Risk Assessment for Bioactive Ingredients in Dietary/Food Supplements

Presented for the IADSA Scientific Group

by

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IADSA Scientific Group

Primary members

- **John Hathcock, USA**
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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

Ingredient	Observed Safe Level
• 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)

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?

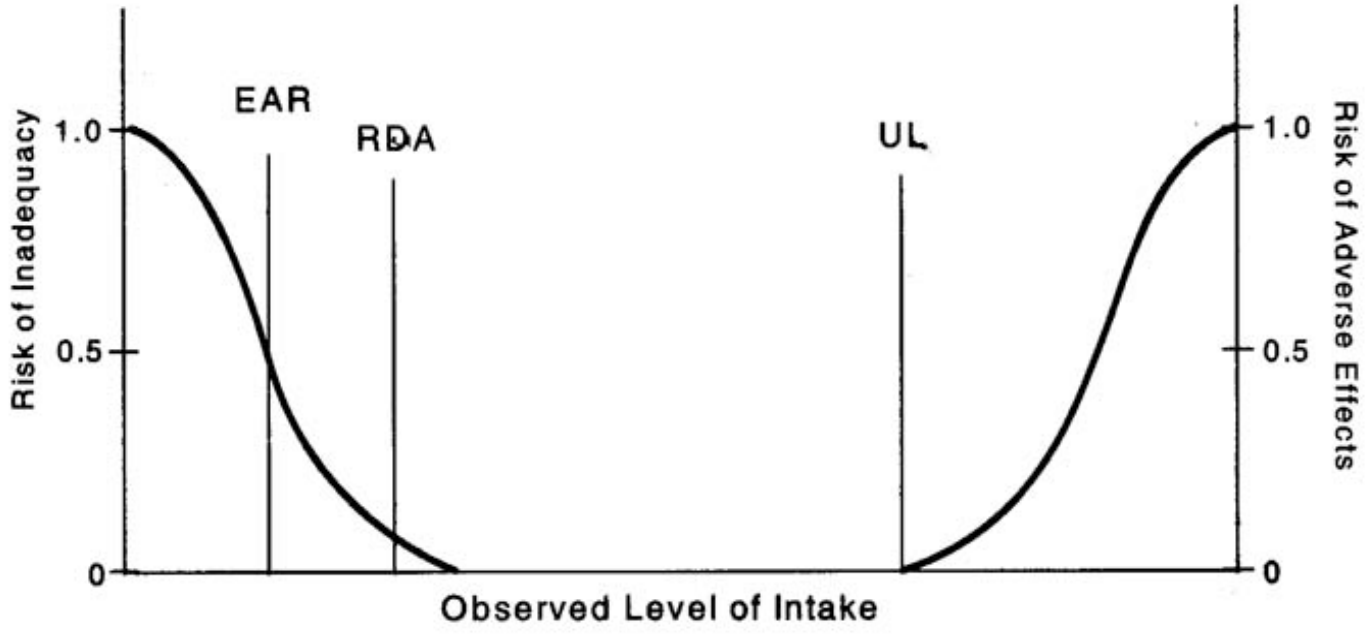
- **Objective scientific basis for decisions related to safety**
- **Help avoid harm from excessive intakes**
- **Advice to the public about safety of high intakes**
- **Establish regulatory maximums for manufactured products—established to help avoid harm from consumption of toxic excesses**
- **Objective 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)**
- **Not included in FAO/WHO nutrient risk assessment report (2006)**
- **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 SSESSMENT

- 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 = 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**
- **UK Expert Group on Vitamins and Minerals, 2003**
  - **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	OSL (HOI)
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)
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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

LCAR	**L-Carnitine**
ALCAR	**Acetyl-L-Carnitine**
PLCAR	**Propionyl-L-Carnitine**

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—6months 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

• 6,000 mg/day	Fishy body odor
• 100 mg/kg/day	Body odor, vague reporting
• 4,000 mg/day	N = only 10, but vague details
• 3,000 mg/day	Small trials, vague reporting
• 2,732 mg/day	Combined treatment, vague
• 2,196 mg/day	Large, long, strong trial
• 2,196 mg/day	Small trial
• 2,064 mg/day	Small trial
• 2,000 mg/day or less	Several trials with no AE

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 mg LCAR equivalents

= 2,000 mg LCAR

= 2,732 mg ALCAR

= 2,906 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

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

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**
  - **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**
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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)**

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