Endpoints – Differences when Considering Deficiency vs. Chronic Disease

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Dietary Reference Intakes Framework

• DRI values based on:
  – Relationships between nutrient intakes and indicators of:
    • Adequacy
    • Adverse effects
  – Data from *apparently healthy populations*
  – Chronic disease (CD) risk reduction *where sufficient data for efficacy and safety exist*
Risk assessment approach to setting DRI values

Demonstration of causality
Hazard Identification = Causal Relationship
  Lit review & interpretation
  Identification & selection of indicator (endpoint)

Intake-Response Relationship
Hazard Characterization = Dose Response
  Establish model

Intake Assessment

Implications & Special Concerns

Dietary Reference Intake
Assumptions of the DRI approach

- “Essentiality” of the substance
- Evidence of causality and intake response
- Threshold for adequacy and adverse effects
- Relevant population
- Biomarkers on causal pathway
- Evidence dictates the absolute nature of the risk

1997-2005 – Generally, DRI values only set for adequacy and adverse effects of high intakes

Assumptions don’t always apply to nutrient-CD relationships
  - Only Adequate Intake values set based on CD endpoints
Comparing the evidence of causality for deficiency and chronic disease endpoints
Assumption: Causal relationship between nutrient intake and endpoint

- Establishing causality and/or dose response
  - RCT
  - Intervention trials
  - Metabolic/balance studies
  - Depletion/repletion
  - ≥3 doses (Intake-Response)
Nature of the evidence differs for CD

- Nutrient-CD evidence mostly associational
- Establishment of causality and/or dose response in absence of RCTs
- Inherent errors/bias associated with study type
  - Confounding and selection bias
  - Self-reported intake
Assumption: Biomarkers on causal pathway

- Direct observation of endpoint
  - Disease of deficiency (EAR), adverse effect (UL)
- Indicators of status on the causal pathway for diseases of deficiency
  - Eg. Serum folate, serum 25(OH)D, serum ferritin
- Higher level of certainty of relationship
CD risk: Use of surrogate or intermediate outcomes

- Nutrient-CD associations often determined using surrogate or intermediate outcomes
  - Higher uncertainty
- Validated biomarkers (including for intake) are few

Comparing the data available for estimating Intake-Response relationships
Assumption: Absolute risk affects all persons, all life-stage groups

Depending on intake level, there is 0 or 100% risk of deficiency or adverse effects
All persons, all life-stage groups: Eg. Vitamin D and bone health
CD risk: Not all persons or life-stage groups

- And often <<50% of population affected by the CD

Source: Diabetes in Canada 2011, Figure 1-4
(data from chronic disease surveillance system)

http://www.med.uottawa.ca/sim/data/Diabetes_e.htm
CD risk: Often defined as Relative risk

- No one is at 0 or 100% risk—they are at higher or lower risk compared to baseline risk
- Changes in relative risk can be small (eg. <10%)

Relative risk: Fibre and coronary heart disease

Greatest effect often at tail(s) of intake distribution – highest or lowest intakes have largest effect

BMJ 2013;347:f6879
Assumption: Threshold for adequacy

- **Threshold effect/Inflection point** between inadequate and adequate intakes
**CD risk: Absence of a threshold**

Nutrient-CD relationships can lack an inflection point  
Eg. Fibre and coronary heart disease

Fibre AI based on median intake to achieve *lowest relative* CHD risk

*BMJ 2013;347:f6879*
Assumption: Threshold for upper intake

Intake > UL increases the risk of adverse effects
CD risk: Absence of an upper threshold

- Nutrient-CD relationships can lack an inflection point
  - Eg. Saturated fats and LDL cholesterol

- * also no “benefit”: Keep intakes as low as possible while consuming a nutritionally adequate diet

Assumption: Interval between beneficial and harmful intakes
Sodium and blood pressure - no threshold and benefit overlaps harm

- Relationship is linear at all doses – NO UPPER THRESHOLD
  - AI (1.5 g) based on adequacy for other nutrients and sweat losses
  - UL (2.3 g) based on the next higher dose in trials

Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate
http://www.nap.edu/catalog/10925.html
CD risk: Potential for overlap between benefit and harm

- A nutrient can be related to multiple chronic diseases with different/overlapping risk relationships

In summary...

- The DRI approach works well for estimating adequate intakes/adverse effects for essential nutrients

- It has not worked well for CD endpoints
  - CDs are complex and can be influenced by many factors including other *food substances*
  - Assumptions used to define EAR/UL do not always apply
  - Available evidence differs significantly from that available for establishing essentiality/toxicity
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