FFI: Harmonization Workshop for Wheat and Maize Flour

Nairobi, April 19-22, 2010

WHO, UNICEF, FAO, GAIN, MI and FFI revised recommendations for iron fortification of wheat and maize flours

Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Richard Hurrell
Laboratory for Human Nutrition
Institute of Food, Nutrition and Health

More people worldwide are deficient in iron than in any other micronutrient

Main reasons are:

- low iron intake/bioavailability from traditional diets of poor people

  cereal and legume based with little or no meat, fruit or vegetables

- increased requirements at certain stage of the life cycle

  growth: infancy, childhood, adolescence, pregnancy

  Fe losses: menstruation

⇩

1 billion people with iron deficiency anaemia (IDA)

(low Hb + no stores, low status of Fe enzymes)

plus

1 billion people with ID (no stores, low Fe enzyme status)

WHO 2007: anaemia prevalence (%) in most at-risk groups

(McLean et al 2007)

	children 0-5yr	women 15-50 yr	pregnant women
Africa	65	44	56
Asia	48	33	42
Latin America	40	23	31
Europe	17	15	19
North America	3	8	6
Oceania	28	20	30
millions with low Hb	**290**	**470**	**60**

No WHO estimates of the prevalence of iron deficiency

- in industrial countries: low Hb mostly due to ID
- in developing countries: ca. 50% anemia is IDA

other reasons for low Hb:

- deficiencies in other micronutrients (vit A, B12, folate, B2)
- infections (inflammatory disorders, malaria)
- hemoglobinopathies (thalassemia, sickle cell)

Negative health outcomes of iron deficiency anaemia

- Reduced physical work capacity: less oxygen, iron enzymes down-regulated. Reduced economic potential.
- Pregnancy:
  - increased risk for severe anaemia
  - higher maternal morbidity and mortality
  - increased risk of preterm delivery, low birth weight
  - increased risk of iron deficiency in infants
- Infancy:
  - increased infant mortality rate
  - delayed mental and motor development
- more frequent upper respiratory infections, risk of severe malarial morbidity increased
- poor iodine utilization; potentially increased Pb burden

Leading global risk factors impacting on health (WHO 2004)

1 underweight

2 unsafe sex

3 high blood pressure

4 tobacco consumption

5 alcohol consumption

6 unsafe drinking water, sanitation and hygiene

7 iron deficiency

8 indoor smoke from solid fuels

9 high cholesterol

10 obesity

Major intervention strategies to correct micronutrient deficiencies

FOOD FORTIFICATION

- ✶ moderate capital expenditure, low running costs, high population coverage
- ✶ best long-term approach for prevention (I/salt, Fe/wheat flour)

SUPPLEMENTATION

- ✶ high dose, high costs, often poor compliance
- ✶ therapeutic, short term intervention for highly deficient groups
- ✶ high dose vitamin A

NUTRITION EDUCATION/ DIET MODIFICATION

- ✶ high cost, moderate impact

BIOFORTIFICATION

plant breeding and genetic engineering techniques

to increase Fe, Zn and β-carotene in staple plant foods

iron fortification of foods

iron is the most difficult mineral to add to foods
and to ensure adequate absorption

- highly absorbable ⇨ color and flavor problems

  organoleptically acceptable ⇨ poorly absorbed

- even the highly absorbable compounds may be poorly absorbed

all major vehicles for iron fortification contain potent absorption inhibitors or are consumed with food containing inhibitors

⇨

manufacturers must protect iron from absorption inhibitors, remove them, or adjust the level of iron fortification accordingly

Stages in the development of an iron-fortified food

I. optimize iron compound: highest potential absorption with no organoleptic problems

select Fe compound with highest relative absorption (WHO Guidelines)

make organoleptic trials: colour and taste panels, storage, food processing, home cooking

II. optimize absorbed iron to meet consumers need

- estimate Fe intake ⇒ current need for Fe
- estimate intake of fortification vehicle
- estimate/measure absorption (± enhancer)

⇒ define fortification level

III. make efficacy study to demonstrate effect on Fe status

monitor prevalence of ID according to WHO/CDC Guidelines

Choice of iron compound

WATER SOLUBLE COMPOUNDS

dissolve instantaneously

ferrous sulfate

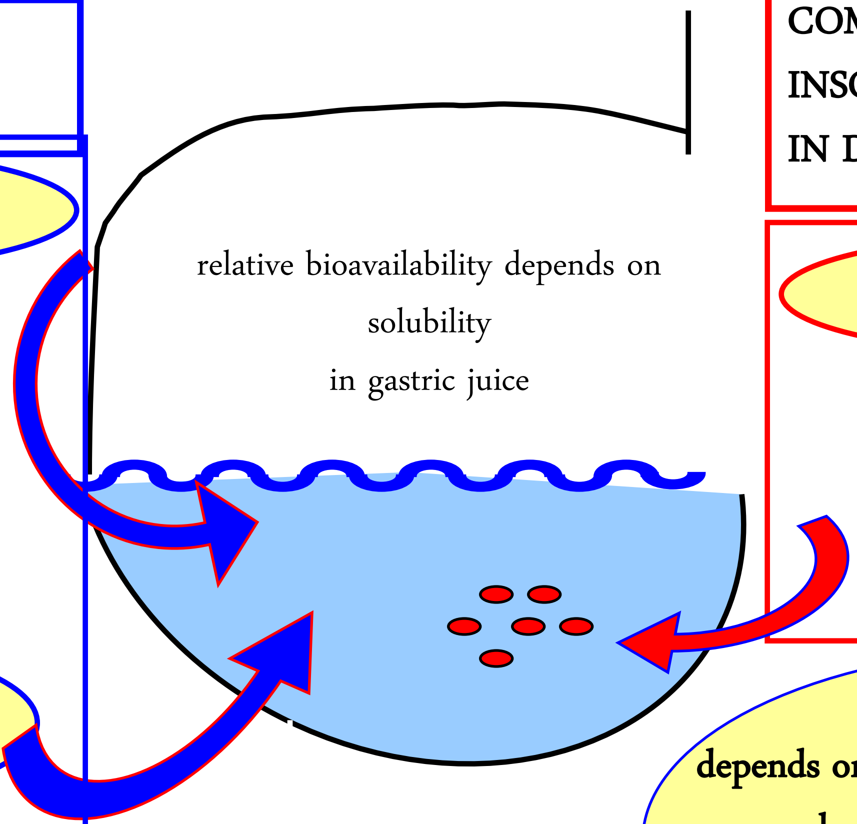
RBV = 100

poorly water soluble/
soluble in dilute HCl

dissolve completely
over time

ferrous fumarate

RBV = 100



COMPOUNDS WATER INSOLUBLE/POORLY SOLUBLE IN DILUTE ACID

never dissolve completely

electrolytic Fe

RBV = ca. 50

ferric pyrophosphate

RBV = 15 -75

absolute absorption
depends on intake of inhibitors (phytate) and enhancers (ascorbic acid) and iron status of consumer

WHO Guidelines (2006) for the choice of iron compound in fortified food

- for most vehicles the order of preference is
  - ferrous sulphate
  - ferrous fumarate
  - encapsulated sulphate or fumarate
  - electrolytic iron (2x amount vs. FS)
  - ferric pyrophosphate (2x amount vs. FS)
  - NaFeEDTA
- for high phytate cereal flours and high peptide sauces (soy, fish)
  - NaFeEDTA
- for liquid milk products and soft drinks
  - ferrous bisglycinate,
  - micronized (dispersible) ferric pyrophosphate
  - ferric ammonium citrate

for infant foods and open-market foods add ascorbic acid as an enhancer at 2:1 molar ratio, for high phytate foods at 4:1

Elemental iron for flour fortification

- Only electrolytic iron is recommended. Only iron powder with sufficiently demonstrated efficacy in humans. Estimated to be half as well absorbed as ferrous sulfate. Add **DOUBLE QUANTITY.**

- It is not recommended to add H-reduced Fe, atomized reduced Fe, carbonyl iron or CO-reduced Fe powders. Little of no support from human studies, and/or animal studies and solubility tests indicate poor absorption.

- Further studies are needed with H-reduced Fe and carbonyl Fe powders.

Recent evolution of flour fortification guidelines

- **Cuernavaca Flour Fortification Guidelines (2004):** Practical approach
  Based on current industry practice, restoration and potential negative sensory changes. Adjusted for flour consumption and iron bioavailability.

- **WHO Fortification Guidelines (2006)**: Scientific approach
  Calculate difference between daily iron intake and requirement. Add to mean flour consumption and adjust for bioavailability.

- **WHO, FAO, UNICEF, MI, GAIN and FFI (2009):** Evidence-based approach
  Iron levels and compounds based on minimum amounts of iron shown to improve iron status of young women in efficacy studies, levels adjusted for mean flour consumption and iron bioavailability.

Evaluation of iron efficacy and effectiveness studies: inclusion/exclusion criteria

- All studies in adult women, adolescents and children which monitor Hb or iron status parameters. No infant studies.
- All food vehicles.
- Studies > 5 months duration.
- Randomized controlled studies with adequate description of methodology and clearly defined iron compounds.
- Studies with added ascorbic acid were excluded, studies with other added micronutrients were included.

Iron efficacy studies with ferrous sulphate

Iron compound	Dose mg/d	Subject / vehicle	Length of study / Country	Impact	Source
Encapsulated Ferrous sulphate [a]	11.8	6-15 year old children salt (bread, fava beans)	9 months Morocco	Very efficacious	Zimmermann (2003)
Ferrous sulphate	10.3	18-40 year old women wheat flour biscuits	9 months Thailand	Very efficacious	Zimmermann (2005)
Ferrous sulphate	11	11-18 year old students wheat flour	6 months China	Moderately efficacious	Sun (2007)
Encapsulated ferrous sulphate [b]	7.1	18-35 year old women wheat flour biscuits	5.5 months Kuwait	Moderately efficacious	Biebinger (2009)

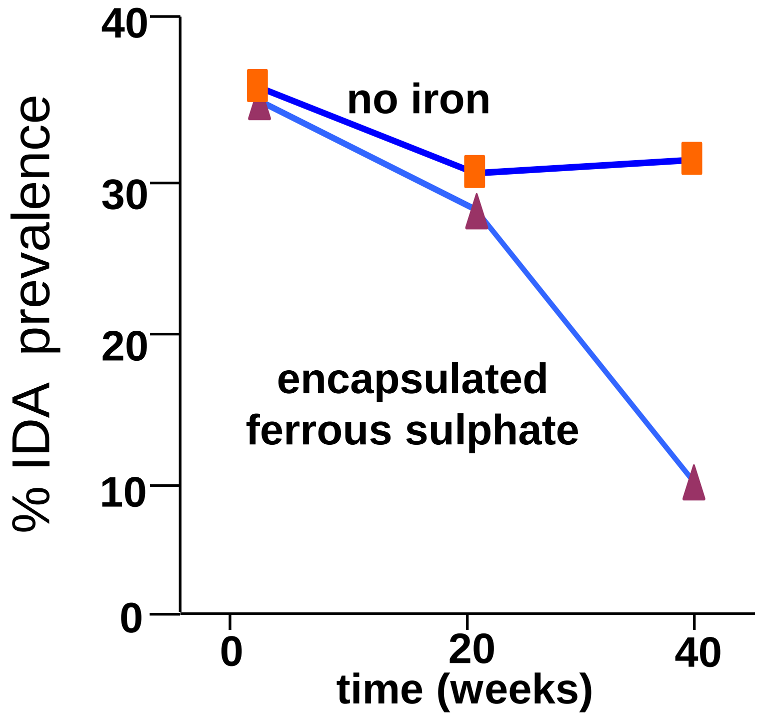
a encapsulated with partially hydrogenated vegetable oil (Balchem)
b encapsulated with hydrogenated palm oil ; mean particle size ca. 40µm

Fortification of salt with encapsulated ferrous sulphate improves iron status in Moroccan school children (Zimmermann et al. 2003)

- encaps. FS prevents colour changes
- dietary iron intake 9-15mg/d, low Fe bioav. (5%), salt intake 7-12g/d,

fortification level defined as 1mg Fe/g

- salt provided to households, much added to bread, fava beans, olives
- 9 months randomized double blind controlled trial in 2x 180 6-15 yr old school children
- monitor Hb, SF and TfR, ZPP



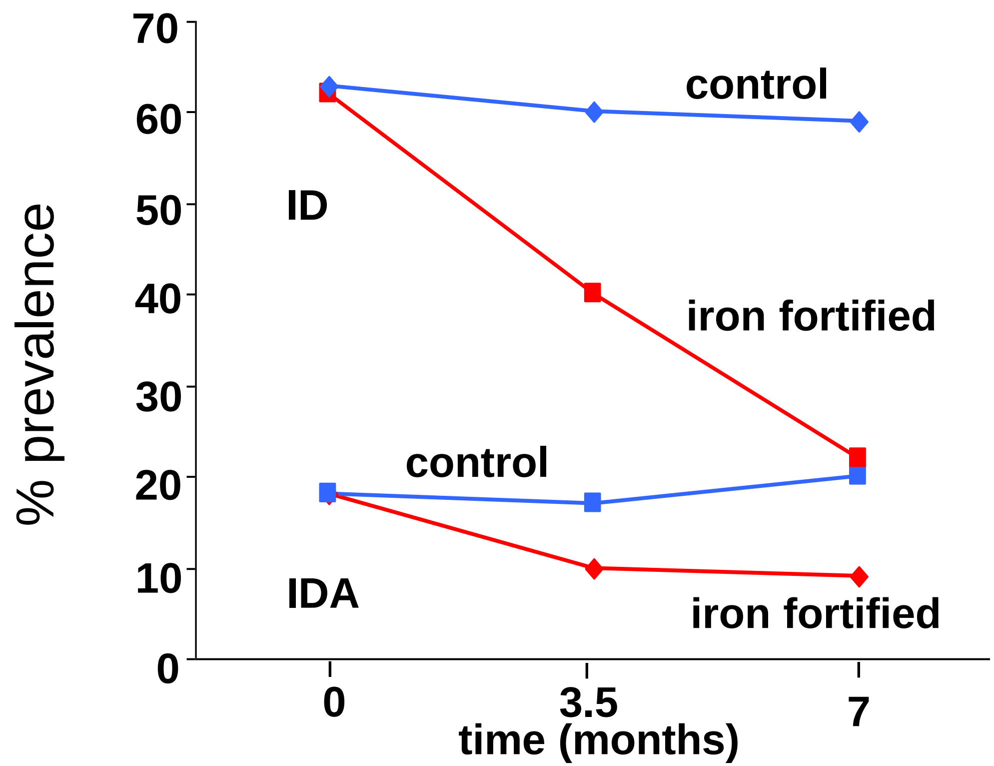
IDA = low Hb +2/3 abnormal iron status parameters

Efficacy and effectiveness studies with NaFeEDTA

Dose mg/d	Subjects/ vehicle	Length of study/ country	Impact	Source
7.1	Both sexes Aged 10+ Curry powder	24 months South Africa	Very efficacious	Ballot (1989)
4.6	Both sexes Aged 1+ sugar	32 months Guatemala	Very efficacious	Viteri (1995)
8.6	Women 17-44 Fish sauce	6 months Vietnam	Moderately efficacious	Thuy (2003)
7.5	Women 16-49 Fish sauce	18 months Vietnam	Very effective	Thuy (2005)
4.9	Both sexes 3+ Soy sauce	18 months China	Very effective	Chen (2005)
7	Both sexes 11-18 Wheat flour	6 months China	Very efficacious	Sun (2007)
7	Children 3-8 Maize porridge	5 months Kenya	Very efficacious	Andang'o (2007)
3.5	Children 3-8 Maize porridge	5 months Kenya	Moderately efficacious	Andang'o (2007)
1.3	Children 6-11 Brown bread	5 months South Africa	No effect on iron status	Van Stuijvenberg (2007abstract)

Fortification of Atta flour with NaFeEDTA improves iron status of Indian School children (Muthayya et al, 2010 unpublished)

- whole grain'atta' wheat flour fortified with NaFeEDTA at 60 ppm
- 7 month randomized double blind controlled trial in 2 x 200 6-13 yrs old children of low Fe status (SF<20μg/L)
- 100g atta flour containing 6 mg Fe as NaFeEDTA fed as chapathis with vegetable dishes 6d/w
- monitor Hb, SF and TfR



Efficacy and effectiveness studies with electrolytic iron

Dose mg/d	Subject/ vehicle	Length of study/ country	Impact	Source
12.5	Women 16 -50 Wheat flour	24 months Sri Lanka	No change in Hb	Nestel (2004)
10	Women 18 -50 Wheat flour biscuits	9 months Thailand	Moderately efficacious No change in Hb	Zimmermann (2005)
3.2	Children 6 -11 Brown bread	7.5 months South Africa	No change in iron status	Van Stuijvenberg (2006)
21	Children 11 -18 Wheat flour	6 months China	Moderately efficacious	Sun (2007)
7	Children 3 -8 Maize porridge	5 months Kenya	No change in iron status	Andang 'o (2007)
4.5	Children 6 -11 Brown bread	8 months South Africa	No change in iron status	Van Stuijvenberg (2007 Abstract)
11	Children 6-14 Wheat flour bisuits	6 months Ivory Coast	No change in iron status	Rohner (2010)

Minimum daily amount of iron from different compounds which have been demonstrated to be efficacious in women

- Ferrous sulfate, 7.1 mg - 4 studies, all efficacious
  NaFeEDTA, 4.6mg - 10 studies, 9 efficacious
  Electrolytic iron 10mg - 7 studies, 2 efficacious

- Evidence-based values from studies with a demonstrated decrease in prevalence of ID/IDA.

Recommended levels of different iron compounds based on demonstrated efficacy

Flour consumption g/d	NaFeEDTA	Ferrous sulphate/ferrous fumarate	Electrolytic iron powder★
> 300	15	25	50
200 - 300	25	35	70
100 - 200	45	70	Not recommended★
< 100	45★	70★	Not recommended

- ★ **electrolytic Fe values increased to be 2 x ferrous sulfate**
- ★ **< 100 g flour/day cannot be fortified to cover iron requirements**
- ★ **< 200 g flour/day required electrolytic iron level too high**

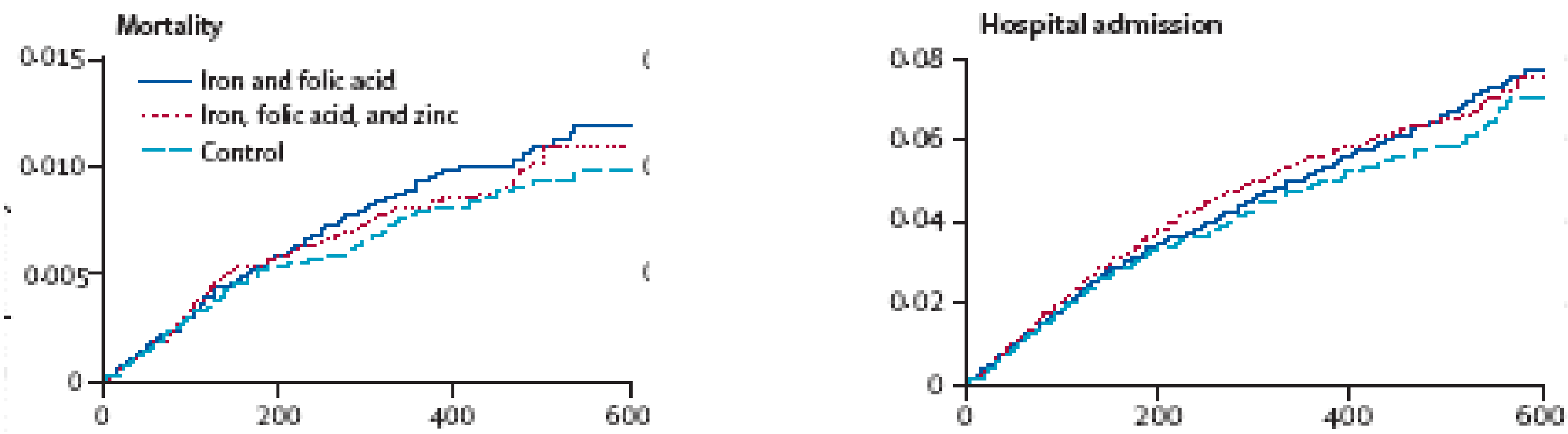
Safety issues with iron fortification

- **GENETIC DISORDERS**
  thalassemia
  sickle cells
  hemochromatosis
  - no public health concerns over heterogeneous trait carriers
  - carriers of α & β thalassemia traits absorb a little more Fe and have modestly increased stores but do not accumulate sufficient Fe to cause tissue damage (Zimmermann 2008)

- **INFECTION**
  - iron supplements may increase malarial infection (Sazawal et al, 2006)
  - no evidence that iron fortification increases infectious morbidity in non-malarious areas (Oppenheimer 2001) but no studies in high malaria areas

Iron and malaria

Historical concerns were reinforced by Pemba study (Sazawal et al.Lancet, 2006) suggesting that universal iron supplementation during early childhood increases the risk of severe morbidity and mortality from malaria and other infections, particularly when supplements are given to individuals who are not iron-deficient.



Nelson-Aalen cumulative hazard estimates for mortality and hospital admission

Cochrane Review: Oral iron supplementation for prevention or treating malaria among children in malaria endemic areas

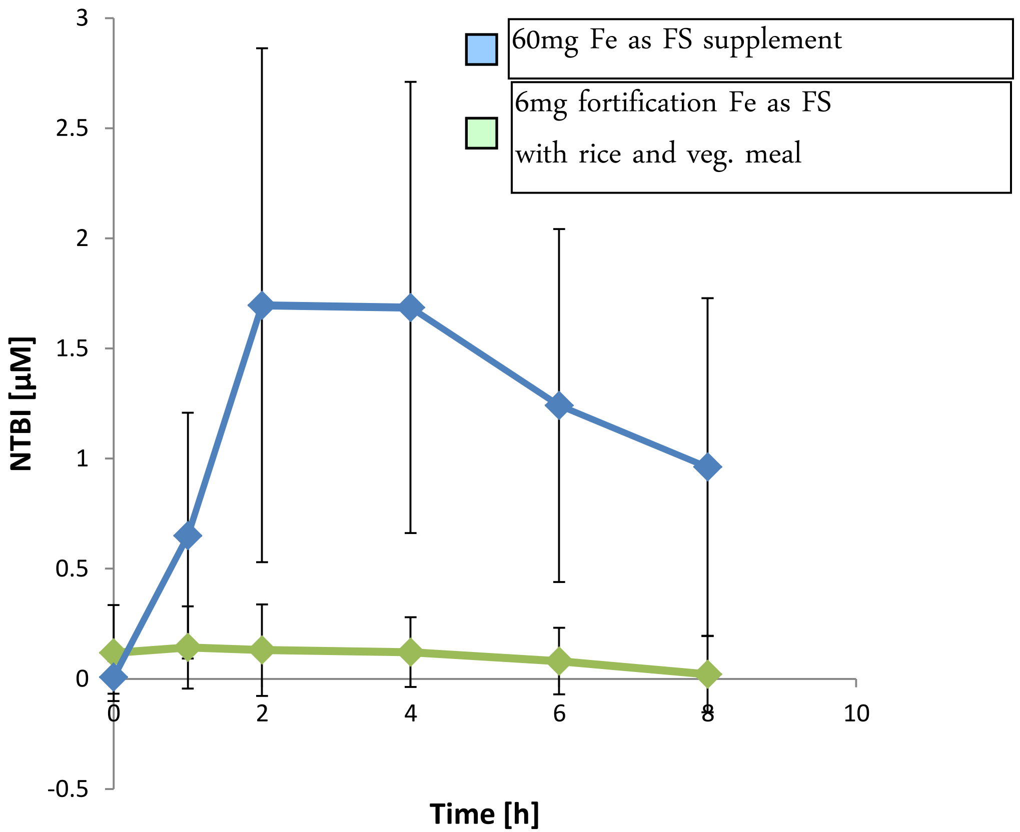
(Ojukwu et al, 2009)

- When comprehensive health care surveillance is available and there is prompt malaria diagnosis and treatment, there ***is no*** increased risk.
- When health care is insufficient there ***is*** an increased risk of malaria.
- Adequate malaria surveillance may not be practiced in all settings. Thus, the safety of iron supplementation in young children remains a concern.
- The concern is primarily in young children where resistance to malaria is not fully developed.

Iron fortification in areas with high malaria level and other infections

- mechanism of negative effect of iron supplementation thought to be modulated by non transferrin bound iron (NTBI)
- serum NTBI far lower with fortification than supplementation
- during infection and inflammation, hepcidin increase, iron abs decrease, and iron from broken down red cells stored in liver
- efficacy of Fe fortification likely to be lower in areas of widespread infection

Serum NTBI in women (SF<25μg/L) after Fe supplement (60mg) or Fe fortified food (6mg) (Egli et al, unpublished)



Final thoughts

- Iron fortification of wheat and maize flours is safe....

- ...and efficacious provided the recommended Fe compounds are used in adequate amounts.
  - electrolytic Fe is the only elemental Fe powder recommended

    H-reduced Fe and atomized reduced Fe powders are widely used and likely to have little or no impact on Fe status
  - efficacy is likely to be lower in areas of widespread infection

- If cereal flour fortification is planned to eliminate ID at a national level, consumption must be >100g/d. If not other food vehicles should also be Fe fortified (salt, sugar, bouillon cubes)

- Electrolytic Fe is not recommended when cereal flour consumption is <200g/d, and where there us widespread infection and inflammation.

The way forward

- The preferred iron compounds for wheat and maize flour fortification are:
  - NaFeEDTA
  - ferrous sulfate, encapsulated ferrous sulfate
  - ferrous fumarate, encapsulated ferrous fumarate
- The second choice iron compound is electrolytic Fe.
- If other elemental iron powders are currently used, this should be discontinued.
- Millers and premix suppliers should adopt these recommendations and governments should legislate for the use of the recommended compounds at the suggested fortification levels.