Inherent Safety of Natural Food Products

Policy and Regulatory View

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What is Safety?

- Safety is a negative concept, i.e.., that nothing adverse will happen
- There is no direct test for safety
- Proof of safety requires the proof of a negative
- It is impossible to prove that something cannot and will not ever happen
- Thus, absolute proof of safety is impossible

Determining Safety

- Evaluation of an ingredient or product for toxicity or adverse effects
- Dose-response evaluation
- Assessment of uncertainty
- Selection of an intake that can be deemed safe
  - to present an acceptably low risk of adverse consequences

What is the Safety Question?

- Ingredient type/origin? Species previously used as food? Whole food? Extract? Metabolite? Derivative of component of metabolite?
- Known effects? Known metabolism, deposition and excretion?
- Any suspected toxicity or adverse effects?
- What is the burden of proof?
  - General safety profile?
  - To evaluate soame specific possibility?

Major Approaches

- **Risk assessment, based on:**
  - **Human CT data**
  - **Data from animal or *in vitro* tests**
  - **Human epidemiology data**
- **History of safe use**
  - **Absence of methods and criteria (at present)**
  - **Most publications have addressed genetically modified plants, not chemicals**

Risk Assessment: UL Method

- Definition: *Tolerable Upper Intake Level* (UL) is the "highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population"
- Accepted by: FAO/WHO, Codex, European Commission, ASEAN, many countries

UL Method Steps

1. Hazard identification (the type of adverse *effect**)
2. Dose-response analysis
3. Uncertainty evaluation
4. Identification of UL

*Codex defines hazard as an *agent*, not the effect

Reasons for Adopting and Using FAO/WHO Risk Assessment Method

- Developed by authoritative international organizations (FAO and WHO)
- Based on UL method developed and sanctioned by major national or regional scientific advisory groups (IOM, EFSA/SCF, EVM)
- Solves the major problem of original method
  - Describes Highest Observed Intake approach for use when no UL can be set
  - Approach adopted by industry and in peer-reviewed literature to avoid misunderstanding of absence of UL

Methods on data uncertainty

- *Old (UL method by FNB, etc)*
  - Select highest possible NOAEL value
  - Assign and use a UF (value carries much uncertainty)
  - Calculate UL
- *New (by CRN/IADSA)—multiple CTs*
  - Evaluate all clinical trial data in decreasing order of intake
  - Identify *possible* NOAEL values, evaluate strength of data
  - Select a NOAEL value that provides high enough confidence to justify UF of 1.0
  - Accepted in several peer-reviewed publications

WHY NOT RDA-BASED LIMITS?

1. Impossible for substances without PRI values
2. RDA are not defined or identified on basis of safety or risk
3. Not valid as an indicator of safety
4. Not accepted in Codex guideline for vitamin and mineral food supplements (2005)
5. Not included in FAO/WHO nutrient risk assessment report (2006)
6. Disproportionate restriction of supplements in comparison with numerous conventional (unfortified) foods
   - A serving of liver may contain about 50x the PRI for vitamin B12
   - Citrus fruits may contain 2 to 3x the RDA for vitamin C
   - Some nutrients may be beneficial at intakes well above current RDAs, e.g., vitamin D

When UL is Not Possible…

Note: UL is not set without identified "hazard" and dose-response data

- this has been a major limitation of the UL for regulatory and policy applications
- UK EVM report avoided this problem
- CRN & IADSA 2004 reports used the Observed Safe Intake (OSL) method
- the January 2006 FAO-WHO report on risk assessment defined a Highest Observed Intake (HOI) in absence of a UL value

Using Risk Assessment to Establish Maximums

1. Risk assessment by UL method consistent with WHO method
   - Where no UL, use HOI (or do not set Maximum)
2. Consider intakes from other food sources
3. Give "due account" to Population Reference Intakes (i.e., the RDA, but do not use it as the Maximum)

What is "Due Account" for PRI (RDA)?

1. **No government or official organization has defined or described "due account"**
2. **The Codex guideline does not allow PRI or RDA values to be the sole basis of Maximums**
3. **EHPM-ERNA risk management model gives a reasonable meaning for "due account"**
4. **Maximum = UL (or HOI) – Intake**
5. **Use of PRI:**

   Population Safety Index = (UL – Intake) ÷ PRI (or RDA)

   (Nutrients with low PSI need careful regulation)

Risk Assessment Values for Bioactive Substances

Ingredient	HOI (published as OSL)
– Carnitine	2,000 mg (LCAR equivalents)
– Chondroitin (as sulfate)	1,200 mg
– Coenzyme Q10	1,200 mg
– Creatine (hydrate)	5.0 g
– Glucosamine (chloride or sulfate)	2,000 mg
– Lutein	20 mg OSL (38 mg animal data)
– Lycopene	75 mg OSL (270 mg animal data)
– Omega-3 fatty acids (IADSA)	3.0 g (total O-3 fatty acids)
– Amino acids	Three published

CRN Risk Assessments for Supplemental Amino Acids

Ingredient	OSL or UL
Arginine	20
Glutamine	14
Taurine	3

- Arg, Glu and Tau based on human clinical trial data
- Safety evaluation of other individual free amino acids depends on
  - Extrapolation from animal data

  OR
  - History of Safe Use

Risk Assessment for Safety of Natural Products

- Identify any known "hazard"
  - If found, apply UL method
  - If not found, apply HOI method
- If data are insufficient for UL or HOI, look for History of Safe Use
- If none of above, new toxicological studies are needed

Assumptions for Natural Products

- Many have no known toxicity
- Some are very toxic
- Presence of potential benefit, but absence of evidence for "essentiality" (e.g., lutein)
- History of Safe Use meaning is debatable
  - "Absence of evidence is not evidence of absence"
  - Some history relates to non-food uses
  - Some history is obvious (rice, wheat, etc)

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