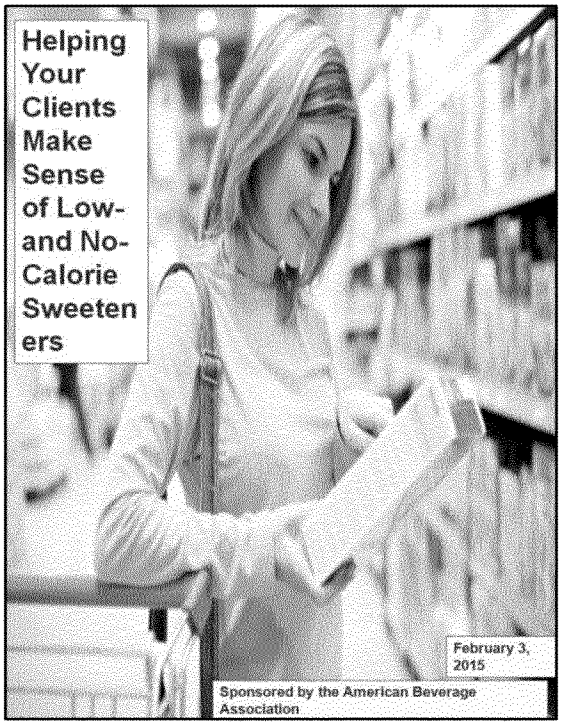


With You Today

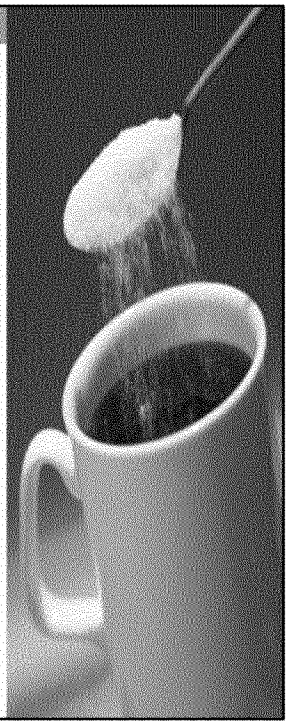
Moderator:
Hope S. Warshaw, MMSc, RD, CDE, BC-ADM
- President of the American Association of Diabetes Educators
- Owner, Hope Warshaw Associates, LLC

Speaker:
Berna Magnuson, PhD
- ATS Fellow
- BMagnuson Consulting

Speaker:
James O. Hill, PhD
- Anschutz Professor and Director of the Anschutz Health and Wellness Center, University of Colorado

Agenda

- Introduction of Speakers
- History, Safety and Regulation
- Weight Control and Low- and No-calorie sweeteners
- Questions/Discussion
- CE Credit Information



Learning Objectives

1. Understand the safety and regulation of low- and no-calorie sweeteners, as well as their long history of use

2. Understand the science that supports the use of low- and no-calorie sweeteners in diabetes prevention and treatment

3. Be able to provide science-based information to answer patients' questions about the efficacy and safety of using low- and no-calorie sweeteners for diabetes management

Disclosures

- Hope Warshaw – Consultant to Calorie Control Council, McNeil Nutritionals, LLC (manufacturers of Splenda® Sweetener Products), Weber Shandwick
- Berna Magnuson – No disclosures
- James O. Hill – Grant support from the American Beverage Association. Consulting income from Coca-Cola, Nestle, McDonalds, Novo Nordisk, General Mills, and Walt Disney

SETTING THE RECORD STRAIGHT:

SAFETY AND REGULATION OF LOW- AND NO-CALORIE SWEETENERS

Berna Magnuson, PhD, ATS Fellow
BMagnuson Consulting

BMAGNUSON CONSULTING

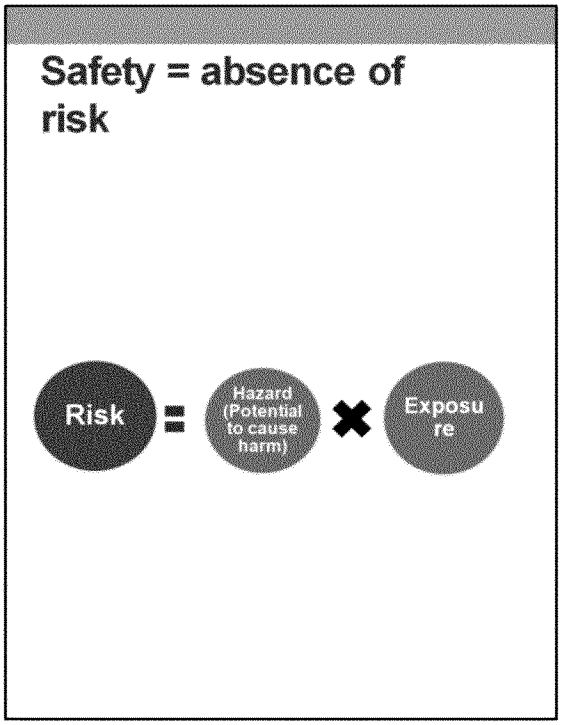
Regulatory Categories of No- and Low-calorie Sweeteners

Food additive	Generally Recognize	Dietary Supplem
• Safety data assessed by FDA before approval • FDA responsible for safety	• Safety data assessed by expert panel • Manufacturer responsible for safety	• Not approved for use in foods and beverages • Manufacturer responsible for safety

http://www.fda.gov/food/ingredientspackaginglabeling/foodadditivesingredients/ucm397716.htm

Sweetener	Regulatory status	Sweetness to sugar	Other names
Acesulfame-K	Food additive	200X	Sunett, Sweet One
Aspartame	Food additive	200X	NutraSweet, Equal
Luo Han Fruit	Generally Recognized as Safe	300X	Monk fruit, Nectresse
Saccharin	FDA-approved interim regulation	300X	Sweet and Low, Sugar Twin
Steviol glycosides	Generally Recognized as Safe	30 – 300X	Truvia, PureVia, and others

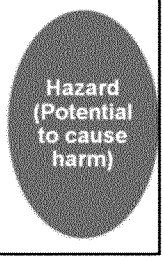
http://www.fda.gov/AboutFDA/Transparency/Basics/ucm214864



Risk is the combination of hazard or potential to cause harm and exposure.

Hazard evaluation of sweeteners

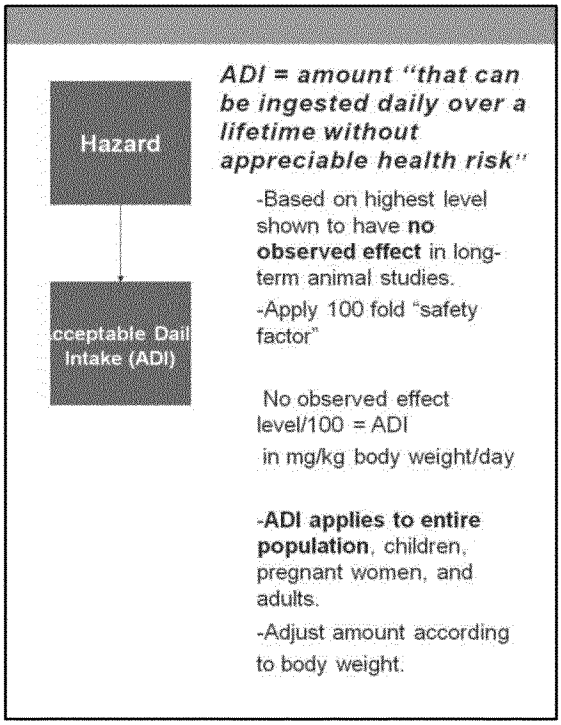
- What is the composition of the sweetener?
- What happens to the compound when we consume it?
- Many safety studies in animals
- And in humans!



Hazard evaluation of sweeteners

Required for approval:

- Short- and long-term toxicity studies
  - Must test in at least 2 animal species, usually more
- Carcinogenicity
- Genetic toxicity
- Reproductive toxicity
  - before and during pregnancy
- Teratogenicity – effect on development
- Also human clinical studies

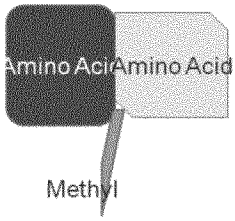


Safe for pregnant women? Children?

Answer = Yes, for approved sweeteners!

This question MUST be answered in safety testing before sweetener is approved for use in foods and beverages!

What is Aspartame?



FDA ADI: 0-50 mg/kg/day

For 150 lb person ~ 97 packets of sweetener/day

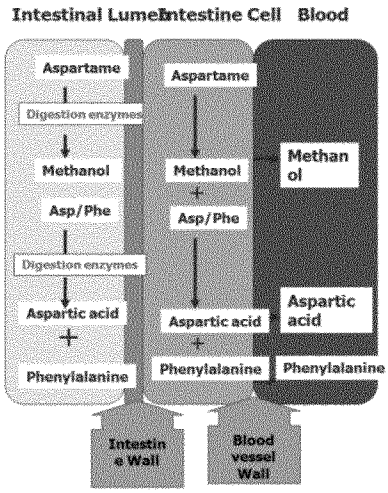
Structure: 2 amino acids & **methyl group**

- Aspartic acid (aspartate)
- Phenylalanine

These are commonly found in foods!

http://www.caloriecontrol.org/sweeteners-and-lite/sugar-substitutes/aspartame

Aspartame digestion



Aspartame does not enter blood or body as a whole.

Just like foods and proteins, aspartame is completely digested in intestine by digestion enzymes.

Components of digestion same as from other foods.

European Food Safety Authority Review of Aspartame, Dec 2013
http://www.efsa.europa.eu/en/topics/topic/aspartame.htm

There are many dietary sources of aspartame digestion products

Food	Phenylalanine (mg)	Aspartic acid (mg)	Methanol (mg)
Aspartame-sweetened Soft drink (34 ml) 	90	72	18
Non-fat milk (340 ml) 	606	953	-
Tomato Juice (340 ml) 	58	346	107
Orange juice	24	180	23

Saccharin

- Currently - limited use in North America
- Most (95%) rapidly absorbed in the small intestine;
- Absorbed saccharin is rapidly excreted in urine.
- **Small amount (5%) to colon** and excreted in feces.
- April 2014 : Health Canada reviews safety and extends allowed uses
- ADI: 0-5 mg/kg/day
- For 150 lb person ~ 8.6 packets of sweetener/day

http://www.hc-sc.gc.ca/fn-an/consult/2013-nop-adp-saccharin-saccharine/index-eng.php;
www.andeal.org/files/Docs/NNSResourceDraft3.pdf

Steviol glycosides

- Purified from the leaves of a South America shrub.
- Are many different forms.
- All have common steviol backbone, different number and position of attachments of glucose.
- Rebaudioside A (Reb A) - sweetest, most abundant steviol glycoside

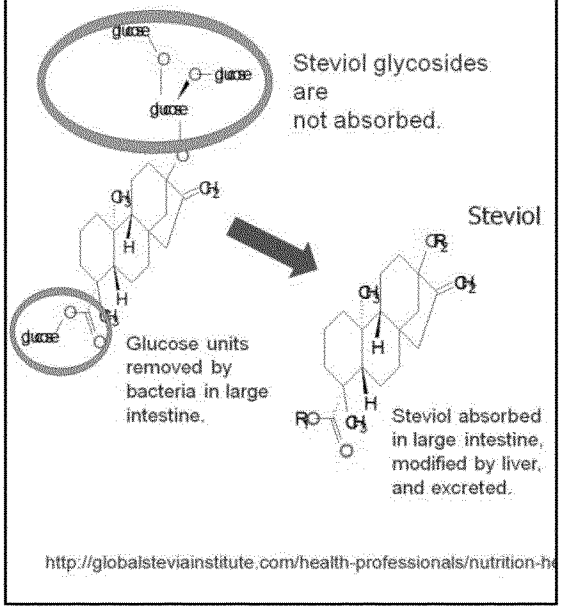
ADI = **0 - 4 mg steviol equivalents/kg body weight/day**

Applies only to extracts purified to contain ≥95% steviol glycosides.

- Need to convert from steviol equivalents to glycosides
- *i.e.* ADI for Reb A = 0 - 12 mg rebaudioside A/kg/day
- 150 lb person ~ 30 packets of tabletop sweetener/day

http://www.caloriecontrol.org/health-professional-library/sweet-facts-about-stevia

Steviol glycosides

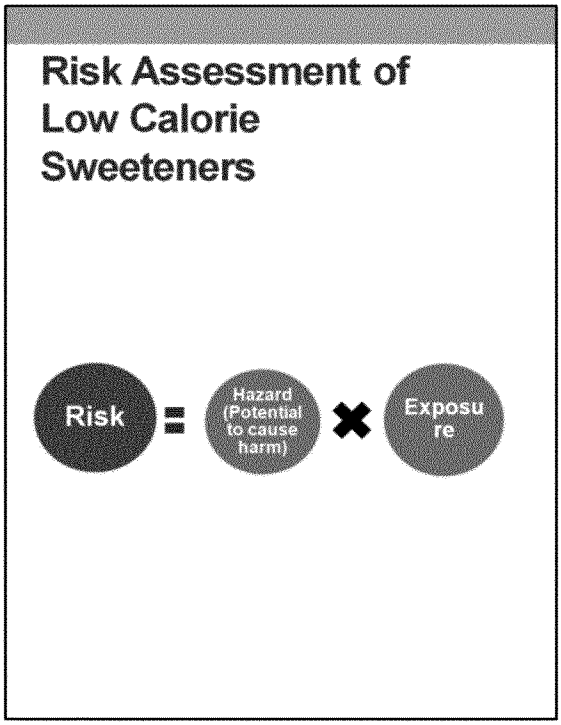


http://globalsteviainstitute.com/health-professionals/nutrition-h

Sucralose

- Structure similar to sugar, but 600X sweetening potency.
- Only a small amount of sucralose is absorbed and excreted in urine.
- Most (85%) of ingested sucralose is not absorbed into the body; is eliminated in the feces unchanged.
- **Gut microflora unable to hydrolyse sucralose**
- ADI: 0-15 mg/kg/day
- For 150 lb person ~ 68.2 packets of sweetener/day

JECFA assessment of sucralose: http://apps.who.int/food-additives-contaminants-jecfa-database/PrintPreview.aspx?chemID=2340
www.andeal.org/files/Docs/NNSResourceDraft3.pdf



Risk is the combination of hazard or potential to cause harm and exposure.

Expos
ure

Intense sweetness = low levels of use

life ÷ 200-600

Sweetness intensity of non-caloric sweetener

Sugar

Sweetness Intensity Means Low Intake

Sweetener	Sweetness Intensity *	Amount to replace 25 g of sugar
Aspartame	~ 200 x	125 mg
Saccharin	~ 300 x	80 mg
Sucralose	~ 600 x	40 mg

*compared to sugar

To determine exposure

Using food intake surveys, calculate consumption of foods that will contain sweetener:

- Average and high users
- Different ages and sex
- Special populations, such as diabetics, children

Intakes must be lower than ADI for all users, including highest consumers.

Example: Aspartame intakes remain well below ADI in recent review by EFSA.

European Food Safety Authority Review of Aspartame, Dec 2013
http://www.efsa.europa.eu/en/topics/topic/aspartame.htm

How much do we eat? Estimated Daily Intake (EDI)

Expos ure

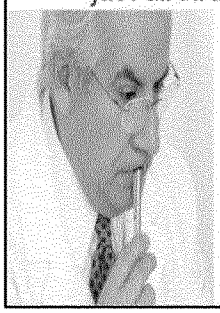
- **Aspartame**: EDI = 6% of ADI at the 90th percentile in general adult population;
- **Saccharin**: EDI = 12% of ADI;
- **Sucralose**: EDI = 32% of ADI for adults and children over age two.

International Food Information Council (IFIC) Foundation

http://www.foodinsight.org/Content/5438/Final%20Revised_LCS%20CPE%20Module_8-1-12.pdf.

But – what about all the studies reporting adverse effects?

- How can we know what to believe?
- How can we explain the different opinions?
- Must look carefully at study, not just abstract or press release!



"Artificial sweeteners induce glucose intolerance by altering the gut microbiota"

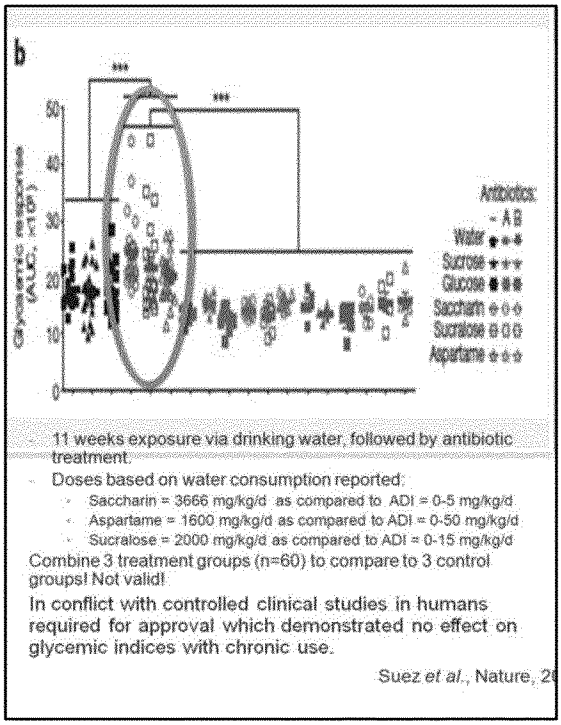
- Compounds tested in mouse study:

  aspartame, saccharin, sucralose.
- All remaining experiments with saccharin and extrapolated results to all "artificial sweeteners".
- Conclude "non-caloric sweeteners directly contribute to glucose intolerance, metabolic disease and obesity".

Suez *et al.*, Nature, 2014

Questions to consider

- How can aspartame affect gut microbiota when does not enter colon?
- How can sucralose affect gut microbiota when not metabolised by microflora?
- What doses were used? Dose response?
- Any effect on other dietary factors that affect gut microbiota or glycemic response?

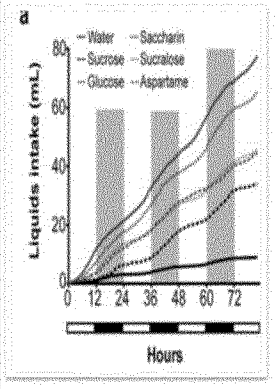


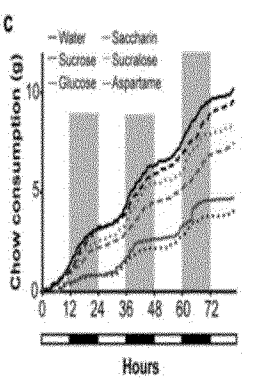
- 11 weeks exposure via drinking water, followed by antibiotic treatment.
- Doses based on water consumption reported:
  - Saccharin = 3666 mg/kg/d as compared to ADI = 0-5 mg/kg/d
  - Aspartame = 1600 mg/kg/d as compared to ADI = 0-50 mg/kg/d
  - Sucralose = 2000 mg/kg/d as compared to ADI = 0-15 mg/kg/d

Combine 3 treatment groups (n=60) to compare to 3 control groups! Not valid!

In conflict with controlled clinical studies in humans required for approval which demonstrated no effect on glycemic indices with chronic use.

Suez *et al.*, Nature, 2





Liquid & food intake shown only for 4 of 20 mice/group and 72 hr of 11 weeks.

Huge differences in water/sugar liquid intake.

Over 50% reduction in mouse chow in some groups.

Dramatic impact on other nutrients, fiber and other fermentable components that affect microbiome. Not considered in paper.

Final Comments

- The safety of use of low calorie sweeteners has been extensively evaluated worldwide.
- But health effect of low-calorie sweeteners continues to be subject of many studies.
- Study design, interpretation of results and consideration of all factors are critical for assessment of validity of conclusions.
- Regulatory agencies worldwide continue to review and confirm safety of use.

For more information

Food and Drug Administration websites:

- http://www.fda.gov/food/ingredientspackaginglabeling/foodadditivesingredients/ucm397716.htm
- http://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm397725.htm#SummaryTable
- http://www.fda.gov/aboutfda/transparency/basics/ucm214864.htm

Calorie Control Council:
http://www.caloriecontrol.org/

European Food Safety Authority:
http://www.efsa.europa.eu/

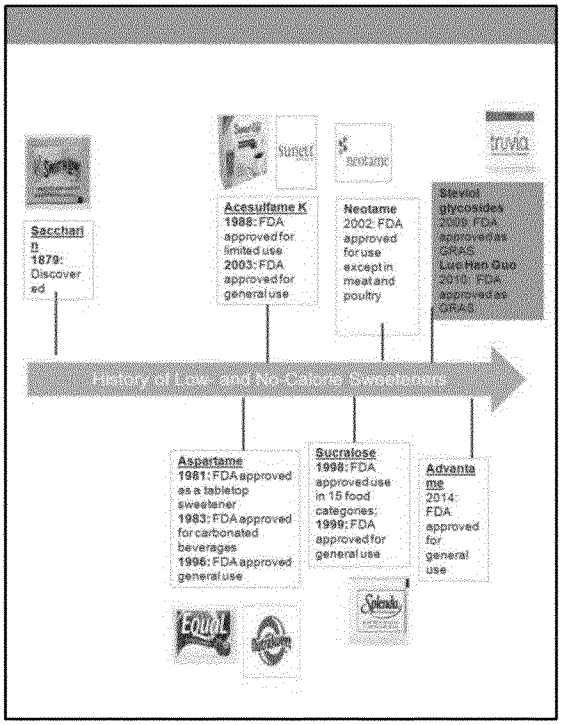
Health Canada

- http://www.hc-sc.gc.ca/fn-an/securit/addit/sweeten-edulcor/index-eng.php

LOW- AND NO-CALORIE SWEETENERS IN WEIGHT MANAGEMENT:

WHAT DOES THE EVIDENCE SHOW?

James O. Hill, PhD
Anschutz Professor, Executive Director
Anschutz Health and Wellness Center
University of Colorado



- **All FDA-approved low calorie sweeteners meet the same standards of safety and are safe for consumption, including pregnant women and children**

- **All FDA-approved sweeteners are safe**
- **http://www.fda.gov/food/ingredientspackaginglabeling/foodadditivesingredients/ucm397725.htm**

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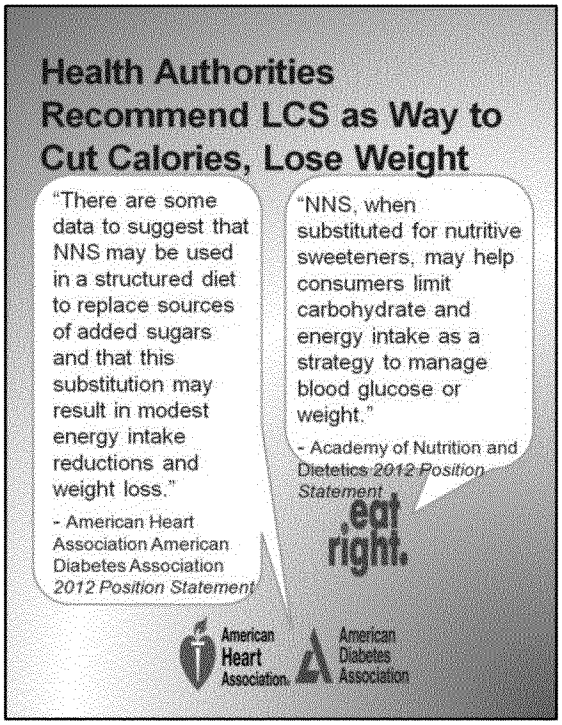
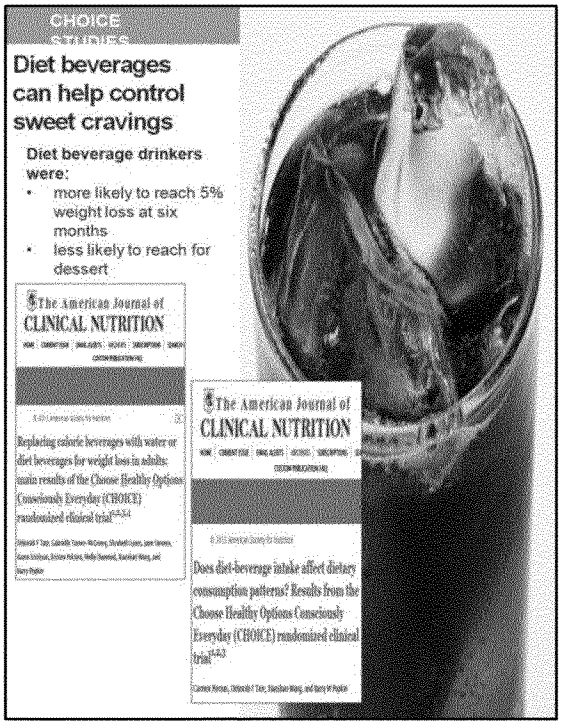
Epidemiologic studies are confusing

- Some studies show association of low- and no-calorie sweeteners (LCS) with:
  - Increased body weight[1,2]
  - Decreased body weight[3] or
  - Both increased/decreased body weight[4]

1. Colditz GA, et al. *Am J Clin Nutr*. 1990;51(6):1100-5; 2. Fowler SP, et al. *Obesity* (Silver Spring). 2008;16(8):1894-900; 3. Mozaffarian D, et al. *N Engl J Med*. 2011;364(25):2392-404; 4. de Koning L, et al. *Am J Clin Nutr*. 2011;93(6):1321-7.



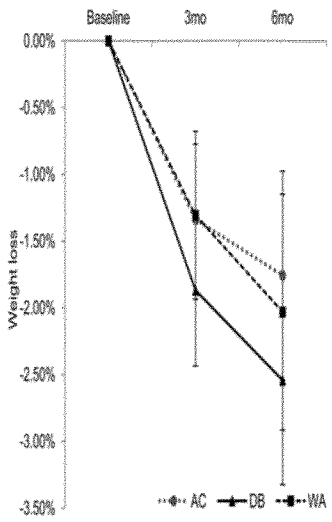


At six months the diet beverage drinkers experienced a greater likelihood of achieving a 5% weight loss than water drinkers. American Journal of Clinical Nutrition. 2012;95:555-563. (Link to abstract: http://ajcn.nutrition.org/content/95/3/555.abstract?sid=e59cd377-7289-4844-bbfe-9a2def4f441a)

An analysis of dietary patterns by Piernas, et al. showed that both study groups reduced total energy, carbohydrates, total sugar, added sugar and other calorie containing nutrients, however, the diet beverage group had a greater reduction of desserts compared to the water drinkers at 6 months

Tate D, et al. 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. American Journal of Clinical Nutrition. 2012;95:555-563. (Link to abstract: http://ajcn.nutrition.org/content/95/3/555.abstract?sid=e59cd377-7289-4844-bbfe-9a2def4f441a)

Low- and No-Calorie Beverage Group Achieved Greatest Weight Loss



WA: water group
DB: diet beverage
AC: attention control

DB vs WA and AC: (P <0.001) and 0–6 months (P <0.001)

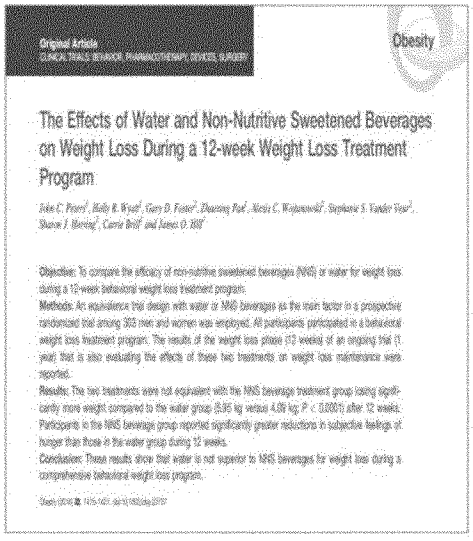
Tate DF, et al. *Am J Clin Nutr.* 2012;95:555-563.

Take-Home Messages

- The **diet beverage group showed a greater likelihood** of achieving a 5% weight loss compared with control
  - OR: 2.29; 95% CI: 1.05, 5.01; *P*=0.04
- The **water group did not significantly differ from control** in odds of achieving 5% weight loss

Tate DF, et al. *Am J Clin Nutr.* 2012;95:555-563.

Intervention Study



Original Article
CLINICAL TRIALS, BEHAVIOR, PHARMACOTHERAPY, DEVICES, SURGERY

Obesity

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

John C. Peters[1], Holly R. Wyatt[1], Gary D. Foster[2], Zhaoxing Pan[3], Maria C. Wojtanowski[3], Stephanie S. Vander Veur[3], Sharon J. Herring[3], Carrie Brill[3] and James O. Hill[1]

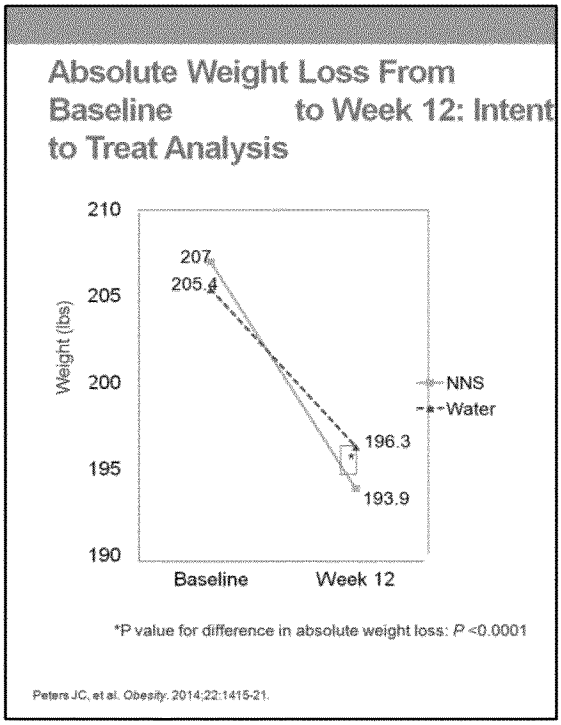
Objective: To compare the efficacy of non-nutritive sweetened beverages (NNS) or water for weight loss during a 12-week behavioral weight loss treatment program.

Methods: An equivalence trial design with water or NNS beverages as the main factor in a prospective randomized trial among 303 men and women was employed. All participants participated in a behavioral weight loss treatment program. The results of the weight loss phase (12 weeks) of an ongoing trial (1 year) that is also evaluating the effects of these two treatments on weight loss maintenance were reported.

Results: The two treatments were not equivalent with the NNS beverage treatment group losing significantly more weight compared to the water group (8.95 kg versus 4.86 kg; $P < 0.0001$) after 12 weeks. Participants in the NNS beverage group reported significantly greater reductions in subjective feelings of hunger than those in the water group during 12 weeks.

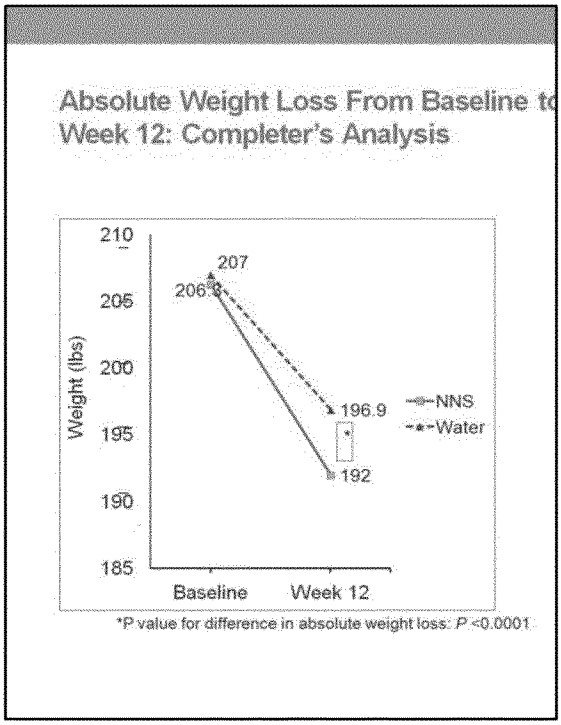
Conclusion: These results show that water is not superior to NNS beverages for weight loss during a comprehensive behavioral weight loss program.

Obesity (2016) 24, 1405–1411. doi:10.1002/oby.21512

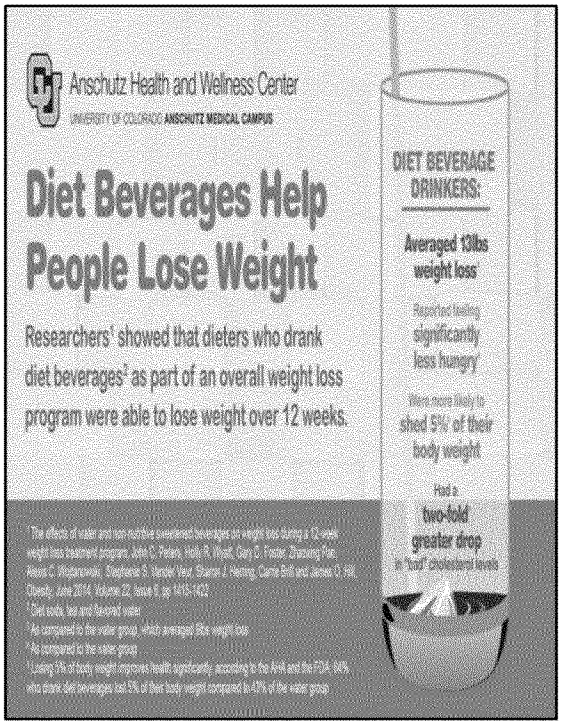


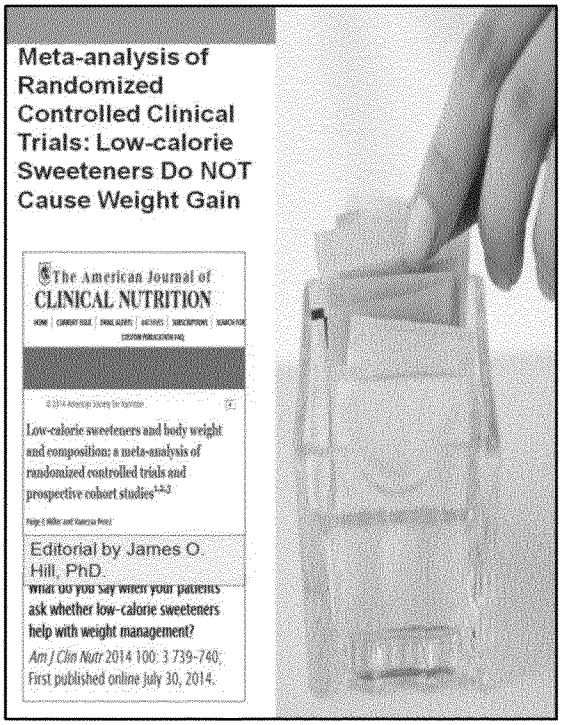
Note: This is the more conservative analysis because we are assuming that those who dropped from the study were not very successful with weight loss.
NNS~ 13 pounds
Water~ 9 pounds

Difference of ~ 4 pounds

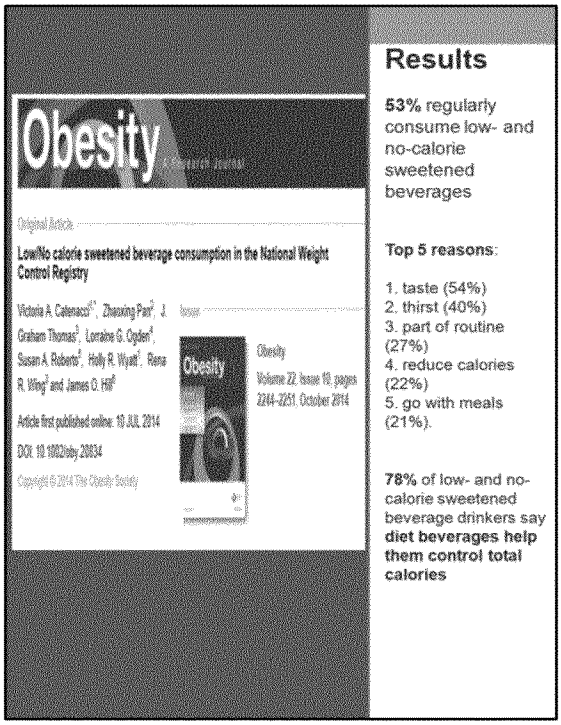


Note: This analysis includes only those that completed the study. Those that dropped are not included. Dropout was similar in both groups.
NNS~ 14 lbs
Water~ 10 lbs





The RCT analysis demonstrated that NNS reduced body weight compared to placebo and modestly, but "significantly" reduced BMI, fat mass, and waist circumference. These results supports existing evidence that judicious substitution of NNS and foods sweetened with them does not cause weight gain and may actually help people manage their weight. No correlation was found between NNS consumption and body weight or fat mass in the nine observational cohort studies analyzed.



Low- and No-Calorie sweetened beverages help “successful losers”

Longer-Term Intervention Trial:
Adding Low- and No-Calorie Sweeteners to a Multidisciplinary Program

- Randomized controlled trial
- N=163 obese women
- Subjects assigned to
  - Aspartame + multidisciplinary program
  - Multidisciplinary program alone (advised to abstain from using aspartame)
- Study duration: 1 year of treatment + 2 year follow-up period

Blackburn GL, et al. *Am J Clin Nutr.* 1997;65(2):409-18.

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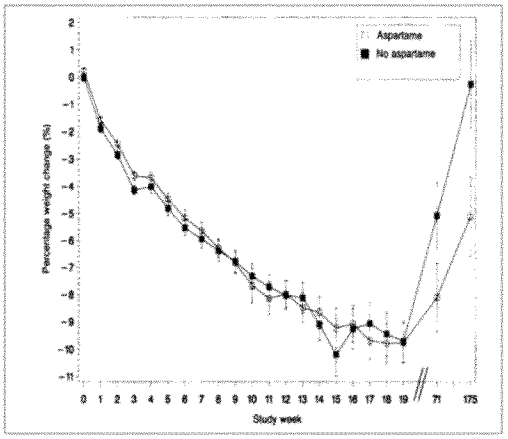
Aspartame Group Achieved Greatest Weigh Loss



Blackburn GL, et al. *Am J Clin Nutr.* 1997;65(2):409-18.

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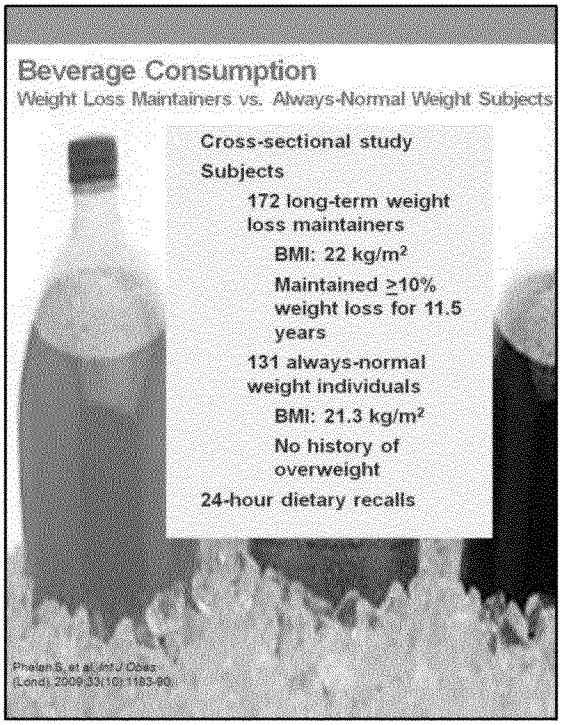
Beverage Consumption
Weight Loss Maintainers vs. Always-Normal Weight Subjects
Cross-sectional study
Subjects
172 long-term weight loss maintainers
BMI: 22 kg/m²
Maintained ≥10% weight loss for 11.5 years
131 always-normal weight individuals
BMI: 21.3 kg/m²
No history of overweight
24-hour dietary recalls
Phelan S, et al. Int J Obes (Lond). 2009;33(10):1183-90.

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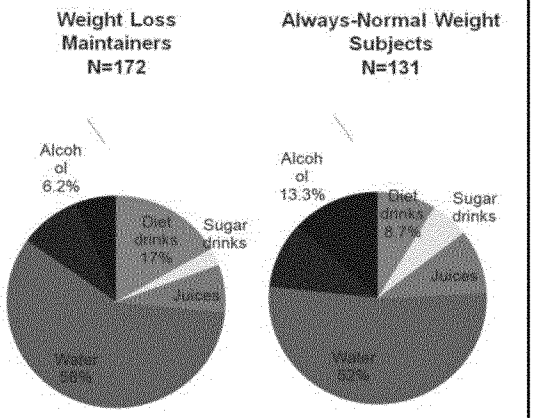
Long-Term Successful Weight Control

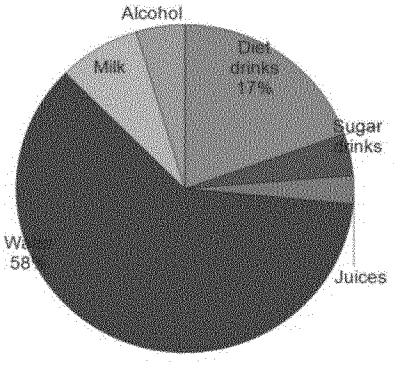


Phelan S, et al. *Int J Obes* (Lond). 2009;33(10):1183-90.

Long-term Successful Weight Control

National Weight Control Registry

Recent enrollees of the NWCR (N=937) who had completed the 2005 version of the Block Food Frequency questionnaire.



Long-term Successful Weight Control

Predictors of one-year weight regain final multivariate model

	B	Beta	T	Sig
Decreased restraint	-.14	-.079	-1.96	.05
Increased disinhibition	.560	.295	7.4	.0001
Decreased water	-.002	.134	-3.4	.001

- Decreasing water intake only beverage related to higher levels of weight regain.
- Neither increases nor decreases in consumption of diet or regular soft drinks related to weight regain.

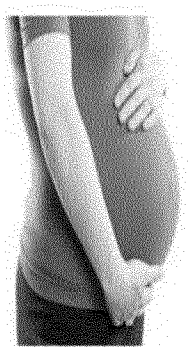
Appetite and Hunger

- Most studies and reviews conclude that non-nutritive sweeteners do not affect appetite or hunger or desire for sweetness in adults[1-4]
- … also note that future research is needed[5,6]

1. Anderson GH, et al. *Appetite*. 1989;13(2):93-103; 2. RogersPJ, et al. *Physiol Behav*. 1995; 93; 3. Blackburn GL, et al. *Am J Clin Nutr*. 1997;65(2):409-18; 4. Anderson GH, et al. J Nutr. 2012 Jun;142(6):1163S-9S C, et al. *Circulation*. 2012;126(4):509-19; 6. Mattes RD, et al. *Am J Clin Nutr*. 2009;89(1):1-14.

Pregnancy

- All FDA-approved low- and no-calorie sweeteners are approved for use by pregnant and lactating women
- The position of the Academy of Nutrition and Dietetics is that their use is acceptable during pregnancy[1]
- One study from 2010 among 59,334 Danish women found an association between intakes of soft drinks with NNS and pre-term births[2]
  - Incidence of pre-term birth was low and finding has not been confirmed in other studies



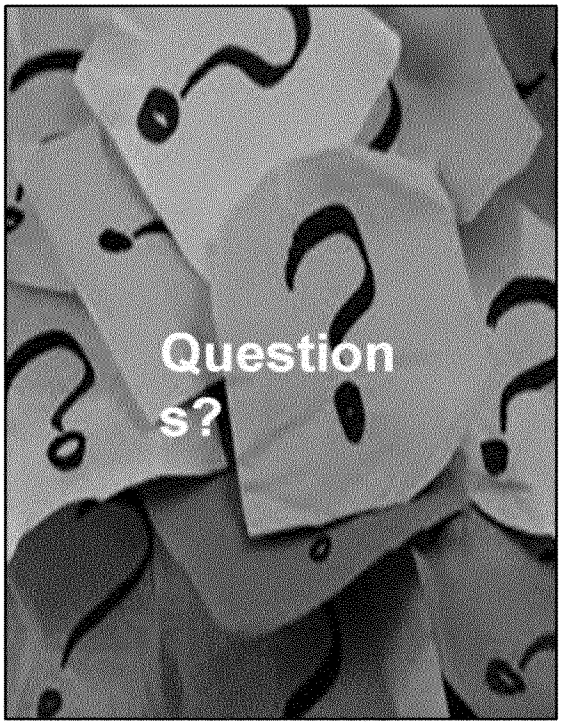
1. http://www.eatright.org/About/Content.aspx?id=8363; 2. Halldorsson TI, et al. *Am J Clin Nutr*. 2010;92:626-33.

Conclusions

- **Strong support** for a modest positive effect on weight with low- and no-calorie sweeteners
- Many research studies in humans with **consistent findings** from prospective studies and randomized controlled trials
- **No current scientific reason to recommend against use** of low- and no-calorie sweeteners for those trying to lose weight

Low- and no-calorie sweeteners are <u>tools</u> that:

- **Improve** glycemic, lipid, HTN control
- **Support** weight loss/control
- **Help prevent** and delay disease progression



For more information

- American Beverage Association: www.letsclearitup.com
- Calorie Control Council www.caloriecontrol.org
- EFSA www.efsa.europa.eu/
- Health Canada www.hc-sc.gc.ca/fn-an/securit/addit/sweeten-edulcor/index-eng.php
- FDA on stevia: www.fda.gov/aboutfda/transparency/basics/ucm214864.htm

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