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Dr. Carel Wreesmann

Ferric sodium EDTA

Now approved also in EU and in India

An update of the global regulatory status

Dar es Salaam – Tanzania
April 5th, 2011

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Lay-out

FeNa-EDTA

JECFA 1993 – 2007

US FDA 2006

WHO 2009

EFSA (EU) 2010

India 2011

Chemical specifications FCC

Determination [Fe] in flour

Human safety of EDTA

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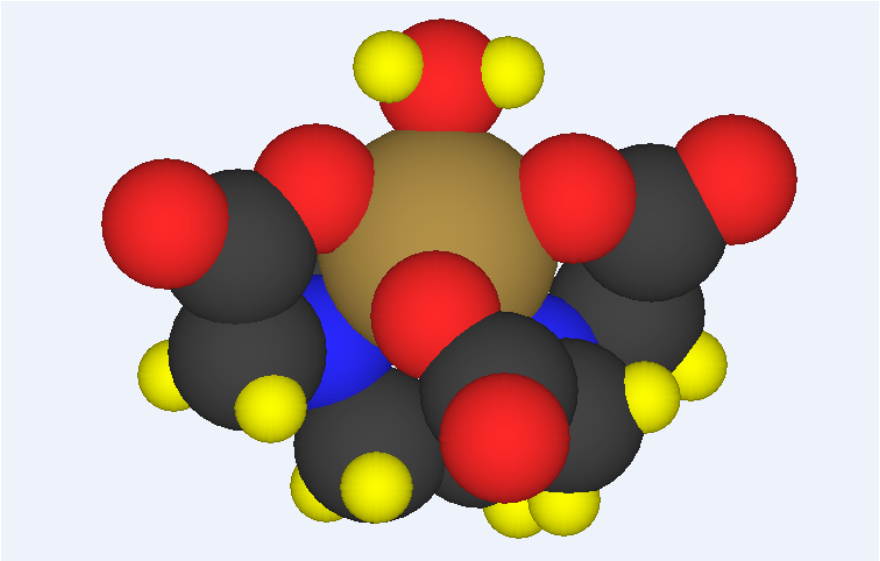
FeNa-EDTA

Ferric sodium EDTA (or sodium iron(III) EDTA)

- food-grade of AkzoNobel ➔ Ferrazone®
- special grade for flour: Ferrazone® XF

$FeNa\text{-}EDTA.3H_2O \rightarrow Na^+ + \{H_2O\text{-}Fe(III)\text{-}EDTA\}^- + 2\ H_2O$



Wageningen University 2007

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JECFA

Joint (FAO/WHO) Expert Committee on Food Additives

1993 *The Committee provisionally concluded that the use of sodium iron EDTA …… would not present a safety problem in supervised food fortification programmes ……*

- http://whqlibdoc.who.int/trs/WHO_TRS_837.pdf

1999 *The Committee concluded that sodium iron EDTA could be considered safe when used in supervised food fortification programmes ……*

- http://whqlibdoc.who.int/trs/WHO_TRS_896.pdf

2007 *Sodium iron EDTA is suitable for use as a source of iron for food fortification ……*

- restriction *supervised food fortification programmes …...* left out
  - http://www.who.int/ipcs/food/jecfa/summaries/summary68.pdf

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US FDA 2006

GRAS: Generally Recognized As Safe

Procedure

- prepare your own dossier
  - strong emphasis on manufacturing details
  - consultant Cantox
- find three prominent US scientists willing to evaluate
  - Prof. Joseph Borzelleca (Virginia Commonwealth University)
  - Prof. Fernando E. Viteri (University California Berkeley)
  - Prof. Dennis D. Miller (Cornell University)
- hold an expert panel meeting
  - Yes, Ferrazone is GRAS

http://www.accessdata.fda.gov/scripts/fcn/gras_notices/grn000178.pdf

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Atlanta Workshop 2008

Second Technical Workshop on Flour Fortification

- US CDC / FFI, Atlanta – USA, April 2008

http://www.sph.emory.edu/wheatflour/atlanta08/summary.html

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Atlanta Recommendations: WHO 2009

Type of flour	Fortificant	Average daily consumption in g/d		
		> 300	150 – 300	< 150
LOW-extraction	**FeNa-EDTA**	**15**	**20**	**40**
	Ferrous sulfate or Ferrous fumarate	20	30	60
	Electrolytic iron	40	60	not recommended
HIGH-extraction	**FeNa-EDTA**	**15**	**20**	**40**

Richard Hurrell et al. Food and Nutrition Bulletin **31** (2010) S7

http://www.who.int/nutrition/publications/micronutrients/wheat_maize_fort.pdf

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EFSA 2010

efsa
European Food Safety Authority

Scientific Opinion

Panel on Food Additives and Nutrient Sources added to Food (ANS)

The Panel concludes that iron is bioavailable from ferric sodium EDTA and that the use of ferric sodium EDTA as a source of iron in food is of no safety concern as long as it does not lead to an exposure to EDTA above 1.9 mg/d.kgbw of EDTA-H_4.

http://www.efsa.europa.eu/en/scdocs/scdoc/1414.htm

Next step in EU: approval by DG SANCO

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Decision European Commission 2010

Decision of June 14th, 2010

ANNEX II

Maximum amounts of Ferric Sodium EDTA (expressed as anhydrous EDTA)

Food supplements (in accordance with Directive 2002/46/EC)	children: 18 mg per daily dose as recommended by the manufacturer
	adults: 75 mg per daily dose as recommended by the manufacturer
Dietetic foods (in accordance with Regulation (EC) No 953/2009)	12 mg EDTA per 100 g of final food
Fortified foods (in accordance with Regulation (EC) No 1925/2006)	12 mg EDTA per 100 g of final food

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:149:0016:0019:EN:PDF

Note: EDTA = EDTA-H_4 12 mg ~ 2.3 mg Fe

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Comments EU approval on FeNa-EDTA

All "other" food products can be fortified with FeNa-EDTA

- all food products as commercially available in the EU

Very lenient approach on maximum ADI issue

12 mg EDTA ~ 2.3 mg Fe as FeNa-EDTA ~ 15% NRV + overage

Food product labeling

- 15% NRV ➔ "contains iron" or "source of iron" = allowed
  - 30% NRV ➔ "rich in iron" = not allowed (not so relevant)

NRV for Fe: 14 mg ➔ 15% NRV = 2.1 mg (Nutrient Reference Value)

Overage: 0.2 mg (= 10% of 2.1 mg; not really required for FeNa-EDTA)

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India 2011

Draft Notification of February 14th, 2011

Food Safety and Standards Authority of India (FSSAI)

FeNa-EDTA is allowed in:

	as such	Fe
	maximum level in ppm	
Drinks ready to serve beverages, carbonated fruit drink and fruit nectars	155	20
Flour atta and maida	200	26

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Global Comparison

Allowed (recommended) levels Fe as Ferrazone (in ppm)

	USA	WHO	EU	India	China
Drinks	**12.5**	**-**	**23**	**20**	**20**
Flour	**-**	**15, 20, 40**	**~ 30 – 50**	**26**	**20**

Note: EU only final foods

1 kg flour ➔ 1.5 – 2 kg bread

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Regulatory Status of FeNa-EDTA

Official statements on safety FeNa-EDTA

- JECFA 1993 (ILSI / US AID)
- JECFA 1999 (ILSI / US AID)
- US FDA 2006 (AkzoNobel)
- JECFA 2007 (AkzoNobel)
- EFSA 2010 (AkzoNobel)

Approved for use

- whole Latin America except Argentina (Kellogg, ILSI)
- China, Vietnam, Philippines, Pakistan (ILSI, other NGO's)
- USA, Malaysia/Indonesia, Australia/NZ, Russia, EU (AkzoNobel)
- India (joint-effort, including AkzoNobel)

Not yet / pending

- Africa, Middle-East

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Chemical Specifications

Food Chemical Codex (FCC)

- monograph in second supplement to the 7th edition

	Check Point	Specification Limits	SMA
1.	Appearance	yellow-brown to light-yellow powder	
2.	Odor	fully odorless	
3.	Iron content %	13.0 – 13.5	347.38
4.	EDTA content %	67.5 – 71.5	928.38
5.	pH of 1% solution	4.5 – 5.5	176.38
6.	Water insoluble matter %	0.1 max	116.38
7.	NTA acid %	0.1 max	975.38
8.	Arsenic mg/kg	1 max	864.38
9.	Lead mg/kg	1 max	864.38
10.	Chloride mg/kg	600 max	269.38
11.	Sulfate mg/kg	600 max	841.38
12.	Free Iron %	0.05 max	952.38
13.	Loss on Drying %	12.5 – 13.5	280.38
14.	Absorbance	0.240 max	978.38

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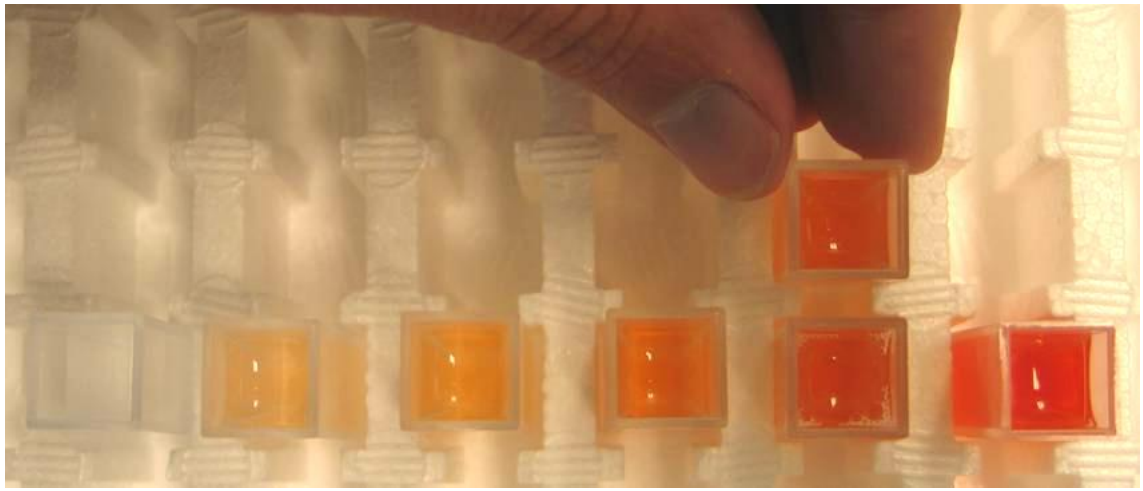
Determination in Flours

Iron EDTA Test (AkzoNobel)

1. extract flour with water
2. separate water from flour
3. add coloring agents
4. measure absorption



0 5 10 15 20 25

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Safety of EDTA: Animal Test Data

Study	highest exposure level to EDTA (in mg/d.kgbw)	Observations
Yang (PhD thesis) 1952	2,500	no particular health problems! group of test animals too small?
Foreman et al. 1954	500	occasionally diarrhea
Oser et al. 1963	**250**	**➔ maximum ADI (JECFA 1974)**
Swenerton & Hurley 1971	1,500	teratogenic effects due to severe zinc deficiency, fully reversible with some extra zinc in the feed
NCI – USA 1977	375	EDTA is NOT carcinogenic

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Can EDTA cause Cancer?

Large animal study of NCI published in 1977

- National Cancer Institute (USA)

Test program

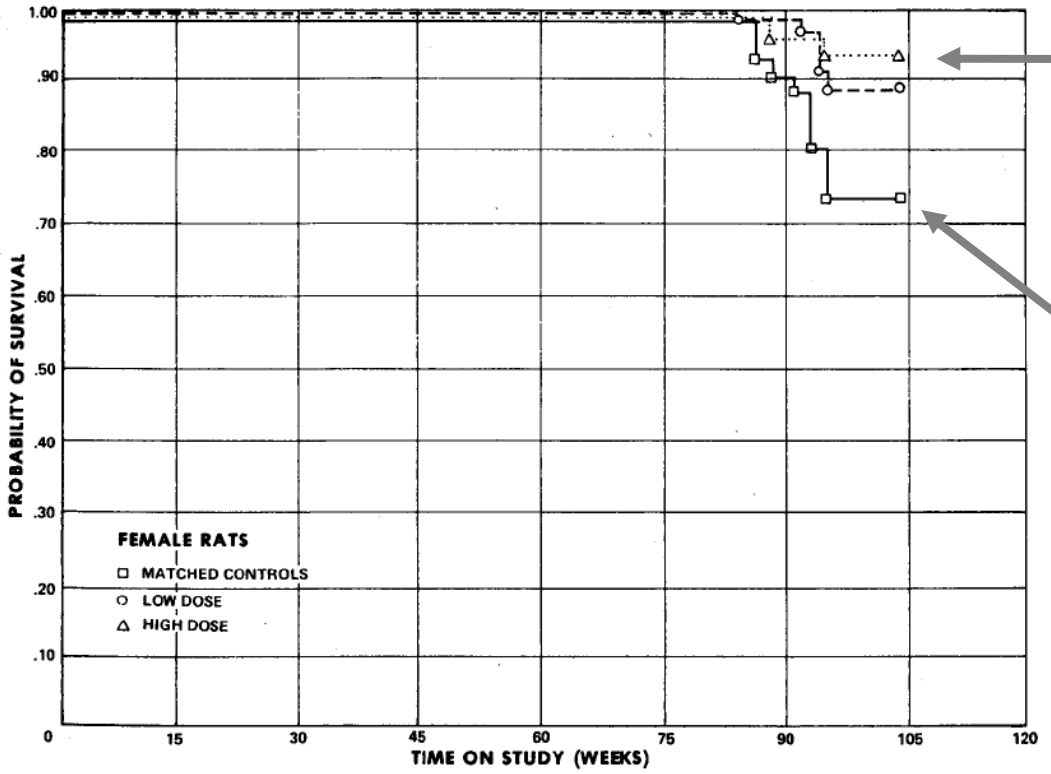
- Na_3H-EDTA.H_2O at 3,750 and 7,500 ppm in feed
- 100 rats and 100 mice during 2 years
  - life expectancy of these rodent ≈ 2 years

Final conclusion for EDTA

- "no evidence of carcinogenicity"
  - same test for NTA: kidney tumors

Survival Curves NCI 1977

Example: female rats



High dosage

Control

Na_3H-EDTA at 375 mg/d.kgbw

(compare 60-kg adult: 22.5 g/d!)

NCI 1977

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Other High-Intake Animal Studies

Highest dose: 250 mg/d.kgbw in rats (2 y) and dogs (1 y)

- *The hematological findings suggest that the dogs at all dosage levels were in a **better** state of health after one year of test feeding than they were originally.*
- basis of current maximum ADI of EDTA = 1.9 mg/d.kgbw

Oser et al. 1963

Highest dose: 2,500 mg/d.kgbw in rats (2 y)

- *The highest mortality occurred in group I [0 = control] and, in decreasing order, in groups II [250] and III [1,000]. There were no deaths in group IV [2,500].*
- data rejected: mortality too high in control group
- otherwise: maximum ADI of EDTA 10 times higher

Yang 1952

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Thank you for your attention!