Risk Assessment for Bioactive Ingredients in Dietary/Food Supplements

Presented for the IADSA Scientific Group

by

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Primary members

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• David Richardson, UK
• Derek Shrimpton, UK
IADSA Risk Assessments for Bioactive Substances

**Purpose:** To provide safety assessment of important non-vitamins an non-minerals (not yet done by authorities)

**Scientists:** IADSA Scientific Group (Hathcock, Ohama, Richardson, Shrimpton)

**Section**  | **Leading author:**
---|---
Methodology | Hathcock
Amino acids | Shrimpton/Ian Grant
Carnitine | Hathcock/Andrew Shao
Chondroitin | Hathcock/Shao
Coenzyme Q10 | Hathcock/Shao
Creatine | Shao/Hathcock
Glucosamine | Hathcock/Shao
Lutein | Shao/Hathcock
Lycopene | Shao/Hathcock
Omega-3 fatty acids | Richardson/Samantha Jennings
# Outcomes: Risk Assessment Values for Bioactive Substances

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Observed Safe Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amino acids</td>
<td>(in process)</td>
</tr>
<tr>
<td>Carnitine</td>
<td>2,000 mg (LCAR equivalents)</td>
</tr>
<tr>
<td>Chondroitin (as sulfate)</td>
<td>1,200 mg</td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td>1,200 mg</td>
</tr>
<tr>
<td>Creatine (hydrate)</td>
<td>5.0 g</td>
</tr>
<tr>
<td>Glucosamine (chloride or sulfate)</td>
<td>2,000 mg</td>
</tr>
<tr>
<td>Lutein</td>
<td>20 mg OSL (38 mg animal data)</td>
</tr>
<tr>
<td>Lycopene</td>
<td>75 mg OSL (270 mg animal data)</td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td>3.0 g (total O-3 fatty acids)</td>
</tr>
</tbody>
</table>
RISK ASSESSMENT

• Scientific process to evaluate probability and consequences of adverse effects resulting from consumption a specific amount of any substance

• Involves four major steps:
  1. Hazard identification (the adverse effect at lowest intake)
  2. Hazard characterization (in three steps)
     • Dose-response analysis
     • Uncertainty evaluation
     • Identification of level without identified risk (or acceptable level of risk)
  3. Exposure assessment
  4. Risk characterization (risk compared with actual intakes)
WHY USE RISK ASSESSMENT?

- Objective scientific basis for decisions related to safety
- Help avoid harm from excessive intakes
- Advice to the public about safety of high intakes
- Establish regulatory maximums for manufactured products—established to help avoid harm from consumption of toxic excesses
- Objective standard for international trade, consistent with WTO (SPS) obligations
WHY NOT RDA-BASED LIMITS?

- RDA are not defined or identified to address safety
- Not valid as an indicator of safety
- RDA limit may preclude benefits at higher intake levels (e.g., chromium, folic acid, selenium)
- Cannot be applied to substances without RDA values
- Not accepted in Codex guideline for vitamin and mineral food supplements (2005)
- Disproportionate restriction of supplements in comparison with numerous conventional (unfortified) foods
  - A serving of beef liver may contain about 50x the RDA for vitamin B12
  - Citrus fruits may contain 2 to 3x the RDA for vitamin C
  - What is the purpose of disproportionate restrictions for supplements?
  - Some nutrients may be beneficial at intakes above current RDAs
PURPOSE OF RISK ASSESSMENT

- To determine if intake is in a “safe” range
HISTORY OF NUTRIENT RISK ASSESSMENT

- Prior to 1980—Biological descriptions with little quantitative information
- 1980s—Adoption of Therapeutic Index as LOAEL/RDA, and later the U-shaped risk curve
- 1990s—Development of UL method by FNB
- 2002—Observed Safe Level (OSL) published by TABD
- 2003—European use/modification of UL method
  - EU and UK give dietary intakes detailed consideration
  - UK included equivalent of OSL, without a name
- 2004—CRN & IADSA publish Observed Safe Level (OSL) extension of UL method
- 2004-5—Codex adopts UL method in supplement guideline
- 2006—FAO/WHO method includes UL, consideration of diet, and Highest Observed Intake (equivalent to OSL)
UL METHOD

1. Identify the “Hazard”—the critical effect (i.e., adverse effect occurring at the lowest intake level)
2. Evaluate dose-response relationship to select NOAEL (or LOAEL)
   • Sensitive groups and related factors considered
   • UL usually applies to total intakes from all sources
3. Assign Uncertainty Factor (UF) consistent with dataset, avoiding arbitrary default values
4. Calculate: $UL = \frac{NOAEL}{UF}$
5. Risk characterization (compare UL to actual intakes)
6. Note: No UL is set without identified “hazard” and D/R data
   • this has been a major limitation of the UL for regulatory and policy applications
   • UK EVM report avoided this problem
   • the CRN/IADSA “Observed Safe Level” (OSL)
   • 2006 FAO/WHO report on risk assessment with its “Highest Observe Intake” (HOI) should help prevent misinterpretation of the absence of a UL
Assumptions in UL Method

- Adverse effects are independent
  - A few recognized exceptions for the vitamins
  - Interactions more common for minerals
  - Mineral antagonism of absorption is most common
- Not all theoretical interactions can be tested
- Food is a complex mixture of nutrients at low to moderate levels
  - Adverse interactions not likely at food levels
Official Methods

- US Food and Nutrition Board, 1997
  - Tolerable Upper Intake Level (UL)
  - Focus on total, with little consideration of dietary intake
- EC Scientific Committee on Food, 2003
  - Upper Level (UL), with focus on total intakes
  - EC FSD requires consideration of other sources
  - Safe Upper Levels (SUL)
  - “Guidance Level”, when no SUL is possible
  - Identified values for total and supplemental (mostly by calculation)
- FAO/WHO report
  - Upper Level (UL)
  - Consideration of all sources, including foods, supplements, water, etc.
  - Expands UL method to include Highest Observed Intake (HOI), when no toxicity is established and no UL can be identified
FAO/WHO Report

• UL for total intakes from all sources
• Careful accounting for intakes from conventional foods, fortified foods and supplements, but not from pharmaceutical products
• Establishes “Highest Observed Intake” (HOI) as estimate of safe level when no toxicity has been observed (no basis for a NOAEL or LOAEL)
  – Very similar to CRN’s Observed Safe Level (OSL) and UK EVM’s unnamed evaluation method for some nutrients
• Provides the method, not specific values (funding needed)
Risk Assessment for Bioactive Substances in Food

• Use CRN/IADSA or FAO/WHO method
  – Look for data as basis of UL
  – If there are no known adverse effects, UL cannot be set
  – In absence of UL, use OSL (or HOI) method
  – The absence of a UL has implied absence of safety data
  – OSL (or HOI) will describe the limits of knowledge of safety of the bioactive ingredient
    • Avoids problems of absence of UL
IADSA Risk Assessment Method for Bioactive Substances

- Use human data, if available
- Identify adverse effects and NOAEL or LOAEL, if possible
- If no NOAEL or LOAEL, examine data for human OSL (HOI) value
- Examine each level of intake for factors that affect confidence in the data
- Consider possible sensitive subpopulations
- Consider extrapolation from test groups to general population
- Select the OSL (HOI) that gives sufficient confidence to not require any numerical adjustment for uncertainty (that is, UF = 1.0) to establish OSL (HOI) for most generally healthy adults
- Compare with authoritative extrapolations from animal data
- Consider other sources, and identify Upper Level for Supplements (ULS)
IADSA APPROACH

Compared with UL Method

- Complete reliance on human NOAEL
- Considers hazard only, not nuisance effects
- Stronger reliance on clinical trials
- Preferential use of direct evidence of adverse effects, not biochemical indicators
- Avoids using LOAEL
- Conservative selection of human supplemental NOAEL, justifying selection of UF = 1.0
- Uses OSL (HOI) when no toxicity is established
Risk Assessment Values for Bioactive Substances

- **Ingredient**
  - Amino acids (in process)
  - 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 3.0 g (total O-3 fatty acids)
Detailed Examples

• Carnitine
• Coenzyme Q10
Carnitine

- L-Carnitine
- None of the clinical trials used DL-carnitine
- Several used acetyl-L-carnitine or propionyl-L-carnitine
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>LCAR</td>
<td>L-Carnitine</td>
</tr>
<tr>
<td>ALCAR</td>
<td>Acetyl-L-Carnitine</td>
</tr>
<tr>
<td>PLCAR</td>
<td>Propionyl-L-Carnitine</td>
</tr>
</tbody>
</table>
Carnitine: Critical Decisions

- Sufficient human clinical trials for risk assessment
  - Therefore animal data not reviewed
- All listings as mg equivalents of LCAR
- Many reports discounted due vagueness regarding possible adverse effects
- No corrections for dietary intake or biosynthesis were made in any clinical trials, and therefore none are required to calculate ULS from OSL (HOI)
Carnitine: Detailed Findings

- 6,000 mg/day—1 yr: large, strong trial
  - Myocardial Infarction patients only
  - No other trials at this dose
  - Good monitoring
  - Significant problem with “fishy” body odor
- 100 mg/kg/day—6 months in hyperactive boys
  - N = 22
  - “unpleasant” body odor
  - Vagueness on monitoring for other effects
- 100 mg/kg/day—8 wks in Rett Syndrome patients
  - “fishy” body odor
  - Vagueness on monitoring for other effects
- 4,000 mg/day—6 months total (3 month cross-over design)
  - N = 20
  - No significant differences in adverse effect incidence
- 3,000 mg/day—90 days, N = 21, vague reporting of no adverse effects
- 3,000 mg/day—120 days, N = 20, vague reporting
- 2,720 mg/day—combination of LCAR and ALCAR
- 2,196 mg/day as ALCAR, N = 431 young Alzheimer's patients
- 2,196 mg as ALCAR, 1 yr, N = 19 diabetics, good monitoring, no adverse effects
- 2,060 mg/day—PLCAR, 90 days, N = 22 peripheral artery disease patients, vague reporting
### Carnitine: Risk Assessment Points

<table>
<thead>
<tr>
<th>Daily Dose</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6,000 mg/day</td>
<td>Fishy body odor</td>
</tr>
<tr>
<td>100 mg/kg/day</td>
<td>Body odor, vague reporting</td>
</tr>
<tr>
<td>4,000 mg/day</td>
<td>N = only 10, but vague details</td>
</tr>
<tr>
<td>3,000 mg/day</td>
<td>Small trials, vague reporting</td>
</tr>
<tr>
<td>2,732 mg/day</td>
<td>Combined treatment, vague</td>
</tr>
<tr>
<td>2,196 mg/day</td>
<td>Large, long, strong trial</td>
</tr>
<tr>
<td>2,196 mg/day</td>
<td>Small trial</td>
</tr>
<tr>
<td>2,064 mg/day</td>
<td>Small trial</td>
</tr>
<tr>
<td>2,000 mg/day or less</td>
<td>Several trials with no AE</td>
</tr>
</tbody>
</table>
Carnitine: Conclusions

- Fishy body odor is a significant problem at higher doses
- No pathological effects are established
- Vague reporting in many trials at high intakes increases uncertainty
- Multiple trials with no adverse effects in range of 2,000 to 2,196 mg/day
- Conservative selection of 2,000 mg equivalents as human OSL (HOI)
Carnitine: Summary

**OSL = ULS**
- $= 2,000 \text{ mg LCAR equivalents}$
- $= 2,000 \text{ mg LCAR}$
- $= 2,732 \text{ mg ALCAR}$
- $= 2,906 \text{ mg PLCAR}$

**Safety**
- Higher intakes are likely to be safe, but the data are not sufficient
- Body odor is a problem at 3,000 mg and higher LCAR
CoQ10 Risk Assessment

- No recognized toxicity
- OSL (HOI) method used
- Clinical trial data are sufficient
CoQ10 Safety: Clinical Trials

- **3,000 mg/day:** Two small uncontrolled trials, one of only 10 days
- **2,400 mg/day:** Properly controlled trial of 16 Parkinson’s disease patients for 8 weeks
- **1,200 mg/day:**
  - One well conducted with 80 Parkinson’s disease patients for 16 months
  - Smaller, shorter trial of 10 Huntington’s disease patients for 6 months found “heartburn”
- **900 mg/day:** Excellent safety study with healthy subjects found no adverse effects in 88 total subjects during 4 weeks of treatment
- **600 mg/day or less:** A large number (>50) of clinical trials in human subjects with various health conditions found no adverse effects that seem to be caused by CoQ10
CoQ10: Important Questions

• Does CoQ10 cause nausea, heartburn or other adverse gastrointestinal effects?
• Is nausea a “hazard” or only a “nuisance?”
• Does “rebound” deficiency occur?
• Can results from diseased groups be generalized to most healthy adults?
CoQ10: Nausea and Related Effects

- The reported cases are not caused by CoQ10 because:
  - Only a small fraction of the trials observed nausea or related effects
  - There is no dose-response relationship between CoQ10 and this type of outcome
    - The incidence is as great with 60 mg/day as with 1,200 mg/day
    - If CoQ10 caused nausea, the incidence and severity would increase with dose
    - The infrequent nausea might be caused by the capsules or inactive ingredients in some of the formulations tested
CoQ10: Conclusions

• CoQ10 is virtually non-toxic
• No pattern of adverse effects is seen with CoQ10 intake up to 3,000 mg/day
• Only repeatedly reported “effect” is nausea and related gastrointestinal effects
  – This cannot be causally related to CoQ10 because there is no dose-response relationship
• The data are sufficient to support
  – A risk assessment using the OSL (HOI) approach
  – A high-confidence conclusion of safety at an oral CoQ10 intake of 1,200 mg/day
• Restrictions related to drug status are not needed to protect the public
CoQ10: Selecting High-Confidence OSL (HOI)

- OSL (HOI) not UL because no adverse effects established for CoQ10
- 1,200 mg selected as high-confidence OSL (HOI) allowing UF = 1.0 because
  - Reported nausea is not caused by CoQ10
  - No adverse effects established at any intake
  - Two trials at 1,200 mg increase confidence (one with 80 subjects had a duration of 16 months)
  - Higher intake trials also show no toxicity
## UF Selections

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>UF</th>
<th>Data type</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E</td>
<td>36</td>
<td>Animal LOAEL</td>
<td>Species different</td>
</tr>
<tr>
<td>Folic acid</td>
<td>5</td>
<td>Human LOAEL</td>
<td>No NOAEL</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>2</td>
<td>Human NOAEL</td>
<td>Small, uncontrolled CTs</td>
</tr>
<tr>
<td>Iron</td>
<td>1.5</td>
<td>Human LOAEL</td>
<td>Large dataset</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>1.5</td>
<td>Human LOAEL</td>
<td>Transient, not-toxic effect (flushing)</td>
</tr>
<tr>
<td>Fluoride</td>
<td>1.0</td>
<td>Human NOAEL</td>
<td>LOAEL is a cosmetic effect (mottling of teeth)</td>
</tr>
<tr>
<td>Manganese</td>
<td>1.0</td>
<td>Human NOAEL</td>
<td>CTs and epidemiology agree</td>
</tr>
<tr>
<td>Vit. B1, B2, B12</td>
<td>--</td>
<td>Human data</td>
<td>No toxicological basis for UL</td>
</tr>
<tr>
<td>CoQ10</td>
<td>1.0</td>
<td>Human OSL</td>
<td>No adverse effects established, higher dose CTs increase confidence at OSL</td>
</tr>
</tbody>
</table>
Uncertainty Evaluation

• Single trial data:
  – Requires very large, long-term trial to have high confidence in the data
  – For Uncertainty Factor of 1.0, the trial might have to involve 1,000 persons for 2 years or more, if no other data were available

• Multiple clinical trial database:
  – Consistency of outcomes reduces uncertainty
  – Confidence at a specified intake is increased by data at higher intakes that also found no adverse effects
CoQ10: UF = 1 at 1,200 mg

- **3,000 mg/day**: Two small uncontrolled trials, one of only 10 days
- **2,400 mg/day**: Properly controlled trial of 16 Parkinson’s disease patients for 8 weeks
- **1,200 mg/day**:
  - One well conducted with 80 Parkinson’s disease patients for 16 months
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- **900 mg/day**: Excellent safety study with healthy subjects found no adverse effects in 88 total subjects during 4 weeks of treatment
- **600 mg/day or less**: A large number (>50) of clinical trials in human subjects with various health conditions found no adverse effects that seem to be caused by CoQ10
Is Nausea a “Hazard?”

- Certainly is undesirable
- Severe nausea with vomiting could reduce net food intake and lead to nutritional deficiencies
- Mild nausea might qualify as a “nuisance” if it did not alter net food intake or consumer’s sense of well-being
- Difficult to classify quantitatively
- Is not an issue for CoQ10 because of
  - The absence of a cause-and-effect relationship
  - The infrequent occurrence with the CoQ10 formulations tested in the clinical trials
Risk of Rebound Deficiency?

- No evidence in the biomedical literature for rebound deficiency of LCAR or CoQ10 after cessation of oral consumption
- Follow up studies show no “deficiency"
- Rebound deficiency a favorite “uncertainty” since mid-1960s paper on vitamin C
  - High-dose vitamin C conditions more rapid return to plasma threshold for renal excretion
  - Does not cause low plasma levels or deficiency
Are Bioactives “Food” or “Drug”?

• Not “vitamins” recognized by authorities
• Occur widely in foods
• Best scientific definitions of “food” and “drug” relate to *intended uses*, not to chemical composition or potency
• No pathological effects
  – Nuisance effects of a few can be avoided by labeling
  – Potency limits by size, cost, or nuisance effects
Extrapolation from Diseased to Healthy Populations?

- Are diseases metabolically related to each other?
- Is any of the diseases metabolically related to the substance being tested?
- Are adverse effects related to the disease in the test subjects?
- Are there any data on healthy subjects?
- Is the ingredient equally safe in subjects with different diseases?
The Future?

- Will FNB new DRI procedures include HOI?
- Will the FAO/WHO method be used to identify internationally accepted UL values?
  - By FAO/WHO?
  - Codex?
- If international UL values are established, will Codex identify product maximums?
- Will risk assessments and guideline expand to cover bioactives?
- How will international differences in “dietary intake” be considered? (e.g., for selenium and retinol)
- Will US FNB, EFSA, FAO/WHO undertake risk assessment for other bioactive ingredients?
- Will industry scientists be allowed to contribute to these processes? (Note: Codex allows NGO participation)
Contact Information

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