VITAMINS, SURVEY

1. Introduction

Vitamins are specific organic compounds that are essential for normal metabolism. Many participate as cofactors in mammalian biochemical reactions. The common thread for the diverse chemical structures of the vitamins is that they are micronutrients. Micronutrients are compounds that are required in only small amounts and are not synthesized by humans, either at all or, at least, in sufficient quantity for metabolic needs. Vitamins are obtained from the diet or as synthetic preparations used in food fortification or supplements.

The term vitamin is derived from *vitamine*, a word created in 1911 (1) when it was believed that the antiberiberi factor (thiamine) was an *amine* essential to the maintenance of life (*vita*). Later discoveries showed that not all vitamins are amines. However, a form of the name has remained.

Using strict definitions, cholecalciferol (D_3) is not essential nor a normal constituent of most diets. Humans living in areas of adequate sunlight and not using excessive amounts of sunscreen can obtain enough vitamin D from a photochemical reaction that converts a normal skin sterol, 7-dehydrocholesterol, into cholecalciferol. As humans consumed less fish, the vitamin no longer was a normal constituent of the diet. (This has been corrected with fortification of milk with one of the two calciferols.) Humans do produce niacin from tryptophan, but it must be remembered that tryptophan is an essential amino acid. Indeed, a niacin deficiency leads to the serious deficiency disease called pellegra.

The history of the vitamins can be divided into five major, overlapping periods (2).

2. Prehistory to ~1900

In this period, the empirical healing of certain diseases by foods was established. Examples were the treatment of night blindness (vitamin A deficiency) with liver in many cultures, of beriberi (vitamin B1 deficiency) by use of unpolished rice by the Japanese navy, of scurvy (vitamin C deficiency) by citrus fruits in the British navy or pine needle extracts by North American natives, and pellagra (niacin deficiency) by a dietary shift away from corn-based foods in many countries (3). An exception to the correction of diet was the discovery that, instead of diet, exposing children in northern latitudes to sunlight cured rickets (vitamin D deficiency) (4).

3. 1880–1905

The ability to induce disease states in animals by manipulation of the diet was established in this period. The classical work by Eijkman (5), in which a beriberi-like condition was induced in chickens fed on polished rice, was significant. These findings led to the concept by Hopkins that small amounts of accessory growth factors are necessary for survival and growth.

4. 1900–1972

During this 70-year period, all 13 of the substances now recognized as vitamins were discovered and isolated in pure form. Structure elucidation for each vitamin was completed, as was their total synthesis (Table 1).

5. 1933–Present

The first commercial synthesis of a vitamin occurred in 1933 when the Reichstein approach was employed to manufacture vitamin C (6). All 13 vitamins are available in commercial quantities, and their biological functions have largely been established (7–10). A list of Nobel Prize winners associated with vitamin research is given in Table 2.

6. 1955–Present

The possibility that vitamins might have physiological functions beyond the prevention of deficiency diseases was first recognized in 1955 with the finding (11) that niacin in pharmacological doses can lower serum cholesterol levels in humans and retinoic acid (active form of vitamin A) is indicated for promyelocytic leukemia. Most recently, there has been a concerted effort under the Institute of Medicine of the U. S. National Academy of Sciences and jointly with Canada to establish optimal vitamin levels that will maintain good health and also evaluate evidence of toxicities when chronically administering large doses of a particular vitamin. This has led to the Dietary Reference Intakes (DRI) (7–10).

Each vitamin can have up to four DRI values based on age, gender, pregnancy, and lactation. They are

1. Estimated Average Requirement (EAR). The intake that meets the estimated nutrient need of 50% of the individuals in that group (ie, infants, children, adult males, adult females, pregnant women, nursing women, and the elderly). The EAR is based on a median rather than a mean.
2. Recommended Dietary Allowance (RDA). The intake that meets the nutrient need of almost all (97–98%) individuals in that group. If the sampling and end points are well defined, the RDA can be calculated from the EAR. They are found in Table 3.

$$\mathrm{RDA} = \mathrm{EAR} + 2\,\mathrm{SD}_{\mathrm{EAR}}$$

   where $\mathrm{SD}_{\mathrm{EAR}}$ = standard deviation above the EAR
3. Adequate Intake (AI). Average observed or experimentally derived intake by a defined population or subgroup that appears to sustain a defined nutritional state, such as normal circulating nutrient values, growth, or other functional indicators of health. It is derived from mean intakes of groups (rather than individuals). The AI becomes most useful when a reliable

EAR is not available. It is used for infants and for the vitamin D family, vitamin K, pantothenic acid (pantothenol), and biotin. They are found in Table 3.

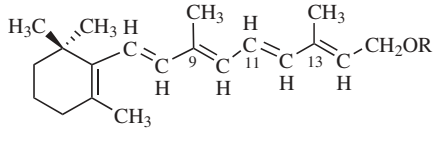
4. Tolerable Upper Intake Level (UL). The maximum intake by an individual that is unlikely to pose risks of adverse health effects in almost all (97–98%) individuals. It includes intake of a nutrient from all sources (food, fortified food, water, and supplements). "Tolerable" is used to "avoid implying any possible beneficial effect". It is the amount can be "tolerated". They are found in Table 4.

An alternative system of stating vitamin requirements is the U. S. Food and Drug Administration's (FDAs) Daily Values (12). They are listed in Table 5. These are part of the nutrition labeling required on most foods sold in the United States. The vitamins are listed as a percent Daily Value (%DV) and are based on a 2000 calorie intake for adults and children 4 or more years of age. Because the DRI values are based on gender and age, the DVs can exceed or be less than a particular RDA or AI.

Vitamin nomenclature and classification has evolved as more vitamins were discovered and their metabolic functions elucidated (Table 6). Initially, there were attempts at using letters of the alphabet. Some are widely used, but as can be seen both are used by the *U.S. Pharmacopeia* (Table 6). Even though the latter is the official compendium for the United States, the DRI manuals published by the National Academy of Sciences do not always use the U.S.P. names.

7. Vitamin A

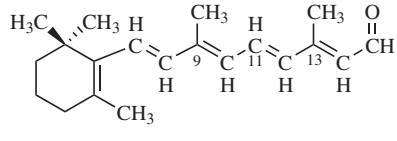
Vitamin A (retinol; R = H) [68-26-8]



Retinol, R = H

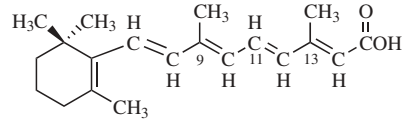
Common commercial forms are vitamin A palmitate ($R = CO(CH_2)_{14}CH_3$) [79-81-2] and vitamin A acetate ($R = COCH_3$) [200720-67-8].

Active forms are retinal [116-31-4] and



Retinal

retinoic acid [302-79-4]



Retinoic acid

7.1. Metabolic Functions. Retinal, as 11-*cis*-retinal, is an essential part of rhodopsin, the visual pigment in the rods of the eye. When light strikes the rods, the 11-*cis* double bond isomerizes to the all-*trans*-retinal, and breaks the enamine bond binding 11-*cis*-retinal to an ϵ-amino group of a lysine in the protein opsin sending an impulse along the optic nerve to the brain.

Retinoic acid is the ligand for the nuclear RAR (retinoic acid receptor) and RXR receptors and is important for cell differentiation. Drugs based on the retinoid structure are ligands for the RAR and RXR receptors. There are risks from teratogenesis when pregnant women take drugs that are retinoids and or whose structures are retinoid based.

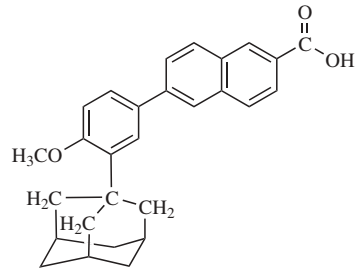
7.2. Deficiency. In adults, night blindness, which is reversible, is caused by lower levels of rhodopsin in the rods resulting in difficulties seeing in dim light or adapting quickly when moving from areas of bright light to dim light. Deficiency in infants can result in permanent blindness.

Vitamin A is required for proper functioning of the immune system including maintenance of the skin and other tissues that are barriers to pathogens. Deficiencies can result in immunodeficiencies. It also is required for proper development of bone.

7.3. Hypervitaminosis A. Chronic ingestion of concentrated vitamin A preparations, such as fish liver oils, causes a nondescript set of symptoms including lethargy, bone and joint pain with possible fracture, severe headaches, scaly skin, brittle nails and irregular menses. Liver cirrhosis is a more severe symptom. Long-term intake of a diet high in the vitamin may promote the development of osteoporotic hip fractures in women (13). This vitamin has UL values.

7.4. Retinoid and Retinoid-based Drugs. *For Acne.*

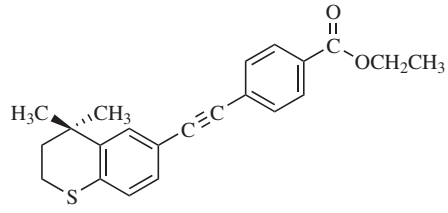
a. Tretinoin (Retin-A; all-*trans*-retinoic acid) [302-79-4].
b. Isotretinoin (Accutane; 13-*cis*-retinoic acid) [4759-48-2].
c. Adapalene (Differin Gel) [106685-40-9].



Adapalene

For Both Acne and Psoriasis.

a. Tazarotene Gel (Tazorac) [118292-40-3].

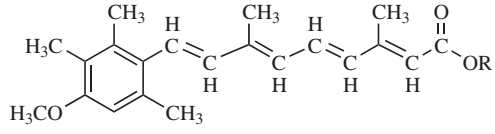


Tazarotene

For Psoriasis.

a. Etretinate (Tegison; R = CH_2CH_3) [54350-48-0].

b. Acitretin (Soriatene; R = H) [55079-83-9].



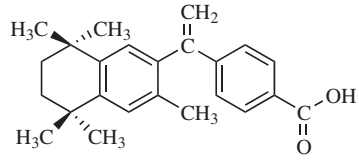
Etretinate, R = ethyl; Acitretin, R = H

For Malignancies.

a. Retinoic acid [302-79-4]: acute promyelocytic leukemia.

b. Alitretinoin (Panretin; 9-*cis*-retinoic acid) [5300-03-8]: Kaposi's sarcoma.

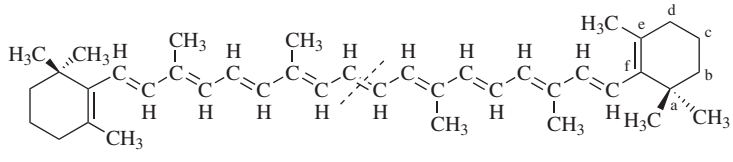
c. Bexarotene (Targretin) [153559-49-0]: refractory cutaneous T cell lymphoma.

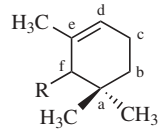


Bexarotene

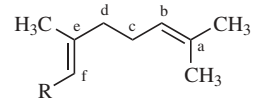
8. Carotenes

These are yellowish pigments found in plants. β-Carotene is a precursor to vitamin A. Oxidative cleavage in the intestinal mucosal produces up two equivalents of retinal. The cleavage of other carotenes is less efficient and are not considered reliable precursors of retinal. The carotenes also function as antioxidants.





(β,α-carotene) [7488-99-5]



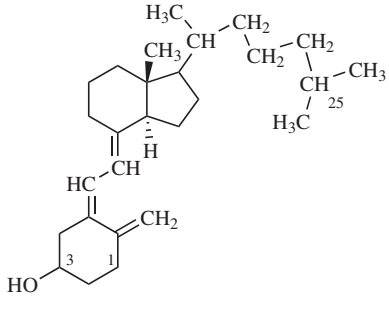
(β,γ-carotene) [472-93-5]

8.1. Hypercarotenosis. Chronic ingestion of carotene-containing foods and products can lead to discoloration of the skin, but, otherwise, do not seem detrimental.

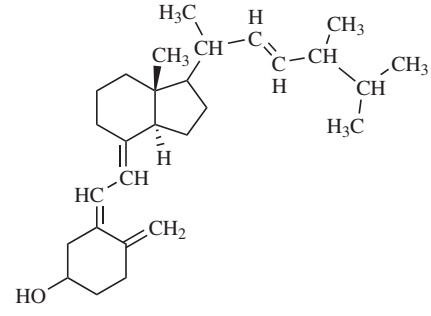
8.2. Dietary Sources. Retinol palmitate is the main form found in fish and mammalian livers, and β-carotene is the source in yellow vegetables (carrots, sweet potatoes, yams, etc). Retinol palmitate also is commonly added to both liquid and powdered milk.

9. Cholecalciferol (Vitamin D_3) and Ergocalciferol (Vitamin D_2)

Both forms of the vitamin are obtained by irradiation of their steroid percursor, cholecalciferol from 7-dehydrocholesterol (animals) and ergocalciferol from ergosterol (plants).



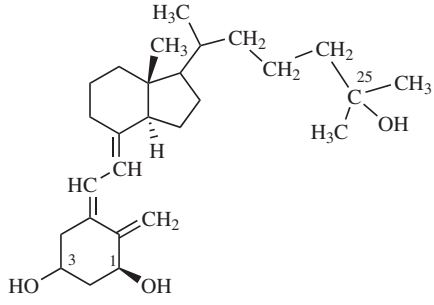
Cholecalciferol (Vitamin D_3) [67-97-0]



Ergocalciferol (Vitamin D_2) [50-14-6]

9.1. Common Commercial Forms. Cholecalciferol is the form found in nonprescription products and added to foods, such as milk. Ergocalciferol is increasingly being restricted to specific medical conditions and is indicated for refractory rickets and hypoparathyroidism.

Active form is 1,25-dihydroxycholecalciferol (calcitrol; 1,25-$(OH)_2$) [32511-63-0].



1,25-Dihydroxycholecalciferol

Cholecalciferol, produced photochemically from 7-dehydrocholesterol in the skin or consumed orally, is transported to the liver for cytochrome P450 hydroxylation at C-25 and then to the kidney for a second cytochrome P450 hydroxylation at C-1. A synthetic form, calcitrol (Rocaltrol), is indicated for refractory rickets. The latter is seen in patients whose kidneys no longer can carry out the final hydroxylation step.

9.2. Metabolic Function. The active form is transported to intestinal mucosa cells where it activates the gene that forms a calcium transport protein. Regulation of calcium transport, excretion, deposition onto and release from bone is an integrated process involving parathyroid hormone, calcitonin, and 1,25-dihydroxycholecalciferol. The latter is also a ligand for the nuclear vitamin D receptor (VDR) and regulates cell division. Nearly every nucleated cell has VDR receptors.

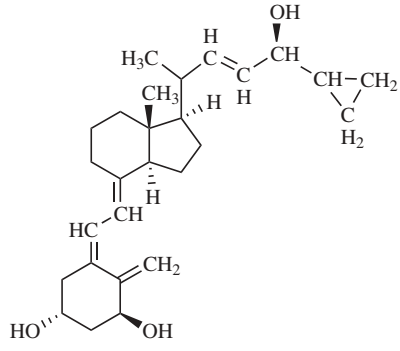
Deltanoid-based structures are ligands for the VDR receptor and are indicated for psoriasis and maintaining calcium homeostasis for patients on kidney dialysis. Large numbers of deltanoids have been synthesized and evaluated for treatment of malignancies (14,15).

9.3. Deficiency. In infants and children, the deficiency disease is called rickets. ("Rachitic" is the adjective form of rickets.) Osteomalacia is the condition in adults. In both cases, there is inadequate calcium being laid down on the cartilage matrix of bone. The cartilage framework cannot support the body causing bowed legs and, in severe cases, collapsed pelvic region. Infants will show a characteristic rachitic rosary in the rib cage. It is difficult to establish a daily requirement because the amount of exposure to sun and degree of skin pigmentation will affect the requirement for vitamin D supplementation. The DRIs for this vitamin are AIs.

9.4. Hypervitaminosis D. Chronic ingestion of the vitamin (as opposed to overexposure to sunlight) causes excessive absorption of dietary calcium. The latter can be deposited in soft tissues. This vitamin has UL values.

9.5. Deltanoids. *For Psoriasis.*

a. Calcipotriene (Dovenex) [112965-21-6]. This drug is used topically. Internal administration can cause hypercalcemia.



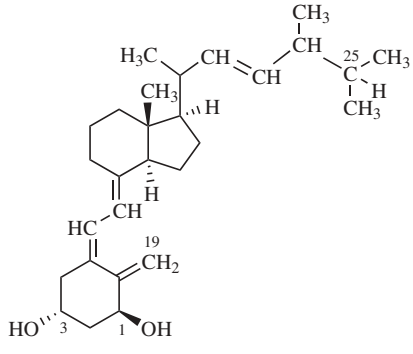
Calcipotriene

For Secondary Hyperparathyroidism Associated with Chronic Renal Failure.

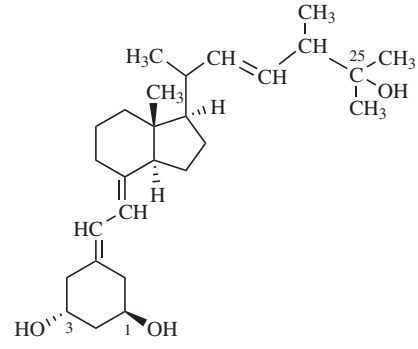
Both are derived from ergocalciferol.

a. Doxercalciferol (Hectoral; 1,3-dihydroxyergocalciferol) [54573-75-0].

b. Paricalcitol (Zemplar; 19-nor-1,3,25-trihydroxyergosterol) [131918-61-1].



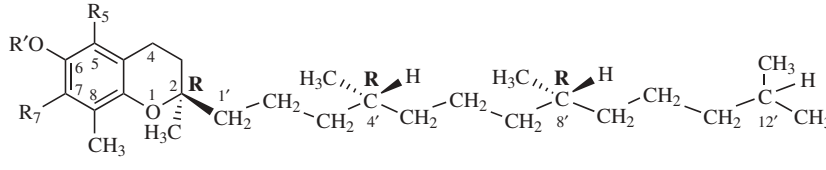
Doxercalciferol



Paricalcitol

9.6. Dietary Sources. Fish liver oils, fish, fortified milk.

10. Vitamin E (α-Tocopherol)



α-Tocopherol ($R_5 = R_7 = CH_3$; $R' = H$) [59-02-9]

Common commercial forms are α-tocopherol acetate ($R' = COCH_3$) [58-95-7] and α-tocopherol hemisuccinate ($R' = COCH_2CH_2COO^-$) [17407-37-3].

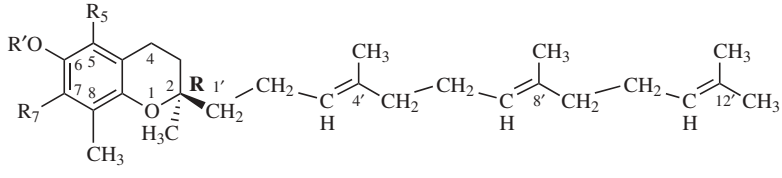
10.1. Vitamin E Family. α-Tocopherol is the predominant member of the vitamin E family found in human tissues. Common dietary sources include three other tocopherols, differing in the presence of methyl groups at positions 5 and 7 and four tocotrienols. The other tocopherols are β-tocopherol ($R_5 = CH_3$; $R_7 = H$; $R' = H$) [148-03-8], γ-tocopherol ($R_5 = H$, $R = CH_3$; $R' = H$) [7616-22-0], and δ-tocopherol ($R_5 = R_7 =$ $R' = H$) [119-13-1]. The methyl substituent pattern of the tocotrienols parallels that of the tocopherols. However, a significant difference between the tocopherols and tocotrienols is that the former has three asymmetric centers and the latter only one at position 2.

α-Tocotrienol ($R_5 = R_7 = CH_3$; $R' = H$) [1721-51-3]

β-Tocotrienol ($R_5 = CH_3$; $R_7 = H$; $R' = H$) [490-23-3]

γ-Tocotrienol ($R_5 = H$, $R = CH_3$; $R' = H$) [14101-61-2]

δ-Tocotrienol ($R_5 = R_7 = R' = H$) [25612-59-3]



10.2. Metabolic Function. In human metabolism, the vitamin E family is considered to be antioxidants and, being lipid soluble, are found in the lipid membranes and lipoproteins including chylomicrons, very low density lipoproteins (VLDL), and low density lipoproteins (LDL). A problem studying this family is finding animal model deficiency conditions that also are found in humans. There is no known human parallel to reproductive failure in rats; muscular dystrophy in many domestic animals including rabbits, turkeys, chicks, lambs, and calves; or an anemia in monkeys.

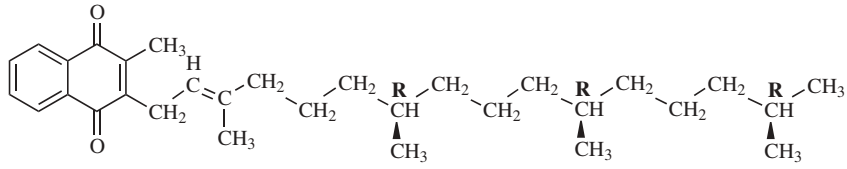
There is debate as to how important the stereochemistry is, particularly in the tocopherol family with its three asymmetric centers. The racemic, synthetic mixture is active. Nevertheless, there appears to be preferential transport for the predominant R isomers (9).

10.3. Deficiency. There is a reversible set of neurological symptoms and a hemolytic anemia in premature infants. Most deficiencies in adults is caused by a malabsorption of lipids from the intestinal tract.

10.4. Hypervitaminosis E. Chronic ingestion of large amounts has been reported to cause clotting disorders, breast enlargement, and severe fatigue.

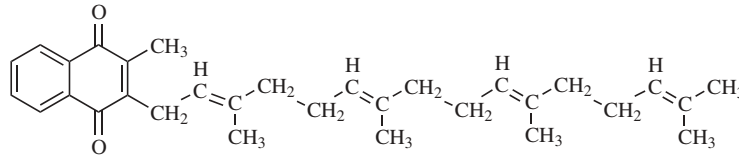
10.5. Dietary Sources. Vegetable oils, cereal grain germ, and nuts.

11. Phytonadione (Vitamin K)



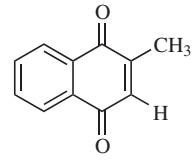
Phytonadione

Commercial form is Phytonadione (Vitamin K_1) [84-80-0].
Another form is Vitamin $K_{2(20)}$ (menaquinone-4) [863-61-6].



Menaquinone-4

Alternate form is Menadione (Synkavite; vitamin K_3; prescription only) [58-27-5].



Menadione

11.1. Metabolic Function. Vitamin K is required for blood clotting. It is a cofactor required for the addition of carbon dioxide to glutamic acid residues forming γ-glutamic acid side chains in several of the clotting proteins including prothrombin, factors VII, IX, and X and clot inhibiting C and S proteins. The γ-glutamyl side chains complex calcium, a process essential for clot formation. (Citrate is added to whole blood to complex the calcium in the donor's blood before the clotting process begins in the bags of whole blood.) The anticoagulant warfarin (Coumadin) inhibits formation of the cofactor form of the vitamin. There is evidence that there are vitamin K receptors that regulate one or more receptor tyrosine kinases (16).

Vitamin K also is required for the formation γ-glutamyl residues in osteocalcin, a protein produced by the bone-forming osteoblast cells. While the exact role of osteocalcin is unclear, it appears to be required for proper mineralization of bone tissue. Some calcium supplements contain vitamin K along with vitamin D.

11.2. Deficiency. Most deficiencies are disease related including intestinal malabsorption of lipids and chronic liver disease preventing adequate

conversion of the K_1 series into $K_{2(20)}$. Increased prothrombin time leads to lessened ability to form clots resulting in hemorrhaging. Because infants are born with sterile intestinal tracts, newborns routinely are administered an intramuscular injection of phytonadione to prevent hemorrhagic disease of the newborn.

There is little evidence that patients on warfarin anticoagulant therapy have increased risk of bone fractures or more severe osteoporosis. Determination of daily requirements is difficult because the bacteria in the human intestinal tract produce forms of vitamin $K_{2(20)}$. Therefore, this vitamin's DRI values are AIs.

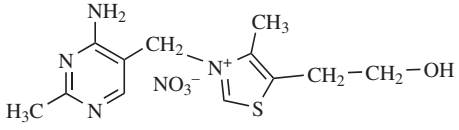
11.3. Hypervitaminosis K. It is considered a nontoxic vitamin. Overdosing does not hasten clot formation.

11.4. Dietary Sources.

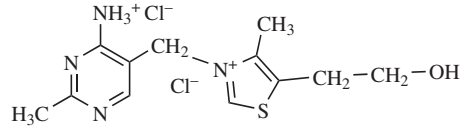
Vitamin K_1 series: green vegetables, some nut oils.

Vitamin K_2 series: fermented dairy products (cheese).

12. Thiamine (Vitamin B_1)



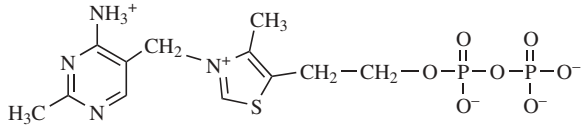
Thiamine mononitrate



Thiamine hydrochloride

Commercial forms are thiamine mononitrate [532-43-4] and thiamine hydrochloride (thiamine chloride hydrochloride) [67-03-8].

Active form is thiamine pyrophosphate (TPP) [136-09-4].



Thiamine pyrophosphate

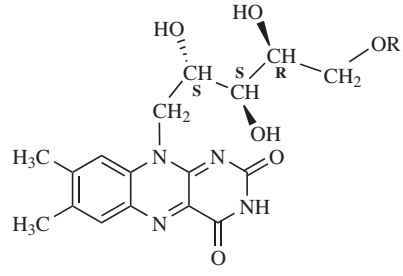
12.1. Metabolic Functions. Thiamine pyrophosphate is the cofactor required for the decarboxylation of α-keto acids (pyruvate to acetyl CoA; α-ketoglutarate to succinyl CoA), and the transketolase reactions in carbohydrate metabolism.

12.2. Deficiency. Beriberi is the disease caused by a deficiency of thiamine. It is characterized by a diseased heart and neurological symptoms including Wernike-Korsakoff Syndrome.

12.3. Hypervitaminosis Thiamine. There are no reported toxicities associated with excessive intake of the vitamin.

12.4. Dietary Sources. Beans, nuts, fruits, animal tissue, and fortified grain containing foods.

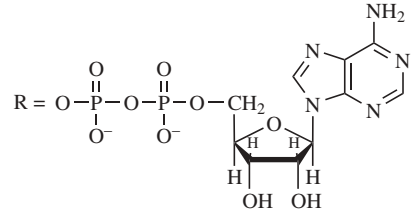
13. Riboflavin (Vitamin B_2)



Riboflavin (R = H)

Commercial forms are riboflavin (R = H) [83-88-5] and riboflavin phosphate (R = phosphate) [146-17-8].

Active forms are flavin mononucleotide (FMN; riboflavin-5′-phosphate, R = phosphate) [146-17-8] and flavin adenine dinucleotide (FAD) [146-14-5].



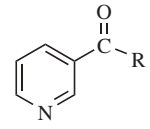
13.1. Metabolic Functions. The flavin cofactors are an integral part of oxidation–reduction reactions. Flavin mononucleotide is part of the respiratory chain in the mitochondria. Flavin adenine dinucleotide is found in both degradative and biosynthetic oxidation-reduction reactions, including the Krebs cycle, fatty acid oxidation and synthesis, monoamine oxidase, and xanthine oxidase. They also are required for transformations that convert pyridoxine and folic acid into their active forms.

13.2. Deficiency. There is no known syndrome associated with a riboflavin deficiency even though the flavin ring system is essential for many oxidation–reduction biochemical reactions. Furthermore, deficiencies are rare as riboflavin in its cofactor forms is a normal constituent of human diets.

13.3. Hypervitaminosis Riboflavin. There are no known toxicities reported for excessive doses of riboflavin.

13.4. Dietary Sources. Liver, kidney, milk, plant and animal tissue, and fortified grain containing foods.

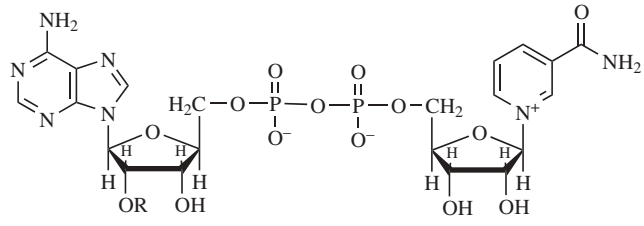
14. Niacin, Niacinamide



Niacin (R = OH)

Commercial forms are niacin (nicotinic acid; R = OH) [59-67-6] and niacinamide (nicotinamide; R = NH_2) [98-92-0].

Active forms are niacinamide adenine dinucleotide (NAD^+; R = H) [53-84-9] and niacinamide adenine dinucleotide phosphate ($NADP^+$; R = phosphate) [53-59-8].



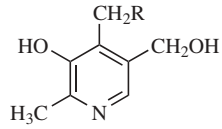
14.1. Metabolic Function. Both cofactor forms of niacinamide are required for numerous oxidation–reduction reactions including the Krebs cycle, aerobic glycolysis, fatty acid synthesis, and degradation.

14.2. Deficiency. Niacin deficiency causes pellegra. The historic names vitamin P and PP stand for pellegra and pellegra prevention, respectively. Pellegra is characterized by a reversible heat-caused dermatitis, diarrhea, dementia, and death.

14.3. Hypervitaminosis Niacin and Niacinamide. The UL for niacin is based on its causing flushing. Niacin causes an uncomfortable flushing reaction because of its vasodilation properties. Niacinamide is found in most vitamin preparations because it does not cause vasodilation. Pharmacological (gram) doses of niacin are very effective at lowering both serum levels of triglycerides (VLDL) and cholesterol (LDL) and increasing levels of high density lipoprotein (HDL). These effects are very beneficial in the management of hyperlipidemias. This response on lipoproteins is not considered related to niacin's vitamin properties. Niacinamide has no lipid lowering properties.

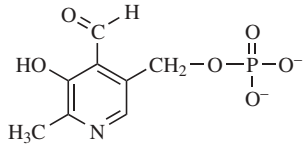
14.4. Dietary Sources. Liver, kidney, other meats, soybean, nuts, and fortified grain containing foods.

15. Pyridoxine (Vitamin B_6)



Commercial forms are pyridoxine (R = OH) [65-23-6] and pyridoxamine ($R = NH_2$) [85-87-0].

Active form is pyridoxal phosphate [54-47-7].



Pyridoxal phosphate

15.1. Metabolic Functions. All transamination reactions require pyridoxal phosphate as do deaminations and decarboxylations of amino acids and formation of glucose-1-phosphate from phosphorylase degradation of glycogen. The neurological deficiency symptoms may be related to pyridoxal phosphate required for the conversion of tyrosine to L-DOPA [DOPA = 3-(3,4-dihydroxy phenyl)alanine], tryptophan to serotonin, and histamine to histidine.

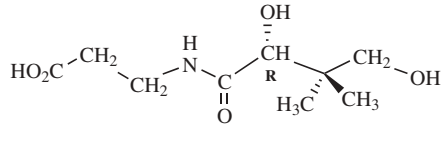
15.2. Deficiencies. In infants, there is a characteristic type of convulsion that is reversible upon administration of the vitamin. Deficiencies in adults cause neuropathies.

15.3. Drug–Nutrient Interactions. Isoniazid, indicated for the treatment of tuberculosis, can induce a pyridoxine deficiency.

15.4. Hypervitaminosis Pyridoxine. There are anecdotal reports of neurological symptoms when taking chronic doses exceeding 2 g/day.

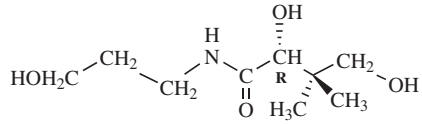
15.5. Dietary Sources. Milk, legumes, plant, and animal tissue.

16. Pantothenic Acid [79-83-4]

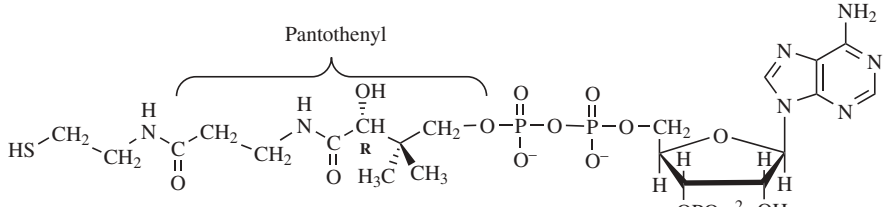


Pantothenic acid

Commercial forms are calcium pantothenate [137-08-6] and pantothenol [81-13-0].



Pantothenol



CoA (CoASH) [85-61-0]

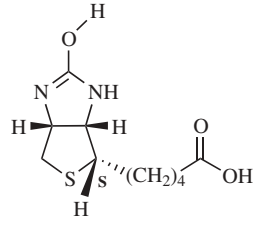
16.1. Metabolic Function. The carbon skeleton is part of CoA. In contrast with the other vitamins that function as cofactors, pantothenic acid does not participate directly in the reaction. Coenzyme A is required for the transfer of many acyl groups. An example is acetyl CoA that transfers acetate to oxalacetate forming citrate in the initial stage of the Krebs cycle.

16.2. Deficiency. Although essential and participating in intermediary metabolism, there is no known deficiency syndrome seen in humans. All DRIs for this vitamin are adequate intakes (AI) because there is not enough data to calculate EAR and RDA values.

16.3. Hypervitaminosis Pantothenic Acid. This vitamin is considered nontoxic.

16.4. Dietary Sources. All animal and plant tissues.

17. Biotin



Biotin (enolic form)

Commercial form is biotin [58-85-5].

17.1. Metabolic Function. Biotin, as a cofactor, is required for many carboxylation reactions in which carbon dioxide is added to the molecule. Examples include formation of methylmalonyl CoA from propionyl CoA in the catabolic metabolism of valine, isoleucine, methionine, and threonine; oxalacetate from

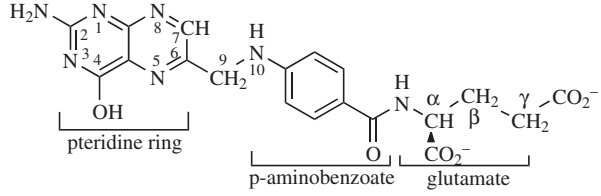
pyruvate in gluconeogenesis; malonyl CoA from acetyl CoA in fatty acid synthesis; and carbamyl phosphate from ammonia in the urea cycle.

17.2. Deficiency. There is no defined syndrome, but a biotin deficient individual exhibits hair loss, conjunctivitis, and a rash around the nose and mouth. A deficiency can be induced by feeding an individual raw egg white. The latter contains a basic protein, avidin, that forms a salt with biotin preventing its absorption. Avidin is not available in cooked egg white, and the yolk contains adequate amounts of biotin. All DRIs for this vitamin are adequate intakes (AI) because there is not enough data to calculate EAR and RDA values.

17.3. Hypervitaminosis Biotin. There are no reported toxicities from ingesting large amounts of this vitamin.

17.4. Dietary Sources. Animal and plant tissue and possibly intestinal bacteria.

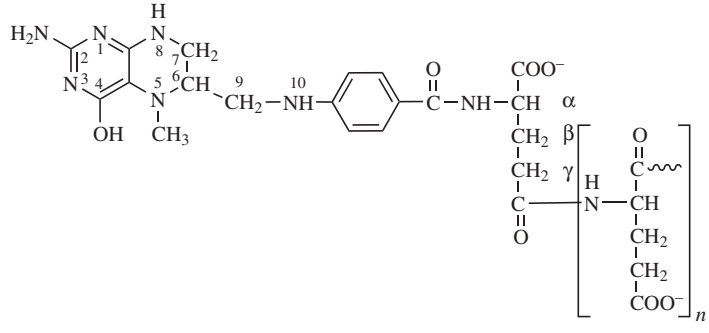
18. Folic Acid



Folic acid

Commercial form is folic acid [59-30-3].

Common *in vivo* form is tetrahydrofolic acid polyglutamate (THF polyglutamate) [138-16-0].

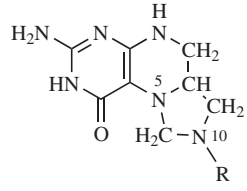


Tetrahydrofolic acid polyglutamate (n = 3,5,7)

18.1. Cofactor Forms.

N^5,N^{10}-Methylene tetrahydrofolic acid [3432-99-3]

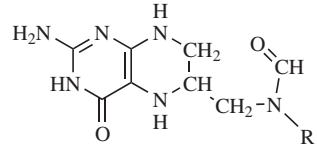
Methylation of deoxyuridylic acid (dUMP) forming deoxythymidylic acid (dTMP) and synthesis of serine from glycine. Part of the methylation of dUMP results in the tetrahydrofolate moiety being oxidized to dihydrofolate. The latter must be reduced to tetrahydrofolate by dihydrofolate reductase before the methylation of another homocysteine can occur.



N^5,N^{10}-Methylene THF

N^{10}-Formyl tetrahydrofolic acid [2800-34-2]

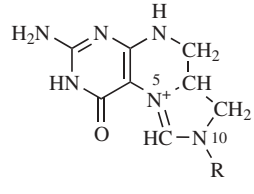
Conversion of aminoimidazole carboxamide ribotide (AICAR) to formaminoimidazole carboxamide ribotide (FAICAR) in purine biosynthesis.



N^{10}-Formyl THF

N^5,N^{10}-Methenyl tetrahydrofolic acid [10360-12-0]

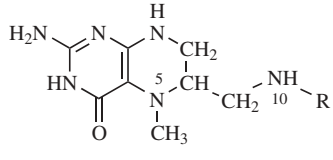
Synthesis of formylglycine ribotide (FGAR) from glycine amide ribotide (GAR) in purine biosynthesis.



N^5,N^{10}-Methenyl THF

N^5-Methyl tetrahydrofolic acid [134-35-0]

Methylation of homocysteine forming methionine. This reaction also requires cobalamin (vitamin B_{12}) and represents a unique relationship between the two vitamins.



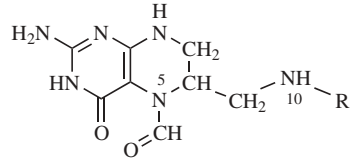
N^5-Methyl THF

18.2. Metabolic Function. Pharmaceutical forms of the vitamin must first be reduced by dihydrofolate reductase into tetrahydrofolate. The four different tetrahydrofolate cofactors are required for one carbon transfers. Two of these tetrahydrofolate cofactors are required for purine synthesis.

18.3. Deficiency. The main deficiency is a characteristic megaloblastic anemia caused by a shortage of nucleotides required for the production of erythrocyte precursors. Two neural tube defects in newborn, spina bifida, and anencephaly, have been associated with inadequate folic acid intake in the early portion of the pregnancy.

Many times, megaloblastic anemia of pregnancy is caused by inadequate intake of the vitamin. Otherwise, deficiencies are caused by malabsorption of the vitamin. Chronic alcohol intake can interfere with absorption from the intestinal tract or storage in the liver. Chronic inflammatory diseases of the intestinal tract interfere with absorption of dietary folate.

18.4. Drug–Nutrient Interactions. *Methotrexate.* This drug widely, used in cancer chemotherapy and as an immunosuppressant, inhibits human dihydrofolate reductase. Its focus is the synthesis of dTMP from dUMP in which N^5,N^{10}-methylene tetrahydrofolate is oxidized to dihydrofolate. Methotrexate prevents the cofactor's reduction to functional tetrahydrofolate. It is common to give doses of such size that the patient could experience significant adverse responses. A noncofactor form of the vitamin, N^5-formyl tetrahydrofolate [58-05-9], is used to "rescue" the patient. Because it already is in the reduced tetrahydrofolate, cells can convert it into any of the four tetrahydrofolate cofactors.



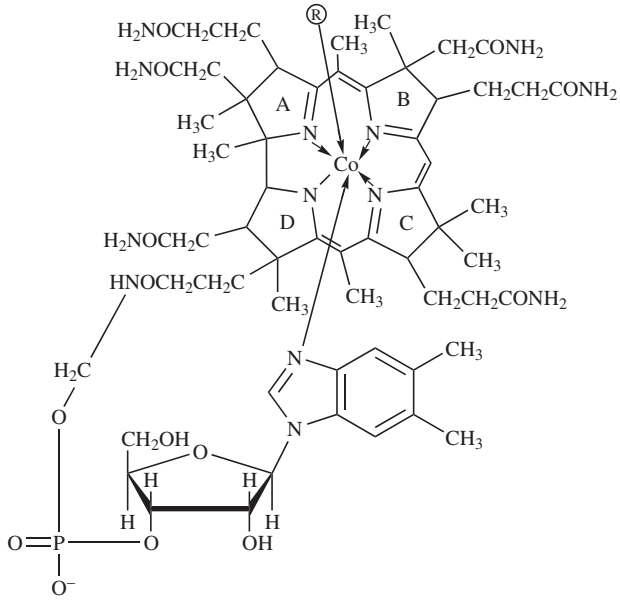
N^5-Formyl THF
(folinic acid; citrovorum factor;
leucovorum)

Phenytoin (Dilantin). The mechanism is uncertain, but there seems to be some type of inhibition of folic acid uptake or utilization.

18.5. Hypervitaminosis Folic Acid. The recommended maximum dose is based on the amount of folic acid that can mask a cobalamin (vitamin B_{12}) deficiency. (See COBALAMIN.) Otherwise, the vitamin is nontoxic.

18.6. Dietary Sources. Deep green leafy vegetables; fortified grain containing foods.

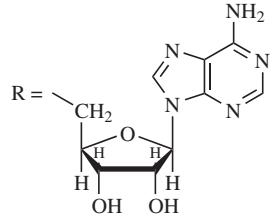
19. Cyanocobalamin (Vitamin B_{12})



Cobalamin

Commercial forms are Cyanocobalamin (R = CN) [68-19-9].

Cofactor forms are methylcobalamin ($R = CH_3$) [13422-55-4] and adenosylcobalamin (5′-deoxyadenosylcobalamin) [13870-90-1].



19.1. Metabolic Functions. Cobalamin has only two known functions in human metabolism. As methylcobalamin, it, with N^5,N^{10}-methylene THF, methylates homocysteine to methionine. The cofactor adenosylcobalamin is required for the rearrangement of methylmalonyl CoA into succinyl CoA.

19.2. Deficiency. Pernicious anemia is caused by a cobalamin deficiency. It is a megaloblastic anemia that, if not treated with cobalamin supplements, will cause destruction of myelin sheath around the nerve fibers resulting in degeneration of the peripheral nerves affecting reflexes and walking, mental deterioration, and eventually death.

Nearly all causes of cobalamin deficiencies are medical. Proper processing of dietary forms of the vitamin require two proteins produced in the stomach, R-factor that is necessary to free cobalamin from food tissues and intrinsic factor

required for intestinal uptake. Bicarbonate and calcium from the pancreas are required to free cobalamin from the R-factor in the intestine before it can combine with intrinsic factor. Thus, absorption of dietary cobalamin requires a functioning stomach, pancreas, and intestine.

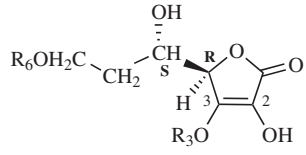
Oral cyanocobalamin dosage forms require intrinsic factor, but not R-factor. Parenteral and nasal dosage forms do not require intrinsic factor or R-factor.

19.3. Hypervitaminosis Cobalamin. There are no reported toxicities associated with high doses of the vitamin.

19.4. Dietary Sources. Meat and dairy products.

20. Ascorbic Acid (Vitamin C)

Commercial forms are ascorbic acid ($R_3 = R_6 = H$) [50-81-7], sodium ascorbate ($R_3 = Na$; $R_6 = H$) [134-03-2] and ascorbic acid palmitate ($R^3 = H$; $R^6 =$ palmitate) [137-66-6].



20.1. Chemistry. Ascorbic acid has two pK_a values. The most acidic, with a pK_a 4.2 is the enolic hydroxyl at position 3. The C-2 hydroxyl's pK_a is 11.6. The palmitic acid ester is used as an antioxidant in foods containing vegetable oil and animal fats. More recently it has appeared in the neutraceutical pantheon under the name "ester-C".

20.2. Metabolic Function. The vitamin is a water-soluble antioxidant and is necessary for the function of the following eight reactions, all of which require an oxidation: (*1*) formation of tyrosine from phenylalanine, (*2*) formation of hydroxyproline from proline, (*3*) formation of hydroxylysine from lysine, (*4*) synthesis of carnitine that is required for fatty acid transport, (*5*) reduction of folic acid to tetrahydrofolate by dihydrofolate reductase, (*6*) antioxidant in the tissues (protect vitamin A; reduce C-reactive protein levels indicating antiinflammatory properties), (*7*) hydroxylation of steroids in the adrenal gland forming hydrocortisone and cortisone, and (*8*) formation of bile acids from cholesterol.

20.3. Deficiency. The outward symptoms of an ascorbic acid deficiency are degeneration of the connective tissues. This probably is related to the inability of praline and lysine to form the hydroxylated amino acids hydroxyproline and hydroxylysine, respectively, that are found in cartilage, elastin, and other related proteins. The result is hemorrhaging, loss of teeth and improper bone growth. The deficiency disease was called scurvy when it was seen in sailors and Barlow's disease on land. The latter was seen in prisons and during the Irish potato famine.

Ascorbic acid is not a vitamin in most animals because they can synthesize it from gulose. Humans lack the ability to synthesize L-gulonolactone and oxidize it to L-ascorbic acid.

20.4. Hypervitaminosis Ascorbic Acid. The vitamin is very nontoxic. Individuals on sodium restricted diets should restrict their use of sodium ascorbate to the recommended dietary allowance (Table 3).

20.5. Dietary Sources. Fresh fruits and vegetables.

21. Vitamin Properties

Because of their diverse structures, there are few common traits to vitamin chemical properties aside from their fat or water solubility and functions. Of general concern is vitamin stability, because of their widespread use in consumer products, medical indications, and animal feed. Formulations include tablets and capsules, aqueous-based oral forms, vegetable oil and aqueous parenteral formulations, additions to commercial foods for human consumption, and a variety of products for domestic animals. Table 7 provides generic information regarding stability under several conditions. Levels of stability vary greatly and are impacted by acid or base strength, light intensity, etc.

The relative instability of many of the vitamins has led to the creation of derivatives and stabilized product forms capable of withstanding the rigors of food, animal feed, and pharmaceutical process conditions. Depending on the vitamin and application, stabilized forms may involve spray drying in a suitable matrix (eg, gelatin), encapsulation (beadletting), or coating with fats or waxes. Esterification protects retinol in the presence of acids and α-tocopherols in the presence of oxygen.

22. Vitamin Production

Preparation of the vitamins in commercial quantities can involve isolation, chemical synthesis, fermentation, and mixed processes, including chemical and fermentation steps. The choice of process is economic, dictated by the need to obtain materials meeting specifications at the lowest cost. It can change as economies of scale change. A summary of process technologies employed for each vitamin are indicated in Table 8.

23. Analytical Methods

Analytical methods for the vitamins involve physical and chemical, chromatographic, microbiological, and biological methods. The method of choice for a particular vitamin depends on the substance being measured, as well as its concentration. For example, detection of biotin, folic acid, and vitamin B_{12} is accurately achieved by high pressure liquid chromatography (hplc) or gas–liquid chromatography (glc). However, chromatographic methods often are not sufficiently sensitive for the low levels at which these vitamins usually are found. Microbiological methods, though slower, more expensive, and usually less accurate, are then employed for these low level assays. Biological assays, although extremely significant in the history of the vitamins, now are rarely used.

Commercial vitamin products for drug use must be assayed by methods defined in the country's pharmacopeia or government agency regulating their sale to the public. In addition to pharmacopeias (17), there are two comprehensive references (18,19).

24. Pseudovitamins

The 13 substances covered in this article have maintained their status as vitamins after years of intensive research into their functions and importance in diet. Over the years, other chemicals have been suggested as vitamins. They include *p*-aminobenzoic acid (PABA), pangamic acid (vitamin B_{15}), vitamin F (essential fatty acids), and choline. The PABA is a component of folic acid, but humans cannot synthesize this vitamin even with PABA present because we cannot make the pteridine ring. Indeed, PABA may overcome the antibacterial action of sulfonamides that act by blocking bacterial synthesis of folic acid. *p*-Aminobenzoic acid's use as a sunscreen is based on its absorbing uv light. There is no defined structure for pangamic acid. It may be *N*,*N*-dimethylglycine or a mixture of the *N*-methylated glycine and calcium gluconate. Although there is no question as to the essentiality of linoleic and α-linolenic acids, they are treated by the nutrition community similar to that of the essential amino acids. There are DRIs for choline (8), but there are questions as to whether dietary requirements are based on the age of the individual. Choline is produced from the nonessential amino acid serine.

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Table 1. **History of the Vitamins**[a]

Vitamin	Discovery	Isolation	Chemical structure	Synthesis
A	1909	1931	1931	1947
D	1918	1932	1936	1959
E	1922	1936	1938	1938
K	1929	1939	1939	1939
B_1	1897	1926	1936	1936
B_2	1920	1933	1935	1935
niacin	1936	1935	1937	1941
B_6	1934	1938	1938	1939
B_{12}	1926	1948	1956	1972
folic acid	1941	1941	1946	1946
pantothenic acid	1931	1938	1940	1940
biotin	1931	1935	1942	1943
C	1912	1928	1933	1933

[a]Adapted from Ref. 4.

Table 2. **Nobel Prizes for Vitamin Research**[a]

Year	Recipient	Field	Citation
1928	Adolf Windaus	chemistry	research into constitution of steroids and connection with vitamins
1929	Christiaan Eijkman	medicine, physiology	discovery of antineuritic vitamins
	Sir Frederick G. Hopkins	medicine, physiology	discovery of growth-stimulating vitamin
1934	George R. Minot, William P. Murphy, George H. Whipple	medicine, physiology	discoveries concerning liver therapy against anemias
1937	Sir Walter H. Haworth	chemistry	research into constitution of carbohydrates and vitamin C
	Paul Karrer	chemistry	research into constitution of carotenoids, flavins, and vitamins A and B_2
	Albert Szent-Györgyi	medicine, physiology	discoveries in connection with biological combustion processes, with special reference to vitamin C and catalysis of fumaric acid
1938	Richard Kuhn	chemistry	work on carotenoids and vitamins
1943	Carl Peter Henrik Dam	medicine, physiology	discovery of vitamin K
	Edward A. Doisy	medicine, physiology	discovery of chemical nature of vitamin K
1953	Fritz A. Lipman	medicine, physiology	discovery of coenzyme A (CoA) and its importance for intermediary metabolism
1964	Konrad E. Bloch, Feodor Lynen	medicine, physiology	discoveries concerning mechanism and regulation of cholesterol and fatty acid metabolism
	Dorothy C. Hodgkin	chemistry	structural determination of vitamin B_{12}
1967	Ragnar A. Granit	medicine, physiology	research that illuminated electrical properties of vision by studying wavelength discrimination by eye
	Halden K. Hartine	medicine, physiology	research on mechanisms of sight
	George Wald	medicine, physiology	research on chemical processes that allow pigments in eye retina to convert light into vision
1965	Robert B. Woodward	chemistry	outstanding achievements in the art of organic synthesis
1981	Kenichi Fukui, Roald Hoffman	chemistry	quantum mechanical studies of chemical reactivity

[a]Updated from Ref. 2.

Table 3. **RDA or AI**[a,b]

Category	Age	Vitamin A, μg/day RAE[c]	Vitamin D, μg/day[d,e]	Vitamin E, mg/day[f]	Phytonadione, μg/day	Thiamine, mg/day	Riboflavin, mg/day	Niacin niacinamide, mg/day[g]	Pyridoxine, mg/day	Pantothenic acid, mg/day	Biotin, μg/day	Folic acid, μg/day[h]	Cyanocobalamin, μg/day	Ascorbic acid, mg/day
infants	0–6 month	400[a]	5[a]	4[a]	2.0[a]	0.2[a]	0.3[a]	2[a]	0.1[a]	1.7[a]	5[a]	65[a]	0.4[a]	40[a]
	7–12 month	400[a]	5[a]	5[a]	2.5[a]	0.3[a]	0.4[a]	4[a]	0.3[a]	1.8[a]	6[a]	80[a]	0.5[a]	50[a]
children	1–3 year	300	5[a]	6	30[a]	0.5	0.5	6	0.5	2[a]	8[a]	150	0.9	15
	4–8 year	400	5[a]	7	55[a]	0.6	0.6	8	0.6	3[a]	12[a]	200	1.2	25
males	9–13 year	600	5[a]	11	60[a]	0.9	0.9	12	1.0	4[a]	20[a]	300	1.8	45
	14–18 year	900	5[a]	15	75[a]	1.2	1.3	16	1.3	5[a]	25[a]	400	2.4	75
	19–30 year	900	5[a]	15	120[a]	1.2	1.3	16	1.3	5[a]	30[a]	400	2.4	90
	31–50 year	900	5[a]	15	120[a]	1.2	1.3	16	1.3	5[a]	30[a]	400	2.4	90
	51–70 year	900	10[a]	15	120[a]	1.2	1.3	16	1.7	5[a]	30[a]	400	2.4	90
	>70 year	900	15[a]	15	120[a]	1.2	1.3	16	1.7	5[a]	30[a]	400	2.4	90
females	9–13 year	600	5[a]	11	60[a]	0.9	0.9	12	1.0	4[a]	20[a]	300	1.8	45
	14–18 year	700	5[a]	15	75[a]	1.0	1.0	14	1.2	5[a]	25[a]	400	2.4	65
	19–30 year	700	5[a]	15	90[a]	1.1	1.1	14	1.3	5[a]	30[a]	400	2.4	75
	31–50 year	700	5[a]	15	90[a]	1.1	1.1	14	1.3	5[a]	30[a]	400	2.4	75
	51–70 year	700	10[a]	15	90[a]	1.1	1.1	14	1.5	5[a]	30[a]	400	2.4	75
	>70 year	700	15[a]	15	90[a]	1.1	1.1	14	1.5	5[a]	30[a]	400	2.4	75
pregnancy	≤18 year	750	5[a]	15	75[a]	1.4	1.4	18	1.9	6[a]	30[a]	600	2.6	80
	19–30 year	770	5[a]	15	90[a]	1.4	1.4	18	1.9	6[a]	30[a]	600	2.6	85
	31–50 year	770	5[a]	15	90[a]	1.4	1.4	18	1.9	6[a]	30[a]	600	2.6	85
lactation	≤18 year	1200	5[a]	19	75[a]	1.4	1.6	17	2.0	7[a]	35[a]	500	2.8	115
	19–30 year	1200	5[a]	19	90[a]	1.4	1.6	17	2.0	7[a]	35[a]	500	2.8	120
	31–50 year	1200	5[a]	19	90[a]	1.4	1.6	17	2.0	7[a]	38[a]	500	2.8	120

[a]Adequate intake.
[b]Adapted from Ref. 10, pp. 770–771.
[c]1 Retinol activity equivalent (RAE) = 1-μg retinol = 12-μg β-carotene = 24-μg α-carotene.
[d]1 μg = 40 IU.
[e]In the absence of adequate exposure to sunlight.
[f]As RRR, RRS, RSR, and RSS α-tocopherol.
[g]As niacin equivalents (NE); 1-mg niacin = 60-mg tryptophan.
[h]As dietary folate equivalents (DFE). 1 DFE = 1-μg food folate = 0.6-μg folate from fortified food = or as a supplement consumed with food = 0.5 μg of a supplement taken on an empty stomach.

Table 4. **Tolerable Upper Limit (UL)**[a]

Category	Age	Vitamin A, μg/day[b]	Vitamin D, μg/day	Vitamin E, mg/day	Niacin, mg/day	Pyridoxine, mg/day	Folic acid, μg/day
infants	0–12 month	600	25	[c]	[c]	[d]	[e]
children	1–3 years	600	50	200	10	30	300
	4–8 years	900	50	300	15	40	400
	9–13 years	1700	50	600	20	60	600
boys	14–18 years	2800	50	800	30	80	800
men	≥19 years	3000	50	1000	35	100	1000
women	14–18 years	2800	50	800	30	80	800
	19–50 years	3000	50	1000	35	100	1000
	≥51 years	3000	50	1000	35	100	1000
pregnancy	14–18 years	2800	50	800	30	80	800
	19 and older	3000	50	1000	35	100	1000
lactation	14–18 years	2800	50	800	30	80	800
	19 and older	3000	50	1000	35	100	1000

[a]Adapted from the individual vitamin monographs in Refs. 7–10.
[b]Preformed vitamin A.
[c]Not possible to establish; source of intake should be from food and formula only.
[d]Source of intake should be formula and food only.
[e]Not possible to establish for supplemental folate.

Table 5. **Reference Values for Nutrition Labeling**[a,b]

Vitamin	Daily value
vitamin A	5000 IU, 1667 μg[c]
cholecalciferol	400 IU, 10 μg[d]
vitamin E	30 IU, 30 mg[e]
phytonadione	80 μg
thiamine	1.5 mg
riboflavin	1.7 mg
niacin/niacinamide	20 mg
pyridoxine	2.0 mg
pantothenic acid	10 mg
biotin	300 μg
folic acid	400 μg
cyanocobalamin	6.0 μg
ascorbic acid	60 mg

[a]Adapted from Ref. 12.
[b]Based on a 2000 calorie intake for adults and children 4 or more years of age.
[c]1 International Unit = 0.3 μg all-*trans* retinol.
[d]40 International Units = 1 μg.
[e]1 International Unit = 1 mg *dl*-α-tocopherol acetate.

Table 6. **Vitamin Nomenclature and Classification by Solubility and Function**[a]

Nomenclature		Classification	
U.S. pharmacopeia	Other names	Solubility	Metabolic functions
vitamin A	retinol	lipid	ligand for nuclear receptors structural component of the visual pigment rhodopsin
a. cholecalciferol b. ergocalciferol	a. vitamin D_3 b. vitamin D_2	lipid	ligand for nuclear receptor regulating cell division signaler for calcium transport across the intestinal mucosa
vitamin E	α-tocopherol	lipid	lipid soluble antioxidant. Possible cofactor
phytonadione	vitamin K_1, vitamin K	lipid	cofactor possible ligand for kinase receptors
thiamine	vitamin B_1	water	cofactor
riboflavin riboflavin-5′-phosphate	vitamin B_2, vitamin G	water	cofactor
a. niacin b. niacinamide	a. nicotinic acid b. nicotinamide a. and b; vitamin B_3, vitamin P or PP	water	cofactor
pyridoxine	vitamin B_6	water	cofactor
pantothenol calcium pantothenate	vitamin B_5 (as pantothenic acid)	water	structural component of CoA
biotin	vitamin H	water	cofactor
folic acid		water	cofactor
cyanocobalamin	vitamin B_{12}	water	cofactor
ascorbic acid	vitamin C	water	water soluble antioxidant. Although not identified as a cofactor, it is required for several oxidation reactions

[a]Even though many biochemistry and nutrition texts still use the term *coenzyme* when referring to the metabolic function of vitamins, the more general term *cofactor* will be used in this article.

Table 7. **Vitamin Stability**[a]

Vitamin	Oxygen	Light	100°C[b]	Acids[b]	Bases[b]
vitamin A[c]	U	U	S	U	S
calciferols	U	U	U	U	U
α-tocopherol[d]	U	U	S	S	S
phytonadione	S	U	S	S	U
thiamine	U	U	U	S	U
riboflavin	S	U	U	S	U
niacin/niacinamide	S	S	S	S	S
pyridoxine	S	U	U	S	S
cyanocobalamin	U	U	U	S	S
folic acid	U	U	U	U	S
pantothenic acid[e]	S	S	U	U	U
biotin	S	S	U	S	S
ascorbic acid	U	U	U	S	U

[a]S = stable; U = unstable.
[b]In absence of oxygen.
[c]Retinol acetate and palmitate are more stable than retinol in the presence of acid.
[d]Tocopherol acetate and succinate are more stable than the unesterified tocopherols in the presence of oxygen.
[e]Pantothenol and calcium pantothenate are more stable at higher temperatures than pantothenic acid.

Table 8. **Vitamin Production Processes**

Isolation	Chemical synthesis	Fermentation	Synthesis/fermentation
α-tocopherol[a]	vitamin A calciferols[b] α-tocopherol[c] phytonadione thiamine niacin/niacinamide pyridoxine folic acid pantothenol/calcium pantothenate biotin	cyanocobalamin	riboflavin ascorbic acid

[a]*(RRR)*- α-Tocopherol.
[b]Ultraviolet (uv) irradiation of 7-dehydrocholesterol or ergosterol.
[c]All-*rac*-α-tocopherol (*d,l*-α-tocopherol).