



This is an expanded version of an editorial published in the British Medical Journal in July 2002 (Bender 2002), updated and revised in February 2007.

Healthy adults use vitamin and other supplements for two reasons:

- a) In the mistaken belief that “modern” foods are nutrient depleted, so that food does not provide adequate amounts of vitamins and minerals;
- b) To promote “optimum health”; this may be defined as current well-being and maximum resistance to future infectious and degenerative diseases. Do supplements achieve this objective?

Estimates of vitamin requirements and tables of recommended or reference intakes are amounts that are calculated to ensure that no-one suffers from deficiency; reference intakes are derived on the basis of average requirement plus twice the standard deviation around that requirement, so are higher than the requirements of almost everyone in the population (Department of Health 1991; Scientific Committee for Food 1993; Institute of Medicine 1997; 1998; 2000; 2001; FAO/WHO 2001).

There are two difficulties. The first is the definition of the word *requirement*. The US usage (Institute of Medicine 1997) is that the requirement is the lowest intake that will “maintain a defined level of nutriture in an individual” – i.e., the lowest amount that will meet a specified criterion of adequacy. The World Health Organization (WHO 1996) defines both a *basal requirement* (the level of intake required to prevent pathologically relevant and clinically detectable signs of deficiency) and a *normative requirement* (the level of intake to maintain a desirable body reserve of the nutrient).

The second difficulty is that in most developed countries vitamin deficiency is no longer a problem. We have very good markers of deficiency, at three levels: clinical, sub-clinical and biochemical, so that it is easy to determine requirements to prevent deficiency. The 2001 FAO/WHO report (FAO/WHO 2001) introduced the term “protective nutrient intake” – an amount greater than the reference intake that may protect against specified health risks of public health importance. Since we have no reliable marker that an individual enjoys “optimum health” (as defined above) it is not possible to set dietary requirements to achieve this state.

The important questions are whether levels of intake higher than current reference intakes may provide health benefits, and whether higher intakes are safe.

Safety of high intakes

Vitamins A, D, B₆ and niacin are all known to be toxic in excess. For vitamin A the intake at which toxic effects occur is about 10 – 12 times the reference intake for adults, and about 3 times the reference intake for infants and pregnant women (although, as noted below, the safety margin for adults, with respect to vitamin D function and bone health, may be considerably smaller than this). Some children are especially sensitive to vitamin D, and develop hypercalcaemia and calcinosis as a result of vitamin D intakes as low as 45 µg/day, compared with a reference intake of 5 – 10 µg (Chesney 1990; Holick 1990).

The European Federation of Health Food Manufacturers has published upper limits of vitamins and minerals for use in over-the-counter supplements (Shrimpton 1997); although these are voluntary, responsible manufacturers are likely to abide by them, and they will be superseded by new regulations in due course.

The UK report on Dietary Reference Intakes (Department of Health 1991) gave “guidance on higher intakes”; the US/Canadian reports (Institute of Medicine 1997; 1998; 2000; 2001) give “tolerable upper levels of intake” derived from the level of intake at which there is no adverse effect, divided by appropriate safety factors. The tolerable upper level is defined as the maximum level of habitual intake that is unlikely to pose any risk of adverse health effects to almost all individuals in the (stated) population group. It is a level of intake that can (with a high degree of probability) be tolerated

biologically, but is not a recommended level, and “there is no established benefit for healthy individuals consuming more than the RDA” (Institute of Medicine 1997).

The UK Foods Standards Agency’s Expert Group on Vitamins and Minerals has published a detailed analysis of the risks and benefits of a wide variety of vitamin and minerals, with safe upper levels of intake where there is adequate evidence, and guidance levels where the data are less clear, but there is evidence of undesirable effects of high levels of intake (Expert Group on Vitamins and Minerals, 2003). These will provide a basis for regulating the amount of specified nutrients permitted in supplements.

Are there benefits from higher levels of intake?

There are two ways of answering this question: to identify biomarkers of optimum nutritional status, rather than the absence of deficiency, or to identify nutrients associated with lower incidence of chronic diseases epidemiologically, followed by intervention trials. Neither has yet provided satisfactory answers, and there is little convincing evidence in favour of supplements (Fairfield & Fletcher 2002).

There are a number of promising suggestions for biomarkers, including metabolic markers of free radical damage, immune responses and damage to DNA. The problem is that we do not yet know how far these biomarkers reflect the likelihood of developing chronic degenerative diseases such as heart disease, cancer, Parkinsonism or Alzheimer’s disease. None of the biomarkers is responsive to only a single nutrient, and all are affected by many non-nutritional factors (Various authors 1996; 1999). To date we do not have any markers that can be used to determine optimum or protective intakes.

The epidemiological evidence has prompted a number of intervention trials, most of which have been disappointing.

Vitamin E and β -carotene

There is clear epidemiological evidence that people with a high plasma concentration of vitamin E are less at risk from cardiovascular disease (Gey, 1995). The Cambridge Heart Antioxidant Study (Stephens *et al.* 1996) showed a reduction in non-fatal, but an increase in fatal, myocardial infarctions. While there are obvious benefits from reducing non-fatal infarctions, this is hardly convincing evidence of the benefits of vitamin E supplements. A meta-analysis of intervention trials with vitamin E supplements (Miller *et al.* 2005) showed an increase in all-cause mortality in many studies, and a significant increase in risk with higher doses of supplements.

In the α -tocopherol β -carotene study (Alpha-Tocopherol Beta-Carotene Cancer Prevention Study Group 1994), there was a lower incidence of, and mortality from, prostate cancer in those people taking the vitamin E supplements (Heinonen *et al.* 1998). There is no clear evidence from a number of other intervention trials that vitamin E reduces cancer risk.

Similarly, there is good epidemiological evidence that high intakes of β -carotene are associated with lower incidence of lung, prostate and other cancers, although β -carotene may simply be a marker of fruit and vegetable consumption. The Physicians’ Health Study (Hennekens *et al.* 1996) was a 12 year trial in USA of β -carotene supplements which showed no effect on the incidence of cardiovascular disease or cancer. In the Linxian study in China (Blot *et al.* 1993), supplements of β -carotene, vitamin E and selenium to a marginally malnourished population reduced mortality from a variety of cancers, especially gastric cancer. By contrast, the results of two major intervention studies with β -carotene, one in Finland among smokers (Alpha-Tocopherol Beta-Carotene Cancer Prevention Study Group 1994) and the other in USA among smokers and people who had been exposed to asbestos (the carotene and retinol efficacy trial (CARET), Omenn *et al.* 1996), both yielded unexpected, and unwanted, results. In the Finnish study more people receiving the supposedly protective supplements died from lung (and other) cancer than those receiving placebo, and the CARET study was ended prematurely because of a 46% excess mortality among the intervention group. In the light of these results, the Food Standards Agency in UK is pressing for a requirement for labels to include a warning that smokers should not take supplements containing β -carotene.

Both vitamin E and carotene are antioxidants and might be expected to reduce the free radical damage that underlies the development of both cancer and cardiovascular disease. However, most

compounds that act as antioxidants do so by forming stable radicals that persist long enough to undergo metabolism to non-radical compounds. By definition they therefore form radicals that can penetrate deeper into tissues and plasma lipoproteins, and potentially cause more damage than the oxygen radicals they have replaced.

In the absence of co-antioxidants such as vitamin C, vitamin E increases the oxidative damage to plasma lipoproteins (Bowry *et al.* 1992; Upston *et al.* 1999). While β -carotene is a radical-trapping antioxidant under conditions of low oxygen availability, under conditions of high oxygen availability, as in the lungs, high intakes may lead to the formation of oxidized metabolites that are pro-oxidants (Burton & Ingold 1984). Indeed, it is instructive to read Burton and Ingold's paper; in the abstract they state that β -carotene "exhibits good radical-trapping antioxidant behavior only at partial pressures of oxygen significantly less than 150 torr, the partial pressure of oxygen in normal air. Such low oxygen partial pressures are found in most tissues under physiological conditions. At higher oxygen pressures, β -carotene loses its antioxidant activity and shows an autocatalytic, pro-oxidant, effect, particularly at relatively high concentrations." It is perhaps unfortunate, to put it mildly, that people apparently took only the title of the paper " β -Carotene, an unusual type of lipid antioxidant" as providing a plausible biological mechanisms to explain the epidemiological studies showing a protective effect of β -carotene before embarking on two large and costly intervention studies that resulted in excess mortality among those people given the apparently protective supplements.

Vitamin C

Vitamin C is an antioxidant, and also inhibits the formation of carcinogenic nitrosamines from dietary amines and nitrites. It might therefore be expected to have protective action against the development of cancer and cardiovascular disease. However, as well as being an antioxidant, vitamin C can be a source of radicals and hence a pro-oxidant. It seems likely that the pro-oxidant actions are of little importance *in vivo*. Except in cases of iron overload there are almost no metal ions in free solution to catalyse radical generation, and because at intakes above about 100 mg /day vitamin C is excreted unchanged, tissue concentrations are unlikely to rise high enough to lead to free radical formation (Halliwell 1996; Carr & Frei 1999).

The epidemiological evidence linking a high intake of vitamin C with reduced cancer incidence is confounded by the fact that the fruits and vegetables that are sources of vitamin C are also rich in a variety of other compounds that may be protective. Studies of 8-hydroxyguanine excretion as a marker of oxidative damage to DNA do not in themselves provide evidence of a protective effect of vitamin C except in people whose intake is low (Halliwell 2001).

Vitamin C deficiency is associated with an increased risk of atherosclerosis, but there is little evidence of protective effects at intakes greater than needed to meet requirements (Jacob, 1998). A systematic review (Ness *et al.* 1996) found limited evidence of benefits of high intakes of vitamin C in reducing the incidence of stroke, but inconsistent evidence with respect to coronary heart disease.

High doses of vitamin C are popularly recommended for the prevention and treatment of the common cold. The evidence from controlled trials is unconvincing. Chalmers (1975) reviewed 15 reports and considered that only 8 met the basic criteria of well-conducted scientific research. Assessment of these 8 reports gave no evidence of any beneficial effects. Similarly, Dykes & Meier (1975), reviewing only those reports which had been published in peer-reviewed journals, concluded that there was no evidence of any significant benefit. Hemila (1992) reviewed a number of studies, and again concluded that there was no evidence of a protective effect against the incidence of colds. He did, however, note that there is consistent evidence of a beneficial effect in reducing the severity and duration of symptoms (a notoriously difficult subject to research). He suggested that this might be due to the antioxidant actions of ascorbate against the oxidizing agents produced by, and released from, activated phagocytes, and hence a decreased inflammatory response. A systematic review (Douglas *et al.* 2000) similarly concluded that there was no beneficial effect in terms of preventing infection, but a modest benefit in terms of reducing the duration of symptoms.

Because vitamin C is excreted in the urine quantitatively with intake at intakes above about 100 mg /day, it has generally been assumed that high intakes are not hazardous. However, excretion of vitamin C will acidify the urine, because vitamin C is an acid. This will have the beneficial effect of reducing the formation of kidney stones of calcium phosphate and magnesium ammonium phosphate,

by increasing their solubility, but will increase the risk of forming kidney stones composed of uric acid, oxalate, cysteine and xanthine, because these compounds are less soluble at an acidic pH.

Perhaps more worryingly, Lee *et al.* (2004) studied post-menopausal women with type II diabetes. Those in the highest quintile of vitamin C intake from supplements had an almost 2-fold increase in coronary artery disease and a 2.5-fold increase in stroke, compared with those in the lowest quintile of intake. The problem here is that vitamin C will react with proteins non-enzymically, in the same way as does glucose in poorly controlled diabetes, forming glycated proteins that are associated with cardiovascular disease and the other consequences of poor glycaemic control.

Vitamin D

An intake of vitamin D above what can be obtained from normal diets (possibly in combination with supplementary calcium) delays the loss of bone with increasing age, so supplements may be advisable to prevent osteoporosis and osteomalacia (Gennari 2001). Vieth (1999) suggested that normal sunlight exposure may provide the equivalent of 20 – 50 µg /day, with possible benefits with respect to the prevention of some cancers, hypertension and the progression of osteoarthritis. For most people increased sunlight exposure is probably more effective than supplements, although we have to balance the beneficial effects on bone against increased risk of skin cancer (see HealthWatch Newsletter no 57, April 2005, for a more detailed discussion of this).

The main actions of vitamin D are mediated by way of receptors that require to form a complex with the vitamin A (retinoid X) receptor – but in the presence of high levels of retinoic acid (derived from vitamin A), the retinoid X receptors dimerise with themselves, so that they are not available to form active complexes with the vitamin D receptor. Excess vitamin A may therefore impair vitamin D function, and there is increasing evidence that intakes of vitamin A only twice the current reference intakes are associated with increased risk of osteoporosis and hip fracture (Penniston & Tanumihardjo, 2006)

Folic acid

The benefits of folic acid supplements taken periconceptually in preventing neural tube defect have been demonstrated convincingly (Department of Health 2000). High intakes of folic acid also reduce plasma homocysteine, a risk factor for cardiovascular disease independent of plasma lipids and other risk factors (Homocysteine Lowering Trialists' Collaboration 1998), and low intakes of folic acid are associated with increased risk of colo-rectal cancer (Choi & Mason 2000). This has led to mandatory fortification of cereal products in USA and elsewhere. To date, although there is evidence of a fall in average blood concentrations of homocysteine, there is no evidence of decreased cardiovascular mortality or cancer incidence.

There are concerns over the safety of widespread enrichment of foods with folic acid, including the masking of early signs of vitamin B₁₂ deficiency due to impaired gastric function in elderly people, antagonism of anti-epileptic medication and possibly enhanced progression of intestinal polyps to cancer. The UK Department of Health (2000) report suggested that if mandatory fortification of flour with folate were to be introduced, a level of 240 µg /100 g flour would provide an acceptable compromise between preventing neural tube defects and putting elderly people at risk from excessive intakes. It is difficult to achieve the necessary precision in flour fortification; at 200 µg /100g the number of neural tube defects prevented decreases, while at 280 µg /100 g the number of elderly people put at risk doubles. There is evidence that in USA and other countries where flour enrichment is mandatory, the amount present in foods is considerably higher than expected. In 2006 the Scientific Advisory Committee on Nutrition of the UK Food Standards Agency published a report (SACN 2006) that recommended mandatory enrichment of flour with folate, but with careful surveillance of the amounts actually added, noting that there was still no evidence of beneficial effects of folate other than in preventing neural tube defects.

Although folic acid lowers plasma homocysteine, there is no evidence from intervention trials that it will reduce cardiovascular disease (or cancer). In the HOPE 2 trial (HOPE 2, 2006) and the NORVIT trial (Bønna *et al.*, 2006), there was a significant reduction in serum homocysteine with folate supplementation; this was accompanied by a reduction in death from stroke (to 75% of the placebo group), but there was no effect on death from myocardial infarction or all-cause mortality. Overall the results of trials to date suggest that while plasma homocysteine is lowered by folate (and other

vitamin) supplements, and some intermediate markers of cardiovascular function show a change in the desired direction, there is no effect on mortality.

So, should healthy adults take a multivitamin tablet every day? These supplements will probably do no good – apart from folic acid taken periconceptually, and possibly vitamin D for the elderly. For children, supplements of vitamins A and D are desirable.

It is worrying that multivitamin tablets are promoted as an aid to “optimum nutrition”, or to make good a diet that is inadequate. It is not possible to show that supplements promote optimum nutrition if the diet is already adequate by WHO standards.

If the diet is not adequate, or if health risks are increased by other factors (e.g. smoking or obesity) then taking a multivitamin tablet is unlikely to help. It is even more hazardous to take a cocktail containing many nutritional supplements “to be on the safe side”. Overloading with one nutrient (e.g. a particular amino acid, vitamin or mineral) may cause disorders of metabolism of other amino acids vitamins or minerals. We evolved on a diet of mixed animal and plant foods in which the balance of nutrients is about right; to alter that balance markedly is not “to be on the safe side”.

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References

- Alpha-Tocopherol Beta-Carotene Cancer Prevention Study Group (1994). The effect of vitamin E and beta carotene on the incidence of lung and other cancers in male smokers. *New England Journal of Medicine* **330**: 1029-35.
- Bender, D. A. (2002). Daily doses of multivitamin tablets. *British Medical Journal* **325**: 173-4.
- Blot, W. J., J. Y. Li, et al. (1993). Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *Journal of the National Cancer Institute* **85**: 1483-92.
- Bønna KH, Njølstad I, Uekland PM et al (2006). Homocysteine lowering and cardiovascular events after acute myocardial infarction. *New England Journal of Medicine* 354: 1578-88.
- Bowry, V. W., K. U. Ingold, et al. (1992). Vitamin E in human low-density lipoprotein. When and how this antioxidant becomes a pro-oxidant. *Biochemical Journal* **288**: 341-4.
- Burton, G. & K. Ingold (1984). β -Carotene, an unusual type of lipid antioxidant. *Science* **224**: 569-73.
- Carr, A. & B. Frei (1999). Does vitamin C act as a pro-oxidant under physiological conditions? *FASEB Journal* **13**: 1007-24.
- Chalmers, T. C. (1975). Effects of ascorbic acid on the common cold. An evaluation of the evidence. *American Journal of Medicine* **58**: 532-6.
- Chesney, R. W. (1990). Requirements and upper limits of vitamin D intake in the term neonate, infant, and older child. *Journal of Pediatrics* **116**: 159-66.
- Choi, S. W. & J. B. Mason (2000). Folate and carcinogenesis: an integrated scheme. *Journal of Nutrition* **130**: 129-32.
- Department of Health (1991). Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. London, Her Majesty's Stationery Office.
- Department of Health (2000). Folic Acid and the Prevention of Disease. London, The Stationery Office.
- Douglas, R. M., E. B. Chalker, et al. (2000). Vitamin C for preventing and treating the common cold. *Cochrane Database Systematic Review* (2): CD000980.
- Dykes, M. H. & P. Meier (1975). Ascorbic acid and the common cold. Evaluation of its efficacy and toxicity. *Journal of the American Medical Association* **231**: 1073-9.
- Expert Group on Vitamins and Minerals (2003). Safe upper levels for vitamins and minerals, available from <http://www.food.gov.uk/multimedia/webpage/vitandmin/120281> (accessed 14/1/2007)
- Fairfield, K. M. & R. H. Fletcher (2002). Vitamins for chronic disease prevention in adults: scientific review. *Journal of the American Medical Association* **287**: 3116-26.
- FAO/WHO (2001). Human Vitamin and Mineral Requirements: Report of a joint FAO/WHO expert consultation, Bangkok, Thailand. Rome, Food and Nutrition Division of the United Nations Food and Agriculture Organization.
- Gennari, C. (2001). Calcium and vitamin D nutrition and bone disease of the elderly. *Public Health Nutrition* **4**: 547-59.

- Gey, K. F. (1995). Cardiovascular disease and vitamins. Concurrent correction of 'suboptimal' plasma antioxidant levels may, as important part of 'optimal' nutrition, help to prevent early stages of cardiovascular disease and cancer, respectively. *Biblio Nutritio et Dieta* **52**: 75-91.
- Halliwell, B. (1996). Vitamin C: antioxidant or pro-oxidant in vivo? *Free Radical Research* **25**: 439-54.
- Halliwell, B. (2001). Vitamin C and genomic stability. *Mutation Research* **475**: 29-35.
- Heinonen, O. P., D. Albanes, et al. (1998). Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. *Journal of the National Cancer Institute* **90**: 440-6.
- Hemila, H. (1992). Vitamin C and the common cold. *British Journal of Nutrition* **67**: 3-16.
- Hennekens, C. H., J. E. Buring, et al. (1996). Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *New England Journal of Medicine* **334**: 1145-9.
- Holick, M. F. (1990). The use and interpretation of assays for vitamin D and its metabolites. *Journal of Nutrition* **120 Suppl 11**: 1464-9.
- Homocysteine Lowering Trialists' Collaboration (1998). Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomized trials. *British Medical Journal* **316**: 894-8.
- HOPE 2, The Heart Outcomes Prevention Evaluation Investigators (2006) Homocysteine lowering with folic acid and B vitamins in vascular disease. *New England Journal of Medicine* **354**: 1567-77.
- Institute of Medicine (1997). Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride. Washington DC, National Academy Press.
- Institute of Medicine (1998). Dietary Reference Values for Thiamin, Riboflavin, Niacin, Vitamin B₆, Folate, Vitamin B₁₂, Pantothenic Acid, Biotin and Choline. Washington DC, National Academy Press.
- Institute of Medicine (2000). Dietary Reference Values for Vitamin C, Vitamin E, Selenium and Carotenoids. Washington DC, National Academy Press.
- Institute of Medicine (2001). Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium and Zinc. Washington DC, National Academy Press.
- Jacob, R. A. (1998). Vitamin C nutriture and risk of atherosclerotic heart disease. *Nutrition Reviews* **56**: 334-7.
- Lee DH, Folsom AR, Harnack L, Halliwell B & Jacobs DR (2004). Does supplemental vitamin C increase cardiovascular disease risk in women with diabetes? *American Journal of Clinical Nutrition* **80**: 1194-200.
- Meleady, R. & I. Graham (1999). Plasma homocysteine as a cardiovascular risk factor: causal, consequential, or of no consequence? *Nutrition Reviews* **57**: 299-305.
- Miller ER, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ & Guallar E (2005) Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Annals of Internal Medicine* **142**: 37-46.
- Ness, A. R., J. W. Powles, et al. (1996). Vitamin C and cardiovascular disease: a systematic review. *Journal of Cardiovascular Risk* **3**: 513-21.
- Omenn, G. S., G. E. Goodman, et al. (1996). Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *New England Journal of Medicine* **334**: 1150-5.
- Penniston KL & Tanumihardjo SA (2006). The acute and chronic toxic effects of vitamin A. *American Journal of Clinical Nutrition* **83**: 191-201.
- SACN Scientific Advisory Committee on Nutrition (2006) Folate and Disease prevention, available from <http://www.sacn.gov.uk/reports/#>, accessed 14/1/2007.
- Scientific Committee for Food (1993). Nutrient and Energy Intakes for the European Community. Luxemburg, Commission of the European Communities.
- Shrimpton, D. (1997). Vitamins and Minerals: A Scientific Evaluation of the Range of Safe Intakes. European Federation of Health Product Manufacturers Associations, Brussels.
- Stephens, N. G., A. Parsons, et al. (1996). Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *Lancet* **347**: 781-6.
- Upston J, Terentis A et al. (1999). Tocopherol-mediated peroxidation of lipoproteins: implications for vitamin E as a potential antiatherogenic supplement. *FASEB Journal* **13**: 977-94.
- Various authors (1996). New Approaches to define Nutrient Requirements. *American Journal of Clinical Nutrition* **63**: 983s-1001s.
- Various authors (1999). Symposium on Optimum Nutrition. *Proceedings of the Nutrition Society* **58**: 395-512.
- Vieth, R. (1999). Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *American Journal of Clinical Nutrition* **69**: 842-56.

WHO (1996). Trace Elements in Human Nutrition and Health. Geneva, World Health Organization.

Footnote

Since this position paper was written, a meta-analysis of trials of antioxidant supplements has been published, which showed increased all-cause mortality among people taking supplements of vitamins A and E, and β -carotene. Vitamin C and selenium supplements had no effect on mortality.

Bjelakovic, G., D. Nikolova, et al. (2007). "Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis." *Journal of the American Medical Association* **297**(8): 842-57.