glycemic and inflammatory responses in the latter. This trial was registered at clinicaltrials.gov as NCT01371266.” As taken from Raatz SK et al. 2015. J. Nutr. 145(10), 2265-72. PubMed, 2016 available at http://www.ncbi.nlm.nih.gov/pubmed/26338891

“OBJECTIVE: The aim of this study was to investigate the protective effects of aspirin (AS) and vitamin C (VC) against cardiac damage induced by chronic corn syrup (CS) consumption via a mechanism involving sirtuin-1 (ST-1), hypoxia-inducible factor-1α (HIF-1α), and the caspase-3 pathway in rats. METHODS: Forty male Sprague-Dawley rats (14-16 weeks) that weighed 250-300 g were randomly distributed into 5 groups, each containing 8 rats: control group, CS+AS group, CS+VC group, CS+AS+VC group, and CS group. AS (10 mg/kg/day) and VC (200 mg/kg/day) were orally given to the rats. F30 (30% fructose syrup solution) was given to the rats in drinking water for 6 weeks. The rats were sacrificed by exsanguination 24 h after the last administration. Blood samples and tissue were collected for biochemical, histopathological, and immunohistochemical examinations. Non-parametric Kruskal-Wallis test and Mann-Whitney U test used for the parameters without normal distribution and ANOVA and post-hoc LSD tests were used for parameters with a normal distribution to compare groups. RESULTS: Uric acid, creatine kinase (CKMB), and lactate dehydrogenase (LDH) levels were increased in the CS group compared with the control group (1.45±0.39 and p=0.011; 3225.64±598.25 and p=0.004; 3906.83±1064.22 and p=0.002, respectively) and decreased in all the treatment groups. In addition, increased levels of MDA and decreased activity of CAT in the CS group (0.172±0.03 and p=0.000; 0.070±0.005 and p=0.007, respectively) were reversed with AS and VC therapy. A decrease in ST-1 activity and increases in caspase-3 and HIF-1 activities corrected by VC and AS therapy were observed. CONCLUSION: AS and VC, which display antioxidant and antiapoptotic activities, ameliorated cardiac damage induced by chronic fructose consumption by increasing the levels of ST-1 and decreasing the levels of HIF-1α and

caspase-3." As taken from Asci H et al. 2016. Anatol. J. Cardiol. 16(9), 648-54. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/26645266

"BACKGROUND: National Health and Nutrition Examination Survey data show an increased risk of cardiovascular disease (CVD) mortality with an increased intake of added sugar. OBJECTIVE: We determined the dose-response effects of consuming beverages sweetened with high-fructose corn syrup (HFCS) at zero, low, medium, and high proportions of energy requirements (Ereq) on circulating lipid/lipoprotein risk factors for CVD and uric acid in adults [age: 18-40 y; body mass index (in kg/m(2)): 18-35]. DESIGN: We conducted a parallel-arm, nonrandomized, double-blinded intervention study in which adults participated in 3.5 inpatient days of baseline testing at the University of California Davis Clinical and Translational Science Center's Clinical Research Center. Participants then consumed beverages sweetened with HFCS at 0% (aspartame sweetened, n = 23), 10% (n = 18), 17.5% (n = 16), or 25% (n = 28) of Ereq during 13 outpatient days and during 3.5 inpatient days of intervention testing at the research center. We conducted 24-h serial blood collections during the baseline and intervention testing periods. RESULTS: Consuming beverages containing 10%, 17.5%, or 25% Ereq from HFCS produced significant linear dose-response increases of lipid/lipoprotein risk factors for CVD and uric acid: postprandial triglyceride (0%: 0 ± 4; 10%: 22 ± 8; 17.5%: 25 ± 5: 25%: 37 ± 5 mg/dL, mean of Δ ± SE, P<0.0001 effect of HFCS-dose), fasting LDL cholesterol (0%: -1.0 ± 3.1; 10%: 7.4 ± 3.2; 17.5%: 8.2 ± 3.1; 25%: 15.9 ± 3.1 mg/dL, P<0.0001), and 24-h mean uric acid concentrations (0%: -0.13 ± 0.07; 10%: 0.15 ± 0.06; 17.5%: 0.30 ± 0.07; 25%: 0.59 ± 0.09 mg/dL, P<0.0001). Compared with beverages containing 0% HFCS, all 3 doses of HFCS-containing beverages increased concentrations of postprandial triglyceride, and the 2 higher doses increased fasting and/or postprandial concentrations of non-HDL cholesterol, LDL cholesterol, apolipoprotein B, apolipoprotein CIII, and uric acid. CONCLUSIONS: Consuming beverages containing 10%, 17.5%, or 25% Ereq from HFCS produced dose-dependent increases in circulating lipid/lipoprotein risk factors for CVD and uric acid within 2 wk. These results provide mechanistic support for the epidemiologic evidence that the risk of cardiovascular mortality is positively associated with consumption of increasing amounts of added sugars. This trial was registered at clinicaltrials.gov as NCT01103921." As taken from Stanhope KL et al. 2015. Am. J. Clin. Nutr. 101(6), 1144-54. PubMed, 2016 available at http://www.ncbi.nlm.nih.gov/pubmed/25904601

"The aim of this study was to evaluate the role of α-lipoic acid (α-LA) on oxidative damage and inflammation that occur in endothelium of aorta and heart while constant consumption of high-fructose corn syrup (HFCS). The rats were randomly divided into three groups with each group containing eight rats. The groups include HFCS, HFCS + α-LA treatment, and control. HFCS was given to the rats at a ratio of 30% of F30 corn syrup in drinking water for 10 weeks. α-LA treatment was given to the rats at a dose of 100 mg/kg/day orally for the last 6 weeks. At the end of the experiment, the rats were killed by cervical dislocation. The blood samples were collected for biochemical studies, and the aortic and cardiac tissues were collected for evaluation of oxidant-antioxidant system, tissue bath, and pathological examination. HFCS had increased the levels of malondialdehyde, creatine kinase MB, lactate dehydrogenase, and uric acid and showed significant structural changes in the heart of the rats by histopathology. Those changes were improved by α-LA treatment as it was found in this treatment group. Immunohistochemical expressions of tumor necrosis factor α and inducible nitric oxide synthase were increased in HFCS group, and these receptor levels were decreased by α-LA treatment. All the tissue bath studies supported these findings. Chronic consumption of HFCS caused several problems like cardiac and

endothelial injury of aorta by hyperuricemia and induced oxidative stress and inflammation. α-LA treatment reduced uric acid levels, oxidative stress, and corrected vascular responses. α-LA can be added to cardiac drugs due to its cardiovascular protective effects against the cardiovascular diseases." As taken from Saygin M et al. 2016. Hum. Exp. Toxicol. 35(2), 194-204. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/25825413

"The objective of the current study was to explore our hypothesis that average consumption of fructose and fructose containing sugars would not increase risk factors for cardiovascular disease (CVD) and the metabolic syndrome (MetS). A randomized, double blind, parallel group study was conducted where 267 individuals with BMI between 23 and 35 kg/m² consumed low fat sugar sweetened milk, daily for ten weeks as part of usual weight-maintenance diet. One group consumed 18% of calories from high fructose corn syrup (HFCS), another group consumed 18% of calories from sucrose, a third group consumed 9% of calories from fructose, and the fourth group consumed 9% of calories from glucose. There was a small change in waist circumference (80.9 ± 9.5 vs. 81.5 ± 9.5 cm) in the entire cohort, as well as in total cholesterol (4.6 ± 1.0 vs. 4.7 ± 1.0 mmol/L, $P<0.01$), triglycerides (TGs) (11.5 ± 6.4 vs. 12.6 ± 8.9 mmol/L, $P<0.01$), and systolic (109.2 ± 10.2 vs. 106.1 ± 10.4 mmHg, $P<0.01$) and diastolic blood pressure (69.8 ± 8.7 vs. 68.1 ± 9.7 mmHg, $P<0.01$). The effects of commonly consumed sugars on components of the MetS and CVD risk factors are minimal, mixed and not clinically significant." As taken from Angelopoulos TJ et al. 2016. Nutrients 8(4), 179. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/27023594

"Dietary guidelines continue to recommend restricting intake of saturated fats. This recommendation follows largely from the observation that saturated fats can raise levels of total serum cholesterol (TC), thereby putatively increasing the risk of atherosclerotic coronary heart disease (CHD). However, TC is only modestly associated with CHD, and more important than the total level of cholesterol in the blood may be the number and size of low-density lipoprotein (LDL) particles that contain it. As for saturated fats, these fats are a diverse class of compounds; different fats may have different effects on LDL and on broader CHD risk based on the specific saturated fatty acids (SFAs) they contain. Importantly, though, people eat foods, not isolated fatty acids. Some food sources of SFAs may pose no risk for CHD or possibly even be protective. Advice to reduce saturated fat in the diet without regard to nuances about LDL, SFAs, or dietary sources could actually increase people's risk of CHD. When saturated fats are replaced with refined carbohydrates, and specifically with added sugars (like sucrose or high fructose corn syrup), the end result is not favorable for heart health. Such replacement leads to changes in LDL, high-density lipoprotein (HDL), and triglycerides that may increase the risk of CHD. Additionally, diets high in sugar may induce many other abnormalities associated with elevated CHD risk, including elevated levels of glucose, insulin, and uric acid, impaired glucose tolerance, insulin and leptin resistance, non-alcoholic fatty liver disease, and altered platelet function. A diet high in added sugars has been found to cause a 3-fold increased risk of death due to cardiovascular disease, but sugars, like saturated fats, are a diverse class of compounds. The monosaccharide, fructose, and fructose-containing sweeteners (e.g., sucrose) produce greater degrees of metabolic abnormalities than does glucose (either isolated as a monomer, or in chains as starch) and may present greater risk of CHD. This paper reviews the evidence linking saturated fats and sugars to CHD, and concludes that the latter is more of a problem than the former. Dietary guidelines should shift focus away from reducing saturated fat, and from replacing saturated fat with carbohydrates, specifically when these carbohydrates are refined. To reduce the burden of CHD, guidelines

should focus particularly on reducing intake of concentrated sugars, specifically the fructose-containing sugars like sucrose and high-fructose corn syrup in the form of ultra-processed foods and beverages." As taken from DiNicolantonio JJ et al. 2016. Prog. Cardiovasc. Dis. 58(5), 464-72. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/26586275

"The impact of sugar consumption on health continues to be a controversial topic. The objective of this review is to discuss the evidence and lack of evidence that allows the controversy to continue, and why resolution of the controversy is important. There are plausible mechanisms and research evidence that supports the suggestion that consumption of excess sugar promotes the development of cardiovascular disease (CVD) and type 2 diabetes (T2DM) both directly and indirectly. The direct pathway involves the unregulated hepatic uptake and metabolism of fructose, leading to liver lipid accumulation, dyslipidemia, decreased insulin sensitivity and increased uric acid levels. The epidemiological data suggest that these direct effects of fructose are pertinent to the consumption of the fructose-containing sugars, sucrose and high fructose corn syrup (HFCS), which are the predominant added sugars. Consumption of added sugar is associated with development and/or prevalence of fatty liver, dyslipidemia, insulin resistance, hyperuricemia, CVD and T2DM, often independent of body weight gain or total energy intake. There are diet intervention studies in which human subjects exhibited increased circulating lipids and decreased insulin sensitivity when consuming high sugar compared with control diets. Most recently, our group has reported that supplementing the ad libitum diets of young adults with beverages containing 0%, 10%, 17.5% or 25% of daily energy requirement (Ereq) as HFCS increased lipid/lipoprotein risk factors for CVD and uric acid in a dose-response manner. However, un-confounded studies conducted in healthy humans under a controlled, energy-balanced diet protocol that enables determination of the effects of sugar with diets that do not allow for body weight gain are lacking. Furthermore, recent reports conclude that there are no adverse effects of consuming beverages containing up to 30% Ereq sucrose or HFCS, and the conclusions from several meta-analyses suggest that fructose has no specific adverse effects relative to any other carbohydrate. Consumption of excess sugar may also promote the development of CVD and T2DM indirectly by causing increased body weight and fat gain, but this is also a topic of controversy. Mechanistically, it is plausible that fructose consumption causes increased energy intake and reduced energy expenditure due to its failure to stimulate leptin production. Functional magnetic resonance imaging (fMRI) of the brain demonstrates that the brain responds differently to fructose or fructose-containing sugars compared with glucose or aspartame. Some epidemiological studies show that sugar consumption is associated with body weight gain, and there are intervention studies in which consumption of ad libitum high-sugar diets promoted increased body weight gain compared with consumption of ad libitum low- sugar diets. However, there are no studies in which energy intake and weight gain were compared in subjects consuming high or low sugar, blinded, ad libitum diets formulated to ensure both groups consumed a comparable macronutrient distribution and the same amounts of fiber. There is also little data to determine whether the form in which added sugar is consumed, as beverage or as solid food, affects its potential to promote weight gain. It will be very challenging to obtain the funding to conduct the clinical diet studies needed to address these evidence gaps, especially at the levels of added sugar that are commonly consumed. Yet, filling these evidence gaps may be necessary for supporting the policy changes that will help to turn the food environment into one that does not promote the development of obesity and metabolic disease." As taken from Stanhope

KL. 2016. Crit. Rev. Clin. Lab. Sci. 53(1), 52-67. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/26376619

“The "Salt Hypothesis" is the notion that an increase in salt intake will increase blood pressure and thus increase the risk of cardiovascular disease (CVD), which has been a point of contention for decades. Despite this, numerous health organizations, dietary guidelines, and government policies advocate population-wide salt restriction. However, there is no conclusive proof that restricting salt intake reduces the risk of hypertension (HTN) and/or CVD events; sodium restriction in fact may paradoxically lead to adverse health outcomes. Importantly, another white crystal, sucrose (or table sugar) but also high-fructose corn syrup are much more detrimental food additives. Indeed, added sugars have the ability to induce hypertension via the promotion of inflammation, oxidative stress, insulin resistance, and obesity. Considering that there is no physiologic requirement for dietary carbohydrate, there is little reason to suspect adverse health consequences from cutting back on sugar. This paper reviews the evidence relating to salt and sugar on HTN and CVD. Based on our review of the scientific literature, guidelines should focus more on reducing sugar rather than salt for the prevention and treatment of HTN and its consequences.” As taken from DiNicolantonio JJ and O'Keefe JH. 2016. Prog. Cardiovasc. Dis. 59(3), 219-225. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/27449852?dopt=AbstractPlus

6.3. Nervous system

“Excessive consumption of added sugars negatively impacts metabolic systems; however, effects on cognitive function are poorly understood. Also unknown is whether negative outcomes associated with consumption of different sugars are exacerbated during critical periods of development (e.g., adolescence). Here we examined the effects of sucrose and high fructose corn syrup-55 (HFCS-55) intake during adolescence or adulthood on cognitive and metabolic outcomes. Adolescent or adult male rats were given 30-day access to chow, water, and either (1) 11% sucrose solution, (2) 11% HFCS-55 solution, or (3) an extra bottle of water (control). In adolescent rats, HFCS-55 intake impaired hippocampal-dependent spatial learning and memory in a Barne's maze, with moderate learning impairment also observed for the sucrose group. The learning and memory impairment is unlikely based on nonspecific behavioral effects as adolescent HFCS-55 consumption did not impact anxiety in the zero maze or performance in a non-spatial response learning task using the same mildly aversive stimuli as the Barne's maze. Protein expression of pro-inflammatory cytokines (interleukin 6, interleukin 1β) was increased in the dorsal hippocampus for the adolescent HFCS-55 group relative to controls with no significant effect in the sucrose group, whereas liver interleukin 1β and plasma insulin levels were elevated for both adolescent-exposed sugar groups. In contrast, intake of HFCS-55 or sucrose in adults did not impact spatial learning, glucose tolerance, anxiety, or neuroinflammatory markers. These data show that consumption of added sugars, particularly HFCS-55, negatively impacts hippocampal function, metabolic outcomes, and neuroinflammation when consumed in excess during the adolescent period of development.” As taken from Hsu TM et al. 2015. Hippocampus 25(2), 227-39. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/25242636

“Several hypotheses for the causes of the obesity epidemic in the US have been proposed. One such hypothesis is that dietary intake patterns have significantly shifted to include unprecedented amounts of refined sugar. We set out to determine if different sugars might promote changes in the hypothalamic mechanisms controlling food intake by measuring several hypothalamic peptides subsequent to overnight access to dilute glucose, sucrose, high fructose corn syrup, or fructose solutions. Rats were given access to food, water and a sugar solution for 24h, after which blood and tissues were collected. Fructose access (as opposed to other sugars that were tested) resulted in a doubling of circulating triglycerides. Glucose consumption resulted in upregulation of 7 satiety-related hypothalamic peptides whereas changes in gene expression were mixed for remaining sugars. Also, following multiple verification assays, 6 satiety related peptides were verified as being affected by sugar intake. These data provide evidence that not all sugars are equally effective in affecting the control of intake.” As taken from Colley DL & Castonguay TW. 2015. Physiol. Behav. 139, 202-9. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/25449399

“Obesogenic dietary factors, such as simple sugars and saturated fatty acids, have been linked to memory impairments and hippocampal dysfunction. Recent evidence suggests that the brain may be particularly vulnerable to the effects of obesogenic diets during early life periods of rapid growth, maturation, and brain development. Investigations utilizing rodent models indicate that early life exposure to "high fat diets" (40-65% kcal derived from fat) or simple sugars (sucrose or high fructose corn syrup) can impair hippocampus-dependent learning and memory processes. In some cases, these deficits occur independent of obesity and metabolic derangement and can persist into adulthood despite dietary intervention. Various neurobiological mechanisms have been identified that may link early life consumption of obesogenic dietary factors with hippocampal dysfunction, including increased neuroinflammation and reduced neurotrophin mediated regulation of neurogenesis and synaptic plasticity. Age, duration of exposure, and dietary composition are key variables contributing to the interaction between early life diet and cognitive dysfunction, however, more research is needed to unravel the precise critical windows of development and causal dietary factors.” As taken from Noble EE and Kanoski SE. 2016. Curr. Opin. Behav. Sci. 9, 7-14. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/26858972

“OBJECTIVES: Added dietary sugars contribute substantially to the diet of children and adolescents in the USA, and recent evidence suggests that consuming sugar-sweetened beverages (SSBs) during early life has deleterious effects on hippocampal-dependent memory function. Here, we test whether the effects of early-life sugar consumption on hippocampal function persist into adulthood when access to sugar is restricted to the juvenile/adolescent phase of development. METHODS: Male rats were given ad libitum access to an 11% weight-by-volume sugar solution (made with high fructose corn syrup-55) throughout the adolescent phase of development (post-natal day (PN) 26-56). The control group received a second bottle of water instead, and both groups received ad libitum standard laboratory chow and water access throughout the study. At PN 56 sugar solutions were removed and at PN 175 rats were subjected to behavioral testing for hippocampal-dependent episodic contextual memory in the novel object in context (NOIC) task, for anxiety-like behavior in the Zero maze, and were given an intraperitoneal glucose tolerance test. RESULTS: Early-life exposure to SSBs conferred long-lasting impairments in hippocampal-dependent memory function later in life- yet had no effect on body weight, anxiety-like behavior, or glucose tolerance. A second experiment demonstrated that NOIC

performance was impaired at PN 175 even when SSB access was limited to 2 hours daily from PN 26-56. DISCUSSION: Our data suggest that even modest SSB consumption throughout early life may have long-term negative consequences on memory function during adulthood." As taken from Noble EE et al. 2019. Nutr. Neurosci. 22(4), 273-283. PubMed, 2019 available at https://www.ncbi.nlm.nih.gov/pubmed/28944721

"BACKGROUND AND PURPOSE: Children and adolescents are the top consumers of high-fructose corn syrup (HFCS) sweetened beverages. Even though the cardiometabolic consequences of HFCS consumption in adolescents are well known, the neuropsychiatric consequences have yet to be determined. EXPERIMENTAL APPROACH: Adolescent rats were fed for a month with 11% weight/volume carbohydrate containing HFCS solution, which is similar to the sugar-sweetened beverages of human consumption. The metabolic, behavioural and electrophysiological characteristics of HFCS-fed rats were determined. Furthermore, the effects of TDZD-8, a highly specific GSK-3B inhibitor, on the HFCS-induced alterations were further explored. KEY RESULTS: HFCS-fed adolescent rats displayed bipolar-like behavioural phenotype with hyperexcitability in hippocampal CA3-CA1 synapses. This hyperexcitability was associated with increased presynaptic release probability and increased readily available pool of AMPA receptors to be incorporated into the postsynaptic membrane, due to decreased expression of the neuron-specific α3-subunit of Na+ /K+ -ATPase and an increased ser845 -phosphorylation of GluA1 subunits (AMPA receptor subunit) respectively. TDZD-8 treatment was found to restore behavioural and electrophysiological disturbances associated with HFCS consumption by inhibition of GSK-3B, the most probable mechanism of action of lithium for its mood-stabilizing effects. CONCLUSION AND IMPLICATIONS: This study shows that HFCS consumption in adolescent rats led to a bipolar-like behavioural phenotype with neuronal hyperexcitability, which is known to be one of the earliest endophenotypic manifestations of bipolar disorder. Inhibition of GSK-3B with TDZD-8 attenuated hyperexcitability and restored HFCS-induced behavioural alterations." As taken from Alten B et al. 2018. Br. J. Pharmacol. 175(24), 4450-4463. PubMed, 2019 available at: https://www.ncbi.nlm.nih.gov/pubmed/30221753

"Glucose intake has been found to improve some aspects of cognitive performance; however, results are often inconsistent. This inconsistency may be related to expectations surrounding glucose, which can have strong effects on performance outcomes. The present study evaluated the independent and interactive effects of acute sugar intake, in the form of high-fructose corn syrup (HFCS), and sugar expectancies on cognitive performance and mood. One hundred five healthy young adults were randomized according to sugar intake and expectation: consumed-sugar/told-sugar, consumed-sugar/told-no-sugar, consumed-no-sugar/told-sugar, and consumed-no-sugar/told-no-sugar. Thirty minutes after sugar or no-sugar intake, participants completed the Profile of Mood States and a battery of cognitive tests, including immediate and delayed recall, the Stroop test, n-back task, and continuous performance task. Tension increased following the expectation of consuming sugar, regardless of sugar consumption ($p < .05$). On the continuous performance task, accuracy and sensitivity were higher (ps $< .05$) and false alarm rate was lower ($p < .05$) following sugar than no sugar intake. No effects of sugar intake or expectation were found for any other mood or cognitive measure (ps $> .05$). The findings suggest that sugar intake in the form of HFCS may benefit certain cognitive processes, such as those that require sustained attention, but that the expectation of sugar intake is not sufficient to produce such benefits."

As taken from Giles GE et al. 2018. Exp. Clin. Psychopharmacol. 26(3), 302-309. PubMed, 2019 available at: https://www.ncbi.nlm.nih.gov/pubmed/29863386

6.4. Other organ systems, dependent on the properties of the substance

Sugar-sweetened beverages and risk of obesity and type 2 diabetes: epidemiologic evidence (Abstract). In recent decades, temporal patterns in SSB intake have shown a close parallel between the upsurge in obesity and rising levels of SSB consumption. SSBs are beverages that contain added caloric sweeteners such as sucrose, high-fructose corn syrup or fruit-juice concentrates, all of which result in similar metabolic effects. They include the full spectrum of soft drinks, carbonated soft drinks, fruitades, fruit drinks, sports drinks, energy and vitamin water drinks, sweetened iced tea, cordial, squashes, and lemonade, which collectively are the largest contributor to added sugar intake in the US. It has long been suspected that SSBs have an etiologic role in the obesity epidemic, however only recently have large epidemiological studies been able to quantify the relationship between SSB consumption and long-term weight gain, type 2 diabetes (T2DM) and cardiovascular disease (CVD) risk. Experimental studies have provided important insight into potential underlying biological mechanisms. It is thought that SSBs contribute to weight gain in part by incomplete compensation for energy at subsequent meals following intake of liquid calories. They may also increase risk of T2DM and CVD as a contributor to a high dietary glycemic load leading to inflammation, insulin resistance and impaired beta-cell function. Additional metabolic effects from the fructose fraction of these beverages may also promote accumulation of visceral adiposity, and increased hepatic de novo lipogenesis, and hypertension due to hyperuricemia. Consumption of SSBs should therefore be replaced by healthy alternatives such as water, to reduce risk of obesity and chronic diseases. As taken from Hu FB, Malik VS. 2010. Physiol. Behav. 100(1), 47-54. PubMed, 2015 available at http://www.ncbi.nlm.nih.gov/pubmed/20138901

Soft drink consumption and obesity: it is all about fructose (Abstract). The purpose of the review is to suggest that fructose, a component of both sucrose (common sugar) and high fructose corn syrup, should be of concern to both healthcare providers and the public.

RECENT FINDINGS: Consumption of sugar-sweetened beverages has increased steadily over the past century and with this increase has come more and more reports associating their use with the risk of overweight, diabetes and cardiometabolic disease. In a meta-analysis of the relationship between soft drink consumption and cardiometabolic risk, there was a 24% overall increased risk comparing the top and bottom quantiles of consumption. Several factors might account for this increased risk, including increased carbohydrate load and increased amounts of dietary fructose. Fructose acutely increases thermogenesis, triglycerides and lipogenesis as well as blood pressure, but has a smaller effect on leptin and insulin release than comparable amounts of glucose. In controlled feeding studies, changes in body weight, fat storage and triglycerides are observed as well as an increase in inflammatory markers. SUMMARY: The present review concludes on the basis of the data assembled here that in the amounts currently consumed, fructose is hazardous to the cardiometabolic health of many children, adolescents and adults. As taken from Bray GA.

Curr Opin Lipidol. 2010 Feb; 21(1):51-7. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/19956074

Diabetes of the liver: the link between nonalcoholic fatty liver disease and HFCS-55 (Abstract). Nonalcoholic fatty liver disease (NAFLD) is associated with obesity and insulin resistance. It is also a predisposing factor for type 2 diabetes. Dietary factors are believed to contribute to all three diseases. NAFLD is characterized by increased intrahepatic fat and mitochondrial dysfunction, and its etiology may be attributed to excessive fructose intake. Consumption of high fructose corn syrup-55 (HFCS-55) stands at up to 15% of the average total daily energy intake in the United States, and is linked to weight gain and obesity. The aim of this study was to establish whether HFCS-55 could contribute to the pathogenesis of NAFLD, by examining the effects of HFCS-55 on hepatocyte lipogenesis, insulin signaling, and cellular function, in vitro and in vivo. Exposure of hepatocytes to HFCS-55 caused a significant increase in hepatocellular triglyceride (TG) and lipogenic proteins. Basal production of reactive oxygen metabolite (ROM) was increased, together with a decreased capacity to respond to an oxidative challenge. HFCS-55 induced a downregulation of the insulin signaling pathway, as indicated by attenuated (ser473)phosphorylation of AKT1. The c-Jun amino-terminal kinase (JNK), which is intimately linked to insulin resistance, was also activated; and this was accompanied by an increase in endoplasmic reticulum (ER) stress and intracellular free calcium perturbation. Hepatocytes exposed to HFCS-55 exhibited mitochondrial dysfunction and released cytochrome C (CytC) into the cytosol. Hepatic steatosis and mitochondrial disruption was induced in vivo by a diet enriched with 20% HFCS 55; accompanied by hypoadiponectinemia and elevated fasting serum insulin and retinol-binding protein-4 (RBP4) levels. Taken together our findings indicate a potential mechanism by which HFCS-55 may contribute to the pathogenesis of NAFLD. As taken from Collison KS et al. Obesity (Silver Spring). 2009 Nov; 17(11):2003-13. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/19282820

Corn syrup sugars: in vitro and in vivo digestibility and clinical tolerance in acute diarrhea of infancy (Abstract). We evaluated the in vitro and in vivo digestibility and clinical tolerance of three corn syrup sugars (DE10, 15, 24) and one infant formula containing corn syrup sugar as the sole carbohydrate source (DE24). In vitro studies were conducted using human duodenal fluid and jejunal mucosa with normal enzyme activities. In vivo studies included intragastric perfusion studies and tolerance tests using the corn syrup sugars and a clinical formula trial in 32 infants with acute diarrhea. Results of the in vitro studies showed that each of the corn syrup sugars was well hydrolyzed by duodenal fluid and by mixtures of duodenal fluids and mucosal homogenates. Similarly, in vivo studies revealed significant hydrolysis in the proximal intestine, as measured during the perfusion studies, and adequate absorption, as indicated by a rise in serum glucose concentration during tolerance tests. Only patients who had a marginal serum glucose rise after a glucose meal had a blunted rise after a corn syrup feeding. More than 85% of the infants beginning the clinical trial tolerated the formula well and gained weight at or above the expected rate for age during the study interval. These data indicate that, except with severe mucosal injury and secondary monosaccharide intolerance, glucose polymers of the dextrose equivalents tested are suitable carbohydrate sources for infants recovering from acute diarrhea. As taken from Lebenthal E et al. J Pediatr. 1983 Jul; 103(1):29-34. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/6345742?dopt=AbstractPlus

A critical examination of the evidence relating high fructose corn syrup and weight gain (Abstract). The use of high fructose corn syrup (HFCS) has increased over the past several decades in the United States while overweight and obesity rates have risen dramatically. Some scientists hypothesize that HFCS consumption has uniquely contributed to the increasing mean body mass index (BMI) of the U.S. population. The Center for Food, Nutrition, and Agriculture Policy convened an expert panel to discuss the published scientific literature examining the relationship between consumption of HFCS or "soft drinks" (proxy for HFCS) and weight gain. The authors conducted original analysis to address certain gaps in the literature. Evidence from ecological studies linking HFCS consumption with rising BMI rates is unreliable. Evidence from epidemiologic studies and randomized controlled trials is inconclusive. Studies analyzing the differences between HFCS and sucrose consumption and their contributions to weight gain do not exist. HFCS and sucrose have similar monosaccharide compositions and sweetness values. The fructose:glucose (F:G) ratio in the U.S. food supply has not appreciably changed since the introduction of HFCS in the 1960s. It is unclear why HFCS would affect satiety or absorption and metabolism of fructose any differently than would sucrose. Based on the currently available evidence, the expert panel concluded that HFCS does not appear to contribute to overweight and obesity any differently than do other energy sources. Research recommendations were made to improve our understanding of the association of HFCS and weight gain. As taken from Forshee RA et al Crit Rev Food Sci Nutr. 2007; 47(6):561-82. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/17653981

"**High-fructose corn syrup causes characteristics of obesity in rats: increased body weight, body fat and triglyceride levels (Abstract).** High-fructose corn syrup (HFCS) accounts for as much as 40% of caloric sweeteners used in the United States. Some studies have shown that short-term access to HFCS can cause increased body weight, but the findings are mixed. The current study examined both short- and long-term effects of HFCS on body weight, body fat, and circulating triglycerides. In Experiment 1, male Sprague-Dawley rats were maintained for short term (8 weeks) on (1) 12 h/day of 8% HFCS, (2) 12 h/day 10% sucrose, (3) 24 h/day HFCS, all with ad libitum rodent chow, or (4) ad libitum chow alone. Rats with 12-h access to HFCS gained significantly more body weight than animals given equal access to 10% sucrose, even though they consumed the same number of total calories, but fewer calories from HFCS than sucrose. In Experiment 2, the long-term effects of HFCS on body weight and obesogenic parameters, as well as gender differences, were explored. Over the course of 6 or 7 months, both male and female rats with access to HFCS gained significantly more body weight than control groups. This increase in body weight with HFCS was accompanied by an increase in adipose fat, notably in the abdominal region, and elevated circulating triglyceride levels. Translated to humans, these results suggest that excessive consumption of HFCS may contribute to the incidence of obesity. As taken from Bocarsly ME et al. Pharmacol Biochem Behav. 2010, Nov; 97(1):101-6. PubMed, 2012 available at http://www.ncbi.nlm.nih.gov/pubmed/20219526?dopt=AbstractPlus

Role of fructose-containing sugars in the epidemics of obesity and metabolic syndrome (Abstract). There is controversy concerning the role of sugar in the epidemics of obesity and metabolic syndrome. There is less controversy concerning the effects of fructose on components of metabolic syndrome; consumption of fructose has been shown to increase visceral adipose deposition and de novo lipogenesis (DNL), produce dyslipidemia, and decrease insulin sensitivity in older, overweight/obese subjects. This

review examines the potential mechanisms of these effects of fructose and considers whether these mechanisms are relevant to the effects of consuming sucrose or high-fructose corn syrup. Evidence demonstrating that the commonly consumed sugars increase visceral adipose deposition, DNL, and insulin insensitivity is limited or inconclusive. Evidence that sugar consumption promotes development of an unfavorable lipid profile is strong and suggests that the upper added sugar consumption limit of 25% of energy or less, suggested in the Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans 2010, may merit re-evaluation. As taken from Stanhope KL. Annu Rev Med. 2012; 63:329-43. PubMed, 2012 available at http://www.ncbi.nlm.nih.gov/pubmed/22034869?dopt=AbstractPlus

“PURPOSE OF REVIEW: The effects of dietary sugar on risk factors and the processes associated with metabolic disease remain a controversial topic, with recent reviews of the available evidence arriving at widely discrepant conclusions. RECENT FINDINGS: There are many recently published epidemiological studies that provide evidence that sugar consumption is associated with metabolic disease. Three recent clinical studies, which investigated the effects of consuming relevant doses of sucrose or high-fructose corn syrup along with ad libitum diets, provide evidence that consumption of these sugars increase the risk factors for cardiovascular disease and metabolic syndrome. Mechanistic studies suggest that these effects result from the rapid hepatic metabolism of fructose catalyzed by fructokinase C, which generates substrate for de novo lipogenesis and leads to increased uric acid levels. Recent clinical studies investigating the effects of consuming less sugar, via educational interventions or by substitution of sugar-sweetened beverages for noncalorically sweetened beverages, provide evidence that such strategies have beneficial effects on risk factors for metabolic disease or on BMI in children. SUMMARY: The accumulating epidemiological evidence, direct clinical evidence, and the evidence suggesting plausible mechanisms support a role for sugar in the epidemics of metabolic syndrome, cardiovascular disease, and type 2 diabetes.” As taken from Stanhope KL et al. 2013. Curr. Opin. Lipidol. 24(3), 198-206. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/23594708

“Fifty adults were divided into five groups often (five of each sex) and orally administered BCS at 0.2, 0.3, 0.4. 0.5 and 0.6 g/kg body weight as indigestible portion. Although no diarrhea was observed in females, BCS at 0.6 g/kg as indigestible portion caused diarrhea in two out of five males. The maximum non-effective dose of indigestible portion of BCS was estimated to be 0.5 g/kg in males and more than 0.6 g/kg in females.”

As taken from Kishimoto Y et al. Acute toxicity and mutagenicity study on branched corn syrup and evaluation of its laxative effect in humans. J Nutr Sci Vitaminol (Tokyo). 2001 Apr; 47(2):126-31, PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/11508703?dopt=Abstract

Recent papers suggest that the consumption of corn syrup (particularly high-fructose corn syrup) may play a role in the epidemic of obesity (Bray et al. 2004) and of type 2 diabetes (Gross et al. 2004) in the US (and presumably other Western countries).

“It has been postulated that fructose-induced triglyceride synthesis is augmented when accompanied by glucose. Chronic elevations could lead to excess fat accumulation in the liver and ectopic fat deposition in muscles, which in turn could contribute to the induction of abnormalities in glucose homeostasis, insulin resistance, and the subsequent development

of type 2 diabetes. Our objective was to evaluate the effect of the addition of commonly consumed fructose- and (or) glucose-containing sugars in the usual diet on liver fat content and intramuscular adipose tissue. For 10 weeks, 64 individuals (mean age, 42.16 ± 11.66 years) consumed low-fat milk sweetened with either high-fructose corn syrup (HFCS) or sucrose; the added sugar matched consumption levels of fructose in the 25th, 50th, and 90th percentiles of the population. The fat content of the liver was measured with unenhanced computed tomography imaging, and the fat content of muscle was assessed with magnetic resonance imaging. When the 6 HFCS and sucrose groups were averaged, there was no change over the course of 10 weeks in the fat content of the liver (13.32% ± 10.49% vs. 13.21% ± 10.75%; P>0.05), vastus lateralis muscle (3.07 ± 0.74 g per 100 mL vs. 3.15 ± 0.84 g per 100 mL; P>0.05), or gluteus maximus muscle (4.08 ± 1.50 g per 100 mL vs. 4.24 ± 1.42 g per 100 mL; P>0.05). Group assignment did not affect the result (interaction > 0.05). These data suggest that when fructose is consumed as part of a typical diet in normally consumed sweeteners, such as sucrose or HFCS, ectopic fat storage in the liver or muscles is not promoted." As taken from Bravo S et al. 2013. Appl. Physiol. Nutr. Metab. 38(6), 681-8. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/23724887

"Peroxisome Proliferator Activated Receptor (PPAR)- δ agonists may serve for treating metabolic diseases. However, the effects of PPAR- δ agonism within the skeletal muscle, which plays a key role in whole-body glucose metabolism, remain unclear. This study aimed to investigate the signaling pathways activated in the gastrocnemius muscle by chronic administration of the selective PPAR- δ agonist, GW0742 (1 mg/kg/day for 16 weeks), in male C57Bl6/J mice treated for 30 weeks with high-fructose corn syrup (HFCS), the major sweetener in foods and soft-drinks (15% wt/vol in drinking water). Mice fed with the HFCS diet exhibited hyperlipidemia, hyperinsulinemia, hyperleptinemia, and hypoadiponectinemia. In the gastrocnemius muscle, HFCS impaired insulin and AMP-activated protein kinase signaling pathways and reduced GLUT-4 and GLUT-5 expression and membrane translocation. GW0742 administration induced PPAR- δ upregulation and improvement in glucose and lipid metabolism. Diet-induced activation of nuclear factor-κB and expression of inducible-nitric-oxide-synthase and intercellular-adhesion-molecule-1 were attenuated by drug treatment. These effects were accompanied by reduction in the serum concentration of interleukin-6 and increase in muscular expression of fibroblast growth factor-21. Overall, here we show that PPAR- δ activation protects the skeletal muscle against the metabolic abnormalities caused by chronic HFCS exposure by affecting multiple levels of the insulin and inflammatory cascades." As taken from Benetti E et al. 2013. Mediators Inflamm. 2013, 509502. PubMed, 2104 available at http://www.ncbi.nlm.nih.gov/pubmed/23861559

"Both controversy and confusion exist concerning fructose, sucrose, and high-fructose corn syrup (HFCS) with respect to their metabolism and health effects. These concerns have often been fueled by speculation based on limited data or animal studies. In retrospect, recent controversies arose when a scientific commentary was published suggesting a possible unique link between HFCS consumption and obesity. Since then, a broad scientific consensus has emerged that there are no metabolic or endocrine response differences between HFCS and sucrose related to obesity or any other adverse health outcome. This equivalence is not surprising given that both of these sugars contain approximately equal amounts of fructose and glucose, contain the same number of calories, possess the same level of sweetness, and are absorbed identically through the gastrointestinal tract. Research comparing pure fructose with pure glucose, although interesting from a scientific point of view, has limited application to human nutrition given that neither is consumed to an

appreciable degree in isolation in the human diet. Whether there is a link between fructose, HFCS, or sucrose and increased risk of heart disease, metabolic syndrome, or fatty infiltration of the liver or muscle remains in dispute with different studies using different methodologies arriving at different conclusions. Further randomized clinical trials are needed to resolve many of these issues. The purpose of this review is to summarize current knowledge about the metabolism, endocrine responses, and potential health effects of sucrose, HFCS, and fructose." As taken from Rippe JM & Angelopoulos TJ. 2013. Adv. Nutr. 4(2), 236-45. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/23493540?dopt=AbstractPlus

"Previous studies have suggested that sugars enhance iron bioavailability, possibly through either chelation or altering the oxidation state of the metal, however, results have been inconclusive. Sugar intake in the last 20 years has increased dramatically, and iron status disorders are significant public health problems worldwide; therefore understanding the nutritional implications of iron-sugar interactions is particularly relevant. In this study we measured the effects of sugars on non-heme iron bioavailability in human intestinal Caco-2 cells and HepG2 hepatoma cells using ferritin formation as a surrogate marker for iron uptake. The effect of sugars on iron oxidation state was examined by measuring ferrous iron formation in different sugar-iron solutions with a ferrozine-based assay. Fructose significantly increased iron-induced ferritin formation in both Caco-2 and HepG2 cells. In addition, high-fructose corn syrup (HFCS-55) increased Caco-2 cell iron-induced ferritin; these effects were negated by the addition of either tannic acid or phytic acid. Fructose combined with FeCl3 increased ferrozine-chelatable ferrous iron levels by approximately 300%. In conclusion, fructose increases iron bioavailability in human intestinal Caco-2 and HepG2 cells. Given the large amount of simple and rapidly digestible sugars in the modern diet their effects on iron bioavailability may have important patho-physiological consequences. Further studies are warranted to characterize these interactions." As taken from Christides T & Sharp P. 2013. PLoS One 8(12), e83031. PubMed, 2014 available at http://www.ncbi.nlm.nih.gov/pubmed/24340076

"Obesity is increasingly prevalent, strongly associated with nonalcoholic liver disease, and a risk factor for numerous cancers. Here, we describe the liver-related consequences of long-term diet-induced obesity. Mice were exposed to an extended obesity model comprising a diet high in trans-fats and fructose corn syrup concurrent with a sedentary lifestyle. Livers were assessed histologically using the nonalcoholic fatty liver disease (NAFLD) activity score (Kleiner system). Mice in the American Lifestyle-Induced Obesity Syndrome (ALIOS) model developed features of early nonalcoholic steatohepatitis at 6 months (mean NAFLD activity score = 2.4) and features of more advanced nonalcoholic steatohepatitis at 12 months, including liver inflammation and bridging fibrosis (mean NAFLD activity score = 5.0). Hepatic expression of lipid metabolism and insulin signaling genes were increased in ALIOS mice compared with normal chow-fed mice. Progressive activation of the mouse hepatic stem cell niche in response to ALIOS correlated with steatosis, fibrosis, and inflammation. Hepatocellular neoplasms were observed in 6 of 10 ALIOS mice after 12 months. Tumors displayed cytological atypia, absence of biliary epithelia, loss of reticulin, alteration of normal perivenular glutamine synthetase staining (absent or diffuse), and variable α-fetoprotein expression. Notably, perivascular tumor cells expressed hepatic stem cell markers. These studies indicate an adipogenic lifestyle alone is sufficient for the development of nonalcoholic steatohepatitis, hepatic stem cell activation, and hepatocarcinogenesis in wild-type mice." As taken from Dowman JK et al. 2014. Am. J.

Pathol. 184(5), 1550-61. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/24650559?dopt=AbstractPlus

“BACKGROUND: Nonalcoholic fatty liver disease (NAFLD) is a common liver disease in obese children. Diets high in added fructose (high fructose corn syrup; HFCS) and glycemic index (GI)/glycemic load (GL) are associated with increased risk of NAFLD. Lifestyle modification is the main treatment, but no guidelines regarding specific dietary interventions for childhood NAFLD exist. We hypothesized that reductions in dietary fructose (total, free, and HFCS)/GI/GL over 6 months would result in improvements in body composition and markers of liver dysfunction and cardiometabolic risk in childhood NAFLD. METHODS: Children and adolescents with NAFLD (n = 12) and healthy controls (n = 14) 7-18 years were studied at baseline and 3 and 6 months post-dietary intervention. Plasma markers of liver dysfunction (ALT, AST, γGT), cardiometabolic risk (TG, total cholesterol, LDL-HDL cholesterol, Apo-B100, Apo-B48, Apo-CIII, insulin, homeostasis model of assessment of insulin resistance [HOMA-IR]), inflammation (TNF-α, IL-6, IL-10), anthropometric, and blood pressure (BP) were studied using validated methodologies. RESULTS: Significant reductions in systolic BP (SBP), percentage body fat (BF), and plasma concentrations of ALT (P = .04), Apo-B100 (P <.001), and HOMA-IR were observed in children with NAFLD at 3 and 6 months (P <.05). Dietary reductions in total/free fructose/HFCS and GL were related to reductions in SBP (P = .01), ALT (P = .004), HOMA-IR (P = .03), and percentage BF in children with NAFLD. Reductions in dietary GI were associated with reduced plasma Apo-B100 (P = .02) in both groups. With the exception of Apo-B100, no changes in laboratory variables were observed in the control group. CONCLUSION: Modest reductions in fructose (total/free, HFCS) and GI/GL intake result in improvements of plasma markers of liver dysfunction and cardiometabolic risk in childhood NAFLD.” As taken from Mager DR et al. 2015. JPEN J. Parenter. Enteral. Nutr. 39(1), 73-84. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/23976771

“PURPOSE: The increased consumption of high-fructose corn syrup (HFCS) may contribute to the worldwide epidemic of fatty liver. In this study, we have investigated whether HFCS intake (20 % beverages) influences lipid synthesis and accumulation in conjunction with insulin receptor substrate-1/2 (IRS-1; IRS-2), endothelial nitric oxide synthase (eNOS), sirtuin 1 (SIRT1) and inducible NOS (iNOS) expressions in liver of rats. Resveratrol was tested for its potential efficacy on changes induced by HFCS. METHODS: Animals were randomly divided into four groups as control, resveratrol, HFCS and resveratrol plus HFCS (resveratrol + HFCS). HFCS was given as 20 % solutions in drinking water. Feeding of all rats was maintained by a standard diet that enriched with or without resveratrol for 12 weeks. RESULTS: Dietary HFCS increased triglyceride content and caused mild microvesicular steatosis in association with up-regulation of fatty acid synthase and sterol regulatory element binding protein (SREBP)-1c in liver of rats. Moreover, HFCS feeding impaired hepatic expression levels of IRS-1, eNOS and SIRT1 mRNA/proteins, but did not change iNOS level. Resveratrol promoted IRS, eNOS and SIRT1, whereas suppressed SREBP-1c expression in rats fed with HFCS. CONCLUSIONS: Resveratrol supplementation considerably restored hepatic changes induced by HFCS. The improvement of hepatic insulin signaling and activation of SIRT1 by resveratrol may be associated with decreased triglyceride content and expression levels of the lipogenic genes of the liver.” As taken from Sadi G et al. 2015. Eur. J. Nutr. 54(6), 895-904. PubMed, 2016 available at: http://www.ncbi.nlm.nih.gov/pubmed/25238689

“OBJECTIVE: To evaluate the trends in the American diet over the last 40 years (1974-2010), during which time the National Health and Nutrition Examination Survey data set has documented an increase in stone prevalence from 3.8% to 8.8%. MATERIALS AND METHODS: We used the National Health and Nutrition Examination Survey reported rates for stone disease (1974-2010) to compare the United States Department of Agriculture's food distribution data during the same period. Three data points for prevalence were used from the literature. We correlated these to changing lithogenic food distributions using linear models to interpolate annual changes in prevalence. Spearman correlations were performed (P ≤.05) using SAS 9.2 (SAS Institute, Cary, NC). RESULTS: Increased total daily calories (rho, 0.96; P<.001), fat (rho, 0.79; P<.001), protein (rho, 0.85; P<.001), fruit (rho, 0.6; P = .01), and vegetables (rho, 0.73; P<.001) correlated strongly with increasing stone prevalence. Dark green vegetables, flour or cereal products, fish or shellfish, corn products (including high fructose corn syrup), and added sugars also showed strong correlations with stone prevalence. Citrus fruits were negatively correlated to stone disease (rho, -0.18; P = .31). Protein, fruits and vegetables, and added sugars actually decreased in proportion to daily caloric per capita increases. CONCLUSION: Increases in caloric intake and several lithogenic foods correlate temporally with increasing stone prevalence. The nature of this relationship is difficult to determine from this data; although, clearly, American diets have changed over the last 4 decades.” As taken from De SK et al. 2014. Urology 84(5), 1030-3. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/25201150

“An epidemic of obesity and type 2 diabetes is linked with the increase in consumption of fructose-containing sugars, such as sucrose and high fructose corn syrup (HFCS). In mammalian cells, fructose is metabolized predominantly via phosphorylation to fructose-1 phosphate by ketohexokinase (KHK) or by alternative pathways. Here we demonstrate that KHK-dependent pathway mediates insulin resistance and inflammatory changes in the visceral fat in response to high fructose.We used mice (males, C57BL/6 background) including littermate wild type control and mice lacking both isoforms of KHK (KHK-null).Fructose diet induced metabolic syndrome including visceral obesity, insulin resistance, proinflammatory changes in the visceral fat (production of proinflammatory adipokines and macrophage infiltration), the endoplasmic reticulum (ER) stress signaling, and decrease of the high molecular weight (HMW) adiponectin followed by decrease in the downstream signaling. KHK-KO mice consuming the same high fructose diet remained lean, with normal insulin sensitivity and healthy visceral adipose tissue with normal adiponectin function not distinguishable from the control by any of the tested parameters.This study demonstrates that blocking KHK and redirecting fructose metabolism to alternative pathways is an effective way to prevent visceral obesity and insulin resistance induced by high fructose, a widespread component of Western diets.” As taken from Marek G et al. 2015. Diabetes 64(2), 508-18. PubMed, 2016 available at: http://www.ncbi.nlm.nih.gov/pubmed/25187370

“BACKGROUND: Concerns have been raised about the concurrent temporal trend between simple sugar intakes, especially of fructose or high-fructose corn syrup (HFCS), and rates of nonalcoholic fatty liver disease (NAFLD) in the United States. OBJECTIVE: We examined the effect of different amounts and forms of dietary fructose on the incidence or prevalence of NAFLD and indexes of liver health in humans. DESIGN: We conducted a systematic review of English-language, human studies of any design in children and adults with low to no alcohol intake and that reported at least one predetermined measure of liver health. The strength of the evidence was evaluated by considering risk of bias, consistency, directness, and precision. RESULTS: Six observational studies and 21 intervention studies met the

inclusion criteria. The overall strength of evidence for observational studies was rated insufficient because of high risk of biases and inconsistent study findings. Of 21 intervention studies, 19 studies were in adults without NAFLD (predominantly healthy, young men) and 1 study each in adults or children with NAFLD. We found a low level of evidence that a hypercaloric fructose diet (supplemented by pure fructose) increases liver fat and aspartate aminotransferase (AST) concentrations in healthy men compared with the consumption of a weight-maintenance diet. In addition, there was a low level of evidence that hypercaloric fructose and glucose diets have similar effects on liver fat and liver enzymes in healthy adults. There was insufficient evidence to draw a conclusion for effects of HFCS or sucrose on NAFLD. CONCLUSIONS: On the basis of indirect comparisons across study findings, the apparent association between indexes of liver health (ie, liver fat, hepatic de novo lipogenesis, alanine aminotransferase, AST, and γ-glutamyl transpeptase) and fructose or sucrose intake appear to be confounded by excessive energy intake. Overall, the available evidence is not sufficiently robust to draw conclusions regarding effects of fructose, HFCS, or sucrose consumption on NAFLD." As taken from Chung M et al. 2014. Am. J. Clin. Nutr. 100(3), 833-49. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/25099546

"AIM: To develop an animal model that encompasses the different facets of non-alcoholic steatohepatitis (NASH), which has been a challenge. METHODS: In this study, we used a high fat diet (HFD) feeding supplemented with fructose and sucrose in the water mimicking the high-fructose corn syrup that is abundant in the diet in the United States. We used C57Bl/6 wild-type mice for short and long-term feedings of 6 and 16 wk respectively, and evaluated the extent of liver damage, steatosis, and inflammasome activation. Our methods included histopathological analysis to assess liver damage and steatosis, which involved H and E and oil-red-o staining; biochemical studies to look at ALT and triglyceride levels; RNA analysis using quantitative polymerase chain reaction; and cytokine analysis, which included the enzyme-linked immunosorbent assay method to look at interleukin (IL)-1β and tumor necrosis factor-α (TNFα) levels. Furthermore, at each length of feeding we also looked at insulin resistance and glucose tolerance using insulin tolerance tests (ITT) and glucose tolerance tests. RESULTS: There was no insulin resistance, steatosis, or inflammasome activation at 6 wk. In contrast, at 16 wk we found significant insulin resistance demonstrated by impaired glucose and ITT in male, but not female mice. In males, elevated alanine aminotransferase and triglyceride levels, indicated liver damage and steatosis, respectively. Increased liver TNFα and monocyte chemoattractant protein-1 mRNA and protein, correlated with steatohepatitis. The inflammasome components, adaptor molecule, Aim2, and NOD-like receptor 4, increased at the mRNA level, and functional inflammasome activation was indicated by increased caspase-1 activity and IL-1β protein levels in male mice fed a long-term HFD. Male mice on HFD had increased α-smooth muscle actin and pro-collagen-1 mRNA indicating evolving fibrosis. In contrast, female mice displayed only elevated triglyceride levels, steatosis, and no fibrosis. CONCLUSION: Our data indicate gender differences in NASH. Male mice fed a long-term HFD display steatohepatitis and inflammasome activation, whereas female mice have steatosis without inflammation." As taken from Ganz M et al. 2014. World J. Gastroenterol. 20(26), 8525-34. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/25024607

"This review examines the current evidence of the relationship between sugar consumption and the development of retinal and other eye diseases including diabetic retinopathy, hypertensive retinopathy, age-related macular degeneration, non-arteritic anterior ischaemic

optic neuropathy and cataract. Sucrose is comprised of fructose and glucose. Sugar consumption has increased five-fold over the last century, with high quantities of sucrose and high-fructose corn syrup found in processed food and soft drinks. This increased consumption is increasingly recognized as a central factor in the rapidly rising rates of obesity and type 2 diabetes. The body metabolizes fructose and glucose differently, with fructose appearing to have the greater propensity to contribute to the metabolic syndrome. This review examines the effect of high rates of dietary consumption of refined carbohydrates on the eye, including the effect of chronic hyperglycaemia on microvascular disease in diabetic retinopathy, and the pathophysiological changes in the retinal circulation in hypertensive retinopathy." As taken from Kearney FM et al. 2014. Clin. Experiment. Ophthalmol. 42(6), 564-73. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/24373051

"Abstract Context: Metabolic syndrome and non-alcoholic fatty liver disease (NAFLD) are the emerging co-morbidities of skin inflammation. Occurrence of skin inflammation such as psoriasis is substantially higher in NAFLD patients than normal. Currently, there are no animal models to study the interaction between these co-morbidities. Objective: The present study seeks to develop a simple mouse model of NAFLD-enhanced skin inflammation and to study the effect of NAFLD on different parameters of skin inflammation. Materials and method: Metabolic syndrome and NAFLD were induced in C57BL/6 mice by feeding high-fat diet (HFD, 60% kcal) and high fructose liquid (HFL, 40% kcal) in drinking water. Skin inflammation was induced by repeated application of oxazolone (1% sensitization and repeated 0.5% challenge) in both normal and NAFLD mice and various parameters of skin inflammation and NAFLD were measured. Results: HFD and HFL diet induced obesity, hyperglycemia, hyperinsulinemia, and histological features of NAFLD in mice. Oxazolone challenge significantly increased ear thickness, ear weight, MPO activity, NF-κB activity, and histological features of skin inflammation in NAFLD mice as compared with normal mice. Overall, induction of oxazolone-induced skin inflammation was more prominent in NAFLD mice than normal mice. Hence, HFD and HFL diet followed by topical oxazolone application develops metabolic syndrome, NAFLD, and enhanced skin inflammation in mice. Discussion and conclusion: This simple model can be utilized to evaluate a therapeutic strategy for the treatment of metabolic syndrome and NAFLD with skin inflammation and also to understand the nexus between these co-morbidities." As taken from Kulkami NM et al. 2015. Pharm. Biol. 53(8), 1110-7. PubMed, 2016 available at: http://www.ncbi.nlm.nih.gov/pubmed/25430922

"BACKGROUND: Intake of added sugar has been shown to correlate with many human metabolic diseases, and rodent models have characterized numerous aspects of the resulting disease phenotypes. However, there is a controversy about whether differential health effects occur because of the consumption of either of the two common types of added sugar-high-fructose corn syrup (fructose and glucose monosaccharides; F/G) or table sugar (sucrose, a fructose and glucose disaccharide). OBJECTIVES: We tested the equivalence of sucrose- vs. F/G-containing diets on mouse (Mus musculus) longevity, reproductive success, and social dominance. METHODS: We fed wild-derived mice, outbred mice descended from wild-caught ancestors, a diet in which 25% of the calories came from either an equal ratio of F/G or an isocaloric amount of sucrose (both diets had 63% of total calories as carbohydrates). Exposure lasted 40 wk, starting at weaning (21 d of age), and then mice (104 females and 56 males) were released into organismal performances assays-seminatural enclosures where mice competed for territories, resources, and mates for 32 wk. Within enclosures all mice consumed the F/G diet.

RESULTS: Females initially fed the F/G diet experienced a mortality rate 1.9 times the rate (P = 0.012) and produced 26.4% fewer offspring than females initially fed sucrose (P = 0.001). This reproductive deficiency was present before mortality differences, suggesting the F/G diet was causing physiologic performance deficits prior to mortality. No differential patterns in survival, reproduction, or social dominance were observed in males, indicating a sex-specific outcome of exposure. CONCLUSION: This study provides experimental evidence that the consumption of human-relevant levels of F/G is more deleterious than an isocaloric amount of sucrose for key organism-level health measures in female mice." As taken from Ruff JS et al. 2015. J. Nutr. 145(3), 434-41. PubMed, 2016 available at http://www.ncbi.nlm.nih.gov/pubmed/25733457

"High-fructose corn syrup-55 (HFCS-55) has been suggested to be more lipogenic than sucrose, which increases the risk for nonalcoholic fatty liver disease (NAFLD) and dyslipidemia. The study objectives were to determine the effects of drinking different sugar-sweetened solutions on hepatic gene expression in relation to liver fatty acid composition and risk of NAFLD. Female rats were randomly assigned (n=7 rats/group) to drink water or water sweetened with 13% (w/v) HFCS-55, sucrose or fructose for 8 weeks. Rats drinking HFCS-55 solution had the highest (P=.03) hepatic total lipid and triglyceride content and histological evidence of fat infiltration. Rats drinking HFCS-55 solution had the highest hepatic de novo lipogenesis indicated by the up-regulation of stearoyl-CoA desaturase-1 and the highest (P<.001) oleic acid (18:1n-9) content. This was accompanied by reduced β-oxidation indicated by down-regulation of hepatic peroxisome proliferator-activated receptor α. Disposal of excess lipids by export of triglyceride-rich lipoprotein from the liver was increased as shown by up-regulation of gene expression of microsomal triglyceride transfer protein in rats drinking sucrose, but not HFCS-55 solution. The observed lipogenic effects were attributed to the slightly higher fructose content of HFCS-55 solution in the absence of differences in macronutrient and total caloric intake between rats drinking HFCS-55 and sucrose solution. Results from gene expression and fatty acid composition analysis showed that, in a hypercaloric state, some types of sugars are more detrimental to the liver. Based on these preclinical study results, excess consumption of caloric sweetened beverage, particularly HFCS-sweetened beverages, should be limited." As taken from Mock K et al. 2017. J. Nutr. Biochem. 39, 32-39. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/27768909

"BACKGROUND: Sugar-sweetened beverage (SSB) consumption and low-grade chronic inflammation are both independently associated with type 2 diabetes and cardiovascular disease. Fructose, a major component of SSBs, may acutely trigger inflammation, which may be one link between SSB consumption and cardiometabolic disease. OBJECTIVE: We sought to determine whether beverages sweetened with fructose, high-fructose corn syrup (HFCS), and glucose differentially influence systemic inflammation [fasting plasma C-reactive protein and interleukin-6 (IL-6) as primary endpoints] acutely and before major changes in body weight. Secondary endpoints included adipose tissue inflammation, intestinal permeability, and plasma fetuin-A as potential mechanistic links between fructose intake and low-grade inflammation. DESIGN: We conducted a randomized, controlled, double-blind, crossover design dietary intervention (the Diet and Systemic Inflammation Study) in 24 normal-weight to obese adults without fructose malabsorption. Participants drank 4 servings/d of fructose-, glucose-, or HFCS-sweetened beverages accounting for 25% of estimated calorie requirements while consuming a standardized diet ad libitum for three 8-d periods. RESULTS: Subjects consumed 116% of their estimated calorie requirement while drinking the beverages with no difference in total energy intake or body

weight between groups as reported previously. Fasting plasma concentrations of C-reactive protein and IL-6 did not differ significantly at the end of the 3 diet periods. We did not detect a consistent differential effect of the diets on measures of adipose tissue inflammation except for adiponectin gene expression in adipose tissue (P = 0.005), which was lowest after the glucose phase. We also did not detect consistent evidence of a differential impact of these sugars on measures of intestinal permeability (lactulose:mannitol test, plasma zonulin, and plasma lipopolysaccharide-binding protein). CONCLUSION: Excessive amounts of fructose, HFCS, and glucose from SSBs consumed over 8 d did not differentially affect low-grade chronic systemic inflammation in normal-weight to obese adults." As taken from Kuzma JN et al. 2016. Am. J. Clin. Nutr. 104(2), 306-14. PubMed, 2017 available at https://www.ncbi.nlm.nih.gov/pubmed/27357093

"Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome; its rising prevalence parallels the rise in obesity and diabetes. Historically thought to result from overnutrition and a sedentary lifestyle, recent evidence suggests that diets high in sugar (from sucrose and/or high-fructose corn syrup [HFCS]) not only increase the risk of NAFLD, but also non-alcoholic steatohepatitis (NASH). Herein, we review the experimental and clinical evidence that fructose precipitates fat accumulation in the liver, due to both increased lipogenesis and impaired fat oxidation. Recent evidence suggests that the predisposition to fatty liver is linked to the metabolism of fructose by fructokinase C, which results in ATP consumption, nucleotide turnover and uric acid generation that mediate fat accumulation. Alterations to gut permeability, the microbiome, and associated endotoxemia contribute to the risk of NAFLD and NASH. Early clinical studies suggest that reducing sugary beverages and total fructose intake, especially from added sugars, may have a significant benefit on reducing hepatic fat accumulation. We suggest larger, more definitive trials to determine if lowering sugar/HFCS intake, and/or blocking uric acid generation, may help reduce NAFLD and its downstream complications of cirrhosis and chronic liver disease." As taken from Jensen T et al. 2018. J. Hepatol. 68(5), 1063-1075. PubMed, 2018 available at https://www.ncbi.nlm.nih.gov/pubmed/29408694

"Non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) are among the most common causes of chronic liver diseases in the westernized world. NAFLD and ALD are frequently accompanied by extrahepatic complications, including hepatocellular carcinoma and cardiovascular diseases, which have a negative impact on patient survival. The chronic ingestion of an excessive daily diet containing sugar/high-fructose corn syrup increases the level of the fructose/glucose metabolite, glyceraldehyde (GA), while the chronic consumption of an excessive number of alcoholic beverages increases the level of the alcohol metabolite, acetaldehyde (AA) in the liver. GA and AA are known to react non-enzymatically with the ε- or α-amino groups of proteins, thereby generating advanced glycation end-products (AGEs, GA-AGEs, and AA-AGEs, respectively) in vivo. The interaction between GA-AGEs and the receptor for AGEs (RAGE) alters intracellular signaling, gene expression, and the release of pro-inflammatory molecules and also elicits the production of reactive oxygen species by human hepatocytes and hepatic stellate cells, all of which may contribute to the pathological changes associated with chronic liver diseases. We herein discuss the pathophysiological roles of GA-AGEs and AA-AGEs (toxic AGEs, TAGE) and a related novel theory for preventing the onset/progression of NAFLD and ALD." As taken from Takeuchi M et al. 2017. Nutrients 9(6), E634. PubMed, 2018 available at https://www.ncbi.nlm.nih.gov/pubmed/28632197

“Fatty liver disease affects up to one out of every two adults in the western world. Data from animal and human studies implicate added sugars (eg, sucrose and high-fructose corn syrup) in the development of fatty liver disease and its consequences. Added fructose in particular, as a component of added sugars, may pose the greatest risk for fatty liver disease. Considering that there is no requirement for added sugars in the diet, dietary guidelines should recommend reducing the intake of added sugars to just 5% of total calories in order to decrease the prevalence of fatty liver disease and its related consequences.” As taken from DiNicolantonio JJ et al. 2017. Open Heart 4(2), e000631. PubMed, 2018 available at https://www.ncbi.nlm.nih.gov/pubmed/29118995

“Dramatic increases in obesity and diabetes have occurred worldwide over the past 30 years. Some investigators have suggested that these increases may be due, in part, to increased added sugars consumption. Several scientific organizations, including the World Health Organization, the Scientific Advisory Council on Nutrition, the Dietary Guidelines Advisory Committee 2015, and the American Heart Association, have recommended significant restrictions on upper limits of sugars consumption. In this review, the scientific evidence related to sugars consumption and its putative link to various chronic conditions such as obesity, diabetes, heart disease, nonalcoholic fatty liver disease, and the metabolic syndrome is examined. While it appears prudent to avoid excessive calories from sugars, the scientific basis for restrictive guidelines is far from settled.” As taken from Rippe JM et al. 2017. Nutr. Rev. 75(1), 18-36. PubMed, 2018 available at https://www.ncbi.nlm.nih.gov/pubmed/27974597

“OBJECTIVE: The use of high fructose corn syrup in the food and beverage industry has shown an increase in the past few decades. Our aims were to evaluate the role of HFCS in inducing nonalcoholic fatty liver disease (NAFLD) and following conditions such as nonalcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. METHODS: In this study, we browsed through the PubMed database by entering the keywords “non-alcoholic fatty liver disease”, “fructose”, “fibrosis” and “cirrhosis”. We also included Basaranoglu’s previous extensive research studies on fructose, NAFLD and NASH. RESULTS: The adverse effects of high fructose corn syrup (HFCS) in cirrhosis formation were demonstrated in animal studies. When mice were fed with excessive trans fat, they developed NASH, however cirrhosis formation was not observed. When the mice were fed a combination of trans fat and HFCS, cirrhosis formation was completed. CONCLUSION: The increased consumption of fructose from food and beverages and the rising rates of obesity have shown a parallel increase. The prevalence of NAFLD, a condition that is associated with obesity, hyperlipidemia and insulin resistance has also shown a similar increase, which may progress to more severe forms such as cirrhosis. In conclusion, we have identified the excessive consumption of fructose in the form of HFCS as a key contributor to the development of cirrhosis.” As taken from Sahin S & Basaranoglu M 2018. Appl. Food Sci. J. 2(1), 8-9. Available at https://www.pulsus.com/scholarly-articles/high-fructose-corn-syrup-hfcs-plays-a-dominant-role-in-the-pathogenesis-of-nafldassociated-cirrhosis-3889.html

“The contribution of high fructose corn syrup (HFCS) to metabolic disorder and obesity, independent of high fat, energy-rich diets, is controversial. While high-fat diets are widely accepted as a rodent model of diet-induced obesity (DIO) and metabolic disorder, the value of HFCS alone as a rodent model of DIO is unclear. Impaired dopamine function is associated with obesity and high fat diet, but the effect of HFCS on the dopamine system has not been investigated. The objective of this study was to test the effect of HFCS on weight gain, glucose regulation, and evoked dopamine release using fast-scan cyclic

voltammetry. Mice (C57BL/6) received either water or 10% HFCS solution in combination with ad libitum chow for 15 weeks. HFCS consumption with chow diet did not induce weight gain compared to water, chow-only controls but did induce glucose dysregulation and reduced evoked dopamine release in the dorsolateral striatum. These data show that HFCS can contribute to metabolic disorder and altered dopamine function independent of weight gain and high-fat diets." As taken from Meyers AM et al. 2017. PLoS One 12(12), e0190206. PubMed, 2018 available at https://www.ncbi.nlm.nih.gov/pubmed/29287121

"OBJECTIVE: This study sought to understand how the dietary source of carbohydrates, either high-fructose corn syrup (HFCS) or complex carbohydrates, affects energy expenditure (EE) measures, appetitive sensations, and hormones during 24 hours of overfeeding. METHODS: Seventeen healthy participants with normal glucose regulation had 24-hour EE measures and fasting blood and 24-hour urine collection during four different 1-day diets, including an energy-balanced diet, fasting, and two 75% carbohydrate diets (5% fat) given at 200% of energy requirements with either HFCS or whole-wheat foods as the carbohydrate source. In eight volunteers, hunger was assessed with visual analog scales the morning after the diets. RESULTS: Compared with energy balance, 24-hour EE increased 12.8% ± 6.9% with carbohydrate overfeeding ($P < 0.0001$). No differences in 24-hour EE or macronutrient utilization were observed between the two high-carbohydrate diets; however, sleeping metabolic rate was higher after the HFCS diet ($\Delta = 35 \pm 48$ kcal [146 ± 200 kJ]; $P = 0.01$). Insulin, ghrelin, and triglycerides increased the morning after both overfeeding diets. Urinary cortisol concentrations (82.8 ± 35.9 vs. 107.6 ± 46.9 nmol/24 h; $P = 0.01$) and morning-after hunger scores ($\Delta = 2.4 \pm 2.0$ cm; $P = 0.01$) were higher with HFCS overfeeding. CONCLUSIONS: The dietary carbohydrate source while overeating did not affect 24-hour EE, but HFCS overconsumption may predispose individuals to further overeating due to increased glucocorticoid release and increased hunger the following morning." As taken from Ibrahim M et al. 2018. Obesity (Silver Spring) 26(1), 141-149. PubMed, 2018 available at https://www.ncbi.nlm.nih.gov/pubmed/29193741

"Objective: Intake of sugary drinks, especially soft drinks, carries increased risk for obesity and diabetes. This article reviews whether sugary drinks carry different risks for metabolic syndrome compared with foods that contain natural or added sugars. Methods: A narrative review was performed to evaluate differences between liquid and solid sugars in their ability to induce metabolic syndrome and to discuss potential mechanisms to account for the differences. Results: Epidemiological studies support liquid added sugars, such as soft drinks, as carrying greater risk for development of metabolic syndrome compared with solid sugar. Some studies suggest that fruit juice may also confer relatively higher risk for weight gain and insulin resistance compared with natural fruits. Experimental evidence suggests this may be due to differences in how fructose is metabolized. Fructose induces metabolic disease by reducing the energy levels in liver cells, mediated by the concentration of fructose to which the cells are exposed. The concentration relates to the quantity and speed at which fructose is ingested, absorbed, and metabolized. Conclusions: Although reduced intake of added sugars (sucrose and high-fructose corn syrup) remains a general recommendation, there is evidence that sugary soft drinks may provide greater health risks relative to sugar-containing foods." As taken from Sundborn G et al. 2019. Obesity (Silver Spring) 27(6), 879-887. PubMed, 2020 available at: https://pubmed.ncbi.nlm.nih.gov/31054268/

“Fructose intake has been associated with non-alcoholic fatty liver disease (NAFLD). The objective of this study was to assess the consumption of dietary fructose according to: 1) classification of hepatic steatosis by two indexes and 2) diagnosis of NAFLD by MRI. We conducted a cross-sectional analysis among 100 young adults from Mexico City. The Hepatic Steatosis Index (HSI) and the Fatty Liver Index (FLI) were estimated using Body Mass Index (BMI), waist circumference, and fasting concentrations of glucose, triglycerides, and hepatic enzymes (ALT, AST, GGT). A semi-quantitative food frequency questionnaire was administered to obtain dietary sources of fructose. We estimated the concordance between the hepatic indices and NAFLD and the correlation between the index scores and the percentage of liver fat. Eighteen percent presented NAFLD; 44% and 46% were classified with hepatic steatosis according to HSI and FLI, respectively. We compared dietary intake of fructose by each outcome: HSI, FLI, and NAFLD. Sugar-sweetened beverages (SSB) and juices were consumed significantly more by those with steatosis by FLI and NAFLD suggesting that SSB intake is linked to metabolic alterations that predict the risk of having NAFLD at a young age.” As taken from Cantoral A et al. 2019. Nutrients 11(3), pii: E522. PubMed, 2019 available at: https://www.ncbi.nlm.nih.gov/pubmed/30823422

“Modern diets have become increasingly rich in fructose, for example through the addition of high-fructose corn syrup to many foods and drinks. It has been suggested that this might lead to hepatotoxicity, including the development of non-alcoholic fatty liver disease. After entering hepatocytes via insulin-independent glucose transporter 2 transmembrane carrier proteins, fructose is phosphorylated to fructose-1-phosphate in a reaction catalysed by fructokinase (ketohexokinase). In turn, fructose-1-phosphate is hydrolysed by aldolase B to glyceraldehydes. Glyceraldehydes may enter gluconeogenesis via fructose-1,6-bisphosphate and fructose-6-phosphate; glyceraldehydes may also enter glycogenolysis via pyruvate. The last pathway involves conversion of pyruvate to acetyl-CoA. Alternatively, pyruvate may be converted, via the action of the hepatic lactate dehydrogenase isoenzyme LDH-5, into lactate. In liver damage, the LDH-5 isoenzyme becomes elevated, predominantly in serum/plasma. We therefore hypothesised that if dietary fructose is associated with hepatotoxicity, there should be a positive correlation between erythrocyte fructose-6-phosphate and plasma LDH-5. This hypothesis was tested by assaying venous blood samples taken from 39 patients at rest, three hours after eating. Quantitative Fourier transform infrared spectrometry following gel electrophoresis was used to assay erythrocyte fructose-6-phosphate levels. Similarly, plasma LDH-5 concentrations were spectrophotometrically analysed, using the pyruvate-lactate reaction, following electrophoretic separation of the LDH isoenzymes. A significant positive correlation was found between the two variables ($r = 0.44$, $p = 0.0047$). This result, which supports our hypothesis, is evidence in favour of the possibility that dietary fructose is associated with hepatotoxicity. In addition to being a marker of hepatic damage, LDH-5 may play a more direct epigenetic role in causing liver damage; acute hepatic injury is associated with nuclear translocation of LDH, causing the production of lactate from pyruvate in the nucleus; in turn, the lactate inhibits histone deacetylase and is associated with upregulation of genes associated with the damage response, leading to cell death.” As taken from Puri BK et al. 2019. Med. Hypotheses 124, 40-41. PubMed, 2019 available at: https://www.ncbi.nlm.nih.gov/pubmed/30798914

“Scientific evidence has identified that the excessive consumption of products made from high-fructose corn syrup is a trigger for obesity, whose prevalence increased in recent years. Due to the metabolic characteristics of fructose, a rapid gastric emptying is produced, altering signals of hunger-satiety and decreasing the appetite. In addition to the hepatic level during catabolism, triose phosphate is generated and adenosine triphosphate (ATP) is reduced, producing uric acid. Triose phosphate triggers the synthesis of fatty acids that increase the production and accumulation of triglycerides, diacylglycerols and ceramides that induce insulin resistance. Hyperlipidemia, insulin resistance and hyperuricemia contribute to the development of hypertension, cardiovascular disease, kidney failure, non-alcoholic fatty liver disease and some kinds of cancer. Understanding the molecular mechanisms and signaling pathways altered by the consumption of fructose is relevant to understand the development of metabolic diseases, as well as to seek therapeutic strategies to improve quality of life.” As taken from Loza-Medrano SS et al. 2019. Rev. Med. Inst. Mex. Seguro Soc. 56(5), 491-504. PubMed, 2019 available at: https://www.ncbi.nlm.nih.gov/pubmed/30777418

“Background: The consumption of high amounts of fructose is associated with metabolic diseases. However, the underlying mechanisms are largely unknown. Objective: To determine the effects of high fructose intake on plasma metabolomics. Study design: We enrolled 12 healthy volunteers (six lean and six obese women, age 24–35 years) in a crossover intervention study. All participants carried out three diets: (1) low fructose (<10 g/day); (2) high fructose (100 g/day) from natural food sources (fruit); and (3) high fructose (100 g/day) from high fructose syrup (HFS). Outcome measures: The primary outcome was changes in plasma metabolites measured by targeted metabolomics. Results: High compared to low fructose diets caused a marked metabolite class separation, especially because of changes in acylcarnitine and lysophosphatidylcholine levels. Both high fructose diets resulted in a decrease in mean acylcarnitine levels in all subjects, and an increase in mean lysophosphatidylcholine and diacyl-phosphatidylcholine levels in obese individuals. Medium chain acylcarnitines were negatively correlated with serum levels of liver enzymes and with the fatty liver index. Discussion: The metabolic shifts induced by high fructose consumption suggest an inhibition of mitochondrial β-oxidation and an increase in lipid peroxidation. The effects tended to be more pronounced following the HFS than the fruit diet.” As taken from Gonzalez-Granda A et al. 2018. Nutrients 10(9), pii: E1254. PubMed, 2019 available at: https://www.ncbi.nlm.nih.gov/pubmed/30200659

“Fructose-, compared to glucose-, sweetened beverages increase liver triglyceride content in the short-term, prior to weight gain. In secondary analyses of a randomized cross-over design study during which 24 healthy adults consumed 25% of their estimated energy requirement in the form of glucose-, fructose-, and high-fructose corn syrup-sweetened beverages in addition to an identical ad libitum diet for three periods of 8 days each, we investigated the hypothesis that fructose in sweetened beverages also triggers insulin resistance in the short term. Total energy intake, body weight, and fasting glucose did not differ among diet phases. However, there was a significant trend for higher fasting insulin ($p = 0.042$ for trend) and, among normal-weight participants, homeostasis model assessment index of insulin resistance ($p = 0.034$ for diet × adiposity interaction) according to the glucose content of the beverages. In conclusion, in contrast to our hypothesis, insulin resistance was increased with higher glucose vs. fructose content of the beverages in this

short-term trial." As taken from Kuzma JN et al. 2019. Eur. J. Clin. Nutr. 73(3), 487-490. PubMed, 2019 available at: https://www.ncbi.nlm.nih.gov/pubmed/30166639

"BACKGROUND: The pathogenesis of nonalcoholic fatty liver disease as a component of metabolic syndrome (MetS) involves the activation of apoptosis in steatotic hepatocytes. Caspase-generated fragments such as cytokeratin-18 (CK-18) in patients with various hepatic impairments are investigated as markers for diagnosis and assessment of disease severity. The goal of the study was to capture early biomarkers of apoptosis and elucidate their role in assessing the presence and extent of hepatic damage in a MetS model. MATERIALS AND METHODS: We used male Wistar rats, divided into two groups (n = 7): control and high-fructose drinking (HFD) (35% fructose corn syrup for 16 weeks). Metabolic disorders and liver damage were studied by histochemistry (hematoxylin and eosin), immunohistochemical, immunological, and biochemical testing. RESULTS: Our results showed significant increase in liver and serum levels of CK-18 and pro/antiapoptotic Bax/Bcl2 ratio, and decreased levels of HMGB1 (marker of necrosis) in the HFD group when compared with the control. All HFD rats developed obesity, hyperglycemia, hepatomegaly, microvesicular steatosis, an imbalance in hepatic antioxidative defense by measuring malondialdehyde and sulfhydryl groups (SH) with no inflammation and fibrosis, elevated serum levels of triglycerides, tumor necrosis factor alpha (TNF-α), and C-reactive protein without changes in serum aminotransferase levels relative to the control group. As a result of the applied regression analysis, we have determined that the variables TNF-α (0.92) and SH (0.659) have a strong complex effect on hepatic CK-18 levels with predicted value of the model R = 0.9. CONCLUSION: The elevated CK-18 serum levels in the HFD group and their association with the histological changes in the liver and biochemical indicators demonstrate the key role of apoptosis in the pathogenesis of HFD-induced liver damage and the reliability of CK-18 as a biomarker for noninvasive assessment of liver damages in MetS." As taken from Bratoeva K et al. 2018. Metab. Syndr. Relat. Disord. 16(7), 350-357. PubMed, 2019 available at: https://www.ncbi.nlm.nih.gov/pubmed/29989845

"Background: Over the past 50 years, the average consumption of sugar worldwide has tripled, also the type of consumed sugar has changed. Due to high price of sucrose and its technological disadvantages, high fructose corn syrup (HFCS) has become one of the most commonly used substitutes. Objective: The aim of the study was to compare, on the animal model, the effect of sugar type (sucrose vs high fructose corn syrup 55% of fructose) and the sugar form (solid vs fluid and solid) on the chosen parameters of carbohydrate-lipid metabolism. Material and methods: The experiment was carried out on 40 Wistar male rats aged 5 months, fed four isocaloric diets, containing: group I (SUC 15%) fodder with 15% sucrose, group II (HFCS 15%) fodder with 15% HFCS-55%, group III (SUC 7.5%+7.5%) – 7.5% sucrose in solid fodder and 7.5% sucrose water solution, group IV (HFCS 7.5%+7.5%) – 7.5% HFCS-55% in solid fodder and 7.5% HFCS water solution. Results: The effect of HFCS-55 on the parameters of carbohydrate and lipid metabolism was not equivalent of the effect of sucrose. Dietary use of HFCS-55 instead of sucrose causes adverse changes in blood parameters of carbohydrate and lipid metabolism, particularly when provided in beverages, as at comparable weight gains to that of sucrose. More intense changes, manifesting in increased blood levels of glucose, triglycerides and uric acid, as well as increased liver fat content, were observed at simultaneous intake of sweeteners in solid foods and fluids, even with less sugar consumption, compared to solid

food only. Conclusions: Dietary use of HFCS-55 causes adverse changes in blood parameters of carbohydrate and lipid metabolism, as at comparable weight gains to that of sucrose. But liquid form of sugar intake is more important insulin resistance and cardiovascular disease risk factor than the sugar type." As taken from Sadowska J and Bruszkowska M. et al. 2019. Rocz. Panstw. Zakl. Hig. 70(1), 59-67. PubMed, 2019 available at: https://www.ncbi.nlm.nih.gov/pubmed/30837747

"OBJECTIVE: To assess the effect of different food sources of fructose-containing sugars on glycaemic control at different levels of energy control. DESIGN: Systematic review and meta-analysis of controlled intervention studies. DATA SOURCES: Medine, Embase, and the Cochrane Library up to 25 April 2018. ELIGIBILITY CRITERIA FOR SELECTING STUDIES: Controlled intervention studies of at least seven days' duration and assessing the effect of different food sources of fructose-containing sugars on glycaemic control in people with and without diabetes were included. Four study designs were prespecified on the basis of energy control: substitution studies (sugars in energy matched comparisons with other macronutrients), addition studies (excess energy from sugars added to diets), subtraction studies (energy from sugars subtracted from diets), and ad libitum studies (sugars freely replaced by other macronutrients without control for energy). Outcomes were glycated haemoglobin (HbA1c), fasting blood glucose, and fasting blood glucose insulin. DATA EXTRACTION AND SYNTHESIS: Four independent reviewers extracted relevant data and assessed risk of bias. Data were pooled by random effects models and overall certainty of the evidence assessed by the GRADE approach (grading of recommendations assessment, development, and evaluation). RESULTS: 155 study comparisons (n=5086) were included. Total fructose-containing sugars had no harmful effect on any outcome in substitution or subtraction studies, with a decrease seen in HbA1c in substitution studies (mean difference -0.22% (95% confidence interval to -0.35% to -0.08%), -25.9 mmol/mol (-27.3 to -24.4)), but a harmful effect was seen on fasting insulin in addition studies (4.68 pmol/L (1.40 to 7.96)) and ad libitum studies (7.24 pmol/L (0.47 to 14.00)). There was interaction by food source, with specific food sources showing beneficial effects (fruit and fruit juice) or harmful effects (sweetened milk and mixed sources) in substitution studies and harmful effects (sugars-sweetened beverages and fruit juice) in addition studies on at least one outcome. Most of the evidence was low quality. CONCLUSIONS: Energy control and food source appear to mediate the effect of fructose-containing sugars on glycaemic control. Although most food sources of these sugars (especially fruit) do not have a harmful effect in energy matched substitutions with other macronutrients, several food sources of fructose-containing sugars (especially sugars-sweetened beverages) adding excess energy to diets have harmful effects. However, certainty in these estimates is low, and more high quality randomised controlled trials are needed." As taken from Choo VL et al. 2018. BMJ 363, k4644. PubMed, 2019 available at: https://www.ncbi.nlm.nih.gov/pubmed/30463844

"We first tested the hypothesis that consuming a high-fructose corn syrup (HFCS)-sweetened soft drink augments kidney vasoconstriction to sympathetic stimulation compared with water (study 1). In a second study, we examined the mechanisms underlying these observations (study 2). In study 1, 13 healthy adults completed a cold pressor test, a sympathoexcitatory maneuver, before (preconsumption) and 30 min after drinking 500 mL of decarbonated HFCS-sweetened soft drink or water (postconsumption). In study 2, venous blood samples were obtained in 12 healthy adults before and 30 min after consumption of 500 mL water or soft drinks matched for caffeine content and taste, which were either artificially sweetened (Diet trial), sucrose-sweetened (Sucrose trial), or

sweetened with HFCS (HFCS trial). In both study 1 and study 2, vascular resistance was calculated as mean arterial pressure divided by blood velocity, which was measured via Doppler ultrasound in renal and segmental arteries. In study 1, HFCS consumption increased vascular resistance in the segmental artery at rest (by 0.5 ± 0.6 mmHg·cm-1·s-1, P = 0.01) and during the cold pressor test (average change: 0.5 ± 1.0 mmHg·cm-1·s-1, main effect: P = 0.05). In study 2, segmental artery vascular resistance increased in the HFCS trial (by 0.8 ± 0.7 mmHg·cm-1·s-1, P = 0.02) but not in the other trials. Increases in serum uric acid were greater in the HFCS trial (0.3 ± 0.4 mg/dL, P ≤ 0.04) compared with the Water and Diet trials, and serum copeptin increased in the HFCS trial (by 0.8 ± 1.0 pmol/L, P = 0.06). These findings indicate that HFCS acutely increases vascular resistance in the kidneys, independent of caffeine content and beverage osmolality, which likely occurs via simultaneous elevations in circulating uric acid and vasopressin." As taken from Chapman CL et al. 2020. Am. J. Physiol. Renal Physiol. 318(4), F1053-F1065. PubMed, 2020 available at https://pubmed.ncbi.nlm.nih.gov/32174139/

"The increased consumption of fructose in the average diet through sweeteners such as high-fructose corn syrup (HFCS) and sucrose has resulted in negative outcomes in society through producing a considerable economic and medical burden on our healthcare system. Ingestion of fructose chronically has contributed to multiple health consequences, such as insulin resistance, obesity, liver disorders, and diabetes. Fructose metabolism starts with fructose phosphorylation by fructose kinase in the liver, and this process is not feedback regulated. Therefore, ingestion of high fructose can deplete ATP, increase uric acid production, and increase nucleotide turnover. This review focuses the discussion on the hepatic manifestations of high fructose-implicated liver metabolic disorders such as insulin resistance, obesity due to enhanced lipogenesis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), and type 2 diabetes. The detrimental effects of high fructose on the liver, contributed potentially by microbiome and leptin, were also discussed. The authors believe that, together with diet management, further studies focusing on disrupting or blocking fructose metabolism in the liver may help with designing novel strategies for prevention and treatment of fructose-induced chronic liver metabolic diseases." As taken from Mai BH et al. 2019. Diabetes Metab. Syndr. Obes. 12, 821-826. PubMed, 2020 available at https://pubmed.ncbi.nlm.nih.gov/31213868/

7. Addiction

JTI is not aware of any information that demonstrates that this ingredient has any addictive effect.

8. Burnt ingredient toxicity

This ingredient was considered as part of an overall safety assessment of ingredients added to tobacco in the manufacture of cigarettes. An expert panel of toxicologists reviewed the open literature and internal toxicology data of 5 tobacco companies to evaluate a composite list of ingredients used in the manufacture of cigarettes. The conclusion of this report was that these ingredients did not increase the inherent biological activity of tobacco cigarettes, and are considered to be acceptable under conditions of intended use (Doull et al., 1994 & 1998).

Tobacco smoke condensates from cigarettes containing Sugars (high fructose corn syrup) and an additive free, reference cigarettes were tested in a battery of *in vitro* and/or *in vivo* test(s). Within the sensitivity and specificity of the bioassay(s) the activity of the condensate was not changed by the addition of Sugars (high fructose corn syrup). Table below provides tested level(s) and specific endpoint(s).

Endpoint	**Tested level (ppm)**	**Reference**
Smoke chemistry	62,507	Carmines, 2002 & Rustemeier et al., 2002
	15,000 20,000	JTI KB Study Report(s)
	65,000	Gaworski et al., 2011 & Coggins et al., 2011a
	42	Roemer et al, 2014
In vitro genotoxicity	62,507	Carmines, 2002 & Roemer et al., 2002
	62,000	Baker et al., 2004c
	15,000 20,000	JTI KB Study Report(s)

	65,000	Gaworski et al., 2011 & Coggins et al., 2011a
	42	Roemer et al, 2014
In vitro cytotoxicity	62,507	Carmines, 2002 & Roemer et al., 2002
	62,000	Baker et al., 2004c
	20,000	JTI KB Study Report(s)
	65,000	Gaworski et al., 2011 & Coggins et al., 2011a
	42	Roemer et al, 2014
Inhalation study	62,507	Carmines, 2002 & Vanscheeuwijck et al., 2002
	62,000	Baker et al., 2004c
	20,000	JTI KB Study Report(s)
	65,000	Gaworski et al., 2011 & Coggins et al., 2011a
	42	Schramke et al, 2014
Skin painting	20,000	JTI KB Study Report(s)
In vivo genotoxicity	42	Schramke et al, 2014

Safety assessment of high fructose corn syrup (HFCS) as an ingredient added to cigarette tobacco (Abstract). A tiered testing strategy has been developed to evaluate the potential for new ingredients, tobacco processes, and technological developments to alter the biological activity that results from burning tobacco. A series of studies was initially conducted with cigarettes containing 3% high fructose corn syrup (HFCS) as an alternate tobacco casing material to corn syrup/invert sugar, including determination of selected mainstream cigarette smoke (MS) constituent yields**,** Ames assay, sister chromatid exchange (SCE) assay in Chinese hamster ovary (CHO) cells, a 30-week dermal tumor-promotion evaluation of cigarette smoke condensate (CSC) in SENCAR mice, and a 13-week subchronic inhalation study of MS in Sprague-Dawley rats**.** A second series of studies was conducted with cigarettes containing 3%, 4% and 5% HFCS including MS chemistry, Ames assay, SCE assay in CHO cells, and a neutral red cytotoxicity assays. Collectively, mainstream smoke chemistry, genotoxicity, dermal tumor-promotion, and inhalation toxicity studies demonstrated no differences between cigarettes with 3% HFCS and cigarettes with 3% corn syrup/invert sugar. Also, mainstream smoke chemistry and genotoxicity of cigarettes with 4% and 5% HFCS were not different from cigarettes with 3% HFCS. In conclusion, the addition of up to 5% HFCS to cigarette does not alter the mainstream smoke chemistry or biological activity of mainstream smoke or mainstream smoke condensate as compared to cigarettes with 3% corn syrup/invert sugar with regard to the parameters investigated and presented. As taken from Stavanja MS et al. Exp Toxicol Pathol. 2006 Mar; 57(4):267-81. PubMed, 2010 available at http://www.ncbi.nlm.nih.gov/pubmed/16426827

Sugars, such as sucrose or invert sugar, have been used as tobacco ingredients in American-blend cigarettes to replenish the sugars lost during curing of the Burley component of the blended tobacco in order to maintain a balanced flavor. Chemical-analytical studies of the mainstream smoke of research cigarettes with various sugar application levels revealed that most of the smoke constituents determined did not show any sugar-related changes in yields (per mg nicotine), while ten constituents were found to either increase (formaldehyde, acrolein, 2-butanone, isoprene, benzene, toluene, benzo[*k*]fluoranthene) or decrease (4-aminobiphenyl, N-nitrosodimethylamine, N-nitrosonornicotine) in a statistically significant manner with increasing sugar application levels. Such constituent yields were modelled into constituent uptake distributions using simulations of nicotine uptake distributions generated on the basis of published nicotine biomonitoring data, which were multiplied by the constituent/nicotine ratios determined in the current analysis. These simulations revealed extensive overlaps for the constituent uptake distributions with and without sugar application….

Moreover, the differences in smoke composition did not lead to relevant changes in the activity in *in vitro* and *in vivo* assays. The potential impact of using sugars as tobacco ingredients was further assessed in an indirect manner by comparing published data from markets with predominantly American-blend or Virginiatype (no added sugars) cigarettes. No relevant difference was found between these markets for smoking prevalence, intensity, some markers of dependence, nicotine uptake, or mortality from smoking-related lung cancer and chronic obstructive pulmonary disease. In conclusion, thorough examination of the data available suggests that the use of sugars as ingredients in cigarette tobacco does not increase the inherent risk and harm of cigarette smoking (Roemer et al. 2012).

When tested in a number of assays in *Salmonella typhimurium* strains TA98 and TA100, the addition of up to 7% high fructose corn syrup to a casing mixture had no significant effect on the mutagenicity of the cigarette smoke condensate when compared to that of a reference cigarette.

9. Heated/vapor emissions toxicity

Total particulate matter (TPM) from heated (tobacco or nicotine) product(s) containing Sugars (High Fructose Corn Syrup) was tested in a battery of *in vitro* and/or *in vivo* test(s). Within the sensitivity and specificity of the bioassay(s) the activity of the TPM was not increased by the addition of Sugars (High Fructose Corn Syrup) when compared to TPM from 3R4F cigarettes. The table below provides tested level(s) and specific endpoint(s).

Endpoint	**Tested level (ppm)**	**Reference**
In vitro genotoxicity	1432	JTI KB Study Report(s)
In vitro cytotoxicity	1432	JTI KB Study Report(s)

Aerosol from an electronic nicotine delivery system (ENDS) product that creates a vapor by heating an e-liquid; the vapor then passes through a capsule containing tobacco granules, containing Sugars (Hydrolyzed starch syrup) was tested in a battery of in vitro and/or in vivo test(s). Under the test conditions and within the sensitivity and specificity of the bioassay(s), no mutagenic, genotoxic or cytotoxic responses were observed when exposed to Aerosol Collected Matter (ACM) and/or aerosol Gas Vapor Phase (GVP) and no adverse findings from a 90-day in vivo repeat-dose inhalation toxicity study were observed after exposure to the aerosol even when exposure concentrations were the maximal amount that could be achieved with the specific product(s). These results are in contrast to those observed with combustible cigarette which showed mutagenic, genotoxic, cytotoxic and adverse effects upon exposure. The table below provides tested level(s) and specific endpoint(s):

Endpoint	**Tested level**	**Reference**
Aerosol chemistry	0.0319 mg/(tobacco portion; 310 mg)	Logic (2019)
In vitro genotoxicity	0.0319 mg/(tobacco portion; 310 mg)	Logic (2019)
In vitro cytotoxicity	0.0319 mg/(tobacco portion; 310 mg)	Logic (2019)

In vivo genotoxicity	0.0319 mg/(tobacco portion; 310 mg)	Logic (2019)
Inhalation study	0.0319 mg/(tobacco portion; 310 mg)	Logic (2019)

10. Ecotoxicity

10.1. Environmental fate

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that hydrolyzed starch syrups (CAS RN 8029-43-4) are of uncertain persistence in the environment.

Data accessed July 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

EPISuite provides the following data for CAS RN 8029-43-4:

Henrys Law Constant (25 deg C) [HENRYWINv3.20]: Bond Method:	9.72E-015 atm-m3/mole (9.85E-010 Pa-m3/mole)
Group Method:	1.62E-026 atm-m3/mole (1.64E-021 Pa-m3/mole)
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:	HLC: 3.153E-014atm-m3/mole (3.195E-009 Pa-m3/mole) VP: 1.33E-007 mmHg (source: MPBPVP) WS: 1E+006 mg/L (source: WSKOWWIN)]

Log Octanol-Air Partition Coefficient (25 deg C)[KOAWIN v1.10]: Log Kow used:	-3.24 (exp database)
Log Kaw used:	-12.401 (Henry Win est)
Log Koa (KOAWIN v1.10 estimate):	9.161
Log Koa (experimental database):	None

Probability of Rapid Biodegradation (BIOWIN v4.10): Biowin1 (Linear Model):Biowin2 (Non-Linear Model):Biowin3 (Ultimate Survey Model):Biowin4 (Primary Survey Model):Biowin5 (MITI Linear Model):Biowin6 (MITI Non-Linear Model):Biowin7 (Anaerobic Linear Model):	1.10810.93153.5922(days-weeks)4.2253(days)1.09500.88291.4659
Ready Biodegradability Prediction:	YES

Hydrocarbon Biodegradation (BioHCwin v1.01): Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C) [AEROWIN v1.00]: Vapor pressure (liquid/subcooled):	1.07E-011 Pa (8.02E-014 mm Hg)
Log Koa (Koawin est):	9.161
Kp (particle/gas partition coef. (m3/ug)):Mackay model: Octanol/air (Koa) model:	2.81E+0050.000356

Fraction sorbed to airborne particulates (phi): Junge-Pankow model:	1
Mackay model:	1
Octanol/air (Koa) model:	0.0277
Atmospheric Oxidation (25 deg C) [AopWin v1.92]: Hydroxyl Radicals Reaction: OVERALL OH Rate Constant =	104.3877E-12 cm3/molecule-sec
Half-Life =	0.102 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life =	1.230 Hrs
Ozone Reaction:	No Ozone Reaction Estimation

Fraction sorbed to airborne particulates (phi): 1 (Junge-Pankow, Mackay avg)

0.0277 (Koa method)

Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00): Koc:	10 L/kg (MCI method)
Log Koc:	1.000 (MCI method)
Koc:	0.01658 L/kg (Kow method)
Log Koc:	-1.781 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]: Rate constants can NOT be estimated for this structure!

Volatilization from Water: Henry LC: 9.72E-015 atm-m3/mole (estimated by Bond SAR Method) Half-Life from Model River:	8.085E+010 hours (3.369E+009 days)
Half-Life from Model Lake:	8.82E+011 hours (3.675E+010 days)
Removal In Wastewater Treatment: Total removal:	1.85 percent
Total biodegradation:	0.09 percent
Total sludge adsorption:	1.75 percent
Total to Air:	0.00 percent

(using 10000 hr Bio P,A,S)

Level III Fugacity Model:	Mass Amount(percent)	Half-Life(hr)	Emissions(kg/hr)
Air	5.06e-007	2.46	1000
Water	28.1	208	1000
Soil	71.8	416	1000
Sediment	0.0592	1.87e+003	0

Persistence Time: 414hr

10.2. Aquatic toxicity

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that hydrolyzed starch syrups (CAS RN 8029-43-4) are not inherently toxic to aquatic organisms and are of low ecotoxicological concern.

Data accessed July 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

ECOSAR version 1.11 reports the following aquatic toxicity data for CAS RN 8029-43-4:

Values used to Generate ECOSAR Profile:

Log Kow: -2.888 (EPISuite Kowwin v1.68 Estimate)

Wat Sol: 5E+005 (mg/L, PhysProp DB exp value)

ECOSAR v1.11 Class-specific Estimations:

Neutral Organics

ECOSAR Class	**Organism**	**Duration**	**End Pt**	**Predicted mg/L (ppm)**
Neutral Organics :	Fish	96-hr	LC50	3.63e+006 *
Neutral Organics :	Daphnid	48-hr	LC50	1.31e+006 *

Neutral Organics	:	Green Algae	96-hr	EC50	1.51e+005
Neutral Organics	:	Fish		ChV	2.08e+005
Neutral Organics	:	Daphnid		ChV	36446.895
Neutral Organics	:	Green Algae		ChV	14500.736
Neutral Organics	:	Fish (SW)	96-hr	LC50	4.44e+006 *
Neutral Organics	:	Mysid	96-hr	LC50	9.04e+007 *
Neutral Organics	:	Fish (SW)		ChV	24350.627
Neutral Organics	:	Mysid (SW)		ChV	3.33e+007 *

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported.

10.3. Sediment toxicity

No data available to us at this time.

10.4. Terrestrial toxicity

ECOSAR version 1.11 reports the following terrestrial toxicity data for CAS RN 8029-43-4:

Values used to Generate ECOSAR Profile:

Log Kow: -2.888 (EPISuite Kowwin v1.68 Estimate)

Wat Sol: 5E+005 (mg/L, PhysProp DB exp value)

ECOSAR v1.11 Class-specific Estimations:

Neutral Organics

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
Neutral Organics :	Earthworm	14-day	LC50	1006.237

“Severe declines in honey bee populations have made it imperative to understand key factors impacting honey bee health. Of major concern is nutrition, as malnutrition in honey bees is associated with immune system impairment and increased pesticide susceptibility. Beekeepers often feed high fructose corn syrup (HFCS) or sucrose after harvesting honey or during periods of nectar dearth. We report that, relative to honey, chronic feeding of either of these two alternative carbohydrate sources elicited hundreds of differences in gene expression in the fat body, a peripheral nutrient-sensing tissue analogous to vertebrate liver and adipose tissues. These expression differences included genes involved in protein metabolism and oxidation-reduction, including some involved in tyrosine and phenylalanine metabolism. Differences between HFCS and sucrose diets were much more subtle and included a few genes involved in carbohydrate and lipid metabolism. Our results suggest that bees receive nutritional components from honey that are not provided by alternative food sources widely used in apiculture.” As taken from Wheeler MM & Robinson GE. 2014. Sci. Rep. 4, 5726. PubMed, 2015 available at: http://www.ncbi.nlm.nih.gov/pubmed/25034029

10.5. All other relevant types of ecotoxicity

The Ecological Categorization Results from the Canadian Domestic Substances List simply state that hydrolysed starch syrups (CAS RN 8029-43-4) are of uncertain bioaccumulative potential in the environment.

Data accessed July 2017 on the OECD website: http://webnet.oecd.org/CCRWeb/Search.aspx

EPISuite provides the following data for CAS RN 8029-43-4:

Bioaccumulation Estimates (BCFBAF v3.01): Log BCF from regression-based method:	0.500 (BCF =3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL):	-3.2387 days (HL = 0.0005772 days)
Log BCF Arnot-Gobas method (upper trophic):	-0.049 (BCF = 0.893)
Log BAF Arnot-Gobas method (upper trophic):	-0.049 (BAF = 0.893)
log Kow used:	-3.24 (exp kow database)

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13. Last audited

June 2020

Substance	*ID Code*	*Rpt No.*	*Year*	*Conclusion**	*21 CFR Section*
Corn Syrup	8029-43-4	50	1976	2	184.1865

SCOGS Opinion:

Corn sugar, commonly referred to as dextrose, is crystalline ?-D-glucose. Glucose is widely distributed in nature both in the free state and in various combined forms, including starch and sucrose. Glucose-yielding carbohydrates constitute one of the main sources of energy in the typical North American diet. Fructose, produced along with glucose in the hydrolysis of sucrose to invert sugar and by isomerization of dextrose, also is a significant calorie source. The absorption and metabolism of these sugars are well established. Biological studies have shown that these substances are devoid of toxic effects at dosage levels well in excess of those that exist in the American diet and, accordingly, at levels that are orders of magnitude higher than those which might occur from the migration of these substances from paper and paperboard products.

Glucose syrup, also called corn syrup when made by the hydrolysis of corn starch, contains in addition to glucose, maltose, and higher saccharides in proportions that depend on the degree of hydrolysis of the starch. The higher conversion syrups may also contain small amounts of disaccharides formed by the recombination of glucose through glucosidic linkages not present in starch. Animal feeding studies have shown that glucose syrups are readily digested and metabolized and have given no evidence of toxic effects.

Fructose-dextrose mixtures have been observed to have hyperlipemic effects when fed at high levels in fat-free diets to adult males and postmenopausal women. There is no evidence, however, that the levels of invert sugar and high-fructose corn syrup in the average diet cause significant elevations in blood lipids and it is unlikely that the consumption of fructose or glucose, ingested as monosaccharides, has a role in coronary heart disease. Although glucose and fructose as well as sucrose have been demonstrated to be cariogenic in animal experiments, epidemiological studies of dietary habits and controlled diets in institutional feeding indicate that the cariogenicity of sucrose and other foods is affected by several factors and not necessarily by the total amount consumed. These factors include the frequency eating, duration of exposure, and the form and physical properties of the food in which the sugar is ingested. Between-meal eating has been demonstrated to be significantly correlated with frequency and severity of caries in both children and adults. Thus, protection is facilitated by limitation of the frequency of consumption of sugar and sugared foods.

Consumption of dextrose and corn syrup has increased markedly in recent years and represented about 21 percent of the sweetener marker in 1974 as compared to about 15 percent in 1970. A major part of the increase resulted from the introduction of high-fructose corn syrup produced the enzymatic isomerization of dextrose in starch hydrolyzates. Level of fructose as the monosaccharide in the diet has increased accordingly but 1974 per capita daily consumption of this

Substance	ID Code	Rpt No.	Year	Conclusion*	21 CFR Section

monosaccharide from all sources was only 6g and no higher than in 1925-29, when apples provided a larger contribution than at present. High-fructose corn syrups are predicted to increase in production and to replace sucrose and invert sugar in up to 30 percent of their applications by 1980-85, based largely on relative costs. There is no evidence that such replacement, per se, would have an adverse effect on public health. However, the Select Committee has expressed concern in its report on sucrose (73) that is this sugar contributes to dental caries in the public at current consumption levels as used in the manner now practiced. It is questionable that replacement of sucrose by syrups and sugars derived from starch would greatly change the cariogenicity of foods containing these sugars. Informing the consumer of the sugar content of foods by appropriate labeling could lead to judicious use of sweetened foods. Choices could be made easier with a greater selection of less sugared foods in the market place. The Select Committee has weighed all of the foregoing and concludes that: Evidence exists that simple sugars, including glucose and fructose [and, therefore, corn sugar(dextrose), corn syrup including high-fructose corn syrup, and invert sugars] are cariogenic. However, in the quantities that these simple sugars are now consumed in processed foods, their contribution to formation of dental caries should be relatively small. If increased usage should occur, as seems likely, the contribution of these sugars to the occurrence of dental caries might become more important. Other than the contribution made to dental caries, there is no evidence in the available information on corn sugar(dextrose), corn syrup, and invert sugar that demonstrated a hazard to the public when they are used at levels that are now current and in the manner now practiced. however, it is not possible to determine without additional data, whether an increase in consumption-that would result if there were a significant increase in the total of corn sugar, corn syrup, invert sugar and sucrose added to foods-would constitute a dietary hazard.

**** denotes Type of Conclusion 1, 2, 3, 4, or 5. Definitions of conclusion types can be found at the end of this report..***

European Food Safety Authority
Published on *European Food Safety Authority* (http://www.efsa.europa.eu)

EFSA will provide scientific advice on the daily intake of added sugar in food by early 2020. The Authority aims to establish a science-based cut-off value for daily exposure to added sugars from all sources which is not associated with adverse health effects. The work will be carried out following a request from Denmark, Finland, Iceland, Norway and Sweden.

Added sugars from all sources comprise sucrose, fructose, glucose, starch hydrolysates such as glucose syrup, high-fructose syrup, and other sugar preparations consumed as such or added during food preparation and manufacturing.

The adverse health effects under consideration will include body weight, glucose intolerance and insulin sensitivity, type-2-diabetes, cardiovascular risk factors, as well as dental caries. In its assessment, EFSA will look at the general healthy population, including children, adolescents, adults and the elderly.

The advice will guide Member States when establishing recommendations for the consumption of added sugars and in planning food-based dietary guidelines.

Sweden is coordinating the request to EFSA on behalf of the five Nordic countries. Annica Sohlström, the Director General of the Swedish National Food Agency, said: "We welcome EFSA's acceptance of the mandate which reflects the need to scientifically evaluate the links between added sugar and health at a European level."

What is going to happen next?

EFSA will establish an ad-hoc working group with expertise in dietary exposure, epidemiology, human nutrition, diet-related chronic diseases and dentistry. The five Nordic countries that initiated this mandate will be invited to the working group as observers.

EFSA will use its established methodology to develop a protocol on how to carry out the assessment. Known as Prometheus – PROmoting METHods for Evidence Use in Scientific assessments – the method shows how EFSA selects evidence, how this evidence contributes to the risk assessment and how EFSA reports on the entire process and it results.

In line with its commitment to openness and transparency, EFSA will engage with stakeholders throughout the assessment process. It will hold two public consultations, inviting feedback on the draft protocol in the first half of 2018 and on the draft opinion in late 2019, which will also involve a face-to-face meeting with stakeholders.

Background

In 2010, EFSA published its Scientific Opinion on Dietary Reference Values for carbohydrates and dietary fibre, which also included sugar. At this time, the available evidence was insufficient to set an upper limit for the daily intake of total or added sugars. New scientific evidence has come to light since then. There has also been growing public interest in the impact of the consumption of sugar-containing foods and beverages on human health.

- Mandate page in the Register of Questions [1]

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

Status:	Final Report
Release Date:	April 4, 2014
Panel Meeting Date:	March 17-18, 2014

The 2014 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This safety assessment was prepared by Monice M. Fiume, Assistant Director/Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

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ABSTRACT

The Expert Panel assessed the safety of 25 monosaccharides, disaccharides, and related ingredients, and concluded these ingredients are safe as used in cosmetics. Many of these ingredients are common dietary sugars, dietary sugar replacements, or very closely related analogs and salts; seven of the ingredients are listed by the FDA as GRAS 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.

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, and the most common use is as a skin conditioning agent (Table 1).[1] Other commonly-reported functions are use as a humectant or as a flavoring agent.

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 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, Authorisation 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, i.e., fucose, galactosyl fructose, galacturonic acid, kefiran, lactulose, mannose, melibiose, and xylobiose, a search for oral toxicity data was performed. Very limited published data were found.

CHEMISTRY

Definition

A monosaccharide is a carbohydrate that cannot be decomposed to a simpler carbohydrate by hydrolysis, and is often called a simple sugar.[6] A disaccharide is a carbohydrate that yields two monosaccharides upon hydrolysis. Many of these ingredients exist in equilibrium between an open chain form and one or more ring forms resulting in a hemiacetal or hemiketal linkage involving the aldehyde (aldose) or ketone (ketose) moiety of the open chain form, with two possible stereochemical configurations (Figure 1). The resulting stereoisomers are called anomers and the stereocenter is referred to as the anomeric carbon.

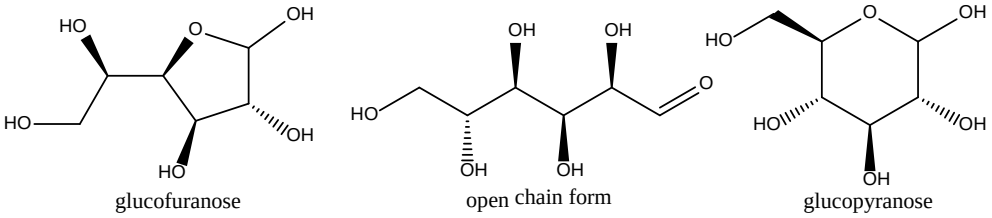


Figure 1. Structural forms of D-glucose (stereoisomer found in natural sources) that exist in equilibrium.

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

Chemical and Physical Properties

Due to the high degree of substitution with hydroxyl groups, the mono- and disaccharides are very hydrophilic and readily dissolve in aqueous solvent systems. These sugars have molecular weights ranging from 142 to 391 Daltons, and are solids at room-temperature, 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 to 15% sucrose), and 2.7% soluble impurities. Sugar cane is extracted with water, clarified to remove mud, evaporated to prepare syrup, crystallized to separate the liquor, and centrifuged to separate molasses from the crystals. Sugar crystals are then dried and may be further refined before bagging for shipment. Sugar beet (water, 75%; sugar, 17%) processing differs in the washing, preparation, and extraction. After washing, the beet is sliced and extracted with water. Sugar refining involves removal of impurities and decolorization. The steps generally followed include affination (mingling and centrifugation), melting, clarification, decolorization (with activated carbon, ion exchange resins, etc.), evaporation, crystallization, and finishing.

Constituents/Impurities

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

USE

Cosmetic

The ingredients included in this safety assessment have a variety of functions in cosmetics. The most common function is as a skin conditioning agent; many also are 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). 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] 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 mono- 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" non-coloring 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 (i.e., in other skin care preparations) and 65% in rinse-off products (i.e., in other personal cleanliness products). However, most of the ingredients are used at less than 1% in leave-on products.

The three ingredients not reported to be used are galactose, galacturonic acid, and lactulose (Table 6).

VCRP data indicate that glucose, lactose, sodium gluconate, sucrose, and trehalose are used in baby products; however concentration of use data for baby products were not reported by industry. Some of the ingredients are used in products that could be incidentally, or are purposely, ingested (e.g., 97.8% glucose in an ingestible oral hygiene product), and some are used near the eye area or mucous membranes (e.g., 2% sucrose in eye lotion and 65% in personal cleanliness products, respectively). Additionally, some of these ingredients are used in cosmetic sprays and powders that could possibly be inhaled (e.g., glucose is used at 1% in a spray body and hand preparation). In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of

droplets/particles <10 µm compared with pump sprays.[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 (i.e., 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]

Non-Cosmetic

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

In Europe, the following are listed in REACH Annex IV: fructose; galactose; glucose; lactose; sodium gluconate; 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 readily absorbed. Some of these ingredients (e.g., gluconic acid, potassium gluconate, and sodium gluconate) are important intermediates in carbohydrate metabolism; gluconic acid is a normal metabolic product of glucose oxidation, and the amounts produced endogenously are much greater than what is consumed.[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 M, 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} M D-[1,3-^{14}C]glucose, supplied as a sterile aq. solution containing 3% alcohol, was placed in the donor cell. After 6 h, the permeability coefficient of glucose was 9.5×10^{-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 four anesthetized monkeys was shaved, a probe holder was taped to the shaved skin, and 0.2 ml of 20% concentrated glucose in distilled water was applied topically through the hole in the probe holder during the course of imaging. The skin was imaged using OCT for 8 min prior to application of the glucose, and then for 2 h after application. The diffusion process was monitored in a 140 µm thick region 210 µm below the dermis region. The mean permeability rate of 20% glucose was calculated to be $(4.41 \pm 0.28) \times 10^{-6}$ cm/sec.

TOXICOLOGICAL STUDIES

Most of the ingredients included in this assessment are found in foods, and the daily exposure from that food use would result in a much larger systemic dose than that resulting from use in cosmetic products. Numerous studies and reviews have been published about the safety of dietary exposure to mono- and disaccharides. 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 mono- and disaccharides as cosmetic ingredients is on the potential for irritation and sensitization. When available, dermal toxicity, ocular irritation, and genotoxicity studies are included.

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

Single Dose (Acute) Toxicity

Dermal

Lactitol

The dermal LD_{50} of lactitol in rabbits is >4500 mg/kg bw.[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 eight male albino rats were fed a diet containing 0.0, 0.5, 1.0, 2.0, or 5.0% (equivalent to 0.0, 1.1, 2.2, 4.0, and 11.3 g/kg bw/day, respectively) of a 50% lactulose syrup for 21 weeks.[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/day of the test material; diarrhea subsides with 3-5 h of feeding. Feed consumption was not statistically significantly affected at any dose level. The organ weights were similar for treated and control animals. A statistically significant increase in cecal weights in the 2 and 5% groups was considered an adaptive reaction. No toxicologically-significant changes in hematology, clinical chemistry, or urinalysis parameters were reported.

Ocular Irritation

In Vitro

Gluconic Acid

The ocular irritation potential of a 50% aq. solution of gluconic acid was evaluated *in vitro* in enucleated rabbit eyes.[9] The test material was applied to four eyes and observed over a period of 4 h following application. Slight corneal swelling and slight permeability of the superficial epithelial cells were not considered to be of any toxicological significance.

Isomalt

A battery of *in vitro* tests were performed to determine the ocular irritation potential of isomalt; based on the overall results of each test included in the battery, isomalt was classified as a non-irritant. A neutral red uptake (NRU) assay was performed in human keratinocytes, and the cytotoxicity of undiluted isomalt to the cells was measured after 24-h exposure.[65] Two experiments were performed. Undiluted isomalt was classified as a non-irritant in this *in vitro* test.

A red blood cell lysis and denaturation (RBC) assay, comprised of two range-finding and denaturation assays and two lysis assays, was performed in calf red blood cells.[66] Concentrations of ≤100,000 mg/l isomalt were tested. Isomalt did not induce hemolysis or protein denaturation, and was classified as a non-irritant. Based on the lack of induction of hemolysis, the predicted *in vivo* ocular irritation potential corresponded to a modified maximum average score of 0.

The third test in the battery was the hen's egg test on the chorioallantoic membrane (HET-CAM) in which isomalt was tested undiluted according to the endpoint assessment and at concentrations of 10 and 50% (w/w) in water according to the reaction-time method.[67] Each aspect of the experiment was performed twice. According to COLIPA (now, Cosmetics Europe) classifications, undiluted isomalt was classified as a slight irritant when tested undiluted in the endpoint assessment; the 10% and 50% concentrations were classified as non-irritant using the reaction-time method.

In Vivo – Non-Human

Gluconic Acid

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

Lactitol

Lactitol was not irritating to rabbit eyes.[20] The study was performed according to the Organisation for Economic Co-operation and Development (OECD) 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-wk safety-in use ophthalmological evaluation.[69] Thirty-one subjects 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/day produced no deleterious effects on breeding, conception, or parturition.[21] (Details were not provided.)

GENOTOXICITY

The genotoxicity of a number of the mono- and disaccharides has been evaluated in *in vitro* and *in vivo* studies. The results of these studies are overwhelmingly negative (Table 10[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 mos in 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 non-human studies, a 50% aq. 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 less than 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 one subject,[76] and irritation was observed in 16% of the subjects 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 (NIOSH) recommended exposure limit (REL) for sucrose is a time-weighted average (TWA) of 10 mg/m^3 (total exposure) and TWA of 5 mg/m^3 (respiratory exposure).[25] The Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) is a TWA of 15 mg/m^3 (total) and TWA of 5 mg/m^3 (respiratory). The American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) is 10 mg/m^3 as TWA; it is in category A4, not classifiable as a human carcinogen.

SUMMARY

This report addresses the safety of 25 monosaccharides, disaccharides, and related ingredients as used in cosmetics. Many of these ingredients are GRAS food substances, direct food additives, or common dietary sugars, dietary sugar replacements, or very closely related analogs; for these ingredients, the focus of this review was on dermal irritation and sensitization. For the ingredients that are not identified as dietary substances, oral toxicity data were 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 varies widely by ingredient and type of use; most of the ingredients are used in leave-on products at less than 1%. Non-cosmetic uses include food use and use as inactive ingredients in approved drugs.

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

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

Lactulose fed to rats at concentrations of up to 5.0% of 50% lactulose syrup for 21 weeks did not result in toxicity. Mild diarrhea was reported for animals fed >2.2 g/kg bw/day of the test material; diarrhea subsides with 3-5 h of feeding. Doses of up to 12 ml/kg/day 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 mos.

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

In non-human studies, a 50% aq. solution of gluconic acid was not a dermal irritant and lactitol was not an irritant or sensitizer in rabbits. In human repeated insult patch tests (HRIPTs), formulations containing 10% rhamnose, 8% glucose, 5% mannose, 2.48% lactose, and less than 1% isomalt, kefiran, lactitol, sucralose, and xylobiose were not irritants or sensitizers. A formulation containing 10% rhamnose did induce a significant irritation reaction in one subject, and irritation was observed in 16% of the subjects during induction in a 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.

DISCUSSION

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

Some of the ingredients, however, are not GRAS 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 (EAFUS) inventory, and/or listed as an inactive ingredient in oral drugs. Moreover, the leave-on use concentrations of these ingredients are typically less than 1%. Therefore, the Panel stated that although oral toxicity data are very limited and reproductive toxicity data are 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 (i.e., 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 a human repeated insult patch test of a hair product that contained 29% sucrose, diluted to 50%, that 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 less than 1% (e.g., glucose is used at 1% in a spray body and hand preparation). In the absence of inhalation data, the Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. The Panel acknowledged that the potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs, but because of the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects.

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

CONCLUSION

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

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

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

TABLES

Table 1. Definitions, Structures, and Reported Functions

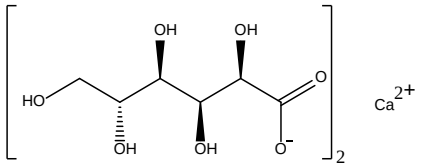
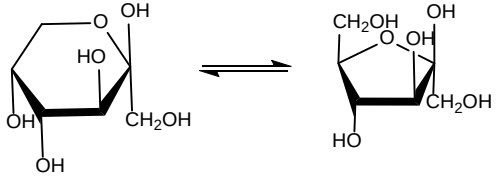
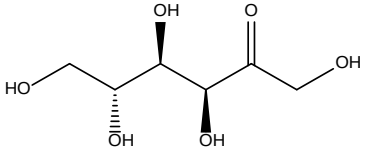
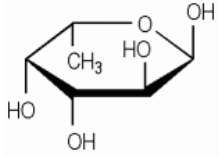
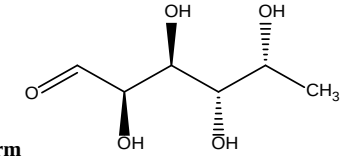
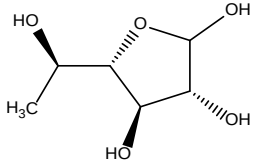
Ingredient (CAS No.)	Definition[1]*	Structure[1]***	Reported Function(s)[1]
Calcium Gluconate 299-28-5	the calcium salt of gluconic acid		chelating agent; skin-conditioning agent - miscellaneous
Fructose 30237-26-4 57-48-7 (D-)	a sugar which occurs in fruit and honey; *fructose exists in solution primarily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

Table 1. Definitions, Structures, and Reported Functions

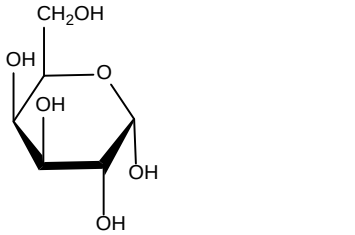
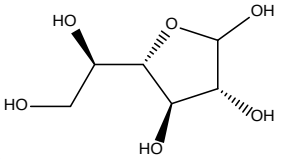
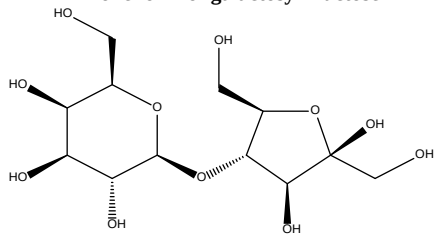
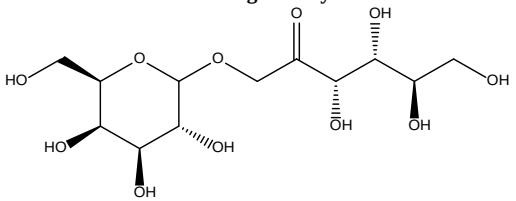
Ingredient (CAS No.)	Definition[1]*	Structure[1]***	Reported Function(s)[1]
Galactose 59-23-4	the sugar that conforms to the formula provided; g*alactose is the C4 epimer of glucose*	 *** open chain form  *** furanose form	skin-conditioning agent - miscellaneous
Galactosyl Fructose 110312-93-1	a disaccharide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

Table 1. Definitions, Structures, and Reported Functions

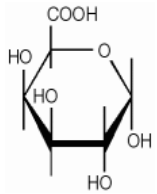
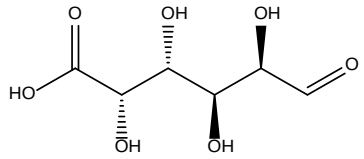
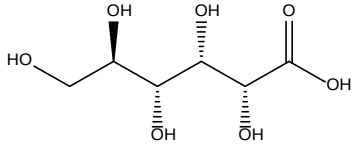
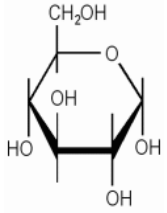
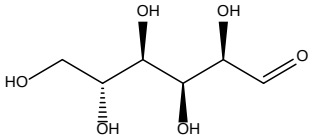
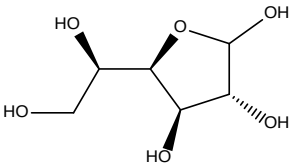
Ingredient (CAS No.)	Definition[1]*	Structure[1]***	Reported Function(s)[1]
Galacturonic Acid 14982-50-4 (DL-) 552-12-5 (D-) 685-73-4 (D-)	the organic compound that conforms to the formula provided; *galacturonic acid is the c-6 oxidation product of galactose*	  *** open chain form	chelating agent; skin-conditioning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

Table 1. Definitions, Structures, and Reported Functions

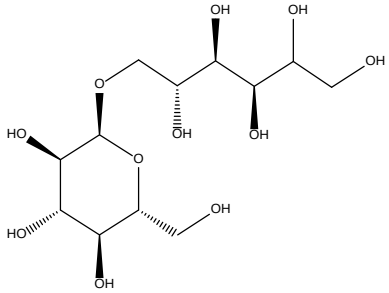
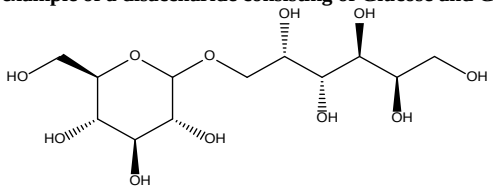
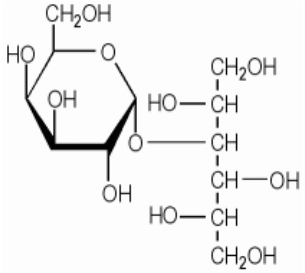
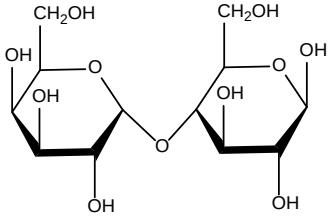
Ingredient (CAS No.)	Definition[1]*	Structure[1]***	Reported Function(s)[1]
Isomalt 64519-82-0	a mixture of polysaccharides produced by the enzymatic rearrangement of sucrose; it consists chiefly of 1-O-α-D-glucopyranosyl-D-mannitol dihydrate and 6-O-α-D-glucopyranosyl-d-sorbitol	***** one example of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

Table 1. Definitions, Structures, and Reported Functions

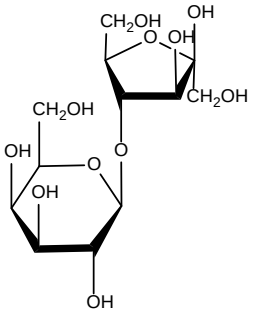
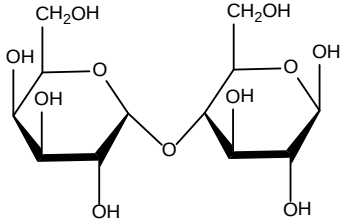
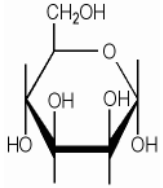
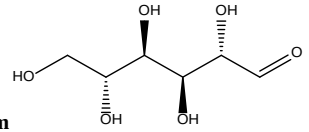
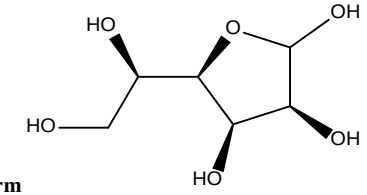
Ingredient (CAS No.)	Definition[1]*	Structure[1]***	Reported Function(s)[1]
Lactulose 4618-18-2	the disaccharide that conforms to the formula provided; *lactulose is the disaccharide (β1 →3) galactopyranosyl-fructo-furanose*		skin-conditioning agent - humectant
Maltose 16984-36-4; 69-79-4	the sugar that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

Table 1. Definitions, Structures, and Reported Functions

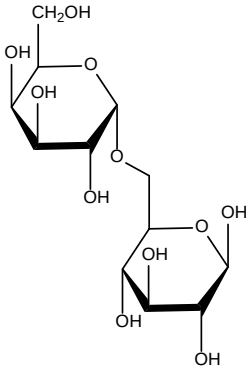
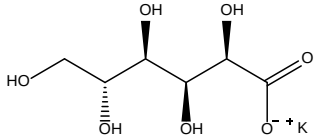
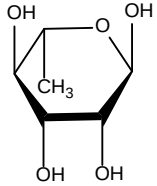
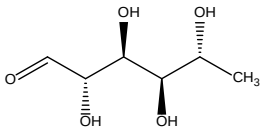
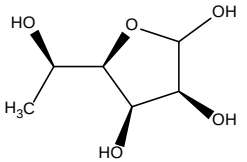
Ingredient (CAS No.)	Definition[1]*	Structure[1]***	Reported Function(s)[1]
Melibiose 5340-95-4; 585-99-9	the carbohydrate that conforms to the formula provided; *melibiose is the disaccharide α(1→6) galactosyl-glucose*		skin-conditioning agent – humectant
Potassium Gluconate 299-27-4	the potassium salt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

Table 1. Definitions, Structures, and Reported Functions

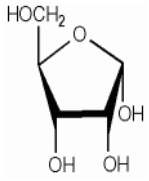
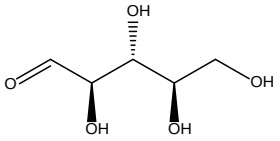
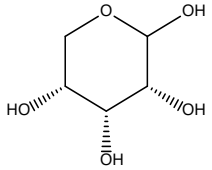
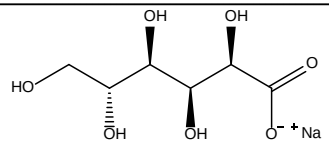
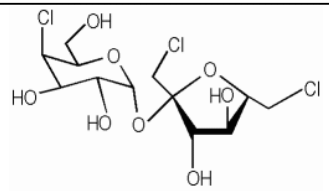
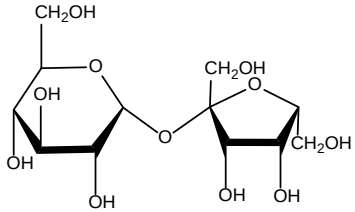
Ingredient (CAS No.)	Definition[1]*	Structure[1]***	Reported Function(s)[1]
Ribose 50-69-1	the sugar that conforms to the formula provided; *ribose is an aldopentose*	 *** open chain form   *** pyranose form	humectant; skin-conditioning agent - humectant
Sodium Gluconate 14906-97-9 527-07-1	the sodium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

Table 1. Definitions, Structures, and Reported Functions

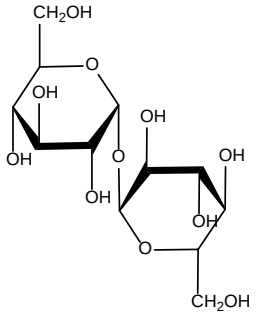
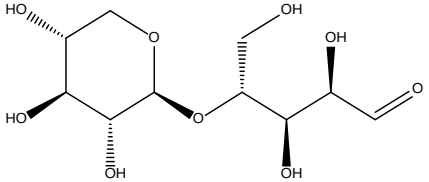
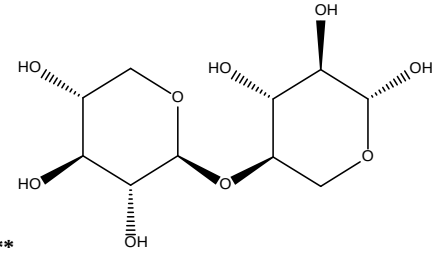
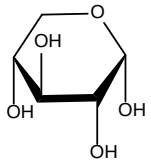
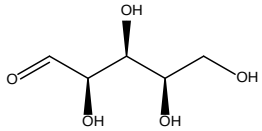
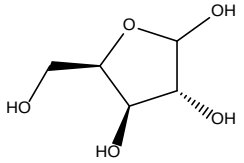
Ingredient (CAS No.)	Definition[1]*	Structure[1]***	Reported Function(s)[1]
Trehalose 99-20-7; 6138-23-4	the disaccharide that conforms to the formula provided; *trehalose is the disaccharide α(1 →1) glucosyl-glucose*		flavoring agent; humectant
Xylobiose 6860-47-5	a disaccharide consisting of two xylose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

Table 1. Definitions, Structures, and Reported Functions

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

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

Table 2. Chemical and Physical Properties

Property	Description	Reference
	Calcium Gluconate	
physical characteristics	odorless, white, crystalline granules or powder	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/cm³ (bulk density)	9
log P_{ow}	-7.51 (estimated)	9
	Fructose	
physical characteristics	D-: orthorhombic, bisphenoidal prisms from alcohol DL-: needles from methanol white crystals or powder	10 11
molecular weight	180.16	10
particle size distribution	crystalline fructose: 170-450 µm powdered fructose: 25-40 µm	12
melting point	D-: decomposes at 103-105°C DL-: 129-130°C	10
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 L-, α-form: minute needles from absolute alcohol	10
molecular weight	164.16	10
melting point	D-, α-form: 144°C L-, α-form: 140°C	10
solubility	D-, α-form: soluble in water; moderately soluble in alcohol L-, α-form: soluble in water and alcohol	10
specific optical rotation (α^{19}_D)	D-, α-form: shows mutarotation; +127.0° (7 min) ⟶ +89.4° (31 min) ⟶ +77.2° (71 min) ⟶ +76.0° (final value 146 min)	10
specific optical rotation (α^{20}_D)	L-, α-form: shows mutarotation, -124.1° (10 min) ⟶ -108.0° (20 min) ⟶ -91.5° (36 min) ⟶ -78.6° (70 min) ⟶ -75.6° (final value, 24 hrs)	10
	Galactose	
physical characteristics	α-form: prisms from water or ethanol β-form: crystals monohydrate: prisms from water	10
molecular weight	180.16	10
melting point	α-form: 167°C β-form: 167°C monohydrate: 118-120°C	10
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) β-form: +52.8° ⟶ +80.2° (water) D-, α-form: (α^{20}_D): +78.0° to 81.5°	10 14
	Galactosyl Fructose	
molecular weight	342.30 (predicted)	15
boiling point	780.1 ± 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 β-form: 166°C	10
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) β-form, (α_D): +27° ⟶ +55.6° (water)	10
	Gluconic Acid	
physical characteristics	crystals; mild acid taste white crystalline powder anhydrous: commercial form is a 50% aq. solution, which is a colorless to brownish liquid.	16 17 9,17
molecular weight	196.16	16

Table 2. Chemical and Physical Properties

Property	Description	Reference
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 aq. solutions, the acid is partially transformed into an equilibrium mixture with γ - and δ-gluconolactones	16
	reacts with strong oxidants	17
	on combustion, forms carbon monoxide	17
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 α-form anhydrous: crystals from hot ethanol or water β-form: crystals from hot water and ethanol, from diluted acetic acid, or from pyridine	10
	white D-glucose: powder with sweet taste	18
molecular weight	180.16	10
melting point	α-form monohydrate: 83°C α-form anhydrous: 146°C β-form: 148-155°C	10
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) α-form anhydrous, (α^{20}_D): +112.2° ⟶ +52.7°C (water) β-form, (α^{20}_D): +18.7° ⟶ +52.7° (water)	10
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 ± 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 monohydrate: white, sweet, odorless crystalline solid; non-hygroscopic dihydrate: white, sweet, odorless crystalline powder	10
molecular weight	344.31 (anhydrous); 362.37 (monohydrate)	3,10
melting point	146°C monohydrate: 94-97°C dihydrate: 75°C (food-grade)	10
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° monohydrate, (α^{22}_D): +12.3° dihydrate, (α^{25}_D): +13.5 – 15.0°	10
	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: 201-202°C	10
solubility	α-lactose monohydrate: practically insoluble in alcohol; insoluble in chloroform, ether	10
specific optical rotation	α-lactose monohydrate, (α^{20}_D): shows mutarotation; +92.6° ⟶ +83.5° (10 min.) ⟶ +69° (50 min) ⟶ +52.3° (22 h) β-lactose, (α^{25}_D): +34° (3 min) ⟶ +39° (6 min) ⟶ +46° (1 hr) ⟶ +52.3° (22 h)	10
K_a (16.5°C)	α-lactose monohydrate: 6.0 x 10^{-13}	10
	Lactulose	
physical characteristics	hexagonal clustered plates from methanol	10
molecular weight	342.30 (anhydrous); 360.32 (monohydrate)	3,10
melting point	168-171°C	10
solubility	freely soluble in water	21
specific optical rotation (α^{22}_D)	shows mutarotation; constant value after 24 h, -51.5°	10

Table 2. Chemical and Physical Properties

Property	Description	Reference
	Maltose	
physical characteristics	monohydrate: crystals from water or diluted alcohol	10
molecular weight	342.30	10
melting point	monohydrate: 102-103°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° ⟶ +130.4°	10
pK_a (21°C)	monohydrate: 12.05	10
	Mannose	
physical characteristics	α-form: crystals from methanol β-form: orthorhombic, bisphenoidal needles from alcohol or acetic acid; sweet taste with bitter aftertaste	10
molecular weight	180.16	10
melting point	α-form: 133°C β-form: decomposes at 132°C	10
specific optical rotation	α-form, (α_D): +29.3° ⟶ +14.2° (water) β-form, (α^{20}_{D}): -17.0° ⟶ +14.2° (water)	10
	Melibiose	
physical characteristics	dihydrate: monoclinic crystals from water of diluted alcohol	10
molecular weight	342.30	10
dihydrate	α-form: 84-85°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	7.5-8.5 (aq. 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 β-form: needles; hygroscopic	10
molecular weight	164.16	10
melting point	α-form: 82-92°C; sublimes at 105°C and 2 mm Hg β-form: 122-126°C	10
specific optical rotation	α-form, (α^{20}D): shows mutarotation; -7.7° ⟶ +8.9° β-form, (α^{20}_{D}): -17.0° ⟶ +31.5°	10
specific gravity (d^{20}_4)	1.4708	10
stability	α-form: loses water of crystallization upon heating, and partially changes to the β-modification β-form: changes into crystals of the α-modification upon exposure to moist air	10
	Ribose	
physical characteristics	plates from absolute alcohol	10
molecular weight	150.13	10
melting point	87°C	10
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 white to tan, granular to fine, crystalline powder technical grade may have a pleasant odor	22 3 16
molecular weight	218.14	16
melting point	170-175°C; decomposes at 196-198°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

Table 2. Chemical and Physical Properties

Property	Description	Reference
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 160-186°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°	10
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	144-145°C	10
solubility	soluble in glycerol, pyridine, hot alcohol	10
specific optical rotation (α^{20}_D)	shows mutarotation; +92° → +18.6° (16 hrs)	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	
	- obtained from glucose in corn syrup by the use of glucose isomerase	3,13
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	
	L-: a common component of many N- and O-linked glycans and glycolipids produced by mammals	48
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

Table 3. Natural Occurrence and /or Methods of Preparation

Ingredient	Natural Occurrence and/or Method of Preparation	Reference
Glucose	- produced by the complete hydrolysis of corn starch with safe and suitable acids or enzymes, followed by refinement and crystallization from the resulting hydrolysate - occurs naturally and in the free state in fruits and other parts of plants; combined in glucosides, in disaccharides and oligosaccharides, in the cellulose and starch of polysaccharides, and in glycogen; manufactured on a large scale from starch; below 50°C, α-D-glucose hydrate is the stable crystalline form, above 50°C, the anhydrous form is obtained, and at higher temperatures, β-D-glucose is formed - normal human blood contains 0.08-0.1%	21CFR184.1857 10
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% - by-product of the cheese industry, produced from whey - β-lactose: obtained by crystallizing concentrated solutions of α-lactose above 93.5°C	10
Lactulose	- synthetic disaccharide composed of galactose and fructose - can be produced from agricultural by-products and from lactose	10 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 α-form: obtained by crystallization from water or ethyl alcohol β-form: prepared by heating α-rhamnose monohydrate on a steam bath	10
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 - synthesized by selective chlorination of sucrose at three of the primary hydroxyl groups - can be synthetized by the reaction of sucrose (or an acetate) with thionyl chloride	10 55 12
Sucrose	- obtained from sugar cane and sugar beet: sugar cane (*Saccharum officinarum*) contains 10-15% sucrose, sugar beet (*Beta vulgaris*) contains 10-17% sucrose - sucrose is obtained by crystallization from sugar cane or sugar beet juice that has been extracted by pressing or diffusion, then clarified and evaporated - most abundant carbohydrate in the sap of land plants	10 21CFR184.1854 49
Trehalose	- found in fungi, bacteria, yeasts, and insects; isolated from the ergot of rye; isolated from yeast - produced from starch using the enzymes maltooligosyl-trehalose synthase and maltooligosyl-trehalose trehalohydrolase	10 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 - produced industrially by hydrolysis of extracts from cotton seed shells, press residue of sugarcane and beech tree chips	10 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: 4.5-5.5% 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, 4.5-6.5%, 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, 4.5-5.5%, monohydrate; NMT 5 µg/g heavy metals; NMT 0.05% residue on ignition[14]

Table 4. Purity specifications

Ingredient	Purity Specifications
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 6.0-7.5% (monohydrate) loss on drying[3] USP: NMT 0.002% heavy metals; NMT 1.0% reducing substances; loss on drying: NMT 3.0%, anhydrous, and 6.0-7.5%, monohydrate [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]

Abbreviation: NMT – not more than

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*	**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[a]; 13[b]	spray: 0.0006-0.1 0.0000075-0.01[a]	1; 62[a]; 50[b]	0.23; aerosol: 0.0002 0.08-2[a]	2[b]	NR
Incidental Inhalation-Powder	2; 13[b]	0.2	50[b]	0.002	2[b]	NR
Dermal Contact	61	0.0000075-1	153	0.0003-20	3	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	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*	**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[b]	NR	2[a]	NR	1; 38[a]; 101[b]	0.24; spray: 1 0.0045-2.9[a]
Incidental Inhalation-Powder	1[b]	NR	NR	NR	3[c]; 101[b]	NR
Dermal Contact	1	NR	2	0.001-0.18	319	0.0001-84
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	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

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]
	Isomalt		**Kefiran**		**Lactitol**	
Totals*	**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[a]; 5[b]	NR	2[b]	NR	NR	NR
Incidental Inhalation-Powder	5[b]	NR	2[b]	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 - Non-Coloring	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*	**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[a]; 10[b]	0.0005[a]; 6[b]	NR	NR	4[a]	NR
Incidental Inhalation-Powder	10[b]	6[b]	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 - Non-Coloring	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*	**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[a]; 3[b]	0.05[a]	4[a]	NR
Incidental Inhalation-Powder	NR	NR	3[b]	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 - Non-Coloring	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

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]
	Ribose		**Sodium Gluconate**		**Sucralose**	
Totals*	**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[a]; 2[b]	NR	29[a]; 27[b]	spray: 0.0006 0.0000075-0.6[a]	3[a]	0.012-0.95[a]
Incidental Inhalation-Powder	2[b]	NR	27[b]	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 - Non-Coloring	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*	**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[a]; 84[b]	0.002; spray: 1; 0.002-2[a]	4; 163[a]; 88[b]	0.002-1[a]	1[a]; 1[b]	0.091[a]
Incidental Inhalation-Powder	4; 84[b]	NR	1; 88[b]; 1[c]	0.12	1[b]	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 - Non-Coloring	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*	**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[a]; 13[b]	pump spray: 0.11		
Incidental Inhalation-Powder	13[b]	NR		
Dermal Contact	28	NR		
Deodorant (underarm)	NR	NR		
Hair - Non-Coloring	47	0.1-0.11		
Hair-Coloring	NR	1		
Nail	NR	NR		
Mucous Membrane	NR	NR		
Baby Products	NR	NR		

* Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types my not equal the sum of total uses

a Includes products that can be sprays, but it is not known whether the reported uses are sprays

b 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

c Includes products that can be powders, but it is not known whether the reported uses are powders

NR – not reported

Table 6. Ingredients Not Reported to be Used

Galactose
Galacturonic Acid
Lactulose

Table 7. Examples of non-cosmetic uses

Ingredient	Use	Reference
Calcium Gluconate	- a direct food additive used as a firming agent, formulation aid, sequestrant, and texturizer	21CFR184.1199
	- used as mineral supplements in pharmaceutical injection solutions	[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]
	- listed in the USP/NF	[14]
	- inactive ingredient for approved drugs; used in oral products	[40]
	- can function as a coating agent, granulation aid, medicated confectionary base, sweetening agent, or tablet and capsule diluent in pharmaceuticals; a non-cariogenic excipient used in tablets or capsules, coatings, sachets, and effervescent tablets; often used in buccal applications	[12]
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 non-cariogenic 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]
	- listed in the *Foods Chemicals Codex* as a processing aid, humectant (anhydrous form), texturizer	[3]
	- inactive ingredient for approved drugs; used in transdermal, oral, sublingual, buccal, inhalation, subcutaneous, vaginal, intravenous, intramuscular, and rectal drugs	[40]
	- in pharmaceuticals, lactose, anhydrous can function as a directly compressible tablet excipient, dry powder inhaler carrier, lyophilization aid, tablet and capsule diluent, tablet and capsule filler; widely used in direct compression tableting applications and as a tablet and capsule filler and binder, and it can be used in i.v. injections	[12]
	- lactose, monohydrate can function as a dry powder inhaler carrier, lyophilization aid, tablet binder, tablet and capsule diluent, tablet and capsule filler; is widely used as a filler and diluent in tablets and capsules	
	- lactose, inhalation can function as a diluent and as a dry powder inhaler carrier; it is widely used as a carrier, diluent, and flow aid in dry powder formulations, and when of suitable particle size, it can be used to prepare soft pellets of dry powder inhaler formulations	
	- lactose, spray-dried can function as a directly compressible tablet excipient, tablet and capsule diluent, tablet and capsule filler; widely used as a binder, filler-binder, and flow aid in direct compression tableting	
Lactulose	- listed in the USP/NF as a concentrate	[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]
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]

Table 7. Examples of non-cosmetic uses

Ingredient	Use	Reference
Sucrose	- as the starting material in the fermentative production of ethanol, butanol, glycerol, citric acid, and levulinic acid	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	- listed 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

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

Nutritive[3,14,42,85]	Non-Nutritive[3,43]
fructose	lactitol
galactose	sucralose
glucose	xylose
isomalt	
lactose	
maltose	
potassium gluconate	
sodium gluconate	
sucrose	
trehalose	

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
	- 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	49
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 ionize 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 to glucose via the pentose phosphate pathway in the liver and other tissues	88
Sodium Gluconate (GRAS)	important intermediate in carbohydrate metabolism	9

Table 9. Summary metabolism data

Ingredient (GRAS foods are noted)	Metabolism Data	Reference
Sucrose	- known to be a relatively efficient source of energy; rapidly metabolizable for utilization and storage - hydrolyzed in the small intestine by sucrose to yield dextrose and fructose, which are then absorbed - there is evidence that sucrose can be absorbed unchanged to a small extent, particularly at high dietary level; nearly all ingested sucrose is absorbed as glucose and fructose, its metabolism is essentially that of these two monosaccharides - excreted unchanged in the urine when administered intravenously	51 12 49 12
	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 - metabolism is essentially identical to that of other disaccharides that are consumed as part of the human diet	12 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 - reaches the large intestine essentially unchanged, where it is metabolized by bacteria with the formation of low molecular weight acids	52 21
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
Sucralose (GRAS)	- highly water-soluble, not lipophilic, and does not bioaccumulate; the major portion of an oral dose of sucralose is unabsorbed and excreted unchanged in the feces of rats, mice, rabbits, dog, and man; only two minor metabolites were detected following oral dosing in the mouse, rat, and man, and only one urinary metabolite was found in the rabbit and the dog - not metabolized or used for energy in mammalian systems	23,55-59,89 60
	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

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	*Saccharomyces 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	≤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]
Sodium Gluconate	0, 1.25,or 2.5 g/kg in physiological saline	chromosomal aberration assay; mice were dosed orally with 1 ml, 1x/day for 4 days	mouse bone marrow cells; C57BL male mice, 2 (control and low dose) or 3 (high dose)/group	not clastogenic; 1 animal of each test group died	[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 h 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 h; micronuclei were evaluated after 6 h, the study was preliminary and was not Good Laboratory Practices (GLP)-compliant	male and female CD-1 COBS Swiss mice; 5/sex/group	negative	[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 h 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]

Table 10. Genotoxicity studies

Test Article	Concentration/Vehicle	Procedure	Test System	Results	Reference
Trehalose	1.25, 2.5, and 5 g/kg in distilled water	micronucleus test; mice were dosed by gavage for 3 days and killed on day 4	male mice; 10/group	negative; no mortality	[53]

Table 11. Irritation and Sensitization Studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			NON-HUMAN		
Gluconic Acid	50% aq. solution 0.5 ml	6 rabbits/group	- 1 sq. in. occlusive patch was applied for 4 h - test sites of one group was abraded - test sites were scored after 24, 48, and 72 h	- slight erythema observed during the initial observation; it is not clear if this is only for abraded skin - no signs of irritation at 72 h	[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 subjects	HRIPT induction: the test material was applied neat under semi-occlusive patches; 9 applications were made over a 3-wk period; the first patch was applied for 48 h, and the remainder for 24 h challenge: the patch was applied after a 2-wk non-treatment period to a previously untreated site; the test sites were scored 48 and 96 h after application.	not an irritant or a sensitizer	.[78]
a leave-in hair product containing **8% glucose**	applied neat 0.2 ml	208 subjects	HRIPT; 24-h, 2 cm^2, semi-occlusive patches were used	not a sensitizer 1% of subjects had a "+" reaction during induction	[77]
mixture containing **isomalt**	final applied concentration of isomalt is 0.94% 20 µl	49 subjects	- single insult patch test; test material was applied to the ventral forearm using Finn Chambers, and the test site was scored 15 min, 24 h, and 48 h after patch removal - SDS (not defined) was used as a positive control - water was the negative control	not an irritant; no reactions to the test formulation were observed	[80]
face and neck product containing **0.1% kefiran**	applied neat	100 subjects	HRIPT using semi-occlusive patches	not an irritant or sensitizer	[69]
paste mask and mud pack containing **0.15% lactitol**	applied neat	28 subjects	4-wk in-use dermal study with open applications	not an irritant	[69]
paste mask and mud pack containing **0.15% lactitol**	applied neat	110 subjects	HRIPT using semi-occlusive patches	not an irritant or sensitizer	[69]
face and neck product containing **2.48% lactose**	applied neat	114 subjects	HRIPT using occlusive patches	not an irritant or sensitizer	[69]

Table 11. Irritation and Sensitization Studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
leave-on facial product containing **5% mannose**	applied neat	103 subjects	HRIPT with 48-72 h occlusive induction patches and a 48-h challenge patch - distilled water was used as a negative control.	not an irritant or a sensitizer	[79]
leave-on formulation containing **10% rhamnose**	applied neat	106 subjects	HRIPT using 48-72 h occlusive patches - distilled water was used as a negative control.	- not a sensitizer - irritation reaction consisting of severe to mild erythema, bulla, coloration, fissuring, and scabbing was observed in one subject	[76]
lip balm formulation containing **0.6% sucralose**	applied neat	50 subjects	modified Draize HRIPT; similar to that described previously, with the exceptions that all the induction patches were applied for 24 h, the challenge patch was applied for 24 h, and the challenge sites scored 24 and 48 h after application	not an irritant or sensitizer	[81]
rinse-off hair product containing **29% sucrose**	diluted to 50% in distilled water 0.02 ml over 50 mm^2	102 subjects	HRIPT using 48-72 h occlusive patches for induction, and a 48-h patch at challenge	- not an irritant or sensitizer - mean irritation index of <0.25; 16% of the subjects presented with score ≥2 reactions during induction	[83]
eye cream formulation containing **0.1% xylobiose**	applied neat	56 subjects	HRIPT using 24-h occlusive patches	not an irritant or sensitizer	[82]

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SAFETY DATA SHEET
GLUCOSE SYRUP 4280R

SECTION 1: Identification of the substance/mixture and of the company/undertaking

1.1 Product identifier:

Product name: **GLUCOSE SYRUP 4280R**
Product No.: 000000201782
Synonyms: 42/43 REGULAR CORN SYRUP
Chemical name: Syrups, hydrolyzed starch
CAS-No.: 8029-43-4

1.2 Relevant identified uses of the substance or mixture and uses advised against:

Identified uses:	Uses advised against:
Industrial., Food., Animal Feed.,	None Reported

1.3 Details of the supplier of the safety data sheet:

Supplier:
ROQUETTE AMERICA Inc.
1003 S. 5th STREET
52632 - 6647 KEOKUK, IA - U.S.A

Telephone: +1 319 524 5757
Fax: +1 319 526 3371
E-mail: sds@roquette.com

1.4 Emergency telephone number:

CHEMTREC USA : 1-800-424-9300 Outside the US: +1 703-527-3887

SECTION 2: Hazards identification

2.1 Classification of the substance or mixture:

This product is not hazardous according to OSHA 29CFR 1910.1200.

2.2 Label elements: Not applicable

2.3 Other hazards: No data available.

SECTION 3: Composition/information on ingredients

3.1 Substance:

Chemical name	Concentration	CAS-No.
Syrups, hydrolyzed starch	>=80%	8029-43-4

SECTION 4: First aid measures

4.1 Description of first aid measures:

Inhalation: Under normal conditions of intended use, this material is not expected to be an inhalation hazard.

Eye contact: Flush thoroughly with water for at least 15 minutes. Get medical assistance.

Skin contact:	Wash with soap and water. For hot product: Immediately immerse in or flush affected area with large amounts of cold water to dissipate heat. Cover with clean cotton sheeting or gauze and get prompt medical attention.
Ingestion:	Product not hazardous when ingested.
4.2 Most important symptoms and effects, both acute and delayed:	Material may be hot. May cause severe thermal burns.

4.3 Indication of any immediate medical attention and special treatment needed:

Treatment:	Treat symptomatically.

SECTION 5: Firefighting measures

5.1 Extinguishing media:

Suitable extinguishing media:	Water spray, foam, dry powder or carbon dioxide.
Unsuitable extinguishing media:	None known.
5.2 Special hazards arising from the substance or mixture:	Fire or excessive heat may produce hazardous decomposition products. See Section 10.

5.3 Advice for firefighters:

Special Fire Fighting Procedures:	Cool containers exposed to heat with water spray and remove container, if no risk is involved.
Special protective equipment for fire-fighters:	Firefighters must use standard protective equipment including flame retardant coat, helmet with face shield, gloves, rubber boots, and in enclosed spaces, SCBA.

SECTION 6: Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures:	Caution: Contaminated surfaces may be slippery. See Section 8 of the SDS for Personal Protective Equipment.
6.2 Environmental precautions:	Not regarded as dangerous for the environment.
6.3 Methods and material for containment and cleaning up:	Absorb spillage with suitable absorbent material. Collect and dispose of spillage as indicated in section 13 of the SDS. Flush area with water.
6.4 Reference to other sections:	For waste disposal, see section 13 of the SDS.

SECTION 7: Handling and storage

7.1 Precautions for safe handling:	Material may be hot. See Section 8 of the SDS for Personal Protective Equipment.
7.2 Conditions for safe storage, including any incompatibilities:	Avoid contact with oxidizing agents. Store in a dry place. Maintain an appropriate temperature to avoid crystallisation problems.
7.3 Specific end use(s):	Industrial., Food., Animal Feed.,

SECTION 8: Exposure controls/personal protection

8.1 Control parameters:

Occupational exposure limits:

This product does not contain any components >1% with specific occupational exposure limits.

8.2 Exposure controls:

Appropriate engineering controls:	No special requirements under ordinary conditions of use and with adequate ventilation.

Individual protection measures, such as personal protective equipment:

Eye/face protection:	If risk of splashing, wear safety goggles or face shield.
Skin protection:	
Hand Protection:	When material is heated, wear gloves to protect against thermal burns.
Other:	Wear suitable protective clothing.
Respiratory Protection:	No specific precautions.
Hygiene measures:	Handle the product in accordance with the good hygiene practices and safety instructions.
Environmental exposure controls:	Not regarded as dangerous for the environment.

SECTION 9: Physical and chemical properties

9.1 Information on basic physical and chemical properties:

Physical State:	Liquid
Form:	Viscous Liquid
Color:	Colorless
Odor:	Odorless
pH:	~ 4.0 at 50 %
Freezing point:	No data available.
Boiling Point:	> 100 °C
Flash Point:	Not Applicable
Flammability (solid, gas):	Not Applicable
Vapor pressure:	< 17 hPa 20 °C
Vapor density (air=1):	~ 0.7

Density:	~ 1.42 g/cm³ (20 °C)
Solubility in Water:	Completely Soluble at 20 °C
Viscosity:	~ 5,000 mPa.s 50 °C

9.2 Other information:

SECTION 10: Stability and reactivity

10.1 Reactivity: Strong oxidizing agents.

10.2 Chemical stability: Material is stable under normal conditions.

10.3 Possibility of hazardous reactions: No hazardous reactions under ordinary conditions of use and storage.

10.4 Conditions to avoid: Solutions may become hazy, partially precipitate from solution, or gel with time on exposure to low temperature.

10.5 Incompatible materials: Strong oxidizing substances.

10.6 Hazardous decomposition products: Carbon Monoxide. Carbon Dioxide.

SECTION 11: Toxicological information

11.1 Information on toxicological effects:

Acute toxicity :

Test / Substance	Species	Type / Result	Exposure	Remarks
OECD 423 D-glucitol	Mouse	LD50 - Oral : >2000 mg/kg No mortalities were reported during the study period.		- REACH data - Data from similar product.

Skin irritation. :

Test / Substance	Species	Result	Exposure	Remarks
OECD 431 Glucose syrups wheat hydrolysed	Human	In vitro Not Irritating	1 h	- REACH data -

Serious eye irritation :

Test / Substance	Species	Result	Exposure	Remarks
OECD 437 Glucose syrups wheat hydrolysed	Bovine cornea.	Not Irritating	4 h	- REACH data -
OECD 405 Glucose syrups wheat hydrolysed	Rabbit	Not Irritating	72 h	- REACH data -

Sensitization :

Test / Substance	Type	Species	Result	Remarks
OECD 429 Glucose syrups wheat hydrolysed	In vivo	Mouse	Non-Sensitising	- REACH data -

Repeated dose toxicity :

Test / Substance	Species	Result	Exposure	Remarks
OECD 453 4-O-a-D-glucopyranosyl-D-glucitol	Rat	No treatment related effects.	52 Week(s).	- REACH data - Data from similar product.

Mutagenesis :

Test / Substance	Type	Species	Result	Remarks
OECD 473 Syrups, hydrolyzed starch, hydrogenated	In vitro	Hamster	Negative	- REACH data - Data from similar product.
OECD 471 (Ames) Syrups, hydrolyzed starch, hydrogenated	In vitro	S. typhimurium	Negative	- REACH data - Data from similar product.
OECD 475 D-glucitol	In vivo	Rat	Negative	- REACH data - Data from similar product.
OECD 474 Syrups, hydrolyzed starch, hydrogenated	In vivo	Mouse	Negative	- REACH data - Data from similar product.
OECD 478 D-glucitol	In vivo	Rat	Negative	- REACH data - Data from similar product.

Carcinogenicity :

Test / Substance	Species	Route of Exposure / Exposure	Result	Remarks
OECD 453 4-O-a-D-glucopyranosyl-D-glucitol	Rat	Oral 2 Year(s)	No treatment related effects.	- REACH data - Data from similar product.

Reproductive toxicity :

Test / Substance	Species	Route of Exposure / Exposure	Result	Remarks
OECD 416 4-O-a-D-glucopyranosyl-D-glucitol	Rat	Oral 12 Week(s).	No treatment related effects.	- REACH data - Data from similar product.
OECD 414 D-glucitol	Hamster	Oral 15 day(s)	No treatment related effects. NOAEL : 1,200 mg/kg	- REACH data - Data from similar product.

SECTION 12: Ecological information

12.1 Toxicity:

Acute toxicity:

Test / Substance	Species	Type/Result	Exposure	Remarks
OECD 203 Glucose syrups wheat hydrolysed	Common Carp	LC50 : > 100 mg/l Non toxic.	96 h	- REACH data -
OECD 202 Glucose syrups wheat hydrolysed	Daphnia magna	LC50 : > 100 mg/l Non toxic.	48 h	- REACH data -
OECD 201 Glucose syrups wheat hydrolysed	Pseudokirchneriella subcapitata	LC50 : > 100 mg/l Non toxic.	72 h	- REACH data -

Chronic Toxicity: No data available.

12.2 Persistence and degradability:

Test / Substance	Result	Remarks
OECD 301b Glucose syrups wheat hydrolysed	> 73 % / 28 d The product is readily biodegradable.	- REACH data -

12.3 Bioaccumulative potential: Potential to bioaccumulate is low.

12.4 Mobility in soil: This material is readily biodegraded and is not likely to bioconcentrate.

12.5 Results of PBT and vPvB assessment: No data available.

12.6 Other adverse effects: None known.

SECTION 13: Disposal considerations

13.1 Waste treatment methods:

Product: Dispose of waste in an appropriate authorised treatment facility in accordance with regulations in force and product characteristics at time of disposal.

Packaging material: Single use packaging. Collect for salvage or disposal.

SECTION 14: Transport information

This material is not subject to transport regulations (DOT, IMDG, IATA).'

SECTION 15: Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture:

This Safety Data Sheet is in conformity with appendix D of the OSHA Hazard Communication Standard 29CFR 1910.1200.

SECTION 16: Other information

Revision Information: Not relevant.

Key literature references and sources for data: No data available.

Abbreviations and acronyms used in the SDS.:

Disclaimer: The information provided in this Safety Data Sheet (SDS) relates only to the specific product designated and may not be applicable when such product is used in combination with other materials or in any process. It is the responsibility of the user to be aware of and to follow the regulations applying to our product for its possession, handling and use.
The information given is designed only as a guidance and is not to be considered a warranty or quality specification.
All information and instructions provided in this SDS are based on the current state of our knowledge at the latest revision date indicated.

SAFETY DATA SHEET

1. Identification

Product identifier	**Tapioca Syrup 27DE**
Other means of identification	Not available.
Synonyms	Glucose syrup
Recommended use	Not available.
Recommended restrictions	None known.

Manufacturer/Importer/Supplier/Distributor information

Company name	Malt Products Corporation
Address	88 Market Street
	Saddle Brook, NJ 07663
Telephone:	1-201-845-4420
E-mail	info@maltproducts.com
Emergency phone number	1-201-845-4420

2. Hazard(s) identification

Physical hazards	Not classified.
Health hazards	Not classified.
OSHA defined hazards	Not classified.
Label elements	
Hazard symbol	None.
Signal word	None.
Hazard statement	The mixture does not meet the criteria for classification.
Precautionary statement	
Prevention	Observe good industrial hygiene practices.
Response	Wash hands after handling.
Storage	Store away from incompatible materials.
Disposal	Dispose of waste and residues in accordance with local authority requirements.
Hazard(s) not otherwise classified (HNOC)	None known.
Supplemental information	Not applicable.

3. Composition/information on ingredients

Mixtures

Chemical name	CAS number	%
Syrups	8029-43-4	100

4. First-aid measures

Inhalation	Move to fresh air. Call a physician if symptoms develop or persist.
Skin contact	Wash off with soap and water. Get medical attention if irritation develops and persists.
Eye contact	Rinse with water. Get medical attention if irritation develops and persists.
Ingestion	Rinse mouth. Get medical attention if symptoms occur.
Most important symptoms/effects, acute and delayed	Direct contact with eyes may cause temporary irritation.
Indication of immediate medical attention and special treatment needed	Treat symptomatically.
General information	Ensure that medical personnel are aware of the material(s) involved, and take precautions to protect themselves.

5. Fire-fighting measures

Suitable extinguishing media	Water fog. Foam. Dry chemical powder. Carbon dioxide (CO2).
Unsuitable extinguishing Media	None known.
Specific hazards arising from the chemical	During fire, gases hazardous to health may be formed.
Special protective equipment and precautions for firefighters	Self-contained breathing apparatus and full protective clothing must be worn in case of fire.
Fire-fighting equipment/instructions	In the event of fire, cool tanks with water spray.
Specific methods	Cool containers exposed to flames with water until well after the fire is out.

6. Accidental release measures

Personal Precautions
Keep unnecessary personnel away. Wear appropriate personal protective equipment. Ensure adequate ventilation.

Spillage
Spillages should be cleared up immediately and the floor surface cleaned.
Spillages should be disposed of in accordance with local, state and federal regulations.

7. Handling and storage

Precautions for safe handling	Use with adequate ventilation. Wear appropriate personal protective equipment. Avoid direct contact with eyes.
Conditions for safe storage, including any incompatibilities	Keep container tightly closed. Store in a well-ventilated place. Store away from incompatible materials (see Section 10 of the SDS).

8. Exposure controls/personal protection

Occupational exposure limits	No exposure limits noted for ingredient(s).
Biological limit values	No biological exposure limits noted for the ingredient(s).
Appropriate engineering Controls	General ventilation normally adequate.

Individual protection measures, such as personal protective equipment

Eye/face protection	If contact is likely, safety glasses with side shields are recommended.
Skin protection	
Hand protection	Wear suitable gloves.
Other	Wear suitable protective clothing.
Respiratory protection	In case of insufficient ventilation, wear suitable respiratory equipment.
Thermal hazards	Wear appropriate thermal protective clothing, when necessary.
General hygiene Considerations	Always observe good personal hygiene measures, such as washing after handling the material and before eating, drinking, and/or smoking. Routinely wash work clothing and protective equipment to remove contaminants.

9. Physical and chemical properties

Appearance	Liquid
Physical state	Liquid.
Form	Liquid.
Color	Colorless to Light Yellow
Odor	Odorless.
Odor threshold	Not available.
pH	4.5-6.2
Melting point/freezing point	Not available.
Initial boiling point and boiling Range	Not available.
Flash point	Not available.
Evaporation rate	Not available.
Flammability (solid, gas)	Not available.

Upper/lower flammability or explosive limits

Flammability limit - lower (%)	Not available.
Flammability limit - upper (%)	Not available.
Explosive limit - lower (%)	Not available.
Explosive limit - upper (%)	Not available.
Vapor pressure	Not available.
Vapor density	Not available.
Relative density	Not available.
Solubility(ies)	
Solubility (water)	Complete
Partition coefficient (n-octanol/water)	Not available.
Auto-ignition temperature	Not available.
Decomposition temperature	Not available.

Viscosity	Not available.

10. Stability and reactivity

Reactivity	The product is stable and non-reactive under normal conditions of use, storage and transport.
Chemical stability	Material is stable under normal conditions.
Possibility of hazardous Reactions	No dangerous reaction known under conditions of normal use.
Conditions to avoid	Contact with incompatible materials.
Incompatible materials	Strong oxidizing agents.
Hazardous decomposition Products	No hazardous decomposition products are known.

11. Toxicological information

Information on likely routes of exposure

Ingestion	No adverse effects due to ingestion are expected.
Inhalation	No adverse effects due to inhalation are expected.
Skin contact	May cause skin irritation.
Eye contact	May cause eye irritation.
Symptoms related to the physical, chemical and toxicological characteristics	Irritant effects.

Information on toxicological effects

Acute toxicity	Occupational exposure to the substance or mixture may cause adverse effects.
Skin corrosion/irritation	Prolonged skin contact may cause temporary irritation.
Serious eye damage/eye Irritation	Direct contact with eyes may cause temporary irritation.
Respiratory or skin sensitization	
Respiratory sensitization	No data available.
Skin sensitization	No data available.
Germ cell mutagenicity	No data available to indicate product or any components present at greater than 0.1% are mutagenic or genotoxic.
Carcinogenicity	This product is not considered to be a carcinogen by IARC, ACGIH, NTP, or OSHA.
Reproductive toxicity	No data available.
Specific target organ toxicity - single exposure	No data available.
Specific target organ toxicity - repeated exposure	No data available.
Aspiration hazard	No data available.

12. Ecological information (Non-Mandatory)

13. Disposal considerations (Non-Mandatory)

Waste Disposal Methods

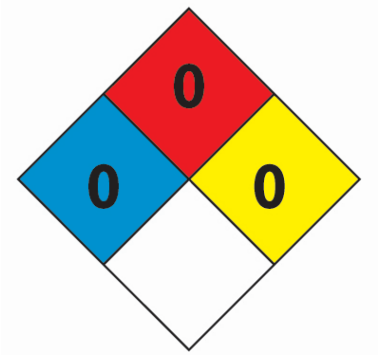
Dispose of in compliance with local, state and federal laws and regulations.

14. Transport information (Non-Mandatory)

15. Regulatory information (Non-Mandatory)

16. Other information, including date of preparation or last revision

Issue date	24-July-2017
Revision date	23-January-2020
Version #	01
NFPA Ratings	



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