Original Article

Fortifying complementary foods with NaFeEDTA – considerations for developing countries

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Abstract

As a highly bioavailable iron compound, sodium iron (iii) ethylenediaminetetraacetate (NaFeEDTA) has been recommended as a food additive for fortification. The amount of a food additive that can be ingested daily over a lifetime without appreciable health risk is termed the acceptable daily intake (ADI). The ADI for NaFeEDTA is based on body weight. For complementary foods and food supplements for infants and young children in low-income countries, where prevalence of underweight is high yet nutrient needs are also high, it is not clear which doses might be appropriate. The objective is to calculate the dosage of NaFeEDTA for fortifying complementary foods assuming different population prevalences of underweight. Mathematical models were used to simulate the dosage of NaFeEDTA for 6- to 8-month-old infants under different prevalences of underweight ranging from 5% to 40%. In order to keep NaFeEDTA intake below the ADI for ethylenediaminetetraacetate (EDTA) recommended by the Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives for 95% of 6- to 8-month-old infants, the daily iron dose from NaFeEDTA in fortified complementary foods should be set between 2.2 mg and 1.8 mg in countries with a prevalence of underweight among 6- to 8-month-old infants between 5% and 40%, respectively. If 2 mg of iron is given to all 6- to 8-month-old infants, the percentage exceeding the ADI for EDTA would be <10% for populations with <30% of children who are underweight, which is the case for many countries. In conclusion, 2 mg of iron from NaFeEDTA could be used for fortifying one daily serving of complementary food to ensure EDTA levels are below the ADI for infants 6–8 months of age. An additional source of iron (such as ferrous sulfate) should be included to increase the iron dose to desired fortification levels.

Keywords: NaFeEDTA, fortified complementary foods, infant, underweight, developing countries.

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Introduction

Iron deficiency is one of the most commonly recognized micronutrient deficiencies for infants and young children around the world. Iron deficiency can result in anaemia, abnormal psychological development and suboptimal physical work capacity (World Health Organization 2001). The causes of iron deficiency

during infancy are related to high iron requirements for growth and relatively low iron content and poor bioavailability in complementary foods in low-income countries (Dewey 2007). The bioavailability of iron is low in plant-based complementary foods, and consumption of foods with high iron bioavailability such as meat, fish and poultry is generally inadequate in the developing world (Dewey 2007).

Iron-fortified complementary food is considered to be a cost-effective way to fulfil infants' iron requirements. Fortification of complementary foods can be done at the site of manufacturer (e.g. a commercially prepared fortified porridge) or at home [e.g. home fortification with multimicronutrient powder [MNP] or fortified soy powder [*Ying Yang Bao* (YYB)]].

Various iron compounds are available for fortifying complementary foods, including ferrous sulfate, ferrous fumarate and electrolytic iron (Allen *et al.* 2006). As a highly bioavailable iron compound, sodium iron (iii) ethylenediaminetetraacetate (NaFeEDTA) has been recommended for food fortification (e.g. wheat flour, soy sauce, fish sauce and sugar) (Allen *et al.* 2006), and the relatively higher cost of NaFeEDTA is offset by its higher bioavailability, particularly in high-phytate diets. Some home fortificants (e.g. MNP and YYB) also use NaFeEDTA as their iron source. Like other EDTA and metal compounds, NaFeEDTA releases iron from EDTA salt in the gastrointestinal tract (mainly intestinal) (Heimbach *et al.* 2000). The iron is absorbed through a pathway similar to other non-haem iron. The EDTA absorption is independent of iron absorption (Heimbach *et al.* 2000). Thus, the safety concern for NaFeEDTA is similar to the concern for other metal-EDTA compounds (Heimbach *et al.* 2000).

The Joint Food and Agriculture Organization (FAO)/ World Health Organization (WHO) Expert Committee on Food Additives (JECFA) states that the total intake of EDTA should not exceed acceptable levels (1.9 mg/kg body weight EDTA) after taking into account the intake of EDTA in the form of food additives based on EDTA compounds (JECFA 2007). Acceptable daily intake (ADI) is a measure of the amount of a food additive that can be consumed on a daily basis over a lifetime without an appreciable health risk. The ADI for NaFeEDTA is based on body

weight, and body weight increases rapidly during 6–24 months of age. Complementary food recommendations are commonly grouped into 6–8 months, 9–11 months and 12–23 months. While the youngest children have a higher iron requirement, their weights are lower, and thus this puts them at greater risk of exceeding the ADI for EDTA.

In addition, the prevalence of underweight for children 6–24 months of age is high and varies across low-income countries (Black *et al.* 2008). Thus, it is not clear which doses would be appropriate for fortifying complementary foods for infants and young children in countries with high burdens of underweight. The purpose of the present analyses is to estimate the dose of NaFeEDTA used in iron-fortified complementary foods in countries with a high burden of underweight. Additionally, the methodology used here has implications for calculating levels of nutrients in foods for this target age group that are also based on body weight (e.g. essential fatty acids).

Materials and methods

The distribution of *z*-score was simulated with normal function with a sample size ($n = 10\,000$). The combined body weight distributions for 6- to 8-month-old male and female reference infants were constructed based on the Box-Cox power exponential method with the formula $\text{weight} = (z\text{-value} * S * L + 1)^{1/L} * M$ (de Onis 2006). The WHO Child Growth Standards parameters (L, M, S) were used for the calculation (de Onis 2006) where ' L ' is the power transformation parameter for normal distribution, ' M ' is the median of weight distribution and ' S ' is the sample standard deviation.

The combined body weight distributions for 6- to 8-month-old infants in high burden countries were constructed under different levels of prevalence of

Key messages

- Two milligrams of iron from sodium iron (iii) ethylenediaminetetraacetate NaFeEDTA could be used for fortifying one daily serving of complementary food to ensure ethylenediaminetetraacetate (EDTA) levels are below the acceptable daily intake for infants 6–8 months of age in many low-income countries.
- An additional source of iron (such as ferrous sulfate) should be included to increase the iron dose to desired fortification levels.

underweight ranging from 5% to 40%, which are typical for many low-income countries. Underweight was defined as weight-for-age z -score < -2 (de Onis 2006). Either mean changes or mean and variance changes were assumed for constructing a new body weight distribution. Both assumptions yielded similar results. Then the newly constructed weight distribution for each prevalence of underweight was used to calculate 2.5th and 5th percentile body weight. Based on the 2.5th percentile and 5th percentile body weight under each prevalence of underweight and ADI for EDTA (1.9 mg/kg body weight), the maximum amount of iron from NaFeEDTA was calculated.

RAND function in the Statistical Analysis System (SAS) was used for normal distribution simulation (SAS version 9.2; SAS Institute Inc., Cary, NC, USA).

Results

Based on Demographic and Health Survey data, the countries with prevalence of underweight between 5% and 40% are shown in Table 1. The combined 6–8 months boy and girl body weight distribution is shown in Fig. 1 with the 2.5th percentile, 5th percentile and median body weight at 6.14 kg, 6.41 kg and 7.97 kg, respectively. By increasing the rates of underweight in the model from 5% to 40%, the 2.5th percentile and 5th percentile body weight decreases from 5.83 kg to 4.76 kg and from 6.08 kg to 4.97 kg, respectively. In order to keep NaFeEDTA intake below the ADI for EDTA recommended by JECFA for 95% of 6- to 8-month-old infants, the daily iron dose from NaFeEDTA in fortified complementary foods cannot exceed 2.2 mg to 1.8 mg, correspondingly (Table 1). In order to keep NaFeEDTA intake below the ADI for EDTA recommended by JECFA for 95% of 6–8 months of age girls, the daily iron dose from NaFeEDTA in fortified complementary foods cannot exceed 2.2 mg to 1.7 mg, correspondingly (data not shown).

The overall prevalence of underweight in low-income countries is about 20%, and only a few countries in South Asia and East Africa have a prevalence $\geq 30\%$. If 2 mg of iron from NaFeEDTA were given to all 6- to 8-month-old infants, the percentage exceeding the ADI for EDTA would be $< 10\%$ for

Table 1. Estimated iron dose (mg) from NaFeEDTA for 6- to 8-month-old children under different prevalences of underweight

Prevalence of underweight	Examples of countries with these prevalences	Body weight at 2.5th percentile (kg)	Maximum iron dose from NaFeEDTA (mg)*	Body weight at 5th (kg)	Maximum iron dose from NaFeEDTA (mg)*
Reference					
5%	Congo (Brazzaville), Lesotho, Swaziland	6.14	2.2	6.41	2.3
10%	Namibia, Senegal, Zambia, Zimbabwe	5.83	2.1	6.08	2.2
15%	Benin, Cameroon, Ghana, Sierra Leone, Haiti	5.51	2.0	5.75	2.1
20%	Congo (DR), Guinea, Liberia, Malawi, Rwanda, Tanzania	5.16	1.9	5.54	2.0
25%	Chad, Ethiopia, Mali, Nigeria, Uganda, Bangladesh	5.04	1.8	5.39	2.0
30%	Niger, Nepal	4.94	1.8	5.26	1.9
35%	Madagascar, India	4.85	1.8	5.15	1.9
40%		4.76	1.7	5.06	1.9
				4.97	1.8

NaFeEDTA, sodium iron (iii) ethylenediaminetetraacetate; DR, Democratic Republic of the Congo. *Based on the acceptable daily intake for EDTA recommended by Joint FAO/WHO Expert Committee on Food Additives (1.9 mg/kg body weight).

Fig. 1. The body weight (kg) distribution for 6- to 8-month male and female infants in World Health Organization reference population.

Table 2. Estimated percentage of children 6–8 months of age whose intake of EDTA would be above upper limit under different prevalences of underweight given a single iron dose (2 mg or 2.5 mg)

Prevalence of underweight (%)	Percentage of children whose intake of EDTA would be above ADI at 2 mg iron (%)	Percentage of children whose intake of EDTA would be above ADI at 2.5 mg iron (%)
5	1.1	18.5
10	2.5	31.3
15	4.1	41.6
20	5.9	50.2
25	7.8	57.6
30	10.0	64.1
35	12.4	69.7
40	15.0	74.7

EDTA, ethylenediaminetetraacetate; ADI, acceptable daily intake.

populations with <30% of children who are underweight, which is the case for most of these countries (Table 2).

However, if 2.5 mg iron were given in NaFeEDTA form to all 6- to 8-month-old infants, 30–64% of infants would be above the ADI of EDTA. For infants 9–11 months, with the use of 2.5 mg, these figures are

5% and 30%, and for those 12–23 months, these figures are 1% and 8% (data not shown).

Discussion

These analyses indicate that the daily iron dose from NaFeEDTA in fortified complementary foods should range from 2.2 mg to 1.8 mg to maintain EDTA intake below the ADI recommended by JECFA for 95% of 6- to 8-month-old infants, as prevalence of underweight of 6- to 8-month-old infants ranges from 5% to 40% in the statistical model. In low-income countries with various prevalences of underweight, 2 mg of iron from NaFeEDTA could be used for fortifying complementary foods for 6-to 24-month older infants and young children. This minimizes the risk of exceeding the ADI in infants 6–8 months of age. If a smaller portion size were suggested for the youngest infants (such as $\frac{1}{2}$ portion per day), a higher level (such as 2.5 mg) could be used for young children 12–23 months of age, but then the infant would not receive sufficient quantities of the other nutrients.

The iron absorption rate from NaFeEDTA is about two to three times greater than that from either ferrous fumarate or ferrous sulfate in high-phytate

diets (Allen *et al.* 2006). This could be very effective for enriching complementary foods or complementary food supplements, as phytate content is generally high in cereal-based complementary foods [International Nutritional Anemia Consultative Group (INACG) 1993; Hurrell *et al.* 2000]. The dose of 1.8–2.2 mg iron from NaFeEDTA would provide about 0.18–0.22 mg absorbed iron, assuming 10% absorption based on MNP intervention studies and isotopic studies (Troesch *et al.* 2009; Troesch *et al.* 2011), which corresponds to 19–24% of iron requirements for 6- to 11-month-old infants and 31–38% of iron requirements for children aged 1–3 years (WHO/FAO 2004). Although this level still only meets about 1/5–1/3 of iron requirements for infants and young children, the EDTA could also enhance the absorption of food iron and soluble iron compounds from other sources (e.g. other iron fortificants) (Allen *et al.* 2006). However, this model also assumes consumption of a fixed daily serving and comparable absorption rates of iron in different settings. It does not take into account infection/inflammation and other factors that can affect iron absorption.

A recent study in South Africa showed that a MNP containing 2.5 mg of iron from NaFeEDTA significantly improved iron status (ferritin, transferrin receptor and body iron) and reduced iron deficiency of children aged ~8 years old when it was added to a maize porridge (Troesch *et al.* 2011). Another study provided 6 mg iron from NaFeEDTA to infants and young children through a fortified full-fat soy powder (YYB) in China (Wang *et al.* 2009). This was an intervention trial for older infants ($n = 1478$) and lasted until the children reached 24 months of age. YYB was given to an intervention group daily and a non-fortified isocaloric rice powder was given to a control group. The results found that YYB significantly decreased the prevalence of anaemia (Wang *et al.* 2009). MNP containing 2.5 mg of iron from NaFeEDTA was also used in a programme in the Kakuma Refugee Camp in Kenya to improve iron status in a malaria-endemic area (World Food Program *et al.* 2009). MNP was offered to children 6–59 months and to non-pregnant women for 13 months. At baseline, mid-term and endline, haemoglobin and iron status were evaluated. Compared to

baseline, iron status was improved at the mid-term and endline, but anaemia did not decrease (Ndemwa *et al.* 2011).

During the complementary feeding period, body weight increases rapidly and iron requirements are lower at 12–23 months of age than at 6–11 months of age. If body weight of 12- to 23-month-old children is used for estimating NaFeEDTA dose for fortifying complementary foods (e.g. if 2.5 mg of iron from NaFeEDTA is given to children aged 12–23 months, 1–8% of the population under 5–30% of prevalence of underweight would be over ADI for EDTA.), there will be higher risk of intakes over the ADI for 6- to 11-month-old infants (e.g. if 2.5 mg of iron from NaFeEDTA is given to children aged 6–11 months, 30–64% of 6- to 8-month-old infants and 5–30% of 9- to 11-month-old infants under 5–30% of prevalence of underweight would be over ADI for EDTA). However, if body weight of 6-month-old infants is used for estimating the NaFeEDTA dose, the iron dose from NaFeEDTA would be relatively small for other older children. Thus, body weights of 6- to 8-month-old infants were combined for estimating NaFeEDTA dose. The 6- to 8-month age group is commonly used for estimating energy and nutrient requirements from complementary foods (Dewey & Brown 2003). Although 6 mg of iron from NaFeEDTA was used in YYB in China and 2.5 mg of iron from NaFeEDTA was used in MNP in Kenya, there were no adverse effects (although the studies were not powered to assess adverse effects) reported in these two projects; 18–64% of 6- to 8-month-old infants would be over ADI of EDTA when 2.5 mg of iron from NaFeEDTA is given to infants and young children where the prevalence of underweight ranges between 5% and 30%.

In conclusion, 2 mg of iron daily from NaFeEDTA could be used for fortifying complementary foods without exceeding the ADI for EDTA for the majority of 6- to 24-month-old infants and young children in developing countries with varying prevalences of underweight. Because this level is below the iron reference nutrient intake (RNI), NaFeEDTA should be one part of the iron fortification used in complementary food and should be in addition to another good source of iron to reach the desired iron levels in the

complementary food. For example, in China, a complementary food supplement included 2.5 mg from EDTA iron and 2.5 mg from ferrous fumarate (Sun *et al.* 2011).

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Conflict of interest

No conflicts of interest exist.

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