Beta-Carotene

Introduction

Beta-carotene is one of many hundreds of food carotenoids, relatively only 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 (Olson 1994; Ross 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 vitamin supplements, and it’s generally safe.

Epidemiological studies have shown that people with high 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 peroxyl 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 results, including the suggestion that the nutrient could have a harmful effect on smokers.

The results of the Carotenoid and Retinol Efficacy Trial (CARET study) (Omenn et al. 1996) and the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC 1994) showed increased rates of lung cancer with beta-carotene supplementation in long-term smokers who continued to smoke. Conversely, the Physicians’ Health Study (PHS) (Hennekens et al. 1996) found that beta-
Beta-carotene had no effect, either helpful or harmful, on any cancer. The ATBC and CARET trials studied populations at very high risk for lung cancer, and because the duration of treatment was far shorter than the induction time for this cancer, these trials ultimately do not support—but also do not disprove—the hypothesis that beta-carotene could be anticarcinogenic in the early stages of cancer.

**Safety Considerations**

Beta-carotene has been considered virtually nontoxic because humans tolerate high dietary dosages without apparent harm (Bendich 1988; Hathcock et al. 1990; Diplock 1995). Standard toxicological tests, including teratogenic, mutagenic, and carcinogenic assays, 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 1994). 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. Intakes as high as 180 mg per day have been given to humans for several months without observed adverse effects other than changes in skin color (Mathews-Roth 1986).

Because of the extensive toxicological safety record of beta-carotene, clinical trials were designed with the assumption that the only likely effects would be beneficial. However, questions about the safety of beta-carotene have been raised by the results of the ATBC and CARET 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 PHS trial, which included more than 2,000 smokers and lasted approximately 12 years, compared with the 5 to 7 years in the ATBC and CARET trials. Three other, shorter-term trials had similar results (Greenberg et al. 1990; Blot et al. 1993; 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; Rimm et al. 1993; Hennekens 1996). 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).

In 2012, the European Food Safety Authority (EFSA) reviewed the possible link between the ingestion of beta-carotene and cancer enhancement in heavy smokers. EFSA noted the findings of the ATBC study and CARET trials and also identified a meta-analysis of randomized controlled trials (RCT), which demonstrated a lack of protection associated with beta-carotene supplementation against cancer risk (Druesne-Pecollo et al. 2010). The meta-analysis, which included the ATBC and CARET trials, indicated an overall increased risk of lung cancers in subjects supplemented with beta-carotene compared with placebo. In subgroup analyses, increased risk of lung cancers was also reported when supplemental beta-carotene was provided in combination with other antioxidants, in individuals supplemented with 20 to 30 mg beta-carotene per day, in populations composed only of smokers or asbestos workers, and in populations with a majority of men. In contrast, no increased lung cancer incidence was reported at supplemental dose levels of beta-carotene varying from 6 to 15 mg per day for about 5 up to 7 years. EFSA concluded that exposure to beta-carotene from its use as a food additive and as a food supplement at a level below 15 mg per day does not give rise to concerns about adverse health effects in the general population, including heavy smokers.

Studies using ferrets, which in contrast to rats and mice metabolize beta-carotene in a manner similar to that of humans, demonstrated inconsistent findings with respect to lung carcinogenesis. Results of one study suggest that high intakes of beta-carotene (in an unstable, nonprotected form) may increase the risk of lung cancer as shown by histopathological changes, especially in the presence of cigarette smoke (Liu et al. 2000; Wolf 2002); however, experiments conducted with protected forms of beta-carotene did not show histopathological changes in the lungs (Kim et al. 2006; Fuster et al. 2008). The limited animal studies 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 clinical trial of the impacts 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 colorectal adenomas; but among smokers and drinkers, beta-carotene increased the risk (Baron et al. 2003). These data provide further evidence that beta-carotene has different effects on smokers and nonsmokers.

**Official Reviews**

**Institute of Medicine (IOM 2000).** The IOM found no effects of high beta-carotene other than carotenodermia, and it judged this effect to be cosmetic rather than adverse. Consequently, the IOM did not set a UL based on this effect. 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.

**European Commission, Scientific Committee on Food (EC SCF 2000).** The EC SCF found a possibly increased risk for smokers with beta-carotene supplementation of 20 mg or more per day, but concluded that there were insufficient data to set a precise figure for a UL. In addition, it noted that the evidence was insufficient to evaluate the safety of different isomeric forms in different preparations.

**Expert Group on Vitamins and Minerals (EVM 2003).** The UK’s 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. Thus, it 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.

**EFSA (2012).** EFSA concluded that beta-carotene exposure at a level below 15 mg per day, from its use as a food additive and as a food supplement, does not give rise to concerns with regard to adverse health effects in the general population. It also stated that no sensitive groups
were identified from the available evidence at this exposure; therefore, the term *general population* encompasses all groups, including heavy smokers.

**CRN Recommendations**

Extensive data show that beta-carotene supplements of 50 mg every other day (the equivalent to 25 mg per day) can be taken for more than a decade without harm in a large group of mostly nonsmokers (Hennekens et al. 1996). An intake of 25 mg per day is therefore selected as the highest observed intake (HOI) 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, then evaluate whether beta-carotene supplements are safe.

**Quantitative Summary for Beta-Carotene**

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<thead>
<tr>
<th></th>
<th>CRN UL, supplemental intake</th>
<th>IOM UL, total intake</th>
<th>EC SCF UL, total intake</th>
<th>EFSA, food additive and supplement maximum</th>
<th>EC supplement maximum</th>
<th>EVM SUL, supplemental intake</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>25 mg/day for nonsmokers; smokers should not use</td>
<td>Not determined</td>
<td>Not determined</td>
<td>&lt;15 mg/day</td>
<td>Not determined</td>
<td>7 mg/day for nonsmokers; smokers should not use</td>
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References


