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FOOD ADDITIVE SAFETY

July 15, 2005

Dr Robert Martin
Division of Biotechnology and GRAS Notice Review (HFS-255)
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Re: GRAS Notification

Dear Dr. Martin:

In accordance with proposed 21 CFR §170.36 [Notice of a claim for exemption based on a Generally Recognized As Safe (GRAS) determination] published in the Federal Register (62 FR 18939-18964), I am submitting in triplicate, as the notifier, Akzo Nobel Chemicals, 525 West Van Buren St., Chicago, IL 60607, a GRAS notification of *Ferrazone*™ (ferric sodium ethylenediaminetetraacetate) for iron fortification of soy and fish sauces, and a GRAS panel report setting forth the basis for the GRAS determination for review by the agency.

Sincerely,

Edwin C. Bisinger, Jr., Ph.D., D.A.B.T.
Manager, Regulatory Toxicology Department
Akzo Nobel Chemicals

Enclosures

AKZO NOBEL

I GRAS Exemption Claim

A. Claim of Exemption From the Requirement for Premarket Approval Pursuant to Proposed 21 CFR §170.36(c)(1) [62 FR 18938 (17 April 1997)]

Ferrazone®, as defined in the report in Appendix I entitled, "**EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF *FERRAZONE™* (FERRIC SODIUM ETHYLENEDIAMINETETRAACETATE) FOR IRON FORTIFICATION OF SOY AND FISH SAUCES**," dated November 4, 2004, has been determined to be Generally Recognized As Safe (GRAS), consistent with Section 201(s) of the *Federal Food, Drug, and Cosmetic Act*. This determination is based on scientific procedures as described in the following sections, under the conditions of its intended use in food, among experts qualified by scientific training and expertise. Therefore, the use of Ferrazone® in food as described below is exempt from the requirement of premarket approval.

Signed,

7/15/05

Edwin C. Bisinger, Jr., Ph.D., D.A.B.T.
Manager, Regulatory Toxicology Department
Akzo Nobel Chemicals Inc.

Date

Phone: 312-544-7191
Email: edwin.bisinger@akzonobel-chemicals.com

B. Name and Address of Notifier

Edwin C. Bisinger, Jr., Ph.D., D.A.B.T.
Manager, Regulatory Toxicology Department
Akzo Nobel Chemicals Inc.
525 West Van Buren St.
Chicago, IL 5605607

C. Common Name of the Notified Substance

The common name of Ferrazone® is ferric sodium ethylenediaminetetraacetate trihydrate, or ferric sodium EDTA (FeNaEDTA).

D. Conditions of Intended Use in Food

Akzo Nobel Chemicals intends to market Ferrazone® as a source of iron in soy and fish sauces. The individual proposed food-uses and use-levels for Ferrazone® are summarized in Table 1.

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

Food Category	Proposed Food-Use	Use-Levels for Ferrazone™ (%)	Use-Levels for Iron (%)	Use Levels for EDTA (%)
Gravies and Sauces	Soy, Fish, Hoisin, and Teriyaki Sauces	0.18	0.024	0.124
	Sweet and Sour Sauce	0.09	0.012	0.062

The consumption of Ferrazone®, and iron and EDTA from all proposed food uses of Ferrazone® were estimated using the United States Department of Agriculture (USDA) 1994-1996 Continuing Survey of Food Intakes by Individuals (USDA CSFII 1994-1996), and the 1998 Supplemental Children's Survey (USDA CSF II 1998) (USDA, 2000). On an all-user basis, the mean intakes of Ferrazone®, iron, and EDTA by the total population from all proposed food-uses were estimated to be 16.37, 2.17, and 11.21 mg/person/day, respectively. The heavy consumer (90th percentile) all-user intakes of Ferrazone®, iron, and EDTA by the total population from all proposed food-uses were 38.44, 5.10, and 26.3 mg/person/day, respectively. On a body weight basis, the intakes of Ferrazone®, iron, and EDTA by the total population are 0.27, 0.036, and 0.19 mg/kg body weight/day (mean) and 0.64, 0.085, and 0.44 mg/kg body weight/day (90th percentile), respectively, assuming an adult body weight of 60 kg.

The impact of fortifying these food products in relation to current iron intakes from food can be determined using data from the 1994-1996, 1998 USDA CSFII, where current background mean iron intake by the total population from the diet is estimated to be 15.02 mg/person/day. With the addition of Ferrazone® to proposed food uses, mean intake of iron from the diet would increase to 15.25 mg/person/day for the total population.

The estimated mean intake of EDTA from all currently regulated food sources is 7.75 mg/person/day (0.13 mg/kg bw/day) (Heimbach *et al.*, 2000). Assuming that the heavy consumer would consume double the mean intake, the 90th percentile intake approximates 0.26 mg/kg bw/day. Adding the 90th percentile intake for current uses of EDTA (0.26 mg/kg bw/day) to the intake of EDTA from proposed fortification uses (0.23 mg/kg bw/day) as a conservative estimate results in a 90th percentile intake of 0.49 mg/kg bw/day). This would represent 0.63 mg/kg bw/day on a $CaNa_2EDTA$ basis and this intake is significantly less than the ADI for $CaNa_2EDTA$ of 2.5 mg/kg bw/day.

Kraft Foods Global (Kraft) recently notified the FDA that FeNaEDTA (Ferrazone®) is GRAS, based on scientific procedures, for use as a source of dietary iron in powdered meal

replacement, flavored milk, and fruit-flavored beverages (GRN 000152). Based on these food uses, Kraft estimated that the mean intake of FeNaEDTA, iron, and EDTA would be 31.4, 4.2, and 21.8 mg/person/day, respectively. The 90th percentile intake of iron and EDTA was estimated to be 8.2 and 43.0 mg/person/day, respectively. Taking into consideration the estimated intake from proposed food uses of both Ferrazone® and Kraft's FeNaEDTA product and the currently regulated food sources of EDTA, the total mean intake of FeNaEDTA, iron, and EDTA would be 47.77, 6.37, and 40.76 mg/person/day, respectively, while the total 90th percentile intake of iron and EDTA would be 13.3 and 84.8 mg/person/day, respectively. On a body weight basis, the 90th percentile intake of EDTA is approximately 1.41 mg/kg body weight/day. This would represent 1.81 mg/kg body weight/day on a $CaNa_2EDTA$ basis which is still well below the ADI of 2.5 mg/kg body weight/day for $CaNa_2EDTA$.

E. Basis for the GRAS Determination

Pursuant to 21 CFR § 170.30, Ferrazone® has been determined to be GRAS on the basis of scientific procedures [see Appendix I – **EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF *FERRAZONE™* (FERRIC SODIUM ETHYLENEDIAMINETETRAACETATE) FOR IRON FORTIFICATION OF SOY AND FISH SAUCES**].

F. Availability of Information

The data and information that serve as the basis for this GRAS Notification will be sent to the U.S. Food and Drug Administration (FDA) upon request, or will be available for review and copying at reasonable times at the offices of:

Regulatory Toxicology Department
Akzo Nobel Chemicals
5 Livingstone Ave.
Dobbs Ferry, NY 10522

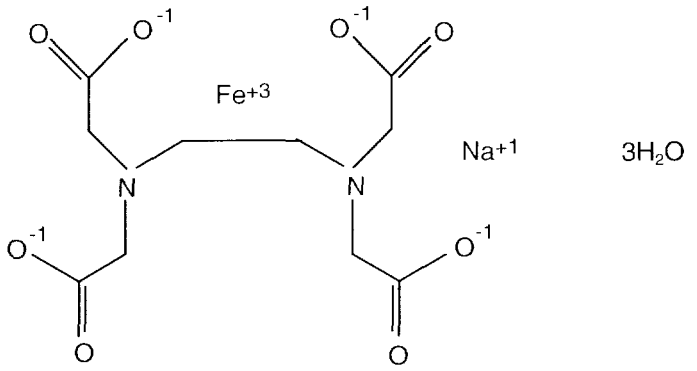
Should the U.S. Food and Drug Administration (FDA) have any questions or additional information requests regarding this notification, Akzo Nobel Chemicals will supply these data and information.

II. Detailed Information About the Identity of the Substance

A. Identity

FeNaEDTA is a free-flowing yellow-brown powder with the chemical composition $FeNa\text{-}EDTA{\cdot}3H_2O$. It can be isolated *via* crystallization with a high level of chemical purity.

Structure:



Synonyms:	ferric sodium ethylenediaminetetraacetate trihydrate; ferric ethylenediaminetetraacetic acid, sodium salt; ferric sodium edetate; ferric sodium EDTA; ferric sodium ethylenediaminetetraacetate; iron monosodium EDTA; iron sodium ethylenediaminetetraacetate; iron sodium ethylenediaminetetraacetate (1:1:1); monosodium ferric EDTA; sodium (ethylenediaminetetraacetato)ferrate(1-); sodium [(ethylenedinitrilo)tetraacetato]ferrate(III); sodium feredetate; sodium ferric EDTA; sodium ferric ethylenediaminetetraacetate; sodium iron EDTA; sodium iron(III) EDTA; sodium iron(III) ethylenediaminetetraacetate; sodium [(ethylenedinitrilo)tetraacetatato]ferrate(III); sodium [(ethylenedinitrilo)tetraacetato]ferrate(III)
Chemical Name:	Ferrate(1-), [[N,N'-1,2-ethanediylbis[N-[(carboxy-kO)methyl]glycinato-kN,kO]] (4-)]-, sodium, (OC-6-21); Ferrate(1-), [[N,N'-1,2-ethanediylbis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']-, sodium, (OC-6-21)
CAS Number:	15708-41-5
Empirical Formula:	$C_{10}H_{12}N_2O_8FeNa{\cdot}3H_2O$
Molecular Weight:	421.1
Solubility in water:	90 g/L water at 20°C 120 g/L water at 30°C 300 g/L water at 70°C
Bulk density:	approx. 950 kg/m^3
Crystal density:	approx. 1.790 kg/m^3

B. Method of Manufacture

Ferric sodium ethylenediaminetetraacetate (FeNaEDTA) is a free-flowing yellow-brown powder with the chemical composition FeNa-EDTA·$3H_2O$. It can be isolated *via* crystallization with a high level of chemical purity. The raw materials used in the manufacture of FeNaEDTA , ferric chloride ($FeCl_3$), tetrasodium EDTA (Na_4-EDTA), and hydrochloric acid (HCl) are prepared internally at Azko Nobel Chemicals and are of technical grade quality. Although they are of

technical grade quality, the levels of contaminating heavy metals are controlled by specification and are similar in level to food grade materials (*e.g.* $FeCl_3$, <0.3 ppm Pb). FeNaEDTA is obtained by crystallization after adding an aqueous solution of ferric chloride to an aqueous solution of tetrasodium EDTA. Hydrochloric acid is used as a pH-adjusting agent. The production of Ferrazone® is conducted in accordance with a HACCP-based food system (HACCP stands for Hazard Analysis Critical Control Points).

As a result of the chemical synthesis method for tetrasodium ethylenediaminetetraacetic acid (Na_4EDTA), small amounts of residual cyanide are found in the Na_4EDTA and controlled by specification (<20 ppm). Thus, levels of cyanide are routinely monitored in different batches of Ferrazone®. No easily released cyanide is found in different batches of Ferrazone® using the ISO 6703 method of cyanide determination in wastewater (detection limit 20 ppm).

Assuming a cyanide detection limit of 20 mg/kg and a 90th percentile daily consumption of 38.4 mg Ferrazone® (26.3 mg EDTA), the maximum potential exposure to cyanide would approximate 0.00077 mg/day. The Agency for Toxic Substances and Disease Registration (ATSDR, 1997) has determined a minimal risk level (MRL) for cyanide of 0.05 mg/kg body weight/day based on a no-observed-adverse-effect level (NOAEL) of 4.5 mg/kg body weight/day in an oral 90-day rat study with sodium cyanide. Thus, a 60 kg individual could consume up to 3 mg of cyanide/day without concern.

C. Specifications for Food Grade Material

The specifications for Ferrazone® are those derived by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) for FeNaEDTA (JECFA, 1999) and are listed in Table 2. Analysis of nonconsecutive representative lots demonstrated compliance with final product specifications.

Table 2 Chemical Specifications for Ferrazone®

Specification Parameter	Specification Value	Analysis Method
Identification		
Solubility	Soluble in water	FNP 52
Test for iron	Pass	FNP 52
Test for sodium	Pass	FNP 52
Purity		
Assay Iron	Not less than 12.5% and not more than 13.5%	FNP 52
EDTA	Not less than 65 5% and not more than 70.5%	FNP 52
PH	3.5-5.5 (1 in 100 solution)	FNP 52
Water insoluble matter	Not more than 0.1%	FNP 52
Nitrilotriacetic acid	Not more than 0.1%	FNP 52
Arsenic	Not more than 1 mg/kg	FNP 52
Lead	Not more than 1 mg/kg	FNP 52

III. Self-Limiting Levels of Use

Although Ferrazone® has more favorable organoleptic properties than other sources of iron, the use of Ferrazone® at levels significantly higher than those proposed will degrade the food product, thus making it unpalatable. The use of Ferrazone® in liquid products, such as soy and fish sauces, also is limited by solubility. Furthermore, given the manner in which soy, fish, hoisin, teriyaki, and sweet and sour sauces are generally used in food preparation and the taste properties of these sauces, it is unlikely that consumption of these products would occur in large amounts. For example, the high salt content of soy sauce limits its use in food preparation (Huo *et al.*, 2002). The potential for excess iron intake from consumption of sauces fortified with Ferrazone® is therefore considered to be negligible.

IV. Basis for GRAS Determination

Pursuant to 21 CFR § 170.30, Ferrazone® has been determined to be GRAS on the basis of scientific procedures. This determination is based on the views of experts who are qualified by scientific training and experience to evaluate the safety of Ferrazone® as a component of food. The safety of Ferrazone® is supported by a number of published studies on ferric sodium EDTA and other sources of EDTA, including *in vitro* and *in vivo* mutagenicity/genotoxicity studies, metabolic studies, acute, subchronic and chronic, and reproductive and developmental toxicity studies in experimental animals, as well as numerous clinical studies investigating the effects of food fortification with ferric sodium EDTA. This determination is further supported by an expert panel evaluation of the health aspects of Ferrazone® [see Appendix I – **EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF *FERRAZONE™* (FERRIC SODIUM ETHYLENEDIAMINETETRAACETATE) FOR IRON FORTIFICATION OF SOY AND FISH SAUCES**].

V. References

ATSDR. 1997. Chapter 7: Regulations and Advisories. Toxicological Profile for Cyanide. Agency for Toxic Substances and Disease Registry. (U.S.) Public Health Service. PB/98/101207/AS; pp. 191-216.

Heimbach, J.; Rieth, S.; Mohamedshah, F.; Slesinski, R.; Samuel-Fernando, P.; Sheehan, T.; Dickmann, R.; Borzelleca, J. 2000. Safety assessment of iron EDTA (sodium iron (Fe^{3+}) ethylenediaminetetraacetic acid): Summary of toxicological, fortification and exposure data. Food Chemical Toxicol 38:99-111.

Huo, J.; Sun, J.; Miao, H.; Yu, B.; Yang, T.; Liu, Z.; Lu, C.; Chen, J.; Zhang, D.; Ma, Y.; Wang, A.; Li Y. 2002. Therapeutic effects of NaFeEDTA-fortified soy sauce in anemic children in China. Asia Pacific J Clin Nutr 11(2):123-137.

JECFA. 1999. Sodium iron (III) ethylenediaminetetraacetate, trihydrate. In: Compendium of Food Additives Specifications. Prepared by the 53rd Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). World Health Organization (WHO); Geneva, Switz., FAO Food and Nutrition Papers 52 Addendum 7, pp. 79-81.

USDA. 2000. 1994-1996, 1998 Continuing Survey of Food Intakes by Individuals (CSFII) and Diet and Health Knowledge Survey (DHKS) (On CD-ROM). U.S. Department of Agriculture (USDA); Riverdale, Maryland. [CD-ROM - PB2000-500027].

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EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF *FERRAZONE*™ (FERRIC SODIUM ETHYLENEDIAMINETETRAACETATE) FOR IRON FORTIFICATION OF SOY AND FISH SAUCES

Akzo Nobel Chemicals
510 Thompson Road #17-00
SLF Building
Singapore 298135

November 4, 2004

EXPERT PANEL CONSENSUS STATEMENT CONCERNING THE GENERALLY RECOGNIZED AS SAFE (GRAS) STATUS OF *FERRAZONE*™ (FERRIC SODIUM ETHYLENEDIAMINETETRAACETATE) FOR IRON FORTIFICATION OF SOY AND FISH SAUCES

November 4, 2004

INTRODUCTION

At the request of Azko Nobel Chemicals, an Expert Panel (the "Panel") of independent scientists, qualified by their relevant national and international experience and scientific training to evaluate the safety of food ingredients, was specially convened to conduct a critical and comprehensive evaluation of the available pertinent data and information, and determine whether, under the conditions of intended use as a source of iron in traditional foods, Ferrazone™ would be "generally recognized as safe" (GRAS), based on scientific procedures. The Panel consisted of the below-signed qualified scientific experts: Joseph F. Borzelleca, Ph.D (Medical College of Virginia), Dennis D. Miller, Ph.D (Cornell University), and Fernando E. Viteri, M.D., Sc.D (University of California, Berkeley, and Children's Hospital Oakland Research Institute). *Curricula vitae* evidencing the Panel members' qualifications for evaluating the safety of food ingredients are provided in Attachment 1.

The Panel, independently and collectively, critically examined a comprehensive package of publicly available scientific information and data compiled from the literature by CANTOX Health Sciences International through June 2004. In addition, the Panel evaluated other information deemed appropriate or necessary, including data and information provided by Azko Nobel Chemicals. The data evaluated by the Panel included information pertaining to the method of manufacture and product specifications, analytical data, intended use levels in specified food products, consumption estimates for all intended uses, and comprehensive literature on the safety of Ferrazone™ and its individual components.

Following independent, critical evaluation of such data and information, the Panel unanimously concluded that under the conditions of intended use in traditional foods described herein, Ferrazone™, meeting appropriate food-grade specifications, and manufactured and used in accordance with current good manufacturing practice, is GRAS based on scientific procedures. A summary of the basis for the Panel's conclusion, excluding confidential data and information, is provided below.

COMPOSITION, MANUFACTURING AND SPECIFICATIONS

Ferric sodium ethylenediaminetetraacetate (FeNaEDTA) is a free-flowing yellow-brown powder with the chemical composition FeNa-EDTA·$3H_2O$. It can be isolated *via* crystallization with a high level of chemical purity. The raw materials used in the manufacture of FeNaEDTA , ferric chloride ($FeCl_3$), tetrasodium EDTA (Na_4-EDTA), and hydrochloric acid (HCl) are prepared internally at Azko Nobel Chemicals and are of technical grade quality. Although they are of technical grade quality, the levels of contaminating heavy metals are controlled by specification and are similar in level to food grade materials (*e.g.* $FeCl_3$, <0.3 ppm Pb). FeNaEDTA is obtained by crystallization after adding an aqueous solution of ferric chloride to an aqueous solution of tetrasodium EDTA. Hydrochloric acid is used as a pH-adjusting agent. The production of Ferrazone™ is conducted in accordance with the Hazard Analysis Critical Control Point (HACCP) system.

The specifications for Ferrazone™ are those derived by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) for FeNaEDTA (JECFA, 1999) and are listed in Table 1. Analysis of nonconsecutive representative lots demonstrated compliance with final product chemical specifications and stability under recommended storage conditions.

As a result of the chemical synthesis method for tetrasodium ethylenediaminetetraacetic acid (Na_4EDTA), small amounts of residual cyanide are found in the Na_4EDTA and controlled by specification (<20 ppm). Thus, levels of cyanide are routinely monitored in different batches of Ferrazone™. No easily released cyanide is found in different batches of Ferrazone using the ISO 6703 method of cyanide determination in wastewater (detection limit 20 ppm).

Additional checks for cyanide contamination are also employed during processing. Cyanide can react with iron to form the highly stable, very low soluble Prussian Blue ($Fe_4[Fe(CN)_6]_3$) which is highly colored and visible. This occurs through the formation of the unstable intermediate forms, hexacyanoferrate (ferrocyanide) and ferric hexacyanoferrate. A blue color is not found in processed batches of Ferrazone™, also confirming the lack of residual cyanide.

Assuming a cyanide detection limit of 20 mg/kg and a 90th percentile daily consumption of 38.4 mg Ferrazone™ (26.3 mg EDTA), the maximum potential exposure to cyanide would approximate 0.00077 mg/day.

The Agency for Toxic Substances and Disease Registration (ATSDR, 1997) has determined a minimal risk level (MRL) for cyanide of 0.05 mg/kg body weight/day based on a no-observed-adverse-effect level (NOAEL) of 4.5 mg/kg body weight/day in an oral 90-day rat study with sodium cyanide. Thus, a 60 kg individual could consume up to 3 mg of cyanide/day without concern.

REGULATORY STATUS

The United States Food and Drug Administration (FDA) have 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 (CFR, 2004).

INTENDED USE AND ESTIMATED EXPOSURE

The individual proposed food uses for Ferrazone™ include fortification of different soy and fish sauces at a proposed level of 3.6 mg of iron from Ferrazone™ per serving size or RACC (reference amount customarily consumed). This information and the corresponding use-levels for iron and EDTA are summarized in Table 2.

The consumption of Ferrazone™, and iron and EDTA from all proposed food uses of Ferrazone™ were estimated using the United States Department of Agriculture (USDA) 1994-1996 Continuing Survey of Food Intakes by Individuals (USDA CSFII 1994-1996), and the 1998 Supplemental Children's Survey (USDA CSF II 1998) (USDA, 2000). On an all-user basis, the mean intakes of Ferrazone™, iron, and EDTA by the total population from all proposed food-uses were estimated to be 16.37, 2.17, and 11.21 mg/person/day, respectively. The heavy consumer (90th percentile) all-user intakes of Ferrazone™, iron, and EDTA by the total population from all proposed food-uses were 38.44, 5.10, and 26.3 mg/person/day, respectively. On a body weight basis, the intakes of Ferrazone™, iron, and EDTA by the total population are 0.27, 0.036, and 0.19 mg/kg body weight/day (mean) and 0.64, 0.085, and 0.44 mg/kg body weight/day (90th percentile), respectively, assuming an adult body weight of 60 kg. Male adults were determined to have the greatest mean all-user intakes of Ferrazone™, iron, and EDTA, 20.23, 2.68, and 13.86 mg/person/day, respectively, and the highest 90th percentile all-user intakes of Ferrazone™, iron, and EDTA, 44.37, 5.90, and 30.30 mg/person/day, respectively. On a body weight basis, the intakes of Ferrazone™, iron, and EDTA by male adults are 0.34, 0.045, and 0.23 mg/kg body weight/day (mean) and 0.73, 0.098, and 0.51 mg/kg body weight/day (90th percentile), respectively, assuming an adult body weight of 60 kg.

The estimated total intakes of Ferrazone™ iron and EDTA from all proposed food uses are summarized in Tables 3, 4, and 5, respectively, on a per person basis (mg/person/day).

The impact of fortifying these food products in relation to current iron intakes from food can be determined using data from the 1994-1996, 1998 USDA CSFII, where current background mean iron intake by the total population from the diet is estimated to be 15.02 mg/person/day. With the addition of Ferrazone™ to proposed food uses, mean intake of iron from the diet would increase to 15.25 mg/person/day for the total population. Considering only users of soy, fish, and other ethnic sauces, consumption of iron from the diet prior to fortification is estimated to be 16.76 mg/person/day, which would increase to 18.93 mg/person/day with the addition of Ferrazone™ to proposed food uses. Iron intake is estimated to be the greatest among male

adults (ages 19 to 50). On an all-user basis, mean intake of iron from the diet prior to the addition of Ferrazone™ to proposed food uses is estimated to be 20.97 mg/person/day amongst male adults, and 23.65 mg/person/day after the fortification of proposed food uses. The intake of iron, pre- and post-fortification, is summarized in Table 6.

DATA PERTAINING TO SAFETY

The safety of Ferrazone™ is based on a subchronic study of FeNaEDTA in rats that demonstrated no significant toxicological effects at the highest dose tested, and is further supported by subchronic studies, reproductive and developmental studies, and carcinogenicity studies of other sources of EDTA in laboratory animals. In addition, numerous clinical studies investigating the effect of iron fortification from FeNaEDTA and other sources also have demonstrated no significant adverse effects, while also demonstrating significant improvements in iron status in iron-deficient individuals. Overall, these studies demonstrate that consumption of FeNaEDTA is safe.

In 1999, JECFA considered the use of FeNaEDTA as a nutritional supplement in foods acceptable when used in supervised food fortification programs that would provide iron intakes of approximately 0.2 mg/kg body weight/day from fortified food (JECFA, 2000). This restriction of use in supervised fortification programs and iron intakes of 0.2 mg/kg body weight/day resulted from the mandate received from the Codex Alimentarius Commission, who requested an evaluation for this specific purpose. This recommended use level was directed towards adult women and did not include children that have an iron requirement significantly higher than this value (IOM, 2001).

The scientific data evaluated by JECFA, as well as those presented in this report, did not reveal any safety concern with regard to the use of FeNaEDTA in fortified foods/drinks of general consumption provided the iron intake from FeNaEDTA is below the above-mentioned level. In particular, dietary iron fortification with FeNaEDTA is not expected to result in iron overload in otherwise normal populations. This conclusion was based on numerous studies of the absorption of iron demonstrating that percent iron absorption from foods is inversely related to dietary iron content, such that it does not increase with increasing levels of iron. Additionally, iron absorption is highest in individuals with low serum ferritin values, and precisely regulated by down-regulation systems in the body.

The current fortification programs have used iron levels well below the tolerable intakes for iron published by JECFA (1983) and the Institute of Medicine (IOM, 2001). JECFA presented a provisional maximum tolerable intake of 0.8 mg/kg body weight/day based on the safe long-term intake of ferrous supplements of 50 mg/day (for a 60 kg individual). The IOM presented a Tolerable Upper Limit of 45 mg/day of iron from all sources based on gastrointestinal effects found in individuals consuming 60 mg of iron from ferrous fumarate as supplemental iron to the diet. The intake of iron was corrected for 10 mg of dietary iron, bringing the total dietary

exposure to 70 mg of iron. An uncertainty factor of 1.5 was applied to the lowest-observed-adverse-effect level (LOAEL) to obtain the Tolerable Upper Limit of 45 mg/day. These values are considerably lower than the apparent safe level of iron derived from rats fed FeNaEDTA. Thus, dietary levels of FeNaEDTA that provide less than 45 mg of iron/day would be considered safe for humans.

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION (ADME)

In general, there are 2 different pathways of absorption for orally administered iron, depending on whether it is of the organic (heme) or inorganic (non-heme) form. Heme iron is highly bioavailable and is relatively unaffected by dietary factors (Viteri *et al.*, 1978; INACG, 1993; IOM, 2001). In contrast, non-heme iron absorption is greatly affected by the presence of ligands in foods, which either enhance (*e.g.*, ascorbic acid), or inhibit (*e.g.*, phytate) absorption (INACG, 1993; IOM, 2001). The iron from FeNaEDTA undergoes the absorptive pathway for the inorganic, non-heme form of iron.

Following oral administration, the iron from FeNaEDTA is separated from the FeEDTA complex before absorption, joining the general non-heme iron pool that is finally incorporated into the circulating hemoglobin (Candela *et al.*, 1984). Thus, iron from FeNaEDTA is subject to similar controls as other inorganic forms of iron. Less than 1% of the intact FeEDTA chelate is absorbed in humans, which is, in turn, rapidly excreted by the kidneys (MacPhail *et al.*, 1981; Candela *et al.*, 1984).

Due to its high solubility at physiological pH, the iron from FeNaEDTA is highly bioavailable when administered in foods, despite the presence of inhibitors of iron absorption (Viteri *et al.*, 1978; Martinez-Torres *et al.*, 1979; MacPhail *et al.*, 1981; Hurrell *et al.*, 2000). Numerous studies comparing the absorption of iron from different sources, such as FeNaEDTA, $FeSO_4$, $Fe_2(SO_4)_3$, $FeCl_3$, and ferrous fumarate, have indicated significantly higher absorption of iron from FeNaEDTA, particularly in subjects with low iron status (Viteri *et al.*, 1978; Martinez-Torres *et al.*, 1979; MacPhail *et al.*, 1981; Hurrell *et al.*, 2000; Walter *et al.*, 2003). These studies also have demonstrated that iron absorption is precisely regulated by the body, with percent iron absorption from foods being inversely related to dietary iron content, such that it does not increase with increasing levels of iron (from 5 to 50 mg Fe as FeNaEDTA), thus protecting against the possibility of iron overload.

TOXICOLOGICAL STUDIES

Acute Studies

FeNaEDTA has been reported to be of low acute oral toxicity in male Sprague-Dawley rats, with an LD_{50} value of 10 g/kg body weight (1.3 g elemental iron/kg body weight) (Whittaker *et al.*, 2002).

Subchronic and Chronic Studies

Dietary treatment with FeNaEDTA, providing iron levels of up to 11 mg/kg body weight/day (84.3 mg FeNaEDTA/kg body weight/day) for a period of up to 61 days, did not result in iron overloading, nor in any other toxicologically significant effects in rats (Appel *et al.*, 2001). Decreased serum total protein, albumin and calcium levels were reported in rats provided with 84.3 mg/kg body weight/day of FeNaEDTA in the diet for 61 days; however, due to the lack of hepatic damage in these rats, these effects were deemed not to be toxicologically significant (Appel *et al.*, 2001). The NOAEL is considered to be 84.3 mg FeNaEDTA/kg body weight/day, providing 11.19 mg iron/kg body weight/day. Based on the results of this study, JECFA (2000) concluded that administration of FeNaEDTA in the diet would not result in a greater uptake of iron once nutritional requirements for iron are met. JECFA concluded that the use of FeNaEDTA would be safe for use in food fortification programs that would provide 0.2 mg iron/kg body weight/day. Studies of other sources of EDTA have likewise demonstrated no significant toxicological effects in rats and dogs (Oser *et al.*, 1963; Chan, 1964). A NOAEL of 250 mg/kg body weight/day was reported for $CaNa_2EDTA$ based on data from 1- and 2-year feeding studies in dogs and rats, respectively (Oser *et al.*, 1963). Based on these data, JECFA (1966, 1974) assigned an ADI of 2.5 mg/kg body weight/day for EDTA.

Reproductive and Developmental Studies

Due to the lack of information regarding the possible reproductive and developmental effects of FeNaEDTA, studies examining the effects of similar EDTA salts, such as Na_2EDTA, Na_3EDTA, Na_4EDTA, and $CaNa_2EDTA$ were considered. No compound-related mortality, reproductive, or teratogenic effects were reported rats orally dosed with 967, 1,243, 1,245, 1,340, or 1,374 mg/kg body weight/day of EDTA, Na_2EDTA, Na_3EDTA, $CaNa_2EDTA$, and Na_4EDTA, respectively, from gestation days (GD) 7 to 14, and these respective doses were considered to be the NOAELs for these compounds (Schardein *et al.*, 1981). In addition, no significant reproductive or developmental effects were observed in multiple generations of rats exposed to diets providing levels of up to 250 mg/kg body weight/day of $CaNa_2EDTA$, which is considered to be the NOAEL in this study (Oser *et al.*, 1963). The route of exposure to EDTA is a critical factor in determining its potential for lethal or teratogenic effects, as fetal resorptions and malformations were reported in rats provided 954 mg/kg body weight/day of Na_2EDTA in the diet, while high incidences of maternal deaths and fetal resorptions were reported in rats subcutaneously injected at a lower dose (375 mg Na_2EDTA/kg body weight) (Kimmel, 1977).

Genotoxicity Studies

Negative results were reported for FeNaEDTA in various *in vitro* genotoxicity assays, including the *Salmonella typhimurium* strains TA97a, TA98, TA100, TA102, TA1535, TA1537, and TA1538, with or without metabolic activation (Dunkel *et al.*, 1999) and in *Escherichia coli* strains IC188 and IC203 (Martínez *et al.*, 2000). Positive results were obtained for FeNaEDTA in the mouse lymphoma assay using L5178Y cells (Dunkel *et al.*, 1999); however, Heimbach *et al.*

(2000) concluded that the mouse lymphoma L5178Y cells were "particularly sensitive to incorporation of excessive quantities of iron salts in the tissue growth medium" given the fact that several iron compounds, including FeNaEDTA, had tested negative for mutagenicity in *S. typhimurium* but positive in the mouse lymphoma assay. This positive result was therefore not considered to be of significance in the overall safety assessment of EDTA.

Carcinogenicity Studies

No carcinogenicity studies have been conducted with FeNaEDTA; however, several studies have been conducted with other EDTA salts, which were considered. The results of 2-year feeding studies indicate that Na_3EDTA, $CaNa_2EDTA$, and Na_2EDTA do not possess carcinogenic activity following administration of up to 2,500 mg/kg body weight/day in rats and 1,125 mg/kg body weight/day in mice (Oser *et al.*, 1963; Yang, 1964; NCI, 1977). FeNaEDTA is likewise not anticipated to possess any carcinogenic activity. Based on the results of these studies, the NOAELs were considered to be 250 mg $CaNa_2EDTA$/kg body weight/day in rats (Oser *et al.*, 1963), 5% Na_2EDTA (approximately 2,500 mg/kg body weight/day) in rats, and 7,500 ppm $Na_3EDTA{\cdot}3H_2O$ (approximately 375 and 1,125 mg/kg body weight/day in rats and mice, respectively) (NCI, 1977).

Clinical Studies

FeNaEDTA has been used in numerous field trials in developing countries for the iron fortification of foods. No adverse effects were reported in humans subjected to long-term (3 to 32 months in duration) FeNaEDTA fortification trials in which fish and soy sauces, sugar, and curry powder were fortified with FeNaEDTA providing levels of 4 to 15 mg iron/day (0.067 to 0.25 mg iron/kg body weight/day) (Garby and Areekul, 1974; Ballot *et al.*, 1989; Viteri *et al.*, 1995; Huo *et al.*, 2002; Thuy *et al.*, 2003). Remarkable improvements in iron status indicators, including serum levels of hemoglobin and ferritin, free erythrocyte protoporphyrin (FEP), total iron binding capacity (TIBC), and iron stores, were reported in the fortified groups compared to the controls (Garby and Areekul, 1974; Ballot *et al.*, 1989; Viteri *et al.*, 1995; Huo *et al.*, 2002; Thuy *et al.*, 2003). The fastest and greatest responses to iron fortification were observed in individuals of the fortified and control groups who were iron-deficient at the start of the fortification study, compared to their iron-repleted counterparts (Ballot *et al.*, 1989; Viteri *et al.*, 1995). Positive responses to iron fortification were reported to decrease with time, as iron deficiencies began to disappear and iron stores started to build up in the subjects (Viteri *et al.*, 1995). The results of these field trials are summarized in Table 7.

NUTRITIONAL SAFETY

A number of studies have investigated the effect of FeNaEDTA on the absorption and metabolism of other nutrients, including zinc, copper, and calcium.

Hurrell *et al.* (1994) investigated the effect of dietary FeNaEDTA on the metabolism of zinc, copper, and calcium in male Sprague-Dawley rats over a period of 21 days and concluded that the use of FeNaEDTA as a food additive, at dietary levels of up to 4.5 mg fortified iron/kg body weight/day and a total of 144 mg EDTA/kg body weight/day, would have beneficial effects on the metabolism of nutritionally-important minerals, such as zinc and copper, while having no effect on the metabolism of calcium in rats. This effect was particularly evident in rats fed a zinc-deficient diet, as significant improvements in copper absorption, zinc absorption and retention, as well as increased weight gain, were observed when FeNaEDTA was administered in place of $FeSO_4$ as the source of iron in the diet. The enhanced zinc and iron absorption in rats administered dietary EDTA was attributed to the formation of soluble metal-EDTA chelates, which are highly absorbable and subsequently prevent the reaction of metals with other ligands that could potentially inhibit absorption, such as phytate. Therefore, the formation of highly absorbable zinc-EDTA chelate resulted in an increased urinary excretion of zinc in the rats.

Studies in humans have likewise demonstrated no adverse effects of FeNaEDTA on the absorption of zinc, calcium, and manganese. Solomons *et al.* (1979) reported no significant effects on absorption of zinc in healthy adult volunteers following consumption of a standard Guatemalan diet fortified with 25 mg of zinc and coffee sweetened with sugar fortified with 15 mg FeNaEDTA when compared to controls. Similarly, no significant differences in zinc absorption were reported following consumption of aqueous solutions containing 25 mg zinc with 15 or 40 mg FeNaEDTA; however, zinc absorption was significantly decreased following consumption of aqueous solutions with 115 or 308 mg FeNaEDTA. The decrease in absorption was attributed to the EDTA moiety. The authors concluded that fortification of sugar with FeNaEDTA at a level of 1,000 ppm would not interfere with zinc nutriture.

Davidsson *et al.* (1994) concluded that the addition of FeNaEDTA to foods would not have detrimental effects on the metabolism of zinc and calcium in humans based on the results of a 28-day crossover study in which healthy women consumed bread fortified with 10 mg iron from either FeNaEDTA or $FeSO_4$. In addition, they concluded that the addition of FeNaEDTA to foods with a low bioavailability might result in increased zinc absorption and iron bioavailability, which will be particularly important in developing countries where low-bioavailable foods form the basis of the staple diet. Hettiarachchi *et al.* (2004) reported significantly increased iron and zinc absorption in a total of 48 Sri Lankan children who, over a period of 14 days, consumed diets containing rice flour fortified with iron (60 mg iron/kg flour, administered as ferrous sulphate) and Na_2EDTA (385.08 mg/kg flour) compared to those whose diets did not contain Na_2EDTA. In a 30-day crossover study, Davidsson *et al.* (1998) reported no significant effects on the on the absorption and urinary excretion of manganese in 10 healthy adult volunteers following consumption of cereals fortified with 100 mg iron/kg dry cereal product (providing approximately 5 mg iron/day) as FeNaEDTA or $FeSO_4$.

OVERVIEW OF FIELD TRIAL EXPOSURE DATA IN COUNTRIES USING OTHER SOURCES OF IRON

Iron sources other than FeNaEDTA have been used in various human trials conducted to assess iron absorption and/or iron status in healthy volunteers and in populations with low iron status. These iron sources include hemoglobin-iron complex (Calvo *et al.*, 1989; Hertrampf *et al.*, 1990), ferrous sulfate (Ashworth and March, 1973; Sayers *et al.*, 1974; Pereira *et al.*, 1979; Rossander *et al.*, 1979; Hallberg and Rossander, 1984; Gotelli *et al.*, 1996; Rapetti *et al.*, 1997; Uicich *et al.*, 1999), iron amino acid chelates (Olivares *et al.*, 1997; Iost *et al.*, 1998; Pizarro *et al.*, 1998; Bovell-Benjamin *et al.*, 2000; de Paula and Fisberg, 2001; Giorgini *et al.*, 2001; Olivares and Pizarro, 2001), and ferrous fumarate (Ashworth and March, 1973; Hertrampf *et al.*, 1980; Sattarzadeh and Zlotkin, 1999; Davidsson *et al.*, 2000; Zlotkin *et al.*, 2001). Other studies also have been designed to compare iron sources and include ferrous succinate, ferric saccharate and ferric pyrophosphate (Hurrell *et al.*, 1989, 1991; Allen *et al.*, 1998; Bovell-Benjamin *et al.*, 2000; Layrisse *et al.*, 2000; van Stuijvenberg *et al.*, 2001). In several studies, ferrous ascorbate was administered as a reference dose under standardized conditions as a means to minimize the effects of individual variations in absorptive capacity (*i.e.*, absorption of iron from a given test meal/carrier food is expressed as a ratio to the reference dose) (Baynes *et al.*, 1987). In general, these trials provided iron levels ranging from 0.2 to 80 mg/day in various carrier foods, with no adverse effects.

SUMMARY

Ferrazone™ (FeNaEDTA) is considered to have low toxicity potential. Under the conditions of intended use of Ferrazone™, the total population mean and 90th percentile all-user daily intakes of Ferrazone™ are estimated to be 16.37 and 38.44 mg/person/day (0.27 and 0.64 mg/kg body weight/day, respectively). The mean intakes of iron and EDTA by the total population from all proposed food-uses of Ferrazone™ were estimated to be 2.17 and 11.21 mg/person/day (0.036 and 0.19 mg/kg body weight/day, respectively). The 90th percentile intakes of iron and EDTA by the total population from all proposed food-uses of Ferrazone™ were estimated to be 5.10 and 26.3 mg/person/day (0.085 and 0.44 mg/kg body weight, respectively). The background *per capita* intake of iron by the total population from the diet is estimated to be 15.02 mg/person/day. With the addition of Ferrazone™ to proposed food uses, the *per capita* intake of iron from the diet would increase to 15.25 mg/person/day for the total population. Thus, the added intake of iron from the proposed level of iron fortification of soy and fish sauces represents a very small proportion of current iron intake.

The levels of intake of iron and EDTA from proposed foods uses of Ferrazone™ are comparable to those obtained in a safety assessment of FeNaEDTA for its intended use as a fortificant in breakfast cereals and cereal bars (Heimbach *et al.*, 2000). In this assessment, the mean intake of iron and EDTA was reported to be 3.93 and 22.17 mg/person/day, respectively, while the 90th percentile intake of EDTA on a body weight basis was reported to be 1.15 mg/kg body

weight/day. Heimbach *et al.* (2000) concluded that this level of exposure was safe based on the fact that the 90th percentile intake of EDTA was less than half of the ADI of 2.5 mg/kg body weight/day for EDTA established by JECFA (1974). The 90th percentile intakes of iron and EDTA from proposed food uses of Ferrazone™ are less than the respective mean intakes estimated by Heimbach *et al.* (2000), thus the intended use of Ferrazone™ in food should pose no safety concerns.

FeNaEDTA has a low acute toxicity, with an oral LD_{50} value of 10 g/kg body weight in rats. Negative results were reported for FeNaEDTA in various *in vitro* genotoxicity assays, using *S. typhimurium* and *E. coli.* Positive results were obtained for FeNaEDTA in the mouse lymphoma assay using L5178Y cells; however, these results may be due to increased sensitivity of the cells to increased iron concentrations and were not considered significant in the overall safety assessment of FeNaEDTA. Dietary treatment with FeNaEDTA, providing iron levels of up to 11 mg/kg body weight/day for a period of up to 61 days produced no toxicologically significant effects in rats. Based on the results of this study, JECFA concluded that administration of FeNaEDTA in the diet would not result in a greater uptake of iron once nutritional requirements for iron are met and that the use of FeNaEDTA would be safe for use in food fortification programs that would provide 0.2 mg iron/kg body weight/day. Studies of other sources of EDTA have likewise demonstrated no significant toxicological effects in rats and dogs. A NOAEL of 250 mg/kg body weight/day was reported for $CaNa_2EDTA$ using 1- and 2-year feeding studies in dogs and rats, respectively. Based on these data, JECFA assigned an ADI of 2.5 mg/kg body weight/day for EDTA. In addition, no compound-related mortality, reproductive, or teratogenic effects were reported in rats orally dosed with 967, 1,243, 1,245, 1,340, and 1,374 mg/kg body weight/day of EDTA, Na_2EDTA, Na_3EDTA, $CaNa_2EDTA$, and Na_4EDTA, respectively, on gestation days 7 to 14. Furthermore, no significant reproductive or developmental effects were observed in multiple generations of rats exposed to diets providing levels of up to 250 mg/kg body weight/day of $CaNa_2EDTA$.

FeNaEDTA has been used in numerous field trials in developing countries for the iron fortification of foods. No adverse effects were reported in humans subjected to long-term FeNaEDTA fortification trials in which fish and soy sauces, sugar, and curry powder were fortified with FeNaEDTA providing levels of 4 to 15 mg iron/day (0.067 to 0.25 mg iron/kg body weight/day). Remarkable improvements in iron status indicators were reported in the fortified groups compared to the controls, with no evidence of iron overload. The fastest and greatest responses to iron fortification were observed in individuals of the fortified and control groups who were iron-deficient at the start of the fortification study, compared to their iron-repleted counterparts. In addition, studies evaluating the nutritional safety of FeNaEDTA in both rats and humans have demonstrated that FeNaEDTA does not adversely affect the absorption of other nutrients, including zinc, copper, and calcium.

Overall, the results of toxicological and clinical studies of FeNaEDTA and other sources of EDTA and iron support the safe intake of Ferrazone™ by humans. The addition of Ferrazone™ to soy

and fish sauces has a minimal impact on the intake of iron from the diet by the total population, and falls well within the level of fortification of 0.2 mg iron/kg body weight/day deemed acceptable by JECFA. It is important to note that iron levels used in current fortification programs are well below the tolerable intakes for iron of 50 mg/day as set by JECFA, or 45 mg/day of iron from all sources as presented by the IOM. Thus, dietary levels of FeNaEDTA that provide less than 45 mg of iron/day would be considered safe for humans. Furthermore, following a review of data similar to those described above, Heimbach *et al.* (2000) concluded that intake of FeNaEDTA would be considered safe at mean intake levels of iron and EDTA that are comparable to respective 90th percentile intakes from proposed uses of Ferrazone™. The scientific evidence presented above indicates that Ferrazone™ would not produce adverse effects on human health under the intended conditions of food use described herein. The data and information summarized in this report support the conclusion that Ferrazone™, meeting appropriate food grade specifications and manufactured in accordance with current good manufacturing practice, would be GRAS based on scientific procedures under the intended conditions of use.

CONCLUSION

We, the Expert Panel, have independently and collectively, critically evaluated the data and information summarized above and conclude that Ferrazone™, meeting appropriate food grade specifications and produced in accordance with current good manufacturing practice, is Generally Recognized As Safe (GRAS) based on scientific procedures under the conditions of intended use in foods specified herein.

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Table 1 Chemical Specifications for Ferrazone™		
Specification Parameter	**Specification Value**	**Analysis Method**
Identification		
Solubility	Soluble in water	FNP 52
Test for iron	Pass	FNP 52
Test for sodium	Pass	FNP 52
Purity		
Assay Iron	Not less than 12.5% and not more than 13.5%	FNP 52
EDTA	Not less than 65.5% and not more than 70.5%	FNP 52
pH	3.5-5.5 (1 in 100 solution)	FNP 52
Water insoluble matter	Not more than 0.1%	FNP 52
Nitrilotriacetic acid	Not more than 0.1%	FNP 52
Arsenic	Not more than 1 mg/kg	FNP 52
Lead	Not more than 1 mg/kg	FNP 52

Table 2 Summary of the Individual Proposed Food Uses for Ferrazone™ and the Corresponding Use-Levels for Iron and EDTA in the U.S.				
Food Category	**Proposed Food-Use**	**Use-Levels for Ferrazone™ (%)**	**Use-Levels for Iron (%)**	**Use Levels for EDTA (%)**
Gravies and Sauces	Soy, Fish, Hoisin, and Teriyaki Sauces	0.18	0.024	0.124
	Sweet and Sour Sauce	0.09	0.012	0.062

Table 3	Summary of the Estimated Daily Intake of Ferrazone™ 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	Mean All-Person Consumption (mg)	All-Users Consumption	
					Mean (mg)	90th Percentile (mg)
Young Children	1-8	NR[a]	NR	0.47	7.38	15.28
Female Children	9-18	NR	NR	0.97	13.90	28.57
Male Children	9-18	NR	NR	1.57	16.15	42.29
Female Adults	19-50	NR	NR	2.04	15.90	37.10
Male Adults	19-50	NR	NR	2.49	20.23	44.37
Female Older Adults	51 and Up	NR	NR	1.05	14.50	31.61
Male Older Adults	51 and Up	NR	NR	1.22	16.97	39.99
Total Population	1 and Up	7.9	1,495	1.60	16.37	38.44

[a] Not reported

Table 4	Summary of the Estimated Daily Intake of Iron from All Proposed Food Categories of Ferrazone™ in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)					
Population Group	Age Group (Years)	% Users	Actual # of Total Users	Mean All-Person Consumption (mg)	All-Users Consumption	
					Mean (mg)	90th Percentile (mg)
Young Children	1-8	NR[a]	NR	0.06	0.98	2.00
Female Children	9-18	NR	NR	0.13	1.84	3.80
Male Children	9-18	NR	NR	0.21	2.14	5.60
Female Adults	19-50	NR	NR	0.27	2.11	4.90
Male Adults	19-50	NR	NR	0.33	2.68	5.90
Female Older Adults	51 and Up	NR	NR	0.14	1.92	4.20
Male Older Adults	51 and Up	NR	NR	0.16	2.25	5.30
Total Population	1 and Up	7.9	1,495	0.21	2.17	5.10

[a] Not reported

Table 5	Summary of the Estimated Daily Intake of EDTA from All Proposed Food Categories of Ferrazone™ in the U.S. by Population Group (1994-1996, 1998 USDA CSFII Data)					
Population Group	Age Group (Years)	% Users	Actual # of Total Users	Mean All-Person Consumption (mg)	All-Users Consumption	
					Mean (mg)	90th Percentile (mg)
Young Children	1-8	NR[a]	NR	0.33	5.05	10.60
Female Children	9-18	NR	NR	0.66	9.53	19.50
Male Children	9-18	NR	NR	1.07	11.06	29.00
Female Adults	19-50	NR	NR	1.40	10.88	25.50
Male Adults	19-50	NR	NR	1.70	13.86	30.30
Female Older Adults	51 and Up	NR	NR	0.72	9.94	21.6
Male Older Adults	51 and Up	NR	NR	0.84	11.62	27.4
Total Population	1 and Up	7.9	1,495	1.10	11.21	26.3

[a] Not reported

Table 6	Summary of the Estimated Daily Intake of Iron from the Diet, Pre and Post Fortification with Ferrazone™ of 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	Mean All-Person Consumption (mg)		Mean All-User Consumption (mg)	
				Pre	Post	Pre	Post
Young Children	1-8	NR[a]	NR	12.65	12.71	12.24	13.22
Female Children	9-18	NR	NR	13.41	13.54	13.66	15.51
Male Children	9-18	NR	NR	18.39	18.60	19.54	21.68
Female Adults	19-50	NR	NR	12.66	12.93	14.12	16.22
Male Adults	19-50	NR	NR	18.73	19.06	20.97	23.65
Female Older Adults	51 and Up	NR	NR	12.12	12.26	13.43	15.35
Male Older Adults	51 and Up	NR	NR	16.93	17.10	19.09	21.33
Total Population	1 and Up	7.9	1,495	15.02	15.25	16.76	18.93

[a] Not reported

Table 7 Summary of Field and Clinical Trials Using FeNaEDTA to Fortify Various Food Vehicles

	Garby and Areekul, 1974	Ballot *et al.*, 1989	Viteri *et al.*, 1995	Huo *et al.*, 2002	Thuy *et al.*, 2003
Geographical region	Thailand	South Africa	Guatemala	China	Vietnam
Population studied	2 rural villages	Urban Indian community in a municipal housing estate	4 rural communities (2 lowlands and 2 highlands)	Children aged 11 to 17 years	Adult women
Design of trial	Controlled (one village); not blinded	Controlled (random allocation by families); double-blinded	Controlled; double-blinded	Controlled, double-blinded, randomized	Controlled, double-blinded, randomized
Sample population	Test village (n=284); Control village (n=330)	263 families (n=672); 129 control families; 134 fortified families; Hb < 9 g/dL excluded	T_1 (n=1,144); T_2 (n=1,756); T_3 (1,645); Control (n=1,095); severely under-nourished children, anemic, pregnant women, Hb < 90 g/L excluded	Control (n=102), low FeNaEDTA (n=102), high FeNaEDTA (n=100)	Control (n=76), Test (n=76)
Food vehicle	Fish-sauce (salt substitute) 30 g NaCl/L, 10 mg Fe/L distributed by village head-man as required	Masala (curry powder) distributed directly to families monthly; free of charge	Off-white sugar distribution: sold to store keepers; purchased by participants (relatively good compliance)	Soy sauce added to soup served daily at lunch	Fish sauce consumed with meals based on noodles or rice
Level of fortification and intake	1 mg Fe/mL; 10-15 mg Fe/person/day	1.4 mg Fe/g; 7.7 mg Fe/person/day	124 mg Fe/kg; 4.3-4.7 mg Fe/person/day	1 mg Fe/mL; 5 and 20 mg Fe/person/day	1 mg Fe/mL; 10 mg Fe/person/day
Duration of trial	12 months	24 months	32 months	3 months	6 months
Abnormal iron status before trial (%)	30-50 of population anemic; 34 PCV below normal	IDA 24 (F), 4 (M) ID 53 (F), 24 (M)	27.3 (T_1), 41.7 (T_2), 10.2 (T_3), 13.9 (Control) of population anemic	100 anemic (all groups)	100 anemic (all groups)
Measurements taken	PCV	Hemoglobin, %Sat, serum ferritin	Hemoglobin, %Sat, FEP, serum ferritin, Fe stores	Hemoglobin, serum iron, serum ferritin, transferritin, TIBC	Hemoglobin, serum ferritin, serum transferrin receptor, serum transferrin receptor:serum ferritin ratio

IDA = iron deficiency anemia; ID = iron deficiency; % Sat = % saturation of transferrin; FEP = free erythrocyte protoporphyrin; PCV = packed cell volume; TIBC = total iron binding capacity

0000026

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Attachment 1

ATTACHMENT 1

CURRICULA VITAE OF EXPERT PANEL MEMBERS

Pages 000034-000069 removed under Exemption 6 of the Freedom of Information Act.

Submission End