UL Research Recommendations

*within the context of an*

International Model for Nutrient Risk Assessment

Report of a Joint FAO/WHO Scientific Workshop on Nutrient Risk Assessment
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Background

- 2005: FAO/WHO international workshop to outline a model for conducting nutrient risk assessment related to upper levels of intake
- No consideration of specific nutrients
- General research recommendations
  

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Goal of Today’s Presentation

- Broad-brush
- Match UL research recommendations into themes sounded during the workshop
- Underscore: Not just lack of data, but need for refined and better model(s)
- Advocate: Time to push the development nutrient risk assessment to its next step
Background: Report Development

- Funds
  - Australia, Food Standards
  - Canada, Health Canada
  - European Commission, SANCO
  - South Korea, KFDA
  - United States, NIH

- 18 participants / 14 countries

  Aggett – UK
  Cheney – Canada
  Gare – US
  Hulthen – Sweden
  Laskovic – France
  Sabzevari – Iran
  Carreira – Brazil
  Giovaco – Canada
  Lartey – Ghana
  Pazynkiewicz – Germany
  Silvekaar – India
  Pham – Korea
  Davy – Guatemala
  Eastbakk – Singapore
  Lartey – US
  Nemeth – UK
  Santos – Brazil
  Stanley – Thailand

Background: Conceptual Underpinnings for the Model

Toxicological principles offer the foundation but need to be modified for the special considerations related to nutrient substances:

- One of a kind homeostatic mechanisms
- Metabolic differences for age/sex and lifestage
- Dual risk curves re: deficiency and excess
- Inability to ‘wait’ until data coalesce / not premarket approval model

Background: ‘Charge’ to Participants

Classic Non-nutrient Toxicological Principles

- ‘Marry’ with Nutrition Principles

Regional Nutrient Risk Assessment

- European Union / EFSA (SCF)
- United Kingdom, Expert Group on Vitamins and Minerals
- United States & Canada, Institute of Medicine
General Themes of the Model

- Outcomes based on available evidence, not on ‘developed data sets’
- Current practice of evidence-based systematic review needs to be adapted for relevance to nutrient risk assessment
- Public health protection choices are part of process and are not necessarily driven by weight of evidence considerations

Research Messages

- ‘First-Step’ Research Message
  - Need research to better allow risk assessors to deal with currently limited data sets
- ‘Second-Step’ Research Message
  - Need research targeted to safety
  - Available research usually focused on efficacy
  - Need way to stimulate and organize research agendas

RESEARCH: 1. Dealing with Existing Data Sets

Guidelines for approach to ‘scientific judgment’
- Researchable issue
- Accountability, documentation and transparency

Examples
- Approaches to combining data to establish link to adverse health effect
- Inclusion/exclusion criteria for and weighting of studies (observational notably)
- Enhanced principles for meta-analysis
RESEARCH:
2. Dealing with Need for Human Intervention Data

- Limited human data sets should not remain the norm, but...
  - Must acknowledge ethical issues
  - Must acknowledge costs and difficulties associated with human trials

- Develop innovative strategies
  - Creative methodologies vis à vis animal models, in-vitro techniques, computer simulations

- Explore more fully:
  - Approaches for comparing sensitivity between animals and humans
  - Extrapolation of data from adults to children
  - Approaches that are more physiological and less default
  - Relevance of changes in easily measured homeostatic mechanisms

UL Recommendations

- Adjustment factors for body size, physical activity, intakes of energy, etc. (G.II.10)
RESEARCH:
3. Identifying Relevant Measurable Endpoints

- Causally-Related Biomarkers
  - Identify, elucidate and validate
  - Specify sensitivity
  - Clarify homeostatic range
  - Clarify time course

UL Recommendations
- Biomarkers (C.IV.01)

RESEARCH:
4. Improving Basic Understanding

- Nature of metabolism, especially at high levels of intake
- Targeted research to elucidate adverse health effects
- Dose range studies
- Specification of interactions
- Bioavailability
UL Recommendations

- General Research (G.I.07)
  - Specific nutrients
    - B-vitamins, folate, pantothenic acid, choline
    - Vitamin C, vitamin E, carotenoids
    - Vitamin K, arsenic, boron, copper, molybdenum, silicon, vanadium (supplements)
  - Amino acids, protein

- Dose-response data (G.I.08)

- Factors affecting uptake and absorption including source (H.I.18)

RESEARCH:

6. Improving and Harmonizing Dietary Intake Assessments

- Approaches to combining data to estimate intake from all sources

- Approaches for estimating intake from aggregated data

- Develop markers of exposure

UL Recommendations

- Quantify intake of dietary supplements (G.I.14)

- Enhance food composition databases (G.II.20)

- Statistical adjustments (G.II.24)
RESEARCH:
5. Adapting Model to Range of 'Nutrient Substances'

- 'Nutrient substances' not specifically defined, but encompass wide range
- Non-essential or non-beneficial – Constituents of food supply
- No threshold response:
  - Trans fat, saturated fat
- Macronutrients vs micronutrients
- Addressing interactions
- Apparent overlap between 'beneficial' intake and risk

UL Recommendations

- Optimal range for macronutrient intake
- Nature of their adverse effects

RESEARCH:
7. Understanding Use/Application of UL and of Risk Characterization

- Studies of risk characterization outcomes to identify:
  - What information was used and how
  - What aspects of characterization were not useful
  - What aspects led to secondary risk assessment requests
- Guidelines for problem formulation
Odds & Ends: Public Health Protection

- Defining what is adverse

- Selecting the critical adverse health effect for UL (age/sex)
  - FAO/WHO: Effect seen at lowest level of intake
  - Not necessarily most severe or 'most evidence'

Odds & Ends: Promoting International Harmonization

- WHO, Codex, and Regions (e.g. EU)

- Create (expand and combine) databases to catalogue and collate information on agreed-upon adverse health effects associated with nutrient substances