

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

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

<http://www.who.int/ipcs/methods/nra/en/index.html>

2

Goal of Today's Presentation

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

3

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	Carriquiry - US	Chang - Korea
Cheney - Canada	Cozzolino - Brazil	Dary - Guatemala
Garza - US	Gourile - Canada	Halliwel - Singapore
Hulthen - Sweden	Lartey - Ghana	Lau - US
Leblanc - France	Przyrembel-Germany	Renwick - UK
Sabzevari - Iran	Sivakumar - India	Srianujata - Thailand

4

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

5

Background:
'Charge' to Participants

Classic Non-nutrient Toxicological Principles
à '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

6

General Themes of the Model

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

Research Messages

- n 'First-Step' Research Message
 - Need research to better allow risk assessors to deal with currently limited data sets
- n '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

- n 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

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

10

RESEARCH:
2. Dealing with Need for Human Intervention Data

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

11

UL Recommendations

- n Adjustment factors for body size, physical activity, intakes of energy, etc. (G.II.10)

12

RESEARCH:
3. **Identifying Relevant Measurable Endpoints**

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

13

UL Recommendations

- n Biomarkers !!! (C.IV.01)

14

RESEARCH:
4. **Improving Basic Understanding**

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

15

UL Recommendations

- n **General Research (G.I.07)**
- n **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
- n **Dose-response data (G.I.08)**
- n **Factors affecting uptake and absorption including source (H.I.18)**

16

RESEARCH:

6. Improving and Harmonizing Dietary Intake Assessments*

- n Approaches to combining data to estimate intake from all sources
- n Approaches for estimating intake from aggregated data
- n Develop markers of exposure

17

UL Recommendations

- n **Quantify intake of dietary supplements (G.I.14)**
- n **Enhance food composition databases (G.II.20)**
- n **Statistical adjustments (G.II.24)**

18

RESEARCH:

5. Adapting Model to Range of 'Nutrient Substances'

- n '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

19

UL Recommendations

- n Optimal range for macronutrient intake (E.1.04), nature of their adverse effects (E.1.10); fats (E.X.25)

20

RESEARCH:

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

- n 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
- n Guidelines for problem formulation

21

**Odds & Ends:
Public Health Protection**

- n Defining what is adverse
- n 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'

22

**Odds & Ends:
Promoting International
Harmonization**

- n WHO, Codex, and Regions (e.g. EU)
- n Create (expand and combine) databases to catalogue and collate information on agreed-upon adverse health effects associated with nutrient substances

23
