Limited Dose-Response Data: What Options Exist for DRIs?

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Problem of Limited Dose-Response Data

- DRI process depends on dose-response data
  > EARs
  > ULs
- Even if extremely limited data on dose-response for many nutrients, DRI panels must establish numeric values
- Resulting DRI values can be “softer” in reality than what might be expected
Example: Data Used to Set Selenium RDA
Possible Biomarkers for Selenium Status

- Diseases—Keshan disease, cancer
- Blood (plasma) selenium concentration
- Plasma selenoprotein concentration maximization
  > this biomarker ultimately selected by DRI panel
Studies that Evaluated Maximization of Plasma Selenoproteins by Supplemental Selenium


New Zealand Study (n=52)

- Baseline selenium intake of subjects averaged 28 µg/day
- Groups given 0, 10, 20, 30, 40 µg/day for 5 mos
- All groups increased GSH-PX but could not be distinguished from one another due to large variation in response
- A conservative EAR of 38 µg/day was chosen (28 µg + 10 µg)

Duffield et al., AJCN 70:896–903, 1999
Chinese Study (n=45)

- Baseline selenium intake of subjects averaged 11 µg/day
- Groups given 0, 10, 30, 60, and 90 µg/day for 8 mos
- Average maximization of plasma GSH-PX achieved at 30 µg/day or total of 41 µg/day
- With weight adjustment to reflect North American body size, EAR would be 52 µg/day

Yang et al., In: Combs et al., Selenium Biol & Med, 1987
Calculation of EAR

- China and New Zealand values were averaged \((38 + 52)/2\)
- Value computed for EAR thus 45 \(\mu\)g/day
- Men and women same because of increased sensitivity to Keshan’s disease seen in women
### EARs and RDAs for Selenium - Adults (µg/day)

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>EAR</th>
<th>RDA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>19+ yrs, M</td>
<td>45</td>
<td>55</td>
</tr>
<tr>
<td>19+ yrs, F</td>
<td>45</td>
<td>55</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>49</td>
<td>60</td>
</tr>
<tr>
<td>Lactation</td>
<td>59</td>
<td>70</td>
</tr>
</tbody>
</table>

*CV of requirements assumed to be 10%
Implications

- EAR for selenium based on a total of < 100 subjects
- Very limited dose-response data
- Dose-response data had to be obtained from nutrient deficient populations (non U.S.)
- Relevance to U.S./Canada?
Solutions to the Problem of Limited Dose-Response Data

- “Statistical” or “modeling” approach
  - Take advantage of large datasets, apply various statistical modeling approaches to characterize dose-response (e.g., in relation to chronic disease or mortality)

- “Biological” approach
  - See background paper for details; relies on animal and *in vitro* studies; will cover briefly here
Statistical Approach: Incorporation of Large Amounts of Data from Chronic Disease Studies

(+): Many studies available; large sample sizes (observational and trials)

(-): Intake data susceptible to measurement error (nutrient-specific; e.g., poor for vitamin E and selenium)

(+) Can examine plasma nutrient status in relation to chronic disease risk (to estimate dose-response) and then tie back to intake data (using metabolic studies etc.)
Examining Dose-Response within Populations: Traditional Single Study Approach

• Quantile (e.g., Highest quintile versus lowest)
  —Examine quantile “dose-response” and test for linear trend across categories

• Continuous (per unit)
  —Model linear relationship between intake and outcome (dose-response)

  —BUT these assume linear relationship…Valid assumption?
Example: Folate Status and Breast Cancer Risk: Non-linear?

- Optimum is not well-defined
- Likely depends on alcohol intake, polymorphisms in folate-related genes
- Source: Ulrich et al., AJCN 86:271, 2007
Restricted Cubic Spline (piecemeal polynomial curves)

- Allows for examination of non-linear effects of continuous variables (e.g., nutrient intake or concentration) in relation to disease risk
  - No functional form needs to be specified
  - Available in standard statistical packages (SAS, BMDP)
  - May reveal non-linear dose-response relationships
Cubic Spline: RR of mortality by serum vitamin E (Wright et al., AJCN 84:1200, 2006)
Examining Dose-Response in Population Studies: Combining Data from Multiple Studies

A. Randomized, nutrient supplementation trials: Systematic review, meta-analysis
   - Meta-analysis originally developed for trials
   - Designed to see if an effect is present or not, BUT
   - Can use meta-regression to get at dose-response across different trials with different doses (and different achieved plasma concentrations)
Figure 3. Hip and Nonvertebral Fracture Efficacies by Achieved 25-Hydroxyvitamin D Levels in 400 IU/d and 700-800 IU/d Vitamin D–Treated Groups

Circles and squares represent relative risks (RRs) and error bars represent 95% confidence intervals. Trendline is based on series of effect sizes (open circles and squares). All trials identified for the primary analyses for both fractures are shown as a reference number outside each circle or square. A meta-regression, which included 9294 individuals, indicated a significant inverse relationship between higher achieved 25-hydroxyvitamin D levels in the treatment group and hip fracture risk (β = -0.009; P = .02; log RR of hip fracture is estimated to decrease by 0.009 per 1-nmol/L increase in 25-hydroxyvitamin D). A meta-regression, which included 9820 individuals, indicated a significant inverse relationship between higher achieved 25-hydroxyvitamin D levels in the treatment group and nonvertebral fracture risk (β = -0.006; P = .03; log RR of nonvertebral fracture is estimated to decrease by 0.006 per 1-nmol/L of 25-hydroxyvitamin D achieved in the treatment group). To convert 25-hydroxyvitamin D to ng/mL, divide values by 2.496.

Bischoff-Ferrari et al., JAMA 2005
Examining Dose-Response in Population Studies: Combining Data from Multiple Studies

B. Observational, epidemiologic studies
   — Application of meta-analysis to observational studies of intake more problematic
   - dose corresponding to “high intake” in one population may be quite different from that in another (and in different parts of dose-response curve)
   — Dose-response meta-analyses across categories can be done (but same caveat as above)
Example: Meta-Analysis, Observational Studies of Selenium Intake and Prostate Cancer Risk

Fig. 1. Forest plot of cohort and case-control studies of any intake (with lowest intake as the reference group) of selenium and risk of prostate cancer.

Source: Etminan et al., CCC 2005
Examining Dose-Response in Population Studies: Combining Data from Multiple Studies

C. Observational, epidemiologic studies
   – Pooled analysis approach: obtain original data from multiple studies, re-analyze all data together
   – Assumption is that intake data across studies is similarly (quantitatively) assessed; an assumption whose validity varies (nutrient-specific)
Fat and Breast Cancer: Pooled Analysis
Pooled RR for Categories of Intake

Relative Risk

% of Energy from Fat

<20  20 - <25  25 - <30  30 - <35  35 - <40  40 - <45  ≥45

Hunter, et al. 1996
Application to Upper Limits

• Instead of modeling risk of inadequacy, model risk of excess
• Similar approaches as described previously can be applied (spline models, meta-analysis, meta-regression, etc)
• Evaluate nutrient concentration or intake level where risk of adverse effect begins to increase
Use of Chronic Disease Endpoints?

- Chronic disease data widely available from U.S./Canadian or similar populations, but causality/confounding difficult to address (correlated nutrients from same foods, etc.)
- Use of plasma biomarkers desirable to examine dose-response, but does not solve confounding problem
“Biological Approach”

- “Mode of action” framework
  - To approximate dose-response, need to understand mode of action
    - straightforward application to UL, but can apply equally well to nutrient deficiency
  - Identify key molecular and biological systems/pathways
Tools/Technologies Available

- Mapping pathways
  - Hypothetically helpful but often we know the pathways involved (e.g., vitamin E deficiency)
- In vitro tests/human cell lines
  - Human “dose” data supercedes
- High-throughput methods
- Microarrays
Tools/Technologies (cont.)

- Computational biology
  - Useful for nutrients that may play a role in signaling pathways

- Physiologically-based pharmacokinetic [pharmacodynamic] models
  - Reasonable approach where animal models of nutrient toxicity/deficiency are available
  - Particularly helpful for different life stages

- Metabolomics? Translational biology?
Trade-Offs: What is the Right Balance?

**Statistical Approach**
Relevant population but limited causal inference?

**Biological**
Mechanistically driven but tenuous link to human dose?
Conclusions

- Newer options exist for examining dose-response in the setting of DRIs
  - none are yet ideal
- Forward progress requires multidisciplinary, integrated approach including biostatisticians and toxicologists working with nutrition scientists
- No obvious advantage of one approach over another

→ Data convergence?