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August 29, 2006

Food and Drug Administration
Office of Nutritional Products, Labeling and Dietary Supplements (CPK1)
Harvey W. Wiley Federal Building
5100 Paint Branch Parkway
College Park, MD 20740-3835

To Whom It May Concern:

On behalf of Cargill, we hereby submit the enclosed health claim petition (an original and one computer readable disk containing the petition) to amend 21 C.F.R. § 101.80 to authorize a noncariogenicity dental health claim for isomaltulose.

Please date stamp a copy of this letter of transmittal and return for our files. If you need additional information or would like to schedule a meeting to discuss the enclosed petition, please do not hesitate to contact me.

Sincerely,

Diane B. McColl

Diane B. McColl
Counsel to Cargill

DBM/vam
Enclosure

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Date: August 29, 2006

Name of Petitioner: Cargill
15407 McGinty Road West
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Subject of the Petition: To amend 21 C.F.R. § 101.80 to authorize a noncariogenicity dental health claim for isomaltulose

U.S. Food and Drug Administration
Office of Nutritional Products, Labeling and Dietary Supplements (HFS-800)
Harvey W. Wiley Federal Building
5100 Paint Branch Parkway
College Park, MD 20740-3835

On behalf of our client, Cargill, we submit this petition pursuant to Section 403(r)(4) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 343(r)(4), requesting that the Food and Drug Administration (FDA) amend 21 C.F.R. § 101.80 to authorize a noncariogenicity dental health claim for isomaltulose. Attached, and constituting a part of this petition, Cargill provides the following:

A. Explanation of 21 C.F.R. § 101.14(b) Compliance.
B. Summary of Scientific Data.
C. Analytical Data.
D. Model Health Claim and Corresponding Regulatory Amendments.
E. Appendices.
F. Claim for a Categorical Exclusion per 21 C.F.R. § 25.32(p).
G. Representative and Balanced Submission Statement.
H. Compliance Statement for GLP, IRB and Informed Consent Requirements.

As counsel to Cargill, the undersigned will serve as the contact person for all communications with FDA concerning this petition.

Sincerely,

By: Diane B. McColl
Diane B. McColl

A. EXPLANATION OF 21 C.F.R. § 101.14(b) COMPLIANCE.

All requirements set forth in 21 C.F.R. § 101.14(b) are satisfied as provided below:

1. Significance of relationship between disease and substance (21 C.F.R. § 101.14(b)(1)).

Dental caries continues to affect a large segment of the United States population, notwithstanding its decline in recent years. The relationship between dietary fermentable carbohydrates, such as sucrose, and dental caries is well-established. As evidenced by the existing dental health claim approval, FDA recognizes the public health benefit resulting from use of non-fermentable sweeteners in place of fermentable sugars. See 21 C.F.R. § 101.80(a), (b).

2. Consumption at decreased dietary levels (21 C.F.R. § 101.14(b)(2)).

Isomaltulose will not be consumed as a component of a conventional food at decreased dietary levels, so this requirement is inapplicable.

3. Consumed at other than decreased dietary levels, the substance contributes taste, aroma, nutritive value or other technical effect, and maintains such effect at levels that justify the health claim (21 C.F.R. § 101.14(b)(3)(i)).

Isomaltulose is intended for use in foods in place of fermentable sugars as a nutritive sweetener. Isomaltulose is a noncariogenic carbohydrate consumed for its sweet taste and nutritive value.

4. Consumed at other than decreased dietary levels, the substance is a safe and lawful food or food ingredient. (21 C.F.R. § 101.14(b)(3)(ii)).

Based on a critical review of the scientific evidence, including, e.g., physical and chemical identity information, manufacturing process, publicly available safety data, corroborating unpublished safety data, intended uses, and consumption estimates, an independent panel of experts (the "Expert Panel"), qualified by scientific training and national and international experience to evaluate the safety of food ingredients, concluded that isomaltulose is generally recognized as safe ("GRAS") based on scientific procedures, under the conditions of intended use in foods. The use of isomaltulose in foods is therefore both safe and lawful.

Furthermore, earlier this year, FDA issued a letter to the Center for Regulatory Services, Inc., on behalf of SÜDZUCKER AG Mannheim/Ochsenfurt (hereinafter "SÜDZUCKER"), in which the agency indicated that it had "no questions" concerning SÜDZUCKER's conclusion that isomaltulose is GRAS under the conditions of use set forth in the company's submission. See FDA Letter to William A. Olson, Ph.D., Center for Regulatory Services, Inc. (GRAS Notice No. GRN 000184) (March 20, 2006). This further supports the safety and lawfulness of isomaltulose.

The Expert Panel's GRAS Report (hereinafter "GRAS Report"), including the references cited therein, is provided in Appendix A. The Expert Panel's GRAS Report and the unpublished data and information attached thereto constitute confidential proprietary trade secret information as well as confidential business information, and are therefore exempt from public disclosure under the Freedom of Information Act, 5 U.S.C. § 552(b)(4).

B. SUMMARY OF SCIENTIFIC DATA

A summary discussion of the scientific data, the evidence of significant scientific agreement and the public health benefit supporting a noncariogenicity dental health claim for isomaltulose are provided below.

1. Indwelling plaque pH data show isomaltulose is noncariogenic.

To qualify for the existing dental health claim, a food must not lower plaque pH below 5.7 by bacterial fermentation either during consumption or up to 30 minutes after consumption, as measured by the indwelling plaque pH test found in "Identification of Low Caries Risk Dietary Components," T.N. Imfeld, Volume 11, *Monographs in Oral Science*, 1983, Karger AG Publishing Co. See 21 C.F.R. § 101.80(c)(2)(ii)(C). Products that do not lower plaque pH below 5.7 by bacterial fermentation under the conditions of this test are considered noncariogenic.

Applying the indwelling plaque pH test cited by FDA in § 101.80, isomaltulose was shown to be noncariogenic in repeated tests (Imfeld, 2005). A copy of the test report is provided in Appendix B.

2. Evidence of significant scientific agreement among experts qualified by scientific training and experience to evaluate dental health claims. (21 C.F.R. § 101.70(f)).

In the dental health claim rulemaking, FDA found significant scientific agreement among qualified experts that the indwelling plaque pH test is the determinative test for evaluating whether a food or food ingredient is noncariogenic. Incorporation of this test into the final dental health claim rule evidences such significant scientific agreement. As described above, isomaltulose has been subjected to this test and found to be noncariogenic.

3. A public health benefit will derive from a dental health claim for isomaltulose. (21 C.F.R. § 101.70(f)).

FDA recognizes that "[t]o the extent that consumers can select foods that contain fewer fermentable carbohydrates, their chances of reducing their risk of developing dental caries are increased." 61 Fed. Reg. 43,433, 43,442 (Aug. 23, 1996) (preamble to final dental health claim rule). When isomaltulose is substituted for fermentable carbohydrates, the finished food contains fewer fermentable carbohydrates. A dental health claim for isomaltulose alerts consumers to the availability of a noncariogenic alternative. A public health benefit will result from a noncariogenicity claim for isomaltulose just as a public health benefit is derived from the existing noncariogenicity claims for sugar alcohols and tagatose.

4. There is no optimum level of isomaltulose beyond which no dental benefit would be expected. (21 C.F.R. § 101.70(f)(B)(1)).

The data summarized above indicate that the noncariogenic properties of isomaltulose are observed when it is used to replace fermentable sugars in formulating sugarfree products. Petitioner therefore proposes that the requested health claim be permitted when isomaltulose

replaces fermentable sugars in food products that otherwise meet the requirements of 21 C.F.R. § 101.80.

5. No known adverse health effects are associated with isomaltulose consumption under conditions of intended use in foods. (21 C.F.R. § 101.70(f)(B)(2)).

As noted above, a specially convened panel of qualified experts critically evaluated all data and information pertinent to the safety of isomaltulose under the conditions of intended use in foods and found such use to be GRAS for all segments of the general population. See GRAS Report (Appendix A).

6. No segment of the general population requires special consideration with respect to a dental health claim for isomaltulose. (21 C.F.R. § 101.70(f)(B)(3)).

All Americans, regardless of age, sex, and other factors, are susceptible to dental caries. Acknowledging this, FDA's regulation states that "Although there has been a decline in the prevalence of dental caries among children in the United States, the disease remains widespread throughout the population, imposing a substantial burden on Americans." 21 C.F.R. § 101.80(a)(3). A dental health claim in the labeling for foods containing isomaltulose would therefore provide important information to all Americans.

7. Other nutritional or health factors that are important to consider with respect to isomaltulose consumption. (21 C.F.R. § 101.70(f)(B)(4)).

The noncariogenic property of isomaltulose is one of its most important health attributes. In addition, in one study, isomaltulose exhibited a less pronounced effect on both the insulin and glucose response following ingestion of a 79 gram dose of isomaltulose as compared to the effects induced by 82 gram of dextrose (NutriScience, 2002).

8. Potential effect of use of isomaltulose on food consumption.

FDA recognizes that the existing dental health claim does not promote "consumption of a particular nutrient rather than focusing on a balanced diet." 61 Fed. Reg. at 43,435. Likewise, a dental health claim for isomaltulose would not encourage consumers to focus solely on a single nutrient. Rather, it would provide public health information enabling consumers to make alternative food choices that can help reduce their risk of dental caries.

9. Isomaltulose conforms to the definition of the term "substance." (21 C.F.R. § 101.14(a)(2)).

Section 101.14(a)(2) of FDA's health claim regulation defines the term "substance" as "a specific food or component of food." As a GRAS substance that may legally be used as a food or food ingredient, isomaltulose is a "substance" eligible for a health claim.

C. ANALYTICAL DATA.

Cargill's HPLC method, "Isomaltulose Purity (minor component quantification)," is provided in Appendix C. Cargill has also developed a validated method for assaying the isomaltulose content in representative foods that would be eligible to bear the dental health claim. The assay method and data establishing the validity of the method for assaying isomaltulose in food are provided in Appendix D. The validation data include a statistical analysis of the analytical and product variability.

D. MODEL HEALTH CLAIM AND CORRESPONDING REGULATORY AMENDMENTS.

1. Amendment to 21 C.F.R. § 101.80.

The model dental health claim proposed for isomaltulose would be the same as that provided for sugar alcohols and tagatose and dental caries in 21 C.F.R. § 101.80(e). Specifically, § 101.80 would be amended as follows:

§ 101.80 Health claims: dietary noncariogenic carbohydrate sweeteners and dental caries.

* * * * *

(c) * * *

(2) * * *

(i) * * *

(C) In specifying the nutrient, the claim shall state "sugar alcohol," "sugar alcohols," or the name or names of the substances listed in paragraph (c)(2)(ii) of this section, e.g., "sorbitol," "isomaltulose." D-tagatose may be identified as "tagatose."

(D) * * *

(E) * * *

(F) * * *

(G) * * *

(H) * * *

(ii) * * *

(D) Isomaltulose.

* * * * *

(e) * * *

(1) * * *

(vi) Frequent eating of foods high in sugars and starches as between-meal snacks can promote tooth decay. Isomaltulose, the sweetening ingredient used to sweeten this food, unlike sugars, does not promote tooth decay.

E. APPENDICES.

Appendix A. Expert Panel Report Concerning the Generally Recognized as Safe (GRAS) Status of Isomaltulose for Use in Foods (May 29, 2003).

GRAS Report (Appendix A) References:

Tab 1: Cheetham, P.S.J. 1982. The human sucrase-isomaltase complex: Physiological, biochemical, nutritional and medical aspects. In: Lee, C.K.; Lindley, M.G. (Eds.). Developments in Food Carbohydrate—3. Disaccharidases. Applied Science Publishers; London, Engl./Englewood, New Jersey, pp. 107-140.

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Tab 3: Goda, T.; Takase, S.; Hosoya, N. 1991. Hydrolysis of palatinose condensates by rat intestinal disaccharidases. Nihon Eiyo Shokuryo Gakkaishi 44(5):395-398.

Tab 4: Götze, H.; Maghdie, A. 1992. Fructosemalabsorption und dysfunktionelle gastrointestinale Beschwerden. Monatsschr Kinderheilkd 140(11):814-817.

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Tab 6: Hall, E.J.; Batt, R.M. 1996. Urinary excretion by dogs of intravenously administered simple sugars. Res Vet Sci 60(3):280-282.

Tab 7: Jonker, D.; Lina, B.A.R.; Kozianowski, G. 2002. 13-week oral toxicity study with isomaltulose (Palatinose®) in rats. Food Chem Toxicol 40(10):1383-1389.

Tab 8: Kashimura, J.; Nakajima, Y.; Benno, Y.; Endo, K.; Mitsuoka, T. 1989. Effects of palatinose and its condensate intake on human fecal microflora. Bifidobact Microflora 8(1):45-50.

Tab 9: Kashimura, J.; Kimura, M.; Kondo, H.; Yokoi, K.; Nishio, K.;

Nakajima, Y.; Itokawa, Y. 1990a. Effects of feeding of Palatinose and its condensates on tissue mineral contents in rats. Nihon Eiyo Shokuryo Gakkaishi 43(2):127-131.

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Tab 11: Kashimura, J.; Kimura, M.; Kondo, H.; Yokoi, K.; Nakajima, Y.; Nishio, K.; Itokawa, Y. 1992. Effects of Palatinose and its condensates on contents of various minerals in rat various tissues. Nihon Eiyo Shokuryo Gakkaishi 45(1):49-54.

Tab 12: Kashimura, J.; Hara, T. and Nakajinma, Y. 1993. Effects of isomaltulose-based oligomers on the human intestinal environment. Nihon Eiyo Shokuryo Gakkaishi 46(2):117-122.

Tab 13: Kawai, K.; Okuda, Y.; Yamashita, K. 1985. Changes in blood glucose and insulin after an oral palatinose administration in normal subjects. Endocrinol Jpn 32(6):933-936.

Tab 14: Kawai, K.; Okuda, Y.; Chiba, Y.; Yamashita, K. 1986. Palatinose as a potential parenteral nutrient: its metabolic effects and fate after oral and intravenous administration to dogs. J Nutr Sci Vitaminol 32:297-306.

Tab 15: Kawai, K.; Yoshikawa, H.; Murayama, Y.; Okuda, Y.; Yamashita, K. 1989. Usefulness of palatinose as a caloric sweetener for diabetic patients. Horm Metab Res 21:338-340.

Tab 16: Liao, Z.-H.; Li, Y.-B.; Yao, B.; Fan, H.-D.; Hu, G.-L.; Weng, J.-P. 2001. The effects of isomaltulose on blood glucose and lipids for diabetic subjects. Diabetes 50 (Suppl. 2):A366 [Abstract No. 1530-P].

Tab 17: Lina, B.A.; Smits-Van Prooije, A.E.; Waalkens-Berendsen, D.H. 1997. Embryotoxicity/teratogenicity study with isomaltulose (Palatinose®) in rats. Food Chem Toxicol 35(3&4):309-314.

Tab 18: Lina, B.A.R.; Jonker, D.; Kozianowski, G. 2002. Isomaltulose (Palatinose®): A review of biological and toxicological studies. Food Chem Toxicol 40(10):1375-1381.

Tab 19: MacDonald, I.; Daniel, J.W. 1983. The bioavailability of isomaltulose in man and rat. Nutr Rep Int 28(5):1083-1090.

Tab 20: Menzies, I.S. 1974. Absorption of intact oligosaccharide in health and disease. Biochem Soc Trans 2(5):1042-1047.

Tab 21: NutriScience. 2002. The Effect of Dextrose and Isomaltulose Ingestion on Serum Glucose and Insulin Levels in Healthy Volunteers. NutriScience Report 72.01.0003.

Tab 22: NutriScience. 2003. Study on the Intestinal Absorption of Isomaltulose, Trehalose, and Soy-Isoflavones. Report on Isomaltulose. NutriScience Report 72.01.0010/B.

Tab 23: Okuda, Y.; Kawai, K.; Chiba, Y.; Koide, Y.; Yamashita, K. 1986. Effects of parenteral palatinose on glucose metabolism in normal and streptozotocin diabetic rats. Horm Metab Res 18:361-364.

Tab 24: Park, Y.K.; Yetley, E.A. 1993. Intakes and food sources of fructose in the United States. Am J Clin Nutr 58(5 Suppl.): 737S-747S.

Tab 25: Porter, M.C.; Kuijpers, M.H.M.; Mercer, G.D.; Hartnagel, R.E. (Jr.); Koeter, H.B.W.M. 1991. Safety evaluation of *Protaminobacter rubrum*: Intravenous pathogenicity and toxigenicity study in rabbits and mice. Food Chem Toxicol 29(10):685-688.

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Tab 29: Truswell, A.S.; Seach, J.M.; Thornburn, A.W. 1988. Incomplete absorption of pure fructose in healthy subjects and the facilitating effect of fructose. Am J Clin Nutr 48(6):1424-1430.

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Tab 31: USDA. 2000. 1994-1996, 1998 Continuing Survey of Food Intakes by Individuals (CSFII) and Diet and Health Knowledge Survey (DHKS)

(On CD-ROM). U.S. Department of Agriculture (USDA); Riverdale, Maryland. [PB2000-500027 Supercedes PB98-500457].

Tab 32: Würsch, P. 1991. Metabolism and tolerance of sugarless sweeteners. In: Rugg-Gunn, A.J. (Ed.). Sugarless: The Way Forward. Elsevier Applied Science; New York, pp. 32-51.

Tab 33: Yamaguchi, K.; Yoshimura, S.; Inada, H.; Matsui, E.; Ohtaki, T.; Ono, H. 1986. A 26-week oral toxicity study of palatinose in rats. Oyo Yakuri 31(5):1015-1031.

Tab 34: Yamaguchi, K.; Yoshimura, S.; Inada, H.; Ozawa, K.; Kato, H.; Ono, H. 1987. A 26-week oral toxicity study of palatinose syrup in rats. Oyo Yakuri 34(1):1-16.

GRAS Report (Appendix A) Attachment 1: Curricula Vitae of Expert Panel

Appendix B. T. Imfeld, "Expert Report on the Safe for Teeth Properties of Isomaltulose Provided by Cerestar R&D Center, B-1800 Vilvoorde" (April 2005).

Appendix C. Cargill, Isomaltulose Purity (minor component quantification).

Appendix D. Cargill, Isomaltulose Methods for Yogurt, Carbonated Soft Drinks, and Tablets (May 2, 2006, May 27, 2006, and April 19, 2006, respectively).

F. CLAIM FOR A CATEGORICAL EXCLUSION PER 21 C.F.R. §25.32(p).

Petitioner claims that the regulatory amendments requested in this health claim petition are categorically excluded under 21 C.F.R. § 25.32(p) and do not require preparation of an environmental assessment or an environmental impact statement.

G. PETITIONER STATEMENT OF RESPONSIBILITY.

The undersigned confirms that to the best of her knowledge and belief this petition is a representative and balanced submission that includes unfavorable information as well as favorable information known to her to be pertinent to the evaluation of the proposed health claim.

Petitioner Cargill

By: _____

Kim Carson
Manager, Regulatory and Scientific Affairs
Cargill

H. PETITIONER STATEMENT OF GOOD LABORATORY PRACTICES, INSTITUTIONAL REVIEW AND INFORMED CONSENT COMPLIANCE

The nonclinical studies conducted by Cargill and described herein were conducted in accordance with good laboratory practices in effect at the time of such investigations.

The indwelling plaque pH test described herein was conducted in compliance with applicable requirements for institutional review and informed consent in effect at the time of such investigation.

By: _____

Kim Carson
Manager, Regulatory and Scientific Affairs
Cargill