

SUMMARIES OF RECENT SCIENTIFIC PUBLICATIONS

SUPPORTING THE USE OF NONNUTRITIVE SWEETENERS (2017 Update)

The research and evidence base for the safety and efficacy of nonnutritive sweeteners [NNS] spans many decades. This bibliography includes relevant publications and is provided by Heartland Food Products Group, LLC, the manufacturer of SPLENDA® Sweetener Products.

(Within each category the publications are listed in reverse chronological order.)

HEALTH ORGANIZATIONS AND PROFESSIONAL ASSOCIATIONS

American Diabetes Association (ADA) – Standards of Medical Care of Diabetes-2017. Lifestyle Management.

Diabetes Care. 2017; 40(Supp 1):S33-S43.

About NNS: “For people who are accustomed to sugar-sweetened products, non-nutritive sweeteners have the potential to reduce overall calorie and carbohydrate intake and may be preferred to sugar when consumed in moderation. Regulatory agencies set acceptable daily intake levels for each non-nutritive sweetener, defined as the amount that can be safely consumed over a person’s lifetime.”

<https://doi.org/10.2337/dc17-S007>

American Cancer Society: Guidelines on Nutrition and Physical Activity for Cancer Prevention and Physical Activity for Cancer Prevention. (Last revised 2016)

About NNS: “There is no proof that these sweeteners, at the levels consumed in human diets, cause cancer. Aspartame, saccharin, and sucralose are a few of the non-nutritive sweeteners approved for use by the FDA. Current evidence does not show a link between these compounds and increased cancer risk...”

<http://www.cancer.org/healthy/eathealthygetactive/acsguidelinesonnutritionphysicalactivityforcancerprevention/acs-guidelines-on-nutrition-and-physical-activity-for-cancer-prevention-common-questions>

Academy of Nutrition and Dietetics Position Paper: Interventions for the Treatment of Overweight and Obesity in Adults.

J Acad Nutr Diet. 2016;116(1):129-147.

Summary: The value of reducing sugar-sweetened beverages (SSBs) to reduce weight is discussed briefly. Data from two RCTs demonstrating greater weight loss with the replacement of low calorie sweetened beverages for SSBs are detailed. These RCTs, by Tate et al. (2012) and Peters et al. (2014) are cited. (See summaries of both below.)

<http://www.eatrightpro.org/~media/eatrightpro%20files/practice/position%20and%20practice%20papers/position%20papers/weightmanagement.ashx>

American Academy of Pediatrics Policy Statement from Council on School Health, Committee on Nutrition. Snacks, Sweetened Beverages, Added Sugars, and Schools

Pediatrics. 2015;135(3):575-583.

About NNS: “Additional improvements in nutrient density of sweet-tasting products could be obtained if nonnutritive sweeteners are used as a tool to replace added sugars and help lower caloric intake. Several nonnutritive sweeteners have been accepted by the US Food and Drug Administration as safe and have shown good safety over time. However, data are scarce on long-term benefits for weight management in children and adolescents or on the consequences of long-term consumption. Continued research is needed.”

<http://pediatrics.aappublications.org/content/pediatrics/early/2015/02/17/peds.2014-3902.full.pdf>

National Cancer Institute, National Institutes of Health.

Do artificial sweeteners cause cancer? (Posted 2014)

Summary: Researchers have conducted studies on the safety of the many nonnutritive sweeteners, including sucralose and others approved by the FDA for sale in the US. There’s no evidence that they cause cancer in humans. Nonnutritive sweeteners available for use in the U.S. have been approved by the FDA. For more information, see the NCI fact sheet on this topic:

<https://www.cancer.gov/about-cancer/causes-prevention/risk/diet/artificial-sweeteners-fact-sheet>.

American Diabetes Association (ADA) Position Statement. Nutrition Therapy Recommendations for the Management of Adults with Diabetes

Evert A, et al. Diabetes Care. 2013;36:3821-3842.

About NNS: “Use of nonnutritive sweeteners (NNSs) has the potential to reduce overall calorie and carbohydrate intake if substituted for caloric sweeteners without compensation by intake of additional calories from other sources.” Regarding safety the statement refers to the reviews and approvals FDA. Regarding glycemic effect, the statement concludes research supports that NNS do not produce a glycemic effect unless other calorie containing ingredients are in the product.

<http://care.diabetesjournals.org/content/36/11/3821.full.pdf+html>

Scientific Statement from the American Diabetes Association and the American Heart Association. Nonnutritive Sweeteners: Current Use and Health Perspectives

Gardener C, et al. Diabetes Care. 2012;35(8):1798-1808; Circulation. 2012;126:509-519.

Summary: This statement, which reviewed evidence published since 2005, concludes reducing the intake of added sugars is an important intervention to achieve a healthy weight and nutrient-dense dietary pattern. The statement also concludes that using NNS may result in small decreases in calorie intake and weight loss when used within a structured eating plan and without caloric compensation.

<http://circ.ahajournals.org/content/early/2012/07/09/CIR.Ob013e31825c42ee.full.pdf+html>

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.”

http://www.eatrightpro.org/~media/eatrightpro%20files/practice/position%20and%20practice%20papers/position%20papers/final_sweetener_position_paper_5-12.ashx

META-ANALYSES, SYSTEMATIC AND LITERATURE REVIEWS

Trends in the Consumption of Low-calorie Sweeteners.

Sylvetsky AC, Rother CL. *Physiology & Behavior*. 2016;164,Part B, 446-450.

Summary: This article reviews NNS consumption trends and summarizes consumption differences among sociodemographic groups. The review reports 20 to 30 percent of children and adults consume NNS daily with beverages sweetened with NNS being consumed most frequently. Men and women 55 to 74 years of age consume the largest amount of NNS. Consumption is highest in non-Hispanic whites, overweight and obese individuals and those with higher income and education.

<http://www.sciencedirect.com/science/article/pii/S0031938416301184>.

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 Obesity*. 2016;40:381-394.

Summary: This systematic review covers a large and lengthy body of evidence including numerous types of animal human studies using varied designs. Studies were conducted with various NNS including several currently available or approved by the U.S. FDA. Conclusions are consistent with other systematic reviews of NNS that demonstrate decreased energy intake and body weight with consumption of NNS used in place of added sugars.

<http://www.nature.com/ijo/journal/vaop/ncurrent/full/ijo2015177a.html>

Substitution of SSBs with Other Beverage Alternatives: A Review of Long-term Health Outcomes.

Zheng M, et al. *J Acad Nutr Diet*. 2015;115(5):767-779.

Summary: This systematic review culled studies from six different literature databases to identify prospective cohort studies (PCS) and randomized controlled trials (RCTs) in children and adults with four month or longer duration. Six PCS and 4 RCTs were included. Results showed that replacing Sugar Sweetened Beverages with a variety of low-calorie beverage alternatives demonstrate a favorable effect on long term body weight.

[http://www.andjrn.org/article/S2212-2672\(15\)00112-4/fulltext](http://www.andjrn.org/article/S2212-2672(15)00112-4/fulltext)

Intense Sweeteners, Appetite for the Sweet Taste, and Relationship to Weight Management.

Bellisle F. *Curr Obes Rep*. 2015;4:106-110.

Summary: This paper, which analyzed research about how human NNS consumption may change the appetite for and intake of sweet tasting products, draws three main conclusions: 1) no consistent relationship exists to demonstrates a heightened appetite for sweet foods, 2) some research shows use of NNS is associated with consumption of less sweets, 3) intervention studies in children and adults show use of NNS can reduce intake of caloric sweeteners and support weight loss efforts.

<http://link.springer.com/article/10.1007%2Fs13679-014-0133-8#page-1>

Low-calorie Sweeteners and Body Weight and Composition: A Meta-Analysis of Randomized Controlled Trials and Prospective Cohort Studies.

Miller PE, et al. *Am J Clin Nutr*. 2014;100:765-77.

Summary: This meta-analysis analyzed results from randomized control trials (RCTs) and prospective cohort studies on NNS and body weight, fat mass, BMI, and waist circumference. It showed that in RCTs NNS reduced body weight compared to placebo and modestly, but “significantly” reduced BMI, fat mass, and waist circumference. This meta-analysis was accompanied by the editorial referenced below by Hill.

<http://ajcn.nutrition.org/content/early/2014/06/18/ajcn.113.082826.full.pdf+html>

What Do You Say When Your Patients Ask Whether Low-calorie Sweeteners Help with Weight Management?

Hill J. *Am J Clin Nutr*. 2014;100: 739-740.

<http://ajcn.nutrition.org/content/early/2014/07/30/ajcn.114.094466.full.pdf>

SAFETY AND CARCINOGENICITY

Biological Fate of Low Calorie Sweeteners.

Magnuson BA, et al., *Nutrition Reviews*. 2016; 74(11):670-689.

Summary: This comprehensive review covers commonly used NNS, including acesulfame potassium, aspartame, saccharin, stevia leaf extract (steviol glycoside) and sucralose. It details the biological fate of these NNS, including their absorption, distribution, metabolism, and excretion pathways. The review also compares the chemical differences between these NNS and notes their global regulatory status. This article helps healthcare providers and their clients overcome potential concerns and hesitancy about using NNS to prevent and/or manage chronic health conditions.

<http://www.pubpdf.com/pub/27753624/Biological-fate-of-low-calorie-sweeteners>

The Safety and Regulatory Process For Low Calorie Sweeteners In The United States.

Roberts A. *Physiology & Behavior*, 2016;164, Part B, 439-444.

Summary: This article provides an in-depth review of the regulatory processes for NNS including the food additive approval process and the Generally Recognized as Safe (GRAS) system used by the U.S. FDA. The same level of scientific evidence is required to support safety and ensure a reasonable certainty of no harm in both review processes. This review covers potential safety concerns, including carcinogenicity, effects on body weight gain, glycemic control and effects on the gut microbiome.

<http://www.sciencedirect.com/science/article/pii/S003193841630083X> (abstract)

Sucralose Non-Carcinogenicity: A Review Of The Scientific And Regulatory Rationale.

Berry C, et al., *Nutrition and Cancer*. 2016 Nov-Dec;68(8):1247-1261.

Summary: This comprehensive safety review of sucralose includes independently conducted and industry-funded research on sucralose chemistry, pharmacokinetics, metabolism, toxicity, genotoxicity, and long-term safety including carcinogenicity. It concludes that sucralose is non-carcinogenic and safe for use by all consumers and 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 intake in humans, toxicity and long-term carcinogenicity studies showed no evidence of carcinogenic potential.

<http://www.tandfonline.com/doi/full/10.1080/01635581.2016.1224366>

GUT HEALTH, GLYCEMIC CONTROL, HUNGER AND APPETITE

Impact of Diet Composition on Blood Glucose Regulation.

Russell WR, et al. *Critical Reviews in Food Science and Nutrition*, 2016;56(4):541-590.

Summary: This comprehensive review explores the research from human studies on a wide range of dietary components and their impact on blood glucose levels with reference to the prevention and management of type 2 diabetes. The review includes impact of the major macronutrients, micronutrients, non-nutrient phytochemicals, low calorie sweeteners (NNS) and several other additional foods. In reference to NNS, this review includes the range of research on various NNS related to glucose regulation including impact on gut hormones and glucose, C-peptide and insulin levels. The article concludes that the use of NNS and food and beverage products containing them by subjects with or without diabetes does not affect blood glucose levels, and that these products are tools that may help people reduce and control calorie consumption. It cites several papers from health associations listed in section one of this bibliography.

<http://dx.doi.org/10.1080/10408398.2013.792772>

Low Calorie Sweeteners: Evidence Remains Lacking For Effects On Human Gut Function.

Bryant C, McLaughlin J. *Physiology & Behavior*, 2016;164, Part B, 482-485.

Summary: This review covers cellular, animal and clinical studies and puts results into context with the gut-brain axis and its regulation of food intake. Authors conclude human studies do not support a clinically meaningful effect of ingested NNS 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. In summarizing the literature in humans, the authors state studies have consistently failed to show that activation of sweet taste receptors by NNS placed in the human gut replicate the effects of caloric sugars on gastric motility, gut hormones or appetitive responses.

<http://www.sciencedirect.com/science/article/pii/S0031938416301627>

Nonnutritive Sweeteners Are Not Supernormal Stimuli.

Antenucci RG, et al. *Int J Obes*. 2015;39(2):254-9.

Summary: Study participants were exposed to a series of taste tests with various caloric and nonnutritive sweeteners. Participants rated perceived sweetness. Results showed participants perceived the sweetness of NNS at lower concentrations than the caloric sweeteners and indicated caloric sweeteners all had higher sweetness ratings than NNS. Researchers concluded that results don't support the claim that NNS produce a negative effect by over-stimulating peoples' sweet taste receptors to produce supernormal stimuli.

<http://www.nature.com/ijo/journal/v39/n2/full/ijo2014109a.html> (abstract)

Non-Nutritive Sweeteners: No Class Effect on the Glycaemic or Appetite Responses to Ingested Glucose.

Bryant CE, et al. *Eur J Clin Nutr*. 2014;68:629-631.

Summary: This study examined the individual effect of acesulfame-K (AceK), aspartame and saccharin responses on glycemia and appetite in humans when consumed in combination with glucose in commonly used amounts. Results showed no additional effect of aspartame or saccharin on glucose response any time during the 60 minute post-ingestion period. No NNS individually had an effect on perceptions of hunger or fullness.

<http://www.nature.com/ejcn/journal/v68/n5/full/ejcn201419a.html> (abstract)

Artificial Sweeteners Have No Effect on Gastric Emptying, Glucagon-like Peptide-1, or Glycemia After Oral Glucose in Healthy Humans.

Wu T, et al. *Diabetes Care*.2013;36:e202-e203.

Summary: This study fed four different drinks to healthy men: 1) water, 2) water with sucralose, 3) water with acesulfame-K (AceK), and 4) water with both sucralose and AceK. 10 minutes after consumption, a 75 gram oral glucose load was administered. Results showed neither sucralose alone, or when combined with AceK, had any acute effect on gastric emptying, GLP-1, or glycemic responses.

<http://care.diabetesjournals.org/content/36/12/e202.full>

WEIGHT MANAGEMENT

Low Calorie Sweetener (LCS) Use And Energy Balance.

Peters, JC, Beck J. *Physiology & Behavior*, 2016;164, Part B, 524-528.

Summary: This review details over thirty years of research and reviews on NNS, energy balance and weight management. The authors summarize the observational longitudinal cohort studies that early on suggested the promotion of weight gain and others, while more recent studies nearly uniformly show either weight loss or the prevention of weight gain. Lastly two recent meta-analyses are summarized (see summaries Miller, Perez and Rogers, et al. below). The authors offer this conclusion about the recent RCTs (see summaries for Peters, et al. and Tate et al. below): "*RCTs are consistent in showing a benefit of LCS which suggest that simple behavioral engagement by individuals attempting to control their weight is a sufficiently strong signal to overcome any potential mechanism that might act to promote energy intake and weight gain.*"

<http://www.sciencedirect.com/science/article/pii/S0031938416301111>

The Use Of Low-Calorie Sweeteners Is Associated With Self-Reported Prior Intent To Lose Weight In A Representative Sample Of U.S. Adults.

Drewnowski A, Rehm CD. *Nutrition & Diabetes*. 2016; 6:e202.

Summary: Use of NNS was determined using data from 24-hour dietary recalls from five cycles of the National Health and Nutrition Examination Survey (1999-2008 NHANES). Data on intent to lose weight was obtained from the weight history questionnaire. Results showed that the use of products sweetened with NNS and NNS-based sweeteners was associated with a higher prevalence of obesity and diabetes. NNS use was also associated with a history of prior weight loss and gain. The authors conclude that any inference of cause and effect between use of NNS and weight control is tempered by the nature of the data and self-reported weight-related data.

<http://www.nature.com/nutd/journal/v6/n3/full/nutd20169a.html>

The Effects of Water and Non-nutritive Sweetened Beverages on Weight Loss During a 12-week Weight Loss Treatment Program.

Peters JC, et al. *Obesity*. 2014;22(6):1415-21.

Summary: The study group in this 12 week weight control RCT trial was instructed to drink 24 fl oz/day diet beverages (any type) and the control group was instructed to drink 24 fl oz/day of water and no diet beverages. Results showed the diet beverage group lost significantly more weight, 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. Diet beverage group experienced significantly less hunger. (Peters et al. 2016, below, summarizes the 9 month maintenance phase of this RCT.)

<http://onlinelibrary.wiley.com/doi/10.1002/oby.20737/epdf>

DIETARY PATTERNS AND QUALITY

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.

Summary: After completing the 9 month maintenance phase of this 1 year behavioral treatment program, the diet beverage group showed statistically significant greater weight loss (6.21 + 7.65 kg) than subjects in the water treatment group (2.45 + 5.59 kg).

<http://onlinelibrary.wiley.com/doi/10.1002/oby.21327/epdf>

Sugar and Artificially Sweetened Beverages and Intrahepatic Fat: A Randomized Controlled Trial.

Campos V, et al. *Obesity*. 2015;23:2335-2339.

Summary: Over a 12 week study period this RCT compared the impact of Artificially Sweetened Beverages (ASB) with Sugar-Sweetened Beverages (SSB) on intrahepatic fat among overweight adults who usually consumed two or more 22- fl.oz. of SSB daily. Results showed participants consuming ASB had significantly decreased total energy, carbohydrate, and sugar intakes. Subjects continuing to consume SSB showed no differences in intake. Dietary changes in the ASB group were accompanied by a significant decrease in intrahepatic fat.

<http://onlinelibrary.wiley.com/doi/10.1002/oby.21310/abstract>

Low/No Calorie Sweetened Beverage Consumption in National Weight Control Registry (NWCR).

Catenacci VA, et al. *Obesity*. 2014;22(10):2244-2251.

Summary: This study surveyed consumption of beverages with NNS in NWCR members with sustained weight loss for > 7 years. Results showed 53% regularly consumed NNS beverages, 10% regularly consumed sugar-sweetened beverages (SSB). 78% of NNS consumers reported they helped control calorie intake. Choice of beverage was "very important" for weight loss (42%) and weight maintenance (40%).

<http://onlinelibrary.wiley.com/doi/10.1002/oby.20834/epdf>

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.

Summary: CHOICE was a 6-month RCT with 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 sweetened beverage with a diet beverage or water, respectively. Results: At 6 months diet beverage drinkers were more likely to achieve a 5% weight loss than water drinkers.

<http://ajcn.nutrition.org/content/95/3/555.full.pdf+html>

Does Diet-Beverage Intake Affect Dietary Consumption Patterns? Results from the Choose Healthy Options Consciously Everyday (CHOICE) Randomized Clinical Trial.

Piernas C, et al. *Am J Clin Nutr*. 2013;97:604-611.

Summary: A secondary analysis Piernas, et al., showed both study groups reduced total energy, carbohydrate, and added sugars. Diet beverage group participants reduced dessert consumption more than water drinkers.

<http://ajcn.nutrition.org/content/97/3/604.full.pdf+html>

Low Calorie Beverage Consumption Is Associated with Energy and Nutrient Intakes and Diet Quality in British Adults.

Gibson SA, et al. *Nutrients*. 2016;8,9:1-15 (e-pub).

Summary: This analysis of adults in the UK National Diet and Nutrition Survey (NDNS) observed associations between consumption of sugar-sweetened beverages (SSB), low-calorie sweetened beverages (LCB), non-consumers of soft drinks (NC) and consumers of both beverages (BB) with energy intake and diet quality. Results showed LCB and NC groups consumed less energy and sugars than consumers of SSB or BB. NC and LCB consumers had higher quality diets compared to SSB and BB consumers. They did not compensate for the sugar or energy deficit with more sugary foods.

<http://www.mdpi.com/2072-6643/8/1/9>

Socio-Demographic Correlates And Trends In Low-Calorie Sweetener Use Among Adults In The United States From 1999 To 2008.

Drewnowski A, Rehm CD. *European Journal of Clinical Nutrition*. (2015) 69, 1035–1041.

Summary: Data from a representative sample of 24-hour dietary recalls for adults were obtained from five cycles of the National Health and Nutrition Examination Survey (1999–2008 NHANES). A single 24-h recall was obtained for adults who consume NNS to determine NNS consumption by product category and sociodemographic status. Results show that about 30% of adults consumed NNS with nearly 20 percent consuming beverages, 11 percent tabletop sweeteners and about 5 percent consuming foods sweetened with a NNS. NNS use was more common among individuals with less incidence of obesity and related chronic diseases, non-Hispanic whites and those with higher education and income.

<http://www.nature.com/ejcn/journal/v69/n9/abs/ejcn201538a.html> (abstract)

Consumption of LCS Among U.S. Adults is Associated With Higher Healthy Eating Index (HEI 2005) Scores and More Physical Activity.

Drewnowski A, et al. *Nutrients*. 2014;6:4389-4403.

Summary: This study analyzed NHANES data from over 22,000 participants between 1999-2008 who consumed beverages, foods and tabletop sweeteners with NNS. The USDA's Healthy Eating Index was used to measure diet quality. Results showed people who use NNS have a higher HEI than non-consumers largely explained by lower calorie intake from solid fats, added sugars and alcohol. NNS users were found to practice other healthy lifestyle behaviors, such as physical activity, and less tobacco and alcohol use.

<http://www.mdpi.com/2072-6643/6/10/4389/htm>

The literature cited in these summaries is consistent with the extensive evidence base on NNS which concludes that NNS can be used safely and efficaciously as part of a healthy eating pattern. Using NNS, including sucralose, the sweetening ingredient in original SPLENDA® Sweetener Products, can assist people with managing their weight and/or various aspects of metabolic health by reducing calories, total carbohydrate and added sugars.

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HRT-SP-9859

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Splenda
SWEETENERS