



Glycemic Research Institute
WASHINGTON, D.C.

METABOLIC IMPACT OF
NON-NUTRITIVE SWEETENERS
FORMULATING WITH SUCRALOSE

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CLINICIAN'S FOCUS

This position paper is a compilation of current findings in the scientific literature regarding non-nutritive sweeteners (NNS), with a specific focus on formulating with Sucralose.

IDENTITY

SUCRALOSE is a non-nutritive sweetener (NNS) that is 600 times sweeter than sucrose. Discovered in 1976, Sucralose is currently used world-wide as an ingredient in processed foods, beverages, Nutraceuticals and Pharmaceuticals.



APPROVALS

Sucralose has been approved by the United States Food and Drug Administration (FDA), and the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Sucralose was first approved for use in Canada (marketed as Splenda) in 1991. Subsequent approvals came in Australia in 1993, in New Zealand in 1996, in the United States in 1998, and in the European Union in 2004. As of 2008, it had been approved in over 80 countries, including United States, Canada, Mexico, Brazil, China, India and Japan.

LARGEST INDEPENDENT ANALYSIS OF SUCRALOSE

In 2000, an international *independent* scientific committee conducted research on the potential toxicity (long and short term), as well as the carcinogenic, metabolic, stability, mutagenicity, immunotoxicity, teratology, and hydrolysis properties of Sucralose. This review by scientists is the largest independent study conducted on Sucralose.

The 25-page in-depth report included biotransformation studies on Sucralose, and addressed whether it could be degraded, possibly to a toxic metabolite, by human gut microflora, particularly if there was prolonged exposure.

The committee of scientists determined the following:

- The structure of the Sucralose molecule is such that it is extremely resistant to hydrolysis and its hydrolysis products, 4-CG and 1,6-DCF, are also resistant to further degradation. Further *in vitro* and *in vivo* studies were carried out to confirm the original data. These additional studies confirmed no hydrolysis problems.
- The 2-year chronic toxicity and carcinogenicity study showed evidence that Sucralose and its by-products are not carcinogenic or toxic.
- Thymus, spleen, white blood cell, lymphocyte, and immune issues related to Sucralose were raised and investigated. The committee concluded from all the relevant studies, (which included a specially enhanced study on cells, tissues and function of the immune system) that there is a clear “*no-effect*” at doses of 3000 mg/kg bw/day for any effects on lymphoid organs and the immune system that might occur from ingesting Sucralose.



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- Reports of thymus, lymphocyte, and total white blood cell problems were reported in test-animals (not humans). Analysis of this data further determined that these side-effects were age-related changes characteristic to the animals tested and not related to Sucralose.
- The committee concluded that Sucralose is acceptable as a sweetener for general food use and that a full Adequate-Daily-Intake (ADI) of 0-15 mg/kg bw/day can be established, based on application of a 100-fold safety factor to the overall *No Effect* of 1500 mg/kg bw/day.

Note: *No Effect* means that there was no negative evidence seen.

SUCRALOSE HYDROLYSIS PRODUCTS

The issue of the potential mutagenicity of Sucralose hydrolysis products, 1,6-DCF was raised by the UK (United Kingdom) Committee on Mutagenicity. This resulted in new *in vivo* and *in vitro* studies on 1,6-DCF, which were more meticulously designed than original studies.

Following ingestion of Sucralose, the new covalent binding (DNA binding) study analyzed tissue radioactivity levels of the liver, kidneys, stomach, small intestine, colon and bone marrow.

Results of the newer studies concluded that “No reproducible induction of UDS was seen following 1,6-DCF treatment.” The scientists and researchers reported that they did not have any further concerns about Sucralose by-products of hydrolysis. Chromosome and DNA aberrations in human lymphocytes *in vitro* were negative.

SUCRALOSE SAFETY ASSESSMENT

An assessment of *independent* safety studies on Sucralose has netted the following information:

- The extent and rate of absorption of Sucralose varies with the species; 30% in the mouse, 10% in the rat, 35% in the dog, and 15% in humans.
- The absorbed material undergoes limited metabolism; less than 1%-2% in humans, and the majority of Sucralose is excreted unchanged in the urine. The two metabolites



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are glucuronide conjugates. There is no evidence of hydrolysis or dechlorination in vivo.

- Sucralose does not interfere with any of the metabolic pathways responsible for glucose homeostasis in the rat or man.

Sucralose exerts no genotoxicity, reproductive/developmental toxicity, neurotoxicity or carcinogenic potential.

- The hydrolysis products of Sucralose are very slowly under acidic conditions, and according to Federal Register, the maximal projected intake of hydrolysis products is 285 micrograms per day (4.7 micrograms/kg/day).
- The hydrolysis products do not possess carcinogenic (cancer-causing) activity at a top dose of 2,000 ppm (100 mg/kg/day).

SUCRALOSE VS SPLENDA

Sucralose and Splenda are not the same formula. Sucralose is the base sweetener added to Splenda, while Splenda is a blend of Sucralose and high glycemic sugars.

SUGAR ALCOHOLS

Sugar alcohols, such as isomalt, xylitol, erythritol, mannitol, and sorbitol, maltitol, isomalt, lactitol, and maltitol, are viewed as alternatives to artificial sweeteners.

The issue with sugar alcohols is their ability to disrupt glycemic responses in humans and trigger gastrointestinal distress.

Researchers acknowledge that sugar alcohols can elevate blood glucose and glycemic levels. According to *Diabetes Spectrum 2004*:

“Despite claims by many food manufacturers, sugar alcohols do affect the postprandial blood glucose response in individuals both with and without diabetes.”

Isomalt, in particular, has been proven to cause disruptions in glycemic levels. In clinical trials, isomalt showed a marked increase in blood glucose levels. In clinical trials, isomalt, a sugar alcohol, was shown to cause moderate to profound gastric distress,



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including diarrhea and flatulence. In children age 4 to 14, isomalt was shown to cause diarrhea in 25 % of the children.

In diabetics, the glycemic response to sugar alcohols can be profound. Sorbitol has been known to elevate blood sugar slower than high glycemic sugars, but rapidly enough to cause postprandial blood sugar elevation. Significant blood sugar elevation is evidenced hours after consuming foods containing sugar alcohols and/or sugar alcohol syrups.

Studies on sugar alcohols have raised health concerns in the scientific community. These include adrenal medullary proliferative lesions, and cytogenetic effects in humans.

Canimoğlu S, Rencüzoğullari E (2006). "The cytogenetic effects of food sweetener maltitol in human peripheral lymphocytes". Drug Chem Toxicol 29 (3): 269–78

Lynch BS, Tischler AS, Capen C, Munro IC, McGirr LM, McClain RM (1996). "Low digestible carbohydrates (polyols and lactose): significance of adrenal medullary proliferative lesions". Regul. Toxicol. Pharmacol. 23 (3): 256–97. doi:10.1006/rtph.1996.0055. PMID 8812969

QUESTIONING THE LONG-TERM SAFETY OF SWEETENERS

Some sweeteners, such as Ace K (Acesulfame Potassium), are considered potentially dangerous and not acceptable for use by humans (*Center for Science in the Public Interest, Wash. D.C.*), yet they can be found in hundreds of foods and beverages in the grocery store. Sweeteners that are considered to be *natural*, such as sugar alcohols, can possess side effects and long-term health concerns. Natural licorice and licorice glycosides can cause spontaneous abortion in the first trimester of pregnancy.

Stevia, a natural product, has raised serious issues regarding safe dosage, form of glycoside, and long-term use in humans. In Vivo studies on Stevia have shown that it may increase insulin secretion through stimulation of the beta cells in the pancreas (*Metabolism, 49,2:208-14, 2000*). Just as cancer concerns have dogged the artificial sweeteners aspartame and saccharin, some researchers worry about the safety of Stevia. The FDA rejected Stevia petitions in the 1990's, after research linked Stevia with infertility in rats, and cancer in a laboratory setting. The FDA now says (2009) that *one* of the currently marketed reformulations of Stevia, rebiana Reb A glycoside, is Generally Recognized As Safe (GRAS).



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Chemistry researcher John Pezzuto isn't convinced. He cites a study he conducted that suggests a certain strain of Stevia can mutate DNA, a possible cancer risk. His findings are in tandem with prior research involving Stevia. "Given that there's the potential for a mutagenic response, why take the risk with Stevia?" asks Pezzuto, Dean of the University of Hawaii at Hilo College of Pharmacy. "I will not be consuming any myself."

In a letter to the Food and Drug Administration (FDA), the *Center for Science in the Public Interest* says the agency should require additional tests, including a key animal study, before accepting rebiana Reb A glycoside (Stevia) as Generally Regarded as Safe, or GRAS.

Even natural table sugar (sucrose) has side-effects such as elevation of blood glucose and insulin levels, increase in fat-cell size, exacerbation of hyperactivity and ADD in children, and cholesterol imbalance. Diligent monitoring of all available studies involving synthetic sweeteners is mandatory for scientists in the nutrition field. If any sweetener is found to possess validated health dangers, it is the obligation of the formulator and manufacturer to remove the offending ingredient from products ingested by humans and/or animals.

Nunes AP, Ferreira-Machado SC, Nunes RM, Dantas FJ, De Mattos JC, Caldeira-de-Araújo A (2007). "Analysis of genotoxic potentiality of stevioside by comet assay". Food Chem. Toxicol. 45 (4): 662-6

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FORMULATING WITH SUCRALOSE

Incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), play an important role in glucose homeostasis in both health and diabetes. Knowledge of the effects of Sucralose, as well as all other sweeteners, on gastric emptying and incretin hormone release is mandatory in formulating any product that will be ingested by humans.

The most prominent issue related to formulating with Sucralose and all other non-nutritive sweeteners (NNS), is the relationship between the sweetener and its ability to promote fat-storage, obesity, insulin resistance, and type 2 diabetes.

In order to formulate products which *do not* increase risk of diabetes, insulin resistance, and obesity, the following factors must be addressed:



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- Cephalic Response
- Glycemic Index & Load
- Diabetic Properties
- Adipose Tissue Fat-Storing Properties
- Kid-Friendly Appropriate Ingredients (see www.GRIKidFriendly.com)
- Insulin Resistance Properties

Many formulators and clinician's are unaware that Sucralose and all other non-nutritive sweeteners (NNS) ***promote hunger*** unless they are formulated with specific Low Glycemic, Non-Cephalic caloric ingredients.

Non-nutritive sweeteners (NNS) are chemosensory signaling compounds that influence ingestive processes and behavior. Therefore, all formulas and products made with artificial sweeteners and non-caloric sweeteners have the ability to stimulate the Cephalic Response and blood glucose excursions, leading to increased fat-storage and risk of type 2 diabetes.

In 2009, the *American Journal of Clinical Nutrition* published a meticulous study showing that:

- The addition of Non-Nutritive Sweeteners (NNS) to diets poses ***no benefit*** for weight loss or reduced weight gain without energy restriction.
- There are long-standing and recent concerns that inclusion of NNS in the diet ***promotes energy intake and contributes to obesity.***

Given the fact that ***non-nutritive sweeteners (NNS) can cause weight gain and stimulate insulin***, formulators are required to use discretionary applications when selecting a sweetening system for orally ingested products.

Documented wide ranges of concentrations and multiple combinations of non-nutritive sweeteners (NNS) in products further complicate the outcome of NNS, as each sweetener carries different metabolic properties.

With a plethora of sweeteners and sugars to choose from, the clinician and professional formulator need to possess an in-depth knowledge of the metabolic responses related to the large variety of sweeteners available for inclusion in orally ingested formulas.



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Without a working knowledge of the metabolic response of sweeteners and sugars used in formulas, the diabetic and obesity properties of foods, beverages, Nutraceuticals and Pharmaceuticals, is an unknown factor.

If the public consumer was made aware of the fat-storing and diabetic-properties of a specific product, they would be *unlikely* to select a product that was fattening and/or increased risk of diabetes and insulin resistance.

To expose the public to products without revealing their underlying metabolic properties is *irresponsible* on the part of the formulator, manufacturer, and marketer.

BUYER BEWARE

FEDERAL REQUIREMENTS FOR NON-NUTRITIVE SWEETENERS (NNS)

Federal government law dictates what information must be provided to consumers regarding sweeteners. Because all of the *approved* NNS are regarded as GRAS, producers and manufacturers are *not required to provide content data* on food labels or to release this information to federal agencies.

Because of these federal laws, consumers are at the mercy of the formulator and manufacturer to protect them from inappropriate dosage and use of non-nutritive sweeteners (NNS).

SUCRALOSE & CEPHALIC RESPONSE

The 2007 journal *NeuroImage* published a study conducted on Sucralose utilizing functional magnet resonance imaging, which proved that non-nutritive sweeteners (NNS) activate different human taste pathways in the human brain than natural sugars, such as sucrose.

The results of the trial are indicative of many other similar clinical trials that illustrate the significance of understanding how non-nutritive sweeteners (NNS) act on the human body.

The trials showed that:

- (1) Both sucrose and Sucralose activate functionally connected primary taste pathways;



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- (2) Taste pleasantness predicts left insula response;
- (3) Sucrose elicits a stronger brain response in the anterior insula, frontal operculum, striatum and anterior cingulate, compared to sucralose;
- (4) Only sucrose, but not Sucralose, stimulation engages dopaminergic midbrain areas in relation to the behavioral pleasantness response.

Thus, the brain response distinguishes the caloric from the non-caloric sweeteners, although the conscious mind does not.

Using non-nutritive sweeteners (NNS) in food, beverage, and Nutraceutical and Pharmaceutical formulas requires an in-depth understanding of the glycemic, insulinogenic, diabetic, and adipose tissue fat-storing properties of non-natural as well as natural sugars and sweeteners.

Without a clear metabolic-picture of the impact of sugars/sweeteners on the human body, the outcome of formulating nutritional supplements is not predictable.

Considering the growing global obesity and diabetes epidemic, Nutraceuticals and Pharmaceuticals should be required to conform to diet-friendly and diabetic-friendly guidelines, or at a minimum, to *reveal* to the public the obesity/diabetic properties of their products.

This objective can be accomplished by submitting food, beverage, nutrition, and Pharma products to the *Glycemic Research Institute for Government Certification Programs*, including *Board Approved Human In Vivo Clinical Trials* that reveal the glycemic, diabetic, Kid-Friendly, and obesity properties of orally ingested consumables.

[NeuroImage](#). Volume 39, 15 February 2008, Pages 1559-1569. Sucrose activates human taste pathways differently from artificial sweetener.

BOTTOM LINE

The bottom line in formulating with Sucralose, and other non-nutritive sweeteners (NNS) is that *all* non-nutritive sweeteners (NNS) used in formulas *must be combined* with a Low Glycemic, Non-Cephalic natural sweetener/sugar.



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This combinatorial equation is essential in *preventing negative metabolic excursions* in humans, such as weight gain and glycemic imbalance. The potential for non-nutritive sweeteners (NNS) to *promote* weight gain was illustrated by the *American Cancer Society* study which was conducted over a one-year period and included 78,694 women. Those who used non-nutritive sweeteners (NNS) were *significantly more likely to gain weight* than were non-users of NNS.

Beverages that contain NNS, with no calories/carbohydrates, or few calories and carbohydrates, are particularly capable of causing weight gain and imbalanced blood glucose levels, due to gastric emptying time.

Certain sweeteners, such as Stevia, though considered *natural*, are not acceptable for use in Non-Cephalic, Low Glycemic formulas.

Foods, beverages, Nutraceutical and Pharmaceutical products designed by formulators that are unfamiliar with the metabolic responses of the sweeteners and sugars they use in producing consumables, are ultimately playing *Russian Roulette* with consumers who expect that the products they ingest have been scrutinized for their ability to instigate increased risk of type 2 diabetes, insulin resistance, weight gain, and obesity.

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