

IFIC.org Foodinsight.org

#### WHAT IS SUCRALOSE?

Sucralose is a no-calorie sweetener that can be used to lower one's intake of added sugars while still providing satisfaction from enjoying the taste of something sweet. While some types of sweeteners in this category are considered low-calorie (e.g., aspartame) and others are no-calorie (e.g., sucralose, monk fruit sweeteners and stevia sweeteners), collectively they are often referred to as sugar substitutes, high-intensity sweeteners, nonnutritive sweeteners or low-calorie sweeteners.

Like other no-calorie sweeteners, sucralose is intensely sweet. It is about 600 times sweeter than sugar, so only small amounts of sucralose are used to match the sweetness provided by sugar. Sucralose is permitted by the U.S. Food and Drug Administration (FDA) for use

as a general-purpose sweetener, meaning it can be used as an ingredient in any type of food or beverage. Sucralose is exceptionally stable, so foods and beverages sweetened with sucralose stav sweet under a wide range of conditions. This includes frozen foods like ice cream and other frozen desserts, as well as foods that need to be heated to high temperatures, like baked goods and foods that require sterilization. However, a recipe that uses sucralose in place of sugar may turn out slightly different because, in addition to sweetness, sugar plays several roles related to volume and texture in recipes but varies based on the type of recipe.

Sucralose is also used in tabletop sweeteners. There are numerous brands of sucralose-based tabletop sweeteners. The most common brand in the U.S. is Splenda® Original.

## HOW IS SUCRALOSE PRODUCED?

Sucralose is made from a process that begins with regular table sugar (sucrose); however, sucralose is not sugar. Three select hydroxyl groups on the sucrose molecule are replaced with three chlorine atoms. Sucralose's structure prevents enzymes in the digestive tract from breaking it down, which is an inherent part of its safety.

# BY THE INTERNATIONAL FOOD INFORMATION COUNCIL



# WHAT HAPPENS TO SUCRALOSE AFTER CONSUMPTION?

Most (about 85 percent) of consumed sucralose is not absorbed by the body and is excreted, unchanged, in the feces.<sup>1,2</sup> Of the small amount that is absorbed (about 15 percent), none is broken down for energy—therefore, sucralose does not provide any calories. All absorbed sucralose is excreted quickly in the urine.<sup>1,2</sup>

## IS SUCRALOSE SAFE TO CONSUME?

YES. More than 100 safety studies representing over 20 years of research have shown sucralose to be safe. In 1998. the FDA approved its use as a sweetener in 15 specific food categories.<sup>3</sup> In 1999, the FDA expanded its regulation to allow sucralose as a "general-purpose sweetener," meaning that it is approved for use in any type of food or beverage. Leading global health authorities such as the European Food Safety Authority (EFSA) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) have concluded that sucralose is safe for its intended use.<sup>4,5</sup> The safety of sucralose has also been confirmed by Japan's Ministry of Health, Labour and Welfare; Food Standards Australia New Zealand: and Health Canada. Based on the conclusions of these global authorities. sucralose is currently permitted for use in more than 100 countries.

The FDA has established an acceptable daily intake (ADI) for sucralose of 5 milligrams (mg) per kilogram (kg) of body weight per day. The JECFA first established an ADI of 0—15 mg/kg of body weight per day for sucralose in 1991. The European Commission's Scientific Committee on Food confirmed JECFA's ADI for sucralose in 2000.6 The ADI represents an amount 100 times less than the

quantity of sucralose found to achieve a no-observed-adverse-effect-level (NOAEL) in toxicology studies. The ADI is a conservative number that the vast majority of people will not reach. Using the ADI established by the FDA, a person weighing 150 pounds (68 kg) would exceed the ADI (340 mg of sucralose) if consuming more than 26 individual tabletop packets of sucralose every day over the course of their lifetime. While precise measurements of the total amount of sucralose people consume in the U.S. is limited, 1.6 mg/kg of body weight per day is a conservative mean estimate of sucralose intake from beverages among adults that has recently been reported.<sup>7</sup> This level of intake is well below the FDA's ADI. Globally, estimated sucralose intake from foods and beverages also remains well below the ADI established by JECFA. A 2018 scientific review found that studies conducted since 2008 raise no concerns for exceeding the ADI of the major lowand no-calorie sweeteners—including sucralose—in the general population.8 For more on how ADIs are set, see the "What is an ADI?" sidebar.

## CAN CHILDREN CONSUME SUCRALOSE?

**YES.** Health and food safety authorities such as the FDA and JECFA have concluded that sucralose is safe for adults and children to consume within the ADI. Sucralose metabolism is not expected to be different in children than it is in adults.<sup>23</sup>

Sucralose can add sweetness to a child's foods and beverages without contributing to calories consumed or added sugars intake. Sucralose is not cariogenic or fermentable like sugars, so it does not increase the risk of dental caries. With a focus on reducing consumption of added sugars in recent decades, the number of food

#### WHAT IS AN ADI?

The acceptable daily intake, or ADI, is the average daily intake over a lifetime that is expected to be safe based on significant research.9 It is derived by determining the no-observed-adverse-effect-level, or NOAEL, which is the highest intake level found to have no adverse effects in lifetime studies in animal models, divided by 100.10 Setting the ADI 100 times lower than the upper level found to have no adverse effects in toxicology studies adds a margin of safety that helps to ensure that human intakes will be safe.

and beverage products containing low-calorie sweeteners has increased. While observational research among U.S. children and adults has shown an increase in the percentage of people reporting daily consumption of products containing low-calorie sweeteners, 2 current intake of low-calorie sweeteners is considered to be well within acceptable levels, both globally and in the U.S. 78

The American Heart Association (AHA) advises against children regularly consuming beverages containing low-calorie sweeteners, instead recommending water and other unsweetened beverages such as plain milk.13 One of the notable exceptions in the 2018 AHA science advisory is made for children with diabetes, whose blood glucose management may be benefitted by consuming lowcalorie-sweetened beverages in place of sugar-sweetened varieties. Citing an absence of data, the 2019 policy statement from the American Academy of Pediatrics (AAP) does not provide



advice on children under two years of age consuming foods or beverages that contain low-calorie sweeteners.14 The 2019 AAP policy statement does, however, acknowledge potential benefits of low-calorie sweeteners for children by reducing calorie intake (especially among children with obesity), incidence of dental caries and glycemic response among children with type 1 and type 2 diabetes. The 2020-2025 Dietary Guidelines for Americans (DGA) do not recommend the consumption of lowcalorie sweeteners or added sugars by children younger than two years of age.15 This DGA recommendation is not related to body weight, diabetes or the safety of added sugars or low-calorie sweeteners. but is instead intended to avoid infants and toddlers developing a preference for overly sweet foods during this formative phase.

# CAN PREGNANT AND BREASTFEEDING WOMEN CONSUME SUCRALOSE?

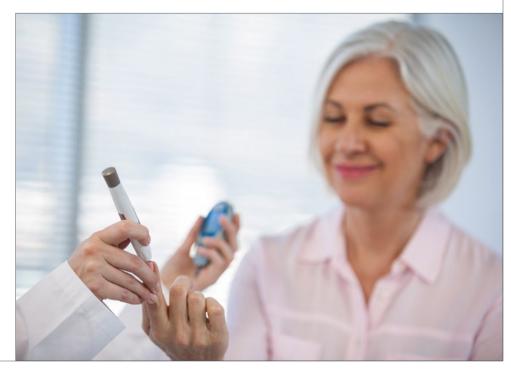
YES. The consumption of low-calorie sweeteners within their respective ADIs is safe for women who are pregnant or breastfeeding according to the EFSA, FDA and JECFA. Research has shown that sucralose has no adverse effects on expecting or nursing mothers or on the fetus, and there are no known side effects of sucralose consumption.<sup>2,16</sup> Because only small amounts of sucralose are absorbed into the bloodstream, the amount of sucralose present in breast milk is very low.<sup>17</sup> All women who are pregnant or nursing need the necessary nutrients and calories for their baby's optimal growth and development, while taking care not to exceed their needs.

# CAN PEOPLE WITH DIABETES CONSUME SUCRALOSE?

**YES.** Foods and beverages made with sucralose are frequently recommended to people with diabetes as an alternative to sugar-sweetened foods and beverages and as a way to help these individuals

satisfy their desire for sweet taste while managing carbohydrate intake. Extensive research shows that sucralose does not raise blood glucose levels or otherwise affect blood glucose management. Recent consensus statements by experts in nutrition, medicine, physical activity and public health cite the neutral effects of low-calorie sweeteners on hemoglobin AIC, insulin and fasting and post-prandial glucose, and conclude that the use of low-calorie sweeteners in diabetes selfcare may contribute to better glycemic management. 22-24

Global health professional organizations have published their own conclusions on the safety and role of low-calorie sweeteners for people with diabetes. The 2021 American Diabetes Association Standards of Medical Care in Diabetes state that, "For some people with diabetes who are accustomed to regularly consuming sugar-sweetened products, nonnutritive sweeteners (containing few or no calories) may be an acceptable substitute for nutritive sweeteners (those containing calories, such as sugar, honey, and agave syrup) when consumed in moderation. Use of nonnutritive sweeteners does not appear



to have a significant effect on glycemic management, but they can reduce overall calorie and carbohydrate intake, as long as individuals are not compensating with additional calories from other food sources." Similar statements addressing the safety and potential use of low- and no-calorie sweeteners such as sucralose for people with diabetes are supported by <u>Diabetes Canada</u> and <u>Diabetes UK.2627</u>

Despite these conclusions, some studies raise questions about sucralose and blood glucose management. For example, a 2013 randomized crossover trial of 17 insulin-sensitive individuals with obesity who did not regularly consume low-calorie sweeteners proposed that sucralose may "prime the pump" to increase blood glucose and insulin concentrations if glucose is consumed soon after sucralose.<sup>28</sup> Results of other randomized and controlled clinical trials do not support this hypothesis.<sup>29-31</sup> Larger and longer clinical trials do not indicate that sucralose adversely affects blood glucose management, 19-21,32 which illustrates the importance of examining the totality of evidence when considering the potential for sucralose (or other low-calorie sweeteners) to impact blood alucose control.

Some observational studies have demonstrated an association between low-calorie sweetener consumption and the risk for type 2 diabetes; 33,34 however, observational studies do not prove cause and effect. Conclusions from observational study designs are at risk of confounding and reverse causality. For instance, many studies do not adjust for obesity status, a direct contributor to developing prediabetes and type 2 diabetes. Given that individuals with overweight and obesity tend to consume more low-calorie-sweetened beverages as compared with lean individuals, 35 this is a critical omission.



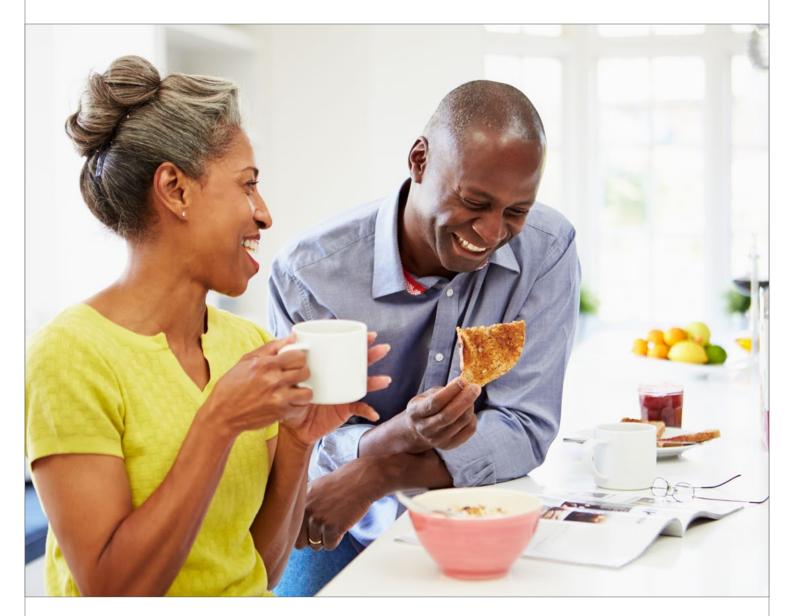
# CAN SUCRALOSE HELP WITH WEIGHT LOSS OR WEIGHT MAINTENANCE?

Substituting foods and beverages sweetened with low- and no-calorie sweeteners like sucralose for their fullsugar counterparts can play a role in weight loss and/or weight management, as demonstrated in numerous clinical trials.<sup>36-39</sup> The National Weight Control Registry (NWCR) is the largest longitudinal study of successful weight loss maintainers who have lost at least 30 pounds and kept if off for more than one year. In an online survey of 434 NWCR members, over 50 percent reported that they regularly consumed low-calorie beverages; 78 percent of these members reported that doing so helped control their calorie intake.40

Conclusions from observational research studying the impact of low-calorie sweeteners on body weight often conflict with data from randomized controlled trials. Some observational studies have reported an association between use of low-calorie sweeteners

and increased body weight and waist circumference in adults.41 A systematic review and meta-analysis of observational studies published in 2017 found that consumption of low-calorie sweeteners was also associated with increases in body mass index (BMI) and higher incidence of obesity and cardiometabolic disease in adults.<sup>42</sup> In children and adolescents, observational studies have shown an association between consumption of low-caloriesweetened beverages and increased body weight, while evidence from randomized controlled trials have not.43,44 Other recent systematic reviews and meta-analyses have concluded that findings from observational studies showed no association between lowcalorie sweetener intake and body weight and a small positive association with higher BMI.36,37,45

While observational studies can be important for generating hypotheses, it is important to note that they have limitations. By their nature, observational studies cannot prove cause and effect. Instead, observational studies examine



the association between an exposure (such as reported sucralose intake) and an outcome (such as body weight or a health condition). Associations found in observational studies can be confounded by various factors and/or may be the result of reverse causality. A common example of this is a person changing their food and beverage choices after being diagnosed with a health condition: The disease led to them making these changes; the changes they made did not lead to the disease.

Additionally, observational studies are not randomized, so they cannot control for all of the other exposures or factors that may be causing or influencing results. For example, one hypothesis is that people may compensate for "caloriefree" choices by eating or drinking more calories in other food choices or future meals.46,47 Think of a person who may justify ordering dessert at a restaurant because they had a diet soda with their meal: The extra calories from the dessert will likely be greater than the calories saved by ordering the diet beverage. These additional calories may contribute to weight gain or prevent further weight loss. This behavior is called the "licensing effect" or "self-licensing," in which an individual justifies giving in

to indulgences by finding reasons to make a behavior that is inconsistent with their goals more acceptable.<sup>48</sup> Although it may occur in some instances, there is little evidence from scientific studies that people consistently and consciously overconsume calories as a result of consuming low-calorie sweeteners or foods and beverages that contain them.<sup>49</sup>

It has also been suggested that people who already have overweight or obesity may begin to choose low-calorie-sweetened foods and beverages as one method for losing weight. This makes it difficult to assume that the use of a low-calorie sweetener can be the cause

of weight gain, since reverse causality may be a factor. A 2019 systematic review and meta-analysis funded by the World Health Organization recommended cautiously interpreting results from observational studies on low-calorie sweeteners and health outcomes while concentrating on plausible confounding and reverse causality.<sup>45</sup>

Data from randomized controlled trials, considered to be the gold standard for assessing causal effects, support that substituting low-calorie sweetener options for regular-calorie versions leads to modest weight loss. 36-39,45,55,56 In a 2016 randomized clinical trial, over 300 participants were assigned to consume either water or low-caloriesweetened beverages for one year as part of a program that included 12 weeks of weight loss followed by 40 weeks of weight maintenance interventions. Those who were assigned to the low-caloriesweetened beverage group lost 6.21 kg on average, while those in the water group lost 2.45 kg.<sup>56</sup>

While a few systematic reviews have concluded that low-calorie sweetener consumption does not lead to appreciable weight loss or weight gain, such findings appear to be the result of how the studies are compared.<sup>42</sup> As stated by Mela, et al.,<sup>53</sup> some study designs allow for the analysis of outcomes between caloric and non-caloric alternatives,<sup>37,39</sup> while others do not.<sup>42</sup>

The Scientific Report of the 2020
Dietary Guidelines Advisory Committee
(DGAC) included a systematic review of
37 studies (six of which were randomized
controlled trials) published between
January 2000 and June 2019 on the
role of low- and no-calorie-sweetened
beverages on adiposity. The DGAC report
concluded that low- and no-calorie
sweeteners should be considered an
option for managing body weight.<sup>57</sup>

It is important to note that losing



#### **SUCRALOSE AT A GLANCE**

**SCIENTIFIC NAME:** Sucralose

MOST COMMON U.S. BRAND NAME: Splenda® Original

**FDA STATUS:** First approved as a sweetener for 15 food categories in 1998. Approval expanded to "general-purpose sweetener" for use in any type of food or beverage in 1999.

and maintaining body weight requires multiple simultaneous approaches.

Making a single change, such as substituting low-calorie sweeteners for full-calorie, sugar-containing products, is just one component. Lifestyle and behavioral practices like eating healthfully, exercising regularly, getting enough sleep, and maintaining social support networks are all important factors in achieving weight loss and weight-maintenance goals.

## CAN SUCRALOSE MAKE ME HUNGRIER?

Highly palatable foods activate brain regions of reward and pleasure. This positive association can enhance appetite, and, if left unchecked, the resulting increase in food intake can lead to overweight and obesity.<sup>58</sup> Low-calorie sweeteners can also lead to a stimulation of reward pathways by activating sweet taste receptors, but they are not a source of calories.

Some have expressed concern that activating reward pathways without delivering calories to the body may have unintended consequences. Some animal studies have demonstrated changes in food intake and appetite-related hormones after consuming low-calorie sweeteners. However, other animal studies show that pathways involved in sugar digestion and preference for sugar are not activated by low-calorie sweeteners. 59.60

Low- and no-calorie sweeteners, including sucralose, have not been found to enhance appetite or cravings in humans.<sup>24,61</sup> Some randomized controlled trials<sup>62</sup> have demonstrated the opposite effect—including a decrease in hunger<sup>47</sup> and reduced dessert intake compared with those who drank water.<sup>63</sup> Others have shown no effect of sucralose on hormones that regulate hunger and fullness<sup>64,65</sup> or on total energy intake and selection of sweet foods.<sup>66,67</sup>

## WHAT ABOUT THE GUT MICROBIOME?

Although research on the gut microbiome is still in its infancy, the microbes living in the intestinal tract have become recognized as potentially significant contributors to health. In rodents that have consumed sucralose, changes in the gut microbiota species profile have been reported.<sup>68,69</sup> However, the clinical meaningfulness of such changes in rodents is not known, and the applicability of animal microbiome studies to humans may be limited.<sup>70</sup>

Currently, no standards exist to define a healthy human microbiome.<sup>71</sup> There are significant differences among the microbiome profiles of different people, and research has shown that the gut



microbiome can quickly respond to normal changes in the diet.<sup>72</sup> International experts have noted that huge variabilities in microbiome profiles makes it difficult to distinguish normal variation from adverse effects.

Sucralose is not metabolized by gut microbiota, and no adverse health effects on the gastrointestinal system are known from either human or well-controlled toxicology studies.<sup>2</sup> Human studies with repeated sucralose consumption show no meaningful effect

on the gut microbiome.<sup>70,73</sup> Consistent with this, a 2019 literature review found no conclusive evidence that low-calorie sweeteners negatively impact gut microbiota.<sup>74</sup> In 2020, a panel of experts on low-calorie sweeteners came to a similar conclusion that, at this time, data on the effects of low-calorie sweeteners on the human gut microbiota are limited and do not provide adequate evidence that they impact gut health at doses that are relevant to human consumption.<sup>24</sup>

#### WHAT'S THE BOTTOM LINE?

All types of foods and beverages, including those made with sucralose, can have a place in a variety of healthy eating patterns. Sucralose has been FDA-approved as a food additive for two decades, and its safety has been acknowledged by many international health authorities. The impact of low-calorie sweeteners on, and association with, chronic conditions like obesity and type 2 diabetes have been extensively studied. Observational studies linking low-calorie sweeteners to weight gain inherently cannot demonstrate a causal relationship and suffer from methodological issues like confounding and reverse causality. In contrast, randomized controlled trials consistently support that low-calorie sweeteners can be useful in nutritional strategies to assist with weight-loss and/or weight-maintenance goals. Sucralose has no impact on blood glucose or insulin levels in randomized controlled trials, and no effect on appetite. While the role of the gut microbiome in health is still being explored, the available research does not suggest that low- and no-calorie sweeteners such as sucralose adversely affect the gut microbiome.

Adopting a healthful, active lifestyle that is tailored to personal goals and priorities is vital to supporting one's well-being. Choosing foods and beverages sweetened with low- and no-calorie sweeteners such as sucralose is one way to reduce consumption of added sugars and keep calories in check—important components in maintaining health and reducing risk for lifestyle-related disease.



#### **REFERENCES**

- Roberts A, Renwick AG, Sims J, Snodin DJ. Sucralose metabolism and pharmacokinetics in man. Food Chem Toxicol. 2000;38 Suppl 2:S31-41.
- Magnuson BA, Roberts A, Nestmann ER. Critical review of the current literature on the safety of sucralose. Food Chem Toxicol. 2017 Aug;106(Pt A):324-355.
- <u>U.S. Food and Drug Administration</u>. Food additives permitted for human consumption. 21 C.F.R. §172.831 (1998).
- EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food). Safety of the proposed extension of use of sucralose (E 955) in foods for special medical purposes in young children. EFSA Journal. 2016 Jan;14(1):4361.
- Joint FAO/WHO Expert Committee on Food
   <u>Additive</u>D. Evaluation of certain food additives and
   contaminants: thirty-seventh report of the Joint FAO/WHO
   Expert Committee on Food Additives. Geneva, Switzerland. 1991.
- European Commission Scientific Committee on Food. Opinion of the Scientific Committee on Food on sucralose. Brussels, Belgium. 2000.
- Tran NL, Barraj LM, Hearty AP, Jack MM. Tiered intake assessment for low- and no-calorie sweeteners in beverages. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2021 Feb;38(2):208-222.
- Martyn D, Darch M, Roberts A, Lee HY, Yaqiong Tian T, Kaburagi N, Belmar P. Low-/No-Calorie Sweeteners: A Review of Global Intakes. Nutrients. 2018 Mar 15;10(3):357.
- World Health Organization, Food and Agriculture Organization
  of the United Nations. Principles and Methods for the Risk
  Assessment of Chemicals in Food, Chapter 5, 2009.
- Renwick AG. Safety factors and establishment of acceptable daily intakes. Food Addit Contam. 1991 Mar-Apr;8(2):135-49.
- <u>U.S. Food and Drug Administration</u>. Health claims: dietary noncariogenic carbohydrate sweeteners and dental caries. 21 C.F.R. §101.80 (2006).
- Sylvetsky AC, Jin Y, Clark EJ, Welsh JA, Rother KI, Talegawkar SA. Consumption of Low-Calorie Sweeteners among Children and Adults in the United States. J Acad Nutr Diet. 2017 Mar;117(3):441-448.e2.
- 13. Johnson RK, Lichtenstein AH, Anderson CAM, Carson JA, Després JP, Hu FB, Kris-Etherton PM, Otten JJ, Towfighi A, Wylie-Rosett J; American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Quality of Care and Outcomes Research; and Stroke Council. Low-Calorie Sweetened Beverages and Cardiometabolic Health: A Science Advisory From the American Heart Association. Circulation. 2018 Aug 28;138(9):e126-e140.
- Baker-Smith CM, de Ferranti SD, Cochran WJ; COMMITTEE ON NUTRITION, SECTION ON GASTROENTEROLOGY, HEPATOLOGY, AND NUTRITION. The Use of Nonnutritive Sweeteners in Children. *Pediatrics*. 2019 Nov;144(5):e20192765.

- U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2020-2025. 9th Edition. December 2020. Available at DietaryGuidelines.gov.
- Grotz VL, Munro IC. An overview of the safety of sucralose. Regul Toxicol Pharmacol. 2009 Oct;55(1):1-5.
- Sylvetsky AC, Gardner AL, Bauman V, Blau JE, Garraffo HM, Walter PJ, Rother KI. Nonnutritive Sweeteners in Breast Milk. J Toxicol Environ Health A. 2015;78(16):1029-32.
- Romo-Romo A, Aguilar-Salinas CA, Brito-Cordova GX, Gomez Diaz RA, Vilchis Valentin D, Almeda-Valdes P. Effects of nonnutritive sweeteners on glucose metabolism and appetite regulating hormones: systematic review of observational prospective studies and clinical trials. *PLoS One*. 2016 Aug 18;11(8):e0161264.
- Nichol AD, Holle MJ, An R. Glycemic impact of non-nutritive sweeteners: a systematic review and meta-analysis of randomized controlled trials. *Eur J Clin Nutr*. 2018 Jun;72(6):796-804.
- Grotz VL, Pi-Sunyer X, Porte D Jr, Roberts A, Richard Trout J. A 12-week randomized clinical trial investigating the potential for sucralose to affect glucose homeostasis. *Regul Toxicol Pharmacol*. 2017 Aug;88:22-33.
- Greyling A, Appleton KM, Raben A, Mela DJ. Acute glycemic and insulinemic effects of low-energy sweeteners: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr. 2020 Oct 1;112(4):1002-1014.
- 22. <u>Serra-Majem L</u>, et al. IberoĐAmerican Consensus on Low- and No-Calorie Sweeteners: Safety, Nutritional Aspects and Benefits in Food and Beverages. *Nutrients*. 2018 Jun 25;10(7):818.
- Evert AB, Dennison M, Gardner CD, Garvey WT, Lau KHK, MacLeod J, Mitri J, Pereira RF, Rawlings K, Robinson S, Saslow L, Uelmen S, Urbanski PB, Yancy WS Jr. Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report. *Diabetes Care*. 2019 May;42(5):731-754.
- 24. Ashwell M, Gibson S, Bellisle F, Buttriss J, Drewnowski A, Fantino M, Gallagher AM, de Graaf K, Goscinny S, Hardman CA, Laviada-Molina H, López-García R, Magnuson B, Mellor D, Rogers PJ, Rowland I, Russell W, Sievenpiper JL, la Vecchia C. Expert consensus on low-calorie sweeteners: facts, research gaps and suggested actions. *Nutr Res Rev.* 2020 Jun;33(1):145-154.
- American Diabetes Association.
   Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes-2020. *Diabetes Care*. 2020 Jan;43(Suppl 1):S48-S65.
- Diabetes Canada Clinical Practice Guidelines Expert Committee, Sievenpiper JL, Chan CB, Dworatzek PD, Freeze C, Williams SL. Nutrition Therapy. Can J Diabetes. 2018 Apr;42 Suppl 1:S64-S79.
- Dyson PA, Twenefour D, Breen C, Duncan A, Elvin E, Goff L, Hill A, Kalsi P, Marsland N, McArdle P, Mellor D, Oliver L, Watson K. Diabetes UK evidence-based nutrition guidelines for the prevention and management of diabetes. *Diabet Med*. 2018 May;35(5):541-547.



- 28. <u>Pepino MY</u>, Tiemann CD, Patterson BW, Wice BM, Klein S. Sucralose affects glycemic and hormonal responses to an oral glucose load. *Diabetes Care*. 2013 Sep;36(9):2530-5.
- Brown AW, Bohan Brown MM, Onken KL, Beitz DC. Short-term consumption of sucralose, a nonnutritive sweetener, is similar to water with regard to select markers of hunger signaling and short-term glucose homeostasis in women. *Nutr Res.* 2011 Dec;31(12):882-8.
- Stellingwerff T, Godin JP, Beaumont M, Tavenard A, Grathwohl D, van Bladeren PJ, Kapp AF, le Coutre J, Damak S. Effects of preexercise sucralose ingestion on carbohydrate oxidation during exercise. *Int J Sport Nutr Exerc Metab*. 2013 Dec;23(6):584-92.
- Temizkan S, Deyneli O, Yasar M, Arpa M, Gunes M, Yazici D, Sirikci O, Haklar G, Imeryuz N, Yavuz DG. Sucralose enhances GLP-1 release and lowers blood glucose in the presence of carbohydrate in healthy subjects but not in patients with type 2 diabetes. Eur J Clin Nutr. 2015 Feb;69(2):162-6.
- Romo-Romo A, Aguilar-Salinas CA, López-Carrasco MG, Guillén-Pineda LE, Brito-Córdova GX, Gómez-Díaz RA, Gómez-Pérez FJ, Almeda-Valdes P. Sucralose Consumption over 2 Weeks in Healthy Subjects Does Not Modify Fasting Plasma Concentrations of Appetite-Regulating Hormones: A Randomized Clinical Trial. J Acad Nutr Diet. 2020 Aug;120(8):1295-1304.
- 33. <u>Sakurai M</u>, Nakamura K, Miura K, Takamura T, Yoshita K, Nagasawa SY, Morikawa Y, Ishizaki M, Kido T, Naruse Y, Suwazono Y, Sasaki S, Nakagawa H. Sugar-sweetened beverage and diet soda consumption and the 7-year risk for type 2 diabetes mellitus in middle-aged Japanese men. *Eur J Nutr.* 2014 Feb;53(1):251-8.
- 34. Imamura F, O'Connor L, Ye Z, Mursu J, Hayashino Y, Bhupathiraju SN, Forouhi NG. Consumption of sugar sweetened beverages, artificially sweetened beverages, and fruit juice and incidence of type 2 diabetes: systematic review, meta-analysis, and estimation of population attributable fraction. BMJ. 2015 Jul 21;351:h3576.
- 35. <u>Bleich SN</u>, Wolfson JA, Vine S, Wang YC. Diet-beverage consumption and caloric intake among US adults, overall and by body weight. *Am J Public Health*. 2014 Mar;104(3):e72-8.
- Miller PE, Perez V. Low-calorie sweeteners and body weight and composition: a meta-analysis of randomized controlled trials and prospective cohort studies. Am J Clin Nutr. 2014 Sep;100(3):765-77.
- 37. Rogers PJ. Hogenkamp PS, de Graaf C, Higgs S, Lluch A, Ness AR, Penfold C, Perry R, Putz P, Yeomans MR, Mela DJ. Does low-energy sweetener consumption affect energy intake and body weight? A systematic review, including meta-analyses, of the evidence from human and animal studies. *Int J Obes* (Lond). 2016 Mar;40(3):381-94.
- Laviada-Molina H, Molina-Segui F, Pérez-Gaxiola G, Cuello-García C, Arjona-Villicaña R, Espinosa-Marrón A, Martinez-Portilla RJ. Effects of nonnutritive sweeteners on body weight and BMI in diverse clinical contexts: Systematic review and meta-analysis. Obes Rev. 2020 Jul;21(7):e13020.

- Rogers PJ, Appleton KM. The effects of low-calorie sweeteners on energy intake and body weight: a systematic review and meta-analyses of sustained intervention studies. *Int J Obes* (Lond), 2021 Mar;45(3):464-478.
- Catenacci VA, Pan Z, Thomas JG, Ogden LG, Roberts SA, Wyatt HR, Wing RR, Hill JO. Low/no calorie sweetened beverage consumption in the National Weight Control Registry. *Obesity* (Silver Spring). 2014 Oct;22(10):2244-51.
- 41. Fowler SPG. Low-calorie sweetener use and energy balance: Results from experimental studies in animals, and large-scale prospective studies in humans. *Physiol Behav.* 2016 Oct 1;164(Pt B):517-523.
- 42. Azad MB, Abou-Setta AM, Chauhan BF, Rabbani R, Lys J, Copstein L, Mann A, Jeyaraman MM, Reid AE, Fiander M, MacKay DS, McGavock J, Wicklow B, Zarychanski R. Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies. CMAJ. 2017 Jul 17;189(28):E929-E939.
- 43. <u>de Ruyter JC</u>, Olthof MR, Seidell JC, Katan MB. A trial of sugarfree or sugar-sweetened beverages and body weight in children. *N Engl J Med*. 2012 Oct 11;367(15):1397-406.
- 44. Young J, Conway EM, Rother KI, Sylvetsky AC. Low-calorie sweetener use, weight, and metabolic health among children: A mini-review. *Pediatr Obes*. 2019 Aug;14(8):e12521.
- 45. Toews I, Lohner S, Küllenberg de Gaudry D, Sommer H, Meerpohl JJ. Association between intake of non-sugar sweeteners and health outcomes: systematic review and metaanalyses of randomised and non-randomised controlled trials and observational studies. BMJ. 2019 Jan 2;364:k4718.
- 46. <u>Mattes RD</u>, Popkin BM. Nonnutritive sweetener consumption in humans: effects on appetite and food intake and their putative mechanisms. *Am J Clin Nutr*. 2009 Jan;89(1):1-14.
- 47. Peters JC, Beck J. Low Calorie Sweetener (LCS) use and energy balance. *Physiol Behav*. 2016 Oct 1;164(Pt B):524-528.
- 48. <u>De Witt Huberts JC</u>, Evers C, De Ridder DT. "Because I am worth it": a theoretical framework and empirical review of a justification-based account of self-regulation failure. *Pers Soc Psychol Rev.* 2014 May;18(2):119-38.
- Rogers PJ. The role of low-calorie sweeteners in the prevention and management of overweight and obesity: evidence v. conjecture. *Proc Nutr Soc.* 2018 Aug;77(3):230-238.
- <u>Drewnowski A</u>, Rehm CD. The use of low-calorie sweeteners is associated with self-reported prior intent to lose weight in a representative sample of US adults. *Nutr Diabetes*. 2016 Mar 7;6:e202.
- Sievenpiper JL, Khan TA, Ha V, Viguiliouk E, Auyeung R. The importance of study design in the assessment of nonnutritive sweeteners and cardiometabolic health. CMAJ. 2017 Nov 20;189(46):E1424-E1425.
- 52. <u>Malik VS</u>. Non-sugar sweeteners and health. *BMJ*. 2019 Jan 3:364:k5005.
- Mela DJ, McLaughlin J, Rogers PJ. Perspective: Standards for Research and Reporting on Low-Energy ("Artificial") Sweeteners. Adv Nutr. 2020 May 1;11(3):484-491.

### 10



#### **SUCRALOSE**

- 54. <u>Sylvetsky AC</u>, Rother KI. Nonnutritive sweeteners in weight management and chronic disease: a review. *Obesity* (Silver Spring), 2018 Apr;26(4):635-640.
- 55. <u>Ebbeling CB</u>, Feldman HA, Steltz SK, Quinn NL, Robinson LM, Ludwig DS. Effects of Sugar-Sweetened, Artificially Sweetened, and Unsweetened Beverages on Cardiometabolic Risk Factors, Body Composition, and Sweet Taste Preference: A Randomized Controlled Trial. *J Am Heart Assoc.* 2020 Aug 4;9(15):e015668.
- Peters JC, Beck J, Cardel M, Wyatt HR, Foster GD, Pan Z, Wojtanowski AC, Vander Veur SS, Herring SJ, Brill C, Hill JO. The effects of water and non-nutritive sweetened beverages on weight loss and weight maintenance: A randomized clinical trial. Obesity (Silver Spring). 2016 Feb;24(2):297–304.
- 57. <u>Dietary Guidelines Advisory Committee</u>. Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC. 2020.
- 58. <u>Singh M. Mood, food, and obesity. Front Psychol.</u> 2014 Sep 1:5:925
- 59. <u>de Araujo IE</u>. Circuit organization of sugar reinforcement. Physiol Behav. 2016 Oct 1;164(Pt B):473-477.
- Tan HE, Sisti AC, Jin H, Vignovich M, Villavicencio M, Tsang KS, Goffer Y, Zuker CS. The gut-brain axis mediates sugar preference. Nature. 2020 Apr;580(7804):511-516.
- 61. Rogers PJ. The role of low-calorie sweeteners in the prevention and management of overweight and obesity: evidence v. conjecture. *Proc Nutr Soc.* 2017 Nov 23:1-9.
- Higgins KA, Mattes RD. A randomized controlled trial contrasting the effects of 4 low-calorie sweeteners and sucrose on body weight in adults with overweight or obesity. Am J Clin Nutr. 2019 May 1;109(5):1288-1301.
- Piernas C, Tate DF, Wang X, Popkin BM. Does diet-beverage intake affect dietary consumption patterns? Results from the Choose Healthy Options Consciously Everyday (CHOICE) randomized clinical trial. Am J Clin Nutr. 2013 Mar;97(3):604-11.
- 64. Ford HE, Peters V, Martin NM, Sleeth ML, Ghatei MA, Frost GS, Bloom SR. Effects of oral ingestion of sucralose on gut hormone response and appetite in healthy normal-weight subjects. *Eur J Clin Nutr.* 2011 Apr;65(4):508-13.
- 65. <u>Steinert RE</u>, Frey F, Töpfer A, Drewe J, Beglinger C. Effects of carbohydrate sugars and artificial sweeteners on appetite and the secretion of gastrointestinal satiety peptides. *Br J Nutr*. 2011 May;105(9):1320-8.
- Bellisle F. Intense Sweeteners, Appetite for the Sweet Taste, and Relationship to Weight Management. *Curr Obes Rep.* 2015 Mar;4(1):106-10.
- Fantino M, Fantino A, Matray M, Mistretta F. Beverages containing low energy sweeteners do not differ from water in their effects on appetite, energy intake and food choices in healthy, non-obese French adults. *Appetite*. 2018 Jun 1;125:557-565.

- Bian X, Chi L, Gao B, Tu P, Ru H, Lu K. Gut Microbiome Response to Sucralose and Its Potential Role in Inducing Liver Inflammation in Mice. Front Physiol. 2017 Jul 24;8:487.
- 69. <u>Uebanso T</u>, Ohnishi A, Kitayama R, Yoshimoto A, Nakahashi M, Shimohata T, Mawatari K, Takahashi A. Effects of Low-Dose Non-Caloric Sweetener Consumption on Gut Microbiota in Mice. *Nutrients*. 2017 Jun 1;9(6):560.
- Ahmad SY, Friel J, Mackay D. The Effects of Non-Nutritive Artificial Sweeteners, Aspartame and Sucralose, on the Gut Microbiome in Healthy Adults: Secondary Outcomes of a Randomized Double-Blinded Crossover Clinical Trial. *Nutrients*. 2020 Nov 6;12(11):3408.
- Merten C, Schoonjans R, Di Gioia D, Peláez C, Sanz Y, Maurici D, Robinson T. Editorial: Exploring the need to include microbiomes into EFSA's scientific assessments. EFSA J. 2020 Jun 29:18(6):e18061.
- David LA, Maurice CF, Carmody RN, Gootenburg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, Biddinger SB, Dutton RJ, Turnbaugh PJ. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014 Jan 23;505(7484):559-63.
- 73. Thomson P, Santibañez R, Aguirre C, Galgani JE, Garrido D. Short-term impact of sucralose consumption on the metabolic response and gut microbiome of healthy adults. Br J Nutr. 2019 Oct 28;122(8):856-862.
- Lobach AR, Roberts A, Rowland IR. Assessing the in vivo data on low/no-calorie sweeteners and the gut microbiota. Food Chem Toxicol. 2019 Feb;124:385-399.