

# SCIENTIFIC PUBLICATIONS SUMMARY

## A Selection of Recent Publications Supporting the Use of Low- and No-Calorie Sweeteners

The research and evidence base for the safety and efficacy low- and no-calorie sweeteners (LNCS)\* spans decades. This summary includes synopses of key publications, reviews and research studies on this topic. (Publications are listed in reverse chronological order within each category.) Find a brief summary of the evaluation and regulatory review of LNCS in the U.S. and globally on the last page. Scientific Publications Summaries from prior years are available at <http://www.splendaprofessional.com/studies-science>. This resource is provided by Heartland Food Products Group, the manufacturer of SPLENDAS® Sweetener Products.

### INTERNATIONAL HEALTH ORGANIZATIONS AND PROFESSIONAL ASSOCIATIONS

#### American Diabetes Association (ADA) – 5. Facilitating behavior change and well-being to improve health outcomes - Standards of medical care of diabetes-2021.

[Diabetes Care. 2021;44\(Supp 1\):S53-S72.](#)

**About LNCS (abridged with relevant statements):** *“The use of nonnutritive sweeteners may have the potential to reduce overall calorie and carbohydrate intake if substituted for caloric (sugar) sweeteners and without compensation by intake of additional calories from other food sources...”*

#### Expert consensus on low-calorie sweeteners: facts, research gaps and suggested actions.

[Ashwell M, et al. Nutr Res Rev. 2020;33\(1\),145-154.](#)

**Summary:** This publication reports conclusions from an expert consensus workshop on LNCS focused on three themes: weight and glucose management, consumption, safety and perception, and lastly nutrition policy. Key conclusions: *“...the safety of LCS is demonstrated by a substantial body of evidence reviewed by regulatory experts and current levels of consumption, even for high users, are within agreed safety margins... More emphasis is required on the role of LCS in helping individuals reduce their sugar and energy intake, which is a public health priority. Based on reviews of clinical evidence to date, the panel concluded that LCS can be beneficial for weight management when they are used to replace sugar in products consumed in the diet (without energy substitution). The available evidence suggests no grounds for concerns about adverse effects of LCS on sweet preference, appetite or glucose control; indeed, LCS may improve diabetic control and dietary compliance. Regarding effects on the human gut microbiota, data are limited and do not provide adequate evidence that LCS affect gut health at doses relevant to human use.”* The experts also agreed on the need to determine optimal ways to communicate the facts about LNCS to consumers, healthcare providers and policy makers.

#### Dietary Guidelines Advisory Committee Scientific Report – 2020-2025

**About LNCS safety and use (Part D, Chapters 10, 12):** The report recommends limiting added sugars to 6% of total calories at most energy levels based on newer evidence about the negative health impacts of added sugars. Regarding safety, the report notes *“The World Health Organization, U.S. Food and Drug Administration, European Food Safety Authority, and other regulatory bodies have*

*issued guidance that the commercially available LNCS are safe when consumed in moderation.”* The report adds: *“Added sugars intakes could be greatly reduced by decreasing intakes of foods and beverages in these categories and by consuming low- or no-sugar-added versions of foods and beverages that can make positive contributions to diet.”*

#### Dietary Guidelines for Americans - 2020-2025.

**About added sugars and LNCS (guideline 4, pages 41-42):** *“When added sugars in foods and beverages exceed 10 percent of calories, a healthy dietary pattern within calories limits is very difficult to achieve. Most Americans have less than 8 percent of calories available for added sugars... an individual who needs 2,000 calories per day (based on age, sex, and physical activity level) has less than 7 percent of calories available for added sugars... It should be noted that replacing added sugars with low- and no-calorie sweeteners may reduce calorie intake in the short-term and aid in weight management...”*

#### American Cancer Society guideline for diet and physical activity for cancer prevention.

[Rock CL, et al. CA—A Cancer Journal for Clinicians. 2020;70:245-271.](#)

**Summary:** These guidelines serve as a foundation for communication, policy and community strategies to reduce cancer risk among Americans and covers numerous topics including a brief discussion on LNCS and cancer. The statement, in part, reads: *“... There is no clear evidence that these sweeteners, at the levels typically consumed in human diets, cause cancer.”*

#### American Academy of Pediatrics. The use of nonnutritive sweeteners in children.

[Baker-Smith CM, et al. Pediatrics. 2019;144\(5\):e20192765.](#)

**Summary:** This policy statement reviews the use and consumption of LNCS in the general pediatric population. The statement includes suggested talking points clinicians can use when counseling. Under Key Findings and Recommendations, the statement reads: 5. *“When substituted for caloric-sweetened foods or beverages, NNS [non-nutritive sweeteners] can reduce weight gain or promote small amounts of weight loss (~1kg) in children (and adults); however, data are limited, and the use of NNSs in isolation is unlikely to lead to substantial weight loss.”* 6. *“Individuals affected by certain conditions (eg, obesity and type 1 or 2 diabetes mellitus) may benefit from the use of NNS if substituted for caloric sweeteners.”* 9. *Health care providers are encouraged to remain alert to new information and sensitive to patient and family preferences.”*

## World Health Organization (WHO), Monographs on ID of carcinogenic hazards to humans and recommended priorities for 2020-2024. 2019.

[IARC Monographs-AG Report-Priorities 2020-2024](#)

**Summary:** IARC periodically convenes advisory groups to ensure that the Monographs evaluations reflect the current state of scientific evidence relevant to carcinogenicity and to recommend substances prioritized for further evaluation. Sucralose was one of hundreds of substances reviewed. The monograph states: “*Sucralose safety tests have indicated no acute, sub-chronic, or chronic toxicity [meaning harm] at levels well above expected human intakes.*” *The report further states that safety tests on sucralose have indicated no harm when observing sucralose consumption at levels well above expected human intakes. This report down graded sucralose to low priority for follow up.*

## Diabetes Canada. 2018 Clinical Practice Guidelines – Nutrition Therapy.

[Sievenpiper JL, et al. Can J Diabetes. 2018;42\(Supp\):S64-79.](#)

**Summary:** The Canadian nutrition therapy guidelines cover a plethora of topics on diabetes and nutrition therapy including LNCS. On LNCS, the statement reads (in part): “*...Although systematic reviews and meta-analyses of prospective cohort studies inclusive of people with diabetes have shown an adverse association of non-nutritive sweetened beverages with weight gain, CVD and stroke, it is well recognized that these data are at high risk of reverse causality. The evidence from systematic reviews and meta-analyses of randomized controlled trials, which give a better protection against bias, have shown a weight loss benefit when non-nutritive sweeteners are used to displace excess calories from added sugars (especially from SSBs) in overweight children and adults without diabetes, a benefit that has been shown to be similar to that seen with other interventions intended to displace excess calories from added sugars, such as water.*”

## Diabetes UK Position Statement. Evidence-based nutrition guidelines for the prevention and management of diabetes.

[Dyson PA, et al. Diabetic Medicine. 2018;35\(5\):541-547.](#)

**Summary:** Diabetes UK reviewed and updated their nutrition guidelines in 2018 for diabetes prevention and management. The statement on LNCS reads: “*Non-nutritive (artificial) sweeteners are safe and may be recommended.*”

## Ibero-American consensus on low- and no-calorie sweeteners: safety, nutritional aspects and benefits in food and beverages.

[Serra-Majem L, et al. Nutrients. 2018;10\(7\):818.](#)

**Summary:** International scientific experts with a range of expertise from nutrition to endocrinology, toxicology and other fields, gathered to develop consensus on this topic and provide a useful, evidence-based, point of reference to assist in efforts to reduce added sugars consumption consistent with public health recommendations. Five conclusions and key messages are stated including the need for continued education on LNCS among healthcare providers and consumers.

## European Food Safety Authority (EFSA). Statement on validity of conclusions of a mouse carcinogenicity study on sucralose (E 955) by Ramazzini Institute.

[Aguilar F, et al. European Food Safety Authority Journal. 2017;15\(5\):4784.](#)

**Summary:** EFSA published a positive scientific opinion on the safety of sucralose regarding carcinogenicity which is consistent with myriad global scientific consensus and regulatory authorities’ conclusions that sucralose is safe and does not cause cancer.

## Academy of Nutrition and Dietetics Position Paper: Use of nutritive and nonnutritive sweeteners.

[J Acad Nutr Diet. 2012;112\(5\):739-758.](#)

**About NNS:** “*It is the position of the Academy of Nutrition and Dietetics that consumers can safely enjoy a range of nutritive and nonnutritive sweeteners when consumed within an eating plan that is guided by current federal nutrition recommendations, such as the Dietary Guidelines for Americans and the Dietary Reference Intakes, as well as individual health goals and personal preference.*”

## IMPORTANCE OF STUDY DESIGN IN LOW- AND NO-CALORIE SWEETENER STUDIES

### Perspective: standards for research and reporting on low-energy (“artificial”) sweeteners.

[Mela DJ, et al. Adv Nutr. 2020;11\(3\):484-491.](#)

**Summary:** Due to widely differing views on the topic of LNCS among experts, policy makers and the general public, these authors provide their perspective on why all aspects of research on this topic should be framed and reported in a balanced manner. They discuss why there may be inconsistencies in understanding the evidence and provide recommendations to better standardize research designs, interpretation and reporting of the evidence.

### Low-energy sweeteners and cardiometabolic health: is there method in the madness.

[Khan TA, et al. Am J Clin Nutr. 2020;112\(4\):917-919.](#)

**Summary:** This editorial, published in response to Greyling A, et al (summarized under the Glycemic Management, Diabetes and Cardiometabolic Health section), discusses the need for careful attention to methodological and design challenges in systematic reviews and meta-analyses in studies assessing the value of LNCS by humans. The authors promote and explain using network meta-analysis in study designs. They advocate for more longer-term pragmatic “real world” RCT using commonly consumed foods and beverages sweetened with LNCS.

## META-ANALYSES, SYSTEMATIC AND LITERATURE REVIEWS AND PRACTICAL GUIDANCE

### The effects of low-calorie sweeteners on energy intake and body weight: a systematic review and meta-analyses of sustained intervention studies.

[Rogers PJ, et al. Int J Obes. 2021;45:464-478.](#)

**Objective:** To resolve various conclusions of systematic reviews and meta-analyses that compare different LNCS and controls including recent relevant RCT.

**Type:** Systematic review and meta-analysis

**Design:** Included 60 articles that reported 88 parallel-groups and crossover studies  $\geq 1$  week in duration reporting either body weight (BW), BMI and/or energy intake (EI) outcomes.

**Conclusions:** The consumption of LNCS instead of added sugars decreases body weight and achieves this by decreasing daily energy intake in adults and children at a healthy weight, or with overweight or obesity.

### Effects of nonnutritive sweeteners on body weight and BMI in diverse clinical contexts: Systematic review and meta-analysis.

[Laviada-Molina H, et al. \*Obes Rev.\* 2020;21\(7\):e13020.](#)

**Objective:** Assess the effects of LNCS on body weight by using only RCTs in participants at any age at a healthy weight or with overweight or obesity.

**Type:** Systematic review and meta-analysis

**Design:** Include only RCTs with a duration  $\geq 4$  weeks. 20 RCTs were determined eligible resulting in 31 interventions/comparisons.

**Conclusions:** Participants using LNCS showed significant weight/BMI differences that favored the use of LNCS compared with nonusers. This was particularly evident in participants with overweight or obesity following an unrestricted eating plan.

### Practical strategies to help reduce added sugars consumption to support glycemic and weight management goals.

[Warshaw H, et al. \*Clin Diabetes.\* 2021;39\(1\):45–56.](#)

**Summary:** This publication offers primary care providers who counsel people with diabetes practical strategies to help clients reduce consumption of added sugars and intake of low-nutrient dense foods and beverages. The article also provides information on the safety of LNCS, summarizes research on LNCS regarding glycemic and weight management. Practical strategies that offer ways to help clients integrate LNCS into their healthy eating pattern are provided.

### Just the facts: What you and your clients need to know about low/no-calorie sweeteners.

[Warshaw H, et al. 2021 \(Jan\). \*ADGES in Practice.\*](#)

**Summary:** This publication aims to dispel myths about the safety and efficacy of using LNCS in people with diabetes including impact on glucose levels, weight management, desire for sweet foods and the gut microbiome. Discussion of the importance of taste in consumer food preferences and the relationship of taste with meal plan adherence. Data showing consumer taste preferences of LNCS is provided.

### Association between intake of non-sugar sweeteners and health outcomes: systematic review and meta-analyses of randomized and non-randomised controlled trials and observational studies.

[Toews I, et al. \*BMJ.\* 2019;364:1-13.](#)

**Objective:** Assess association between intake of LCS and potential health benefits in generally healthy or overweight/obese adults and children.

**Type:** Systematic review

**Design:** Included 56 studies, 17 RCTs. Studies allowed direct comparison of no intake or lower intake of LCS with higher LCS intake. Intervention duration  $> 7$  days.

**Conclusions:** Several health benefits were found. Reduction in calorie consumption, no effect on feelings of hunger or appetite, not causing a rise in glucose levels and not contributing to tooth decay.

### Stevia leaf to stevia sweetener: Exploring its science, benefits, and future potential.

[Samuel P, et al. \*J Nutr.\* 2018;148\(7\):1186S-1205S.](#)

**Objective:** This global comprehensive report, based on a symposium held after the 2017 American Society for Nutrition meeting, aims to cover the science, safety, ADI and potential health benefits of high-purity steviol glycosides.

**Type:** Comprehensive report

**Conclusions:** Regarding science and safety, the report states: “all major global scientific and regulatory bodies have determined, through their rigorous evaluation processes, that high-purity steviol glycosides are safe for the general population.” In healthy individuals and those with diabetes the use of steviol glycosides, in place of some carbohydrate and sugars, support reduction in postprandial glucose levels and reduced carbohydrate and sugar intake.

### 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.

[Rogers PJ, et al. \*Int J Obes.\* 2016;40:381–394.](#)

**Objective:** Review a large and lengthy body of evidence including numerous types of animal and human studies on LCS.

**Type:** Systematic review with meta-analyses

**Conclusions:** Consistent with other systematic reviews of LCS, this study demonstrated decreased energy intake and body weight with consumption of LCS used in place of added sugars.

## GLYCEMIC MANAGEMENT, DIABETES AND CARDIOMETABOLIC HEALTH

### Acute glycemic and insulinemic effect of low-energy sweeteners: a systematic review and meta-analysis of randomized controlled trials.

[Greyling A, et al. \*Am J Clin Nutr.\* 2020;112\(4\):1002-1014.](#)

**Objective:** Examine the acute effect of LNCS consumption on postprandial glucose (PPG) and postprandial insulin (PPI) responses to quantify these relationships.

**Type:** Systematic review with meta-analyses

**Design:** 26 RCT included with 34 PPG trials and 29 PPI trials.

**Conclusions:** Consumption of LNCS, given alone or in combination with a nutrient-containing preload, resulted in no acute effects on the mean change in PPG or PPI responses compared with the control intervention. While there was a small beneficial effect on PPG in studies with subjects with type 2 diabetes, the effects did not differ by LNCS type or dose, or fasting glucose or insulin levels.

\*See Khan et al, editorial under section IMPORTANCE OF STUDY DESIGN IN LOW- AND NO-CALORIE SWEETENER STUDIES)

### The effect of the artificial sweeteners on glucose metabolism in healthy adults: a randomized, double-blinded, crossover clinical trial.

[Ahmad SY, et al. \*Appl Physiol Nutr Metab.\* 2020;45:606-612.](#)

**Objective:** Determine the effect of realistic amounts of the pure forms of sucralose aspartame on indicators of glucose metabolism.

**Type:** Randomized double-blinded crossover study

**Design:** 17 healthy subjects between 18–45 years of age whose BMI was between 20–25 were studied. A 4-week baseline period initiated the study during which no LNCS were consumed. Two 14-day treatment periods were separated by a 4-week washout period. The LNCS consumed were a standardized dose of 14% (0.425 g) of ADI for aspartame and 20% (0.136 g) of ADI for sucralose. Dosages were based on patterns of regular soft drink intake in Canadian men and women. Blood samples were collected and analyzed for glucose, insulin, active glucagon-like peptide-1 (GLP-1), and leptin.

**Conclusions:** Total area under the curve glucose, insulin, active GLP-1 and leptin values were similar in the treatment groups compared with subjects' baseline results. No change in insulin sensitivity occurred after either treatment in comparison to baseline. Conclusions suggest that daily and repeated consumption of pure aspartame or sucralose for 2 weeks had no effect on glucose metabolism among healthy adults with normoglycemia.

### A prospective study of artificially sweetened beverage intake and cardiometabolic health among women at high risk.

[Hinkle SN, et al. Am J Clin Nutr 2019;110:221–232.](#)

**Objective:** The aim of this study was to examine associations of LNCS beverage intake and cardiometabolic health among high-risk women with prior gestational diabetes mellitus (GDM).

**Type:** Prospective study

**Design:** 607 women with history of GDM in the Danish National Birth Cohort and followed in the Diabetes & Women's Health (DWH) studies (9–16 years) were assessed for LNCS beverage intake using FFQs during both studies. Observed cardiometabolic outcomes and estimated percentage differences in continuous cardiometabolic markers and relative risks (RRs) for clinical endpoints during pregnancy and at follow-up adjusted for pre-pregnancy BMI, diet, and lifestyle factors. Sensitivity analyses to account for reverse causation were performed.

**Conclusions:** Consumption of LNCS beverages, during pregnancy and at follow-up, was associated with higher HbA1c, insulin, HOMA-IR, triglycerides, liver fat, and adiposity and with lower HDL at follow-up. However, after careful consideration and analyses for reverse causality and confounding, the associations were not significantly associated with beneficial or detrimental cardiometabolic profiles.

### Associations of diet soda and non-caloric artificial sweetener use with markers of glucose and insulin homeostasis and incident diabetes: the Strong Heart Family Study.

[Jensen PN, et al. Eur J Clin Nutr. 2019; doi:10.1038/s41430-019-0461-6.](#)

**Objective:** Assess associations of diet soda and LNCS consumption with: 1) early markers of insulin and glucose homeostasis (cross-sectionally) and 2) incidence of a diabetes diagnosis (over average of 8 years follow-up) in American Indian population with high rates of obesity and type 2 diabetes.

**Type:** Retrospective analysis using the SHFS database. (SHFS is a family-based longitudinal study of genetics and risk factors for CVD in 12 AI communities in AZ, OK, ND, and SD.)

**Design:** 1359 SHFS participants without CVD diabetes who participated in the 2007–2009 study exam. LNCS beverages and LNCS consumption were assessed and FPG and insulin levels were measured during the study exam. Participants were followed for diagnosis of diabetes through 2017 with a phone interview and medical record review.

**Conclusions:** 40% of participants reported regularly consuming diet soda. 41% used LNCS to sweeten beverages. 98 cases of diabetes were found. Data indicate no statistically significant associations of diet soda or LNCS consumption with fasting insulin, fasting glucose, or incident diabetes.

### Effects of a rare sugar, D-allulose, coingested with fat on postprandial glycemia and lipidemia in young women.

[Kuzawa K, et al. J Nutr Hum Health. 2019;3\(1\):1-6.](#)

**Objective:** Study the effect of ingesting D-allulose (a C-3 epimer of D-fructose which is an alternative zero-calorie sweetener to natural sugars) with fat cream on postprandial glycemia and lipidemia in young women.

**Type:** Randomized single-blinded crossover design

**Design:** 11 young Japanese female university students were studied on 4 occasions and ingested one of 4 beverages after a 12-h fast: fat cream with water (F trial), fat cream with D-allulose (FA trial), fat cream with fructose (FFr trial), or fat cream with sucrose (FS trial). Venous blood samples were obtained before ingestion (0 h) and at 0.5, 1, 2, 4, and 6 h after ingestion.

**Conclusions:** When ingested with fat, D-allulose showed almost no glycemic response in contrast to fructose or sucrose. However, ingesting D-allulose with fat may delay postprandial lipidemia similar to these sugars. The rise of serum concentration of D-allulose was slower, compared with glucose or fructose, probably due to slower absorption. D-Allulose was effective for preventing postprandial glycemic response.

### Glycemic impact of non-nutritive sweeteners: a systematic review and meta-analysis of randomized controlled trials.

[Nichol AD, et al. Eur J Clin Nutr. 2018;72:796-804.](#)

**Objective:** Quantitatively synthesize existing research from RCT on the impact of 4 LCS (aspartame, saccharin, steviosides and sucralose) on glycemia in normoglycemic individuals and a subset of people with diabetes.

**Type:** Systematic review with meta-analyses

**Design:** Search PubMed and Web of Science databases for 29 RCT. Used PRISMA guidelines. Two authors screened the titles and abstracts of candidate publications. The third author was consulted to resolve discrepancies. A total of 741 subjects were included in the analysis.

**Conclusions:** The LNCS studied did not increase blood glucose levels rather levels gradually decreased. However, the impact of LNCS on glycemia varied to some extent by age, body weight and whether people had diabetes or not.

### A 12-week randomized clinical trial investigating the potential for sucralose to affect glucose homeostasis.

[Grotz VL, et al. Regul Toxicol Pharmacol. 2017;88:22-33.](#)

**Objective:** Study impact of sucralose on glucose control and other metabolic parameters over 12 weeks.

**Type:** Randomized controlled trial, double-blind, parallel design

**Design:** Study included 47 normoglycemic male volunteers who consumed ~333.3 mg encapsulated sucralose or placebo three times a day at mealtimes. This amount was equivalent to ~200 g of added sugars per meal. A1c, fasting glucose, insulin, and C-peptide levels were measured weekly. Adherence was carefully measured.

**Conclusions:** Results showed glucose, insulin, C-peptide and A1c levels were within normal ranges. Findings support that sucralose has no effect on glycemic control. Discussion section offers valuable review of recent research on LNCS, glucose control and impact of gastrointestinal sweet taste receptors.

### Impact of diet composition on blood glucose regulation.

[Russell WR, et al. Crit Rev Food Sci Nutr. 2016;56\(4\):541-590.](#)

**Objective:** Explore human studies focused on various dietary components and their impact on blood glucose levels to prevent and manage type 2 diabetes. This included the impact of the major macronutrients, micronutrients, nonnutrient phytochemicals, and LNCS as well as research on various LNCS related to glucose regulation including impact on gut hormones and glucose, C-peptide and insulin levels.

**Type:** Review

**Conclusions:** The use of LNCS in subjects with or without diabetes does not affect glucose levels, however, dietary components have significant and clinically relevant effects on blood glucose modulation.

## GUT HEALTH AND MICROBIOME, HUNGER AND APPETITE

### The effect of the artificial sweeteners, aspartame and sucralose, on the gut microbiome in healthy adults: Secondary outcomes of a randomized, double-blinded, crossover clinical trial.

[Ahmad SY, et al. \*Nutrients\*. 2020;12\(11\):3408.](#)

**Objective:** Determine the effect of sucralose and aspartame consumption on gut microbiota composition using realistic amounts of the pure forms of these LNCS.

**Type:** Randomized double-blinded crossover study (secondary outcomes study – see primary study by Ahmad SY, et al. under glycemic management, diabetes and cardiometabolic health.)

**Design:** 17 healthy subjects between 18 and 45 years of age whose BMI was between 20–25 were studied. Two 14-day treatment periods were separated by a 4-week washout period. The sweeteners consumed were a standardized dose of 14% (0.425 g) of ADI for aspartame and 20% (0.136 g) of ADI for sucralose. Before and after fecal samples were collected and analyzed for microbiome and short-chain fatty acids (SCFAs).

**Conclusions:** No differences were found in the median relative proportions of the most abundant bacterial taxa (family and genus) before and after treatments with both LNCS nor were any obvious differences found in the microbiota community structure. No differences were found in fecal SCFAs after consuming both LNCS. Authors conclude that daily and repeated consumption of pure aspartame or sucralose in typical amounts of what would be considered high use result in minimal effect on gut microbiota composition or SCFA production.

### Do low-calorie sweetened beverages help to control food cravings? Two experimental studies.

[Maloney NG, et al. \*Phys Behav\*. 2019;208:112500.](#)

**Objective:** Investigate the effect of priming hedonic eating motivations on ad libitum energy intake in frequent and non-consumers of LNCS beverages.

**Type:** Prospective experimental, human

**Design:** In study 1 (N=120) frequent and non-consumers of beverages sweetened with LNCS were exposed to either chocolate or neutral cues (craving vs. control condition) and then completed several tests. Ad libitum energy intake from sweet and savory snacks and beverages (including LNCS) was then assessed. Study 2 followed a similar protocol, but included only frequent consumers (N=172) and manipulated the availability of LNCS beverages in the ad libitum eating context (available vs. unavailable). Measures of guilt and perceived behavioral control were also included.

**Conclusions:** LNCS beverages did not consistently protect consumers from craving-induced increases in energy intake. However, frequent consumers of LNCS beverages consumed fewer calories overall when they were available. These participants also perceived more control over their food intake and felt less guilty.

### Assessing the *in vivo* data on low/no-calorie sweeteners and the gut microbiota.

[Lobach AR, et al. \*Food Chemical Toxicol\*. 2019;124:385-399.](#)

**Objective:** Explore the literature for any published studies with gut microbiome measures in either animal or human subjects exposed

to LCS and studies that investigated the general nature of the gut microbiome.

**Type:** Systematic review

**Conclusions:** No credible evidence is revealed that LCS adversely affect health through an effect on the gut microbiome. Authors found clear evidence that dietary changes unrelated to LCS consumption are likely the major determinants of change in gut microbiota numbers and phyla.

### 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.

[Fantino M, et al. \*Appetite\*. 2018;125:557-565.](#)

**Objective:** Determine if beverages sweetened with LNCS, when consumed with meals, would differ or not, from plain water in impact on mean energy intake, either before or after LNCS habituation, in the laboratory or at home.

**Type:** Randomized controlled trial, two-arm, cross over design

**Design:** 166 healthy non-obese French adult men and women ages 18-45 naïve to regular LNCS consumption.

**Conclusions:** Results showed no difference between the consumption of water and LNCS beverages in their effects on total energy intake, macronutrient intakes, and selection of sweet foods and on motivational ratings. Results were similar in subjects who had not previously consumed LNCS on a regular basis and those who consumed them regularly during the study.

### Low calorie sweeteners: evidence remains lacking for effects on human gut function.

[Bryant C, McLaughlin J. \*Phys Behav\*. 2016;164, Part B, 482–485.](#)

**Objective:** To review the cellular, animal, and clinical studies on human gut function and put the results into context with the gut-brain axis and its regulation of food intake.

**Type:** Review

**Conclusions:** Human studies do not support a clinically meaningful effect of ingested LNCS on hormones involved in gut signaling. Sucralose, aspartame and ace-K had no greater effect than water on secretion of GLP-1, insulin, PYY, or ghrelin, nor any impact on appetite.

## STUDIES ADDRESSING GLYCEMIC MANAGEMENT, DIABETES AND CARDIOMETABOLIC HEALTH AND GUT HEALTH AND MICROBIOME, HUNGER AND APPETITE

### A rational review on the effects of sweeteners and sweetness enhancers on appetite, food reward and metabolic/adiposity outcomes in adults. *Food & Function*.

[O'Connor D, et al. \*Food & Function\*. 2021.](#)

**Objective:** 1) Assess the impact of LNCS on eating behavior, including subjective appetite, food intake, food reward and sensory stimulation; 2) Assess the metabolic impact of LNCS on body weight regulation, glucose homeostasis and gut health.

**Type:** Rationale review

**Design:** Conduct a comprehensive literature review with key terms. Use a search pathway that selects studies with the presence of at least both an intervention group and comparison group in healthy and metabolically healthy adults with obesity. Both between- and within-subject comparisons were included, to verify food intake, subjective appetite, food hedonics, body weight, energy, glucose metabolism and adiposity markers.

**Conclusions:** The evidence suggests that while some sweeteners have the potential to increase subjective appetite, these effects do not translate in changes in food intake. Overall, the data reviewed suggests that LNCS can facilitate a reduction in energy intake without significant negative effects on food intake behavior or metabolism. Findings support the role of LNCS in the prevention of obesity as a complementary strategy to other weight management approaches.

### Effects of Sugar-Sweetened, Artificially Sweetened, and Unsweetened Beverages on Cardiometabolic Risk Factors, Body Composition, and Sweet Taste Preference: A Randomized Controlled Trial.

[Ebbeling CB, et al. J Am Heart Assoc. 2020;22:e015668.](#)

**Objective:** Compare effects of consuming sugar-sweetened beverages (SSBs), artificially sweetened beverages (ASBs) or unsweetened beverages (USBs) in adults who habitually consumed SSBs.

**Type:** Randomized controlled trial

**Design:** 203 adults (121 males, 82 females; 91.6% retention), who regularly drank SSBs were randomly assigned to 3 groups and received a 12-month intervention, including free home-delivered beverages to promote consumption. Check in phone calls were made and written messages were delivered as part of the intervention. Serum triglyceride to high-density lipoprotein cholesterol ratio (primary), body weight, and sweet taste preference (experimental assessment, 0%–18% sucrose solutions) were measured at 2 visits during the 12-month study.

**Conclusions:** Replacing SSBs with noncaloric beverages (both ASBs and USBs) for 12 months did not affect serum triglyceride to high-density lipoprotein cholesterol ratio. Among individuals with central adiposity, replacing SSBs with either ASBs or USBs lowered body weight.

### Short-term impact of sucralose consumption on the metabolic response and gut microbiome of healthy adults.

[Thomson P, et al. Brit J Nutr. 2019;122:856–862.](#)

**Objective:** Examine short-term effect of sucralose consumption on glucose homeostasis and gut microbiome of healthy male volunteers.

**Type:** Randomized, double-blind study

**Design:** 34 subjects randomized into 2 groups. One was administered sucralose capsules (780 mg/d) for 7 days. The control group was given placebo. Before and after the intervention, glycemic and insulin responses were assessed with a oral glucose load (75 g). Insulin resistance was determined using homeostasis model assessment of insulin resistance and Matsuda indexes. The gut microbiome was evaluated before and after the intervention by 16S rRNA sequencing.

**Conclusions:** Glycaemic control and insulin resistance were not affected during the 7 day period. At the phylum level, gut microbiome was not modified in any group. Independent of consuming sucralose or placebo, individuals with a higher insulin response after the intervention had lower bacteroidetes and higher firmicutes abundances. High doses of sucralose for 7 d does not alter glycaemic control, insulin resistance, or gut microbiome in healthy individuals. However, subjects with an increase vs. decrease in insulin response after sucralose and placebo were found to have different gut microbiome compositions.

### A randomized controlled trial contrasting the effects of 4 low-calorie sweeteners and sucrose on body weight in adults with overweight or obesity.

[Higgins KA, Mattes RD. Am J Clin Nutr. 2019; 109:1288–1301.](#)

**Objective:** Compare effects of consumption of 4 LNCS and sucrose on body weight, ingestive behaviors, and glucose tolerance over 12-wk intervention in overweight or obese adults.

**Type:** Randomized controlled trial

**Design:** In a parallel-arm design, 154 participants consumed either 1.25–1.75 L of beverage sweetened with sucrose, aspartame, saccharin, sucralose, or reb A daily for 12 weeks. Sucrose containing beverage contained 400–560 kcal/d. The LNCS beverages contained <5kcal/d. Anthropometric indexes, energy intake, energy expenditure, appetite, and glucose tolerance were measured at baseline. Body weight measured every 2 weeks with energy intake, expenditure, and appetite assessed every 4 wk. Compliance was determined.

**Conclusions:** Subjects (123 completers) in sucrose and saccharin groups had significant increases in body weight compared with aspartame, reb A, and sucralose. Weight change in sucralose group was greater than saccharin, aspartame, and reb A groups. LNCS should be categorized as distinct entities because of their differing effects on body weight.

### The role of low-calorie sweeteners in the prevention and management of overweight and obesity: evidence v. conjecture.

[Rogers PJ. Proceedings of the Nutrition Society. 2017;77\(3\):230-238.](#)

**Objective:** Examine 3 common claims about the effects of LNCS on energy intake and preference for sweetness: 1) the sweet taste confusion hypothesis; 2) the sweetness without calories and sweet tooth hypothesis; and 3) the conscious overcompensation hypothesis.

**Type:** Literature review

**Conclusions:** The author substantiates the lack of evidence for the 3 claims and concludes that intervention studies generally show consumption of LNCS in place of (some) sugar reduces energy intake and body weight.

### d-Allulose enhances postprandial fat oxidation in healthy humans.

[Kimura T, et al. Nutrition. 2017;\(43-44\):16-20.](#)

**Objective:** To examine the effects of a single ingestion of a small amount of d-allulose on postprandial energy metabolism in healthy participants. The proposed mechanism of d-allulose in weight management is that it suppresses hepatic lipogenesis and increases hepatic fatty acid oxidation, resulting in enhanced energy expenditure.

**Type:** Randomized, single-blind crossover design

**Design:** 13 healthy men and women (mean age of 35.7 + 2.1 yrs) and normal BMI were studied. At 30 min after taking 5 g of d-allulose or 10 mg of aspartame without any sugar as a control, overnight-fasted participants ingested a standardized meal. Energy metabolism was evaluated by a breath-by-breath method. Blood was collected and plasma glucose, insulin, total cholesterol, triacylglycerol, and free fatty acids were analyzed.

**Conclusions:** d-Allulose enhanced postprandial fat oxidation in these subjects. In addition, plasma glucose levels were lower and free fatty acid levels were higher in subjects fed d-allulose. The other parameters measured were not changed. Results show that d-allulose could be a novel sweetener to control and maintain healthy body weight, probably through enhanced energy metabolism.

## WEIGHT MANAGEMENT AND ENERGY INTAKE

**Low calorie sweetener (LCS) use and energy balance.**

[Peters, JC, Beck J. Phys Behav. 2016;164, Part B, 524-528.](#)

**Objective:** Review over 30 years of research and reviews on LNCS, energy balance and weight management.

**Type:** Literature review

**Conclusions:** Where older observational longitudinal cohort studies suggested that LNCS may promote weight gain, more recent studies nearly uniformly show either weight loss or the prevention of weight gain.

**The effects of water and non-nutritive sweetened beverages on weight loss and weight maintenance: a randomized clinical trial.**

[Peters JC, et al. Obesity. 2016;24\(2\):297-304.](#)

**Objective:** Evaluate the effects of water vs. beverages sweetened with LNCS on body weight in subjects enrolled in a year-long behavioral weight loss treatment program at 12 weeks and 1 year.

**Type:** Randomized equivalence design trial (2 study sites)

**Design:** 303 people with overweight or obesity were randomized. The study group was instructed to drink 24 fl oz/day diet beverages (DB) and the control group 24 fl oz/day of water and no diet beverages. All participants participated in the same weight loss program.

**Conclusions:** DB group lost significantly more weight at 12 weeks, average of 13 pounds, or 44 percent more than control group (average 9 pounds). 64% of study group lost >5% of body weight, compared with 43% of control group. DB group experienced significantly less hunger. At one year, after completing the 9 month maintenance phase, the DB group showed statistically significant > weight loss than subjects in the water treatment group.

**Low/no calorie sweetened beverage consumption in national weight control registry (NWCR).**

[Catenacci VA, et al. Obesity. 2014;22\(10\):2244-2251.](#)

**Objective:** Evaluate prevalence of and strategies behind low/no calorie sweetened beverage (LNCSB) consumption in successful weight loss maintainers.

**Type:** Cross-sectional

**Design:** Administer an online survey to 434 members of the National Weight Control Registry (NWCR) who have lost > 13.6 and maintained weight loss for > 1 year to determine consumption of beverages sweetened with LCS.

**Conclusions:** Greater than half the participants surveyed reported regularly consuming LCS beverages, 10% regularly consumed SSB. 78% of LCS beverage consumers reported these helped them control calorie intake and noted that their choice of beverage was “very important” for weight loss (42%) and weight maintenance (40%).

**Weight-reducing effect and safety evaluation of rare sugar syrup by a randomized double-blind, parallel-group study in humans.**

[Hayashi N, et al. J Functional Foods. 2014;11:152-159.](#)

**Objective:** Learn about an effective safe dose of rare sugar syrup (RSS), as an alternative to high-fructose corn syrup (HFCS) and evaluate biomarkers during long-term consumption.

**Type:** Randomized double-blind, two-group parallel, placebo-controlled comparison study

**Design:** 34 men and women with average BMI of 25.6 kg/m<sup>2</sup> were divided into two groups. Subjects consumed either a test drink containing RSS or a drink (isocaloric) with HFCS before breakfast on a daily basis for 12 weeks. The 20-week study was 4 pre-treatment weeks for observation, 12 weeks for treatment, and 4 weeks for posttreatment

observation. Testing was done during weeks 0, 2, 4, 8 and 12 of the and at the end of the post-treatment observation period.

**Conclusions:** Significant reductions of body weight, body fat percentage and waist circumference in the RSS group were observed compared to the HFCS group. No adverse effects or abnormal blood parameters for lipid and carbohydrate metabolism, hepatic and renal functions were observed. Continuous use of a RSS could assist weight management.

**Replacing caloric beverages with water or diet beverages for weight loss in adults: main result of the choose healthy options consciously everyday (choice) randomized control trial.**

[Tate D, et al. Am J Clin Nutr. 2012;95:555-563.](#)

**Objective:** Compare the replacement of calorie-containing beverages with water or diet beverages (DBs) as a method to reduce weight in overweight or obese adults over 6 months in adults and attention controls (ACs).

**Type:** Randomized controlled trial

**Design:** 318 adults randomized into 3 groups: 1) diet beverage, 2) water or 3) control. Eligible subjects had to consume > 280 kcal/day sweetened beverages and commit to making a dietary change. Diet beverage and water groups substituted >2 servings/day of SSB with a DB or water, respectively.

**Conclusions:** At 6 months DB drinkers were more likely to achieve a 5% weight loss than water drinkers.

## HEALTHY DIETARY PATTERNS WITH LCS INTAKE AND LCS CONSUMPTION LEVELS

**Intake of low and no-calorie sweeteners (LNCS) by the Brazilian population.**

[Barraj L, et al. Food Addit Contam. 2020;12L442-465.](#)

**Objective:** Estimate the intake of 6 LNCS from foods and beverages and tabletop sweeteners by the Brazilian population compared to ADI.

**Type:** Cross sectional survey

**Design:** Intake estimates were based on consumption data from a nationwide cross-sectional survey (ages 10 years and older) conducted among the Brazilian population in 2008–2009 and rates of LNCS use and product market share. Two intake scenarios were applied: 1) conservative brand loyal consumer scenario that assumes all LNCS-containing foods and beverages and tabletop sweeteners contain the maximum reported LNCS concentrations; 2) scenario that represents general consumer population that uses a market share weighted average of the reported concentrations.

**Conclusions:** Intake of LNCS up to the 95th percentile did not exceed their respective ADI for all subpopulations considered, in either the general consumer scenario or the brand loyal scenario. For the brand loyal scenario consumers the 95th percentile intakes of LNCS ranged from 6.8% to 54% of their respective ADI and for the general consumer scenario from <1% to 6.0% of their respective ADI.

**Daily Eating Frequency in US Adults: Associations with Low-Calorie Sweeteners, Body Mass Index, and Nutrient Intake (NHANES 2007–2016).**

[Hunt KJ, et al. Nutrients. 2020;12\(9\):2566.](#)

**Objective:** Address, for the 2020 Dietary Guidelines Advisory Committee, how the frequency of consuming LNCS is observed among US adults aged ≥19 years with NHANES 2007–2016 data with

respect to timing, calorie intake, and body mass index (BMI).

**Type:** Cross sectional data analysis

**Design:** Use of the first 24 hr dietary recall from 5 consecutive cycles of NHANES 2007–2016. Data from 25,411 US adults with normal weight, overweight or obese BMIs was included. Researchers examined eating frequency data and food and beverage consumption patterns using several approaches.

**Conclusions:** LNCS items were consumed without concurrent calories from other sources in fewer than 2.7% of all episodes. Within normal weight participants (29.4%), overweight (33.6%) and obese BMIs (37.1%, LCS consumers (35.2% overall) showed more eating occasions/day; and intake of fewer calories, carbohydrates, fats, and protein, per occasion. People consuming LNCS had lower total calories and higher fiber intake per day yet consumption was associated with higher BMI. These results did not show that LCS consumption was associated with increased caloric intake from other dietary sources.

### Estimation of exposures to non-nutritive sweeteners from consumption of tabletop sweetener products: a review.

[Tennant DR. Food Addit Contam. Part A, 36:3, 359-365. 2019;1566784.](#)

**Objective:** Reliable estimation of intake of LNCS is complex, in part because there's considerable variation in the forms of Tabletop Sweeteners (TTS) products. This paper examines the suitability of existing food consumption databases for estimation of LNCS intake from (TTS) and proposes an alternate method for estimates.

**Type:** Review and analysis

**Design:** Review current intake estimation models for TTS.

**Conclusions:** Data suggest that using upper percentile consumption figures for powdered forms is a critical factor in intake estimations and may be a more realistic method by which overall exposure estimates could be obtained. When estimates are based on maximum concentration levels in powdered TTS products, and 95th percentile consumption figures for TTS intakes are below ADI values for all LNCS.

### Low-calorie beverage consumption, diet quality and cardiometabolic risk factor in British adults.

[Patel L, et al. Nutrients. 2018;10:1261.](#)

**Objective:** Verify the association between LNCS beverage consumption, diet quality and cardiometabolic risk factors in British adults.

**Type:** Cross-sectional study

**Design:** Data from over 5,000 individuals 16 years of age and older obtained from two waves of the National Diet and Nutrition Survey Rolling Programme (2008–2012 and 2013–2014) was analyzed.

**Conclusions:** LNCS beverage consumption, compared with SSB was associated lower energy consumption, lower free [added] sugar intake. Consumption of other nutrients was not significantly different. Nor was plasma glucose, total cholesterol, LDL, HDL or triglycerides. Replacing LNCS beverage for SSB can positively impact diet quality and energy consumption.

### Low-/No-calorie sweeteners: A review of global intakes.

[Martyn D, et al. Nutrients. 2018;10\(3\):357.](#)

**Objective:** Examine published data since 2008 to determine the global intake of the seven most commonly used LNCS, including: aspartame, acesulfame-K, saccharin, sucralose, cyclamate, thaumatin and steviol glycosides.

**Type:** Literature review

**Conclusions:** The review raised no concern regarding excess intake of these 7 LNCS among the general population and other sub populations like children and people with diabetes. The data did not demonstrate any significant increase or decrease of LNCS over the 10-year period

but do suggest a possible increase in the numbers people consuming products containing LNCS.

## SAFETY AND CARCINOGENICITY (INTERNATIONAL HEALTH ORGANIZATIONS, HEALTH PROFESSIONAL ASSOCIATIONS AND EXPERT CONSENSUS REPORTS)

### Metabolic fate in adult and pediatric population of steviol glycosides produced from stevia leaf extract by different production technologies.

[Purkayastha S, et al. Regul Toxicol Pharmacol. 2020;116:104727.](#)

**Objective:** Investigate the metabolic fate of steviol glycosides in the colonic microbiota of adults and children.

**Type:** Human study

**Design:** In vitro incubation tests conducted in human fecal homogenates from children and adults.

**Conclusions:** Results showed that steviol glycosides produced by extraction from the stevia leaf or enzymatic conversion of the stevia leaf extract share the same metabolic fate in the human gut microbiota in children and adults. This supports the safety of all steviol glycosides produced in one of these ways.

### Lack of potential carcinogenicity for sucralose – Systematic evaluation and integration of mechanistic data into the totality of the evidence.

[Chappell GA, et al. Food Chem Toxicol. 2019.](#)

**Objective:** Conduct a systematic assessment on the potential carcinogenicity of sucralose.

**Type:** Systematic assessment of mechanistic data

**Design:** Researchers used a framework developed for the quantitative integration of data related to the proposed key characteristics of carcinogens (KCCs). Data from peer-reviewed literature and the ToxCast/Tox21 database were evaluated using an algorithm that weighs data for quality and relevance.

**Conclusions:** The overall lack of activity for sucralose as tested in various models and across mechanistic endpoints organized by KCCs, coupled with the lack of carcinogenicity in standard two-year cancer bioassays in rodents, reinforces regulatory conclusions that sucralose does not present carcinogenic hazard to humans.

### FDA regulatory approach to steviol glycosides.

[Perrier JD, et al. Food Chem Toxicol. 2018;122:132-142.](#)

**Objective:** Provide detail on FDA's practices for filing and evaluating the Generally Recognized As Safe (GRAS) notices for high-purity steviol glycosides as sweeteners in foods.

**Type:** Review (Written by FDA employees).

**Conclusions:** The FDA has not questioned the GRAS status of more than 50 GRAS applications for use of numerous steviol glycosides as general-purpose sweeteners in foods, beverages and tabletop sweeteners. Includes discussion of new technologies to produce higher volumes of steviol glycosides to scale production and meet demand and table summarizing data in the GRAS notices filed with FDA.

### Critical review of the current literature on the safety of sucralose.

[Magnuson BA, et al. Food Chem Toxicol. 2017;106: 324-355.](#)

**Objective:** Provide an in-depth review of studies conducted over past forty years including the effects of sucralose on growth, development,

reproduction, neurotoxicity, immunotoxicity, carcinogenicity and overall health status. The review of more recent studies focused on the effect of sucralose on the gut microflora and glycemic control.

**Type:** Literature review

**Conclusions:** Sucralose is safe for its intended use as a LCS.

### Biological fate of low calorie sweeteners.

[Magnuson BA, et al, Nutr Rev. 2016; 74\(11\):670–689.](#)

**Objective:** Provide comprehensive review on commonly used LNCS, including acesulfame potassium, aspartame, saccharin, stevia leaf extract (steviol glycoside) and sucralose detailing biological fates, including absorption, distribution, metabolism, and excretion pathways (ADME). The review also compares the chemical differences between LNCS and details global regulatory status.

**Type:** Literature review

**Conclusions:** The only trait that LNCS have in common is that they impart sweetness. Beyond this they are a diverse group of compounds with important differences in their metabolic fate including: ADME. An extensive body of evidence exists on ADME in both animal models and humans because it is a prerequisite for approval by global regulatory agencies. It's critical to use the existing knowledge of ADME to address potential controversies surrounding their use. Safety concerns about their use can often be addressed with this knowledge.

### The safety and regulatory process for low calorie sweeteners in the United States.

[Roberts A. Physiol Behav. 2016;164, Part B, 439–444.](#)

**Objective:** Provide an in-depth review of the regulatory processes for LCS including Food Additive approval and Generally Recognized as Safe (GRAS) used by the FDA including potential safety concerns, including carcinogenicity, effects on body weight gain, glycemic control and effects on the gut microbiome.

**Type:** Review

**Conclusions:** The regulatory process and review time of the Food Additive and GRAS evaluation processes by the FDA differ, however, the same level of scientific evidence is required to support safety and ensure a reasonable certainty of no harm.

### Sucralose non-carcinogenicity: a review of the scientific and regulatory rationale.

[Berry C, et al., Nutr Cancer. 2016 Nov-Dec;68\(8\):1247-1261.](#)

**Objective:** To comprehensively review the safety literature on sucralose through a database search using key terms. Studies include independently conducted and industry-funded research on sucralose chemistry, pharmacokinetics, metabolism, toxicity, genotoxicity, and long-term safety, including carcinogenicity.

**Type:** Literature review

**Conclusions:** Sucralose is non-carcinogenic and safe for all consumers. The review supports four key points: 1) there is no evidence of chemical concerns or toxicity; 2) no metabolites in sucralose were found to be carcinogenic; 3) no changes to genes were observed to indicate any cancer-causing effects; 4) at doses thousands of times the maximum expected daily human intake toxicity and long-term carcinogenicity studies showed no evidence of carcinogenic potential.

## Safety Evaluation and Regulatory Review of Low- and No-Calorie Sweeteners in U.S. and Globally

**United States:** The U.S. Food and Drug Administration (FDA) regulates low calorie sweeteners either through the Food Additive approval process or the Generally Recognized as Safe (GRAS) process.(1,2) Both processes follow established rigorous protocols and meet the FDA standard of safety.(1,2) Whether the LCS is evaluated as a Food Additive or GRAS ingredient, they are allowed for use by the entire population, including children, pregnant and lactating women and people with diabetes.

**Food Additive review process:** The manufacturer or entity submits a food additive petition for review to FDA. The petition must provide a complete safety assessment of the ingredient based on the principles of food toxicology.(3) The ingredient is not allowed to be used in foods until FDA completes their review and grants approval. Sucralose, the sweetening ingredient in SPLENDA® Original, is an example of a LCS that received FDA approval as a Food Additive.

**GRAS review process:** The general recognition of safety of these ingredients is based on data in the public domain therefore FDA does not require a complete safety assessment. Rather the manufacturer or entity seeking to use the ingredient in foods obtains review from experts and submits the review to FDA as a "GRAS Notification." In essence, this notifies the FDA of their intent to use the ingredient. FDA responds to a GRAS notification with either a No Objection letter, meaning FDA has no questions about the use of this ingredient, or a notification that the ingredient does not provide a basis for use as a GRAS ingredient. To date FDA has reviewed many GRAS notifications for steviol glycosides. Based on No Objection letters, these ingredients are allowed in the food supply.(4) As an example, the steviol glycosides Reb A and D, the sweetening ingredients in SPLENDA® Naturals Stevia, are GRAS.

**Global:** The safety evaluation and regulatory processes to allow the use of LCS around the globe depends on the country or area of the world. Some have their country or area-based regulatory body. As examples, Canada has their regulatory body, Health and Welfare Canada and countries in Europe look to the European Food Safety Authority (EFSA). Many countries use guidance from the Joint Expert Committees for Food Additives (JECFA) administered jointly by the Food and Agriculture Organization of the United Nations and the World Health Organization.(5)

Sucralose, the sweetening ingredient in SPLENDA® Original and steviol glycosides, the sweetening ingredients in SPLENDA® Naturals, have been authorized or adopted for use across the globe by many regulatory bodies, including Health and Welfare Canada.(6,7)

<sup>1</sup>Rulis, AM, Levitt JA: FDA's food ingredient approval process. Safety assurance based on scientific assessment. Regul Toxicol Pharmacol. 2009; 53:20-31. <sup>2</sup>Roberts, A. The safety and regulatory process for low-calorie sweeteners in the United States. Physiol Behav. 2016;164, Part B, 439-444. <sup>3</sup>FDA. Generally Recognized as Safe. [www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras](http://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras). April 1, 2021. <sup>4</sup>Guidance for industry and other stakeholders: Toxicological principles for the safety assessment of food ingredients (Redbook). [www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-and-other-stakeholders-redbook-2000](http://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-and-other-stakeholders-redbook-2000). Accessed April 1, 2021. <sup>5</sup>Perrier JD, Mihalov JJ, Carlson SJ: FDA regulatory approach to steviol glycosides. Food Chem Toxicol. 2018;122:132-142. <sup>6</sup>Samuel P, Ayoob KT, Magnuson BA, et al. Stevia leaf to stevia sweetener: Exploring its science, benefits, and future potential. J Nutr. 2018;148(7):1186S-1205S. <sup>7</sup>World Health Organization. Joint FAO/WHO Expert Committee on Food Additives (JECFA). [www.who.int/foodsafety/areas\\_work/chemical-risks/jecfa/en/](http://www.who.int/foodsafety/areas_work/chemical-risks/jecfa/en/). (Accessed April 1, 2021.) +Article reviewed within this publication.

\*This summary uses the term low- and no-calorie sweeteners with the abbreviation LNCS, however, various synonymous terms are used in the literature such as: low-calorie sweeteners, nonnutritive sweeteners, low-energy sweeteners, high intensity sweeteners, and others. In addition, when referring to beverages sweetened with LNCS, the term artificially sweetened beverages (ASB) is often used. This summary refers to them as LNCS beverages.

The literature cited here is consistent with the extensive evidence base on LNCS which concludes they can be used safely and efficaciously as part of a healthy eating pattern to help manage weight, glycemia, and/or various aspects of cardiometabolic health by reducing calories, total carbohydrate and added sugars.

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