Toxicology Due to Excess and Deficiency

Peter J Aggett
University of Central Lancashire
Outline of Presentation:

- Nutrient Risk Assessment: Excess
- Requirements
- Commonalities of Inadequacy and Toxicity
- Biologically Based Approach
Risk - Benefit Analysis Needs

1. A common method of risk assessment (hazard and dose-response assessment)

2. A common currency to describe the health impacts

(EFSA 2007 Symposium 6)
“Science is what you know, philosophy is what you do not know”

Bertrand Russell
Idealised Acceptable Range of Oral Intake (IPCS 2002)
Idealised Acceptable Range of Oral Intake (IPCS 2002)
Issues of Risk-Benefit or Benefit-Risk Analysis

- Disciplines of the assessors
- Toxicologists or Nutritionists
  - (The Profession is in the Dose)
- Confounded by mutual respect and possibly misplaced trust
- “Quality” of the data bases
  - External and internal exposure
  - Critical health effects
Issues of Risk-Benefit or Benefit-Risk Analysis: 2

- Is there an interdisciplinary commonality or currency in the entire knowledge base?
- A highest common denominator of quality for the knowledge base
- Different approaches to dealing with uncertainty and variability
- Risk and Benefit are not antonyms
Risk

- The probability or likelihood that a hazard will actually cause harm to an individual or population group.
Hazard (of Excess)

• The inherent property of a nutrient or related substance to cause adverse health effects depending upon the level of intake.
  – (WHO/FAO 2007)
Hazard (of Inadequacy)

• The inherent property of ("a low intake/exposure") of a nutrient or related substance to cause adverse health effects depending upon the level of intake.
Benefit

Avoiding deficiency or toxicity…or?
Hazard-Benefit-Hazard: 3

- Balance of Hazards and “Benefits” rather than Risk-Benefit Analysis
- Characterisation of Adverse (Critical) Health Events
Risk Benefit Analysis

- Principles and Methods for the Assessment of Risk from Essential Trace Elements
- IPCS: EHC 228; 2002
A Biologically Based Approach to Risk Assessment

• An exploration of a homeostatic approach to RA of exposure to Essential Trace Elements.
• Difficulties in balancing beneficial and adverse events
• Setting an “Acceptable Range of Oral Intake” AROI

(IPCS. WHO 2002)
Hazard-Benefit-Hazard Spectrum

Fig. 5.

- **Inadequacy**
- **Adequacy**
- **Excess**

- **Deficiency**
- **Toxicity**

Range of acceptable daily oral intake

RDA

WHO 01.335
Hazard-Benefit-Hazard Responses to Inadequate and Excess Exposure to a Micronutrient (IPCS, WHO 2002)
Hazard-Benefit-Hazard Responses to Inadequate and Excess Exposure to a Micronutrient (IPCS, WHO 2002)
A Model for Establishing Upper Levels of Intake for Nutrients and Related Substances

- Critical evaluation of experience using risk assessment approach
- Valued the potential rigour and transparency of the process
- Reappraisal of AHEs, Uncertainty, and exposure assessment
- Biologically Based Model
  - (Joint FAO/WHO Technical Workshop 2006)
Metabolic template for Metals: critical event

INTAKE

Uptake
Transfer
Portal/ (lymphatics)

Liver

Systemic Distribution (Plasma)

Haematopoietic
R.E.S.
Pancreas
Endothelia (CVD)
Brain
Epithelia
Bone
Skin
Hair

Release and Presentation from diet

Non absorbed and excreted

Uptake Deposition- store, enzymes, metabolised, sequestered

Faeces

Urine
Adverse Health Effects Used In Hazard Characterisation

1. Biochemical changes within homeostatic range and no adverse sequelae

2. Biochemical changes outside the homeostatic range without known sequelae

3. Biochemical changes outside the homeostatic range: a marker of potential adverse effects due to excess

4. Clinical symptoms indicative of a minor but reversible change

5. Clinical symptoms of significant but reversible effects

6. Clinical signs indicative of significant reversible organ damage

7. Clinical signs indicative of irreversible organ damage
   (Renwick et al 2004)
**Flow of Phenomena against Increases in Exposure**

1. Biochemical changes within homeostatic range and no adverse sequelae

2. Biochemical changes outside the homeostatic range without known sequelae

3. Biochemical changes outside the homeostatic range: a marker of potential adverse effects due to excess

4. Clinical symptoms indicative of a minor but reversible change

5. Clinical symptoms of significant but reversible effects

6. Clinical signs indicative of significant reversible organ damage

7. Clinical signs indicative of irreversible organ damage

(Renwick et al 2004)
Cascade Of Effects And Of Markers: Opportunities For Critical Marker Identification

1. *Biochemical changes within homeostatic range and no adverse sequelae*

2. *Biochemical changes outside the homeostatic range without known sequelae*

3. *Biochemical changes outside the homeostatic range: a marker of potential adverse effects due to excess*

4. *Clinical symptoms indicative of a minor but reversible changes*

5. *Clinical symptoms of significant but reversible effects*

6. *Clinical signs indicative of significant reversible organ damage*

7. *Clinical signs indicative of irreversible organ damage*

Opportunities For Critical Marker Identification: Marker chain and dose relationship

1. Biochemical changes within homeostatic range and no adverse sequelae

2. Biochemical changes outside the homeostatic range without known sequelae

3. Biochemical changes outside the homeostatic range: a marker of potential adverse effects due to excess

4. Clinical symptoms indicative of a minor but reversible changes

5. Clinical symptoms of significant but reversible effects

6. Clinical signs indicative of significant reversible organ damage

7. Clinical signs indicative of irreversible organ damage

Hazard-Benefit-Hazard Responses to Inadequate and Excess Exposure to a Micronutrient (IPCS, WHO 2002)
Hazard-Benefit-Hazard Responses to Inadequate and Excess Exposure to a Micronutrient (IPCS, WHO 2002)
Avoiding AHEs of Deficiency

- What is the critical event?
- What is the best marker?
- Difficult decision, data are often not available.

Identify AHEs with diminishing “intakes”
Or Gaining Beneficial Health Effects

- What is the critical event?
- What is the best marker?
- Difficult decision, data are often not available.

Identify Beneficial Health Effects with increasing “intakes”
Flow of Phenomena against Reduced Exposure/Dosage

1. Biochemical changes within homeostatic range and no adverse sequelae

2. Biochemical changes outside the homeostatic range without known sequelae

3. Biochemical changes outside the homeostatic range: a marker of potential adverse effects due to deficiency

4. Clinical symptoms indicative of a minor but reversible change

5. Clinical symptoms of significant but reversible metabolic and functional effects

6. Clinical signs indicative of significant reversible architectural organ damage

7. Clinical signs indicative of irreversible organ damage
Hazard-Benefit-Hazard Responses to Inadequate and Excess Exposure to a Micronutrient (IPCS, WHO 2002)
Recommended Dietary Allowance (USA)
Reference Nutrient Intake (UK)
Population Reference Intake (EU)

Population distribution of requirements for a nutrient

Frequency (number of subjects)

2 standard deviations

Estimated average requirement - EAR

RDA/ PRI/ RNI

Sao Paulo, November 2005
Distributions of Intake and Requirements

![Graph showing distributions of intake and requirements for zinc intake.](image)

- **Probability of inadequacy**
- **Probability of excess**

**Hypothetical intake distributions**

**Zinc intake (mg/day)**

Frequency ( )

Probability ( . . . )

IPCS 2002
CVs of Human Variability

**Benefit**
EU Scientific Committee on Food: 15% by the SCF
USA Institute of Medicine: 10%

**Toxicity**
Drug kinetics monomorphic pathways: ~ 30-50%
Drug kinetics polymorphic pathways: ~ 40-65%
Drug dynamics: ~ 50%

Overall: 45%
Attempts At Rationalisation

- International Harmonisation of Approaches for Developing Nutrient-Based Dietary Standards
- Food Nutrition Bulletin 2007 (March) 28; 1, S3-S153
Nutrient Intake Values

• Conceptual exercise
• Advocated Two derived or primary values:
  – Average Nutrient Requirement
  – Upper Nutrient Level

(UNU/WHO/FAO 2007)
Population distribution of requirements for a nutrient

- Frequency (number of subjects)
- Nutrient Requirement

- Average Nutrient Requirement - ANR
- Upper Nutrient Level - UL
- Individual Nutrient Level - INL

Apply own estimate for variability
Harmonisation Task Group

• Advocated
  – A more systematic approach to data acquisition and application
  – Biologically based models
  – Essentially the ADME approach
Nutrient in diet

Absorption

Gut mucosa

Not absorbed

Metabolism

Lipid soluble compartment

Water soluble compartment

Liver

stable

intact

active

Systemic circulation

Extra-hepatic organs utilisation, metabolism and deposition

Kinetics

Cell sites & functions

Dynamics

Faeces

Intraluminal metabolism microflora

Nutrient Safety and Metabolism

Excretion

Not absorbed
Metabolic template for Metals: critical event

- **INTAKE**
- **Uptake**
- **Transfer**
- **Portal/(lymphatics)**
- **Haematopoietic**
  - R.E.S.
  - Pancreas
- **Pancreas**
- **Endothelia**
  - (CVD)
- **Brain**
- **Epithelia**
- **Bone**
- **Skin**
- **Hair**
- **Systemic Distribution (Plasma)**
  - Uptake
  - Deposition, store, enzymes, metabolised, sequestered
- **Liver**
- **Release and Presentation from diet**
- **Non absorbed and excreted**
- **Faeces**
- **Urine**

Release and Presentation from diet
“Critical Events” (The Homeostatic Swan)
Metabolic template for Metals: critical event

INTAKE

Uptake

Transfer

Portal/lymphatics

Uptake Deposition - store, enzymes, metabolised, sequestered

Systemic Distribution (Plasma)

Liver

Haematopoietic

R.E.S.

Pancreas

Endothelia (CVD)

Brain

Epithelia

Bone

Skin

Hair

Control Points

Non absorbed and excreted

Release and Presentation from diet

Faeces

Urine
An Illustrative Spectrum: Copper

Mixed Data Bases
Few Systematic Exposure Response Curves
Very Limited Intake or Exposure Data
Few Human Data
Copper: Metabolism

**Dietary Cu**
0.6-2.0mg daily

Copper absorbed comes from dietary intake, saliva, gut, and hepato-biliary excretions/secretions

Peripheral uptake by endocytosis of caeruloplasmin

**Uptake**

**Transfer**

Portal (on albumin, transcuprein, aas)

**INTAKE**

**Uptake**

**Transfer**

**Systemic Plasma Cu; Cp**

**Enzymes**

1. **Uptake**
2. **Transfer**

**Store** (Metallothionein)

**Caeruloplasmin**

**Biliary Excretory Degraded caeruloplasmin**

**Sulfur compounds**

**Faeces**
0.5-1.5mg

**Urine**
30-60 microgm

**Haematopoietic**

R.E.S.
Pancreas
Gonads
Brain
Muscle
Bone
Skin
Hair

Entericirculation
Copper: Deficiency.

INTAKE

Uptake
Transfer
Portal

Systemic Plasma Cu; Cp

Enzymes Caeruloplasmin

Excretory
Store metallothionein

Urinary Cu

1 2 3 4 5 6

Haematopoietic
R.E.S.
Pancreas
Gonads
Brain
Muscle
Bone
Skin
Hair

1
2
3?

Cu; Cp
## A Postulated Spectrum of Copper Metabolism:
### Approximate Daily Intakes ug/kg body weight

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>5000</th>
<th>DEATH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;5000</td>
<td>Gross disturbance of nutrient metabolism.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tissue architectural damage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatic “detoxification” and homeostasis overwhelmed</td>
</tr>
<tr>
<td>ADEQUACY</td>
<td>100</td>
<td>GI metallothionein induced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cu absorption down regulated</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>Hepatic metallothionein increased ++;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lysosomal excretion of copper</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>Hepatic uptake, sequestration and excretion effect homeostasis:</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>GI uptake efficient, Hepatobiliary excretion</td>
</tr>
<tr>
<td></td>
<td>8.5</td>
<td>Biliary excretion reduced</td>
</tr>
<tr>
<td></td>
<td>5.2</td>
<td>Hepatic deposition depleted</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Gastrointestinal absorption increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative copper balance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cu enzyme activities reduced,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Impaired substrate metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Peripheral pools disrupted</td>
</tr>
<tr>
<td>DEFICIENCY</td>
<td>2</td>
<td>Disturbed function and substrate metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DEATH</td>
</tr>
</tbody>
</table>
Copper: Dose Response “Human Data”

- Black dots: Cu Absorption (%)
- Open circles: Cu Absorption (mg)
From Scott Baker
Variability and Uncertainty

Variability
- Inter-individual differences arising from e.g.
  - Functional Polymorphisms
  - Programming
  - Age
  - Gender
  - Physiological maturation

Uncertainty
- Factors which are unknown or imprecise e.g.
  - Exposure (inc Bioavailability)
  - Internal exposure
  - Adaptation
  - Measurements
  - Methodologies
  - Extrapolations
  - Manifestation of impact
A “Biological Based Model” would:

- Use of nutrient kinetics (ADME) and dynamics
- Mechanisms of observed effects: homeostasis and pathological events
- Work from a critical effect to identify a more convenient marker, exploiting information on the pathogenesis of the adverse event related to inadequate and excessive intakes
- Facilitate characterisation of U & V for ULs from NOAEL, and extrapolations from ANR
Summary 2: The model would

- Characterisation and validation of markers for key homeostatic events
- Enable exploitation of quantitative data on (genomics), proteomics and (metabolomics) either as markers in their own right or to validate other markers
- Develop and exploit predictive markers for short and long term outcomes
- Allow for temporal patterns of exposure duration and the risk and the long-term latency of effects
Summary 3: The model would support the

- Acquisition of appropriate intake/dose-response data
- Assessment of human variability (and uncertainty) and of Interspecies uncertainty in extrapolation from animal models to humans and a
- Founding of a common spectrum for dose-response relationships for both toxicity and deficiency