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Risk Assessment of Nutrients and Related Compounds

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The increasing use of fortified foods, special foods for dietetic uses, and dietary supplements including vitamins and minerals results in the potential for excessive intakes of nutrients and related compounds. According to the recent vitamin and mineral usage surveys, 45% of the middle-aged and the elderly, and more than one-third of the children and adolescents consume some forms of vitamins and mineral supplements in Korea. In addition, a wide varieties of 'functional foods for health' containing nutrients and related compounds are being used by 40~60% of the population groups at various life stages in Korea. A significant proportion of the vitamin and mineral users are found to consume 150~3,100% of the recommended levels for vitamins E, B6 and C, and iron, which can pose a public health risk. Tolerable or safe upper intake levels (UL) of nutrients and possibly of related compounds are needed to address the potential problem for adverse effects of consuming excessive amounts of nutrients. Nutrients and related compounds differ from many other types of substances that commonly are the subject of risk assessment in that they confer benefit as well as the potential for risk. Nutrient risk assessment model include 4 steps: Hazard identification, Hazard characterization, Dietary exposure assessment, and Risk characterization. Hazard identification step involves the collection, organization, and evaluation of all information pertaining to the adverse effects associated with a given nutrient. Hazard characterization step is the detailed evaluation of the nature of the adverse effects associated with the nutrient. As it rests largely on the assessment of a dose-response, it is often called the dose-response assessment. The end result of the first 2 steps is the UL for specific nutrient or related compound. Dietary intake assessment is the process of compiling and analyzing data on the usual (habitual) intake of the nutrient for the population of interest. In the risk characterization step the proportion of the population who may have intakes that exceed the UL is identified and the degree to which their intakes exceed the UL. It should be noted that the UL is neither a recommended intake nor a level for fortification or supplementation. Utilizing the above risk assessement model, a newly launched 2005 Korea Dietary Reference Intakes includes tolerable upper intake levels for vitamins and minerals with known documented adverse effects. We utilized the odels developed by the US Institute of Medicine, European Union Scientific Committee on Food, United Kingdom Expert Groups on Vitamins and Minerals. We also reviewed the set of ULs for vitamins and minerals which had been recently published in Australia/New Zealand and Japan.

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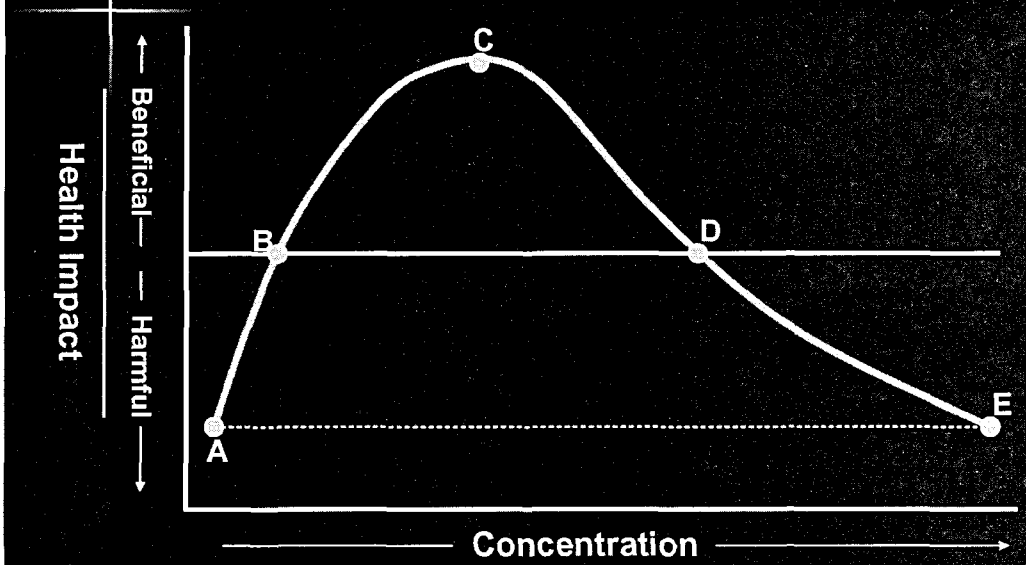
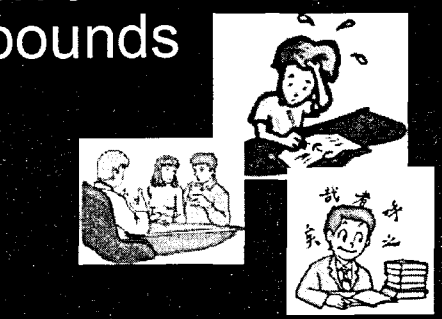
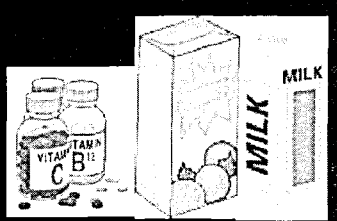
Impact of nutrient concentrations on health



Sources of Excessive Nutrients and Related Compounds

- **Vitamin & Mineral Preparations**
- **Tonic Drinks**
- **Food Fortification**
- **Food Additives**
- **Mineral Water**
- **Functional Foods for Health**



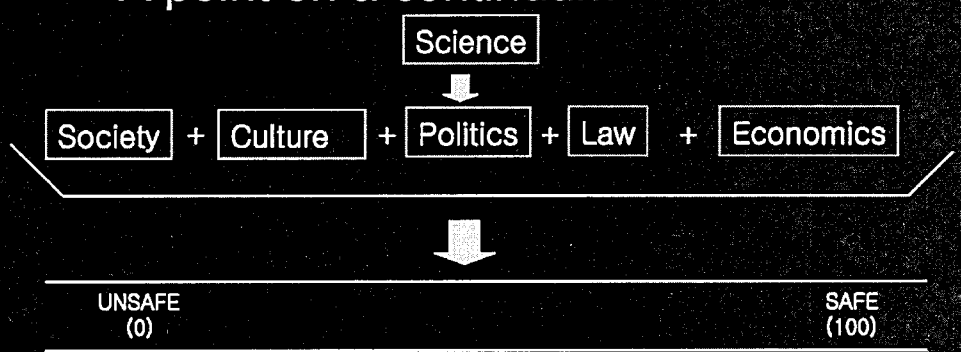


Key Issues in the Development of a Model for Nutrients and Related Compounds

- Safety vs. risk
- Limitations of traditional models
- Unique characteristics of nutrients

Characteristics of the Concept of Safety

- An intellectual concept
- Not an inherent biological property
- A point on a continuum



Definition of Risk

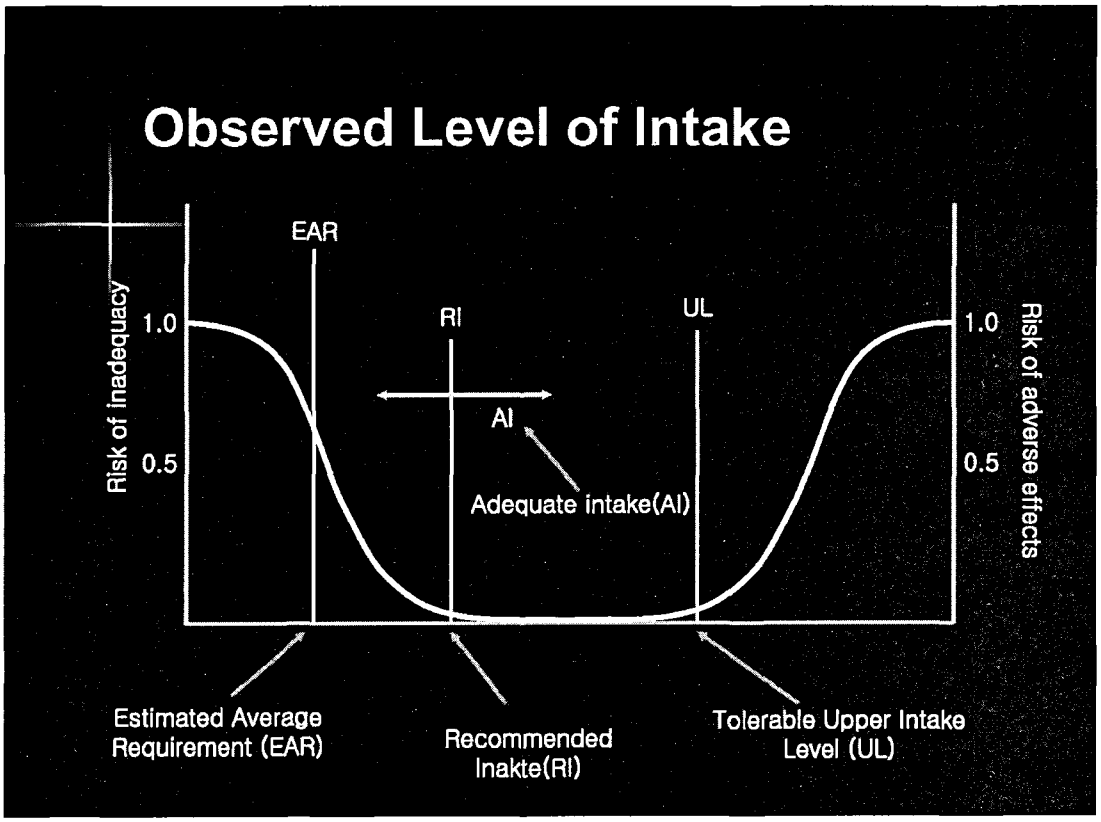
- Risk is defined as the probability of an adverse effect occurring at some specified level of exposure
- Risk assessment is a scientific exercise, not influenced by value judgement

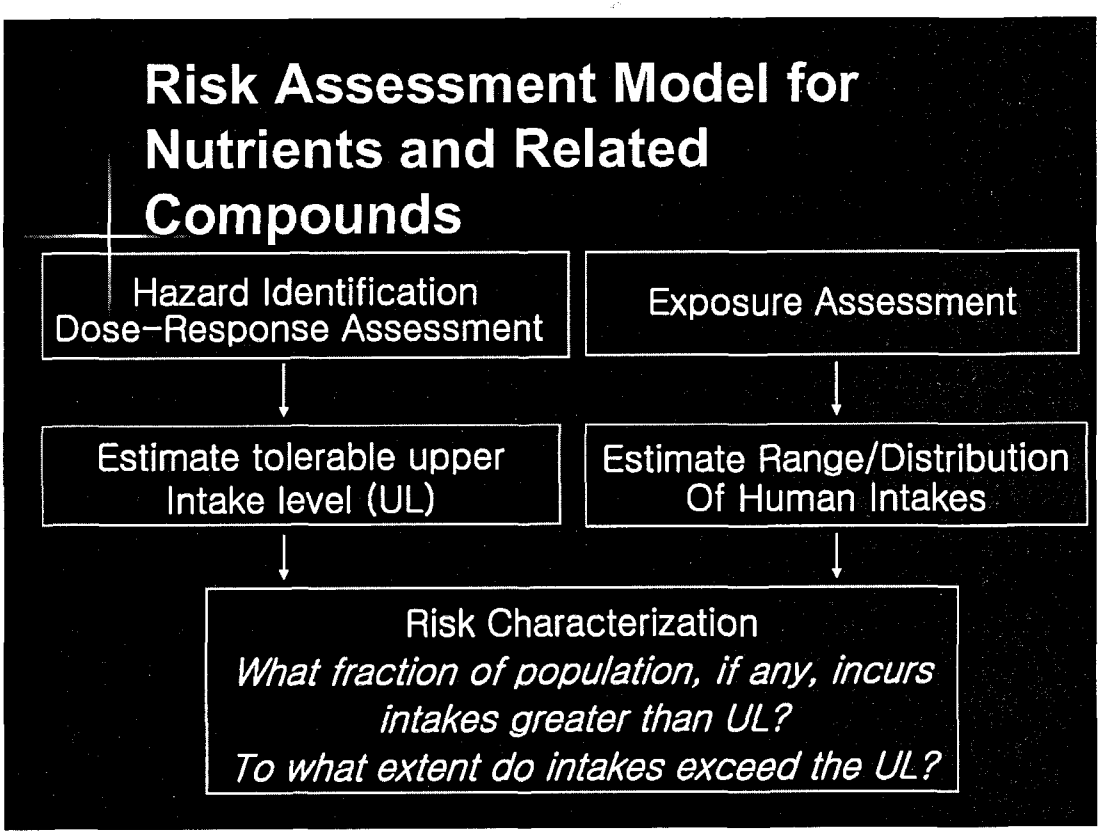
Unique Characteristics of Nutrients

- Absence of dose-response data
- Few available human or animal chronic studies
- Few surveillance studies to establish NOAEL
- Available databases concentrate on supplement intake not total
- Significant differences in bioavailability

What is a Tolerable Upper Intake Level (UL)?

√ ***The highest average daily nutrient intake level likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the potential risk of adverse effects increases.***


Observed Level of Intake
EAR
RI
UL
AI
Adequate intake(AI)
Risk of inadequacy
1.0
0.5
1.0
0.5
Risk of adverse effects
Estimated Average Requirement (EAR)
Recommended Inakte(RI)
Tolerable Upper Intake Level (UL)


Risk Assessment Model for Nutrients and Related Compounds
Hazard Identification Dose-Response Assessment
Exposure Assessment
Estimate tolerable upper Intake level (UL)
Estimate Range/Distribution Of Human Intakes
Risk Characterization
What fraction of population, if any, incurs intakes greater than UL?
To what extent do intakes exceed the UL?

Steps in the Risk Assessment Process

- Step 1 : Hazard identification
- Step 2 : Dose-response assessment
- Step 3 : Intake assessment
- Step 4 : Risk characterization

↓ ↓

Risk Management

Risk Assessment Model for Nutrient Adverse Effects

Hazard Identification

Determination of adverse health effects caused by high intakes of the nutrient or food component

Dose-Response Assessment

- Selection of critical data set
- Identification of NOAEL (or LOAEL)
- Assessment of uncertainty (UF)
- Derivation of Tolerable Upper Intake Level (UL)

Risk Assessment Model for Nutrient Adverse Effects

Intake Assessment

Evaluation of the range and the distribution of human intakes of the nutrient or the food component

Risk Characterization

- Estimation of the fraction of the population, if any, with intakes greater than the UL
- Evaluation of the magnitude with which these excess intakes exceed the UL

Components of Hazard Identification

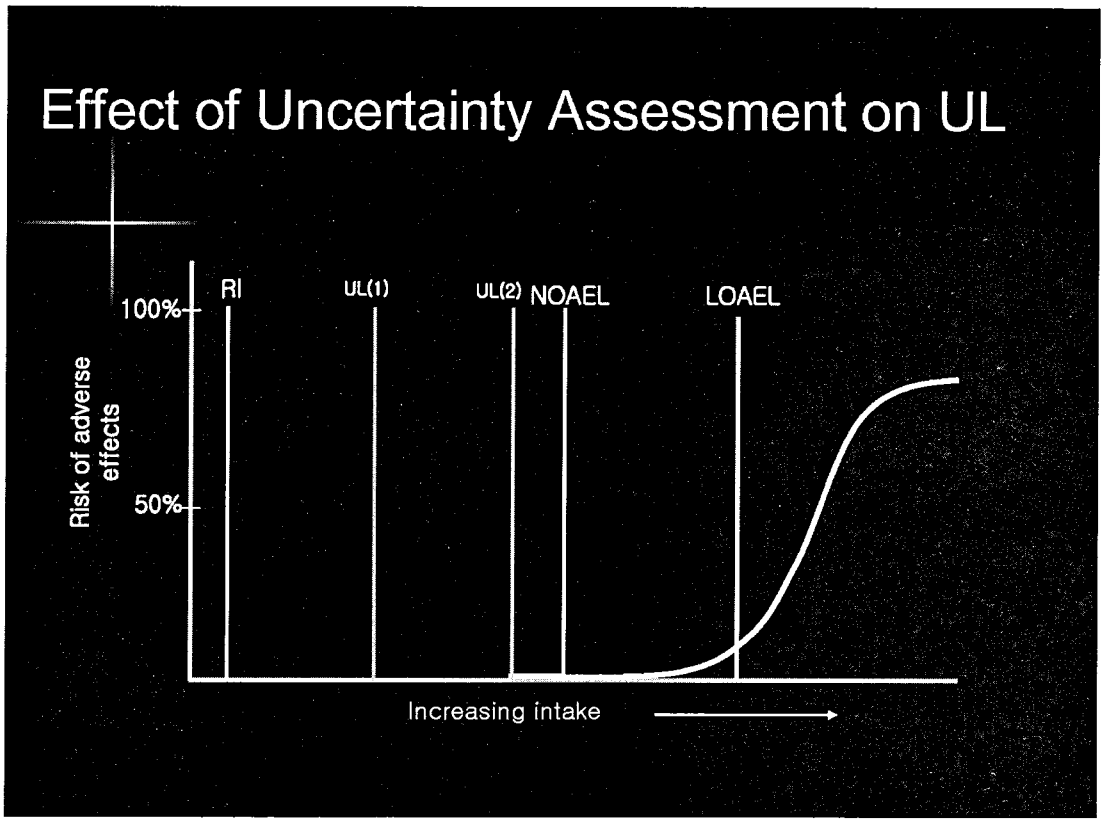
- Evidence of adverse effects in humans
- Causality
- Relevance of experimental data
- Pharmacokinetic and metabolic data
- Mechanisms of toxic action
- Quality and completeness of the database
- Identification of distinct and highly sensitive subpopulations

Components of Dose-Response Assessment

- Data selection and identification of critical endpoints
- Identification of no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) and critical endpoint
- Assessment of uncertainty and data on variability in response
- Derivation of a UL
- Characterization of the estimate and special considerations

Uncertainty Assessment

- Interindividual variation in sensitivity
- Experimental animal data extrapolated to humans
- LOAEL to NOAEL
- Subchronic NOAEL to predict chronic NOAEL



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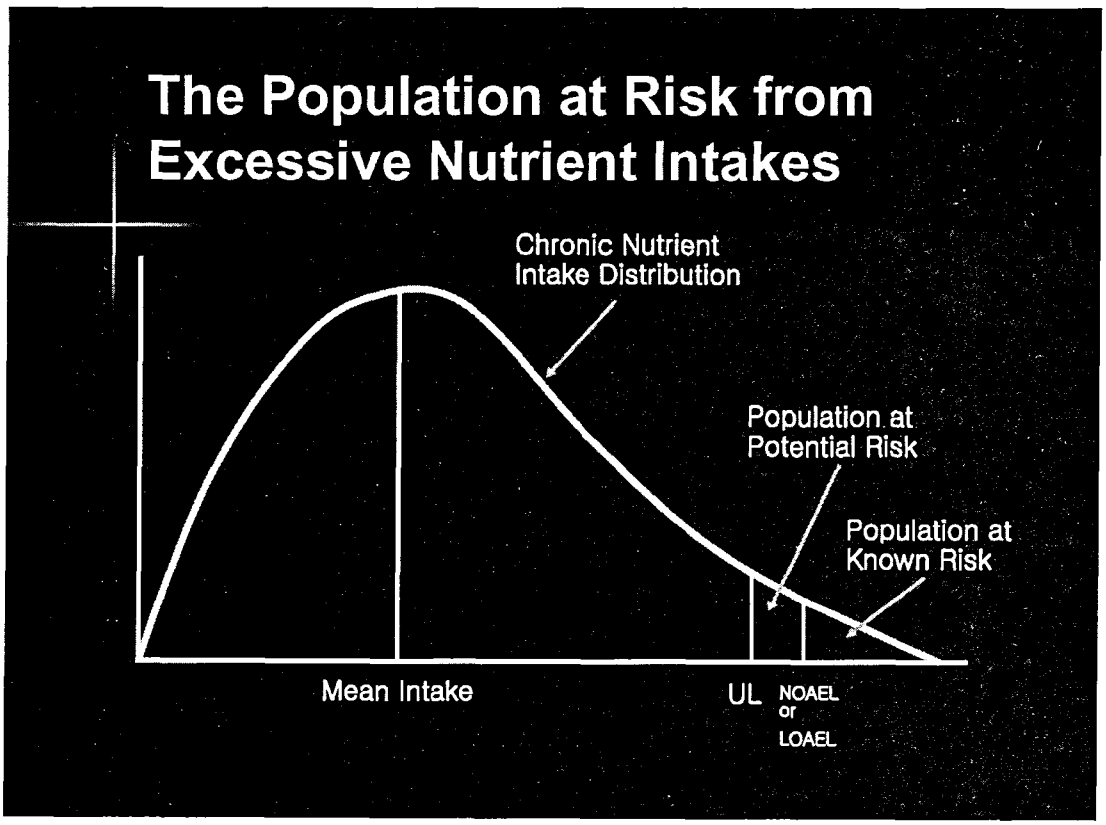
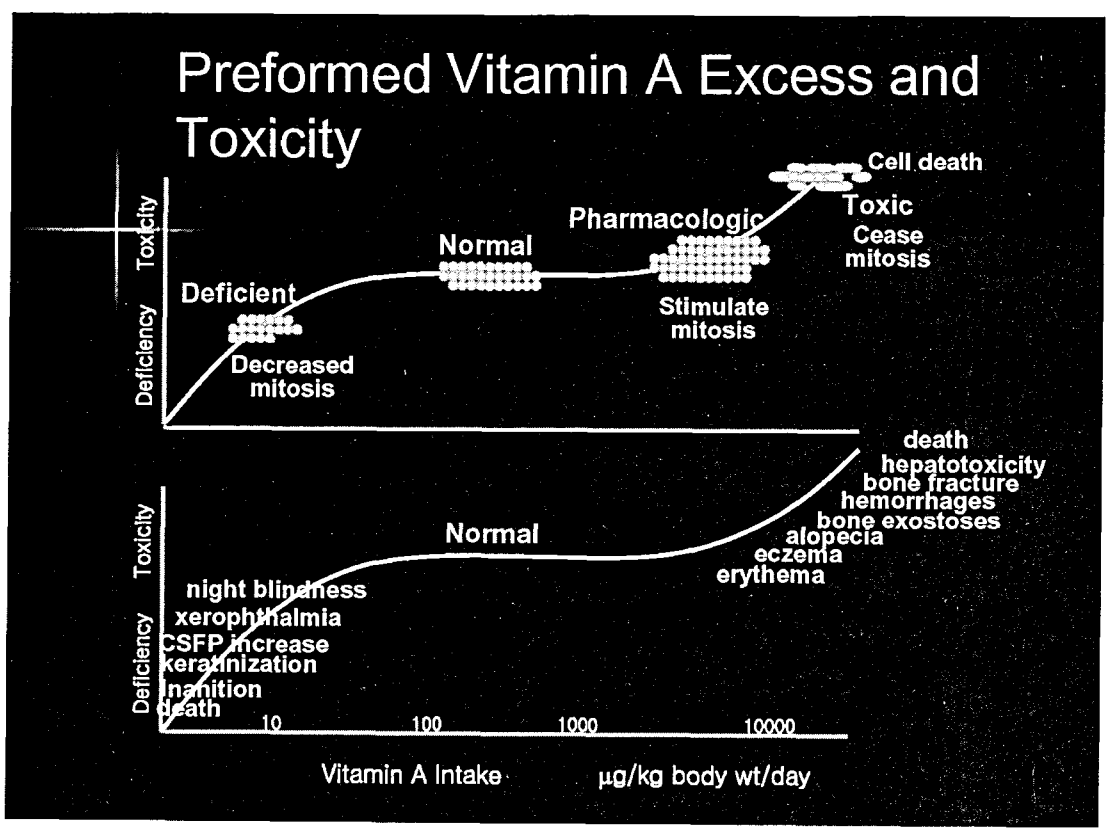

The Population at Risk from Excessive Nutrient Intakes
Chronic Nutrient Intake Distribution
Population at Potential Risk
Population at Known Risk
Mean Intake
UL
NOAEL or LOAEL


Preformed Vitamin A Excess and Toxicity
Toxicity
Deficiency
Deficient
Decreased mitosis
Normal
Pharmacologic
Stimulate mitosis
Toxic
Cease mitosis
Cell death
Toxicity
Deficiency
night blindness
xerophthalmia
CSFP increase
keratinization
inanition
death
Normal
erythema
eczema
alopecia
bone exostoses
hemorrhages
bone fracture
hepatotoxicity
death
10
100
1000
10000
Vitamin A Intake
μg/kg body wt/day

Upper Levels for Preformed Retinol (1)

1. Step 1: Hazard identification
   Critical adverse effect로
   성인의 경우 liver abnormalities
   가임여성의 경우는 teratogenicity
2. Step 2: Dose-response assessment
   · Women of reproductive age
   - 자료 선택: 인체 연구 결과가 충분하여 동물연구 결과는 선택 하지 않음
   - NOAEL 규명: 4,500 ㎍/d
   - Uncertainty assessment: UF 1.5 was selected on the basis of inter-individual variability
   - UL 도출: NOAEL/UF = 4,500㎍/d /1.5 = 3,000㎍/d

Continued...

Upper Levels for Preformed Retinol (2)

· All other adults
-자료 선정: 인체 연구 결과 liver abnormalities를 critical adverse effect로 선정
-LOAEL: 14,000㎍/d
-Uncertainty assessment: UF 5.0 for the severe irreversible adverse effect, LOAEL to NOAEL extrapolation
-UL 도출: 14,000/5 = 3,000 ㎍/d
· Infants
-자료 선정: 인체 연구 결과 bulging fontanel을 critical adverse effect로 선정
-LOAEL 6,000㎍/d
-Uncertainty factor: 10 uncertainty of extrapolating a LOAEL to a NOAEL, interindividual variation
-UL: 6,000/10 = 600㎍/d

Upper Levels Compared: Vitamins

NUTRIENT	FNB	SCF	EVM 2003	DRI-K 2005
Preformed Vit A, μg	3,000	3,000	1,500 bone fragility 3,000 birth defects	3,000
Beta-carotene, mg	Not for smokers	20 smokers	7	25 Not for smokers
Vit D, μg	50	50	25	60
Vit E, mg	1,000	300	800 IU = 540 mg	540 mg α TE
Vit K	--	--	1,000 μg	--
Vit B-1, mg	--	--	100 suppl	--
Vit B-2, mg	--	--	40 suppl	--
Vit B-6, mg	100	25 (100/4)	10 (50/300x60)	100
Folic acid, μg	1,000	1,000	1,000 suppl	1,000
Vit B-12, μg	--	--	2,000	--
Nicotinic acid, mg	35	10	17 suppl	35
Nicotinamide, mg	(w/NA)	900	500 suppl	1,000
Pantothenic acid, mg	--	--	200 suppl (2,000/10)	--
Biotin, μg	--	--	900 suppl (9 mg/10)	--

Upper Levels Compared: MINERALS

NUTRIENT	FNB	SCF	EVM 2003	DRI-K 2005
Calcium, mg	2,500	--	1,500 suppl	2,500
Phosphorus, mg	4,000	--	250 suppl	3,500
Potassium, mg	--*	--	3,750 w/ minor AE	--
Magnesium, mg	350 free	250 free	400 suppl	350 free
Boron, mg	20	--	9.6	--
Chromium, μg	--	--	10 mg (not picolinate)	--
Copper, mg	10	5	10	10
Fluoride, mg	10	--	--	--
Iodide, μg	1,100	--	940 total, 500 suppl	3,000
Iron, mg	45 (empty stomach)	--	17	65 (full stomach)
Manganese, mg	11	--	12 total, 4 suppl	11
Molybdenum, μg	2,000	600	230 diet, 0 suppl	600
Selenium, μg	400	300	450 total, 350 suppl	400
Zinc, mg	40	25	25 suppl	35

THE FUTURE: Vitamins and Minerals

- FAO/WHO project to establish international ULs for use by Codex (CCNFSDU) – currently undergoing
- Codex (CCNFSDU) set maximums for supplement products, but only after scientific committees have set UL values for nutrients

THE FUTURE: Other Ingredients

Apply UL method to safety evaluation

- Other nutrients (e.g., amino acids, fatty acids)
- Vitamin-like substances in diet (e.g., lutein, lycopene, etc.)
- Metabolites in physiology and/or diet (e.g., carnitine, creatine, pyruvate, CoQ_{10}, etc.)
- Complex materials (botanical ingredients and extracts, e.g., garlic, ginkgo, ginseng, etc.)

Candidate ingredients for application of expanded methodology

- Amino acids
- Fatty acids
- Carnitine
- Carotenoids such as lutein and lycopene
- Chondroitin
- Coenzyme Q-10
- Creatine
- Glucosamine
- Melatonin
- Etc.

Researches are needed

- Quantitative analysis on sources of nutrients and related compounds: food, water, supplements
- Identification of vulnerable population groups
- Long-term effects of chronic excessive intake of nutrients and related compounds