Current Framework for DRI Development: What are the Pros and Cons?

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How should the RDAs be Revised? 1994

- Link to “Reduction in Chronic Disease Risk”
- Several reference points for several uses
DRI Concept

First Problem: Not Understood
Problems with the Original Paradigm
<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Nutrient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>Manganese</td>
</tr>
<tr>
<td>Chloride</td>
<td>Sodium</td>
</tr>
<tr>
<td>Chromium</td>
<td>Vitamin D</td>
</tr>
<tr>
<td>Fluoride</td>
<td>Vitamin K</td>
</tr>
<tr>
<td>Potassium</td>
<td></td>
</tr>
</tbody>
</table>
For Example, Calcium AI (vs. EAR)

- Uncertainty re: methods used in older balance studies

- Lack of concordance between observational vs. experimental data (mean intakes lower than values need to achieve Ca retention)

- Lack of longitudinal, dose response data to verify an association between amount of intake needed for retention vs. fracture, bone loss
For Example, Vitamin D AI (vs. EAR)

- Not known how much dietary D needed to maintain normal calcium metabolism and bone health (sunlight, pigmentation, latitude, clothing)

- Uncertainties as to fortified levels and food composition data base
Four AIs Set by Disease Endpoints
(No EARs by Disease Endpoints)

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Disease Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>calcium retention, bone density</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>circulating 25-OHD levels, bone density, fracture</td>
</tr>
<tr>
<td>Fluoride</td>
<td>dental carries</td>
</tr>
<tr>
<td>Potassium</td>
<td>hypertension, kidney stones</td>
</tr>
<tr>
<td>Fiber</td>
<td>coronary heart disease</td>
</tr>
</tbody>
</table>
To Establish a RDA From an EAR

- Determine indicator of adequacy
- Determine average requirement (EAR)
- Assess variability
- Calculate $\text{RDA} = \text{EAR} + 2 \text{ SD}_{\text{EAR}}$

Problem: Variance not known; therefore CV is assumed
A 10% CV Assumed For:

- Thiamine
- Riboflavin
- Niacin
- Vitamin B6
- Folate
- Vitamin B12
- Vitamin C
- Vitamin E
- Selenium
- Zinc
EAR for Vitamin A Using Dark Adaptation

- Pooled four studies (13 individuals)
- EAR = 300ug (900 IU)
- But, CV = 40%; therefore, no RDA established using dark adaptation.
A Variety of Endpoints (EAR) Were Used

<table>
<thead>
<tr>
<th>Biochemical Functions-</th>
<th>Selenium</th>
<th>Maximal Glutathione Reductase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factorial-</td>
<td>Vitamin A, Zinc, Iron</td>
<td></td>
</tr>
<tr>
<td>Nutrient Concentrations-</td>
<td>Vitamin C</td>
<td>Neutrophil with minimal urinary loss</td>
</tr>
<tr>
<td></td>
<td>Pi</td>
<td></td>
</tr>
<tr>
<td>Physiologic Function-</td>
<td>Vitamin E (Vitamin A)</td>
<td>$H_2O_2$ induced hemolysis</td>
</tr>
<tr>
<td></td>
<td>Vitamin B12</td>
<td>To maintain hematologic status</td>
</tr>
<tr>
<td>Turnover-</td>
<td>Iodine</td>
<td></td>
</tr>
</tbody>
</table>
Data Gaps

- Lack of defined health related endpoints associated with status
- Lack of biomarkers to use to define chronic disease
- Lack of age specific data (extrapolations)
- Lack of information on variability of responses (RDAs)
- Lack of dose response data (AIs)
- Lack of long term studies
Tolerable Upper Intake Level

The highest level of daily nutrient intake that is likely to pose no risks of adverse health effects to almost all individuals in the general population

- Not a recommended level of intake
- Not a level that is desirable to attain
UL = \frac{\text{NOAEL or LOAEL}}{\text{UF}}
Sources of Uncertainty

1) Interindividual Variation
2) Animal to Human Extrapolations
3) Short Term vs. Chronic Exposures
4) Use of a LOAEL instead of a NOAEL
5) Small numbers
6) Severity

UF = 1-10
Example: Adverse Effects Considered in Setting North American UL for Vit. A

- Bone mineral density
- Liver toxicity
- Teratogenicity (women of reproductive age)
- Bulging fontanel (infants)
# Daily Dietary intake of Retinol Associated with Risk for Hip Fracture

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariate Analysis (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinol Intake</td>
<td></td>
</tr>
<tr>
<td>0.5 mg/d</td>
<td>1.0</td>
</tr>
<tr>
<td>0.51-1.0 mg/d</td>
<td>0.92</td>
</tr>
<tr>
<td>1.01-1.5 mg/d</td>
<td>1.34</td>
</tr>
<tr>
<td>&gt;1.5 mg/d</td>
<td>2.05</td>
</tr>
<tr>
<td>Per category</td>
<td>1.33 p = .006</td>
</tr>
<tr>
<td>Continuous per mg</td>
<td>1.68 p = .004</td>
</tr>
</tbody>
</table>

Upper Levels for Vitamin A (US)

Women of reproductive age
Teratogenicity = 3,000 µg/day*

All other adults
Liver Toxicity = 3,000 µg/day

*Rothman NEJM, 1995 (EU NOAEL = 3000 µg/day via regression curve)
Vitamin A (UK; EU)

UK- Evidence base considered inadequate to establish an UL (Rothman biased). Intakes greater than 1500 µg/day may be inappropriate. No vitamin A supplements if pregnant.

EU- UL = 3000 µg/day (NOAEL for teratogenicity, using Rothman- no U.F. as other studies show true threshold probably higher). Covers risk of hepatoxicity.
Upper Levels for Vitamin A (US) (Jiggering the UF)

Women of reproductive age

NOAEL (teratogenicity) = 4,500 µg/day = 3,000 µg/day*

UF 1.5

All other adults

LOAEL (liver toxicity) = 14,000 µg/day = 3,000 µg/day

UF 5

*Rothman NEJM, 1995 (EU NOAEL = 3000 µg/day via regression curve)
Data Gaps

- Lack of defined critical endpoints associated with status
- Lack of biomarkers to use to define chronic disease
- Lack of age specific data (extrapolations)
- Lack of information on variability of responses (RDAs)
- Lack of dose response data (AIs)
- Lack of long term studies
- Lack of knowledge as to which systems dysfunction with excess
- Lack of uniform rules as to how to apply UFss
Problems with Infants/Children (example)

- 56% WIC infants (4-5 months old) eating above UL (600 RAE/d) for vitamin A

<table>
<thead>
<tr>
<th>Life stage</th>
<th>Criterion</th>
<th>RDA</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 mo</td>
<td>Breast milk</td>
<td>400</td>
<td>600</td>
</tr>
<tr>
<td>7-12 mo</td>
<td>Extrapolated up</td>
<td>500</td>
<td>600</td>
</tr>
<tr>
<td>1-3 y</td>
<td>Both extrapolated down</td>
<td>300</td>
<td>600</td>
</tr>
<tr>
<td>4-8 y</td>
<td>Both extrapolated down</td>
<td>400</td>
<td>900</td>
</tr>
<tr>
<td>9-13 y</td>
<td>Both extrapolated down</td>
<td>600</td>
<td>1700</td>
</tr>
</tbody>
</table>
Fat

EAR, RDA, Al not provided, as not essential and no beneficial role. Rather, AMDR (Acceptable Macronutrient Distribution Range) = 20-35% of calories.

UL not provided for saturated and trans-fat intakes on LDL, or for cholesterol, as CHD risk increases progressively.
1) AI* as effect on CHD occurs continuously across a range of intakes

<table>
<thead>
<tr>
<th>Age</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>28g</td>
<td>25g</td>
</tr>
<tr>
<td>&gt;50</td>
<td>30g</td>
<td>21g</td>
</tr>
</tbody>
</table>

*basis = heart disease prevention

2) No UL as confounded by phytate
Estimated Energy Requirement

1) To maintain healthy weight (BMI 18.5-24.9) at an acceptable level of physical activity (PAL 1.7).

*Determined TEE for normal BMI, and then factored out BEE for PAL

2) EER based on energy balance (no weight gain); not based on reduction of disease risk.
Selection of End Points

1) Availability of data
2) Public health protection
   – ULs!

Not on:
1) Strength or consistency of evidence
2) Severity or clinical importance of endpoint
No Decision is not an Option

- Goal for individuals
- Dietary assessment
- Planning and procuring food supplies
- Food fortification and supplementation policies
- Planning and evaluating food assistance
- Food labeling policies
- Agricultural policies
- Dietary guidance policies (Dietary Guidelines)
- Planning education programs
Future Selection of Endpoints

- Identify markers that correlate with a disease or a physiologic state
  a. Markers should be attributable to the nutrient in question (animal, human)
  b. Markers should be responsive to the nutrient in question
- Use Evidence Based Reviews to answer key questions such as (a) and (b) above
- Rank quality of the evidence according to the degree of confidence in the conclusion (consistent guidelines)
- Correlate dietary intake with selected marker
- Rank overall quality of data
Evidence Based Reviews

- Independent, unbiased reviews of a defined topic (no stake in outcome)
- Can account for confounders in ranking (e.g. supplements)
- Can answer tough questions (extrapolation)
- Increases transparency of how and why decisions made (replicability)
When Data Just Aren’t There or Inadequate

- An approximate (e.g. interpolated) EAR scientifically based, but (if so) how expressed will make more useful
- Develop consistent guidelines for setting UF5
- Develop consistent guidelines for a rating of the overall evidence for a DRI value (strength, consistency, public health relevance, applicability to persons of interest)
### Epidemiological Studies of β-Carotene and Lung Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Parameter Measured</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Willett et al, 1984</td>
<td>Serum carotenes</td>
<td>0</td>
</tr>
<tr>
<td>Nomura et al, 1985</td>
<td>Serum β-carotene</td>
<td>+</td>
</tr>
<tr>
<td>Menkes et al, 1986</td>
<td>Serum β-carotene</td>
<td>+</td>
</tr>
<tr>
<td>Gey et al, 1987</td>
<td>Serum β-carotene</td>
<td>+</td>
</tr>
<tr>
<td>Wald et al, 1988</td>
<td>Serum β-carotene</td>
<td>+</td>
</tr>
<tr>
<td>Kune et al, 1989</td>
<td>Serum β-carotene</td>
<td>+</td>
</tr>
<tr>
<td>Connett et al, 1989</td>
<td>Serum β-carotene</td>
<td>+</td>
</tr>
<tr>
<td>Knekt et al, 1990</td>
<td>Plasma total carotene</td>
<td>+</td>
</tr>
<tr>
<td>Stäheline et al, 1991</td>
<td>Plasma total carotene</td>
<td>+</td>
</tr>
<tr>
<td>ATBC Trial, 1994</td>
<td>Serum β-carotene</td>
<td>+</td>
</tr>
</tbody>
</table>
ATBC Trial

Number of cases

Vit E  No Vit E  β-car  No β-car
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</th>
<th>Daily Dose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATBC (ATBC Cancer Prevention Group, 1994)</td>
<td>29,133 men 50-69 yr. Duration: 6 yr</td>
<td>20 mg β-carotene and/or 50 mg vitamin E</td>
<td>18% ↑ lung cancer in smokers</td>
</tr>
<tr>
<td>CARET (Omenn et al, 1996)</td>
<td>18,254 smokers and asbestos workers, 45-69 yr Duration: 4 yr</td>
<td>30 mg β-carotene and 25,000 IU retinol</td>
<td>25% ↑ lung cancer</td>
</tr>
<tr>
<td>PHS (Hennekens et al., 1996)</td>
<td>22,071 male physicians, 40-48 yr Duration: 12 yr</td>
<td>50 mg β-carotene (alternate days)</td>
<td>NS effects on cancer, including smokers</td>
</tr>
</tbody>
</table>

1 primary Prevention Randomized, Double-Blind, Placebo-Controlled
FDA Analysis

1) The available studies were primarily observational in nature

2) The number of studies available was significant. For example, at the time of the 1991 proposal:
   a. Retrospective studies of dietary and serum carotenoids and cancer- 8
   b. Prospective studies of dietary carotenoids and cancer- 4
   c. Prospective studies of serum or plasma carotenoids and cancer- 5
   d. Premalignancy and beta-carotene- 6
   e. Chemoprevention intervention trials with beta-carotene- 4 case control
1) Criteria used in evaluating the studies:

a. Did available studies allow attribution of the nutrient(s) per se to observed health effects, not simply to diets/dietary patterns that were rich sources of these nutrients; or to serum/plasma levels that could be markers of diets rich in these nutrients?

b. Did the available studies provide a sufficient basis for relating intakes to actual reduced risk of cancer (i.e. because there were no validated biomarkers at the time relative to serving as surrogates for cancer sites)?
This negative analysis weathered the test of time, as it did not result in premature health claims that touted the benefits of antioxidant vitamins for reducing the risk of cancer - a relationship that still lacks confirmation and/or has been refuted by evolving evidence.
How Useful is the Present DRI Framework?

- Planning for groups not useful (WIC) as WIC package not entire diet (Meals on Wheels, school lunch, etc.)
  - a. too many assumptions including that distribution of intakes won’t change with intervention
- Planning for individuals
  - a. RDA is a goal- either met or not
- Assessing individual dietary adequacy
  - a. equations too cumbersome to use (only 5% of dieticians use)
- Assessing intakes of group (WIC) worked well
Another Quandary for Application:

Na, K, Ca, vitamin D, vitamin E, and linoleic acid unrealistic values to use given the North American food supply and dietary habits.
Quandaries for the Food Label

1) What if no DRI (trans fat)?
2) What if an AI (calcium)?
3) What if a distribution range? - how to identify a single DV?
4) Use an EAR or a RDA?

(people use the label to chose among various food products)
Pros
- Comprehensive review of scientific literature on time
- Risk assessment model developed
- Framework for assessment of group dietary intakes worked well (EAR cut point for prevalence of inadequacy)

Cons
- Not based on health endpoints, data not fit
- Lack of variance data
- Extrapolations
- Little long term data
- UF for ULs subjective