

Beta-carotene

Function

Beta-carotene is one of many hundreds of food carotenoids, relatively few of which have been studied in relation to their impact on human physiology. Beta-carotene is the most abundant form of provitamin A in fruits and vegetables (Ross 1999; Olson 1999). The other two carotenoids with vitamin A activity, alpha-carotene and beta-cryptoxanthin, are not prevalent in foods. Beta-carotene is an effective source of vitamin A in both conventional foods and dietary supplements.

Epidemiological studies have shown that people with high dietary intakes of beta-carotene or high blood levels of this nutrient have a reduced risk of various diseases, including cancer and heart disease (van Poppel and Goldbohm 1995). The chemical abilities of beta-carotene to quench singlet oxygen and to inhibit peroxy free-radical reactions are well established (Sies and Stahl 1995). In addition to this antioxidant property, beta-carotene and some other carotenoids may play an important role in facilitating normal cell-to-cell communication through gap junctions (Acevedo and Bertram 1995). Because many carcinogens inhibit gap junction communications (Gregus and Klaassen 1996), protection of this activity by dietary substances could be an important function in the protection against cancer.

The suggestion that beta-carotene might reduce the risk of cancer is based on epidemiological evidence but has not been confirmed by clinical trials. The few clinical trials that have directly sought to determine whether beta-carotene supplements would reduce the risk of cancer have led to surprising and controversial results, including the indication that the nutrient could have a harmful effect on smokers.

Safety Evidence

Beta-carotene has been considered virtually nontoxic because humans tolerate high dietary intake without apparent harm (Bendich 1988; Hathcock et al. 1990; Diplock 1995). Standard toxicological tests, including teratogenic, mutagenic, and carcinogenic assay, have been performed on beta-carotene without any evidence of harmful effects. There is no evidence that conversion of beta-carotene to vitamin A contributes to vitamin A toxicity, even when beta-carotene is ingested in large amounts (Olson 1999). The only documented biological effect of high beta-carotene intake has been discoloration of the skin related to hypercarotenemia, but this occurs only at extremely high intake levels. Intake as high as 180 mg per day has been given to humans for several months without observed adverse effects other than changes in skin color (Mathews-Roth 1986).

Because of the extensive safety record of beta-carotene, clinical trials were designed with the assumption that the only likely effects would be beneficial. Questions about the safety of beta-carotene have been raised by the results of the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC 1994) and Carotenoid and Retinol Efficacy Trial (CARET) (Omenn et al. 1996) trials, which observed significant increases in lung cancer risk for long-term smokers and asbestos workers who were given beta-carotene supplements of 20 or 30 mg per day. On the other hand, there was evidence in the CARET study that beta-carotene may reduce the risk of lung cancer in former smokers. In contrast to the unexpected increases in lung cancer risk in the ATBC and CARET trials, no increased risk was observed in the Physicians' Health Study (PHS) (Hennekens et al. 1996) which included more than 2,000 smokers and lasted approximately twelve years, compared with the five to seven years in the ATBC and CARET trials. Three other, shorter-term trials had similar results (Blot et al. 1993; Greenberg et al. 1990; Greenberg et al. 1994). Moreover, observational studies have found that a reduced risk of lung cancer and other diseases accompanies increased beta-carotene intake (Menkes et al. 1986; Hennekens et al. 1996; Rimm et al. 1993). It has been postulated that the effects of alcohol or of high levels of retinol intake on the liver might explain the adverse outcomes with beta-carotene in the ATBC and CARET studies (Lachance 1996).

New studies using ferrets, animals that, in contrast to rats and mice, metabolize beta-carotene in a manner similar to that of humans, also suggest that high intake of beta-carotene may increase the risk of cancer, especially in the presence of cigarette smoke (Liu et al. 2000). The animal studies, however, are not sufficient to confirm a cancer risk in humans, and also do not provide an adequate basis for a quantitative extrapolation to a safe or unsafe human intake.

A recent clinical trial of the impact of beta-carotene (25 mg per day) and/or vitamins C and E (1,000 mg and 400 IU, respectively) indicated that among subjects who neither smoked nor drank alcohol, beta-carotene strongly reduced the risk of recurrent adenomas; but among smokers and drinkers, beta-carotene increased such risk (Baron et al. 2003). These data provide further evidence that beta-carotene has different effects on smokers and nonsmokers.

Published Official Reviews of Beta-carotene Safety

The FNB found no effects of high beta-carotene intake other than carotenoderma, and judged this effect to be cosmetic rather than adverse. Consequently, FNB did not set a UL based on this effect (Food and Nutrition Board 2000). The organization did find that there was a potential for beta-carotene to increase the risk of lung cancer in smokers, but considered the evidence to be inconsistent and not sufficient for a dose-response assessment and the derivation of a UL value.

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The EC SCF found a possibly increased risk for smokers with beta-carotene supplementation of 20 mg or more per day (Scientific Committee on Food 2000). In addition, EC SCF noted that the evidence was insufficient to evaluate the safety of different isomeric forms in different preparations.

The UK EVM considered the evidence of increased cancer risk in smokers consuming 20 mg of beta-carotene per day to be compelling, but of uncertain application to other persons (Expert Group on Vitamins and Minerals 2003). Thus, UK EVM identified a LOAEL of 20 mg and cautiously selected a UF of 3 to derive an SUL of 7 mg for most adults. Furthermore, it recommended that smokers or those exposed to asbestos refrain from taking any supplemental beta-carotene.

CRN ULS for Beta-carotene

Extensive data show that beta-carotene supplements of 50 mg every other day (the equivalent of 25 mg per day) can be taken for more than a decade without harm based on study of a large group of mostly nonsmokers (Hennekens et al. 1996). An intake of 25 mg per day is therefore selected as the OSL for nonsmokers. Skin discoloration may occur with larger amounts, but this effect should be considered undesirable rather than adverse. It is harmless and self-correcting with intake reduction.

The only evidence of adverse effects of beta-carotene comes from the ATBC and CARET studies, which involved long-term heavy smokers and asbestos workers. These data suggest a LOAEL of 20 mg per day for smokers or asbestos workers, but disparities between the ATBC and CARET results and other data prevent confident identification of any LOAEL for beta-carotene. Smokers and asbestos workers should first control these health risks.

Comparison of Safety Values for Beta-carotene

CRN ULS (OSL method)	25 mg, nonsmokers; (no supplement for smokers)
US FNB UL	Reviewed but not established; smokers should not use
EC SCF UL	Reviewed but not established; risk for smokers
EC supplement maximum	Not established (as of May 2004)
UK EVM SUL, supplement (LOAEL , 3)	7 mg (smokers should not use)

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