



March 31, 2004

**Food and Drug Administration
Office of Nutritional Products, Labeling and Dietary Supplements (HFS-800)
5100 Paint Branch Parkway
College Park, MD 20740-3835**

To Whom It May Concern:

McNeil Nutritionals, Division of McNeil – PPC, Inc., hereby submits a health claim petition (original and one copy) to amend 21 CFR §101.80 to permit the use of a noncariogenicity dental health claim for sucralose.

Please communicate with the undersigned regarding questions, additional information needs, or to schedule a meeting with the petitioner.

Sincerely,

**Richard R. Reo
Director, Regulatory Affairs
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2004P-0294

CP 1

March 31, 2004

Name of Petitioner: McNeil Nutritionals
317 George Street
P.O Box 2400
New Brunswick, NJ 08903-2400

Subject of the Petition: To amend 21 CFR § 101.80 to authorize a noncariogenicity dental health claim for sucralose

**Food and Drug Administration
Office of Nutritional Products, Labeling and Dietary Supplements (HFS-800)
5100 Paint Branch Parkway
College Park, MD 20740-3835**

The undersigned, McNeil Nutritionals, submits this petition pursuant to Section 403(r)(4) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 343(r)(4), with respect to a noncariogenic dental health claim for the nonnutritive sweetener, sucralose.

Attached hereto, and constituting a part of this petition are the following:

- A. Preliminary Requirements
- B. Summary of Scientific Data
- C. Analytical Data
- D. Model Health Claim Language
- E. Appendices
- F. Claim for Categorical Exclusion under 21 C.F.R. § 25.32(p)
- G. Representative and Balanced Submission Statement

The undersigned will serve as the McNeil Nutritionals contact for all communications with FDA regarding this petition.

Sincerely,



Richard R. Reo
Director, Regulatory Affairs
for McNeil Nutritionals

A. **Preliminary Requirements: Eligibility for Health Claim under 21 CFR §101.14(b)**

In accordance with the requirements identified in 21 CFR § 101.14(b), the discussion that follows demonstrates the eligibility of sucralose for the proposed noncariogenic dental health claim:

1. **Association between a disease and the ingredient (21 CFR §101.14(b)(1)).**

A large body of scientific literature recognizes the relationship between dental caries and fermentable carbohydrates and has led FDA to establish a dental health claim regulation (21 CFR § 101.80) for sugar alcohols and other non-fermentable substances. The scientific literature establishing the relationship between dental caries and fermentable carbohydrate is described and referenced in the final rule for the "Sugar Alcohols and Dental Caries" health claim [Federal Register, Vol.: 61, 43433-43447 (1996)]. Additionally, the current dental health claim regulation observes that a large proportion of the US population continues to be affected by this disease. Under the current dental health claim regulation, a number of noncariogenic sweeteners and other food ingredients can be used to replace fermentable carbohydrates*.

*Note: Chemically, sucralose may be classified as a substituted carbohydrate. It is made from sucrose by a process that selectively replaces three of the sucrose molecule's hydroxyl groups with three chlorine atoms. Extensive data show that sucralose is not metabolized for energy in animals, man, or by oral bacteria. Accordingly, sucralose fits the definition of a non-fermentable carbohydrate.

2. **Consumption at decreased dietary levels (21 CFR § 101.14(b)(2)).**

Sucralose will not be consumed as a component of a conventional food at decreased dietary levels, thus this requirement does not apply.

3. Consumed at other than decreased dietary levels, the substance contributes taste, aroma, nutritive value, or other technical effect to the food and retains that attribute when consumed at levels that are necessary to justify that claim. (21 CFR § 101.14(b)(3)(i)).

As defined in 21 CFR 170.3(o)(19), sucralose is a nonnutritive sweetener, that is regulated as a direct food additive in accordance with 21 CFR §172.831: “for use as a sweetener in foods generally in accordance with current good manufacturing practice in an amount not to exceed that which is reasonably required to produce the intended technical effect”. Sucralose can be used to replace fermentable carbohydrates such as sugar, high-fructose corn syrup, honey, etc. It is not metabolized for energy in the body and is not metabolized by oral bacteria. Accordingly, it does not produce plaque and or acid (not “acidogenic”), both of which are conditions that contribute to caries formation. Sucralose also is highly stable to a broad range of food processing and shelf-storage conditions and, thus, retains its sweetness and non-fermentability, regardless of the use levels employed. Please refer to Federal Register, Vol.: 63, 16417-16433 (1998) and to Food Additive Petition, FAP 7A3987, which we incorporate by cross-reference, for information on the studies done to assess sucralose metabolism in animals and man. Please also refer to the appended published reports for information on the metabolism of sucralose by oral bacteria.

4. Consumed at other than decreased dietary levels, the substance must be a food ingredient and demonstrated to be safe and lawful to FDA’s satisfaction. (21 CFR § 101.14(b)(3)(ii)).

FDA has fully evaluated the use of sucralose in the food supply, concluded that it is safe for use as a direct food additive, and promulgated a regulation (21 CFR 172.831) setting out its conditions of use. Under this regulation, sucralose may be used in conventional foods and dietary supplements as a general-purpose sweetener in accordance with current GMPs. Thus, the use of sucralose is both safe and lawful. On April 3, 1998, FDA permitted the use of sucralose in 15 food and beverage categories (Federal Register, Vol.: 63,

16417-16433). On August 12, 1999, FDA broadened the approval by permitting the use of sucralose as a general-purpose sweetener (Federal Register, Vol.: 64, 43908-43909).

B. Summary of Scientific Data

1. Sucralose is noncariogenic as determined by various methodologies.

Over the last two decades, several scientific studies have investigated the potential for sucralose to either (a) support the growth of oral bacteria and plaque or (b) for such organisms to produce acid where sucralose is the only carbon-based substrate present. A review of the literature stemming from these investigations can be found in *Dental Considerations in Sucralose Use*, I. D. Mandel and V. L. Grotz, along with a general literature review. (Appendix E).

Well-designed studies, summarized below and found in the Appendix E, relied on a variety of *in vivo* (both human and animal) and *in vitro* test methodologies (see note below). Collectively, these studies have produced consistent results and demonstrate that there is significant scientific agreement among experts qualified to evaluate such claims that sucralose neither supports the growth of oral bacteria nor allows such bacteria to lower oral pH below 5.7. These scientific conclusions underscore the fact that sucralose is non-fermentable, noncariogenic and that it qualifies for a noncariogenic dental health claim.

Note: In order for a food to be able to bear the noncariogenic dental health claim, it must not lower plaque pH below 5.7 through the action of bacterial fermentation of its carbohydrate content. This pH represents a reasonable limit below which the production of acid in the mouth could begin to produce dental caries. The application of a plaque pH test arose from considering the possibility that while a non-fermentable sugar alcohol in and of itself would not drop plaque pH below 5.7, it could be present in foods with fermentable carbohydrates that could lower pH below this level. Consequently FDA

adopted a test protocol in 21 CFR § 101.80 (2)(ii)(C), i.e., the indwelling plaque pH test published in 1983 by T.N. Imfeld. However, the FDA stated that it does not require manufacturers who wish to make the health claim to perform the plaque pH test. Nor does FDA require that a specific procedure be used. Manufacturers are free to decide whether or how to satisfy themselves that their products are in compliance with the plaque pH test. FDA stated that the T. N. Imfeld protocol is the method that it would use to determine whether or not a health claim for a particular product was in compliance with the plaque pH requirement (*Federal Register*, 61: 43442 (1996)). We agree with the Agency policy allowing companies the discretion to use other appropriate science and technologies, as they evolve, to evaluate the potential for substances to undergo fermentation with subsequent acid production.

2. Significant Agreement From Publicly Available Scientific Literature and Among Qualified Experts In Supporting the Dental Health Claim (21 CFR § 101.70(f))

- A. D. A. Young and W. H. Bowen, *The Influence of Sucralose on Bacterial Metabolism* (1990)

This in vitro study examined the effects of sucralose on the growth of 10 different oral microorganisms and on plaque. The authors concluded that sucralose did not exhibit any ability to support the growth of these organisms nor was there any effect on plaque. Further, neither the organisms nor the plaque appeared to have the ability to produce acid from sucralose. The pH, for periods of up to one hour, in the test systems remained constant at 7.0. At the end of this period sucrose was added to the test systems resulting in a dramatic drop in pH to below 4.

- B. L. M. Steinberg, F. Odusola, J. Yip and I. D. Mandel, *Effect of Aqueous Solutions of Sucralose on Plaque pH* (1995)

This in vivo human study (N = 10) examined the effect of rinses containing sucralose alone, sucralose + maltodextrin, or sucralose + maltodextrin and

dextrose, on plaque pH. These were compared to equi-sweet solutions of sucrose. Plaque pH was measured in time intervals ranging from 2-60 minutes utilizing a glass reference and an antimony microelectrode. The minimum pH during that time interval was reported. The minimum pH for sucralose was reported as 6.56 compared to sucrose at 5.29. The authors concluded that sucralose is non-acidogenic and that commercial forms of sucralose-based table sweeteners are likely to be less cariogenic than sucrose.

C. W. H. Bowen, D. A. Young and S. K. Pearson, *The Effects of Sucralose on Coronal and Root-surface Caries* (1990)

This *in vivo* study used both normal and desalivated rats. The animals were variously infected with *S. mutans* (sobrinus) 6715-17 and with *Actinomyces viscosus* OMZ105E. Infection was monitored and, after 5 weeks, the animals were sacrificed. Caries were observed, as was cultivable flora. The authors concluded that the substitution of sucrose by sucralose in the diet did not promote colonization by *S. mutans* or the development of coronal caries. There was also a dramatic decrease in root-surface caries with sucralose compared to sucrose. The authors concluded that sucralose was non-cariogenic in rats.

D. D. B. Drucker and J. Verran, *Comparative Effects of the Substance-Sweeteners Glucose, Sorbitol, Sucrose, Xylitol, and Trichlorosucrose On Lowering Of pH By Two Oral Streptococcus Mutans Strains In Vitro* (1980)

This *in vitro* study investigated the acidogenicity of the subject sweeteners (Note: trichlorosucrose is a synonym for sucralose) and the effects of suspension media on results. The study demonstrated that sucralose very closely matches the acidogenicity of xylitol in all suspended media tested. Depending upon the suspending media, sucralose was shown to be less acidogenic than xylitol. The pH summary results for an incubation time of 2 hours are:

<u>Sweetener</u>	<u>Saline Media</u>	<u>Buffer Media</u>	<u>Broth Media</u>
Sucralose	5.62	6.89	6.48
Xylitol	5.32	6.99	6.41

- E. C. Meyerowitz, E. P. Syrrakou and R. F. Raubertas, Effect of Sucralose – Alone or Bulked with Maltodextrin and/or Dextrose – on Plaque pH in Humans (1996)

This *in vivo* study examined plaque pH by the use of a miniature pH electrode at time intervals from 2-60 minutes, after rinsing with a tea beverage. The minimum pH recorded during the 60 minutes was used as the basis for assessing relative acidogenic potential. The following are the results:

<u>Beverage</u>	<u>pH</u>
Unsweetened Tea	6.79
Tea with Sucralose	6.73
Tea with Sucrose	5.46
Tea with Sucralose + maltodextrin	6.20
Tea with Sucralose + dextrose/maltodextrin	6.02

The authors concluded that sucralose alone or in combination with maltodextrin, or dextrose/maltodextrin is significantly less acidogenic than sucrose when used as a sweetener in iced tea.

- F. W. H. Bowen, S. K. Pearson and J. L. Falany, Influence of Sweetening Agents in Solution on Dental Caries in Desalivated Rats (1990)

This *in vivo* study involved the use of desalivated Sprague-Dawley rats that were infected with *Streptococcus sobrinus* (6715-15) and *Actinomyces viscosus* (OMZ105E). Desalivated rats were used as a more severe test for cariogenicity. The authors looked at both caries formation and bacterial populations after 25 days. The rats were fed by gavage. The study also assessed the effects of fluoride. For the portion of the study that evaluated

caries formation in the absence of fluoride, the authors concluded that sucralose is noncariogenic.

Influence of Sweeteners on Caries in Desalivated Rats

	Control (distilled water)	Sucralose 16.7 mg%	Aspartame 55.6 mg%	Sorbitol 20%	Fructose 7.7%	Sucrose 10%
Sulcal (SD)	16.3 (9.8)	11.2 (4.9)	13.2 (7.2)	9.7 (7.2)	38.6 (3.6)	41.3 (6.7)
DS* (SD)	0	0	0	0.6 (1.1)	27.9 (7.2)	22.1 (10.2)
Smooth Surface (SD)	0	0	0	2.2 (6.4)	46.3 (14.3)	70.9 (28.8)

*DS = Slight dentinal involvement

3. A public health benefit will derive from the proposed dental health claim for sucralose (21 CFR § 101.70(f))

In the preamble to the final rule for "Food Labeling: Health Claims; Sugar Alcohols and Dental Caries" [*Federal Register 61:43433-43447 (1996)*], FDA establishes the need, the basis, and the method to enable consumers to make better-informed choices in foods to help protect their oral health. The reduction in dietary intake of fermentable carbohydrates is a cornerstone of this effort. Substituting sucralose for fermentable carbohydrates over a very wide range of foods and beverages would play a significant role to achieving this end. A noncariogenic dental health claim for sucralose will be an important addition to the list of substances now covered by the existing claim and will inform consumers of a wider variety of existing products that are noncariogenic.

Additional Summary Issues In Support of the Health Claim

1. With respect to replacing fermentable carbohydrates, particularly sucrose, there is no optimum sucralose use level beyond which no benefit would be expected. (21 CFR § 101.70(f)(B)(1))

2. Sucralose is a general-purpose sweetener regulated under 21 CFR § 172.831. The safety of sucralose for its intended use as a direct food additive has been thoroughly evaluated by the FDA. Sucralose poses no risk to any segment of the population from its intended use in foods and beverages. (21 CFR § 101.70(f)(B)(2))
3. There are no identifiable populations that would require special considerations. FDA has stated in the preamble to the final Health Claims rule in *61 Fed. Reg. 43436-43437 (1996)*: "Further, dental caries is a disease for which the general U. S. population, or an identified subgroup, is at risk, and the condition is prevalent in the general population.... The disease remains one of the most prevalent infectious diseases that causes substantial expense, pain, and work loss... Consequently, dental caries continues to be a disease of public health concern in this country." A dental health claim for foods and beverages containing sucralose and that are in compliance with 21 CFR § 101.80 would assist consumers by providing valuable information to permit them to make good oral care dietary choices. (21 CFR § 101.70(f)(B)(3))
4. Additional nutritional and health factors related to the consumption of sucralose-containing foods and beverages resides in the fact that sucralose provides sweetness without calories. The use of sucralose, to either partially or wholly replace sucrose, reduces caloric density while providing a satisfying, sugar-like taste to those products it sweetens. Sucralose-sweetened products can play an important role in decreasing caloric intake and helping to manage weight, one of the most significant and widely recognized health problems in America today. Sucralose-sweetened products are also a useful dietary tool for individuals with diabetes. Its use as a calorie-reducing ingredient, a replacement for sucrose, and its noncariogenicity are benefits that allow the U.S. population to simultaneously address multiple dietary health concerns.

The use of a noncariogenic dental health claim for those foods and beverages that contain sucralose and that meet the requirements of 21 CFR § 101.80 would not change dietary habits or other consumption patterns to cause individuals to restrict their dietary intake to a narrow spectrum of foods while at the same time ignoring the benefits of a varied and healthy diet. Sucralose would be one of several ingredients, like the sugar alcohols, to widen the dietary choices for consumers regarding their decisions aimed at helping to reduce dental caries. (21 CFR § 101.70(f)(B)(4))

5. Sucralose conforms to the definition of the term “substance” in 21 CFR § 101.14(a)(2). The general requirements for health claims define a “substance” as “a specific food or component of food”. Since sucralose is a regulated food ingredient intended for use as a component of conventional foods, it meets the eligibility requirement for a health claim.

C. Analytical Data (21 CFR § 101.70(f)(C))

There is no Association of Official Analytical Chemists (AOAC) methodology for assaying the sucralose content in the foods or beverages that would bear the dental health claim. Validated methods for assaying the sucralose content of a variety of foods and beverages are provided in the sucralose food additive petitions reviewed by FDA. Accordingly, we incorporate by reference the sucralose assay methods contained in FAP 7A3987 (Docket No. 87F-0086) and FAP 8A4624 (Docket No. 99F-0001).

D. Model Health Claim and Regulatory Amendments to: 21 CFR § 101.80

The following is added:

(c) (2) (ii) (C) sucralose

(e) (v) “Frequent eating of foods high in sugars and starches as between-meal snacks can promote tooth decay. Sucralose,

the sweetening ingredient used to sweeten this food, unlike sugars, may reduce the risk of dental caries.”

- (vi) “Frequent between-meal consumption of foods high in sugars and starches promote tooth decay. Sucralose, the sweetening ingredient in (name of food), unlike sugars, does not promote tooth decay.”

(2) Examples of the shortened claim for small packages:

- (v) “Sucralose does not promote tooth decay.”
(vi) “Sucralose may reduce the risk of tooth decay.”

E. Appendices

All references listed are attached in Appendix E.

F. Claim for a Categorical Exclusion from 21 C. F. R. § 25.32(p)

The Petitioner claims that the amendments submitted in this health claim petition are categorically excluded under 21 CFR § 25.32(p) and do not require either an Environmental Assessment or an Environmental Impact Statement. An environmental assessment of sucralose was conducted as part of the petition for the approval of sucralose as a direct food additive. As a result of this assessment, FDA concluded that sucralose would have no significant impact on the environment and that an environmental impact statement was unnecessary (*Federal Register*, Vol. 64, No. 155, pp. 43908-43909, August 12, 1999.)

G. Petitioner Statement of Responsibility

The undersigned acknowledges that to the best of his knowledge, this petition

is a representative and balanced submission that includes unfavorable information as well as favorable information, known to him to be pertinent to the evaluation of the proposed health claim.

Petitioner McNeil Nutritionals

Richard R. Reo, Director, Regulatory Affairs

APPENDIX E

A copy of each of the following is appended:

1. General literature search: *Dental Aspects of Sucralose*, March 16, 2004.
2. Mandel, ID, Grotz, VL: Dental Considerations in Sucralose Use. *J. Clinical Chem.* 13: 116-118, 2002.
3. Young, DA, Bowen, WH: The Influence of Sucralose on Bacterial Metabolism. *J. Dent. Res.* 69: 1480-1484, 1990.
4. Steinberg, LM, Odusola, F, Yip, J, Mandel, ID: Effect of Aqueous Solutions of Sucralose on Plaque pH. *Am. J. of Dent.* 8: 209-211, 1995.
5. Bowen, WH, Young, DA, Pearson, SK: The Effects of Sucralose on Coronal and Root-surface Caries. *J. Dent. Res.* 69: 1485-1487, 1990.
6. Drucker, DB, Verran, J: Comparative Effects of the Substance-Sweeteners Glucose, Sorbitol, Sucrose, Xylitol and Trichlorosucrose on Lowering of pH by Two Oral *Streptococcus Mutans* Strains *In Vitro*. *Arch. Oral Biol.* 24: 965-970, 1980.
7. Meyerowitz, C, Syrrakou, EP, Raubertas, RF: Effect of Sucralose – Alone or Bulked with Maltodextrin and/or Dextrose – on Plaque pH in Humans. *Caries Res.* 30: 439-444, 1996.
8. Bowen, WH, Pearson, SK, Falany, JL: Influence of Sweetening Agents in Solution on Dental Caries in Desalivated Rats. *Archs. Oral Biol.* 35: 839-844, 1990.