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# Overview of Micronutrients: Iron and Folate

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# Disclaimers

- I am not an expert in iron and folate, but only a professional working in public health programs, who is trying to understand the reasons and origin of current recommendations.
- If something that I say does not make sense, please tell us so, and we would discuss an appropriate compromise, as our “truths” (i.e. recommendations) are limited by the advance in the reduction of our ignorance.
- I am happy to be here for learning of the science and experience of many others, especially those working with realities.

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# Outline

1. What are the consequences of iron and folate deficiency? Examples of corrections.
2. Are there adverse effects due to excesses?
3. Are there biomarkers of iron and folate status?
4. How much is too little and how much is too much?
5. Then, how to add additional amounts in a safe and efficacious manner?
6. Questions and discussion.

# Causes of anemia

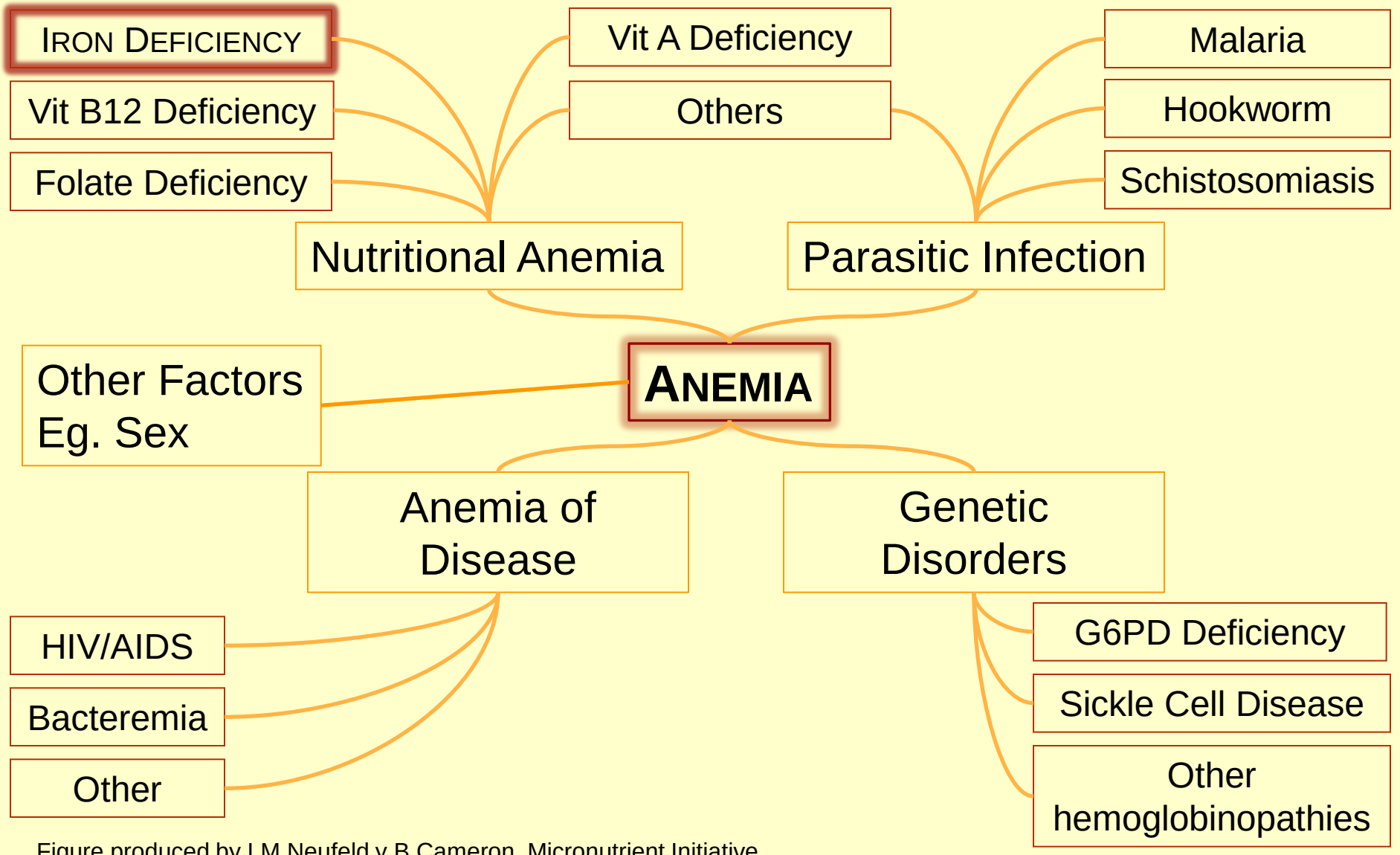


Figure produced by LM Neufeld y B Cameron, Micronutrient Initiative

Micronutrient Initiative

# Consequences of iron deficiency

- Tiredness, lack of energy
- Deterioration in detoxifying process
- Impairment of the immunological response
- Irreversible cognitive retardation (< 2 years old)
- Anemia
- Maternal mortality (when severe)

# An example of benefit by increasing iron intake in an iron-deficient population

Percent of low scores of motor development at 9 months under different scenarios of iron supplementation (Hebei, China)

| | | Pregnant women (96 mg Fe/day; 400 µg Folic Acid/day) | |
|---|---|---|---|
| | | **Placebo** | **+ Iron** |
| Infants (1 mg Fe/kg from 6 weeks) | **Placebo** | - 24 % | - 29 % |
| | **+ Iron** | - 16 % | - 19 % |

**Source:** Angulo Barroso *et al*., *Pediatrics* 2016; **137**: e20153547.





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# Iron homeostasis during pregnancy

- Women should start pregnancy with 500 mg of stored iron
- During pregnancy: + 480-1150 mg Fe
- Transfer to fetus during the last 10 weeks of gestation; 270 mg Fe; 5.6 mg Fe/day
- Delayed cord clamping: until cord stops pulsing: 30% more blood volume; 60 % more iron in RBC; 75 mg iron
- During third trimester of pregnancy: 3-8 mg Fe/day
- Iron intake during third trimester of pregnancy?

  5% bioavailability: 60 – 160 mg Fe/day
  10 % bioavailability: 30 – 80 mg Fe/day
  20 % bioavailability: 15 – 40 mg Fe/day

- One iron receptor in human placenta (hemochromial; depend on transferrin-bound Fe), the proton-coupled folate transporter (PCFT), shows two orders of magnitude higher affinity for folate.

**Source:** Cao & O'Brien, *Nutr Rev* 2013; **71**35-51.





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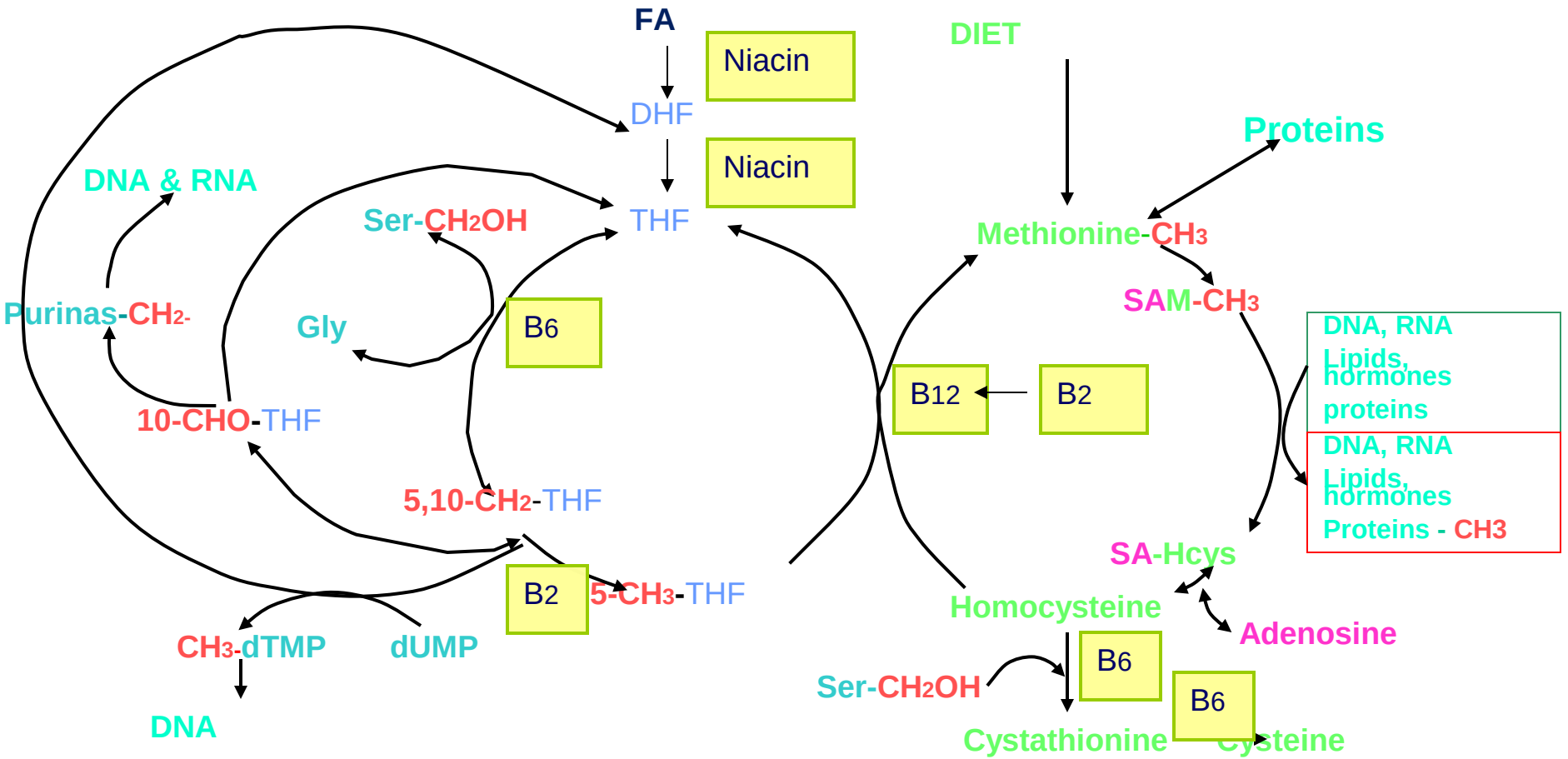
# Roles of folate (and other vitamins)



# Consequences of folate (and/or B12 deficiencies)

Neural tube defects within 28 days after conception.

**Incapacities:**

- Leg paralysis
- Hydrocephaly
- Bad control of bladder and intestinal evacuations
- Learning difficulties

Other consequences:

- Fetal growth retardation
- Low birth weight
- Pre-term delivery
- Macrocytic anemia
- Risk to cancers: leukemia, lymphoma, colorectal, breast, prostate

Modified from Jorge Rosenthal

# Folic acid reduces recurrence of NTDs

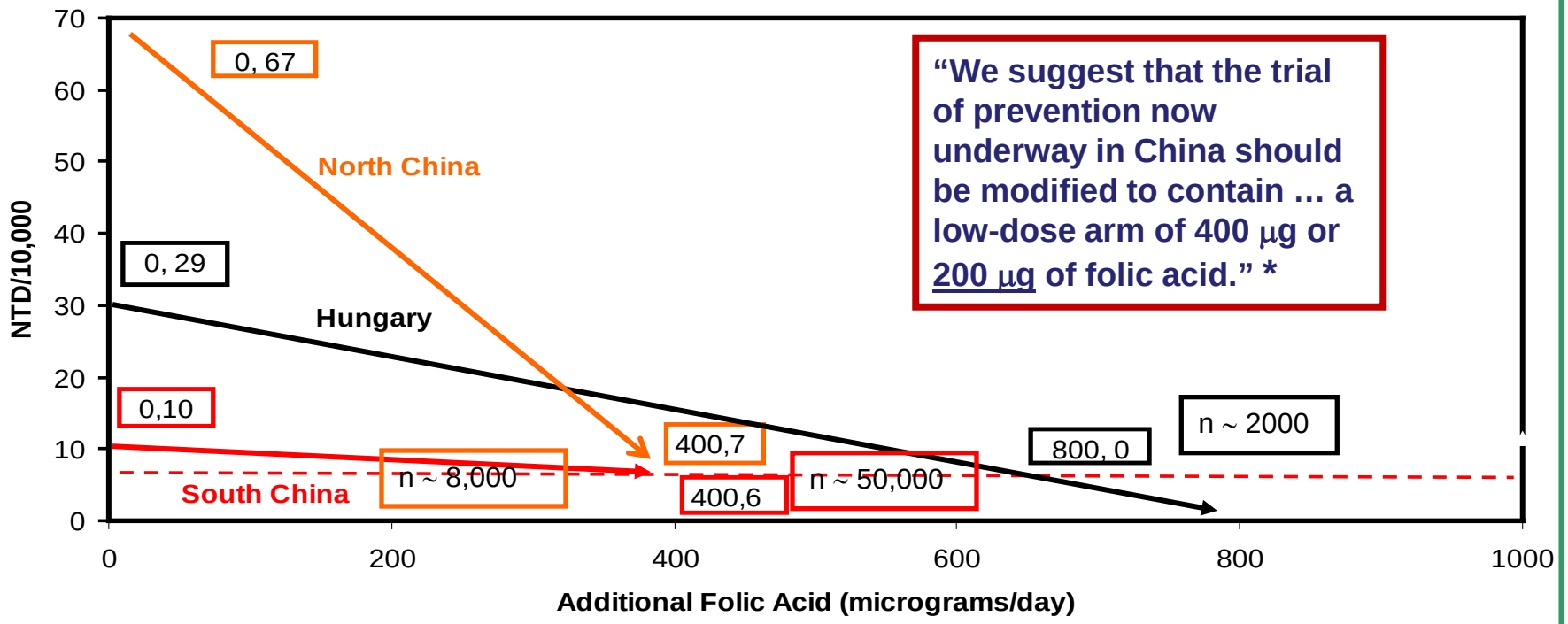
## NTD/10,000 pregnancies

| Country | Year | Control | + Min. & Vit. No Folic Acid | + Min. & Vit. + Folic Acid | + Folic Acid | Reference |
|---|---|---|---|---|---|---|
| U.K. | 1976 and before | 470 | - | 70 [360 µg/d] | - | 1 |
| Inter-country | 1983-91 | 423 | 272 | 117 [4000 µg/d] | 78 [4000 µg/d] | 2 |
| Ireland | 1981-88 | 291 | 112 | 0 [360 µg/d] | 0 [360 µg/d] | 3 |


**References:**

1. Smithells et al., *Lancet* 1983; i:1027-1031.
2. MRC. *Lancet* 1991; 338:131-137.
3. *Kirke et al., Arch Dis Child 1992; 1442-1446*

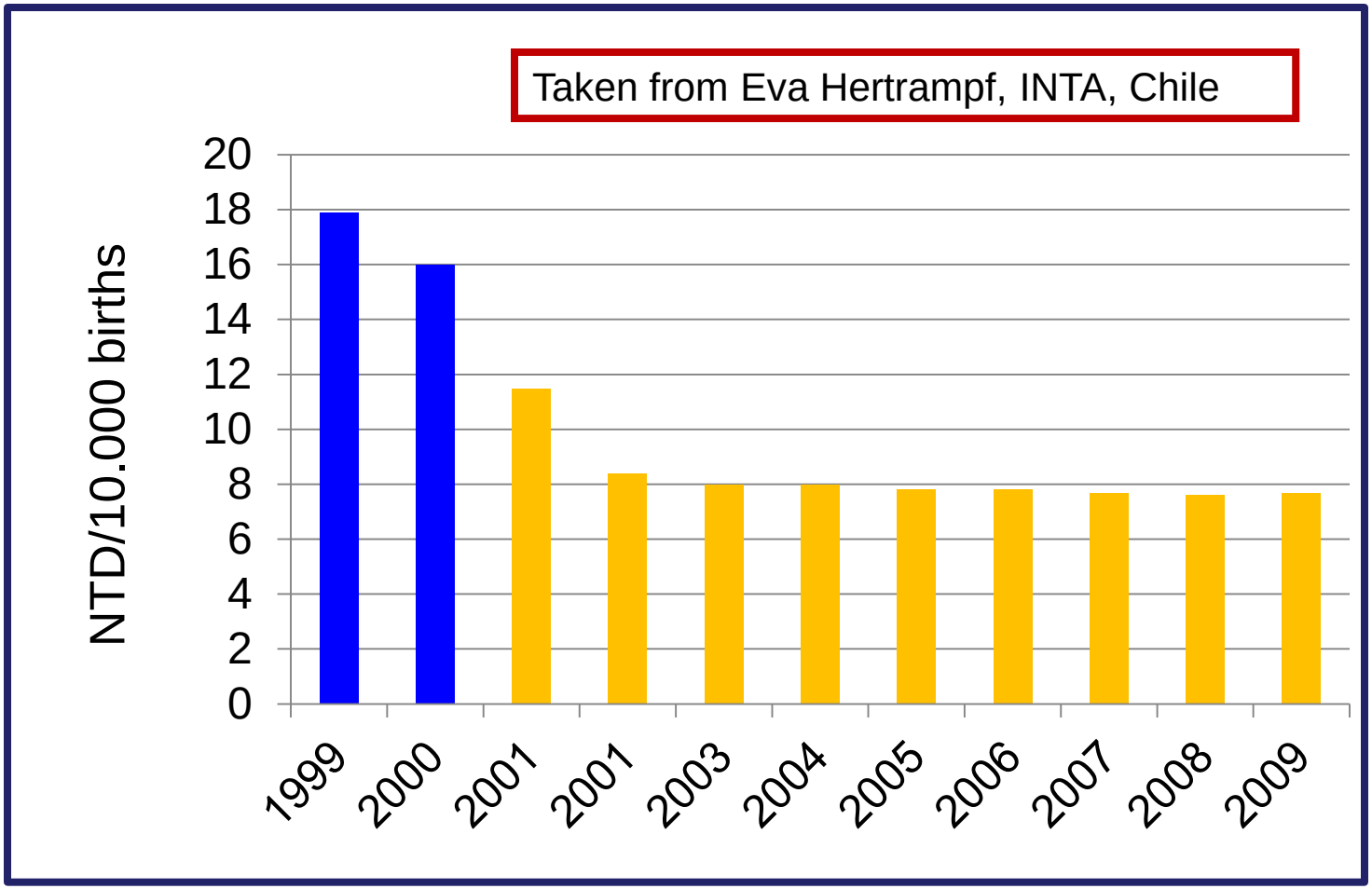
# Prevention of first occurrence of NTDs



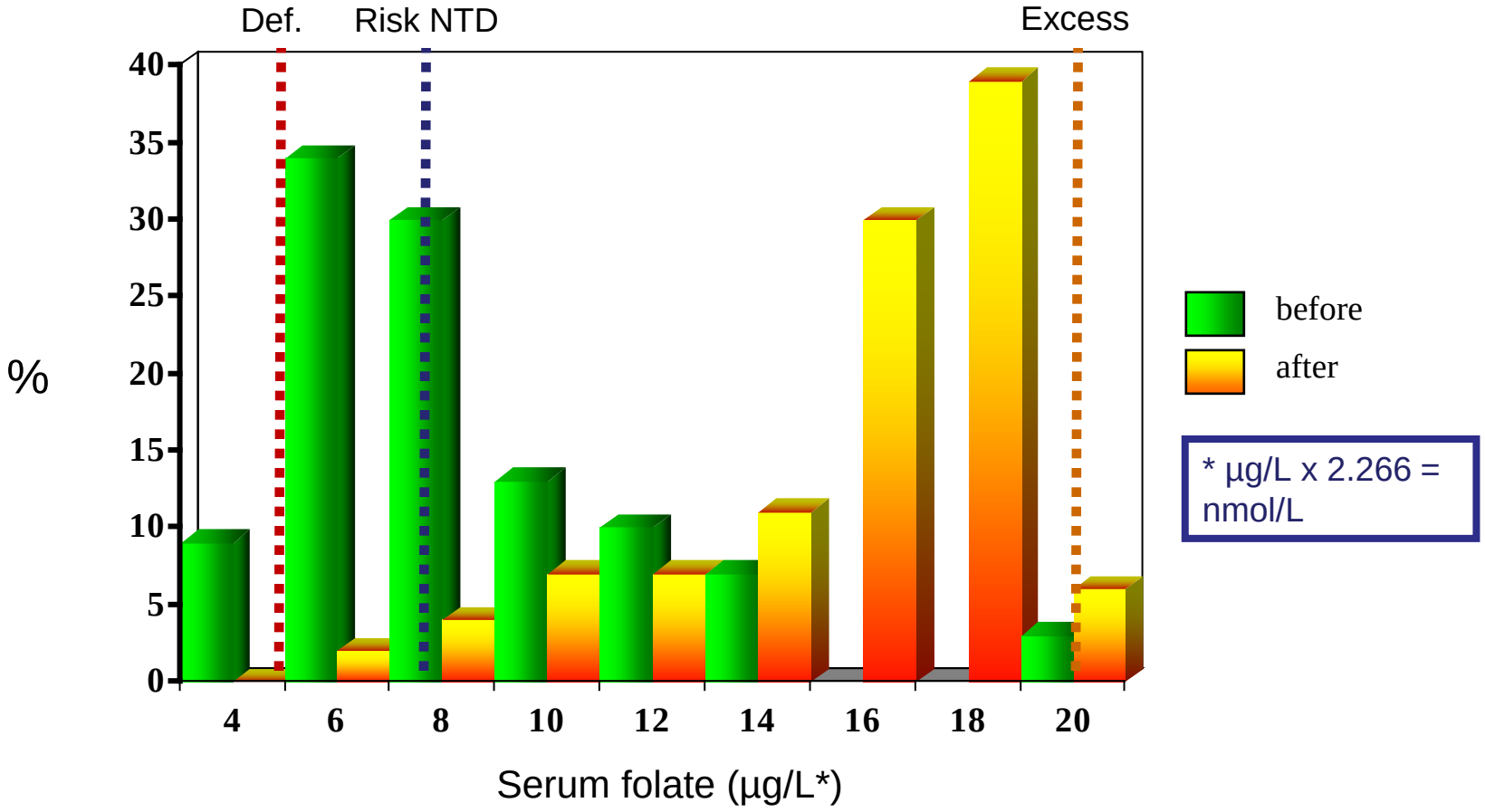


**References**:
**Hungary:** Czeizel and Dudás *N Engl J Med* 1992;**327**:1832.
**China:** Berry et al. *N Engl J Med* 1999;**341**:1485.
* Scott JM et al. *Lancet* 1991;**338**:505.

# Impact of folic acid (2 mg/kg) through wheat flour in Chile (200 g/day of flour intake)

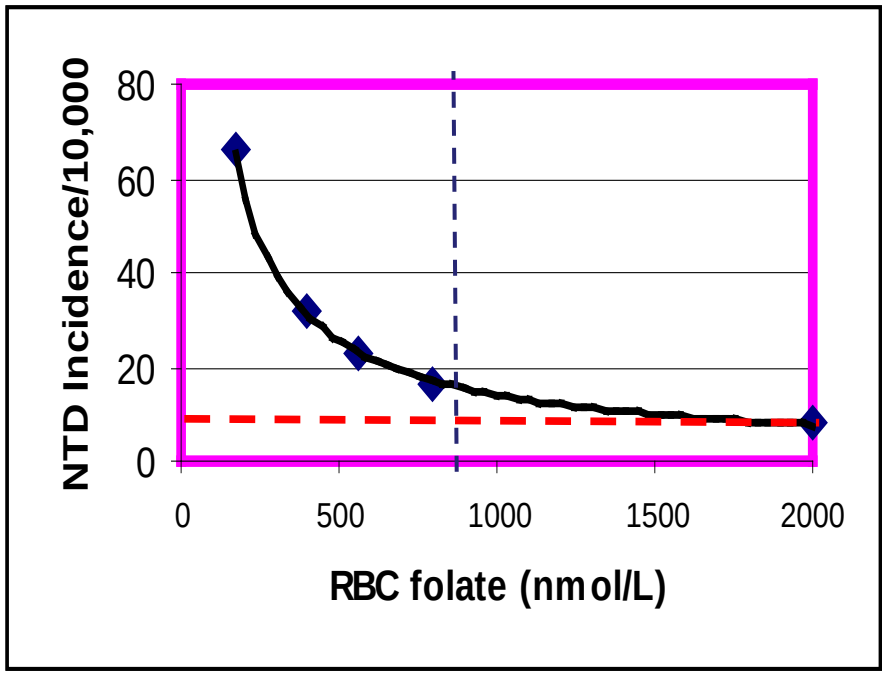


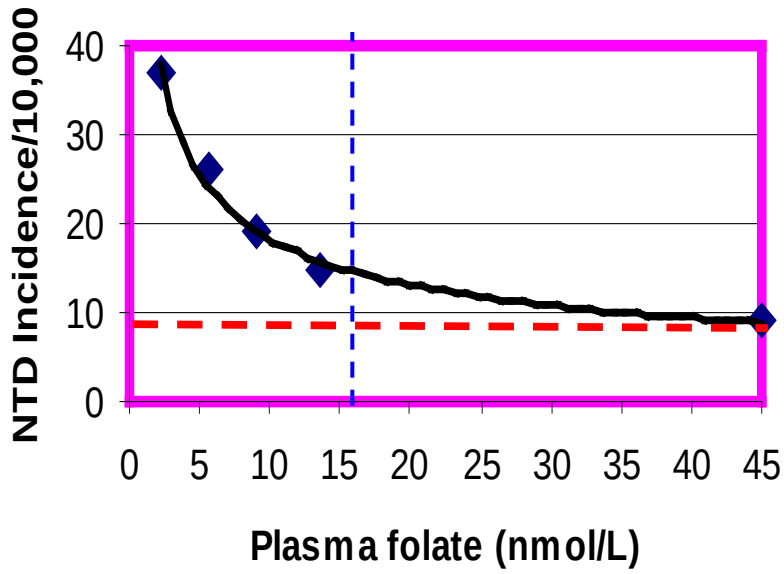
# What other changes occurred in the Chilean population?




**Source:** Hirsch *et al*., J Nutr 2011.

# Association between blood-folate and NTDs

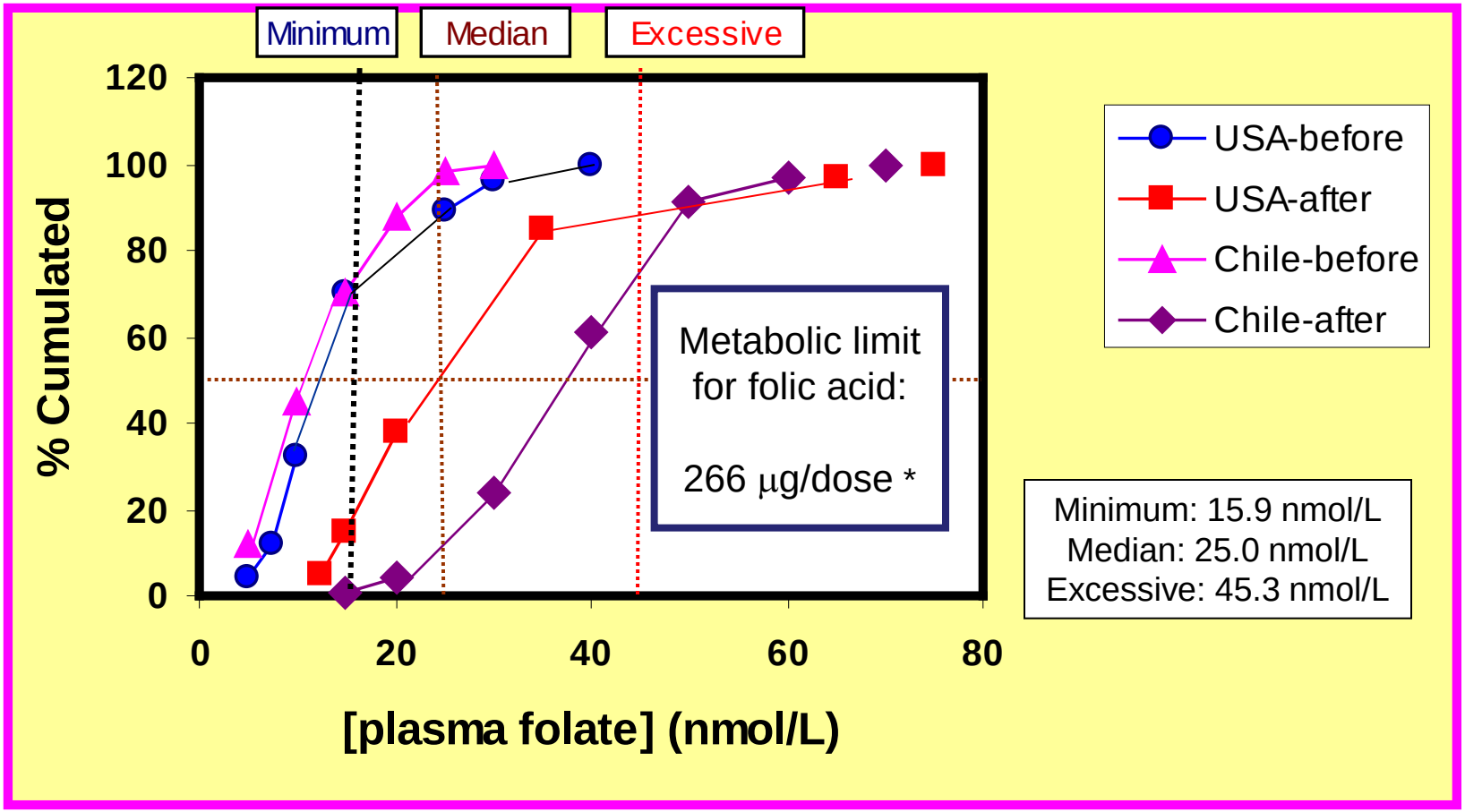



**Reference:** Daly LE et al.,*J Am Med Sci* 1995;**274**:1698-1762.

Data from Ireland.

# Serum-folate changes in USA and Chile




Adapted from Pfeiffer et al., *Am J Clin Nutr* 2005; 82:442-50; and Hertrampf et al., J Nutr 2003; 133:3166-69.

***** Kelly et al. *Am J Clin Nutr* 1997;**65**:1790.

# Median of serum folate (nmol/L) before and after flour fortification with folic acid

## Women of child-bearing age

| Countries | Chile | USA | C.Rica | W.Bank | Ecuador |
|---|---|---|---|---|---|
| **Before** | 9 | 10 | 22 | 18.5-23.8 | 14 |
| **After** | 38 | 22 | 25 | - | |

## Children 1-5 years old

| Countries | Ecuador |
|---|---|
| **Before** | 25.4 |
| **After** | |

**Reference:** National Survey of Nutrition of Ecuador, 2013.

However, folic acid is being promoted in addition to the provision of dietary folate, as well as it is incorporated into MNP for children. Do we know that these additional amount are needed? Do we know if those are safe*?

**See:** Oppenheimer & Cashin. *Transactions of the Royal Society of Tropical Medicine and Hygiene 1986;* **80**, 169–171; Metz J. *Food Nutr Bull* 2007; **28**(4 Suppl):S540-549.

# Meta-Analysis of Trials of Iron +/- Folic Acid for Prevention or Treatment of Anemia

- **All malaria settings**

| | RR | 95% CI |
|---|---|---|
| – Any parasitemia | 1.13 | 1.01 - 1.26 |

- **Settings with no routine malaria surveillance**

| – Clinical Malaria | RR | 95% CI |
|---|---|---|
| Pemba | 1.16 | 1.00 - 1.34 |
| Five other trials | 1.16 | 0.43 - 1.45 |
| Total | 1.16 | 1.03 - 1.31 |

**Source: Ojukwu, et al, Cochrane 2009**

**Slide from:** Robert Black, JHU, 2015

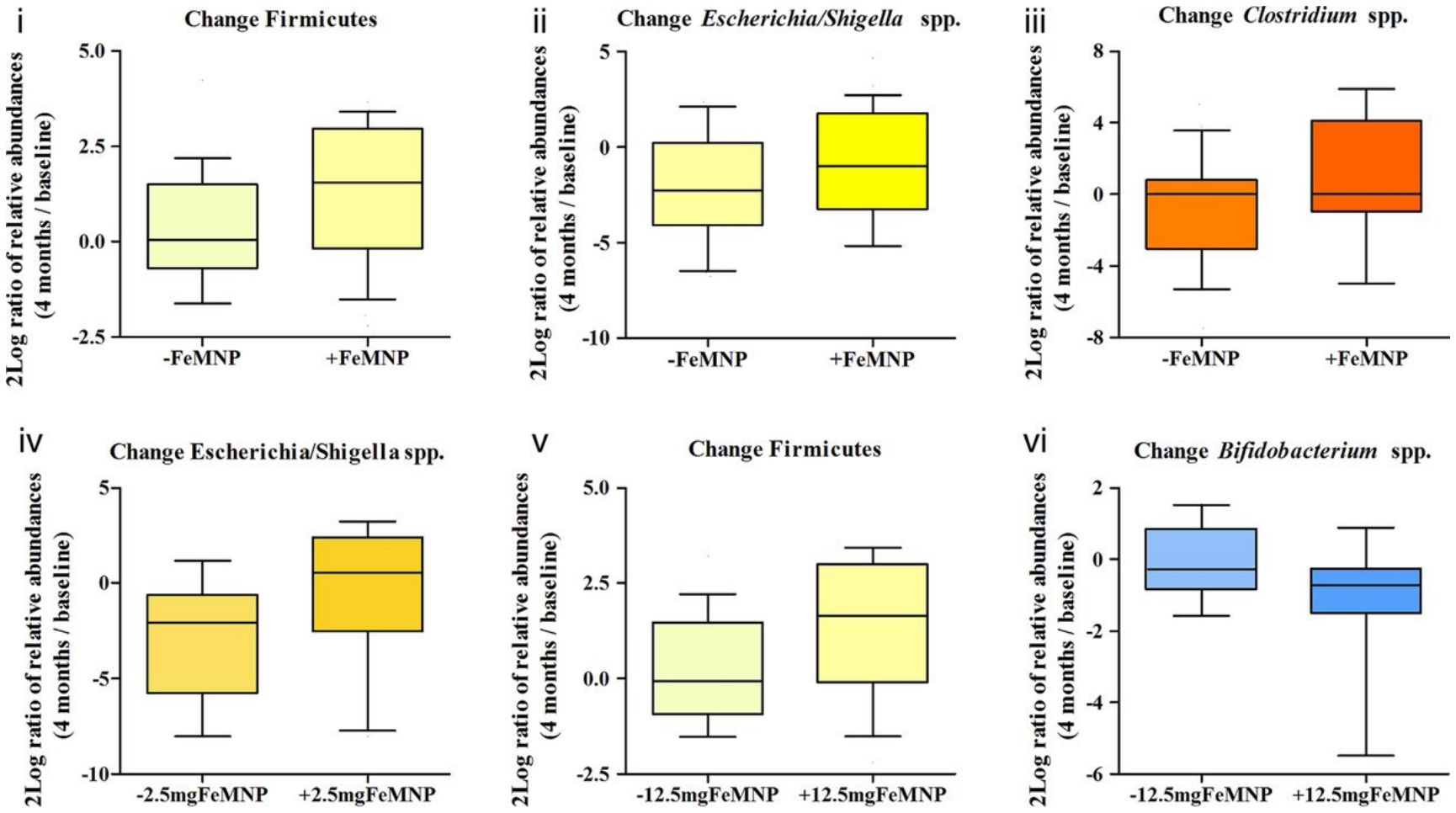
# Adverse negative consequence of supplying iron: Severity of diarrhea in pre-schoolers from Pakistan

| Age (6-18 months) | Control | | MNP without zinc | | MNP with zinc | |
|---|---|---|---|---|---|---|
| | Incidence* | RR | Incidence* | RR | Incidence | RR |
| Any type | 3.73 | 1.0 | 4.16 | 1.05 (0.04-1.17) | 4.16 | 1.05 (0.04-1.17) |
| Diarrhea with blood | 0.08 | 1.0 | 0.16 | 1.63 (1.12-2.39) | 0.17 | 1.88 ( 1.29-2.74) |
| Severe diarrhea (>6/d) | 1.31 | 1.0 | 1.94 | 1.28 (1.03-1.57) | 1.69 | 1.17 (0.95-1.45) |
| Persistent diarrhea | 0.06 | 1.0 | 0.10 | 1.41 (0.87-2.28) | 0.09 | 1.33 (0.82-2.16) |

* Incidence per children-years

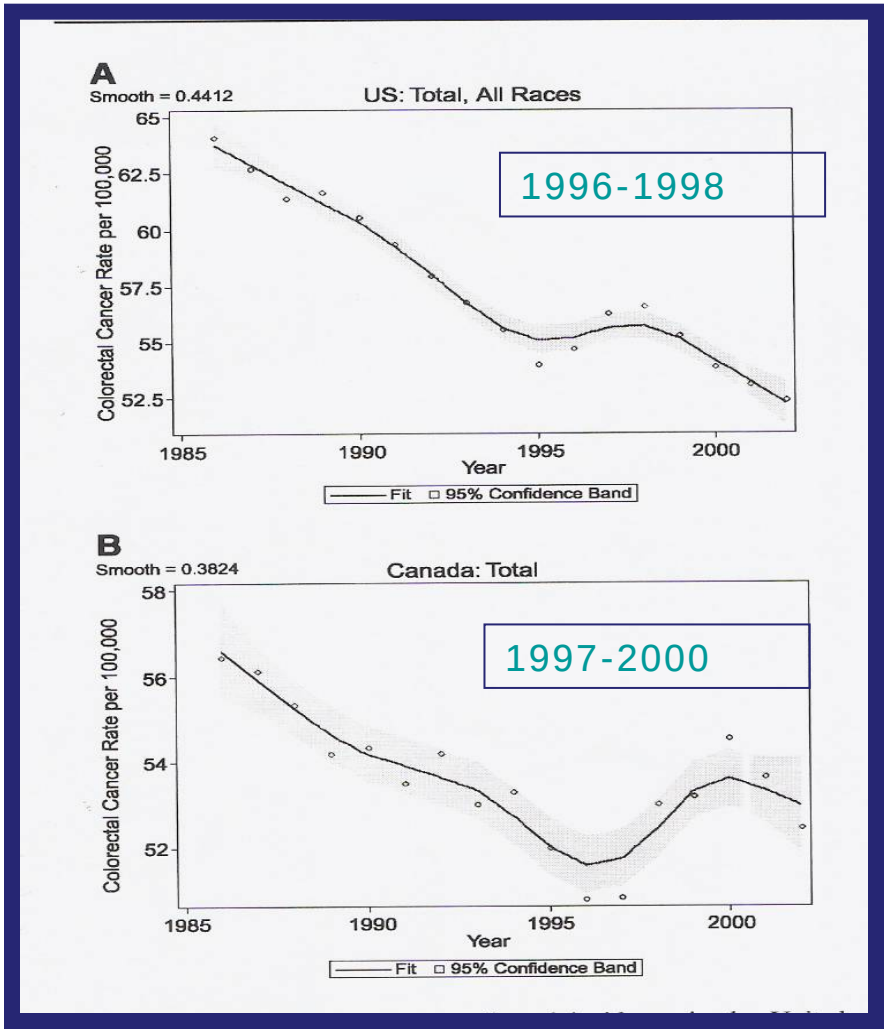
**Source:** Soofi *et al.,* Lancet 2013; **382**:29-40.

# Excessive iron supply favor pathogenic intestinal bacteria in Kenyan children




**Source:** Jaeggi *et al.*, doi:10.1136/gutjnl-2014-307720

# Probable adverse effects due to excess of folic acid

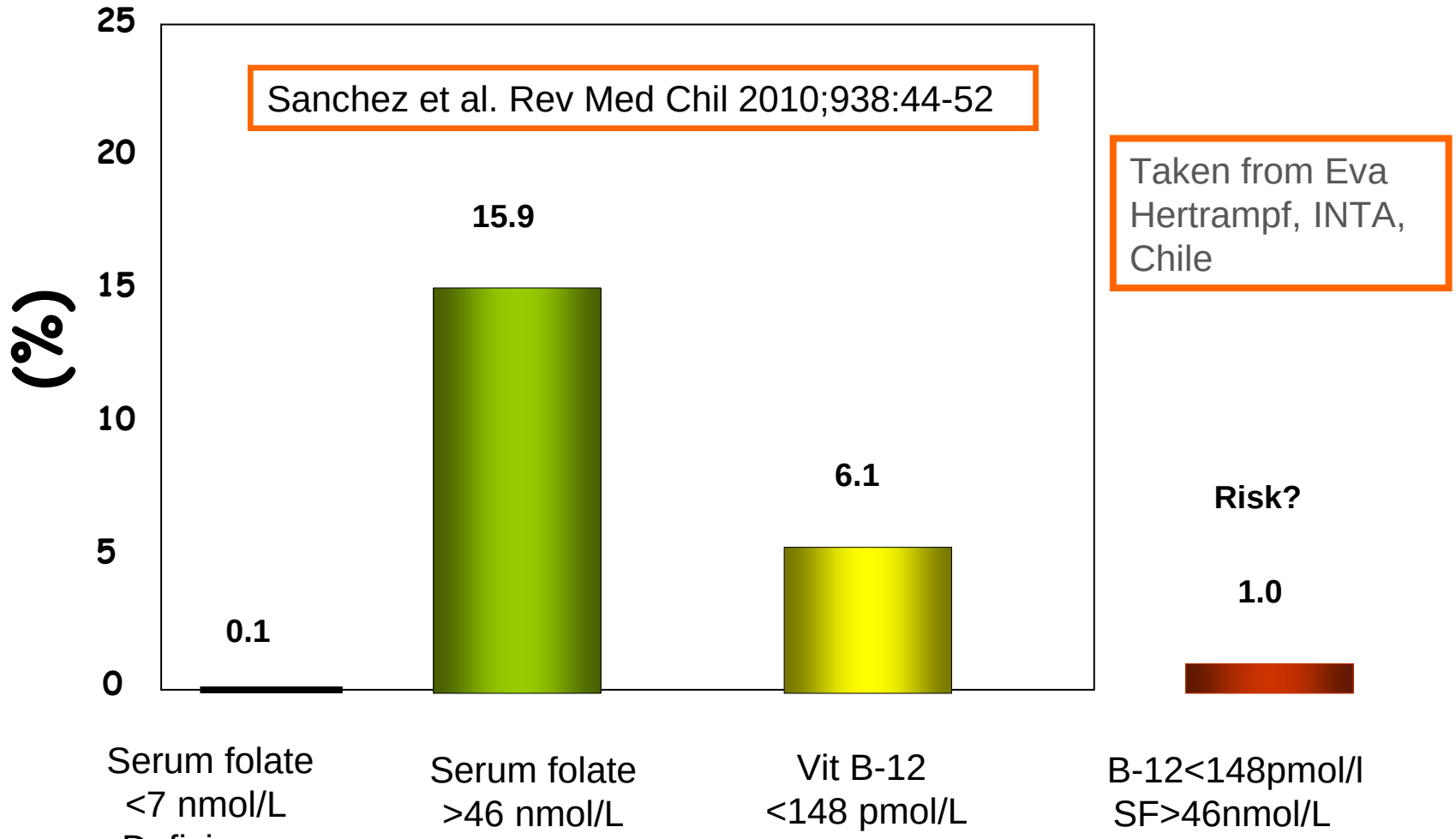



**Other potential risks:**

- Masking of megaloblastic anemia, but not other consequences of vitamin B-12 deficiency.
- Antagonist of some anti-malaria drugs (probable high levels of folic acid are required)
- Antagonist of anti-cancer medications, and eczema treatment.
- Prostate cancer.

**Reference:** Mason J, Dickstein A, Jacques P, Haggarty P, Selhub J, Dallale G, Rosemberg I. *Cancer Epidemiol Biomarkers Prev* 2007; **16**(7).

# The risk of unbalances



# Understanding biomarkers associated to nutrients

Amount consumed x [Nutrient] = Additional intake

[BIOAVAILABILITY

**NUTRIENT BIOEFFICACY** → &

BIOCONVERSION]

**EFFECTS**
(Physiology changes)

**FUNCTION**
(Tissues)

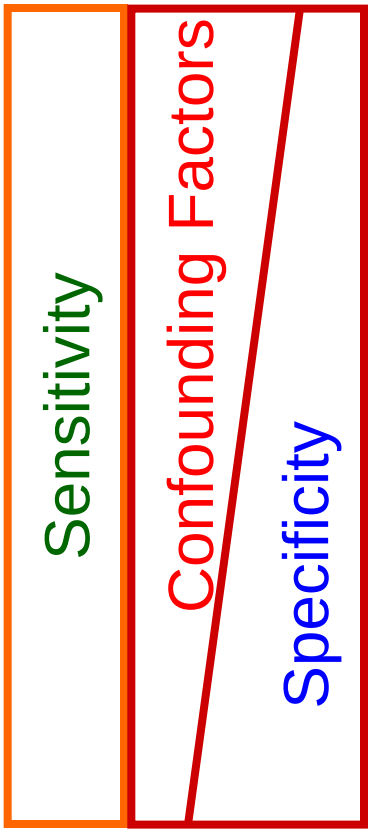
**STATUS**
(Metabolic biomarkers)

**EXPOSURE**
(Biomarkers of intake)

Basal bio-form → **Additional bio-form** → Total bio-form

Impact requires: Need + Additional micronutrient intake + Coverage

# Micronutrient indicators: Assessing needs and impact




**EFFECT**
(Physiology changes)

↑

**FUNCTION**
(Tissues)

↑

**STATUS**
(Metabolic biomarkers)

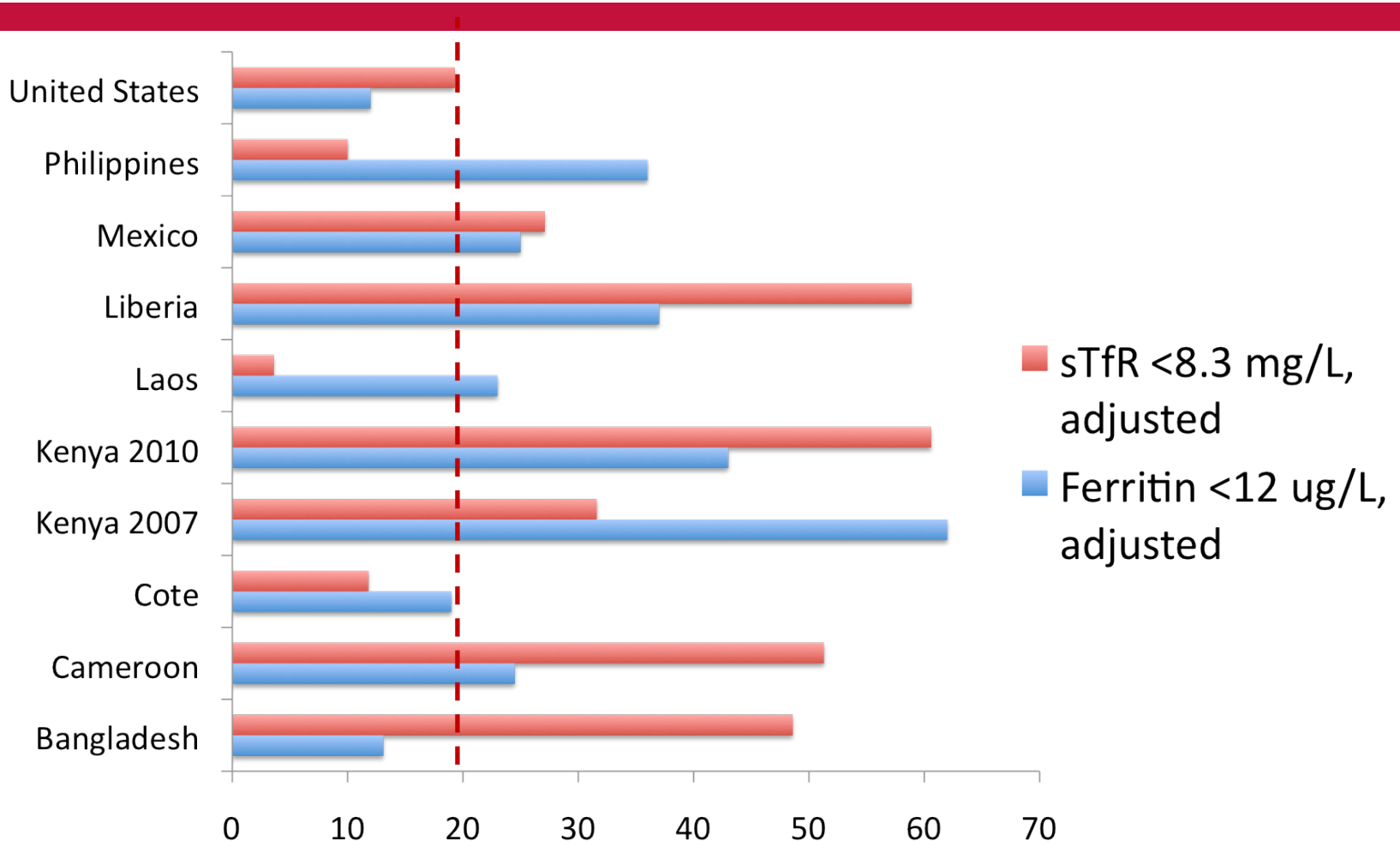
↑

**EXPOSURE**
(Biomarkers of intake)

| Iron | Folate |
|---|---|
| IQ, endurance | NTD |
| Anemia | Anemia, p-homocysteine |
| Serum- Ferritin Soluble-TfR | RBC-folate |
| - | Serum-folate |

What of these are being used?

# Prevalence of iron deficiency in pre-schoolers using two biomarkers




**Source:** Namaste et al. (SPRING/USAID) Unpublished data of the BRINDA project.

# Why the anemia prevalence is too different in three recent surveys in Guatemala?

| Year | Source | Age (months) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 6-8 | 9-11 | 12-17 | 18-23 | 24-35 | 36-47 | 48-59 |
| 08-09 | ENSMI-2009 | 72.1% | | 58.7% | | 47.9% | 40.9% | 31.0% |
| 2013 | SIVESNU | 25.4% | | 16.0% | | 10.0% | 2.2% | 1.5% |
| 2015 | ENSMI(DHS) | 64.3% | | 39.6% | | 19.1% | 14.8% | 9.1% |

**Notes:**

1. The three used finger pricking and Hemo-cue, but in 2013 blood was collected in a microtiter tube before loading the Hemo-cue cuvette.
2. In 2015 better attention was given for avoiding “milking” of the finger.
3. **Question:** Do we need to use different cut-off points to diagnose anemia in small children? (WHO cut-off point is 11 g/dL from 6-59 months of age).

# Cut-off of serum/plasma and RBC folate

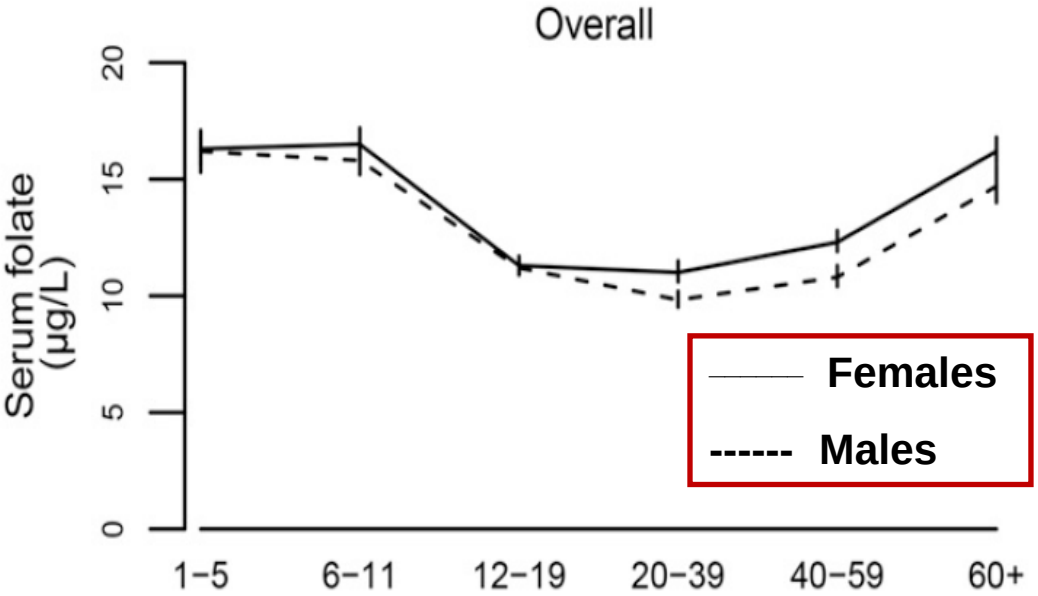
| Variable | Negative balance (megaloblastic anemia) | Increment of homocysteine | Occurrence of NTDs | Supra-physiological |
|---|---|---|---|---|
| Serum Folate (nmol/L)* | < 7.0 | < 10.0 | < 15.9 | ≥ 45.3 |
| RBC folate (nmol/L)* | < 305 | < 340 | < 906 | ? |
| DFE (µg/day) | < 205 | < 294 | < 474 | ≥ 1370 |
| Folic Acid (µg/day)** | < 120 | < 173 | < 279 | ≥ 806 |

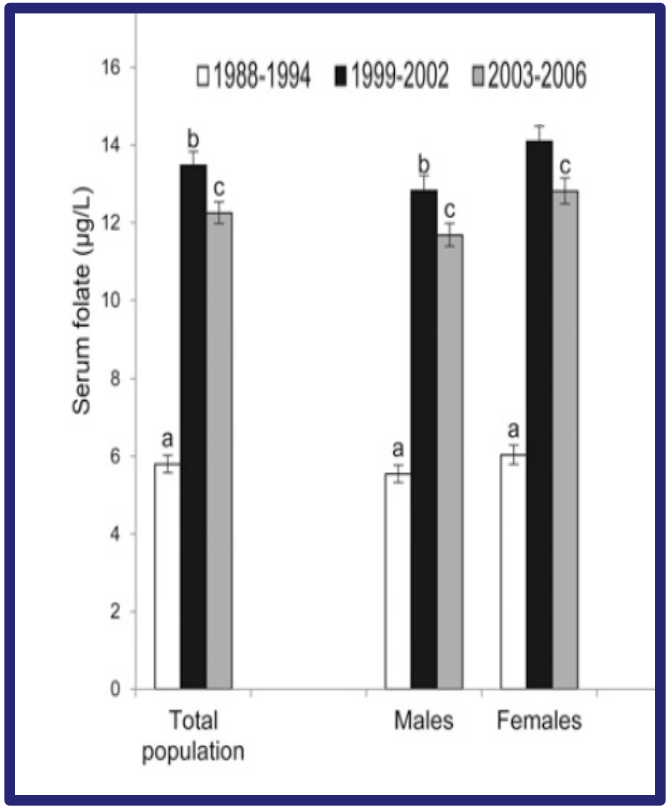
*** µg/L = nmol/L / 2.266**

**** Folic acid = DFE/ 1.7**

**See**: Dary O. Nutritional interpretations of folic acid interventions. *Nutr Rev* 2009; **67**:235-244.

# Variation of serum folate along the life course (years) in USA*




**nmol/L = µg/L x 2.226**

**Source**: Bailey *et al.* From NHANES, 2003-2006. *J Nutr* 2015; doi: 10.3945/jn.114.206599..

# How much is too little, and how much is too much? (adults)

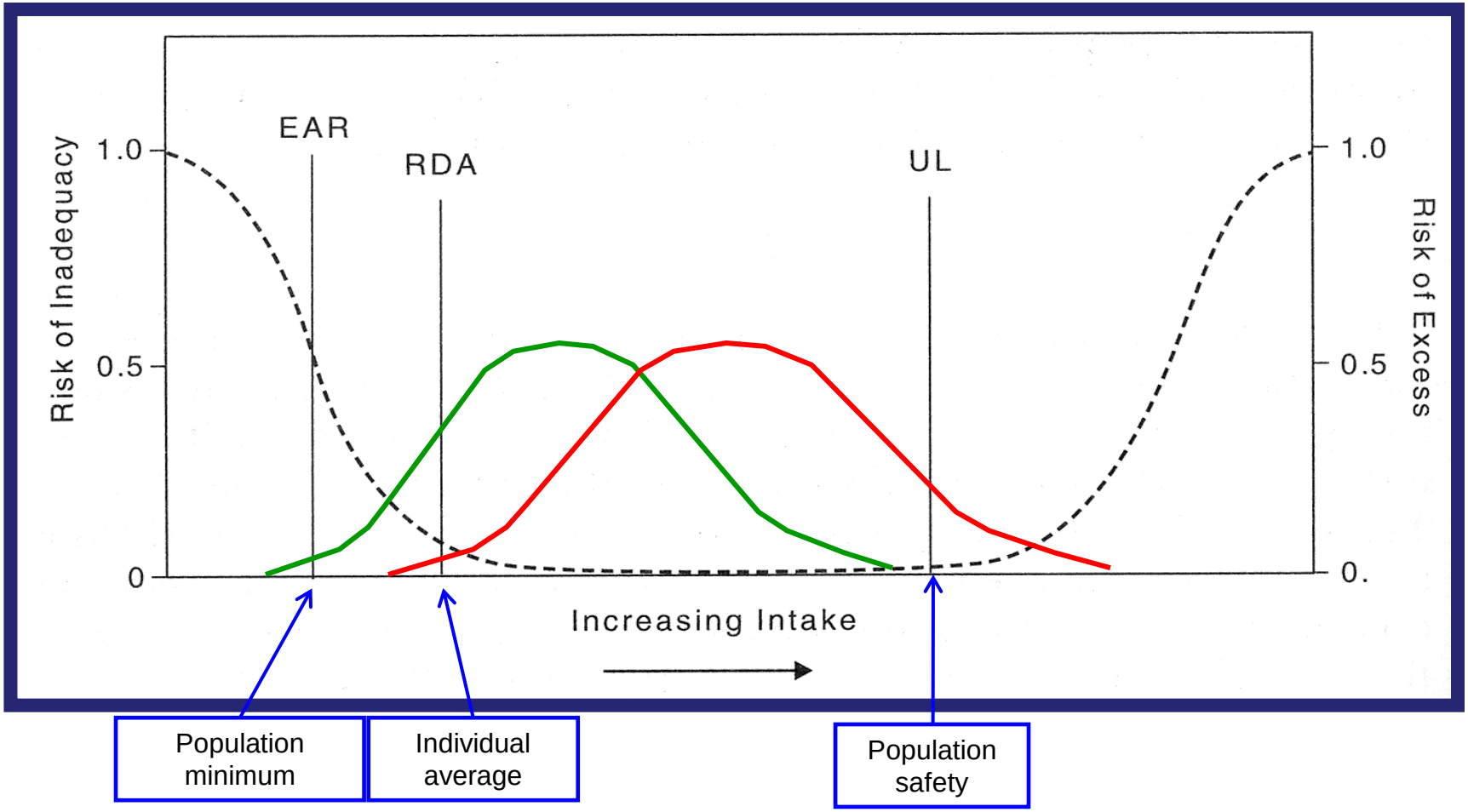
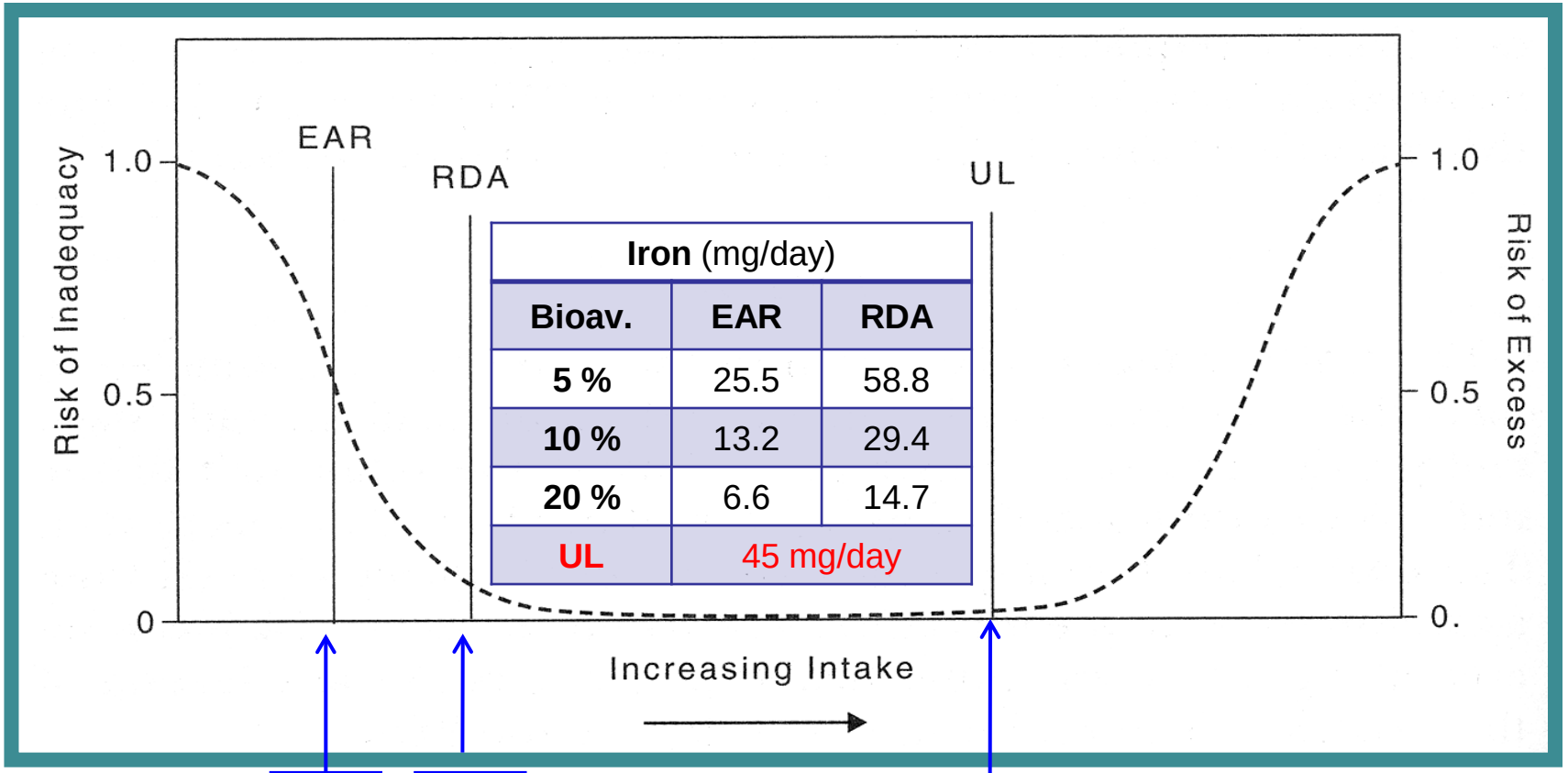



Figure modified from Institute of Medicine, the Academies of Science, USA..

# Dietary reference intakes (DRI) of iron and folate for healthy adult females

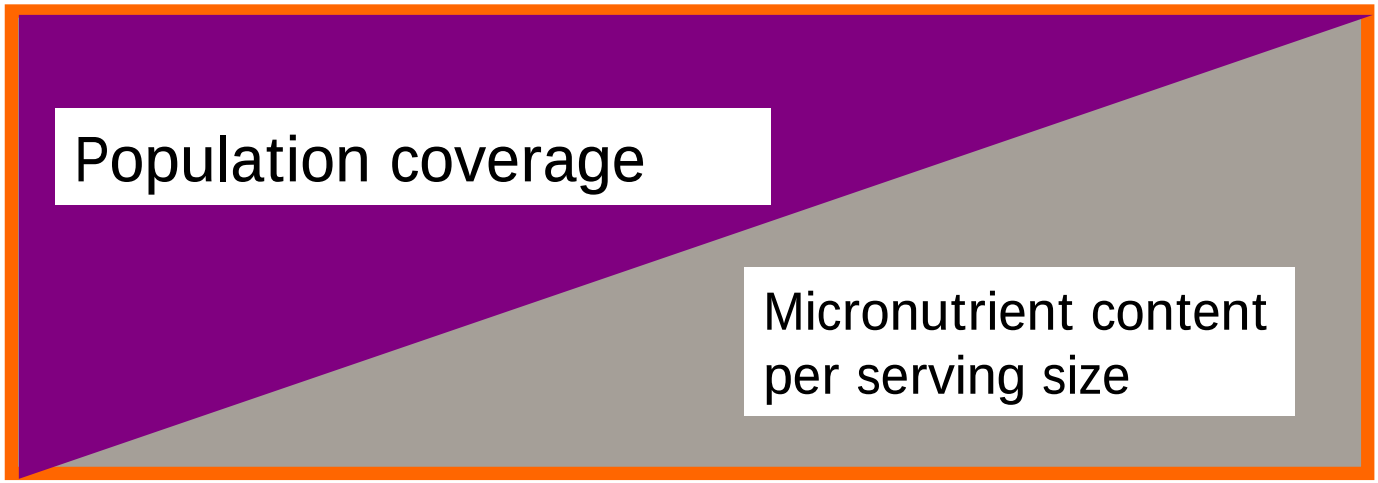



**Iron** (mg/day)

| Bioav. | EAR | RDA |
|---|---|---|
| 5 % | 25.5 | 58.8 |
| 10 % | 13.2 | 29.4 |
| 20 % | 6.6 | 14.7 |
| UL | 45 mg/day | |

Figure modified from Institute of Medicine, the Academies of Science, USA.. EAR, RDA/RNI, UL values are a combination from WHO and IOM.

# Strategies for increasing micronutrient intakes




**Mass fortification:** flours, oil, sugar, milk, salt, rice

**Target fortification:** Complementary foods, RUTF, RUSF, LNS

**Supplementation:** including MNP for home "fortification"

**Dietary Diversity ("Nutrition"-Sensitive) – Including breast-feeding**

# Supply of iron and folate by different food groups

| Minerals/ Others | Milk | Eggs | FMP[1] | Cereals, roots tubers | Pulses nuts seeds | ProVA fruits & vgt. | Other fruits & vgt. | Oil, ref. flours, sugar |
|---|---|---|---|---|---|---|---|---|
| Iron | - | (+) | +++ | (++) | (+++) | (++) | (++) | - |
| Folate (B-9) | - | + | + | + | ++++ | + | ++ | - |
| | | | | | | | | |
| Fiber | - | - | - | XX | XX | X | XX | - |
| Phytates | - | - | - | X | XX | - | - | - |
| Polyphenols | - | - | - | - | XX | - | - | - |
| Oxalates | - | - | - | | | | XX | - |

Notes: [1] FMP = Fish, meat, poultry; X = relative density, non-nutrient;
+ = Relative density of the micronutrient.; ( ) low absorption in humans

# Comparison of micronutrient-delivering strategies

| Characteristic | Diet | Food Fortification | Supplementation |
|---|---|---|---|
| **Principle** | Increase nutrient content through selection and appropriate combination of foods | Incorporation of micronutrients to the edible vehicles during the manufacturing process | Syrups/tablets/powders of micronutrients consumed with/without foods (home-"fortification") |
| **Impact** | Additional quantity and quality of the supplied micronutrients (very little to do with the mechanism of delivery) | | |
| **PROGRAMMATIC EFFICIENCY (Sustainability)** | | | |
| Feasible | √ | √√ | √√√ |
| Easy to deliver | √√ | √√√ | √ |
| Accessed by consumers | √√ | √√√ | √ |
| Practical to monitor | √ | √√ | √√√ |
| Viable <u>total</u> cost. | √√√ | √√ | √ |