

# Food Update



Winter 2012

Volume 3, Issue 1

## The Pathway to Regulatory Approval for Steviol Glycosides

The recent approval of steviol glycosides in Europe represents a major victory in a journey that started over 20 years ago when the European Union's Scientific Committee of Food was one of the first authorities to review the safety of Stevia extracts. Over that time, several safety and quality hurdles were encountered and overcome, thereby allowing several regulatory authorities to accept the use of this novel sweetener. These hurdles included the definition of the material and questions on preclinical and human safety.

### Specifications and Purity

When the safety of Stevia extracts was first considered, there was no consistency in reporting the test material used in the safety studies. As a result, some short-term safety studies were raising potential red flags, whereas longer term studies, in which the test material was defined, were demonstrating a lack of safety concern. Without consistently defined material, the safety of Stevia extracts in comparison to commercially available materials could not be determined.

This issue was resolved by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) during their 63<sup>rd</sup> meeting in 2004. JECFA established temporary specifications for Stevia extracts, such that the preparations must contain at least 95% steviol glycosides, with the sum of stevioside and rebaudioside A being not less than 70% of the total, and established a common naming for these preparations called "steviol glycosides". Subsequent to the 63<sup>rd</sup> meeting, the specifications for steviol glycosides have been revised with the growing knowledge of safety and individual steviol glycosides present within primary extract. Today, the purity specification for steviol glycosides states that the preparation must contain at least 95% steviol glycosides, as a combination of 9 individual glycosides (stevioside, rebaudioside A, B, C, D, and F, dulcoside A, rubusoside, and steviolbioside).

### Preclinical Safety

With the advent of defined material, the relevance of early studies could be determined. The fertility effects reported in female rats administered crude Stevia extracts were discounted as not relevant, especially in light of the lack of reproductive effects in longer term studies conducted with higher doses of steviol glycosides. However, questions regarding the metabolism of high-purity steviol glycosides and the long-term safety in additional species still remained.

continued on page 2...

### Inside this Issue:

#### The Pathway to Regulatory Approval for Steviol Glycosides

*...read more page 1*

#### Recent Publications

*...read more page 2*

#### Follow Intertek Cantox on LinkedIn...

*...read more page 3*

#### Good Reporting is Integral to Good Science – Seems a No-Brainer, But Why Is It Not Happening?...

*read more page 3*

#### Regulatory News

*...read more page 4*

#### Upcoming Events

*...read more page 4*

#### Workshop on the Regulation of Animal Feed Ingredients in the US

*...read more page 5*

#### Omega-3s: Can There Be Too Much of a Good Thing?

*...read more page 5*

#### In Profile with... Ilana Platt, PhD.

*...read more page 6*

## The Pathway to Regulatory Approval for Steviol Glycosides ...cont'd

continued from page 1...

In 2006, JECFA concluded that the metabolic fate of steviol glycosides is similar between rats and humans, in that the glycosides are metabolised to the aglycone, steviol, in the colon by the sequential removal of glucose units by the intestinal bacteria. Steviol is subsequently absorbed, rapidly glucuronidated, and excreted. These conclusions were further corroborated by studies published in 2009, in which the metabolic fate of stevioside and rebaudioside A were compared in rats and humans. The only difference noted in the metabolism of the glycosides between rats and humans was the route of excretion, such that steviol glucuronides were extracted in the faeces of rats and in the urine of humans.

The long-term safety of steviol glycosides would finally be confirmed in 2009 following the publication of 2 subchronic toxicity studies and a 2-generation reproductive toxicity study conducted with high-purity rebaudioside A. These studies corroborated the lack of toxicologically relevant findings of earlier studies conducted with high-purity stevioside. As a result of the similar metabolic pathways and findings from toxicity studies, safety data on an individual steviol glycoside could be extrapolated to steviol glycosides, in general, it was considered that the rat was an acceptable model to determine the safety of steviol glycosides in humans.

### Human Safety

Although a temporary acceptable daily intake (ADI) for steviol glycosides was established by JECFA in 2006, questions regarding the potential pharmacological effects of steviol glycosides in normotensive and hypotensive individuals, as well as in insulin-dependent and non-insulin dependent diabetics limited the designation of a full ADI. However, in 2009, studies conducted in the population groups of interest demonstrated that the consumption of high-purity material did not cause pharmacological effects. Subsequently, JECFA removed the temporary designation and established a full ADI of 0 to 4 mg/kg body weight, calculated as steviol equivalents.

### Continuing the Journey

Presently, steviol glycosides are accepted for use in several jurisdictions beyond Europe, including the United States, Australia and New Zealand, South America, and Asia. The use of steviol glycosides in Canada, however, remains limited to natural health products (a.k.a. dietary supplements). Should Canada approve their use in foods, steviol glycosides will be the first all natural non-nutritive sweetener with widespread approval.

## Recent Publications

### Toxicological risk assessments: addressing concerns about exposure to potentially hazardous substances

Card JW, Fikree H (2011). Regul Focus (Sep.):14-17.

### A review of the efficacy and safety of nanoparticle-based oral insulin delivery systems

Card JW, Magnuson BA (2011). Am J Physiol Gastrointest Liver Physiol 301(6):G956-G967.

### Subchronic toxicity evaluation of potato protein isolate

Lynch B, Simon RR, van Otterdijk FM, Emmen HH, Giuseppin ML, Kemme-Kroonsberg C (2011). Food Chem Toxicol [advance electronic publication – Oct. 7, 2011].

### A brief review of the occurrence, use, and safety of food-related nanomaterials.

Magnuson BA, Jonaitis TS, Card JW (2011). J Food Sci 76(6):R126-R133.

### Vitamin D and sterol composition of 10 types of mushrooms from retail suppliers in the United States.

Phillips KM, Ruggio DM, Horst RL, Minor B, Simon RR, Feeney MJ, Byrdwell WC, Haytowitz DB (2011). J Agric Food Chem 59(14):7841-7853.

### Postprandial effects of almond consumption on human osteoclast precursors - an ex vivo study.

Platt ID, Josse AR, Kendall CW, Jenkins DJ, El-Sohemy A (2011). Metabolism 60(7):923-929.

### Vitamin D mushrooms: comparison of the composition of button mushrooms (*Agaricus bisporus*) treated postharvest with UVB light or sunlight.

Simon RR, Phillips KM, Horst RL, Munro IC (2011). J Agric Food Chem 59(16):8724-8732.

### Impact of low v. moderate intakes of long-chain n-3 fatty acids on risk of coronary heart disease.

Musa-Veloso K, Binns MA, Kocenas A, Chung C, Rice H, Oppedal-Olsen H, Lloyd H, Lemke S (2011). Br J Nutr 106(8):1129-1141.

### A comparison of the LDL-cholesterol lowering efficacy of plant stanols and plant sterols over a continuous dose range: Results of a meta-analysis of randomized, placebo-controlled trials.

Musa-Veloso K, Poon TH, Elliot JA, Chung C (2011). Prostaglandins Leukot Essent Fatty Acids 85(1):9-28.



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### Good Reporting is Integral to Good Science – Seems a No-Brainer, But Why Is It Not Happening?

Intertek Cantox had the honour of having Dr. David Moher, Ottawa Hospital Research Institute, present a talk titled, “The intellectual return on our investments in health research: a paradigm shift” wherein the current state of health research reporting in publications was discussed.

Based on his presentation, it appears the current state of health research reporting in publications is abysmal. Indeed, the quality of research reporting is well below an acceptable level - - authors do not adequately describe basic essential information of their research studies!

A review of 262 randomized trials from prominent oncology journals revealed that a small minority (11%) adequately reported 10 pre-specified elements related to the characterization of the intervention. Moreover, in a review of 199 randomized trials investigating effects on diabetes, 53% were of low methodological quality, and many were missing pertinent information pertaining to characterization of the intervention, randomization, and the identification of the primary outcome(s).

Dr. Moher’s findings revealed that the lack of adequate research reporting is apparent ‘across the board’, regardless of the “prestige” of the journal, how well the study is funded, and the research area. Considering that a manuscript is reviewed in-house by multiple researchers (typically), by the journal editor, as well as at least 3 peer-reviewers, Dr. Moher’s findings are quite remarkable.

#### What is at the heart of inadequate research reporting?

It is difficult to pinpoint but is likely related to a lack of awareness of quality reporting requirements (*i.e.*, a lack of education), funding limitations, time, and the “publish or perish” mentality of getting research published as fast as possible.

#### What can be done to correct this systemic failure?

1. More training on peer-reviewing and research-reporting or, more specifically, a stronger emphasis on the importance of “Journalology” – the study of all aspects related to writing, (peer)-reviewing, and research reporting.
2. The consistent use and application of reporting guidelines and checklists (*e.g.*, CONSORT) – research shows that they work!
3. Compensating peer-reviewers to ensure they are qualified to peer-review, and are given sufficient time to fully review manuscripts.
4. Requiring the submission of protocols/study reports with manuscripts to allow for a direct comparison of ‘planned’ *versus* ‘reported’ study features.
5. Central publication of clinical trial protocols online (some databases are available).
6. Completion of a “Transparency Pledge” by researchers, in manuscripts, to encourage the comprehensiveness and objectivity of data presentation.

#### Key Links:

- CONSORT (Consolidated Standards of Reporting Trials) provides information on initiatives to help alleviate the problems related to inadequate reporting of randomized control trials (<http://www.consort-statement.org/>)
- Prisma provides guidance that focuses on ways in which authors can ensure the transparent and complete reporting of systematic reviews and meta-analyses (<http://www.prisma-statement.org/conceptual.htm>)
- Prospero (International prospective register of systematic reviews) is a database that acts as a permanent record of systematic reviews (<http://www.crd.york.ac.uk/prospero/>)
- The Equator-Network is an international initiative committed to the provision of resources/reporting guidelines to researchers in a wide range of disciplines (<http://www.equator-network.org/>)

## Regulatory News

### Health Canada's New Policy for Caffeinated Energy Drinks

Health Canada is changing the way caffeinated energy drinks are regulated in response to growing concerns regarding the intakes of high levels of caffeine from these products. Currently regulated as Natural Health Products (NHPs), caffeinated energy drinks will soon be regulated as foods. With this new policy comes more stringent composition and labelling requirements, as well as incident reporting requirements for industry. For further information, see Health Canada's proposed approach, which was released in October (<http://www.hc-sc.gc.ca/fn-an/legislation/pol/energy-drinks-boissons-energisantes-eng.php>).

### Health Claims Updates in the EU

The European Food Safety Authority (EFSA) has released its 2 most recent batches of Article 13.1 health claim opinions on June 30 and July 28, 2011. A total of 78 opinions were released for the 2 batches, including 571 claims, 22 of which received favourable opinions. In addition, EFSA has released a draft guidance document for health claims related to neurological and psychological function in order to define the scientific requirements for supporting these types of claims. Comments on the draft document are due by December 16, 2011. For further information, see EFSA's open consultation information page (<http://www.efsa.europa.eu/en/consultations/call/111017.htm>).

### The New EU Food Information Regulation

The new EU Food Information for Consumers Regulation, Regulation (EU) No 1169/2011, was published in the Official Journal of the European Union on October 25 which initiates the formal adoption of the regulation. This regulation will replace Directives 2000/13/EC and 90/496/EEC to bring together EU rules on general and nutritional labelling for simplification purposes. Changes to existing legislation include origin labelling of meat, nutrition labelling for processed foods, labelling for high caffeine content drinks, allergen labelling for non pre-packed food, and font size minimums. The new food labelling rules will be mandatory as of 2014 and nutrition declaration will be mandatory as of 2016.

### FSANZ Food and Processing Aid Updates

Food Standards Australia New Zealand (FSANZ) has recently approved the use of endoprotease, a new processing aid sourced from genetically modified *Aspergillus niger*. FSANZ also has recently received an application for approval for food derived from corn line 5307, which has been genetically modified for protection against insect pests.

### USDA Office Closures

In an effort to reduce costs, the U.S. Department of Agriculture (USDA) is intending to close 259 offices, facilities, and laboratories nationwide, as well as 7 foreign offices. The closures will affect local Farm Service Agency offices, the USDA's Food, Nutrition, and Consumer Services department, Agricultural Research Service labs, and the Food Safety and Inspection Service. The announced closures raise concerns about the potential effects on food safety; however, USDA has indicated that there will not be a reduction in inspectors or inspection work, and no risk to consumers.

## Upcoming Events

### Nutracon

March 7 - 8, 2012  
Anaheim, California  
<http://www.nutraconference.com/nutracon12/public/enter.aspx>

### Natural Products Expo West 2012

March 8 - 11, 2012  
Anaheim, California  
<http://www.expowest.com>

### Engredea Ingredients & Innovation

March 9 - 12, 2012  
Anaheim, California  
Visit us at booth 725  
<http://engredea.com/engredea12/Public/enter.aspx>

### Wellness 12

March 28 - 29, 2012  
Rosemont, Illinois  
*Don't miss Dr. Kathy Musa-Veloso's presentation on, "Functional Foods, Dietary Ingredients, and Health Claims in the EU & U.S.: Are Regulators Closing the Doors on Innovation?"*  
<http://www.ift.org/meetings-and-events/wellness.aspx>

### Supplieside East

May 8 - 10, 2012  
New York City, New York  
<http://www.suppliesideshow.com/2012/east/exhibit.html>

### Vitafoods Europe

May 22 - 24, 2012  
Paris, France  
*Visit us at booth SP34*  
<http://www.vitafoods.eu.com/>

### IFIA Japan (International Food Ingredients and Additives)

May 23 - 25, 2012  
Tokyo, Japan  
*Visit us at our booth*  
<http://www.ifiajapan.com/2012/en/index.html>

### IFT (Institute for Food Technologists)

June 26 - 28, 2012  
Las Vegas, Nevada  
*Visit us at booth 2839*  
<http://www.am-fe.ift.org/cms/>

# Workshop on the Regulation of Animal Feed Ingredients in the U.S. 16 February 2012 in Brussels, Belgium

Regulatory processes in the US are changing, and it is critical to understand the options open to any company wishing to gain acceptance to market a new feed ingredient. This workshop will provide a comparison of the current approval processes, with up-to-date information on the regulatory options available to companies seeking to market their ingredients in animal feed. Don't miss this exciting learning opportunity hosted by Intertek Cantox, featuring presentations by an AAFCO official and Dr. David A. Dzanis, DVM, DACVN.

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**Space is limited - Register early to avoid disappointment!**

## Omega-3s: Can There Be Too Much of a Good Thing?

For some time now, people have been hearing about the health benefits of omega-3 fatty acids (such as eicosapentanoic acid [EPA], docosahexanoic acid [DHA], and alpha-linolenic acid [ALA]), which are typically consumed in the diet from fish and plant oils. Some of the key benefits are related to cardiovascular, vision, and brain health, amongst others. With increased interest in these fatty acids and many food and supplement manufacturers jumping at the opportunity to provide consumers with additional sources of these essential unsaturated fatty acids, government agencies around the globe are honing in on exactly how much should individuals be consuming to get these benefits and whether there are risks with consuming too much.

On December 5<sup>th</sup>, the European Commission and various Member States voted on a number of health claims associated with maintenance of normal vision (with DHA), maintenance of brain function (with DHA), normal heart function (with EPA/DHA), and maintenance of normal blood cholesterol levels (with ALA), with the associated daily intake requirements. In the United States (U.S.), the U.S. Food and Drug Administration (U.S. FDA) has permitted qualified health claims regarding EPA/DHA intake and a possible reduction in coronary heart disease, since 2004.

However, in the European Union, health claims associated with DHA (or EPA/DHA/ALA) and normal triglyceride level maintenance, and EPA/DHA/ALA and normal blood pressure were not included in the "Article 13.1 list", that was recently given a positive vote for adoption by the Standing Committee on the Foodchain and Animal Health, because concerns have been raised by certain Member States about the safety of these fatty acids at the intake levels that would be required to achieve these benefits.

The German Federal Risk Assessment Agency discussed a safe upper limit of intake of 1.5 g omega-3 fatty acids/day, based on scientific evidence that indicates that very high

levels of intake of DHA/EPA may be associated with elevated cholesterol levels, impairment of natural immune defence (in particular in older people), and thinning of the blood. Meanwhile, the U.S. FDA has recommended not exceeding 3 g (EPA/DHA)/day from the diet with a maximum of 2 g/day from supplements.

Consequently, the European Food Safety Authority (EFSA) (the European Union's food safety risk assessor) is being requested by Member States to review the available scientific data on these omega-3 fatty acids to determine an upper safe level of intake, as well as consider their safety in various subpopulations (*i.e.*, children, infants, pregnant/breastfeeding women). The results of this review by EFSA will be closely watched by government agencies around the world that are aware of the potential for increased consumption of omega-3 fatty acids by their citizens and by industry stakeholders interested in strengthening the arguments for the health claims of these supplements in their respective countries.

Leading up to this EFSA review, efforts are underway to calculate current intakes of omega-3 fatty acids from the background (*i.e.*, naturally occurring), as well as from dietary supplements and fortified foods. These estimates will provide EFSA with information about the scale of current intake and the potential intake from increased supplement use and food fortification. Additionally, the Norwegian Scientific Committee for Food Safety is carrying out a study to evaluate the negative and positive health effects of omega-3 fatty acids as constituents of food supplements and fortified foods, the results of which are expected to be published soon.

The results of these assessments will provide additional guidance to global government agencies in understanding the state of affairs surrounding omega-3 fatty acids, their consumption, and potential health claims.

**Stay tuned for more details.**



## In Profile with...Ilana Platt, PhD

Dr. Platt, a Scientific and Regulatory Consultant in Intertek Cantox's Food and Nutrition Group, obtained her PhD in Nutritional Sciences from the University of Toronto where the focus of her research pertained to the role of dietary fats in bone health. Following her PhD studies, and just prior to joining Intertek Cantox, Dr. Platt completed a postdoctoral research fellowship at the Harvard Schools of Medicine and Dental, where she further refined her expertise in the field of bone biology.

As Intertek Cantox's resident 'bone' expert, and as member of the Food and Nutrition Group's health claims division where Dr. Platt applies her expertise in nutritional sciences to critically evaluate

and interpret the body of scientific literature for the assessment of food health claim substantiation, Dr. Platt is especially suited to advise on and complete health claim feasibility assessments and substantiation dossiers for bone health claims. Earlier this year, the European Food Safety Authority (EFSA) published their Draft Guidance on the scientific requirements for health claims related to bone, joints, oral health and connective tissue (EFSA-Q-2010-01184), which was open for public consultation. EFSA's Technical report resulting from this consultation will be presented to the Panel on Dietetic Products, Nutrition and Allergies for possible endorsement. EFSA's Guidance on such claims provides an opportunity to ensure that substantiation dossiers are congruent with EFSA's standards for claim substantiation, and are met with favorable Opinions from EFSA. Please contact Dr. Platt ([iplatt@cantox.com](mailto:iplatt@cantox.com)) to find out how she can help your company succeed with a successful health claim petition.

At Intertek Cantox, our expertise and experience have been successfully applied to obtain and maintain international regulatory approvals for new products and our internationally-recognized product safety assessments have been used extensively in the development and commercialization of foods and personal care products.

Intertek Cantox is well-positioned to assist your company in evaluating the safety and efficacy of their products, as well as in the preparation of the necessary regulatory submissions to obtain pre-market approval in the intended jurisdictions. For more information on any of our services contact us at: [food@cantox.com](mailto:food@cantox.com)

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