European Food Safety Authority

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SCIENTIFIC OPINION

Statement on the safety of β-carotene use in heavy smokers[1]

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS)[2,]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following a request by the European Commission the Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to conclude on the possible link between the ingestion of β-carotene and cancer enhancement in heavy smokers. The safety of (synthetic) β-carotene [E 160a (ii)] has been evaluated previously by JECFA (1975) and by the SCF (2000a). In 2000, the SCF concluded that there were insufficient data to set a precise figure for a Tolerable Upper Intake Level (UL) of β-carotene (SCF, 2000b). Unexpectedly, two independent trials revealed that heavy smokers (at least 1 package/day for 36 years on average) receiving long-term β-carotene (20 mg/day) supplementation or β-carotene (30 mg/day) + retinol (25 000 International Unit (IU) vitamin A) supplementation, showed increased rather than decreased incidences of lung cancer. A meta-analysis of randomized controlled trials (RCT) demonstrated absence of any protective effect associated with β-carotene supplementation with regard to cancer risk. Epidemiological studies reported no increased lung cancer incidence in heavy smokers at supplemental dose levels of β-carotene varying from 6 – 15 mg/day for about 5 up to 7 years. The Panel concluded that exposure to β-carotene from its use as food additive and as food supplement at a level below 15 mg/day do not give rise to concerns about adverse health effects in the general population, including heavy smokers.

KEY WORDS

Safety, β-carotene, heavy smokers

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SUMMARY

Following a request by the European Commission the Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to conclude on the possible link between the ingestion of β-carotene and cancer enhancement in heavy smokers.

The safety of (synthetic) β-carotene [E 160a (ii)] has been evaluated previously by JECFA (1975) en the SCF (2000a). In 2000, the SCF concluded that there were insufficient data to set a precise figure for a Tolerable Upper Intake Level (UL) of β-carotene (SCF, 2000b).

In the past, high serum β-carotene levels have been associated with a decrease in incidence of cancer, including lung cancer, in humans (Mayne, 1996; Ziegler et al., 1996). However, the ATBC study and CARET trials (ATBC Study group, 1994; Omenn et al., 1996a; 1996b; Omenn, 1998) unexpectedly revealed that heavy smokers (at least 1 package/day for 36 years on average) receiving long-term β-carotene (20 mg/day) supplementation (ATBC) or β-carotene (30 mg/day) + retinol (25 000 International Unit (IU) vitamin A) supplementation (CARET), showed increased rather than decreased incidences of lung cancer.

In 2010, Druesne-Pecollo et al. performed a meta-analysis of randomized controlled trials (RCT) investigating β-carotene supplementation and cancer risk. They found absence of any protective effect associated with β-carotene supplementation with regard to primary cancer risk. However, their analyses indicated an increased risk of lung cancers in individuals supplemented with β-carotene at dose levels equal to or greater than 20 mg/day as well as in smokers and asbestos workers supplemented with β-carotene. A statistically significant interaction was found between β-carotene intake and smoking status.

Epidemiological studies reported no increased lung cancer incidence in heavy smokers at supplemental dose levels of β-carotene varying from 6 – 15 mg/day for about 5 up to 7 years (Druesne-Pecollo et al., 2010).

The Panel concluded that exposure to β-carotene from its use as food additive and as food supplement at a level below 15 mg/day do not give rise to concerns about adverse health effects in the general population, including heavy smokers.

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BACKGROUND AS PROVIDED BY EUROPEAN COMMISSION

On 14th of March 2012 the ANS Panel published the scientific opinion on the re-evaluation of mixed carotenes (E 160a (i) and β-carotene (E 160a (ii) as a food additive. However, in the view of the European Commission, this opinion did not specifically conclude on the possible link between the ingestion of β-carotene and cancer enhancement in heavy smokers, nor does it provide the Commission with an upper safe level for β-carotene for this category of the population, as requested in the initial mandate of 27th of February 2009.

The European Food Safety Authority (EFSA) has informed the Scientific Panel on Food Additives and Nutrient Sources added to food (ANS) that on 25th of June 2012, the European Commission has requested EFSA to give further guidance on the basis of the previous mandate on safe use of β-carotene sent to EFSA (ref: EFSA-Q-2009-00830); i.e. to review the existing data on the possible link between β-carotene and cancer enhancement in heavy smokers, to advise the Commission on an upper safe level of intake (UL) of β-carotene in heavy smokers, and if not possible to set an UL, to provide advice on a daily intake of β-carotene that does not give rise to concerns about adverse health effects in heavy smokers.

TERMS OF REFERENCE AS PROVIDED BY EUROPEAN COMMISSION

The ANS will produce a Panel Statement on the above request for the European Commission to provide advice on a daily intake of β-carotene that does not give rise to concerns about adverse health effects in heavy smokers.

EVALUATION

Following a request by the European Commission the Scientific Panel on Food Additives and Nutrient Sources added to Food (ANS) was asked to conclude on the possible link between the ingestion of β-carotene and cancer enhancement in heavy smokers.

The safety of (synthetic) β-carotene [E 160a (ii)] has been evaluated previously by Joint FAO/WHO Expert Committee on Food Additives JECFA (1975) and by the Scientific Committee for Food (SCF) (2000a). In 2000, the SCF concluded that there was insufficient data to set a precise figure for a Tolerable Upper Intake Level (UL) of β-carotene (SCF, 2000b).

In the past, high serum β-carotene levels have been associated with a decrease in incidence of cancer, including lung cancer, in humans (Mayne, 1996; Ziegler et al., 1996). However, the ATBC study and CARET trials (ATBC Study group, 1994; Omenn et al., 1996a; 1996b; Omenn, 1998) unexpectedly revealed that heavy smokers (at least 1 package/day for 36 years on average) receiving long-term β-carotene (20 mg/day) supplementation (ATBC) or β-carotene (30 mg/day) + retinol (25 000 International Unit (IU) vitamin A) supplementation (CARET), showed increased rather than decreased incidences of lung cancer.

In 2009, DSM conducted an extensive review of the scientific literature, published since 2000 on the relationship between β-carotene supplementation and cancer risk. The negative effects observed in heavy smokers in the ATBC and CARET studies were not seen in any other intervention study. Therefore, the authors concluded that the increased lung cancer incidence in β-carotene supplemented smokers has been demonstrated to be specific to individuals who chronically smoke more than 20 cigarettes per day.

Druesne-Pecollo et al. (2010) performed a systematic review and meta-analysis of randomized controlled trials (RCT) investigating β-carotene supplementation and cancer risk. The meta-analysis from these studies, including 180 702 subjects and 1852 cases of lung cancer, gave a significant overall increased Relative Risk (RR) of 1.13 (95% Confidence Interval (CI), 1.04 – 1.24) in subjects supplemented with β-carotene compared to those receiving placebo. Compared to corresponding placebo groups, the risk of lung cancer was significantly increased in subjects supplemented either with β-carotene in combination with other antioxidants (RR of 1.16; 95% CI, 1.04 – 1.29) or with doses of 20 mg/day of β-carotene and above (RR, 1.16; 95% CI, 1.06 – 1.27). Significantly increased overall RR were also found for subjects supplemented with β-carotene in populations exclusively composed of smokers or asbestos workers (RR, 1.20; 95% CI, 1.07 – 1.34) as well as in populations with a majority of men (RR, 1.14; 95% CI, 1.04 – 1.25) compared to the control groups. No significant effect of β-carotene supplementation was observed in the other subgroup analyses.

The authors found absence of any protective effect associated with β-carotene supplementation with regard to primary cancer risk. However, their analyses indicated an increased risk of lung cancers in individuals supplemented with β-carotene at dose levels equal to or greater than 20 mg/day as well as in smokers and asbestos workers supplemented with β-carotene. A statistically significant interaction was found between β-carotene intake and smoking status.

Epidemiological studies reported no increased lung cancer incidence in heavy smokers at supplemental dose levels of β-carotene varying from 6 – 15 mg/day for about 5 up to 7 years (Druesne-Pecollo et al., 2010).

CONCLUSIONS

The Panel concluded that exposure to beta-carotene from its use as food additive and as food supplement at a level below 15 mg/day do not give rise to concerns about adverse health effects in the general population. The Panel noted that as no sensitive groups were identified from the available evidence at this exposure, the term general population covers all groups including heavy smokers.

DOCUMENTATION PROVIDED TO EFSA

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GLOSSARY/ABBREVIATIONS

ANS	Scientific Panel on Food Additives and Nutrient Sources added to Food
CARET	β-Carotene and Retinol Efficacy Trial
CI	Confidence Interval
EFSA	European Food Safety Authority
IU	International Unit
JECFA	Joint FAO/WHO Expert Committee on Food Additives
UL	Tolerable Upper Intake Level
RR	Relative Risk
RCT	Randomized Controlled Trials
SCF	Scientific Committee for Food