Low Calorie Sweetener Health Effects: Science Vs Myths?

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Low Calorie Sweeteners (LCS)

- Approved for use in foods and beverages to reduce sugar and caloric content
- Useful for individuals wishing to manage blood sugar levels and calorie intake
- Extensive toxicology testing prior to approval conducted to ensure no adverse health effects.

So, what about the controversial reports?

In many cases, controversy and myths are[4] resulting from :

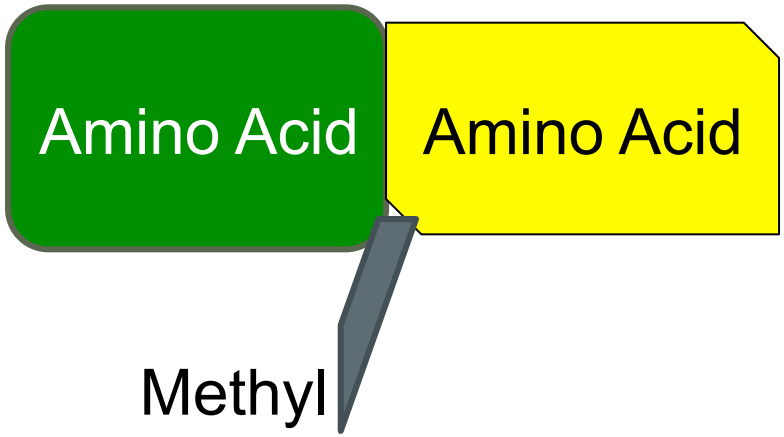
- Lack of understanding of biological fate of LCS;
- Focus on one study, ignore overall weight of evidence;
- Flaws in experimental design and data analysis and/or reporting;
- Associations in observational studies interpreted as causation;
- Controversies make the news headlines.

Outline:

- Provide overview of biological fate of LCS following consumption.
- Discuss key studies fueling controversies
- Discuss use by children
- Conclusions

Biological Fate of LCS

Aspartame



2 amino acids & methyl group

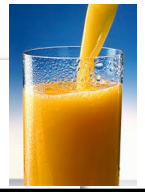
- Aspartic acid (aspartate)
- Phenylalanine

Not absorbed intact.

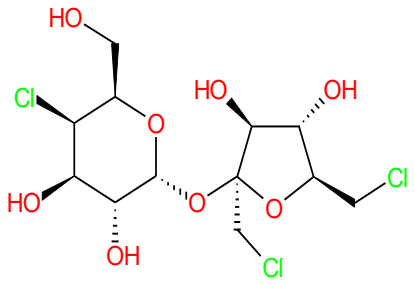
Completely digested into these components which are all commonly found in foods!

Magnuson *et al*., 2007

There are many dietary sources of aspartame digestion products

Food	Phenylalanine (mg)	Aspartic acid (mg)	Methanol (mg)
Aspartame-sweetened Soft drink (340 ml)	90	72	18
Non-fat milk (340 ml) 	606	953	-
Tomato Juice (340 ml) 	58	346	107
Orange juice (340 ml) 	24	180	23

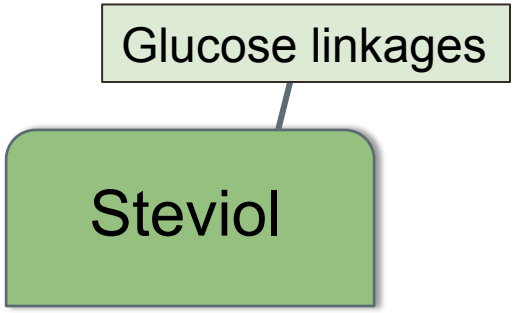
Sucralose



- Structure similar to sugar (disaccharide) with 3 Cl, which makes much sweeter.
- Cannot be digested into monosaccharides, – no impact on blood glucose, no calories.
- Most unabsorbed and excreted in feces. Small amount absorbed, small fraction is conjugated, and excreted in urine.
- Gut microflora unable to metabolize sucralose.

Grice and Goldsmith, 2000

Steviol glycosides



Many different glycosides; Varying glucose number & position

- Stevioside – 2 glucose units
- Reb A – 4 glucose units
- Reb D - 5 glucose units

- Extensive metabolism by colonic gut microflora to remove linkages and form common metabolite, steviol.
- Steviol absorbed and conjugated in liver for excretion.
- Is why ADI expressed as “steviol equivalents”.

Carakostas *et al*., 2008

	Aspartame	Sucralose	Steviol glycosides	Ace K	Saccharin
Absorption into blood	0% as aspartame, only digestion products	15%, most not absorbed	0% as glycoside, 100% as steviol	100%	85-95%
Metabolism	Digested in small intestine	No digestion or hydrolysis	Gut microflora and liver	No	No
Excretion	Amino acids into amino acid pool, methanol to CO_2	Primarily excreted as unchanged sucralose in feces	Metabolites of steviol in urine	Urine	Urine, but also feces with high doses

(Magnuson *et al.*, Nutr Rev 2016)

Summary

- **The absorption, metabolism and excretion of all approved sweeteners is well understood.**
- **However, many studies do not consider this information!**

Consumption of LCS does NOT lead to cancer

Toxicology testing of LCS required to establish levels that have:

- No effect in lifetime studies**.**
- **No effect on cancer (genetics and animal studies).**
- No effect on pregnancy or offspring.
- No effect on growth, development or maturation.
- No effect on any organ, blood chemistry or any chronic disease endpoints.

- **The No Observed Effect Level (NOEL) is the basis for the human ADI (Acceptable Daily Intake)**

Controversy: studies by Soffritti from Ramazzini Institute

- **Studies on aspartame** (Soffritti et al., 2006, 2007, 2010) and **sucralose** (Soffritti et al., 2016) reported increased incidence of some cancers.
- Are in **conflict with all previous long term and genetox studies** on these LCS showing no effect.
- Lead to extensive reviews by many experts worldwide.

Expert reviews of LCS and cancer studies

Aspartame: EFSA 2006, 2009, 2011, 2013; Agence Franciase de Securite Santarie des Aliments, 2006; Health Canada; Magnuson et al., 2007; National Experts Report on Aspartame, 2010; Schoeb et al., 2009; Schoeb and McConnell, 2011.

Sucralose: Berry *et al.*, 2016. EFSA 2017; Gift *et al*., 2013, Hayes *et al*., 2011; U.S. EPA 2012.

Conclusions by all: Soffritti studies on LCS are unreliable. No evidence of carcinogenic potential.

Problems identified with many aspects of studies by Soffritti et al including:

- health of the animals, to high background incidences of chronic infection
- diet and housing practices,
- rigorousness of test procedures,
- histopathology procedures,
- application of historical control data,
- statistical evaluations and statistical extrapolations of data generated,
- lack of evidence of plausible biological mechanism.

Overwhelming number of epidemiological studies find no association between LCS and cancer

Author	Type of study (N)	Consumption	Conclusions
Gurney (1997)	56 brain tumor cases 94 controls	Dietary recall - Personal interview	**No association**
Hardell (2001)	30 brain tumor cases 45 controls	Recall of low-calorie soft drinks.	**No association**
Bunin (2005)	315 child brain tumor cases, 315 controls	Food frequency by mothers	**No association**
Lim (2006)	Prospective 473,984 subjects, 5 yr. Hematopoietic and brain cancers	Food frequency questionnaires	**No associations**
Gallus (2007)	Case control; various cancers (8976 cases, 7028 controls)	Food frequency questionnaires	**No association**
Bosetti (2009)	Case control; various cancers (1010 cases, 2107 controls)	Food frequency questionnaires	**No association**
Schernhammer (2012)	Prospective: 22 yr. Nurses' Health (77,218 F); Health Professionals (47,810 M). Hematopoietic cancers	Food frequency questionnaires every 4 years	**No association when combined cohorts. Weak positive with separate**
McCullough (2014)	Prospective: 10 yr. Cancer Prevention cohort; (100,442 M&F) Non-Hodgkin lymphoma	Food frequency questionnaires every 2 years	**No association** with aspartame or diet beverage consumption

American Cancer Society®

Do non-nutritive sweeteners or sugar substitutes cause cancer?

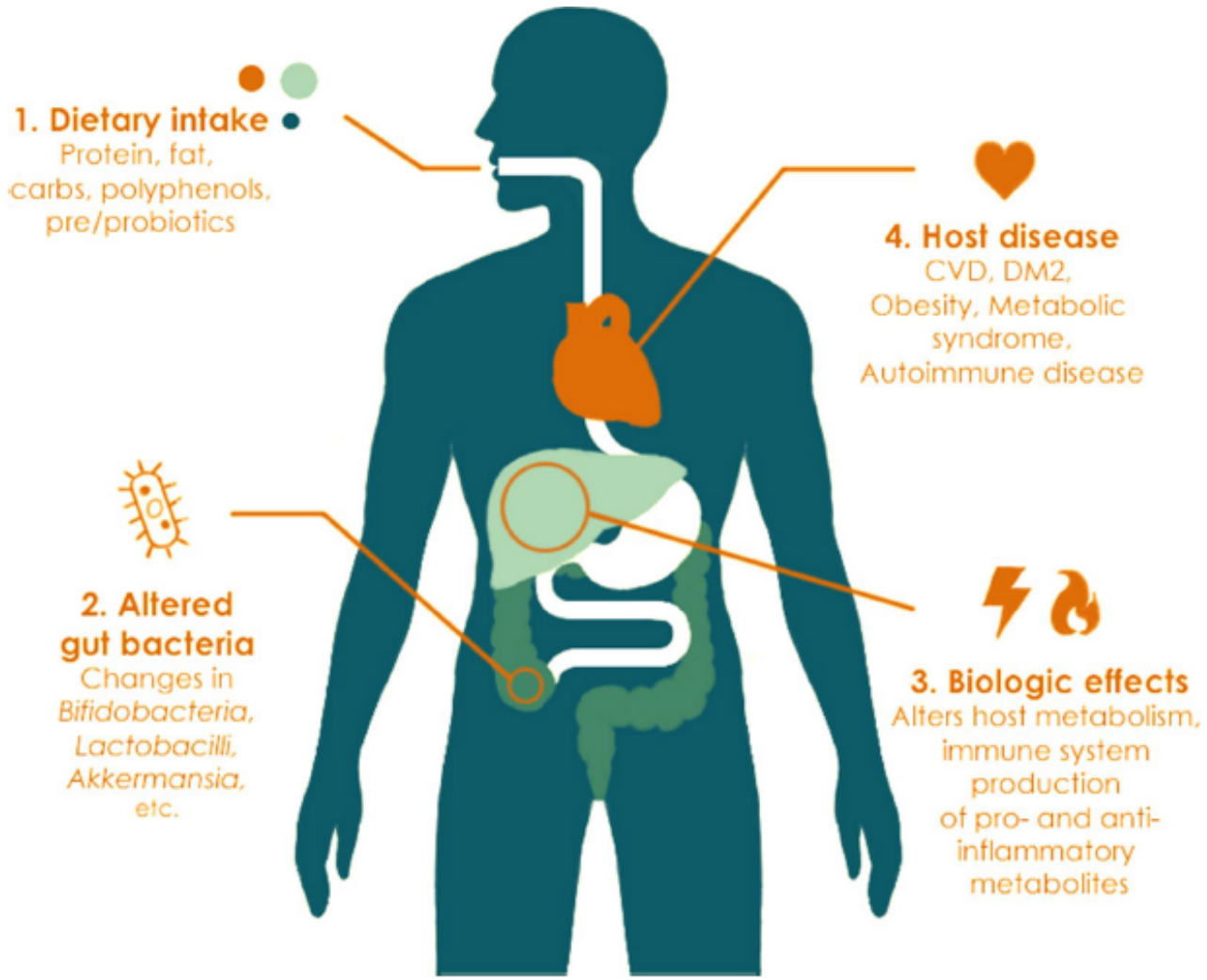
No. There is no proof that these sweeteners, at the levels consumed in human diets, cause cancer.

Does being overweight increase cancer risk?

Yes. Being overweight or obese is linked with an increased risk of cancers of the breast, colon and rectum, endometrium, esophagus, kidney, and pancreas, and ..gallbladder. Also… increased risk of cancers of the liver, cervix, and ovary, as well as non-Hodgkin lymphoma, multiple myeloma, and aggressive forms of prostate cancer.

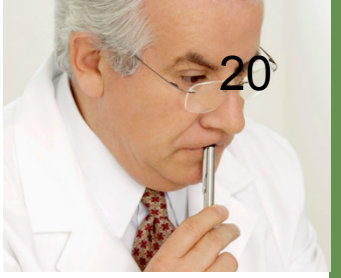
https://www.cancer.org/healthy/eat-healthy-get-active/acs-guidelines-nutrition-physical-activity-cancer-prevention/common-questions.html

Controversy: LSC and gut microbiome?



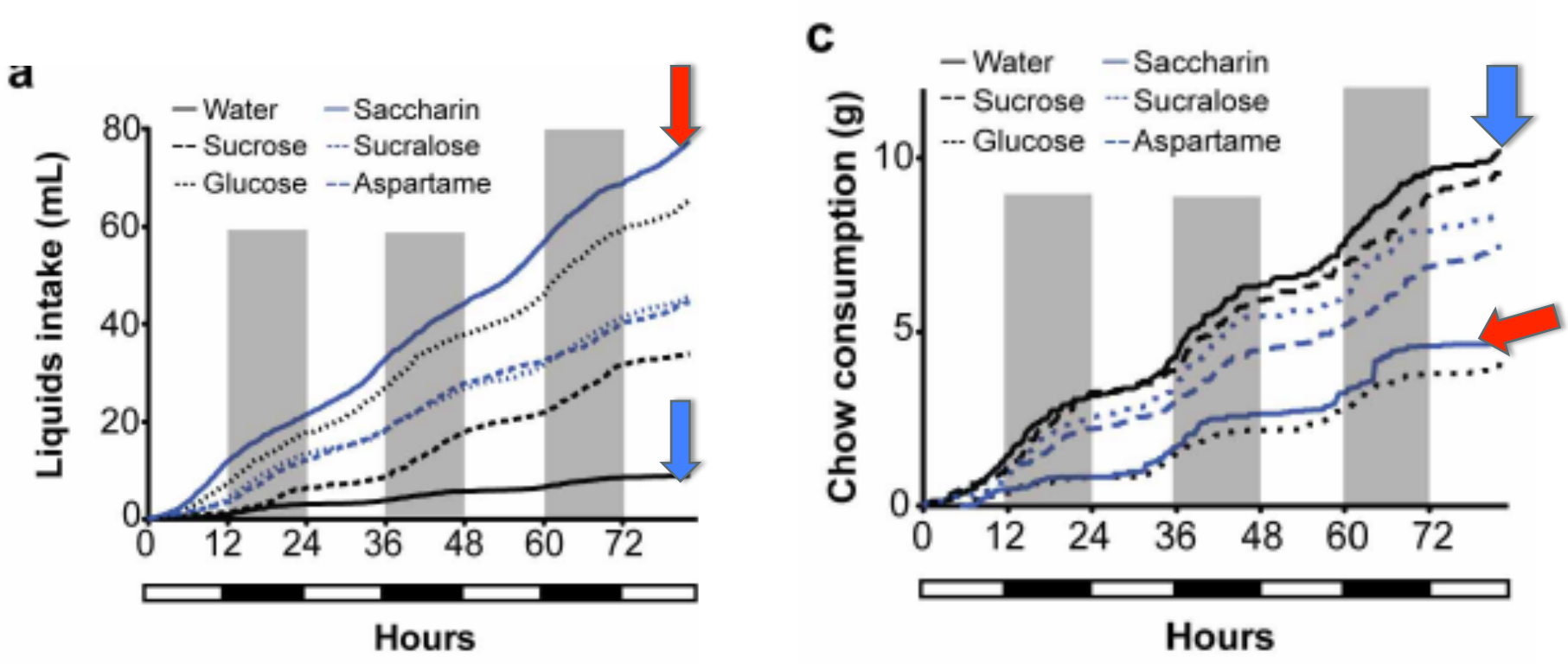
Singh *et al*. J Transl Med (2017) 15:73

Microbiome Study Design is Critical



Suez *et al*., (Nature, 2014) reported LSC cause changes in microbiota lead to effects on blood glucose control, but many problems with study

- Protocol resulted in very significant changes in total diet intake in mice (see next slide); not considered!
- Experts agree that for microbiome studies, environmental and lifestyle variables including **dietary intake and composition need to be carefully controlled** (Goodrich *et al*., 2014)
- Ignored extensive well-controlled human clinical studies showing sweeteners do not effect blood glucose response (review: Russell *et al*., 2016)



- **Blue arrows= water group; Red arrow: saccharin group**
- **First graph – liquids intake, Second graph – Food intake.**

- **>50% drop in food consumption by saccharin group!**
- **CANNOT attribute any observed effects to LCS!**
- **Not physiologically relevant to human consumption**

Suez *et al*., Nature, 2014; Extended Data Figure 3a & c.

Potential benefit of LCS for blood glucose control: Position statements

Acknowledge potential benefit of use of LCS **as substitute for caloric sweeteners** for management of blood glucose in individuals with diabetes.

American Diabetes Association (ADA) 2017

http://www.sweeteners.org/category/5/research/214/adas-2017-guidelines-support-thebeneficial-role-of-low-calorie-sweeteners-in-diabetesmanagement)

European Food Safety Authority (EFSA)

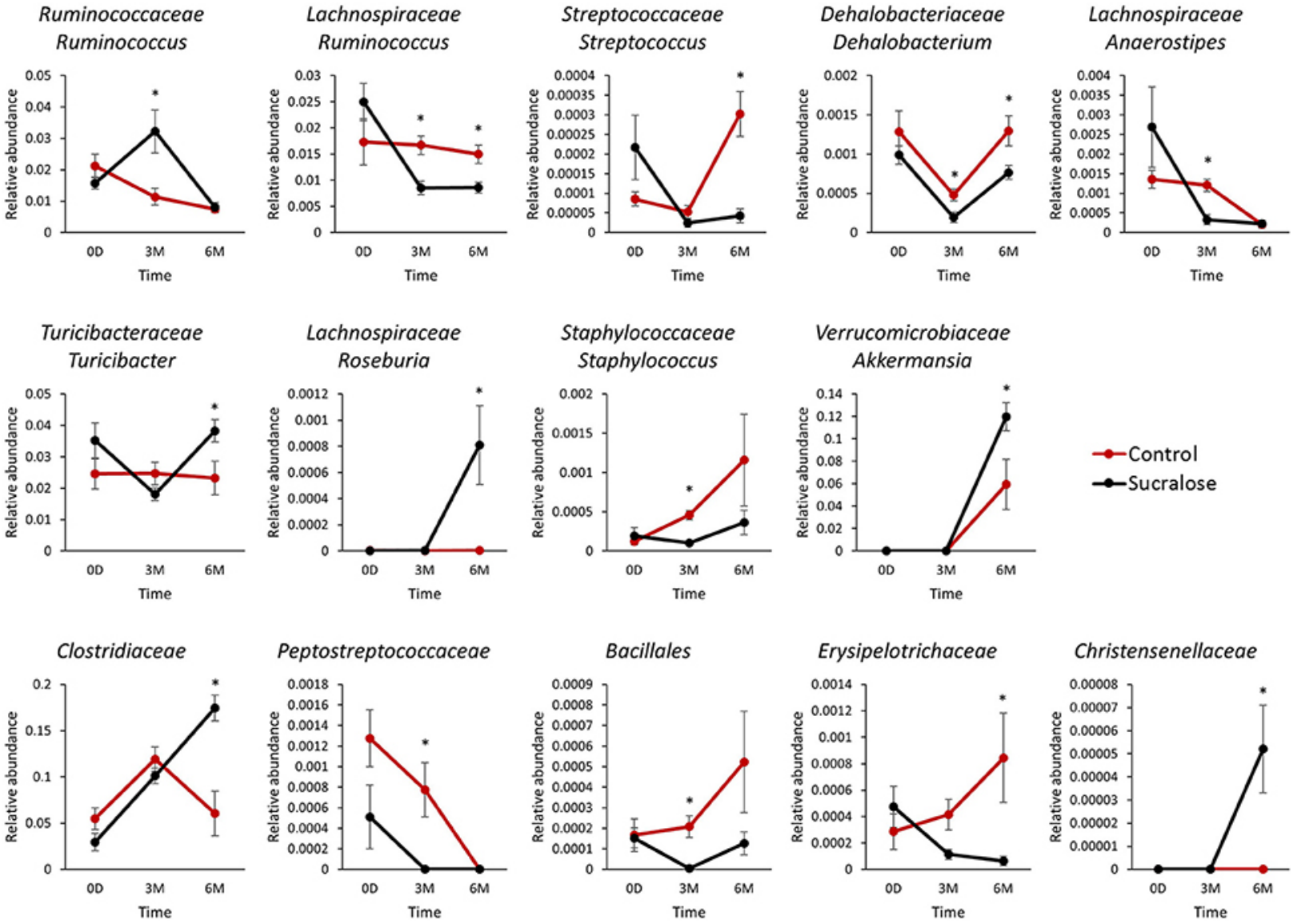
(http://www.sweeteners.org/category /38/benefits/50/benefits-for-people-with-diabetes)".

Changes in microflora in control group as much as treatment group

- **Abstract states that sucralose affects gut microflora and may cause liver inflammation in mice.**
- **Is in conflict with well conducted previous toxicology studies showing no effect on either parameter when fed sucralose at high doses for life. (See: Magnuson et al., Food Chem Toxicol. 2017 Aug;106(Pt A):324-355 (freely available)**
- **LOOK at the microflora DATA (in next slide)**
- **Note: No evaluation of liver pathology, speculation based on gene expression (PCR) of some liver proteins.**
- **No evaluation of food or water consumption to evaluate potential impact.**

Bian et al., 2017

Microflora in Control group changes as much as sucralose group! No consistent effect.



Summary

- **Well conducted studies provide no evidence of adverse effects of LCS due to alterations in the gut microbota.**
- **Many studies on LCS and microbiota have deficiencies in design and data reporting; conflicting results.**
- **The low amounts of LCS consumed and their biological fate make it unlikely that LCS significantly affect the gut microbiome.**

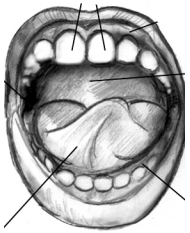
Controversy: LCS and Appetite or Hunger

- Conflicting results from studies with animals and fruit flies lead to headlines. Results depend on study design. (Wang et al., 2006, 2017; Park et al., 2017 in Cell Metabolism).

- Most human studies and clinical reviews conclude that **LCS do not affect appetite or hunger** or desire for sweetness.
- RCTs 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.

Controversy: sweet taste receptors and gut hormones

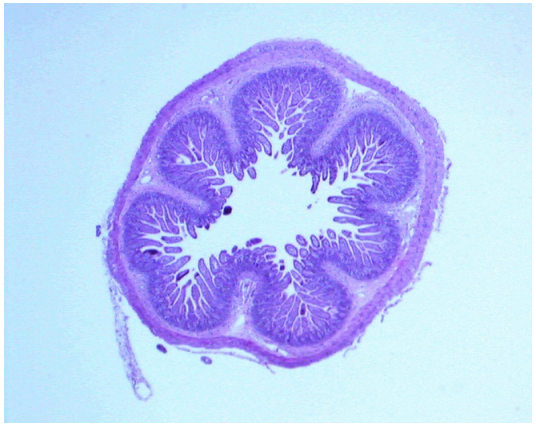


Taste receptors on tongue

Activation by sweet compounds

Signals to brain
Perceive sweetness

Taste receptors in gut cells



Activation by glucose and other sugars

Release of gut hormones

? -Do non-nutritive sweeteners stimulate these gut receptors?
-Functional significance?

Sucralose and Gut Hormones

In vitro studies:

- Sucralose activates of receptors, release of gut hormones

Subsequent acute animal and human feeding studies on gut hormones and function:

- Different designs, healthy and diabetic subjects,
- Most report no effect on gut hormones,
- No **adverse effect** on functions related to gut hormones including blood glucose and insulin levels, appetite, and gastric emptying.

Confirms long-term daily consumption RCTs:

- No adverse effects of use in healthy individuals and individuals with diabetes.

Reviews: Bryant & McLaughlin, 2016; Meyer-Gerspach *et al.*, 2016, Magnuson *et al*., 2017

LCS Consumption

Intense sweetness = little needed

Sugar

÷ 200-300

Sweetness intensity of non-caloric sweetener

Mg of LCS to replace Grams of sugar

Sweetener	Sweetness Intensity (compared to sucrose)	Amount to replace 100 calories or 25 g of sugar
Acesulfame K	~ 200 x	125 mg
Aspartame	~ 200 x	125 mg
Cyclamate	~30 x	800 mg
Saccharin	~ 300 x	80 mg
Sucralose	~ 600 x	40 mg
Steviol glycosides	200 - 300 x	80-125 mg

Estimated aspartame consumption below ADI even in highest uses using very conservative estimates

	Toddler	Children	Adolescent	Adults
Mean	1.6-16.3	1.8-12.6	0.8-4.0	0.7-8.5
High level	7.5-36.0	6.3-32.4	2.3-13.2	2.4-27.5

- **mg/kg bw/day**
- **min-max across all 26 dietary surveys conducted in 17 different European countries**
- **assumed that all processed foods contained aspartame at MPL or highest reported use level**

(EFSA 2013)

Study finds little chance for T1D children to exceed LCS ADIs

Children with Type 1 diabetes (4-18 yr)

- food frequency questionnaire
- Tier 2 (maximum concentration) and Tier 3 (maximum used concentrations) method of exposure assessment used.

Conclude: ".. little chance for T1D children to exceed ADIs for acesulfame-k, aspartame, neohesperidin, sucralose, saccharin, steviol glycosides and neotame."

Alteration between different food and beverage products containing different LCS reduces chances of exceeding the ADI.

Dewinter *et al*. (2016)
Food Additives & Contam. v33

When are LCS beneficial for children?
To reduce sugar and calories for control of childhood diabetes and obesity.

Are products containing LCS safe for consumption by children? YES!

Example: Aspartame (Magnuson *et al*., 2007)

- **Metabolism of aspartame**
  - No differences between children and adult
- **No effect on learning and behavior**
  - **Animal studies**: Up to 4000 mg/kg/d, no effect on neuronal function, learning or behavior despite changes in blood and brain amino acids levels
  - **Human Clinical studies:** Normal children, hyperactive children, children with PKU, aggressive school boys, sugar-sensitive children
- **No effect on childhood cancers**

LCS are safe for children (>1 yr) at levels found in foods and beverages

Conclusions

- Well conducted studies carefully reviewed by regulatory agency experts worldwide confirm lack of adverse health effects of consumption of LCS at approved use levels.
- **Many myths exist. Careful examination of study design, interpretation of results and consideration of all factors is critical** for assessment of validity of controversial studies.
- Intakes of LCS remain below the ADIs.
- **There is strong scientific evidence supporting safety of use of LCS.**

Questions?

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