Vitamins E, C and the B complex

Their uses and misuses

Recommended dietary allowances for nutrients have important limitations in acting as a reference point for a normal vitamin usage by an individual. Many of the claims for the efficacy of large doses of vitamins are not well substantiated.

M L Wahlqvist

M L Wahlqvist, BMedSc, MD, BS, MD, FRACP, is Professor of Human Nutrition at the Department of Human Nutrition, Deakin University, Victoria.

D R Briggs

D R Briggs, MSc, PhD, DipAppChem, ARACI, AAIFST, is Lecturer in Food Chemistry at the Department of Human Nutrition, Deakin University, Victoria.

G P Jones

G P Jones, BSc, PhD, AAIFST, is Lecturer in Food Chemistry at the Department of Human Nutrition, Deakin University, Victoria.

To make a judgement on what constitutes acceptable use of vitamins it is necessary to have a reference point for normal vitamin use. This reference point is the recommended dietary allowance (RDA) and it is important that the limitations of these values be understood. RDAs for vitamins are recommendations for the average daily amounts of nutrients that are considered adequate to meet the known nutritional needs of practically all healthy persons.[1]

The RDAs are group requirements and as such do not indicate the requirements of a specific individual. There are many limitations in the use of RDAs;[2] in particular, they are recommendations for healthy people and do not allow for factors such as infections, chronic diseases or interactions with certain drugs.

Furthermore, the RDAs are calculated as the average amounts required to maintain good health; there is no indication of a level of intake above which toxic effects may be observed. Thus there is a degree of uncertainty for any individual about what constitutes an adequate amount of a given vitamin to maintain good health and what constitutes a hazardous amount.

In Australia, the dietary allowances[3] do not include values for vitamins E and B_6 or for several important minerals; it is considered likely that if a diet contains adequate amounts of the major nutrients that *are* listed, then the diet will at the same time contain adequate amounts of the nutrients that have not been listed. The most complete statement on dietary allowances is for the United States and is available from the National Academy of Science.[1] A comparison of daily allowances for selected vitamins is given in *Table 1.* Data on the nutrient content of food may be obtained from 'Tables of composition of Australian foods'[4] and a comprehensive compilation produced in the United Kingdom.[5]

Vitamin supplements

Supplementation may involve either single vitamin or mineral preparations or combined vitamin and mineral preparations. The amounts of the various nutrients in these products may not relate to the recommended daily allowance and there may be a potential hazard associated with large dosage in long term nutrient supplementation.

For those people who are at risk of nutrient deficiency and whose nutrient levels have been depleted, a period of supplementation to restore the levels rapidly may be desirable.

A recent 'Draft standard for vitamin and mineral preparations' from the National Health and Medical Research Council[6] has generated considerable controversy, mainly because of misinterpretation of the status, content and intention of this document. The Draft concluded that 'there was no need for people who consume a balanced diet to supplement their vitamin and mineral intake with supplements' and that 'the majority of those people using vitamin and mineral preparations were not those with dietary imbalances'.

Table 1
Daily allowances of selected vitamins for the adult[3] in Australia and the United States

		Vitamin E (milligram)	Vitamin C (milligram)	Thiamin (milligram)	Riboflavin (milligram)	Niacin equivalents (milligram)	Vitamin B_6 (milligram)	Vitamin B_{12} (microgram)
Australia[3]:	M	–	30	1.1	1.4	18	–	2
	F	–	30	0.8	1.0	13	–	2
United States[1]:	M	10	60	1.4	1.6	18	2.2	3
	F	8	60	1.0	1.2	13	2.0	3

The Draft considered that people using high dosage vitamin or mineral preparations or both should do so under medical supervision, especially when such preparations are used for a long period. Hazards associated with the use of vitamins E, C and the vitamin B complex are considered in the following discussion. The preferred name for these vitamins is given in *Table 2.*

Vitamin E

Vitamin E activity is shown by a number of structurally related compounds which differ in biological activity. Vitamin E activity is defined in terms of international units (IU): 1 IU is defined as having the activity of 1mg of *dl-α*-tocopheryl acetate.

The various forms of vitamin E are distributed widely in food, with vegetable and seed oils being the major contributors to the diet. Other important sources are almonds, peanuts and margarine. Eggs, liver and fish are moderate sources; small amounts are present in fruit and vegetables. In general, the largest amounts are found in the skin of fruit and in the dark green tissues of vegetables, compared with very small amounts in white tissues. Most animal products are poor sources of vitamin E.

Physiological role

There is no unified concept of the overall function of vitamin E but its most widely accepted nutritive and therapeutic role is as an antioxidant.[7]

Vitamin E deficiency is rare in man. Deficiency has been observed only in adults with an inability to absorb fat. Thus, vitamin E deficiency can develop with cystic fibrosis of the pancreas. Low birth weight infants fed infant formulae with high polyunsaturated fat and low vitamin E content have developed a form of anaemia attributed to vitamin E deficiency.[8]

Nutritional requirements

The human requirement for vitamin E depends on the polyunsaturated fatty acid (PUFA) content of the diet — which is reflected in the fatty acid composition of the tissues. The higher the PUFA composition of the diet the higher the vitamin E requirement. Daily allowances for males and females are given in *Table 1.* Such levels can be expected from a normal balanced diet. The additional requirement during pregnancy and lactation — two and three mg a day of *d-α*-tocopherol respectively — is likely to be concomitant with the additional energy requirement. Diets which are high in PUFA (with the exception of those high in marine oils) are also likely to have higher vitamin E activity.

Toxicity

Compared with the fat soluble vitamins A and D, vitamin E has a low toxicity. The literature contains a number of inconsistent and isolated reports on the adverse effects of large doses of vitamin E *(Table 3).*[9] Although other non specific complaints have been reported, it appears that at daily levels below 300 IU vitamin E is tolerated by adults.

● RDAs do not indicate nutritional requirements for an individual but the average amounts necessary to maintain health for most people. They do not indicate the levels at which an adverse response will be observed.

Table 2
Nomenclature of vitamins

Preferred name	Other names (including specific compounds)
Thiamin	vitamin B_1, vitamin F, aneurin, anti-beri beri vitamin.
Riboflavin	vitamin B_2, vitamin G, lactoflavin(e), riboflavine.
Niacin	nicotinamide, nicotinic acid, anti-pellagra factor, vitamin PP.
Vitamin B_6	pyridoxal, pyridoxine, pyridoxamine, adermin.
Vitamin B_{12}	cyano-, aqua-, hydroxo-, nitrito-cobalamin, anti-pernicious anaemia factor.
Vitamin C	ascorbic acid, L-ascorbic acid, dehydroascorbic acid, L-dehydroascorbic acid, anti-scorbutic vitamin.
Vitamin E	α-, β-, γ-, δ-tocopherol, α-, β-, γ-, δ-tocotrienol, tocopheryl and tocotrienyl esters, anti-sterility vitamin.

Clinical applications

There is a considerable amount of literature and controversy about the therapeutic efficacy of vitamin E in a wide variety of diseases. There are well established benefits of the use of vitamin E supplementation for low birth weight infants deficient in vitamin E and in dietary fat malabsorption syndromes.[10] Among adults, intermittent claudication has also been treated with vitamin E. There is no conclusive evidence that vitamin E therapy is beneficial in treating sterility or preventing abortion in humans.

Many individuals dose themselves regularly with relatively large amounts of vitamin E supplements available at retail outlets. Claims about the beneficial effects of these large doses of vitamin E are largely unsubstantiated. Several therapeutic claims which have been supported by 'good evidence' can be explained in terms of concurrent poor absorption of fat, or the consumption of abnormally large amounts of PUFAs.[11]

A well publicised claim is that vitamin E therapy protects against and is useful in the treatment of coronary heart disease; despite several attempts to do so this claim has not been confirmed.

In view of the possible side effects of large doses of vitamin E and lack of evidence of the therapeutic value of such doses considerable care should be exercised in prescribing large doses.

Table 3
Adverse responses to high dose of vitamin E[9]

Fatigue and weakness
Increased urinary creatine excretion
Allergic contact dermatitis
Ecchymoses, altered coagulation factors or both
Elevated plasma lipids
Reduced response to iron therapy
Increased urinary androgen excretion

Vitamin C

Vitamin C activity is shown by L-ascorbic acid and its oxidation product, L-dehydroascorbic acid. Further oxidation to 2,3-diketogulonic acid results in loss of vitamin C activity.

Fresh, canned and frozen citrus fruits are good sources of vitamin C. Some aboriginal bushfoods are very high in vitamin C.[12] In addition, significant quantities of this vitamin can be obtained from fruits such as blackberries, raspberries, blackcurrant juice, strawberries, peaches and pineapples, and vegetables such as cabbage, broccoli, asparagus, peas, cauliflower and potatoes.

Vitamin C can be rapidly lost during food preparation because of its water solubility and ease of oxidation. Retention can be maximised by using a minimum of water, not peeling or cutting the food, boiling water prior to addition of food, not keeping the food warm for prolonged periods and not using baking soda to preserve the colour of cooked greens.

Nutritional requirement and physiological role

The human requirement for vitamin C is difficult to estimate. The amount that will prevent scurvy is between 10 and 20 mg a day. These amounts are not necessarily the optimum intake for man, and tissue concentrations greater than that necessary to prevent scurvy may be required to

maintain other essential physiological functions. The wider role of vitamin C has generated much controversy about the optimum intake of this vitamin. A number of factors alter human requirements for vitamin C, for example: emotional and environmental stress, smoking, use of oral contraceptives, lactation, pregnancy, age and sex.[1]

The recommended intake of vitamin C varies from country to country. In Australia and the United Kingdom, the allowance for adult men is 30 mg daily. In the United States the daily allowance is 60 mg. This intake will maintain an ascorbate body pool of 1500 mg which will protect against scurvy and maintain a metabolic pool sufficient to prevent scurvy developing for several weeks on deficient diets.

Vitamin C has been credited with a role in areas other than that of scurvy prevention:

- the modification of cholesterol and other body lipids
- a possible relationship to mental depression
- weakness and fatigue due to decreased skeletal muscle function
- modification of potentially toxic substances
- susceptibility to infectious diseases.

This is the subject of a recent critical review.[13]

Pharmacological intakes of vitamin C

Large doses of vitamin C, far in excess of nutritional requirements, have been claimed to reduce the frequency and severity of the symptoms of the common cold.[14] Daily amounts of 2000 to 3000 mg and above have been suggested. In carefully controlled trials the results either have not been reproducible or have shown only a slight beneficial effect.[15]

Adverse effects of 'megadoses' of vitamin C

Several studies have suggested hazards (although rare) and potential hazards associated with the regular intake of large doses of vitamin C. Interactions with other drugs and interference with clinical measurements have also been observed.[9,13,15] In view of these factors and the lack of evidence of substantial benefits from large doses of the vitamin, it is suggested that the routine intake of such amounts is unwarranted.

Vitamin B complex

The vitamin B complex are a group of vitamins which differ widely in chemical structure and biological activity. They occur together in cereal germ, liver and yeast, and were discovered by separation from what was known originally as 'vitamin B' — hence the use of the term vitamin B complex for this group — which includes thiamin, riboflavin, niacin, vitamin B_6 and vitamin B_{12}.

Thiamin

Thiamin is essential for reactions involved in energy metabolism, particularly carbohydrate metabolism, and the requirement for thiamin has been related to energy intake. The dietary allowance in Australia has been based on 0.1 mg per 1000 kilojoules.

Good sources of thiamin are peas, beans, nuts, yeast, fortified breakfast cereals and the germ of cereals; other significant sources include fruit, other vegetables, and meat.

Thiamin is water soluble and is lost almost entirely if cooking water is discarded. The use of baking powder to maintain the green colour of vegetables should be avoided because it destroys thiamin almost totally.

Thiamin deficiency, when it affects nerve function, results in 'dry' or atrophic beri beri. As a consequence there may be impairment of sensation, loss of reflexes and ataxia. If the brain is affected the disorder is known as the Wernicke-Korsakoff syndrome. This condition occurs in chronic alcoholics when decreased food consumption, impaired absorption and an increased requirement of thiamin are important aetiological factors in thiamin deficiency.[1]

The consumption of raw fish containing thiaminase or large amounts of tea containing a thiamin antagonist can also cause thiamin deficiency, especially in those who have a marginal thiamin intake.

Thiamin deficiency can also result in 'wet' beri beri which is characterised by oedema and high output cardiac failure.

- The most widely accepted nutritive and therapeutic function of vitamin E is its role as an antioxidant.

● The amount of vitamin C necessary to prevent scurvy does not necessarily indicate the optimum intake required to maintain other essential physiological functions.

Toxicity

No toxic effects from oral thiamin have been reported but serious clinical consequences have followed high parenteral doses. These have included death from anaphylactic shock, ataxia, nausea, anorexia and hypotension.[9]

Riboflavin

Riboflavin is a constituent of two coenzymes which are essential to a number of oxidative enzyme systems. The riboflavin requirements are related to energy needs and in Australia the allowance has been set at 0.12 mg per 1000 kilojoules for adults, infants and children. Liver, kidney and heart are good sources of riboflavin as well as dairy products, eggs, yeast and green vegetables. Riboflavin is relatively stable to heat in the absence of light and major losses are likely to be due to leaching during cooking.

Deficiency of riboflavin is characterised by angular stomatitis, glossitis, seborrheic dermatitis about the nose and scrotum, and vascularisation of the cornea. Orally administered riboflavin has a low level of toxicity and doses of up to 20 mg a day have been used for treatment of deficiency.

Niacin

Niacin is a generic term for compounds which exhibit the biological activity of nicotinic acid. Deficiency of niacin results in pellagra which in the initial stages is characterised by weakness, lassitude, anorexia and indigestion, followed later by dermatitis on parts of the body exposed to sunlight or mild trauma, inflammation of the mucous membranes, diarrhoea, and in severe cases dementia.

Tryptophan is a precursor of niacin in man and therefore protein intake will influence the niacin requirement. On average, 60 mg of tryptophan is converted to 1 mg of niacin which is one niacin equivalent. In Australia, a dietary allowance of 1.6 niacin equivalents per 1000 kilojoules has been adopted. Frequently, food composition tables give only the amounts of niacin. The tryptophan content of food can be estimated by assuming that approximately one per cent of protein is tryptophan. Thus, the niacin equivalent (mg) for a food is the niacin content (mg) + 0.16 x protein content (grams). In some foods, particularly corn and wheat, all of the niacin may not be available biologically to the body. This factor must be considered if these foods provide a substantial portion of the daily niacin intake.

Good sources of niacin equivalents are fortified breakfast cereal, meat, liver, kidney, fish, peanuts and yeast. Niacin is stable during food preparation and greatest losses occur in discarded cooking water or meat exudate.

Niacin, usually in the form of the amide nicotinamide, is used therapeutically in amounts of about 10 times the daily allowance for the treatment of deficiency. In addition, niacin has been used in much larger doses in the treatment of psychiatric conditions, Hartnup's disease, hyperlipidaemia, and some circulatory disorders.[9,16,17]

Adverse reactions to the therapeutic use of niacin have been reported, including flushing, itching, gastrointestinal irritation and altered glucose tolerance.[9] Gout may be precipitated in susceptible individuals.

Vitamin B_6

Vitamin B_6 is three naturally occurring chemically related compounds — pyridoxine, pyridoxal and pyridoxamine — which have multiple roles in amino acid metabolism. There is no dietary allowance for vitamin B_6 recommended in Australia although this is currently under review.[18] The recommended dietary allowance in the United States varies from 0.3 mg for infants to 2.2 mg for adults.

Vitamin B_6 is widely distributed in food. Cereal and cereal products, kidney, liver, beef, pork, nuts, potatoes, peas, carrots, cauliflower and avocados are good sources. The vitamin B_6 content of vegetables and fruit in general is rather low.

Deficiencies in vitamin B_6 produce a number of ill defined symptoms such as insomnia, irritability, nervousness and difficulty in walking. This is followed by more characteristic symptoms including

● Adverse responses to high doses of riboflavin, vitamin B_6 and vitamin B_{12} are relatively infrequent.

mental depression, poor growth, convulsions, pellagra like dermatitis, cheilosis, angular stomatitis, glossitis, peripheral neuropathy, anaemia, impairment of antibody formation and alteration in formation of hormones affecting carbohydrate metabolism.

The requirement for vitamin B_6 is increased in a number of situations. The use of steroid oral contraceptives results in abnormal tryptophan metabolism which has been corrected by supplementation with dietary vitamin B_6. The increased requirement is considered minor and the current evidence does not appear to warrant the use of routine supplementation. Increased tryptophan excretion during pregnancy has also been prevented by vitamin B_6 supplementation, although clinical trials have suggested that there is little benefit from routine supplementation during pregnancy.[1]

Others who may be susceptible to vitamin B_6 deficiency are the elderly and alcohol abusers. The drugs isoniazid, cycloserine and penicillamin increase the requirement for vitamin B_6. Deficiency manifestations are prevented by the use of vitamin B_6 supplementation. Supplementation is also indicated in cases of inborn errors of vitamin B_6 metabolism, and vitamin B_6 responsive anaemia. There may also be an additional requirement for vitamin B_6 in thyrotoxicosis.[19]

Toxicity

The toxicity of vitamin B_6 by any route of administration is very low. The administration of vitamin B_6 has been reported as reducing the beneficial effects of L-dopa therapy in Parkinson's disease.[19]

Vitamin B_{12}

The term vitamin B_{12} should be used as a generic descriptor for all compounds exhibiting the activity of cyanocobalamin. There are a number of cobalamins containing anionic groups other than cyanide which exhibit vitamin B_{12} activity, for example aquacobalamin, hydroxocobalamin and methylcobalamin. In most clinical situations all forms of vitamin B_{12} appear equipotent. The dietary allowance of vitamin B_{12} in Australia for adults is 2 μg a day. In Australia deficiency of vitamin B_{12} resulting from an inadequate dietary intake is rare and is likely to occur only in people consuming strict vegan or faddist diets which are devoid of all animal products.

Good food sources of vitamin B_{12} are kidney, liver, brain, heart, oysters and egg yolk. Moderate quantities are found in meat, dairy products and fish. Fruit, vegetables and cereals and other plant foods usually do not contain this vitamin, unless contaminated by soil or fecal matter. Naturally occurring vitamin B_{12} is produced by micro-organisms and microbial contamination may be a source of dietary vitamin B_{12} in vegan diets. Losses of vitamin B_{12} during food preparation are generally small.

Deficiency

Most cases of vitamin B_{12} deficency are due to inadequate absorption from the gastrointestinal tract. This may be due to a number of factors such as inadequate production or unavailability of intrinsic factor, a glycoprotein produced by normal gastric parietal cells; interference with intrinsic factor function or competition for vitamin B_{12} (for example by fish tapeworm); a general or specialised malabsorption syndrome (for example, lack of releasing enzyme in intestinal juice). The claim that large doses of vitamin C taken with meals could lead to vitamin B_{12} deficiency has not been supported.[20]

Deficiency results in haematological and neurological changes.[21] The anaemia which develops is characterised by macrocytosis.

Vitamin B_{12} therapy

The only established therapeutic use of vitamin B_{12} is in treating a deficiency of this vitamin. There is inadequate evidence supporting claims for other clinical uses[21] except perhaps the use of hydroxocobalamin in the treatment of tobacco amblyopia.[22]

Toxicity

Vitamin B_{12} has very low systemic toxicity and clinically the most common adverse reactions have been hypersensitivity responses involving flushing, headache and skin reactions and in extreme cases anaphylactic shock.

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Reprint request —
Professor M L Wahlqvist
Department of Human Nutrition
Deakin University
Geelong 3217