

# Comparison of Regulations in India and EU

## A Case Study

### EDTA - Ferric Sodium EDTA



ILSI - India  
April 30<sup>th</sup>, 2011

EDTA

FeNa-EDTA

JECFA 1993 – 2007

US FDA 2006

WHO 2009

EFSA / EU 2010

India 2011

Chemical specifications FCC

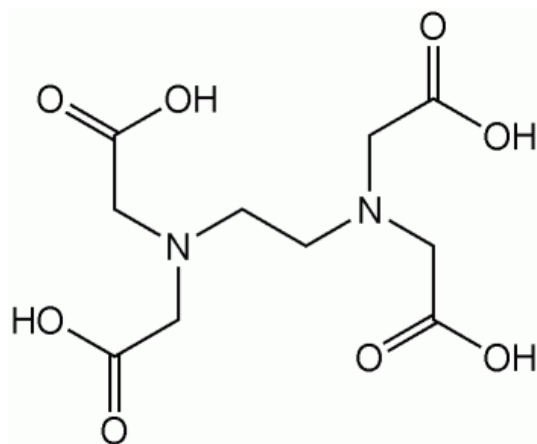
Determination [Fe] in flour

Human safety of EDTA



# EDTA

EDTA: EDTA-H<sub>4</sub>



H<sub>4</sub> → Na<sub>4</sub> →

Me(II)Na<sub>2</sub> or Me(III)Na

EDTA-Na<sub>4</sub>

- industrial cleaning agent
  - dissolves calcium salts

EDTA-CaNa<sub>2</sub>

- food preservative
  - prevents rancidity and discoloration

EDTA-FeNa

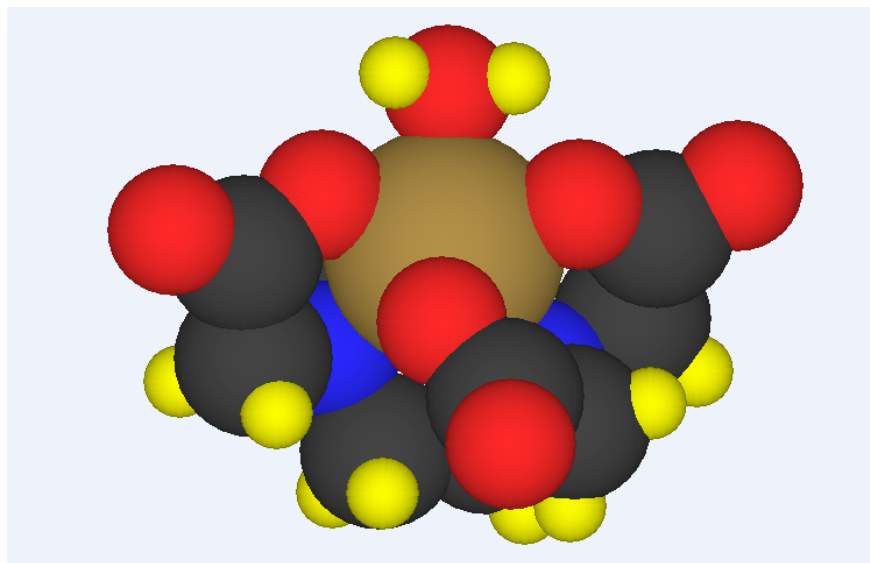
- food fortificant
  - ensures adequate iron absorption



# FeNa-EDTA

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

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



Wageningen University 2007



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## 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](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](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>



## 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](http://www.accessdata.fda.gov/scripts/fcn/gras_notices/grn000178.pdf)



# 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>



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

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



**World Health Organization**

**Recommendations on Wheat and Maize Flour Fortification  
Meeting Report: Interim Consensus Statement**

[http://www.who.int/nutrition/publications/micronutrients/wheat\\_maize\\_fort.pdf](http://www.who.int/nutrition/publications/micronutrients/wheat_maize_fort.pdf)







## 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<sub>4</sub>.*

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



# Decision European Commission 2010

Decision of June 14<sup>th</sup>, 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<sub>4</sub>

12 mg ~ 2.3 mg Fe



# 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)



# India 2011

Draft Notification of February 14<sup>th</sup>, 2011

Food Safety and Standards Authority of India (FSSAI)

FeNa-EDTA is allowed in:

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



# 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



# 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



# Chemical Specifications

## Food Chemical Codex (FCC)

- monograph in 2<sup>nd</sup> supplement to the 7<sup>th</sup> edition (2011)

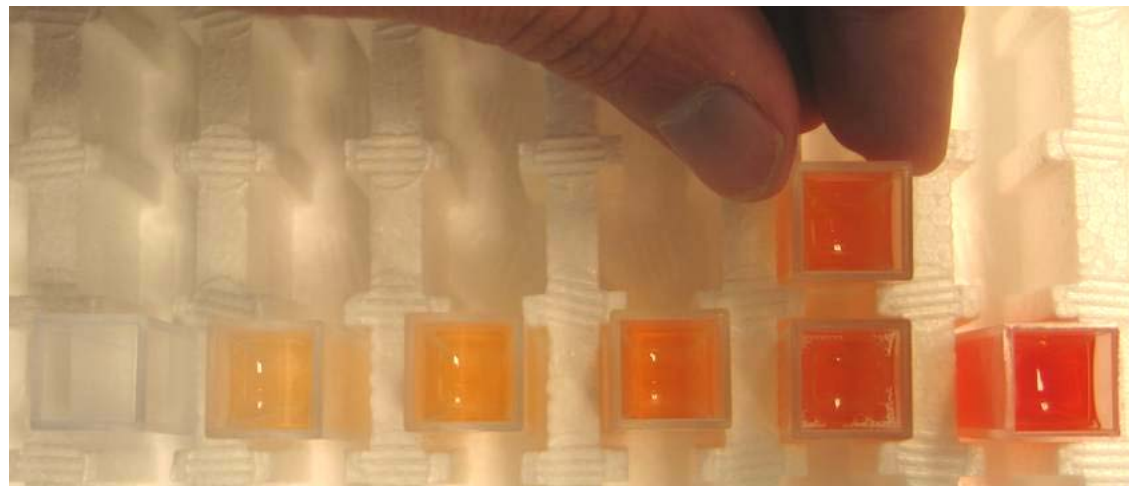
	Check Point	Specification Limits	SMA
1.	Appearance	yellow-brown to light-yellow powder	
2.	Odor	fully odorless	
3.	Iron content %	13.0 – 13.5	347.38
4.	EDTA content %	67.5 – 71.5	928.38
5.	pH of 1% solution	4.5 – 5.5	176.38
6.	Water insoluble matter %	0.1 max	116.38
7.	NTA acid %	0.1 max	975.38
8.	Arsenic 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



# 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





# 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
<b>Oser et al. 1963</b>	<b>250</b>	<b>→ maximum ADI (JECFA 1974)</b>
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



# Can EDTA cause Cancer?

Large animal study of NCI published in 1977

- National Cancer Institute (USA)

Test program

- $\text{Na}_3\text{H-EDTA}\cdot\text{H}_2\text{O}$  at 3,750 and 7,500 ppm in feed
- 100 rats and 100 mice during 2 years
  - life expectancy of these rodents  $\approx$  2 years

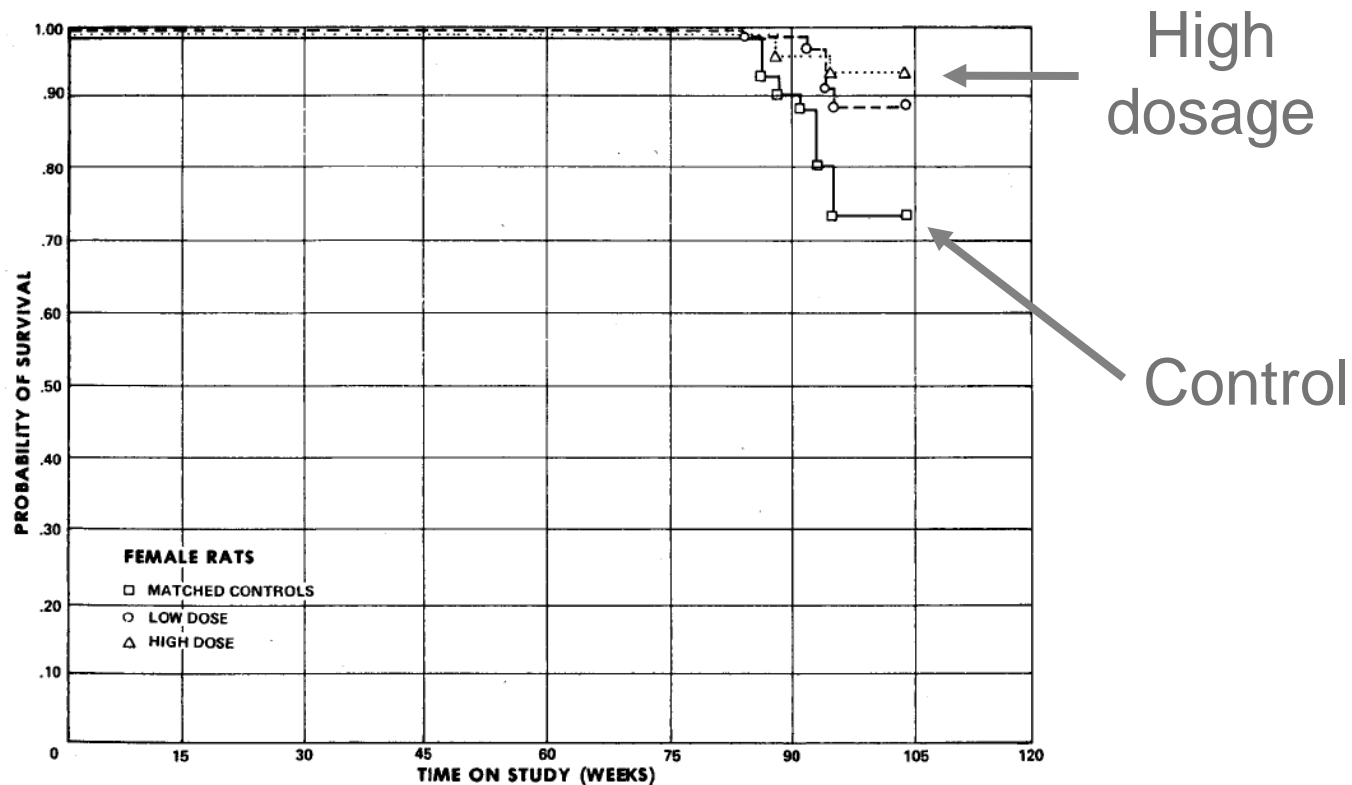
Final conclusion for EDTA

- “no evidence of carcinogenicity”



# Survival Curves NCI 1977

Example: female rats



Na<sub>3</sub>H-EDTA at 375 mg/d.kgbw  
(compare 60-kg adult: 22.5 g/d!)

NCI 1977



## 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].*
- JECFA rejected these data in 1974: mortality too high in control group
- otherwise: maximum ADI of EDTA could have been 10 times higher

Yang 1952



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*Thank you for your attention!*

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