ELECTRONIC SUBMISSION

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Re: "Sugars that Are Metabolized Differently Than Traditional Sugars" (Docket No. FDA-2020-N-1359)

Dear Sir or Madam,

BENEO Inc. ("BENEO") welcomes the opportunity provided by U.S. Food and Drug Administration ("FDA") to submit a comment and information on sugars that are metabolized differently than traditional sugars.

BENEO Inc. is the operating division of the BENEO group in the USA, headquartered in Parsippany, NJ. The BENEO group is a global organization specializing in plant-based food ingredients with nutritional and technical benefits. The BENEO group companies include BENEO-Palatinit GmbH (producer of isomaltulose and isomalt), BENEO-Orafti S.A. (producer of inulin and oligofructose from chicory), and BENEO-Remy N.V. (producer of rice ingredients). BENEO Inc. serves over 150 customers, including customers of isomaltulose (Palatinose™) whose finished products range from e.g. beverages, meal replacements, cereal based products, confectionery to snacks.

This comment will largely provide relevant information on Palatinose™ ("isomaltulose"), a non-traditional sugar that is metabolized differently than traditional sugars.

A. General Information About Sugars That Are Metabolized Differently Than Traditional Sugars

1. Isomaltulose

As noted by the agency in the invitation to provide information, isomaltulose is metabolized differently in the body than traditional sugars. While FDA may already be aware of isomaltulose, we would like to provide information to the docket about isomaltulose and its properties to underline its classification as “non-traditional sugar.”

Isomaltulose is a disaccharide consisting of one glucose and one fructose moiety linked via an α-1,6 glycosidic bond. The difference between sucrose and isomaltulose is the linkage between the glucose and fructose molecule – sucrose includes a α-1,2 glycosidic bond, which is much weaker than the α-1,6 linkage. This different linkage determines the physical and physiological properties of isomaltulose, which largely differ from those of sucrose and other traditional sugars. Isomaltulose occurs naturally in small quantities in honey and sugar cane juices.[1] It is approximately 50% as sweet as sucrose while it is mainly used in food applications as carbohydrate alternative for its different physiological properties. As shown in Figure 1, isomaltulose (Palatinose™) is manufactured by enzymatic conversion from sucrose by turning the α-1,2 glycosidic bond of sucrose into a much more stable α-1,6 glycosidic bond.

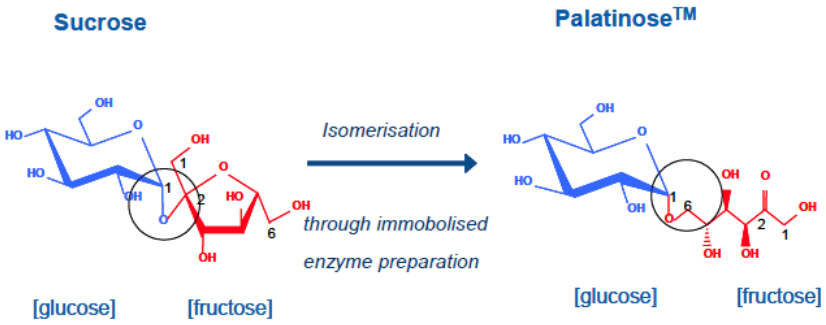

Figure 1. Enzymatic rearrangement of sucrose to isomaltulose (Palatinose™).

[1] Siddiqui IR, Furgala B (1967) Isolation and characterization of oligosaccharides from honey, Part I: Disaccharides. J Agric Res 6, 139-145; Eggleston G, Grisham M (2003) Oligosaccharides in cane and their formation on cane deterioration, In: ACS Symposium Series 849, Chapter 16, 211-232.

Due to the α-1,6 linkage, isomaltulose is metabolized differently than traditional sugars. It is slowly hydrolyzed and absorbed in the small intestine and has a positive, i.e. low effect on blood glucose and insulin levels, it creates an improved metabolic profile including the promotion of fat oxidation, and it does not promote dental caries compared to traditional sugars. It should be noted that FDA acknowledged GRAS status for isomaltulose in March 2006.[2]

a. Isomaltulose is slowly hydrolyzed and absorbed and has a positive, i.e. low effect on blood glucose and insulin compared to traditional sugars

Consuming traditional sugars leads to a very fast digestion and absorption reflected in a rapid rise in blood glucose levels, followed by a high insulin release and an insulin-induced rapid return of blood glucose concentrations to baseline levels or below. Isomaltulose does not have the same effect on blood glucose and insulin levels as traditional sugars. In contrast to traditional sugars, the blood glucose response of isomaltulose is characterized by an overall lower rise in blood glucose and insulin levels, less blood glucose fluctuations, and an extended glucose supply and processing over a longer period of time.

These 'low glycemic' properties of isomaltulose are the result of its different linkage and its resulting slower release and uptake from the small intestine into the blood: Due to its α-1,6 glycosidic bond, isomaltulose is digested more slowly than sucrose. For instance, it takes about 4 to 5 times longer for the enzymes to split isomaltulose in comparison with sucrose (enzyme kinetic data reveal a difference in Vmax by a factor of 4 to 5),[3] and its digestion and absorption occur along the entire length of the small intestine. The slower and sustained glucose release from isomaltulose leads to its lower and slower increases in blood glucose and insulin. This is reflected in the blood glucose response and insulin curves shown in Figure 2.

[2] *See* GRAS Notices, GRN No. 184, available at https://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices&id=184&sort=GRN_No&order=DESC&startrow=1&type=basic&search=184.

[3] Sentko, A, Bernard, J: Isomaltulose. In: O'Brien Nabors (Hrsg.): Alternative Sweeteners. 4. Auflage. CRC Press, Taylor & Francis Group, Boca Raton, London, New York 2011, S. 423–438.

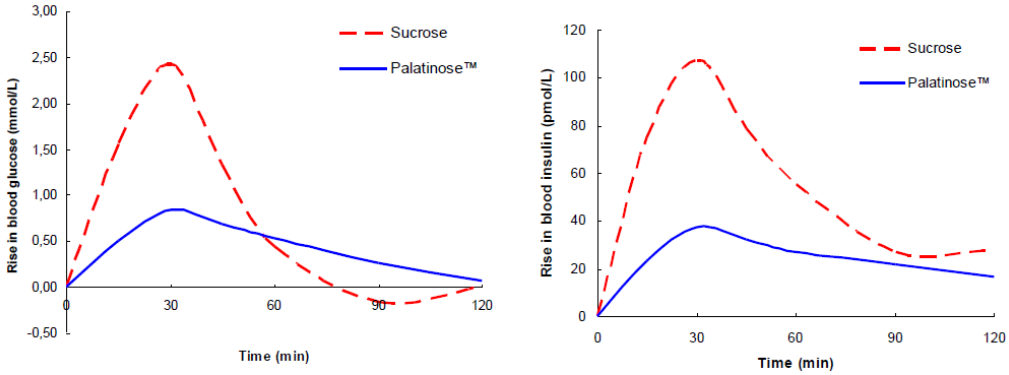

Figure 2. Typical blood glucose curve (left) and insulin curve (right) in response to isomaltulose (Palatinose™) and sucrose, as mean values of blood glucose and insulin measurements after intake of 50 g isomaltulose or sucrose in healthy adults.[4]

The effect of isomaltulose on blood glucose levels can also be quantified through the Glycemic Index (GI). The GI is a measure used to quantitatively compare how foods affect blood glucose levels.[5] Glycemic Index Testing at Sydney University following standard methodology revealed that isomaltulose has a much lower glycemic index of only 32, compared to traditional sugars like sucrose with a GI of 68 or glucose with a GI of 100 (used as reference).[6] Accordingly, isomaltulose classifies as a 'low GI' food (GI ≤ 55). Its low effects on blood glucose and insulin levels have been confirmed in a large number of clinical trials.[7] When compared to sucrose, these studies consistently show a lower

[4] Maresch CC et al (2017) Low glycemic index prototype isomaltulose – update of clinical trials. Nutrients 9(4). pii: E381.

[5] The Glycemic Index is defined as "the incremental area under the blood glucose response curve of a 50 g carbohydrate portion of a test food expressed as a percent of the response to the same carbohydrate from a standard food taken by the same subject." FAO Food and Nutrition Paper - 66, Carbohydrates in human nutrition, Chapter 4, The role of the glycemic index in food choice, available at http://www.fao.org/3/w8079e/w8079e0a.htm

[6] Sydney University's Glycaemic Research Service (SUGiRS) (2002) Glycaemic Index Report – Isomaltulose (Unpublished). See GI database at www.glycemicindex.com

[7] Ang M, Linn T (2014) Comparison of the effects of slowly and rapidly absorbed carbohydrates on postprandial glucose metabolism in type 2 diabetes mellitus patients: a randomized trial. In Am J Clin Nutr 100 (4) 1059-1068; Holub I et al (2010) Novel findings on the metabolic effects of the low glycaemic carbohydrate isomaltulose (Palatinose), Br J Nutr 103(12), 1730-7; Kahlhöfer J et al (2016) Effect of low glycemic-sugar-sweetened beverages on glucose metabolism and macronutrient oxidation in healthy men, Int J Obes (Lond) 40(6):990–997; Kawai K et al (1985) Changes in blood glucose and insulin after an oral Palatinose administration in normal subjects, Endocrinologia Japonica 32(6), 933-6; Kawai K et al (1989) Usefulness of palatinose as a caloric sweetener for diabetic patients, Hormone and metabolic research 21(6), 338-40; König D et al (2012) Postprandial substrate use in overweight subjects with the metabolic syndrome after isomaltulose (Palatinose™)

peak concentration in the blood glucose response curves: The maximum rise in blood glucose concentrations was on average 20% lower, and the maximum rise in insulin concentrations was on average 40% lower with isomaltulose versus sucrose. Corresponding blood glucose curves show a 20 to 50% lower iAUC after intake of isomaltulose versus sucrose.[8] These results were consistent across multiple study populations, including healthy adults, overweight to obese adults, adults with diabetes, and children.

Eating foods with low GI reduces the elevation of blood glucose concentrations after a meal, and studies have shown that diets low in GI induce more weight loss and lower glycated hemoglobin than other diets.[9] A scientific consensus statement by the International Carbohydrate Quality Consortium, a group of world-wide leading scientists in the area of GI / GL research, concluded from a recognized comprehensive literature review that reducing postprandial glycemia is a beneficial physiological effect with relevance to the prevention and management of diabetes mellitus (improving insulin sensitivity and beta-cell function) and the prevention of coronary heart disease (improving blood lipids and inflammatory markers), and with probable evidence also in weight management (reducing body fat mass).[10] Being a low GI carbohydrate, isomaltulose can contribute to a carbohydrate-based low glycemic diet and at the same time positively influence the metabolism towards higher fat oxidation.[11] Unlike traditional sugars, isomaltulose can also help to provide more

ingestion. Nutrition 28 (6), 651–656 ; Liao Z et al (2001) Effect of isomaltulose on blood glucose and lipids of diabetic subjects, Yingyang Xuebao 23(4), 373-375; Macdonald I, Daniel JW (1983) The bioavailability of isomaltulose in man and rat, Nutrition Reports International 28(5), 1083-90; Maeda A et al (2013) Effects of the naturally-occurring disaccharides, palatinose and sucrose, on incretin secretion in healthy non-obese subjects. J Diabetes Investig 4 (3) 281-6; Pfeiffer AFH, Keyhani-Nejad F (2018) High glycemic index metabolic damage - a pivotal role of GIP and GLP-1, Trends Endocrinol Metab 29(5):289-299; Tan WS et al (2017) Ethnic variability in glycemic response to sucrose and isomaltulose. Nutrients 9(4), pii: E347; van Can JGP et al (2009) Reduced glycaemic and insulinaemic responses following isomaltulose ingestion: implications for postprandial substrate use, Br J Nutr. 102 (10) 1408-13**;** Yamori Y et al (2007) Japanese perspective on reduction in lifestyle disease risk in immigrant japanese brazillans: a double-blind, placebo-controlled intervention study on palatinose. Clin Exp Pharmacol Physiol 34, S5.

[8] Maresch CC et al (2017) Low glycemic index prototype isomaltulose – update of clinical trials. Nutrients 9(4). pii: E381.

[9] Maresch CC et al (2017) Low glycemic index prototype isomaltulose – update of clinical trials. Nutrients 9(4). pii: E381.

[10] Augustin LS et al (2015) Glycemic index, glycemic load and glycemic response: An international scientific consensus summit from the international carbohydrate quality consortium (ICQC). Nutr Metab Cardiovasc Dis 25(9):795-815.

[11] Henry CJ et al (2017) A low glycaemic index diet incorporating isomaltulose is associated with lower glycaemic response and variability, and promotes fat oxidation in Asians. Nutrients 9(5), pii: E473;

healthy food choices to consumers and contribute to a diet that has increasingly been recognized to support metabolic health.

Regulators in Europe have recognized this beneficial property of isomaltulose. For example, the European Food Safety Authority has issued an opinion confirming that consuming isomaltulose instead of traditional sugars leads to a reduced increase in blood glucose.[12] This beneficial health effect is also subject to a corresponding EU health claim: Consumption of foods/drinks containing isomaltulose instead of other sugars induces a lower blood glucose rise after their consumption compared to sugar-containing foods/drinks.[13]

b. Despite being fully metabolized, isomaltulose promotes fat oxidation which leads to less fat storage

Isomaltulose is fully metabolized, providing four calories per gram (same as any other available carbohydrate).[14] However, examining caloric contribution alone does not tell the entire story of how isomaltulose is metabolized. As noted previously, the stable α-1,6 glycosidic bond leads isomaltulose to be digested more slowly, 4 to 5 times more slowly compared to sucrose, which leads to lower blood glucose and insulin levels. It also leads to a more favorable response of incretin hormones. It was demonstrated in human intervention studies in healthy and diabetic people that isomaltulose triggers less GIP release in early parts of the small intestine, and a higher GLP-1 release in later parts of the small intestine, the exact opposite of the incretin response to sucrose and other traditional sugars.[15]

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[12] European Food Safety Authority, Scientific Opinion on the substantiation of health claims related to the sugar replacers xylitol, sorbitol, mannitol, maltitol, lactitol, isomalt, erythritol, D-tagatose, isomaltulose, sucralose and polydextrose and maintenance of tooth mineralisation by decreasing tooth demineralisation (ID 463, 464, 563, 618, 647, 1182, 1591, 2907, 2921, 4300), and reduction of post-prandial glycaemic responses (ID 617, 619, 669, 1590, 1762, 2903, 2908, 2920) pursuant to Article 13(1) of Regulation (EC) No 1924/2006, Jan. 28, 2011, available at https://www.efsa.europa.eu/en/efsajournal/pub/2076.

[13] *See* Commission Regulation (EU) No 432/2012 of 16 May 2012 establishing a list of permitted health claims made on foods, other than those referring to the reduction of disease risk and to children's development and health; available at: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:136:0001:0040:EN:PDF (*"Consumption of foods/drinks containing <isomaltulose> instead of other sugars induces a lower blood glucose rise after their consumption compared to sugar containing foods/drinks."*).

[14] Holub I, et al (2010) Novel findings on the metabolic effects of the low glycaemic carbohydrate isomaltulose (Palatinose), Br J Nutr 103(12), 1730-7.

[15] Ang M, Linn T (2014) Comparison of the effects of slowly and rapidly absorbed carbohydrates on postprandial glucose metabolism in type 2 diabetes mellitus patients: a randomized trial. Am J Clin Nutr 100(4):1059–1068; Maeda A, Miyagawa J, Miuchi M, Nagai E, Konishi K, Matsuo T, Tokuda M, Kusunoki Y, Ochi H, Murai K, Katsuno T, Hamaguchi T, Harano Y, Namba M (2013) Effects of the naturally-occurring disaccharides, palatinose and sucrose, on incretin secretion in healthy non-obese subjects. J Diabetes Investig. 4(3):281–286; Keyhani-Nejad F, Kemper M, Schueler R, Pivovarova O, Rudovich N, Pfeiffer AF (2016) Effects of Palatinose

The hormone GIP promotes energy storage and plays an important role for metabolic effects and the quality of carbohydrates, as outlined in the review by Pfeiffer & Keyhani-Nejad.[16]

As a result of its slower and sustained carbohydrate energy supply, isomaltulose will also have less of an inhibitory effect on fat mobilization from adipose tissue and fat utilization in muscles. This means there are higher levels of fat oxidation and less storage of fat in adipose and non-adipose tissues when compared to traditional sugars. Insulin effects play a role: High insulin levels promote the predominant utilization of carbohydrate sources for energy gain and the storage of fat in muscle and adipose tissue. High glycemic diets suppress fat oxidation to a larger extent, resulting in enhanced fat storage. Isomaltulose causes less insulin release. It promotes greater utilization of fat in energy metabolism than traditional sugars (including fructose) and other high glycemic carbohydrates. Higher level of fat oxidation with isomaltulose compared to sucrose or other traditional sugars, or maltodextrins has been confirmed in a number of human intervention studies.[17] In addition, long-term effects on body weight and body composition have been observed in several studies including animal and human intervention studies. For example, consuming isomaltulose was associated with less fat accumulation in abdominal fat tissue (visceral fat) and in liver fat.[18] In a mice study, isomaltulose

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and Sucrose Intake on Glucose Metabolism and Incretin Secretion in Subjects With Type 2 Diabetes. Diabetes Care 39(3):e38-e39.

[16] Pfeiffer AFH, Keyhani-Nejad F (2018) High glycemic index metabolic damage – a pivotal role of GIP and GLP-1. Trends Endocrinol Metab 29(5):289-299.

[17] König D et al (2012) Postprandial substrate use in overweight subjects with the metabolic syndrome after isomaltulose (Palatinose™) ingestion, Nutrition 28 (6) 651-6; van Can JGP, Ijzerman TH, van Loon LJC, Brouns F, Blaak E (2009) Reduced glycaemic and insulinaemic responses following isomaltulose ingestion: implications for postprandial substrate use, Br J Nutr. 102 (10) 1408-13; van Can JG et al (2012) Reduced glycaemic and insulinaemic responses following trehalose and isomaltulose ingestion: implications for postprandial substrate use in impaired glucose-tolerant subjects, Br J Nutr. 108 (7) 1210-7; Arai et al 2007, Effects of a Palatinose-based liquid diet (Inslow) on glycemic control and the second-meal effect in healthy men. Metab Clin Exp 56, 115-121; Lightowler H, Schweitzer L, Theis S, Henry CJ (2019) Changes in weight and substrate oxidation in overweight adults following isomaltulose intake during a 12-week weight loss intervention: A randomized, double-blind, controlled trial. Nutrients 11(10), pii: E2367. doi: 10.3390/nu11102367; König D, Theis S, Kozianowski G, Berg A (2012) Postprandial substrate use in overweight subjects with the metabolic syndrome after isomaltulose (Palatinose™) ingestion. Nutrition 28 (6) 651-6; König D, Zdzieblik D, Holz A, Theis S, Gollhofer A (2016) Substrate utilization and cycling performance following Palatinose™ ingestion: A randomized, double-blind, controlled trial. Nutrients 8(7). pii: E390; Achten J, Jentjens RL, Brouns F, Jeukendrup AE (2007) Exogenous oxidation of isomaltulose is lower than that of sucrose during exercise in men, J Nutr 137, 1143-1148; West DJ, Morton RD, Stephens JW, Bain SC, Kilduff LP, Luzio S, Still R, Bracken RM (2011a) Isomaltulose improves postexercise glycemia by reducing CHO oxidation in T1DM, Med Sci Sports Exerc 43 (2) 204-10.

[18] Yamori et al (2007) Japanese perspective on reduction in lifestyle disease risk in immigrant. Japanese Brazilians: A double-blind, placebo-controlled intervention study on palatinose. Clinical and Experimental Pharmacology and Physiology 34, suppl. 1, S5-S7; Oizumi T, Daimon M, Jimbu Y, Kameda W, Arawaka N, Yamaguchi H, Ohnuma H, Sasaki H, Kato T (2007) A palatinose-based balanced formula improves glucose

feeding resulted in improvements in glucose tolerance and less liver fat, which can be regarded as indication for preventive effects regarding the development of non-alcoholic fatty liver disease and insulin resistance (diabetes mellitus). The link with less GIP release was confirmed experimentally in the same study.[19] Positive effects of isomaltulose on body weight have been described as well: Lightowler et al (2019) observed in their 12-weeks human intervention study, that a calorie-restricted diet in which sucrose was replaced for isomaltulose (at equal caloric intake) was more effective in reducing body weight, linked with the demonstrated effect of isomaltulose to increase fat oxidation.

Hence, the resulting overall improved metabolic profile with isomaltulose has long-term benefits related to blood glucose control, body weight management, and body composition, as documented by numerous animal and human clinical studies. The four calories per gram contributed by isomaltulose are not “empty calories” that can lead to issues with weight management and obesity, which concern formed the basis of FDA’s rationale for requiring the declaration of added sugars.[20] The four calories in isomaltulose do not have the same detrimental impact as four calories from traditional sugars.

Moreover, the fact that isomaltulose is fully metabolized provides an advantage over other sugar substitutes. Sugar substitutes that have a reduced or no caloric contribution are not fully metabolized by the body. This may cause gastrointestinal distress.[21] Many food manufacturers are hesitant to use such sugar substitutes for this reason. Isomaltulose, in contrast, is completely digestible. If consumed, it does not lead to gastrointestinal distress, even at high intake levels. In fact,

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tolerance, serum free fatty acid levels and body fat composition. Tohoku J Exp Med 212(2):91–99; Okuno M, Kim MK, Mizu M, Mori M, Mori H, Yamori Y (2010) Palatinose-blended sugar compared with sucrose: different effects on insulin sensitivity after 12 weeks supplementation in sedentary adults. Int J Food Sci Nutr 61(6):643–651. Keyhani-Nejad F, Irmler M, Isken F, Wirth EK, Beckers J, Birkenfeld AL, Pfeiffer, Andreas F H (2015) Nutritional strategy to prevent fatty liver and insulin resistance independent of obesity by reducing glucose-dependent insulinotropic polypeptide responses in mice. Diabetologia 58(2):374–383.

[19] Keyhani-Nejad F, Irmler M, Isken F, Wirth EK, Beckers J, Birkenfeld AL, Pfeiffer, Andreas F H (2015) Nutritional strategy to prevent fatty liver and insulin resistance independent of obesity by reducing glucose-dependent insulinotropic polypeptide responses in mice. Diabetologia 58(2):374–383.

[20] *See, e.g.*, 81 Fed. Reg. at 33815, 33788.

[21] For example, a clinical study of allulose showed that high levels of consumption of allulose lead to severe symptoms of diarrhea and GI symptoms: Han Y, Choi BR, Kim SY, Kim S-B, Kim YH, Kwon E-Y, Choi M-S (2018) Gastrointestinal Tolerance of D-Allulose in Healthy and Young Adults. A Non-Randomized Controlled Trial. Nutrients 10(12). Iida T, Kishimoto Y, Yoshikawa Y, Okuma K, YAGI K, Tatsuhiro M, Izumori K (2007) Estimation of maximum Non-effect level of D-Psicose in causing diarrheo in human subjects. J Advanced Food Ingred(10):15–19. Gastrointestinal tolerance was also observed with tagatose: Buemann B, Toubro S, Raben A, Astrup A (1999) Human tolerance to a single, high dose of D-tagatose. Regul Toxicol Pharmacol 29(2 Pt 2):S66-70. Buemann B, Toubro S, Astrup A (1999) Human gastrointestinal tolerance to D-tagatose. Regul Toxicol Pharmacol 29(2 Pt 2):S71-7. Lee A, Storey DM. Comparative gastrointestinal tolerance of sucrose, lactitol, or D-tagatose in chocolate. Regul Toxicol Pharmacol. 1999 Apr;29(2 Pt 2):S78-82.

the gastrointestinal tolerance of isomaltulose is comparable to sucrose.[22] Therefore, although isomaltulose does provide a caloric contribution, it is a desirable substitute over traditional sugars because it offers the benefits described above without the digestive challenges.

c. Isomaltulose does not promote tooth decay unlike traditional sugars

Isomaltulose is non-cariogenic. Unlike traditional sugars, it is largely resistant to utilization/fermentation by oral bacteria. The resistance leads to negligible acid production and thus, unlike traditional sugars, isomaltulose does not decrease pH below the value of 5.7 leading to tooth decay. Therefore, it does not promote tooth decay. This is reflected in FDA's health claim regulation describing isomaltulose as a dietary non-cariogenic carbohydrate sweetener and authorizing claims for isomaltulose and reduced risk of dental caries.[23] The dental health benefits of isomaltulose are also recognized in the EU with a corresponding health claim.[24]

2. Consumer Research

BENEO's consumer research which was conducted in 2019 in partnership with wizer (N=1007) shows that 60% of consumers and 66% of consumers limiting or avoiding traditional sugars are aware that some carbohydrates are more slowly released than others (Appendix 1). 49% of consumers and 56% of consumers limiting or avoiding traditional sugars believe that carbohydrates that are more slowly released are better for their health. 43% of consumers and 49% of consumers limiting or avoiding traditional sugars believe that low glycemic carbohydrates are better for their health. The data show that consumers possibly understand the differences between isomaltulose and traditional sugars. Therefore, when consumers are looking at the NFL, they would likely expect to see only traditional sugars are being accounted for total and added sugars.

In addition, our research shows that when consumers are considering the ideal carbohydrate in their food or beverage, consumers are not only concerned about the calories. They are also concerned with whether the carbohydrate will cause an energy crash, affect their teeth, or impact their blood glucose levels. In all of these respects, isomaltulose is different from traditional sugars.

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[22] Maresch CC et al (2017) Low glycemic index prototype isomaltulose – update of clinical trials. Nutrients 9(4). pii: E381.

[23] 21 CFR § 101.80(c)(2)(ii)(B).

[24] Commission Regulation (EU) No 432/2012 of 16 May 2012 establishing a list of permitted health claims made on foods, other than those referring to the reduction of disease risk and to children's development and health; available at: https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:136:0001:0040:EN:PDF (*"Consumption of foods/drinks containing <isomaltulose> instead of other sugars contributes to the maintenance of tooth mineralisation."*)

B. Declaration of Total Sugars

Total Sugars is the sum of all free mono-and disaccharides (such as glucose, fructose, lactose, and sucrose).[25] In the Final Guidance for Industry, "The Declaration of Allulose and Calories from Allulose on Nutrition and Supplement Facts Labels"[26] ("Allulose Guidance") FDA shifted its position from only considering the chemical structure for determining whether a sugar needed to be captured under Total Sugars. FDA also considered other evidence such as link to dental caries and how the ingredient is metabolized, including caloric contribution and effect on blood glucose and insulin levels. In its conclusion, FDA stated it would exercise enforcement discretion for excluding allulose from Total Sugars. The agency cited the fact that allulose did not promote dental caries, negligibly increases glycemic and insulinemic responses, and is virtually unmetabolized as reasons for its discretion.

FDA should take the same approach with isomaltulose and exercise enforcement discretion for the exclusion of isomaltulose from Total Sugars. When consumers see Total Sugar on the NFL, they think of traditional sugars. Consumers are not thinking about non-traditional sugars such as isomaltulose. To lump isomaltulose with traditional sugars in Total Sugars would be misleading and would prevent consumers from profiting from the physiological benefits of isomaltulose. As cited above, isomaltulose is different than traditional sugars in ways that are meaningful to consumers. Isomaltulose causes a lower level of glucose and insulin response. It promotes fat oxidation which leads to less fat storage. It does not promote dental caries. Therefore, we believe isomaltulose is distinct enough from traditional sugars to warrant exclusion from Total Sugars.

We believe adjusting the gram amount of the Total Sugars declaration based on caloric contribution to the diet would not be appropriate since it may mislead consumers. Non-traditional sugars may be negligible in calories, but have other properties that would not fit into FDA's goal of helping consumers maintain healthy dietary practices. An adjusted gram amount based on caloric contribution may lead consumers into thinking that a food or beverage that contains a non-traditional sugar negligible in calories is better for their health than a product containing isomaltulose just because the Total Sugars amount is less. That is not necessarily the case. There are consumers who would benefit from a product that contains isomaltulose, because it has an extended glucose supply, promotes fat oxidation, and does not cause the gastrointestinal distress caused by some non-caloric non-traditional sugars, but who might not pick up the product because of the higher amount of Total Sugars declared. Caloric contribution should not be the sole consideration for adjusting the gram amount. FDA should consider other factors such as glucose and insulin response, promotion of fat oxidation, and promotion of dental caries if it plans to take this route.

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[25] 21 CFR 101.9(c)(6)(ii).

[26] FDA, *Guidance for Industry: The Declaration of Allulose and Calories from Allulose on Nutrition and Supplement Facts Labels* (Oct. 2020).

In the Allulose Guidance, FDA considered pH of dental plaque after consumption, caloric value, and glucose and insulin response to determine whether a non-traditional sugar should be excluded from Total Sugars. FDA considered these additional factors because it believed it "should consider not only the chemical structure of sugars, but also other evidence."[27] In support of its rationale, it cited the goal of section 403(q) of the Federal Food, Drug, and Cosmetic Act ("FDCA") to help consumers maintain healthy dietary practices. With that rationale in mind, we believe FDA should take a holistic approach when considering whether to allow the exclusion of a non-traditional sugar from Total Sugars. The additional evidence or factors FDA considers should be based on the goal of helping consumers maintain healthy dietary practices.

While caloric value could be one consideration, it should not negatively impact FDA's decision to exclude a non-traditional sugar from the Total Sugars declaration. Carbohydrates serve as a central supply of energy for the body. The World Health Organization (WHO/FAO 2003) recommends that 55-75% of the daily energy intake should come from carbohydrates. Some carbohydrates are better than others. FDA should, therefore, consider the metabolic properties of the individual carbohydrate, or non-traditional sugar, when determining whether it should be excluded from the declaration of Total Sugars. Non-traditional sugars that are metabolized over a longer period of time and have an extended glucose supply are good sources of energy. Hence, such substances should only be included along with the other carbohydrates under Total Carbohydrates. Isomaltulose is one of those non-traditional sugars which is a quality and nutritive carbohydrate. As noted above, it serves as a good source of energy without the negative properties traditional sugars may provide (e.g. dramatic spikes in glucose and insulin responses and contribution to dental caries). Although it provides the same 4 kcal/g that traditional sugars, and also starches provide, isomaltulose is entering the body in a slow and balanced way leading to lower blood glucose rise. This makes isomaltulose an ideal source for energy.

Glucose and insulin responses are important considerations for determining whether a non-traditional sugar should be excluded from Total Sugars. As mentioned above, glucose and insulin responses correlate with metabolic regulation and fat oxidation, fat storage, obesity, and chronic disease. Lower insulin levels and higher fat oxidation lead to less fat storage which reduces the risk of obesity and chronic disease. Thus, in addition to glucose and insulin responses, FDA should consider a non-traditional sugar's ability to promote fat oxidation and overall metabolic health. The Dietary Guidelines for Americans 2015 ("Dietary Guidelines") set forth goals to encourage healthy eating practices in order to reduce the risk of chronic disease. FDA cited the Dietary Guidelines as a primary reason for revamping the NFL's sugar declaration. If FDA considers low glycemic modes of carbohydrate energy supply and promotion of fat oxidation, FDA would be keeping in the spirit of both the Dietary Guidelines and the agency's rationale for revising the NFL. As noted above, isomaltulose

[27] Allulose Guidance at 6.

is not “empty calories.” It in fact promotes fat oxidation which reduces the storage of fat and reduces the inhibitory effects on fat mobilization and utilization. Studies have shown when compared to sucrose, isomaltulose showed greater fat oxidation which led to a reduction in visceral fat. Since the goals of the Dietary Guidelines include reducing the risk of obesity and chronic disease, isomaltulose, as an alternative to traditional sugars, can help accomplish these goals. Fat oxidation, therefore, is a factor FDA should consider when determining whether to require a non-traditional sugar to be included in Total Sugars.

By considering these additional factors, FDA would be adhering to the goals of the Dietary Guidelines to promote healthy dietary practices and reduce the risk of obesity and chronic disease. After considering these new factors, FDA will find that isomaltulose has very different properties than traditional sugars. Therefore, it should not be lumped in with traditional sugars under Total Sugars, but instead excluded.

C. Declaration of Added Sugars

We recognize that added sugars consumption is a public health concern. The Dietary Guidelines recommend that consumers limit the intake of calories from added sugars. The excess calories from added sugars was found to lead to adiposity in adults and children, which further led to chronic disease. When FDA revised the NFL to mandate a separate line for Added Sugars, it took this into account. FDA also stated the goal of the revision was to help consumers maintain healthy dietary practices. We recognize that FDA did not base the Added Sugars declaration on risk associated with any disease or condition. Rather, the goal was to assist consumers in making choices that would lead to less consumption of added sugars. The ability for consumers to readily understand the information on the labels was important to the agency.[28]

We believe excluding isomaltulose from the Added Sugars declaration helps to accomplish FDA’s goals. We believe isomaltulose should be excluded from the Added Sugars declaration for the same reasons as stated above for Total Sugars. Although isomaltulose provides the same calories per gram as traditional sugars, its metabolic profile as a slow releasing carbohydrate and its promotion of fat oxidation makes it a better alternative to traditional sugars. Such properties have been shown to lead to less visceral fat and help in weight management when compared to traditional sugars. If isomaltulose is excluded from Added Sugars, a consumer can easily and readily pick up products with less traditional sugars based on the Added Sugars declaration. For the same reason as stated above for Total Sugars, we do not believe it would be appropriate to adjust the gram amount or %DV solely based on the caloric contribution of a non-traditional sugar.

[28] 79 FR 11879 at 11891.

We also note two impending events that may be relevant for manufacturer and consumer decision-making about added sugars. First, we understand that the 2020-2025 Dietary Guidelines are likely to recommend even lower intakes of added sugars than the prior version. Second, we understand that FDA is working on updates to its "healthy" nutrient content claim regulation, which likely will include limits on added sugars for products bearing this claim. These updates will provide food manufacturers with additional incentives to lower the added sugars content of their products. Isomaltulose offers another tool in the toolkit for reducing the traditional sugars that deliver the negative attributes of added sugars about which the Dietary Guidelines and FDA are concerned. And excluding isomaltulose from the Added Sugars declaration (as well as the Total Sugars declaration) will help consumers choose products they enjoy and which comport with the latest Dietary Guidelines and FDA's definition of "healthy."

D. Label Declarations

As stated above, we believe isomaltulose should be excluded from the Total Sugars and Added Sugars declaration because it has different properties than traditional sugars. Since isomaltulose is already accounted for in Total Carbohydrates on the NFL, and is listed as an ingredient, there is no need to mandate any additional declarations for isomaltulose.

Specifically, we believe it is not appropriate to combine sugar alcohols with non-traditional sugars that are metabolized differently than traditional sugars into one collective declaration. By combining all the non-traditional sugars with sugar alcohols into one declaration, FDA would be signaling that they are all the same. In particular, isomaltulose is vastly different than sugar alcohols in many respects. For example, isomaltulose is metabolized in its entirety while sugar alcohols and the other non-traditional sugars allulose and D-tagatose are not. The caloric contribution and glucose and insulin responses of isomaltulose are completely different than sugar alcohols. Whereas isomaltulose can be relied on by consumers as a good source of energy, sugar alcohols cannot because they are low to negligible in calories and hardly supply glucose. Polyols mostly function as sugar replacers providing bulk and some sweetness to food. Lastly, sugar alcohols like other low-digestible carbohydrates have been shown to cause gastrointestinal side effects when consumed in excess quantities. Lumping all the non-traditional sugars, including isomaltulose, together with sugar alcohols into one declaration would be misleading and confusing to consumers. Consumers who want to avoid sugar alcohols would not readily be able to rely on the NFL. Therefore, we do not support combing non-traditional sugars with sugar alcohols into one declaration. Consequently, we do not believe there is a scientifically appropriate name that would encompass a variety of non-traditional sugars and sugar alcohols collectively since they all have vastly different metabolic properties.

Conclusion

BENEO believes isomaltulose is a more nutritive alternative to traditional sugars. Based on its metabolic properties, its effects on the body are different and support a healthy diet. Therefore, FDA should exercise its discretion to exclude isomaltulose from the Total Sugars and Added Sugars declarations. Its exclusion would minimize consumer confusion and help consumers make healthy dietary choices. We urge FDA to issue a guidance document promptly announcing its enforcement discretion for excluding isomaltulose from these declarations, as the agency has done for allulose, and to promulgate an interim final rule updating its regulations at 21 C.F.R. § 101.9(c)(6)(ii) and (iii) to reflect that isomaltulose is excluded from Total Sugars and Added Sugars.

Respectfully Submitted,

Jon Peters
President BENEO Inc.

i.V. Alexander Schoch
Dr. Alexander Schoch
Head of Regulatory Affairs, BENEO GmbH

Appendix 1

connecting nutrition and health

Extract from Isomaltulose (Palatinose™) Consumer Research 2019 by BENEO

SÜDZUCKER GROUP

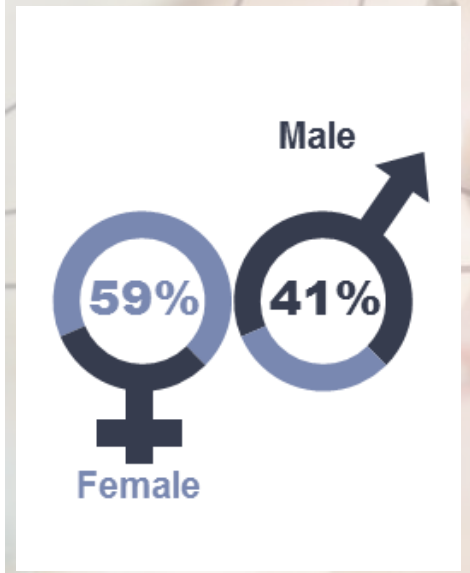
Research Details

Project

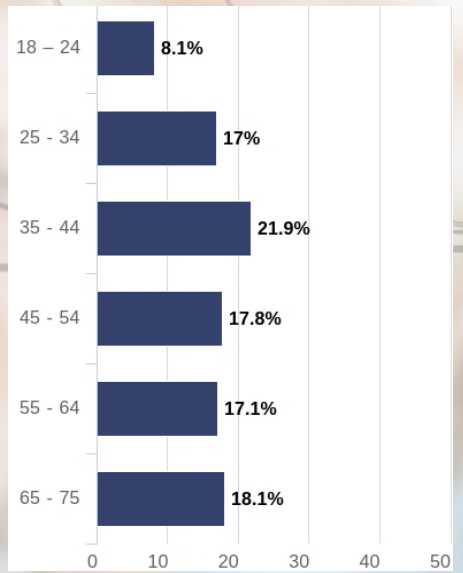
2019 QUANTITATIVE RESEARCH IN USA
IN PARTNERSHIP WITH wizer

Key Demographics

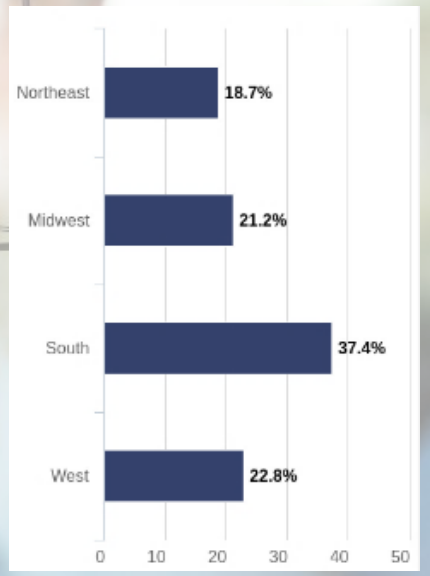
GENDER



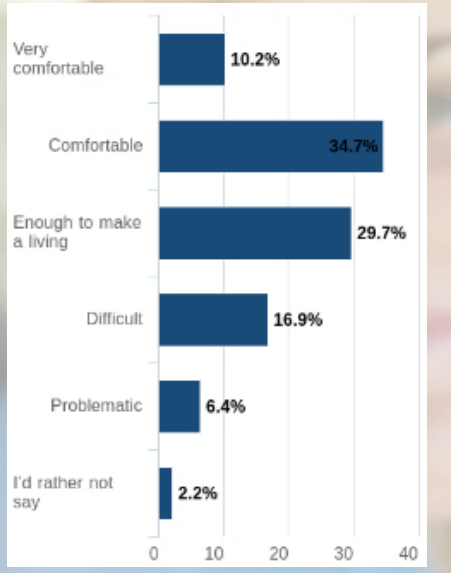
AGE



REGION



FINANCES



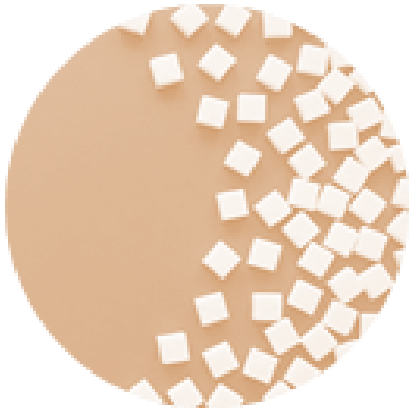
Source: BENEO Consumer Research on Functional Carbs in USA 2019 (N = 1007)

Research Details

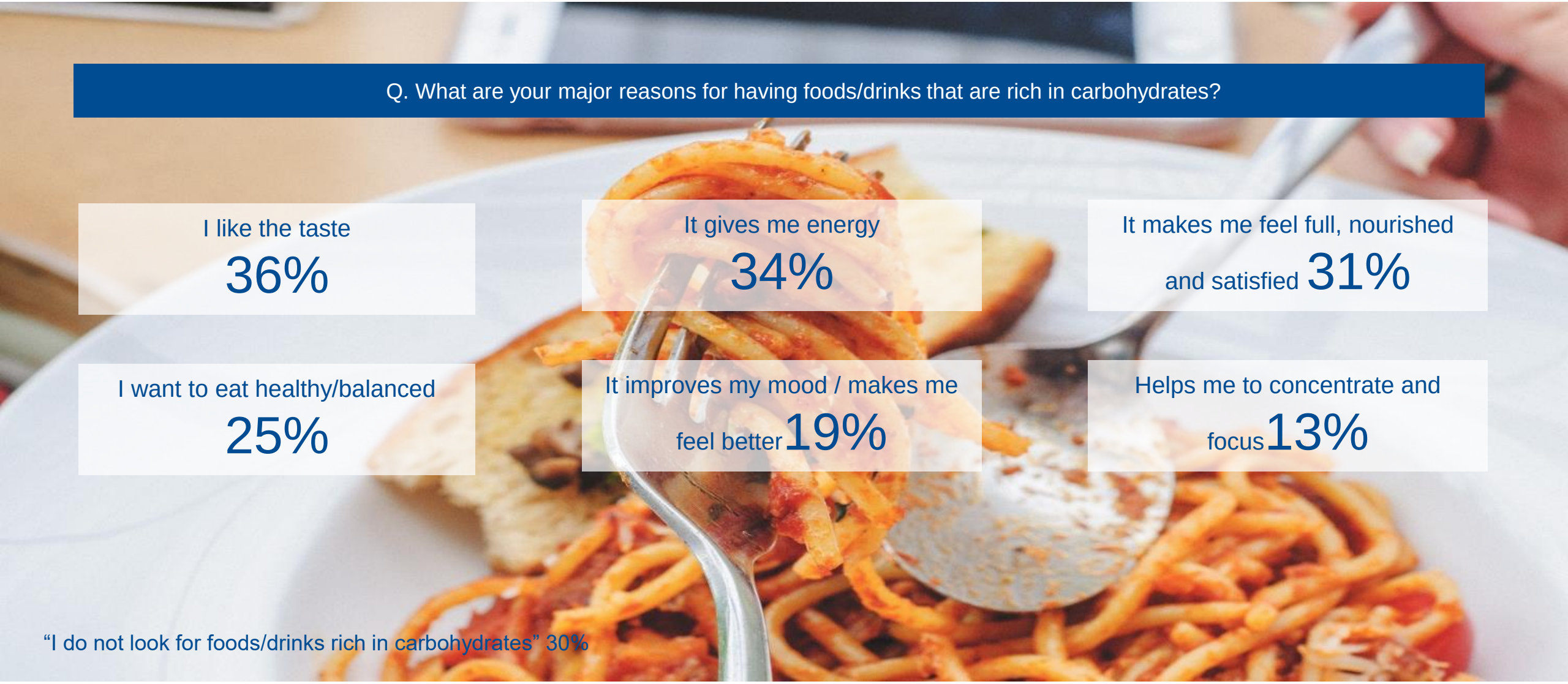
Source: BENEO Consumer Research on Functional Carbs in USA 2019 (N = 1007)


BENEO
STASERA
BENEO
White Rice
oral flora
Inulin and
replacement

Carbs & Sugar



Taste and energy are the main reasons for choosing foods/drinks rich in carbs



Q. What are your major reasons for having foods/drinks that are rich in carbohydrates?

I like the taste **36%**

It gives me energy **34%**

It makes me feel full, nourished and satisfied **31%**

I want to eat healthy/balanced **25%**

It improves my mood / makes me feel better **19%**

Helps me to concentrate and focus **13%**

"I do not look for foods/drinks rich in carbohydrates" 30%

Source: BENEO Consumer Research on Functional Carbs in USA 2019 (N = 1007)

Though weight control is key in avoiding carbs, consumers also highly consider the overall health

39% of shoppers say they try to limit or avoid carbohydrates in the diet

Q. Why do you try to limit or avoid carbohydrates (foods/drinks rich in carbohydrates)?*

Weight Management

I want to control my weight

61%

"I don't limit my carb intake" 2%

Blood Sugar Management

I am concerned about my blood sugar levels

27%

I am afraid of diabetes

20%

Carb Crash

I feel tired/sluggish after having eaten too many carbohydrates

29%

I feel too full/heavy when eating too many carbohydrates

21%

Healthy Lifestyle

I want to eat healthy

45%

I want to prevent a future health condition

29%

I want to manage an existing health condition

18%

Source: BENEO Consumer Research on Functional Carbs in USA 2019 (N = 1007)

* Asked to those who limit/avoid carbs (N = 394)

Slow carbs, an understandable and credible concept

67% believes that carbohydrates are an essential part of a balanced diet

People limiting/avoiding sugar: 69%

61% believes that different carbohydrates have a different effect on the body

People limiting/avoiding sugar 67%

60% are aware that some carbohydrates are more slowly released than others

People limiting/avoiding sugar 66%

49% believes that carbohydrates that are more slowly released are better for health

People limiting/avoiding sugar 56%

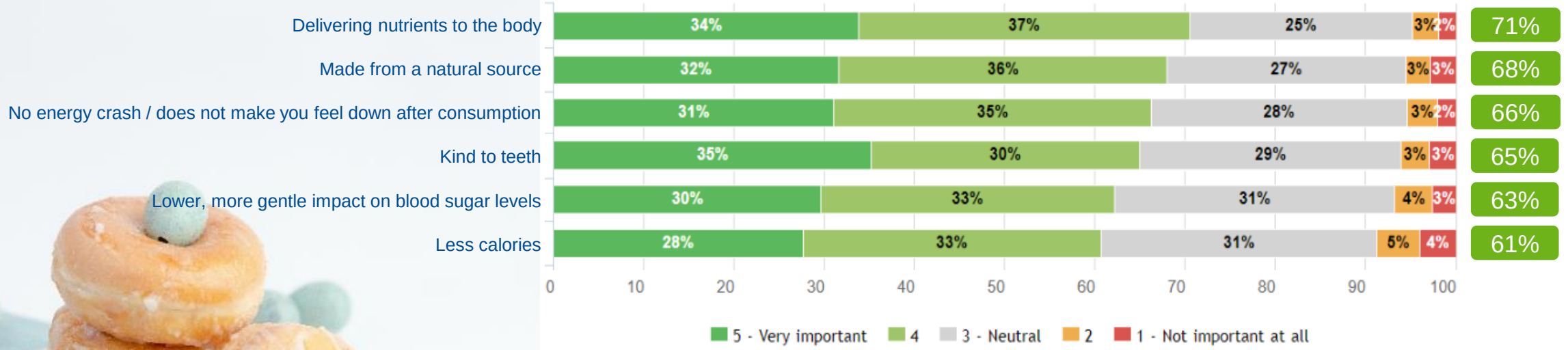
43% believes that low glycemic carbohydrates are better for health

People limiting/avoiding sugar 49%

Source: BENEO Consumer Research on Functional Carbs in USA 2019 (N = 1007) Top 2 answer: completely agree/agree

The ideal carb delivers nutrients, is made from a natural source and avoids an energy crash after consumption

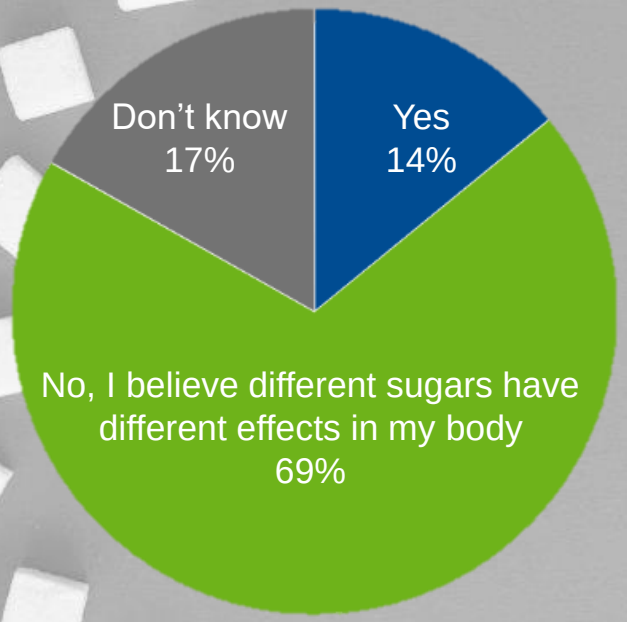
Q. How important do you consider the following criteria when thinking about an “ideal” carbohydrate being used in your foods/drinks?



Source: BENEO Consumer Research on Functional Carbs in USA 2019 (N = 1007)

Close to 70% believes that different sugars can have different effects and prefer the natural kind over low-calorie

Q. Do you think all sugars have the same effect in your body?



Q. What makes some sugars different than others?*

"**Some sugars** are simple and are broken down very quickly by our bodies while others **are complex, taking long to break down**. I think a balance of the two is probably ideal, but **simple sugars** have to be watched carefully because they will more readily **cause spikes in our blood sugar levels**."

"It makes a difference on **whether you have a sugar crash, also how it is processed** through the body."

"**Natural verses artificial is important.** Also how that sugar is released inside one's body."

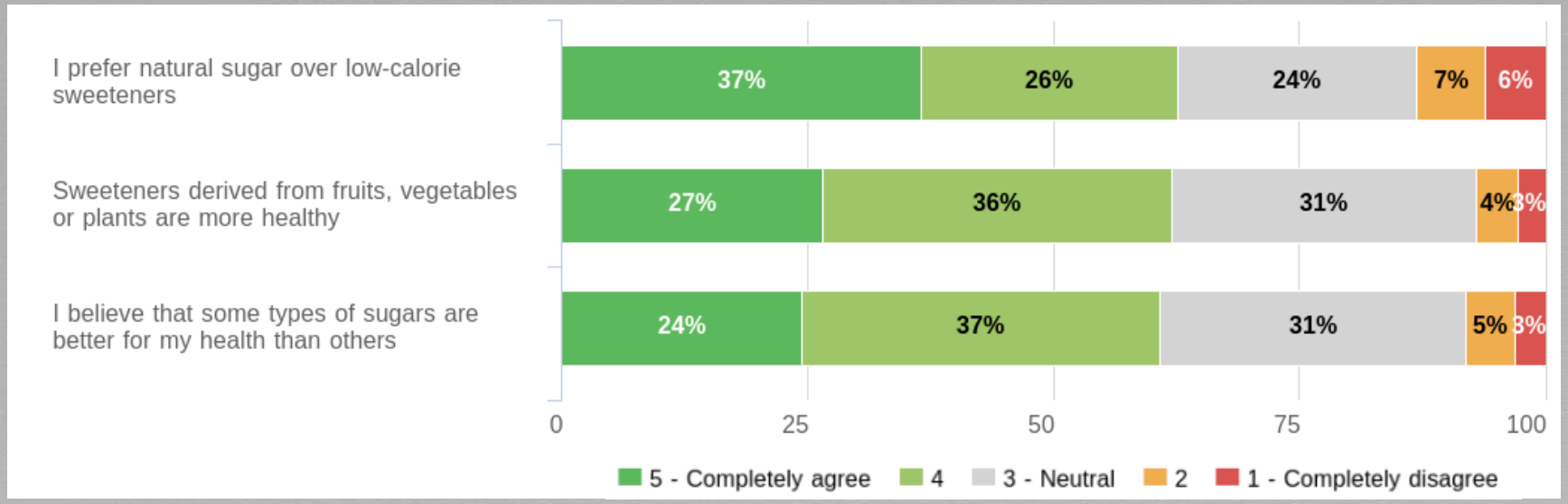
"**Some sugars** I eat or my kids eat **give a quick burst of energy**. **Some seem to give energy that lasts a long time**. I've always believed that sugars from fruits and vegetables are healthier than those derived from things like candy and some starches**. I worry about the chemicals in artificial sweeteners**."

Source: BENEO Consumer Research on Functional Carbs in USA 2019 (N = 1007)

* Asked to those who believe different sugars have different effects

While generally sugars can be part of a healthy and balanced diet, over 60% do believes that some types are better for health than others

Q. To what extent do you agree or disagree with each of the following statements?



Source: BENEO Consumer Research on Functional Carbs in USA 2019 (N = 1007)