Excess Iron Intake: Defining Toxic Effects and Upper Limits in Vulnerable Populations

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...but what is “excess intake”?

Tolerable Upper Intake Level or Upper Limit (UL)
The maximum amount of chronic daily intake of a nutrient that is unlikely to pose risk of adverse health effects (toxicity) in almost all (97.5%) healthy individuals in an age- and sex-specific population group.

Set at different levels by various groups – no universal agreement on upper limits (ULs)
Adverse Effects (toxicity)

Adverse effects = “any significant alteration in the structure or function of the human organism or any impairment of a physiologically important function”, including one nutrient’s negative impact on the absorption or effectiveness of another.
## Selected Adverse Effects of Excess Intake

<table>
<thead>
<tr>
<th></th>
<th>Iron</th>
<th>Folic Acid</th>
<th>Vitamin A</th>
<th>Vitamin D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td>GI distress and corrosion</td>
<td>Antagonist to antifolate drugs</td>
<td>Increased intracranial pressure (bulging fontanelles, headaches, blurred vision, vertigo)</td>
<td>Hypercalcemia</td>
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<tr>
<td></td>
<td>Organ damage</td>
<td></td>
<td>GL symptoms</td>
<td>GI symptoms</td>
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<td></td>
<td>Lethal at extremely high doses</td>
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<td></td>
<td>Impaired renal function</td>
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<td><strong>Chronic</strong></td>
<td>Liver fibrosis</td>
<td>Neurological damage via masking of vitamin B12 deficiency</td>
<td>Hepatotoxicity</td>
<td>Irreversible calcification of tissues and bone demineralization</td>
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<tr>
<td></td>
<td>Carcinogenesis</td>
<td></td>
<td>Reduced bone mineral density</td>
<td>Kidney stones</td>
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<td></td>
<td>Inhibition of zinc absorption</td>
<td></td>
<td>Birth defects</td>
<td>Infant growth retardation</td>
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</tbody>
</table>
Published UL Recommendations

- 8 from government + FAO/WHO recommendations
- Consistency in approach: risk assessment framework
- Variability in application of framework
- Incongruence in outcomes
Published UL Recommendations

- USA & Canada: 1998-2011
- FAO/WHO: 2004
- UK: 2003
- EU: 2012-2015
- Nordic countries: 2012
- Japan: 2015
- Korea: 2015
- China: 2013
- Australia & NZ: 2006
Risk Assessment: 4 steps

1. Hazard Identification
2. Dose-response assessment
3. Intake assessment
4. Risk characterization
The Big Picture
Risk

Safe

Unsafe

LOAEL

NOAEL

UL

UFs

RDA

Risk

Intake

Risk of inadequacy

Risk of adverse effect
Variabilities in Application of Risk Assessment (cont’d)

- Whether ULs reflect total or supplementary intake
- Whether ULs were set for children (and how)
  - *If extrapolated, which equation and which reference weights were used*
- Level of confidence in ULs set (e.g., “guidance levels” with significant uncertainty)
ULs for children

- Scarcity of evidence
- Extrapolation downwards from adult values
- Population intakes may be greater than UL
- Some organizations do not set
- Critical endpoint may not be relevant
# UL Ranges for Infants and Young Children vs Population Intakes

<table>
<thead>
<tr>
<th></th>
<th>0-12 month UL range (total intake)</th>
<th>1-3 years UL range (total intake)</th>
<th>Intake from national surveys</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>20-40 mg</td>
<td>20-40 mg</td>
<td>NHANES 2-5y: Mean 12.3 mg; 95&lt;sup&gt;th&lt;/sup&gt; percentile 13.1 mg ENFCS 6-35m: Median 10 mg</td>
</tr>
<tr>
<td>Folic acid</td>
<td>no UL</td>
<td>200-300 µg</td>
<td>NHANES 2-5y: Mean 509 µg; 95&lt;sup&gt;th&lt;/sup&gt; percentile 536 µg ENSANUT 1-4y: Mean 246 µg</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>600 µg*</td>
<td>600-800 µg*</td>
<td>NHANES 2-5y: Mean 549 µg; 95&lt;sup&gt;th&lt;/sup&gt; percentile 607 µg ENFCS 6-35m: Median 9 µg ENSANUT 1-4y: Mean 563 µg</td>
</tr>
</tbody>
</table>

* NNR UL is 3 mg/day for “entire population”
Challenges with Risk Assessment in UL-setting

- Scarcity of quality data, especially for children
  - *Ethical limitations*
  - *Studies often not designed to assess adverse effects*
  - *Small, short duration*
  - *Heterogeneity in types of evidence*

- ULs assume chronic intake but are often based on acute adverse effects
- Lack of understanding of how nutrients interact with each other in excess
Ultimately...

- There is considerable uncertainty in UL values, especially for children.
- ULs were developed to apply to healthy populations and should not be assumed directly applicable to malnourished populations.
- Caution must be exercised in interpreting risk for populations receiving public health interventions.
  - E.g. high-dose vitamin A supplementation.
- For nutrients with limited evidence of toxicity in children, population intake data may provide better insight for setting ULs than inappropriate extrapolation form adult ULs.
Iron Supplementation in Malaria Endemic Areas

- Taking iron does not make a child more likely to be infected with malaria

- However, children taking iron may get sicker than children not taking iron:
  - IF they become infected and;
  - IF they do not receive treatment promptly

- Iron supplementation is important in treating anemia
  - Providing iron in the context of malaria control will have a greater impact on anemia than malaria control alone

- Therefore, iron-containing MNP must always be provided in the context of an active malaria control program
Key Health Messages

MNP program beneficiaries should be told:

- Malaria is a preventable and treatable illness which people can get from a mosquito bite
- Malaria causes fever
- All children, including those receiving MNP, should sleep under a bed net every night
- Children with a fever should be tested for malaria without delay
- Children who test positive should be treated with the first line antimalarial

Coordination of efforts between malaria control and nutrition programs providing MNP can help to ensure improved health outcomes for children

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Thank you!