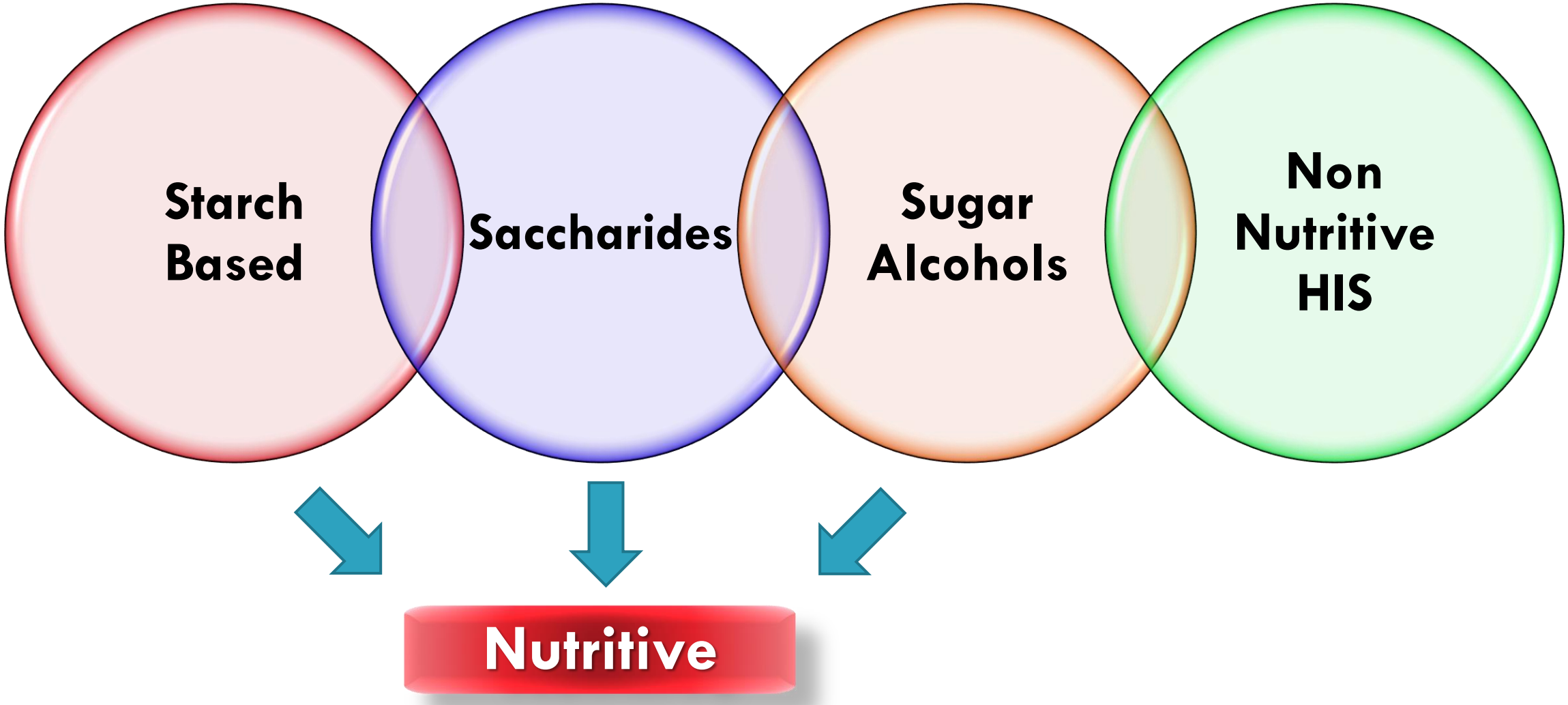

THANK
YOU


artificial
Sweetener


artificial
Sweetener

Artificial Sweetener Family



Non-nutritive Artificial Sweeteners (NNAS)

Controversy Continues

Despite of the fact

- Extensive premarket safety studies used in the rigorous approval process by various FDAs…
- Various PMS research, RWE, Meta-analysis etc…
- Various Global Diabetes, Endocrine, Dietetic Associations and National Cancer Institute hold positions that FDA approved nonnutritive sweeteners are safe to use…

Diabetes Care 2003;26:S51–S61

J Am Diet Assoc. 2004;104:255-275

You are not alone

in this.

Taking our scientific discussion ahead

ORIGINAL ARTICLE

Clearing the Myths around non-nutritive/noncaloric Sweeteners: An Efficacy and Safety Evaluation

Mangesh Tiwaskar[1], Viswanathan Mohan[2*]

Received: 27 November 2021; *Accepted:* 10 March 2022

ABSTRACT

Non-nutritive sweeteners (NNSs) are used to substitute sugar in the diet and are approved by the regulatory bodies in many countries, including the Food and Agriculture Organization (FAO)/the World Health Organization (WHO). Non-nutritive sweeteners are here to stay, as it is an effective strategy to reduce sugar and caloric intake which is a public health priority today. It is a tool to increase dietary compliance in the management of obesity and diabetes and is a partner for fitness seekers. However, the debate on its safety and efficacy continues, including several myths associated with its usage. This review has evaluated the scientific literature in-depth and concludes that NNSs are safe to use within an acceptable daily intake (ADI). Non-nutritive sweeteners are beneficial for their intended use, including weight management and diabetes control when consumed as a part of a dietary management program. The current data do not provide sufficient evidence that NNSs can affect the gut microbiome, and more research, particularly at relevant doses, is required. We also need more randomized control trials (RCTs) among the Indian population on the impact of sugar reduction with NNSs and its health benefits to strengthen the evidence for its use in medical nutrition management and preventive health, helping the individual make an informed choice.

Journal of the Association of Physicians of India (2022): 10.5005/japi-11001-0029

Topics Covered in the publication:

- ✓ Characteristics of NNS
- ✓ Effect on Body Weight / Body Mass Index
- ✓ Effect on Metabolic Health: A Focus on Diabetes
- ✓ Effect on Dental Health
- ✓ NNS and Cancer
- ✓ NNS and Gut Microbiota
- ✓ NNS and Renal Toxicity

ORIGINAL ARTICLE

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Mangesh Tiwaskar[1], Viswanathan Mohan[2*]

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Abstract

Non-nutritive sweeteners (NNSs) are used to substitute sugar in the diet and are approved by the regulatory bodies in many countries, including the Food and Agriculture Organization (FAO)/the World Health Organization (WHO). Non-nutritive sweeteners are here to stay, as it is an effective strategy to reduce sugar and caloric intake which is a public health priority today. It is a tool to increase dietary compliance in the management of obesity and diabetes and is a partner for fitness seekers. However, the debate on its safety and efficacy continues, including several myths associated with its usage. This review has evaluated the scientific literature in-depth and concludes that NNSs are safe to use within an acceptable daily intake (ADI). Non-nutritive sweeteners are beneficial for their intended use, including weight management and diabetes control when consumed as a part of a dietary management program. The current data do not provide sufficient evidence that NNSs can affect the gut microbiome, and more research, particularly at relevant doses, is required. We also need more randomized control trials (RCTs) among the Indian population on the impact of sugar reduction with NNSs and its health benefits to strengthen the evidence for its use in medical nutrition management and preventive health, helping the individual make an informed choice.

Journal of the Association of Physicians of India (2022): 10.5005/japi-11001-0029

Introduction

Non-nutritive/noncaloric sweeteners are defined as food additives that are used to replace sugar and give food a sweet taste, thus helping in decreasing caloric and sugar intake. The tabletop sweeteners are products that consist of or include permitted NNSs [approved by regulatory bodies like the United States Food and Drug Administration (USFDA) Joint FAO/WHO Expert Committee on Food Additives (JECFA), country-specific regulatory bodies, etc.] and are intended for use as an alternative to sugar, to their ultimate customers. Predominantly there are two kinds of sweeteners—caloric sweeteners and noncaloric/NNSs/low-caloric sweeteners (LCSs). Sucrose, glucose, and fructose are the foremost bulk caloric sweeteners used in food and beverages or packed in small containers for retail sale. Caloric sweeteners add bulk and calories to the food. These sweeteners are generally carbohydrates or sugar alcohols that have a similar sweetness to sugar, for example, sorbitol, sorbitol syrup, mannitol, isomalt, polyglycitol syrup, maltitol, maltitol syrup, lactitol, xylitol, etc. Sugars add 4 kcal/gm to foods, while sugar alcohols add calories ranging from 0.2 to 2.6 kcal/gm. Conversely, high-intensity sweeteners/NNSs have a sweet taste, are noncaloric, do not provide bulk to the food, have multifold sweetness than sugar, and are consequently used in small amounts. These include steviol glycoside, thaumatin, aspartame, sucralose, neotame, acesulfame potassium, saccharin, etc.[1]

Sugar is deemed as the major contributing factor for the increased risk of obesity since it adds caloric value to the food.[1-3] Obesity is a major public health concern worldwide,[2-4] and its prevalence has increased evidently over the past few decades.[3] It is considered as the major cause of comorbidities leading to diabetes mellitus, cardiovascular disorders, hypertension, certain cancers, and other health problems.[3,4] Owing to a high burden of the disease, the WHO has recommended that the total added sugars should be restricted to below 10% (preferably 5%) of the total energy intake.[4-7] Therefore the regulatory bodies around the world have recommended reducing the intake of sugar to combat the issue of obesity and related comorbidities.[2] The use of NNSs is one of the most important strategies that may help in substituting the sugar due to their sweetness, palatability, and addition of none or few calories to food.[2-5]

Several studies have demonstrated that substituting sugars with NNSs has been useful in preventing and managing obesity and associated disorders.[2,3] In 2011, the European Food Safety Authority (EFSA) concluded that there was sufficient scientific evidence to support the claims that NNSs like sucralose reduced postprandial blood sugar levels and maintained tooth mineralization by decreasing tooth demineralization.[8]

Despite the consistent reassurances from food safety authorities, there exists some distrust regarding the use of NNSs among healthcare professionals.[2] The present succinct review focuses on busting the myths surrounding the efficacy and safety of NNSs in humans by deliberating their safety and efficacy on health outcomes.

Non-nutritive Sweeteners: The Journey from Discovery to Human Use

Non-nutritive sweeteners have an intensely sweet taste that provides very low or zero calories. These agents are used in minimal quantities as they have greater sweetness than sugar.[1,3] Non-nutritive sweeteners have been used safely in food and drinks all over the world for over a century. Saccharin was the first NNS to be discovered in 1879 by Remsen and Fahlberg. This was followed by the discovery of stevia, cyclamate, aspartame, acesulfame potassium, sucralose, and neotame. Non-nutritive sweeteners differ from each other in terms of their sweetness, unique structure, metabolic fate, and technical characteristics.[9] The properties of the most used NNSs are summarized in Table 1.

Health Outcomes of NNSs

Several studies have established the effectiveness of NNSs in the maintenance of body weight, treatment of obesity, management of diabetes, and prevention/reduction of dental caries.[1] However, there

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How to cite this article: Tiwaskar M, Mohan V. Clearing the Myths around non-nutritive/noncaloric Sweeteners: An Efficacy and Safety Evaluation. J Assoc Physicians India 2022;70(7):18–26.

Reference:

Tiwaskar M, Mohan V. Clearing the Myths around non-nutritive/non-caloric Sweeteners: An Efficacy and Safety Evaluation. J Assoc Physicians India. 2022 Jul;70(7):11-12. doi: 10.5005/japi-11001-0029. PMID: 35833391.

Artificial Sweeteners: An Update

A Presentation by Dr Mangesh Tiwaskar

Disclaimer

- Discussion based on ADA, AHA, NIH, EASD, RSSDI, National Cancer Institute Guidance and review of some published literature in peer reviewed International Journals…

- There are no Conflicts of Interest…

Time will ----

- Details of the other sweeteners
- Details of specific drug
- Details on Metabolic Aspects
- Details of any RCTs

Few Abbreviations…

- ★ **NNS/LCS** : Non Nutritive Sweeteners / Low Calory Sweeteners…
- ★ **GRAS** : Generally Regarded As Safe…
- ★ **ADI** : Acceptable Daily Intake…
- ★ **NOAEL** : No Observed Adverse Effect Level…
- ★ **EFSA** : European Food Safety Authority…
- ★ **FSSAI** : Food Safety and Standards Authority of India…
- ★ **JECFA** : Joint (FAO/WHO) Expert Committee on Food Additives…

Need for Non Nutritive Sweeteners:

Data shows increasing sugar consumption in India

As per WHO, 2015[2] there is a:

- Strong Recommendation to reduce intake of free sugar throughout the life course. Consumption, should be less than 10% of total energy intake.
- Conditional Recommendation: further reduce intake of free sugars to below 5% of total energy intake

Dental caries in kids

Indians are at high risk of developing obesity, metabolic syndrome and diabetes[3].

References:

1. Gulati S, Misra A. Sugar Intake, Obesity, and Diabetes in India. Nutrients. 2014; 6(12):5955-5974. https://doi.org/10.3390/nu6125955
2. Guideline: Sugars intake for adults and children. Geneva: World Health Organization; 2015.
3. Wells, J. C., Pomeroy, E., Walimbe, S. R., Popkin, B. M., & Yajnik, C. S. (2016). The Elevated Susceptibility to Diabetes in India: An Evolutionary Perspective. Frontiers in public health, 4, 145. https://doi.org/10.3389/fpubh.2016.00145

What are LC NNA HIS?

- **Non-nutritive low-caloric** substances used for Sweetening…
- Interact with taste receptors to give a sense of sweetness…
- **Much sweeter** than Sucrose (Sweetness Factor Index of 1)…
- Can exceed sweetness of sucrose by **30 - 37,000** times!…

Non Nutritive sweeteners can help in reducing added sugar intake while maintaining diet palatability

Non nutritive Sweeteners: Current Use and Health Perspectives: A Scientific Statement from the American Heart Association and the American Diabetes Association[1]

"The evidence reviewed suggests that when used judiciously, NNS could facilitate reductions in added sugars intake, thereby resulting in decreased total energy and weight loss/weight control, and promoting beneficial effects on related metabolic parameters. However, these potential benefits will not be fully realized if there is a compensatory increase in energy intake from other sources"

American Diabetes Association®

American Heart Association®

BDA: The association of UK Dietitians[2]:

"Opting for an artificial sweeteners may assist in the management of weight and in the management of other health conditions such as diabetes mellitus in some individuals. A tailored individualized approach is required"

BDA The Association of UK Dietitians

EFSA: European Food Safety Authority[3]

Scientific Opinion on the substantiation of health claims related to intense sweetener

"Panel considers that the reduction of post-prandial glycaemic responses (as long as post-prandial insulinaemic responses are not disproportionally increased) may be a beneficial physiological effect"

efsa European Food Safety Authority

References:

1. Diabetes Care 2012 Aug; 35(8): 1798-1808. https://doi.org/10.2337/dc12-9002. https://care.diabetesjournals.org/content/35/8/1798
2. https://www.bda.uk.com/uploads/assets/11ea5867-96eb-43df-b61f2cbe9673530d/policystatementsweetners.pdf, accessed on 28th July 2021
3. https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2011.2229, accessed on 28th July 2021

There are 2 kinds of sweeteners:

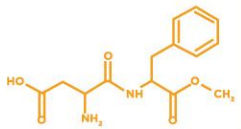
Novel NNS

- Aspartame
- Sucralose
- Stevia
- Neotame
- Ace K^+

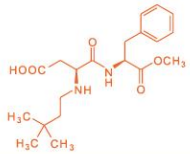
Non Nutritive Sweeteners

Includes:

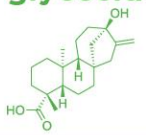
Aspartame



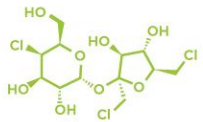
Neotame



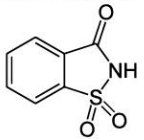
Steviol glycosides



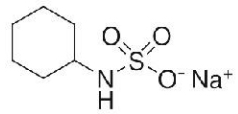
Sucralose



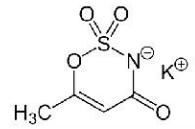
Saccharin



Cyclamate



Acesulfame potassium



References:

1. Diabetes Care 2012 Aug; 35(8): 1798-1808. https://doi.org/10.2337/dc12-9002. https://care.diabetesjournals.org/content/35/8/1798
2. https://www.bda.uk.com/uploads/assets/11ea5867-96eb-43df-b61f2cbe9673530d/policystatementsweetners.pdf, accessed on 28th July 2021
3. https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2011.2229, accessed on 28th July 2021

Let's look at the history of Non Nutritive Sweeteners its Discovery and first approval.

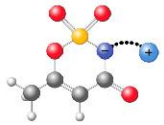
Fun Fact

Saccharine, Aspartame and Sucralose were discovered "**Accidentally !!**"

Steviol Glycosides
Sucalose
Aspartame
Neotame

References:
Sugar substitutes: Health controversy over perceived benefits; Kirtida R. Tandel, J Pharmacol Pharmacother, 2011 Oct-Dec, 2(4): 236-243. doi: 10.4103/0976-500X.85936

Key characteristics of common non nutritive sweeteners[1,2]

Name of NNS	Chemical Composition/ Plant Source	Sweetening power (compared to sucrose)	Caloric value	Acceptable Daily Intake (ADI)	Global regulatory status
Acesulfame-K (First Generation) 	Is a combination of an organic acid and potassium	Approx. 200 times sweeter than sucrose	Calorie-free	As per JECFA: 15 mg/kg/day	1988: Usage approved in specific categories (US - FDA) 2003: Approved as General Purpose Sweetener (US- FDA) **Approved for use in over 90 countries** **More than 90 studies support its safety** (US- FDA)
Aspartame (First Generation) 	Consists of Methyl ester of amino acids, aspartic acid and phenylalanine	Approx. 200 times sweeter than sucrose	Negligible	As per JECFA: 40 mg/kg/day	1981: Approved for use in few categories (US-FDA) 1996: Approved as General Purpose Sweetener (US-FDA) **Approved for use in 100 countries** More than 100 studies supporting its safety. (US- FDA) PKU patients: to avoid the usage.
Sucralose (Second Generation) 	Disaccharide made from sucrose by substituting 3 chlorine molecules for 3 hydroxyl groups on sucrose molecule	Approx. 600 times sweeter than sucrose	Calorie-free	As per JECFA: 15 mg/kg/day	1998: approved for 15 food categories (US- FDA) 1999: Approved as general purpose sweetener (US- FDA) **Approved for use in 80 countries** Extensively studied. More than 110 safety studies (US- FDA)
Steviol glycosides (Third Generation) 	Sweetener present in leaves, from grp of compound – steviol glycosides. High purity extract with 95% of steviol glycosides are approved for use. Stevia sweetener refers to approved high purity leaf extract.	Approx. 200 to 300 times sweeter than sucrose (depending on the glycoside)	Calorie-free	ADI for steviol glycosides is expressed as 4 mg of steviol equivalent / kg/day.	Approved for use by JECFA in 2009 Approved for use in 49 countries
Neotame (Third Generation) 	Derivative of aspartic acid and phenylalanine	7000 – 13000 times sweeter than sugar	Negligible	As per JECFA: 2 mg/kg/day	2002: Approved as general purpose sweetener (US- FDA) **Approved for use in 40 countries** **More than 113 animal and human studies reviewed to determine the safety** (US- FDA)

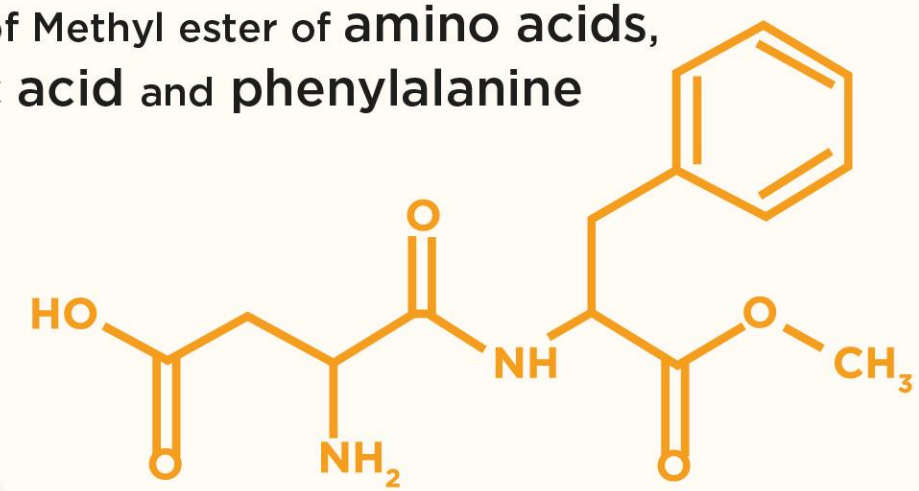
References:

1. ILSI, Low calorie/ non nutritive sweetener fact sheet , Sept 2015
2. https://www.fda.gov/food/food-additives-petitions/additional-information-about-high-intensity-sweeteners-permitted-use-food-united-states, accessed on 28th July 2021

Aspartame *(First Generation)*

Chemical Composition

Consists of Methyl ester of **amino acids**, **aspartic acid** and **phenylalanine**



Global regulatory status

- 1981: Approved for use in few categories (US-FDA)
- 1996: Approved as General Purpose Sweetener (US-FDA)
- Approved for use in 100 countries
- More than 100 studies supporting its safety. (US- FDA)
- PKU patients: to avoid the usage.

Sweetening power (compared to sucrose)

Approx. **200 times sweeter** than sucrose

Caloric value

Negligible

Acceptable Daily Intake (ADI)

As per JECFA:
40 mg/kg/day

References:

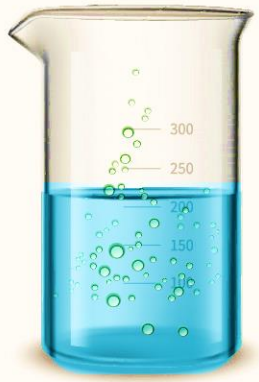
ILSI, Low calorie/ non nutritive sweetener fact sheet , Sept 2015

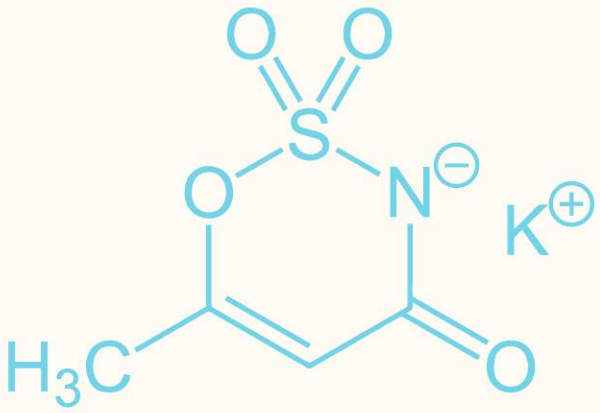
https://www.fda.gov/food/food-additives-petitions/additional-information-about-high-intensity-sweeteners-permitted-use-food-united-states, accessed on 28th July 2021

Acesulfame-K *(First Generation)*

Chemical Composition

Is a combination of an **organic acid** and **potassium**





Global regulatory status

- 1988: Usage approved in specific categories (US - FDA)
- 2003: Approved as General Purpose Sweetener (US- FDA)
- **Approved for use in over 90 countries**
- More than 90 studies support its safety (US- FDA)

Sweetening power (compared to sucrose)

Approx. **200 times sweeter** than sucrose

Caloric value

Calorie-free

Acceptable Daily Intake (ADI)

As per JECFA:
15 mg/kg/day

References:

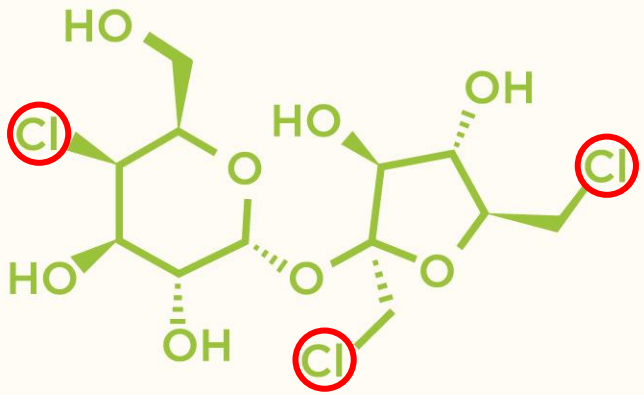
ILSI, Low calorie/ non nutritive sweetener fact sheet , Sept 2015

https://www.fda.gov/food/food-additives-petitions/additional-information-about-high-intensity-sweeteners-permitted-use-food-united-states, accessed on 28th July 2021

Sucralose *(Second Generation)*

Chemical Composition

Disaccharide made from sucrose by substituting 3 chlorine molecules for 3 hydroxyl groups on sucrose molecule



Global regulatory status

- 1998: approved for 15 food categories (US- FDA)
- 1999: Approved as general purpose sweetener (US- FDA)
- **Approved for use in 80 countries**
- **Extensively studied. More than 110 safety studies (US- FDA)**

Sweetening power (compared to sucrose)

Approx. 600 times sweeter than sucrose

Caloric value

Calorie-free

Acceptable Daily Intake (ADI)

As per JECFA:
15 mg/kg/day

References:

ILSI, Low calorie/ non nutritive sweetener fact sheet , Sept 2015

https://www.fda.gov/food/food-additives-petitions/additional-information-about-high-intensity-sweeteners-permitted-use-food-united-states, accessed on 28th July 2021

Steviol Glycosides *(Third Generation)*

Plant Source

Sweetener present in leaves, from group of compound – steviol glycosides. High purity extract with 95% of steviol glycosides are approved for use. Stevia sweetener refers to approved high purity leaf extract.

Global regulatory status

- Approved for use by JECFA in 2009
- **Approved for use in 49 countries**

Sweetening power (compared to sucrose)

Approx. 200 to 300 times sweeter than sucrose (depending on the glycoside)

Caloric value

Calorie-free

Acceptable Daily Intake (ADI)

ADI for steviol glycosides is expressed as 4 mg of steviol equivalent /kg/day.

References:

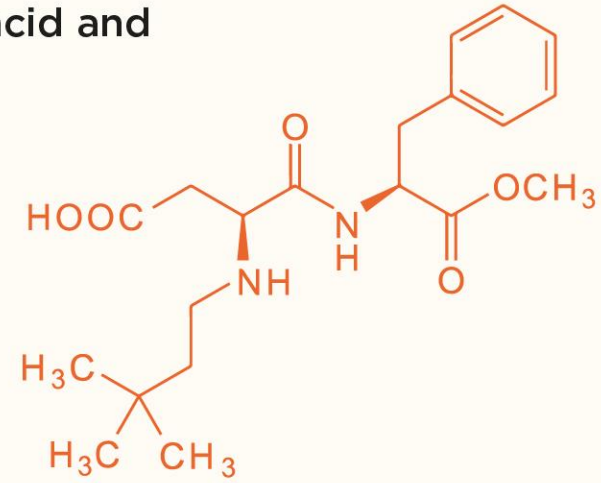
ILSI, Low calorie/ non nutritive sweetener fact sheet , Sept 2015

https://www.fda.gov/food/food-additives-petitions/additional-information-about-high-intensity-sweeteners-permitted-use-food-united-states, accessed on 28th July 2021

Neotame *(Third Generation)*

Chemical Composition

Derivative of aspartic acid and phenylalanine



Global regulatory status

- 2002: Approved as general purpose sweetener (US- FDA)
- Approved for use in 40 countries
- More than 113 animal and human studies reviewed to determine the safety (US- FDA)

Sweetening power (compared to sucrose)

Approx. **7000-13000 times sweeter** than sugar

Caloric value

Negligible

Acceptable Daily Intake (ADI)

As per JECFA:
2 mg/kg/day

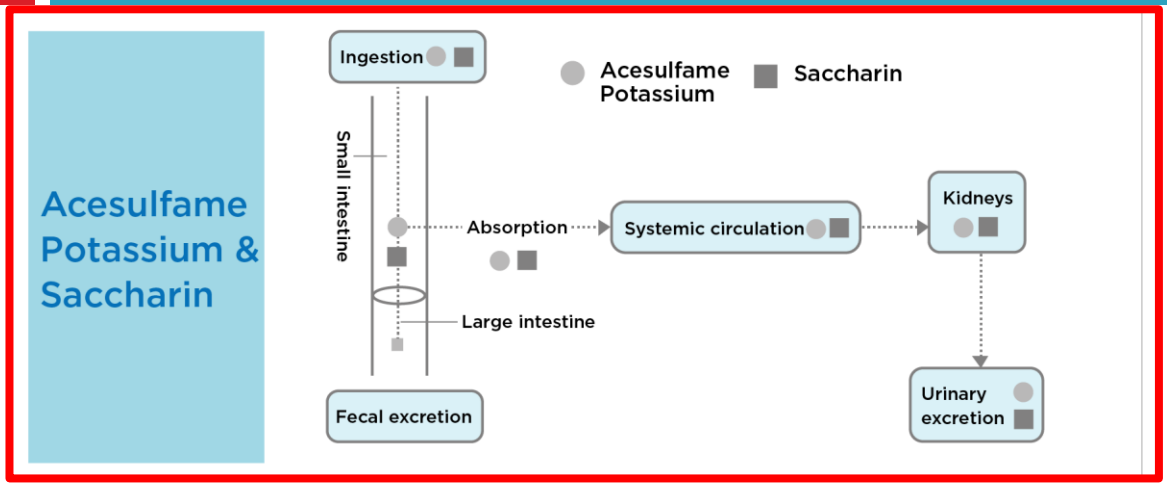
References:

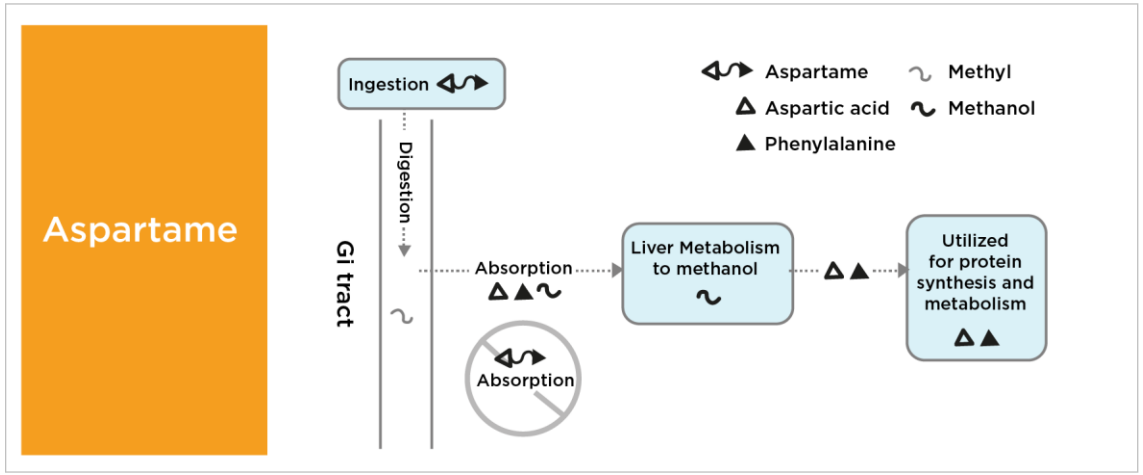
ILSI, Low calorie/ non nutritive sweetener fact sheet , Sept 2015

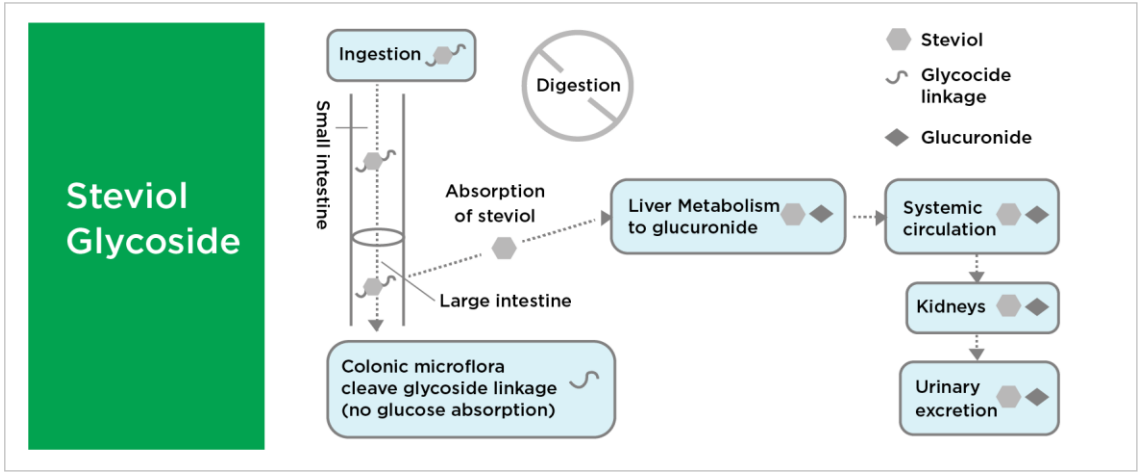
https://www.fda.gov/food/food-additives-petitions/additional-information-about-high-intensity-sweeteners-permitted-use-food-united-states, accessed on 28th July 2021

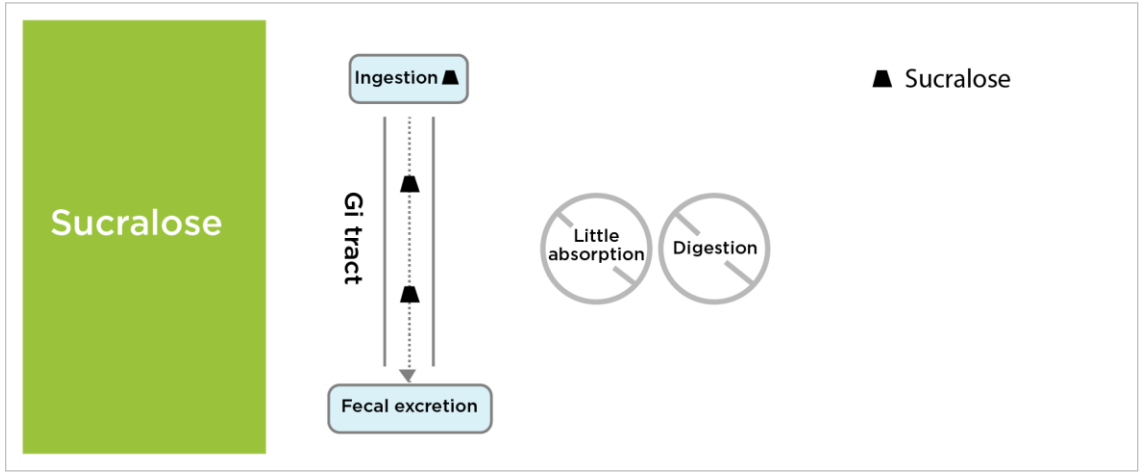
NNS in our Daily Life

Biological fate of NNS in body





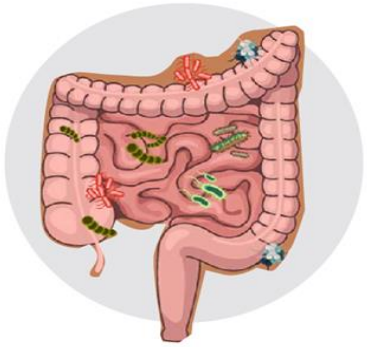




Reference:
Magnuson BA, Carakostas MC, Moore NH, Poulos SP, Renwick AG. Biological fate of low-calorie sweeteners. Nutr Rev. 2016 Nov;74(11):670-689. doi: 10.1093/nutrit/nuw032. PMID: 27753624.

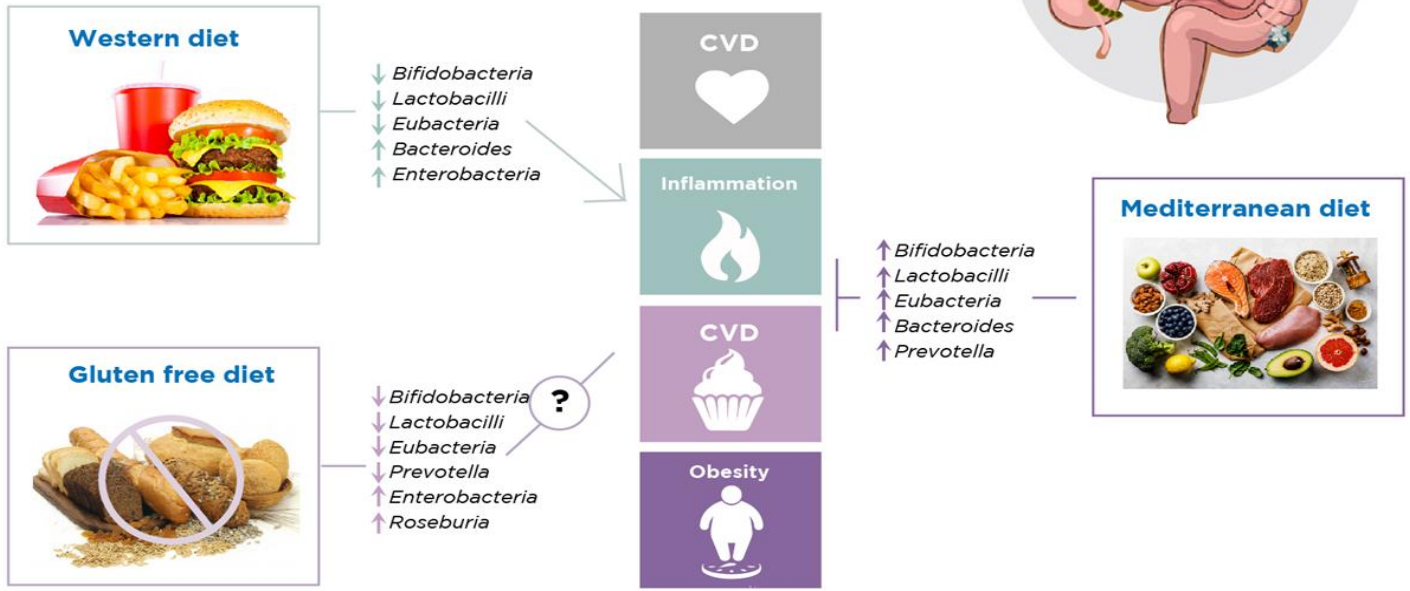
They have been well addressed…

On the contrary, high intake of sugar is linked to "inflammatory" gut microbiome. Available literature shows association of Western diets with changes in Gut microbiota and cardio metabolic disease.



"Higher intake of animal foods, processed foods, alcohol and sugar, corresponds to a microbial environment that is characteristic of inflammation, and is associated with higher levels of intestinal inflammatory markers."[1]

Published in BMJ, GUT, 2021



Impact of various diets on intestinal microbiota and cardiometabolic disease[2].

References:

1. Bolte, L. A., Vich Vila, A., Imhann, F., Collij, V., Gacesa, R., Peters, V., Wijmenga, C., Kurilshikov, A., Campmans-Kuijpers, M., Fu, J., Dijkstra, G., Zhernakova, A., & Weersma, R. K. (2021). Long-term dietary patterns are associated with pro-inflammatory and anti-inflammatory features of the gut microbiome. Gut, 70(7), 1287–1298. https://doi.org/10.1136/gutjnl-2020-322670
2. Singh, R. K., Chang, H. W., Yan, D., Lee, K. M., Ucmak, D., Wong, K., Abrouk, M., Farahnik, B., Nakamura, M., Zhu, T. H., Bhutani, T., & Liao, W. (2017). Influence of diet on the gut microbiome and implications for human health. Journal of translational medicine, 15(1), 73. https://doi.org/10.1186/s12967-017-1175-y

Questions Asked…

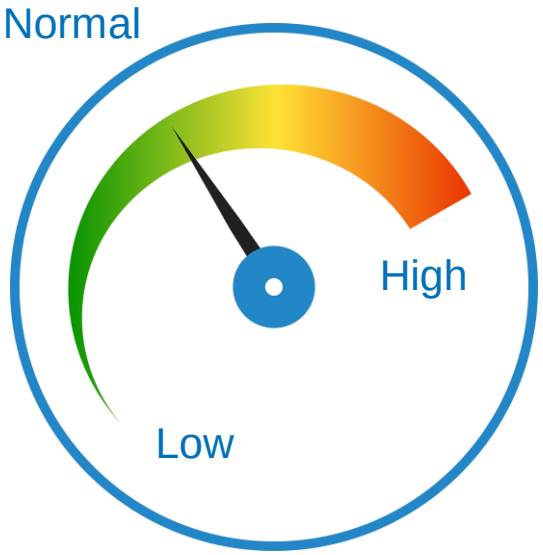
- Will cause Obesity…
- Will cause ↑IR and affect Glucose metabolism…
- Will reduce endogenous GLP1 and GIP secretion…

Effect on Metabolic Health: A Focus on Diabetes

Clinical evidence supports use of

LCS.

LCS associated with **no increase in blood glucose levels**, hemoglobin A_{1C}, fasting and postprandial glucose, and insulin levels in subjects with or without diabetes



Blood Sugar Level

Lets discuss the outcomes of various studies highlighting the effects of NNSs on glycemia and glucose hemostasis

Characteristics of human studies investigating the effect of specific artificial sweeteners on glucose homeostasis.

References	Study type	Duration	Participants	Dosage artificial sweetener	Comparator	Measure of glucose homeostasis	Statistical significance
Aspartame							
(39)	RCT	Acute	Healthy	169 mg	Water	Glucose levels	N.S
(40)	RCT	Acute	Obese	500 ml beverage	Water	Glucose levels	N.S.
(43)	RCT	Acute	T2DM	400 mg in beverage	Unsweetened flavored beverage	Glucose levels	N.S.
(44)	RCT	Acute	Healthy, overweight	250 mg	Water	Glucose levels	N.S.
(45)	RCT	Acute	Healthy	400 mg	Placebo (corn flour)	Glucose levels	N.S.

Impact of continuous covariates on PPG and PPI responses to LES[1]

	PPG mean change difference			PPI mean change difference		
Covariates	β	SE	P	β	SE	P
Baseline fasting glucose per 1-mmol/L increase	−0.059	0.04	0.15	2.17	2.87	0.45
Baseline fasting insulin per 1-pmol/L increase	−0.001	0.001	0.32	−0.04	0.11	0.75
Sucralose dose per 10-mg increase	0.004	0.003	0.22	0.08	0.19	0.66
L-Arabinose dose per 1000-mg increase	0.001	0.024	0.96	0.96	3.93	0.81

[1]LES, low-energy sweeteners; PPG, postprandial glucose; PPI, postprandial insulin.

(52)	RCT	Acute	Healthy	50 ml beverage	Water	Glucose levels	N.S.
(53)	RCT	Acute	Healthy	80 mg infusion	Saline infusion	Glucose levels	N.S.
(42)	RCT	Acute	Healthy	960 mg infusion	Saline infusion	Glucose levels	N.S.
(46)	RCT	Acute	Healthy, T2DM	24 mg	Water	Glucose levels	N.S.
(54)	RCT	10 days	Healthy	60 mg in beverage	-	Insulin sensitivity	N.S.
(54)	RCT	10 days	Healthy	60 mg + maltodextrin	-	Insulin sensitivity	↓, $P < 0.043$
(47)	RCT	2 weeks	Healthy	0.136 mg/day	-	Insulin sensitivity	N.S.
(38)	RCT	2 weeks	Healthy	36 mg/day + maltodextrin/ dextrose	Control group	Insulin sensitivity	−17.7%, $P < 0.04$
(55)	RCT	13 weeks	T2DM	667 mg/day	Placebo (cellulose)	HbA1c	N.S.

Effect of NNSs on glycemia and glucose hemostasis

Table 4: Effect of NNSs on glycemia and glucose hemostasis

Author (year)	*Study type*	*Study population*	*Study duration*	*LCS used*	*Comparator*	*Conclusion*
Kim et al. (2020)[42]	Randomized, crossover trial	39 healthy individuals	2 weeks intervention 4 weeks washout period	Acesulfame potassium + aspartame	Mineral water	No effect on glucose, insulin, and insulin sensitivity
Higgins et al. (2018)[43]	Parallel-arm design	100 healthy, lean adults	12 weeks	Aspartame	–	No effect on glycemia, appetite, or bodyweight
Engel et al. (2018)[44]	Secondary analysis of a 6-month RCT	60 overweight and obese subjects	6 months	Aspartame	Sucrose	No effect of aspartame on long-term glycemic (fasting glucose and insulin) or on insulin sensitivity
Tey et al. (2017)[45]	Randomized, crossover study	10 healthy males	24 hours	Aspartame, stevia	Sucrose	Minimal effect on 24-hour glucose profiles with LCS
Grotz et al. (2017)[46]	Double-blind, parallel, randomized clinical trial	47 healthy males	12 weeks	Sucralose	Placebo	Sucralose does not affect glycemic control
Sylvetsky et al. (2016)[47]	Four-period, crossover study	61 healthy adults	24 hours	Diet soda with sucralose, acesulfame potassium, aspartame	Water with sucralose Seltzer water with NNS	Diet sodas augmented GLP-1 responses to oral glucose
Temizkan et al. (2015)[48]	Prospective study	8 healthy volunteers and 8 newly diagnosed, drug-naive T2DM patients	Not specified	Sucralose, aspartame	Water	Sucralose lowers blood glucose in healthy subjects by enhancing GLP-1 release; however, this is not observed in newly diagnosed T2DM patients
Hazali et al. (2014)[49]	Prospective study	32 healthy subjects	24 hours	Stevia	Sucrose	Stevia maintained blood glucose even when consumed in a short length of time
Bryant et al. 2014[50]	Prospective study	10 healthy subjects	Not specified	Aspartame, saccharin, acesulfame potassium	–	No additional effect of aspartame or saccharin on blood glucose
Pepino et al. (2013)[51]	Randomized crossover design	17 obese subjects	2 days with 7 days washout period	Sucralose	Water	Sucralose increased peak plasma glucose concentrations, C-peptide, and insulin concentrations, and total insulin AUC after an oral glucose load
Brown et al. (2009)[52]	Prospective study	22 healthy subjects	24 hours	Sucralose and acesulfame potassium	Carbonated water	Increase in GLP-1 secretion

GLP, Glucagon-like peptide; T2DM, Type II diabetes mellitus; AUC, Area under curve

Reference:
Tiwaskar M, Mohan V. Clearing the Myths around non-nutritive/noncaloric Sweeteners: An Efficacy and Safety Evaluation. J Assoc Physicians India. 2022 Jul;70(7):11-12. doi: 10.5005/japi-11001-0029. PMID: 35833391.

Highlighting a recent Systematic review and meta-analysis:

“

Data indicate that **replacing sugar with NNS leads to weight reduction**, an effect that is particularly evident in adults, subjects with overweight/ obesity, and those under an unrestricted diet”

Reference:

Laviada, Hugo & Molina Segui, Fernanda & Perez-Gaxiola, Giordano & Cuello-Garcia, Carlos & Arjona-Villicaña, Ruy & Espinosa, Alan & Martínez Portilla, Raigam. (2020). Effects of nonnutritive sweeteners on body weight and BMI in diverse clinical contexts: Systematic review and meta-analysis. Obesity Reviews. 21. 10.1111/obr.13020.

Received: 3 January 2020 | Revised: 2 March 2020 | Accepted: 3 March 2020

DOI: 10.1111/obr.13020

ETIOLOGY AND PATHOPHYSIOLOGY

OBESITY Reviews WILEY

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

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Summary

There is an ongoing debate about the possible influences of nonnutritive sweeteners (NNS) on body weight. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) with NNS to assess their impact on body weight. We systematically searched for RCTs at least 4 weeks in duration, evaluating the effect of NNS on body weight, both in subjects with healthy weight and in subjects with overweight/obesity at any age, and compared the effects of NNS vs caloric and non-caloric comparators. The primary outcome was the difference in body weight between NNS and comparators. Twenty studies were eligible (n = 2914). Participants consuming NNS showed significant weight/BMI differences favouring NNS compared with nonusers. Grouping by nature of comparator revealed that NNS vs placebo/no intervention and NNS vs water produced no effect. When comparing NNS vs sucrose, significant weight/BMI differences appeared favouring NNS. Consumption of NNS led to significantly negative weight/BMI differences in unrestricted energy diets, but not in weight-reduction diets. Participants with overweight/obesity and adults showed significant favourable weight/BMI differences with NNS. Data suggest that replacing sugar with NNS leads to weight reduction, particularly in participants with overweight/obesity under an unrestricted diet, information that could be utilized for evidence-based public policy decisions.

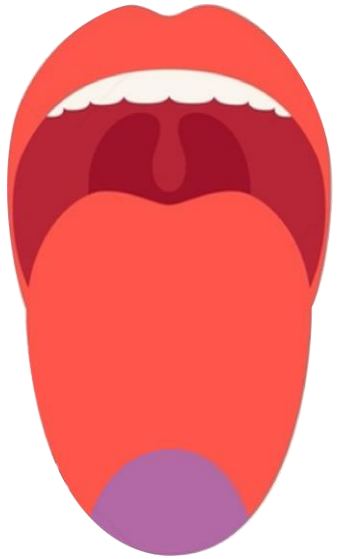
KEYWORDS

artificial sweeteners, body weight, obesity, systematic review

Effect on Taste Receptor and Incretin Secretion

Taste receptors - involved in the modulation of multiple metabolic processes like **satiation, glucose homeostasis**, and **gut motility**.

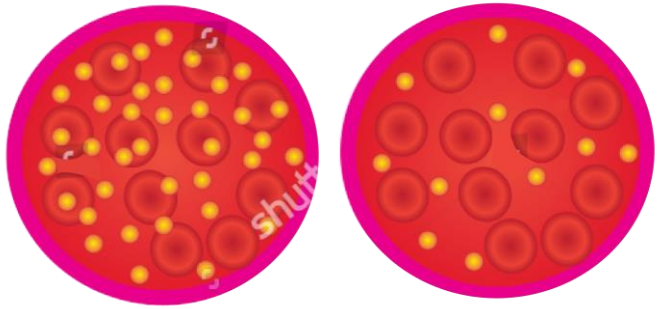
Activation of sweet-taste receptors in the gut plays a role in the **regulation of glucose absorption** and **promoting insulin release**.



Exposure to food, sugars, or nutrient triggers physiological responses that result in the release of insulin or **incretin to reduce blood glucose levels**.

Contrary to the findings of in vitro studies, in vivo studies and human trials have shown to **have no effects on circulating incretin levels**.

A recent review stated that **NNSs do not directly induce incretin secretion** and activation of the sweet-taste receptors by **LCSs fails to replicate any of the effects on gut hormones**, gastric motility, or appetitive responses evoked by caloric sugars



High blood Sugar

Normal blood Sugar

Reference:
Pang MD, Goossens GH, Blaak EE. The impact of artificial sweeteners on body weight control and glucose homeostasis. Front Nutr 2021;7:598340.

LCS and its effect on Appetite or Hunger

Most human studies and clinical reviews have however, concluded that LCS do not affect appetite or hunger or desire for sweetness. Randomized Control Trials (RCT) that measured hunger and food choices demonstrate either no or possible overall beneficial effect (Anderson et al. 1989; Drewnowski et al., 1994, Rogers et al. 1995; Blackburn et al.. 1997; Mattes et al.. 2009; Anderson et al. 2012; Gardner et al., 2012; Piernas et al., 2013, Peters et al., 2016). 'Most of these studies reported no effect on gut hormones, no adverse effect on functions related to gut hormones including blood glucose and insulin levels, appetite and gastric emptying.
Thus, it has been revealed that there is no adverse effect of LCS use with respect to hunger and appetite in healthy individuals and individuals with diabetes (Bryant & McLaughlin, 2016; Meyer-Gerspach et al., 2016, Magnuson et al., 2017).

Reference:
NNS Monograph on sweetness: Role of Sugar and low calorie Sweeteners

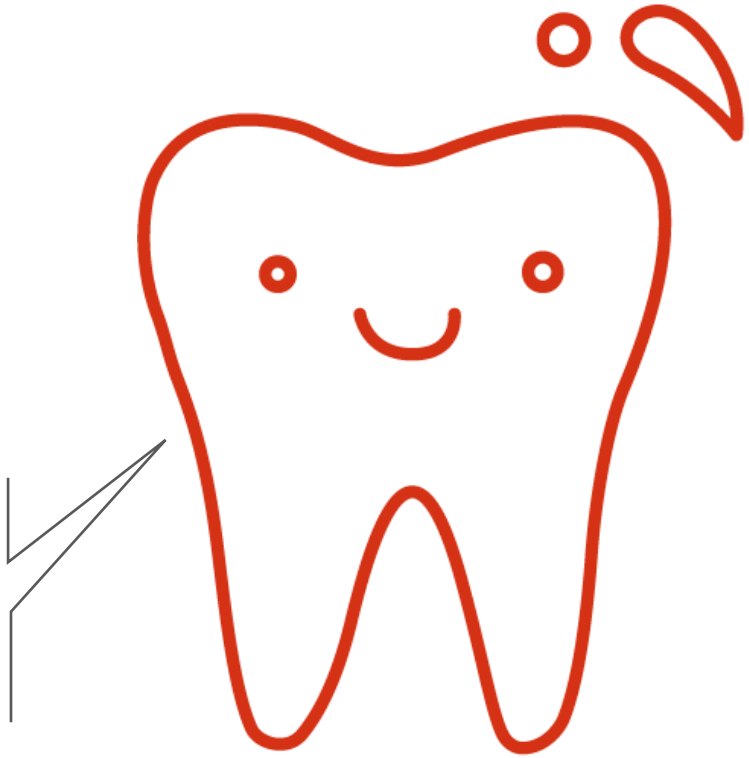
Diabetes and Dental Health

Diabetics – at a higher risk for both **gingivitis** (early-stage gum disease) and **periodontitis** (advanced gum disease).

Patients with long-standing, poorly controlled diabetes are **at risk of** developing **oral candidiasis**

Diabetes is believed to **promote** periodontitis through an exaggerated inflammatory response to the **periodontal microflora**

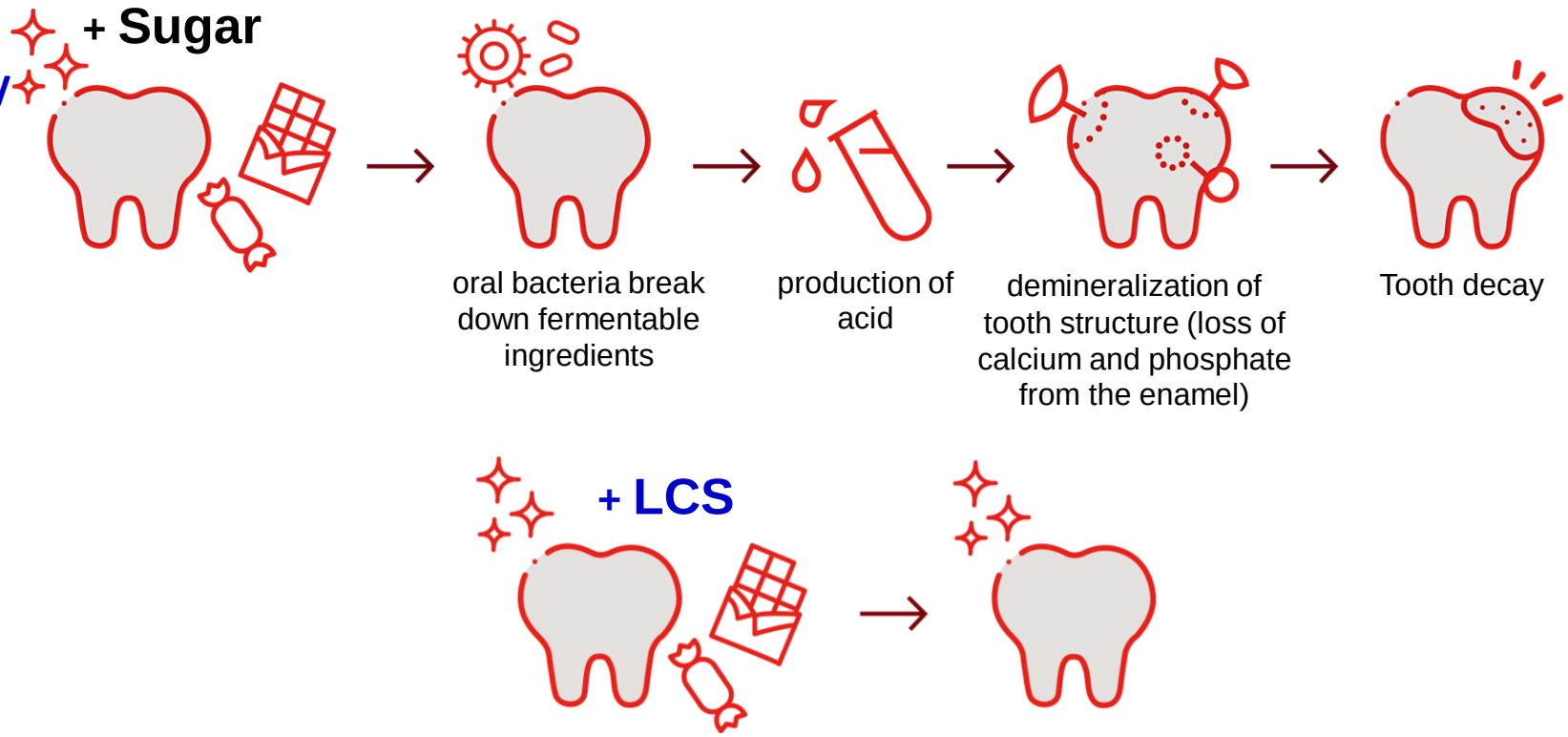
Dental Health is crucial for Diabetics



Reference:
Lamster IB, Lalla E, Borgnakke WS, Taylor GW. The relationship between oral health and diabetes mellitus. J Am Dent Assoc. 2008 Oct;139 Suppl:19S-24S. doi: 10.14219/jada.archive.2008.0363. PMID: 18809650

Effect of NNS on Dental Health

- Relationship exists between amount of free sugar intake and the development of dental caries across age groups. **Limiting free sugar intake to <10% of daily energy intake diminishes the risk of dental caries** throughout the life course.
- Evidence reveals that use of NNSs influences **microbial composition of the oral mucosa** that may be utilized to **reduce the risk of the development of dental caries**.
- In vitro studies have uncovered that **aspartame, saccharin**, and **sucralose** have antimicrobial activity against common periodontal pathogens.

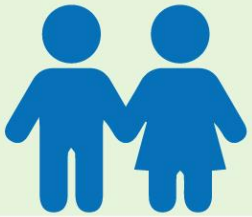


Reference:
Sylvetsky AC, Rother KI. Non-nutritive sweeteners in weight management and chronic disease: a review. Obesity (Silver Spring) 2018;26(4):635–640.

Use of NNS Among children and in Pregnancy

"2013 EFSA publishes its first full risk assessment of aspartame. The opinion concludes that aspartame and its breakdown products are safe for the general population (including infants, children and pregnant women)[1]."

Safety of the proposed extension of use of sucralose (E 955) in foods for special medical purposes in young children[2]



"Extension of use of sucralose (E 955) in FSMP in young children aged from 1 to 3 years would not be of safety concern."

efsa
European Food Safety Authority

References:
1. https://www.efsa.europa.eu/en/topics/topic/aspartame
2. https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2016.4361

Use of NNS Among children and in Pregnancy

"Scientists in Health Canada's Food Directorate identified no toxicological concerns with the use of steviol glycosides and consider it safe for consumption in foods by the general population, including pregnant women and children, as well as individuals with diabetes, at dose levels not greater than 4 mg/kg bw/day, expressed as steviol equivalents. This value is consistent with that derived by JECFA."[3]

Government of Canada

"Considering the conservative nature of the dietary exposure estimate, based on maximum use levels applied to all food consumed from categories with permissions for use in the countries assessed, steviol glycosides are not likely to present a health concern for any age group[4].

Food and Agriculture Organization of the United Nations

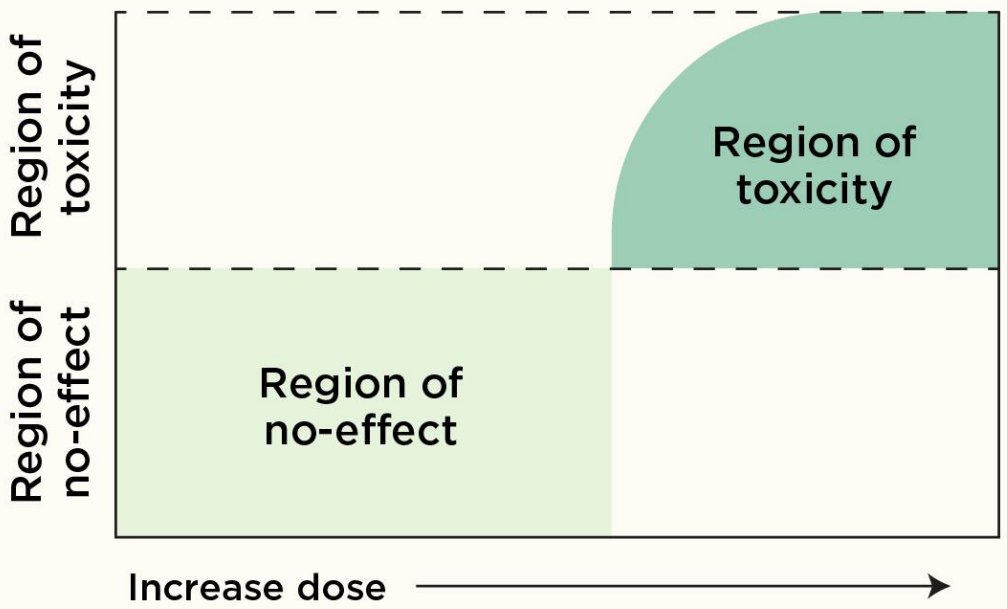
World Health Organization

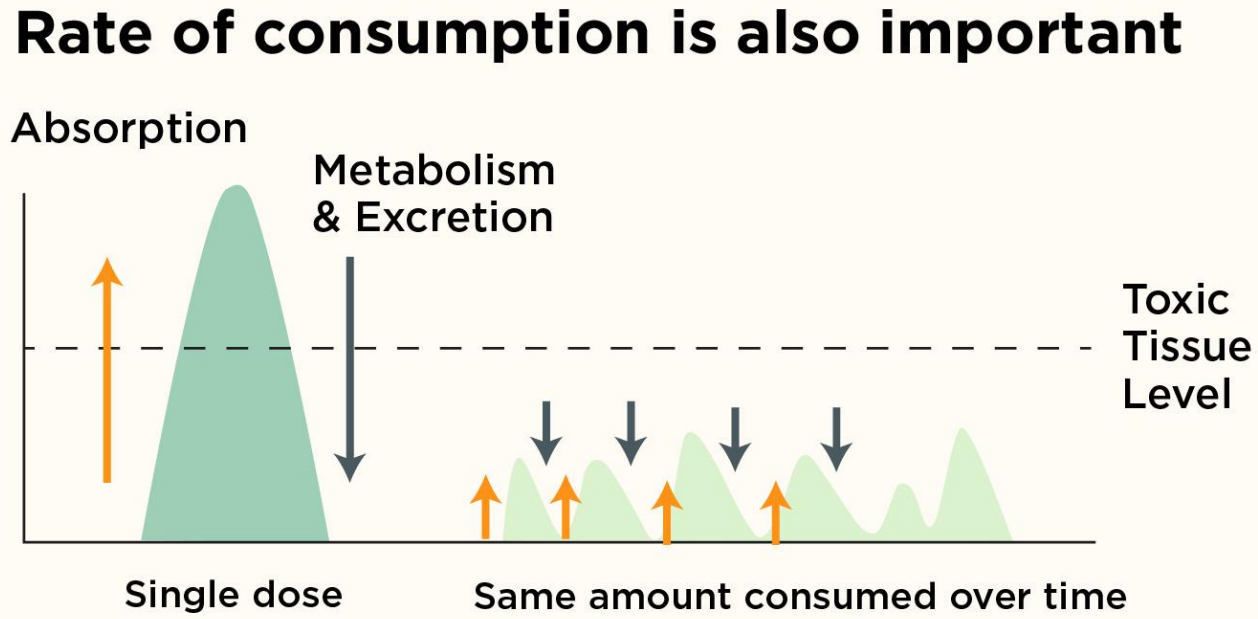
FSSAI, 2021 has also **recently removed** the "NOT RECOMMENDED FOR CHIILDREN", declaration from Table Top sweeteners which was earlier a Mandatory declaration. This acknowledges its safety for children[5].

References:

3. https://www.canada.ca/en/health-canada/services/food-nutrition/public-involvement-partnerships/technical-consultation-proposal-allow-use-food-additive-steviol-glycosides-table-top-sweetener/consultation.html
4. 82nd Joint FAO/WHO Expert Committee on Food Additives (JECFA) meeting – Food additives Summary and conclusions, 2016 Geneva, 7–16 June 2016
5. Food Safety and standards (Food Product Standards and Food Additive) Amendment Regulations, 2021. Effective from Nov. 2021

Safety of sweeteners and level of exposure





Max amount of NNS that can be consumed in a day

Low-Calorie Sweetner	Brand Names	Sweetness as compared with sugar	Acceptable Daily Intake* (maximum number of tabletop sweetner packets per day)
Aspartame	Equal®, NutraSweet® Sugar Twin®	200 times sweeter than sugar	75**
Acesulfame-K	Sunett®, Sweet One®	200 times sweeter than sugar	23
Saccharin	Sweet'N Low®, Sweet Twin®, Necta Sweet®	200-700 times sweeter than sugar	45
Sucralose	Splenda®	600 times sweeter than sugar	23
Neotame	Newtame®	7,000-13,000 times sweeter than sugar	23
Advantame	No brand names	20,000 times sweeter than sugar	4,920

Acceptable Daily Intake is the maximum amount of a substance that can be consumed daily over the course of a person's lifetime with no appreciable health risk, and is based on the highest intake that does not lead to observable adverse effects. Calculations are based on a 132 pound individual.

Eg. Indian Aspartame based Table Top Sweetener

Safe for daily consumption:

155 PELLETS /DAY

Acceptable Daily Intake of Aspartame is 40 mg/kg of body weight which translates to 155 pellets/day

For a 70 kg body weight

1 PELLET = 1 TEASPOON OF SUGAR (5 g) IN SWEETNESS

155 Pellets can replace 155 tsp of Sugar (775 gms of sugar)!

We would never consume this amount!!

References:
https://www.hsph.harvard.edu/nutritionsource/healthy-drinks/artificial-sweeteners/, accessed on 28th July 2021

Ideally NNS should have…

Sweetness with no unpleasant after taste

Have little or no calories

Not have any side effect

Commercially and economically viable

Able to survive cooking/ baking


Thank You !