Outline

• How DRIs are derived for infants & children.
• Issues identified from their application, and implications.
• Major knowledge gaps identified in reports.
• Can the gaps be filled?

How DRIs are established for infants

• **0-6 mo** (except energy)
  Al = average volume of breast milk X concentration of each nutrient

• **7-12 mo** (except energy, protein, iron & zinc, vit D, F)
  Al = nutrient intake from breast milk + solid food (if data available), OR
  For 46% of nutrients, extrapolation up from 0-6 mo, and/or down from older age (usually adults), if no dietary data.
Limitations of AIs, 0-6 months

- Limited data on breast milk composition
  - values vary widely within and among studies
  - small numbers, changes with time postpartum (e.g. zinc), supplement use and fortification, sampling and analysis problems.
- AI is likely to exceed true requirement
- No EAR to estimate adequacy of intake, or with which to plan complementary foods.

Iron and vitamin A content of milk

IRON: “The average concentration is 0.35 mg/L”
- Values considered at 1-3 mo (mg/L):
  0.20, 0.25, 0.25, 0.26, 0.35, 0.49, (0.80), (0.88)
- New data Sweden (n=86), 0.29 mg/L (Domeloff, 2004)

VITAMIN A: “an average of 485 ug/L during the first 6 months of lactation”
- Values considered (ug/L):
  329 (Navajo, n=23 at 1 mo), 314, 485 (n=6 at <6 mo, serial measures), 600 (n=12 at 1 mo), 640 (n=5 at >1 mo)

Vitamin B-12 content of milk

“Using the higher value of 0.42 ug/L”…..

Values considered at 3 months:
- 0.31 (vegans), 0.42 (3 mo, n=22), 0.34 (3 mo, Brazil, WN, serial, n=9), 0.91 (n=22, Brazil, prenatal supplements).

Problems: releasing B-12 from haptocorrin, older assays, few studies or subjects, supplementation.

Folate analysis has been controversial.
**Setting (AI) for infants 7-12 months**

Must consider intake from breast milk + food:

Values using ≥ 2 methods compared (50% extrapolated)
1. Extrapolation up from 0-6 month AI (niacin, choline, biotin, B-12, A, K, Mo)
2. Extrapolation up from 6 mo and down from adult EAR or AI (B-1, B-2, B-6, folate, pantothenic)
3. Mean intake from breast milk (600 mL/day) + mean intake from foods (Ca, P, Mg, Cu, Cr, vit. C) from CFSII.
4. Factorial method (protein, Fe, Zn)
5. Other – energy, vitamin D, fluoride

---

**12-23 months; DRIs that were not extrapolated**

- Energy (from birth; TEE + growth)
- Protein (N balance, protein deposition)
- Linoleic, linolenic (breast milk + median intake CSFII)
- Vitamin D (from birth; serum 25(OH)D)
- Calcium (factorial, balance)
- Phosphorus (factorial)
- Iron (factorial, assumes 10% bioavailable)
- Zinc (factorial)
- Fluoride (caries prevention)

---

**Extrapolation?**

- Adult
- 7-12 mo: 1.5 yr – 2.5 yr

---
Extrapolations

- UP from AI for 0-6 mo, to AI for 7-12 mo, based on body wt increase^{0.75}

- DOWN from adult EAR to child EAR:
  \[ \text{EAR}_{\text{child}} = \text{EAR}_{\text{adult}} \cdot F \]
  where \( F = \left( \frac{\text{Weight}_{\text{child}}}{\text{Weight}_{\text{adult}}} \right)^{0.75} (1 + \text{growth factor}) \)

Reference weights adapted from NHANES III

Extrapolating Data from Adults to Children (continued)

Growth factors based on the approximate proportional increase in protein requirements for growth (FAO/WHO/UNU, 1985):

- 0.3 for children to \( \leq 3 \) years
- 0.15 for boys 4 through 18 years and girls 4 through 13 years

Problems with interpolation

Uncertainties about:
- Factor for growth (all used incremental protein requirements),
- Some nutrients deposited in large amounts during growth (e.g. protein, Ca), others not.

Also:
- If adult value is AI, child value must also be AI
Atkinson and Koletzko, 2006. Reviewed approaches to extrapolation in 13 reports and 1 review.

### Extrapolations: different approaches

<table>
<thead>
<tr>
<th></th>
<th>Actual weight</th>
<th>Ref. weight</th>
<th>Metabol. weight</th>
<th>Energy</th>
<th>Interpolated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can/USA</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caribb.</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-A-CH</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EU</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>None?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>X?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Conclusions from review

- IOM derived heights and BMIs from NHANES III ('88-'94) and CDC ('02) for macronutrients. **The new WHO Growth Standards should now be used for age 0-5 y; weight, length/height, BMI.**
- BW: for nutrients not associated with metabolic rate
- BW^{0.75}: for those related to metabolic rate
- Cut-offs for age categories should be based on biology.
Derivation of Upper Levels

- For infants and children, reliable data to estimate UL only for vitamin A, D, K, fluoride, selenium, zinc and iron (based on reported adverse effects in children).
- Mostly extrapolated down from adults, based on weight.
- Probably only relevant to supplements, not foods.
- For some nutrients UL is very close to AI (e.g. vitamin A, zinc).
- Interpret cautiously.

Emerging inconsistencies

1. Recommendations for 7-12 mo > than 12-23 mo

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>7-12 mo</th>
<th>12-23 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vit A (ug RAE)</td>
<td>500</td>
<td>300</td>
</tr>
<tr>
<td>Vit C (mg)</td>
<td>50</td>
<td>15</td>
</tr>
<tr>
<td>Iodine (ug)</td>
<td>130</td>
<td>90</td>
</tr>
<tr>
<td>Iron (mg)</td>
<td>11</td>
<td>7</td>
</tr>
</tbody>
</table>

Why? Vitamins A and C are high in complementary foods.

2. Large increase from 7-12 mo to 12-23 mo

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>7-12 mo</th>
<th>12-23 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folate (ug)</td>
<td>80</td>
<td>150</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>270</td>
<td>500</td>
</tr>
<tr>
<td>Phosphorus (mg)</td>
<td>275</td>
<td>460</td>
</tr>
<tr>
<td>Vit K (ug)</td>
<td>2.5</td>
<td>30</td>
</tr>
</tbody>
</table>

Why? Adult values high or extrapolation model wrong?
3. Recommended fibre intakes for children are too high?

Limitations of DRI: Fiber

- No AI for infants because none in milk, and no data on food.
- AI extrapolated from adult AI of 14 g/1000 kcal based on reduction in CVD in adults.
- Low fiber intake is risk factor for constipation, but AI impossible to achieve?

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>AI (g/d)</th>
<th>Intake range</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>19</td>
<td>5-12 (1-2 y)</td>
</tr>
<tr>
<td>4-8</td>
<td>25</td>
<td>6-18</td>
</tr>
<tr>
<td>9-13</td>
<td>26-31</td>
<td>9-11 (10-12 y)</td>
</tr>
<tr>
<td>Adult</td>
<td>25-38</td>
<td></td>
</tr>
</tbody>
</table>

Problems identified through application

1. Inadequate nutrients may be wrongly identified

For children aged 1-2 y in CSFII (Devaney et al., 2004),
- 58% intakes vitamin E (<EAR), but
- <1% consume an inadequate intake of any other nutrient.

For schoolers in CSFII (Suitor & Gleason, 2002),
- 79% intakes vitamin E <EAR
- 36% intakes Mg <EAR
- 20% intakes P <EAR
Using DRI method to estimate % inadequate intakes in schoolers (Suitor & Gleason, CSFII, n=2692, 2002)

Problems identified through application

2. High prevalence of intakes >UL in CSFII
   • For 0-11 months:
     – 90% exceed Zn UL
     – 39% exceed vitamin A UL
   • For 1-4 years:
     – 55% exceed Zn UL
     – 20% exceed vitamin A UL
     – 86% exceed Na UL
     – (but <1% exceed UL for Fe, Zn, B-6, C)

Knowledge gaps identified in reports (43 identified)

MICRONUTRIENTS

“Studies needed to set child and adolescent EARs for vitamins B1, B2, B6, folate, niacin, pantothenic, C, E, Se….
using graded levels of intake with clearly defined cut-offs for adequacy and inadequacy (biomarkers), for sufficient duration” (11).

Is this feasible in children?
How do we improve knowledge of vitamin requirements?

**Feasibility:** how to determine cut-offs for adequacy and inadequacy, when vitamin deficiencies are rare?
- Test responses to interventions in populations with a high prevalence of deficiency.
- Feed slightly below and above EARs, long enough to see changes in biomarkers? (Expensive, time-consuming, difficult).
- Studies with stable isotopes (e.g. deuterated retinol, D) or nano tracers (\(^{14}\)C-folate and \(^{14}\)C-tocopherol by AMS):
  - % absorption from breast milk and food
  - kinetic modeling (population-based plasma kinetics)
  - intake that maintains pool size.

**EAR = intake required maintain pool size?**

<table>
<thead>
<tr>
<th>Intake (ug RAE/day)</th>
<th>Initial - Final Pool (ug RAE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-1000</td>
</tr>
<tr>
<td>200</td>
<td>-500</td>
</tr>
<tr>
<td>400</td>
<td>0</td>
</tr>
<tr>
<td>600</td>
<td>500</td>
</tr>
<tr>
<td>800</td>
<td>1000</td>
</tr>
</tbody>
</table>

"Paired DRD technique"
Haskell et al., 2005

How do we improve knowledge of mineral requirements?

**Stable isotope tracers** e.g. iron, zinc

- Measure bioavailability e.g. absorption of \(^{58}\)Fe from breast milk = 16% in Swedish infants (Domeloff et al. 2002); and effects of foods on breast milk Fe absorption (Abrams et al.), based on erythrocyte incorporation.
- Measure absorption, excretion, pool size, turnover \(\rightarrow\) requirements e.g. Zn (Krebs et al.).
Knowledge gaps in reports: Ca, P, Mg, vitamin D

1. Intakes of Ca, P, Mg, D to maximize bone mineral accretion (1-18 y) (1)
   FEASIBLE:
   • Ca, P and Mg balance & retention at varying levels of intake
   • Stable isotopes of Ca, Mg to measure absorption, pools, excretion etc.
     Dual Ca isotope tracer + timed urine collection (Abrams 2005).
   • More data on relationship of D intake and serum 25(OH)D to PTH (e.g. Hollis studies), bone turnover markers, immune function, BMD.

2. Relationship between absorbed P and serum P (1)
   FEASIBILITY:
   • AI for P in adults is based on intake that maintains normal serum P. Could be done in children if know normal value. Not an important gap?

Knowledge gaps in reports: Macronutrients

1. Form, frequency, duration, intensity of activity for management of body weight in children across age, gender, ethnicities (3), and effects on substrate utilization and energy depots (2)
2. More DLW studies to determine TEE in children (incl. obese), & link TEE to weight (2)
3. Methods to measure PAL and classify activity level in free-living children (1)
   THESE ARE ALL FEASIBLE

Knowledge gaps in reports: water & electrolytes

1. Electrolyte (Na, K) and water needs of infants and children (4), vs activity level and climate (2)
   FEASIBILITY:
   • Electrolyte needs difficult to establish;
     – urinary excretion is proportional to intake and few balance data in adults or children.
     – adult AI for Na based on intake from DASH diet, and K intake to lower BP in salt hypersensitivity etc. i.e. inappropriate end-points for children.
   • Water turnover can be measured from disappearance of deuterium from labeled water over time.
2. Intake of Na and K in infancy and blood pressure and bone health in later life (3). This will be difficult!
Summary: what needs to be done for children...

- More analysis of breast milk, collected appropriately.
- If extrapolating, use new WHO standards.
- More nutrient intake data (especially from complementary foods), related to biomarkers that are validated in children.
- Studies with stable and nano tracers to determine vitamin and mineral bioavailability, change in pool size on different intakes, kinetics etc.
- DLW to measure energy expenditure and water turnover.
- D requirements based on relationship of intake to 25(OH)D, PTH, bone markers etc.

Measuring children is difficult……..

But children are NOT just little adults.

They need their own evidence-based DRIs.

Wrong DRIs can affect health, identify wrong nutrient intake problems (inadequacy and excess), and lead to wrong dietary recommendations for child feeding programs.