Background Information
IOM/FNB Workshop on Dietary Reference Intakes
The Development of DRIs 1994-2004: Lessons Learned & New Challenges
September 18-20, 2007
Washington, DC

Information Compiled and Posted July 11, 2007

Purpose: To Provide Useful/Relevant Information for
Workshop Participants and Attendees

Opportunity for interested parties to comment electronically through August 11, 2007:
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DOCUMENT:
Comparison of Outcomes/Approaches Among DRI Nutrients

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Date: 2007

TABLE 1 Indicators of Adequacy for EAR or AI

Nutrient	Reference Value	Indicators considered in estimating requirements
Calcium	AI	• Calcium intake and fracture risk • Bone mass measurements (bone mineral content (BMC) and bone mineral density (BMD) • Calcium intake and bone mass • **Calcium retention –desirable rates as determined by Ca balance studies, factorial estimates of requirements, BMD and BMC** • Calcium intake and risk of chronic diseases other than osteoporosis (hypertension, colon cancer)
Phosphorus	EAR	• **Phosphorus balance (children and adolescents)** • **Serum P_i (adults)**
Magnesium	EAR	• Serum magnesium • Plasma ionized magnesium • Intracellular magnesium • **Magnesium balance studies (all age groups)** • Estimates of tissue accretion during growth • Magnesium tolerance test • Epidemiological studies and meta-analyses (cardiovascular disease and osteoporosis)
Vitamin D	AI	• **Serum 25(OH)D (older infants, children, adolescents, adults)** • Serum vitamin D • Serum 1,25(OH_2)D • **Evaluation of skeletal health (infants < 6 mos: linear growth and bone mass; adults >50 to 70 yrs: bone loss; adults >70 yrs: bone loss, fractures, parathyroid hormone)**
Fluoride	AI	• **Prevention of Dental Caries** • Bone mineral content • Fluoride Balance
Thiamin	EAR	• **Urinary thiamin excretion (all age groups except infants, extrapolation from young adult males)** • Erythrocyte transketolase activity • Erythrocyte thiamin

Nutrient	Reference Value	Indicators considered in estimating requirements
Riboflavin	EAR	• Erythrocyte glutathione reductase (EGR) • Erythrocyte flavin • Urinary flavin • Clinical signs of deficiency • Indicators of CHO metabolism (lactic and pyruvic acid concentrations) • Possible reduction of chronic disease risk (site-specific cancers (e.g. esophageal); lens opacities – risk of cataracts) • **Concurrent analyses (EGR activity coefficient; urinary excretion, erythrocyte flavin, clinical signs of deficiency) (all age groups except infants, children extrapolated from adults)**
Niacin	EAR	• **Urinary excretion of N^1-methylnicotinamide and its 2-pyridone derivative N^1-methyl-2-pyridone-5-carboxamide (all age groups except infants; children extrapolated from adults)** • Plasma concentration of the 2-pyridone derivative • Erythrocyte NAD concentration • Transfer of adenosine diphosphate ribose (functional measure of polyadenosine diphosphate ribosylation – assays to assess status not available) • Pellagra
Vitamin B_6	EAR	• Plasma pyridoxal 5′-phosphate (reflects tissue stores) (adult women) • Erythrocyte and total blood pyridoxal 5′-phosphate • Blood total vitamin concentrations • Urinary pyridoxic acid and total vitamin B_6 • Erythrocyte aspartate aminotransferase (α-EAST) and alanine aminotransferase (α-EALT) • Tryptophan metabolites • Plasma homocysteine • Possible reduction of chronic disease risk (MI and CHD) • Cognitive function • **Concurrent analyses (plasma PLP, urinary pyridoxic acid, tryptophan metabolites, α-EAST, α-EALT) (children and adolescents except infants extrapolated from adults)**
Folate	EAR	• Erythrocyte folate • Plasma homocysteine • Serum folate • Urinary folate • Indicators of hematological status • Risk of neural tube defects and chronic degenerative diseases (EAR does not accommodate NTD prevention as appropriate criterion because by definition only 50% protection) • **Combination of erythrocyte folate, serum or plasma folate and plasma homocsyteine (children and adolescents except infants extrapolated from adults)**

Nutrient	Reference Value	Indicators considered in estimating requirements
Vitamin B_{12}	EAR	• **Indicators of hematological response (stable hemoglobin value, normal MCV, normal reticulocyte response) (primary criterion) (children and adolescents except infants extrapolated from adults)** • **Serum and plasma vitamin B_{12}** • Methylmalonic acid • Homocysteine • Formiminoglutamic acid, propionate and methylcitrate • Holotranscobalamin II
Pantothenic Acid	AI	• Urinary excretion • Blood levels of pantothenic acid - whole blood - serum, plasma - erythrocytes • **Pantothenic acid intakes (children, adolescents extrapolated from adults)**
Biotin	AI	• Biotin and 3-Hydroxyisovalerate excretion • Plasma biotin • Odd-chain fatty acid composition of plasma lipids • **Biotin intake of infants fed exclusively on human milk (extrapolated to older infants, children, adolescents and adults)**
Choline	AI	• **Markers of liver dysfunction(amounts to prevent increases in alanine aminotransferase in men extrapolated to children and adolescents and adult females)** • Plasma concentrations • Reduction in risk of chronic disease (dementia, cardiovascular disease, cancer)
Vitamin C	EAR	• Antioxidant functions • **Antioxidant functions in leukocytes (Near maximal neutrophil concentration with minimal urinary excretion ascorbate) (extrapolated to children and adolescents and adult females)** • Oxidative deoxyribonucleic acid and chromosome damage (cellular DNA damage, urinary markers of DNA damage, ex vivo damage, cancer biomarkers) • Immune function • Collagen metabolism • Carnitine biosynthesis • Periodontal health • Relationship of vitamin C intake to chronic disease - Cardiovascular disease - Cancer (breast, cervical, colorectal, pancreatic, lung, gastric) - Cataract - Asthma and obstructive pulmonary disease - Common cold - Cognitive function and memory

Nutrient	Reference Value	Indicators considered in estimating requirements
Vitamin E	EAR	• Lipid peroxidation markers • Oxidation products of DNA or proteins • Vitamin E metabolite excretion • Vitamin E biokinetics • Vitamin E deficiency symptoms • **Plasma α-tocopherol concentration (extrapolated to children and adolescents and women)** • **Hydrogen peroxide-induced hemolysis (extrapolated to children and adolescents and women)** • Relationship of vitamin E intake to chronic disease - Cardiovascular disease - Diabetes mellitus (oxidative stress, platelet hyperactivity, diabetic neuropathy) - Cancer - Immune function - Cataracts - CNS disorders (Parkinson's Disease, Alzheimer's Disease and Down's Syndrome, Tardive Dyskinesia)
Selenium	EAR	• Keshan Disease • Selenium in hair and nails • Selenium in blood • **Glutathione peroxidases and selenoprotein P in blood (levels to achieve plateau concentrations of plasma selenoproteins/) (extrapolated from adults to children and adolescents)** • Cancer • Urinary selenium • Labeled selenium
β-Carotene & other Carotenoids	----	• Vitamin A equivalency (requirements for carotenoids based on vitamin A activity considered with the evaluation of the requirements for vitamin A) • Markers of antioxidant activity • Gap junctional communication • Immune function • Relationship of carotenoid intake to chronic disease - All-cause mortality - Cancer (all cancers combined, lung, oral cavity, pharynx, larynx, cervical) - Cardiovascular disease - Age-related macular degeneration - Cataracts • **Plasma and Tissue Concentrations (3-6 mg β-carotene/day from food sources "prudent" to maintain plasma β-carotene levels in the range associated with a lower risk of various chronic disease outcomes)**

Nutrient	Reference Value	Indicators considered in estimating requirements
Vitamin A	EAR	• Dark adaptation • Plasma retinol concentration • Total liver reserves by isotopic dilution • Relative dose response and modified relative dose response • Conjunctival impression cytology • Immune function • **Amount dietary vitamin A required to maintain a given body-pool size in well-nourished adults** A x B x C x D x E x F A= Percent of body vitamin A stores lost per day when ingesting a vitamin A-free diet B = Minimum acceptable liver vitamin A reserve C = The liver weight:body weight ratio D = Reference weight for a specific age group and gender E = Ratio of total body:liver vitamin A reserves F = Efficiency of storage of ingested vitamin A (children and adolescents extrapolated from adults)
Vitamin K	AI	• Prothrombin time • Factor VII • Plasma and serum phylloquinone • Urinary γ-carboxyl glutamyl residues • Undercarboxylated prothrombin (PIVKA) • Under-γ-carboxylated osteocalcin • Relationship of vitamin K intake to chronic disease - Osteoporosis - Atherosclerosis • **Vitamin K intakes of apparently healthy groups (adults, children and adolescents except infants)**
Chromium	AI	• Balance studies • Urinary chromium excretion • Plasma chromium concentration • Blood glucose and insulin concentrations • **Chromium content per 1000 kcal in well-balanced designed adult diets times the highest energy intakes for adults and extrapolated to children and adolescents**

Nutrient	Reference Value	Indicators considered in estimating requirements
Copper	EAR	• Ceruloplasmin concentration • Erythrocyte superoxide dismutase activity • Platelet copper concentration and cytochrome c oxidase activity • Urinary copper • Leukocyte copper concentration • Lysyl oxidase activity • Peptidyl glycine α-amidating monooxygenase activity • Diamine oxidase activity • Copper balance • Factorial analysis • **Combination of ceruloplasmin concentration, erythrocyte superoxide dismutase activity, platelet copper concentration and cytochrome c oxidase activity, plasma copper concentration and factorial analysis**
Iodine	EAR	• **Iodine accumulation and turnover (adults extrapolated to children and adolescents 9-18 yrs)** • Urinary iodine • Thyroid size • **Iodine balance (children 1-8 yrs)** • Serum thyroid stimulating hormone concentration • Serum thyroglobulin concentration • Thyroxine and triiodothyroxine concentrations
Iron	EAR	• Functional indicators (associated with degree of iron deficiency sufficient to cause measurable anemia – decreased physical work capacity, delayed psychomotor development in infants, impaired cognitive function) • Biochemical Indicators - Serum ferritin concentration - Total iron binding capacity - Early iron deficiency - Serum transferring saturation - Erythrocyte protopophyrin concentration - Soluble serum transferrin receptor concentration - Iron deficiency anemia - Hemoglobin concentration and hematocrit - Erythrocyte indexes (MCH, MCV) - Surrogate laboratory indicators (Ferritin model: serum ferritin concentration, erythrocyte protoporphyrin concentration and transferrin saturation / MCV model: MCV, transferring saturation and erythrocyte protoporphyrin concentration – 2 or more abnormal indicators indicative of iron deficiency) • Factorial modeling used when distribution of nutrient requirements is skewed. • Iron balance studies • **Indicator of adequacy – normal functional iron concentration but only minimal stores (serum ferritin 15 µg/L) calculated by factorial modeling because distribution of iron requirements is skewed.**

Nutrient	Reference Value	Indicators considered in estimating requirements
Manganese	AI	• Balance and depletion studies • Serum and plasma manganese concentrations • Blood manganese concentrations • Urinary manganese • Arginase activity • Manganese-superoxide dismutase activity • **Intake levels used as basis for AI. Adult AIs based on highest intake levels reported for 4 age groups due to underreporting of intakes. Children's AI based on mean intakes.**
Molybdenum	EAR	• Plasma and serum molybdenum concentrations • Urinary molybdenum • **Molybdenum balance (children and adolescents extrapolated from adult male data)**
Zinc	EAR	• **Minimal quantity of absorbed zinc required to match the total excretion of endogenous zinc plus growth where appropriate calculated using the factorial method adjusted for fractional absorption (older infants, children, adolescents, adults)** • **Physical growth response to zinc supplementation (used to check EAR derived by factorial method in older infants and young children 7 mos – 3 yrs)** • Size and turnover rates of zinc pools • Plasma and serum zinc concentrations • Zinc concentration in erythrocytes • Zinc concentration in hair • Activity of zinc-dependent enzymes • Metallothionein and zinc-regulated gene markers • Indexes of immune status • Hormones • Circulating hepatic proteins
Arsenic	-	
Boron	-	
Nickel	-	
Silicon	-	
Vanadium	-	

Nutrient	Reference Value	Indicators considered in estimating requirements
Dietary Carbohydrates	EAR	• **Glucose utilization by the brain** The amount of digestible CHO in an energy sufficient diet that would provide the brain (CNS) with an adequate supply of glucose fuel without the requirement for additional glucose production from ingested proteins or triacylglycerols
Sugars	-	
Starches	-	
Total Fiber	AI	• Prevention of hyperlipidema, hypertension and coronary heart disease; **Prevention of CHD** • Colon health (constipation, laxation, fecal weight; fiber fermentation products – energy source for colon; prevention of diverticular disease) • Prevention of colon cancer • Protection against breast cancer • Other cancers (endometrial, ovarian) • Glucose tolerance, insulin response and amelioration of diabetes • Fiber intake, satiety and weight maintenance
Dietary Fiber	-	
Functional Fiber	-	
Total Fat	-	
Saturated Fatty Acids	-	• Not essential in the diet
MUFA	-	• Not essential in the diet
n-6 PUFA	AI	• Correction of deficiency in infants and adults on TPN • **Median intakes US population**
n-3 PUFA	AI	• Correction of deficiency in patients on TPN • **Median intakes US population**
Trans-Fatty Acids	-	• No known requirements for physiological functions
Cholesterol	-	• No evidence for dietary requirement
Protein & Amino Acids	EAR	• **N Balance** • Factorial method

Nutrient	Reference Value	Indicators considered in estimating requirements
Water	AI	• Water balance • **Hydration status measured by serum osmolality** • AI based on median intakes of total water NHANES III
Potassium	AI	• Potassium balance • Serum potassium concentration • Hypokalemia • **Salt-sensitive blood pressure (children and adolescents extrapolated from adults on basis of median energy intakes)** • **Blood pressure** • **Prevention of kidney stones** • Prevention of cardiovascular disease • Prevention of bone demineralization • Prevention of impaired pulmonary function
Sodium	AI	• Sodium balance • Chloride balance • Serum or plasma sodium concentration • Plasma renin activity • Elevation in blood pressure • Blood lipid concentrations • Insulin resistance • **Amount based on meeting the sodium needs of moderately active apparently healthy individuals in a temperate climate as well as that of other important nutrients using foods found in a western-type diet (children and adolescents extrapolated from adults using relative energy intakes)**
Chloride	AI	• Equimolar with sodium
Sulfate	-	• Requirements met by requirements for sulfur amino acids

[a] Bolded indicator is the indicator selected for the reference value.

TABLE 2 Indicators of Excess for Upper Level

Nutrient	Reference Value	Indicators of Excess[a]
Calcium	UL	• Nephrolithiasis • **Hypercalcemia and renal insufficiency (Milk Alkali Syndrome)** • Calcium/mineral interaction (iron, zinc, magnesium, phosphorus)
Phosphorus	UL	• **Hyperphosphatemia** leading to risk of - adjustments in calcium-regulating hormones (PTH) - metastatic calcification of soft tissues - skeletal porosity - interference with calcium absorption
Magnesium	UL	• **Diarrhea (applies to nonfood sources of magnesium only)**
Vitamin D	UL	• **Hypercalcemia of hypervitaminosis D** • Renal disease (calcification of renal tissue not associated with hypercalcemia) • Cardiovascular effects (arteriosclerosis with calcium deposition)
Fluoride	UL	• **Adverse cosmetic effect: enamel fluorosis (infants and children 0 to 8 yrs)** • **Adverse functional effect: skeletal fluorosis (all age groups > 8yrs)**
Thiamin	-	• Anaphylaxis (parenteral administration) • Allergic sensitivity and pruritis (parenteral administration) • No adverse effects reported for ingested thiamin at high doses
Riboflavin	-	• No adverse effects reported for ingested riboflavin at high doses • in vitro studies showing formation of active oxygen species on intense exposure to visible or ultraviolet light (relevance to human health effects in vivo questionable but theoretically plausible riboflavin could increase photosensitivity to ultraviolet irradiation)
Niacin	UL	• **Vasodilatory effects (flushing) applies only to nicotinic acid and nicotinamide as supplements, food fortificants or pharmacologic agents** • Gastrointestinal effects • Hepatotoxicity (jaundice, increased levels serum transaminases, fulminant hepatitis …) • Glucose intolerance • Ocular effects (blurred vision, toxic ambylopia, macular edema and cystic maculopathy) reversible and dose-dependent
Vitamin B_6	UL	• **Sensory neuropathy (evidence from high doses of pyridoxine and not vitamin B_6 from food)** • Other adverse effects - dermatological lesions - congenital defects and vitamin B_6 dependency of the newborn (not confirmed; no evidence of teratogenicity in experimental animals)

Nutrient	Reference Value	Indicators of Excess[a]
Folate	UL	• **Neurological effects of supplemental folate in individuals with vitamin B_{12} deficiency (because a number of apparently healthy individuals are vitamin B_{12} deficient, considered part of the general population in setting the UL)** • Neurotoxicity and epileptogenicity in experimental animals (no clear evidence of folate-induced neurotoxicity in humans) • General toxicity • Reproductive and developmental effects (no studies designed to assess the safety of supplemental folate taken to prevent NTDs) • Carcinogenicity (positive association between supplemental folate and incidence of cancer of the oropharynx and hypopharynx and of total cancer not corrected for confounders, alcohol and smoking; other studies suggest folate anticarcinogenic) • Hypersensitivity • Intestinal zinc absorption
Vitamin B_{12}	-	
Pantothenic Acid	-	
Biotin	-	
Choline	UL	• **Body odor, sweating and salivation (fishy body odor, vomiting, GI effects) (secondary indicator)** • **Hypotension (primary indicator)** • Hepatotoxicity (attributed to salicylate in choline salt) • Nonspecific toxicity (tinnitus, pruritus attributed to salicylate in choline salt)
Vitamin C	UL	• **Gastrointestinal effects (nausea, abdominal cramps, diarrhea)** • Increased oxalate excretion and kidney stone formation • Increased uric acid excretion • Excess iron absorption • Lowered vitamin B_{12} levels • Systemic conditioning to high levels • Prooxidant effects • Other adverse effects - high altitude resistance - delayed-type allergic response - erosion of dental enamel

Nutrient	Reference Value	Indicators of Excess[a]
Vitamin E	UL	• Hemorrhagic toxicity in humans (stroke) • **Hemorrhagic toxicity in experimental animals** • Platelet effects in humans (in vitro inhibition of platelet aggregation and adhesion) • Other adverse effects in humans (uncontrolled studies: fatigue, emotional disturbances, thrombophlebitis, breast soreness, creatinuria, altered serum lipid and lipoprotein levels, GI disturbances and thyroid effects) • Adverse effects in premature infants (increased incidence of necrotizing enterocolitis, intracranial hemorrhage) • Other adverse effects in animals (lung lesions)
Selenium	UL	• **Chronic selenosis (hair and nail brittleness and loss**; other symptoms: GI disturbance, skin rash, garlic breath odor, fatigue, irritability, nervous system abnormalities) • Acute toxic effects – fatal or near fatal selenium poisoning • Biochemical indicators of selenium toxicity (total tissue concentration including plasma and blood; chronic intake of protein-bound selenium as toxic as inorganic selenium)
β-Carotene & other Carotenoids	-	
Vitamin A	UL	• Acute toxicity (nausea, vomiting, headache, increased cerebrospinal fluid pressure, vertigo, blurred vision, muscular incoordination) • Bone mineral density • **Teratogenicity (basis for UL in women of child -bearing age)** • **Liver abnormalities** (reversibly elevated liver enzyme activity → widespread fibrosis and cirrhosis → sometimes death) **(basis for UL for adults; children and adolescents extrapolated on basis of relative body wt)** • Adverse interactions (alcohol) • **Adverse effects in infants and children** (intracranial (bulging fontanel) and skeletal abnormalities, bone tenderness and pain, increased intracranial pressure, desquamation, brittle nails, mouth fissures, alopecia, fever, headache, lethargy, irritability, weight loss, vomiting and hepatomegaly) (**basis for infant UL)**
Vitamin K	-	
Chromium	-	• Chronic renal failure • Genotoxicity • Carcinogenicity • Hepatic dysfunction • Reproductive effects • Other adverse effects (rhabdomyolysis)

Nutrient	Reference Value	Indicators of Excess[a]
Copper	UL	• Gastrointestinal effects (abdominal pain, cramps, nausea, diarrhea, vomiting) • **Liver damage (extrapolated to children and adolescents on basis relative body weight)** • Other systemic effects (data inadequate to asses reproductive or developmental effects in humans; little convincing evidence copper associated with development of cancer in humans)
Iodine	UL	• Acute iodine poisoning (burning mouth, throat, stomach, abdominal pain, fever, nausea, vomiting, diarrhea, weak pulse, cardiac irritability, coma, cyanosis • Hypothyroidism, **elevated thyroid stimulating hormone (extrapolated to children and adolescents on basis of reference body weights)** • Goiter • Thyroid papillary cancer • Thyroid effects in newborns • Other adverse effects (iodermia, hyperthyroidism)
Iron	UL	• Acute adverse effects (vomiting, diarrhea, with involvement of 5 organ systems – cardiovascular, CNS, kidney, liver and hematological) • Iron-zinc interactions • **Gastrointestinal effects** (constipation, nausea, vomiting, diarrhea) • Secondary iron overload (parenteral iron, blood transfusions, hematological disorders) • Cardiovascular disease • Cancer
Manganese	UL	• **Elevated blood manganese and neurotoxicity (children and adolescents extrapolated from adults on basis of relative body weight)** • Neurotoxicity in laboratory animals • Ecological studies in humans (high level of Mn in drinking water associated with neuromotor deficits similar to Parkinson's disease)
Molybdenum	UL	• Renal failure (rats, rabbits) • Increased uric acid in plasma and urine in humans (hyperuricemia and arthralgias observed in one study but not confirmed in 2 others) • Impaired copper utilization (ruminants) • **Reproductive effects in rats and mice (rats: prolonged estrus cycle, decreased gestational weight gain in pups, adverse effects on embryogenesis; mice: early deaths of offspring, dead litters, maternal deaths and failure to breed) (children and adolescents extrapolated from adults on basis of relative body weights)** • Cancer (no evidence humans and animals) • Hemoglogin and hematocrit decrease (rabbits) • Growth depression (rats, guinea pigs)

Nutrient	Reference Value	Indicators of Excess[a]
Zinc	UL	• Acute effects (epigastric pain, nausea, vomiting, loss of appetite, abdominal cramps, diarrhea and headaches) • Immunological response (functional impairment) • Lipoprotein and cholesterol (decreased HDL and LDL – not consistently observed) • **Reduced copper status (decreased erythrocyte copper-zinc superoxide dismutase activity) (adult UL)** • Zinc-iron interactions (not shown in food) • Other endpoints (insufficient evidence of carcinogenicity from human or animal studies) • **Serum copper and cholesterol concentrations in infants (UL extrapolated to children and adolescents based on relative body weight)**
Arsenic	-	
Boron	UL	• Acute effects (nausea, gastric discomfort, vomiting, diarrhea, skin flushing, excitation, convulsions, depression and vascular collapse • Chronic effects in humans (dermatitis, alopecia, anorexia, indigestion) • Genotoxicity (not a concern) • **Reproductive and developmental effects in animals (rats, dogs and mice: adverse effects in the testes and on male fertility) (children and adolescents extrapolated from adult UL on basis of relative body weight)** • Other effects (mice: increased mortality, extramedullary hematopoiesis, hyperkeratosis and hyperplasia of forestomach; rats and mice: testicular atrophy)
Nickel	UL	• UL applies to excess nickel intake as soluble nickel salts • Acute effects in humans (nausea, abdominal pain, diarrhea, vomiting, shortness of breath, altered hematological parameters, transient hemianopsia, contact dermatitis-like symptoms • **Subchronic and chronic effects in animals (children and adolescents extrapolated from adult UL on basis of relative weight)** - increased mortality - **clinical signs of general systemic toxicity** - **decreased body weight gains** - changes in absolute and relative organ weights - fetotoxicity and interference in reproductive capacity male rats (quality of data insufficient for UL determination)
Silicon	-	

Nutrient	Reference Value	Indicators of Excess[a]
Vanadium	UL	• UL applies to total vanadium from food, water and supplements (used by athletes and borderline diabetics considered part of the apparently healthy general population) • Acute toxicity (rats: desquamation enteritis, mild liver congestion with fatty changes and slight parenchymal degeneration of the renal convoluted tubules; mice: acute tubular necrosis • **Renal toxicity (rats: histopathological lesions and increased urea, uric acid and creatine, decreased weight gain; mice: acute tubular necrosis) (UL for nonpregnant non-lactating adults only, other groups should not take supplements)** • Gastrointestinal effects in humans (abdominal cramps, loose stool) • Hematological effects (humans: no adverse effects shown; animals: may cause anemia and changes in leukocyte system) • Cardiovascular effects (rats: increased blood pressure and heart rate) • Reproductive effects (humans: none, rats: decrease in pregnancy rate) • Other adverse effects in humans (green tongue, fatigue, lethargy, focal neurological lesions)
Dietary Carbohydrates	-	
Sugars	-	
Starches		
Total Fiber	-	
Dietary Fiber	-	
Functional Fiber	-	
Total Fat		
Saturated Fatty Acids	-	
MUFA	-	
n-6 PUFA	-	
n-3 PUFA	-	
trans-Fatty Acids	-	
Cholesterol	-	

Nutrient	Reference Value	Indicators of Excess[a]
Protein & Amino Acids	-	
Water	-	
Potassium	-	
Sodium	UL	• **Blood pressure (adult UL extrapolated to children and adolescents based on median energy intakes)** • Stroke • Coronary heart disease • Renal disease • Left ventricular mass • Calcium excretion, bone mineral density, and kidney stones • Pulmonary function (asthma) • Gastric cancer
Chloride	UL	• Equimolar to sodium
Sulfate	-	

[a] Indicator used in setting the UL is bolded.

TABLE 3 Rationale for Setting AI

Nutrient	Reference Value	Rationale for AI or no value rather than EAR	
		Evidence Reviewed	**Conclusions**
Calcium	AI	Note: • Calcium Panel proposed that a statistical model be used to estimate an intake of calcium that would result in maximum calcium retention that would be used to establish the EAR. The DRI Committee determined that an AI should be established instead. Concerns with the model led the DRI Committee to apply the model to establish AIs based on the intake of calcium sufficient to achieve a *defined desirable level* of calcium retention specific to each age group. Evidence reviewed: • Calcium intakes and fracture risks (studies on optimal calcium intakes to minimize later osteoporotic fractures not available; observational studies cannot be used to estimate EAR) • Bone mass measurements (bone mineral density (BMD), bone mineral content (BMC)) • Calcium intake and bone mass (cross-sectional studies cannot account for long term calcium intakes and influence of other factors on bone mass; intervention studies in adults best evaluated in second or later years of intervention because of bone remodeling transient) • Calcium retention (influenced by genetics, calciotropic hormones and weight-bearing exercise as well as calcium intakes) • Desirable calcium retention: Data from calcium balance studies, factorial estimates of requirements and limited data on BMC and BMD used to obtain information on calcium intakes and retention to develop non-linear regression model to derive an intake of calcium adequate to achieve predetermined desirable calcium retention. • Hypertension (effect of calcium on blood pressure "modest and variable" in the general population and intake for effect on blood pressure likely less than that required for the desirable level of skeletal calcium retention) • Colon cancer (evidence inconsistent and prospective trials lacking)	AI established because of • uncertainties inherent in balance study methodology and the nutritional significance of the values obtained from the studies that form the basis of the desirable retention model; • lack of concordance between observational and experimental data (mean Ca intakes in the US and Canada much lower than the experimentally derived values predicted to be required to achieve a desirable level of calcium retention); • lack of longitudinal data that could be used to verify the association of the experimentally derived calcium intakes for achieving a predetermined level of calcium retention with the rate and extent of long-term bone loss and its clinical consequences, such as fracture
Phosphorus	EAR		
Magnesium	EAR		

Nutrient	Reference Value	Rationale for AI or no value rather than EAR Evidence Reviewed	Conclusions
Vitamin D	AI	• Serum 25(OH)D was the primary indicator of vit D adequacy. Normal range of serum 25(OH)D concentration was determined to be the mean ± 2SD in a group of healthy persons. • Serum vitamin D (not indicative of D status – measure of recent exposure) • Serum 1,25 $(OH)_2D$ (not a good indicator of vit D status, levels tightly regulated) • Skeletal health (infants and children: bone development, prevention of rickets, serum 25(OH)D and PTH concentrations; adults: BMC, BMD, fracture risk, serum 25(OH)D and PTH)	• All humans can meet Vit D requirements through adequate sun exposure. Cutaneous synthesis of Vit D, however, is affected by many factors – melanin pigmentation, latitude, time of day, season, weather conditions, amount of skin exposed and use of sunscreen. • Difficult to determine an accurate value for an EAR as most of the studies are subject to one or more of the above variables especially exposure to sunlight. Studies in subjects deprived of sunlight do not account for vit D stores from previous sun exposure. • Vit D is a hormone. An EAR would represent a "gross estimate" of the need for the active hormone. • The vit D content of the diet is uncertain. Levels of added vit D in foods shown to be highly variable and the content of naturally occurring vit D in foods varies with the season.
Fluoride	AI	• Dental caries • Bone mineral content (data inconsistent) • Fluoride balance (no data on long term effects of negative balance on enamel or caries development)	• "Because data are not available to determine an EAR, the reference value that will be used for F is the AI." • AI of 0.05 mg/kg/day from all sources is based on maximum reduction in dental caries without causing adverse effects including moderate dental fluorosis. The AI for each age group is based on reference weights.
Thiamin	EAR		
Riboflavin	EAR		
Niacin	EAR		
Vitamin B_6	EAR		
Folate	EAR		
Vitamin B_{12}	EAR		
Pantothenic Acid	AI	Indicators for estimating requirements • Urinary excretion (strongly dependent on intake) • Whole blood levels of pantothenic acid (blood levels fell during the first 28 days on a PA free diet but not during the next 35 days; 10 mg PA per day for 9 weeks did not increase PA levels) • Serum or plasma pantothenic acid (do not	• AI based on usual intake of PA in adults supported by the results of the one study in adults relating dietary intake of PA to urinary excretion. Although it was a dose response study with 3 levels of PA, uncertainties about the accuracy of the published values for the amounts of pantothenic acid in foods used to estimate intakes, small number of subjects studied (6 young females) and lack of

Nutrient	Reference Value	Rationale for AI or no value rather than EAR	
		Evidence Reviewed	**Conclusions**
		correlate with whole blood levels) • Erythrocyte pantothenic acid (model to predict levels from intake and urine concentrations only explained 30% of variance)	information about the effects of intake on the efficiency of absorption and storage did not permit the establishment of an EAR.
Biotin	AI	• Evidence comes from clinical observations of patients receiving biotin-free TPN, individuals with inborn errors of metabolism, persons consuming large amounts of raw egg white; 2 studies of avidin-induced biotin deficiency and less than 10 studies of biotin bioavailability and pharmacokinetics. • Abnormally decreased biotin excretion and abnormally increased excretion of 3-hydroxyisovalerate are most validated measures of biotin status but no mention made of their suitability for determining requirements. • Low plasma biotin concentration – not sensitive indicator of inadequate biotin intake • Odd-chain fatty acid composition of plasma lipids thought to result from propionyl-CoA carboxylase deficiency • Different methods for analyzing biotin result in a 20 fold difference in mean plasma biotin.	• No definitive studies demonstrating evidence of biotin deficiency in normal individuals. • Evidence for biotin requirement minimal and "does not justify" setting an EAR. • AI for children, adolescents and adults extrapolated on basis of relative body weight from infant AI based on biotin content of human milk.
Choline	AI	Indicators for Estimating Requirements • Markers of liver dysfunction produced by choline deficiency (human: elevated alanine aminotransferase, fatty infiltration (difficult to measure); rat: decreased hepatic Choline and metabolites including phosphocholine) • Plasma Choline concentration (varies with choline intake; in subjects fasted for > 1 week, did not decrease below 50% of normal due possibly to hydrolysis of membrane phospholipids – not suitable as indicator) • Reduction of risk of chronic disease - Dementia (rats: Choline in early life decreases severity of memory deficits in old age; humans: data are for Choline used as treatment rather than preventative) - Cardiovascular disease (phosphatidylcholine lowers cholesterol in humans and betaine lowers homocysteine. More studies needed.) - Cancer (rodents: deficiency associated with increased incidence of liver cancer; no human data)	• AI because estimate is uncertain (single study, lack of dose response data) and may need revision. • AI based on single study in which 500 mg/day (7 mg/kg) prevented alanine transaminase abnormalities in healthy men. Two other studies showed that 2 mg/kg produced deficiency, 31 mg/kg restored Choline status.
Vitamin C	EAR		

Nutrient	Reference Value	Rationale for AI or no value rather than EAR Evidence Reviewed	 Conclusions
Vitamin E	EAR		
Selenium	EAR		
β-Carotene & other Carotenoids	----		No requirement set for β-carotene separate from that for vitamin A
Vitamin A	EAR		
Vitamin K	AI	• Indicators related to vitamin K dependent clotting factors (prothrombin time, Factor VII. PIVKA-II) were deemed to be too insensitive or in the case of PIKA-II, lacking data because results of older studies could not be compared with newer results because of changes in methodology. Dose-response data lacking. • Plasma and serum phylloquinone reflects recent intakes but not the average intake of K and increases with age in parallel with increases in triglycerides. • Urinary γ-carboxylglutamyl (Gla) residues respond to vitamin K intakes after a period of several days and are affected by age. • Under-γ-carboxylated osteocalcin (ucOC) – although vit K does decrease the percentage of ucOC, methodological issues and physiological significance of the %ucOC ruled out use of this indicator. • Relationship of vitamin K to chronic disease: - Osteoporosis: study results not consistent. Vitamin K deficient patients due to warfarin therapy found not to have reduced BMD at most sites, mice lacking the gene for osteocalcin had greater bone mass and stronger bones. - Atherosclerosis – association of osteocalcin and matrix Gla proteins with atherosclerotic plaques and extensive arterial calcification in the matrix Gla protein knock-out mouse. Requires further investigation.	• Clinically significant vitamin K deficiency is limited to individuals with malabsorption syndromes or those treated with drugs that interfere with vitamin K metabolism. • indicators sensitive to vitamin K intake, though useful to describe relative diet-induced changes in vitamin K status, were not used for establishing an EAR because of uncertainty about their true physiological significance (ucOC) and the lack of sufficient dose-response data (PIVKA-II).
Chromium	AI	• Chromium balance: Results of two studies reviewed (total n = 24). Few details given • Urinary chromium excretion deemed to be related to recent chromium intake and not useful as a predictor of chromium status • Plasma chromium close to the detection limits for graphite furnace atomic absorption, not useful as a clinical indicator. • Blood glucose and insulin concentration: one study suggesting influence of chromium on	• Data are lacking to establish an EAR. • No national survey data are available on chromium intakes.

Nutrient	Reference Value	Rationale for AI or no value rather than EAR	
		Evidence Reviewed	**Conclusions**
		blood glucose concentration but lacking dose response data.	
Copper	EAR		
Iodine	EAR		
Iron	EAR		
Manganese	AI	• Balance and depletion studies: "problematic" for determining requirements because Mn rapidly excreted in the bile and Mn balances during short-and moderate term studies appear not to be proportional to intakes. • Serum, and plasma manganese concentrations: in a depletion-repletion study, plasma Mn was not significantly correlated with intake; in a second study, serum Mn did not respond to variations in Mn intake. • Blood manganese concentration: extremely variable. • Urinary manganese: results of studies not consistent. Urinary Mn decreased with depletion in one study but not in another. Mn supplementation did not increase excretion. • Arginase activity: decreased in liver of Mn deficient rats. Enzyme influenced by protein intake and liver disease. • Manganese-superoxide dismutase activity: low in Mn deficient experimental animals. Lymphocyte Mn-SOD increased in women supplemented with Mn but enzyme affected by alcohol and PUFA intake.	• Balance data could not be used to set EAR because a wide range of manganese intakes can result in manganese balance. The results of several balance studies would result in an RDA higher than the median intake observed in the Total Diet Study. • The lack of overt symptoms of Mn deficiency led to conclusion that "an RDA based on balance data most likely overestimates the requirement for most North American individuals." • Intake data are used to set an AI for manganese.
Molybdenum	EAR		
Zinc	EAR		
Arsenic	-	Lack of human data to identify a biological role of arsenic in humans.	Did not set either an EAR or AI
Boron	-	Evidence supports a biological role for boron in some microorganisms; in higher animals, boron has a role in reproduction and development but a clear biological function for boron has not yet been established in humans.	Did not set EAR or AI
Nickel	-	Nickel may serve as a cofactor or structural component of certain metalloenzymes and facilitate iron absorption or metabolism in microorganisms. No reported studies on	Did not set EAR or AI

Nutrient	Reference Value	Rationale for AI or no value rather than EAR	
		Evidence Reviewed	**Conclusions**
		biological role of nickel in higher animals or humans.	
Silicon	-	Silicon appears to be involved in the formation of collagen and bone in animals. A biological role for silicon in humans has not been identified.	Did not set EAR or AI
Vanadium	-	In experimental animals, vanadium mimics insulin and inhibits the activity of various enzymes. Vanadium deficiency results in increased abortion rates. Biological role in humans not established.	Did not set EAR or AI
Dietary Carbohydrates	EAR		
Sugars	-		
Starches	-		
Total Fiber	AI	• Prevention of hyperlipidemia, hypertension and CHD - epidemiological studies – prospective cohort studies observed reduced risk of CHD with increasing intakes of DF especially from cereals. - Intervention studies with viscous fibers reduced total and LDL cholesterol levels but the effects of dietary fibre in reducing CHD cannot be attributed solely to the cholesterol lowering effect. • Gastrointestinal health - duodenal ulcer: prospective cohort study showed intake of viscous fibers from fruit, vegetables and legumes associated with reduced risk - Dietary fiber, functional fiber and colon health: fiber has beneficial effects on constipation, laxation and increases stool weight, fiber fermentation produces butyrate and fiber intake is protective against diverticular disease. • Prevention of colon cancer: Epidemiological studies: prospective cohort studies: weak or nonexistent association between fiber intake and risk of colon cancer; case-control studies: inverse association between fiber intake and cancer risk; Intervention studies: no effect of fiber; Colonic adenomas: no effect • Protection against breast cancer: evidence of relationship strongest for cereal consumption but not dietary fiber (observational studies)	• "Data on the relationship between dietary fiber intake and risk of CHD based on epidemiological, clinical and mechanistic data are strong enough to warrant using this relationship as a basis for setting a recommended level of intake." (Caveat – data from epi studies are on fiber-containing foods (some studies analyzed diets for fiber content, others used indicators of dietary fiber intake such as cereals, legumes etc) • "Prospective studies have shown that the impact of dietary fiber on the advent of CHD occurs continuously across a range of intakes, Therefore, an EAR cannot be set." • Total fiber reduces risk of type-2 diabetes, used as secondary endpoint to support AI set using CHD endpoint. • Evidence supports role of fiber in GI health; fiber intakes based on prevention of CHD should be sufficient. • Evidence for reduced risk of colon cancer inconsistent.

Nutrient	Reference Value	Rationale for AI or no value rather than EAR	
		Evidence Reviewed	**Conclusions**
		except in case control studies. Intervention studies: fiber shown to reduce estrogen concentrations . • Glucose tolerance, insulin response and amelioration of diabetes: results of two prospective cohort studies suggest high glycemic load, low fiber diets are associated with risk of type-2 diabetes; 66 % of intervention studies with viscous fibers showed reductions in glycemic response but blood glucose response of intact foods is more closely related to nonviscous fiber content. • Satiety and Weight Maintenance: strongest evidence from epidemiological studies; intervention studies gave mixed results on effects of fiber on subsequent energy intakes.	
Dietary Fiber	-		
Functional Fiber	-		
Total Fat		Clinical endpoints of fat intake are trends rather than defined endpoints and cannot be used to set an EAR.	AMDR set instead.
Saturated Fatty Acids	-		Not essential in the diet.
MUFA	-		Not essential in the diet.
n-6 PUFA	AI	• n-6 deficiency found only in patients with chronic fat malabsorption or on parenteral nutrition. Studies of requirements to correct deficiency confined to patients on TPN. • Plasma ratio of eicosatrienoic acid:arachidonic acid	• Optimal plasma or tissue lipid concentrations of n-6 fatty acids or ratios of n-6:n-3 fatty acids have not been established. • Because of the lack of data on n-6 requirements in healthy individuals, EAR cannot be set based on correction of a deficiency.
n-3 PUFA	AI	• Evidence of essentiality of n-3 fatty acids from studies of patients on TPN or tube-feeding. • No accepted normal ranges for EPA or DHA levels in plasma ant tissues. • Growth and neural development: results of studies in infants fed formulas containing DHA ± arachidonic acid.	• EAR cannot be set based on correction of a deficiency because of lack of data on the n-3 fatty acid requirement in health individuals. • Randomized clinical studies on growth and neural development in term infants gave conflicting results on the requirements for n-3 fatty acids but raise concerns over supplementation with long chain n-3 without arachidonic acid. "For these reasons, growth and neural development could not be used to set an EAR."
Trans-Fatty Acids	-		No known requirements for physiological functions

Nutrient	Reference Value	Rationale for AI or no value rather than EAR	
		Evidence Reviewed	**Conclusions**
Cholesterol	-		No evidence for dietary requirement
Protein & Amino Acids	EAR		
Water	AI	(Utility for use in estimating water requirements not mentioned for most of the indicators) • Water balance studies: estimates of minimum requirements • Methods for estimating hydration status : plasma osmolality selected as measure of hydration status • Urine indicators • Body weight changes • Thirst • Dehydration, health and performance • Dehydration and chronic diseases	• It is not possible to estimate an EAR for water. Given the extreme variation in water needs depending on environmental conditions and activity as well as differences in metabolism, a single level of intake could not be set that would ensure adequate hydration and optimal health for half of all apparently healthy persons in all environmental conditions.
Potassium	AI	• Potassium balance: affected by diet, subject can be in balance at levels low enough for adverse effects to occur. • Serum potassium concentrations: signs and symptoms of K deficiency can occur in the absence of frank hypokalemia; not a sensitive indicator in terms of mitigating chronic disease. • Hypokalemia: moderate K deficiency can occur without hypokalemia. • Salt-sensitive blood pressure: supplemental K (as bicarbonate) mitigates the effects of salt in a dose-dependent manner. • Blood pressure: BP inversely associated with K intake, directly associated with Na intake and the Na:K ratio. BP more closely associated with Na:K ratio than intake of either Na or K. Intervention trials used K supplements (anions - chloride, bicarbonate, citrate)or foods rich in K in nonhypertensive and hypertensive subjects. In a number of studies, K in diet was not recorded. No studies used more than 2 levels of K. K most effective in lowering BP if Na intake high. • Prevention of CVD: in animal models, K supplements reduced stroke mortality and bicarbonate and citrate forms attenuated hypertension; inverse relationship between K intake at baseline and subsequent morbidity and mortality from stroke seen in some but not all cross-sectional and cohort studies. • Prevention of bone demineralization: observational and intervention studies:	• Insufficient dose response data to set an EAR level that would reduce blood pressure, mitigate salt sensitivity or decrease the risk of kidney stones in 50 % of subjects • Requirement for K could depend on level of dietary Na but data inadequate to set requirement based on Na intake or Na:K ratio.

Nutrient	Reference Value	Rationale for AI or no value rather than EAR	
		Evidence Reviewed	**Conclusions**
		positive effect of K on BMD attributed to decrease in net endogenous acid production. Mole for mole basis, hypocalciuric effect of K overrides hypercalciuric effect of Na. • Prevention of kidney stones: stone occurrence highly significantly related to urinary Na:K ratio but not significantly to urinary potassium. Reducing Na:K ratio in children with idiopathic hypercalcuria reduced Ca excretion. In clinical trial of K citrate in recurrent stone formers, stone formation rate significantly reduced.	
Sodium	AI	• Sodium balance: obligatory Na losses very low ≤ 180 mg/day • Serum or plasma sodium concentration: hyponatremia not caused by low Na intakes • Plasma rennin activity: plasma rennin activity inversely related to sodium intake but insufficient evidence to support claim that this is a deleterious response. • Elevation in blood pressure: Increases in BP with reduction in Na intake due to greater activation of the rennin-angiotension-alderosterone axis; reductions in BP, the reverse. Apparent rise in BP in response to reduced Na intake cannot be used as an indicator of adequate Na. • Blood lipid concentrations: extremely low Na intakes significantly increased total and LDL cholesterol (13/19 trials). Modest Na reductions (1l7 g/day) showed no effect on total, HDL and LDH cholesterol, dose response study (1.1 g, 2.3 g and 3.4 g) showed no effect. • Insulin resistance: evidence inconsistent and limited.	• EAR not set because dose response data unavailable on indicator of adequacy to permit assessment of the level at which half the individuals would demonstrate inadequacy for that indicator. • AI set at level - At which needs for other nutrients can be met, - Which exceeds the levels of Na intake associated with adverse effects on blood lipid levels and insulin resistance; - Which allows for excess sodium loss in sweat by unacclimatized people who are exposed to high temperatures or who are moderately physically active.
Chloride	AI		Equimolar with sodium
Sulfate	-		Requirements met by requirements for sulfur amino acids

TABLE 3a Rationale for AI (abbreviated version of Table 3)

Nutrient	Reference Value Adequate Intake	Rationale for AI rather than EAR
Calcium	AI	1. Uncertainties inherent in balance study methodology and the nutritional significance of the values obtained from these studies that form the basis of the desirable retention model; 2. Lack of concordance between observational and experimental data (mean Ca intakes in the US and Canada much lower than the experimentally derived values predicted to be required to achieve a desirable level of calcium retention); 3. The lack of longitudinal data that could be used to verify the association of the experimentally derived calcium intakes for achieving a predetermined level of calcium retention with the rate and extent of long-term bone loss and its clinical sequelae, such as fracture.
Phosphorus	EAR	
Magnesium	EAR	
Vitamin D	AI	1. All humans can meet Vit D requirements through adequate sun exposure. Cutaneous synthesis of Vit D, however, is affected by degree of pigmentation, latitude, time of day, season, weather conditions, amount of skin exposed and use of sunscreen. Difficult to determine an accurate value for an EAR as most of the studies are subject to one or more of these variables especially exposure to sunlight. Studies in subjects deprived of sunlight do not account for vit D stores from previous sun exposure. 2. The vit D content of the diet is uncertain. Levels of added vit D are highly variable and the content of naturally occurring vit D varies with the season.
Fluoride	AI	Lack of data to determine EAR..
Thiamin	EAR	
Riboflavin	EAR	
Niacin	EAR	
Vitamin B6	EAR	
Folate	EAR	
Vitamin B12	EAR	
Pantothenic Acid	AI	1. Uncertainties in the accuracy of the published values for the amounts of pantothenic acid in foods used to estimate intakes in studies; 2. Small number of subjects studied; 3. Lack of information about the effects of intake on the efficiency of absorption and storage.

Nutrient	Reference Value Adequate Intake	Rationale for AI rather than EAR
Biotin	AI	Lack of evidence including no definitive studies demonstrating evidence of biotin deficiency in normal individuals.
Choline	AI	Lack of data.
Vitamin C	EAR	
Vitamin E	EAR	
Selenium	EAR	
β-Carotene & other Carotenoids	----	No requirement set for β-carotene separate from that for vitamin A.
Vitamin A	EAR	
Vitamin K	AI	1. Clinically significant vitamin K deficiency is limited to individuals with malabsorption syndromes or those treated with drugs known to interfere with vitamin K metabolism. 2. Recently developed indicators sensitive to vitamin K intake, though useful to describe relative diet-induced changes in vitamin K status, were not used for establishing an EAR because of uncertainty about their true physiological significance and the lack of sufficient dose-response data.
Chromium	AI	Lack of data.
Copper	EAR	
Iodine	EAR	
Iron	EAR	
Manganese	AI	Balance data could not be used to set EAR because a wide range of manganese intakes can result in manganese balance. The results of several balance studies would result in an RDA higher than the median intake observed in the Total Diet Study. The lack of overt symptoms of Mn deficiency led to conclusion that "an RDA based on balance data most likely overestimates the requirement for most North American individuals." Therefore, intake data are used to set an AI for manganese.
Molybdenum	EAR	
Zinc	EAR	
Arsenic	-	Insufficient data to set EAR or AI.
Boron	-	Insufficient data to set EAR or AI.

Nutrient	Reference Value Adequate Intake	Rationale for AI rather than EAR
Nickel	-	Insufficient data to set EAR or AI.
Silicon	-	Insufficient data to set EAR or AI.
Vanadium	-	Insufficient data to set EAR or AI.
Dietary Carbohydrates	EAR	
Sugars	-	
Starches	-	
Total Fiber	AI	Dietary fiber reduces risk of CHD across a range of intakes.
Dietary Fiber	-	
Functional Fiber	-	
Total Fat	-	Clinical endpoints of fat intake are trends rather than defined endpoints.
Saturated Fatty Acids	-	Not essential in the diet.
MUFA	-	Not essential in the diet.
n-6 PUFA	AI	Inadequate data to set EAR.
n-3 PUFA	AI	Inadequate data to set an EAR.
Trans-Fatty Acids	-	No known requirements for physiological functions.
Cholesterol	-	No evidence for dietary requirement.
Protein & Amino Acids	EAR	
Water	AI	Water needs vary with environmental conditions and activity as well as differences in metabolism consequently a single level of intake could not be set that would ensure adequate hydration and optimal health for half of all apparently healthy persons in all environmental conditions.
Potassium	AI	Data lacking to set an EAR level that would reduce blood pressure, mitigate salt sensitivity or decrease the risk of kidney stones in 50 % of subjects.

Nutrient	Reference Value Adequate Intake	Rationale for AI rather than EAR
Sodium	AI	Data unavailable on indicator of adequacy evaluated at multiple levels of intake to permit assessment of the level at which half the individuals would demonstrate inadequacy for that indicator.
Chloride	AI	Equimolar with sodium.
Sulfate	-	Requirements met by requirements for sulfur amino acids.

TABLE 4 Rationale for not setting Upper Level

Nutrient	Rationale for not setting Upper Level	
	Evidence reviewed	**Conclusions**
Thiamin	• Occasional reports of serious and fatal anaphylaxis to parenteral administration • One case of pruritus after IM administration but not with oral exposures • Lack of toxicity explained by rapid decline in absorption with intakes >5 mg	• No evidence of adverse effects from consumption of excess thiamin from food and supplements. • Data inadequate for quantitative risk assessment; absence of known toxic effects by ingestion inability to determine LOAEL and NOAEL. • Possible adverse effects (AEs) not systematically studied; supplements containing up to 50 mg/d are widely available but effects of this level not studied systematically.
Riboflavin	• No AEs with IV high intakes • 1/49 patients w/d from study with gastric upset – may be an anomaly • Lack of harm may be due to limited solubility and limited capacity for absorption • No data from animal studies suggesting hazard for fetus or newborn • Only evidence of AEs is from in vitro studies but relevance to humans is questionable • Other AEs are theoretical	• No evidence of adverse effects from consumption of excess riboflavin from food and supplements. • Available studies not designed to systematically evaluate. • Data not sufficient for quantitative risk assessment**.**
Vitamin B12	• Weak evidence from animal studies contradicted by human data; • Questionable relevance and quality of acne studies • Parenteral administration to pernicious anemia patients support lack of AEs • Only small % of high oral doses is absorbed	• No evidence of adverse effects from consumption of excess B12 from food and supplements. • Evidence insufficient for quantitative risk assessment and to derive UL.
Pantothenic Acid	• Lit search no evidence of toxicity • No toxic effects in study on wound healing • Cocktail of nutrients including pantothenic acid associated with ↑transaminase levels but can't attribute effect to pantothenic acid • No subgroups distinctly susceptible to AEs were identified	• No evidence of adverse effects of oral pantothenic acid in humans or animals. • Can not do quantitative risk assessment. • Absence of known toxic effects by ingestion, cannot determine LOAEL and NOAEL.
Biotin	• No toxicity in patients treated with high oral and IV doses • Animal studies suggesting toxicity lack relevance to humans and poor study quality	• No evidence of adverse effects of biotin in humans or animals. • Data not sufficient for quantitative risk assessment.
β-Carotene & other Carotenoids	• No AEs other than carotenodermia with ß-carotene from foods – harmless • No side affects from therapeutic uses at high doses • No evidence of teratogenicity, mutagenicity, or carcinogenicity in long-term animal studies • No increase in serum retinol with long-term human supplementation	• Conflicting data on ß-carotene and lung cancer not sufficient for D-R assessment. • Supplement intakes of 30 mg/d or more associated with carotenodermia but is considered harmless. • No data on other carotenoids.
Vitamin K	• No evidence of toxicity associated with intake of either the phylloquinone or menaquinone forms of vitamin K	• No adverse effects associated with vit K consumption from food or supplements have been reported in

Nutrient	Rationale for not setting Upper Level	
	Evidence reviewed	**Conclusions**
	• Menadione, a synthetic form of vitamin K was associated with liver damage and no longer used therapeutically • Significant association between intramuscularly administered vit K and childhood cancer particularly leukemia reported in one study (195 cases, 558 controls) (p=0.002; observed risk 1.97 95% CI 1.3 – 3.0). No significantly increased risk reported in children given oral vit K. • Evidence from other population studies failed to confirm an association between vit K and any one or all childhood cancers combined • Data from animal models have shown no toxicity of vitamin K. No adverse effects were reported with administration of up to 25 g/kg of phylloquinone either parenterally or orally to laboratory animals	humans or animals. • Findings of association between intramuscular vit K doses and cancer have limited relevance to ULs based on oral intakes and have not been supported by other larger studies. • A quantitative risk assessment cannot be performed and a UL cannot be derived.
Chromium	• The toxicity of chromium depends on the valence state. Review was limited to trivalent chromium (III) the principal form of chromium found in food and supplements. Hexavalent chromium (VI), which has a much higher level of toxicity than trivalent chromium, is not found in food. • Chronic Renal Failure: Chronic interstitial nephritis in humans has been attributed to ingestion of chromium picolinate in two case reports. No evidence of kidney damage in experimental animals exposed for up to 2 years to oral chromium as chromium chloride, chromium trichloride, - chromium picolinate, or chromium acetate. • Genotoxicity: Chromium VI is a well established human carcinogen, mutagen, and clastogen, but chromium III compounds are not. In vivo genotoxicity assays for chromium III have been negative. Most studies of genotoxicity in cellular systems have yielded negative results as well. Positive results of chromium III were found in intact cells; however, it was concluded that these results could be due to contamination of the test compounds with traces of chromium VI, which is readily taken up by cells. Several studies suggest that chromium III picolinate and tri-picolinate may cause DNA damage through the generation of hydroxyl radicals. • Carcinogenicity: There is little evidence of carcinogenicity in humans or animals after oral intake of chromium III. One study attributed increased mortality due to stomach cancer in gold miners to chromium dust but did not adjust for possible confounding factors (e.g., role of dietary habits) and failed to show a dose response. A 2-year feeding study in rats showed no carcinogenicity after intake (5 days/week for 2 years) of 1, 2, or 5	• The studies on renal, hepatic, reproductive, and DNA damaging effects of chromium III do not provide dose-response information or clear indications of a LOAEL or NOAEL. • There are insufficient data to establish a UL for soluble chromium III salts. • No adverse effects have been convincingly associated with excess intake of chromium from food or supplements but this does not mean that there is no potential for adverse effects at high intakes • Because of the current widespread use of chromium supplements, more research is needed to assess the safety of high-dose chromium intake from supplements.

Nutrient	Rationale for not setting Upper Level	
	Evidence reviewed	**Conclusions**
	percent chromium oxide (Cr_2O_3) baked in bread. • Hepatic Dysfunction: There are no reports of hepatic adverse effects in humans Several rat studies show no morphological changes in livers following long-term ingestion of chromium compounds. • Reproductive Effects: There are no studies in humans to suggest that chromium III is a reproductive or developmental toxicant. Studies of various chromium III compounds in mice and rats have shown reduced fertility and adverse effects on the testes. • Rhabdomyolysis: the study did not take into account other possible causes.	
Arsenic	• Acute Effects/Poisoning: Inorganic arsenic is an established human poison resulting in encephalopathy and GI symptoms at doses greater than 10 mg/kg/day and anemia and hepatotoxicity at doses of 1 mg/kg/day or greater. • Arsenicism: Chronic intake of 10 µg/kg/day or greater of inorganic arsenic produces arsenicism, a condition characterized by alteration of skin pigmentation and keratosis In some regions, an occlusive peripheral vascular disease also occurs resulting in gangrene of the extremities, especially of the feet, thus termed blackfoot disease • Peripheral Neuropathy: Intermediate and chronic exposures of arsenic up to levels of 11 mg/L of water are associated with symmetrical peripheral neuropathy. However, in some populations exposures of 5 mg/L of water did not result in clinical or subclinical neuropathy • Developmental Toxicity: Developmental effects in humans have not been demonstrated. In experimental animals, single doses of arsenic administered orally, intragastrically or IP caused fetal death and malformations. • Genotoxicity: Inorganic arsenic demonstrated to have mutagenic effects in bacteria and cultured human cells. Sodium methanearsonates did not have mutagenic activity in bacteria. • Carcinogenicity: Ingestion of inorganic arsenic is associated with risk of cancers of the skin, bladder, and lung. Increased risks of other cancers such as kidney and liver have also been reported, but the strength of the association is not great. There are no studies of cancer in humans after exposure to organic arsenicals. Most studies of a positive association with cancer involve intake of inorganic arsenic in drinking water. A large-scale survey of 40,421 Taiwanese in an area where the well water has a high concentration of arsenic found that the	• No data on the possible adverse effects of organic arsenic compounds in food were found. • Animals do not appear to be good quantitative models for inorganic arsenic toxicity in humans perhaps because of the species diversity of erythrocyte-binding of arsenic and inorganic arsenic methyltransferase activity, a detoxification mechanism • High intakes of inorganic arsenic are associated with various toxicities, including increased risks of several cancers with chronic exposure to high levels in drinking water. • Not possible to establish a health-based level of inorganic arsenic in food and drinking water because of lack of evidence to define the mechanisms of arsenic carcinogenesis and no data to support a threshold. • Because arsenicism may be associated with arsenic intakes higher than those causing other adverse effects, it was not selected as a critical adverse effect to set a UL. • Although no UL was set for arsenic, there is no justification for adding arsenic to food and there may be a risk of adverse effects with consumption of organic arsenic in food or with intake of inorganic arsenic in water supplies at the current MCL of 50 µg/L in the United States. Substantial numbers of individuals in North America, however, are exposed to arsenic levels exceeding the MCL

Nutrient	Rationale for not setting Upper Level	
	Evidence reviewed	**Conclusions**
	prevalence rates for skin cancer, and arsenicism showed an ascending gradient which correlated with the arsenic content of the well water. The risk of bladder cancer in Taiwan, Japan and Chile was increased with intake of arsenic from water. Studies in U.S. populations exposed to arsenic in drinking water have not identified cancer increases. These epidemiological associations have to some extent been replicated in animal experiments, however, the mechanisms of arsenic carcinogenesis are not established, but may involve genetic effects or perturbation of cellular signaling pathways.	
Silicon	• Urolithiasis: Limited reports indicate that magnesium trisilicate used as an antacid in large amounts for long periods (i.e., several years) may be associated with the development of urolithiasis due to the formation, in vivo, of silicon-containing stones. Less than 30 cases of urolithiasis reported to be associated with intake of silicates (in the form of antacids) could be found even though antacids containing silicon have been sold since the 1930s. • Carcinogenicity: There was no evidence that orally administered silica induced tumors in rats and mice fed amorphous silica for approximately two years..	• There is no evidence that silicon that occurs naturally in food and water produces adverse health effects.apart from scattered reports of urolithiasis. • There are no adequate data demonstrating a no-observed-adverse-effect level (NOAEL) for silicon • Due to lack of data indicating adverse effects of silicon, it is not possible to establish a UL.
Dietary Carbohydrates	Adverse effects high CHO diet considered in development of AMDR	
Sugars	• **Behavior*:*** Hypothesis that sugar intake is related to hyperactivity not supported by a meta-analysis of 23 studies conducted over a 12-year period which concluded that sugar intake does not affect either behavior or cognitive performance in children. • **Dental Caries*:*** Dental caries is significantly associated with sugar consumption in all age groups, however, there is not a simple cause and effect relationship because of multifactorial causation of caries. Therefore, it is not possible to determine an intake level of sugar at which increased risk of dental caries can occur. • **Triacylglycerol, LDL-, and HDL- Cholesterol Concentrations:** Reviewed studies relating increasing sugars intake to increasing concentrations of TAG, LDL and decreasing concentration of HDL-C. Came to no over-all conclusions • **Coronary Heart Disease:** Four epidemiological studies have shown no risk of coronary heart disease (CHD) from consuming naturally occurring or added sugars. • **Insulin Sensitivity and Type 2 Diabetes**: Two	• Review of available data on dental caries, behavior, cancer, risk of obesity and risk of hyperlipidemia, the evidence was insufficient to establish UL for total or added sugars. AMDR set instead.

Nutrient	Rationale for not setting Upper Level	
	Evidence reviewed	**Conclusions**
	prospective cohort studies showed no risk of diabetes from consuming increased amounts of sugar and a negative association was observed between increased sucrose intake and risk of diabetes. Intervention studies that have evaluated the effect of sugar intakes on insulin concentration and insulin resistance gave mixed results. • **Obesity**: Effects of total sugars on energy intakes mixed. Intakes of added sugars most often associated with increased energy intake. Reports disagree on whether there is a direct link between a trend to higher intakes of sugars and increased rates of obesity. Results are confounded by under-reporting of intakes of high sugar foods. • Physical Activity: The studies of the effects of carbohydrates on physical activity had conflicting results. • Lung Cancer: One case control study reported that foods rich in sugar, total sugars intake, sugars/dietary fibre ratio and glycemic index associated with increased risk of lung cancer. • Breast Cancer: Evidence was insufficient to determine role of sugars. Insulin resistance and insulin growth factor may play a role. • Prostate Cancer: Fructose from fruit and non-fruit sources reduces risk but evidence to suggest role in prostate cancer lacking. • Colorectal Cancer: Five case control studies showed increased colorectal polyps and cancer risk with increasing intakes of sugars. High consumption of fruits and vegetables and avoidance of foods containing highly refined sugars associated with decreased risk. Positive association of high sugars consumption and colorectal cancer related to dietary patterns generally associated with increased cancer risk and not biological effect of sugars.	
Starches		
Total Fiber		
Dietary Fiber	• Mineral Bioavailability: Most studies on calcium absorption showed no effect of dietary fiber. 16 g of purified cellulose, a functional fiber, increased Ca excretion by 200 mg. Magnesium absorption was unaffected by dietary fiber. Absorption of zinc and iron is adversely affected by both the phytate contained in fibre and by fibre itself. • Gastrointestinal Distress • Limited studies show high chronic intakes of fibre result in GI distress with flatulence and excessive fullness as symptoms.	• Composition of dietary fibers is variable so difficult to link specific fiber with specific adverse effect. High intake of dietary fiber will not produce deleterious effects in healthy people.

Nutrient	Rationale for not setting Upper Level	
	Evidence reviewed	**Conclusions**
Functional Fiber	• Due to bulky nature of fibers, excess consumption is likely to be self-limiting.	
Total Fat		Lack of defined level of intake at which an adverse effect such as obesity can occur. AMDR set instead.
Saturated Fatty Acids	• Elevated LDL-Cholesterol Concentration and Risk of CHD: Hundreds of studies have shown that total and LDL cholesterol increase as intake of SFA increases. Positive linear relationship between serum total and LDL cholesterol and risk of CHD or mortality from CHD. Majority but not all epidemiological studies show positive relationship between SFA intake and CHD risk and CHD mortality. Mixed results may be due to differences in the effects on individual SFAs on serum cholesterol with stearate having neutral effect. • Mortality: Increased risk of non-CHD mortality especially cancer at low serum cholesterol concentrations suggesting a U or J shaped risk curve has been attributed to confounders. • Obesity: Studies linking SFA intake and BMI had mixed results. • Impaired Glucose Tolerance and Risk of Diabetes: Several large epidemiological studies showed increased risk of diabetes with increasing SFA intakes. One study concluded that diets high in SFA independent predictor for both fasting and postprandial insulin. Short term intervention studies suggest lack of adverse effect on risk indicators for diabetes. Several studies showed no effect on postprandial glucose and insulin concentration or sensitivity. One study found a high intake of SFA impaired insulin sensitivity.	• No threshold could be determined below which SFA did not increase serum cholesterol levels so no UL could be established. Any incremental increase in saturated fatty acid intake increases CHD risk. • "Impractical to make recommendations for SFA on basis of individual fatty acids." • Neither possible nor advisable to achieve 0% energy from SFA in typical whole food diets. Consume diet low in SFA (chapter on AMDRs)
MUFA	• Cardiovascular Disease: Within the usual range of intakes of n-9 MUFAs, there are no clearly established adverse effects. Evidence in non-human primates that a diet rich in n-9 promotes atherosclerosis as much as diets containing isocaloric amounts of SFA or PUFA. Overconsumption of energy on high n-9 diet and high fat diet may increase intakes of SFA because occur together in animal fats. n-7 MUFA palmitoleic acid acts like SFA to increase LDL-C concentrations. • Cancer: Most epidemiological studies show MUFA are not associated with increased risk of cancer. A few studies have shown a positive association between MUFA and breast cancer, colorectal cancer, advanced prostate cancer and lung cancer.	• Lack of adequate data to set UL.
n-6 PUFA	• Nil. Adverse effects reviewed in AMDR chapter.	• Lack of a defined intake level at which an adverse effect can occur. AMDR set instead.

Nutrient	Rationale for not setting Upper Level	
	Evidence reviewed	**Conclusions**
n-3 PUFA	• Immune Function: Suppression of various measures of human immune function in vitro and ex vivo occurred in individuals supplemented with fish oils compared to baseline. The levels of EPA and DHA were 7-15 times greater than typical US intakes. Concluded that EPA and DHA at these levels decreased the potential of the immune system to attack pathogens. These levels also decreased the inflammatory response, a potential beneficial effect in autoimmune diseases. Studies using comparisons across treatment groups on the other hand did not show adverse effects of EPA and DHA. These studies support a lack of long term adverse effects of fish oil supplementation on cytokine activity. Reasons for difference in results within individuals and across treatment groups not known. Animal model not available for further study. Conclude that there are insufficient data to establish UL for EPA and DHA based on infectious responsiveness. • Bleeding and Increased Risk of Hemorrhagic Stroke: The results of studies on effects of EPA and DHA on bleeding times have been mixed. There was no dose response for the effect of EPA and DHA on per cent increase in bleeding time. • Oxidative Damage: Studies in experimental animals showed increased lipid peroxidation and oxidative damage to erythrocytes, liver and kidney membranes and bone marrow DNA with consumption of DHA. These AEs could be decreased or prevented with co-consumption of vitamin E.	• Evidence suggests high intakes of EPA and DHA may impair immune responses and result in excessively prolonged bleeding times, however, cannot establish a UL. • Studies of immune function carried out in vitro and cannot extrapolate to in vivo response. • Data on effect of EPA and DHA on bleeding times are mixed and a dose response effect was not observed. • EPA and DHA supplements should be taken with caution until more information is available. • Special Considerations: The following groups were singled out for particular caution about supplements: - individuals with glucose intolerance or diabetic conditions which require increased doses of hypoglycemic agents; - individuals with familial hypercholesterolemia suffering from increased nosebleeds; - individuals on anticoagulant therapy with already prolonged bleeding times.
trans-Fatty Acids	• Total and LDL Cholesterol Concentrations: Dose dependant relationship between TFA intake and LDL:HDL ratio. Magnitude of the effect is greater for TFA than SFA. • HDL Cholesterol Concentrations: Data on effect of TFA on HDL-C less consistent than on LDL-C but preponderance of data show TFAs lower HDL-C relative to SFAs. • Lp(a) Concentrations: Increases in Lp(a) associated with TFA intakes would not be predicted to have a physiologically significant effect on CVD risk. • Hemostatic Factors; No effect of TFA compared with SFA. • Susceptibility of LDL-C to Oxidation: Little to no effect observed. • Blood Pressure: No effect • Coronary Heart Disease: Positive linear trend between TFA and LDL-C coupled with evidence that TFA produce lower HDL-C resulting in a higher TC or LDL-C:HDL-C ratio results in concern that TFA more deleterious with respect to	• Positive linear trend between TFA intake and LDL-C and therefore increased risk of CHD. UL not set for TFA because any incremental increase in *trans* fatty acid intake increases CHD risk.

Nutrient	Rationale for not setting Upper Level	
	Evidence reviewed	**Conclusions**
	CHD than SFA.	
Cholesterol	• Effects of dietary cholesterol on total and lipoprotein cholesterol concentrations: Large numbers of studies on the effects of increasing intakes of dietary cholesterol on total serum cholesterol concentration show a linear relationship. Other studies show a curvilinear univariate relationship quasi-linear in the range of 0 to 300-400 mg/d added dietary cholesterol. As baseline dietary cholesterol increases, there is a decrease in the response to increments of dietary cholesterol above baseline. Dietary cholesterol has been shown to increase total cholesterol:HDL cholesterol ratio. Predictive formulas been developed that indicate that 100 mg added dietary cholesterol results in an increase of 0.05 mmol/L LDL-C and 0.01 mmol/L HDL-C. Considerable evidence of interindividual variation in serum cholesterol response which can range from 0 to 100% in response to dietary cholesterol. May be related to differences in cholesterol absorption, suppression of hepatic synthesis and LDL catabolism. Increasing evidence that these differences which are stable within an individual have a genetic basis. This is supported by studies in animal models. • Cardiovascular Disease and Coronary Heart Disease: Prospective epidemiological studies have shown an association between dietary cholesterol and risk of CHD morbidity and mortality (7 Countries, Honolulu Heart Program, Western Electric, UK Health Conscious) however number of other epidemiological studies have not demonstrated a significant independent relationship of cholesterol intake to risk of MI and fatal CHD (Health Professionals, Nurses). Uncertainties: Lack of consistency relating dietary cholesterol to CVD and CHD endpoints may be due to limited ability to detect effects of a small increase in LDL-C due to inaccuracy in dietary data, difficulty distinguishing effect of dietary cholesterol independent of energy and other substances which affect serum cholesterol and CHD risk, effect of increase in HDL-C and effects of interindividual variation in response. • Cancer: No consistent significant association established between dietary cholesterol intake and cancer including lung, breast, colon and prostate. Several case control studies suggest high consumption of cholesterol increased risk of lung cancer. A positive association was found in one case control study but not in two others.	• The main adverse effect of dietary cholesterol is to increase serum LDL-C which would be predicted to increase risk of CHD. Effect of the lesser increase in serum HDL-C uncertain. Increase of 100 mg dietary cholesterol leads to 0.05 mmol – 0.1mmol/L increase in total cholesterol of which 80% is LDL-C. Although the effect of dietary cholesterol is highly variable among individuals and attenuated at higher baseline intakes, the increase in LDL-C concentration would predict approximately a 1-2% increase in CHD. • Epidemiological studies have limited power to detect effects of this magnitude and do not provide meaningful basis for establishing adverse effects of dietary cholesterol. • Cannot establish a LOAEL because no studies have examined the effects of very small increments of dietary cholesterol in numbers of subjects sufficiently large for statistical treatment of data. • Not appropriate to set UL for dietary cholesterol because increased risk may occur at a very low intake level and at a level that is exceeded by usual diets.
Protein & Amino Acid	• Historical experience of explorers and others on high meat diets suggests that the presence of fat	• Data on potential of high protein diets to produce AEs conflicting.

Nutrient	Rationale for not setting Upper Level	
	Evidence reviewed	**Conclusions**
	high meat diets suggests that the presence of fat reduces the protein content to less than 50% of energy. Eating lean meat for prolonged period resulted in death ("rabbit starvation") • N Balance studies: No negative balances have been reported on high protein intakes. • Maximum Urea Synthesis: Determined to be 65 mg urea N/hr/kgBW$^{0.75}$. At higher intakes of protein the rate did not increase but continued longer. In 70 kg adult, this amounts to 250 g protein and about 45% of energy. In line with historical experience but study did not allow a period of adaptation as seen in experimental animals. • Chronic Disease: High protein intakes have been associated with osteoporosis, renal stones, renal insufficiency, cancer, CHD and obesity. Evidence does not permit the setting of a UL based on chronic disease risk.	AEs conflicting. • Data do not provide dose-response information or clear indication of LOAEL or NOAEL. • Insufficient data to establish a UL. • Caution warranted with high protein supplements. • Individuals with idiopathic hypercalcuria should not consume more than RDA of protein (although stated that no evidence that a decreased intake of protein will reduce kidney stones).
Water	• Hyponatremia: Water intoxication results in a decrease in extracellular fluid (ECF) sodium concentration which causes fluid to move to the intracellular fluid (ICF) space leading to CNS edema, lung congestion, muscle weakness and ultimately death. Most often observed in infants, seen also in psychiatric patients with polydipsia, patients on psychotropic drugs, individuals participating in prolonged athletic events(>6 hrs) and military recruits. Exacerbated by impaired renal water excretion. Persons with certain mutations of the cystic fibrosis transmembrane regulatory gene are susceptible to hyponatremia. • Bladder Lesions: Excess consumption (e.g. >20 L/day) results in irreversible bladder lesions. Possible association with thinner bladder muscles, delayed bladder sensation and flow rate impairment.	• No data on habitual consumption of elevated water intakes resulting in identifiable hazards in healthy people. • UL not set due to significant ability to self-regulate excessive water consumption by healthy people in temperate climates.
Potassium	• Gastrointestinal Discomfort: Confined to certain forms of K supplements. Reports of ulceration of GI tract and perforation of small bowel with KCl supplements. No reports of AEs due to K in food. • Arrhythmias from hyperkalemia: Hyperkalemia leads to conduction abnormalities on ECG then cardiac arrhythmias which can be life-threatening. Arrhythmias can result from either high plasma K concentrations or rapid and extreme changes in plasma K concentrations. Uncertainty about level at which arrhythmias occur but likely at concentrations >5.5 mmol/L. • Acute toxicity of limited value in assessing potential hazards of chronic ingestion of high K levels. Healthy individuals tolerated K supplements up to 15.6 g/day (400 mmol) over 5 days. Maximum	• In otherwise healthy individuals without impaired urinary K excretion from medical condition or drug therapy, no evidence that a high intake of K from foods has adverse effects, therefore a UL is not set. • Supplemental potassium can lead to acute toxicity in healthy individuals and chronic consumption of high levels of K can lead to hyperkalemia in individuals with impaired urinary K excretion. Supplemental K should only be provided under medical supervision. • Infants and children: since the renal secretory ability of normal infants is not full developed, K intake should be limited to that contained in formula and complementary foods. • Special considerations: - Problem Pregnancy: High concentrations of antikaliuretic hormone progesterone may make

Nutrient	Rationale for not setting Upper Level	
	Evidence reviewed	**Conclusions**
	excretory rate after adaptation estimated at 31.3 g/day (800 mmol) for adults. • Life-threatening hyperkalemia reported in individuals with impaired urinary K excretion due to either drug therapy or medical condition. These patients at risk for both hypo-and hyper-kalemia.	woman with undetected renal dysfunction or with sudden decrease in GFR more likely to develop hyperkalemia when K intake is high. - Other Situations: Clinical settings – type 1 diabetes, chronic renal insufficiency, sever heart failure and adrenal insufficiency. Medical supervision typically provided and K intake below the AI often appropriate.
Sulfate	• Diarrhea -- Adults: Sulfate levels in water of 1200 mg/L did not cause diarrhea in two studies. Single dose of 8 g sodium sulfate caused severe diarrhea but when divided into 4 hourly doses, there was no effect. • Diarrhea -- Infants: study of infants exposed to sulfate in well water showed no difference in sulfate intakes between those with and those without diarrhea. Small case history study suggests that sulfate concentrations in water of >600 mg/L may cause diarrhea. Study of neonatal piglets showed diarrhea appeared at sulfate concentration in the water of >1200 mg/L, 50% of piglets had diarrhea at 1600-1800 mg/L and 100% at 2000-2200 mg/L. • Acidosis: Metabolic acidosis resulted from consumption of flowers of sulfur (elemental sulfur). No reports of acidosis with consumption of chondroitan sulfate supplements. • Ulcerative Colitis: Sulfate and undigested sulfur compounds in colon implicated in etiology of ulcerative colitis through production of hydrogen sulfide by action of sulfate-reducing bacteria. Excess luminal sulfide thought to overburden mucosal detoxification systems leading to impaired butyrate oxidation and epithelial inflammation. Fecal sulfide levels are elevated in patients with ulcerative colitis. Drug therapy is aimed at reducing hydrogen sulfide production. In a rat model of ulcerative colitis, exacerbation of the colitis by dietary iron supplementation was ameliorated by vitamin E. Since there was no effect on measures of oxidative stress, the vitamin E may be acting by another mechanism to reduce inflammation.	• Not possible to identify a UL for adults based on either diarrhea or possible role in ulcerative colitis. • Data are inadequate to set a UL for infants based on diarrhea but based on data in neonatal piglets levels of sulfate intake >1500 mg/day may cause some degree of diarrhea. • Special Considerations - Renal Failure: Hypersulfatemia of chronic renal failure results in complexing with calcium which may in part explain parathyroid stimulation and may directly effect trans-sulfuration pathway and contribute to severity of homocysteinemia. - Hyperthyroidism increases basal metabolic rate and protein catabolism leading to increased serum sulfate levels.

TABLE 4a Rationale for Not Setting Upper Level (abbreviated version, Table 4)

Nutrient	Reference Value Upper Level	Rationale for Not Setting Upper Level
Calcium	UL	
Phosphorus	UL	
Magnesium	UL	
Vitamin D	UL	
Fluoride	UL	
Thiamin	-	No evidence of adverse effects from consumption of excess thiamin from food and supplements.
Riboflavin	-	No evidence of adverse effects from consumption of excess riboflavin from food and supplements.
Niacin	UL	
Vitamin B6	UL	
Folate	UL	
Vitamin B12	-	No evidence of adverse effects from consumption of excess B12 from food and supplements.
Pantothenic Acid	-	No evidence of adverse effects of oral pantothenic acid in humans or animals.
Biotin	-	No evidence of adverse effects of biotin in humans or animals.
Choline	UL	
Vitamin C	UL	
Vitamin E	UL	
Selenium	UL	
β-Carotene & other Carotenoids	-	Increased risk of lung cancer from β-carotene supplements could not be used to establish UL due to conflicting data and lack of dose response data. Carotenodermia considered harmless.
Vitamin A	UL	
Vitamin K	-	No evidence of adverse effects of vitamin K from food or supplements in humans or animals.

Nutrient	Reference Value Upper Level	Rationale for Not Setting Upper Level
Chromium	-	Insufficient data to establish a UL for soluble chromium III salts. No adverse effects have been convincingly associated with excess intake of chromium from food or supplements but this does not mean that there is no potential for adverse effects at high intakes.
Copper	UL	
Iodine	UL	
Iron	UL	
Manganese	UL	
Molybdenum	UL	
Zinc	UL	
Arsenic	-	No evidence linking organic arsenic in food to any adverse effect. Not possible to establish a health-based level of inorganic arsenic in food and drinking water because of lack of evidence to define the mechanisms of arsenic carcinogenesis and no data to support a threshold.
Boron	UL	
Nickel	UL	
Silicon	-	No evidence that silicon occurring naturally in food and water produces adverse health effects.
Vanadium	UL	
Dietary Carbohydrates	-	Adverse effects high CHO diet considered in development of AMDR
Sugars	-	Review of available data on dental caries, behavior, cancer, risk of obesity and risk of hyperlipidemia, the evidence was insufficient to establish UL for total or added sugars. AMDR set instead.
Starches		
Total Fiber	-	
Dietary Fiber	-	Composition of dietary fibers is variable so difficult to link specific fiber with specific adverse effect. High intake of dietary fiber will not produce deleterious effects in healthy people.
Functional Fiber	-	Due to bulky nature of fibers, excess consumption is likely to be self-limiting.

Nutrient	Reference Value Upper Level	Rationale for Not Setting Upper Level
Total Fat		Lack of defined level of intake at which an adverse effect such as obesity can occur. AMDR set instead.
Saturated Fatty Acids	-	No threshold could be determined. Any incremental increase in saturated fatty acid intake increases CHD risk.
MUFA	-	Lack of adequate data.
n-6 PUFA	-	Lack of a defined intake level at which an adverse effect can occur. AMDR set instead.
n-3 PUFA	-	Lack of adequate data on adverse effects to set UL but EPA/DHA supplements should be used with caution.
trans-Fatty Acids	-	No threshold could be determined. Any incremental increase in *trans* fatty acid intake increases CHD risk.
Cholesterol	-	Cannot set UL because increased risk may occur at a very low intake level and at a level that is exceeded by usual diets.
Protein & Amino Acids	-	Data on adverse effects of protein often conflicting and lack dose-response information and indications of LOAEL and NOAEL.
Water	-	No data on habitual consumption of elevated water intakes resulting in identifiable hazards in healthy people. UL not set due to significant ability to self-regulate excessive water consumption by healthy people in temperate climates.
Potassium	-	In healthy individuals no evidence that a high intake from foods has adverse effects. Supplemental potassium should only be used under medical supervision because of potential for toxicity.
Sodium	UL	
Chloride	UL	
Sulfate	-	Not possible to identify a UL based on either of the two adverse effects identified.

TABLE 5 EAR/AI Nutrient/Nutrient Interactions

Nutrient	Reference Value	Interaction reviewed?	Effect on ref value?	Nutrients
Calcium	AI	Yes	No	Sodium: increases calcium excretion; Protein: increases calcium excretion
Phosphorus	EAR	Yes	No	Calcium (Ca:P ratio)
Magnesium	EAR	Yes	No	Phosphorus (phytate) effect on absorption Calcium: effect on retention not significant; Protein: effect on Mg retention needs additional study
Vitamin D	AI	No	No	None mentioned
Fluoride	AI	Yes	No	Calcium-rich foods: decrease F absorption
Thiamin	EAR	No	No	None mentioned
Riboflavin	EAR	Yes	No	Proportions fat and CHO in diet - ↓fat ↑CHO ↓ riboflavin req't; niacin (requires FAD); vit B_6 (requires FMN)
Niacin	EAR	Yes	No	Riboflavin, vit B6 (FMN for formation PLP) req'd for conversion tryptophan to niacin; Tr-niacin pathway req FAD, PLP and Fe
Vitamin B_6	EAR	Yes	No	Protein – as intake ↑, B_6 req't ↑; "no compelling evidence to adjust B_6 req'ts based on protein intakes"
Folate	EAR	Yes	No	No other nutrients increase or decrease folate req'ts. Coexisting Fe or B12 deficiency may interfere with diagnosis anemia due to folate deficiency
Vitamin B_{12}	EAR	Yes	No	Folate –may "mitigate effects of B12 deficiency on red cell formation, does not affect req't for B12. Vit C – low B12 levels artifact due to effects of C on B12 assay
Pantothenic Acid	AI	Yes	No	One study suggests that thiamin and riboflavin may affect pantothenic acid metabolism and excretion
Biotin	AI	No	No	None mentioned
Choline	AI	Yes	No	Methyl donors – methionine, folate act with Choline in conversion homocysteine to Me. Deficiency of Choline or folate leads to depletion of other.

Nutrient	Reference Value	Interaction reviewed?	Effect on ref value?	Nutrients
Vitamin C	EAR	No	No	Glutathione – vit C acts to maintain reduced glutathione levels; Tocopherol: vit C can regenerate or spare α-tocopherol in experimental animals and in vitro ; Iron: vit C reduction of iron to ferrous state in iron transfer and storage, effect on bioavailability; Copper: excess vit C reported to inhibit intestinal absorption and ceruloplasmin oxidase activity and labilization o f ceruloplasmin-bound copper for transport. Significance in humans questionable
Vitamin E	EAR	Yes	No because amt req'd for mean PUFA intake already met	Vit C , glutathione, ubiquinols can regenerate α-tocopherol (extent of recycling in vivo in humans unknown); ↑PUFA reported to increase vit E req'ts; conclude high PUFA intakes should be accompanied by high vit E intakes.
Selenium	EAR	No	No	None mentioned
B-Carotene & other Carotenoids	-----			
Vitamin A	EAR	Yes		Iron: vit A deficiency impairs iron mobilization form stores. Zinc req'd for hepatic synthesis and secretion of retinol binding protein so deficiency can affect mobilization vit A from liver
Vitamin K	AI	Yes	No	Vit E: elevated intakes antagonize vit K action by inhibiting microsomal vit K-dependent carboxylase and affecting phylloquinone absorption. No reports in healthy humans but supplementation of anticoagulated patients with vit E resulted in nonsignificant decreases in prothrombin concentrations; Carotenoids: competitive interactions affecting absorption of different Carotenoids. Alcohol: ethanol consumption depletes hepatic vit A in exptl animals and humans
Chromium	AI	Yes	No	Vit C enhances absorption of $CrCl_3$; Diet high in simple sugars (35% en) increased urinary Cr excretion. Phytate at high levels decreased absorption in rats.
Copper	EAR	Yes	No	Zinc: high intakes (in excess of diet) can decrease Cu absorption; Iron: high intakes may interfere with Cu absorption in infants; Fructose: high levels increased severity of Cu deficiency in rats but not in pigs. Fructose at 20% en resulted in inconsistent effects in humans but did not result in Cu depletion.

Nutrient	Reference Value	Interaction reviewed?	Effect on ref value?	Nutrients
Iodine	EAR	No	No	None mentioned
Iron	EAR	Yes	Yes	Ascorbic acid, other organic acids (citric, malic and lactic acids), meat, fish, poultry enhance nonheme iron absorption; Phytate, polyphenols, vegetable proteins inhibit absorption of nonheme iron; calcium inhibits absorption of both heme and nonheme iron.
Manganese	AI	No	No	Phytate affects Mn absorption; high ferritin concentrations associated with reduced Mn absorption.
Molybdenum	EAR	Yes	No	Mb:Tungsten ratio: Tungsten used as an antagonist of Mb absorption to produce Mb deficiency in experimental animals. Not relevant to human nutrition. Mb:Cu and Sulfate ratios: excess Mb produces Cu deficiency in ruminants.
Zinc	EAR	Yes	Yes	Iron: high levels of supplemental iron decrease zinc absorption; Calcium and phosphorus: excess Ca reduces zinc absorption in swine and produces parakeratosis. Studies in humans equivocal with calcium phosphate decreasing Zn absorption while calcium citrate malate did not. Conclude calcium-rich diet should not have major effect on Zn absorption when Zn intake is adequate. Phytate and phosphorus-rich proteins tightly bind Zn and decrease its absorption. Copper: Zn induces intestinal metallothionen which binds Cu.
Arsenic	----			
Boron	----			
Nickel	---			
Silicon	---			
Vanadium	---			
Dietary Carbohydrates	EAR	NO	No	
Sugars	---			
Starches	---			

Nutrient	Reference Value	Interaction reviewed?	Effect on ref value?	Nutrients
Total Fiber	AI	No	No	None mentioned
Dietary Fiber	---			
Functional Fiber	---			
Total Fat	---			
n-3 PUFA	AI	No	No	None mentioned
n-6 PUFA	AI	No	No	None mentioned
Saturated Fatty Acids	---			
Trans-Fatty Acids	----			
MUFA	---			
Cholesterol	----			
Protein & Amino Acids	EAR	No	No	None mentioned
Water	AI	No	No	None mentioned
Potassium	AI	Yes	No	Sodium: effects of K depend on intake of Na. K reduces effect of Na on BP, increased intact of K bicarbonate mitigates salt sensitivity and lowers urinary Ca excretion. Effect of K on BP greater at higher levels of Na intake than at lower; relationship of kidney stones to Na:K ratio direct and highly significant; hypocalciuric effect of K bicarbonate diminished by dietary NaCl.
Sodium	AI	Yes	No	Potassium: K salts increase urinary Na excretion ; Calcium: high intakes of sodium increase urinary Ca excretion
Chloride	AI	Yes	Yes	AI equimolar with sodium
Sulfate	----			

TABLE 6 Tolerable Upper Intake Level: Uncertainty Factors

Nutrient	Age group	UF	NOAEL LOAEL	Critical Adverse Effect	UF Rationale
Calcium	Adults 19-70 y Adult UL applied to children 1-18 y and adults 71 y+	2	LOAEL	Hypercalcemia and renal insufficiency (milk-alkali syndrome)	• 12 percent of the American population is estimated to have renal stones. • Hypercalciuria has been shown to occur with intakes as low as 1,700 mg (42.5 mmol)/day in male and 870 mg (21.7 mmol)/day in female patients with renal stones. • Concern for the potential increased risk of mineral depletion in vulnerable populations due to the interference of calcium on mineral bioavailability, especially iron and zinc. (p.140)
Phosphorus	Children 1-8 y	3.3	NOAEL	Hyperphosphatemia	• Potentially increased susceptibility due to smaller body size. (p.187)
	Adults 19-70 y Adult UL applied to children 9-18 y	2.5	NOAEL	Hyperphosphatemia	• No benefit is evident from serum P_i values above the usual normal range in adults. • Lack of information on potential adverse effects in the zone between normal P_i levels and levels associated with ectopic mineralization. • UF in keeping with the pharmacokinetic practice where the relationship between intake and blood level is known. (p.187)
	Adults 71 y +	3.3	NOAEL	Hyperphosphatemia	• UF increased because of increasing prevalence of impaired renal function after age 70. (p.188)
Magnesium * UL applies to supplemental magnesium	Children 9–18 y; Adults 19 y + UL extrapolated to children 1-8 y	~1	LOAEL	Diarrhea	• Very mild, reversible nature of osmotic diarrhea caused by ingestion of magnesium salts. • Osmotic diarrhea is quite apparent to the individual and thus is not a symptom that is masked until serious consequences result. (p.245)
Vitamin D Vitamin D	Infants 0-12 mo.	1.8	NOAEL	Retarded linear growth	• The insensitivity of the endpoint. • Small sample sizes. • Little data about sensitivity at the tails of the distributions. (p.284)

Nutrient	Age group	UF	NOAEL LOAEL	Critical Adverse Effect	UF Rationale
	Adults 19 y + Adult UL applied to children 1-18 y	1.2	NOAEL	Hypercalcemia	• NOAEL based only on one study with small sample size and of short duration. • Uncertainty whether any increase in serum calcium, even though still within normal limits, might be adverse for sensitive individuals. • UF of 1.2 was judged to be sufficiently conservative to account for the uncertainties in this data set. • Larger UF judged unnecessary due to the "availability of human data and a reasonably well-defined NOAEL in a healthy population". (p.282)
Fluoride	Infants and children 0-8 y	1	LOAEL	Moderate enamel fluorosis	• Relationship between fluoride intake and enamel fluorosis is based on human studies. • Enamel fluorosis cosmetic rather than functional effect. (p.309)
	Children 9–18 y; Adults 19 y +	1	NOAEL	Skeletal fluorosis	• NOAEL derived from human studies. • Lack of evidence for symptomatic skeletal fluorosis observed at level of NOAEL. (p.310)
Thiamin	N/A				
Riboflavin	N/A				
Niacin * UL applies to synthetic forms only	Adults 19 y + UL extrapolated to children 1-18 y	1.5	LOAEL	Vasodilation (flushing; can involve burning, tingling, and itching sensation, as well as reddened skin; occasionally accompanied by pain)	• Transient nature of the flushing effect • Use of LOAEL rather than NOAEL. (p.143)
Vitamin B6	Adults 19 y + UL extrapolated to children 1-18 y	2	NOAEL	Sensory neuropathy	• Limitations of the data involving pyridoxine doses of less than 500mg/day. (p.186)
Folate	Adults 19 y +	5	LOAEL	Precipitation or	• Severity of the neurological complications observed.

Nutrient	Age group	UF	NOAEL LOAEL	Critical Adverse Effect	UF Rationale
				exacerbation of neuropathy in vitamin B_{12} deficient-individuals	• Use of a LOAEL rather than a NOAEL to derive UL. • The UF is not larger than 5 on the basis of the uncontrolled observation that millions of people have been exposed to self-treatment with about one-tenth of the LOAEL without reported harm. (p.279-280)
* UL applies to synthetic forms only	UL extrapolated to children 1-18 y				
Vitamin B12	N/A				
Pantothenic Acid	N/A				
Biotin	N/A				
Choline	Adults 19 y +	2	LOAEL	Hypotension; fishy body odor as 2nd consideration	• Limited data regarding hypotension. • The interindividual variation in response to cholingergic effects. (p.410)
	UL extrapolated to children 1-18 y				
Vitamin C	Adults 19 y +	1.5	LOAEL	Osmotic diarrhea and related gastrointestinal disturbances	• Little uncertainty regarding the range of vitamin C intakes likely to induce osmotic diarrhea. • Extrapolation from a LOAEL to a NOAEL. • The database has no other significant sources of uncertainty. • Mild, reversible nature of osmotic diarrhea. (p.162)
	UL extrapolated to children 1-18 y				
Vitamin E	Adults 19 y +	36	LOAEL	Increased tendency to haemorrhage (Based on hemorrhagic toxicity in rats)	• Extrapolation from a LOAEL to a NOAEL (UF=2). • Severity of hemorrhagic effects justifies UF greater than 1. • Extrapolation from subchronic to chronic intake (UF=2). • Extrapolation from experimental animals to humans (UF=3). • Data showing some similarities between animal and human responses. • Interindividual variation in sensitivity (UF=3) • Based on pharmacokinetic data showing plasma saturation of α-tocopherol concentrations with increasingly higher intakes in humans. • Various UFs combined = 2 x 2 x 3 x 3 = 36 (p.256-257)
* UL applies to synthetic vit. E (any form)	UL extrapolated to children 1-18 y				

Nutrient	Age group	UF	NOAEL LOAEL	Critical Adverse Effect	UF Rationale
Selenium	Infants 0–6 mo.	1	NOAEL	Chronic selenosis	• No evidence that maternal intake associated with a human milk level of 60 micrograms/L results in infant or maternal toxicity. • Infant UL and adult UL are similar on a body-weight basis. • No evidence indicating increased sensitivity to selenium toxicity for any age group. (p.316)
	UL extrapolated to infants 7-12 mo. and children 1-18 y				
	Adults 19 y +	2	NOAEL	Chronic selenosis (Hair and nail brittleness and loss)	• Toxic effect is not severe, but may not be readily reversible. (p.315)
B-Carotene & other Carotenoids	N/A				
Vitamin A * UL applies to preformed vit. A	Infants 0–12 mo.	10	LOAEL	Hypervitaminosis A	• Uncertainty in extrapolating a LOAEL to a NOAEL for a nonsevere and reversible effect (i.e., bulging fontanel). • Inter-individual variability in sensitivity. (p.144)
	Females 19-50 y (including pregnant and lactating)	1.5	NOAEL	Teratogenicity	• Inter-individual variability in susceptibility. • A higher UF was not justified because of substantial data showing no adverse effects at doses up to 3000 micrograms/day of vitamin A supplements. (p.139)
	UL extrapolated to females 14-18 y				
	Adults 19 y +, other than women of childbearing age	5	LOAEL	Liver abnormalities	• The severe, irreversible nature of the adverse effect. • Extrapolation from a LOAEL to a NOAEL. • Inter-individual variation in sensitivity. • In addition: "This UL is the same as that set for women of reproductive age, given that the UL is defined as the highest level of daily nutrient intake likely to pose no risk of adverse health effects to almost all of the general population." (p.143)
	UL extrapolated to children 1-18 y				
Vitamin K	N/A				
Chromium	N/A				

Nutrient	Age group	UF	NOAEL LOAEL	Critical Adverse Effect	UF Rationale
Copper	Adults 19 y + UL extrapolated to children 1-18 y	1	NOAEL	Liver damage	• The NOAEL of 10 mg/day was considered to be protective of the general population. •A larger UF was considered unnecessary in view of: • The large international database in humans indicating no adverse effects from daily consumption of 10 to 12 mg/day of copper in foods. • The rarity of observed liver damage from copper exposures in human populations with normal copper homeostasis. (p.249)
Iodine	Adults 19 y + UL extrapolated to children 1-18 y	1.5	LOAEL	Thyroid dysfunction shown by elevated TSH concentrations	• Little uncertainty regarding the range of iodine intakes that are likely to induce elevated TSH concentration over baseline. • Extrapolation from a LOAEL to a NOAEL. • The mild, reversible nature of elevated TSH over baseline. (p.281)
Iron	Infants 0–12 mo; children 1-3 y UL applied to children 4-13 y	1	NOAEL	Gastrointestinal distress	• Little uncertainty regarding the range of intakes that is likely to induce GI effects in infants and young children. (p.376)
	Adults 19 y + UL applied to children 14-18 y	1.5	LOAEL	Gastrointestinal distress	• Extrapolation from a LOAEL to a NOAEL. • The self-limiting nature of the observed GI effects. (p.374)
Manganese	Adults 19 y + UL extrapolated to children 1-18 y	1	NOAEL	Elevated blood manganese concentrations and neurotoxicity	• Lack of evidence of human toxicity from doses less than the NOAEL from food. (p.412)
Molybdenum	Adults 19 y + UL extrapolated to children 1-18 y	30	NOAEL	Impaired reproduction and growth (in animal studies)	• Extrapolation from experimental animals to humans (UF=10). • Intraspecies variation (UF=3); based on the expected similarity in pharmokinetics of molybdenum among humans.

Nutrient	Age group	UF	NOAEL LOAEL	Critical Adverse Effect	UF Rationale
					• Various UFs combined = 10 x 3 = 30 (p.436)
Zinc	Infants 0–6 mo. UL extrapolated to infants 7-12mo. and children 1-18 y	1	NOAEL	Reduced copper status	• The length of the study and the high number of subjects. (p.487)
	Adults 19 y +	1.5	LOAEL	Reduced copper status	• Inter-individual variability in sensitivity. • Extrapolation from a LOAEL to a NOAEL. • Higher UF not justified because reduced copper status is rare in humans. (p.486)
Arsenic	N/A				
Boron	Adults 19 y + UL extrapolated to children 1-18 y	30	NOAEL	Reproductive and development effects (in animal studies)	• Extrapolation from experimental animals to humans (UF=10). • Intraspecies variability (UF=3); based on the expected similarity in pharmokinetics among humans. • Various UFs combined = 10 x 3 = 30 (p.518)
Nickel	Adults 19 y + UL extrapolated to children 1-18 y	300	NOAEL	General systemic toxicity (i.e., decreased body weight gain in subchronic and chronic rat studies)	• Extrapolation from experimental animals to humans (UF=10). • Incorporates uncertainties about the nature of the dose-response curve for nickel toxicity and uncertainties about the sensitivity of rats as compared with humans in respect to nickel toxicity. • Potential variation in the human population, especially in regard to hypersensitivity reactions (UF=10). • Concerns that nickel may be a reproductive toxin at levels lower than the NOAEL observed (UF=3). • Various UFs combined = 10 x 10 x 3 = 300 (p.526)
Silicon	N/A				
Vanadium	Adults 19 y +	300	LOAEL	Renal toxicity (in subchronic and chronic animal studies)	• Extrapolation from a LOAEL to a NOAEL (UF=3) • Severity of kidney lesions justified a UF higher than 1. • Extrapolation from experimental animals to humans (UF=10).

Nutrient	Age group	UF	NOAEL LOAEL	Critical Adverse Effect	UF Rationale
					• Intraspecies variability (UF=10). • Various UFs combined = 3 x 10 x 10 = 300 (p.540-541)
Digestible Carbohydrates	N/A				
Sugars	N/A				
Total Fiber	N/A				
Total Fat	N/A				
n-3 PUFA	N/A				
n-6 PUFA	N/A				
Saturated Fatty Acids	N/A				
Trans-Fatty Acids	N/A				
MUFA	N/A				
Cholesterol	N/A				
Protein & Amino Acids	N/A				
Water	N/A				
Potassium	N/A				
Sodium	Adults 19–50 y UL applied to children 14-18 y and adults 51 y + UL extrapolated to children 1-13 y	1.0	LOAEL	Elevated blood pressure	• No UF applied for extrapolation from LOAEL to NOAEL despite there being large numbers of persons who would achieve an even lower blood pressure by reducing their sodium intake from the LOAEL to lower levels because: • Choosing a level of sodium intake at which no one would experience a rise in blood pressure would be difficult because there is heterogeneity in both the extent of blood pressure reduction that would be achieved and in the extent of cardiovascular disease risk reduction. • Consuming a diet with sodium intake level at the NOAEL may well result in a diet inadequate in other essential nutrients, particularly for those with lower levels of energy expenditure. •UF of approximately 1.6 or higher would lead to a UL below the AI. (p.380)
Chloride	N/A UL for chloride set on equimolar basis				

Nutrient	Age group	UF	NOAEL LOAEL	Critical Adverse Effect	UF Rationale
	to that for sodium				
Sulfate	N/A				

TABLE 7 DRI Values that have been Extrapolated

Nutrient	Ref Value	Extrapolation Group	Basis Group (extrapolated from)	Method of Extrapolation	Rationale
Calcium	AI	1-3 y	4-8 y	Extrapolation of desirable calcium retention (Using estimate of calcium retention from data in children 4-8 y) (p.99)	Available data indicate net accretion of 100mg/day in ages1-3y; using estimate of 20% net calcium retention in children 4-8y yields AI of 500 mg/day.
Phosphorus	N/A	No values determined solely via extrapolation			
Magnesium	EAR	1-8 y	9-13 y	Based on (old) reference body weight. Balance studies in older children yield an estimated EAR of 5 mg/kg/day; this is multiplied by reference body weight. (p.216)	Absence of adequate data in children 1-8y.
	UL	1-8 y	9-70 y+	Based on (old) reference body weight. UL for adults adjusted on body-weight basis. (p.246)	Assumed that children are as susceptible to adverse effect as adults.
Vitamin D	N/A	No values determined solely via extrapolation			
Fluoride	AI	Infants 7-12 mo 1-71 y+	N/A AI set at 0.05 mg/kg/day for all ages greater than 6 months	Based on (old) reference body weight. (p.302)	This level confers a high level of protection against dental caries and is associated with no known unwanted health effects

Nutrient	Ref Value	Extrapolation Group	Basis Group (extrapolated from)	Method of Extrapolation	Rationale
Thiamin	AI	Infants 7-12 mo	19-50 y	Adjustment for metabolic body weight and growth[1] (p.66)	Maintenance needs for B vitamins and Choline expressed per kg metabolic body weight are the same for adults and children. Using $BW^{0.75}$ adjusts for metabolic differences related to body weight; extra B vitamins and Choline needed for growth comparable to the percentage extra protein needed for growth.
	EAR	1-18 y	19-50 y	Adjustment for metabolic body weight and growth[1] (p.66)	Absence of adequate data in children 1-18y. Maintenance needs for B vitamins per kg metabolic body weight are the same for adults and children.
		Pregnant F	Non-pregnant F	Adjustment for increased maternal needs (approx. 30%) (p.77)	Increased growth in maternal and fetal compartments (~20%) and increase in energy utilization (~10%). No apparent increase in absorption capacity.
Riboflavin	AI	Infants 7-12 mo	0-6 mo AND adults 19-70 y	Metabolic weight ratio[2] (p.105) AND Adjustment for metabolic body weight and growth[1] (p.105)	Both methods yielded similar estimates. Metabolic weight ratio does not adjust for growth because it is based on a value for a growing infant.
	EAR	1–18 y	19-70 y	Adjustment for metabolic body weight and growth[1] (p.106)	Absence of adequate data in children 1-18y. Maintenance needs for B vitamins per kg metabolic body weight are the same for adults and children.

Nutrient	Ref Value	Extrapolation Group	Basis Group (extrapolated from)	Method of Extrapolation	Rationale
Niacin	AI	Infants 7-12 mo	19-70 y+	Adjustment for metabolic body weight and growth[1] (p.131)	Maintenance needs for B vitamins per kg metabolic body weight are the same for adults and children. Seems to be the middle value of three different calculations – extrapolation up from infants, extrapolation down from adults, and niacin in human milk + niacin in solid foods.
	EAR	1-18 y	19-70 y+	Adjustment for metabolic body weight and growth[1] (p.131)	Absence of adequate data in children 1-18y. Maintenance needs for B vitamins per kg metabolic body weight are the same for adults and children.
	UL	1-18 y	19-70 y+	Adjustment for metabolic body weight[3] (p.143)	Adjustment yields a conservative UL to protect sensitive individuals in each age group.
Vitamin B6	AI	Infants 7-12 mo	0-6 mo AND adults 51-70 y+	Metabolic weight ratio[2] (p.167) AND Adjustment for metabolic body weight and growth[1] (p.167)	The mean obtained from the two types of extrapolation was used.
	EAR	1-18 y	19-50 y	Adjustment for metabolic body weight and growth[1] (p.169)	Absence of adequate data in children 1-18y. Maintenance needs for B vitamins per kg metabolic body weight are the same for adults and children.
Vitamin B6	UL	1-18 y	19-70 y+	Adjustment for metabolic body weight[3] (p.186)	Adjustment yields a conservative UL to protect sensitive individuals in each age group.
Folate	AI	Infants 7-12 mo	0-6 mo AND adults 19-70 y+	Metabolic weight ratio[2] (p.215) AND Adjustment for metabolic body weight and growth[1] (p.216)	Both methods yielded similar estimates. Data from research studies supports the calculated AI.

Nutrient	Ref Value	Extrapolation Group	Basis Group (extrapolated from)	Method of Extrapolation	Rationale
	EAR	1-18 y	19-70 y+	Adjustment for metabolic body weight and growth[1] (p.217,220)	Absence of adequate data in children 1-18y. Maintenance needs for B vitamins per kg metabolic body weight are the same for adults and children.
	UL	1-18 y	19-70 y+	Adjustment for metabolic body weight[3] (p.280)	Adjustment yields a conservative UL to protect sensitive individuals in each age group.
Vitamin B12	AI	Infants 7-12 mo	0-6 mo	Metabolic weight ratio[2] (p.325)	Only somewhat lower than value obtained by extrapolating down from adult EAR.
	EAR	1-18 y	19-50 y	Adjustment for metabolic body weight and growth[1] (p.326)	Absence of adequate data in children 1-18y. Maintenance needs for B vitamins per kg metabolic body weight are the same for adults and children.
Pantothenic Acid	AI	Infants 7-12 mo	0-6 mo AND adults 19-50 y	Metabolic weight ratio[2] (p.363) AND Adjustment for metabolic body weight and growth[1] (p.363)	The mean obtained from the two types of extrapolation was used.
		1-18 y	19-50 y	Adjustment for metabolic body weight and growth[1] (p.364,365)	Absence of adequate data in children 1-18y. AI for these ages is consistent with additional information reviewed.
Biotin	AI	Infants 7-12 mo 1-70 y+	0-6 mo	Metabolic weight ratio[2] (p.380)	Absence of adequate data in all age groups (other than biotin content of human milk).
Choline	AI	Infants 7-12 mo	0-6 mo AND adults 19-70 y+	Metabolic weight ratio[2] (p.401) AND Adjustment for metabolic body weight and growth[1] (p.401)	Both methods yielded similar estimates.
		1-18 y	19-70 y+	Adjustment for metabolic body weight and growth[1] (p.403)	Absence of data in children 1-18y.

Nutrient	Ref Value	Extrapolation Group	Basis Group (extrapolated from)	Method of Extrapolation	Rationale
	UL	1-18 y	19-70 y+	Adjustment for metabolic body weight[3] (p.412)	Adjustment yields a conservative UL to protect sensitive individuals in each age group.
Vitamin C	EAR	1-18 y Women 19-30 y 31-70 y+	Men 19-30 y	Based on (old) reference body weight. EAR for adults adjusted on body-weight basis. (p.138, 147)	Absence of adequate data in all age groups except men 19-30y. Vitamin C is water-soluble and males have a larger lean body mass and total body water than females.
	UL	1-18 y	19-70 y+	Based on (old) reference body weight. UL for adults adjusted on body-weight basis. (p.163)	Results of available studies are consistent with data on adverse effects in adults on a body weight basis.
Vitamin E	AI	Infants 7-12 mo	0-6 mo	Metabolic weight ratio[2] (p.230)	Metabolic weight ratio does not adjust for growth because it is based on a value for a growing infant.
	EAR	1-18 y	19-30 y	Adjustment for metabolic body weight and growth[1] (p.231)	Absence of data in children 1-18y. Maintenance needs for vit E expressed per kg metabolic body weight are the same for adults and children; extra vit E needed for growth comparable to the percent extra protein needed for growth.
	UL	1-18 y	19-70 y+	Based on (old) reference body weight. UL for adults adjusted on body-weight basis. (p.258)	Absence of data in children 1-18y.
Selenium	EAR	1-18 y	19-50 y	Adjustment for metabolic body weight and growth[1] (p.299). Reference weights for males are used for both sexes given the reported slightly increased susceptibility of females to developing Keshan disease.	Absence of adequate data in children 1-18y. Maintenance needs for selenium expressed per kg metabolic body weight are the same for adults and children; extra selenium needed for growth comparable to the percentage extra protein needed for growth.
	UL	Infants 7-12 mo	0-6 mo	Based on (old) reference	There is no evidence indicating

Nutrient	Ref Value	Extrapolation Group	Basis Group (extrapolated from)	Method of Extrapolation	Rationale
		1-18 y		body weight. UL of 7 mcg/kg/day derived for 2-6 month old infants; this is multiplied by reference body weight. (p.316)	increased sensitivity to selenium toxicity for any age group. The infant UL and the adult UL are similar on a body weight basis.
B-Carotene & other Carotenoids	-----				
Vitamin A	AI	Infants 7-12 mo	0-6 mo	Metabolic weight ratio[2] (p.111)	Amount of vitamin A in human milk + vitamin A in solid foods supports AI.
	EAR	1-18 y	19-70 y+	Adjustment for metabolic body weight and growth[1] (p.112).	Absence of adequate data in children 1-18y. Maintenance needs for vitamin A expressed per kg metabolic body weight are the same for adults and children; extra vitamin A needed for growth comparable to the percentage extra protein needed for growth. Extrapolation using total body weight yielded values associated with inadequate serum retinol concentrations in preschoolers.
	UL	1-18 y	19-70 y+	Based on (old) reference body weight. UL for adults adjusted on body-weight basis. (p.144)	Absence of adequate data in children 1-18y.
Vitamin K	AI	Infants 7-12 mo	0-6 mo	Metabolic weight ratio[2] (p.178)	No adverse clinical outcomes associated with this level of intake. Metabolic weight ratio does not adjust for growth because it is based on a value for a growing infant.
Chromium	AI	1-18 y	19-70 y+ (*also established using extrapolation)	Adjustment for metabolic body weight and growth[1] (p.112).	Absence of data in children 1-18y. Metabolic weight used rather than total body weight because urinary excretion of chromium is known to increase with exercise.

Nutrient	Ref Value	Extrapolation Group	Basis Group (extrapolated from)	Method of Extrapolation	Rationale
		19-70 y+	N/A Mean chromium content of diets designed by nutritionists was 13.4 mcg/1000 kcal	Energy intake basis. Value of 13.4 mcg/1000kcal multiplied by mean energy intake from NHANES III. Values for 19-30y used for 19-50y; values for 51-70y used for 51-70y+. (p.208, 209)	Absence of data in adults.
		Pregnant F	Non-pregnant F	Metabolic weight ratio[4]. Reference body weight for pregnancy assumed to be 16 kg more than non-pregnant. (p.210)	Absence of data to estimate additional chromium requirement during pregnancy.
Copper	EAR	1-18 y	19-70 y+	Adjustment for metabolic body weight and growth[1] (p.238).	Absence of data in children 1-18y. Metabolic weight used rather than total body weight because of the structural and functional role of copper in a number of enzymes.
	UL	1-18 y	19-70 y+	Based on (old) reference body weight. UL for adults adjusted on body-weight basis. (p.250)	Absence of adequate data in children 1-18y.
Iodine	AI	Infants 7-12 mo	0-6 mo	Metabolic weight ratio[2] (p.268)	Metabolic weight ratio does not adjust for growth because it is based on a value for a growing infant.
	EAR	9-18 y	19-70 y+	Adjustment for metabolic body weight and growth[1] (p.272).	Extrapolation yielded higher estimates than other methods (balance studies, urinary iodine concentration). Metabolic weight used rather than total body weight because thyroid hormones involved in metabolic rate.
	UL	1-18 y	19-70 y+	Based on (old) reference body weight. UL for adults adjusted on body-weight basis. (p.282)	Absence of data in children 1-18y.

Nutrient	Ref Value	Extrapolation Group	Basis Group (extrapolated from)	Method of Extrapolation	Rationale
Iron	N/A	No values determined solely via extrapolation			
Manganese	AI	Infants 7-12 mo	Adults 19-70 y+	Adjustment for metabolic body weight and growth[1] (p.404)	Amount of manganese in human milk + manganese in solid foods supports AI.
		Pregnant F	Non-pregnant F	Metabolic weight ratio[4]. Reference body weight for pregnancy assumed to be 16 kg more than non-pregnant. (p.407)	Absence of data to estimate additional manganese requirement during pregnancy.
	UL	1-18 y	19-70 y+	Based on (old) reference body weight. UL for adults adjusted on body-weight basis. (p.413)	Absence of data in children 1-18y.
Molybdenum	AI	Infants 7-12 mo	0-6 mo	Metabolic weight ratio[2] (p.426)	Absence of adequate data in infants 7-12 months.
	EAR	1-18 y	19-70 y+	Adjustment for metabolic body weight and growth[1] (p.427).	Absence of data in children 1-18y. Metabolic weight used rather than total body weight because of functional role of molybdenum in a select number of enzymes.
		Pregnant F	Non-pregnant F	Metabolic weight ratio[4]. Reference body weight for pregnancy assumed to be 16 kg more than non-pregnant. (p.431)	Absence of data to estimate additional molybdenum requirement during pregnancy.
	UL	1-18 y	19-70 y+	Based on (old) reference body weight. UL for adults adjusted on body-weight basis. (p.437)	Absence of data in children 1-18y.

Nutrient	Ref Value	Extrapolation Group	Basis Group (extrapolated from)	Method of Extrapolation	Rationale
Zinc	EAR	Infants 7-12 mo Children 1-18y	19-50 y	Components of factorial analysis extrapolated on body-weight basis	Note: for infants 7-12 mo and children 1-18 y; each component of the factorial analysis to derive EAR was extrapolated from adults based on (old) reference weight (p.463, 467-70). EAR calculated by factorial analysis consistent with that derived from extrapolation down from adults based on adjustment for metabolic body weight and growth[1] (p.465, 467-70)
	UL	Infants 7-12 mo 1-18 y	Infants 0-6 mo	Based on (old) reference body weight. UL for infants 0-6 mo adjusted on body-weight basis. (p.487)	Absence of data in older infants and children 1-18y.
Arsenic	----				
Boron	UL	1-18y 19-70 y+	N/A UL determined to be 0.3 mg/kg/day based on animal data	Based on (old) reference body weight. UL of 0.3 mg/kg/day multiplied by reference body weight. For 14-18y and 19y+, female body weight was used. (p.519)	No data on adverse effects in humans. Reasons listed supporting use of animal data (p.517)
Nickel	UL	1-18y 19-70 y+	N/A UL determined to be 0.017 mg/kg/day based on animal data	Based on (old) reference body weight. UL of 0.017 mg/kg/day multiplied by reference body weight. For 14-18y and 19y+, female body weight was used. (p.527)	No data on adverse effects in humans relevant to dietary exposure.
Silicon	---				
Vanadium	UL	19-70 y+	N/A UL determined to be 0.026 mg/kg/day based on animal data	UL of 0.026 mg/kg/day multiplied by (old) reference body weight (average of male + female) (p.541)	Specificity and dose-response relationship of adverse (gastro-intestinal) effects in humans not as clearly defined as adverse kidney effects demonstrated in animals.

Nutrient	Ref Value	Extrapolation Group	Basis Group (extrapolated from)	Method of Extrapolation	Rationale
					(p.539)
Digestible Carbohydrates	N/A	No values determined solely via extrapolation			
Sugars	- - -				
Total Fiber	AI	1-18 y 19-70 y+	N/A Data in adults showed 14g/1000 kcal reduced the risk of CHD	Energy intake basis. Value of 14g/1000kcal multiplied by median energy intake from CSFII. (p.386, 388)	No information to indicate that fibre intake, as a function of energy intake, differs during the lifecycle.
Total Fat	N/A	No values determined solely via extrapolation			
n-3 PUFA	N/A	No values determined solely via extrapolation			
n-6 PUFA	N/A	No values determined solely via extrapolation			
Saturated Fatty Acids	---				
Trans-Fatty Acids	----				
MUFA	---				
Cholesterol	----				
Protein & Amino Acids	EAR	None		* Note: RDA is also expressed in g/d in addition to g/kg/d. This is obtained by multiplying RDA in g/kg/d by (new) reference body weights.	
Water	N/A	No values determined solely via extrapolation			
Potassium	AI	1-18 y	19-50 y	Relative energy intake basis. AI for adults extrapolated	Adjustment based on energy intake deemed most appropriate because

Nutrient	Ref Value	Extrapolation Group	Basis Group (extrapolated from)	Method of Extrapolation	Rationale
				based on median energy intake from CSFII. (Energy intake level used for adults was average of median energy intakes of M&F 19-50y). (p.233)	of concern that adjustment based on weight might lead to a relatively low and potentially inadequate intake of potassium. Children also have high energy intake relative to their weight and potential for high sodium intake due to their high energy intake. (p.233) No adjustment done for 51-70y+ because of increased risk of hypertension with aging.
Sodium	AI	1-8 y 51-70 y+	19-50 y	Relative energy intake basis. AI for adults extrapolated based on median energy intake from CSFII. (Energy intake level used for adults was average of median energy intakes of M&F 19-50y). AI for adults applied to ages 9-18 y because median energy intake similar to that of adults. (p.306) For adults 51-70y and 71+ y, median energy intakes for both genders were averaged. (p.312)	Adjustment on basis of energy intake used rather than basis of body weight because high levels of physical activity have an effect on losses of electrolytes in sweat. (p.45) Relative energy intake chosen because the AI for adults is based on an intake of sodium from foods found in the Western diet which allows for adequate consumption of other nutrients. (p.306)
	UL	1-13 y	19-50 y	Relative energy intake basis. UL for adults extrapolated based on median energy intake from CSFII. UL for adults applied to ages 14-18 y because median energy intake similar to that of adults. (p.386) UL for 19-50y applied to ages 51+. (p.382)	Energy intake used as the basis for extrapolation rather than body weight to be consistent with method for setting AI. (p.45)

Nutrient	Ref Value	Extrapolation Group	Basis Group (extrapolated from)	Method of Extrapolation	Rationale
Chloride	AI UL			Set at a level equivalent on a molar basis to that of sodium.	Almost all dietary chloride comes with the sodium added during processing or consumption of foods. (p.270)
Sulfate	----				

Extrapolation formulas used:

1) **Extrapolating EAR/AI down from adults:** (p.31-32, B vitamins; p.66 Antioxidants; p.52 Micronutrients)
$EAR_{child} = EAR_{adult} * (Ref.wt_{child} / Ref.wt_{adult})^{0.75} * (1 + growth\ factor)$

If the EAR differs for adult men and women, the reference weight used for adults differs by gender. Otherwise, the average reference weight for men and women is used, unless the EAR for women is derived from data on men.
If only an AI has been set for adults, it is substituted for the EAR in the above formula and an AI is calculated.

2) **Extrapolating AI up from young infants:** (p.33 B vitamins; p.66 Antioxidants; p.53 Micronutrients)

$AI_{child} = AI_{0\text{-}6\ mo} * (Ref.wt_{child} / Ref.wt_{0\text{-}6\ mo})^{0.75}$

3) **Extrapolating UL down from adults:** (p.56 B vitamins)

$UL_{child} = UL_{adult} * (Ref.wt_{child\ (Female)} / Ref.wt_{adult\ (Male)})^{0.75}$

The reference weight for female children and adolescents and the reference weight for adult males are used in the formula above.

4) **Extrapolating EAR/AI from non-pregnant females:** (p.54, Micronutrients)
$EAR_{Preg} = EAR_{Non\text{-}preg} * ([Ref.wt_{Non\text{-}preg} + 16] / Ref.wt_{Non\text{-}preg})^{0.75}$

Reference weights for use in formulas and other adjustments

Age group	OLD Reference Weight (kg)		NEW Reference Weight (kg)	
	Males	Females	Males	Females
2-6 mo.	7	7	6	6
7-11 mo.	9	9	9	9
1-3 y	13	13	12	12
4-8 y	22	22	20	20
9-13 y	40	40	36	37
14-18 y	64	57	61	54
19-30 y (and older)	76	61	70	57

Note: Old reference weights have been used in all extrapolation formulas listed above

Growth factors used to extrapolate down from adults

Age group	Growth factor	Notes:
7 mo. – 3 y	0.30	• The proportional increase in protein requirements for growth from FAO/WHO/UNA (1985) was used to estimate the growth factor indicated.
4-8 y	0.15	
9-13 y	0.15	
14-18 y, Males	0.15	• Growth beyond age 13 for females is assumed to represent a negligible increased requirement for vitamins.
14-18 y, Females	0.00	