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FOOD ADDITIVE SAFETY

VIA HAND DELIVERY

June 3, 2004

George Pauli, Ph.D.
Office of Premarket Approval (HFF-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
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College Park, MD 20740-3835

AAC
CONSULTING GROUP

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Rockville, Maryland 20855-2765
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RE: Submission of GRAS Notification of Sodium Iron EDTA for Use as a Fortificant in Dry Mix Beverage on behalf of Kraft Foods, Inc.

Dear Dr. Pauli:

In accordance with proposed 21 CFR § 170.36 (Notice of a claim for exemption based on a GRAS determination) published in the Federal Register (62 FR 18939-18964), I am submitting in triplicate, as the agent to the notifier, Kraft Foods, Inc., a GRAS Notification of sodium iron EDTA for use as a fortificant in dry mix beverage. Also enclosed is a GRAS panel report setting forth the basis for the GRAS determination, a dossier by CanTox International, and a report by CanTox International on food intake of those beverages intended for the proposed use.

Please let me know if you have any questions.

Sincerely

Edward A. Steele
Vice President
Food, Dietary Supplement & Cosmetic Consulting

Enclosures

A subsidiary of Kendle International Inc.

OPINION OF AN EXPERT PANEL ON THE GENERALLY RECOGNIZED AS SAFE (GRAS) USE OF SODIUM IRON ETHYLENEDIAMINETETRAACETIC ACID (EDTA) FOR IRON FORTIFICATION OF DRY MIX BEVERAGE

The undersigned, an independent panel of recognized experts (hereinafter referred to as Expert Panel), qualified by their scientific training and relevant national and international experience to evaluate the safety of food and food ingredients, was requested by Kraft Foods to determine the Generally Recognized as Safe (GRAS) status of sodium iron EDTA ($NaFe^{+3}EDTA$) for use as an iron fortificant added to a powdered soft drink beverage. The ingredient is intended for use in amounts not to exceed 2.5 mg iron/200 ml reconstituted beverage. A comprehensive search of the scientific literature for safety and toxicity information on EDTA was conducted through January 2003 and made available to the Expert Panel. Following independent, critical evaluation, the Expert Panel conferred and unanimously agreed to the decision described herein.

Description of Sodium Iron EDTA

Common Name or Usual Name: Sodium iron EDTA (NaFeEDTA)

Chemical Names: Ferric sodium EDTA; Ferric sodium edetate; Ferric sodium ethylenediaminetetraacetic acid; Sodium feredetate; Sodium ferric EDTA; Sodium ferric ethylenediaminetetraacetate; Sodium iron(III) ethylenediaminetetraacetate; Sodium ironedetate; Monosodium ferric EDTA; Monosodium ferric ethylenediaminetetraacetate

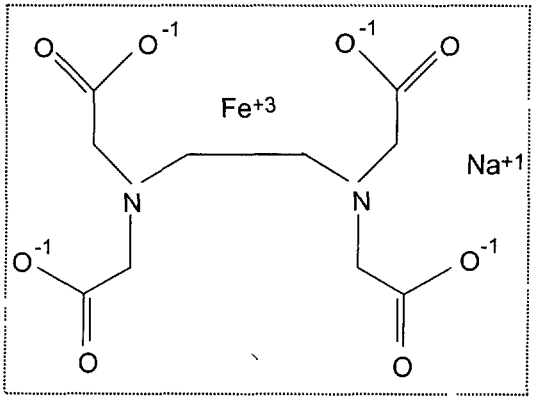
Chemical Abstracts Services (CAS) Number

CAS No. 15708-41-5

Empirical Formula and Formula Weight

$C_{10}H_{12}FeN_2NaO_8 \cdot 3H_2O$ 421.09 (trihydrate)

Structural Formula



Chemical and Physical Characteristics

NaFeEDTA occurs as a pale yellow powder that is very soluble in water at pH 7.0, with approximately 50% solubility at pH's of up to 7.4 (MacPhail *et al.*, 1981; INACG, 1993; Viteri *et al.*, 1995; JECFA, 1999). It is relatively stable and suitable in foods that are stored for long periods of time, or prepared at high temperatures (Garby and Areekul, 1974; INACG, 1993; Viteri *et al.*, 1995; Bovell-Benjamin *et al.*, 1999; JECFA, 1999; García-Casal and Layrisse, 2001).

Specifications

Food grade specifications for NaFeEDTA appropriate for food fortification programs have been developed by WHO/FAO Joint Expert Committee on Food Additives JECFA (1999) and are summarized below.

Specification Parameter	Specification
Identification Tests	
Solubility	Soluble in water
Test for iron	Passes test
Test for sodium	Passes test
Purity	
Assay	Not less than 12.5% and not more than 13.5% iron on trihydrate basis Not less than 65.5% and not more than 70.5% EDTA on trihydrate basis
PH	3.5-5.5 (1 in 100 solution)
Water insoluble matter	Not more than 0.1%
Nitrilotriacetic acid	Not more than 0.1%
Arsenic	Not more than 1 mg/kg
Lead	Not more than 1 mg/kg

JECFA, 1999

Chemical Properties of EDTA

EDTA is a hexadentate chelating agent able to combine stoichiometrically with virtually every metal ion in the periodic table (Chaberck and Martell, 1959). The effectiveness of EDTA as a chelating agent for a particular metal ion is given by its stability constant with the metal ion. In solution, metal ions with higher affinity displace ions with lower affinities from the EDTA complex. Chelation potential is affected by pH, the molar ratio of chelate to metal ion, and the presence of competing metal ions capable of forming complexes with EDTA (Plumb *et al.*, 1950; Martell, 1960; Hart, 1984). The stability constants for different metal-EDTA complexes vary significantly.

Manufacturing Process

NaFeEDTA is manufactured to meet the WHO/FAO Joint Expert Committee on Food Additives (JECFA) food grade specifications cited above.

Intended Use and Estimated Exposure

Kraft Foods proposes to use sodium iron EDTA for iron fortification of powdered soft drinks in areas of the world with a high prevalence of iron deficiency. Powdered soft drinks are considered ideal for such purposes given the stability of sodium iron EDTA in dry, powdered form, the stability and solubility of sodium iron EDTA in the reconstituted drink, the volume of soft drink beverage that is typically consumed, and economic considerations regarding transportation, storage and initial product costs. Such factors are critical toward making practicable iron fortification programs in underdeveloped areas of the world. The proposed level of fortification is 2.5 mg iron/200 ml of reconstituted beverage or 14.1 mg EDTA/200 ml of reconstituted beverage. As infants and children regularly consume more food and drink on a body weight basis (per kg of body weight) than adults, they represent the highest consumers of iron EDTA on a mg/kg body weight basis. Consequently, the following estimated intakes of sodium iron EDTA are focused on infants 0-2 years of age and children 3 to 11 years of age to assure that exposure to iron on a body weight basis is not underestimated.

Using the USDA Continuing Survey of Food Intake by Individuals (CSFII, 1994-96, 1998 Food Codes for all proposed uses) a food consumption study conducted by CanTox International (see attached document) found that iron intake by all age groups and all users of the proposed uses of iron EDTA to be 4.2 mg iron (at the mean) and 8.2 mg iron (at the 90th percentile). For infants, 0-2 years of age (users only), the mean and 90th percentile are 2.4 and 4.6 mg iron, respectively. Children, 3-11 years of age (users only), consume 3.2 and 6.4 mg iron at the mean and 90th percentile, respectively. When viewed on a body weight basis, iron consumption for all ages (users only) is 0.09 and 0.2 mg iron/kg bw, respectively. For infants 0-2 years of age (users only), the mean and 90th percentile are 0.18 and 0.38 mg iron/kg bw and for children 3—11 years of age (users only), the mean is 0.13mg iron/kg bw and the 90th percentile is 0.27 mg iron/kg bw.

It should be recognized that these estimates overstate actual consumption as they are based on short term surveys of 2 to 3 days as compared to the more accurate 14-day studies sometimes available. For instance, aspartame and neotame petitions used Market Research Corporation of America (MRCA) 14-day survey data for consumption of diet soft drinks at the 90th percentile. Consumption values in the 14-day study were only a third of that reported in the three day studies. Thus, we believe consumption estimates for users only at the 90th percentile exaggerates actual consumption by a factor of at least 2. Realistically, consumption of iron by these infants and children consuming iron EDTA fortified powdered soft drinks at the 90th percentile would be less than 0.2 mg iron/kg body weight. The tendency of 2 or 3 day food consumption survey data to over estimate exposure by a factor of 2 to 3 fold is well documented by studies conducted within several European countries (IEFS, 1998). Consumption of EDTA from sodium iron EDTA as proposed would be 0.49 mg EDTA/kg bw (mean) and 1.03 mg EDTA/kg bw (90th percentile) for all ages and users only, 0.96 mg EDTA/kg bw (mean) and 1.98 mg EDTA/kg bw (90th percentile) for infants (users only) and 0.7 mg EDTA/kg bw (mean) and 1.42 mg EDTA/kg bw for children (users only). Realistically, given the inherent exaggeration produced by short term surveys, consumption of EDTA over a 14-day period would not exceed 1.0 mg EDTA/kg bw/day for any age group.

Current International Regulatory Status

JECFA, in 1992, provisionally approved the use of NaFeEDTA in supervised food fortification programs, under the condition that additional studies be conducted, assessing the site of deposition of iron administered as NaFeEDTA and the metabolic fate of NaFeEDTA (JECFA, 1993). JECFA has since re-evaluated NaFeEDTA in 1999, and has lifted the provisional status of the approval stating that the use of NaFeEDTA as a nutritional supplement in foods is considered acceptable when used in supervised food fortification programs that would provide iron intakes of approximately 0.2 mg/kg body weight/day (JECFA, 2000). This restriction of use in supervised fortification programs resulted from the mandate received from the Codex Committee for Food Additives who requested an evaluation for this specific purpose.

A number of developing countries have approved NaFeEDTA for use in supervised fortification programs (see Section 4.4.7 of the CanTox dossier). NaFeEDTA is currently considered as Generally Recognized As Safe (GRAS) in the United States for use in the iron fortification of RTE cereals, toaster pastries, cereal-based breakfast bars and granola bars; foods that already are permitted to be fortified with iron (Heimbach *et al.,* 2000). The United States Food and Drug Administration (FDA) have also approved the use of EDTA and several of its salts, calcium disodium EDTA ($CaNa_2EDTA$) and disodium EDTA (Na_2EDTA) as direct additives to food under 21 C.F.R. §172.120 and §172.135 (FDA, 2002).

Safety Issues Related to Intended Use of Sodium Iron EDTA

Several questions of safety come to mind with respect to the intended use of sodium iron EDTA. First, and most obvious, is the question of possible iron overload, excessive amounts of iron resulting in iron mediated toxicity. Secondly, and just as obvious, is the question of possible nutritional imbalances in copper, zinc or calcium being mediated by either excess iron or by EDTA. Other issues include the possibility of acute toxicity, known to occur in children from over doses of dietary supplements containing iron, and questions of safety related to whether iron EDTA is absorbed intact and may, as a consequence, pose a risk of toxicity. Finally, there is the issue of mutagenicity of sodium iron EDTA. The Expert Panel has addressed each of these matters as discussed below and concludes that all such issues have been resolved in favor of the safety of the intended use of sodium iron EDTA.

Resolution of Safety Concerns

Iron overload

The possibility of iron overload under the proposed conditions of intended use (realistic 90th percentile 0.2 mg iron/kg body weight) has been addressed by JECFA (JECFA 2000) which has concluded that such levels of iron pose no risk of iron overload in normal individuals who may or may not be iron deficient. This conclusion was reevaluated by CanTox (CanTox 2003) following review of more recent findings and concurs with the JECFA conclusion. Important to this reevaluation was the review of a rat study by Appel et al (2001) which showed no evidence of iron overload at doses as high as 11 mg iron/kg

body weight/day, 50-times higher than the upper 90th percentile proposed use intended for humans. Based on these studies and the results of numerous field trials with sodium iron EDTA in developing countries (Garby an Areekul, 1974; Solomons, et al., 1979; Ballot et al., 1989b; Viteri et al., 19950) in which doses of between 5 and 15 mg/kg body weight/day were given, equivalent to 75-times the intended proposed use level at the 90th percentile, the Expert Panel concludes there is no basis to support a concern for the possibility of iron overload under the proposed intended conditions of use of sodium iron EDTA in normal individuals.

Interference with absorption of copper, zinc, magnesium and calcium
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 trails (Garby and Areekul, 1974; Soalomons, et al., 1979; Ballot et al., 1989b; Viteri et al., 1995). Doses ranged up to 15 mg iron/kg body weight, approximately 75-times greater than the proposed intended use at the upper 90th percentile of consumption. Based on these observations and findings in rats (Hurrel et al. , 1994; Appel et al., 2002), the Expert Panel agrees with the JECFA assessment (2000) and the CanTox (2003) conclusion 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.

Acute toxicity in children
Acute toxicity from iron is mediated through iron overload. As iron overload does not occur in normal individuals at the levels of iron proposed as discussed above, there is no reason to believe that such levels could be acutely toxic to children. Indeed, Whittaker et al., 2002 has discussed acute toxicity of iron in children and indicated that acute toxicity may begin at doses as low as 25 mg iron/kg body weight (more than 100-times the proposed 90th percentile use level as proposed here for sodium iron EDTA). Acute ingestion of 25 mg iron/kg body weight (usually in the form of ferrous sulfate) may produce symptoms of iron poisoning but 60 mg iron/kg body weight is required to result in clinically significant iron poisoning, equivalent to about 100 liters of reconstituted beverage containing 2.5 mg iron per 200 ml of reconstituted soft drink. Acute exposure to 250 mg/kg body weight (equivalent to over 400 liters of reconstituted soft drink) may have lethal consequences for a young child. Clearly, the doses of iron required to exhibit acute toxicity or lethality in young children is hundreds of times greater than the proposed intended use of sodium iron EDTA at the 90th percentile of consumption. Thus, in consideration of the above, the Expert Panel concludes that the proposed intended use of sodium iron EDTA does not pose a risk of acute toxicity.

Is iron EDTA absorbed intact from the gastrointestinal tract and does it pose a risk of toxicity?
Absorption of orally administered sodium iron EDTA as iron (Fe^{55}) and radioactive C^{14}-EDTA in pigs was described by Candela et al. (1984). In contrast to Fe^{55} only small percentages of C^{14} could be detected in plasma at any time indicating that the majority of iron from EDTA was not absorbed as intact iron EDTA. Between 72 to 91% of the administered iron and EDTA were found in the feces but only 3-4% of the iron present was in the form of intact iron EDTA indicating that the remaining 96 to 97% was transformed into insoluble iron compounds. The conclusion that can be derived from these findings is that very little if any iron EDTA is absorbed intact.

Studies in rats conducted by Appel et al. (2002) in which the deposition of iron from the oral administration of sodium iron EDTA was compared to ferrous sulfate. While there were slight differences in deposition patterns between the two iron substances with respect to liver, spleen and kidney, the differences were minimal when compared against the increases in iron that resulted from dietary fortification with either iron containing substance. For example, iron deposition in liver doubled at high doses of either iron EDTA or ferrous sulfate after 61-days of supplementation but the difference in liver deposition between the substances was less than 10%. Similarly, iron deposition in kidneys tripled with both iron containing substances yet there was only a 2% difference between iron EDTA and ferrous sulfate in term of iron deposition in the kidney. The largest difference in deposition between the two iron containing substances occurred with deposition in the spleen (about 20%) but the increase in deposition above base line was huge, 35-43-fold. Were significant amounts of iron absorbed intact as iron EDTA, a very different pattern of deposition and excretion would be expected when EDTA iron is compared to ferrous sulfate iron. These findings are considered consistent with and help confirm those of Candela et al. (1984).

Iron absorption studies in human subjects using radioactive Fe^{59} in sodium iron EDTA led to conclusions similar to those drawn here (Candela et al. (1984)). Approximately 12% of the iron in sodium iron EDTA was absorbed and incorporated as Fe^{59} into circulating hemoglobin while only 0.3% of administered Fe^{59} was excreted in the urine. Similar results were obtained by MacPhail et al., 1981, who reported less than 1% of the administered dose of iron was excreted in urine which they attributed to intact iron EDTA.

Based on the above results from studies in rats, pigs and human subjects, sodium iron EDTA dissociates in the gastrointestinal tract resulting in virtually all its iron entering the same iron absorption pathway used by iron salts such as ferrous sulfate. Thus, the means by which iron from iron EDTA is absorbed does not raise any questions of safety consistent with experience and observations of the safe use of sodium iron EDTA in field trials with human subjects.

Mutagenicity of sodium iron EDTA

Iron EDTA and iron salts were found not to be mutagenic in the Ames *Salmonella* assay with or without activation (Dunkel et al., 1999). However, these same iron salts and iron EDTA were found to increase the mutation frequency in the L5178Y mouse lymphoma TK assay by about 2 to 3 fold at high iron concentrations. Iron EDTA was slightly less active than ferrous sulfate. As the finding with iron EDTA is typical of the other iron salts tested, and was not the highest response observed, it is considered to reflect the sensitivity of L5178Y cells to abnormally high iron concentrations. Thus, the findings with iron EDTA applies to iron in general and has no implications for safety of the intended use of iron EDTA as proposed here.

Safety Profile of Sodium Iron EDTA

Many animal studies have been conducted with EDTA or various salts of EDTA, as described in the following section, but relatively few have focused on iron EDTA per se. However, because iron EDTA dissociates in the gastrointestinal tract allowing iron and

EDTA to be absorbed independently, the studies with salts of EDTA are considered relevant. In addition to non-iron EDTA studies, there are a few studies with iron EDTA that are described in this section.

Absorption and deposition of iron from iron EDTA
Absorption of iron from dietary iron EDTA and improvement in iron status has been well documented in several human studies reviewed in CanTox (2003). One of the most extensive of these studies was by Hurrell et al. (2000) who compared iron absorption of several iron containing compounds, including ferrous sulfate and iron EDTA in a wheat or wheat-soy infant cereal. In one set of studies, iron absorption from mixtures of sodium EDTA and ferrous sulfate using different molar ratios of sodium EDTA with ferrous sulfate was assessed. The results showed the absorption of iron from ferrous sulfate increased as the molar ratio of EDTA to iron was increased and as it approached 1. This finding is consistent with the conclusion that iron EDTA dissociates in the gastrointestinal tract allowing iron to be absorbed by the non-heme iron absorption pathway. EDTA's effect in improving iron absorption is considered to be a result of EDTA protecting iron from being precipitated by the formation of insoluble iron complexes (e.g. iron phytate) with dietary components (e.g. phytic and its salts) present in the gastrointestinal tract. Deposition studies in the rat conducted by Appel et al. (2002) show, as discussed above, that the tissue distribution/deposition of iron is essentially the same whether ferrous sulfate or sodium iron EDTA is orally administered further supporting the conclusion that iron from EDTA is absorbed by the gastrointestinal tract by the same mechanism as iron from ferrous sulfate is absorbed.

Acute toxicity
The oral LD50 in rats for ferrous sulfate and sodium iron EDTA is about one gram iron/kg body weight, or more exactly 1.1 iron g/kg body weight and 1.3 iron g/kg body weight (Whittaker et al. 2002)), respectively. Since the animals were dosed by gavage, inhibitory influences of dietary components were probably minimal causing the quantities of absorbed iron to be reasonably similar between ferrous sulfate and iron EDTA. The similar LD50's, therefore, are consistent with the concept that iron from both substances is absorbed following dissociation of iron from ferrous sulfate and sodium iron EDTA, and both compounds fully dissociate.

Subchronic toxicity
Su *et al.* (1999) administered NaFeEDTA in the diet to groups of Wistar rats (18/sex/group) at doses of approximately 0, 250, 1,250 and 2,500 mg NaFeEDTA/kg body weight for a period of 90 days. The general condition, body weight and food consumption of animals were evaluated throughout the duration of the study. In addition, parameter measurements of haematology and blood chemistry values, as well as organ weights and histopathology of the rats were conducted on days 45 and 90 of feeding. Food consumption in the NaFeEDTA-treated groups of rats was reported not to be significantly different from the controls. The mean growth of rats in the 2,500 mg NaFeEDTA/kg body weight dose group was reported to be significantly decreased in males at week 2, and in females at week 5 of the study; however, no significant differences in growth were reported in the other NaFeEDTA dose groups and the controls. With the exception of the significantly decreased mean body weights of rats administered 1,250 mg/kg body weight of NaFeEDTA at weeks 1 and 2 of the study, the mean body weights of NaFeEDTA-

treated rats were not significantly different from controls. There were no deaths reported in any of the rats administered 0, 250 and 1,250 mg/kg body weight of NaFeEDTA; however, deaths were reported in 4 female, 1 male and 1 female rats treated with the highest dose of NaFeEDTA (2,500 mg/kg body weight) at weeks 2, 3, and 7, respectively. At day 45 of the study, it was reported that haemoglobin content, as well as red and white blood cell counts were not significantly different between NaFeEDTA-treated and control groups of rats. At day 90 of the study, rats administered 2,500 mg/kg body weight of NaFeEDTA had significantly lower haemoglobin content and significantly higher white blood cell counts (polymorphonuclear leukocytes, in particular) than controls. There were no significant differences in serum transaminase activity, total protein, albumin, globulin, urea-nitrogen, glucose, total cholesterol and triglyceride levels reported among the 4 different treatment groups at days 45 and 90; however, serum total protein and albumin levels of rats in the 2,500 mg NaFeEDTA/kg body weight dose group were significantly lower at day 90 than the controls. Relative organ weights were not significantly different among the different treatment groups at day 45, but significantly increased spleen and stomach weights in males, as well as liver weights in females were reported in the 2,500 mg NaFeEDTA/kg body weight dose group at day 90 of the study. Upon histopathological examination it was found that rats administered 2,500 mg/kg body weight of NaFeEDTA exhibited greater incidence and severity of lesions, necrotic foci and connective tissue hyperplasia of the liver, at day 90 (75% frequency) than at day 45 (25% frequency) of the study. Additionally, inflammation of the colonic mucosa and necrosis of the intestinal mucosa also were reported in this group of rats at day 90. Small liver necrosis foci and slight liver connective tissue hyperplasia were reported in rats administered 1,250 mg/kg body weight of NaFeEDTA, while no histopathological changes were reported in rats administered 250 mg/kg body weight of NaFeEDTA. The authors concluded that the minimum dose, which would provide subchronic toxicity effects in rats, was 1,250 mg/kg body weight of NaFeEDTA, and that the NOAEL must lie between 250 and 1,250 mg NaFeEDTA/kg body weight doses.

In a more recent study in which more realistic doses were used, the disposition, accumulation and toxicity of NaFeEDTA were studied in groups of male Sprague-Dawley rats (40/group) administered approximately 3, 6, or 12 mg iron/kg body weight as NaFeEDTA (Appel *et al.*, 2001). For control, another 3 groups of rats (40/group) were provided with 3, 6, or 12 mg iron/kg body weight as $FeSO_4$. Baseline levels of the analytical parameters were obtained from the euthanasia of 10 untreated rats at the beginning of the study period. After 31 days of feeding, 20 rats/group were euthanized for examination, while the remaining 20 rats/group were kept and euthanized after a total feeding period of 61 days. Evaluated parameters included body weights, food and iron intake, haematology, clinical chemistry values and histopathological examinations of various organs (*i.e.*, adrenals, brain, cecum, colon, heart, kidneys, liver, esophagus, rectum, small intestines, spleen, stomach, testes, and thymus). No significant differences were seen in the distribution of iron between the test and control diets, with mean daily intakes of 2.81, 5.67, and 11.19 mg iron/kg body weight for NaFeEDTA and 2.84, 5.69, and 11.54 mg iron/kg body weight for $FeSO_4$, for the low-, mid- and high-doses, respectively. There also were no significant differences in the mean body weights and overall mean food consumption reported between the test and control groups. Clinical signs were reported, including encrustations around the eyes, malocclusion of incisors, nasal encrustations and red discharge from the nose, sniffing, sparsely haired skin, dermal encrustations, and

dermal wounds; however, these were randomly distributed among the various groups and considered not to be compound-related. There also were no compound-related histopathological changes reported in the control or NaFeEDTA groups of rats. Mean corpuscular haemoglobin levels were reported to be significantly increased in the high-dose $FeSO_4$ and NaFeEDTA groups (12 mg iron/kg body weight), as well as the mid-dose NaFeEDTA group (6 mg iron/kg body weight), after 31 days of feeding. In addition, the high-dose NaFeEDTA group was reported to have a significantly greater number of eosinophils after 31 days of feeding than the mid-dose $FeSO_4$ group or the other NaFeEDTA dose groups. No significant differences in red blood cell, coagulation variables, or white blood cell counts were reported after 61 days of feeding. Decreased alkaline phosphatase activity in the mid-dose NaFeEDTA group, as well as increased total bilirubin levels in the mid-dose $FeSO_4$ group (6 mg iron/kg body weight) were reported at day 32, but not at day 62 of feeding. The authors did report significantly lower total plasma protein concentrations in the NaFeEDTA groups than the controls at day 62 of feeding. They also reported significantly lower plasma albumin levels in the mid- and high-dose NaFeEDTA groups than the low-dose NaFeEDTA and low- and mid-dose $FeSO_4$ groups; significantly lower calcium levels in the high-dose NaFeEDTA group than the low-dose NaFeEDTA and low- and mid-dose $FeSO_4$ groups; and significantly decreased sodium concentrations in the high-dose NaFeEDTA and $FeSO_4$ groups, compared to the low-dose $FeSO_4$ group at day 62. The authors attributed the lower plasma calcium levels reported for the high-dose NaFeEDTA group, for the most part, to the concurrent decrease in plasma albumin levels. However, due to the lack of hepatic damage reported in NaFeEDTA-treated rats, the decreased plasma levels of calcium were deemed by the authors not to be toxicologically significant.

The authors reported no significant differences in the absolute and relative thymus weights of NaFeEDTA and control groups of rats after 31 days of feeding. However, after 61 days, the absolute and relative thymus weights of the low-dose NaFeEDTA group were significantly greater than those in the low-dose $FeSO_4$ and the mid- and high-dose NaFeEDTA groups. After 31 days of feeding, plasma concentrations of chloride were reported to significantly decrease with increasing iron levels in both the NaFeEDTA and $FeSO_4$ diets. No such trend was observed at the end of 61 days of feeding. In general, plasma triglyceride levels increased with time (*i.e.*, higher after 61 days than after 31 days of feeding), which could be attributed to the natural growth of rats in the study. There was no significant difference in the plasma triglyceride levels of NaFeEDTA-treated and control rats throughout the duration of the study, except for significantly decreased levels in the low-dose $FeSO_4$ group at day 31 of feeding, compared to the high-dose NaFeEDTA group. This difference was no longer present at day 61 of feeding. The authors reported a decreasing trend in the mean daily intake of iron/kg body weight in both NaFeEDTA and $FeSO_4$ groups with increasing age of rats, which they attributed to decreasing food consumption in aging rats. The significantly higher levels of iron in the plasma of low- and mid-dose NaFeEDTA groups reported at day 31 were not observed at day 61. There were no statistically significant differences in mean TIBC in the blood plasma of NaFeEDTA-treated and control groups of rats at day 31. After 61 days of feeding, however, the low-dose $FeSO_4$ group was reported to have a significantly higher TIBC than any of the other groups, while the mid-dose $FeSO_4$ and low-dose NaFeEDTA groups were reported to have significantly increased TIBC compared to the high-dose NaFeEDTA group.

In general, levels of non-heme iron in the liver, spleen and kidney of rats were reported to increase with increasing iron concentrations in the diet. Rats fed with NaFeEDTA were reported to have significantly lower non-heme iron levels in the liver and spleen than those fed with $FeSO_4$ though, as discussed above the difference was small when compared to the huge increase over baseline (control values). There was no significant difference in the levels of non-heme iron identified in the kidneys of both control and NaFeEDTA-treated rats.

The authors concluded that dietary treatment with $FeSO_4$ or NaFeEDTA, which provide iron at levels of up to 11.5 mg/kg body weight/day does not result in iron overloading, nor in any other toxicologically significant effects in rats.

Conclusions about the safety of sodium iron EDTA under conditions of intended use

Sodium iron EDTA is absorbed by the same means and mechanism as iron salts typically used to fortify foods (e.g. ferrous sulfate). Sodium iron EDTA has the advantage over ferrous sulfate of being stable in aqueous foods and beverages, particularly at low pH. Iron EDTA's acute and longer term toxicity, at doses thousands of times higher than the intended use in food fortification, are due to iron overload and in that respect is comparable to ferrous sulfate. In view of the finding that the intended use of iron EDTA in powdered soft drinks consumed by infants and young children at the 90th percentile does not exceed the JECFA ADI (0.2 mg/kg body weight), when food consumption data are properly adjusted for survey duration, the proposed use level of sodium iron EDTA is considered safe. Furthermore, this conclusion is confirmed by toxicological and clinical studies discussed herein.

Safety Profile EDTA

Numerous experimental studies have been undertaken over the years to assess acute and chronic toxicity, reproduction, carcinogenicity, genotoxicity, and teratogenicity of EDTA and its salts. Most of these studies were compiled by JECFA (1974, 1993) and FDA (Whittaker *et al.* 1993) for their final comprehensive evaluations and reports.

Absorption, metabolism and effects on essential elements
Extensive biochemical, pharmacologic, and clinical studies have been conducted with EDTA and its salts with a view toward their medicinal use. The results of these studies indicate that EDTA is readily absorbed but not metabolized. Foreman and Trujillo (1954) found C^{14}-labeled calcium EDTA to be eliminated unchanged in studies with humans. In large doses, EDTA may interfere with the absorption, or may reduce body reserves, of minerals. In moderate dosage, EDTA is generally considered to be innocuous (Oser *et al.* 1963).

Acute toxicity studies
The acute oral LD_{50} of calcium EDTA for the rat was found to be 10.0 ± 0.74 g/kg bw and for the rabbit and dog, approximately 7 and 12 g/kg bw, respectively. The oral LD_{50} in rats is not affected by the presence of food in the stomach or by pre-existing deficiency in Ca, Fe, Cu or Mn (Oser *et al.* 1963).

Results of acute oral toxicity studies with $CaNa_2EDTA$

Test species	LD_{50} (mg/kg bw)
Rat	10,000±740
Rabbit	7,000 approx.
Dog	12,000 approx.

After Oser *et al.* 1963

Short- term studies
In one study, five male rats received 250 or 500 mg/kg bw/day $CaNa_2EDTA$ intraperitoneally, for three to twenty-one days and some were observed for an additional two weeks. Weight gain was adequate and the histology of various organs was normal. The only exception was the mild to moderate renal hydropic changes with focal subcapsular swelling and proliferation in glomerular loops at 500 mg/kg bw/day dose. There was only slight involvement with complete recovery at the 250 mg/kg bw/day level (Reuber and Schmieller, 1962).

In a rat study reported by Yang in 1964, three male and three female rats were fed a low-mineral diet (one-half the usual portion of salt mixture, *i.e.* 1.25% instead of 2.50%) containing 0% and 1.5% $CaNa_2EDTA$ for four months. The test group showed a reduced weight gain, but there was no distinct difference in the general condition of the animals.

In another experiment, three groups of eight to thirteen male and female rats were fed a low-mineral diet containing 0, 0.5, and 1% of $CaNa_2EDTA$ for 250 days. No significant differences from the controls were found for body weight gain, mortality, gross pathology or histopathology of the organs. Blood calcium levels, total bone ash and blood coagulation times were unaffected. Basal metabolism was also within normal range (Chan, 1964).

Studies in dogs were performed in four groups of one male and three female mongrels. They were fed diets resulting in exposures of 0, 50, 100 and 250 mg/kg bw $CaNa_2EDTA$ daily for 12 months. All appeared in good health. There were no significant changes in hemoglobin, blood cells or urine. Blood sugar and prothrombin time remained normal. X-rays of long bones and ribs showed no changes at the highest dose tested. All test subjects survived the full year. Gross and microscopic findings were unremarkable (Oser *et al.* 1963). The NOEL in dogs was the highest dose fed, 250 mg/kg bw/day.

Long-term toxicity/reproductive studies
Oser *et al.* (1963) conducted a rat study involving four groups of 25 males and 25 females fed diets resulting in exposures of 0, 50, 125 and 250 mg/kg bw/day $CaNa_2EDTA$ for two years. Four successive generations were studied for reproduction, lactation, and the long-term effects of $CaNa_2EDTA$ in the diet. Final observations were made on animals

receiving the diets for 6, 12 and 24 months. In the two-year feeding study, no significant treatment related changes were reported in body weight gain, food conversion efficiency (body weight gain/100 g of diet), blood glucose, hematopoiesis, blood nonprotein nitrogen, serum calcium, urine albumin and glucose, and organ weights. No differences were obsevered with histopathologic evaluation of the heart, liver, kidney, spleen, adrenals, thyroid, and gonads. No treatment related effects on mineral metabolism were seen. There was no evidence of abnormal calcification in the tibias of rats sacrificed at 12 weeks, or at the end of the 2-year treatment. The ash content of the tibias of control rats was the same as that in rats fed the highest dose level. Based on the results of this study, the NOEL is the highest dose fed, 250 mg/kg bw/day.

The results of this study showed that $CaNa_2EDTA$ had no effect on fertility, gestation, viability, or lactation indices, and the growth responses for all dose levels were not different from control groups of the same sex and generation. This study was reviewed by the Food and Agriculture Organization/World Health Organization (FAO/WHO) Joint Committee on Food Additives (JECFA) and was used by them to calculate the ADI of $CaNa_2EDTA$ (JECFA, 1966, 1974).

Teratogenicity studies

Tuchmann-Duplessis and Mercier-Parot (1956) were the first to report potential teratogenicity of EDTA salts. Rats received EDTA intramuscularly at doses up to 40 mg/kg on Day 6 or 10 of gestation. Polydactyly and tail defects were identified as possibly related to treatment with EDTA.

Swenerton and Hurley (1971) reported gross congenital malformations in the full–term young, when pregnant female rats were fed diets containing 20 and 30 g Na_2EDTA/kg diet, approximately 1000 and 1500 mg/kg bw/day, respectively. However, when Na_2EDTA was fed simultaneously in a diet supplemented with zinc (from the basal diet level of 100 to 1000 mg Zn/kg), no effects were observed. The study suggested that the congenital defects likely resulted from zinc deficiency caused by chelation of zinc by EDTA.

In other experiments with EDTA, Kimmel (1977) reported significant differences in teratogenic effects in CD rats administered the compound through various routes. Na_2EDTA was administered to pregnant rats on Days 7 to 14 of gestation by dietary admixture, by gavage, and by subcutaneous injection. Malformations were increased when EDTA was administered as a dietary admixture resulting in an exposure of 954 mg/kg bw/day and when given by gastric intubation at doses of 1250 or 1500 mg/kg/day. No increase in malformations was observed when EDTA was administered subcutaneously at a dose of 375 mg/kg bw/day despite significant maternal toxicity (24 % mortality among treated dams).

In contrast to these findings, Schardein *et al.* (1981) found no teratogenic effects in pregnant CD rats receiving 1000 mg EDTA/kg/day from Days 7-14 when the disodium, trisodium, calcium and tetrasodium salts of EDTA were given by gastric intubation. The difference in findings between the Kimmel (1977) study and this study may be attributed to the differences in housing, feed and drinking water. In the Kimmel study, the animals were maintained on deionized water, a semipurified diet and housed on nonmetallic caging. These conditions are more conducive than in Schardein *et al.* (1981) to the

development of zinc (or other essential element) deficiency, which are considered ultimately responsible for the teratogenic effects. Thus, the differences in both toxicity and teratogenicity reported in the published studies are considered due principally to differences in the availability of zinc and possibly other essential metal ions as the result of chelation by EDTA (Kimmel, 1977 and Whittaker *et al.* 1993).

Carcinogenicity Studies

The National Cancer Institute (NCI, 1977) reported results of a standard rodent bioassay for assessing potential carcinogenicity of trisodium EDTA (Na_3EDTA) which was administered for 103 weeks to Fischer 344 rats and B6C3F1 mice at dietary levels of 0.375 and 0.75%, approximately equivalent to 200 and 400 mg/kg bw/day in the rat and 540 and 1080 mg/kg bw/day in the mouse, respectively. Various tumors were observed in treated and control groups of both species but these were found not to be dose-related. NCI concluded there was no evidence of carcinogenicity for EDTA at the concentrations tested. Survival in treated and control groups were comparable and no signs of clinical toxicity were observed.

Genotoxicity studies

EDTA has been tested for genotoxicity in assays measuring gene mutation and chromosomal effects. Dunkel *et al.* (1985) reported the results from a four-laboratory study in which Na_3EDTA was tested for mutagenicity in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 and in *Escherichia coli* WP2 *uvrA* both with and without metabolic activation, using liver S-9 preparations from Aroclor 1254-induced Fischer 344 rats, B6C3F1 mice, and Syrian hamsters. The results were negative. McGregor *et al.* (1988) concluded that Na_3EDTA did not increase the mutant frequency in the L5178Y tk^+/tk^- mouse lymphoma cell forward mutation assay in either the absence or presence of a metabolic activation system. In studies sponsored by the National Toxicology Program (Whittaker *et al.* 1993), Na_3EDTA was tested for its ability to induce chromosomal aberrations or sister chromatid exchanges in mammalian cells in culture. These test results were also negative. Available evidence indicated that EDTA is not genotoxic.

Allergic reactions

In a skin sensitization study, Raymond and Gross (1969) reported a 6% (3/50) positive response to $CaNa_2EDTA$, with 2 of the 3 positively responding individuals cross-reacting with ethylenediamine. It was concluded that $CaNa_2EDTA$ is a weak sensitizing compound. Later experimental studies by Henck *et al.* (1985) to evaluate the sensitizing potential of Na_3EDTA in guinea pigs, were found to be negative. Therefore, the researchers concluded that the potential for EDTA and its salts to produce a human skin sensitization response is very low.

Safety Summary of EDTA and Conclusions

EDTA is absorbed and eliminated intact by the kidney. EDTA has a low order of acute toxicity and low potential for skin sensitization. The teratogenic effects of EDTA are due to its chelation properties, especially its ability to chelate zinc. EDTA was shown to be non-mutagenic and non-carcinogenic in standard tests. EDTA has been shown to be non-toxic at levels below those that significantly affect mineral balance and metabolism.

The Joint WHO/FAO Expert Committee on Food Additives (JECFA) established an ADI of 2.5 mg/kg bw/day for EDTA based on the $CaNa_2EDTA$ rat study by Oser *et al.* (1963). The ADI was calculated by using the highest dose tested in the rat (250 mg/kg bw/day) as the no-observed-effect level (NOEL) with a 100-fold safety factor which resulted in an ADI of 2.5 mg/kg/day, equivalent to 150 mg/person/day for a 60 kg individual. Further, when the relative toxicities of Na_2EDTA and $CaNa_2EDTA$ were compared, JECFA concluded that the use of $CaNa_2EDTA$ is preferable to that of Na_2EDTA because Na_2EDTA is more effective at sequestering physiological calcium (JECFA, 1974).

The findings of the study on EDTA by Oser *et al.* (1963) were confirmed in a 2-year cancer bioassay in rats and mice (NCI, 1977). The NCI study showed survival was not affected by treatment with EDTA and no treatment related neoplastic or non-neoplastic responses were identified. Therefore, on the strength of these data, the ADI was confirmed at 2.5 mg/kg bw/day. Based on these determinations, it is concluded that the intended use of sodium iron EDTA will not raise a question of safety with respect to EDTA exposure for the 90th percentile consumer, including young children exposed to 1.2 EDTA mg/kg body weight/day. The safety evaluation must also take into consideration other sources of EDTA in the diet. Combining exposures to these sources of EDTA (using the intake estimates developed by the FDA, see section below) with EDTA exposure from the proposed fortification use in young children, it can be shown that the JECFA ADI of 2.5 mg EDTA/kg body weight/day is not exceeded, see section below.

Estimated Exposure to EDTA from Regulated Uses

The Food and Drug Administration has reviewed and reassessed the EDI for EDTA since it was originally established in 1969. In 1992, the agency updated its estimate of chronic daily exposure to EDTA by utilizing available food intake information and Monte Carlo simulation methodology (Rubinstein, 1981) to calculate a 90th percentile exposure. The Monte Carlo technique uses a distribution of values for a variable instead of a discrete value. The food intake distributions were taken from the Market Research Corporation of America (MRCA) Information Services (Northbrook, IL) 5-Year Menu Census (1982-1987), and portion sizes used from the 1987-1988 U. S. Department of Agriculture-Nationwide Food Consumption Survey (USDA-NFCS). For use level distribution, typical values were estimated to be 80-90% of the maximum; minimum values were estimated to be 60-70% of the maximum. The following two assumptions were employed when the expected mean values were calculated: "all foods that may contain EDTA under FDA's regulation do contain EDTA, and the presence of EDTA in food does not affect a consumer's choice relating to that food" (Whittaker *et al.* 1993).

Sources of exposure to EDTA from individually regulated foods are outlined in 21 CFR §172.120 and 21 CFR §172.135. Due to the multiplicity of uses for EDTA, all consumers are considered eaters of EDTA; therefore, eaters-only exposure is equivalent to the total-sample. Mean overall exposure to EDTA has been estimated to be 0.25 mg/kg/day. In the Monte Carlo simulation, the 90th percentile exposure is 0.43 mg/kg/day and the 50th is 0.22 mg/kg/day. The difference in formula weight between $CaNa_2EDTA$ and Na_2EDTA was not considered, as it would amount to no more than about 1 mg/person/day.

As a test of this method, the amount of EDTA utilized in the food supply was obtained. The total quantity of EDTA salt reported by weight in the NAS update for 1987 was 186,000 pounds (NAS, 1989). This amount yielded a per capita estimate of exposure of 1.6 mg/person/day, one-tenth of the Monte Carlo estimate. Thus, this test of the Monte Carlo method shows that it has not underestimated exposure but is likely over stating actual exposure to EDTA containing foods. Consequently, it is unlikely that even children with 90th percentile exposure would exceed 0.43 mg EDTA/kg body weight/day. Adding this estimate to the estimated 90th percentile exposure from the proposed fortification use (0.43 mg EDTA/kg/day + 1.0 mg EDTA/kg/day) gives the value, 1.43 mg EDTA/kg/day, still below the JECFA ADI for EDTA of 2.5 mg/kg/day.

Conclusion of the Expert Panel

Based upon a critical evaluation of the information summarized above, the Expert Panel has established that sodium iron EDTA (meeting food grade specifications as set forth on page 2) is generally recognized as safe when used for iron fortification of a powdered soft drink at levels not to exceed 2.5 mg iron/200ml beverage in accordance with current Good Manufacturing Practice.

W. Gary Flamm, Ph.D., FACT, FATS — 5/19/04 Date

Donald Hughes, Ph.D. — 5/21/04 Date

Stanley M. Tarka, Jr., Ph.D. — May 14, 2004 Date

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I. GRAS Exemption Claim

A. Claim of Exemption From the Requirement for Premarket Approval Pursuant to Proposed 21 CFR § 170.36 (c)(1)

Sodium iron EDTA has been determined to be generally recognized as safe, and therefore, exempt from the requirement of premarket approval, under the conditions of its intended use as described below. The basis for this finding is described in the following sections.

Signed,

_____ Date 6/3/04

Edward A. Steele:

Agent for:

Kraft Foods Global

Three Lakes Drive

Northfield, Illinois 60093

B. Name and Address of Notifier

Edward A. Steele, Vice President for Food, Dietary Supplement and Cosmetic Consulting

AAC Consulting Group

7361 Calhoun Place, Suite 500

Rockville, MD. 20855

C. Common Name of the Notified Substance

Sodium iron EDTA.

D. Conditions of Use

Sodium iron EDTA is intended to be used for iron fortification of powdered soft drinks in areas of the world with a high prevalence of iron deficiency. The proposed level of fortification is 2.5 mg iron/200 ml reconstituted beverage or 14.1 mg EDTA/200 ml reconstituted beverage. Given infants and children consume more food and drink on a body weight basis than adults and will therefore be the highest consumers of iron or EDTA on a mg/kg basis, estimated intakes of sodium iron EDTA are focused on infants, 0-2 years of age, and children, 3 to 11 years. The USDA Continuing Survey of Food Intake by Individuals (CSFII, 1994-96, 1998 Food Codes for all proposed uses) was used for all intake estimates (see CanTox International Report entitled "Estimated Daily Intakes of Iron and EDTA by the US Population from the Proposed Food Fortificant Uses of Sodium Iron EDTA Trihydrate"). For infants, 0-2 years (users only), the mean and 90th percentile intakes of iron are 2.4 and 4.6 mg, respectively. Children, 3-11 years (users only), consume 3.2 and 6.4 mg iron at the mean and 90th percentile, respectively. On a body weight basis, the mean and 90th percentile consumption of iron by infants from the intended uses are 0.18 and 0.38 mg iron/kg body weight, respectively; and for 3-11 year olds, the mean and 90th percentile are 0.13 and 0.27 mg iron/kg body weight, respectively. Consumption of EDTA from sodium iron EDTA as proposed would be 0.96 mg EDTA/kg bw (mean) and 1.98 mg EDTA/kg bw (90th percentile) for infants (users only) and 0.7 mg EDTA/kg bw (mean) and 1.42 mg EDTA/kg bw for children (users only).

It should be recognized that these estimates overstate actual consumption as they are based on short term surveys of 2 to 3 days as compared to the more accurate 14-day studies sometimes available. For instance, aspartame and neotame petitions used Market Research Corporation of America (MRCA) 14-day survey data for consumption of diet soft drinks at the 90th percentile. Consumption values in the 14-day study were only a third of that reported in the three day studies. The tendency of 2 or 3 day food consumption survey data to over estimate exposure by

a factor of 2 to 3 fold is well documented by studies conducted within several European countries (IEFS, 1998). Thus, we believe consumption estimates for users only at the 90th percentile exaggerates actual consumption by a factor of at least 2. Realistically, consumption of iron by these infants and children consuming iron EDTA fortified powdered soft drinks at the 90th percentile would be less than 0.2 mg iron/kg body weight. Furthermore, consumption of EDTA over a 14-day period would not exceed 1.0 mg EDTA/kg bw/day for any age group.

E. Basis for the GRAS Determination

Pursuant to 21 CFR § 170.30, sodium iron EDTA has been determined GRAS by scientific procedures for its intended use. This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of sodium iron EDTA as a component of food. The safety of sodium iron EDTA is supported by a number of published studies including metabolic studies, acute, and medium-term toxicity studies in experimental animals, mutagenicity studies, and clinical studies on the nutritional effects of sodium iron EDTA. In addition, the GRAS status of iron salts and the safety of EDTA is supported by numerous published studies regarding metabolism and safety in experimental and clinical studies. This determination is further supported by a published safety assessment of sodium iron EDTA by the Joint WHO/FAO Expert Committee on Food Additives (See attached – EXPERT PANEL REPORT "Opinion of an Expert Panel on the GRAS Use of Sodium Iron EDTA for Iron Fortication of Dry Mix Beverage").

F. Availability of Information

The data and information that serve as a basis for this GRAS determination are available for the Food and Drug Administration's (FDA) review and copying at a reasonable time at the offices of:

Edward A. Steele

AAC Consulting Group

7361 Calhoun Place

Rockville, Md. 20855

Phone (301) 838-3120

Alternatively, copies of data and information can be provided to FDA upon request, by contacting Ed Steele.

II. Detailed Information About the Identity of the Substance

A. Identity

NaFeEDTA occurs as a pale yellow powder that is very soluble in water at pH 7.0, with approximately 50% solubility at pH's of up to 7.4. It is relatively stable and suitable in foods that are stored for long periods of time, or prepared at high temperatures.

Common Name or Usual Name: Sodium iron EDTA (NaFeEDTA)

Chemical Names: Ferric sodium EDTA; Ferric sodium edetate; Ferric sodium ethylenediaminetetraacetic acid; Sodium feredetate; Sodium ferric EDTA; Sodium ferric ethylenediaminetetraacetate; Sodium iron(III) ethylenediaminetetraacetate; Sodium ironedetate; Monosodium ferric EDTA; Monosodium ferric ethylenediaminetetraacetate

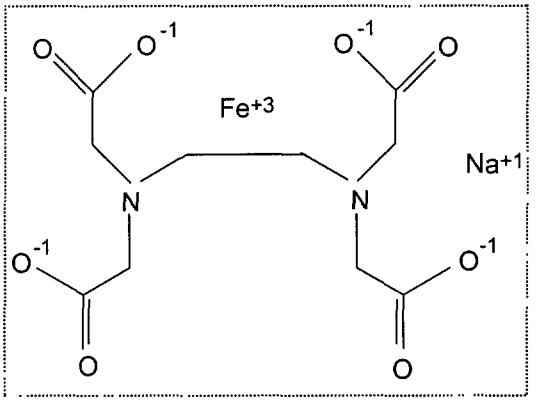
Chemical Abstracts Services (CAS) Number

CAS No. 15708-41-5

Empirical Formula and Formula Weight

$C_{10}H_{12}FeN_2NaO_8 \cdot 3H_2O$ 421.09 (trihydrate)

Structural Formula



B. Method of Manufacture

NaFeEDTA is manufactured to meet the WHO/FAO Joint Expert Committee on Food Additives (JECFA) food grade specifications cited below.

C. Specifications for Food Grade Material

Food grade specifications for NaFeEDTA appropriate for food fortification programs have been developed by WHO/FAO Joint Expert Committee on Food Additives JECFA (1999) and are summarized below.

Specification Parameter	Specification
Identification Tests	
Solubility	Soluble in water
Test for iron	Passes test
Test for sodium	Passes test
Purity	
Assay	Not less than 12.5% and not more than 13.5% iron on trihydrate basis Not less than 65.5% and not more than 70.5% EDTA on trihydrate basis
PH	3.5-5.5 (1 in 100 solution)
Water insoluble matter	Not more than 0.1%
Nitrilotriacetic acid	Not more than 0.1%
Arsenic	Not more than 1 mg/kg
Lead	Not more than 1 mg/kg

JECFA, 1999

III. Self-Limiting Levels of Use

Self-limiting concentrations of sodium iron EDTA have not been determined for dry mix beverage but the level to be added under current good manufacturing practice will not exceed 2.5 mg iron/200 ml of reconstituted beverage.

IV. Basis for GRAS Determination

The determination that sodium iron EDTA is GRAS is on the basis of scientific procedures. See attached - EXPERT PANEL REPORT: "Opinion of an Expert Panel on the GRAS Use of Sodium Iron EDTA for Iron Fortication of Dry Mix Beverage"

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ESTIMATED DAILY INTAKES OF IRON AND ETHYLENEDIAMINETETRAACETATE BY THE U.S. POPULATION FROM PROPOSED FOOD FORTIFICANT USES OF SODIUM IRON (III) ETHYLENEDIAMINETETRAACETATE TRIHYDRATE

- Draft for Discussion -

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1.0 INTRODUCTION

CANTOX HEALTH SCIENCES INTERNATIONAL (CANTOX) has completed an assessment of the consumption of iron and ethylenediaminetetraacetate (EDTA), by the U.S. population from the proposed fortificant use of Sodium Iron (III) EthylenediaminetetraacetateTrihydrate (NaFeEDTA) in dry mix beverages such as meal replacements, flavored milks, and fruit-flavored drinks. The proposed level of fortification would provide 2.5 mg of iron per 200mL serving of reconstituted beverage.

Estimates for the intakes of iron and EDTA were based on the proposed use-levels and food consumption data included in the United States Department of Agriculture (USDA) 1994-1996 Continuing Survey of Food Intakes by Individuals (CSFII 1994-1996) and the 1998 Supplemental Children's Survey (CSFII 1998) (USDA, 2000). Calculations for the mean and 90th percentile all-person and all-user intakes, and percent consumed were performed for each of the individual proposed food-uses. Similar calculations were used to determine the estimated total intakes of iron and EDTA from all proposed food-uses combined. In both cases, the per person and per kilogram body weight intakes were reported for the following population groups:

infants, ages 0 to 2;
children, ages 3 to 11;
female teenagers, ages 12 to 19;
male teenagers, ages 12 to 19;
female adults, ages 20 and up;
male adults, ages 20 and up; and
total population (all population and gender groups combined).

2.0 FOOD CONSUMPTION SURVEY DATA

2.1 Survey Description

USDA, CSFII 1994-1996 provides food consumption data on persons of all ages; whereas, CSFII 1998 is limited to children birth through 9 years of age. Combined, these surveys provide the most up-to-date data for evaluating food-use and food-consumption patterns in the United States, containing 4 years of data on individuals selected *via* stratified, multistage area probability sampling of American households within all 50 states. CSFII 1994-1996, 1998 survey data were collected from individuals and households *via* 24-hour dietary recalls administered on 2 non-consecutive days (Day 1 and Day 2) throughout all 4 seasons of the year. Data was collected in-person, a minimum of 3 days apart, on different days of the week, to achieve the desired degree of statistical independence. CSFII 1994-1996 contains 2-day dietary food consumption data for more than 15,000 individuals of all ages, and 1-day data for 16,103 individuals. CSFII 1998 contributes data from an additional 5,559 children birth through 9 years of age to data reported for 4,253 children of the same ages within CSFII 1994-1996. The overall CSFII 1994-1996, 1998 response rate for individuals selected for participation in the survey was 81.5 and 77.5% for Day 1 and Day 2, respectively.

In addition to collecting information on the types and quantities of foods being consumed, CSFII 1994-1996, 1998 collected physiological and demographic information from individual participants in the survey, such as sex, age, self-reported height and weight, and other variables useful in characterizing consumption. The inclusion of this information allows for further assessment of food intake based on consumption by specific population groups of interest within the total population. USDA sample weights were developed and incorporated with CSFII 1994-1996, 1998 to compensate for the potential under-representation of intakes from specific population groups as a result of sample variability due to survey design, differential nonresponse rates, or other factors, such as deficiencies in the sampling frame (USDA, 2000).

2.2 Statistical Methods

Consumption data from individual dietary records, detailing food items ingested by each survey participant on each of the 2 survey days, were collated by computer and used to generate estimates for the intake of iron and EDTA by the U.S. population. Estimates for the daily intakes of iron and EDTA represent projected 2-day averages for each individual from Day 1 and Day 2 of CSFII 1994-96, 1998 data; these average amounts comprised the distribution from which mean and percentile intake estimates were produced. Mean and percentile estimates were generated using ratio estimation and nonparametric techniques, respectively, incorporating USDA survey weights in order to provide representative intakes for the entire U.S. population. All-person intake refers to the estimated intakes of iron and EDTA averaged over all individuals

surveyed regardless of whether they consumed food products in which NaFeEDTA is currently proposed for use as an iron fortificant, and therefore includes "zero" consumers (those who reported no intake of the proposed food-use products during the two survey days). All-user intake refers to the estimated intakes of iron and EDTA by those individuals consuming food products in which the use of NaFeEDTA is under consideration, hence the 'all-user' designation. Individuals were considered users if they consumed 1 or more food products in which NaFeEDTA is proposed for use on either Day 1 or Day 2 of the survey.

2.3 Sample Size Criteria

Mean or percentile intake estimates based on small sample sizes or with high variability relative to the mean (assessed using the coefficient of variation) may be less statistically reliable than estimates based on adequate sample sizes (LSRO, 1995). Data presented in Appendices A to D for the estimated daily intakes of iron and EDTA from proposed food-uses, follow the guidelines proposed by the Human Nutrition Information Service/National Center for Health Statistics Analytic Working Group for evaluating the reliability of statistical estimates based on specified design effects, adopted in the "Third Report on Nutrition Monitoring in the United States" (LSRO, 1995). A "broadly calculated" design effect accounts for the variability associated with an estimate as a result of the complex sample design or survey weighting procedures. An estimated mean may be unreliable if the sample size is less than 30 times the average design effect, while estimates at or above the 75th percentile may be questionable if the sample size is less than 8 times the average design effect divided by 1 minus the percentile of interest (expressed as a fraction) (LSRO, 1995). For data from the CSFII 1994-1996, 1998, USDA has used a variance inflation factor (VIF) to approximate the design effect, based on the coefficient of variation for the survey sampling weights (USDA, 2000). The CSFII 1994-1996, 1998 uses several different VIFs based on the 4-year weights for certain age groups. VIF values for 2-day survey respondents are presented in Table 2.3-1, in conjunction with the minimum sample-sizes required to ensure the statistical reliability of mean and 90th percentile intake estimates generated from CSFII 1994-1996, 1998 data, calculated as described above.

Table 2.3-1 Summary of the Variance Inflation Factors (VIF) and Minimum-Sample Sizes Required to Ensure the Statistical Reliability of Mean and 90th Percentile Intake Estimates Generated from CSFII 1994-1996, 1998 Data

Age Group (Years)	VIF	Minimum Sample-Size Requirements (n)	
		Mean	90th Percentile
0-19	2.50	75	200
20 and Up	1.54	47	124
All Ages	2.50	75	200

Therefore, using a VIF of 2.50 for the total population, mean and 90th percentile intake estimates based on sample sizes of less than 75 and 200, respectively, may not be considered statistically reliable due to the limited sampling size (LSRO, 1995). In accordance with these minimum sample-size guidelines, estimated means or percentiles presented in Appendices A through D for the intakes of iron and EDTA that may be statistically unreliable are marked with an asterisk, and were not considered when assessing the relative contribution of specific food-uses to total iron and EDTA consumption.

3.0 FOOD USAGE DATA

The individual proposed use-levels employed in the current intake analysis are summarized in Table 3-1. These use levels are based on a fortification level that would provide 2.5 mg iron per 200 mL serving of reconstituted beverage. Food codes representative of each proposed food-use were chosen from the USDA CSFII 1994-1996, 1998 consumption surveys (USDA, 2000) and grouped in food-use categories according to Title 21, Section § 170.3 of the *Code of Federal Regulations* (CFR, 2001). Product specific adjustment factors were developed based on data provided in the standard recipe file for the USDA CSFII 1994-1996, 1998 survey (USDA, 2000). All food codes included in the current intake assessment are listed in Appendix E.

Table 3.1-1 Summary of the Individual Proposed Food-Uses and Use-Levels for Iron and the Corresponding Use-levels for EDTA in the U.S.

Food Category	Proposed Food-Use	Iron Use-Level (%)	EDTA Use-Level (%)
Beverages and Beverage Bases	Meal Replacements (Powder)	0.02	0.1
Milk Products	Flavored Milk and Milk Drinks (Powder)	0.02	0.1
Processed Fruits and Fruit Juices	Fruit-Flavored Drinks	0.0013	0.0066
	Fruit-Flavored Drinks (Powder)	0.02	0.1

4.0 FOOD SURVEY RESULTS

Estimates for the total daily intakes of iron and EDTA from all proposed food-uses are provided in Tables 4.1-1 and 4.1-2. Estimates for the daily intake of iron from individual proposed food-uses in the U.S. are summarized in Tables A-1 to A-7 and B-1 to B-7 of Appendix A and B, respectively, and that of EDTA in Tables C-1 to C-7 and D-1 to D-7 of Appendix C and D, respectively. Tables A-1 to A-7 and C-1 to C-7 provide estimates for daily intakes per person (mg/day), whereas Tables B-1 to B-7 and D-1 to D-7 provide estimates for daily intakes on a per kilogram body weight basis (mg/kg body weight/day).

4.1 Estimated Daily Intake of Iron from All Proposed Food-Uses

Table 4.1-1 summarizes the estimated total intake of iron from all proposed food-uses in the U.S. by population group. Table 4.1-2 presents this data on a per kilogram body weight basis.

Approximately 9.6% of the total U.S. population was identified as consumers of iron from the proposed food-uses (2,581 actual users identified). Consumption of these types of foods by the total U.S. population resulted in estimated mean all-person and all-user intakes of iron of 0.4 mg/person/day (0.01 mg/kg body weight/day) and 4.2 mg/person/day (0.09 mg/kg body weight/day), respectively (Tables 4.1-1 and 4.1-2). On an individual population basis, male teenagers were determined to have the greatest mean all-person (0.9 mg/person/day) and all-user (5.7 mg/person/day) intake of iron on an absolute basis. Infants and female adults had the lowest mean all-person intakes of iron on an absolute basis, with a mean intake of 0.3 mg/person/day, while infants had the lowest all-user consumption of 2.4 mg/person/day. On a body weight basis, children had the highest all-person iron intake of 0.03 mg/kg body weight/day, while infants had the highest all user intake of 0.18 mg/kg body weight/day. Female and male adults were estimated to have the lowest intakes of iron on a body weight basis, with an all-person consumption of <0.01 mg/kg body weight/day and an all-user iron intake of 0.06 mg/kg body weight/day.

Table 4.1-1 Summary of the Estimated Daily Intake of Iron from All Proposed Food Categories in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Infant	0-2	13.0	404	0.3	1.1	2.4	4.6
Child	3-11	19.8	1,330	0.6	2.3	3.2	6.4
Female Teenager	12-19	11.9	89	0.6	2.2*	4.7	9.0*
Male Teenager	12-19	15.4	118	0.9	3.0*	5.7	11.3*
Female Adult	20 and Up	7.1	328	0.3	na	4.0	7.5
Male Adult	20 and Up	6.6	312	0.4	na	5.1	11.4
Total Population	All Ages	9.6	2,581	0.4	na	4.2	8.2

*Indicates an intake estimate that may not be statistically reliable as the sample size does not meet the minimum reporting requirements described in Section 2.3.

When heavy consumers (90th percentile) were assessed, all-person intakes of iron from all proposed food-uses were also determined to be greatest in male teenagers, 3.0 mg/person/day, while all-user intakes were greatest in male adults, 11.4 mg/person/day, on an absolute basis.

90th Percentile all-person and all-user intakes were lowest in infants, 1.1 and 4.6 mg/person/day, respectively, on an absolute basis (Table 4.1-1). On a body weight basis, children were determined to have the greatest all-person 90th percentile intakes of iron of 0.09 mg/kg body weight/day, while infants were determined to have the greatest all-user 90th percentile intakes, 0.18 mg/kg body weight/day (Table 4.1-2). Both female and male adults were identified as having the lowest all-person 90th percentile intakes of iron on a body weight basis, <0.01 mg/kg body weight/day, while female adults had the lowest all-user 90th percentile intakes, 0.12 mg/kg body weight/day.

Table 4.1-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of Iron from All Proposed Food Categories in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Infant	0-2	13.0	404	0.02	0.08	0.18	0.38
Child	3-11	19.8	1,330	0.03	0.09	0.13	0.27
Female Teenager	12-19	11.9	89	0.01	0.04	0.08	0.15
Male Teenager	12-19	15.4	118	0.01	0.05	0.09	0.17
Female Adult	20 and Up	7.1	328	<0.01	na	0.06	0.12
Male Adult	20 and Up	6.6	312	<0.01	na	0.06	0.13
Total Population	All Ages	9.6	2,581	0.01	na	0.09	0.20

4.2 Estimated Daily Intake of EDTA from All Proposed Food-Uses

Table 4.2-2 summarizes the estimated total intake of EDTA from all proposed food-uses in the U.S. by population group. Table 4.2-2 presents this data on a per kilogram body weight basis.

The estimated total intake of EDTA from all proposed food-uses of Na Fe EDTA as an iron fortificant in the U.S. by population group is summarized in Table 4.2-1. Table 4.2-2 presents this data on a per kilogram body weight basis.

Table 4.2-1 Summary of the Estimated Daily Intake of EDTA from All Proposed Food Categories in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Infant	0-2	13.0	404	1.6	5.9	12.4	24.2
Child	3-11	19.8	1,330	3.3	12.3	16.7	33.4
Female Teenager	12-19	11.9	89	2.9	11.8	24.5	47.2
Male Teenager	12-19	15.4	118	4.6	15.7	29.8	59.0
Female Adult	20 and Up	7.1	328	1.5	na	21.2	39.3
Male Adult	20 and Up	6.6	312	1.8	na	26.6	59.9
Total Population	All Ages	9.6	2,581	2.1	na	21.8	43.0

Approximately 9.6% of the total U.S. population was identified as consumers of EDTA from the proposed food-uses (2,581 actual users identified). Consumption of these types of foods by the total U.S. population resulted in estimated mean all-person and all-user intakes of EDTA of 2.1 mg/person/day (0.05 mg/kg body weight/day) and 21.8 mg/person/day (0.49 mg/kg body weight/day), respectively (Tables 4.2-1 and 4.2-2). On an individual population basis, male teenagers were determined to have the greatest mean all-person (4.6 mg/person/day) and all-user (29.8 mg/person/day) intake of EDTA on an absolute basis. Female adults had the lowest mean all-person intakes of EDTA on an absolute basis, with a mean intake of 1.5 mg/person/day, while infants had the lowest all-user consumption of 12.4 mg/person/day. On a body weight basis, children had the highest all-person EDTA intake of 0.14 mg/kg body weight/day, while infants had the highest all user intake of 0.96 mg/kg body weight/day. Both female and male adults were estimated to have the lowest all-person intakes of EDTA on a body weight basis at 0.02 mg/kg body weight/day, while females had the lowest all-user EDTA intake of 0.32 mg/kg body weight/day.

When heavy consumers (90th percentile) were assessed all-person intakes of EDTA from all proposed food-uses were also determined to be greatest in male teenagers, 15.7 mg/person/day, while all-user intakes were greatest in male adults, 59.9 mg/person/day, on an absolute basis. 90th percentile all-person and all-user intakes were lowest in infants, 5.9 and 24.2 mg/person/day, respectively, on an absolute basis (Table 4.1-1). On a body weight basis, children were determined to have the greatest all-person 90th percentile intakes of EDTA of 0.50 mg/kg body weight/day, while infants were determined to have the greatest all-user 90th percentile intakes, 1.98 mg/kg body weight/day (Table 4.1-2). Both female and male adults were identified as having the lowest all-person 90th percentile intakes of EDTA on a body weight basis,

0.02 mg/kg body weight/day, while female adults had the lowest all-user 90th percentile intakes, 0.32 mg/kg body weight/day.

Table 4.2-2 Summary of the Estimated Daily Per Kilogram Body Weight Intake of EDTA from All Proposed Food Categories in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)

Population Group	Age Group (Years)	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
				Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Infant	0-2	13.0	404	0.12	0.41	0.96	1.98
Child	3-11	19.8	1,330	0.14	0.50	0.70	1.42
Female Teenager	12-19	11.9	89	0.05	0.19	0.44	0.78
Male Teenager	12-19	15.4	118	0.07	0.25	0.49	0.91
Female Adult	20 and Up	7.1	328	0.02	na	0.32	0.65
Male Adult	20 and Up	6.6	312	0.02	na	0.33	0.71
Total Population	All Ages	9.6	2,581	0.05	na	0.49	1.03

Based on the proposed food uses and uses levels for iron fortification as outline in Table3.1-1, consumption of the proposed foods by the total U.S. population resulted in estimated mean all-person and all-user intakes of NaFeEDTA of 3.02 mg/person/day (0.07 mg/kg body weight/day) and 31.4 mg/person/day (0.70 mg/kg body weight/day), respectively.

4.3 Estimated Daily Intake of Iron and EDTA from the Individual Proposed Food-Uses

4.3.1 All-Person Intakes

Estimates for the mean and 90th percentile daily intakes on a mg/person/day basis for iron and EDTA from each individual food category are summarized in Tables A-1 to A-7 and C-1 to C-7, respectively, and on a mg/kg body weight/day basis in Tables B-1 to B-7 and D-1 to D-7. Fruit-flavored drinks consumed by the total population made the most significant contribution to the mean all-person intake of iron, 0.37 mg/ person/day (0.01 mg/kg body weight/day) and EDTA 1.93 mg/person/day (0.04 mg/kg body weight/day), respectively. Consumption of meal replacement beverages, and flavored milk drinks, made lesser contributions to the intakes of iron, ranging from <0.01 to 0.02 mg/person/day (<0.1 mg/kg body weight/day) and EDTA, ranging from 0.01 to 0.11 mg/person/day (<0.1 mg/kg body weight/day). All-person 90th percentile intakes could not be interpreted.

Approximately 23 individuals within the total population reported consuming powdered fruit-flavored drinks, while meal replacement beverages had 41 consumers and 92 individuals consumed flavored milk drinks. For the total CSFII 1994-1996, 1998 surveyed sample, mean and 90th percentile intake estimates based on sample sizes of less than 75 and 200, respectively, may not be statistically reliable due to the small sample sizes (Section 2.3). As a result, estimates for the intakes of iron and EDTA based on the consumption of these foods by the total U.S. population should be interpreted with caution, as they may be unreliable.

4.3.2 All-User Intakes

Estimates for the mean all-user intakes on a mg/person/day basis for iron and EDTA from each individual food category are summarized in Tables A-1 to A-7 and C-1 to C-7, respectively, and on a mg/kg body weight/day basis in Tables B-1 to B-7 and D-1 to D-7. In contrast to the results observed for the all-person intakes of iron and EDTA, meal replacement beverage consumers were identified as having the greatest mean and 90th percentile all-user intakes of iron and EDTA.

Estimates for the mean and 90th percentile all-user intakes of iron by the total population from meal replacement beverages were 7.38 mg/person/day (0.11 mg/kg body weight/day) and 14.8 mg/person/day (0.20 mg/kg body weight/day), respectively. Estimates for the mean and 90th percentile all-user intakes of EDTA by the total population from meal replacement beverages were 38.7 mg/person/day (0.57 mg/kg body weight/day) and 77.6 mg/person/day (1.04 mg/kg body weight/day), respectively. However, only 0.3% of the total population was identified as meal replacement beverage consumers. When the relative contribution of each of the proposed food-uses to the total intakes of iron and EDTA from all proposed food-uses is examined, meal replacement beverages have a smaller impact on the total all-user intakes of iron and EDTA by the U.S. population, relative to the consumption of fruit-flavored drinks. The mean and 90th percentile all-user intakes of iron from fruit-flavored drinks were 4.06 mg/person/day (0.09 mg/kg body weight/day) and 7.74 mg/person/day (0.19 mg/kg body weight/day), respectively. The mean and 90th percentile all-user intakes of EDTA from fruit-flavored drinks were 21.3 mg/person/day (0.48 mg/kg body weight/day) and 40.5 mg/person/day (1.02 mg/kg body weight/day), respectively.

The consumption of flavored milk and milk drinks make a contribution to iron and EDTA all-user intakes, however, only 0.11 to 0.18% of the total population was identified as consumers of these proposed food-uses, therefore these categories actually have a minor impact on the total all-user intake of iron and EDTA relative to fruit-flavored drinks.

On an individual population group basis (Tables A-1 to A-6, B-1 to B-6, C-1 to C-6, and D-1 to D-6) intake estimates for many of the proposed food uses, with the exception of fruit-flavored drinks, were unreliable due to small numbers of users, as described in Section 2.3. Thus,

consumption of fruit-flavored drinks only is considered. Male teenagers consuming fruit-flavored drinks experienced the highest mean all-user intakes of iron, 5.6 mg/person/day and the highest 90th percentile intakes, 10.5 mg/person/day. Male teenagers consuming fruit-flavored drinks also consumed the most EDTA, with mean all-user intakes of 29.3 mg/person/day and 90th percentile intakes of 55.0 mg/person/day. On a per kilogram body weight basis, infants consuming fruit-flavored drinks experienced the highest mean all-user intakes of iron, 0.19 mg/kg body weight/day and highest 90th percentile intakes of 0.38 mg/kg body weight/day. Intakes of EDTA on a per kilogram body weight basis for populations consuming fruit-flavored drinks were highest in infants for the mean, 0.99 mg/kg body weight/day, and the 90th percentile, 1.99 mg/kg body weight/day.

5.0 CONCLUSIONS

Consumption data and information pertaining to the individual proposed food-uses were used to estimate the all-person and all-user intakes of iron and EDTA, from the addition of NaFeEDTA as an iron fortificant, for specific demographic groups and for the total U.S. population. This type of intake methodology is generally considered to be 'worst case' as a result of several conservative assumptions made in the consumption estimates. For example, it is often assumed that all food products within a food category contain the ingredient at the maximum specified level of use. In addition, it is well established that the length of a dietary survey affects the estimated consumption of individual users. Short-term surveys, such as the typical 2 or 3-day dietary surveys, overestimate consumption of food products that are consumed relatively infrequently.

In summary, on an all-user basis, the mean intake of iron by the total U.S. population from all proposed food-uses was estimated to be 4.2 mg/person/day or 0.09 mg/kg body weight/day. The mean intake of EDTA on an all-user basis by the total U.S. population from all proposed food-uses was estimated to be 21.8 mg/person/day or 0.49 mg/kg body weight/day. The heavy consumer (90th percentile) all-user intake of iron by the total U.S. population from all proposed food-uses was estimated to be 8.2 mg/person/day or 0.20 mg/kg body weight/day, while that of EDTA was 43.0 mg/person/day or 1.03 mg/person/day.

6.0 REFERENCES

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APPENDIX A

Estimated Daily Intake of Iron from Individual Proposed Food-Uses by Different Population Groups Within the United States

Table A-1 Estimated Daily Intake of Iron from Individual Proposed Food-Uses by Infants Aged 0 to 2 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Beverages and Beverage Bases						
Meal Replacements (Powder)	0.03	1	<0.01*	na	3.70*	3.70*
Milk Products						
Flavored Milk and Milk Drinks (Powder)	0.74	24	0.01*	na	1.13*	2.20*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	12.26	378	0.30	0.78	2.42	4.63
Fruit-Flavored Drinks (Powder)	0.11	4	<0.01*	na	0.84*	1.40*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

Table A-2 Estimated Daily Intake of Iron from Individual Proposed Food-Uses by Children Aged 3 to 11 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Beverages and Beverage Bases						
Meal Replacements (Powder)	0.18	11	0.01*	na	4.87*	7.40*
Milk Products						
Flavored Milk and Milk Drinks (Powder)	0.64	61	0.01*	na	1.80*	4.40*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	18.90	1,258	0.60	2.28	3.18	6.25
Fruit-Flavored Drinks (Powder)	0.12	8	0.01*	na	9.10*	13.60*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

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Table A-3 Estimated Daily Intake of Iron from Individual Proposed Food-Uses by Female Teenagers Aged 12 to 19 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Beverages and Beverage Bases						
Meal Replacements (Powder)	0.15	1	<0.01*	na	3.70*	3.70*
Milk Products						
Flavored Milk and Milk Drinks (Powder)	0.25	1	<0.01*	na	0.60*	0.60*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	11.33	85	0.51	1.95*	4.53	9.00*
Fruit-Flavored Drinks (Powder)	0.18	2	0.03*	na	19.20*	32.40*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

Table A-4 Estimated Daily Intake of Iron from Individual Proposed Food-Uses by the Male Teenagers Aged 12 to 19 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Beverages and Beverage Bases						
Meal Replacements (Powder)	0.37	2	0.02*	na	5.23*	7.40*
Milk Products						
Flavored Milk and Milk Drinks (Powder)	0	0	na	na	Na	na
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	15.19	116	0.85	3.0*	5.60	10.50*
Fruit-Flavored Drinks (Powder)	0.04	1	0.01*	na	20.00*	20.00*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

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Table A-5 Estimated Daily Intake of Iron from Individual Proposed Food-Uses by Female Adults Aged 20 and Over Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Beverages and Beverage Bases						
Meal Replacements (Powder)	0.39	13	0.02*	na	6.21*	7.40*
Milk Products						
Flavored Milk and Milk Drinks (Powder)	0.08	4	<0.01*	na	0.75*	1.80*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	6.63	311	0.26	na	3.97	7.50
Fruit-Flavored Drinks (Powder)	0.07	2	<0.01*	na	0.83*	0.90*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

Table A-6 Estimated Daily Intake of Iron from Individual Proposed Food-Uses by Male Adults Aged 20 and Over Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Beverages and Beverage Bases						
Meal Replacements (Powder)	0.31	13	0.03*	na	10.20*	21.50*
Milk Products						
Flavored Milk and Milk Drinks (Powder)	0.05	2	<0.01*	na	2.65*	6.60*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	6.16	293	0.30	na	4.83	10.00
Fruit-Flavored Drinks (Powder)	0.14	6	0.01*	na	4.51*	11.50*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

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Table A-7 Estimated Daily Intake of Iron from Individual Proposed Food-Uses by the Total Population (All Ages) Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Beverages and Beverage Bases						
Meal Replacements (Powder)	0.30	41	0.02*	na	7.38*	14.80*
Milk Products						
Flavored Milk and Milk Drinks (Powder)	0.18	92	<0.01	na	1.49	4.40*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	9.08	2,441	0.37	na	4.06	7.74
Fruit-Flavored Drinks (Powder)	0.11	23	0.01*	na	5.87*	13.60*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

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APPENDIX B

Estimated Daily Per Kilogram Body Weight Intake of Iron from Individual Proposed Food-Uses by Different Population Groups Within the United States

Table B-1 Estimated Daily Per Kilogram Body Weight Intake of Iron from Individual Proposed Food-Uses by Infants Aged 0 to 2 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Beverages and Beverage Bases						
Meal Replacements	0.03	1	<0.01*	na	0.22*	0.22*
Milk Products						
Flavored Milk and Milk Drinks	0.74	24	<0.01*	na	0.08*	0.16*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	12.26	378	0.02	0.07	0.19	0.38
Fruit-Flavored Drinks (Powder)	0.11	4	<0.01*	na	0.07*	0.14*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

Table B-2 Estimated Daily Per Kilogram Body Weight Intake of Iron from Individual Proposed Food-Uses by Children Aged 3 to 11 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Beverages and Beverage Bases						
Meal Replacements	0.18	11	<0.01*	na	0.18*	0.21*
Milk Products						
Flavored Milk and Milk Drinks	0.64	61	<0.01*	na	0.08*	0.20*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	18.9	1,258	0.02	0.09	0.13	0.27
Fruit-Flavored Drinks (Powder)	0.12	8	<0.01*	na	0.47*	0.88*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

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Table B-3 Estimated Daily Per Kilogram Body Weight Intake of Iron from Individual Proposed Food-Uses by Female Teenagers Aged 12 to 19 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Beverages and Beverage Bases						
Meal Replacements	0.15	1	<0.01*	na	0.06*	0.06*
Milk Products						
Flavored Milk and Milk Drinks	0.25	1	<0.01*	na	0.01*	0.01*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	11.33	85	0.01	0.03*	0.08	0.14*
Fruit-Flavored Drinks (Powder)	0.18	2	<0.01*	na	0.36*	0.72*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

Table B-4 Estimated Daily Per Kilogram Body Weight Intake of Iron from Individual Proposed Food-Uses by Male Teenagers Aged 12 to 19 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Beverages and Beverage Bases						
Meal Replacements	0.37	2	<0.01*	na	0.08*	0.09*
Milk Products						
Flavored Milk and Milk Drinks	0	0	na	na	na	na
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	15.19	116	0.01	0.05*	0.09	0.17*
Fruit-Flavored Drinks (Powder)	0.04	1	<0.01*	na	0.32*	0.32*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

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Table B-5 Estimated Daily Per Kilogram Body Weight Intake of Iron from Individual Proposed Food-Uses by Female Adults Aged 20 and Over Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Beverages and Beverage Bases						
Meal Replacements	0.39	13	<0.01*	na	0.10*	0.15*
Milk Products						
Flavored Milk and Milk Drinks	0.08	4	<0.01*	na	0.01*	0.04*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	6.63	311	<0.01	na	0.06	0.11
Fruit-Flavored Drinks (Powder)	0.07	2	<0.01*	na	0.01*	0.01*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

Table B-6 Estimated Daily Per Kilogram Body Weight Intake of Iron from Individual Proposed Food-Uses by Male Adults Aged 20 and Over Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Beverages and Beverage Bases						
Meal Replacements	0.31	13	<0.01*	na	0.11*	0.20*
Milk Products						
Flavored Milk and Milk Drinks	0.05	2	<0.01*	na	0.03*	0.07*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	6.16	293	<0.01	na	0.06	0.13
Fruit-Flavored Drinks (Powder)	0.14	6	<0.01*	na	0.05*	0.14*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

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Table B-7 Estimated Daily Per Kilogram Body Weight Intake of Iron from Individual Proposed Food-Uses by the Total Population (All Ages) Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Beverages and Beverage Bases						
Meal Replacements	0.30	41	<0.01*	na	0.11*	0.20*
Milk Products						
Flavored Milk and Milk Drinks	0.18	92	<0.01	na	0.06	0.16*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	9.08	2441	0.01	na	0.09	0.19
Fruit-Flavored Drinks (Powder)	0.11	23	<0.01*	na	0.14*	0.60*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

000133

APPENDIX C

Estimated Daily Intake of EDTA from Individual Proposed Food-Uses by Different Population Groups Within the United States

Table C-1 Estimated Daily Intake of EDTA from Individual Proposed Food-Uses by Infants Aged 0 to 2 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Beverages and Beverage Bases						
Meal Replacements (Powder)	0.03	1	0.01*	na	19.40*	19.40*
Milk Products						
Flavored Milk and Milk Drinks (Powder)	0.74	24	0.04*	na	5.93*	11.50*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	12.26	378	1.56	4.09	12.70	24.20
Fruit-Flavored Drinks (Powder)	0.11	4	<0.01*	na	4.41*	7.34*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

Table C-2 Estimated Daily Intake of EDTA from Individual Proposed Food-Uses by Children Aged 3 to 11 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Beverages and Beverage Bases						
Meal Replacements (Powder)	0.18	11	0.05*	na	25.50*	38.80*
Milk Products						
Flavored Milk and Milk Drinks (Powder)	0.64	61	0.06*	na	9.42*	23.10*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	18.9	1,258	3.15	12.0	16.70	32.80
Fruit-Flavored Drinks (Powder)	0.12	8	0.05*	na	47.70*	71.30*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

000135

Table C-3 Estimated Daily Intake of EDTA from Individual Proposed Food-Uses by Female Teenagers Aged 12 to 19 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Beverages and Beverage Bases						
Meal Replacements (Powder)	0.15	1	0.03*	na	19.40*	19.40*
Milk Products						
Flavored Milk and Milk Drinks (Powder)	0.25	1	0.01*	na	3.14*	3.14*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	11.33	85	2.69	10.20*	23.80	47.20*
Fruit-Flavored Drinks (Powder)	0.18	2	0.18*	na	101.00*	170.00*

*Indicates an intake estimate that may not be statistically reliable as the sample size does not meet the minimum reporting requirements described in Section 2.3

Table C-4 Estimated Daily Intake of EDTA from Individual Proposed Food-Uses by the Male Teenagers Aged 12 to 19 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Beverages and Beverage Bases						
Meal Replacements (Powder)	0.37	2	0.10*	na	27.40*	38.80*
Milk Products						
Flavored Milk and Milk Drinks (Powder)	0	0	na	na	na	Na
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	15.19	116	4.45	15.70*	29.30	55.00*
Fruit-Flavored Drinks (Powder)	0.04	1	0.04*	na	105.00*	105.00*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

000136

Table C-5 Estimated Daily Intake of EDTA from Individual Proposed Food-Uses by Female Adults Aged 20 and Over Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Beverages and Beverage Bases						
Meal Replacements (Powder)	0.39	13	0.13*	na	32.5*	38.80*
Milk Products						
Flavored Milk and Milk Drinks (Powder)	0.08	4	<0.01*	na	3.95*	9.43*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	6.63	311	1.38	na	20.80	57.30
Fruit-Flavored Drinks (Powder)	0.07	2	<0.01*	na	4.36*	4.74*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

Table C-6 Estimated Daily Intake of EDTA from Individual Proposed Food-Uses by Male Adults Aged 20 and Over Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Beverages and Beverage Bases						
Meal Replacements (Powder)	0.31	13	0.16*	na	53.60*	113.00*
Milk Products						
Flavored Milk and Milk Drinks (Powder)	0.05	2	0.01*	na	13.90*	34.60*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	6.16	293	1.56	na	25.30	52.60
Fruit-Flavored Drinks (Powder)	0.14	6	0.03*	na	23.60*	60.30*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

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Table C-7 Estimated Daily Intake of EDTA from Individual Proposed Food-Uses by the Total Population (All Ages) Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg)	90th Percentile (mg)	Mean (mg)	90th Percentile (mg)
Beverages and Beverage Bases						
Meal Replacements (Powder)	0.30	41	0.11*	na	38.70*	77.60*
Milk Products						
Flavored Milk and Milk Drinks (Powder)	0.18	92	0.01	na	7.83	23.10*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	9.08	2,441	1.93	na	21.30	40.50
Fruit-Flavored Drinks (Powder)	0.11	23	0.03*	na	30.70*	71.30*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

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APPENDIX D

Estimated Daily Per Kilogram Body Weight Intake of EDTA from Individual Proposed Food-Uses by Different Population Groups Within the United States

Table D-1 Estimated Daily Per Kilogram Body Weight Intake of EDTA from Individual Proposed Food-Uses by Infants Aged 0 to 2 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Beverages and Beverage Bases						
Meal Replacements	0.03	1	<0.01*	na	1.16*	1.16*
Milk Products						
Flavored Milk and Milk Drinks	0.74	24	<0.01*	na	0.41*	0.85*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	12.26	378	0.12	0.39	0.99	1.99
Fruit-Flavored Drinks (Powder)	0.11	4	<0.01*	na	0.38*	0.74*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

Table D-2 Estimated Daily Per Kilogram Body Weight Intake of EDTA from Individual Proposed Food-Uses by Children Aged 3 to 11 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Beverages and Beverage Bases						
Meal Replacements	0.18	11	<0.01*	na	0.95*	1.13*
Milk Products						
Flavored Milk and Milk Drinks	0.64	61	<0.01*	na	0.44*	1.04*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	18.9	1,258	0.13	0.47	0.70	1.40
Fruit-Flavored Drinks (Powder)	0.12	8	<0.01*	na	2.48*	4.64*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

000140

Table D-3 Estimated Daily Per Kilogram Body Weight Intake of EDTA from Individual Proposed Food-Uses by Female Teenagers Aged 12 to 19 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Beverages and Beverage Bases						
Meal Replacements	0.15	1	<0.01*	na	0.32*	0.32*
Milk Products						
Flavored Milk and Milk Drinks	0.25	1	<0.01*	na	0.06*	0.06*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	11.33	85	0.05	0.17*	0.43	0.73*
Fruit-Flavored Drinks (Powder)	0.18	2	<0.01*	na	1.90*	3.76*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

Table D-4 Estimated Daily Per Kilogram Body Weight Intake of EDTA from Individual Proposed Food-Uses by Male Teenagers Aged 12 to 19 Years Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Beverages and Beverage Bases						
Meal Replacements	0.37	2	<0.01*	na	0.40*	0.45*
Milk Products						
Flavored Milk and Milk Drinks	0	0	na	na	na	na
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	15.19	116	0.07	0.25*	0.48	0.91*
Fruit-Flavored Drinks (Powder)	0.04	1	<0.01*	na	1.66*	1.66*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

000141

Table D-5 Estimated Daily Per Kilogram Body Weight Intake of EDTA from Individual Proposed Food-Uses by Female Adults Aged 20 and Over Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Beverages and Beverage Bases						
Meal Replacements	0.39	13	<0.01*	na	0.52*	0.80*
Milk Products						
Flavored Milk and Milk Drinks	0.08	4	<0.01*	na	0.07*	0.19*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	6.63	311	0.02	na	0.32	0.60
Fruit-Flavored Drinks (Powder)	0.07	2	<0.01*	na	0.08*	0.08*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

Table D-6 Estimated Daily Per Kilogram Body Weight Intake of EDTA from Individual Proposed Food-Uses by Male Adults Aged 20 and Over Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Beverages and Beverage Bases						
Meal Replacements	0.31	13	<0.01*	na	0.60*	1.04*
Milk Products						
Flavored Milk and Milk Drinks	0.05	2	<0.01*	na	0.15*	0.37*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	6.16	293	0.02	na	0.31	0.68
Fruit-Flavored Drinks (Powder)	0.14	6	<0.01*	na	0.29*	0.72*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

000142

Table D-7 Estimated Daily Per Kilogram Body Weight Intake of EDTA from Individual Proposed Food-Uses by the Total Population (All Ages) Within the United States (1994-1996, 1998 USDA CSFII Data)

Food-Use Category	% Users	Actual # of Total Users	All-Person Consumption		All-Users Consumption	
			Mean (mg/kg)	90th Percentile (mg/kg)	Mean (mg/kg)	90th Percentile (mg/kg)
Beverages and Beverage Bases						
Meal Replacements	0.30	41	<0.01*	na	0.57*	1.04*
Milk Products						
Flavored Milk and Milk Drinks	0.18	92	<0.01	na	0.32	0.84*
Processed Fruits and Fruit Juices						
Fruit-Flavored Drinks	9.08	2441	0.04	na	0.48	1.02
Fruit-Flavored Drinks (Powder)	0.11	23	<0.01*	na	0.73*	3.15*

*Indicates an intake estimate that may not be statistically reliable, as the sample size does not meet the minimum reporting requirements described in Section 2.3.

000143

APPENDIX E

Representative USDA CSFII 1994-1996, 1998 Food Codes for All Proposed Food-Uses for Sodium Iron (III) Ethylenediaminetetraacetate, Trihydrate, as an Iron Fortificant in the United States

Representative USDA CSFII 1994-1996, 1998 Food Codes for All Proposed Food-Uses for Iron in the United States

Beverages and Beverage Bases

Meal Replacements
(adjustment for reconstitution, assuming 15 g of powder to 240 ml of water)
[Iron] = 2.0 $\times 10^{-2}$%

11830800	Instant breakfast, powder, not reconstituted
11830810	Instant breakfast, powder, sweetened with low calorie sweetener, not reconstituted

Milk Products

Flavored Milk and Milk Drinks
(adjustment for reconstitution, assuming 15g of powder to 240 ml of milk)
[Iron] = 2.0 $\times 10^{-2}$%

11830400	Milk beverage, powder, dry mix, not reconstituted, flavors other than chocolate

Processed Fruits and Fruit Juices

Fruit-Flavored Drinks
(Iron concentration of 3.0 mg/RACC, RACC of 240 ml)
[Iron] = 1.3 $\times 10^{-3}$%

92541010	Fruit-flavored drink, made from sweetened powdered mix (fortified with vitamin C)
92541020	Lemonade-flavored drink, made from powdered mix, with sugar and vitamin C added
92541040	Lemonade-flavored drink, made from powdered mix, low calorie, with vitamin C added
92541100	Apple cider-flavored drink, made from powdered mix, with sugar and vitamin C added
92541120	Apple cider-flavored drink, made from powdered mix, low calorie, with vitamin C added
92542000	Fruit-flavored drink, made from powdered mix, mainly sugar, with high vitamin C added
92544000	Fruit-flavored drink, made from unsweetened powdered mix (fortified with vitamin C), with sugar added
92552000	Fruit-flavored drink, made from powdered mix with high vitamin C added, low calorie
92731000	Fruit-flavored drink, non-carbonated, made from powdered mix, with sugar
92741000	Fruit-flavored drink, non-carbonated, made from low calorie powdered mix

Fruit-Flavored Drinks
(adjustment for reconstitution, assuming 15g of powder to 240 ml of water)
[Iron] = 2.0 $\times 10^{-2}$%

92900100	Tang, dry concentrate
92900110	Fruit-flavored concentrate, dry powder, with sugar and vitamin C added
92900200	Fruit-flavored beverage, dry concentrate, low calorie, not reconstituted
92900300	Fruit-flavored thirst quencher beverage, dry concentrate, not reconstituted

000145

SUBMISSION END

AM

04-05904P96927-ARNV

04-06-15A 7:38 RCVD

VIA FEDERAL EXPRESS

June 10, 2004

Robert Martin, Ph.D.
Office of Premarket Approval (HFF-200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

AAC CONSULTING GROUP

7361 Calhoun Place,
Suite 500
Rockville, Maryland 20855-2765
301.838.3120
fax: 301.838.3182

RE: Submission of GRAS Notification of Sodium Iron EDTA for Use as a Fortificant in Dry Mix Beverage on behalf of Kraft Foods, Inc.

Dear Dr. Martin:

Enclosed please find three (3) original GRAS Exemption Claim pages signed by Edward A. Steele. This page was inadvertently left unsigned when the original GRAS Notification was submitted.

Please let me know if you have any questions.

Sincerely, (b) (6)

(b) (6)

BEST ORIGINAL COPY

Edward A. Steele
Vice President
Food, Dietary Supplement & Cosmetic Consulting

Enclosures

000147

AM

Fasano, Jeremiah

From: James Barnett [jbarnett@aacgroup.com]
Sent: Wednesday, October 06, 2004 9:30 AM
To: Ed Steele; Jeremiah Fasano
Cc: Katherine Trivelli
Subject: RE: GRN 152 (NaFeEDTA) Request for Clarifications

Ed/Dr. Fasano:
I spoke to Dr. Flamm this AM and will forward the inquiry FEDEX today. He and I will work together to prepare a response to Dr. Fasano's questions. Ed, could you send me an electronic copy of the GRAS determination? Alternatively, I could pick up a hard copy Friday in Rockville. Thanks Jim Barnett

-----Original Message-----
From: Fasano, Jeremiah [mailto:Jeremiah.Fasano@cfsan.fda.gov]
Sent: Tuesday, October 05, 2004 8:02 PM
To: Ed Steele
Cc: Glew, Jeanette G
Subject: Re: GRN 152 (NaFeEDTA) Request for Clarifications

Dear Mr. Steele:

Per our phone conversation of this afternoon, I am relaying to you in written form the points on which we would like clarification of Kraft's GRAS notice (GRN 152) for the use of sodium iron EDTA as an iron fortificant in powdered beverage mixes in areas of the world with a high prevalence of iron deficiency.

1) The notice includes a report prepared for Kraft by CANTOX Health Sciences. The report is stamped 'Confidential' on every page. We would like to clarify our understanding that this report should no longer be considered confidential business information.

2) The notice does not contain a method of manufacture for sodium iron EDTA. We would like to see either a description of the intended method of manufacture or a reference to a published method.

3) Although the notice does not mention infant formula, it includes estimates of exposure for infants (ages 0-2 years). Since the category of intended use is powdered beverages, we would like to confirm our understanding that the intended use does not include infant formulas.

4) The notice does not discuss the estimated contribution of sodium iron EDTA to total dietary intake of iron, although it does address the potential for acute iron poisoning. We recognize that a conventional exposure estimate for total dietary intake similar to that calculated for EDTA in the notice may be difficult given the intended use. However, we consider that it would be appropriate to provide a statement elaborating on the estimated contribution of sodium iron EDTA to total dietary intake of iron in populations where the ingredient would be used. Such a statement should consider the intake of iron from other dietary sources and the Institute of Medicine's tolerable upper limit of iron intake.

000155

We would appreciate written confirmation of our understanding on points 1 and 3, a description or reference to the intended method of manufacture, and a statement on point 4 as soon as conveniently possible. You indicated in our

AM

Fasano, Jeremiah

From: James Barnett [jbarnett@aacgroup.com]
Sent: Thursday, October 28, 2004 9:57 AM
To: Fasano, Jeremiah
Cc: Gary Flamm
Subject: RE: GRN 152 (NaFeEDTA) Request for Clarifications

Dear Dr. Fasano:
In my last communication with Dr. Flamm, he and the client thought the response should be relatively straightforward and agreed that they would handle the response. Therefore, I am requesting by this e-mail that Dr. Flamm respond to your inquiry. Regards, Jim Barnett

-----Original Message-----
From: Fasano, Jeremiah [mailto:Jeremiah.Fasano@cfsan.fda.gov]
Sent: Wednesday, October 27, 2004 5:23 PM
To: 'James Barnett'
Subject: RE: GRN 152 (NaFeEDTA) Request for Clarifications

Dr. Barnett:

This is just a quick note to get a feel for your progress in preparing a response to our questions of October 5th regarding GRAS Notice 000152 (sodium iron EDTA). Do you know when we are likely to see it?

Regards-

-Jeremiah Fasano

Jeremiah Fasano, Ph.D.
Consumer Safety Officer
DBGNR/OFAS/CFSAN/FDA

jfasano@cfsan.fda.gov
Phone: 202-418-3352
Fax: 202-418-3179

HFS-255
5100 Paint Branch Parkway
College Park, MD 20740
-----Original Message-----
From: James Barnett [mailto:jbarnett@aacgroup.com]
Sent: Wednesday, October 06, 2004 9:30 AM
To: Ed Steele; Jeremiah Fasano
Cc: Katherine Trivelli
Subject: RE: GRN 152 (NaFeEDTA) Request for Clarifications

Ed/Dr. Fasano:
I spoke to Dr. Flamm this AM and will forward the inquiry FEDEX today. He and I will work together to prepare a response to Dr. Fasano's questions. Ed, could you send me an electronic copy of the GRAS determination? Alternatively, I could pick up a hard copy Friday in Rockville. Thanks Jim Barnett

-----Original Message-----
From: Fasano, Jeremiah [mailto:Jeremiah.Fasano@cfsan.fda.gov]
Sent: Tuesday, October 05, 2004 8:02 PM

AM

Fasano, Jeremiah

From: Ed Steele [esteele@aacgroup.com]
Sent: Saturday, November 13, 2004 2:32 PM
To: Jeremiah.Fasano@cfsan.fda.gov
Cc: Gary Flamm; Katherine Trivelli
Subject: GRN 152 (NaFeEDTA) - Clarification

Dear Dr. Fasano:

This responds to your e-mail of October 5, 2004 concerning AAC's submission of GRAS Notice GRN 152 on behalf of Kraft Foods Global. There were four points on which clarification was sought. I will address each point separately:

Point 1:

The first point concerned the CanTox report which was stamped confidential. We confirm that the CanTox report should no longer be considered confidential.

Point 2:

This response addresses point 2 in your e-mail in which we were requested to provide either a description of the intended method or a reference to a published method.

Kraft Foods Global intends to obtain sodium iron EDTA from Akzo Nobel (US address: Akzo Nobel Functional Chemicals, 1747 Fort Amanda Road, Lima, Ohio 45804-1864). Akzo Nobel is a principal manufacturer of sodium iron EDTA under the trade name Ferrazone (www.ferrazone.com). Ferrazone is produced under GMP conditions and meets JECFA specifications. The manufacturing process is given in the attached file, Ferrazone Production Process, which is marked confidential. We request that such manufacturing information be treated as confidential in accordance with 21 CFR 20.44. As indicated, the manufacturing process involves only GRAS affirmed and GRAS listed (under Part 182) substances, and an additive approved for direct addition to human food. The process is conducted under mild conditions in water and does not require extensive purification to meet JECFA specification. Thus, the process is simple and straightforward and does not raise any questions of safety.

Point 3:

Relative to point 3, we confirm your understanding that the intended use of sodium iron EDTA does not include infant formulas.

Point 4:

You have requested we provide a statement elaborating on the estimated contribution of sodium iron EDTA to total dietary iron in populations where the ingredient would be used and to consider the intake of iron from other dietary sources and the Institute of Medicine's (IOM) tolerable upper limit (TUL) of iron.

The IOM's TUL is based on gastrointestinal effects in individuals consuming 60 mg of iron from ferrous fumarate as supplemental iron to the diet. Dietary iron was assumed to be 10 mg bringing the total iron consumed daily to 70 mg. An uncertainty factor of 1.5 was applied to this value to obtain the TUL of 45 mg/day. This value is considerably lower than the apparent safe level of iron as determined from rats fed sodium iron EDTA. Nevertheless, such gastrointestinal effects would be expected to limit exposures to iron thus preventing the development of serious adverse effects which would be expected only at far higher levels of exposure. Thus, such gastrointestinal effects represent a self limiting factor on the consumption of an iron fortified beverage.

Representative populations where the ingredient would be used are listed in the attached tables with their respective assessment of iron status. These are Latin American Countries where iron deficiency anemia occurs in 30 to 70% of susceptible subpopulations. While the level of dietary iron consumed by these populations is not precisely known, it can be readily assumed that, in general, it is substantially less than the amount of iron required, 18 mg iron/ person/day or 0.9 mg iron/100 calories. The IOM estimate of 10 mg of dietary iron used in their calculation of the TUL for those taking iron supplements is considered a reasonable estimate. Using that estimate of 10 mg of dietary iron, we calculate that one serving (or 200 ml) of the fortified beverage delivers 2.5 mg iron or 25% of dietary iron consumed by such populations. Even if an entire liter of the fortified beverage were consumed (which is well above the 90th percentile consumption in the US), only 12.5 mg of fortified iron would be ingested representing about a doubling of the non-fortified dietary iron intake and a total consumption of only 22.5 mg iron. The TUL is not reached in these populations until 2800 ml (2.8 liters) of the fortified beverage is consumed. Such an amount is well beyond any expected consumption particularly on a chronic basis. Thus, it can be concluded that such iron fortification as intended would not result in the subject populations exceeding the TUL as established by IOM.

I trust this adequately addresses the points raised. If you need any additional information, please let me know.

Sincerely,

Edward A. Steele

President

AAC Consulting Group, Inc.

301-838-3120 ext 125

301-838-3182 fax

<<LA Nutritional Mapping - Summary.doc>> <<Ferrazone Production Process.pdf>>

NUTRITIONAL MAPPING – Latin America

ANDEAN COUNTRIES				
BOLIVIA – D	ECUADOR - D	VENEZUELA - T	COLOMBIA - T	PERU - D
Chronic malnutrition in children under three M-L (9)	Protein-energy malnutrition in children under 5 years (low weight-for-age) – 26%. M-H (9)	Malnutrition in children: under 2 years (11.7%), 2-6 years (22.4%), and 7-14 years (24.4%) – M (7)	Overall Malnutrition: declining in the group under 5 years. Chronic malnutrition: Decl.: 13.5% children <5. M (7)	Malnutrition in children under 5: 7.9% weight-for-age deficits; 25.9% low height-for-age. L – M (6)
	Obesity and dyslipidemia in schoolchildren: 19% and 22% respectively. L-M (5)	Overweight: increasing for all age groups and in the population under 15. M (7)		
Diabetes mellitus - 20% in individuals aged 60-64 H (10)	Mortality by Diabetes mellitus: 27 per 100,000	Diabetes mellitus: 3rd cause of death (highest risk in females above 45. H (10)		Diabetes: between 7% to 8%. M (7)
Hypertension -18.6%: M(8)		Hypertension in adults is 20%-30%. M-H (10)	Hypertension : 21%. M – H (9) Cardiovascular diseases: one of the leading causes of death (11)	Hypertension in adults: 17% in men and 9% in women. M (7) Hypercholesterolemia: 30% in men, 24% in women. (11)
Vitamin A deficiency - significant: sub-clinical in up to 20% of young children; National Vitamin A Program for fortifying sugar. M(8)	Vitamin A deficiency - moderately serious problem: 9.6% to 25.6%.M-H(9)			Vitamin A deficiency – public health problem, affect 50% of children under 5.H(12)
Iron deficiency: anemia: 67% of children under three; 35% of children aged 8-12 years; 57% of pregnant women. 31% of subjects of all ages may be iron deficient M-H (9)	Iron deficiency: 22.2% anemia in children 6-59 months of age. Highest in boys, 61% of pregnant M(8)	Iron deficiency anemia: Mandatory fortification of corn and wheat flour decreased deficiency but still exists L-M(6)	Anemia: in children under 5 years increased from 18% (97) to 23% (95); higher in the 12-23-month-old group (36.7%) and in rural areas (27.2%) M(8)	Iron deficiency: significant among children – anemia affect 50% of children under 5, 20-30% of school children and 30% women 15-49. H(12)
Iodine deficiency controlled through salt iodization Program L(1)	Iodine deficiency – may be under control. (National Iodine Program) L(1)	Iodine deficiency has been a public health problem Mandatory iodization reduced deficiency but might still exists. L(3)		Iodine deficiency has declined in recent years (salt iodization Program) and has brought under control. L(1)

000161

SOUTHERN CONE COUNTRIES

ARGENTINA – T	CHILE – T	PARAGUAY – T	URUGUAY – T	BRAZIL - T
Malnutrition: growth retardation (height-for-age deficit) frequent among pre-school and school-aged children due to chronic malnutrition (4.2%). L (3)	Child malnutrition (weight-for-age): tendency to decrease - 15% (1975) to 5% (1993) to 0.7 (current). 74% Children under 6 with normal nutritional status. L (1)	Malnutrition (height-for-age) in schoolchildren: 10.3% L (4)	Malnutrition: 28% of the children under 5 (height-for-age). M – H (9)	Malnutrition: declining. L – M (5)
Overweight and obesity: respectively 19.5% and 4.1% L – M(5)	Overweight – females 23% to 25%; pregant women 46% (1994); 22% of children are overweight or obese. M-h (8)	Elevated triglyceride levels : 17.2% men, 10.4% women. M(7). Obesity: 53.8% of the total study population (45.8% men and 57.4% women).M-H (10)	Obesity: 3% - 9% of the children, 47% of men and 58% of women. M – H (9) Fat consumption high (32 % of VCT). (10)	Obesity: growing in all income groups. M – H (8)
	Prevalence of diabetes: 3.0% to 5.6% L (4)	Prevalence of diabetes: 6.1%; glucose intolerance 11.5% M(6)	Diabetes: 7.6% in men over 18 years of age and 10.0% in women in the same age group. fifth cause of death.M(8)	Prevalence of Diabetes: 7.6% in the urban population aged 30–69 years.M(7)
Hypertension : 13% of males and 7% of females among adults 18 to 59 years of age. L-M(5)	Cardiovascular diseases: 1/4 of all deaths.(9) Hypertensive disease frequently associated. M-H(8)	High blood pressure: 11.5% of the population (9.5% men and 12.4% women). M(5)	Hypertension: 20% of the adult population. M-H(9)	Cardiovascular diseases: leading cause of death in all regions of the country (11)
		Vitamin deficiencies are commom. M-H(8)	Blindness due to vitamin A deficiency is not a public health problem. L(2)	Vitamin A deficiency: important micronutrient deficiency. M-H(9)
Prevalence of iron deficiency anemia in children: 24% to 47%; correlation with socioeconomic level.M-H(8)	Anemia: 20% among children (6-24 months) and 20% among pregnant women. L-M(6)	Anemia is commom M-H(8)		Iron Deficiency anemia: pregnant women 25%-44%; children under 5, 59%-70%. H(12)
Iodine deficiency: : reported in the age group 1–6 years old. L(3)	Iodine deficiency: 9% of school populations (1995) have goiter, although 97% of salt is iodized L(3)	Endemic goiter is commom M-H(8)	Endemic goiter is not public health problem. Table salt has been iodized since 1963. L(2)	Under control. L(1)

000162

CENTRAL AMERICA COUNTRIES			
COSTA RICA – T	DOMINICAN R. – T	EL SALVADOR – T	GUATEMALA - D
Malnutrition decreasing – 5.1% (96) x 8.6% (80) in preschoolers L(4)	Malnutrition: serious problem – 6-11% in children. Height for age deficit (20%). Low birth weight M(6)	Malnutrition: important public health issue - overall malnutrition 14.9%; chronic, 25.5%; acute, 3.8%. 58% of the pregnant women does not meet their caloric needs and 40.5% are not getting enough protein.M-H(9)	Malnutrition: (protein-energy) has declined since the 1970s. Last data: 84% girls and 83% boys under 9 (94) M-H(11)
14.9% children overweight. L-M(5)			
Diabetes mellitus was the ninth leading cause of death: : 2.2% males; 3.4% females. L(3)	Diabetes: growing problem (4.2% of deaths). L(4)		
Cardiovascular disease was the leading cause of death. H(11)			
Vitamin A deficiency in preschoolers: 8.7%. L(4)	Vitamin A deficiency in children under 15: 19%. M(8)	Vitamin A deficincy is an important public health problem Vit A intake is insufficient for a very large proportion of the population. H(11)	Vitamin A deficiency: still a public health problem (WHO). Prevalende – children 1 - 5: 15 %, regardless sugar fortification with vitamin A. M-H(9)
	Iron deficiency in children under 15: 30% M(8)	Iron deficiency is important public health problem - only 8.5% of the families has an adequate intake. 12-17yo most affected – 51%. Fortification of wheat flour with iron initiated in January 1996.H(11)	Iron deficiency anemia most common among young children and women of reproductive age, prevalence (1995). Wheat flour fortification with iron implemented since the late 1980s M(8)
Iodine deficiency: endemic goiter reported in 1994, 91% female, 63% in the childbearing age.	Iodine deficiency in children under 15: 74% H(9)	Iodine deficiency used to be an important public health problem Salt iodized since 1996.L-M(5)	Iodine deficincy - the situation is good: Iodine deficiency appear to be on the decline (1995 info). Fortified salt.L(2)

CENTRAL AMERICA COUNTRIES			
HONDURAS – T	NICARAGUA – D	PANAMA - T	
Malnutrition is widespread, affecting 14-40% of the in population. Hhas declined significantly since the 1970s M-H (8)	Prevalence of malnutrition 19% of children in urban areas. Caloric intake of children - 88.9% of the recommended daily allowance.M(8)	Malnutrition: - One-quarter of the children under 5: 5.2% (weight-for-age), 3.4% (weight-for-height), 5.2% (height-for-age). L-M(4)	
		Diabetes mellitus: 8th most common cause of death. M(8)	
	Cardiovascular disease M(8) and hypertension – 31% of deaths M(8)	Hypertension: 6th general cause of morbidity (mainly in the 20–59 age group and in the group aged over 60 M(8)	
Significant subclinical vitamin A deficiency (13% of the aged 1–3) , public health problem (WHO). Sugar fortification since the 1970s. 75% of all families consume less than 50% of their RDI. M(8)	Vitamin A deficiency: public health problem: Subclinical in 31% of children aged 1-5.. Diets delivering less than 80% of RDI to 84% children (rural) H(11)		
Iron deficiency: is prevalent - highest in young children and pregnant women - 30.2% of children aged 1–3; anemic, 26% women of childbearing age and 32% of pregnant M(8)	Iron deficiency anemia: public health problem:. prevalent in 30-55% of young children; in 33.6% among adult women. 57% of children have iron intakes less than the recommended daily amount.H (9)	Prevalence of anemia: children under 1 - 43.4%, children 1 to 4 - 38.4%, schoolchildren - 20.2%, and pregnant women - 38.9%. Children 12 to 59 months old 18% (1992). M-H(10)	
Iodine deficiency: is not a major problem (95); prevalence has declined in the past two decades. Salt iodization since the 1970s. L(3)	Iodine deficiency: not a public health problem (salt fortification) - Total goiter rate declined over the last years, may still exist deficiency in some high risk groups (20%). L(3)	Iodine deficiency – incidence of goiter - 12.3%. to 23.2% in schoolchildren (1991).M(7)	

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CARIBBEAN COUNTRIES				
ANTIGUA & BARBUDA-T	BAHAMAS – T	BELIZE – T	BARBADOS – T	CAYMAN ISLANDS - T
Protein-Calorie Malnutrition: not a major problem - national rate for mild/moderate malnutrition less than 0.87%. L(1)	Protein-energy malnutrition: among children 0–5 not a serious public health problem L(1)	Malnutrition: Deficiencies in weight and height for age in preschool children M(8)	Nutrition programs aiming at improving the nutritional status of the Barbadian population	Protein-energy malnutrition: not a significant presence in children. L(1)
Obesity: a national rate 4.6%. Women over 40 –> 60% obese; of these, 33% grossly obese. Men over 40 -> 25% obese. M(8)	Obesity: Serious problem. Overall, 48.6 % of the population, females (53.6%), males (43%); children 5–14 years 6.7%; (1988–89) H(9)	Obesity: is a problem (data from 1995). Nutritional problems range from deficiency to obesity. M-H(9)		Obesity: among children and adults starting to cause concern, but there are no current data on its prevalence.
	Type II diabetes; serious problem. H(9)	Diabetes : among the 10 leading causes of mortality (50 and over). M(6)	Diabetes mellitus – serious problem. H(9)	
Cardiovascular diseases - high prevalence of hypertension and heart disease.	Hypertension: 13% of the population 15–64 years; 38% elderly (65). L-M(5) Cardiovascular diseases: serious problem. M(8)	Cardiovascular diseases accounted for 30% of deaths in 1993–1996. Heart diseases leading cause of death.H(11)	Heart disease – serious problem M(8)	Diseases of the circulatory system were responsible for 41.9% of deaths. Data on hypertension not available H(9)
	Vit. A: Deficiencies of micronutrients – not serious problem. L(1)	Vitamin A deficiency: deficiencies in vitamin A in preschool children. M(8)		fortificated food from US. supplements are routinely provided to pregnant women and preschool children. L(1)
Prevalence of iron deficiency anemia: 2.5% in children under 5; 6.3% among pregnant women. L(2)	Iron deficiency anemia: 19% of the pregnant Deficiencies of micronutrients – not serious problem. L(2)	Iron deficiency anemia: deficiencies in serum iron in preschool children. M(8)		fortificated food from US. supplements are routinely provided to pregnant women and preschool children L(1)
	Iodine deficiency: deficiencies of micronutrients – not serious problem. L(1)			There have been no cases showing evidence of iodine deficiency disorders L(1)

CARIBBEAN COUNTRIES				
FRENCH GUIANA- T	GRENADA	GUADALOUPE	GUYANA – T	MARTINIQUE
Protein-energy malnutrition: affects the black population				
				Obesity and high cholesterol – tendence of increasing M(7)
		Prevalence of diabetes: 6.6 % M(6)		Diabetes: serious problem tending to increase. M(8)
		Cardiovascular Diseases, including Hypertension: leading cause of death (33% of all deaths). M(7)	Cardiovacular diseases: 38.6% of all deaths. M(8)	Cardiovascular disorders: leading cause of mortality Hypertension is estimated to occur in 20% of the general population. H(9)
	no active monitoring of the prevalence of vitamin A deficiency			
	Iron deficiency anemia: 30% of pregnant women; 55% children under age 1. H(10)		Iron deficiency anemia: 52% pregnant women and 42.2% adults aged 15-30. H(9)	
	no active monitoring of the prevalence of iodine deficiency		Iodine deficiency: 3.9% in females and 2.5% in males (5-14-year-old group); 2.1% in pregnant women. L(3)	

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CARIBBEAN COUNTRIES				
HAITI – T	JAMAICA - T	NETHERLANDS ANTILLES (CURAÇAO) - T	SAINT VINCENT AND THE GRENADINES	TRINIDAD & TOBAGO
Malnutrition: High rates of malnutrition ; one-third of children with severe growth retardation. H(12)	Prevalence of malnutrition of children under 5 declining 39.0%-31.9%, severe malnutrition 10.8%-8%.H(10)	Malnutrition: 3% of children under one year of age, 5% among children 2 and 3 years old. L(2)		
		Obesity: More than 50% of women; 60% in the group aged 45–64. H(10)		Obesity: early obesity reported. Body-mass index is high. M(8)
Prevalence of diabetes: 2%–8% for different parts of the country; L-M(5)	Diabetes - serious problem M(8)	Prevalence of diabetes: 10% in the population over 18 years of age; 30%–35% group 45 years and over.H(9)	Diabetes is an important health problem, although prevalences are unknown. M(8)	Prevalende of Diabetes: high and increasing (11% in the adult population 35 years old and older) H(9)
Cardiovascular Diseases: for 40% of patient admissions; Prevalence of high blood pressure: 13%–15% in the adult pop. over 18. M(6)	Cardiovascular disease and hypertension – serious problems. M(8)	Hypertension is the most frequently reported disease (11.4 % of men and 16.7% of women) M(7)	Hypertension is an important health problem, although prevalence are unknown. M(8)	Cardiovascular disease: is the highest-ranking cause of death. H(10) Hypertension: high prevalence. H(10)
Vitamin A deficiency: Public health problem: children consume 34% RDI. M(8)				
Iron deficiency anemia: 30% of preschool children and 38% of women. L1	Iron deficiency anemia: 28.9 % of pregnant women; 25% of children under age 5. M(8)			Iron deficiency anemia: 21% in pregnant women M(7)
Iodine deficiency: prevalence is low. Not a Public Health Problem.				

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Manufacturing Method of Ferrazone™

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www.ferrazone.com

AM

Fasano, Jeremiah

From: Ed Steele [esteele@aacgroup.com]
Sent: Friday, December 03, 2004 11:47 AM
To: Jeremiah.Fasano@cfsan.fda.gov
Cc: Gary Flamm (wgflamm@attglobal.net); dskrypec@kraft.com
Subject: Method of Manufacture - GRN 152 (NaFeEDTA)

Dr. Fasano:

Attached is a description of the non-confidential manufacturing process you requested in your phone call earlier this week:

> Sodium iron EDTA meeting JECFA specifications is prepared by complexing sodium EDTA with an iron chloride salt under acidic conditions, followed by filtering and drying, in a facility certified as in accordance with Hazard Analysis Critical Control Point (HACCP) system.

I hope this is sufficient to allow FDA to proceed with the review of this notice.

Please let me know if you need any additional information.

Edward A. Steele

President

AAC Consulting Group, Inc./Kendle

301-838-3120 ext 125

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