FOOD STANDARDS
Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

**12 December 2007**
**[8-07]**

# DRAFT ASSESSMENT REPORT

# APPLICATION A570

# FERRIC SODIUM EDETATE AS A PERMITTED FORM OF IRON

**DEADLINE FOR PUBLIC SUBMISSIONS: 6pm (Canberra time) 6 February 2008**
**SUBMISSIONS RECEIVED AFTER THIS DEADLINE WILL NOT BE CONSIDERED**
*(See 'Invitation for Public Submissions' for details)*

For Information on matters relating to this Assessment Report or the assessment process generally, please refer to http://www.foodstandards.gov.au/standardsdevelopment/

## Executive Summary

An unpaid Application was received from Axiome Pty Ltd, on behalf of Akzo Nobel Pty Ltd (the Applicant) seeking to amend Standard 1.1.1 – Preliminary Provisions – Application, Interpretation and General Prohibitions of the *Australia New Zealand Food Standards Code* (the Code), to approve sodium iron(III) **e**thylene**d**iamine**t**etra**a**cetate (common name ferric sodium edetate or ferric sodium EDTA) as a permitted form of the mineral iron.

At Draft Assessment, dietary exposure estimates suggested total exposure to EDTA from ferric sodium EDTA would be likely to exceed acceptable levels if the request to permit use of this form of iron in all food categories captured under the original Application was pursued. FSANZ presented the Applicant with alternative suggestions to amend the Application. The Applicant chose to withdraw breakfast cereals and formulated supplementary foods for young children aged one to three years from the Application.

The amended Application seeks to vary the Schedule to Standard 1.1.1 to include ferric sodium EDTA as a permitted form of the mineral iron. Fortification of food with iron is only permitted in the Code if the iron is in one of the forms listed in the Schedule to Standard 1.1.1. This Application does not seek to change any permission in the Code for voluntary addition of iron to food. The justification for use of ferric sodium EDTA provided by the Applicant is that it has superior biological and technological properties in comparison to the forms of iron currently permitted.

Approval of this Application would allow manufacturers of the following foods, which already have permission to contain added iron, to choose to add iron in the form of ferric sodium EDTA: (in accordance with Standard 1.3.2 – Vitamins and Minerals) to biscuits, bread, cereal flours, pasta, extracts of meat, vegetables or yeast, analogues of meat derived from legumes, and formulated beverages; (in accordance with Standard 2.9.3 – Formulated Meal Replacements and Formulated Supplementary Foods) to formulated meal replacements and formulated supplementary foods; (and in accordance with Standard 2.9.4 – Formulated Supplementary Sports Foods) to formulated supplementary sports foods.

**Purpose**

The Applicant seeks approval for the use of ferric sodium EDTA as an alternative permitted form of the mineral iron within existing voluntary permissions for addition of iron to food. The objective of this assessment is to determine whether or not a permission in the Code to use ferric sodium EDTA will be safe and efficacious.

**Risk Assessment**

FSANZ has undertaken a comprehensive risk assessment of ferric sodium EDTA and concluded that its use in a range of foods for voluntary fortification purposes does not raise public health and safety concerns.

Over the long-term, absorption of iron is effectively down-regulated by the body, including the iron in ferric sodium EDTA. As iron requirements decline, the body adjusts by absorbing less iron. In test meals high in phytic acid (a potent inhibitor of iron absorption) the iron in ferric sodium EDTA is two to three times better absorbed than the iron in ferrous sulphate.

Vegetarians, a group over-represented amongst iron deficient populations, may follow diets that mimic these test conditions. Vegetarians, depending on their iron status and dietary patterns, may potentially benefit from approval of this Application. The usual diet of most New Zealanders and Australians is unlikely to mimic these test conditions however. Given this and the down-regulation of iron absorption, ferric sodium EDTA is unlikely to offer any particular biological advantage or disadvantage to the general population compared with use of other permitted iron forms.

The Applicant's claim that ferric sodium EDTA has superior technological properties has been considered. While there is evidence that ferric sodium EDTA is technologically superior to other forms of iron in certain food vehicles, including some cereals, soy sauce and fish sauce, the effects of adding ferric sodium EDTA would need to be assessed in different food vehicles before it is used since the effects can be highly variable and not readily predictable. Recently published reports suggest ferric sodium EDTA is more expensive than other forms of iron.

FSANZ has determined that the Acceptable Daily Intake (ADI) established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1974 for other compounds of EDTA is applicable for ferric sodium EDTA. In July 2007, JECFA updated and subsequently reaffirmed its earlier evaluations on the safety of ferric sodium EDTA, which had been published in 1993 and 1999, and concluded that ferric sodium EDTA is suitable for use as a source of iron for food fortification provided that the total intake of iron does not exceed the provisional maximum tolerable daily intake of 0.8 mg/kg body weight (bw). Total intake of EDTA compounds should not exceed the ADI of 0-2.5 mg/kg bw, equivalent to up to 1.9 mg/kg bw EDTA.

The dietary exposure model used in this assessment includes exposure to EDTA through ingestion of foods containing permitted additive calcium disodium EDTA and the proposed levels of ferric sodium EDTA. According to the 'realistic' scenario modelled, for the most highly exposed group by virtue of body weight, namely the 2-6 year olds, the aggregate exposure at the 90$^{th}$ percentile is around 80% of the ADI. All other population subgroups have exposures less than 80% of the ADI. Exposures to EDTA compounds may increase above the ADI in future should there be an increase in the availability of foods fortified with iron within existing iron fortification permissions and ferric sodium EDTA were the only fortificant used. Increased use of the additive calcium disodium EDTA by the food industry would further increase exposures to EDTA. However as there would be 17 forms of iron for industry to select from, it is considered extremely unlikely that ferric sodium EDTA will be the only fortificant used.

**Risk Management**

The FSANZ risk assessment confirms the safety of ferric sodium EDTA. As an iron fortificant, for the general population, ferric sodium EDTA appears to offer no biological advantage or disadvantage to most Australians and New Zealanders. Also, due to the body's effective down-regulation of iron absorption, there appears to be no additional risk of iron overload through the use of ferric sodium EDTA in place of other forms of iron currently permitted in the Code.

In relation to the EDTA component, the dietary exposure assessment reveals that given current uptake of iron fortification permissions by the food industry, the potential use of ferric sodium EDTA in a range of foods for voluntary fortification purposes does not raise public health and safety concerns. However, there is potential for changes in food industry practice which could increase exposures of EDTA towards the 'worst case' scenario as modelled by FSANZ. Although this scenario is considered unlikely, FSANZ recommends monitoring estimated exposures to ferric sodium EDTA as part of its future fortification monitoring programs.

The key focus of the FSANZ risk assessment was the safety aspects of this new form of iron. However, the risk assessment also discussed the incidental finding that ferric sodium EDTA may potentially benefit vegetarians. As noted in Section 5.2, ferric sodium EDTA could reduce the inhibitory effect of phytic acid and enable the absorption of more iron by vegetarians than if iron was consumed by them as ferrous sulphate.

The food industry could benefit from the technologically superior properties of ferric sodium EDTA where evident, and either reformulate existing iron-fortified products or introduce new products onto the market.

Approval to use ferric sodium EDTA will not result in any changes to the current labelling requirements for foods containing added iron, in either the ingredient list or the nutrition information panel on food labels. While manufacturers may choose to declare the form of iron used, there are no requirements within the Code for foods containing added iron to declare the permitted form of iron that has been added to the food, though the ingredient list must declare 'iron' or 'mineral (iron)'.

**Impact of Regulatory Options**

The only regulatory options identified were to approve or not approve the use of ferric sodium EDTA as an alternative permitted form of the mineral iron within the existing voluntary permissions for addition of iron to foods under Standard 1.3.2 (except breakfast cereals, as purchased), Standard 2.9.3 (except formulated supplementary foods for young children) and Standard 2.9.4. Analysis of the potential costs and benefits of each option on parties likely to be affected (consumers, the food industry and government), indicates that approval of this Application provides a greater net benefit than the alternative.

## Preferred Approach

The preferred regulatory approach for Application A570 is to amend Standard 1.1.1 Preliminary Provisions – Application, Interpretation and General Prohibitions to include ferric sodium EDTA as a permitted form of iron. Subsequent amendments to Standard 1.3.2 – Vitamins and Minerals, and Standard 2.9.3 – Formulated Meal Replacements and Formulated Supplementary Foods are also required to clearly exclude the use of ferric sodium EDTA in 'breakfast cereal, as purchased' and 'formulated supplementary foods for young children'.

## Reasons for Preferred Approach

The draft variations to the Code are proposed for the following reasons:

- it is consistent with the section 18 objectives of the FSANZ Act;
- it does not raise any public health and safety concerns; and
- it has the potential to provide a net benefit to the food industry.

**Consultation**

The Initial Assessment Report was available for public comment between 13 December 2006 and 7 February 2007. Seven submissions were received including three from industry and four from government. Submitters either supported the option to amend Standard 1.1.1 and/or supported the progression of the Application. FSANZ has taken submitters' comments into account in preparing the Draft Assessment for this Application.

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## INVITATION FOR PUBLIC SUBMISSIONS

FSANZ invites public comment on this Draft Assessment Report based on regulation impact principles and the draft variations to the Code for the purpose of preparing an amendment to the Code for approval by the FSANZ Board.

Written submissions are invited from interested individuals and organisations to assist FSANZ in preparing the Draft Assessment of this Application. Submissions should, where possible, address the objectives of FSANZ as set out in section 18 of the FSANZ Act. Information providing details of potential costs and benefits of the proposed change to the Code from stakeholders is highly desirable. Claims made in submissions should be supported wherever possible by referencing or including relevant studies, research findings, trials, surveys etc. Technical information should be in sufficient detail to allow independent scientific assessment.

The processes of FSANZ are open to public scrutiny, and any submissions received will ordinarily be placed on the public register of FSANZ and made available for inspection. If you wish any information contained in a submission to remain confidential to FSANZ, you should clearly identify the sensitive information and provide justification for treating it as commercial-in-confidence. Section 114 of the FSANZ Act requires FSANZ to treat in-confidence, trade secrets relating to food and any other information relating to food, the commercial value of which would be, or could reasonably be expected to be, destroyed or diminished by disclosure.

Submissions must be made in writing and should clearly be marked with the word 'Submission' and quote the correct project number and name. Submissions may be sent to one of the following addresses:

**Food Standards Australia New Zealand**
**PO Box 7186**
**Canberra BC ACT 2610**
**AUSTRALIA**
**Tel (02) 6271 2222**
**www.foodstandards.gov.au**

**Food Standards Australia New Zealand**
**PO Box 10559**
**The Terrace WELLINGTON 6036**
**NEW ZEALAND**
**Tel (04) 473 9942**
**www.foodstandards.govt.nz**

**Submissions need to be received by FSANZ by 6pm (Canberra time) 6 February 2008.**

Submissions received after this date will not be considered, unless agreement for an extension has been given prior to this closing date. Agreement to an extension of time will only be given if extraordinary circumstances warrant an extension to the submission period. Any agreed extension will be notified on the FSANZ website and will apply to all submitters.

While FSANZ accepts submissions in hard copy to our offices, it is more convenient and quicker to receive submissions electronically through the FSANZ website using the Standards Development tab and then through Documents for Public Comment. Questions relating to making submissions or the application process can be directed to the Standards Management Officer at the above address or by emailing standards.management@foodstandards.gov.au.

Assessment reports are available for viewing and downloading from the FSANZ website. Alternatively, requests for paper copies of reports or other general inquiries can be directed to FSANZ's Information Officer at either of the above addresses or by emailing info@foodstandards.gov.au.

# INTRODUCTION

Food Standards Australia New Zealand (FSANZ) received an unpaid Application from Axiome Pty Ltd on behalf of Akzo Nobel Pty Ltd (the Applicant) on 11 August 2005 seeking to amend Standard 1.1.1 – Preliminary Provisions – Application, Interpretation and General Prohibitions in the Code, to approve sodium iron(III) **e**thylene**d**iamine**t**etra**a**cetate (common name ferric sodium edetate or ferric sodium EDTA) as a permitted form of the mineral iron. The Applicant sought permission to use this new form of the mineral iron within the existing voluntary permissions for addition of iron to food. This Application has not sought to change any permission in the Code for voluntary addition of iron to food.

At Draft Assessment, dietary exposure estimates undertaken by FSANZ suggested that total exposure to EDTA would be likely to exceed acceptable levels if the request to permit use of ferric sodium EDTA in all food categories captured under the original Application was pursued. FSANZ presented the Applicant with alternative suggestions to amend the Application. The Applicant chose to withdraw breakfast cereals and formulated supplementary foods for young children aged one to three years from the Application.

This Draft Assessment Report discusses the issues involved in the amended Application and seeks comments from stakeholders on a preferred approach to assist FSANZ in making a final assessment of this Application.

## 1. Background

The Applicant has requested that the Schedule to Standard 1.1.1 be amended to include ferric sodium EDTA as a permitted form of iron. Fortification of certain food with iron is permitted in the Code only if the iron is in one of the forms listed in the Schedule to Standard 1.1.1. There is currently no listing of ferric sodium EDTA in Standard 1.1.1, and therefore an amendment to this Standard is required before ferric sodium EDTA would be permitted for use. The justification for use of ferric sodium EDTA provided by the Applicant is that it has superior biological and technological properties in comparison to the forms of iron currently permitted.

The Applicant has not requested permission for use of ferric sodium EDTA in infant formula or foods for infants. These foods are regulated by Standards 2.9.1 and 2.9.2 respectively, which contain their own separate lists of iron forms permitted for addition.

The amended Application seeks to vary the Schedule to Standard 1.1.1 to include ferric sodium EDTA as a permitted form of the mineral iron where addition of iron is currently permitted in accordance with the Standards listed under Table 1 below. This would enable manufacturers of foods which already have permission to contain added iron to choose to add iron in the form of ferric sodium EDTA.

### 1.1 Current Standards

#### *1.1.1 Permitted chemical forms of iron*

Standards 1.3.2, 2.9.3 and 2.9.4 permit the addition of iron to certain foods only if the added iron is in one of the forms listed in the Schedule to Standard 1.1.1.

There are currently 16 permitted forms of iron listed in the Schedule to Standard 1.1.1. There is currently no listing of ferric sodium EDTA in Standard 1.1.1.

*1.1.2 Recommended Dietary Intakes of iron*

The Schedule to Standard 1.1.1 provides the Recommended Dietary Intakes (RDI) that apply generally to the Code. For iron the RDI is 12 mg, except for children aged one to three years where the RDI is 6 mg.

*1.1.3 Existing voluntary permissions for addition of iron to food*

The Code contains permissions to add iron in any of the permitted forms listed in the Schedule to Standard 1.1.1, to foods under Standard 1.3.2, foods under Standard 2.9.3, and foods under Standard 2.9.4.

**Table 1: Foods captured under this Application with existing permissions for the voluntary addition of iron**

| Food | Reference quantity | Maximum claim per reference quantity (proportion RDI) |
|---|---|---|
| **Standard 1.3.2 – Vitamins and Minerals** | | |
| Biscuits containing not more than 200g/kg fat and not more than 50g/kg sugars | 35 g | 3.0 mg (25%) |
| Bread | 50 g | 3.0 mg (25%) |
| Cereal flours | 35 g | 3.0 mg (25%) |
| Pasta | That quantity which is equivalent to 35 g of uncooked dried pasta | 3.0 mg (25%) |
| Extracts of meat, vegetables or yeast | 5 g | 1.8 mg (15%) |
| Analogues of meat derived from legumes | 100 g | 3.5 mg (30%) |
| Formulated beverages | 600 mL | 3.0 mg (25%) |
| **Standard 2.9.3 – Formulated Meal Replacements and Formulated Supplementary Foods** | | |
| Formulated meal replacements | One meal serving | 4.8 mg (40%) |
| Formulated supplementary foods | One serving | 6.0 mg (50%) |
| **Standard 2.9.4 – Formulated Supplementary Sports Foods** | | |
| Formulated supplementary sports foods | One day quantity | 12 mg (100%) |

*1.1.4 Labelling of foods containing added iron*

There are no requirements within the Code for foods containing added iron to declare the permitted form of iron that has been added to the food. Standard 1.2.4 – Labelling of Ingredients, requires all ingredients to be listed in a statement of ingredients.

The ingredient list on the label of foods containing added iron must declare the added iron but could declare 'iron' or the class name 'mineral' followed by '(iron)' without declaring the form of iron that has been added to the food. Manufacturers may volunteer to declare the form of added iron in the ingredient list if they wish to do so.

The nutrition information panel on a food containing added iron is not required to include a declaration of the iron content of the food unless a nutrition claim is made about the iron content of the food (refer to Division 2 of Standard 1.2.8 – Nutrition Information Requirements). Manufacturers may include a voluntary declaration of the iron content of the food in the nutrition information panel if they wish to do so.

### *1.1.5 Existing permissions in the Code for compounds containing EDTA*

Calcium disodium EDTA is currently permitted in the Code as a food additive in a range of foods including, fully preserved fish including canned fish, fruit drink, water-based flavoured drinks and sauces and toppings, at levels ranging from 33 to 250 mg/kg. This is the only EDTA compound permitted in the Code.

## 1.2 Overseas and International Regulations

There are no international standards relating to use of ferric sodium EDTA. The use of ferric sodium EDTA has mostly been restricted to food fortification programs.

### *1.2.1 Codex General Standard for Food Additives*

There are two EDTA compounds listed as permitted food additives in the Codex General Standard for Food Additives (GSFA). These are calcium disodium EDTA (INS no. 385) and disodium EDTA (INS no. 386). Codex has not recognised ferric sodium EDTA as a permitted food additive under the GSFA (CODEX 2007).

### *1.2.2 United States of America*

Ferric sodium EDTA is not currently recognised by the Food and Drug Administration (FDA) as a direct food additive. Pre-approval of food additives is required in the United States unless the use of the substance is generally recognised as safe (GRAS) by qualified experts. Any person may notify the FDA of a determination by that person that a particular use of a substance is GRAS. The FDA evaluates whether notices provide a sufficient basis for a GRAS determination. The FDA has provided GRAS status to ferric sodium EDTA through two notices.

In December 2004, the FDA evaluated a notice submitted on behalf of Kraft Foods Global in which Kraft concluded that ferric sodium EDTA is GRAS when used as a source of dietary iron in powdered meal replacements, flavoured milk, and fruit-flavoured beverages designed for fortification programs in areas of the world with a high prevalence of iron deficiency. While the FDA did not make its own determination regarding the GRAS status of the subject use of ferric sodium EDTA, the FDA stated that it had no questions regarding Kraft's conclusions (USFDA 2004).

In January 2006, responding to a notice submitted by Akzo Nobel Chemicals, ferric sodium EDTA was determined to be GRAS for use as a source of dietary iron in the iron fortification of soy, fish, teriyaki, and hoisin sauces. Again, the FDA did not make its own determination regarding the GRAS status but stated that it had no questions regarding Akzo Nobel's conclusions (USFDA 2006).

### *1.2.3 European Union*

Currently, the use of ferric sodium EDTA is not permitted in the European Union as a source of iron in foods and food supplements. An Application was submitted to the European Food Safety Authority (EFSA) by Akzo Nobel in July 2006 for approval of ferric sodium EDTA as a direct replacement for permitted forms of iron in the European Union for use in foods for particular nutritional uses (PARNUTS products) and food supplements. The Application seeks permission to use ferric sodium EDTA within both regulated and not yet regulated categories of PARNUTS products (special purpose foods) other than baby foods and infant formula. The Application does not include general purpose foods (Akzo Nobel Functional Chemicals, 2006). The EFSA does not expect a scientific opinion on this Application before the end of 2008 (personal communication).

### *1.2.4 Canada*

In 2005, Health Canada released a Proposed Policy and Implementation Plan on the Addition of Vitamins and Minerals to Foods. Under this Policy, Canada currently permits iron to be added to certain foods and has a list of 15 forms of iron permitted for use. Ferric sodium EDTA is not a permitted form of iron in Canada (Health Canada 2005).

## 1.3 Nutrition Background

### *1.3.1 Iron nutrition*

Iron is a component of a number of proteins in the body: haem-containing proteins (e.g. haemoglobin and myoglobin); transport proteins (e.g. transferrin); and storage proteins (e.g. ferritin or haemosiderin). It is also utilised in iron-containing enzymes used in redox reactions, such as cytochromes. Approximately two thirds of the body's iron is found in circulating red blood cells as haemoglobin, which is the protein responsible for carrying oxygen around the body. Twenty to thirty per cent of the body's iron is found in storage proteins and about ten per cent is located in iron-containing enzymes (NHMRC, 2006).

### *1.3.2 Sources of iron*

Two broad categories of dietary iron are present naturally in food: haem- and non-haem iron. Haem iron is found in haemoglobin and myoglobin proteins of animal meat and fish. Non-haem iron is derived from various sources (e.g. vegetable foods, dairy products and dietary iron fortificants) (NHMRC, 2006). A wide variety of iron compounds are currently permitted to be used to voluntarily fortify food. The Schedule to Standard 1.1.1 lists 16 permitted forms of iron for use in New Zealand and Australia.

### *1.3.3 Estimated dietary intakes in New Zealand and Australia against recommended upper levels of intake*

FSANZ has determined that there is a considerable margin between current population levels of iron intake at the 95th percentile and recommended upper levels for intake of iron.

The existing permissions in the Code for addition of iron to food are long standing. The addition of formulated beverages to Standard 1.3.2 in November 2006 is the only recent amendment to the Code that provided a new permission for the addition of iron to food. During consideration of Application A470 – Formulated Beverages, FSANZ estimated dietary intakes of iron, before and after formulated beverages would be on the market. FSANZ concluded that for the general population, the addition of iron to formulated beverages at a level of 3 mg per 600 mL serve posed no appreciable public health and safety risk. The conclusion was based on exposure estimates that showed intakes even at the 95th percentile would still be much lower than the concentrations of iron found to result in adverse effects. The highest values (95th percentiles) from the dietary intake estimates for iron from Application A470 are shown below, compared to the UL for iron now available following the recent publication of Nutrient Reference Values for Australia and New Zealand (NHMRC, 2006). The UL is the highest average daily nutrient intake level likely to pose no adverse health effects to almost all individuals in the general population.

**Table 2: Estimated dietary intakes of iron after introduction of formulated beverages containing added iron into the Code, compared to upper levels of intake (UL)**

| Age group | 95th percentile intake mg/day Scenario 2* (A) | Upper level of intake (UL) mg/day (B) | 95th percentile intake as proportion of UL (A/B x 100%) |
|---|---|---|---|
| 1-3 years, Aus | - | 20 | 65% |
| 2-3 years, Aus | 13.4 | - | |
| 4-8 years, Aus | 15.5 | 40 | 40% |
| 9-13 years, Aus | 23.2 | 40 | 60% |
| 14-18 years, Aus | 29.4 | 45 | 65% |
| 15-18 years, NZ | 25.2 | 45 | 55% |
| ≥19 years, Aus | 22.9 | 45 | 50% |
| ≥ 19 years, NZ | 22.0 | 45 | 50% |

(Source: Application A470 Formulated Beverages Final Assessment Report Attachment 6) (FSANZ 2005)
Scenario 2* = when people substitute all water based flavoured drink, bottled water and fruit juices and drinks they consumed with formulated beverages.

Specific detail on the assumptions made in the dietary exposure estimates shown in Table 2 can be found in the Final Assessment Report for Application A470 on the FSANZ website.

### *1.3.4 Iron status of Australians and New Zealanders*

A reduction in iron status, often referred to as 'iron deficiency' can be categorised into three stages:

- iron depletion – iron stores are depleted but there is enough circulating iron to ensure red blood cell production is not compromised;

- iron-deficient erythropoiesis – iron stores are empty and lower circulating levels of iron begin to compromise red blood cell production;

- iron deficiency anaemia – the amount of circulating iron is very low and red cell production is dramatically reduced. Severe anaemia is associated with fatigue, weakness and potentially heart failure (MacPhail, 2002).

Data from one New Zealand (Ferguson *et al*., 2001) and two Australian studies (Salder and Blight, 1996; Rangan *et al*., 1997) show that the prevalence of iron deficiency amongst Australian and New Zealand women is approximately 7-14%. These figures are slightly better than other developed countries, where adult female rates are 20-30% for iron depletion/iron deficient erythropoiesis and 2-8% for iron deficiency anaemia (WHO and FAO, 2004). FSANZ has been unable to obtain further data on iron deficiency rates for other sectors of the population.

There are three dimensions which affect iron status. These are demographic factors (e.g. being female, an athlete or a teenager), dietary factors (e.g. being vegetarian), and social or physical factors (e.g. poverty, alcohol abuse or poor dentition) (Australian Iron Status Advisory Panel 2007). Because there are many variables affecting iron status, the development of iron deficiency in an individual will depend on how many of these risk factors operate at once and over what period of time, making it difficult to predict. Vegetarians as a group would be expected to be over-represented amongst iron deficient populations given they consistently expose themselves to dietary factors such as low haem iron, and possibly excess phytic acid also.

## 2. The Issue

Standards 1.3.2, 2.9.3 and 2.9.4 permit the addition of iron to certain foods only if the added iron is in one of the forms listed in Standard 1.1.1. There is currently no listing of ferric sodium EDTA in Standard 1.1.1, and therefore an amendment to this Standard is required before ferric sodium EDTA can be permitted for use as a form of iron for addition to certain foods.

## 3. Objectives

In developing or varying a food standard, FSANZ is required by its legislation to meet three primary objectives which are set out in section 18 of the FSANZ Act. These are:

- the protection of public health and safety;

- the provision of adequate information relating to food to enable consumers to make informed choices; and

- the prevention of misleading or deceptive conduct.

In developing and varying standards, FSANZ must also have regard to:

- the need for standards to be based on risk analysis using the best available scientific evidence;

- the promotion of consistency between domestic and international food standards;
- the desirability of an efficient and internationally competitive food industry;
- the promotion of fair trading in food; and
- any written policy guidelines formulated by the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council).

The objective of this assessment is to determine whether or not a permission in the Code to use ferric sodium EDTA would be safe and efficacious.

### 3.1 Ministerial Policy Guideline

The Ministerial Council Policy Guideline of potential relevance to this Application is titled Fortification of Food with Vitamins and Minerals. This Policy Guideline was adopted by Ministers in May 2004. The Policy Guideline provides guidance on development of new permissions for the addition of vitamins and minerals to food (Ministerial Council 2004).

This Application seeks to add ferric sodium EDTA to the list of permitted forms of iron in the Code so that manufacturers of foods which already have permission to add iron may choose to add iron in the form of ferric sodium EDTA. This Application does not seek to extend the range of foods in which voluntary fortification is currently permitted. The risk assessment has therefore focused on the bioavailability[1] of ferric sodium EDTA compared to other forms of iron, particularly ferrous sulphate, in terms of nutritional safety and efficacy. The assessment is therefore consistent with the Policy Guideline endorsed by the Ministerial Council.

# RISK ASSESSMENT

A detailed Nutrition Assessment is provided at Attachment 2.

A detailed Safety Assessment is provided at Attachment 3.

A detailed Food Technology Report is provided at Attachment 4.

The Dietary Exposure Assessment Report is provided at Attachment 5.

This risk assessment addresses the following key risk assessment questions.

## 4. Key Assessment Questions

At Draft Assessment, the key assessment questions are:

1. Are there potential risks and/or benefits to the Australian and New Zealand populations from permitting ferric sodium EDTA as a form of iron?

[1] Bioavailability is the proportion of the ingested nutrient absorbed and utilised through normal metabolic pathways (Hurrell, 2002). It is influenced by dietary factors and host related factors (Gibson, 2007).

To answer this question the following will be assessed:

a. Is ferric sodium EDTA a bioavailable form of iron compared to the forms of iron currently permitted in the Code?
b. Within the existing permission for voluntary iron fortification of foods, would ferric sodium EDTA as a new iron fortificant, potentially benefit any population groups?
c. Within the existing permission for voluntary iron fortification of foods, would ferric sodium EDTA as a new iron fortificant, pose any risks for any population groups?

2. Are there potential risks to the Australian and New Zealand populations from increasing EDTA intakes as a result of permitting the use of ferric sodium EDTA as a form of iron?

To answer this question the following will be assessed:

a. Is there a maximum level of intake of EDTA (a reference health standard) above which adverse reactions could occur?
b. What is the level of exposure to EDTA for Australian and New Zealand population groups should ferric sodium EDTA be permitted as a form of iron?
c. Is there a risk of excessive EDTA intakes in Australian and New Zealand population groups?

3. Is ferric sodium EDTA a technologically superior form of iron?

# 5. Ferric Sodium EDTA as a Permitted Form of Iron

## 5.1 Bioavailability

The bioavailability of iron from ferric sodium EDTA is most often compared to ferrous sulphate because ferrous sulphate is widely used. This Assessment reports on the bioavailability of iron from ferric sodium EDTA compared to iron from ferrous sulphate only. The bioavailability of iron from other forms of iron currently permitted in the Code relative to ferric sodium EDTA has rarely been reported, and therefore is largely unknown.

Under test conditions where test meals are high in phytic acid (a potent inhibitor of iron absorption), the iron in ferric sodium EDTA is two to three times better absorbed and incorporated into red blood cells than the iron in ferrous sulphate. Under these conditions, the iron in ferric sodium EDTA can be said to be two to three times more bioavailable than the iron in ferrous sulphate. This improvement in bioavailability is due to ferric sodium EDTA reducing the effect of the iron absorption inhibitor phytic acid.

Over the long-term, absorption of iron is effectively down-regulated by the body, including the iron in ferric sodium EDTA. As iron requirements decline, the body adjusts by absorbing less iron. The usual diet of most New Zealanders and Australians is unlikely to mimic test conditions where absorption of iron from ferric sodium EDTA would be expected to be greater than absorption of iron from ferrous sulphate.

Given also that these populations are mostly iron replete and that down-regulation of iron absorption applies over time regardless of the form of iron consumed, the iron in ferric sodium EDTA is unlikely to offer any particular biological advantage or disadvantage to the general population compared with use of other permitted iron forms.

## 5.2 Potential Benefits

Within the existing permission for voluntary iron fortification of foods, would ferric sodium EDTA as a new iron fortificant, potentially benefit any population groups? Vegetarians may potentially benefit from ferric sodium EDTA as a new iron fortificant depending on their dietary pattern and iron status. Vegetarians as a group would be expected to be over-represented amongst iron deficient populations. A vegetarian with low iron status would be expected to absorb more iron from their diet than an iron replete individual. If the vegetarian's diet was high in phytic acid also, providing iron in the form of ferric sodium EDTA to such an individual would reduce the inhibitory effect of the phytic acid and enable the vegetarian to absorb two to three times more iron than they would if they consumed the iron as ferrous sulphate. The phytic acid content of vegetarian diets consumed in Australia and New Zealand is not known and would be variable, so this potential benefit to vegetarians as a group should be considered as a possibility only.

## 5.3 Potential Risks

Within the existing permission for voluntary iron fortification of foods, would ferric sodium EDTA as a new iron fortificant, pose any risks for any population groups?

### *5.3.1 Iron overload*

Within the existing permission for voluntary iron fortification of foods, ferric sodium EDTA as a new iron fortificant would not pose any additional risks to the general population. The absorption of iron is well controlled and down-regulated by the body. As iron status improves and iron requirements decline, the body adjusts by absorbing less iron. Studies with ferric sodium EDTA have shown that down-regulation occurs when iron is consumed in that form (Yeung *et al*., 2004). The potential introduction of ferric sodium EDTA as a new form of added iron into the diet of New Zealanders and Australians should confer no additional risk of iron-overload (excess stored iron) in the general population, due to the well controlled absorption of iron through down-regulation.

A sub-population of individuals (e.g. haemochromatosis sufferers) is susceptible to iron-overload, even at normal dietary iron intakes. Development of iron overload disease cannot be prevented in an undiagnosed individual and occurs regardless of the dietary iron source. Iron overload must be clinically managed once diagnosed. Therefore, the risk to this sub-population would not be increased by consumption of iron from ferric sodium EDTA.

### *5.3.2 Iron and Coronary Heart Disease*

The proposition that iron status is linked with prevalence of coronary heart disease has been noted briefly in this assessment because the proposed link was raised by a submitter at Initial Assessment. A summary of submissions at Initial Assessment is provided at Attachment 6. Published reviews indicate that there is not strong evidence for an association between iron and heart disease at this time.

### 5.4 Summary of Potential Benefits and/or Risks

The iron in ferric sodium EDTA is two to three times better absorbed than the iron in ferrous sulphate where test meals are high in phytic acid. Ferric sodium EDTA reduces the inhibitory effect of phytic acid on iron absorption. Compared to ferrous sulphate, ferric sodium EDTA is unlikely to offer any particular biological advantage or disadvantage to the general populations of Australia and New Zealand. However, vegetarians may potentially benefit, depending on their iron status and the phytic acid content of their diet. The potential risk of iron overload to both the general population and the sub-population of individuals susceptible to iron overload would not be increased by consumption of iron from ferric sodium EDTA.

## 6. Potential Risks from Increasing Exposures to EDTA

### 6.1 Reference Health Standard

Ferric sodium EDTA, like other EDTA-metal complexes, dissociates in the gastrointestinal tract to release bioavailable non-haem iron and an EDTA salt. Since the absorption of iron and EDTA are independent processes a consideration of any toxicological data on EDTA containing compounds other than ferric sodium EDTA is relevant for a safety assessment. The absorption of iron which is released from ferric sodium EDTA in the small intestine is controlled through the same physiological mechanisms as other permitted forms of iron, such as ferric sulphate, ferrous sulphate, ferric citrate, and ferrous fumarate.

Following oral administration, the iron in ferric sodium EDTA, which is separated from the EDTA complex in the lumen of the gut, forms part of the general non-haem iron pool in the diet that is mainly used in haemoglobin synthesis for physiological erythrocyte development. The absorption of iron from ferric sodium EDTA is controlled through the same physiological mechanisms as other forms of iron. Less than 1% of the intact ferric sodium EDTA chelate is absorbed and excreted unchanged by the kidneys. Following dissociation from ferric sodium EDTA, most (95%) of the EDTA is found in the faeces, while less than 5% is absorbed and excreted in the urine (JECFA 1999).

Ferric sodium EDTA has very low acute oral toxicity ($LD_{50}$ = 10,000 mg/kg bw). EDTA compounds do not cause reproductive or developmental effects when fed in a nutrient-sufficient diet or in a minimal diet supplemented with zinc (Swenerton and Hurley, 1971). In chronic toxicity studies, diets containing as much as 1% EDTA were without any adverse effects. EDTA compounds were not carcinogenic in experimental animal bioassays and are unlikely to be genotoxic (JECFA 1993).

In a two-year feeding study in rats treated with calcium disodium EDTA, no effects were observed at the highest tested dose of 250 mg/kg bw/day. Using a conventional 100-fold safety factor to take account of intra-and inter-species variability, the acceptable daily intake (ADI) for calcium disodium EDTA was calculated to be 2.5 mg/kg bw. Owing to the independence of the absorption kinetics for EDTA, this group ADI is also applicable for all other EDTA-containing compounds such as ferric sodium EDTA. For ferric sodium EDTA the theoretical bioavailable iron concentration at the maximal ADI of 2.5 mg/kg bw would be around 0.3-0.4 mg/kg bw/day. This concentration is well below the provisional tolerable daily intake of 0-0.8 mg/kg bw for iron (JECFA 2007).

### *6.1.1 Existing Safety Standards*

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) ( 1974) evaluated the safety of calcium disodium EDTA and disodium EDTA as food additives and recommended that these compounds be permitted as food additives at doses up to an ADI of 2.5 mg/kg bw/day.

In 1993, JECFA provisionally concluded that ferric sodium EDTA was safe when used in supervised food fortification programmes in iron-deficient populations. However, JECFA also requested that additional studies be conducted to assess the site of iron deposition and metabolic fate of ferric sodium EDTA following long-term administration (JECFA 1993).

In 1999, JECFA reviewed the results of new studies, including a short-term toxicity study in rats designed to address JECFA's concerns on iron deposition and metabolism of ferric sodium EDTA and concluded that 'sodium iron EDTA could be considered safe for use in supervised food fortification programmes, when public health officials had determined the need for iron supplementation of the diet of a population.' These programmes were required to provide daily iron intake of approximately 0.2 mg/kg bw (JECFA 1999).

In 2007, JECFA reviewed several new studies on the biochemical and toxicological aspects and on the efficacy of ferric sodium EDTA. JECFA concluded that ferric sodium EDTA is suitable for use as a source of iron for food fortification provided that the total intake of iron does not exceed PMTDI of 0.8 mg/kg bw. Total intake of EDTA compounds should not exceed the ADI of 0-2.5 mg/kg bw, equivalent to up to 1.9 mg/kg bw EDTA (JECFA 2007).

### *6.1.2 Nutritional risks associated with increased intakes of EDTA from ferric sodium EDTA*

There is a plausible biological explanation for the theoretical concern that consumption of compounds that release EDTA could impact on the nutritional status of important minerals such as zinc, copper, calcium or magnesium. The potential risk cannot be classified with confidence on the basis of published evidence because of the very limited published information that tests this theoretical risk. JECFA included studies regarding interference with mineral metabolism in its consideration of the evidence assessed by the Committee when establishing the ADI that is being used by FSANZ for this assessment. Therefore, provided the ADI for EDTA of 2.5 mg/kg body weight is not exceeded, the potential for EDTA from ferric sodium EDTA to have adverse effects on nutrient interactions should not be a concern.

## 6.2 Estimates of Total Dietary Exposure to EDTA

The dietary exposure model used in this assessment aggregates the likely exposure to EDTA through ingestion of foods containing permitted calcium disodium EDTA and the levels of ferric sodium EDTA proposed by the Applicant. These two compounds are the only potential sources of EDTA in foods in New Zealand and Australia. According to the 'realistic' scenario modelled, for the most highly exposed group namely the 2-6 year olds by virtue of body weight, the aggregate exposure at the 90$^{th}$ percentile is around 80% of the ADI. All other population subgroups have exposures less than 80% of the ADI under this scenario.

### 6.3 Potential Risk of Excessive EDTA Exposure

There is potential for changes in food industry practice which would increase exposures to EDTA towards the 'worst case' scenario as modelled by FSANZ. Under this scenario, estimated exposures would exceed the ADI. This could occur should there be an increase in the availability of foods fortified with iron within existing iron fortification permissions and ferric sodium EDTA were the only fortificant used. Increased use of the additive calcium disodium EDTA by the food industry would further increase exposures to EDTA. However as there would be 17 forms of iron for industry to select from, it is considered unlikely that ferric sodium EDTA will be the only fortificant used. Therefore dietary exposures to EDTA from ferric sodium EDTA will be lower than predicted (models assumed ferric sodium EDTA was the only iron fortificant).

## 7. Food Technology Issues

### 7.1 Is Ferric Sodium EDTA a Technologically Superior Form of Iron?

#### *7.1.1 Iron compounds*

Iron has been acknowledged as the most challenging micronutrient to add to foods because the iron compounds that have the best bioavailability tend to be those that produce undesirable changes to the sensory properties of the food vehicle such as the taste, colour or texture of the food. Iron in certain foods can cause rancidity and off flavours during prolonged storage. Sensory changes are highly variable and can be unpredictable also. It is not true to say that a form of iron will be equally suitable in a particular food vehicle under all situations. The cost of available iron compounds is also variable (WHO FAO, 2006).

#### *7.1.2 Ferric sodium EDTA as a form of iron*

Ferric sodium EDTA has the molecular formula:

$$C_{10}H_{12}N_2O_8FeNa{\cdot}3H_2O \text{ (trihydrate)}$$

The advantages of using ferric sodium EDTA as a food fortificant are that it has excellent stability during food processing. This means that the iron does not catalyse the oxidation of food components leading to undesirable odours, flavours and colours, which can occur with other forms of iron fortificants. Ferric sodium EDTA is slowly soluble in water. It causes fewer organoleptic problems than other water-soluble iron compounds but further data on the technical aspects of its use is required. The effects of adding ferric sodium EDTA as a fortificant for different food types needs to be assessed before it is used since the effects can be highly variable and not readily predictable. It may cause colour changes in some foods such as tea, coffee or cocoa. It does not promote lipid oxidation in stored cereals or the formation of precipitates in foods that are high in free peptides such as soy sauce and fish sauce (Bothwell and MacPhail, 2004). The main disadvantage of using ferric sodium EDTA is that it is reportedly more expensive than other iron fortificants (WHO FAO, 2006).

## 8. Risk Characterisation

Consideration has been given to the proposed use of ferric sodium EDTA as an alternative permitted form of the mineral iron within existing voluntary permissions for addition of iron to food.

Under test conditions where test meals are high in phytic acid, the iron in ferric sodium EDTA is two to three times better absorbed than the iron in ferrous sulphate. Vegetarians, a group over-represented amongst iron deficient populations, may follow diets that mimic these test conditions. Vegetarians, depending on their iron status and dietary patterns, may potentially benefit from approval of this Application. However, ferric sodium EDTA is unlikely to offer any particular biological advantage or disadvantage to the general populations of Australia and New Zealand.

Provided the total dietary intake of EDTA from existing permissions for use of the additive calcium disodium EDTA (refer section 1.1.5) and the proposed permissions for ferric sodium EDTA does not exceed the ADI of 2.5 mg/kg body weight, the proposed use of ferric sodium EDTA does not raise any public health and safety concerns in New Zealand or Australia.

# RISK MANAGEMENT

FSANZ has considered the management of any risks identified through the risk assessment and submissions received during the public consultation period. FSANZ has also considered possible nutritional benefits which have been identified.

## 9. Public Health and Safety Considerations

### 9.1 Ferric Sodium EDTA as an Iron Fortificant

FSANZ's risk assessment indicates that as a source of iron for the general population, ferric sodium EDTA probably offers no biological advantage or disadvantage to most Australians and New Zealanders. Also, due to the body's effective down-regulation of iron absorption, there appears to be no additional risk of iron overload through the use of ferric sodium EDTA in place of other forms of iron currently permitted in the Code.

Individuals with diagnosed haemochromatosis are treated through the removal of blood by venesection (sometimes called phlebotomy) at regular intervals (Haemochromatosis Society Australia Inc., 2007). The Haemochromatosis Society of Australia outlines there is no specific diet for haemochromatosis but it is accepted that people with this disorder should not enhance iron uptake out of their diet (Haemochromatosis Society Australia Inc. 2007). The New Zealand Haemochromatosis Support and Awareness Group recommends that in addition to avoiding iron supplements, foods that are fortified with iron should also be avoided (IRONZ 2007). Iron-fortified foods are readily identifiable by mandatory ingredient lists on food labels in Australia and New Zealand, so any consumer wishing to avoid iron-fortified foods, including foods that would be fortified with ferric sodium EDTA, could easily do so.

As indicated in the Nutrition Assessment (see Attachment 2), the development of iron-overload cannot be prevented in individuals with undiagnosed haemochromatosis, and once diagnosed, their condition is clinically managed. Therefore, the risk to such individuals would not be increased by consumption of iron from ferric sodium EDTA.

The impact of iron on other nutrients has not been considered as part of the risk assessment because it has previously been considered in allocating voluntary fortification permissions (Standard 1.3.2 – Vitamins and Minerals). This Application is only introducing another form of iron rather than a new permission.

The Nutrition Assessment also highlights that published reviews indicate that there is not strong evidence for an association between iron and heart disease at this time.

*9.1.1 Potential change in industry practice*

The Applicant has highlighted the superior technological properties of ferric sodium EDTA compared with other forms of iron for the fortification of food products. The FSANZ Food Technology Report (see Attachment 4) supports these claims. However, it also indicates that ferric sodium EDTA is not ideal for use in all products and that there are reports of it being more expensive than other iron fortificants, citing a recent publication by the World Health Organization (WHO) (WHO FAO, 2006).

The Applicant has provided data highlighting the cost benefit of ferric sodium EDTA to address iron deficiency through mass fortification programs. The Applicant also contends that cost comparison of limited iron fortification (voluntary fortification) in niche products is not a key factor. Considering this is an Application for voluntary fortification, the decision of whether industry will use this product will be based on a business case; balancing the cost and technological benefits. It is therefore possible that the level of fortification of food with iron within existing permissions may increase through the use of ferric sodium EDTA.

Based on a FSANZ assessment of current iron-fortified foods in Australia and information from the New Zealand Manufactured Food Database (Manufactured Food Database, 2006), it is evident there is potential for expansion within categories in which there are permissions. In Australia and New Zealand there appears to be very few iron-fortified breads and soy beverages. In Australia there appears to be no iron-fortified biscuits (containing not more than 200 g/kg fat and not more than 50 g/kg sugars), cereal flours or pasta. In New Zealand, there are few iron-fortified biscuits (containing not more than 200 g/kg fat and not more than 50 g/kg sugars) and pastas. FSANZ recently approved the voluntary addition of iron to formulated beverages. Growth in the availability of formulated beverages in the near future is likely to be modest.

If the availability of iron-fortified foods increased this could lead to an increase in consumption of such foods, and thereby increase iron intakes. Section 1.3.3 presented a comparison of iron intakes, from a previous conservative dietary intake assessment conducted by FSANZ (FSANZ 2005), as a proportion of the UL. Intakes are well below the UL. Even if there was an increase in the number of foods being fortified within existing voluntary permissions, it is likely that intakes of iron would still be within the level of safety.

**Question to submitters**

Will manufacturers substitute ferric sodium EDTA for other permitted forms of iron or fortify new products not currently fortified with iron, and if so, why?

### *9.1.2 Potential change in consumer behaviour*

There is no evidence to suggest that food consumption behaviour would change through permitting the use of ferric sodium EDTA as an iron fortificant. However there are a number of factors that may result in changes in individual consumption behaviour. These include:

1. consumers are presented with different information, for example through manufacturers making permitted nutrition content or function claims;
2. changes in sensory properties of the product, for example taste, colour, odour and texture;
3. changes in the price of products; and
4. changes in the availability of products.

#### 9.1.2.1 Information available to consumers

If consumers are presented with new or different information, consumption behaviour may change. However this will be muted to the extent that generally, vitamins and minerals are of less interest to consumers than macro-nutrients such as fat and sugar. Recent survey research by FSANZ (unpublished data) found that information about vitamins and minerals were searched for by approximately 20% of consumers. There are also socio-economic gradients in the reported search and use of this information, with women tending to report higher levels of use. However, even though up to 20% of people search for information about vitamins and minerals, FSANZ's quantitative research shows there appears to be no significant impact on actual behaviour.

Consumers currently have access to information about iron fortified foods through the mandatory ingredient list provisions and through voluntary nutrition claims and associated iron content information in the NIP on such foods. A change in the form of iron used by a manufacturer of an iron fortified food may not be evident to the consumer through the ingredient list unless the manufacturer had chosen to specify the type of iron used. The mandatory requirement for ingredient lists on iron fortified foods is that the list contains 'iron' or 'mineral (iron)'. The form of iron may be volunteered.

#### 9.1.2.2 Sensory properties

Food sensory properties are a key motivator underpinning food choices. If ferric sodium EDTA changes the taste, odour, colour and texture of products, consumers may respond to the change by increasing or decreasing their consumption of the food. It is envisaged that if manufacturers substituted ferric sodium EDTA for another form of iron currently used in their product, they would attempt to match the sensory properties.

#### 9.1.2.3 Price

Price is another key motivator underpinning food choices. If the use of ferric sodium EDTA results in increases or decreases in product prices then consumption behaviour may change. It is unknown what additional manufacturing costs would result in the production of foods voluntarily fortified with ferric sodium EDTA and what, if any costs, would be passed on to consumers.

9.1.2.4 Industry growth

The availability of ferric sodium EDTA may provide opportunities for the food industry to innovate and provide a greater range of iron-fortified foods to consumers. An increase in the number of iron-fortified foods within food categories in which there are existing iron-fortification permissions, may result in changes in consumption behaviour.

## 9.2 EDTA

### *9.2.1 Exposure to EDTA based on current levels of iron fortification*

FSANZ's risk assessment investigated the safety of the proposed addition of ferric sodium EDTA as an iron fortificant with respect to the EDTA component. The Applicant initially sought the use of ferric sodium EDTA in **all** foods permitted to be fortified with iron in Standards 1.3.2; 2.9.3; and 2.9.4. As indicated in Section 1 of this Report, at Draft Assessment the Applicant agreed to amend the Application on the basis that estimated exposures to EDTA would exceed acceptable levels. The amended Application excludes breakfast cereals and formulated supplementary foods for young children from the list of foods seeking permission to be fortified with ferric sodium EDTA.

With the exclusion of these foods, the risk assessment concludes that, based on current levels of iron fortification by industry, there are no public health and safety concerns for EDTA when ferric sodium EDTA is used as an iron fortificant. This conclusion is based on the dietary exposure assessment that indicated the estimated dietary exposure for all population groups is below the ADI, which encompasses the potential adverse effect EDTA may have on nutrient metabolism.

FSANZ notes that ferric sodium EDTA is safely used in various countries for large-scale iron fortification programs (Van *et al*., 2005; Chen *et al*., 2005; NUTRA Ingredients 2007). The WHO recommends the use of ferric sodium EDTA for the mass fortification of high-phytate cereal flours and for sauces with a high peptide content (WHO FAO, 2006).

### *9.2.2 Exposure to EDTA based on possible future levels of iron fortification*

The Dietary Exposure Assessment (see Attachment 5) reveals that should there be an increase in the availability of foods fortified with iron within existing iron fortification permissions and ferric sodium EDTA were the only fortificant used, estimated exposures to EDTA would increase to levels above the ADI (refer Scenario 2 exposure estimates). Increased use of the additive calcium disodium EDTA by the food industry would further increase exposures to EDTA. However, the assumptions made in the exposure estimates for EDTA under Scenario 2 (worst case) are unlikely to be met i.e. that all iron-fortified foods would contain ferric sodium EDTA. With the addition of ferric sodium EDTA to the Schedule of Standard 1.1.1, there would be 17 forms of iron for industry to select from when using iron fortification permissions. It is unrealistic to assume that all will choose ferric sodium EDTA. However, FSANZ recommends including ferric sodium EDTA in future fortification monitoring programs. The measurement of current food consumption patterns is either underway or planned for Australian and New Zealand population groups. The results of these surveys will be useful in refining future EDTA dietary exposure estimates.

### 9.3 Consideration of Nutritional Benefit

The risk assessment primarily focussed on the potential risks to public health and safety through the permission to added ferric sodium EDTA as an iron fortificant. Vegetarians were identified as a population group in which providing iron in the form of ferric sodium EDTA could potentially prove beneficial. Single source data from Roy Morgan Research indicates 10% of the Australian and 8% of the New Zealand populations aged 14 years and above identify themselves as vegetarians[2] (Roy Morgan Research, 2007). This represents a small proportion of the population.

### 9.4 Labelling

The purpose of food labelling is to provide consumers with information about food to enable them to make informed food choices. Labelling provides an important source of information for consumers regarding fortification and enables consumers to make informed decisions regarding their consumption of fortified foods.

The generic labelling requirements of the Code applicable to packaged foods that are fortified with iron include:

- listing of ingredients (Standard 1.2.4);
- nutrition information requirements for foods making nutrition claims (Standard 1.2.8); and
- the conditions applying to nutrition claims about vitamins and minerals (Standard 1.3.2).

The ingredient list enables consumers to select or avoid iron fortified foods as they wish. As is the case under existing permissions, foods voluntarily fortified with iron must list the iron in the ingredient list. This requirement would apply to foods containing ferric sodium EDTA also. If a nutrition claim is made, the iron content of the food will be required to be listed in the NIP on the label, as is currently the case. FSANZ considers the generic requirements of the Code to be appropriate for providing consumers with information regarding iron fortification with ferric sodium EDTA.

FSANZ is currently considering new regulations around nutrition, health and related claims under Proposal P293, which will be contained within Standard 1.2.7. This process is not expected to be finalised until mid-2008. Under this Proposal, the current approach is that claims about the bioavailability of iron in general purpose foods and foods standardised by Standards 2.9.3 and 2.9.4 would be regulated under Standard 1.2.7. Such claims would be permitted (assuming any applicable conditions were met) and it would depend on the wording of the claim as to whether the claim was regulated as a nutrition content claim or health claim under this Standard.

## 10. Regulatory Options

Since Initial Assessment, the Application has been amended to exclude breakfast cereals and formulated supplementary foods for young children aged one to three years. On this basis, FSANZ is proposing the following two regulatory options at Draft Assessment:

[2] Survey participants were asked to agree or disagree with the statement 'The food I eat is all, or almost all, vegetarian'.

### 10.1 Option 1 – Maintain *Status Quo*

Maintain the *status quo* by not amending the Code and thus not approving ferric sodium EDTA as a permitted form of iron in Standard 1.1.1.

### 10.2 Option 2 – Amend Standard 1.1.1

Amend Standard 1.1.1 to include ferric sodium EDTA as a permitted form of iron where addition of iron is currently permitted, with the exception of 'breakfast cereals, as purchased' and 'formulated supplementary foods for young children'.

Under this option, ferric sodium EDTA would be permitted to be added to certain foods contained within three Standards of the Code, as shown in Table 1.

## 11. Impact Analysis

### 11.1 Affected Parties

The parties likely to be affected by the Application are: **consumers**; **industry** comprising Australian and New Zealand manufacturers and/or suppliers of specialty ingredients for application in foods and manufacturers or importers of foods with added iron; and the **Governments** of Australia and New Zealand.

### 11.2 Cost-Benefit Analysis

This analysis assesses the immediate and tangible impacts of the current Standard under Option 1 and the proposed amendment under Option 2.

*11.2.1 Option 1 – Maintain status quo*

11.2.1.1 Consumers

By maintaining the *status quo* consumers would still have access to products fortified with iron in the forms currently permitted in Standard 1.1.1. Therefore, consumers would continue to have the choice to consume iron-fortified products. However, vegetarians were identified as a population sub-group who may potentially benefit from ferric sodium EDTA. This opportunity to benefit would be unavailable under the *status quo*.

11.2.1.2 Industry

By maintaining the *status quo* manufacturers could continue to add iron to foods in the permitted forms listed in Standard 1.1.1. However, maintaining the *status quo* would deny manufacturers the opportunity to capitalise on the potential technologically superior properties of ferric sodium EDTA in comparison with other forms of iron.

11.2.1.3 Government

There is likely to be no impact on the Australian and New Zealand Governments as a result of maintaining the *status quo*.

*11.2.2 Option 2 – Amend Standard 1.1.1*

11.2.2.1 Consumers

Approving ferric sodium EDTA as a permitted form of iron may potentially benefit vegetarians as well as the population as a whole due to the possible increase in availability of iron-fortified foods. Consumers may be offered greater choice under Option 2.

It is unknown what additional manufacturing costs would result in the production of foods with ferric sodium EDTA and what, if any costs, would be passed on to consumers.

11.2.2.2 Industry

Option 2 would provide an additional option for food manufacturers when adding iron to foods. Manufacturers could benefit from the technologically superior properties of ferric sodium EDTA where evident, and either reformulate existing iron-fortified products or introduce new products onto the market.

11.2.2.3 Government

Option 2 would impact upon the Australian and New Zealand Governments in relation to monitoring exposures to EDTA as recommended in Section 9.2.2. However, as FSANZ has already undertaken to develop a monitoring system for voluntary fortification permissions, ferric sodium EDTA could be included in this program.

### 11.3 Comparison of Options

A comparison of the Options presented at Draft Assessment indicates that maintaining both the status quo (Option 1) and approving ferric sodium EDTA as a permitted form of iron (Option 2) would continue to protect the health and safety of the Australian and New Zealand populations.

Option 2 may offer manufacturers a more technologically superior form of iron for food fortification. There is no apparent risk to the population due to excessive iron intakes or excessive exposure to EDTA. Monitoring is recommended to ensure the level of risk remains low. An incidental finding is that vegetarians are a population sub-group who may potentially benefit from the increased bioavailability of ferric sodium EDTA.

Therefore, at Draft Assessment, a comparison of options indicates Option 2 provides a greater net benefit than Option 1.

# COMMUNICATION AND CONSULTATION STRATEGY

## 12. Consultation and Communication

FSANZ has reviewed the nature of the feedback received from submitters at Initial Assessment (see Attachment 6) and does not intend to undertake specific communication and consultation work in addition to the two statutory consultation periods. FSANZ will review the nature of the feedback received from submitters to this Draft Assessment, and determine whether additional communication strategies will be required prior to Final Assessment.

### 12.1 Initial Assessment

The Initial Assessment Report was available for public submissions during the six week public consultation period of 13 December 2006 to 7 February 2007. A total of seven submissions were received, including three from industry and four from government. Submitters either supported the option to amend Standard 1.1.1 and/or supported the progression of the Application which would be further reviewed at Draft Assessment.

Issues raised in submissions included:

- the impact of the increased bioavailability of iron from ferric sodium EDTA;
- the impact of exposure to EDTA;
- how at risk consumers will identify foods fortified with ferric sodium EDTA;
- the impact of ferric sodium EDTA on other nutrients in the diet; and
- the association between iron intakes and coronary heart disease.

A full summary of submissions received at Initial Assessment is in Attachment 6. The issues raised have been fully considered as part of this assessment.

### 12.2 Draft Assessment

FSANZ is now seeking comment in relation to this Draft Assessment Report. Comments received in response to this Report will be used to assist in the development of a Final Assessment Report.

Submitters are invited to provide comment in relation to issues discussed in this Report and the proposed regulatory options, and potential impacts in relation to these options.

### 12.3 World Trade Organization (WTO)

As members of the World Trade Organization (WTO), Australia and New Zealand are obligated to notify WTO member nations where proposed mandatory regulatory measures are inconsistent with any existing or imminent international standards and the proposed measure may have a significant effect on trade.

There are no relevant international standards relating to the use of ferric sodium EDTA as a permitted form of iron. Amending the Code to allow ferric sodium EDTA as a permitted form of iron in general purpose foods under Standard 1.3.2 and special purpose foods under Standards 2.9.3 and 2.9.4 of the Code, is unlikely to have a significant effect on international trade as these measures do not change any existing permission for addition of iron to food and addition of a permitted form of iron to food in New Zealand and Australia is voluntary.

It will not be necessary to notify the WTO of the proposed measure.

# CONCLUSION

## 13. Conclusion and Preferred Approach

### Preferred Approach

The preferred regulatory approach for Application A570 is to amend Standard 1.1.1 Preliminary Provisions – Application, Interpretation and General Prohibitions to include ferric sodium EDTA as a permitted form of iron. Subsequent amendments to Standard 1.3.2 – Vitamins and Minerals, and Standard 2.9.3 – Formulated Meal Replacements and Formulated Supplementary Foods are also required to clearly exclude the use of ferric sodium EDTA in 'breakfast cereal, as purchased' and 'formulated supplementary foods for young children'.

The considerations made in reaching this preferred approach are as follows:

- it is consistent with the section 18 objectives of the FSANZ Act;
- it does not raise any public health and safety concerns; and
- it has the potential to provide a net benefit to the food industry.

FSANZ therefore recommends the proposed draft variations to the Code that are provided in Attachment 1.

## 14. Implementation and Review

Following the consultation period for this document, a Final Assessment of the Application will be completed and draft variations to the Code considered for approval by the FSANZ Board. The FSANZ Board's resulting decision will then be notified to the Ministerial Council.

Following notification, the proposed draft variation to the Code is expected to come into effect on gazettal, subject to any request from the Ministerial Council for a review of FSANZ's decision. FSANZ will recommend monitoring industry use of ferric sodium EDTA and calcium disodium EDTA permissions in future monitoring programs. These results, combined with updated data on food consumption patterns, will be useful in refining future EDTA dietary exposure assessments.

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## Attachments

1. Draft variations to the *Australia New Zealand Food Standards Code*
2. Nutrition Assessment Report
3. Safety Assessment Report
4. Food Technology Report
5. Dietary Exposure Assessment Report
6. Summary of Submissions at Initial Assessment

**Attachment 1**

## Draft variations to the *Australia New Zealand Food Standards Code*

*Standards or variations to standards are considered to be legislative instruments for the purposes of the Legislative Instruments Act (2003) and are not subject to disallowance or sunsetting.*

**To commence: on gazettal**

**[1]** ***Standard 1.1.1*** *of the Australia New Zealand Food Standards Code is varied by inserting in* Column 2 *of the* Schedule*, in the entry for* Iron –

Ferric sodium EDTA (This form of iron is not permitted to be added to breakfast cereals, as purchased under Standard 1.3.2 and to formulated supplementary foods for young children as regulated in Standard 2.9.3.)

**[2]** ***Standard 1.3.2*** *of the Australia New Zealand Food Standards Code is varied by omitting from* Column 3 *of the* Table to clause 3, *under the heading* Breakfast cereals, as purchased, *the entry for* Iron, *substituting* –

Iron – except
ferric sodium
EDTA

**[3]** ***Standard 2.9.3*** *of the Australia New Zealand Food Standards Code is varied by omitting from* Column 1 *of* Table 3, *in the* Schedule, *the entry for* Iron, *substituting* –

Iron – except ferric sodium EDTA for formulated supplementary foods for young children

## Attachment 2

# Nutrition Assessment Report

### APPLICATION A570 – FERRIC SODIUM EDETATE AS A PERMITTED FORM OF IRON

**Summary**

FSANZ has received an application to approve ferric sodium edetate (ferric sodium EDTA) as a permitted form of the mineral iron in foods permitted to contain added iron under Standards 1.3.2 (except breakfast cereals), 2.9.3 (except formulated supplementary foods for young children aged one to three years) and 2.9.4. FSANZ has reviewed the available literature and has focused its consideration on the bioavailability of iron from ferric sodium EDTA, the potential risk of iron-overload, and the potential nutritional risks associated with increased intake of EDTA from ferric sodium EDTA.

Bioavailability of iron from ferric sodium EDTA

There is insufficient data to compare the bioavailability of iron from ferric sodium EDTA against the bioavailability of iron from forms of iron currently permitted in the Code other than ferrous sulphate. Under test conditions where test meals are high in phytic acid (a potent inhibitor of iron absorption), the iron in ferric sodium EDTA is two to three times better absorbed and incorporated into red blood cells than the iron in ferrous sulphate. Ferric sodium EDTA reduces the effect of the inhibitor phytic acid. The iron from ferric sodium EDTA can be said to be two to three times more bioavailable than the iron from ferrous sulphate under these conditions. It is unlikely that the usual diets of most New Zealanders and Australians will mimic these test conditions. Instead, the usual diets of these populations are more likely to mimic conditions where the difference in bioavailability of ferric sodium EDTA compared to ferrous sulphate has been less significant or has not been shown to be significant. Vegetarians may potentially benefit from ferric sodium EDTA as a new iron fortificant, because the dietary pattern of vegetarians may mimic these test conditions and vegetarians are a group over-represented amongst iron deficient populations.

Over the long-term, absorption of iron is effectively down-regulated by the body, including the iron in ferric sodium EDTA. Given the varied diet of Australians and New Zealanders and the mostly iron replete status of those populations, ferric sodium EDTA is unlikely to offer any particular biological advantage or disadvantage to the general populations of Australia and New Zealand.

Iron overload

The absorption of iron is well controlled and down-regulated by the body. As iron status improves and iron requirements decline, the body adjusts by absorbing less iron. Studies with ferric sodium EDTA have shown that down-regulation occurs when iron is consumed in that form. The potential introduction of ferric sodium EDTA as a new form of added iron into the diet of New Zealanders and Australians should offer no additional risk of iron-overload (excess stored iron) in the general population, due to the well controlled absorption of iron through down-regulation.

A sub-population of individuals is susceptible to iron-overload, even at normal dietary iron intakes. This sub-population includes sufferers of haemochromatosis or other diseases or conditions that can cause iron overload. The accumulation of iron in someone susceptible to iron overload occurs regardless of the dietary iron source. Development of iron overload disease cannot be prevented in an undiagnosed susceptible individual, but must be clinically managed once diagnosed. Therefore, the risk to such individuals would not be increased by consumption of iron from ferric sodium EDTA.

Iron and coronary heart disease

The proposition that iron status is linked with prevalence of coronary heart disease has been noted briefly in this assessment because the proposed link was raised by a submitter at Initial Assessment. Published reviews indicate that there is not strong evidence for an association between iron and heart disease at this time.

Nutritional risks associated with increased intakes of EDTA from ferric sodium EDTA

There is a plausible biological explanation for the theoretical concern that consumption of compounds that release EDTA could impact on the nutritional status of important minerals such as zinc, copper, calcium or magnesium. The potential risk cannot be classified with confidence on the basis of published research results, because of the very limited published information that tests this theoretical risk. However, in establishing the ADI for EDTA that FSANZ has applied to this Assessment, JECFA considered the effects of EDTA on mineral metabolism. Therefore, provided the ADI for EDTA is not exceeded, the potential for EDTA from ferric sodium EDTA to have adverse effects on nutrient interactions should not be a concern.

**Introduction**

Iron is important for oxygen transport and other cell functions. Iron is a component of a number of proteins in the body: storage proteins (e.g. ferritin and haemosiderin); transport proteins (e.g. transferrin and lactoferrin); and haem-containing proteins (e.g. haemoglobin). Iron is also a component of certain enzymes. The iron in the body (iron status) can be measured through these various biochemical parameters, and using these measures, iron deficiency is defined in degrees ranging from moderate to severe. Over time, the iron content of the body is highly conserved and the effect of additional dietary iron cumulates slowly (NHMRC, 2006).

There are many factors that determine the proportion of iron absorbed from food; both dietary factors and host related factors. Iron is absorbed better by individuals who are iron deficient compared to individuals who are not. Dietary iron comes in two different forms: haem and non-haem. These forms of iron are not equally available to the body. Generally speaking, haem iron is better absorbed and comes from animal food sources. The iron from plant sources is in the non-haem form and is not absorbed as well. The absorption of non-haem iron can be enhanced by other nutrients such as ascorbic acid (vitamin C) or other foods such as meat, fish or poultry consumed at the same time. In contrast, the absorption of non-haem iron can be inhibited by phytates found in grains and legumes, polyphenols found in tea, vegetable protein or other nutrients such as calcium and zinc. There are complex interactions between iron and other minerals in the diet. Minerals such as calcium and zinc can inhibit iron absorption.

On the other hand, high intakes of iron can affect the absorption of calcium and zinc (NHMRC, 2006). The scope of this assessment does not include consideration of dietary iron intake on the absorption of other minerals from the diet.

The Applicant has sought permission to approve ferric sodium EDTA as a permitted form of iron, claiming ferric sodium EDTA is biologically and technologically superior to other forms. The bioavailability[3] of iron from ferric sodium EDTA is the main issue considered under this assessment. Potential risk of iron overload is assessed in light of evidence regarding the bioavailability of iron from ferric sodium EDTA.

Ferric sodium EDTA is a compound that is slowly soluble in water. The iron in ferric sodium EDTA is absorbed in the same manner as non-haem iron. The EDTA in ferric sodium EDTA is a complexing agent or chelate that can combine with virtually every metal in the periodic table. This chelating action creates the potential for consumed EDTA to impact on the status of nutritionally important minerals such as zinc, calcium, copper or magnesium (Bothwell and MacPhail, 2004). This assessment considers the potential nutritional risk associated with increased EDTA intake.

## IRON

### Bioavailability of iron sourced from ferric sodium EDTA

FSANZ has reviewed several papers published over the last thirty years that report results of human radio-labelled iron absorption studies involving ferric sodium EDTA. Particular features of the studies relevant to Application A570 are presented in Table 1 below. Because of the widespread use of ferrous sulphate ($FeSO_{4)}$ which is a very inexpensive water-soluble form of iron, the relative bioavailability of different iron compounds are often ranked in relation to $FeSO_4$. The main points noted by FSANZ in this assessment include the various food vehicles considered in these studies, the various levels of iron added to those food vehicles for test purposes, the presence or absence of inhibitors of iron absorption in the foods tested and the absorption of iron from ferric sodium EDTA relative to the absorption of iron from $FeSO_4$ in these tests. The results of a small human study (n=10) conducted in the Philippines have not been included in this assessment as there were too many inconsistencies between the results and discussion presented in that particular paper (Trinidad *et al*., 2002).

<u>Applicability of absorption studies to assessing the bioavailability of iron from ferric sodium EDTA</u>

Most of the studies reviewed employed a similar protocol using the double radio-iron method. Generally speaking, the studies measure the relative absorption of iron from $^{59}$ferric sodium EDTA compared to $^{55}FeSO_4$, measuring iron absorption as the amount of radio-labelled iron incorporated into red blood cells after 14 days. Sixty to seventy per cent of the body's iron is in haemoglobin in red blood cells, i.e. the majority of the functional iron in the body (NHMRC, 2006). Therefore, it is appropriate to refer to the bioavailability of iron when considering the measures of iron absorption from the majority of these studies, where those measures of iron absorption reflect the incorporation of iron into red blood cells.

[3] Bioavailability is the proportion of the ingested nutrient absorbed and utilised through normal metabolic pathways (Hurrell, 2002). It is influenced by dietary factors and host related factors (Gibson, 2007).

One study did not follow this protocol but measured absorption of iron across the gut only, so results from that study do not fit with the definition of bioavailability employed here (Huo *et al*., 2007).

Some limitations of the absorption studies reviewed here

The most important limitation to note for the purposes of this Assessment is that these absorption studies are short term. Part of the objective of this Assessment is to determine the nutritional efficacy of ferric sodium EDTA. While the short term absorption studies reviewed enable the relative bioavailability of ferric sodium EDTA to be ranked against ferrous sulphate under test conditions, they do not reveal what the result of consuming foods containing small doses of added iron in one form or another as part of a varied diet over the long term might be.

FSANZ notes that in all studies reported here absorption tests were carried out on small groups of subjects, usually involving only six to eight subjects and rarely more than 12 subjects. In some of the studies, the tests of absorption of iron from ferric sodium EDTA and $FeSO_4$ were not conducted in the same individuals (Layrisse and Martinez-Torres, 1977; Martinez-Torres *et al*., 1979). MacPhail *et al* (1981) reported using a reference standard to provide an index of the absorbing capacity of each individual in the test. Use of references such as this was not consistently reported in the studies reviewed here.

Because of these limitations, results should at least be replicated consistently across several studies before ranking the relative bioavailability of ferric sodium EDTA compared to ferrous sulphate under test conditions. Then, careful consideration of the limitations of short term studies should be acknowledged before suggesting how the results of such tests might extrapolate to long term consumption of ferric sodium EDTA by humans in free living situations.

Studies involving children

Very few of the reviewed studies involved children. The old study by Viteri *et al* (1978) included n=7 children, and Davidsson and colleagues (2002) involved n=11 12-13 year old girls in tests comparing ferric sodium EDTA to $FeSO_4$. This assessment by FSANZ has deliberately excluded evidence relating to infants because infant foods are not included in the request submitted to FSANZ under this Application. However, children other than infants would be consumers of foods covered by this Application. There is insufficient evidence to assess the absorption of iron from ferric sodium EDTA by children.

**Table 1: Human studies on the absorption of iron from ferric sodium EDTA**

| Study | Key features of study design | Study participants | Iron dose | Food vehicle(s) | Mean iron absorption from Ferric sodium EDTA | Mean iron absorption from $FeSO_4$ | Key elements and outcomes of relevance to A570 |
|---|---|---|---|---|---|---|---|
| Layrisse *et al* (1977) | Labelled $^{59}Fe$ and $^{55}Fe$. Test meals day 1, 2, and day 15, 16. Blood sampled day 15 and 30. | N=147 adult peasants in Venezuela. | 5 mg, 25 mg or 50 mg in meal tests. 5 mg only in milk tests. | 1. Base meal = black beans, plantain, rice, maize-soybean dough. 2. Base meal without meat and with orange juice. 3. Base meal with meat. 4. Milk. | For 25 mg iron: 6.3% (no meat) 8.9% (no meat plus orange juice) 8.5% (meat)<br>For 5 mg iron: 6.2% (no meat) 4.1% (with meat)<br>For 5 mg iron in milk – 11.6% | For 25 mg iron: 1.8% (no meat) 1.5% (no meat plus orange juice) 2.6% (meat)<br>For 5 mg iron: 2.7% (no meat) 3.2% (with meat)<br>For 5 mg iron in milk – 7% | In general, when meals contain low amounts of iron, a higher percentage of iron is absorbed from those meals compared to meals that contain more iron. There were many tests reported in this paper using different iron doses in various meals. Mean values presented here are a sample of results only. Overall absorption of iron from ferric sodium EDTA in the various tests reported in this paper was about twice as high as the absorption of iron from $FeSO_4$. |
| Viteri *et al* (1978) | Labelled $^{59}Fe$ and $^{55}Fe$. Test meals day 1, 2, and day 16, 17. Blood sampled day 16 and 32. | N=7 pre-school children and N=98 adults in Guatemala | 5 mg | Children – milk, rice, sugar. Adults – various tests. 1. Pepsi cola 2. Black bean gruel, tortillas, coffee. 3. Black bean gruel, tortillas, coffee and orange flavoured drink | Children – 2.6 X higher than $FeSO_4$. Healthy adults – higher but not significantly different compared to $FeSO_4$. Deficient adult males – 2.7 X higher than $FeSO_4$. | | This study used ferric sulphate, not ferrous sulphate. The authors' rationale was that ferrous sulphate is oxidised to ferric sulphate, particularly when heated, so ferric sulphate would be the form actually ingested when ferrous sulphate is used for fortification. |

| Study | Key features of study design | Study participants | Iron dose | Food vehicle(s) | Mean iron absorption from Ferric sodium EDTA | Mean iron absorption from $FeSO_4$ | Key elements and outcomes of relevance to A570 |
|---|---|---|---|---|---|---|---|
| Martinez-Torres *et al(1979)* | Labelled $^{59}Fe$ and $^{55}Fe$. Test meals day 1, 2, and day 15, 16. Blood sampled day 15 and 30. | N=107 adult peasants in Venezuela. | 3 mg | 1. Sugar and sugar cane syrup alone.<br>2. Enriched sugar cane syrup with wheat or maize.<br>3. Enriched sugar cane syrup with a range of traditional Guatemalan foods containing various proportions of toasted maize flour, sweet manioc flour, white cheese, coconut milk, milk powder, butter and spices. | 21.7% from syrup alone*<br><br>Range of 8% to 13% | 7.1% from syrup alone*<br><br>Range of 2% to 30% | An atypical finding in this paper compared to other papers reviewed here was the approximate three fold better absorption of iron from $FeSO_4$ compared to iron from ferric sodium EDTA when the food vehicle was sugar cane syrup alone.<br>* These absorption values were calibrated to results from a reference dose in an attempt to correct for variation in iron status between subjects in the study.<br><br>Given variability in the range of absorption values found, authors concluded that ferrous sulphate is very sensitive to inhibitors of iron absorption present in food vehicles while the absorption of iron from ferric sodium EDTA is only slightly affected by such substances. |
| MacPhail *et al* (1981) | Labelled $^{59}Fe$ and $^{55}Fe$. Test meals day 1, 2. Reference Fe salt in solution day 15. Blood sampled day 16, 30. | N=153 Multiparous Indian women living in South Africa. | 3 mg or 5 mg | Cane sugar and maize porridge with tea, dhal and a reference drink containing ascorbic acid. | Two times higher than $FeSO_4$. | | Tea inhibited the absorption of iron from ferric sodium EDTA 7-fold. The other inhibitory substances in the meal had less impact on absorption of iron from ferric sodium EDTA than absorption of iron from $FeSO_4$. The authors postulate that iron present in the chelated from remains in solution and is relatively well absorbed because it is protected from inhibitory ligands. |

| Study | Key features of study design | Study participants | Iron dose | Food vehicle(s) | Mean iron absorption from Ferric sodium EDTA | Mean iron absorption from $FeSO_4$ | Key elements and outcomes of relevance to A570 |
|---|---|---|---|---|---|---|---|
| Hurrell *et al* (2000) | Labelled $^{59}Fe$ and $^{55}Fe$. Test meals day 2, 3 and day 15, 16. Blood sampled day 1, 17, and 32. | N=84 healthy adults | 5 mg or 15 mg in infant cereals. 2.15 mg or 2.5 mg in bread rolls. | Infant cereals:<br>1. Wheat-based, 123 mg phytic acid.<br>2. Quinoa-based, 763 mg phytic acid.<br>3. Wheat-soybean-based, 770 mg phytic acid.<br>Wheat bread rolls:<br>1. Low phytic acid<br>2. High phytic acid | 2-4 times higher than $FeSO_4$. | | Absorption of iron from ferric sodium EDTA is reduced by inhibitors but to a much less extent than the absorption of iron from $FeSO_4$ when inhibitors are present. So, ferric sodium EDTA, while improving absorption of iron where inhibitors are present, does not remove the affect of inhibitors altogether. |
| Mendoza *et al* (2001) | Labelled $^{59}Fe$ and $^{55}Fe$. Test meals day 1, 2, 13 and 14. Blood sampled day 1, 12 and 24. | N=14 non-anaemic women | 4.4 mg total (1 mg from added $^{59}Fe$) | Porridge containing:<br>1. Genetically modified maize low in phytic acid.<br>2. Wild type maize. | GM maize – 5.40%.<br>Wild-type maize – 5.73%. | GM maize – 1.91%.<br>Wild-type maize – 1.69%. | The study showed that iron from ferric sodium EDTA is better absorbed than iron from $FeSO_4$ regardless of maize type. |
| Davidsson *et al(2002)* | $^{57}Fe$ crossover design. Test meals day 1, 2 and day 15, 16. Blood sampled day 1, 16, and 31. | Guatemala. n=11 girls in tests comparing Ferric sodium EDTA and $FeSO_4$. | 4.2 mg total (2 mg from added $^{57}Fe$) | Tortillas from corn masa flour (high phytic acid) and black bean paste. | 9.0% (±1SD: 3.2%-25.5%) | 5.5% (±1SD: 1.8%-16.5%) | In meals containing high levels of phytic acid, absorption of iron from ferric sodium EDTA is 1.5 to 2 times higher than absorption of iron from $FeSO_4$. |
| Fidler *et al* (2003) | $^{57}Fe$ and $^{58}Fe$. Erythrocyte incorporation after 14 days only. | N=10 women in each of 5 tests (total n=50) in Switzerland | 5 mg | Fortified fish sauce or fortified soy sauce.<br>1. Rice and sauce.<br>2. Rice and vegetables and sauce. | Fish sauce – 3.3%.<br>Soy sauce – 6.1%. | Fish sauce – 3.1%.<br>Soy sauce – 5.6%. | No significant difference between the absorption of iron from ferric sodium EDTA or $FeSO_4$ fortified fish sauce or soy sauce was found. These food vehicles are low in phytic acid. |

| Study | Key features of study design | Study participants | Iron dose | Food vehicle(s) | Mean iron absorption from Ferric sodium EDTA | Mean iron absorption from $FeSO_4$ | Key elements and outcomes of relevance to A570 |
|---|---|---|---|---|---|---|---|
| Mendoza *et al* (2004) | Labelled meal fed to each subject 1 day at 7 day intervals | N=13 20-31 yr old women | 14.7 mg | A food supplement fortified with various vitamins and minerals provided to pre-school children in Peru (low phytic acid content). | 1.7 X better than $FeSO_4$. | | Study was designed to evaluate the effect of calcium on zinc and iron absorption. The food vehicle was novel and sample size was small, so results are of limited relevance to Application A570. |
| Huo *et al(2007)* | Stable isotope tracer method. 15 days study duration. $^{54}FeSO_4$ and $^{58}$Ferric sodium EDTA given days 4 and 5. Compare total intake of labelled isotopes against measured loss in faeces. | N=10 healthy 18-22 yr old Chinese women. | 6 mg $^{54}$Fe in $^{54}FeSO_4$ and 3 mg $^{58}$Fe in $^{58}$Ferric sodium EDTA. Total dietary Fe intake from 15-day controlled diet not specified. | Iron-fortified soy sauce given on days 4 and 5 during a 15 day controlled diet based on typical dietary pattern of Chinese women. Test diet had high plant content and approximately 80 g meat per day. | 10.51% ± 2.83% | 4.73% ± 2.15% | This study estimated iron absorption by measuring the content of labelled iron in faeces and comparing this with the measured intake of labelled iron (total intake minus iron in faeces as a percentage of total intake). Absorption of iron across the gut was 2.2 times higher from ferric sodium EDTA than $FeSO_4$ under these test conditions. These measures are not comparable with the measures of bioavailability of iron from ferric sodium EDTA in the absorption tests above because the utilisation of iron through normal metabolic pathways is not accounted for in this study design. |

Key results comparing absorption of iron from ferrous sulphate and ferric sodium EDTA

The most consistent finding from the iron absorption studies summarised in Table 1 is that where the food vehicle in the test was high in phytic acid, absorption of iron from ferric sodium EDTA was about two to three times better than iron absorption from $FeSO_4$. Improvements in iron absorption of this magnitude were reported by Hurrell *et al* (2000), MacPhail *et al* (1981), Mendoza *et al* (2001) (tests conducted on wild-type maize), and Layrisse *et al* (1977). Viteri *et al* (1978) reported similar findings for the iron-deficient adults and children in that study. In the paper by Davidsson *et al* (2002) the higher absorption from ferric sodium EDTA was of a lower magnitude (approximately 0.65 times higher than $FeSO_4$), and in the paper by Mendoza *et al* (2004) it was only 1.7 times higher. A study not included in Table 1 found that iron absorption was approximately four times better from ferric sodium EDTA than various other iron sources from a food vehicle that is very high in phytic acid (corn masa flour, a staple in Central America) (Walter *et al*., 2003). The paper by Walter and colleagues has not been included in Table 1 because absorption of iron from ferric sodium EDTA was only tested in one meal on a small number of subjects, and was not the focus of the study design. The study was designed to find the best iron fortificant for use in corn-masa flour. Another short duration study on 10 healthy iron-replete women of child-bearing age in Switzerland, which investigated the effect of ferric sodium EDTA on absorption and retention of zinc and calcium, found iron absorption values were four times higher from the ferric sodium EDTA fortified bread tested compared to $FeSO_4$ (see Table 5 below) (Davidsson *et al*., 1994).

In tests where food vehicles were low in phytic acid, there were limited reports of occasions where use of ferric sodium EDTA improved absorption of iron significantly, i.e. where results showed no effect of phytic acid on absorption. The study by Layrisse *et al* (1977), which tested milk, found iron from ferric sodium EDTA was absorbed 1.6 times better than iron from $FeSO_4$. Mendoza *et al* (2001) reported iron absorption from maize genetically modified to be low in phytic acid was 2.8 times higher if the iron was provided in ferric sodium EDTA rather than $FeSO_4$. This is an interesting finding because it showed, in a test situation where the phytic acid content of food vehicles was the only variable, that the relative bioavailability of ferric sodium EDTA could be better than $FeSO_4$ without dependence on the presence of phytic acid. This brings to question whether it was perhaps not just the level of the phytic acid that made ferric sodium EDTA more bioavailable in the test meals reported elsewhere ((Layrisse and Martinez-Torres, 1977; Viteri *et al*., 1978; MacPhail *et al*., 1981; Hurrell *et al*., 2000; Mendoza *et al*., 2001; Walter *et al*., 2003) or if it was phytic acid plus something else in the test meals or in the design of those studies that produced the reported result. Mendoza *et al* is the only published paper that provides a good test of this theory, and on its own, that paper does not provide enough evidence to explore alternate explanations for the apparent association between phytic acid and the bioavailability of ferric sodium EDTA further.

Two of the studies found no significant difference in the absorption of iron from ferric sodium EDTA compared to $FeSO_4$. This was reported for the subset of healthy adults involved in the research by Viteri *et al* (1978), and in the study by Fidler *et al* (2003), which compared iron absorption in women fed test meals with iron-fortified fish sauce or iron-fortified soy sauce, food vehicles both low in phytic acid.

The absorption studies considered here rarely report that absorption of iron was reduced if ferric sodium EDTA was used instead of $FeSO_4$.

An unusual exception to this was the finding that when administered with sugar cane syrup alone, iron from $FeSO_4$ was absorbed about three times better than iron from ferric sodium EDTA (Martinez-Torres *et al*., 1979).

The effect of inhibitors on iron absorption

When studies were designed specifically to test the effect of inhibitors on iron absorption, researchers found that using ferric sodium EDTA did not remove the effect of different inhibitors of iron absorption altogether. MacPhail *et al* (1981) found the inhibitors in cereals (bran or maize) did not decrease the amount of iron absorbed from ferric sodium EDTA, while bran decreased absorption of iron from ferrous sulphate 11-fold. However, tea decreased absorption from ferric sodium EDTA seven-fold. Other researchers found tea consumed with low phytic acid wheat rolls significantly decreased the absorption of iron from $FeSO_4$ and ferric sodium EDTA (Hurrell *et al*., 2000). Results showed that absorption of iron from ferric sodium EDTA was affected by phytic acid (absorption was 3.91% in rolls containing phytic acid compared to 11.5% in rolls where the phytic acid had been degraded). However, absorption of iron was better in the rolls containing ferric sodium EDTA than those with $FeSO_4$ (for rolls containing $FeSO_4$, absorption was 0.99% in those with phytic acid compared to 5.7% in rolls where the phytic acid had been degraded). A small study, not included in Table 1, reported the inhibitory effect of coffee on non-haem iron absorption in humans (Morck *et al*., 1983). In that small study (n=10), the authors found, that like tea, coffee reduced iron absorption by 70% from both ferric sodium EDTA and $FeCl_3$. As patterns of consumption and methods of coffee preparation would also influence iron absorption, this small study alone does not provide sufficient information to determine the impact of coffee on iron absorption from a varied diet. However, taken together the studies reviewed here do show that ferric sodium EDTA, while improving absorption of iron where inhibitors, specifically phytic acid, are present, does not remove the effect of inhibitors altogether.

The effect of iron status on iron absorption

While the iron status of the subjects in the studies presented in Table 1 has not been detailed in the Table, FSANZ notes that mostly healthy adults but also some adults with some degree of iron-deficiency participated in these tests. Generally speaking, the collection of recent studies published from 2000-2004 involved healthy adults (Hurrell *et al*., 2000; Mendoza *et al*., 2001; Fidler *et al*., 2003; Mendoza *et al*., 2004). In Hurrell *et al* (2000), the authors noted that in most cases, individual iron absorption values were highest in those subjects with the lowest serum ferritin values. The older absorption studies published from 1977-1981, conducted in Venezuela, Guatemala and South Africa, involved subjects from low socio-economic groups in which iron deficiency is more common (Layrisse and Martinez-Torres, 1977; Viteri *et al*., 1978; Martinez-Torres *et al*., 1979; MacPhail *et al*., 1981). Conclusions about the absorption or bioavailability of iron from ferric sodium EDTA under this assessment are confined to adults, but those who are iron-deficient and iron-replete.

*FSANZ assessment*

Conclusions about the bioavailability of iron from ferric sodium EDTA under this assessment are confined to adults. The published evidence usually compares absorption of iron from ferric sodium EDTA with absorption of iron from $FeSO_4$, and therefore the absorption of iron from ferric sodium EDTA compared to forms of iron other than $FeSO_4$ cannot be determined at this time.

Notwithstanding limitations of the published literature identified by FSANZ, it seems reasonable to generalise that the iron in ferric sodium EDTA is two to three times better absorbed than the iron in $FeSO_4$ when consumed in test meals containing inhibitors of non-haem iron absorption, specifically phytic acid. Measures of this order of improved iron absorption from ferric sodium EDTA in high phytic acid test meals have been found reasonably consistently in the studies reviewed here. The absorption of iron from ferric sodium EDTA is reduced by the presence of inhibitors such as the polyphenols in tea. Use of ferric sodium EDTA as a source of iron does not remove the potential impact of inhibitors of iron absorption altogether.

Generally speaking, the diets of New Zealanders and Australians include frequent and adequate consumption of meat and ascorbic acid (vitamin C) which enhance the absorption of iron. It is unlikely that the usual diets of most New Zealanders and Australians will mimic the test conditions of meals high in inhibitors of iron absorption, where it has been shown that iron from ferric sodium EDTA is more bioavailable. Instead, the usual diets of these populations are more likely to mimic conditions where the difference in bioavailability of ferric sodium EDTA compared to ferrous sulphate has been less significant or has not been shown to be significant. Given this and the down regulation of iron absorption over time, compared to ferrous sulphate, ferric sodium EDTA is unlikely to offer any particular biological advantage or disadvantage to the general populations of Australia and New Zealand.

While short term study results suggest two to three times improved bioavailability of ferric sodium EDTA compared to $FeSO_4$ from test meals high in phytic acid, it is not known if this relativity is maintained over long term consumption of foods containing low doses of ferric sodium EDTA as part of a varied diet. Vegetarians are a particular group who might receive added benefit from the opportunity to consume foods fortified with ferric sodium EDTA. The bioavailability of iron from ferric sodium EDTA might be two to three times better than iron from foods containing ferrous sulphate consumed by vegetarians, given the absence of most haem-iron from their diet, the possibility that a vegetarian diet high in plant foods might be high in phytic acid, and the fact that vegetarians as a group are over represented amongst iron-deficient populations. A vegetarian diet may be likely to sometimes or often mimic the test conditions where improved bioavailability of iron from ferric sodium EDTA has been shown. And a vegetarian would be expected to absorb more iron from their diet if they have a poor iron status. But vegetarian diets are variable and may not always be high in phytic acid. Host-related factors and diet-related factors (e.g. consumption of tea and ascorbic acid (vitamin C) containing foods) would still have an influence on the absorption of iron from ferric sodium EDTA by this group and the potential benefit to vegetarians could vary from one person to the next.

**Human intervention trials to address iron-deficiency with ferric sodium EDTA**

A total of seven human intervention trials have been considered by FSANZ and details are provided in Table 2 below. The trials all had the specific objective of testing the efficacy of ferric sodium EDTA to address population iron-deficiency. These types of studies involve human populations numbered in the 100s or 1000s, living their normal lives. A national iron fortification program has been initiated in Vietnam following the results of the 18 month fish-sauce trial. The program being implemented in Vietnam will fortify fish sauce with ferric sodium EDTA at a level of 39 mg/100 mL fish sauce (Van *et al*., 2005). There is also a large project underway in Western China involving fortification of wheat with ferric sodium EDTA (Chen *et al*., 2005).

In this assessment, FSANZ has considered relevant literature published within the last 30 years. The results of a fortification trial reported in 1974 have not been considered by FSANZ (Garby and Areekul, 1974). On the basis of a brief report of the results of this trial in the review by Bothwell and MacPhail (2004), FSANZ expects that the results of the study by Garby and Areekul would accord with the other studies reviewed here, and would not alter this assessment.

Key features of study design

Three of these trials were of relatively short duration: Huo *et al* (2002) was a three-month trial, Andang'o *et al* (2007) was a five-month trial and Van Thuy *et al* (2003) was a six-month trial. The three short trials used higher levels of fortification and had small sample sizes when compared to the longer fortification studies.

An 18 month trial enrolled 14,000 subjects in China and provided 29.6 mg Fe/100 mL soy sauce to household members in the group receiving fortified soy sauce (Chen *et al*., 2005). Van Thuy *et al* (2005) was also an 18 month trial that enrolled 576 women in Vietnam and provided 50.3 mg Fe/100 mL fish sauce for household use by subjects assigned to the group receiving the fortified food vehicle. In this study, all members of households provided with ferric sodium EDTA fortified fish sauce consumed that fish sauce, but only the women in the household were studied. These two studies in Asia used a similar food vehicle for the same period of time, but the level of ferric sodium EDTA trialled in the Vietnamese study was 66% higher than the levels tested on subjects in the study in China. The study in Vietnam did not attempt to evaluate impact of ferric sodium EDTA fortification on children, while the study in China did. A two year study conducted in South Africa provided iron to 984 enrolled subjects aged 10 years and over as ferric sodium EDTA in curry powder, where each person received an average of 7.7 mg iron per day from this form (Ballot *et al*., 1989). A slightly longer study in Guatemala, which lasted 32 months, provided iron to 5,640 subjects through sugar fortified with 130 mg Fe/kg sugar which provided less total iron (4.3-4.7 mg/person/day) than the study in South Africa (Viteri *et al*., 1995). The study in Guatemala included children aged 1 year and over.

**Table 2: Human intervention trials to address iron-deficiency with ferric sodium EDTA**

| Study | Country | Study participants | Study duration | Food vehicle(s) | Ferric sodium EDTA | Endpoints measured | Key elements and outcomes of relevance to A570 |
|---|---|---|---|---|---|---|---|
| Andang'o *et al* (2007) | Kenya | (n=516 enrolled; n=505 completed the study) 3-8 year old school children | 5 months | Porridge from whole maize flour fed 5 times a week (high phytate content) at school. Target daily intake was 700 mL porridge (containing 100 g flour) per day (3-5 yrs). Target daily intake was 1000 mL porridge (containing 150 g flour) per day (6-8 years). | High target dose 5.6 mg ferric sodium EDTA/day (=36-40% RDA). Low target dose 2.8 mg ferric sodium EDTA/day (=18-20% RDA). | Haemoglobin. Serum ferritin. Transferrin receptor. 1º outcome iron-deficiency anaemia. | Randomised controlled trial with intention to treat. The subjects' usual diet is monotonous, predominantly maize with a low content of animal products. Dietary iron intake/person/day was not estimated. Subjects had high rates of malaria (49%) and iron-deficiency anaemia (11%). Flour fortified with iron also contained supplemental vitamins A, B1, B2 and B3. The high dose ferric sodium EDTA improved all measured indicators of iron status and the effect was three times greater in children with iron-deficiency anaemia compared to iron-replete children. Compared to controls, prevalence of iron-deficiency anaemia was 90% lower in children fed high-dose ferric sodium EDTA. Low-dose ferric sodium EDTA also reduced iron deficiency by 70% but did not change the prevalence of anaemia. Unilever and Akzo Nobel Chemicals provided funds. |

| Study | Country | Study participants | Study duration | Food vehicle(s) | Ferric sodium EDTA | Endpoints measured | Key elements and outcomes of relevance to A570 |
|---|---|---|---|---|---|---|---|
| Chen *et al* (2005) | China | (n=14,000 enrolled) (about 1/3 evaluated as representative subset) Household members aged 3+ | 18 months | Soy sauce provided for household use | 29.6 mg Fe/ 100 mL soy sauce | Food consumption (FFQ). Haemoglobin. Plasma ferritin. Serum retinol. For 3-6 yr olds haemoglobin only. | Randomised, double-blind, controlled trial. The subjects' usual diet is primarily plant based with very little meat. Blood samples were collected and a food frequency questionnaire was administered at baseline, 6, 12 and 18 months to about one third of participants. The evaluation cohort was representative of the whole population. Population estimates of total dietary iron intake met or exceeded recommended amounts (mean adult intakes range 22.1-27.5 mg/day). Persons in the ferric sodium EDTA fortified group consumed on average (based on predicted uptake) an extra 4.9 mg (range 4.7-5.1) iron per day. All age and sex subgroups (except men aged 55+ and children 3-6 years) in the fortified group had significantly higher haemoglobin, and a lower prevalence of anaemia than controls. The adults aged 55+ in the control group had higher plasma ferritin at the end of the trial than the fortified group, a discrepancy not explained. Differences became significant after six months and remained for the duration of the study period. This study was an ILSI collaboration. |
| Van Thuy *et al* (2005) | Vietnam | (n=576 enrolled; 33% lost to follow-up) Anaemic women of child-bearing age evaluated, though all household members exposed | 18 months | Fish sauce provided for household use | 50.3 mg Fe/ 100 mL fish sauce. | Food consumption (24h recall). Haemoglobin (anaemia hb<120g/L). Serum ferritin (iron deficiency SF<12µg/L). Serum retinol. | Randomised (by village), double-blind, controlled trial with intention to treat. The subjects had a high prevalence of anaemia (>20%) and an average iron intake of ~50% RDA from a cereal-based diet. The control group had baseline dietary intakes of 8.9 mg Fe/person/day and the fortified group 9.8 mg Fe/person/day, i.e. excluding fortification iron. Data collection was at baseline, 6, 12 and 18 months. The prevalence of iron deficiency decreased from 22.3% to 4% and prevalence of anaemia decreased from 24.7% to 8.5% in the fortified groups at the end of the trial. Mean haemoglobin was significantly higher in the fortified group at 12 and 18 months compared to the control group. Most of the improvement in iron status occurred within the first 12 months of the trial. |

| Study | Country | Study participants | Study duration | Food vehicle(s) | Ferric sodium EDTA | Endpoints measured | Key elements and outcomes of relevance to A570 |
|---|---|---|---|---|---|---|---|
| Van Thuy *et al* (2003) | Vietnam | (n=152 enrolled, n=136 evaluated) Anaemic female factory workers 17-49 years old. | 6 months | Fish sauce and noodle snack provided once daily at worksite six days per week | 100 mg Fe/ 100 mL fish sauce. | Haemoglobin. Serum ferritin. Serum transferrin receptor. | Randomised, double-blind, controlled trial. The subjects had a high prevalence of anaemia. Mean baseline dietary Fe intakes were 8.9 mg/day for the fortified group and 8.6 mg/day for controls. This study employed a high level of fortification (1 mg Fe/1 mL fish sauce) because of the short study duration. Data was gathered at baseline, 3 and 6 months. At the end of the trial, the prevalence of anaemia was significantly reduced (33.8% decrease) in the women consuming the fortified fish sauce compared to controls. |
| Huo *et al* (2002) | China | (n=304 enrolled, results given for n=240) Anaemic 11-17 year olds at boarding school | 3 months | Soy sauce (5 mL) in soup given once daily at boarding school | High dose (400 mg Fe/ 100 mL sauce: 20 mg Fe/person/day) Low dose (100 mg Fe/ 100 mL sauce; 5 mg Fe/ person/day) | Haemoglobin, serum iron, serum ferritin, free erythrocytic porphyrin, total iron binding capability, transferritin. | This was a short pilot study for a larger fortification trial. Students were located in three different schools. This study employed a high level of fortification (1 or 4 mg Fe/1 mL soy sauce). From the paper, it is unclear why results were not reported for all 304 students enrolled in the study. Three-day weighed food intakes were used to estimate average daily iron intake from school cafeteria diets of 17 mg/person/day, mostly from plant-based sources. Improved iron status measures were observed in the groups receiving fortified soy sauce but not the control groups. Fortification resulted in progressively higher concentrations of haemoglobin; concentrations were significantly higher in the groups fed the high dose after one, two and three months, while at the lower level the significant change was after two and three months. The differences between the high dose and lower dose groups were not statistically significant after three months. Note that the 'lower' dose in this study corresponds to the high level of fortification used by Van Thuy *et al* (2003). |

| Study | Country | Study participants | Study duration | Food vehicle(s) | Ferric sodium EDTA | Endpoints measured | Key elements and outcomes of relevance to A570 |
|---|---|---|---|---|---|---|---|
| Viteri *et al* (1995) | Guatemala | (n=5,640 enrolled) Iron deficient low-income semi-rural persons aged 1 year+. | 32 months | Sugar provided to store keepers for retail sale | 130 mg Fe/kg sugar. 4.3-4.7 mg Fe/person/day. | Haemoglobin, total iron binding capacity, free erythrocyte protoporphyrin, serum ferritin. Blood folate. Plasma vitamin B12. Plasma and urine iron, copper and zinc. | Controlled, double-blind trial, not randomised. Baseline dietary iron intake data not presented. Sugar in Guatemala is fortified with Vitamin A. The objective of this study was to test the field application of also fortifying sugar with ferric sodium EDTA and to measure effectiveness with regard to iron deficiency. Two highland communities (one control, one fortified) where dietary iron deficiency prevails, as well as two lowland communities (both fortified) where hookworm aggravates the dietary situation, were studied. Iron nutrition was estimated at 8, 20 and 32 months. The key result was that fortified communities demonstrated significant improvements in iron status. The fastest and highest increments occurred among the more deficient groups at the start of fortification. With time these rates of improvement in iron status generally became slower as iron stores improved and stabilised. The other results of this study, including dietary intake data and changes in plasma and urinary trace mineral concentrations (iron, copper and zinc) were not presented in this paper. The authors indicated their intention to present those results in another publication, and stated in this paper that no undesirable effects of sugar fortification with ferric sodium EDTA were detected under the conditions of this trial. FSANZ has not located the results of measures of urinary copper or zinc from this fortification trial in any other published paper by these authors. |

| Study | Country | Study participants | Study duration | Food vehicle(s) | Ferric sodium EDTA | Endpoints measured | Key elements and outcomes of relevance to A570 |
|---|---|---|---|---|---|---|---|
| Ballot *et al* (1989) | South Africa | (n=984 enrolled, n=672 after 2 yrs, i.e. 27% lost to follow-up) Iron-deficient aged 10 yrs+ of Indian descent in an urban housing estate | 24 months | Curry powder provided for household use | 10 mg ferric sodium EDTA/g curry powder = 7.7 mg Fe/ person/day from fortified curry powder. | Haemoglobin, ferritin, body iron stores. 1° outcome iron-deficiency anaemia. | This was a targeted, double-blind clinical trial randomised by families conducted as a pilot fortification program. Total baseline dietary iron intakes were not provided. Though 27% of the sample was lost to follow up, after 2 years there had not been significant differences in the number or category of dropouts between the fortified and control groups. Subjects provided an annual blood sample. In all groups, there was an improvement with time in all measurements of iron status except the transferrin saturation. The greatest response was seen in the most iron-deficient subjects. Two random groups of 30 subjects (30 controls and 30 from the fortified group; each group comprising 13 males and 17 females) had plasma zinc levels determined at the end of the trial to compare the two groups, though baseline plasma zinc levels had not been measured. The mean zinc level of the fortified group after 2 years was 15.8 ± 2.6 µmol/L compared to the unfortified group which was 15.7 ± 4.1 µmol/L. These results were not significantly different ($p > 0.1$). The study also provides a small sample of iron-replete males who showed no significant change in body iron stores between control and fortified groups. |

Key results

The results of the human intervention trials show that ferric sodium EDTA is an efficacious source of iron for iron-fortification programs in populations with endemic iron-deficiency. Some authors reported that the greatest response was seen in the most iron-deficient subjects (Ballot *et al*., 1989; Viteri *et al*., 1995; Andang'o *et al*., 2007). Also, the fastest and highest increments occurred among the more deficient groups at the start of fortification. With time, these rates of improvement in iron status generally became slower as iron stores improved and stabilised (Viteri *et al*., 1995). Chen *et al* (2005) reported that differences became significant after six months while Thuy *et al* (2005) found that most of the improvement in iron status occurred within the first 12 months of the trial.

Absence of study endpoints of most relevance to Application A570

All seven trials involved collection of blood and measured endpoints that provide information about levels of iron in the body: where iron is present in haem-containing proteins (e.g. haemoglobin), transport proteins (e.g. transferrin) or storage proteins (e.g. ferritin). Chen *et al* (2005) and Van Thuy *et al* (2003) also measured serum retinol levels because Vitamin A deficiency is known to cause anaemia and can exacerbate iron-deficiency. But of the seven trials, only two included measures of other nutrition-related endpoints as part of their design. The trial involving ferric sodium EDTA-fortified sugar in Guatemala, reported that blood folate, plasma vitamin B12 and plasma and urine iron, copper and zinc were measured in that study (Viteri *et al*., 1995). The results of measures of iron, copper and zinc from the subjects in this 32 month fortification trial might be of interest in terms of assessing whether there was an impact from consuming ferric sodium EDTA on the metabolism of these minerals. However these results were not included in this paper and FSANZ has not been able to locate the results in any other publication.

Ballot *et al* (1989), measured plasma zinc levels in two subgroups of 30 individuals from their trial: 30 subjects from the control group and 30 subjects who had been consuming ferric sodium EDTA fortified curry powder for two years. The mean plasma zinc levels of these two groups were not significantly different after the two year trial. The baseline zinc levels of these two groups of thirty people had not been measured. If these long term trials had compared ferric sodium EDTA to another form of iron and not just to a placebo, they might have provided evidence about the relative bioavailability of ferric sodium EDTA consumed over an extended time period, i.e. whether one form of iron addressed iron deficiency more quickly than the other. Because the comparisons in this study are with a placebo only, the studies do not add to the body of evidence about the bioavailability of ferric sodium EDTA and its nutritional efficacy in that sense. On the whole, the nature of the design of these fortification trials and the results reported do not provide information to help FSANZ to assess the impact of long-term exposure to ferric sodium EDTA on the metabolism of nutritionally important minerals other than iron (an issue discussed in more depth below) or in terms of its bioavailability relative to other iron forms.

*FSANZ assessment*

The factors that are of most interest to FSANZ for the purposes of considering this evidence under Application A570 are:

- All of the studies involved iron-deficient populations.

- The studies were conducted in geographic areas where problems such as malaria and parasite infestations and the prevalence of other nutrient deficiencies such as vitamin A deficiency cause anaemia, and therefore exacerbate the problem of iron-deficiency.
- Many of the characteristics of the study populations were typical of persons living in developing countries (e.g. low socio-economic status).
- The usual diets of the subjects in these studies are largely plant-based, somewhat monotonous, and typically have a low-content of animal products.

Most of these characteristics and circumstances do not translate to the diets and living conditions of the general populations of New Zealand and Australia.

As iron status improves, iron absorption declines, an issue explored further below under the section on iron overload. There is some evidence from these trials to support that observation. However, none of the evidence from the human trials conducted provides information about the long-term effect of exposing populations to ferric sodium EDTA, particularly in terms of the bioavailability of ferric sodium EDTA compared to other forms of iron or the potential concern about interactions between EDTA and other minerals, also discussed below. The information from these human trials is not very applicable to considering use of ferric sodium EDTA in general purpose and special purpose foods in New Zealand and Australia.

**Potential risk of iron overload**

FSANZ has concluded that iron from ferric sodium EDTA would be expected to be absorbed in amounts two to three times better than iron from ferrous sulphate under test conditions where meals are high in phytic acid. At high levels, iron is toxic. Could broad use of ferric sodium EDTA lead to or exacerbate iron overload (excess stored iron) in some populations in New Zealand and Australia?

Down-regulation of iron absorption

Down-regulation refers to the inverse relationship between iron absorption and iron status. In various human studies considered in this assessment, researchers have found that subjects with lower iron status absorb more iron than subjects who are iron-replete (Ballot *et al*., 1989; Viteri *et al*., 1995; Hurrell *et al*., 2000; Andang'o *et al*., 2007). The absorption of iron declines as subjects' iron status improves (Viteri *et al*., 1995). It has also been noted that this regulation occurs with both haem and non-haem iron, but there is a greater response with non-haem iron (Yeung *et al*., 2004).

The iron in ferric sodium EDTA is absorbed in the same manner as non-haem iron. Studies with ferric sodium EDTA have shown that down-regulation occurs when iron is consumed in that form.

The down-regulation of iron absorption is well controlled in rats (Yeung *et al*., 2004). Yeung *et al* (2004) undertook a comprehensive rat study that compared the down-regulation of iron from $FeSO_4$ and ferric sodium EDTA in rats with elevated iron status.

**Table 3: Percentage absorption of iron from $FeSO_4$ and ferric sodium EDTA in iron-replete and iron-loaded rats**

| Basal rats (n=18) | | Iron-loaded rats (n=18) | |
|---|---|---|---|
| $^{59}FeSO_4$ | $^{59}$Ferric sodium EDTA | $^{59}FeSO_4$ | $^{59}$Ferric sodium EDTA |
| 64.7% Fe absorption | 49.4% Fe absorption | 12.8% Fe absorption | 10.2% Fe absorption |

**(Source: Yeung *et al* (2004)**

Half of the rats in this study received a basal diet containing 35 mg Fe/kg. These rats were not anaemic. The other half were fed 30,000 mg Fe/kg for 29 days in order to become loaded with iron. The two groups were then divided in half and fed labelled iron to compare the absorption of iron from $FeSO_4$ and ferric sodium EDTA. The researchers found that iron absorption from $FeSO_4$ and ferric sodium EDTA was about 80% lower in iron-loaded rats regardless of the form in which the iron was given to them. Both groups of rats absorbed more iron from $FeSO_4$ than ferric sodium EDTA. This suggests that ferric sodium EDTA is no more likely than $FeSO_4$ to lead to or exacerbate iron overload in rats.

Haemochromatosis

Haemochromatosis is a disease which causes the body to absorb more iron than usual from the diet. Even at normal dietary intakes, and irrespective of the form of dietary iron, individuals with haemochromatosis can accumulate excess stored iron in their bodies. Excess stored iron is toxic to the body and can lead to organ damage, particularly damage to the liver, heart or pancreas. Another name for haemochromatosis is iron overload disease. Other diseases or conditions can cause iron overload, such as certain anaemias, chronic liver disease such as hepatitis or rare inherited diseases (National Heart Lung and Blood Institute 2007).

Haemochromatosis as an overt clinical condition occurs when an individual inherits a copy of the haemochromatosis gene from both parents (homozygous). It is estimated that 0.5% of Caucasians are homozygous for the condition. However, individuals who are homozygous will not necessarily develop signs and symptoms of the disease. If an individual is homozygous and undiagnosed, development of iron overload disease cannot be prevented. But not everyone who is homozygous develops iron overload disease (National Heart Lung and Blood Institute 2007). A population based study conducted in Australia found only half of those who were homozygous had clinical features of haemochromatosis (Olynyk *et al*., 1999). The seriousness of the disease varies from person to person.

Some people show no symptoms, while in others, if left untreated haemochromatosis can lead to organ failure and even death. If an individual inherits only one copy (heterozygous), then they become a carrier of the condition and rarely express any adverse clinical symptoms. Haemochromatosis is more common in men than women. Signs and symptoms do not usually appear in men until aged 40-60 and in women signs and symptoms do not usually appear until after menopause. Young children rarely develop haemochromatosis (National Heart Lung and Blood Institute 2007).

Individuals susceptible to iron overload are usually identified only when enough iron has accumulated in their system to produce adverse effects. Early diagnosis and treatment are important.

Once identified, the principal treatment for individuals is clinical management, through regular phlebotomy (taking of blood), or if phlebotomy is not possible, through prescription medication (HealthAtoZ 2007; Haemochromatosis Society Australia 2007; National Heart Lung and Blood Institute 2007; IRONZ 2007).

*FSANZ assessment*

Overall, FSANZ concludes that there would be no additional risk of iron-overload in the populations of New Zealand and Australia if permission was given to use ferric sodium EDTA as a source of iron in the foods captured under this Application.

Studies with ferric sodium EDTA have shown that down-regulation of iron occurs when iron is consumed in that form. The potential introduction of ferric sodium EDTA as a new form of added iron into the diet of New Zealanders and Australians should offer no additional risk of iron-overload (excess stored iron) in the general population, given this well controlled down-regulation. While iron from ferric sodium EDTA may be better absorbed by individuals following a vegetarian diet, down-regulation of iron absorption would protect those individuals from iron-overload in the same way that the general population is expected to be protected.

A sub-population of individuals is susceptible to iron-overload, even at normal dietary iron intakes. This sub-population includes sufferers of haemochromatosis or other diseases or conditions that can cause iron overload. The accumulation of iron in someone susceptible to iron overload can occur regardless of the dietary iron source. The condition is clinically managed once diagnosed. Because development of iron overload disease cannot be prevented in an undiagnosed susceptible individual, but must be clinically managed once diagnosed, the risk to such individuals would not be increased by consumption of iron from ferric sodium EDTA.

**Iron and coronary heart disease**

The proposition that iron status is linked with prevalence of coronary heart disease (CHD) was brought to the attention of FSANZ through a submission by the Australian Food and Grocery Council (AFGC) at the Initial Assessment phase of this Application. The AFGC expressed the view that there is not good evidence of a correlation between excessive iron intake and CHD (refer Attachment 6 of the A570 Draft Assessment Report).

In 1999, a meta-analysis of 12 prospective cohort studies which involved a combined total of 7,800 CHD cases was published. The authors looked at risk ratios for CHD against markers of iron status as well as estimated total dietary iron intake where these characteristics had been measured in the prospective studies. The analysis did not find either strongly positive or strongly negative epidemiological associations between iron status and CHD. The possibility of weak associations could not be ruled out (Danesh and Appleby, 1999).

A more recent review considered the results of the meta-analysis noted above as well as reviews of other epidemiological studies including case-control studies and cross-sectional studies. This author reported that the question of the importance of iron stores in development of CHD remains a topic of investigation. However, the author concluded that the preponderance of studies does not support a strong association between high iron stores and CHD (Wood, 2004).

A recently published randomised controlled trial investigated the proposition that accumulated excess iron is related to risk of cardiovascular disease (Zacharski *et al*., 2007). This trial approached the proposition from a different position compared to the epidemiological studies included in the reviews by authors above. The trial tested whether reducing body iron stores through phlebotomy would influence all cause mortality (primary end point) or death plus nonfatal myocardial infarction and stroke (secondary end point). It was a secondary prevention trial involving patients with symptomatic but stable peripheral arterial disease. The authors reported no significant differences for primary or secondary study end points between control groups and those subjects who had their iron levels reduced by phlebotomy. Commentary published in the Journal of the American Medical Association since the publication of this trial, by other experts interested in the iron/heart disease debate (who criticised the study by Zacharski *et al* for not achieving full iron-depletion, for having the limitations of a secondary prevention study, and for not having sufficient power to consider subgroups by age) and the trial authors' reply, suggest the debate about iron and heart disease is set to continue (JAMA Related Letters 2007).

*FSANZ assessment*

The proposition that iron status is linked with prevalence of coronary heart disease has been noted briefly in this assessment because the proposed link was raised by a submitter at Initial Assessment. It has not been researched in depth given the submitter expressed no particular concerns and published reviews indicate that there is not strong evidence for an association between iron and heart disease at this time.

## EDTA

### Potential nutritional risks associated with increased EDTA from ferric sodium EDTA

Digestion and absorption of EDTA from ferric sodium EDTA

When consumed orally, most of the EDTA from ferric sodium EDTA passes through the digestive tract rather than being absorbed. A labelled isotope absorption study investigated the fate of the iron and the fate of the EDTA when ferric sodium EDTA is consumed by swine (Candela *et al*., 1984). With regard to the EDTA, the study showed that only 5% of the EDTA was absorbed and eliminated by the kidney. Almost all of the EDTA was eliminated in the faeces, approximately 80% in a soluble fraction. A more recent rat study also showed that iron is dissociated from EDTA prior to or during intestinal absorption. In the rat study, some fraction of the dissociated EDTA was absorbed separately (Zhu *et al*., 2006).

The ability of EDTA to bind metals might present a nutritional risk

The EDTA in ferric sodium EDTA is a complexing agent or chelate that can combine with virtually every metal in the periodic table. When compounds containing EDTA are consumed, the EDTA is released as the compound passes along the digestive tract making the EDTA available to re-bind with other minerals present in the digestive system. If intake of EDTA is increased, there is a theoretical concern that nutritionally important minerals could be bound by EDTA in the digestive system and be excreted in the faeces rather than absorbed (Bothwell and MacPhail, 2004). If ferric sodium EDTA was permitted to be used as a source of iron, the potential nutritional risk that might accompany this permission, via increasing the intake of EDTA, needs to be assessed.

The ability of EDTA to bind metals depends on a measure known as the stability constant of the metal complex, as well as the pH, the molar ratio of the EDTA to the metal and whether competing metal ions are present.

**Table 4: Stability constants of EDTA metal complexes and optimal pH**

| Metal ion | Stability constant | Optimal pH |
|---|---|---|
| $Fe^{3+}$ | 25.1 | 1 |
| $Cu^{2+}$ | 18.4 | 3 |
| $Zn^{2+}$ | 16.1 | 4 |
| $Fe^{2+}$ | 14.6 | 5 |
| $Mn^{2+}$ | 13.5 | 5.5 |
| $Ca^{2+}$ | 10.6 | 7.5 |
| $Mg^{2+}$ | 8.7 | 10 |

(Source: (Bothwell and MacPhail, 2004)

Iron has a high stability constant therefore a strong potential to bind with EDTA and this potential is strongest in the acidic environment of the stomach.

Beyond the stomach, the environment becomes more alkaline so it is predicted that the iron in ferric sodium EDTA becomes unbound from EDTA after it leaves the stomach, freeing the EDTA to bind with other minerals. Any mineral could presumably bind with EDTA, but zinc, copper, calcium and magnesium are of particular interest because these nutritionally important minerals have relatively high stability constants for EDTA and can complex with EDTA in alkaline conditions.

Solomons *et al* (1979), using pharmacological doses of zinc salts, found high doses of ferric sodium EDTA (>115 mg) progressively inhibited zinc absorption. The authors also found that it was the EDTA moiety, not the iron, inhibiting zinc absorption. The design of this old human study had considerable limitations and because of these and certain aspects of the study design, such as the molar ratio of EDTA to metal ions used in the study, the results cannot readily be compared with results from more recent research. The results of more recent research, a rat study by Hurrell *et al* (1994), and two short duration human studies involving small sample sizes by Davidsson *et al* (1994) and Davidsson *et al* (1998) are summarised in the table below.

**Table 5: Studies on interactions between ferric sodium EDTA and nutritionally important minerals (mean values presented)**

| **Study** | **Hurrell *et al* (1994)** | | | | **Davidsson *et al* (1994)** | | **Davidsson *et al* (1998)** | |
|---|---|---|---|---|---|---|---|---|
| **Study design** | Chemical balance studies in rats. Eight test diets to test $FeSO_4$ and ferric sodium EDTA under zinc–deficient and zinc-sufficient circumstances; four groups of EDTA levels (0, 200, 500 and 1000 mg/kg). Test diets for 17 days; urine and faeces collected days 18-21; rats killed day 21 and femurs analysed for zinc and calcium. | | | | Randomised, cross-over chemical balance study. Total daily test intakes ~ 18 mg Fe, 11 mg Zn, 803 mg Ca, 60 mg ascorbic acid, and no red meat or offal to minimise haem iron intake. Compared $FeSO_4$ and ferric sodium EDTA. Stable isotopes of zinc and calcium given on day 6 of each 14-day trial period, with a 4 week washout phase. Total amounts of zinc and calcium in samples of diet, faeces and urine were measured. | | Crossover labelled isotope absorption study. Test meals with labelled $^{54}Mn$ day 1 and day 28. Measured whole body retention of $^{54}Mn$ over 4 weeks after each test meal. | |
| **Subjects** | Rats (n=64; 8 rats per test diet) | | | | Healthy iron-replete women of child-bearing age (n=10) | | Healthy adult humans (n=10) | |
| **Food vehicle** | Soya-bean based diets | | | | Wheat bread rolls (high extraction) | | Weaning cereal based on wheat and soy, relatively high in phytic acid | |
| **Iron dose** | 50.1 mg/kg | | | | 18 mg/day (10 mg from fortificant) | | 19.7 mg Fe/kg dry cereal | |
| **Iron fortificant** | **FeSO4** | | **Ferric sodium EDTA** | | **$FeSO_4$** | **Ferric sodium EDTA** | **$FeSO_4$ + ascorbic acid** | **Ferric sodium EDTA** |
| | **A** | **B** | **A^** | **B^** | | | | |
| **Iron absorption** | Was not measured under this study design | | | | | 4X higher than $FeSO_4$ | Was not measured under this study design | |
| **Zinc absorption** | 50.2% | 16.0% | 67.4 – 79.4% | 20.4-30.4% | 20.9 ± 4.4% | 33.5 ± 17.3% | | |
| **Zinc urinary excretion** | 2% | 0.7% | 4 – 15.6% | 1.7-5.9% | 0.29 ± 0.21% | 0.91 ± 0.34% | | |
| **Calcium absorption** | 57.1% | 56.2% | 53.3-57.7% | 56.4-58.8% | 53.3 ± 6.5%* | 53.3 ± 11.2% | | |
| **Calcium urinary excretion** | 1.2% | 0.9% | 1.1-2.3% | 0.6-1.7% | 8.8 ± 1.9% | 9.8 ± 2.2% | | |
| **Copper absorption** | 27.5% | 30.8% | 31.1-38.2% | 32.1-33.7% | Was not measured under this study design | | | |
| **Copper urinary excretion** | 3.9% | 2.5% | 3.8-4.1% | 2.8% at all [EDTA] | | | | |
| **Manganese absorption*** | Was not measured under this study design | | | | | | 0.91±0.35% | 1.1±0.15% |
| **Manganese urinary excretion*** | | | | | | | 0.72±0.53% of absorbed dose | 1.1±0.55% of absorbed dose |

**A** = Zinc-deficient diet (6.1 mg Zn/kg) and **B** = Zinc-sufficient diet (30 mg Zn/kg)
^ = range of mean absorption values measured across test diets containing 200, 500 and 1000 mg/kg EDTA. The low end of the range does not necessarily correspond with the lowest EDTA dose.
* Results were <u>not</u> significantly different between $FeSO_4$ and ferric sodium EDTA.

The results presented in Table 5 above show that ingestion of ferric sodium EDTA rather than $FeSO_4$ can significantly increase the absorption of zinc in rats and humans. This evidence is highlighted by shaded cells in Table 5. The absorption of calcium, copper and manganese, was not significantly different if using ferric sodium EDTA rather than $FeSO_4$ where tested. When ferric sodium EDTA is used, measured levels of urinary excretion of zinc, calcium, copper and manganese show either a slight or no significant increase. In the rat study the authors note that overall retention of calcium and copper (intake – (urinary excretion + faecal loss) was not influenced by ferric sodium EDTA. Overall retention of zinc was significantly increased by ferric sodium EDTA despite the increase in urinary excretion of zinc because the losses in urine only contribute slightly to zinc metabolism and the increases in zinc absorption easily compensated for this loss (Hurrell *et al*., 1994). The above results suggest that ferric sodium EDTA added to foods could have a beneficial, not detrimental effect on zinc metabolism, while having limited or no effect on the metabolism of calcium, copper or manganese.

Davidsson *et al* (2005) have published one other paper on EDTA and mineral interactions. This study has limited relevance to Application A570 because it involved 11 infants aged 18-27 weeks. Application A570 does not include foods for this age group. However this paper is noted because it is reportedly the first and only published attempt to measure an effect of EDTA on apparent absorption of magnesium in humans.

Limitations of the available literature

While methodologically sound studies, the results from the three published papers presented in Table 5 do not amount to a significant body of evidence. Caution should be exercised before extrapolating results from animal studies to humans. And caution should be exercised before generalising results from short-term human studies that have yet to be replicated, and which involved small numbers of individuals. The authors of this literature noted in 2005 that 'Only limited information is available on the influence of ferric sodium EDTA on the absorption and excretion of other nutritionally important minerals and trace elements' (Davidsson *et al*., 2005).

At this time, there are no published human studies reporting the influence of EDTA compounds on copper absorption and very limited data on the influence of EDTA compounds on the absorption and metabolism of potentially-toxic minerals.

The ability of EDTA to bind metals depends on many variables which can be manipulated and controlled to a certain extent under test conditions. The molar ratio of EDTA to minerals of interest in the diet of Australians and New Zealanders is difficult to estimate and would not necessarily correspond with the molar ratios used in the rat study or human studies presented in Table 5.

While various human intervention trials using ferric sodium EDTA (Table 2 above) have been conducted over an extended period, there are no published results from these trials relating to the interaction between EDTA from ferric sodium EDTA and minerals other than iron, except for brief results provided by Ballot *et al* (1989) (discussed above).

Baseline EDTA intakes in New Zealand and Australia

In New Zealand and Australia certain foods have permission to contain the additive calcium disodium EDTA. As a result of these permissions, Australians and New Zealanders may be consuming EDTA from their diet at this time. If there has been long-term population exposure to EDTA with no apparent negative effect on metabolism of nutritionally important minerals, such information would add to the totality of evidence regarding EDTA and potential nutrient interactions.

Exposure estimates for EDTA are in the report at Attachment 5 of the Application A570 Draft Assessment. It is reported there that the highest baseline estimates of EDTA from calcium disodium EDTA, for children aged two to six years at the 90$^{th}$ percentile, range from 10% of the ADI based on current apparent use of calcium disodium EDTA, to 50% of the ADI if all permissions to use calcium disodium EDTA were followed by the food industry. The lower estimate, i.e. 10% at the 90$^{th}$ percentile, is the more realistic of the two estimates. Because two to six year old children, given their low body weight, are the group with highest exposure when exposure is expressed as a proportion of the ADI, it is likely baseline exposure of the general population to EDTA compounds is very low.

Comparison of estimated EDTA intakes with reference health standards for EDTA

The reference health standard for EDTA used by FSANZ for the purpose of this assessment is the Acceptable Daily Intake (ADI) established by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) for calcium disodium EDTA (JECFA 1974). After recently reviewing additional literature, JECFA stated that 'Total intake of EDTA should not exceed acceptable levels, also taking into account the intake of EDTA from the food additive use of other EDTA compounds' (JECFA 2007). In accordance with JECFA, the ADI for EDTA used by FSANZ for the purpose of this assessment is 0-2.5 mg/kg body weight. JECFA has established and recently reaffirmed this ADI taking biochemical and toxicological studies into account. JECFA included studies regarding interference with mineral metabolism in its consideration of the evidence assessed by the Committee when establishing the ADI.

*FSANZ assessment*

There is a plausible biological explanation for the theoretical concern that consumption of compounds that release EDTA could impact on the nutritional status of important minerals such as zinc, copper, calcium or magnesium. The potential risk relates most to the unknown long-term effects of EDTA intake by human populations.

The published evidence of studies designed to test this theoretical risk is very limited, and on its own would be insufficient to classify the potential risk with confidence. However, JECFA included studies regarding interference with mineral metabolism in its consideration of the evidence assessed by the Committee when establishing the ADI that is being used by FSANZ for this assessment. FSANZ therefore concludes that provided the ADI for EDTA is not exceeded, the potential for EDTA from ferric sodium EDTA to have adverse effects on nutrient interactions should not be a concern.

**Conclusions**

FSANZ has received an Application to approve ferric sodium EDTA as a permitted form of the mineral iron in foods permitted to contain added iron under Standards 1.3.2 (except breakfast cereals), 2.9.3 (except formulated supplementary foods for young children aged one to three years) and 2.9.4 of the *Code*. FSANZ has reviewed the available literature and has focused its consideration on the bioavailability of iron from ferric sodium EDTA, the potential risk of iron-overload, and the potential nutritional risks associated with increased intake of EDTA from ferric sodium EDTA. FSANZ has drawn the following conclusions:

Bioavailability of iron from ferric sodium EDTA

- Conclusions about the bioavailability of iron from ferric sodium EDTA under this assessment may be confined to adults generally, due to an absence of data testing the bioavailability of iron from ferric sodium EDTA in children.

- As a source of iron for the general population, ferric sodium EDTA probably offers no biological advantage or disadvantage to most New Zealanders and Australians, where their diets typically contain adequate amounts of meat and vitamin C (enhancers of iron absorption).

- Under test conditions, the iron in ferric sodium EDTA is two to three times better absorbed than the iron in $FeSO_4$ when consumed with inhibitors of non-haem iron absorption, particularly phytic acid.

- Vegetarians may potentially benefit from approval of this Application, depending on their iron status and dietary pattern. The iron from foods containing ferric sodium EDTA may be absorbed two to three times better by vegetarians given the absence of most haem-iron from their diet and the possibility that their diet rich in plant foods may be high in phytic acid also.

Iron overload

- Overall, FSANZ concludes that there would be no additional risk of iron-overload in the populations of New Zealand and Australia if permission was given to use ferric sodium EDTA as a source of iron in the foods captured under this Application, due to the well controlled absorption of iron through down-regulation.

- A sub-population of individuals, including sufferers of haemochromatosis, is susceptible to iron-overload, even at normal dietary iron intakes. The accumulation of iron in someone susceptible to iron overload occurs regardless of the dietary iron source. Because development of iron overload disease cannot be prevented in an undiagnosed susceptible individual and the condition is clinically managed once diagnosed, the risk to such individuals would not be increased by consumption of iron from ferric sodium EDTA.

Iron and coronary heart disease

Published reviews indicate that there is not strong evidence for an association between iron and heart disease at this time.

Nutritional risks associated with increased intakes of EDTA from ferric sodium EDTA

There is a plausible biological explanation for the theoretical concern that consumption of compounds that release EDTA could impact on the nutritional status of important minerals such as zinc, copper, calcium or magnesium. Provided the ADI for EDTA is not exceeded, the potential for EDTA from ferric sodium EDTA to have adverse effects on nutrient interactions should not be a concern.

**Search Details**

The body of evidence considered in this nutrition risk assessment includes material provided by the Applicant and submitters to the Initial Assessment Report for Application A570 as well as literature located by FSANZ. In this assessment, FSANZ has considered relevant literature published within the last 30 years.

FSANZ used the U.S. National Library of Medicine's premiere search system for health information PubMed® available free on the Internet at http://pubmed.gov. The search was limited to publications in English. Where detail in abstracts indicated strong relevance to A570, the Related Links in PubMed® were explored. Twenty-six full text articles were retrieved following the first search. The reference lists in located articles were hand searched to check for any additional studies that would be related to this Application, and where necessary, additional articles were retrieved. To further cross check for any published material potentially related to Application A570, FSANZ conducted a search of several of the lead authors identified in the authoritative reviews and pivotal studies it had located.

Searches in PubMed® were conducted for the following subject terms:

1. Ferric sodium edetate
2. Ferric sodium EDTA
3. NaFeEDTA
4. 1 or 2 or 3 and nutrient interactions
5. 1 or 2 or 3 and nutrient absorption
6. 1 or 2 or 3 and nutritional status
7. 1 or 2 or 3 and mineral absorption
8. Ironstrene
9. Iron and nutrient interactions
10. Iron and other nutrients
11. Iron influence on nutrient status
12. Iron fortification and zinc status
13. Iron fortification and copper status

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## Attachment 3

# Safety Assessment Report

### APPLICATION A570 – FERRIC SODIUM EDETATE AS A PERMITTED FORM OF IRON

#### Summary and Conclusions

Iron ($Fe^{3+}$) sodium ethylenediaminetetraacetic acid or ferric sodium EDTA, which has been shown to have a beneficial effect on iron status by increasing iron bioavailability in human diets, has been proposed for use as a direct substitute for other permitted fortificant forms of iron in food.

Ferric sodium EDTA, like other EDTA-metal complexes, dissociates in the gastrointestinal tract to release bioavailable non-haem iron and an EDTA salt. Since the absorption of iron and EDTA are independent processes a consideration of any toxicological data on EDTA containing compounds other than ferric sodium EDTA is relevant for a safety assessment. The absorption of iron which is released from ferric sodium EDTA in the small intestine is controlled through the same physiological mechanisms as other permitted forms of iron, such as ferric sulphate, ferrous sulphate, ferric citrate, and ferrous fumarate.

Following oral administration, the iron in ferric sodium EDTA, which is separated from the EDTA complex in the lumen of the gut, forms part of the general non-haem iron pool in the diet that is mainly used in haemoglobin synthesis for physiological erythrocyte development. The absorption of iron from ferric sodium EDTA is controlled through the same physiological mechanisms as other forms of iron. Less than 1% of the intact ferric sodium EDTA chelate is absorbed and excreted unchanged by the kidneys. Following dissociation from ferric sodium EDTA, most (95%) of the EDTA is found in the faeces, while less than 5% is absorbed and excreted in the urine.

Ferric sodium EDTA has very low acute oral toxicity ($LD_{50}$ = 10,000 mg/kg bw). EDTA compounds do not cause reproductive or developmental effects when fed in a nutrient-sufficient diet or in a minimal diet supplemented with zinc. In chronic toxicity studies, diets containing as much as 1% EDTA were without any adverse effects. EDTA compounds were not carcinogenic in experimental animal bioassays and are unlikely to be genotoxic.

In a two-year feeding study in rats treated with calcium disodium EDTA no effects were observed at the highest tested dose of 250 mg/kg bw/day. Using a conventional 100-fold safety factor to take account of intra-and inter-species variability the ADI for calcium disodium EDTA was calculated to be 2.5 mg/kg bw/day. Owing to the independence of the absorption kinetics for EDTA this group ADI is also applicable for all other EDTA-containing compounds, such as ferric sodium EDTA. For ferric sodium EDTA the theoretical bioavailable iron concentration at the maximal ADI of 2.5 mg/kg bw would be around 0.3-0.4 mg/kg bw/day. This concentration is well below the provisional tolerable daily intake of 0-0.8 mg/kg bw for iron (JECFA, 2007).

The dietary exposure model used in this assessment includes aggregating the likely exposure to EDTA through ingestion of foods containing permitted calcium disodium EDTA and the proposed levels of ferric sodium EDTA.

For the most highly exposed group, namely the 2-6 year olds, the aggregate exposure at the 90$^{th}$ percentile is around 80% of the ADI. All other population subgroups have values less than 80% of the ADI. However, there is potential for changes in food industry practice or consumer behaviour to increase the intake of EDTA towards the 'worst case' scenario of dietary exposure to EDTA modelled by FSANZ. Such circumstances could result in EDTA intakes exceeding the ADI.

**Existing Permissions in the Code**

Calcium disodium EDTA is currently permitted in the Code as a food additive in a range of foods including, fully preserved fish including canned fish, fruit drink, water-based flavoured drinks and sauces and toppings, at levels ranging from 33 to 250 mg/kg.

**Existing Safety Standards**

JECFA (1974) evaluated the safety of calcium disodium EDTA and disodium EDTA as food additives and recommended that these compounds be permitted as food additives at doses up to an ADI of 2.5 mg/kg bw/day.

In 1993, JECFA provisionally concluded that ferric sodium EDTA was safe when used in supervised food fortification programmes in iron-deficient populations. However, JECFA also requested that additional studies be conducted to assess the site of iron deposition and metabolic fate of ferric sodium EDTA following long-term administration.

In 1999, JECFA reviewed the results of new studies, including a short-term toxicity study in rats designed to address JECFA's concerns on iron deposition and metabolism of ferric sodium EDTA and concluded that 'sodium iron EDTA could be considered safe for use in supervised food fortification programmes, when public health officials had determined the need for iron supplementation of the diet of a population.' These programmes were required to provide daily iron intake of approximately 0.2 mg/kg bw.

In 2007, JECFA reviewed several new studies on the biochemical and toxicological aspects and on the efficacy of ferric sodium EDTA. JECFA concluded that ferric sodium EDTA is suitable for use as a source of iron for food fortification provided that the total intake of iron does not exceed PMTDI of 0.8 mg/kg bw. Total intake of EDTA compounds should not exceed the ADI of 0-2.5 mg/kg bw, equivalent to up to 1.9 mg/kg bw EDTA.

## 1. INTRODUCTION

Akzo Nobel Pty Ltd (the Applicant) is seeking to amend Standard 1.1.1 to approve ferric sodium edetate as a permitted form of the mineral iron.

Ferric sodium edetate is one of the common names for sodium iron (III) ethylene-diamine-tetraacetate, also known as ferric sodium EDTA and sodium feredetate. In keeping consistency with the Code, it will be referred to as ferric sodium EDTA in this Report.

The Applicant stated that the justification for use of ferric sodium EDTA for iron fortification, and addition to food, where iron fortification or addition is currently permitted, was based on its superior biological and food technological performance relative to the forms of iron currently permitted.

## 2. HISTORY OF USE

Ferric sodium EDTA is emerging as an alternative iron fortificant in recent years for use in supervised food fortification programs to improve iron status in populations where iron deficiency is highly prevalent.

JECFA evaluated the safety of ferric sodium EDTA as an iron fortificant in foods and concluded that it could be considered safe when used in supervised food fortification programs (JECFA 1999). Ferric sodium EDTA was intended for use in response to a need for iron supplementation in a population as determined by public health officials. Such programs would provide a daily iron intake of approximately 0.2 mg/kg of body weight.

In 2004, US FDA designated ferric sodium EDTA as Generally Recognised as Safe (GRAS) as a dietary source of iron for food fortification purpose in various foods in response to Kraft's GRAS notice (No. GRN 000152). Kraft intended ferric sodium EDTA for iron fortification in powered meal replacement, flavoured milk, and fruit-flavoured beverages at a level not to exceed 2.5 mg of iron per 200 mL of reconstituted beverage and in areas of the world with a high prevalence of iron deficiency.

In 2006, USFDA designated ferric sodium EDTA as GRAS for use as a source of dietary iron for fortification purposes in soy, fish, teriyaki, and hoisin sauces at a level of 0.024% iron by weight, and in sweet and sour sauce at a level of 0.012% iron by weight in response to Akzo Nobel's GRAS Notice No. GRN 000178.

## 3. STRUCTURE AND PROPERTIES

### 3.1 Chemistry

JECFA (1993) reviewed chemical properties of EDTA metal complexes to facilitate understanding of the biochemistry and toxicology of these complexes. A summary of JECFA's evaluation is presented here.

EDTA is capable of chelating stoichiometrically with virtually every metal ion in the periodic table. The measure of EDTA as a chelator for any particular metal ion is its stability constant.

The stability constants and optimal pH of EDTA complexes formed with the nutritionally important metals are shown in Table 1 (Source: JECFA 1993, Bothwell and MacPhail, 2004)

**Table 1: Stability constants of EDTA metal complexes and optimal pH**

| Metal ion | Stability constant | Optimal pH |
|---|---|---|
| $Fe^{3+}$ | 25.1 | 1 |
| $Cu^{2+}$ | 18.4 | 3 |
| $Zn^{2+}$ | 16.1 | 4 |
| $Fe^{2+}$ | 14.6 | 5 |
| $Mn^{2+}$ | 13.5 | 5.5 |
| $Ca^{2+}$ | 10.6 | 7.5 |
| $Mg^{2+}$ | 8.7 | 10 |
| $Na^{+}$ | 1.7 | / |

Chelated metal ions are prevented from reacting with competing anions and its solubility is significantly increased. The measure of chelation potential is its stability constant which is dependent on pH, the molar ratio of chelator to metal ion, and the presence of competing metal ions.

Based on these characteristics, it is expected that when ferric sodium EDTA is ingested with foods, the $Fe^{3+}$ ion would be expected to remain firmly bound to the EDTA moiety during passage through the gastric juice, but could be exchanged for $Cu^{2+}$, $Zn^{2+}$, $Fe^{2+}$ or $Ca^{2+}$ in the duodenum. As for Mg-EDTA chelate, due to it low stability constant and high pH optimum it is less likely that EDTA reacts with this metal in the duodenum.

### 3.2 Solubility and stability

Ferric sodium EDTA is a stable and un-reactive compound with the iron bound tightly to the EDTA moiety especially at low pH. A study conducted by Garcia-Casal and Layrisse (2001) to compare solubility of different iron compounds at different pH revealed that within tested pH range (pH 2-6), ferric sodium EDTA remained completely soluble while other iron compounds such as ferrous sulphate and ferrous fumarate showed decreased solubility with the increase of pH.

## 4. SAFETY OF FERRIC SODIUM EDTA

Considerations of different EDTA metal complexes, including calcium disodium EDTA and disodium EDTA, are relevant in evaluating the toxicological effects of ferric sodium EDTA due to the chelating property of EDTA and metal ion replacement facilitated by the changing pH range through the GI tract.

Earlier toxicity studies of EDTA compounds were often conducted using calcium disodium EDTA and disodium EDTA. Together with these earlier studies, more recent studies using ferric sodium EDTA, including an acute toxicity (Whittaker et al., 2002), a short-term toxicity (Appel et al., 2001) and a genotoxicity study (Dunkel et al., 1999) were also considered in this assessment.

### 4.1 Toxicological data

*4.2.1 Absorption, distribution and excretion*

The ferric form of food iron is poorly absorbed from the upper small intestine where most non-haem iron is absorbed due to its low solubility in media above pH 3.5. However, in the presence of EDTA, iron (primarily the ferric form) is firmly bound to EDTA in the acidic environment of stomach. The chelate remains soluble in the upper small intestine where pH increases. The increased pH allows exchange of chelated iron with other metal ions and thereby releases iron for absorption.

Studies carried out prior to 1993 on iron absorption and excretion from ferric sodium EDTA and EDTA absorption and excretion from other EDTA metal chelates were reviewed by JECFA (1993).

Oral delivery studies in swine using a double labelled ($^{55}Fe$ and $^{14}C$) ferric sodium EDTA preparation showed different absorption kinetics of iron and EDTA.

Iron was rapidly absorbed with the peak concentration in plasma being observed after 1 hour while EDTA was absorbed over an extended period (5-20 hours). This difference in $T_{max}$ suggests independent absorption processes for Fe and EDTA. A total of about 5% EDTA was absorbed and quantitatively excreted in urine. Similar absorption studies in humans revealed that between 3 to 25 % iron was absorbed and the small amount of intact ferric sodium EDTA complex absorbed were expected to be excreted in 24 hours.

JECFA concluded that most of the iron in ferric sodium EDTA was released from the chelate to the physiological mucosal uptake system before absorption. Less than 1% ferric sodium EDTA complex was absorbed as the intact form and was completely excreted in the urine. Less than 5% EDTA moiety was absorbed and also completely eliminated in the urine.

More recently, a study in rats was performed to compare the disposition, accumulation of iron fed as ferric sodium EDTA or as ferrous sulphate (Appel et al., 2001). The feeding was carried out for 31 and 61 day using iron doses of 2.8, 5.7 or 11.4 mg /kg bw/day. The results indicated that iron was accumulated from the diet in liver, spleen and kidneys in a dose-dependent manner and iron derived from ferric sodium EDTA was accumulated less efficiently in liver and spleen than iron from ferrous sulphate. No excess iron accumulation in tissues was observed in spite of feeding iron up to 11.4 mg/kg bw/day in a form of either ferrous soleplate or ferric sodium EDTA.

*4.2.2 Toxicity*

Iron

Iron is an essential element in the human body, especially an essential constituent in haem proteins, such as haemoglobin, myoglobin and cytochrome, which are involved in oxygen transport or mitochondrial electron transfer. However excess iron is toxic. Iron poisoning occurs by accidental overdose of iron tablets and predominantly by children. Iron toxicity can be classified as corrosive or cellular (Spanierman, 2007). Large amount of ingested elemental iron is very corrosive to the GI tract and it acts on the mucosal tissues and manifests as haematemesis and diarrhoea. The absorption of excessive quantities of ingested iron results in systemic iron toxicity.

At cellular level, it causes impaired oxidative phosphorylation and mitochondrial dysfunction, which can result in cell death. Many organs are affected by systemic iron toxicity, including liver, heart, kidneys, lungs and haematological systems etc, but the most affected organ is liver.

Ingestion of iron in the range between 20-40 mg/kg bw results in symptoms of GI toxicity. Moderate to severe intoxication occurs when ingestion of iron ranges between 40 to 60 mg/kg bw. It may be lethal when ingestion of iron exceeds 60 mg/kg although it is estimated that the fatal amount of elemental iron to be between 200- 300 mg /kg bw (UK Expert Group on Vitamins and Minerals, 2003).

In relation to chronic iron overload, the UK expert group on vitamins and minerals (2003) concluded: ‘Iron overload as a result of dietary intake is unusual in the normal population and only a handful of case reports exist describing this phenomenon. This may be due to the reduction in iron absorption that occurs as exposure increases.’

Although the body has the ability to modulate iron absorption according to its needs, individuals with hereditary haemochromatosis are more susceptible to iron overload than the remainder of the population, even at normal dietary iron intakes. As such, those with haemochromatosis are advised to avoid iron supplements and iron fortified foods (NHMRC, 2006a).

EDTA metal complexes

*Acute toxicity studies*

JECFA's 1993 evaluation summarised acute toxicity studies with calcium disodium EDTA and disodium EDTA. The oral studies are presented in Table 2.

**Table 2: $LD_{50}$ of EDTA Compounds in Different Species**

| Animal | Compound | $LD_{50}$ (mg/kg bw) |
|---|---|---|
| Rat | $Na_2EDTA$ | 2000-2200 |
| Rabbit | $Na_2EDTA$ | 2300 |
| Rat | $CaNa_2EDTA$ | 10,000±740 |
| Rabbit | $CaNa_2EDTA$ | 7,000 approx |
| Dog | $CaNa_2EDTA$ | 12,000 approx |

These results suggest that the acute toxicity of disodium EDTA is 3 to 5 times as high as that of calcium disodium EDTA depending on the test animal.

The acute toxicity of ferric sodium EDTA was compared to that of carbonyl iron and ferrous sulphate in young male Sprague-Dawley rats (Whittaker et al. 2002). The iron doses (mg/kg bw) tested were 900, 1000, 1100, 1200, 1300 and 1400 for ferrous sulphate; 40,000 and 50,000 for carbonyl iron; 650, 1300, 1625, 1950, 2600, 3900 and 5200 for ferric sodium EDTA. The test compounds were administered by gavage. Eight rats were used in most the dose groups, except the highest does group for ferrous sulphate where 4 animals were used and the 3900 and 5200 dose groups for ferric sodium EDTA where 4 and 6 animals were used respectively. The study indicated $LD_{50}$ for ferric sodium EDTA, carbonyl iron, ferrous sulphate to be 1,300 Fe mg/kg bw, 50,000 Fe mg/kg bw, and 1,100 Fe mg/kg bw respectively.

For ferric sodium EDTA, an $LD_{50}$ of 1,300 Fe mg/kg bw is approximately equivalent to 10,000 mg /kg bw of ferric sodium EDTA.

*Short-term toxicity studies*

Short-term oral studies in rats with other calcium disodium EDTA or disodium EDTA were review by JECFA in 1993. In the study using calcium disodium EDTA, three males and three females per group were fed for four months on a low mineral diet (1.25%) containing one-half the usual portion of salt mixture (2.5%). Calcium disodium EDTA was added to the diet at a concentration of 0 or 1.5%. The test group showed a reduced weight gain, but there was no other differences in general conditions of the animals (Yang 1964, as in JECFA 1993).

Another short-term study involved the use of disodium EDTA (Chan 1964, as in JECFA 1993). Three groups of 10 to 13 males and females were feed a low mineral diet (0.5% Ca and 0.013% Fe) with the addition of 0, 0.5% and 1% disodium EDTA for 205 days.

Certain adverse effects were observed in the group on 1% disodium EDTA diet, including: growth retardation of the males, lowered erythrocyte and leukocyte counts, a prolonged blood coagulation time, a significant lower ash content of the bone, considerable erosion of the molars and diarrhoea. Gross and histological examination of the major organs revealed no abnormalities.

The short-term toxicity of ferric sodium EDTA was compared with that of ferrous sulphate in rats (Appel et al., 2001). The study involved six groups with 40 males/group; three test groups receiving different levels of ferric sodium EDTA (35, 70, or 140 mg Fe/kg diet) and three control groups receiving different levels of ferrous sulphate (35, 70, or 140 mg Fe/kg diet). Twenty rats in each group were sacrificed after 31 days and the remainder after 61 days. The mean iron daily intake for three ferric sodium EDTA groups was 2.8, 5.7, and 11.2 mg/kg bw, and similar amount for the ferrous sulphate groups. These doses are equivalent to ferric sodium EDTA daily intake of 22, 44, 86 mg/kg bw respectively. No treatment related effects in clinical signs, body weight, food consumption, food conversion efficiency, haematology, clinical chemistry and pathology of selected organs were observed.

Oser et al. (1963, as in JECFA 1993) reported a feeding study using calcium disodium EDTA in dogs. Four groups of 4-6 month old mongrel dogs were fed diets providing 0, 50, 100, or 200 mg calcium disodium EDTA/kg bw/day for a year. Body weight gain was not affected by the treatment. There were no differences in haematology, blood chemistry, urine composition, or histopathology of various organs, and there was no evidence of skeletal changes.

The long term toxicity and reproduction studies using disodium EDTA, trisodium EDTA and calcium disodium EDTA through oral route were review by JECFA (1993). The summary of the evaluations is presented as follows:

*Long-term toxicity studies*

In a two year study, groups of 33 rats were fed 0, 0.5, 1 or 5% disodium EDTA. Apart from diarrhoea and reduced food consumption in the 5% group, no other treatment related effects were observed (Yang 1964, as in JECFA 1993).

Two animal species were used in a 103 week study with trisodium EDTA. Groups of rats or mice (50/sex/group) were fed a diet containing trisodium EDTA at concentrations of 0.375% or 0.75% diet. The control groups consisted of 20 males and 20 females of corresponding animals. No treatment related effects were observed in rats. In mice, the only observed effect was a reduced body weight gain in males and females in the highest dose group (NCI 1977, as in JECFA 1993).

*Reproduction toxicity studies*

Yang (1964, as in JECFA 1993) used groups of six rats maintained for 12 weeks on diets containing 0, 0.5, 1 or 5% disodium EDTA. Mating in each group was allowed when the animals were 100 days old and mating was repeated 10 days after weaning the first litter. Normal litters were produced from all groups except the 5% group which failed to produce litters.

Calcium disodium EDTA was used in a two-year rat study. Four groups of 25 male and 25 female rats were fed diets providing a daily intake of calcium disodium EDTA at 0, 50, 125 or 250 mg/kg bw. Feeding was carried on through four successive generations. Rats were mated after 12 week feeding and were allowed to lactate for three weeks. After one week resting, the rats were mated again to produce the second litter. Ten male and 10 female rats of F1 generation from each group and similar F2 and F3 generation groups were allowed to produce two litters. No significant abnormalities in appearance and be behaviour were noted during the 12 weeks of the post weaning period in all generations. No significant differences in weight gain, food conversion efficiency, haematological parameters, organ weight and histopathology of liver, kidney, spleen, heart, adrenals, thyroid and gonads. Fertility, lactation and weaning were not adversely affected. There was no evidence of any chelating effect on calcification of bone and teeth (Oser et al. 1963, as in JECFA 1993). Owing to the absence of any toxicological findings the NOEL in this study was 250 mg/kg bw/day.

*Developmental toxicity studies*

Groups of 5-16 pregnant female Sprague-Dawley rats were fed disodium EDTA in standard diets (containing 100 ppm zinc) at levels of 0%, 2% or 3% from day 1 to day 21 of gestation. A fourth group received 3% disodium EDTA and 1000 ppm zinc from day 6 to 21 of gestation. On day 21 of gestation, foetuses were removed and examined. In rats fed 2% disodium EDTA, the litter size was normal and foetuses were alive. Gross congenital malformations were apparent in 7% of the foetuses. In the 3% group, nearly half of the implantation sites had dead foetuses or resorptions. Full term foetuses were significantly smaller than the controls and 100% of them were malformed. Malformations included severe brain malformation, cleft palate, malformed digits, clubbed legs and malformed tails. Maternal toxicity as manifested by diarrhoea was observed in rats on both 2 and 3% diets. The teratogenic effects of disodium EDTA were prevented by supplementation of the diet with 1000 ppm zinc suggesting that EDTA could interfere with metals uptake. Although zinc was able to prevent the teratogenic effects of disodium EDTA other metal-EDTA complexes with higher stability constants relative to sodium may also have achieved the same outcome (Swenerton & Hurley, 1977).

In another similar reproduction study, 42 pregnant CD rats were fed diets containing disodium EDTA at 0 and 3% of the diet (daily intake at 0 and 954 mg/kg bw) from gestation day 7 to 14. Foetuses were removed and examined at day 21 of gestation.

In the treatment group, there was a significant increase in fetal death and 71% of the foetuses were malformed. Maternal toxicity, i.e. decreased food consumption, diarrhoea and diminished weight gain was observed in the treatment group (Kimmel 1977, as in JECFA 1993).

*Genotoxicity*

Ferric sodium EDTA did not increase the mutation frequency in the Ames test (plate incorporation and pre-incubation method) using Salmonella *typhimurium* strains TA97a, TA98, TA100, TA102, TA1535, TA1537, and TA1538 at concentrations up to 10,000 μg/plate of iron as ferric sodium EDTA, with or without metabolic activation (Dunkel *et al*., 1999).

In the mouse lymphoma assay of L5178Y cells, ferric sodium EDTA was tested at concentrations providing 1.3, 2.6, 162.5, or 325.0 µg/mL of iron in the absence of metabolic activation, and at concentrations providing 0.026, 0.052, 1.625, 3.250, or 6.500 µg/mL of iron in the presence of metabolic activation. In the absence of metabolic activation, an increase in mutation frequency at the highest tested concentration (325.0 µg/mL) was observed to be more than double that of the negative control. However, at the highest dose appreciable cytotoxicity was apparent with the relative total growth being only 33.5% of the control value. In the presence of metabolic activation, a dose-dependent increase in mutation frequency (2-fold that of the negative control) were observed at the three highest concentrations tested (1.625, 3.250, and 6.500 µg iron/mL). However, these increases in mutation frequency were associated with a reduction in cell growth of 47%, 62%, and 81% of control, respectively. Based on similar increases in mutation frequency in the mouse lymphoma assay with other ferrous or ferric iron salts the investigators attributed the increased number of mutations to the iron component of iron sodium EDTA. Moreover, disodium EDTA produced negative results in the mouse lymphoma assay with or without metabolic activation (Dunkel *et al*., 1999).

### 4.2 JECFA evaluations

JECFA (1974) evaluated the safety of calcium disodium EDTA and disodium EDTA as food additives and established an ADI of 0-2.5 mg $CaNa_2EDTA$/kg bw. The data indicated that calcium disodium EDTA was poorly absorbed from the gut, metabolically inert and did not bioaccumulate. A long-term feeding study in rats using doses of up to 250 mg/kg bw/day revealed no evidence of interference with minerals metabolism.

In 1993, JECFA was asked to provide an opinion on the safety of ferric sodium EDTA in supervised food fortification programmes in populations in which iron-deficiency anaemia was prevalent. After reviewing the existing data on iron and EDTA JECFA concluded that ferric sodium EDTA was unlikely to represent a safety problem when used in supervised food fortification programmes in iron-deficient populations. However, JECFA noted the absence of appropriate studies to determine iron deposition and metabolic fate of ferric sodium EDTA following repeat dosing.

In 1999, JECFA reviewed the results of new studies, including a short-term toxicity study in rats designed to investigate iron deposition and metabolism of ferric sodium EDTA.

JECFA re-affirmed that ‘sodium iron EDTA could be considered safe for use in supervised food fortification programs, when public health officials had determined the need for iron supplementation of the diet of a population.’ These programmes were required to provide daily iron intake of approximately 0.2 mg/kg bw.

In 2007 JECFA reviewed several new studies on ferric sodium EDTA and re-affirmed that ferric sodium EDTA was suitable for use as a source of iron in food fortification provided that the total intake of iron does not exceed the provisional maximal tolerable daily intake of 0.8 mg/kg bw. The total intake of EDTA-containing compounds should not exceed the ADI of 0-2.5 mg/kg bw, equivalent to 1.9 mg/kg bw EDTA (JECFA, 2007).

### 4.3 Risk Characterisation

As there is an existing approval for calcium disodium EDTA in the Code, it is appropriate that an aggregate risk assessment be performed to consider the possibility that consumers will be simultaneously exposed to EDTA from the presence of calcium disodium EDTA and ferric sodium EDTA.

The dietary exposure model has considered the highest exposure for 2-6 year olds based on the maximum permitted levels for calcium disodium EDTA and ferric sodium EDTA, and the exposure arising from more realistic estimates of market share data and actual usage by the food industry (see Table 3).

**Table 3: Dietary Exposure Modelling (expressed as per cent of the ADI - 2.5 mg/kg bw) for 2-6 Year Old Children**

| Baseline Type | Exposure | Baseline | Scenario1[c] | Scenerio2[d] |
|---|---|---|---|---|
| Baseline | Mean | 20 | **190** | 60 |
| Maximum[a] | 90$^{th}$ Percentile | 50 | **360** | 100 |
| Baseline | Mean | 4 | 180 | **45** |
| Refined[b] | 90$^{th}$ Percentile | 10 | 350 | **80** |

a: Baseline maximum - to estimate the current exposure to EDTA from permission for all foods at the Maximum Permitted Level for calcium disodium EDTA (385) in the Code (Standard 1.3.1).

b: Baseline refined - to estimate the current exposure to EDTA from selected food groups based on uptake by the food industry of current permissions for calcium disodium EDTA (385) (excluding beverages and preparations of food additives) at the Maximum Permitted Level of use.

c: Scenario 1 – EDTA exposures assuming all the foods (excluding breakfast cereals) currently permitted to be fortified with iron as per the Code (Standards 1.3.2, 2.9.3 and 2.9.4) will be substituted with ferric sodium EDTA at its maximum claimable amount, in addition to baseline EDTA uses.

d: Scenario 2 – EDTA exposures assuming the foods (excluding breakfast cereals) currently permitted to be fortified with iron as per the Code (Scenario 1) with some market share data, in addition to baseline EDTA uses.

The exposure described in Scenario 2 with the refined baseline represents a realistic dietary exposure to EDTA compounds. In this scenario, the mean and 90$^{th}$ percentile estimated dietary exposure to EDTA compounds for all population groups is below the ADI, including the 2-6 year old group (Table 3), indicating no public health and safety concerns at this level of exposure.

However, should the food industry increase the uptake of current permissions for calcium disodium EDTA and/or increase market share of permitted ferric sodium EDTA fortified food in future, the exposure to EDTA compounds may increase towards Scenario 1 with maximum baseline exposure. It is therefore necessary to monitor the exposure to EDTA compounds periodically in future to ensure appropriate risk management measures implemented should this Application be approved.

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## Attachment 4

# Food Technology Report

### APPLICATION A570 – FERRIC SODIUM EDETATE AS A PERMITTED FORM OF IRON


**Summary**

This review assesses ferric sodium edetate (ferric sodium EDTA) as an alternative source for iron fortification of food from a food technology point of view. The effects of adding ferric sodium EDTA as a fortificant for different food types needs to be assessed before it is used since the effects can be highly variable and not readily predictable.

The advantages of using ferric sodium EDTA as a food fortificant are that it has excellent stability during food processing so the iron does not catalyse the oxidation of food components which leads to undesirable odours, flavours and colours, which can occur with other forms of iron fortificants. The main disadvantage of using ferric sodium EDTA is that it is reportedly more expensive than other iron fortificants.


**Introduction**

The Application is seeking permission to use ferric sodium EDTA as a permitted form of iron in the Code, to allow for the substance to be used to fortify food where permissions exist for iron fortification.

Iron has been acknowledged as the most challenging micronutrient to add to foods because the iron compounds that have the best bioavailability[4] tend to be those that produce undesirable changes to the sensory properties of the food vehicle, such as the taste, colour or texture of the food. Iron in certain foods can cause rancidity and off flavours during prolonged storage. Sensory changes are highly variable and can be unpredictable also. It is not true to say that a form of iron will be equally suitable in a particular food vehicle under all situations. The cost of available iron compounds is also variable (WHO FAO, 2006).

**The Chemistry of Ferric Sodium EDTA**

The Applicant refers to the chemical as ferric sodium edetate, while its food additive name used by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in its specification is sodium iron (III) ethylenediaminetetraacetate, trihydrate. Alternative names are ferric sodium edetate, sodium iron EDTA and sodium feredetate. In this report it is abbreviated to ferric sodium EDTA.

The molecular structure of the compound is:

$C_{10}H_{12}FeN_2NaO_8.3H_2O$.

The molecular weight of the trihydrate is 421.09.

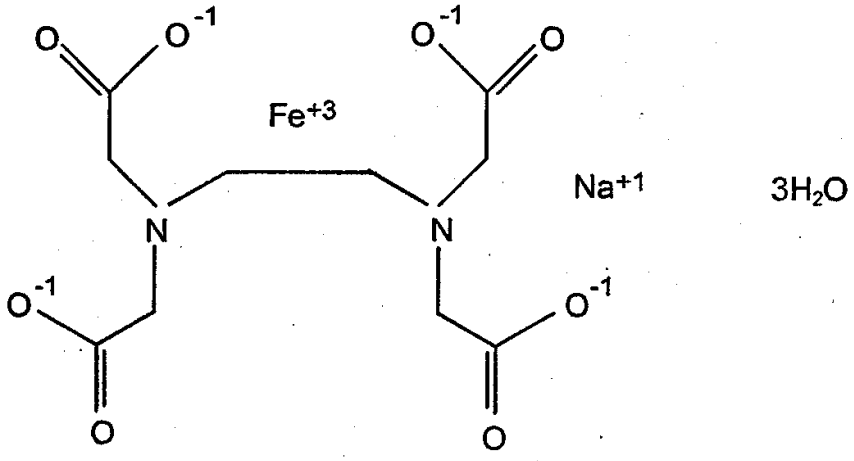
[4] Bioavailability is the proportion of the ingested nutrient absorbed and utilised through normal metabolic pathways (Hurrell, 2002). It is influenced by dietary factors and host related factors (Gibson, 2007).

The Chemical Abstracts System number (CAS number) is: 15708-41-5

Ethylenediaminetetraacetic acid (EDTA) is a chelating ligand which is able to bind to most metal ions. Calcium disodium EDTA (INS 385) is approved as a food additive in Schedule 1 of Standard 1.3.1. Calcium disodium EDTA has the technical function of an antioxidant, preservative and sequestrant.

In the case of the ferric (Fe(III)) ion it is strongly bound to three carboxyl oxygens and the two nitrogen atoms of the diamine bridge producing a quite stable bond. The sodium ion coordinates with the other carboxyl oxygen ion. A representation of the structure (copied from the Application) is provided below.

JECFA prepared a specification for ferric sodium EDTA in 1999 (JECFA 1999). It is published in their consolidated specifications, which is a primary source for specifications in Standard 1.3.4, in subclause 2(a) of the Standard. Therefore, if the substance is approved as a permitted form of iron in the Code then a separate specification will not be required to be written.




**Technological Advantages and Disadvantages of Ferric Sodium EDTA use in Food**

The Application is proposing permission for the use of ferric sodium EDTA as it has a number of claimed advantages over some other permitted forms of iron used for food fortification. The technological advantages and disadvantages of using ferric sodium EDTA in food are summarised below.

*Advantages*

It is claimed to have excellent stability when added to food under food processing and storage conditions. This is since the iron is strongly bound within the EDTA chelate molecule. The stability constant of the ferric EDTA complex is greater than the other metals of biological significance indicating the strength of the bond. The iron is strongly bound to EDTA so it is not available to catalyse the oxidation of fats and oils in food which produce undesirable flavours, odours and colours, which occurs for some other less inert forms of iron.

The substance is slowly soluble in water and is virtually tasteless and odourless.

*Disadvantages*

It is reportedly more expensive than more commonly used iron fortificants, being around 6-8 times more expensive than ferrous sulphate (WHO FAO, 2006).

**Food Vehicle Use**

The following section summarises food technology information found in the literature relating to using the substance as a fortificant in various food types.

The World Health Organization indicates that it is important to assess the effects of the added iron fortificant on each food type prior to use because the effects on different foods can be highly variable and not readily predictable (WHO FAO, 2006).

A lot of the following information on the different food vehicle use with ferric sodium EDTA has been taken from Bothwell and MacPhail (2004). Information was also drawn from an earlier review by Heimbach *et al* (2000).

*Cereals*

There have been positive reports about the use of the substance to fortify cereals and cereal based products. It has been noted that ferric sodium EDTA does not provoke fat oxidation reactions in wheat flour. Rancid oxidised by-products of the reaction of fat oxidation leads to unacceptable odour and flavour problems (which is a noted problem for other iron fortificants).

Wheat flour stored at 37°C for six months was found to be acceptable, having little fat oxidation problems. One report did note concerns with dough viscosity and the specific volume of bread produced using ferric sodium EDTA fortified flour. Breakfast cereals were also fortified with the compound in Latin America for a short period. FSANZ has been unable to determine the reason for withdrawal of these breakfast cereal products from the market. The compound has been recommended as a fortificant for nixtamalised (where the corn kernel is soaked and cooked in alkaline solution to remove the clear pericarb outer hull before the kernel is crushed to improve the extraction) corn flour. Nixtamalisation is a process used in preparing corn for tortillas, tacos and corn chips. Maize meal and flour has been successfully fortified in Kenya to produce uji, a type of porridge product (Andang'o *et al*., 2007). However, South African research indicated colour and taste differences occurred when fortified maize meal and wheat flour was used to cook products (porridge and bread).

*Sugar*

Ferric sodium EDTA causes slight colour changes when added to sugar. When fortified sugar is then added to both tea and coffee darkening occurs, presumably due to the formation of complexes with tannins.

*Salt*

Salt has not been fortified with ferric sodium EDTA, but it is suggested in the literature that colour changes may be expected.

*Milk*

Fortification of milk has not been extensively investigated, however as above for the case of sugar, it is expected that colour changes will occur when fortified milk is added to tea, coffee or cocoa. Some other products in this category have shown colour issues; these are chocolate milk powder, infant cereals containing banana and other fruits, cornstarch puddings and gruels.

*Condiments*

As for cereals and cereal based products the fortification of condiments with ferric sodium EDTA has been investigated with positive results. Fortification trials have been successful using fish sauce, soy sauce and curry powder. There have not been any unacceptable organoleptic (odour, taste and colour) problems. However some technical issues have been noted.

Ferric sodium EDTA is stable to heating up to 100°C, however processing at higher temperatures can cause problems. Losses have been noted due to exposure of fortified fish sauce (but not the darker soy sauce) to sunlight. Storage in dark bottles could be a solution to this problem.

**References**

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WHO FAO (2006) *Guidelines on food fortification with micronutrients*. In: Allen, L., de Benoist, B., Dary, O., and Hurrell, R. eds.

## Attachment 5

# Dietary Exposure Assessment Report

### APPLICATION A570 – FERRIC SODIUM EDETATE AS A PERMITTED FORM OF IRON

### EXECUTIVE SUMMARY

The Applicant has requested the permission to add ferric sodium edetate (ferric sodium EDTA) in foods up to the maximum claimable amount where fortification or addition of iron is currently permitted in the Code. The Applicant provided FSANZ with information on proposed levels of use for ferric sodium EDTA. Food consumption data from the 1995 Australian and 1997 New Zealand National Nutrition Surveys were used for the dietary exposure assessments. The population groups assessed were the Australian population (2 years and above), the New Zealand population (15 years and above) and children (2-6 years) for Australia only.

Since ferric sodium EDTA was proposed to replace iron sources currently permitted, iron intakes were not investigated, as the replacement posed no additional public health and safety concern. However, a dietary exposure assessment was deemed necessary to estimate the potential dietary exposure to the 'EDTA[5]' component and the impact of allowing the use of the ferric sodium EDTA in the food supply on public health and safety.

JECFA (1974) evaluated the safety of calcium disodium EDTA and disodium EDTA as food additives and established an ADI of 2.5 mg calcium disodium EDTA /kg bw/day. JECFA (2007) reconfirmed that the total intake of EDTA compounds, including calcium disodium EDTA, disodium EDTA and ferric sodium EDTA, should not exceed the ADI of 0-2.5 mg/kg bw/day, equivalent to up to 1.9 mg/kg bw/day EDTA.

The dietary exposure assessments were undertaken based on the maximum permitted levels (MPLs) of calcium disodium EDTA and proposed use of ferric sodium EDTA. For the purpose of assessing this Application, dietary exposures were calculated in two ways:

- **'Maximum' assessment** (based on *all foods permitted* to add calcium disodium EDTA, assuming MPLs in the Code plus use of ferric sodium EDTA); and
- **'Refined' assessment** (based on *current market use* of calcium disodium EDTA in foods assuming MPLs in the Code plus use of ferric sodium EDTA)

For each of these assessments, three scenarios were considered:

- *Baseline Scenario* (where the contributions to EDTA exposures were only from calcium disodium EDTA)
- *Scenario 1 – replacement* (i.e. all iron in foods permitted to be fortified with iron replaced with ferric sodium EDTA in addition to baseline EDTA exposures from calcium disodium EDTA)

[5] EDTA refers to dietary exposures from both the EDTA component of calcium disodium EDTA and ferric sodium EDTA.

- *Scenario 2 – market share* (i.e. all iron in iron fortified foods replaced with ferric sodium EDTA but based on current market uptake for iron fortified foods in addition to baseline EDTA exposures from calcium disodium EDTA)

Among the population groups assessed, Australian children aged 2-6 years had the highest dietary exposures to EDTA on a body weight basis. Estimated mean and the 90$^{th}$ percentile exposures for the Australian children aged 2-6 years were above the ADI for the *replacement* scenarios and were below the ADI for all the other scenarios. Similarly, estimated mean and the 90$^{th}$ percentile exposures for the Australian population aged 2 years and above were below the ADI for all the scenarios except for the 90$^{th}$ percentile exposure for the *replacement* scenarios. Estimated mean and the 90$^{th}$ percentile exposures for all scenarios were below the ADI for New Zealand population aged 15 years and above.

The major contributors to total EDTA dietary exposure for the *baseline* scenarios for the *maximum* assessments for all the population groups assessed were beverages, sauces and toppings and fully preserved fish. The *refined* assessment excluded beverages from the assessment based on the current market use of calcium disodium EDTA; therefore the major contributors were sauces and toppings and fully preserved fish.

The major contributors to total EDTA dietary exposure were plain breads, followed by fruit and vegetable juices for the *replacement (scenario 1)* and beverages for the *market share (scenario 2)* scenario for both the maximum and refined assessments. An exception was for children aged 2-6 years in Australia where the major contributors for the *maximum market share* scenario were beverages (29%), followed by bread (25%).

## 1. Background

This Application seeks to have ferric sodium EDTA as a permitted form of iron fortificant; i.e. ferric sodium EDTA may replace other permitted forms of iron at levels currently permitted in the Code.

Since ferric sodium EDTA was proposed to replace iron sources currently permitted, iron intakes were not investigated, as the replacement posed no additional public health and safety concern. However, a dietary exposure assessment was deemed necessary to estimate the potential dietary exposure to the 'EDTA[1]' component and the impact of allowing the use of the ferric sodium EDTA in the food supply on public health and safety.

### 1.1 Proposed use of ferric sodium EDTA

The Applicant has provided the proposed use of ferric sodium EDTA in foods (as shown in Table 1)

**Table 1: Proposed uses of ferric sodium EDTA in foods, as provided by the Applicant**

| Food Name | Concentration Level (units) |
|---|---|
| Include foods listed in<br>Standard 1.3.2 – Vitamins and Minerals except breakfast cereals,<br><br>Standard 2.9.3 – Formulated meal replacements and formulated supplementary foods, except FSFYC aged 1-3 years; and<br><br>Standard 2.9.4- Formulated supplementary sports foods. | 90.484 mg Ferric sodium EDTA is equivalent to 12 mg Iron<br>Maximum amount of iron that can be claimed for the particular food. |

The Applicant has withdrawn the request to fortify breakfast cereals and formulated supplementary foods for young children aged one to three years from the Application. This amendment follows advice from FSANZ that estimated dietary exposure to EDTA[1] by young children would too easily exceed the Acceptable Daily Intake (ADI) of 2.5 mg/kg bw/day (JECFA, 2007), if the request to permit use of ferric sodium EDTA in all foods where fortification or addition of iron is currently permitted in the Code were to be approved.

### 1.2 Current permissions in the Code for EDTA

The chelating agent EDTA is permitted to be used in certain foods in Australia and New Zealand. The current permissions under Standard 1.3.1 of the Code for the additive allow EDTA from calcium disodium EDTA (385) as a colour retention agent or flavouring agent as a food additive. The potential use of calcium disodium EDTA was recently expanded by permission to use the additive in formulated beverages, with an amendment to the Code gazetted in November 2006. Permitted uses of calcium disodium EDTA in the Code are as shown in Table 2.

**Table 2: Permitted uses of calcium disodium EDTA in the Code**

| Food Code | Food Name | mg of calcium disodium EDTA /kg |
|---|---|---|
| | | Baseline |
| 0.1 | Preparation of food additives | 500 |
| 9.4 | Fully preserved fish including canned fish product | 250 |
| 14.1.2.2 | Fruit drinks (carbonated products only) | 33 |
| 14.1.3 | Water based flavoured drinks (products containing fruit flavouring, juice or pulp or orange peel extract only) | 33 |
| 14.1.4 | Formulated beverages (products containing fruit flavouring, juice or pulp or orange peel extract only) | 33 |
| 20.2 | Sauces and toppings (including mayonnaises and salad dressings) | 75 |

### 1.3 Current permissions in the Code for Iron fortification

There are currently 16 permitted forms of iron listed in the Schedule to Standard 1.1.1 and ferric sodium EDTA is not currently listed as a permitted form. The Code provided the maximum claimable amount of iron permitted per reference quantity (proportion of Recommended Dietary Intake) as shown in Table 3.

The Applicant has not requested permission for use of ferric sodium EDTA in infant formula or foods for infants. These foods are regulated by Standards 2.9.1 and 2.9.2 respectively, which contain their own separate lists of iron forms permitted for addition.

**Table 3: Addition of iron currently permitted in the Code considered for this Application[♣]**

| Foods | Reference Quantity | Maximum Claim Per Reference Quantity (proportion RDI) |
|---|---|---|
| **Standard 1.3.2 – Vitamins and Minerals** | | |
| **Cereals and cereal products** | | |
| Biscuits containing not more than 200 g/kg fat and not more than 50 g/kg sugars | 35 g | 3.0 mg (25%) |
| Bread | 50 g | 3.0 mg (25%) |
| Cereal flours | 35 g | 3.0 mg (25%) |
| Pasta | That quantity which is equivalent to 35 g of uncooked dried pasta | 3.0 mg (25%) |
| Extracts of meat, vegetables or yeast (including modified yeast) and foods containing no less than 800 g/kg of extracts of meat, vegetables or yeast (including modified yeast) | 5 g | 1.8 mg (15%) |
| Analogues of meat, where no less than 12% of the energy value of the food is derived from protein, and the food contains 5 g protein per serve of the food | 100 g | 3.5 mg (30%) |
| Formulated Beverages | 600 mL | 3.0 mg (25%) |
| **Standard 2.9.3– Formulated meal replacements and formulated supplementary foods** | | |
| Formulated meal replacements | Per serve | 4.8 mg (40%) |
| Formulated supplementary foods | Per serve | 6 mg (50%) |
| **Standard 2.9.4 – Formulated Supplementary Sports Foods** | | |
| Formulated supplementary sports foods | Per one day | 12 mg/day |

[♣] The Applicant has withdrawn breakfast cereals and formulated supplementary foods for young children (FSFYC) aged one to three years from the Application.

## 2. Dietary Exposure Assessments

### 2.1 What is dietary modelling?

Dietary modelling is a tool used to estimate exposures to food chemicals from the diet as part of the risk assessment process. To estimate dietary exposure to food chemicals records of what foods people have eaten are required and information on how much of the food chemical is in each food. The accuracy of these exposure estimates depend on the quality of the data used in the dietary exposure assessments. Sometimes not all of the data required are available or there is uncertainty about the accuracy so assumptions are made, either about the foods eaten or about chemical levels, based on previous knowledge and experience. The models are generally set up according to international conventions for food chemical exposure estimates, however, each modelling process requires decisions to be made about how to set the model up and what assumptions to make; a different decision may result in a different answer.

Therefore, FSANZ documents clearly all such decisions and model assumptions to enable the results to be understood in the context of the data available and so that risk managers can make informed decisions.

### 2.2 Population groups assessed

The dietary exposure assessment was conducted for the Australian population aged 2 years and above, the New Zealand population aged 15 years and above and Australian children aged 2-6 years. An exposure assessment was conducted on children aged 2-6 years because children generally have higher dietary exposures per kilogram body weight due to their smaller body weight and the fact that they consume more food per kilogram of body weight compared to adults. They also consume many foods proposed to contain ferric sodium EDTA, such as processed cereal and meal products, breads, biscuits and fruit and vegetable juice products. It is important to note that, while children aged 2-6 years have been assessed as a separate group, this group has also been included in the dietary exposure assessment for Australians two years and above.

### 2.3 Dietary Modelling Approach for consideration of EDTA

The dietary exposure assessment was conducted using dietary modelling techniques that combine food consumption data with food chemical concentration data to estimate the exposure to the food chemical from the diet. The dietary exposure assessment was conducted using FSANZ's dietary modelling computer program, DIAMOND.

Dietary exposure = food chemical concentration x food consumption

The dietary exposure to EDTA was estimated by combining usual patterns of food consumption, as derived from national nutrition survey (NNS) data, with current concentrations of EDTA in food, in addition to the proposed levels of ferric sodium EDTA in foods. This Application proposes ferric sodium EDTA to be added to the food supply. Dietary exposure for the 'EDTA' refers to exposures from both calcium disodium EDTA and ferric sodium EDTA. Both compounds had similar molecular weights.

The dietary modelling approach used for the exposure assessment of EDTA for Australian and New Zealand population is as shown in Figure 1.

In the Code, fruit and vegetable juices are not permitted to have added iron but in the current market there are iron fortified fruit juices that are labelled as formulated supplementary drinks. The Applicant claims ferric sodium EDTA can overcome many of the common food technology problems for fruit juices associated with the forms of iron currently listed in Standard 1.1.1. These problems include rancidity and off colours, and undesirable reactions with other nutrients (such as ascorbic acid) that can degrade important food components. Based on this information and the claimed benefits for ferric sodium EDTA, consumption of fruit and vegetable juices was included for modelling purposes. For the market share scenario it was assumed iron fortified fruit and vegetable juices had a 10% market share.

Formulated beverages (FBs) were not reported as consumed when the dietary surveys were conducted in 1995 (Australia) and 1997 (NZ).

For the purpose of this Application, it was assumed that FB consumption substituted for consumption of other like-beverages (such as soft drink, bottled water, cordial etc), assuming a 5% market share, based on up to date information obtained for another recent application (A470 - Formulated beverages). For example, a reported consumption of 300 mL cordial was assumed to be 95% of cordial with the EDTA concentration of cordial and 5% of FBs to which the concentration of EDTA permitted was assigned.

Dietary exposure assessments of EDTA were compared with the ADI of 2.5 mg/kg bw/day (JECFA 2007) for all calcium and ferric compounds containing EDTA, equivalent to the ADI of 1.9 mg/kg/bw/day for the EDTA component.

### 2.4 Dietary survey data

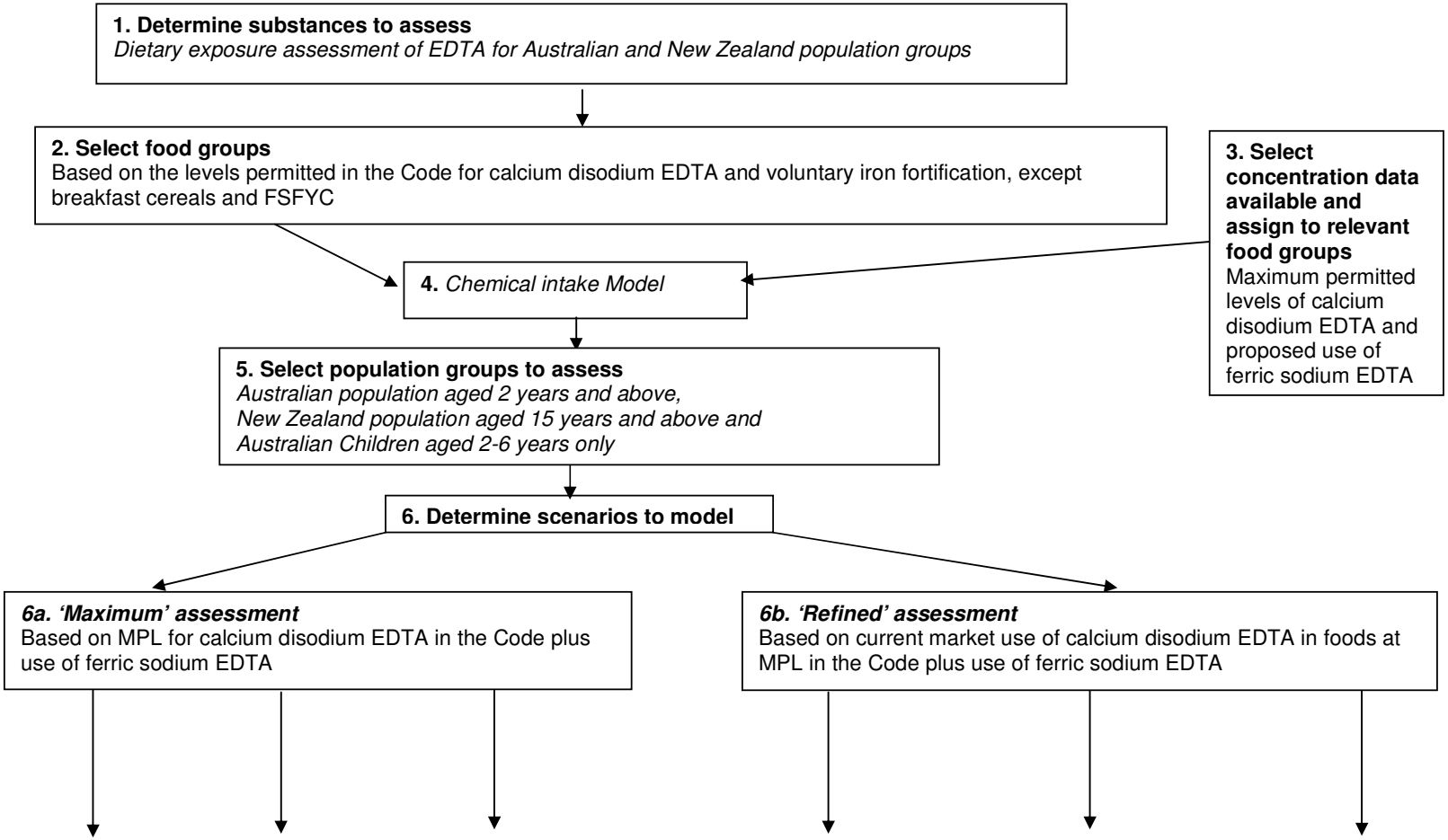
DIAMOND contains dietary survey data for both Australia and New Zealand; the 1995 NNS from Australia that surveyed 13 858 people aged 2 years and above, and the 1997 New Zealand NNS that surveyed 4 636 people aged 15 years and above. Both of the NNSs used a 24-hour food recall methodology.

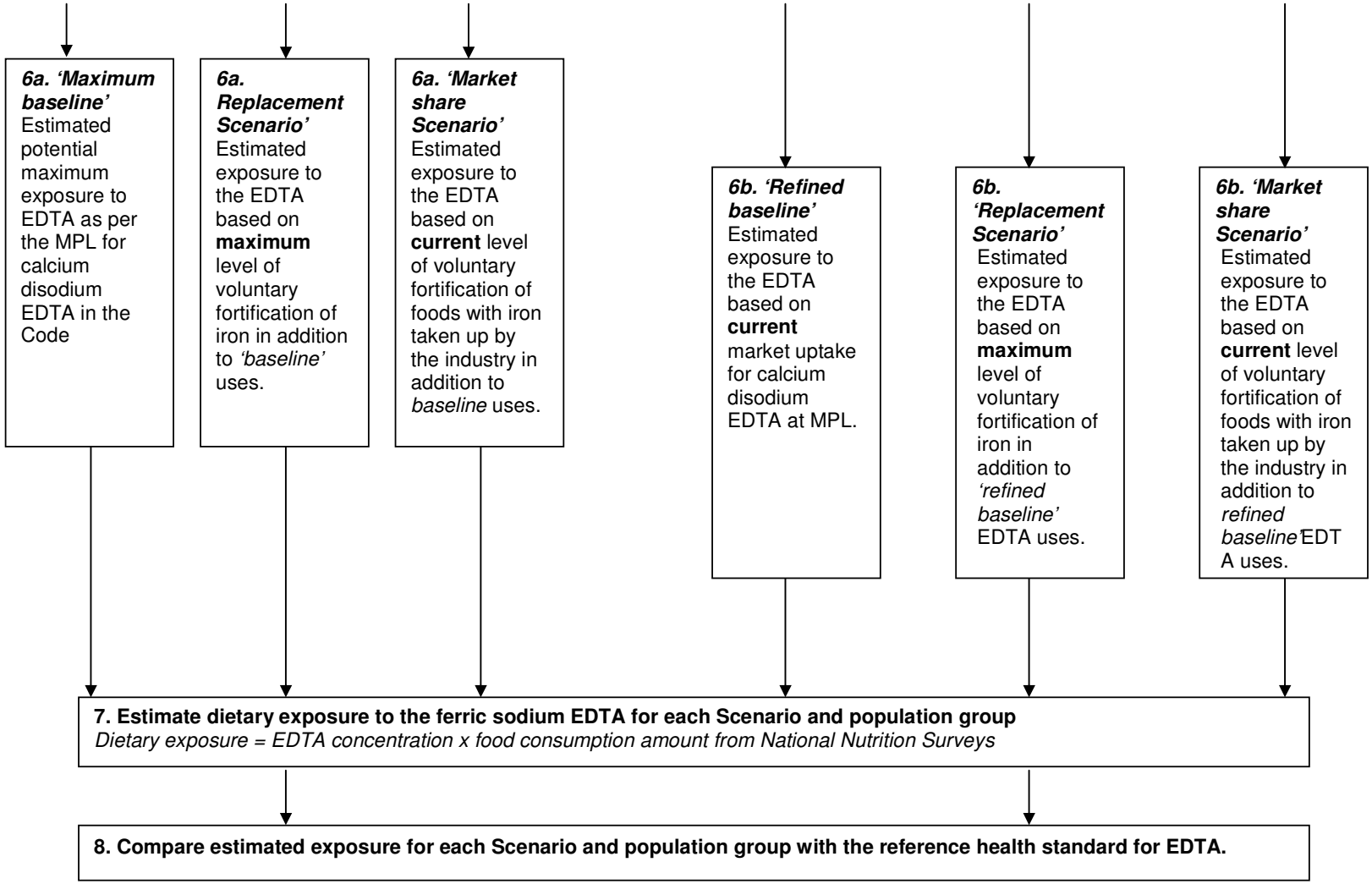
It is recognised that these survey data have several limitations. For a complete list of limitations see the Section 7 Limitations of the dietary modelling.

### 2.5 Additional food consumption data or other relevant data

No further information was required or identified for the purpose of refining the dietary exposure estimates for this Application.

*Figure 1: Dietary modelling approach used for the Ferric sodium EDTA for the Australian and New Zealand population groups*




6a. 'Maximum baseline' Estimated potential maximum exposure to EDTA as per the MPL for calcium disodium EDTA in the Code
6a. Replacement Scenario' Estimated exposure to the EDTA based on maximum level of voluntary fortification of iron in addition to 'baseline' uses.
6a. 'Market share Scenario' Estimated exposure to the EDTA based on current level of voluntary fortification of foods with iron taken up by the industry in addition to baseline uses.
6b. 'Refined baseline' Estimated exposure to the EDTA based on current market uptake for calcium disodium EDTA at MPL.
6b. 'Replacement Scenario' Estimated exposure to the EDTA based on maximum level of voluntary fortification of iron in addition to 'refined baseline' EDTA uses.
6b. 'Market share Scenario' Estimated exposure to the EDTA based on current level of voluntary fortification of foods with iron taken up by the industry in addition to refined baseline EDTA uses.
7. Estimate dietary exposure to the ferric sodium EDTA for each Scenario and population group
Dietary exposure = EDTA concentration x food consumption amount from National Nutrition Surveys
8. Compare estimated exposure for each Scenario and population group with the reference health standard for EDTA.

## 3 Ferric sodium EDTA concentration levels

The levels of ferric sodium EDTA in foods that were used in the dietary exposure assessment were derived from the Application. The Application states that, 90.484 mg ferric sodium EDTA is equivalent to 12 mg iron, the Recommended Dietary Intake for iron as specified in the Code for labelling purposes. The Code provided the maximum claimable amount of iron permitted per reference quantity (proportion of Recommended Dietary Intake) as shown in Table 3. Concentration levels were assigned to food groups based on the claimable amount. An example of the calculations for ferric sodium EDTA concentration for the purpose of estimating the exposure assessment is as explained in Figure 2. The foods and proposed levels of use for ferric sodium EDTA are shown in Table 5.

**As per the permissions in the Code:**

| | |
|---|---|
| maximum claim per reference quantity for bread | **= 3.0 mg (25%)/ 50g** |
| i.e. mg of ferric sodium EDTA per reference quantity | = (90.484 mg ferric sodium EDTA x 0.25) per 50 g serve<br>= 22.6 x (1000/50) mg/kg<br>= 452 mg/kg |

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| | |
|---|---|
| Market share values were assigned for some foods based on current Market uptake for fortified foods | |
| i.e. if 20% of breads are currently fortified with one or more nutrients | =452 mg/kg x 0.20<br>=90 mg/kg |

*Figure 2: Ferric sodium EDTA concentration for the purpose of estimating the exposure assessment*

Concentrations of ferric sodium EDTA were assigned to food groups using DIAMOND food classification codes. These codes are based on the Australian New Zealand Food Classification System (ANZFCS) used in Standard 1.3.1 (for example 6.4.2 represents Pasta). The foods proposed to contain ferric sodium EDTA (as shown in Table 3) were matched to the most appropriate ANZFSC code(s) for dietary modelling purposes.

Reference quantities provided in the Code were used as the serve sizes for the related food groups. Where the reference quantities were not provided in the Code label information was used to derive the serve sizes.

In the Code, the maximum claim per reference quantity to fortify pasta is for uncooked dried pasta. Dehydration factors were applied to the proposed concentration levels for pasta reported consumed as cooked in the dietary modelling to represent the levels of EDTA that would be present in the food as a dry ingredient.

**Table 1: Permitted levels of calcium disodium EDTA in foods used in the dietary exposure assessment for estimating the *baseline* concentrations**

| Food Code | Food Name | mg of calcium disodium EDTA /kg | |
|---|---|---|---|
| | | Maximum baseline | Refined baseline |
| 0.1 | Preparation of food additives | 500 | 500 |
| 9.4 | Fully preserved fish including canned fish product | 250 | 250 |
| 14.1.2.2 | Fruit drinks (carbonated products only) | 33 | 0 |
| 14.1.3 | Water based flavoured drinks (products containing fruit flavouring, juice or pulp or orange peel extract only) | 33 | 0 |
| 14.1.4 | Formulated beverages (products containing fruit flavouring, juice or pulp or orange peel extract only) | 33 | 0 |
| 20.2 | Sauces and toppings (including mayonnaises and salad dressings) | 75 | 75 |

**Table 2: Proposed use of ferric sodium EDTA in foods and levels of use used in the dietary exposure assessment**

| Food Code | Food Name | mg of ferric sodium EDTA /kg | |
|---|---|---|---|
| | | Replacement | Market share |
| 4.3.8 | Fruit and vegetable based products | 271 | * |
| 6.2 | Cereal Flours | 646 | * |
| 6.4.2 | Pasta | 215♦ | 5.3[1] |
| 7.1.1 | Plain bread | 452 | 90[2] |
| 7.1.2 | Fancy breads | 452 | 90[2] |
| 7.2.1.1 | Biscuits, savoury | 646 | * |
| 12.5.2 | Yeast extract spreads and beef extract | 2715 | 135.8[3] |
| 12.6 | Vegetable protein products | 271 | * |
| 13.3.1 | Solid formulated meal replacements and | 603 | * |
| 13.3.2 | liquid formulated meal replacements | 145 | * |
| 13.3.4 | liquid formulated supplementary foods | 259 | * |
| 13.4 | Formulated supplementary sports foods | 393 | * |
| 14.1.0.1 | Formulated beverages | 1.9 | * |
| 14.1.2.1 | Fruit and vegetable juices | 259 | 25.9[4] |
| 20.1.1.7 | Beverage flavouring, dry, fortified | 259 | 164[5] |

[*] Proposed levels of ferric sodium EDTA remain same for both the scenarios

♦ Dehydration factors were applied where consumption of cooked pasta was reported

[1] 2.5% market share

[2] 20% market share

[3] 5% market share

[4] 10% market share

[5] Serve size assumed to be 275 mL/serve in the market share scenarios to reflect the fact the brand with 85% market recommends this serve size; the minimum serve size recommended on labels of fortified dry beverages of 175 mL/serve was used for the replacement scenario (conservative approach since this results in a higher EDTA concentration per 100 mL)

## 4 Scenarios for dietary exposure assessment

For the purpose of assessing this Application, dietary exposures were calculated in two ways:

- **'Maximum' assessment** (based on MPL for calcium disodium EDTA in the Code plus use of ferric sodium EDTA); and
- **'Refined' assessment** (based on current market use of calcium disodium EDTA in foods and MPL in the Code plus use of ferric sodium EDTA).

For each of these assessments, another three scenarios were assessed and they were:

- *Baseline* Scenario
- *Scenario 1 – replacement* Scenario
- *Scenario 2 – market share* Scenario

The scenarios used for the dietary exposure assessment of EDTA for Australian and New Zealand population are as shown in.

### 4.1 'Maximum' assessments

#### 4.1.1 'Maximum Baseline' Scenario

*Maximum baseline* scenario estimates the exposure to EDTA from permissions for all foods at the Maximum Permitted Level for calcium disodium EDTA (385) in the Code (Standard 1.3.1) (see Table 4).

#### 4.1.2 *Scenario 1 – Replacement* Scenario

This scenario deems a situation where for all the foods currently permitted to be voluntarily fortified with iron as per to the Code (except breakfast cereals and FSFYC), replace with ferric sodium EDTA as the fortificant at its maximum claimable amount (worst case scenario). Based on this assumption the concentrations of ferric sodium EDTA were assigned to food groups up to the levels that would provide maximum claimable amount of iron per reference quantity (see Table 5).

#### 4.1.3 *Scenario 2 – Market share* Scenario

Realistically 100% the foods in the market would not be iron fortified foods. The market uptakes for iron fortified foods were analysed and market share values were used for some food groups in conjunction with the specified concentrations assigned in *maximum replacement* scenario.

Based on these dietary exposures to ferric sodium EDTA is estimated for *maximum market share scenario (Scenario two)*. The foods and proposed levels of use for ferric sodium EDTA are shown in Table 2.

### 4.2 'Refined' assessments

#### 4.2.1 *Refined Baseline* Scenario

*Refined baseline* scenario estimates the current exposure to EDTA from selected food groups, as per the maximum permitted levels (MPL) for calcium disodium EDTA in the Code except beverages and preparations of food additives Table 4.

These food groups were excluded based on evidence from the FSANZ label database (Food Standards Australia New Zealand, 2007) that the calcium disodium EDTA permissions for sauces and toppings and the fully preserved fish including canned fish products has been taken up by the industry but it was not being added to beverages and preparations of food additives.

### 4.2.2 S *Scenario 1 – Replacement* Scenario

Same as per the *replacement scenario* in the 'maximum' assessment (2.7.1.2), except using the *refined baseline*.

### 4.2.3 *Scenario 2 – Market share* Scenario

As per the 'market share maximum' scenario in the maximum assessment (2.7.1.3), except using the *refined baseline*.

## 5. Assumptions used in the dietary modelling

The aim of the dietary exposure assessment was to make as realistic an estimate of dietary exposure as possible. However, where significant uncertainties in the data existed, conservative assumptions were generally used to ensure that the dietary exposure assessment did not underestimate exposure.

The assumptions made in the dietary modelling are listed below, broken down into several categories.

***Concentration data***

- Where a permission is given to a food classification code, all foods in that group contain EDTA;
- all the foods within the group contain EDTA at the levels specified in Table 4 and Table 5. Unless otherwise specified, the maximum concentration of EDTA in each food category has been used;
- where a food or food group has a zero concentration of EDTA, it was not included in the intake assessment;
- where a food was not included in the exposure assessment, it was assumed to contain a zero concentration of EDTA;
- where a food has a specified EDTA concentration, this concentration is carried over to mixed foods where the food has been used as an ingredient e.g. biscuits used in cheese cakes; and
- all mixed foods with recipes in DIAMOND were assumed to be prepared in the home (and not produced commercially). Therefore, if a recipe uses an ingredient that is permitted to contain EDTA, the quantities of EDTA from the ingredient will carry-over into the mixed food. It was assumed that carry-over from cereal flours would not occur to breads or biscuits.

*Consumption data*

- consumption of foods as recorded in the NNS represent current food consumption patterns; and

- Australian children 2-6 years are representative of New Zealand children of the same age in terms of food consumption and dietary exposure to EDTA;

*Consumer behaviour*

- consumers always select products containing calcium disodium EDTA or ferric sodium EDTA;
- consumers do not alter their food consumption habits to substitute non EDTA containing products with EDTA containing products; and
- consumers do not increase their consumption of foods upon foods containing ferric sodium EDTA becoming available.

*General*

- market share for the use of ferric sodium EDTA were assumed for different foods based on current market uptake for iron fortification;
- there are no reductions in EDTA concentrations from food preparation or due to cooking;
- for the purpose of this assessment, it is assumed that 1 mL is equal to 1 g for all liquid and semi-liquid foods (e.g. milk, yoghurt); and
- foods voluntarily fortified with iron use ferric sodium EDTA as the fortificant and uses at its maximum claimable amount.

These assumptions are likely to lead to a conservative estimate for EDTA dietary exposure.

## 6. Results

### 6.1 Estimated dietary exposures to EDTA

The estimated mean and the 90$^{th}$ percentile dietary exposures to EDTA for *maximum* assessments are as shown in Figure 3 and *refined* assessments are as shown in Figure 4 (full results for both scenarios can be found in Table 2.1 and Table 2.2 in Appendix 2).

Dietary exposures to EDTA were at their lowest for the *baseline* scenarios where the contributions to the EDTA exposures were only from calcium disodium EDTA. As expected, dietary exposures to EDTA from the *replacement* scenario and *market share* scenario were higher than the baseline estimates since exposures from both EDTA compounds were included.

The estimated dietary exposure to EDTA was higher for the *replacement* scenarios because a conservative approach was taken to estimate the exposure to EDTA, (i.e. all the foods fortified with iron will be replaced with ferric sodium EDTA on top of the EDTA exposures from calcium disodium EDTA) while a more realistic approach was taken in the *market share* scenarios..

### *6.1.1 Maximum assessments*

*Australia – 2 years and above*

The estimated mean and 90$^{th}$ percentile exposures for EDTA were 0.2 mg/kg bw/day and 0.4 mg/kg bw/day for the *baseline* scenario; 1.7 mg/kg bw/day and 3.5 mg/kg bw/day for the *replacement* scenario and 0.5 mg/kg bw/day and 1.1 mg/kg bw/day for the *market share* scenario.

*Australia – 2-6 years*

The estimated mean and 90$^{th}$ percentile exposures for EDTA were 0.5 mg/kg bw/day and 1.3 mg/kg bw/day for the *baseline* scenario; 4.8 mg/kg bw/day and 9.0 mg/kg bw/day for the *replacement* scenario and 1.4 mg/kg bw/day and 2.6 mg/kg bw/day for the *market share* scenario.

*New Zealand – 15 years and above*

The estimated mean and 90$^{th}$ percentile exposures for EDTA were 0.1 mg/kg bw/day and 0.3 mg/kg bw/day for the *baseline* scenario; 1.3 mg/kg bw/day and 2.4 mg/kg bw/day for the *replacement* scenario and 0.4 mg/kg bw/day and 0.8 mg/kg bw/day for the *market share* scenario.

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### *6.1.2 Refined assessments*

*Australia – 2 years and above*

The estimated mean and 90$^{th}$ percentile exposures for EDTA were 0.1 mg/kg bw/day and 0.2 mg/kg bw/day for the *baseline* scenario; 1.6 mg/kg bw/day and 3.3 mg/kg bw/day for the *replacement* scenario and 0.4 mg/kg bw/day and 0.9 mg/kg bw/day for the *market share* scenario.

*Australia – 2-6 years*

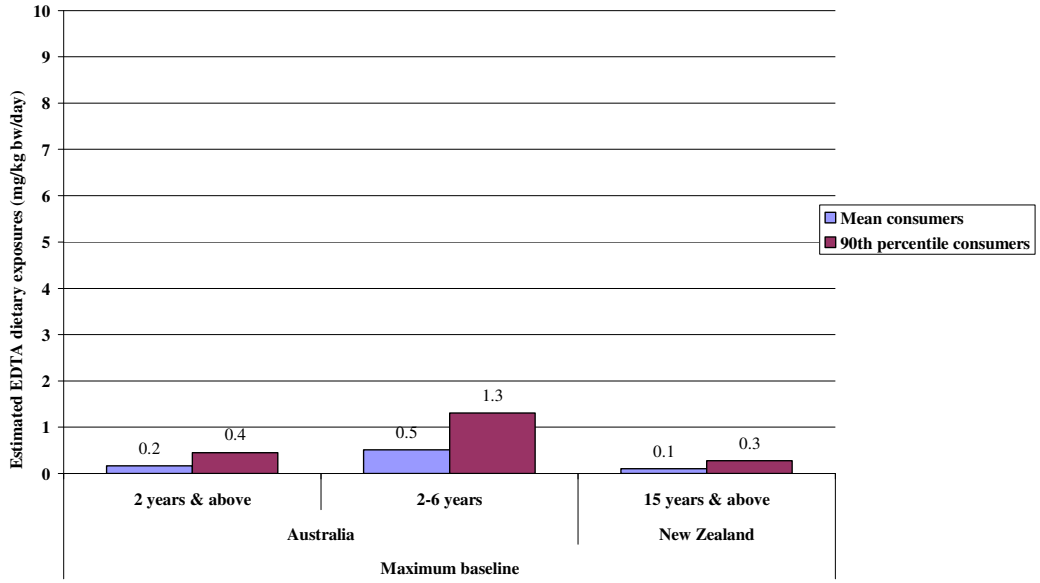
The estimated mean and 90$^{th}$ percentile exposures for EDTA were 0.1 mg/kg bw/day and 0.3 mg/kg bw/day for the *baseline* scenario; 4.5 mg/kg bw/day and 8.7 mg/kg bw/day for the *replacement* scenario and 1.1 mg/kg bw/day and 2.0 mg/kg bw/day for the *market share* scenario.

*New Zealand – 15 years and above*

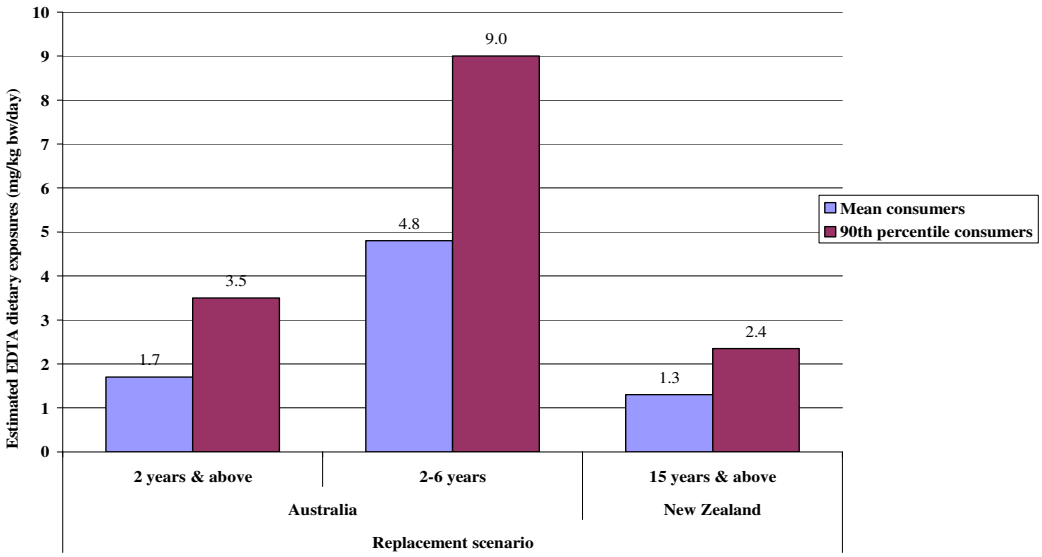
The estimated mean and 90$^{th}$ percentile exposures for EDTA were 0.1 mg/kg bw/day and 0.2 mg/kg bw/day for the *baseline* scenario; 1.2 mg/kg bw/day and 2.4 mg/kg bw/day for the *replacement* scenario and 0.4 mg/kg bw/day and 0.7 mg/kg bw/day for the *market share* scenario.

*Figure 3: Estimated mean and the 90th percentile dietary exposures to EDTA for* maximum *assessment*

a Maximum baseline




b *Scenario 1 – Replacement* scenario



c *Scenario 2 – Market share* scenario

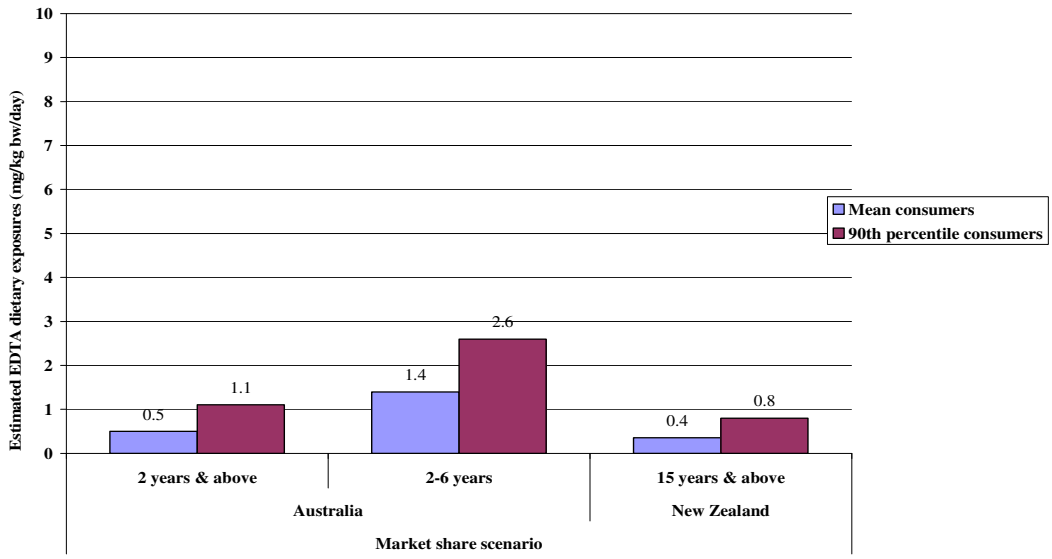
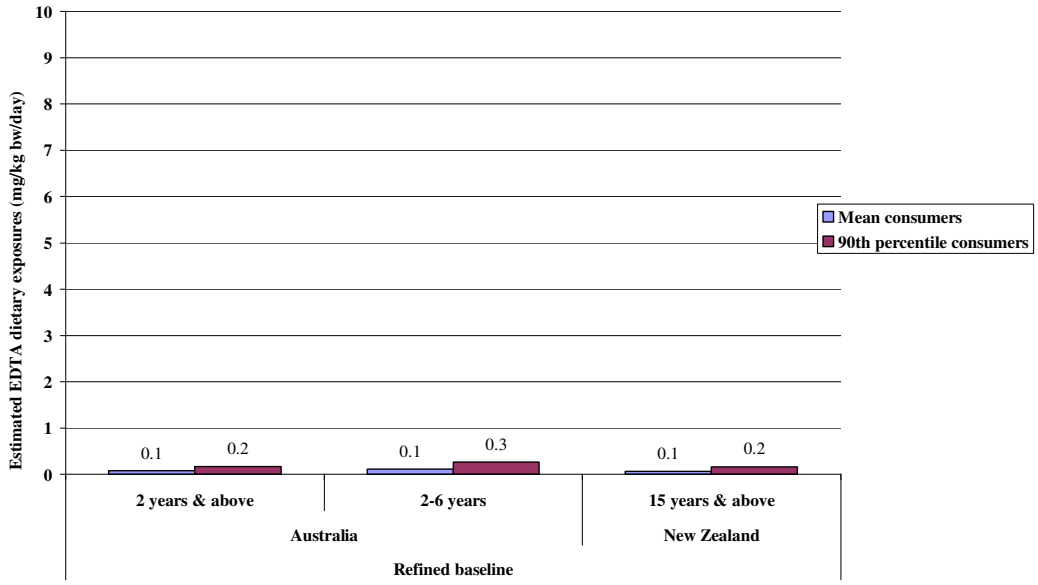
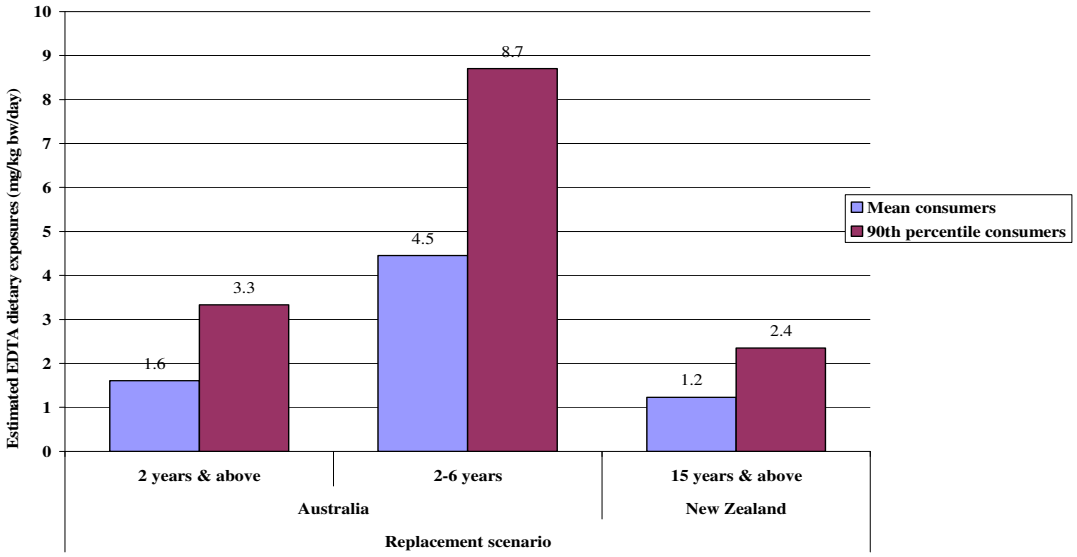



*Figure 4: Estimated mean and the 90th percentile dietary exposures to EDTA for* refined *assessment*

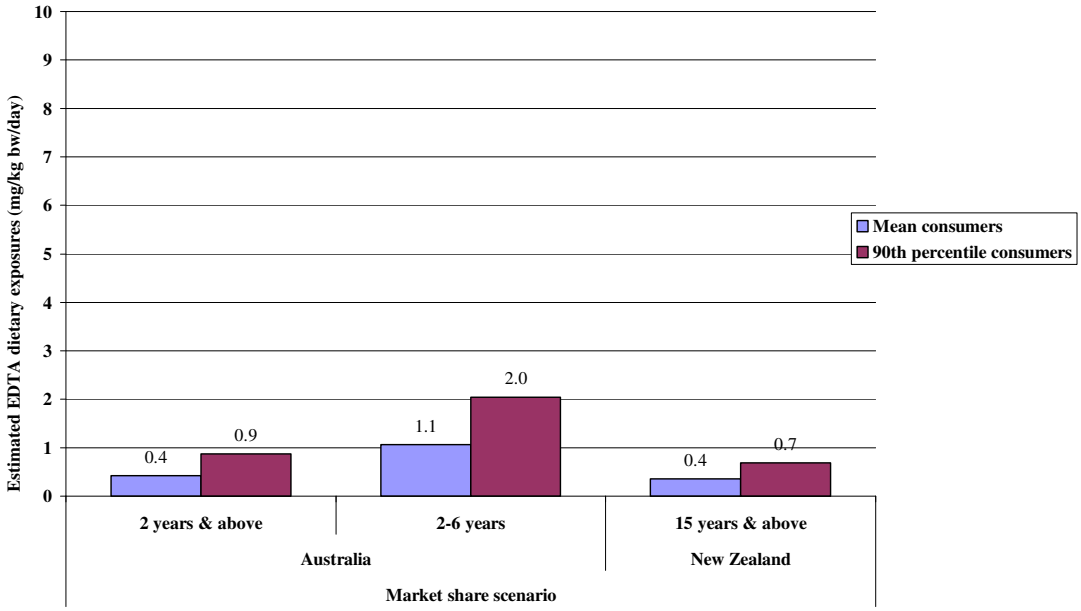
a *Refined baseline*



b *Scenario 1 – Replacement* scenario




c *Scenario 2 – Market share* scenario




## 6.2 Major contributing foods to total estimated dietary exposures to EDTA

A full list of all the food groups and their contributions to total EDTA dietary exposure can be found in Table A2.3 in Appendix 2. The major contributors (≥5%) are shown in Figure 5a for Australians aged 2 years and above, Figure 5b for Australians aged 2-6 years and Figure 5c for New Zealanders aged 15 years and above.

The highest contributors for *replacement* scenario and *market share* scenario for both the *maximum* and *refined* assessments for all the population groups assessed were from plain breads, followed by fruit and vegetable juices for the *replacement* scenario and beverages for the *market share* scenario*,* except for children 2-6 years Australia for the *maximum market share* scenario. The highest contributors for children 2-6 years for *maximum market share* scenario were beverages (29%), followed by bread (25%).

### *6.2.1 Maximum assessments*

The major contributors for the *baseline* scenarios for the maximum assessments for all the population groups assessed were beverages (47-84%), sauces and toppings (10-35%) and fully preserved fish (3-19%).

*Australia – 2 years and above*

The major contributors for *replacement scenario* were plain breads (49%), fruit and vegetable juices (20%), pasta (6%), beverages (5%) and fancy breads (5%). The major contributors for *market share* scenario were plain breads (32%), beverages (17%), flours, meals and starches (13%), Biscuits, savoury (10%), fruit and vegetable juices (7%),sauces and toppings (6%) and beverage flavourings, dry (5%).

*Australia – 2-6 years*

The major contributors for *replacement* scenario were plain breads (38%), fruit and vegetable juices (32%), beverages (9%) and pasta (5%). The major contributors for *market share* scenario were beverages (29%), plain breads (25%), Biscuits, savoury (12%), fruit and vegetable juices (11%), beverage flavourings, dry fortified (8%) and flours , meals and starches (7%).

*New Zealand – 15 years and above*

The major contributors for *replacement* scenario were plain breads (57%), fruit and vegetable juices (12%), fancy breads (5%) and flours, meals and starches (5%). The major contributors *market share* scenario were plain breads (37%), flours , meals and starches (15%),beverages (11%), beverage flavourings, dry (8%), biscuits, savoury (8%) and sauces and toppings (7%).

### *6.2.1 Refined assessments*

The refined assessment excluded beverages from the baseline scenarios based on the evidence from the FSANZ label database (Food Standards Australia New Zealand, 2007); therefore the major contributors for all the population groups assessed were sauces and toppings (63-77%) and fully preserved fish (23-37%).

*Australia – 2 years and above*

The major contributors for *replacement* scenario were plain breads (51%), fruit and vegetable juices (21%), pasta (6%) and fancy breads (5%). The major contributors for *market share* scenario were plain breads (38%), flours, meals and starches (15%), Biscuits, savoury (12%), fruit and vegetable juices (8%),sauces and toppings (7%) and beverage flavourings, dry (6%).

*Australia – 2-6 years*

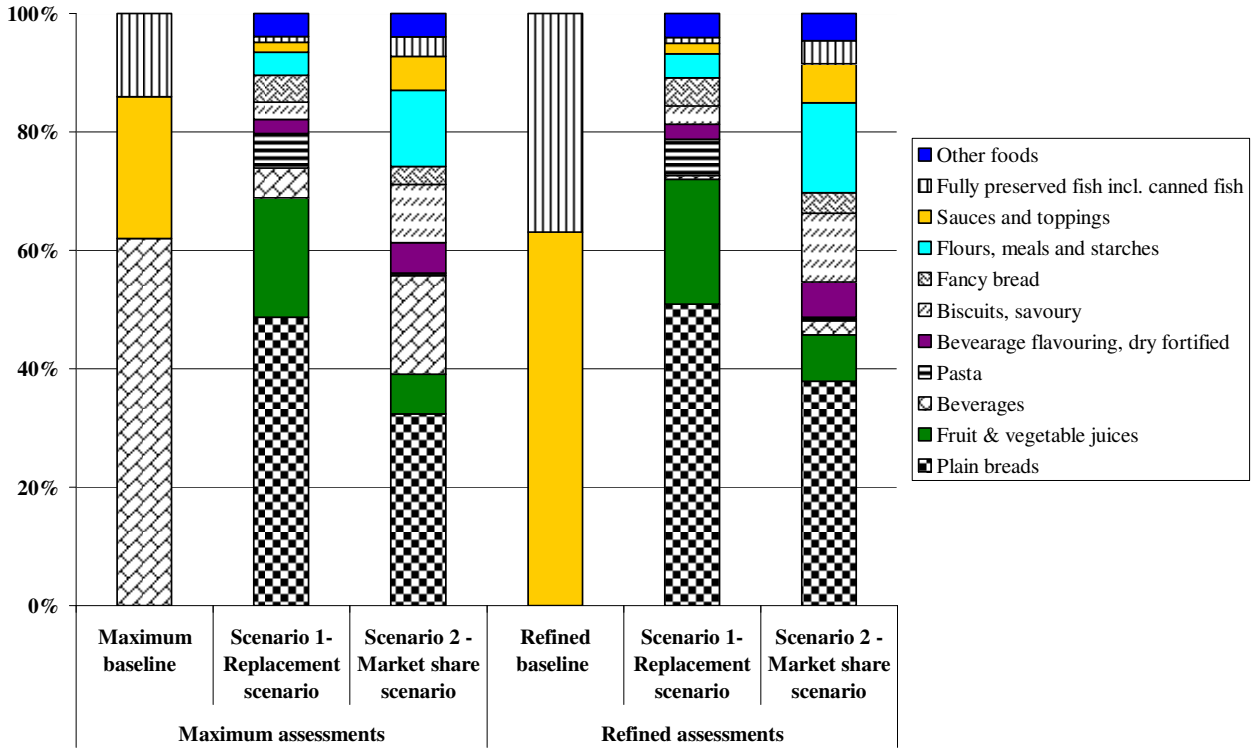
The major contributors for *replacement* scenario were plain breads (41%), fruit and vegetable juices (35%) and pasta (5%). The major contributors for *market share* scenario were plain breads (34%), Biscuits, savoury (16%), fruit and vegetable juices (15%), beverage flavourings, dry fortified (11%) and flours, meals and starches (9%).

*New Zealand – 15 years and above*

The major contributors for *replacement* scenario were plain breads (59%), fruit and vegetable juices (13%), fancy breads (6%) and flours, meals and starches (5%). The major contributors for *market share* scenario were plain breads (41%), flours, meals and starches (16%), beverage flavourings, dry (9%), biscuits, savoury (9%) and sauces and toppings (8%).

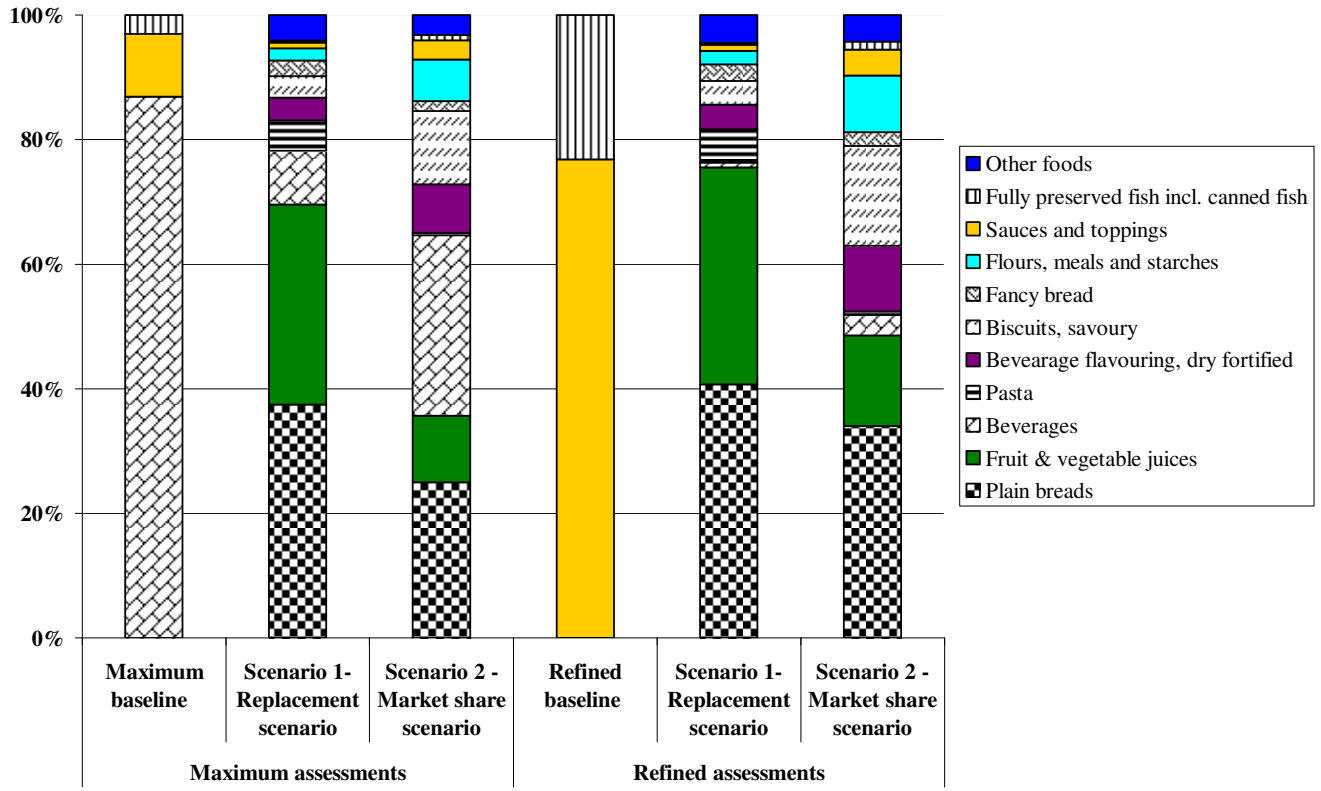
*Figure 5: Major contributors to total EDTA dietary exposures for Australia and New Zealand, and for different population group*

a Australia 2 years and above[€]



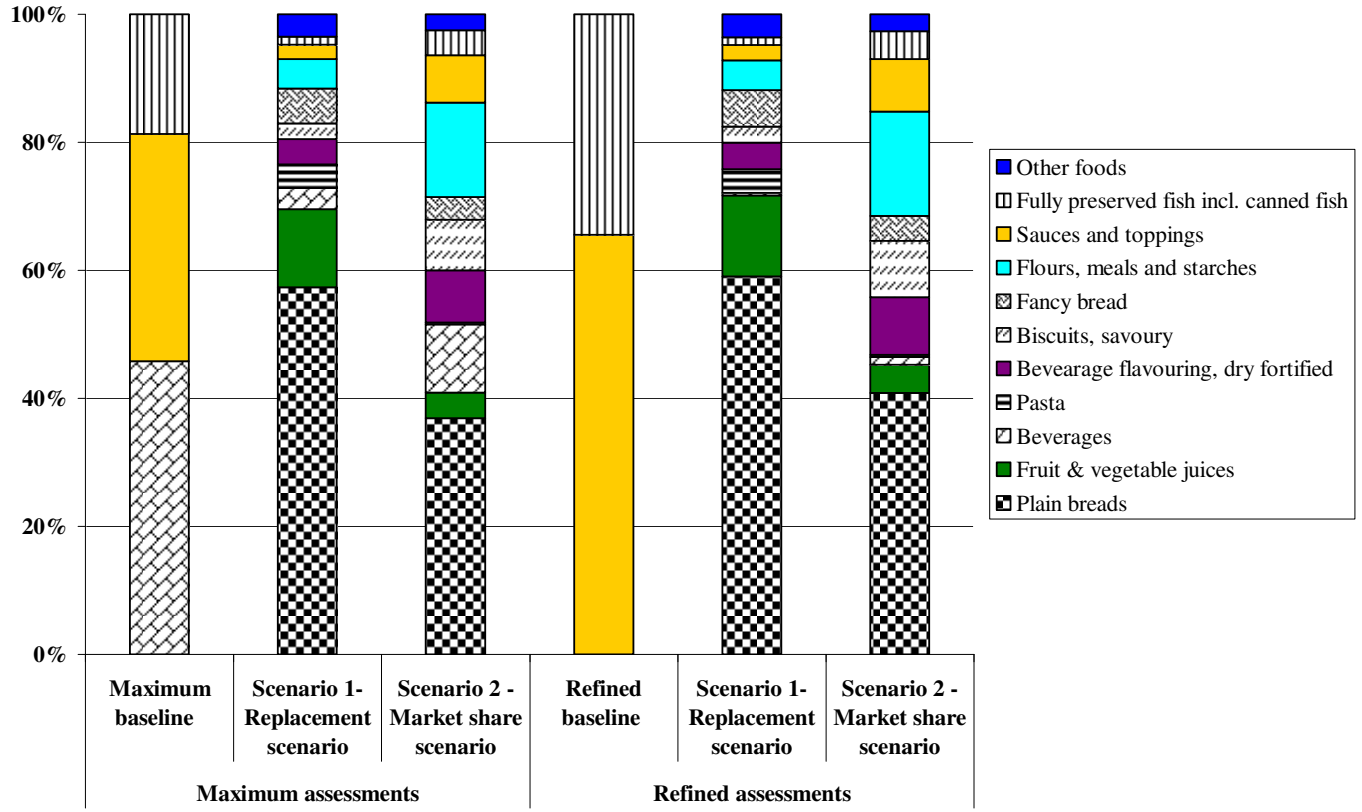

[€] Note: The percent contribution of each food group is based on total EDTA exposures for all consumers in the population groups assessed. Therefore the total EDTA exposures differ for each population group and each scenario

b Australian children 2-6 years[€]




€ Note: The per cent contribution of each food group is based on total EDTA exposures for all consumers in the population groups assessed. Therefore the total EDTA exposures differ for each population group and each scenario.

c New Zealand 15 years and above[€]




[€] Note: The per cent contribution of each food group is based on total EDTA exposures for all consumers in the population groups assessed. Therefore the total EDTA exposures differ for each population group and each scenario.

## 7 Limitations of the dietary modelling

Dietary modelling based on 1995 or 1997 NNS food consumption data provides the best estimate of actual consumption of a food and the resulting estimated dietary intake of a nutrient for the population. However, it should be noted that the NNS data does have its limitations. These limitations relate to the age of the data and the changes in eating patterns that may have occurred since the data were collected. Generally, consumption of staple foods such as fruit, vegetables, meat, dairy products and cereal products, which make up the majority of most people's diet, is unlikely to have changed markedly since 1995/1997(Cook *et al*., 2001a; Cook *et al*., 2001b). However, there is uncertainty associated with the consumption of foods that may have changed in consumption since 1995/1997, or that have been introduced to the market since 1995/1997.

Daily food consumption amounts for occasionally consumed foods based on 24 hour food consumption data tend to be higher than daily food consumption amounts for those foods based on a longer period of time. This specifically affects the food groups in this assessment such as sauces and toppings. The 90$^{th}$ percentile dietary exposures have been reported to represent the potential exposures for high consumers on a daily basis over a lifetime of exposure.

Over time, there may be changes to the ways in which manufacturers and retailers make and present foods for sale. Since the data were collected for the Australian and New Zealand NNSs, there have been significant changes to the Food Standards Code to allow more innovation in the food industry. As a consequence, another limitation of the dietary modelling is that some of the foods that are currently available in the food supply were either not available or were not as commonly available in 1995/1997. Since the data were collected for the NNSs, there has been an increase in the range of products that are fortified with nutrients.

While the results of NNSs can be used to describe the usual intake of groups of people, they cannot be used to describe the usual intake of an individual (Rutishauser, 2000). In particular, they cannot be used to predict how consumers will change their eating patterns as a result of an external influence such as the availability of a new type of food.

As ferric sodium EDTA is not currently permitted to be added to foods in Australia or New Zealand it is difficult to predict what concentrations of EDTA will be used, and the proportion of food groups that may contain EDTA.

## 8 Comparison of estimates against a reference health standard

In order to determine if the level of exposure to EDTA will be a public health and safety concern, the estimated dietary exposures were compared to the reference health standard, an Acceptable Daily Intake (ADI) of 2.5 mg/kg bw/day set by JECFA in 1974 (JECFA, 1974) and reconfirmed in 2007 (JECFA 2007). The ADI is defined as an estimate of the amount of a chemical that can be ingested daily over a lifetime without appreciable risk to health (WHO, 2001).

The estimated dietary exposures for EDTA, as compared to the ADI for the *maximum* assessments are as shown in Figure 6 and for the *refined* assessments are as shown in Figure 7 (full results in Table A3.1 and Table A3.2 in Appendix 3).

Among the population groups assessed, Australian children 2-6 years had the highest dietary exposures to EDTA. Estimated mean and the 90th percentile exposures for the Australian children 2-6 years were below the ADI for all the scenarios except for the *replacement* scenarios. Estimated mean and the 90th percentile exposures for the Australian population 2 years and above were below the ADI for all the scenarios except for the 90th percentile exposure for the *replacement* scenarios. Estimated mean and the 90th percentile exposures for all scenarios were below the ADI for New Zealand population 15 years and above.

### 8.1. Maximum assessments

*Australia – 2 years and above*

Estimated mean and 90th percentile exposures for consumers of EDTA were 7% of the ADI and 20% of the ADI for the *baseline* scenario; 70% of the ADI and 140% of the ADI for the *replacement* scenario and 20% of the ADI and 45% of the ADI for the *market share* scenario.

*Australia – 2-6 years*

Estimated mean and 90th percentile exposures for consumers of EDTA were 20% of the ADI and 50% of the ADI for the *baseline* scenario; 190% of the ADI and 360% of the ADI for the *replacement* scenario and 60% of the ADI and 100% of the ADI for the *market share* scenario.

*New Zealand – 15 years and above*

Estimated mean and 90th percentile exposures for consumers of EDTA were 4% of the ADI and 10% of the ADI for the *baseline* scenario; 50% of the ADI and 95% of the ADI for the *replacement* scenario and 15% of the ADI and 30% of the ADI for the *market share* scenario.

### 8.2 Refined assessments

*Australia – 2 years and above*

Estimated mean and 90th percentile exposures for consumers of EDTA were 3% of the ADI and 7% of the ADI for the *baseline* scenario; 65% of the ADI and 130% of the ADI for the *replacement* scenario and 15% of the ADI and 35% of the ADI for the *market share* scenario.

*Australia – 2-6 years*

Estimated mean and 90th percentile exposures for consumers of EDTA were 4% of the ADI and 10% of the ADI for the *baseline* scenario; 180% of the ADI and 350% of the ADI for the *replacement* scenario and 45% of the ADI and 80% of the ADI for the *market share* scenario.

*New Zealand – 15 years and above*

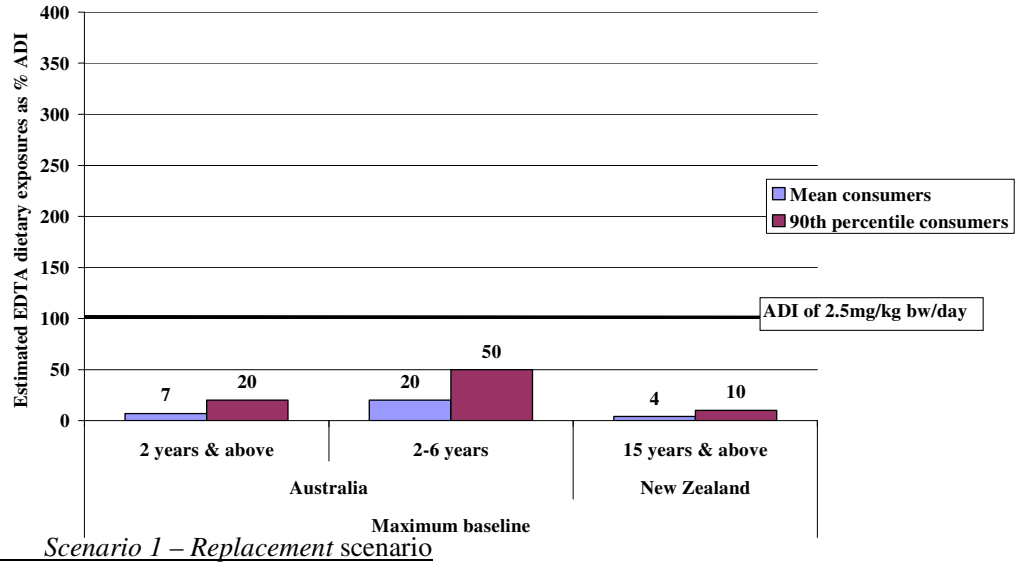
Estimated mean and 90th percentile exposures for consumers of EDTA were 3% of the ADI and 6% of the ADI for the *baseline* scenario; 50% of the ADI and 95% of the ADI for the *replacement* scenario and 15% of the ADI and 30% of the ADI for the *market share* scenario.

Realistically 100% the foods in the market would not be iron fortified foods. Also if this Application is approved, ferric sodium EDTA will be one of the 17 forms of iron listed in the Code, permitted for use in the general food supply. Thus as a realistic approach ferric sodium EDTA does not substitute 100% of current market for iron fortification.

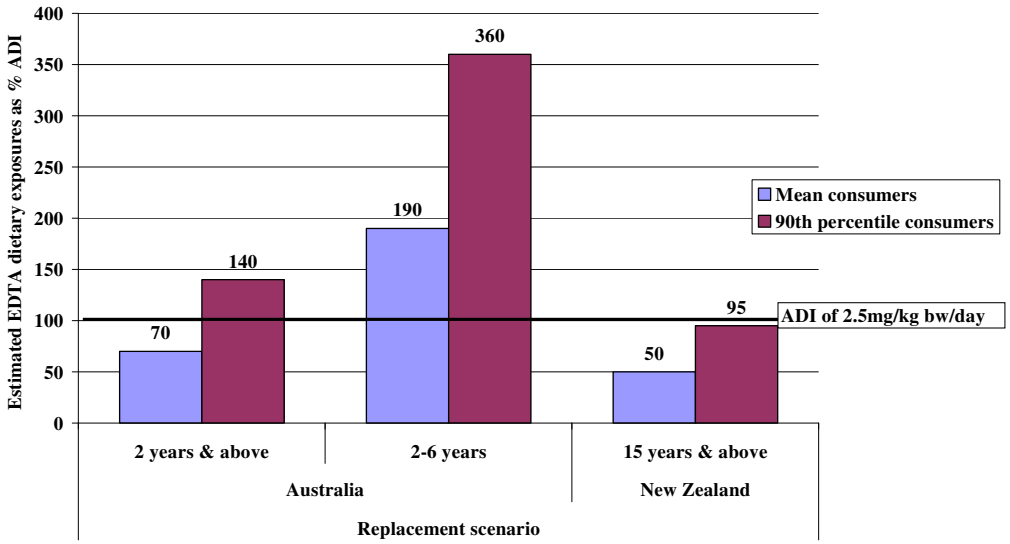
The children 2-6 years had higher percentile exposures compared to general population when expressed as a per kilogram body weight basis due to their higher consumption per kilogram body weight and relatively higher consumption of beverages.

*Figure 6: Estimated dietary exposures to EDTA, as a percentage of ADI for 'maximum assessment*

a *Maximum Baseline*




b *Scenario 1 – Replacement* scenario



c *Scenario 2 – Market share* scenario

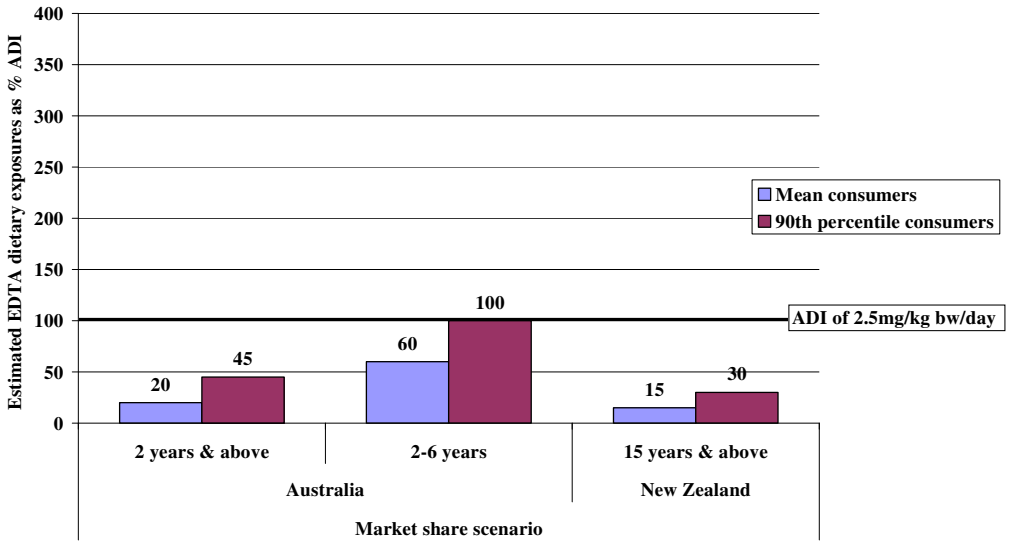
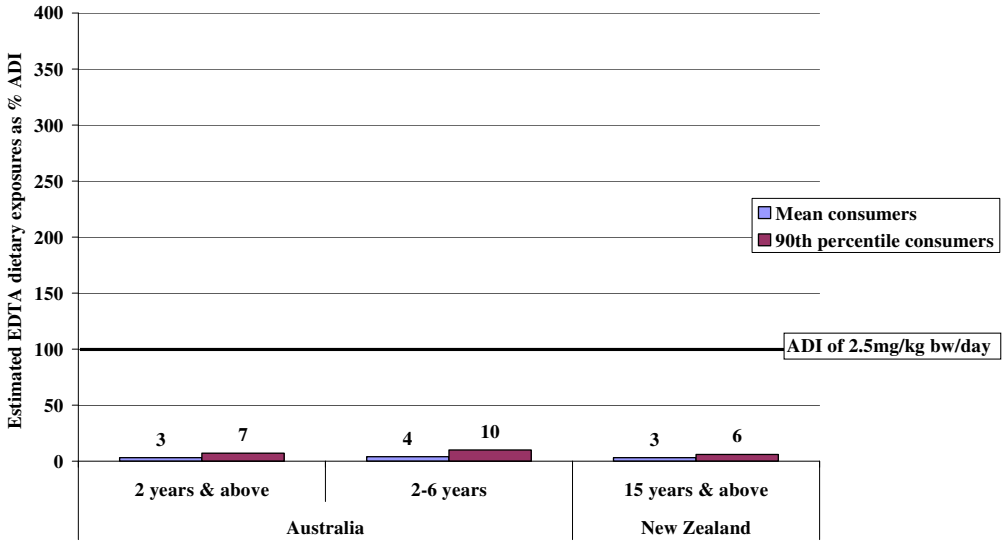
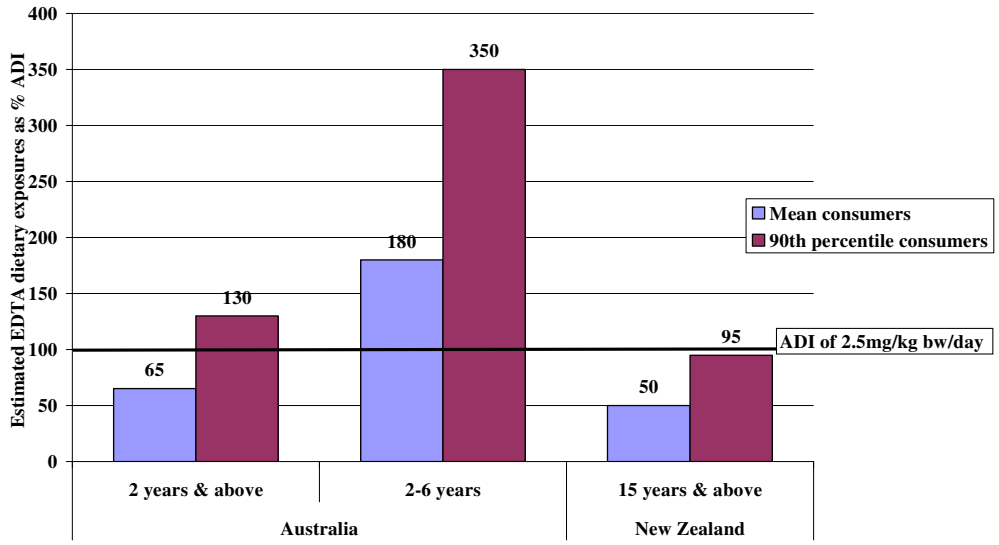



*Figure 7: Estimated dietary exposures to EDTA, as a percentage of ADI for 'refined' assessment*

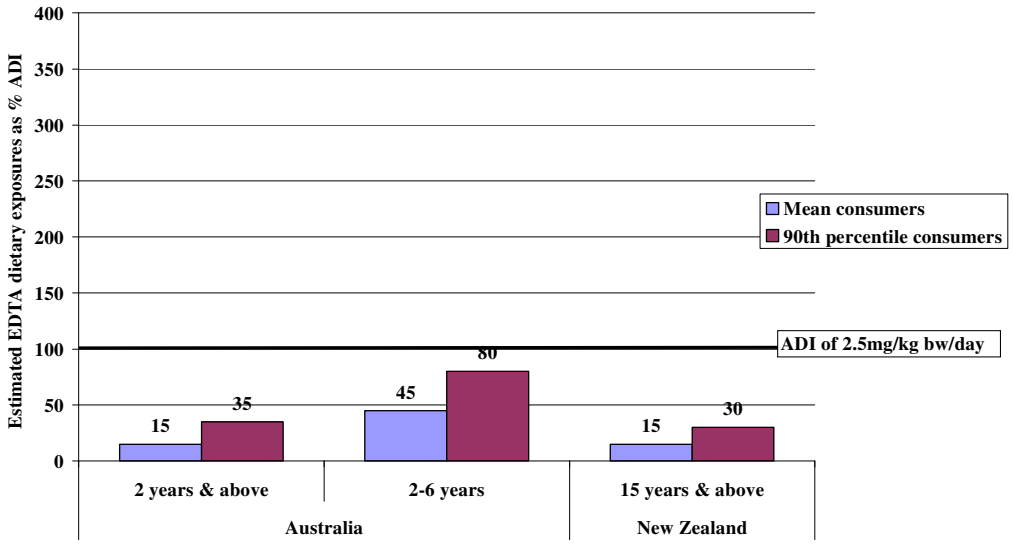
a *Refined baseline*



b *Scenario 1 – Replacement* scenario




c *Scenario 2 – Market share* scenario



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JECFA (2007) *Summary and conclusions of the Sixty-third meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA).* JECFA, pp1-18. http://www.fao.org/ag/AGN/agns/jecfa_new_en.asp. Accessed on

Lambe, J., Kearney, J., Leclercrq, C., Berardi, D., Zunft, H.F.J., De Henauw, S., De Volder, M., Lamberg-Allardt, C.J.E., Karkkainen, M.U.M., Dunne, A. and Gibney, N.J. (2000) Enhancing the capacity of food consumption surveys of short duration to estimate long term consumer-only intakes by combination with a qualitative food frequency questionnaire. *Food Additives and Contaminants* 17(3):177-187.

Rutishauser, I. (2000) Getting it right:- how to use the data from the 1995 National Nutrition Survey. Commonwealth of Australia, Canberra.

WHO (2001) *Summary of Evaluations Performed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA 1956-2003) (First through fifty-seventh meetings) Internet Edition*. ILSI Press International Life Sciences Institute, Washington DC.

# Appendix 1

## How were the estimated dietary exposures calculated?

### A1.1 How were estimated dietary exposures calculated?

Ferric sodium EDTA is proposed to be used for iron fortification and dietary exposure assessments were done to the EDTA component. The DIAMOND program allows EDTA concentrations to be assigned to food groups. Consumption of all of these food groups can be separated as required. For example for Standard 2.9.3 - Formulated meal replacements and formulated supplementary foods, EDTA concentrations were assigned separately for liquid and solid foods as the maximum claimable amount permitted in the Code is per serve size.

The exposures to EDTA were calculated for each individual in the NNSs using his or her individual food records from the dietary survey. The DIAMOND program multiplies the specified concentration of EDTA by the amount of food that an individual consumed from that group in order to estimate the exposure to EDTA from each food. Once this has been completed for all of the foods specified to contain EDTA, the total amount of EDTA consumed from all foods is summed for each individual. Population statistics (mean, median and high percentile exposures) are then derived from the individuals' ranked exposures.

Where estimated dietary exposures are expressed per kilogram of body weight, each individuals' total dietary exposure is divided by their own body weight, the results ranked, and population statistics derived. A small number of NNS respondents did not provide a body weight. These respondents are not included in calculations of estimated dietary intakes that are expressed per kilogram of body weight.

Where estimated exposures are expressed as a percentage of the reference health standard, each individual's total exposure is calculated as a percentage of the reference health standard (either using the total exposures in units per day or units per kilogram of body weight per day, depending on the units of the reference health standard), the results are then ranked, and population statistics derived.

Food consumption amounts for each individual take into account where each food in a classification code is consumed alone and as an ingredient in mixed foods. For example, bread eaten as a slice of bread, bread in a sandwich, and bread on a crumbed foods are all included in the consumption of bread Where a higher level food classification code (e.g. 6.3 Processed cereal and meal products) is given a EDTA concentration, as well as a sub-category (e.g. 6.3.2 Breakfast bars), the consumption of the foods in the sub-classification is not included in the higher level classification code.

In DIAMOND, all mixed foods in classification codes 20 and 21 have a recipe. Recipes are used to break down mixed foods into component ingredients which are in classification codes 1-14.

The data for consumption of the ingredients from the recipe are then used in models and multiplied by EDTA concentrations for each of the raw ingredients. This only occurs if the *Mixed food* classification code (classification code 20) is not assigned its own EDTA permission. If the *Mixed foods* classification is assigned a EDTA concentration, the total consumption of the mixed food is multiplied by the proposed level, and the recipes are not used for that food group.

When a food that does not have a recipe is classified in two food groups in classification codes 1-14, and these food groups are assigned different permissions, DIAMOND will assume the food is in the food group with the highest assigned EDTA level to assume a worst-case scenario. If the food groups have the same permitted EDTA level, DIAMOND will assume the food is in the food group that appears first, based numerically on the ANZFCS.

In DIAMOND, hydration factors are applied to some foods to convert the amount of food consumed in the dietary survey to the equivalent amount of the food in the form to which a food chemical permission is given. For example, consumption figures for beverage flavourings are converted into the equivalent quantities of a beverage. Dehydration factors were applied to the proposed concentration levels for pasta in the dietary modelling to represent the levels of EDTA that would be present in the food as a dry ingredient.

When a food is classified in two food groups (for example, mixed fruit juice may be entered in the apple and pear groups), and these food groups are assigned different EDTA permissions, DIAMOND will assume the food is in the food group with the highest assigned EDTA level to assume a worst case scenario. If the food groups have the same permitted EDTA level, DIAMOND will assume the food is in the food group that appears first, based alpha-numerically on the DIAMOND food code.

In DIAMOND, hydration and raw equivalence factors are applied to some foods to convert the amount of food consumed in the dietary survey to the equivalent amount of the food in the form to which a food chemical concentration is assigned. Factors are only applied to individual foods, and not major food group codes. For example, consumption figures for instant coffee powder are converted into the equivalent quantities of coffee beans; consumption figures for tomato paste are converted into the equivalent quantities of raw tomatoes.

### A1.2 How were percentage contributions calculated?

Percentage contributions of each food group to total estimated exposures are calculated by summing the exposures for a food group from each individual in the population group who consumed a food from that group. This is the dividing by the sum of the exposures of all individuals from all food groups containing cadmium and multiplying this by 100.

### A1.3 Reporting of dietary exposure assessment results for high consumers

Under the FSANZ Science Strategy 2006-2009, FSANZ agreed to review its dietary modelling procedures. As part of this review an international peer review was sought. FSANZ has previously reported chronic dietary exposures for high consumers of food chemicals at the 95$^{th}$ percentile. The recommendation of the peer review by an international dietary exposure assessment expert from the US Food and Drug Administration was that FSANZ should consider reporting food chemical dietary exposures at the 90th percentile not the 95$^{th}$ percentile, if only one 24 hour recall record per person was used for the assessment to align with international best practice. Ninety fifth percentile results are likely to be an overestimate of a daily consumption amount for high consumers, particularly for occasionally consumed foods where estimates may be 2-5 fold higher than the mean for consumers(WHO, 1983; Lambe *et al*., 2000). Hence use of 95$^{th}$ percentile estimates may potentially result in an overly conservative risk management approach.

## Appendix 2

# Complete information on dietary exposure assessment results

**Table A2.1: Estimated dietary exposures to EDTA for maximum assessment**

a Maximum baseline[♣]

| Country | Population group | Number of consumers of calcium disodium EDTA | Consumers[♦] as a % of total respondents[#] | Mean all respondents | Mean consumers | 90th percentile consumers |
|---|---|---|---|---|---|---|
| | | | | mg/day (mg/kg bw/day) | | |
| | | | | Maximum baseline | | |
| **Australia** | 2 years & above | 10528 | 76.0 | 6.54 (0.13) | 8.60 (0.17) | 23.42 (0.45) |
| | 2-6 years | 828 | 83.7 | 8.04 (0.43) | 9.60 (0.51) | 25.60 (1.30) |
| **New Zealand** | 15 years & above | 3500 | 75.5 | 5.81 (0.08) | 7.70 (0.10) | 19.95 (0.28) |

b *Scenario 1- Replacement* scenario® and *Scenario 2 – Market share* scenario[m]

| Country | Population group | Number of consumers of ferric sodium EDTA | Consumers[£] as a % of total respondents[#] | Mean all respondents | | Mean consumers | | 90th percentile consumers | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | mg/day (mg/kg bw/day) | | | | | |
| | | | | Replacement Scenario | Market Share Scenario | Replacement Scenario | Market Share Scenario | Replacement Scenario | Market Share Scenario |
| **Australia** | 2 years & above | 13714 | 99.0 | 92.28 (1.68) | 27.67 (0.50) | 93.24 (1.70) | 27.96 (0.51) | 179.73 (3.52) | 53.59 (1.10) |
| | 2-6 years | 984 | 99.5 | 87.91 (4.81) | 26.29 (1.43) | 88.36 (4.83) | 26.43 (1.44) | 164.31 (8.98) | 48.83 (2.60) |
| **New Zealand** | 15 years & above | 4562 | 98.4 | 89.95 (1.24) | 27.79 (0.38) | 91.41 (1.26) | 28.24 (0.39) | 170.01 (2.40) | 55.07 (0.77) |

# Total number of respondents for Australia: whole population = 13 858, 2-6 years = 989; New Zealand: whole population = 4 636. Respondents include all members of the survey population whether or not they consumed a food that contains EDTA.

[£]Consumers only – This only includes the people who have consumed a food that contains EDTA.

[♣] Maximum baseline: - to estimate the current exposure to EDTA from permissions for all foods at the Maximum Permitted Level for calcium disodium EDTA (385) in the Code (Standard 1.3.1).

®Scenario 1 'Replacement' scenario:- EDTA exposures assuming all the foods (excluding breakfast cereals and FSFYC) currently permitted to be fortified with iron as per the Code (Standard 1.3.2, 2.9.3 & 2.9.4) will be substituted with Ferric Sodium EDTA at its maximum claimable amount (worst case scenario), in addition to baseline EDTA uses.

[m]Scenario 2 'Market share scenario:- EDTA exposures assuming foods (excluding breakfast cereals and FSFYC)currently permitted to be fortified with iron as per to the Code (Scenario 1) with some market share data, in addition to baseline EDTA uses.

**Table A2.2: Estimated dietary exposures to EDTA for *refined assessment***

a *Refined baseline*[♣]

| Country | Population group | Number of consumers of calcium disodium EDTA | Consumers[£] as a % of total respondents[#] | Mean all respondents | Mean consumers mg/day (mg/kg bw/day) | 90th percentile consumers |
|---|---|---|---|---|---|---|
| | | | | Refined baseline | | |
| **Australia** | 2 years & above | 7857 | 56.7 | 2.48 (0.04) | 4.38 (0.07) | 10.50 (0.17) |
| | 2-6 years | 509 | 51.5 | 1.05 (0.06) | 2.04 (0.11) | 4.88 (0.27) |
| **New Zealand** | 15 years & above | 3050 | 65.8 | 3.14 (0.04) | 4.77 (0.07) | 11.12 (0.16) |

b Scenario 1 – *Replacement* scenario® and Scenario 2 – *Market share* scenario[m]

| Country | Population group | Number of consumers of ferric sodium EDTA | Consumers ♦ as a % of total respondents[#] | Mean all respondents | | Mean consumers mg/day (mg/kg bw/day) | | 90th percentile consumers | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Replacement Scenario | Market Share Scenario | Replacement Scenario | Market Share Scenario | Replacement Scenario | Market Share Scenario |
| **Australia** | 2 years & above | 13714 | 99.0 | 88.22 (1.59) | 23.62 (0.42) | 89.15 (1.61) | 23.87 (0.42) | 174.24 (3.33) | 45.43 (0.88) |
| | 2-6 years | 984 | 99.5 | 80.93 (4.43) | 19.31 (1.06) | 81.34 (4.46) | 19.41 (1.07) | 157.61 (8.67) | 36.14 (2.05) |
| **New Zealand** | 15 years & above | 4562 | 98.4 | 87.27 (1.21) | 25.11 (0.35) | 88.69 (1.23) | 25.52 (0.35) | 166.46 (2.35) | 49.23 (0.69) |

# Total number of respondents for Australia: whole population = 13 858, 2-6 years = 989; New Zealand: whole population = 4 636. Respondents include all members of the survey population whether or not they consumed a food that contains EDTA.
[£]Consumers only – This only includes the people who have consumed a food that contains EDTA.

♣ Refined baseline: - estimates the current exposure to EDTA from selected food groups based on uptake by the food industry of current permissions for calcium disodium EDTA (385) (excludes beverages and preparations of food additives) at Maximum Permitted Level of use.

®Scenario 1 'Replacement' scenario:- Scenario 1 - EDTA exposures assuming all the foods (excluding breakfast cereals and FSFYC) currently permitted to be fortified with iron as per the Code (Standard 1.3.2, 2.9.3 & 2.9.4) will be substituted with Ferric Sodium EDTA at its maximum claimable amount (worst case scenario), in addition to baseline EDTA uses.

[m]Scenario 2 'Market share scenario:- EDTA exposures assuming foods (excluding breakfast cereals and FSFYC)currently permitted to be fortified with iron as per to the Code (Scenario 1) with some market share data, in addition to baseline EDTA uses.

**Table A2.3: Major contributors to total EDTA dietary exposures for Australia and New Zealand, and for different population groups**

| Population groups | | Food Name | % Contribution to EDTA dietary exposure | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Maximum | | | Refined | | |
| | | | *Maximum baseline*[♣] | *Scenario 1- Replacement scenario*[®] | *Scenario 2 - Market share scenario*[m] | *Refined baseline*[•] | *Scenario 1- Replacement scenario*[®] | *Scenario 2 - Market share scenario*[m] |
| **Australia** | **2 years & above** | **Plain breads** | NA | 49 | 32 | NA | 51 | 38 |
| | | **Fruit & vegetable juices** | NA | 20 | 7 | NA | 21 | 8 |
| | | **Beverages** | 62 | <5 | 17 | NA | <5 | <5 |
| | | **Pasta** | NA | 6 | <5 | NA | 6 | <5 |
| | | **Beverage flavouring, dry fortified** | NA | <5 | 5 | NA | <5 | 6 |
| | | **Biscuits, savoury** | NA | <5 | 10 | NA | <5 | 12 |
| | | **Fancy bread** | NA | <5 | <5 | NA | <5 | <5 |
| | | **Flours, meals and starches** | NA | <5 | 13 | NA | <5 | 15 |
| | | Sauces toppings and mayonnaises, salad dressings | 24 | <5 | 6 | 63 | <5 | 7 |
| | | Fully preserved fish incl. canned fish | 14 | <5 | <5 | 37 | <5 | <5 |
| | | **Other foods** | 0 | <5 | <5 | 0 | <5 | 5 |
| | **2-6 years** | **Plain breads** | NA | 38 | 25 | NA | 41 | 34 |
| | | **Fruit & vegetable juices** | NA | 32 | 11 | NA | 35 | 15 |
| | | **Beverages** | 87 | 9 | 29 | NA | <5 | <5 |
| | | **Pasta** | NA | <5 | <5 | NA | 5 | <5 |
| | | **Beverage flavouring, dry fortified** | NA | <5 | 8 | NA | <5 | 11 |
| | | **Biscuits, savoury** | NA | <5 | 12 | NA | <5 | 16 |

| Population groups | | Food Name | % Contribution to EDTA dietary exposure | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Maximum | | | Refined | | |
| | | | *Maximum baseline*[♣] | *Scenario 1- Replacement scenario*[®] | *Scenario 2 - Market share scenario*[m] | *Refined baseline*[•] | *Scenario 1- Replacement scenario*[®] | *Scenario 2 - Market share scenario*[m] |
| | | **Fancy bread** | NA | <5 | <5 | | <5 | <5 |
| | | **Flours, meals and starches** | NA | <5 | 7 | NA | <5 | 9 |
| | | Sauces toppings and mayonnaises, salad dressings | 10 | <5 | <5 | 77 | <5 | <5 |
| | | Fully preserved fish incl. canned fish | <5 | <5 | <5 | 23 | <5 | <5 |
| | | **Other foods** | 0 | <5 | <5 | 0 | <5 | <5 |
| **New Zealand** | **15 years & above** | **Plain breads** | NA | 57 | 37 | NA | 59 | 41 |
| | | **Fruit & vegetable juices** | NA | 12 | <5 | NA | 13 | <5 |
| | | **Beverages** | 46 | <5 | 11 | NA | <5 | <5 |
| | | **Pasta** | NA | <5 | <5 | NA | <5 | <5 |
| | | **Beverage flavouring, dry fortified** | NA | <5 | 8 | NA | <5 | 9 |
| | | **Biscuits, savoury** | NA | <5 | 8 | NA | <5 | 9 |
| | | **Fancy bread** | NA | 5 | <5 | NA | 6 | <5 |
| | | **Flours, meals and starches** | NA | <5 | 15 | NA | <5 | 16 |
| | | Sauces toppings and mayonnaises, salad dressings | 35 | <5 | 7 | 66 | <5 | 8 |
| | | Fully preserved fish incl. canned fish | 19 | <5 | <5 | 34 | <5 | <5 |
| | | **Other foods** | 0 | <5 | <5 | 0 | <5 | <5 |

[♣] Maximum baseline: - to estimate the current exposure to EDTA from permissions for all foods at the Maximum Permitted Level for calcium disodium EDTA (385) in the Code (Standard 1.3.1).

• Refined baseline: - estimates the current exposure to EDTA from selected food groups based on uptake by the food industry of current permissions for calcium disodium EDTA (385) (excludes beverages and preparations of food additives) at Maximum Permitted Level of use.

®Scenario 1 'Replacement' scenario:- EDTA exposures assuming all the foods (excluding breakfast cereals and FSFYC) currently permitted to be fortified with iron as per the Code (Standard 1.3.2, 2.9.3 & 2.9.4) will be substituted with Ferric Sodium EDTA at its maximum claimable amount (worst case scenario), in addition to baseline EDTA uses.

[m]Scenario 2 'Market share scenario:- EDTA exposures assuming foods (excluding breakfast cereals and FSFYC)currently permitted to be fortified with iron as per to the Code (Scenario 1) with some market share data, in addition to baseline EDTA uses.

## Appendix 3

# Complete information on risk characterisation

### Table A3.1: Estimated dietary exposures to EDTA for maximum assessment, as a percentage of ADI

a Maximum baseline♣

| Country | Population group | Number of consumers of calcium disodium EDTA | Consumers♦ as a % of total respondents# | Estimated dietary exposures to calcium disodium EDTA | |
|---|---|---|---|---|---|
| | | | | Mean consumers | 90th percentile consumers |
| | | | | Maximum baseline | |
| | | | | (% ADI*) | (% ADI*) |
| **Australia** | 2 years & above | 10528 | 76.0 | 7 | 20 |
| | 2-6 years | 828 | 83.7 | 20 | 50 |
| **New Zealand** | 15 years & above | 3500 | 75.5 | 4 | 10 |

*b Scenario 1 – Replacement scenario® and Scenario 2 – Market share scenario[m]*

| Country | Population group | Number of consumers of ferric sodium EDTA | Consumers♦ as a % of total respondents# | Estimated dietary exposures to ferric sodium EDTA | | | |
|---|---|---|---|---|---|---|---|
| | | | | Mean consumers | | 90th percentile consumers | |
| | | | | Replacement Scenario | Market Share scenario | Replacement Scenario | Market Share scenario |
| | | | | (% ADI*) | | (% ADI*) | |
| **Australia** | 2 years & above | 13714 | 99.0 | 70 | 20 | 140 | 45 |
| | 2-6 years | 984 | 99.5 | 190 | 60 | 360 | 100 |
| **New Zealand** | 15 years & above | 4562 | 98.4 | 50 | 15 | 95 | 30 |

# Total number of respondents for Australia: whole population = 13 858, 2-6 years = 989; New Zealand: whole population = 4 636. Respondents include all members of the survey population whether or not they consumed a food that contains EDTA.
♦ Consumers only – This only includes the people who have consumed a food that contains EDTA.
♣ Maximum baseline: - to estimate the current exposure to EDTA from permissions for all foods at the Maximum Permitted Level for calcium disodium EDTA (385) in the Code (Standard 1.3.1).
®Scenario 1 'Replacement' scenario:- EDTA exposures assuming all the foods (excluding breakfast cereals and FSFYC) currently permitted to be fortified with iron as per the Code (Standard 1.3.2, 2.9.3 & 2.9.4) will be substituted with Ferric Sodium EDTA at its maximum claimable amount (worst case scenario), in addition to baseline EDTA uses.
[m]Scenario 2 'Market share scenario:- EDTA exposures assuming foods (excluding breakfast cereals and FSFYC) currently permitted to be fortified with iron as per to the Code (Scenario 1) with some market share data, in addition to baseline EDTA uses.
* ADI = 2.5 mg/kg/bw/day

**Table A3.2: Estimated dietary exposures to ferric sodium EDTA for refined assessment, as a percentage of ADI**

a *Refined baseline*[♣]

| Country | Population group | Number of consumers of calcium disodium EDTA | Consumers[♦] as a % of total respondents[#] | Estimated dietary exposures to calcium disodium EDTA | |
|---|---|---|---|---|---|
| | | | | Mean consumers | 90th percentile consumers |
| | | | | Refined baseline | |
| | | | | (% ADI*) | (% ADI*) |
| **Australia** | 2 years & above | 7857 | 56.7 | 3 | 7 |
| | 2-6 years | 509 | 51.5 | 4 | 10 |
| **New Zealand** | 15 years & above | 3050 | 65.8 | 3 | 6 |

*b Scenario 1- Replacement* scenario® *and Scenario 2 – Market share* scenario [m]

| Country | Population group | Number of consumers of ferric sodium EDTA | Consumers[♦] as a % of total respondents[#] | Estimated dietary exposures to ferric sodium EDTA | | | |
|---|---|---|---|---|---|---|---|
| | | | | Mean consumers | | 90th percentile consumers | |
| | | | | Replacement Scenario | Market Share scenario | Replacement Scenario | Market Share scenario |
| | | | | (% ADI*) | | (% ADI*) | |
| **Australia** | 2 years & above | 13714 | 99.0 | 65 | 15 | 130 | 35 |
| | 2-6 years | 984 | 99.5 | 180 | 45 | 350 | 80 |
| **New Zealand** | 15 years & above | 4562 | 98.4 | 50 | 15 | 95 | 30 |

# Total number of respondents for Australia: whole population = 13 858, 2-6 years = 989; New Zealand: whole population = 4 636. Respondents include all members of the survey population whether or not they consumed a food that contains EDTA.

♦ Consumers only – This only includes the people who have consumed a food that contains EDTA.

♣ Refined baseline: - estimates the current exposure to EDTA from selected food groups based on uptake by the food industry of current permissions for calcium disodium EDTA (385) (excludes beverages and preparations of food additives) at Maximum Permitted Level of use.

®Scenario 1 'Replacement' scenario:- EDTA exposures assuming all the foods (excluding breakfast cereals and FSFYC) currently permitted to be fortified with iron as per the Code (Standard 1.3.2, 2.9.3 & 2.9.4) will be substituted with Ferric Sodium EDTA at its maximum claimable amount (worst case scenario), in addition to baseline EDTA uses.

[m]Scenario 2 'Market share scenario:- EDTA exposures assuming foods (excluding breakfast cereals and FSFYC) currently permitted to be fortified with iron as per to the Code (Scenario 1) with some market share data, in addition to baseline EDTA uses.

* ADI = 2.5 mg/kg/bw/day

## Attachment 6

## Summary of Submissions at Initial Assessment

### APPLICATION A570 – FERRIC SODIUM EDETATE AS A PERMITTED FORM OF IRON

The Initial Assessment Report was available for public submissions during the six week public consultation period of 13 December 2006 to 7 February 2007. A total of seven submissions were received including three from industry and four from government. A summary of submitter comments is provided in the table below.

The two regulatory options presented in the Initial Assessment were:

**Option 1** Maintain the *status quo*
**Option 2** Approve ferric sodium edetate (ferric sodium EDTA) as a permitted form of iron in Standard 1.1.1

| Submitter | Submission Comments |
|---|---|
| **Industry** | |
| **Australian Food and Grocery Council**<br><br>Kim Leighton | **Supports Option 2, subject to FSANZ's safety assessment**<br><br>• Notes basis of Application is that ferric sodium EDTA overcomes some technological problems associated with other forms of iron.<br>• Notes applicant claims iron remains available and is effectively absorbed, making it a more effective and efficient means of iron food fortification.<br>• Considers a broad cross-section of the community is at increased risk of iron deficiency and would benefit from increased availability of iron.<br>• Those with haemochromatosis or other conditions of iron overload, as well as those with some liver diseases, may experience effects from iron intakes well below upper level of safe consumption by normal population. Declaration of iron content via NIP is one way to avoid excessive consumption.<br>• Studies do not provide good evidence that excessive iron intake correlates with coronary heart disease. References provided. However quotes two large studies that report increased dietary haem iron, but not total dietary iron, to be associated with increased risk of myocardial infarction. |

| Submitter | Submission Comments |
|---|---|
| **Unilever Australasia**<br><br>Julie Newlands | **Supports progressing Application and will comment further at Draft Assessment**<br><br>• Issues requiring investigation include:<br><br>- increased bioavailability of ferric sodium EDTA compared to current forms in the mostly replete population; and<br>- additional dietary contribution to EDTA intake when it is already present through calcium disodium EDTA.<br><br>• Recommends FSANZ use reviews of ferric sodium EDTA undertaken by other regulatory bodies to assist risk assessment and management. |
| **The Food Technology Association of Australia (formerly FTA Vic)**<br><br>David Gill | **Supports Option 2**<br><br>• No supporting information provided. |
| **Government** | |
| **NZ Food Safety Authority**<br><br>Carole Inkster | **Supports further assessment of Application**<br><br>• Will review the Draft Assessment. |
| **NSW Food Authority**<br><br>David Cusack | **Supports progression of the Application**<br><br>• Recommends the following issues be assessed:<br><br>- bioavailability of iron from ferric sodium EDTA and risk of iron overload in general population and at risk consumers (young children and those with haemochromatosis);<br>- how at risk consumers will identify food fortified with ferric sodium EDTA;<br>- impact of ferric sodium EDTA on bioavailability of other nutrients in diet e.g. zinc, magnesium and calcium;<br>- impact of direct dietary source of EDTA on human health and nutrition; and<br>- increased availability and use in general food supply compared with a supervised food program. |
| **Queensland Health**<br><br>Tenille Fort | **Support not finalised. Will comment further at Draft Assessment.**<br><br>• Consideration should be given to implementing JECFA's acceptable daily intake for EDTA.<br>• Provides two WebPages with information on ferric sodium EDTA which may assist FSANZ assessment.<br><br>http://www.food.gov.uk/multimedia/pdfs/ferricsodiumedta.pdf<br>http://www.inchem.org/documants/jecfa/jecmono/v32je14.htm |
| **Dept of Human Services, Victoria**<br><br>Victor Di Paola | **Support will be finalised after reviewing Draft Assessment** |