New Expert Recommendations on Wheat Flour Fortification

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Outline

AkzoNobel

Iron and the human body
  iron deficiency anemia: what can be done?

Fortification of wheat flour
  why not effective so far? how to fulfill body iron needs?

FeNa-EDTA (Ferrazone®)
  field trials, applications, new expert recommendations
  analysis in flour, product information
Akzo Nobel: Key Figures

- Net sales: €14 bln / year
- Number of employees: approx. 60,000

Decorative Paints
Specialty Chemicals
Performance Coatings

Ferrazone ® => Specialty Chemicals
Business Unit Functional Chemicals
Iron in Human Body

- Oxygen transport
  - hemoglobin, myoglobin

- Immune system

- Formation of new cells

- No excretion of iron
  - too much iron = toxic!

- Regulation of absorption is extremely tight!

- Total body iron: 3 – 4 g

Andrews 1999
Iron Absorption and Requirement

Absorption only to compensate for losses desquamation (skin cells), menstruation, ...

Body iron requirements (in mg/d)

- adult men: $1 – 1\frac{1}{2}$
- adult women: $1 – 3$
- pregnant women: $\sim 4$
- Infants (6 – 12 months): $\sim 1$

Absorption Fe: maximum 10 – 20% !

When less is absorbed over several years (e.g. 0.5 rather than 1.0 mg/d)

$\rightarrow$ iron deficiency anemia

US IoM 2001
Even after 19 Years

Children in Costa Rica recruited at 2 years of age in poor neighborhoods

one group: good iron status
other group: chronic iron-deficiency

At the age of 19: gap in “cognitive scores” is still widening!

Lozoff et al. 2006
Why is IDA prevalence so high?

Developing countries
up to 50% women and children; mild to severe anemia
Inhibitory diets
no (virtually no) meat
rich in phytate due to high-extraction flours
(consumption of tea)
Diseases
hookworm, malaria, …

Industrialized world
up to 10% adolescent girls (infants?); mainly iron deficiency
too low intake of meat?
What can be done?

Dietary changes
  meat, vitamin C  long-term option, expensive

Supplementation
  tablets, syrups (medicines)  only small part of a population

Fortification
  staple foods  whole population
  beverages, snacks  target groups
about 2/3 of the countries in the world run wheat flour fortification programs…

Source: Flour Fortification Initiative (FFI) at
http://www.sph.emory.edu/wheatflour/globalmap.php
Level of iron is sufficient but absorption is too low
form of iron fortificant is critically important

Suitability iron fortificants for flour fortification
sufficient level of absorption and no rancidity upon storage

*Electrolytic iron (and other elemental iron types)*

*Ferrous sulfate (FeSO₄) / Ferrous fumarate*

*Ferric sodium EDTA (FeNa-EDTA; Ferrazone®)*
Elemental Iron

Cheap, no taste effect, *not really effective either*

At low pH: elemental iron (Fe\(^0\)) ➔ ferrous (Fe\(^{2+}\)) ions
- pH = 2 (empty stomach) ➔ rapid dissolution
- pH ≥ 4 (full meal) ➔ dissolution much slower (if at all?)

Tablets, fortified snacks:
- can be effective (pH stomach still low)

Full meals (food fortification + phytate):
- *not* effective (pH stomach too high)
pH in the Stomach

pH measured with probes inside the esophagus at three different spots in the stomach.

Simonian et al. 2005
Manufactured from iron (Fe) and sulfuric acid (H$_2$SO$_4$)

After crystallization: $\Rightarrow$ FeSO$_4$·7H$_2$O

- **green** or **hydrated**
  - dissolves readily in water
  - risk of rancidity upon storage

After additional drying step: $\Rightarrow$ FeSO$_4$·xH$_2$O ($x \approx 1$)

- **white** or **dried**
  - no risk of rancidity
  - somewhat more expensive
  - dissolves well in water, but only at an extremely slow rate

Hurrell et al. 1989
Ferrous Fumarate

Manufactured from ferrous salt and fumaric acid red-brown powder

Solubility in water
poor at pH = 7 (food)
excellent at pH = 2 (stomach …)

Absorption characteristics
in all human studies fully equal to FeSO$_4$
Manufactured from a ferric salt and EDTA-Na4 after crystallization (pH < 7): FeNa-EDTA.3H2O yellow-brown powder

In water:
FeNa-EDTA.3H2O ➔

Na+ + 2 H2O + {Fe(III)-EDTA-OH2}−

Wageningen University 2007
Cereals ➔ Mill ➔ Flour

husks and shells separated from kernels by sieving
husks and shells: vitamins, minerals and phytate
kernels: starch

High-extraction (high in phytic acid and iron)
unleavened (flat) bread (South Asia, Middle-East)

Low-extraction (low in phytic acid and iron)
leavened (western style) bread
pasta products: instant noodles, spaghetti
Phytic Acid

Inositol hexaphosphoric acid

Strongly binds non-heme iron in food
Recent study Wageningen University (NL) on foods from China
Guansheng Ma et al. 2005

**Data on Wheat Flour**

<table>
<thead>
<tr>
<th>Extraction rate</th>
<th>[phytic acid]</th>
<th>[Fe]</th>
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<tbody>
<tr>
<td>Low (50%)</td>
<td>0.04%</td>
<td>4 ppm</td>
</tr>
<tr>
<td>High (85%)</td>
<td>0.4%</td>
<td>14 ppm</td>
</tr>
</tbody>
</table>

Note: 1% = 10,000 ppm
Iron Absorption FeSO\textsubscript{4} vs. FeNa-EDTA

Mean iron absorption (%) from fortified wheat bread rolls

- **Low-extraction wheat flour**
  - FeSO\textsubscript{4}: 5.70
  - NaFeEDTA: 11.50

- **High-extraction wheat flour**
  - FeSO\textsubscript{4}: 0.99
  - NaFeEDTA: 3.91

Hurrell et al. 2000
Expert view around 2000

Elemental iron

suitable at all for staple food fortification?

pH stomach >> 2 not yet known

Ferrous sulfate / ferrous fumarate

both well-effective, including in full meals

sensitive to the phytate content in a meal

FeNa-EDTA

much more effective than above-mentioned ferrous salts

particularly in the presence of phytate

uncertain regulatory status
Iron absorption is needed to balance daily losses
  dead skin cells (both adult men and women): ~ 1 mg/d
  monthly periods (adult women only): ~ 1 to 2 mg/d extra!
    average is ~ 1 mg/d, only 5% as much as ~ 2 mg/d Fe,

How to ensure absorption of 1 mg/d Fe from food?

Should food fortification provide at least 1 mg/d Fe
  adult men (and children): > 95% iron sufficient
  children until 2 years of age: special infant foods
  women of childbearing age: 50 – 80% OK as well
    high monthly blood losses (20 – 50%): iron-fortified niche products
Iron Absorption from Intrinsic Iron

All food products contain intrinsic iron
  = naturally present iron, range: 1 – 20 ppm
  heme iron (meat) and non-heme iron (vegetables)

Like FeSO₄ absorption of non-heme iron is poor
in the presence of high levels of phytate

Total absorption: added + intrinsic iron
Plants grown with radio-active labeled $^{55}$Fe iron

- meals with $^{55}$Fe intrinsic iron

Added iron: $^{59}$Fe FeNa-EDTA

Absorption from intrinsic iron (black bars) in same meal is higher than in separate meals!

MacPhail 1985
Intrinsic Iron and FeNa-EDTA (2)

Studies in meals prepared from radio-active labeled plants INACG 1993

<table>
<thead>
<tr>
<th>meal</th>
<th>addition</th>
<th>FeNa-EDTA</th>
<th>intrinsic Fe</th>
<th>ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>maize</td>
<td>sugar</td>
<td>12.9</td>
<td>4.9</td>
<td>2.6</td>
</tr>
<tr>
<td>maize</td>
<td>cooked into the meal</td>
<td>8.1</td>
<td>5.5</td>
<td>1.2</td>
</tr>
<tr>
<td>lentils</td>
<td>mixed with the dough</td>
<td>5.4</td>
<td>5.2</td>
<td>1.04</td>
</tr>
<tr>
<td>maize</td>
<td>mixed with the dough</td>
<td>4.8</td>
<td>4.0</td>
<td>1.3</td>
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<tr>
<td>maize</td>
<td>mixed with the dough</td>
<td>6.2</td>
<td>5.1</td>
<td>1.2</td>
</tr>
<tr>
<td>wheat</td>
<td></td>
<td>9.6</td>
<td>8.6</td>
<td>1.1</td>
</tr>
</tbody>
</table>

55Fe intrinsic iron
59Fe FeNa-EDTA ~ equal amounts
FeNa-EDTA

After having delivered its ferric ion the remaining, empty EDTA molecule can bind a new one from the intrinsic, non-heme iron pool and present it to the intestinal cells as well.

EDTA acts as a shuttle for intrinsic iron!

Absorption from intrinsic seems to be somewhat lower than from FeNa-EDTA itself. Not all intrinsic iron can be shuttled?

Unfortunately only scarce data available from 1970’s

Only way to explain high effectiveness in field trials.
High-extraction wheat flour at 300 g/d
iron content, both intrinsic and added: 15 ppm ~ 9 mg/d Fe

Absorption levels
No fortification: 1% from intrinsic Fe only
→ 0.045 mg/d
FeSO₄: 1% from FeSO₄ and from intrinsic Fe
→ 0.090 mg/d (extra: 0.045)
FeNa-EDTA: 4% from FeNa-EDTA and 3% from intrinsic Fe
→ 0.315 mg/d (extra: 0.270 = 6 times FeSO₄!)
Calculation example: total iron absorption \( \sim 0.3 \) mg/d (still < 1)

Example of 4%: volunteers with 20 µg/L serum ferritin  
Hurrell 2000

Iron absorption \( \sim \) serum ferritin (SF)  
Lynch et al. 1989

Iron deficiency: SF < 12 µg/L  
WHO guidelines

Iron absorption 3 times higher: 0.3 \( \Rightarrow \) 0.9 mg/d (\( \approx \) 1)
iron absorption from other food products as well

FeSO\(_4\): 0.1 \( \Rightarrow \) 0.3 mg/d, still < 1
Iron Absorption vs. Serum Ferritin

Relationship
serum ferritin (SF)
and iron absorption (IA)

SF two times lower
IA about two times up

Lynch et al. 1989

Needs refinement!
So far however only few additional data
FeNa-EDTA: Field Trials

So far 8 field trials, all with excellent results
Thailand, South Africa, Guatemala, China (2x), Vietnam, Kenya, India
Dosage range 4 – 10 mg/d Fe as FeNa-EDTA
Kenya, India: ultra inhibitory diets

Why so effective at such a low level?
clues for a possible explanation in previous sheets

Safe for use?
field trials: no single adverse health effect ever
as in decades-long use as a medicine for infants in France and UK
Official statements on safe use


JECFA 2007: Sodium iron EDTA is suitable for use as a source of iron for food fortification to fulfill nutritional iron requirements … approval for use in Brazil, China, India, …

Currents uses of FeNa-EDTA in food

1. China: soy sauce and wheat flour
2. Brazil: Tang powdered beverage
3. Pakistan: atta flour

Expert recommendations

flour: US CDC / FFI ➔ FAO/WHO
Low-extraction wheat flour

<table>
<thead>
<tr>
<th>Recommended iron fortificant</th>
<th>Average daily consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Above 200 g/d</td>
</tr>
<tr>
<td>Ferrous sulfate or ferrous fumarate</td>
<td>30 ppm Fe</td>
</tr>
<tr>
<td>Electrolytic iron</td>
<td>60 ppm Fe</td>
</tr>
<tr>
<td></td>
<td>Below 200 g/d</td>
</tr>
<tr>
<td></td>
<td>45 ppm Fe</td>
</tr>
<tr>
<td></td>
<td>90 ppm Fe</td>
</tr>
</tbody>
</table>

High-extraction wheat flour

FeNa-EDTA: 30 ppm Fe
Summary: iron fortification
(page 111)

- NaFeEDTA is recommended for the mass fortification of high-phytate cereal flours and for sauces with a high peptide content (e.g. fish sauce, soy sauce).
Second Technical Workshop on Flour Fortification
US CDC / FFI, Atlanta – USA, April 2008
http://www.sph.emory.edu/wheatflour/atlanta08/Atlantabackgrounddocument3finaldraft.doc

Follow-up of Cuernavaca 2004

Slight modification recommended levels
both high- and low-extraction wheat flour

Closer look at low-extraction wheat flour
threshold inhibitory effect of phytic acid
FeSO₄:  dried vs. hydrated
elemental iron: effective?
Phytic Acid in Low-Extraction Flour

No inhibitory effect phytic acid (PA) on iron absorption
molar ratio PA:Fe < 1:1, preferably < 0.4:1
(weight ratio < 12:1, preferably < 5:1)
Hurrell 2004

Food applications from low-extraction wheat flour
leavened bread: yeast for leavening, phytase  \[ \text{[PA]} = 0 \]
 instant noodles, spaghetti (pasta): no yeast  \[ \text{[PA]} > 0 \]
Guansheng Ma 2005: [PA] in pasta \( \approx 1,000 – 2,000 \) ppm
 [Fe]: > 80 – 160 ppm, preferably: > 200 – 400 ppm …
\[ \text{[PA]} = 0 \]  \( \Rightarrow \) FeNa-EDTA, FeSO\(_4\) or ferrous fumarate
\[ \text{[PA]} > 0 \]  \( \Rightarrow \) FeNa-EDTA
Atlanta Recommendations

<table>
<thead>
<tr>
<th>Type of flour</th>
<th>Fortificant</th>
<th>Average daily consumption in g/d</th>
</tr>
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<tr>
<td></td>
<td></td>
<td>&gt; 300</td>
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<tr>
<td>LOW-extraction</td>
<td>FeNa-EDTA</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Ferrous sulfate or Ferrous fumarate</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Electrolytic iron</td>
<td>40</td>
</tr>
<tr>
<td>HIGH-extraction</td>
<td>FeNa-EDTA</td>
<td>15</td>
</tr>
</tbody>
</table>

* The preferred order of iron fortificants is: FeNa-EDTA, FeSO4 and ferrous fumarate. If these cannot be used, add electrolytic iron.

Minimum levels of Fe consumed:
1. FeNa-EDTA 4 mg/d
2. Ferrous salts 7 mg/d
3. Electrolytic iron 14 mg/d
Endorsements in 2009

GAIN

http://www.gainhealth.org/2009EOIFFP

2.3 Appropriate Fortificant: The actual vitamin and mineral compound used to fortify the food or condiment must follow the latest international standard recommendations … for wheat flour and maize meal. (= “Atlanta 2008”) …

WHO

http://www.who.int/nutrition/publications/micronutrients/wheat_maize_fort.pdf
How to check \([\text{Fe}]\) as \(\text{FeNa-EDTA}\) in flours?

**Method as developed by AkzoNobel for FeNa-EDTA**

(based on existing colorimetric tests)

1. extraction with water (or water/methanol)
2. separation water from flour by filtration or centrifuging
3. addition of coloring reagents (phenanthroline)
4. evaluation of resulting orange color
   by spectrophotometric determination or visual assessment
Visual Comparison

Example: Indian atta flour fortified with 19 ppm Fe as Ferrazone Reference samples ([Fe] in ppm) prepared from FeSO$_4$.
EDTA

EthyleneDiamine TetraAcetic acid

\[ \text{HOOC} - \text{CH}_2 - \text{N} - \text{CH}_2 - \text{CH}_2 - \text{N} - \text{CH}_2 - \text{COOH} \]

\[ \text{CH}_2 - \text{COOH} \]
Ferric Sodium EDTA

FeNa-EDTA.3H₂O

Fe³⁺

H₂O

Na⁺

2 H₂O

HOOC - CH₂

N - CH₂ - CH₂ - N

HOOC - CH₂

CH₂ - COOH

CH₂ - COOH
Ferrazone® Product Range

Food-grade ferric sodium EDTA ex AkzoNobel

→ Ferrazone® (www.ferrazone.com)

Ferrazone®

Sodium Iron (III) Ethylenediaminetetraacetate

Ferrazone® is a stable, water soluble iron compound that meets JECFA specifications for food fortification. Ferrazone® is Generally Recognized As Safe (GRAS) by the US FDA. Ferrazone® manufacturing is certified to be in accordance with the HACCP requirements.

<table>
<thead>
<tr>
<th>Checksheet</th>
<th>Specification</th>
<th>Units</th>
<th>Method</th>
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<tbody>
<tr>
<td>Appearance</td>
<td>Yellowish brown coloured powder</td>
<td>Visual</td>
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<tr>
<td>Iron content</td>
<td>15.0-15.2</td>
<td>%</td>
<td>JECFA</td>
</tr>
<tr>
<td>EDTA content</td>
<td>65.0-70.5</td>
<td>%</td>
<td>JECFA</td>
</tr>
<tr>
<td>Identification</td>
<td>Phone tests</td>
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<tr>
<td>Phosphate ion</td>
<td>0.5 max.</td>
<td>%</td>
<td>JECFA</td>
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<tr>
<td>Nitrate ion</td>
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<td>%</td>
<td>JECFA</td>
</tr>
<tr>
<td>Ammonia</td>
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<td>mg/kg</td>
<td>JECFA</td>
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<tr>
<td>Lead</td>
<td>0.1 max.</td>
<td>mg/kg</td>
<td>JECFA</td>
</tr>
</tbody>
</table>

Net Weight: 25 kg

Ferrazone® XF

Sodium Iron (III) Ethylenediaminetetraacetate

Ferrazone® XF is a stable, water soluble iron compound that meets JECFA specifications for food fortification. Ferrazone® XF is Generally Recognized As Safe (GRAS) by the US FDA. Ferrazone® XF manufacturing is certified to be in accordance with the HACCP requirements.

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<tr>
<td>Iron content</td>
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<td>%</td>
<td>JECFA</td>
</tr>
<tr>
<td>EDTA content</td>
<td>65.0-70.5</td>
<td>%</td>
<td>JECFA</td>
</tr>
<tr>
<td>Identification</td>
<td>Phone tests</td>
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<td></td>
</tr>
<tr>
<td>Phosphate ion</td>
<td>0.5 max.</td>
<td>%</td>
<td>JECFA</td>
</tr>
<tr>
<td>Nitrate ion</td>
<td>0.5 max.</td>
<td>%</td>
<td>JECFA</td>
</tr>
<tr>
<td>Ammonia</td>
<td>&lt; 0.1</td>
<td>mg/kg</td>
<td>JECFA</td>
</tr>
<tr>
<td>Lead</td>
<td>&lt; 0.1</td>
<td>mg/kg</td>
<td>JECFA</td>
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</tbody>
</table>

Net Weight: 25 kg

Ferrazone® BP

Sodium Formate

Ferrazone® BP is a stable, water soluble iron compound that meets British Pharmacopoeia specifications for pharmaceutical application. Ferrazone® BP is Generally Recognized As Safe (GRAS) by the US FDA. Ferrazone® BP manufacturing is certified to be in accordance with the HACCP requirements.

<table>
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<td>Yellowish brown coloured powder</td>
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<td></td>
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<tr>
<td>Iron content</td>
<td>15.0-15.2</td>
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<td>JECFA</td>
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<td>Formate ion</td>
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<td>Identification</td>
<td>Phone tests</td>
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<td></td>
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<tr>
<td>Potassium</td>
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<td>Chloride</td>
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<td>mg/kg</td>
<td>JECFA</td>
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<td>Loss on drying</td>
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<td>%</td>
<td>JECFA</td>
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<tr>
<td>Heavy metal 5% Pb</td>
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<td>JECFA</td>
</tr>
<tr>
<td>Free and/or EDTA</td>
<td>0.01 max.</td>
<td>mg/kg</td>
<td>JECFA</td>
</tr>
</tbody>
</table>

Net Weight: 25 kg

< 500 micron

Food & Beverages

< 150 micron

Wheat Flour

< 500 micron

Pharmaceuticals
Finally

Please have a closer look at www.ferrazone.com

New Expert Recommendations on Wheat Flour Fortification:
Thank you for your attention!