Stevia:
A Naturally Sweet Alternative

Webinar for:
Food and Culinary Professionals
and Nutrition Education for the Public DPGs
December 4, 2009

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A Naturally Sweet Alternative

Beth Hubrich, MS, RD

- Current Position: Executive Director, Calorie Control Council
- Reviews and communicates the science of low and reduced-calorie sweeteners to nutrition professionals, other HCPs and food industry partners
- Frequently quoted by media about low-calorie sweeteners
- Active member ADA, founding member Weight Management DPG

Claire Kruger, PhD

- Chief Executive Officer and Director of Health Sciences, Spherix Inc, where she provides scientific, regulatory, and strategic support to food, drug, and dietary supplement manufacturers, agricultural producers, biotechnology companies, trade associations, and law firms around the world
- Over 20 years experience as a toxicology consultant, focusing on foods, consumer products and pharmaceuticals
- PhD in toxicology

Michael Carakostas, DVM, PhD, DACVP

- Senior Consultant with ToxStrategies, a scientific consulting firm, leads the Food and Supplement Safety Practice
- Board certified veterinary clinical pathologist
- Extensive experience in food ingredient safety assessment, food regulatory affairs
- Lead a multi-year research effort while at Coca-Cola to fill the safety assessment gaps on stevia which led to numerous publications

Hope Warshaw, MMSc, RD, CDE

- Owner, Hope Warshaw Associates, LLC, consultant, freelance writer/author and diabetes educator
- Background in no calorie sweeteners as diabetes educator and consultant to food and ingredient manufacturers, including McNeil Nutritionals, LLC
- Member of ongoing ADA Evidence Analysis project on caloric and non-caloric sweeteners to support position paper update 2010
- Active volunteer Diabetes Care and Education and Weight Management DPGs

Program Flow

- Introductions
- FDA and International Regulatory Overview
  - Beth Hubrich, MS, RD
- Stevia History & GRAS Approvals
  - Claire Kruger, PhD
- Research Evidence-base for Safety
  - Michael Carakostas, DVM, PhD, DACVP
- Stevia in Tabletop Sweeteners & Foods and Beverages
  - Hope Warshaw, MMSc, RD, CDE
- Q & A

Navigating GRAS/Regulatory Approval

Beth Hubrich, MS, RD
Calorie Control Council

Food Ingredient Safety

- US Food and Drug Administration (FDA) oversees food ingredient safety
- Overview: "FDA's Food Ingredient Approval Process, Safety Assurance Based on Scientific Assessment"
  - *Regulatory Toxicology and Pharmacology, 2008*
  - http://www.caloriecontrol.org/pdf/Rulis_08.pdf

Food Ingredient Safety

- "Food Additive" – becomes a component or affects characteristic of a food and **is not *Generally Recognized As Safe (GRAS)***
- New food additive is unsafe until proven safe and burden of proof of safety lies with ***petitioner***

Food Ingredient Safety

- Safety review includes:
  - Intake
  - Cumulative effect of all uses
  - Toxicology data to support safety
  - Must meet law's safety standard of "reasonable certainty of no harm."

Food Ingredient Safety

- Unlike drugs, review does not look at benefits
- Must have low toxic potential
- Must be safe for everyone (pregnant women, children, etc.)

GRAS

- Generally Recognized As Safe
- There is general consensus by qualified experts that the ingredient is safe for its intended use
- Same safety standard as food ingredients – "reasonable certainty of no harm"

GRAS vs. Food Ingredient

- Information/Common knowledge regarding safety
- General availability and general acceptance of information; widely known
- Clearly outlined in 1997 Federal Register
- Both require same strength of evidence

GRAS

- FDA does not "approve" a GRAS notice
- Issues letter: "no questions at this time about the conclusions…."
- GRAS claimant must fully address any potential controversy

Historical Use of Stevia, Mapping the Road to GRAS and Overcoming Obstacles

Claire L. Kruger, Ph.D., D.A.B.T.
CEO

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Historical Use of Stevia as a Sweetener

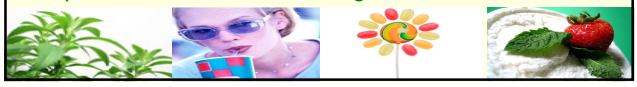
- *Stevia rebaudiana* (Bertoni) Bertoni
  - Plant native to S. America
  - Naturally sweet
  - Used for centuries
- Extracts permitted in several countries
  - In Japan, 40% of sweetener market

What Makes Stevia Sweet?

- *Steviol glycosides*
  - Molecules with very similar structures
    - Stevioside, Rebaudioside A, Dulcoside, etc.
  - Natural, low calorie, and ~300X sweeter than sugar

U.S. Regulatory History

- Stevia sold in herbal and health food stores; unregulated in the 1970s and 80s
- GRAS Affirmation petition (2G0390) submitted to FDA on behalf of American Herbal Products Association: basis cited as pre-1958 history of use. Approval denied; safety concerns cited
- Stevia permitted for use as a dietary supplement under Dietary Supplement Health & Education Act of 1994 (DSHEA); safety concerns prohibited use as a food ingredient



Consideration by the Joint FAO/WHO Expert Committee on Food Additives (JECFA)

- JECFA reviewed steviol glycosides at its 58th, 63rd, 68th, 69th meetings
- At the 58th and 63rd meetings, temporary specifications and a temporary acceptable daily intake (ADI) were assigned; safety concerns cited
- At the 68th meeting, final specifications were put in place and the temporary ADI was extended
- At the 69th meeting (2009), a **final ADI of 0-4 mg/kg bw** expressed as steviol, was established

Steviol Glycosides

- Information needed to assure safety and secure regulatory approval:
  - Food-grade specifications
  - Estimated daily intake
  - Acceptable daily intake
    - Absorption, distribution, metabolism and excretion (ADME)
    - Systemic toxicity
    - Physiologic/pharmacologic activity

Composition of Stevia Leaf

- Structural compounds
  - Fiber, cellulose, membrane lipids, waxes
- Primary metabolites (needed for nutrition and essential metabolic processes)
  - Chlorophylls, phytosterols, organic acids
- Secondary metabolites (not necessary for nutrition and growth, but may confer an ecological advantage; includes steviol glycosides)

Specification Problem:

Not all Stevia extracts are created equal

- Aqueous solutions vs. dried extracts
- Purity of material
- Proportion of the different steviol glycosides
  - Historically extracts high in stevioside
  - Newer extracts are higher in rebaudioside A
    - Taste

Basis for the Specifications and Subsequent Safety Evaluation

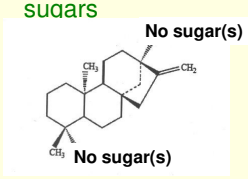
- Based on steviol equivalents

> How much steviol are we consuming?
>
> (not how much of any one steviol glycoside)

- 1 g steviol glycoside = 0.3 – 0.4 g steviol

Steviol Glycoside Metabolism
(Rats and Humans)

- Not digested
- Gut microflora clip off sugars



steviol

- ≈80% of steviol glycosides are absorbed as free steviol
- Steviol undergoes glucuronidation and rapidly eliminated in urine (humans) or feces (rats)

Basis for Regulatory Acceptance

- The basis for generation of appropriate specifications for steviol glycosides and subsequent safety evaluation is derived from:
  - comparative metabolism (rat studies are a good model) and;
  - metabolic disposition studies in rodents and humans (steviol is the common metabolite for steviol glycosides)

Basis for Regulatory Acceptance Specifications

- JECFA allows for seven steviol glycosides (rebaudioside A, stevioside, rebaudioside B, steviolbioside, rebaudioside C, dulcoside A and rubusoside) to be present, the sum of which accounts for a minimum of 95% of the dried substance (JECFA 2007)

Basis for Regulatory Acceptance Toxicology

- Steviol glycosides have very low acute toxicity in animals and there is no evidence of health risk, including repeat dose systemic toxicity, carcinogenicity, developmental, or reproductive effects. Weight of the evidence indicates that steviol glycosides are not genotoxic.

Basis for Regulatory Acceptance

- Safety of ingestion of steviol glycosides in humans has been corroborated in clinical trials; measures of tolerance, body weight, clinical chemistry, hematology and urinalysis did not show any evidence of untoward effects; no untoward effects on blood pressure or glucose control.

Basis for Regulatory Acceptance

- Estimates of intake for steviol glycosides, when used as a sweetener, were determined to be within established safe levels.

GRAS Notifications

GRAS Notices (filed in 2008-2009) for use of steviol glycoside extracts as a sweetener in food products:

GRN 252, 253, 275, 278, 282, 287, 303, 304

Notices highlighted in red have no questions or letters; others pending

Safety Studies Supporting GRAS and International Regulatory Requirements

Michael Carakostas, DVM, PhD, DACVP
Senior Consultant
ToxStrategies, Inc
St. Helena Island, SC

How Safety Information Gaps Were Addressed: *Reviews of Existing Studies*

Carcinogenicity:
- used an existing two-year rat carcinogenicity study on stevioside plus several other supportive steviol glycoside carcinogenicity studies and metabolism studies

Genotoxicity:
- written review by expert

Intestinal microflora effects:
- written review by experts

Intake assessment:
- used existing NNS intake data

How Safety Information Gaps Were Addressed: *New Studies*

Reproductive safety concerns:
- short and intermediate term general oral toxicity studies and pre-clinical reproductive safety study

Kidney and liver safety concerns:
- short and intermediate term toxicity studies

Carcinogenicity requirements:
- comparative metabolism studies (plus existing studies)

How Safety Information Gaps Were Addressed: *New Studies*

Safety in subjects with lower blood pressure:
- clinical study with sufficient power to predict

Safety in subjects with Type II diabetes:
- clinical study with sufficient power to predict

Safety Summary – Existing Studies

Study	Summary
Pre-clinical Safety	Pre-2008 90-day studies on stevioside, but not reb-A. Some reported adverse renal effects not observed in later studies. Mid-2008 publication of a 90-day study reported a 2000 mg/kg/day no observed adverse effect level (NOAEL) and no adverse effects with reb-A. Previously published reproductive safety studies – adverse effects reported with unrefined or uncharacterized stevia
Genetic Toxicity and Cancer	Previous genotoxicity concerns about steviol – expert review concluded these were in-vitro test specific artifacts. Previous 2-year carcinogenicity study on stevioside had NOAEL of approx. 1000 mg/kg/day (400 mg/kg/day steviol equiv.)

Safety Summary – Existing Studies

Study	Summary
Microbial effects	Review of literature indicated no potential for adverse effects on normal intestinal microflora.
Clinical studies on blood pressure and glucose effects	A number of previous small studies and anecdotal reports touting stevia as an herbal treatment for high blood pressure and glucose control in diabetics. 2007 e-publication of combined clinical study that looked at blood pressure and glucose homeostasis in same subjects. No pharmacological effects observed but considered too small to provide acceptable predictive by regulatory authorities at that time. Subsequently, used successfully in at least one GRAS notification without other supporting documentation of clinical safety.

Safety Summary

Study	Summary
Intake Assessment	Estimated intake based on actual NNS intake studies was accepted by both FDA and JECFA. High-consuming (95th percentile) adult intake 3.4 mg/kg/day; high consuming children 5.0 mg/kg/day; and 4.5 mg/kg/day for children with diabetes. 5 mg/kg/day reb-A = 1.6 mg/kg/day in steviol equivalents.
Metabolism	Human and rodent metabolism are similar – all steviol glycosides are metabolized to steviol. Some differences in primary route of excretion: • rat primarily via feces as steviol • human primarily via urine as soluble steviol glucuronide **Confirms that stevioside safety studies can be used for safety assessment of all steviol glycosides**

Safety Summary

Study	Summary
General safety / renal and hepatic safety	Very high doses tested in 28-day pre-clinical study (up to 10% of diet) with no adverse effects observed. In 90-day pre-clinical study (doses up to 5% of diet), no adverse effects observed. NOAEL approx. 4000 mg reb-A/kg/day
Reproductive Safety	No effects on male reproductive system at very high doses used for 28- and 90-day preclinical studies. No functional or structural effects observed in 2-generation reproductive safety study. No effects on off-spring. NOAEL approx. 2500 mg reb-A/kg/day
Microbial effects	Review of literature indicated no potential for adverse effects on normal intestinal microflora.

Safety Summary

Study	Summary
Blood Pressure	4-week clinical study on human subjects with low to low-normal blood pressure. No effects observed (80% power to detect a 4.5 mmHg change in resting seated systolic bp).
Diabetes	16-week clinical study in subjects with type II diabetes – no effects on multiple measures of glucose homeostasis including HbA1c (90% power to detect a 0.5% change in HbA1c from baseline to end of study).

Safety Summary

- On a steviol-equivalent basis, pre-clinical safety studies support a NOAEL of 400 mg steviol/kg/day based on the results of the carcinogenicity study with supporting safety data from the other pre-clinical studies at higher NOAELs.
- A 100-fold safety factor provides an ADI of 0-4 mg steviol/kg/day equivalent to 12 mg reb-A/kg/day.
- The intake assessment showed that high-percentile consumers would be expected to ingest no more than 5 mg reb-A/kg/day.

Safety Summary

- No adverse effects in special populations:
  - subjects with low blood pressure
  - subjects with Type-2 diabetes
- Important for GRAS:
  All studies published in peer reviewed journal to establish "general recognition"

Stevia: Tabletop Sweeteners

Stevia: Tabletop Sweeteners

- Uses:
  - Sweeten foods & beverages
  - Cooking and baking
- Forms of stevia:
  - Rebaudioside A, abbreviated as Reb A or Rebiana;
  - Stevia extract: numerous steviol glycosides, mainly rebaudioside A
- Bulking ingredients:
  - Used with stevia form to provide volume/bulk
    - similar to all NCS, used due to sweetness intensity
  - Used to obtain optimal taste profile
  - Different bulking ingredients used in products

PureVia
All Natural Zero Calorie Sweetener

- Manufacturer: Whole Earth Sweetener Company
- Website: purevia.com
- Stevia form: Rebaudioside A (abbrev. Reb A)
- Product form: Sticks, 1 = 2 tsp sweetness
- Ingredients*: Erythritol, isomaltulose, Reb A (Stevia extract), Contains 1% or less of Cellulose Powder and each Natural Flavor
- Nutrition Facts (svg): Cal: 0^, CHO: 2g, Sugars: <1g, Erythritol: 1 g

*Order listed on package
^FDA – less than 5 cals/svg can be listed as 0

Stevia in the Raw
100% Natural Zero Calorie Sweetener

- Manufacturer: Cumberland Packing Corp.
- Website: steviaextractintheraw.com
- Stevia form: Rebiana
- Product form: Packets, 1 = 2 tsp sweetness
  Granulated = cup for cup
- Ingredients*: Packets - Dextrose, Stevia extract (rebiana)
  - Granulated = maltodextrin, Stevia extract
- Nutrition Facts (svg): Cal: 0, CHO: <1g, Sugars: <1g

*Order listed on package

Sun Crystals
all-natural sweetener

- Manufacturer: McNeil Nutritionals, LLC
- Website: suncrystals.com
- Stevia form: stevia extract
- Product form(s): Packets, 1 = 2 tsp sweetness, Granulated blend: ½ cup = 1 cup sweetness
- Ingredients*: packet and granulated: cane sugar, stevia
- Nutrition Facts (svg):
  - Pkt: Cal: 5, CHO: 1g, Sugars: 1g
  - Granulated (1/2 tsp): Cal: 5, CHO: 2g, Sugars: 2g

*Order listed on package

Sweet Leaf
All Natural Stevia Plus

- Manufacturer: Wisdom Natural Brands
- Website: sweetleaf.com
- Stevia form: Stevia extract
- Product form(s): Packets 1 = 2 tsp sweetness; Shaker jar (shake to taste); Tablets 1 = 1 tsp sugar (pure stevia)
- Ingredients*: inulin, stevia extract
  - (inulin: polysaccharide found in fruits, veg; blend of fructose polymers synthesized from sucrose or extracted from chicory root [sweet leaf])
- Nutrition Facts: Cal: 0, CHO: 0g, Sugars: 0g

*Order listed on package

Truvia
Nature's Calorie-Free Sweetener

- Manufacturer: The Truvia Company, Cargill, Inc.
- Website: truvia.com
- Stevia form: rebiana
- Product form(s): Packets, 1 = 2 tsp sweetness
- Ingredients*: Erythritol, rebiana, natural flavors
- Nutrition Facts (svg): Pkt: Cal: 0, CHO: 3g, Erythritol: 3g

*Order listed on package

Stevia in Foods & Beverages

Stevia in Foods & Beverages

- Form: Stevia, no bulking ingredients
- To date:
  - Mainly beverages, few foods
  - Large and small brands
  - Products sweetened mainly with PureVia or Truvia
    - Many Coca-Cola products with Truvia
    - Several PepsiCo products with PureVia
    - Enliten sold to food and beverage producers
  - Some products with Truvia/PureVia logo
  - Distribution nationwide or natural food stores, or Whole Foods
- Expect more foods and beverage due to manufacturer's interest, consumer desire/demand

Pure Via
truvia
Enliten

Foods & Beverages:
with Truvia (available nationwide/Coca-Cola)

- Odwalla reduced calorie juices
  - Quenchers & lemon/limeade
  - 50 cals/8 oz – 4 flavors
- Glacéau vitaminwater
  - 10 cals/8 oz – 8 flavors
  - 0 cals/8 oz – 7 flavors
- Sprite Green – soft drink/Coca Cola
  - 50 cals/8.5 oz (sugar)
  - Only in some markets


Foods & Beverages: with Truvia (select/natural retailers)

- Nature's Splash/Kraft (4 flavors)
  - 25 cals/8oz, dry powdered sticks
  - 1st ingredient: evaporated cane juice
- True Lemon: O cal/packet
- Hansen's Natural Lo-Cal Juices (4 Flavors)
  - 40 cals/8 oz
- All Sport, naturally zero
  - 0 cals/8 oz
- Blue Sky Free soft drink in 12 oz cans (4 flavors)
  - 0 cals/8 oz
- Sweet Freedom/Blue Bunny frozen desserts (sticks/3 flavors)
  - 60 - 90 cals/svg (1 stick)

Foods & Beverages: with PureVia (available nationwide/PepsiCo)

- SoBe Lifewaters (5 flavors)
  - 0 cals/8 oz
- Trop50 (3 types: calcium/vit D fortified, some pulp, no pulp)
  - 50 cals/8 oz, CHO: 13 g


Stevia as 2010 Food Trend

- Stevia identified as 2010 food trend in The Next Wave: Wellness Food Trends for 2010 www.foodprocessing.com/articles/2009/wellnesstrendsfor2010.html
  - With it's natural credentials, stevia opens up the low calorie sweetener marketplace…
  - "…consumers are driving innovation in the low-sugar beverage area…"
  - "2010 is going to be the year of reb-A,…you're going to see a number of product intros in beverage and dairy especially."
  - Warning about the downside of stevia marketplace: "There are newcomers [reb-A suppliers] who don't have GRAS documentation…. so beware….look for [reb-A suppliers] with GRAS documentation…"

Conclusions

- Safety studies and long term use demonstrate safety
  - ***studies conducted across metabolism, pharmacology and toxicology clearly support safe intake by the general population***
- FDA's GRAS self-affirmation process used, no objection to use
- Growing marketplace/consumer demand/desire for tabletop sweeteners and foods & beverages with natural ingredients
- Stay posted, watch your supermarket aisles…

Q and A

Still Have Questions?

Calorie Control Council
www.caloriecontrol.org

www.steviabenefits.org