# Evidence for the Safety of Fortifying Flour with Iron in the Presence of Thalassemia and Other Blood Disorders

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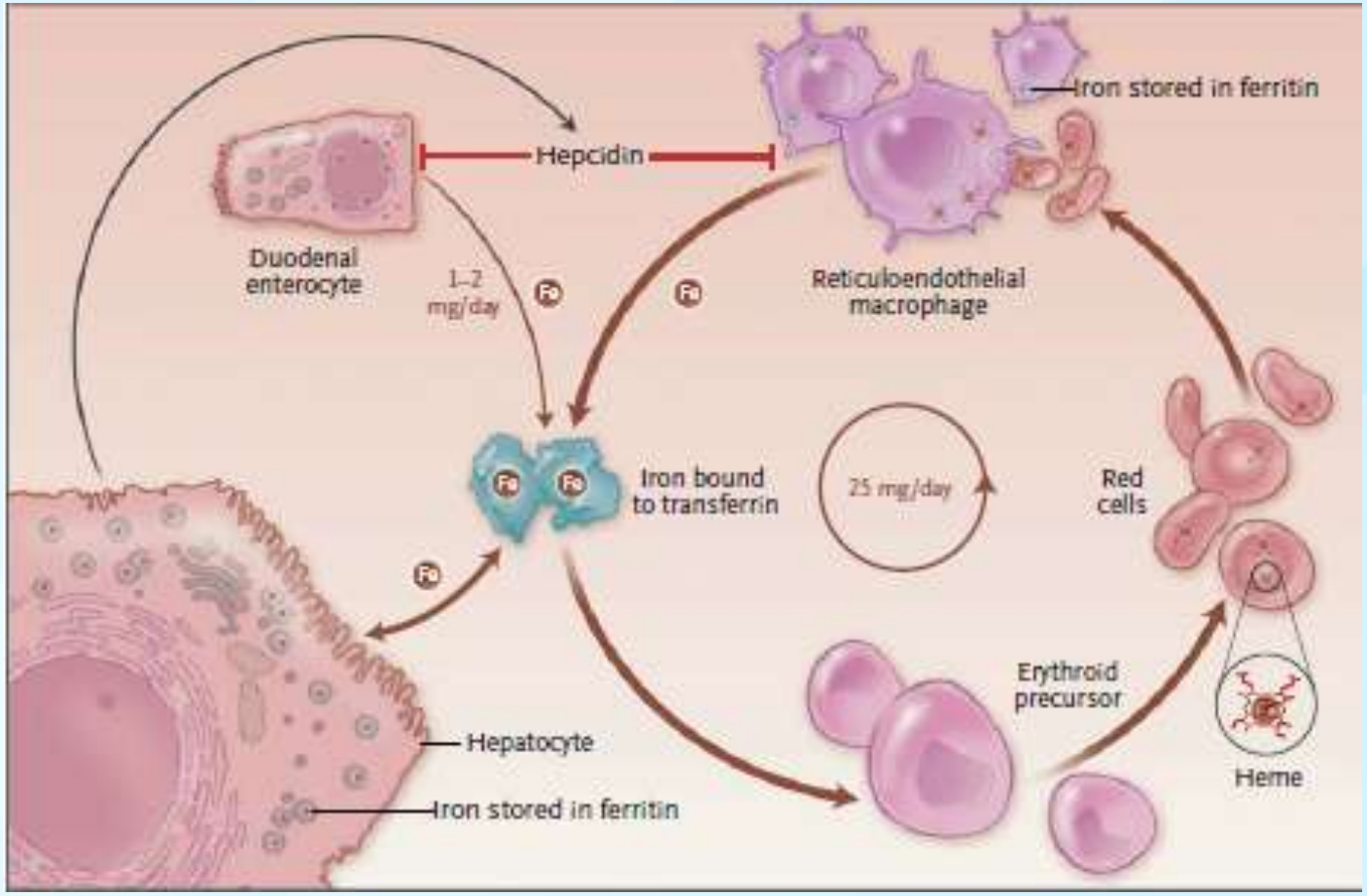
*The findings and conclusions in this presentation are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention*

# Dietary Iron

- **Essential micronutrient**
- **Most contained in red blood cells and recycled**
- **No mechanism for excretion**
- **Iron levels controlled by absorption**
- **Loss only through blood loss or sloughing**
  - Normally lose 1 mg per day
  - Menstruation – 10 mg per cycle (more for heavy bleeders)
  - Blood Donation- 250mg
  - Increased demand due to pregnancy – 700mg
- **Absorption is generally 5-10% of dietary intake**

# Iron Absorption and Transport




Fleming, Robert E, and Prem Ponka. 2012. "Iron overload in human disease." *The New England journal of medicine* 366 (4) (January 26): 348-59. doi:10.1056/NEJMra1004967. http://www.ncbi.nlm.nih.gov/pubmed/22276824.

# Secondary Iron Overload

- **Iron absorption mediated by hepcidin**
- **Secondary iron overload caused by ineffective erythropoiesis**
  - Hepcidin expression is decreased when erythropoiesis is increased
  - Due to downregulation of hepcidin
  - Failure to inhibit ferroportin
  - Increase iron export from enterocyte into plasma
- **This is seen in "iron-loading anemias"**

Fleming, R. E., & Ponka, P. (2012). Iron overload in human disease. *The New England journal of medicine*, *366*(4), 348-59. doi:10.1056/NEJMra1004967

# Some causes of secondary iron overload.

- Hereditary disorders
  - **Thalassemia**
  - Pyruvate kinase deficiency
  - Dyserythropoietic anemia
  - Glucose-6-phosphate dehydrogenase (G6PD) deficiency
  - Hereditary spherocytosis
  - Sideroblastic anemia (ALA-S deficiency)
- Acquired disorders
  - Sideroblastic and other dyserythropoietic anemias
  - Any anemia, except for that due to blood loss, in which multiple transfusions are required.

Beutler, Ernest, a Victor Hoffbrand, and James D Cook. 2003. "Iron deficiency and overload." *Hematology* (January): 40-61. http://www.ncbi.nlm.nih.gov/pubmed/14633776.

# Common Types of Alpha Thalassemia

| # of Affected Genes (out of 4) | Alpha Thalassemia | Clinical Significance |
|---|---|---|
| 1 | Silent Carrier | No symptoms |
| 2 | α Thal trait | Microcytosis +/- Mild anemia |
| 3 | Hb H Disease | Moderate to severe anemia |
| 4 | α Thal Major (Hydrops Fetalis) | Usually die before or shortly after birth |

# Common Types of Beta Thalassemia

| # of Affected Genes (out of 2) | Beta Thalassemia | Clinical Significance |
|---|---|---|
| 1 | βThal trait/minor | Microcytosis, mild anemia |
| 2 | β Thal intermedia or β Thal Major (Cooley's Anemia) | TI - moderate anemia, not transfusion-dependent; TM - transfusion dependent |

# Thalassemia and Iron Overload

- Complication
  - **Iron overload** → organ damage
- Mechanism for Development of Iron Overload
  1. Blood transfusion
     - Blood transfusions (every 2-4 weeks for TM)
  2. Increased absorption of dietary iron due to ineffective erythropoiesis
- Treatment
  - Iron chelation therapy
    - Deferoxamine (standard therapy given overnight through a needle/pump under the skin)
    - Deferasirox (daily pill)

# Life Expectancy - Thalassemia

| Therapy | Life expectancy |
|---|---|
| No regular transfusion | <5 years |
| Regular transfusion+ no chelation | 10-15 years |
| Regular transfusions + desferrioxamine (DFO) chelation – Poor adherence | 15- 25 years |
| Regular transfusions + (DFO) chelation – Good adherence | At least 50 years |
| Regular transfusions + diverse chelation modalities [DFO, deferiprone (DFP), deferasirox (DFX), combination DFO and DFP] and improved monitoring of liver and myocardial iron content by magnetic resonance imaging | > 50 years |

Telfer, P. (2009). Update on survival in thalassemia major. *Hemoglobin*, *33 Suppl 1*, S76-80. doi:10.3109/03630260903347336

# Mechanisms of iron overload and which thalassemia patients are at risk

Transfused

- Thalassemia Major
  - When patients are transfused (e.g. b-thal major)
  - Accumulation is doubled compared to Thal intermedia

Non-transfused Thalassemia

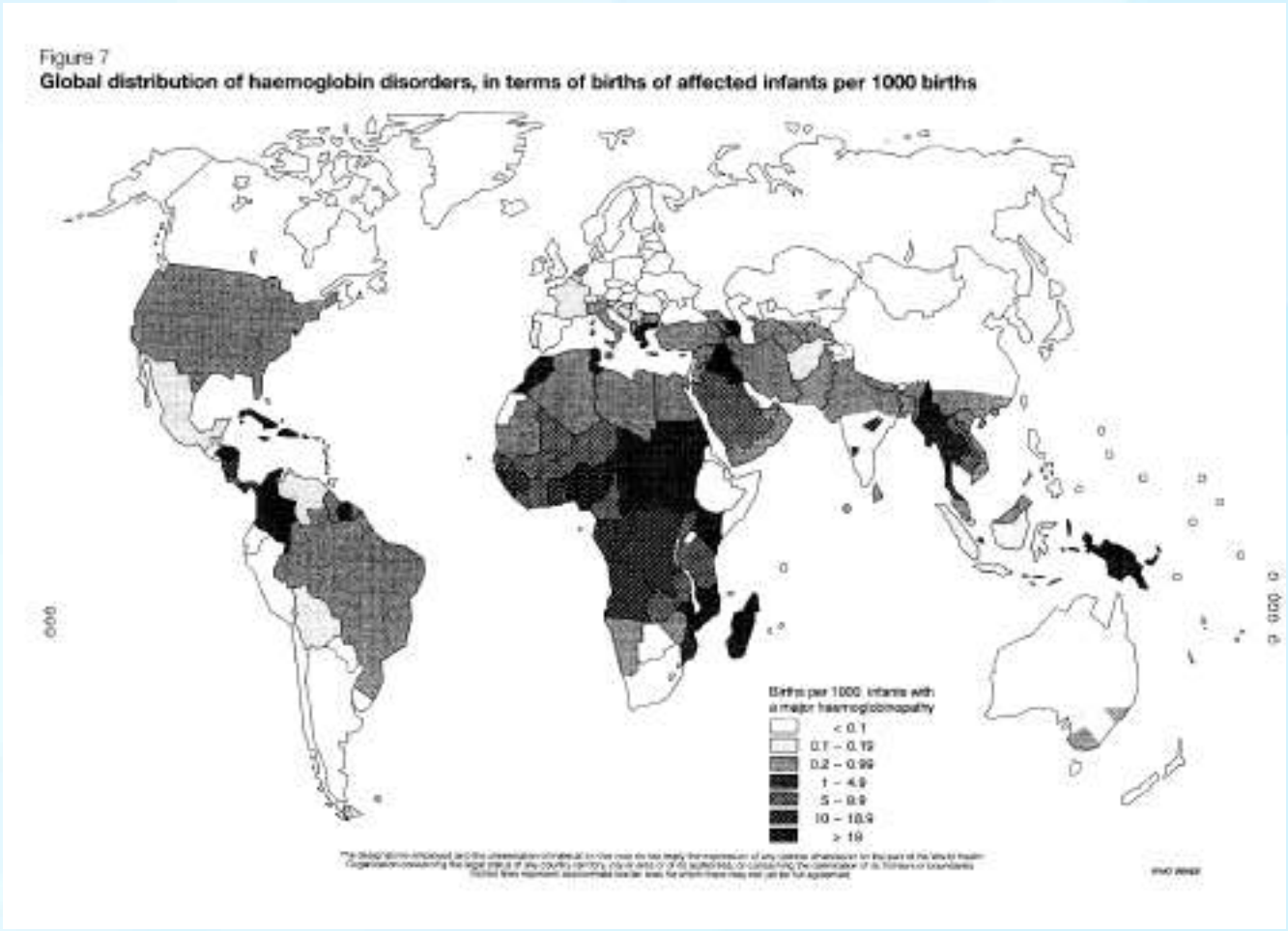
- Thalassemia Intermedia
  - Rate of iron loading from The GI tract is 3-4 times greater than normal
  - Results in an increased iron burden between 2-5g per year
  - May need chelation as they get older

# Mechanisms of iron overload and which thalassemia patients are at risk

Non-transfused

- Thalassemia Minor /Carriers
  - There are very few reports in the literature and studies present conflicting results
  - Evidence in total suggests that carriers are not at higher risk of iron-overload from dietary iron unless certain circumstances exist
    - Associated with coincidental HFE and other hemochromatosis causing gene mutations
    - Inappropriate therapy with very high levels of iron

# Who Does Sickle Cell and Thalassemia Affect?




Data from: Control of Hereditary Diseases. WHO Technical Report Series 865. WHO, Geneva, Switzerland.

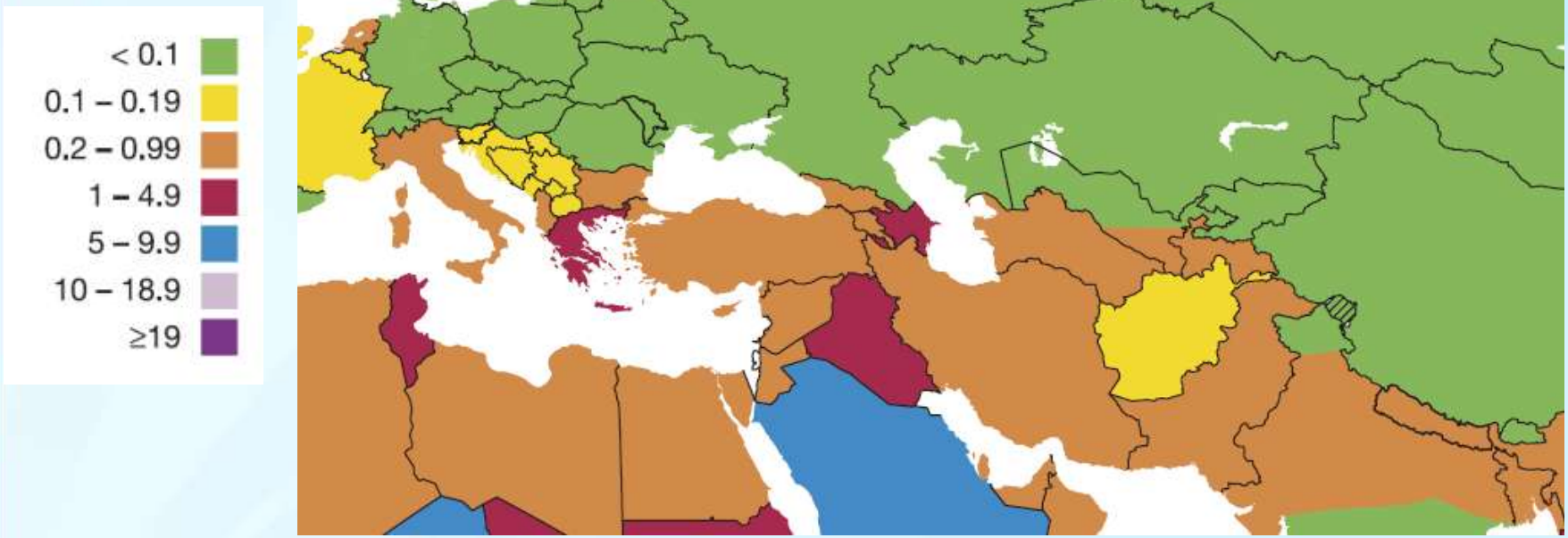
# Distribution of β-Thalassemia Carriers (CEE/CIS)

| Country | % with Thal Trait | Reference |
|---|---|---|
| Albania | 8.4 | Baghernajad-S L, 2009 |
| Armenian | 1-2 | Kuliev AM, 1994 |
| Azerbaijan | >6 (0-20) | Kuliev AM, 1994 |
| Bosnia | 1.5 | Efremov GD,1992 |
| Bulgaria | 2.5 (0.5-19.9) | Petkov GH 2007 |
| Croatia (Dalmation Coast) | 0.8 (6.9) | Efremov GD, 1992 |
| Georgia | Up to 3 | Kuliev AM, 1994 |

# Distribution of β-Thalassemia Carriers (CEE/CIS)

| Country | % with Thal Trait | Reference |
|---|---|---|
| Kosovo | 2.0 | Efremov GD, 1992 |
| Macedonia | 2.6 (1%-10%) | Efremov GD, 2007 |
| Montenegro | 1.9 | Efremov GD, 1992 |
| Romania | 0.5% | Talmaci R, 2004 |
| Serbia | 1.8 | Efremov GD,1992 |
| Tajikistan | Estimated 10% | Baranov VS, 1993 |
| Turkey (Adiyaman) | 1.91 | Genc A , 2012 |
| Turkey (Konya) | 2.0 | Guler, E, 2007 |
| Turkey | 1.66 (1 -13) | Cavdar AO, 1971 |
| Turkey | 3.9 | Koçak R, 1995 |
| Turkmenistan | Estimated 10% | Baranov VS, 1993 |
| Uzbekistan | Estimated 10% | Baranov VS,1993 |

# Births with Pathological Hemoglobin Disorders per 1,000 Live Births (CEE/CIS)




Data from: Control of Hereditary Diseases. WHO Technical Report Series 865. WHO, Geneva, Switzerland.
Map reformatted in: March of Dimes Global Report on Birth Defects – The Hidden Toll of Dying and Disabled Children

# Conclusions

- Among those with thalassemia, evidence suggests that only thalassemia major and intermedia are at risk of secondary iron overload
- Prevalence of clinically significant (Major and Intermedia) thalassemia  is low in CEE/CIS
- Early identification and appropriate clinical management should address risk of iron overload in persons with thalassemia major and intermedia

# Potential Recommendations

- **In populations with a high prevalence of thalassemias and thalassemia traits**
  - Early identification (screening for hemoglobinopathies) to identify persons with thalassemia major and intermedia
  - Regular monitoring of individuals for iron overload throughout lifespan if they have thalassemia
  - Education of patients thalassemia major and intermedia to avoid iron containing supplements and iron-rich foods
  - Population monitoring (public health surveillance) for iron deficiency AND for possible iron overload to assess effect of any program

# Thank You

**For more information please contact Centers for Disease Control and Prevention**

1600 Clifton Road NE, Atlanta, GA 30333
Telephone, 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov Web: www.cdc.gov

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