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**Nutrition Noteworthy**

**Title**

NaFeEDTA-Fortified Fish Sauce: The Cure to Iron Deficiency Anemia in Vietnam?

**Permalink**

<https://escholarship.org/uc/item/4ws8w4s7>

**Journal**

Nutrition Noteworthy, 7(1)

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**Publication Date**

2005

Peer reviewed

## **Introduction**

Iron deficiency affects 2 out of 3 people in developing nations, well over 3.5 billion people, and is the most common nutritional disorder in the world according to the World Health Organization (WHO) (1). These staggering numbers correlate with significantly poorer performance on psychomotor and mental development scales and behavioral ratings in infants, lower scores on cognitive function tests in preschool children, lower scores in cognitive function tests and educational achievement tests in school-age children (2), and poor pregnancy outcome (3). According to Allen, iron deficiency anemia in pregnancy is a strong determinant for preterm delivery and subsequent low birth weight, and possibly for inferior neonatal health. The most severe form of iron deficiency is iron deficiency anemia (IDA). IDA is associated with low work productivity in adults (4). The most commonly affected populations are young children, pregnant and postpartum women. IDA affects these populations because of the high iron demands of infant growth and pregnancy. Mental retardation of children and maternal and perinatal mortality are regarded as the most severe outcomes of IDA (1). IDA was clinically defined as having a hemoglobin concentration of <120g/L and low iron stores were defined as a serum ferritin concentration of <12 micrograms/L (5). Although the statistics look grave, IDA is a curable and more importantly, preventable disease. Fortification of staple foods or condiments with absorbable iron in these affected regions can eliminate this growing problem. Fortification of food is also a much more cost-effective intervention as compared to supplementation of iron through other means (6).

## **Iron Deficiency in Southeast Asia, namely Vietnam**

According to the World Health Organization, over 90 percent of the individuals affected with anemia live in developing countries and more than six hundred million live in Southeast Asia. In 1995, a national survey of Vietnam estimated that the prevalence of anemia is 60 percent in children fewer than two years of age, 53 percent in pregnant women, and 40 percent in non-pregnant women (1). Food production and availability in Vietnam has shown an upward trend in the past ten years with daily caloric requirements being met. However, the overall pattern of food production has shown little change. Rice production is continuing to account for a predominant part of food production. There is no evidence of a significant uptrend with respect to production of milk, horticultural products, poultry or meat production in Vietnam (7). A unique and unfortunate feature of the nutrition situation in Southeast-Asian countries is that the incidence of low birth weight deliveries. This is a reflection of poor maternal nutrition in pregnancy. Florid nutritional deficiency diseases have shown a steep decline over the last twenty years, but goiters and IDA continue to be major public health problems in Vietnam (7).

## **Recommendations on How to Prevent and Cure IDA**

Current WHO and UNICEF guidelines recommend that interventions for the prevention and the control of iron deficiency and IDA should follow an integrated, long-term approach. IDA must be addressed by a multidisciplinary approach, including the

following elements: 1) increased iron intake (i.e., iron-rich diets, increasing iron absorption, and iron and folate supplements, fortification of wheat flour and other complementary foods with iron and other micronutrients, where appropriate); 2) infection control (i.e., public health measures to control hookworm infections, malaria, and schistosomiasis); 3) improved nutritional status (i.e., control of major nutrient deficiencies, diet diversification, and infection prevention) (1,8).

### **NaFeEDTA-Fortified Fish Sauce...Vietnam's Hope**

In 1998, two Project IDEA (Iron Deficiency Elimination Action) workshops on food fortification were held in Vietnam to discuss potentially useful food vehicles and iron fortificants for the control of iron deficiency (9). Fish sauce (nuoc mam) was suggested as a good vehicle for iron fortification programs because more than 80% of the population regularly consumes fish sauce (5). Fish Sauce is a staple condiment and ingredient in the Vietnamese and Southeast Asian diet. It is estimated that about 10-15 ml is consumed per person/day. There is a network of fish sauce factories under the supervision of the Ministry of Fishery (9). This will allow for easier access to and regulation of the fortification process. A recent study on fish sauce production in Vietnam concluded that iron fortification of fish sauce can be made before bottling the product with only minor modifications to the production process (9).

### **Barriers of Iron Fortification**

Iron is the most difficult mineral to fortify foods with because of high rate of inadequate absorption. The most bioavailable form of iron are the water-soluble iron compounds. However, fortification of food with these compounds often leads to the development of unacceptable color and flavor changes in the food vehicle. The main barriers to successful iron fortification are the following: 1) finding an iron compound that is adequately absorbed but causes no sensory changes to the food vehicle; and 2) overcoming the inhibitory effect on iron absorption of dietary components such as phytic acid, phenolic compounds and calcium (10). Water-soluble iron often causes rancidity when added to cereal flours and lead to color changes when added to low quality salt. Insoluble compounds, such as elemental iron powders, on the other hand, do not cause sensory changes but may be so poorly absorbed as to be of little or no nutritional benefit (10). Selection of the iron compound is not the only problem. The other major difficulty to ensuring adequate absorption is the presence of iron absorption inhibitors in the fortification vehicle itself, or in the accompanying diet. The main inhibitory compound is phytic acid (myo-inositol 6-phosphate) (11), which is widely present in cereal grains and legume seeds (12). Phytic acid binds iron strongly in the gastrointestinal tract and can decrease the absorption of even the most bioavailable iron compounds to very low levels (13).

### **NaFeEDTA: Iron Fortificant**

NaFeEDTA as a fortificant is advantageous in many ways. Iron from NaFeEDTA is absorbed 2 to 3 times better than from ferrous sulfate in the presence of phytic acid (13).

Unlike many other soluble iron compounds, it does not cause precipitation of peptides when added to fish sauce or soy sauce. In the absence of phytic acid, NaFeEDTA has an absorption spectrum similar to that of ferrous sulfate (10). Its main advantage, however, is that it has been demonstrated several times to be efficacious for food fortification, improving the iron status of target populations consuming NaFeEDTA fortified fish sauce, curry powder and sugar (10). Its disadvantages are higher cost (~6 times as expensive as ferrous sulfate) (10). Another potential disadvantage of NaFeEDTA as a fortificant was its susceptibility to photodegradation in aqueous solution (14). Losses of up to 35% of NaFeEDTA occurred over a 2 to 6 week period with fortified fish sauce stored in clear bottles exposed to direct sunlight. However, this loss can be avoided by storing the fish sauce in amber bottles in areas with indirect sunlight or in the dark (14).

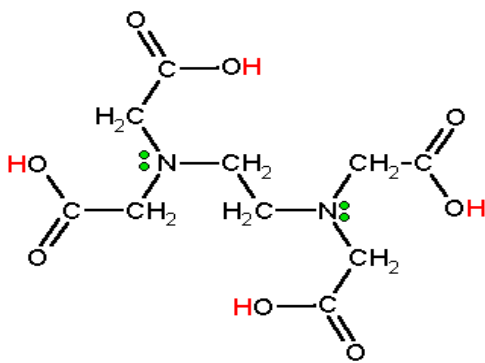


Figure 2. EDTA or ethylenediaminetetraacetic acid is a novel molecule for complexing metal ions. It is a polyprotic acid containing four carboxylic acid groups (acidic hydrogens are red) and two amine groups with lone pair electrons (green dots). The classic structural formula is given here (15).

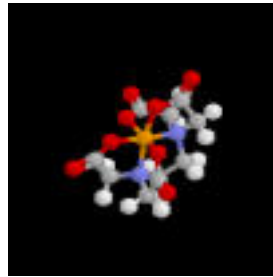


Figure 1. Octahedral coordination of the Fe-EDTA (15).

### Efficacy Trials of NaFeEDTA-fortified Fish Sauce

In 2000, a landmark randomized double blind controlled trial was conducted to evaluate the efficacy of NaFeEDTA-fortified fish sauce to improve iron status of anemic women in Vietnam. The six-month study consisted of an experimental group that received 10mL of fortified fish sauce and the control group that received 10mL of unfortified fish sauce. All 152 women were served a complete meal mainly by noodles or rice, six days per week, under strict supervision. Hemoglobin increased significantly in the fortified group and by the end of the study, the prevalence of anemia had decreased by 33% in this group. Serum-ferritin increased significantly in the fortified group. No significant changes occurred in the non-fortified group. Thus, regular consumption of iron fortified fish sauce during 6 months improved iron status significantly and decreased the prevalence of anemia in Vietnamese anemic women (5). Iron fortification of fish sauce is thus a promising approach to control iron deficiency anemia in Vietnam.

An 18-month study will begin in two similar communities with a total population of 12,000. The overall purpose of this randomized double-blind trial is to determine whether or not fish sauce fortified with NaFeEDTA is an effective intervention to combat

iron deficiency and iron deficiency anemia in Vietnam under realistic conditions. More realistic conditions in this study would include a longer duration of 18 months and the use of fish sauce fortified with NaFeEDTA at 0.5mg Fe/mL, half of the originally studied concentration (5).

### **Economic Cost and Impact of Reducing Iron Deficiency**

According to Baltussen and associates, iron fortification is a cost-effective means of preventing and treating IDA worldwide (6). They estimated the health and economic gains from iron supplementation to be twice as much as from iron fortification. However, the estimated the cost of iron supplementation to 95 percent of the Southeast Asia to be \$286,217,588 and the cost of fortification to be \$38,831,752, nearly one—eighth the cost. It is clear that fortification is less costly than supplementation and appears to be more cost effective than iron supplementation. It was concluded that iron fortification is economically more attractive than iron supplementation. The existing work of fish-sauce factories, which are supervised by the Ministry of Fishery, would also facilitate the implementation of the fortification program, and the additional cost has been estimated to be \$0.02/L (16).

### **Conclusion**

Iron deficiency is the most common nutritional disorder in the world. The numbers are staggering: as many as 4-5 billion people, 66-80% of the world's population, may be iron deficient. However, 90 percent, of the iron deficiency is found in developing nations. It is very important to implement a form of intervention that is both effective and economically sound. Iron fortification programs have been implemented worldwide. For Southeast Asia, NaFeEDTA-Fortified fish sauce is the key. Recent studies clearly show that fish sauce fortified with NaFeEDTA is efficacious in improving iron status and reducing the prevalence of IDA in anemic Vietnamese women (5). These results add to growing body of evidence that food fortification with iron compounds having high bioavailability is a useful approach to combat iron deficiency and IDA. Previous studies have reported positive results with NaFeEDTA fortification of fish sauce in Thailand (17), of sugar in Central America (18), and of curry powder in South Africa (19) after a 12 to 24 month study period. We shall await the publication of the results from the large-scale more realistic trial before recommending the implementation of an iron-fortification program nationally in Vietnam or elsewhere in Southeast Asia.

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