DRIs

Dietary Reference Intakes

Procedures for Development of Tolerable Upper Intake Levels for Nutrients 1994-2004

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Today’s Presentation

- Previous discussions/reports impacting need to develop a new process for setting reference values
- Overview of US/Canada DRI Process
- In-depth look at steps in developing ULs
- Examples of UL derivation
Previous Reports that Set the Stage for the Development ULs

- 1983 Recommended Nutrient Intakes—Health & Welfare, Canada
- 1991 UK Dietary Reference Values Report—COMA
The Concept of a Safe Intake Range

Observed level of intake

Deficient
Average Requirement
RDA
Safe Range of Intake
Upper Safe

Risk of inadequacy
Risk of excess

Adapted from Health and Welfare, Canada, 1983; 1991 UK Report, COMA
DRI Framework

- Reference values to meet variety of uses
- Concepts of reduction of risk to chronic disease
- Reviews of other food components
- In-depth rationale for functional end points used
- Open dialog with interested groups
- Estimates of upper limits of intake
Why DRIs?

Conceptual Approach

- Quantitative dietary reference values need to address multiple users and meet multiple needs
  - Labeling
  - Limits for fortification
  - Assessing adequacy of diets of population groups
- One number can’t do it all if a science-based approach is to be followed
Relationship of the DRIs

- **Observed level of intake**
- **UL**
- **Risk of inadequacy**
- **Risk of excess**
- **0.5**
- **RDA**
- **AI**
- **Increase**
- **EAR**

Graph illustrating the relationship between different dietary intake levels and the associated risks of inadequacy or excess.
Dietary Reference Intakes

Standing Committee on the Scientific Evaluation of Dietary Reference Intakes

Panels

Ca, Vitamin D, Phosphorus, Mg, F

Folate, B₁₂, Other B Vitamins, Choline

Vitamins C and E, Se, β-carotene and Other Carotenoids

Vitamins A and K, As, B, Cr, Cu, Fe, I₂, Mn, Mo, Ni, Si, V, Zn

Energy and Macronutrients

Electrolytes, Water

[Other Food Components]

Uses of DRIs Subcommittee

Upper Reference Levels Subcommittee

10 years, $US ~7.5 M
Flow Chart of DRI Activities—FNB/IOM Process

Reports Released

NRC REVIEW

SCIENTIFIC AND USER COMMUNITIES

Solicits Nominees

DRI COMMITTEE—Scientific Evaluation of DRIs

NUTRIENT GROUP PANEL(S)

1) Holds Workshops and Meetings
2) Develops Scientific Basis for Nutrient Needs and Sets Tentative Reference Values, Including EARs, Variances, RDAs, AIs, and ULs

Forwards Drafts

UPPER REFERENCE LEVELS SUBCOMMITTEE

Forwards Drafts

Develops Guidelines for use with Emphasis on Policy, Guidance & Education

USES OF DRIs SUBCOMMITTEE
DRI Reports 1997-2004
DRI Funding Provided By

- United States: DHHS (Office of Disease Prevention and Health Promotion, Food and Drug Administration, Centers for Disease Control and Prevention, and NIH); USDA; U.S. Army
- Health Canada
- NGOs: the Dannon Institute; International Life Sciences Institute
- the DRI Corporate Donors’ Fund: Daiichi Fine Chemicals; Kemin Foods; M&M/Mars; Mead Johnson Nutritionals; Nabisco Foods Group; Natural Source Vitamin E Association; Roche Vitamins; U.S. Borax; and Weider Nutritional Group
Subcommittee on Upper Reference Levels of Nutrients

Original Subcommittee 1995+
- IAN C. MUNRO, chair, CanTox, Inc., Mississauga, Ontario
- WALTER MERTZ, Retired, USDA, Beltsville, MD
- RITA B. MESSING, Minnesota Dept of Health
- SANFORD A. MILLER, Georgetown University, Washington, DC
- SUZANNE P. MURPHY, University of California, Berkeley
- JOSEPH V. RODRICKS, The Life Sciences Consultancy, Arlington, VA
- IRVIN H. ROSENBERG, USDA & Tufts University, Boston
- STEVE L. TAYLOR, Univ. of Nebraska, Lincoln
- ROBERT H. WASSERMAN, Cornell University, Ithaca, NY

Additional Members 1999-2004
- G. HARVEY ANDERSON, University of Toronto
- GEORGE C. BECKING, Phoenix OHC, Kingston, Ontario
- ELAINE FOUSTMAN, University of Washington, Seattle
- SUZANNE HENDRICH, Iowa State University, Ames
- RENATE D. KIMBROUGH, Institute for Evaluating Health Risks
- HARRIS PASTIDES, University of South Carolina, Columbia
- JOHN A. THOMAS, San Antonio
- GARY M. WILLIAMS, New York Medical College
Key Issues in the Development of a Model for Upper Levels of Nutrients

- Safety versus risk
- Limitations of traditional models
- Unique characteristics of nutrients
- Sparse documentation of adverse effects of chronic overconsumption
- Coordinating the work of the nutrient review panels with the subcommittees
Characteristics of the Concept of Safety

Safety is:

- An intellectual concept
- Not an inherent biological property
- A point on a continuum

UK DRV Report in 1991 had used the term “Upper Safe Level of Intake”
Safety: A Point on a Continuum

SCIENCE

SOCIETY + CULTURE + POLITICS + LAW + ECONOMICS

UNSAFE (0) SAFE (100)
Definition of Risk

- Risk is defined as the probability of an adverse effect occurring at some specified level of exposure.
- Risk assessment is a scientific exercise, not influenced by value judgments.
- Risk management = approaches to take to mitigate identified risk --- not part of risk assessment.
Limitations of Traditional Toxicology Models in Use in 1994

- Focused on establishing *safe intakes* not tolerable upper intake levels
- Reliance on animal data
- Most involved the concept of establishing an Acceptable Daily Intake (ADI) ---somewhat equivalent to other terms such as US EPA’s Oral Reference Dose (RfD) or US ATSDR’s Minimum Risk Level (MRL)
Typical Studies Required for Food Ingredients (Usually for Non-Essential Additives)

- Acute toxicity - 2 species
- Sub-chronic toxicity - 2 species
- Multi-generation studies
- Teratology studies
- Long-term/carcinogenicity studies - 2 species
- Absorption, distribution, metabolism and excretion studies
- Genotoxicity studies - *in vitro / in vivo*

Calculation of Acceptable Daily Intake (ADI)

\[
\text{ADI (mg/kg bw-man)} = \frac{\text{NOAEL}^1 \text{ (mg/kg bw-animal)}}{\text{Safety Factor (usually 100)}}
\]

Note: Safety Factor designed to compensate for:

a) Animal to man extrapolation
b) Intrahuman sensitivities (children, elderly, gender)
c) Differences in test population size

\(^1\text{No Adverse Effect Level}\)
Unique Characteristics of Data on Overconsumption of Nutrients

- Absence of dose-response data
- Few available human or animal chronic studies
- Few surveillance studies to establish NOAEL
- Available databases have concentrated on supplement intake, but not total
- Significant differences in bioavailability, particularly for trace elements
Problem Identified When Standard Uncertainty Factors Used with *Essential* Nutrients

US EPA’s RfD (oral reference dose) for zinc for children was *less* than the 1989 RDA for zinc for young boys
Risk Assessment Model

- Hazard Identification
- Dose-Response Assessment
- Exposure Assessment
- Risk Characterization

Risk Management
The highest daily nutrient intake level that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects may increase(s). The UL is not a recommended level of intake and is not a level that is desirable to attain.

NOTE: Words in italics added in later DRI reports
UL
Tolerable Upper Intake Level
Aspects Important to Consider when Applying to Nutrients

- Limited data available due to few human studies
- Depending on clinical significance of observed adverse effects, uncertainty factor used will vary
- Observed effects may vary depending on form of intake
Step 1: Hazard Identification

Components

- Evidence of adverse effects in humans
- Causality
- Relevance of experimental data
- Mechanism of toxic action
- Quality and completeness of the data base
- Identification of distinct and highly sensitive subpopulations
Step 2: Dose-Response Assessment

Components

- Data selection
- Identification of no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) and critical endpoint
- Uncertainty assessment
- Derivation of a UL
- Characterization of the estimate and special considerations
Step 3: Uncertainty Assessment

Depends on

- Inter-individual variation in sensitivity
- Experimental animal data extrapolated to humans
- LOAEL used in absence of NOAEL
- Sub-chronic NOAEL used to predict chronic NOAEL
UL Calculations

Almost always based on data for adults, then typically decreased for younger age groups

\[
\text{LOAEL} \quad \text{Uncertainty Factor} = \quad \text{UL}
\]
Effect of Uncertainty Assessment on UL

Risk of Adverse Effects

- 100%
- 50%
- 100%
- 50%

RDA  UL  NOAEL  LOAEL

Increasing Intake
Idealized Benefit/Risk Curve

Probability that stipulated intake is inadequate for a randomly selected individual

Probability that stipulated intake is excessive for a randomly selected individual

Increasing Intake
Importance of Knowing Distributions for Dietary Recommendations

- Frequency
- Requirement
- Intake Distribution
- Adverse Effects

- Requirement
- Intake
- Population Index
- AI
- EAR
- RDA
- X

S. Murphy, 2015
Distributions for Dietary Recommendations—Possibly Overlapping Distributions

- Requirement
- Intake Distribution
- Idealized Adverse Effects
- Actual Adverse Effects

X_{EAR} \quad RDA \quad X_{\text{Intake}} \quad \text{Pop. Index} \quad \text{Al}

Reference: S. Murphy, 2015
Example of Overlapping Requirements Distribution with Distribution of Adverse Effects: Caries Experience and Dental Fluorosis Index Versus Fluoride Concentration of Drinking Water
Example: Establishing a UL For Folate
## UL Adverse Effects from 1998 B-Vitamin Report

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Adverse Effect</th>
<th>(\text{N(L)})OAEL</th>
<th>UF</th>
<th>Adult UL/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin(^1)</td>
<td>Flushing</td>
<td>(L = 50 \text{ mg})</td>
<td>1.5</td>
<td>(~35 \text{ mg})</td>
</tr>
<tr>
<td>Vitamin B(_6)</td>
<td>Sensory neuropathy</td>
<td>(N = 200 \text{ mg})</td>
<td>2.0</td>
<td>100 mg</td>
</tr>
<tr>
<td>Folate(^1)</td>
<td>Neuropathy in B(_{12})-deficient individuals</td>
<td>(L = 5 \text{ mg})</td>
<td>5.0</td>
<td>1,000 µg</td>
</tr>
<tr>
<td>Choline</td>
<td>Hypotension, fishy body odor</td>
<td>(L = 7.5 \text{ g})</td>
<td>2.0</td>
<td>3.5 g</td>
</tr>
<tr>
<td>Vitamin B(_{12})</td>
<td>None identified as of concern</td>
<td>(\text{---})</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)From supplements only
UL for Folate
Dose Response Assessment
Adverse Effect Selection

• Possible adverse effects in the literature
  – Neurological damage in Vitamin B-12 deficient individuals
  – General toxicity: mental changes, sleep disturbances, and GI effects of 15 mg/d
  – Increased cancer of oropharynx and hypopharynx and total cancer rates – epidemiological study
  – Hypersensitivity – rare, 1 mg/d
  – Intestinal zinc malabsorption
UL for Folate
Dose Response Assessment
Identification of NOAEL (or LOAEL)

- Supplemental folate $\geq 5$ mg/d ~100 reported cases
- $\leq 5$ mg/d (0.33 to 2.5 mg/d), only 8 well-documented
- Folate supplementation maintained patients in remission of pernicious anemia symptoms
- Background intake of folate from food was not specified in reports
UL for Folate
Dose Response Assessment
Uncertainty Assessment

-UF chosen was 5

-Why so high when there is dose-response data available?
  - Due to severity of neurological complications
  - Complications are irreversible
  - Only have LOAEL, not NOAEL

-Not higher than 5 as have uncontrolled observations of millions of people exposed to 1/10th the LOAEL without reported harm
UL for Folate Calculations

All adults

\[
\text{LOAEL (Masking B-12 deficiency)} \quad \frac{5 \text{ mg/day}}{5} = 1 \text{ mg/day} = \text{UL}
\]
Example:
Establishing a UL For β-Carotene
Why Not a UL for β-Carotene?

- Supplemental β-carotene increased the risk of lung cancer in two major trials (doses used 20 mg/d; 30 mg/d + vit. A)
- However, the data are conflicting with a third major trial (dose 50 mg/every other day) reporting no adverse effects with up to 12 years intervention
- Therefore, conflicting data did not allow determination of a UL
Plasma β-Carotene Concentrations in Large Population Studies

U.S. 5th to 95th%
0.09 – 0.9 (5 – 49)

"Threshold" >0.4 μmol/L (>20 μg/dL)

U.S. 5th to 95th%
0.09 – 0.9 (5 – 49)

Blood β-carotene concentration
μmol/L (μg/dL)

1.9 (100)
3.8 (200)
5.6 (300)
7.5 (400)

Linxian (15 mg/day)

PHS (50 mg every other day)

ATBC (20 mg/day)

CARET (30 mg/day)
Supplemental β-Carotene and Lung Cancer Risk

Report conclusion: “Based on evidence that β-carotene supplements have not been shown to confer any benefit...and may cause harm in certain subgroups (possible lung cancer risk in smokers), it is concluded that β-carotene supplements are not advisable, other than as a provitamin A source and for the prevention and control of vitamin A deficiency in at-risk populations.”
Example:
Establishing a UL For Vitamin A
Adverse Effects Considered in Setting the Upper Level for Vitamin A

- Bone mineral density
- Liver toxicity
- Teratogenicity (women of reproductive age)
- Bulging fontanel (infants)
Upper Levels for Vitamin A

**Women of reproductive age**

\[
\text{NOAEL (teratogenicity)} = 4,500 \, \mu g/\text{day} = 3,000 \, \mu g/\text{day} \\
\text{UF} = 1.5
\]

**All other adults**

\[
\text{LOAEL (liver toxicity)} = 14,000 \, \mu g/\text{day} = 3,000 \, \mu g/\text{day} \\
\text{UF} = 5
\]
<table>
<thead>
<tr>
<th>Life Stage</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–6 mo</td>
<td>600</td>
</tr>
<tr>
<td>7–12 mo</td>
<td>600</td>
</tr>
<tr>
<td>1–3 y</td>
<td>600</td>
</tr>
<tr>
<td>4–8 y</td>
<td>900 (same as RDA for adult male)</td>
</tr>
<tr>
<td>9–13 y</td>
<td>1,700</td>
</tr>
<tr>
<td>14–18 y</td>
<td>2,800</td>
</tr>
<tr>
<td>≥19 y</td>
<td>3,000</td>
</tr>
<tr>
<td>Preg, Lact</td>
<td>See age group</td>
</tr>
</tbody>
</table>
Example:
Establishing a UL For Iron
Adverse Effects Considered for Setting the Upper Level for Iron*

- Gastrointestinal distress
- Impaired zinc absorption
- Cardiovascular disease
- Cancer

\[
UL = \text{LOAEL} \times \frac{UF}{1.5} = 70 \text{ mg/day} \approx 45 \text{ mg/day} \]

*May not protect individuals with hemochromatosis
Critical Points in Establishing Useful ULs

- Integrate nutrient requirements analysis with evaluation of adverse effects—can’t be isolated activities—and must involve both nutritionists and toxicologists.
- Evaluate existence of food and supplement intake data to assure that adequate exposure (intake) estimates exist for relevant sub-population groups.
- Dietary guidance needs to reflect varied population needs as well as potential adverse effects—depends on the seriousness of the adverse effects.
- Risk managers determine how to incorporate risk assessment into policy—Final Dietary Guidelines, label values, etc.
21st Century Paradox in the U.S.: Overnutrition & Malnutrition

Percent of inadequate intakes in U.S. compared to nutrient requirements, using individual DRI EARs to determine prevalence of inadequacy; WWEIA intake surveys now include estimates from supplements as well as food to allow comparison with ULs.

What We Eat in America, NHANES

WWEIA 2001-2002, 1 day, 1+y
FSRG/ARS/USDA
Synthesis Report Submitted as CRD 1 for Codex Committee on Nutrition and Foods for Special Dietary Uses in 1998

All DRI reports are downloadable on National Academies Press website: www.nap.edu
Search term: DRI

Also, 2015 Dietary Guidelines for Americans Advisory Committee Report from February 2015 available online; final 2015 Dietary Guidelines Report not yet available