

Stevia: The Journey From GRAS to Grocery

Webinar for:
WM, DCE and SCAN DPGs
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Stevia: The Journey From GRAS to Grocery



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
- 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



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

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Comparison of Regulatory Paths

FOOD ADDITIVE	GRAS	DIETARY SUPPLEMENT
Becomes a component of conventional food	Becomes a component of conventional food	Supplements the diet (vitamin, mineral, herb in tablet, capsule, liquid form)
The Federal Food, Drug and Cosmetic Act 1938	Exemption to Food Additives Definition 1958 Notification Process Promulgated 1997	DSHEA 1994
Food Additive Petition	General Recognition of Safety by Expert Panel: GRAS dossier (self-GRAS or Notification)	Pre-1994: No FDA Notification Post-1994: New Dietary Ingredient (NDI) Notification to FDA
Premarket FDA <u>Approval</u> mandatory	No premarket FDA approval: <u>Notification</u> to FDA optional	Premarket FDA <u>Notification</u> mandatory (post-1994)
Information and data remain confidential	Pivotal information and data must be published; Notification publicly available	Information and data may be unpublished; Notification publicly available



GRAS Ingredients

- General recognition of safety is based on the views of experts qualified by scientific training and experience
- Safety is based on the consensus of reasonable certainty that a substance is not harmful under its intended conditions of use
- Pivotal information must be publicly available



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?

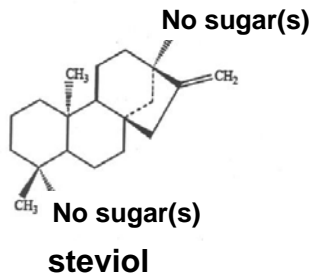
(not how much of any one steviol glycoside)

- 1 g steviol glycoside = 0.3 – 0.4 g steviol



Steviol Glycoside Metabolism (Rats and Humans)

- Not digested
- Gut microflora clip off sugars
- $\approx 80\%$ 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 2008-2010) for use of steviol glycoside extracts as a sweetener in food products:

GRN 252, 253, 275, 278, 282, 287, 303, 304, 318, 323, 329

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



Safety Studies Supporting GRAS and International Regulatory Requirements

Michael Carakostas, DVM, PhD, DACVP
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How Pre-Clinical Safety Information Gaps Were Addressed

Reproductive safety concerns:

new short and intermediate term general oral toxicity studies
new pre-clinical two-generation reproductive safety study

Kidney and liver safety concerns:

short and intermediate term toxicity studies

Comparative metabolism concerns:

new rat and human comparative metabolism studies



How Pre-Clinical Safety Information Gaps Were Addressed

Carcinogenicity:

used an existing carcinogenicity study on stevioside
several older supportive carcinogenicity studies
comparative metabolism studies

Intestinal microflora effects:

written review by experts

Intake assessment:

used existing NNS intake data based on real usage



Summary of Pre-clinical Safety Results

- No concerns about genotoxicity or carcinogenicity
- Reproductive safety study demonstrated safety in both males and females
- Oral toxicity studies demonstrated that there are no adverse effects on the kidney
- No Observed Adverse Effect Level (NOAEL) = 400 mg steviol/kg/day (from “lifetime” rat safety study)
- No concerns about adverse effects on intestinal microflora



Safety Summary

Study	Summary
Intake Assessment	<p>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.</p> <p>5 mg/kg/day reb-A = 1.6 mg/kg/day in steviol equivalents.</p>
Metabolism	<p>All steviol glycosides are metabolized to steviol.</p> <p>Some differences in primary route of excretion:</p> <ul style="list-style-type: none"> • rat primarily via feces as steviol • human primarily via urine as soluble steviol glucuronide <p>Confirms that stevioside safety studies can be used for safety assessment of all steviol glycosides</p>

How Clinical Safety Information Gaps Were Addressed

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



Existing Clinical Studies

- A number of previous small studies and anecdotal reports touting stevia as an herbal treatment for high blood pressure and glucose control in diabetics. *This was not helpful.*
- 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 US and International regulatory authorities at that time.



Clinical 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: Sachets, 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, Erythritol: 1 g



*Order listed on package
[^]FDA – less than 5 cal/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 forms:
 - Packets, 1 = 2 tsp sweetness
 - Granulated, 1 cup = 1 cup sweetness
- Ingredients*: Dextrose, Stevia extract (rebiana)
- Nutrition Facts (svg):
 - Packet: Cal: 0, CHO: <1g
 - Granulated (1 tsp): Cal: 0, CHO: <0.5g



*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
 - Granulated (1/2 tsp): Cal: 5, CHO: 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

*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, small, national, regional 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 (only)
 - 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



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

- Odwalla reduced calorie juice
 - Quenchers & lemon/limeade
 - 50 cal/8 oz – 4 flavors
- Glacéau vitaminwater
 - 10 cal/8 oz – 8 flavors
 - 0 cal/8 oz – 7 flavors
- Powerade Play
 - 60 cal/12oz – 4 flavors
- Minute Maid Pomegranate
 - 40 cal/8 oz
- Sprite Green (some markets)
 - 50 cal/8.5 oz (contains sugar)



Foods & Beverages: with Truvia (varied manufacturers)

- Nature's Splash/Kraft (4 flavors)
 - 50 cal/dry pkt stick, makes 16.9 oz
 - 1st ingredient: evaporated cane juice
- True Lemon: 10 cal/pkt, makes 16.9 oz
- Hansen's Natural Lo-Cal Juices (4 Flavors)
 - 40 cal/8 oz
- All Sport, naturally zero
 - 0 cal/8 oz
- Blue Sky Free soft drink in 12 oz cans (4 flavors)
 - 0 cal/8 oz



Foods & Beverages: with Truvia (varied manufacturers)

- Velamints (3 flavors)
 - 5 cal/3 mints
- Dippin Dots Chillz (>3 flavors)
 - 50 – 80 cal/2.6 oz svg/pouch
- Breyer's YoCrunch (5 flavors)
 - 100 cal/3.75 oz cup



Foods & Beverages: (with PureVia/PepsiCo)

- SoBe Lifewaters (7 flavors)
 - 0 cal/8 oz
- Trop50 (3 types: calcium/vit D fortified, some pulp, no pulp)
 - 50 cal/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 its 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."



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



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