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November 17, 2010

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Division of
Biotechnology and

BY FEDEX

Office of Food Additive Safety (HFS-255)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

Subject: Notice of a GRAS Exemption for Calcium Disodium EDTA and Disodium EDTA

Dear Sir/Madam:

Pursuant to the proposed rule outlined at 62 Fed. Reg. 18939 (April 17, 1997), Del Monte Foods hereby submits notification that use of calcium disodium EDTA and disodium EDTA as color, flavor, and/or texture retention agents in select packaged cooked sweet corn products with or without sauce, including mixed vegetable and similar products that contain less than 50% corn by weight, is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because the notifier has determined that such use is generally recognized as safe (GRAS).

To facilitate your review, this notification is submitted in the format suggested under proposed 21 C.F.R. § 170.36(c) (see 62 Fed. Reg. at 18961). Enclosed are three copies of the GRAS Exemption Claim, Additional Information summary, and GRAS Expert Panel Opinion.

Sincerely,

(b) (6)

Ricardo Carvajal
Counsel to Del Monte Foods

RC/sas
Enclosures

GRAS EXEMPTION CLAIM

We hereby claim that the use of calcium disodium ethylenediaminetetraacetic acid ("calcium disodium EDTA") and disodium ethylenediaminetetraacetic acid ("disodium EDTA") as color, flavor, and/or texture retention agents in select packaged cooked sweet corn products with or without sauce, including mixed vegetable and similar products that contain less than 50% corn by weight, is exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act because we have determined that such use of calcium disodium EDTA and disodium EDTA is generally recognized as safe (GRAS).

(1) Name and address of the notifier:

Name: Steven Bautista
Title: Director, Research & Development, Del Monte Foods
Address: 205 N. Wiget Lane, Walnut Creek, CA 94598
Phone: 925-944-7266
Fax: 412-222-4254

(2) Common or usual name of the substances that are the subject of the GRAS exemption claim:

Calcium disodium EDTA and disodium EDTA

(3) Applicable conditions of use of the notified substance:

(a) Foods in which the substance is to be used:

Packaged cooked sweet corn products with or without sauce, including mixed vegetable and similar products that contain less than 50% corn by weight.

(b) Levels of use in such foods:

Calcium disodium EDTA would be used at a maximum use level of 200 ppm, and disodium EDTA would be used at a maximum use level of 165 ppm.

(c) Purposes for which the substances are used:

Color, flavor, and/or texture retention agents.

(d) Description of the population expected to consume the substance:

Members of the general population who consume at least one of the products described above.

(4) Basis for the GRAS determination:

The basis of the GRAS determination is through scientific procedures.

(5) Review and Copying Statement:

The data and information that are the basis for Del Monte's GRAS determination are available for the Food and Drug Administration's (FDA's) review and copying at reasonable times at the offices of the notifier, or will be sent to FDA upon request.

(b) (6)

Name: Steven Bautista
Title: Director, R&D

Please address correspondence to:

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Additional Information
Summary

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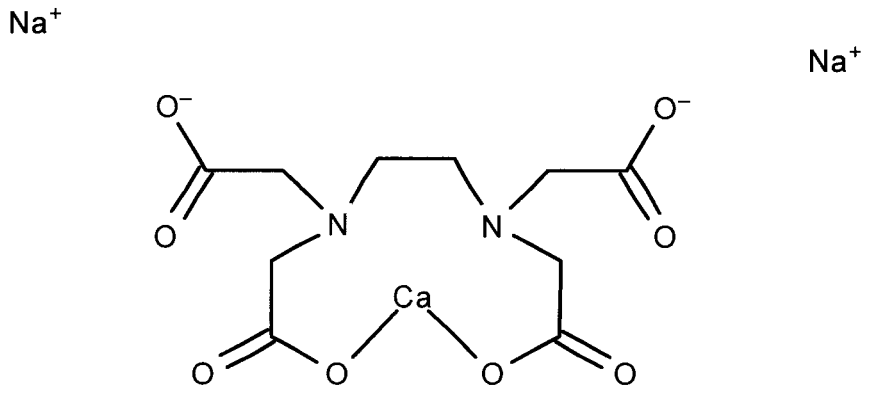
ADDITIONAL INFORMATION - GRAS Notice for Use of Calcium Disodium EDTA and Disodium EDTA as Color, Flavor, and/or Texture Retention Agents in Select Packaged Cooked Sweet Corn Products

I. Identity and Manufacture of the Notified Substance (proposed 21 C.F.R. § 170.36(c)(2)

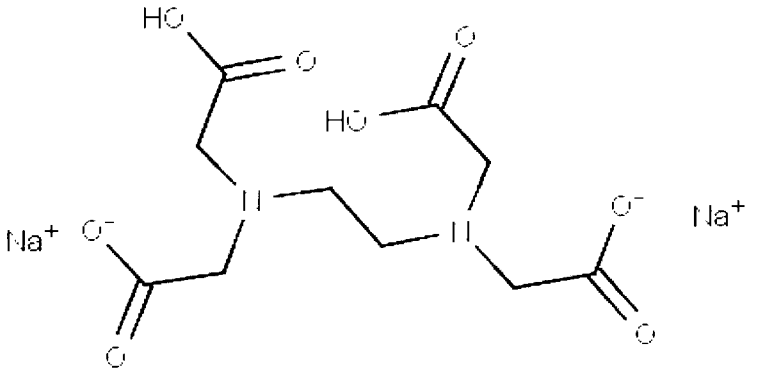
Calcium disodium ethylenediaminetetraacetic acid ($C_{10}H_{12}CaN_2Na_2O_8$; CAS No. 23411-34-9), commonly called calcium disodium EDTA, is a white to off-white, crystalline or granular powder with a faint, saline-like taste that is odorless and hygroscopic. It has a molecular weight of 410.3 and its physical structure is depicted in Figure 1.

Figure 1. Calcium Disodium EDTA structure



Disodium ethylenediaminetetraacetic acid ($C_{10}H_{16}N_2Na_2O_8$; CAS No. 139-33-3), commonly called disodium EDTA, is a white to off-white, odorless crystalline powder. It has a molecular weight of 372.24 and its physical structure is depicted in Figure 2.

Figure 2. Disodium EDTA Structure



The calcium disodium EDTA and disodium EDTA products that are the subject of this GRAS determination meet appropriate food-grade specifications, as published in the Food Chemicals Codex ("FCC"). The calcium disodium EDTA and disodium EDTA that are the subject of this GRAS determination are produced consistent with cGMP in the same manner as the approved food additives calcium disodium EDTA and disodium EDTA. Additional information on the method of manufacture can be provided upon request.

II. Information on Any Self-Limiting Levels of Use (proposed 21 C.F.R. § 170.36(c)(3)

There are no known self-limiting levels of use for calcium disodium EDTA or disodium EDTA. The levels to be added will not exceed 200 ppm and 165 ppm, respectively.

III. Detailed Summary of Basis for GRAS Determination (proposed 21 C.F.R. § 170.36(c)(4)

A. Discussion of Scientific Information Relied on to Establish Safety

1. Exposure

The consumption of packaged cooked sweet corn from the proposed new uses was based on food consumption records collected as part of the National Health and Nutrition

Examination Surveys (NHANES) conducted in 2003-2004 and 2005-2006. Using the NHANES consumption data, the estimated 2-day average intakes of packaged cooked sweet corn from proposed new uses in canned corn products for the U.S. population 2 years and older was estimated (as used in reference to the proposed corn products, the term "canned" encompasses all hermetically sealed containers.) The intakes of EDTA from cooked sweet corn in select products were calculated by multiplying each NHANES respondent's 2-day average cooked sweet corn intake with the maximum proposed level of EDTA (200 ppm). The estimate of 90th percentile per user EDTA intake from the proposed new use in select packaged cooked sweet corn products is 0.34 mg/kg bw/day (see Table 1).

Estimated total dietary intake of EDTA includes currently approved/existing uses and the proposed new uses of calcium disodium EDTA and disodium EDTA. In the most recent GRAS Notification (GRN 000178, 2005) for sodium iron EDTA, Akzo Nobel estimated the 90th percentile combined intake of EDTA from the food uses of sodium iron EDTA in GRN 000152, GRN 00178, and currently regulated uses of calcium disodium EDTA and disodium EDTA to be 1.4 mg/kg bw/day (for a 60 kg person). Taken together with the per user 90th percentile intake of EDTA from the proposed use of calcium disodium EDTA or disodium EDTA at a maximum concentration of 200 ppm in select packaged cooked sweet corn products, the calculated cumulative intake of EDTA was conservatively estimated to be 1.74 mg/kg bw/day (i.e., 1.4 mg/kg bw/day + 0.34 mg/kg bw/day = 1.74 mg/kg bw/day).

This estimate of total intake represents an overestimation, since it assumes that all packaged cooked sweet corn consumed from one of these food categories contained EDTA at 200 ppm and that the individual also consumed other foods containing EDTA (e.g., that they consume 1.4 mg/kg bw/day from other foods and that they are the upper 90th percentile user) plus 0.34 mg/kg bw/day from the proposed corn-containing foods (and they are also the 90th percentile user from this category).

Table 1. Estimated Daily Intake of EDTA from Cooked Sweet Corn in Select Products by the U.S. Population 2+ yr; NHANES 2003-2006, 2-day average (mg/kg bw/day)

EDTA	N	Per Capita		Per User	
		Mean	90th	Mean	90th
U.S. Population 2+ yr	1,257	0.01*	0*	0.15	0.34

*Based upon the NHANES survey, less than 5% of the population consumes a sweet corn containing food on any given day. Therefore, the per capita consumption amount is 0 even at the 90th percentile of the total population. The per capita estimate of the mean intake includes consumers and non consumers. The per capita mean is thus larger than the 90th percentile for these foods since it includes the 5% percent of the population who did consume a sweet corn containing food.

2. Safety

The safety of calcium disodium EDTA, disodium EDTA, and many other salts of EDTA has been reviewed by the FDA, the EPA, JECFA and the Cosmetics Ingredient Review Board (CIRB, Lanigan and Yamarik 2002), and has been the subject of reviews in the public literature. Metal ions on the EDTA-metal complex are freely exchanged once in the digestive tract. Therefore, the various EDTA salt forms are expected to have essentially similar toxicological potential and metabolic fate in the body, regardless of whether EDTA is consumed as the calcium, sodium, or sodium-iron salt form. Hence, the following safety review focuses on EDTA, irrespective of the EDTA-metal complex to which exposure occurred. An overall summary of available safety information in animals and humans follows.

(i) Preclinical Studies

Absorption, Distribution, Metabolism, and Excretion

EDTA is poorly absorbed following ingestion by humans as well as animals. EPA (2006) indicated an upper limit of absorption of 20%, with elimination occurring primarily via the kidneys (95%). Studies in humans with radiolabelled CaEDTA in gelatin capsules indicated that a maximum of 5% of the radioactivity associated with EDTA was absorbed. Most of the dose (approximately 95%) was recovered unaltered in the feces and urine within 3 days of administration. Intravenous and intramuscular administration of CaEDTA in humans produced similar results, with >98% of the dose being excreted unaltered primarily in the urine (Foreman and Trujillo 1954, as cited in Heimbach et al 2000). Similar results have been reported following ingestion of radiolabelled CaEDTA in rats, with 98% of the dose appearing unaltered in the feces and urine within 24 hours of administration. Less than 0.1% of the radioactivity was reported in respiratory CO_2, indicating a lack of metabolism of EDTA (Foreman et al 1953, as cited in Heimbach et al 2000). Rats fed disodium EDTA at dietary levels of 0.5, 1.0, and 5.0% excreted 99.2, 98.2, and 95.7% of the dose in the feces (JECFA 1967).

Acute Toxicity

EPA (2006) states that EDTA chemicals are not acutely toxic via the oral route of exposure and are mild skin irritants and severe eye irritants. Oral LD50 values of 7,000-12,000 mg/kg have been reported in various animal species for calcium disodium EDTA and 2,000-2,200 mg/kg for disodium EDTA (JECFA 1967; Heimbach et al 2000). Diarrhea has been reported in rats following a single oral dose of 250 mg EDTA/animal (Foreman et al 1953).

Subchronic Toxicity

Numerous studies have been conducted in animals employing calcium disodium EDTA and disodium EDTA. Rats were fed a diet containing 0, 0.5, 1.0, or 5.0% disodium EDTA (equivalent to approximately 0, 500, 1000, or 5000 mg/kg/day) and 0 or 1.5% calcium disodium EDTA (equivalent to approximately 1500 mg/kg/day) in normal or low-mineral diets for 90-120 days, with diarrhea and reduced food consumption reported in only high-dose group rats fed disodium EDTA (Yang 1952, as cited in Heimbach et al 2000) and reduced weight gain in rats fed calcium disodium EDTA at 1500 mg/kg/day.

Chan (1956, as cited in Heimbach 2000) fed weanling albino rats a purified, low-mineral diet (0.54% Ca and 0.013% Fe) containing either 0.5 or 1.0% disodium EDTA or calcium disodium EDTA for 90 days (equivalent to approximately 500 or 1000 mg/kg bw/day, respectively). Signs of diarrhea and growth retardation were observed in the 1% disodium EDTA dose group only. Extension of dosing for an additional 115 days (205 days total) resulted in growth retardation in the groups fed diets containing 1.0% of each EDTA chelate, and increased blood coagulation times, blood serum calcium levels, and an anemic appearance in the group fed a 1.0% disodium EDTA diet. The authors speculated that complexing of calcium in the blood may have interfered with the coagulation mechanism. Gross and histological examinations of the liver, kidney and spleen revealed no significant abnormalities. A substantial degree of dental erosion and lower ash content of bone was observed in animals receiving a low mineral diet with 1% disodium EDTA, but not in rats fed a 1% disodium EDTA diet with adequate mineral levels.

In 1964, BIBRA reviewed the subchronic toxicity studies of Yang and Chan on calcium disodium EDTA and disodium EDTA summarized above and concluded that "the presence of minute quantities of disodium EDTA (10-100 ppm) in foods would not be expected to have any significant effect on health," and that adult diet containing as much as 4000 ppm EDTA would still be far less than the lowest quantity fed to rats (0.5% in the diet) (Heimbach et al 2000). EPA (2006) concluded that any EDTA-related toxic effects were related to metal deficiencies, especially in zinc that result from the chelating properties of EDTA. Provided that the trace metals needed by the body are maintained, EDTA can be consumed at very high exposure levels of 1000 mg/kg bw /day or greater without adverse effect.

Chronic Toxicity

Chronic toxicity studies have been conducted in rats, mice, rabbits, and dogs with various EDTA compounds including calcium disodium EDTA and disodium EDTA (Heimbach et al 2000). Mongrel dogs (one male and three females/group) were fed 0, 50, 100, or 250 mg/kg/day of calcium disodium EDTA in the diet for 12 months. No adverse effects were

noted in appearance, health status, hematology, urinalysis or blood chemistry parameters, bone or dental calcification, or gross and histopathological findings (Oser et al 1963).

Rabbits were treated orally with 250 mg/kg/day calcium disodium EDTA for 2 years without adverse effect (FDA 1998b, as cited in Lanigan and Yamarik 2002).

Trisodium EDTA was studied by the National Cancer Institute (NCI) in a 2-year carcinogenicity study in male and female Fischer 344 rats and $B6C3F_1$ mice. Mice were fed trisodium EDTA in the diet at concentrations of 0, 3750, or 7500 ppm (equivalent to approximately 535 and 1070 mg/kg/day in mice and 375 and 750 mg/kg/day in rats) for 103 weeks. Trisodium EDTA was not associated with any adverse effects on clinical signs of toxicity or survival or an increased incidence of tumors in either rats or mice. In addition, as an extension of the 90-day study (Yang 1952, as cited in Heimbach 2000) reported above, rats were fed up to 5% disodium EDTA in the diet for 2 years without continued observation of the diarrhea and reduced food consumption observed at 90 days. EPA (2006) has concluded that there is no concern for EDTA with regard to carcinogenicity.

Reproductive and Developmental Toxicity

Numerous reproductive and developmental toxicity studies have been conducted in animals and have been reviewed by EPA, JECFA, and Heimbach et al (2000). A multigeneration study (Oser et al 1963) was conducted in Wistar rats (25 animals/sex/group) administered calcium disodium EDTA in a nutritionally adequate diet for four successive generations at doses of 0, 50, 125, and 250 mg/kg/day for up to 2 years. Potential adverse effects on reproduction and lactation were examined. Ten rats from each treatment group representing the F_1 generation were raised to maturity and allowed to produce two litters; a similar regimen was followed for the F_2 and F_3 litters. The second litters from each generation (control and 250 mg/kg bw/day groups only) were maintained without change in dietary treatment until the end of the 2-year period for the F_0 generation. The study design allowed for observations to be made on rats receiving test diets for 0.5, 1, 1.5, or 2 years in the F_3, F_2, F_1 and F_0 generations, respectively. The authors reported no treatment-related differences in growth, survival, gross or histopathological findings, reproductive performance, or hematology, urinalysis or blood chemistry parameters when animals were fed up to 250 mg/kg bw/day calcium disodium EDTA in the diet (reported by the authors to be equivalent to a dietary concentration of 5000 ppm) for four generations. The authors concluded that nutritionally adequate diets (as were administered in this study) are required to avoid mineral deficiencies that can result in reproductive and developmental toxicity in animals.

Numerous studies with disodium EDTA administration in the diet resulted in adverse effects on reproductive and developmental endpoints including impaired reproduction and an increased incidence of malformations (Swenerton and Hurley 1971, Kimmel 1977, and Schardein et al 1981, as cited in Heimbach et al 2000). However, the reproductive and developmental effects only occurred in studies where the trace metals were removed from the maternal body, thus were not available to the developing fetus, and where dams were not fed nutritionally adequate diets that could replenish those essential nutrients, especially zinc.

Swenerton and Hurley (1971) fed pregnant female Sprague-Dawley rats a purified diet containing 2 or 3% disodium EDTA (equivalent to approximately 2000 or 3000 mg/kg bw/day, respectively) and 100 ppm zinc carbonate during gestation. All females fed disodium EDTA had moderate to severe diarrhea. The 2% disodium EDTA diet caused a slight impairment of reproduction and an increased incidence of malformations (including brain, cleft palate, malformed digits, clubbed legs and malformed tails). The 3% disodium EDTA diet severely affected reproduction. In a second study, pregnant females were fed either the control diet with 100 ppm zinc, 3% disodium EDTA with 100 ppm zinc or 3% disodium ETDA supplemented with 1000 ppm zinc on gestation days 6-21. Significant increases in malformations were seen in animals given 3% disodium EDTA at the low zinc level of 100 ppm but not with 1000 ppm zinc. The investigators concluded that the observed teratogenic effects were not attributable to EDTA itself but rather to an induced deficiency of zinc that was insufficient to support normal fetal development.

Kimmel (1977) demonstrated that the route of administration of disodium EDTA had a marked effect on reproductive and developmental toxicity. Groups of pregnant rats were given disodium EDTA in a semipurified diet at a dose of 954 mg/kg bw/day (3% in diet); by gavage at a dose of 1250 mg/kg bw/day (given as a split dose of 625 mg/kg bw twice/day) or 1500 mg/kg bw/day (given as a split dose of 750 mg/kg bw twice/day); or by subcutaneous injection at a dose of 375 mg/kg bw/day. Animals in all groups were dosed on gestation days 7 through 14 and fetuses were examined on gestation day 21 for skeletal and visceral malformations. Maternal toxicity was evident by decreased food consumption, diarrhea, and reduced weight gain in groups treated by all three dose routes. Dietary administration of EDTA resulted in no maternal deaths, but malformations were seen in 71% of the offspring. By gavage, EDTA was more toxic to the dams, but resulted in fewer malformed offspring (20.5% at 1250 mg/kg bw/day) than did dietary administration. By subcutaneous injection (at a dose about one-third to one-half that of the other routes), EDTA was lethal to 24% of the dams, but produced a low rate (4.3%) of malformed offspring. The authors speculated that the mechanism by which EDTA induced developmental toxicity was the binding of zinc by EDTA resulting in zinc deficiency during embryonic development. In support of this proposed mechanism, Kimmel noted

that the observed malformations were similar to those seen in zinc-deficient rats, and that the findings of their laboratory were consistent with Swenerton and Hurley (1971) when a low-zinc diet was employed.

Shardein et al. (1981) investigated the developmental toxicity of EDTA (acid form), disodium EDTA, trisodium EDTA, tetrasodium EDTA or calcium disodiumEDTA. Equimolar doses of 1000 mg/kg bw/day were given in two split doses by gavage on days 7-14 of gestation to groups of 20 pregnant rats that were maintained on a nutritionally complete, standard lab chow diet. Dams were sacrificed on day 21 of gestation and fetuses were examined for abnormalities. Diarrhea and decreased food intake and weight gain were observed in all treated groups. EDTA, disodium EDTA, and tetrasodium EDTA had the greatest effects on weight gain. None of the test compounds significantly affected litter size, fetal mortality, or rate of malformations. The absence of reproductive and developmental abnormalities in this gavage study contrasts with the high incidence of malformations noted by Kimmel (1977) in gavage studies performed with animals receiving a semipurified diet with limited levels of zinc and other micronutrients.

Genotoxicity

Numerous *in vitro* and *in vivo* assays have been conducted with a number of EDTA salts. A literature review by Heindorf et al (1983, as cited in Heimbach et al 2000) indicated that EDTA inhibited DNA synthesis and repair and produced a low degree of chromosomal damage and gene mutations *in vitro*. However, FDA has concluded that the effects noted were most likely spurious indications of genotoxic potential resulting from the chelation of cations important as enzymatic cofactors involved in cellular DNA synthesis (Lerner et al 1986, as cited in Heimbach et al 2000). Trisodium EDTA was not mutagenic in the Ames assay (*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 and *Escherichia coli* WP uvrA) and the L5178Y mouse lymphoma cell forward mutation assay with or without metabolic activation. Heimbach et al (2000) observed that the overall genotoxic findings associated with EDTA indicated that EDTA-metal complexes lack significant genotoxic potential under conditions that do not deplete essential trace elements required for normal cell function.

Allergenicity

Disodium EDTA was evaluated for the potential to produce an allergic response in male guinea pigs administered on alternate days 10 injections of 0.1 ml of a 0.1% disodium EDTA solution (Yang 1952, as cited in Heimbach 2000). No sign of allergenicity was noted after a challenge injection of a 0.1% solution given 2 weeks after the last injection. In a human skin-sensitization study with calcium disodium EDTA, Raymond and Gross

(1969, as cited in Heimbach 2000) reported a positive response in 3/50 individuals that cross-reacted with ethylenediamine. They concluded that given the widespread experience with calcium disodium EDTA and the absence of reports of adverse reactions, it was at most a weak sensitizing agent.

(ii) Human Studies

Calcium disodium EDTA and disodium EDTA are commonly employed as parenterally administered chelating agents in the treatment of heavy metal toxicity. The heavy metal poison is exchanged with the calcium molecule, mobilized, and then removed via the kidneys. A long history of use in clinical applications has demonstrated its lack of accumulation in the body and safety in man.

EDTA is used therapeutically in adults and pregnant women. A therapeutic dose of 1.2 to 2.0 grams per day is generally given to adults. EDTA treatment of pregnant women is possible without affecting the development of the fetus. Treatments of EDTA to pregnant women include 75 mg/kg/day calcium disodium EDTA for 7 days, and 1 gram twice a day for 3 days, under medical supervision. Healthy, normal infants were delivered 4 weeks and 8 days after chelation therapy, respectively (EPA, 2006).

In addition, no adverse effects on the balance of minerals, such as calcium, copper, zinc and magnesium were reported in individuals administered sodium iron EDTA-fortified foods in long term trials (Garby and Areekul, 1974; Solomons, et al., 1979; Ballot et al., 1989b; Viteri et al., 1995, as cited in GRAS Notification No.152; http://www.accessdata.fda.gov/scripts/fcn/gras_notices/grn_152.pdf). Doses ranged up to 15 mg iron/kg body weight, approximately 75-times greater than the proposed use at the upper 90th percentile of consumption. Based on these observations and findings in rats (Hurrel et al., 1994; Appel et al., 2002, as cited in GRAS Notification No. 152), the Expert Panel for GRAS Notification No. 152 concluded that sodium iron EDTA at the levels of iron EDTA proposed would not interfere with the absorption of other metals such as copper, zinc, magnesium and calcium.

GRAS Notification No. 178 also cited studies in humans that demonstrated no adverse effects of FeNaEDTA on the absorption of zinc, calcium, and manganese. Solomons et al. (1979, as cited in GRAS Notice 178) reported no significant effects on absorption of zinc in healthy adult volunteers following consumption of a standard Guatemalan diet fortified with 25 mg of zinc and coffee sweetened with sugar fortified with 15 mg FeNaEDTA when compared to controls. Similarly, no significant differences in zinc absorption were reported following consumption of aqueous solutions containing 25 mg zinc with 15 or 40 mg FeNaEDTA; however, zinc absorption was significantly decreased following consumption of aqueous solutions with 115 or 308 mg FeNaEDTA. The decrease in absorption was

attributed to the EDTA moiety. The authors concluded that fortification of sugar with FeNaEDTA at a level of 1,000 ppm would not interfere with zinc nutriture. Davidsson et al (1994, as cited in GRAS Notice 178) concluded that the addition of FeNaEDTA to foods would not have detrimental effects on the metabolism of zinc and calcium in humans based on the results of a 28-day crossover study in which healthy women consumed bread fortified with 10 mg iron from either FeNaEDTA or FeSO. In addition, they concluded that the addition of FeNaEDTA to foods with a low bioavailability might result in increased zinc absorption and iron bioavailability, which will be particularly important in developing countries where low-bioavailable foods form the basis of the staple diet.

(iii) Safety Study Summary

Calcium disodium EDTA, disodium EDTA, and related EDTA salts are poorly absorbed in the GI tract and are not acutely toxic. They are not mutagenic or genotoxic under conditions that do not deplete essential trace elements required for normal cell function. EDTA compounds are not carcinogenic in rodent bioassays and have no reproductive or developmental toxic effects when diets are supplemented with essential nutrients including zinc. Subchronic and chronic toxicity studies conducted in animals reveal that EDTA compounds exhibit general adverse effects only at very high exposure levels of approximately 1000 mg/kg bw/day and greater. In addition, calcium disodium EDTA as well as disodium EDTA have a long history of safe use as FDA approved direct food additives.

B. Discussion of Information Inconsistent With the GRAS Determination

We are not aware of any reports of investigations or other information that may appear to be inconsistent with the GRAS determination.

C. Basis for Conclusion That There Is Consensus Regarding Safety

The enclosed GRAS Expert Panel Opinion provides the basis for concluding that there is consensus among experts qualified by scientific training and experience to evaluate the safety of substances added to food that there is reasonable certainty that the substance is not harmful under the intended conditions of use.

References

Environmental Protection Agency (EPA). 2006. Ethylendiaminetetraacetic acid chemicals: exemptions from the requirement of a tolerance. Federal Register, March 8. 71(45): 11563-11570.

Food Chemical Codex, V6. 2008. Monographs of calcium disodium EDTA and disodium EDTA, pp. 131-132, 283-284. United Book Press, Inc., Baltimore, MD.

Foreman, H., Vier, M., and Magee, M. 1953. The metabolism of C^{14}-labeled ethylenediamintetraacetic acid in the rat. J. Biol. Chem. 203: 1045-1053.

Heimbach, J., Rieth, S., Mohamedshah, R., Slesinski, R., Samuel-Fernando, P., Sheehan, T., Dickmann, R., and Borzelleca, J. 2000. Safety assessment of iron EDTA (sodium iron (Fe3) ethylenediaminetetraacetic acid): summary of toxicological, fortification and exposure data. Food and Chemical Toxicology. 38: 99-111.

JECFA. 1967. Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour-treatment agents, acids and bases. Joint FAO/WHO Expert Committee on Food Additives. WHO Tech. Rep. Ser. No. 339.

JECFA. 1974. Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers and thickening agents. Joint FAO/WHO Expert Committee on Food Additives. WHO Tech. Rep. Ser. No. 539.

Kimmel, C.A. 1977. Effect of route of administration on the toxicity and teratogenicity of EDTA in the rat. Toxicology and Applied Pharmacology 40: 299-306.

Lanigan, R.S. and Yamarik, T.A. 2002. Final report on the safety assessment of EDTA, calcium disodium EDTA, diammonium EDTA, dipotassium EDTA, disodium EDTA, TEA-EDTA, tetrasodium EDTA, tripotassium EDTA, trisodium EDTA, HEDTA, and trisodium HEDTA. Int. J. Toxicol. Suppl 2: 95-142.

Oser, B.L., Oser, M., and Spencer, H.C. 1963. Safety evaluation studies of calcium EDTA. Toxicology and Applied Pharmacology 5: 142-162.

Schardein, J.L., Sakowski, R., Petrere, J., and Humphrey, R.R. 1981. Teratogenesis studies with EDTA and its salts in rats. Toxicology and Applied Pharmacology 61: 423-428.

Swenerton, H. and Hurley, L.S. 1971. Teratogenic effects of a chelating agent and their prevention by zinc. Science 173: 62-64.

U.S. Food and Drug Administration. 2004. Agency Response Letter GRAS Notice No. GRN 000152. December 9. http://www.cfsan.fda.gov/~rdb/opa-g152.html.

U.S. Food and Drug Administration. 2004. GRAS Notice No. GRN 000152. December 9. http://www.accessdata.fda.gov/scripts/fcn/gras_notices/grn_152.pdf

U.S. Food and Drug Administration. 2006. Agency Response Letter GRAS Notice No. GRN 000178. January 11. http://www.cfsan.fda.gov/~rdb/opa-g178.html.

U.S. Food and Drug Administration. 2006. GRAS Notice No. GRN 000178. January 11. http://www.accessdata.fda.gov/scripts/fcn/gras_notices/grn000178.pdf

Whittaker P., Vanderveen J.E., Dinovi, M.J., Kuznesof, P.M., and Dunkel V.C. 1993. Toxicological profile, current use, and regulatory issues of EDTA compounds for assessing use of sodium iron EDTA for food fortification. Reg. Tox. Pharm. 18: 419-427.

GRAS Expert Panel Opinion

000019

EXPERT PANEL OPINION
THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF CALCIUM DISODIUM EDTA AND DISODIUM EDTA AS COLOR, FLAVOR, AND/OR TEXTURE RETENTION AGENTS IN SELECT PACKAGED COOKED SWEET CORN PRODUCTS

Introduction

The undersigned, an independent panel of experts, qualified by their scientific training and national and international experience to evaluate the safety of food and food ingredients (the "Expert Panel"), was specially convened by Del Monte Foods, and asked to evaluate the safety and Generally Recognized as Safe (GRAS) status of the proposed use of calcium disodium ethylenediaminetetraacetic acid ("calcium disodium EDTA") and disodium ethylenediaminetetraacetic acid ("disodium EDTA") as color, flavor, and/or texture retention agents in select packaged cooked sweet corn products. Calcium disodium EDTA and disodium EDTA are proposed for use as color, flavor, and/or texture retention agents in select packaged cooked sweet corn products with or without sauce, including mixed vegetable and similar products that contain less than 50% corn by weight. Calcium disodium EDTA would be added to the packaged cooked sweet corn products at levels up to 200 ppm and disodium EDTA would be added at levels up to 165 ppm.

Exponent Inc. performed a comprehensive search of the scientific literature, through August 2010, relating to the safety/toxicity and dietary intake/consumption of calcium disodium EDTA and disodium EDTA. Exponent Inc. summarized the results of the literature search and prepared a safety assessment, "GRAS Determination of Calcium Disodium EDTA and Disodium EDTA as Color, Flavor, and/or Texture Retention Agents in Select Packaged Cooked Sweet Corn Products," for consideration by the Expert Panel.

The Expert Panel reviewed Exponent Inc.'s safety assessment documentation, as well as other available data and information that the Panel members believed to be pertinent to safety of calcium disodium EDTA and disodium EDTA under the conditions of intended use in select

packaged cooked sweet corn products. In addition, the Expert Panel reviewed the methods of manufacture and specifications for calcium disodium EDTA and disodium EDTA, analytical data confirming compliance with food-grade specifications, the conditions of intended uses in select cooked sweet corn products and the estimated dietary exposure to calcium disodium EDTA and disodium EDTA. The Expert Panel consulted by telephone on October 26, 2010, and independently and jointly unanimously concluded that the intended use of calcium disodium EDTA and disodium EDTA, produced consistent with current good manufacturing practice (cGMP) and meeting appropriate food-grade specifications, as color, flavor, and/or texture retention agents in select packaged cooked sweet corn products, with or without sauce, including mixed vegetable and similar products that contain less than 50% corn by weight, is safe. The Expert Panel further concluded that the intended use is GRAS based on scientific procedures. It is also our opinion that other qualified experts would concur with our conclusions. Summarized below is the scientific analysis supporting our conclusions.

Description

Calcium disodium EDTA ($C_{10}H_{12}CaN_2Na_2O_8$; CAS No. 23411-34-9) is a white to off-white, crystalline or granular powder with a faint, saline-like taste that is odorless and hygroscopic. Disodium EDTA ($C_{10}H_{16}N_2Na_2O_8$; CAS No. 139-33-3) is a white to off-white, odorless crystalline powder. The calcium disodium EDTA and disodium EDTA products that are the subject of this GRAS determination meet appropriate food-grade specifications, as published in the Food Chemicals Codex ("FCC").

Calcium disodium EDTA is approved by the U.S. Food and Drug Administration (FDA) as a food additive in 21 CFR 172.120 for use in foods under limited conditions of use. Specifically, its approved uses are as a preservative, sequestrant, flavor retention agent, color retention agent, texture retention agent, and antigushing agent at particular use levels in pickled cabbage, canned carbonated soft drinks, canned white potatoes, cooked canned clams, cooked canned crabmeat, pickled cucumbers, distilled alcoholic beverages, non-standardized dressings, cooked canned dried lima beans, hard-cooked egg products (consisting of, in cylindrical shape, egg white with inner core of egg yolk), fermented malt beverages, French dressing, cooked canned legumes (other than dried lima beans, pink beans and red beans), mayonnaise, cooked canned

mushrooms, oleomargarine, pecan pie fillings, cooked canned pink beans, potato salad, processed dry pinto beans, cooked canned red beans, salad dressings, sandwich spreads, sauces, cooked canned shrimp, spice extractives in soluble carriers, and artificially colored and lemon-flavored or orange-flavored spreads. The approved food additive conditions of use do not encompass the proposed use as a color, flavor and/or texture retention agent in packaged cooked sweet corn products, with or without sauce, including mixed vegetable and similar products that contain less than 50% corn by weight. The proposed use was not requested in a food additive petition filed with the agency.

Disodium EDTA is approved as a food additive in 21 CFR 172.135 under limited conditions of use. Specifically, its approved conditions of use are as a preservative, sequestrant, flavor retention agent, and color retention agent at particular use levels in aqueous multivitamin preparations, canned black-eyed peas, canned kidney beans, canned strawberry pie fillings, cooked sausage, nonstandardized dressings, French dressing, frozen white potatoes including cut potatoes, gefilte fish balls or patties in packing medium, legumes (all cooked canned, other than black-eyed peas), mayonnaise, ready-to-eat-cereal products containing dried bananas, salad dressings, sandwich spreads, sauces, and saccharin nonnutritive sweeteners. The approved food additive conditions of use do not encompass the proposed use as a color, flavor and/or texture retention agent in packaged cooked sweet corn products, with or without sauce, including mixed vegetable and similar products that contain less than 50% corn by weight. The proposed use was not requested in a food additive petition filed with the agency.

Manufacturing Process

The calcium disodium EDTA and disodium EDTA that are the subject of this GRAS determination are produced consistent with cGMP in the same manner as the approved food additives calcium disodium EDTA and disodium EDTA. The calcium disodium EDTA and disodium EDTA that are the subject of this GRAS evaluation meet appropriate food grade specifications, as published in the FCC.

Intended Use

Calcium disodium EDTA and disodium EDTA are proposed for use as color, flavor, and/or texture retention agents in select packaged cooked sweet corn products with or without sauce, including mixed vegetable and similar products that contain less than 50% corn by weight. Calcium disodium EDTA would be employed at a maximum use level of 200 ppm and disodium EDTA at a maximum use level of 165 ppm. Calcium disodium EDTA and disodium EDTA may each be used alone or in combination.

Exposure

The consumption of packaged cooked sweet corn from the proposed new uses was based on food consumption records collected as part of the National Health and Nutrition Examination Surveys (NHANES) conducted in 2003-2004 and 2005-2006. Using the NHANES consumption data, Exponent estimated 2-day average intakes of packaged cooked sweet corn from proposed new uses in canned corn products for the U.S. population 2 years and older (as used in reference to the proposed corn products, the term "canned" encompasses all hermetically sealed containers.) The intakes of EDTA from cooked sweet corn in select products were calculated by multiplying each NHANES respondent's 2-day average cooked sweet corn intake with the maximum proposed level of EDTA (200 ppm). The estimate of 90th percentile *per user* EDTA intake from the proposed new use in select packaged cooked sweet corn products is 0.34 mg/kg bw/day.

Estimated total dietary intake of EDTA includes currently approved/existing uses and the proposed new uses of calcium disodium EDTA and disodium EDTA. In the most recent GRAS Notification (GRN 000178, 2005) for sodium iron EDTA, Akzo Nobel estimated the 90th percentile combined intake of EDTA from the food uses of sodium iron EDTA in GRN 000152, GRN 00178, and currently regulated uses of calcium disodium EDTA and disodium EDTA to be 1.4 mg/kg bw/day (for a 60 kg person). Taken together with the per user 90th percentile intake of EDTA from the proposed use of calcium disodium EDTA or disodium EDTA at a maximum concentration of 200 ppm in select packaged cooked sweet corn products, the calculated cumulative intake of EDTA was conservatively estimated to be 1.74 mg/kg bw/day (i.e., 1.4 mg/kg bw/day + 0.34 mg/kg bw/day = 1.74 mg/kg bw/day).

This estimate of total intake represents an overestimation, since it assumes that all packaged cooked sweet corn consumed from one of these food categories contained EDTA at 200 ppm and that the individual also consumed other foods containing EDTA (e.g., that they consume 1.4 mg/kg bw/day from other foods and that they are the upper 90th percentile user) plus 0.34 mg/kg bw/day from the proposed corn-containing foods (and they are also the 90th percentile user from this category).

Safety Data

The safety of calcium disodium EDTA, disodium EDTA, and many other salts of EDTA has been reviewed by the FDA, the U.S. Environmental Protection Agency ("EPA"), the WHO/FAO Joint Expert Committee on Food Additives ("JECFA") and the Cosmetics Ingredient Review Board (CIRB, Lanigan and Yamarik 2002), and has been the subject of reviews in the public literature. Metal ions on the EDTA-metal complex are freely exchanged once in the digestive tract. Therefore, the various EDTA salt forms are expected to have essentially similar toxicological potential and metabolic fate in the body, regardless of whether EDTA is consumed as the calcium, sodium, or sodium-iron salt form. Hence, this GRAS determination focuses on EDTA, irrespective of the EDTA-metal complex to which exposure may have occurred.

JECFA considered the safety of numerous food additives, including calcium disodium EDTA, in 1974 (JECFA 1974). JECFA recommended that calcium disodium EDTA and disodium EDTA be permitted as food additives and established an acceptable daily intake ("ADI") of 2.5 mg EDTA/kg bw/day. The ADI was set based on the facts that (1) EDTA salts are poorly absorbed in the G-I tract; (2) EDTA salts have a history of use in treating metal poisoning in humans; and (3) EDTA is essentially not metabolized (Heimbach et al, 2000).

An extensive toxicologic database provides a sufficient basis for an assessment of the safety of calcium disodium EDTA and disodium EDTA for the proposed use as color, flavor, and/or texture retention agents at maximum concentrations in select packaged cooked sweet corn products of 200 ppm and 165 ppm respectively. Calcium disodium EDTA, disodium EDTA, and related EDTA salts are poorly absorbed in the gastrointestinal tract and are not acutely toxic. They are not mutagenic or genotoxic under conditions that do not deplete essential trace

elements required for normal cell function. EDTA compounds are not carcinogenic in rodent bioassays and have no reproductive or developmental toxic effects when diets are supplemented with essential nutrients including zinc. Subchronic and chronic toxicity studies conducted in animals reveal that EDTA compounds exhibit general adverse effects only at very high exposure levels of approximately 1000 mg/kg bw/day and greater. In addition, calcium disodium EDTA as well as disodium EDTA has a long history of safe use as FDA-approved food additives.

Summary

Our summary resulting from this critical evaluation is presented below.

- The substances that are the subject of this GRAS determination are calcium disodium EDTA and disodium EDTA. Calcium disodium EDTA and disodium EDTA, produced consistent with cGMP, meet appropriate food-grade specifications, as published in the FCC.

- Calcium disodium EDTA and disodium EDTA have a long history of safe use in foods as FDA-approved food additives.

- Calcium disodium EDTA and disodium EDTA are proposed for use as color, flavor, and/or texture retention agents in select packaged cooked sweet corn products with or without sauce, including mixed vegetable and similar products that contain less than 50% corn by weight. Calcium disodium EDTA and disodium EDTA will be added to such corn products at levels up to 200 ppm and 165 ppm, respectively.

- Total estimated dietary intake of EDTA by U.S. population includes current FDA-approved and GRAS-notified uses as well as the proposed new uses of calcium disodium EDTA and disodium EDTA. In the most recent GRAS Notification (GRN 000178, 2005), Akzo Nobel estimated the 90th percentile combined intake of EDTA from the food uses in GRN 000152, GRN 00178, and currently regulated uses to be 1.4 mg/kg bw/day (for a 60 kg person). Taken together with the per user 90th percentile intake of EDTA from the proposed use of calcium disodium EDTA or disodium EDTA at a maximum concentration of 200 ppm in select packaged cooked sweet corn products (i.e., 0.34 mg/kg bw/day), the cumulative dietary intake of EDTA was conservatively estimated to

be 1.74 mg/kg bw/day (i.e., 1.4 mg/kg bw/day + 0.34 mg/kg bw/day = 1.74 mg/kg bw/day).

- JECFA considered the safety of several food additives including calcium disodium EDTA, in 1974. JECFA recommended that calcium disodium EDTA and disodium EDTA be permitted as food additives and established an ADI of 2.5 mg EDTA/kg bw/day. The ADI was set based on the facts that (1) EDTA salts are poorly absorbed in the G-I tract; (2) EDTA salts have a history of use in treating metal poisoning in humans; and (3) EDTA is essentially not metabolized. The estimated cumulative daily intake of EDTA has been conservatively estimated to be 1.74 mg/kg bw/day (i.e., 1.4 mg/kg bw/day + 0.34 mg/kg bw/day = 1.74 mg/kg bw/day) which is below the ADI of 2.5 mg/kg bw/day set by JECFA. In addition, the available preclinical and clinical studies on various salt forms of EDTA do not indicate any serious adverse effects related to treatment/ingestion at the proposed levels of use.

Expert Panel Conclusion

We, the undersigned expert panel members, have individually and collectively critically evaluated published and unpublished data and information pertinent to safety, and unanimously conclude that the use of calcium disodium EDTA and disodium EDTA, produced consistent with cGMP and meeting appropriate food-grade specifications, as color, flavor, and/or texture retention agents in select packaged cooked sweet corn products with or without sauce, including mixed vegetable and similar products that contain less than 50% corn by weight, at levels up to 200 ppm and 165 ppm, respectively, is safe.

We further conclude that the intended use of calcium disodium EDTA and disodium EDTA, produced consistent with cGMP and meeting appropriate food-grade specifications, as color, flavor, and/or texture retention agents in select packaged cooked sweet corn products with or without sauce, including mixed vegetable and similar products that contain less than 50% corn by weight, at levels up to 200 ppm and 165 ppm, respectively, is "generally recognized as safe" ("GRAS") based on scientific procedures.

It is our opinion that other qualified experts would concur with our conclusions.

By:

(b) (6)

James W. Anderson, M.D.
Professor of Medicine and Clinical Nutrition, Emeritus
University of Kentucky

Oct. 28, 2010
Date

Thomas J. Sobotka, Ph.D.

Date

John A. Thomas, Ph.D.
Adjunct Professor
Indiana University School of Medicine

Date

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James W. Anderson, M.D.
Professor of Medicine and Clinical Nutrition, Emeritus
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10/28/2010
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James W. Anderson, M.D. Date
Professor of Medicine and Clinical Nutrition, Emeritus
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Thomas J. Sobotka, Ph.D. Date

(b) (6)

_____ 10/28/10

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References

Environmental Protection Agency (EPA). 2006. Ethylendiaminetetraacetic acid chemicals: exemptions from the requirement of a tolerance. Federal Register, March 8. 71(45): 11563-11570.

Heimbach, J., Rieth, S., Mohamedshah, R., Slesinski, R., Samuel-Fernando, P., Sheehan, T., Dickmann, R., and Borzelleca, J. 2000. Safety assessment of iron EDTA (sodium iron (Fe3) ethylenediaminetetraacetic acid): summary of toxicological, fortification and exposure data. Food and Chemical Toxicology. 38: 99-111.

JECFA. 1967. Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour-treatment agents, acids and bases. Joint FAO/WHO Expert Committee on Food Additives. WHO Tech. Rep. Ser. No. 339.

JECFA. 1974. Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers and thickening agents. Joint FAO/WHO Expert Committee on Food Additives. WHO Tech. Rep. Ser. No. 539.

Lanigan, R.S. and Yamarik, T.A. 2002. Final report on the safety assessment of EDTA, calcium disodium EDTA, diammonium EDTA, dipotassium EDTA, disodium EDTA, TEA-EDTA, tetrasodium EDTA, tripotassium EDTA, trisodium EDTA, HEDTA, and trisodium HEDTA. Int. J. Toxicol. Suppl 2: 95-142.

U.S. Food and Drug Administration. 2004. Agency Response Letter GRAS Notice No. GRN 000152. December 9. http://www.cfsan.fda.gov/~rdb/opa-g152.html.

U.S. Food and Drug Administration. 2004. GRAS Notice No. GRN 000152. December 9. http://www.accessdata.fda.gov/scripts/fcn/gras_notices/grn_152.pdf

U.S. Food and Drug Administration. 2006. Agency Response Letter GRAS Notice No. GRN 000178. January 11. http://www.cfsan.fda.gov/~rdb/opa-g178.html.

U.S. Food and Drug Administration. 2006. GRAS Notice No. GRN 000178. January 11. http://www.accessdata.fda.gov/scripts/fcn/gras_notices/grn000178.pdf.

References

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