



WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

^{SE}
IARC Handbooks of Cancer Prevention

Carotenoids

Volume 2

This publication represents the views and expert opinions
of an IARC Working Group on the
Evaluation of Cancer-preventive Agents,
which met in Lyon,

10–16 December 1997

1998

Published by the International Agency for Research on Cancer,
150 cours Albert Thomas, F-69372 Lyon cedex 08, France

© International Agency for Research on Cancer, 1998

Distributed by Oxford University Press, Walton Street, Oxford, UK OX2 6DP (Fax: +44 1865 267782) and in
the USA by Oxford University Press, 2001 Evans Road, Carey, NC 27513, USA (Fax: +1 919 677 1303).

All IARC publications can also be ordered directly from IARC Press
(Fax: +33 4 72 73 83 02; E-mail: press@iarc.fr).

Publications of the World Health Organization enjoy copyright protection in
accordance with the provisions of Protocol 2 of the Universal Copyright Convention.
All rights reserved.

The designations used and the presentation of the material in this publication do not imply the
expression of any opinion whatsoever on the part of the Secretariat of the World Health Organization
concerning the legal status of any country, territory, city, or area or of its authorities,
or concerning the delimitation of its frontiers or boundaries.

The mention of specific companies or of certain manufacturers' products does not imply
that they are endorsed or recommended by the World Health Organization in preference to others
of a similar nature that are not mentioned. Errors and omissions excepted,
the names of proprietary products are distinguished by initial capital letters.

The authors alone are responsible for the views expressed in this publication.

The International Agency for Research on Cancer welcomes requests for permission to
reproduce or translate its publications, in part or in full. Applications and enquiries should be addressed
to the Editorial & Publications Service, International Agency for Research on Cancer,
which will be glad to provide the latest information on any changes made to the text, plans for new
editions, and reprints and translations already available.

IARC Library Cataloguing in Publication Data

Carotenoids/
IARC Working Group on the Evaluation of
Cancer Preventive Agents (1997 : Lyon,
France)

(IARC handbooks of cancer prevention ; 2)

1. Carotenoids – congresses. I. IARC Working Group on the Evaluation of Cancer Preventive Agents II Series

ISBN 92 832 3002 7
ISSN 1027-5622

(NLM Classification: W1)

16491

International Agency For Research On Cancer

The International Agency for Research on Cancer (IARC) was established in 1965 by the World Health Assembly, as an independently financed organization within the framework of the World Health Organization. The headquarters of the Agency are in Lyon, France.

The Agency conducts a programme of research concentrating particularly on the epidemiology of cancer and the study of potential carcinogens in the human environment. Its field studies are supplemented by biological and chemical research carried out in the Agency's laboratories in Lyon and, through collaborative research agreements, in national research institutions in many countries. The Agency also conducts a programme for the education and training of personnel for cancer research.

The publications of the Agency contribute to the dissemination of authoritative information on different aspects of cancer research. A complete list is printed at the back of this book. Information about IARC publications, and how to order them, is also available via the Internet at: <http://www.iarc.fr/>

167491

icer,
se

: +44 1865 267782) and in
(Fax: +1 919 677 1303).
Press

tection in
ht Convention.

ion do not imply the
rld Health Organization
its authorities,
as.

ts does not imply
n preference to others
excepted,
ital letters.

publication.

for permission to
ies should be addressed
arch on Cancer,
the text, plans for new
s.

on the Evaluation of Cancer

cation: W1)

Contents

List of Participants	1
-----------------------------------	---

Preamble	3
-----------------------	---

General Remarks	15
------------------------------	----

Carotenoids

1	Chemical and physical characteristics of carotenoids	23
1.1	Structure and nomenclature	23
1.2	General properties	27
	1.2.1 Relationships between structure, properties and biological activity	27
	1.2.2 Molecular size and shape	27
	1.2.3 Solubility	27
	1.2.4 Properties and molecular interactions of carotenoids <i>in vivo</i>	27
1.3	Properties of the conjugated polyene chain	28
	1.3.1 Light absorption and photochemical properties	28
	1.3.2 Chemical properties	28
1.4	Isolation and analysis	29
	1.4.1 General methods	29
	1.4.2 Identification	30
	1.4.3 Quantitative analysis	30
1.5	Data on individual compounds	30
	1.5.1 β -Carotene	30
	1.5.2 α -Carotene	31
	1.5.3 Lycopene	31
	1.5.4 Lutein	32
	1.5.5 Canthaxanthin	33
	1.5.6 Zeaxanthin	33
	1.5.7 β -Cryptoxanthin	34
	1.5.8 α -Cryptoxanthin	34
	1.5.9 Zeinoxanthin	35
2	Occurrence, commercial sources, use and application, analysis and human exposure 35	
2.1	Carotenes	36
	2.1.1 β -Carotene	36
	2.1.2 α -Carotene	41
	2.1.3 Lycopene	43
2.2	Xanthophylls	44
	2.2.1 Lutein and zeaxanthin	44
	2.2.2 Cryptoxanthin	45
	2.2.3 Canthaxanthin	46

3	Metabolism, kinetics and genetic variation	46	
3.1	Humans	47	
	3.1.1 Intestinal digestion and absorption	47	
	3.1.2 Transport in plasma	48	
	3.1.3 Serum carotenoid concentrations	49	
	3.1.3.1 Effects of β -carotene supplements	50	
	3.1.3.2 Effects of tobacco smoking	51	
	3.1.3.3 Effects of alcohol drinking	51	
	3.1.3.4 Effects of other modulators	52	
	3.1.4 Tissue carotenoid concentrations	52	4.3
	3.1.4.1 Effects of dietary intake	52	
	3.1.4.2 Effects of supplemental intake	54	
	3.1.5 Kinetics	54	
	3.1.6 Metabolism	55	
	3.1.6.1 β -Carotene	55	
	3.1.6.2 β -Apocarotenoids	57	
	3.1.6.3 Other carotenoids	57	
	3.1.7 Genetic variation	58	
3.2	Experimental models	58	5
	3.2.1 Non-human primates	58	5.1
	3.2.2 Preruminant calves and cows	59	5.2
	3.2.3 Ferrets	61	5.3
	3.2.4 Rats	62	5.4
	3.2.5 Other animal species	63	
	3.2.6 Conclusion	64	6
			6.1
4.	Preventive effects	64	
4.1	Humans	64	
	4.1.1 Studies of cancer occurrence	64	
	4.1.1.1 Observational studies based on blood and other tissue measures of carotenoids	64	6.2
	4.1.1.2 Observational studies based on dietary questionnaires	92	6.3
	4.1.1.3 Intervention trials	118	7
	4.1.2 Studies of intermediate end-points	130	7.1
	4.1.2.1 Observational studies of dietary and serum carotenoids	130	
	4.1.2.2 Experimental studies of colorectal adenoma	131	
	4.1.2.3 Experimental studies of cellular dysplasia and atypia	131	7.2
	4.1.2.4 Experimental studies of oral leukoplakia	132	
	4.1.2.5 Experimental studies of cell proliferation	133	
	4.1.2.6 Experimental studies of chromosomal damage	134	7.3
	4.1.2.7 Experimental studies of immunological end-points	135	
	4.1.2.8 Summary	136	
4.2	Experimental models	137	
	4.2.1 Experimental animals	137	
	4.2.1.1 β -Carotene	137	
	4.2.1.2 β -Carotene with other potential inhibitors	179	
	4.2.1.3 Canthaxanthin	191	
	4.2.1.4 Canthaxanthin with other potential inhibitors	205	
	4.2.1.5 Lycopene	207	

.....	46	4.2.1.6 Lutein	211
.....	47	4.2.1.7 α -Carotene	212
.....	47	4.2.1.8 Fucoxanthin	215
.....	48	4.2.1.9 Astaxanthin	215
.....	49	4.2.1.10 Crocetin	216
.....	50	4.2.1.11 Mixtures of carotenoids	216
.....	51	4.2.1.12 Other end-points	219
.....	51	4.2.2 Cells	220
.....	52	4.2.2.1 Mammalian cells <i>in vitro</i>	220
.....	52	4.2.2.2 Antimutagenicity in short-term tests	229
.....	52	4.3 Mechanisms of cancer prevention	251
.....	54	4.3.1 Antioxidant properties	251
.....	54	4.3.2 Modulation of carcinogen metabolism	254
.....	55	4.3.3 Effects on cell transformation and differentiation	254
.....	55	4.3.4 Effects on cell-to-cell communication	254
.....	57	4.3.5 Inhibition of cell proliferation and oncogene expression	254
.....	57	4.3.6 Effects on immune function	254
.....	58	4.3.7 Inhibition of endogenous formation of carcinogens	254
.....	58	5 Other beneficial effects	255
.....	58	5.1 Photosensitivity disorders	255
.....	59	5.2 Cardiovascular disease	255
.....	61	5.3 Age-related macular degeneration and cataract	257
.....	62	5.4 Other effects	259
.....	63	6 Carcinogenicity	259
.....	64	6.1 Humans	259
.....	64	6.1.1 ATBC study	259
.....	64	6.1.2 CARET	259
.....	64	6.1.3 Interpretation of trials suggesting carcinogenicity	260
.....	64	6.2 Experimental animals	261
.....	64	6.3 Mechanisms of carcinogenicity	262
.....	92	7 Other toxic effects	263
.....	118	7.1 Toxic and other adverse effects	263
.....	130	7.1.1 Humans	263
.....	130	7.1.2 Experimental animals	264
.....	131	7.2 Reproductive and developmental effects	264
.....	131	7.2.1 Humans	264
.....	132	7.2.2 Experimental animals	265
.....	133	7.3 Genetic and related effects	266
.....	134	7.3.1 Humans	265
.....	135	7.3.2 Experimental systems	266
.....	136	7.3.2.1 <i>In vitro</i>	266
.....	137	7.3.2.2 <i>In vivo</i>	270
.....	137		
.....	137		
.....	179		
.....	191		
.....	205		
.....	207		

8	Summary of data	270
8.1	Chemistry, occurrence and human exposure	270
8.2	Metabolism and kinetics	270
	8.2.1 Humans	270
	8.2.2 Experimental models	271
8.3	Cancer-preventive effects	271
	8.3.1 Humans	271
	8.3.2 Experimental systems	271
	8.3.2.1 Cancer-preventive activity	272
	8.3.2.2 Genetic and related effects	272
	8.3.3 Mechanisms of cancer prevention	275
8.4	Other beneficial effects	275
8.5	Carcinogenic effects	276
	8.5.1 Humans	276
	8.5.2 Experimental animals	276
8.6	Other toxic effects	276
	8.6.1 Humans	276
	8.6.2 Experimental systems	276
9	Recommendations for research	276
10	Evaluation	278
10.1	Cancer-preventive activity	278
	10.1.1 Humans	278
	10.1.2 Experimental animals	278
10.2	Overall evaluation	278
11	References	281
Appendix 1	The concept of activity profiles of mutagenicity	323
Appendix 2	Definitions of test codes	326

List of participants

Volume 2. Carotenoids

Lyon, 10-16 December 1997

.....270
270
270
270
271
271
271
271
271
272
272
275
275
276
276
276
276
276
276
276
276
276
278
278
278
278
278
278
281
323
326

J.A. Baron
 7927 Rubin Bldg
 Dartmouth-Hitchcock Medical Center
 1 Medical Center Drive
 Dartmouth Medical School
 Lebanon, NH 03756
 USA

J.S. Bertram
 Cancer Research Center of Hawaii
 University of Hawaii
 1236 Lauhala St
 Honolulu, HI 96813
 USA

G. Britton
 The University of Liverpool
 Life Sciences Building
 School of Biological Sciences
 Crown Street
 Liverpool L69 7ZB
 United Kingdom

E. Buiatti
 Centro di Documentazione per la Salute
 Via Triacchini 17
 40100 Bologna
 Italy

S. De Flora
 Institute of Hygiene and Preventive Medicine
 University of Genoa
 Via A. Pastore 1
 16132 Genoa
 Italy

V.J. Feron
 TNO-Nutrition and Food Research Institute
 Toxicology Division
 PO Box 360
 3700 AJ Zeist
 The Netherlands

M. Gerber
 Centre de Recherche en Cancerologie
 Centre Val d'Aurelle
 Parc Euromedicine
 34298 Montpellier Cedex 5
 France

E.R. Greenberg
 Norris Cotton Cancer Center
 Dartmouth-Hitchcock Medical Center
 1 Medical Center Drive
 Lebanon, NH 03756
 USA

R.J. Kavlock
 Reproductive Toxicology Division (MD-71)
 United States Environmental Protection Agency
 NHEERL
 Research Triangle Park, NC 27711
 USA

P. Knekt
 National Public Health Institute
 Mannerheimintie 166
 00300 Helsinki
 Finland

W. Malone
 Chemoprevention Branch
 National Cancer Institute
 Executive Plaza North
 Suite 201
 Bethesda, MD 20892
 USA

S.T. Mayne
 Department of Epidemiology and Public Health
 School of Medicine
 Yale University,
 60 College Street
 PO Box 208034
 New Haven, CT 06520-8034
 USA

H. Nishino
 Department of Biochemistry
 Kyoto Prefectural University of Medicine
 Kawaramachi-Hirokoji
 Kamigyo-ku
 Kyoto 602
 Japan

J.A. Olson
 Iowa State University
 Biochemistry and Biophysics Department
 Ames, Iowa 50011
 USA

H. Pfander
Department of Chemistry and Biochemistry
University of Bern
Freiestrasse 3
3012 Bern
Switzerland

W. Stahl
Institut für Physiologische Chemie I
Heinrich-Heine Universität
Postfach 10 37 51
4000 Dusseldorf
Germany

D.I. Thurnham
Howard Professor of Human Nutrition
University of Ulster
Coleraine County, Londonderry
BT52 1SA
United Kingdom

J. Virtamo
National Public Health Institute
Mannerheimintie 166
00300 Helsinki
Finland

R.G. Ziegler
Nutritional Epidemiology Branch
National Cancer Institute
Executive Plaza North 430
Bethesda, MD 20892
USA

Observers:

P. Astorg
INRA, Centre de Recherches de Dijon
Unité de Toxicologie Nutritionnelle
BP 1540
17 rue Sully
21034 Dijon Cedex
France

R. Goralczyk
F. Hoffmann-La Roche Ltd
Vitamins & Fine Chemicals
Human Nutrition and Health
Carotenoid Research Group
CH-4070 Basel
Switzerland

R.M. Salkeld
F. Hoffmann-La Roche Ltd
Vitamins & Fine Chemicals
Human Nutrition and Health
Vitamin Research Group
CH-4070 Basel
Switzerland

J.F. Steghens
Fédération de Biochimie
Hôpital Edouard Herriot
69437 Lyon Cedex 03
France

Secretariat:

P. Boffetta
E. Heseltine (*Editor*)
R. Kaaks
V. Krutovskikh
C. Malaveille
A.B. Miller
H. Ohshima
B. Pignatelli
M. Plummer
M. Rautalahti
E. Riboli
R. Sankaranarayanan
H. Vainio (*Responsible Officer*)
J. Wilbourn
M.L. Zaidan Dagli

Technical Assistance:

M. Lézère
A. Meneghel
D. Mietton
S. Ruiz
J. Mitchell
S. Reynaud
J. Thévenoux

Unable to attend:

H.K. Biesalski, Universität Hohenheim, Institut für Biologische Chemie, Institut 140, Fruwirthstr. 12, 70599 Stuttgart, Germany
G.S. Omenn, Executive Vice President for Medical Affairs, 608 Fleming Administration Building, Ann Arbor, Michigan 48109-1340, USA

Prean of Ca

The prevention
tives of the Inte
Cancer (IARC).
exposures to k
increasing host
chemopreventic
aim of the IARC
ate carcinogenic
ical, physical a
scientific basis
decisions on av
the series of IAR
to evaluate scie
interventions th
mortality from
into two parts.
scope, objective
The second desc
cancer-preventi

Part One

Scope

Preventive strat
logical, dietary
may retard, blo
or reduce under
prevention' is
pharmaceutical
chemicals to re
Handbooks add
nisms of cancer
quacy of the a
timing, dose, di

Preventive s
continuum of
(2) subgroups
or environmen
susceptibility t
cerous lesions;
second primary

conflicting results. In one study (Mukherjee *et al.*, 1991), oral administration of 27 mg/kg bw β -carotene significantly enhanced the frequencies of both micronuclei and chromosomal aberrations in bone-marrow cells of Swiss albino mice over that in controls receiving the solvent (olive oil) only. In contrast, another study (Umegaki *et al.*, 1994a) showed that β -carotene given by gavage or incorporated into a *Dunaliella bardawil* diet reduced the 'spontaneous' frequency of micronuclei in peripheral blood reticulocytes of ICR mice.

8. Summary of Data

8.1 Chemistry, occurrence and human exposure

The carotenoids are hydrophobic, lipophilic substances which, after ingestion, are absorbed with other lipids. The state in which the carotenoids occur in the food matrix, e.g. crystalline or not, their concentration, the availability of fat or oil and the presence of bile acids are major factors in determining their bioavailability. About 600 carotenoids have been isolated from natural sources, and some 100 or so of these are likely to be present in the human diet; however, of the carotenoids in serum, only six or seven have been studied in any depth, of which three are provitamin A carotenoids, i.e. β -carotene, α -carotene and β -cryptoxanthin. The main carotenoids that are addressed in this *Handbook* are found widely in fruits and vegetables and products derived from them; small amounts are also found in foods of animal origin such as some fish and crustaceans, egg yolk and dairy products. Some carotenoids, notably β -carotene, are used widely as food colourants and are produced synthetically or from biological sources for this purpose. Supplements of β -carotene, natural and synthetic, are widely available.

Fruits and green vegetables are the main sources of β -carotene and lutein in the human diet. Carrots are rich in β -carotene and are often the main source of α -carotene in temperate climates, depending on strain or variety. Tomatoes and tomato products are rich in

lycopene. Yellow maize provides zeaxanthin and β -cryptoxanthin; various fruits such as oranges, peaches, apricots, mangoes and papayas, also contain β -cryptoxanthin. There is no major dietary source of canthaxanthin, although it is found in trout, crustaceans and sometimes in egg yolk after its use as an additive in feed. Canthaxanthin has been marketed in the past as an orally administered 'tanning' agent, but this use has been discontinued in several countries. A balanced diet provides a daily intake of a few milligrams of some of these compounds; the total might range from 4 to 10 mg/day. Much higher intakes can be achieved from certain foods such as carrots, red palm oil, mangos and concentrated tomato products. If supplements are taken, the intake increases accordingly. The daily intake of each of the other carotenoids listed, namely zeaxanthin, β -cryptoxanthin, canthaxanthin and α -carotene, is likely to be 1–5 mg.

In the body, all carotenoids are found in lipid environments, especially fatty tissues and membranes. Their presence in membranes may be important in relation to their biological actions.

The long system of conjugated double bonds that constitutes the light-absorbing chromophore of the carotenoids also makes these molecules rather unstable and very reactive towards oxidizing agents and free radicals. They can have antioxidant or pro-oxidant actions *in vitro*. Although antioxidant activity *in vivo* has not been proven, this has been proposed as a possible mechanism by which carotenoids could protect against cancer and other degenerative diseases.

Routine methods for the qualitative and quantitative analysis of carotenoids in foods and in blood and body tissues are usually based on reverse-phase high-performance liquid chromatography with the use of an in-line photodiode-array detector to generate ultraviolet or visible-absorption spectra. Mass spectrometry and co-chromatography with authentic samples are required additionally for proper identification.

8.2 Metabolism and kinetics

8.2.1 Humans

In humans, carotenes and many xanthophylls are absorbed in the small intestine and appear

in lipoproteins. 20 carotenoid components are absorbed, and the amounts absorbed are those in the diet, but they are essentially being the addition of carotenoids to plasma, with

Factors that affect the concentration of carotenoids in tissues include the intake of acidic fibre and alcohol, the intake of antioxidants, and the presence of certain nutrients. In general, the concentration of carotenoids in tissues is increased by supplementation with carotenoids, either as natural or synthetic products, or by the use of a given carotenoid in a particular subject on the plasma

The only carotenoid in humans is β -carotene, and of the approximately 20 carotenoids, only β -carotene is cleaved to retinal, and although st

8.2.2 Exp

Distinct kinetics of intestinal absorption, and, to a lesser extent, in tissues. Most carotenoids are not stored in humans; they have been described in humans: they are absorbed with the information

provides zeaxanthin in various fruits such as peaches, mangoes and cryptoxanthin. There is also a source of canthaxanthin, found in trout, crustaceans and after its use as an xanthin has been normally administered 'tanned' has been discontinued. A balanced diet provides a milligram of some of which might range from 4 to 10 mg. Higher intakes can be obtained from foods such as carrots, red concentrated tomato and other sources. If these are taken, the intake of each is estimated, namely zeaxanthin and α -carotene, 5 mg.

Carotenoids are found in animal fatty tissues and in membranes may be involved in their biological actions.

The conjugated double bond system of the light-absorbing carotenoids also makes them chemically stable and very reactive towards free radicals. As antioxidants and free radical scavengers or pro-oxidant agents, their antioxidant activity is dependent on this mechanism by which they act against cancer and other diseases.

The qualitative and quantitative analysis of carotenoids in foods and tissues are usually based on the performance liquid chromatography of an in-line photodiode array ultraviolet or visible light spectrometry and the use of authentic samples are necessary for proper identification.

Metabolism

In many xanthophylls, the xanthophylls in the intestine and appear

in lipoproteins of the plasma. Although more than 20 carotenoids are found in plasma, the major components are lycopene, lutein, β -carotene, zeaxanthin, β -cryptoxanthin and α -carotene. The types and amounts of carotenoids in the plasma reflect those in the diet. Plasma carotenoids are taken up by essentially all tissues, the major repositories being the adipose tissue, liver and skin. The pattern of carotenoids in tissues reflects that in the plasma, with few exceptions.

Factors that influence serum carotenoid concentrations and presumably also those of tissues include the dietary intake of carotenoids, the fat content of the diet, the acidic fibre content of the diet, smoking, alcohol intake and food processing. The determinants of absorption and resulting blood and tissue concentrations are not well understood. In general, increased intake of both dietary and supplemental carotenoids leads to higher blood concentrations, but the bioavailability of purified or synthetic preparations is greater than that of dietary components. Oral supplements of a given carotenoid markedly increase its concentrations in plasma and tissues. In vitamin A-sufficient subjects, carotenoid intake has little effect on the plasma concentrations of retinol.

The only known function of carotenoids in humans is as precursors of vitamin A. Only 50 of the approximately 600 carotenoids in nature, however, serve this role. The major pathway of enzymatic conversion is central cleavage of the carotenoid molecule, although asymmetric cleavage can also occur. Carotenoids can also be oxidized at other positions in the molecule, although such reactions have been little studied.

8.2.2 Experimental models

Distinct interspecies differences exist in the biokinetics of carotenoids and particularly in their intestinal absorption, their transport in plasma and, to a lesser extent, their metabolism in tissues. Most of the common laboratory animals are not suitable models for biokinetics in humans; however, two animal models have been developed to mimic the situation in humans: the ferret and the preruminant calf. Although both have some limitations, studies with these species have provided important information on carotenoid uptake and metabo-

lism. Use of non-human primates has provided promising results, but further evaluation of these models is needed. Other species, such as rats, chicks and pigs, may be considered for investigating specific aspects such as metabolism.

Carotenoids are metabolized differently in different species. The most marked difference is between vertebrates that efficiently absorb intact carotenoids, such as humans, other primates, cows and birds, and those that do not, such as most rodents and pigs. Because of these differences, research in humans is particularly important.

8.3 Cancer-preventive effects

8.3.1 Humans

The results of epidemiological studies, viewed in aggregate, do not support the notion that β -carotene has generalized cancer-preventive effects. The observational data suggesting cancer-preventive effects are most consistent for lung, oral and pharyngeal cancers, the incidences of which tend to be inversely related to β -carotene (or provitamin A carotenoid) intake or blood concentrations. One difficulty in interpreting these findings is that β -carotene may be only a marker of the intake of other beneficial substances in fruits and vegetables or perhaps other lifestyle habits. No clinical trial of β -carotene as a single agent, however, has shown a reduction in the risk for cancer at any specific site, and there is evidence of an increase in the risk for lung cancer among smokers and asbestos workers receiving β -carotene supplements at high doses, which resulted in blood concentrations an average of 10–15 times higher than normal. It is worth noting that the information from clinical trials reflects the first 12 years of intervention, and, at present, there are no data on the possible effects of longer intervention. There is virtually no information on β -carotene supplementation early in the carcinogenic process. Lastly, the doses used in the intervention trials greatly exceeded those consumed in normal diets. There is only limited, inconsistent information on carotenoids other than β -carotene.

Summarized below are the results of studies on β -carotene pertaining to specific cancers. The data for other cancer sites were generally less extensive and not indicative of either protection or harm.

Lung cancer

The most extensive results with regard to β -carotene pertain to cancers of the lung and bronchus. The vast majority of observational studies of dietary intake indicate a decreased risk with higher intake of carotene. There are also extensive, consistent findings that higher blood concentrations of β -carotene are associated with a decreased risk for lung cancer. In general, people with the highest intake or blood concentration have been found to have a 20–50% lower risk than those with the lowest values. In contrast, no clinical trial of β -carotene supplementation has shown a reduction in risk, and two of the three large trials found an increase in lung cancer occurrence among smokers; one also suggested an increase in asbestos workers.

Skin cancer

The results of epidemiological studies show no reduction in the risk for skin cancer associated with β -carotene intake or blood concentrations. One clinical trial indicated no reduction in the risk for basal- or squamous-cell skin cancer after supplementation for up to five years.

Oral and pharyngeal cancers

Some observational studies have shown inverse associations between dietary intake of β -carotene (or carotene), blood carotene concentrations and the risk for oral and pharyngeal cancers. Intervention trials of intermediate markers of oral carcinogenesis (oral leukoplakia or micronuclei) with supplemental β -carotene, alone and in combination with other agents, have shown regression. Many of these trials, however, have methodological limitations.

Oesophageal cancer

Observational studies of dietary intake of provitamin A carotenoids generally suggest inverse associations with the risk for oesophageal cancer. The results of two related intervention trials are available. In one trial, supplemental β -carotene given in combination with vitamin E and selenium had no effect on the rate of mortality from oesophageal cancer. In a related trial in the same population but restricted to persons with oesophageal

dysplasia, supplemental β -carotene given with several other micronutrients was also of no benefit in preventing death from oesophageal cancer.

Gastric cancer

Some observational studies of either dietary or blood β -carotene concentrations showed inverse associations with gastric cancer or pre-cancerous gastric lesions. The results of three intervention trials are available. In one trial, supplemental β -carotene given in combination with vitamin E and selenium showed a reduction of borderline significance in the risk for gastric cancer. The population studied was known to have several micronutrient deficiencies, and the relevance of these results for well-nourished populations is unclear. In a related trial in the same population but restricted to persons with oesophageal dysplasia, supplemental β -carotene given with several other micronutrients was of no benefit in preventing mortality from gastric cancer. In a third trial, no reduction in gastric cancer risk was observed.

Colorectal cancer and adenoma

Epidemiological studies show no clear pattern of reduced risk for either invasive cancer or adenoma in relation to β -carotene intake. Two clinical trials showed no reduction in the occurrence of adenoma after supplementation with β -carotene. None of the large trials of β -carotene supplementation suggests a decrease in the occurrence of colorectal cancer.

Cervical cancer

Some observational studies have shown inverse associations between dietary intake of various carotenoids or blood carotenoid concentrations and the risk for cervical neoplasia. One trial of low-dose β -carotene supplementation in women with cervical dysplasia in the Netherlands gave no evidence of greater regression in this group.

8.3.2 Experimental systems**8.3.2.1 Cancer-preventive activity** *β -Carotene*

The cancer-preventive efficacy of β -carotene has been assessed in mouse, rat and hamster

models, virus-induced inoculated tumour

In models of respiratory β -carotene was ineffective in hamsters, and the weak enhancement in models of lung cancer. β -carotene was ineffective

The effects of β -carotene on lung carcinogenesis induced in mice were investigated in mice; β -carotene was ineffective in the two studies in which it was administered at the late stages of carcinogenesis. It was effective in preventing carcinogenesis in hamsters but was ineffective in mice given after tumour induction. It was also effective in preventing carcinogenesis in most of the studies in which it was administered. In those studies in which it was administered in combination with nitrosodiethylamine, conflicting results were observed. It did not affect the incidence of tumours in a strain of mice with spontaneous tumours. In other studies, the preventive effects of β -carotene on carcinogenesis were observed in mice and in several studies in rats. In some results were found, but they do not explain the difference in pancreatic cancer incidence. In one of two studies, a different strain emerged to explain the preventive effect of β -carotene on carcinogenesis was demonstrated in mice but not in rats. It prevented urinary tumours in one of two studies during and after tumour induction but not in one study in models of small intestine. In two studies in rats, β -carotene had effects against salivary gland tumours. In one of three studies

In one model of lung cancer in rats, β -carotene showed no effect on the incidences of pre-invasive adenocarcinomas a

-carotene given with
ents was also of no
th from oesophageal

es of either dietary or
centrations showed
gastric cancer or pre-
The results of three
ailable. In one trial,
given in combination
ium showed a reduc-
cance in the risk for
ulation studied was
icronutrient deficien-
these results for well-
unclear. In a related
ion but restricted to
al dysplasia, supple-
with several other
benefit in preventing
ncer. In a third trial,
ic cancer risk was

ma
how no clear pattern
er invasive cancer or
-carotene intake. Two
to reduction in the
fter supplementation
the large trials of β -
n suggests a decrease
rectal cancer.

es have shown inverse
ary intake of various
tenoid concentrations
eoplasia. One trial of
ementation in women
the Nether-lands gave
ression in this group.

ams activity

fficacy of β -carotene
use, rat and hamster

models, virus-induced tumour models and
inoculated tumour cells.

In models of respiratory-tract carcinogenesis,
 β -carotene was ineffective in three studies in
hamsters, and there were even indications of
weak enhancement in two of these studies. In
models of lung carcinogenesis in mice, β -
carotene was ineffective in two studies.

The effects of β -carotene against skin car-
cinogenesis induced by various carcinogens
were investigated in more than 20 studies in
mice; β -carotene was effective in almost all. In
the two studies in which it was ineffective, it
was administered only before initiation or in
the late stages of carcinogenesis. β -Carotene
was effective in preventing buccal pouch car-
cinogenesis in hamsters in about 20 studies. It
was ineffective in only one study when also
given after tumour development. β -Carotene
was also effective in preventing liver carcino-
genesis in most of about 20 studies in male rats.
In those studies involving administration of *N*-
nitrosodiethylamine or 2-acetylaminofluorene,
conflicting results were obtained. β -Carotene
did not affect the incidence of liver tumours in
a strain of mice with a high incidence of spon-
taneous tumours at this site. The cancer-pre-
ventive effects of β -carotene in models of colon
carcinogenesis were investigated in one study
in mice and in seven studies in rats. Conflicting
results were found, and no pattern emerged to
explain the differences. β -Carotene prevented
pancreatic cancer in two of three studies in rats
and in one of two studies in hamsters. No pat-
tern emerged to explain the differences. The
preventive effect of β -carotene on gastric car-
cinogenesis was demonstrated in one study in
mice but not in one study in rats. β -Carotene
prevented urinary bladder carcinogenesis in
one of two studies in mice when given before,
during and after carcinogen administration,
but not in one study in rats. It was ineffective
in models of small intestine carcinogenesis in
two studies in rats. It showed some preventive
effects against salivary gland carcinogenesis in
one of three studies in rats.

In one model of multiorgan carcinogenesis in
rats, β -carotene showed a tendency to decrease
the incidences of preneoplastic liver foci, colon
adenocarcinomas and nephroblastomas.

β -Carotene was effective in three studies in
models of malignant tumours induced in mice
by Moloney murine sarcoma virus. In several
studies in mice and rats inoculated with
tumour cells, subsequent administration of β -
carotene inhibited tumour growth, enhanced
survival and in some cases resulted in tumour
regression.

The cancer-preventive effects of β -carotene
combined with other chemicals (vitamin C,
vitamin E, retinol, glutathione, oltipraz,
4-hydroxyphenylretinamide, selenium, wheat
bran or perilla oil) were investigated in three
studies in rats and one study in hamsters with
regard to pancreatic carcinogenesis, in three
studies on buccal pouch cancer in hamsters, in
two studies on colon carcinogenesis in rats, in
one study on respiratory tract tumours in ham-
sters and in one study on lung tumours in mice.
In all of these studies, the combinations were as
effective or more effective than β -carotene
alone, except for one study in hamsters in
which β -carotene alone or combined with vita-
min C was ineffective in preventing pancreatic
carcinogenesis and one study in mice in which
 β -carotene alone or in combination with
retinol was ineffective in preventing lung
tumours.

β -Carotene inhibited neoplastic transforma-
tion in four studies. The effect required contin-
uous treatment during the post-initiation phase
of carcinogenesis and was reversible after with-
drawal of treatment. β -Carotene inhibited the
formation of aberrant lesions in mouse mam-
mary cells in one study. Maximum inhibition
was seen when treatment was simultaneous and
continued for the duration of the experiment.

Canthaxanthin

The cancer-preventive efficacy of canthaxan-
thin was assessed in several mouse, rat and
hamster models. It prevented skin carcinogene-
sis in eight studies in mice in which ultraviolet
B irradiation was used as the carcinogen; con-
flicting results were obtained in two studies in
which 7,12-dimethylbenz[*a*]anthracene was
the carcinogen. Canthaxanthin was effective in
all six studies in hamsters in which the buccal
pouch was the target organ. It showed cancer-
preventive effects in one of four studies of liver

carcinogenesis in rats. The cancer-preventive efficacy of canthaxanthin was investigated in 10 studies in rats in models of cancers of the colon, mammary gland, tongue, small intestine, glandular stomach and salivary glands. In single studies, it was effective against cancers of the tongue and glandular stomach and ineffective against cancers of the salivary glands and small intestine. In studies of the colon and mammary gland, canthaxanthin was effective in one study and ineffective in another; the positive finding in mammary glands was associated with treatment before carcinogen administration. In two studies in mice, canthaxanthin had no preventive effect against urinary bladder cancer.

In one study in mice inoculated with malignant thymoma cells, canthaxanthin inhibited tumour growth when administered before and after tumour inoculation and appeared to be ineffective when given only after inoculation. It inhibited neoplastic transformation in cell cultures *in vitro*.

α-Carotene

In single studies in mice, *α*-carotene reduced the incidences of tumours of the liver, lung and skin, and in one study in rats it inhibited colon carcinogenesis. It inhibited neoplastic transformation *in vitro*.

Lycopene

A slight effect of lycopene was seen in two studies in rats in the aberrant crypt foci model of colon carcinogenesis. In models of liver carcinogenesis in rats, lycopene was ineffective in two studies and effective in one. In one study in mice, lycopene reduced the incidence of spontaneous mammary gland tumours but enhanced the development of preneoplastic mammary nodules. In another study, lycopene reduced the incidence of spontaneous liver tumours in mice. It was effective in one study of lung carcinogenesis in male but not female mice. It inhibited neoplastic transformation *in vitro*.

Lutein

In one study in rats, oral administration of lutein had preventive activity in the aberrant

crypt foci model of colon carcinogenesis. In one study in mice, it was effective against skin carcinogenesis. In one study in mice inoculated with murine mammary tumour cells, lutein inhibited tumour growth. It inhibited neoplastic transformation *in vitro*.

Fucoxanthin

In single studies in mice, fucoxanthin applied to the skin was found to have preventive effects against skin tumours. Fucoxanthin in drinking-water inhibited the formation of tumours of the duodenum.

Mixtures

In four studies, *Spirulina-Dunaliella* extracts (containing 15–30% *β*-carotene, 20–25% zeaxanthin, 20–25% *β*-cryptoxanthin, 10–15% myxoxanthin, 10–15% echinenone and other carotenoids) were found to prevent cheek pouch carcinogenesis in hamsters. In one study in mice, diets supplemented with *Dunaliella* powder or *Dunaliella* extract (containing 0.03% *β*-carotene) reduced the incidence of spontaneous mammary gland tumours. In single studies in mice, palm-oil carotene was effective in reducing the incidence of spontaneous liver cancer and of chemically induced carcinogenesis in the skin, lung, small intestine and stomach. In one study in rats, palm-oil carotene had no preventive effect in the aberrant crypt foci model of colon carcinogenesis.

8.3.2.2 Genetic and related effects

A number of carotenoids were evaluated for their ability to inhibit genetic and related effects *in vitro*. In most studies, carotenoids exerted protective effects against promutagens and mutagens that induce oxidative damage, whereas they did not affect the potency of directly acting mutagens. These findings were not always consistent, depending on the test compound and the laboratory that conducted the study. In addition to the usual limitations of *in vitro* studies, resulting from the high concentrations of both genotoxic agents and modulators, the delivery system for carotenoids in these studies is very different from those *in vivo*.

In studies of the ability of orally administered carotenoids (mostly *β*-carotene) to

inhibit genetic and hamsters t or chemical car ed production DNA of liver tions in T lymj or chromosom cells and bind most of the st tective effects

8.3.3 Mechanisms

The following proposed or cancer-preven of these mech *in vitro*, and me dietary comp are likely to o

All of the oxidative or synthetic or involving fre species may l the multistej noids can inte and they hav peroxidation.

In experiu been shown t tion of norm tiation. Carc tional comm an effect pcc proliferation five studies, were not cy proliferation reported to carotene. In normal and cells. The pr formation at formation c from carote can modula metabolizin.

Caroteno effects that c tems, possit

on carcinogenesis. In effective against skin idy in mice inoculated tumour cells, lutein . It inhibited neoplas- .

, fucoxanthin applied ave preventive effects oxanthin in drinking- ation of tumours of

sa-Dunaliella extracts rotene, 20–25% zeaxanthin, 10–15% chixinone and other d to prevent cheek amsters. In one study nted with *Dunaliella* act (containing 0.03% incidence of spon- l tumours. In single carotene was effective e of spontaneous liver induced carcinogene- ll intestine and stom- palm-oil carotene had e aberrant crypt foci nesis.

ad effects

ls were evaluated for genetic and related studies, carotenoids against promutagens ce oxidative damage, t the potency of direct- se findings were not ling on the test com- y that conducted the usual limitations of ing from the high genotoxic agents and ystem for carotenoids rent from those *in vivo*. ty of orally adminis- tly β -carotene) to

inhibit genetic and related effects in mice, rats and hamsters treated with a variety of physical or chemical carcinogens, the end-points includ- ed production of single-strand breaks in the DNA of liver or forestomach mucosa, muta- tions in T lymphocytes, micronucleus formation or chromosomal aberrations in bone-marrow cells and binding to liver DNA. The results of most of the studies were consistent with pro- tective effects of carotenoids.

8.3.3 Mechanisms of cancer prevention

The following mechanisms of action have been proposed or suspected to contribute to any cancer-preventive effects of carotenoids. Most of these mechanisms have been studied only *in vitro*, and more complex interactions among dietary components and mechanistic pathways are likely to occur *in vivo*.

All of the carotenoids examined inhibited oxidative or free-radical-initiated damage to synthetic or biological membranes. Processes involving free radicals and reactive oxygen species may be important at various stages of the multistep carcinogenic process. Carote- noids can interact with reactive oxygen species, and they have also been shown to inhibit lipid peroxidation.

In experimental models, carotenoids have been shown to prevent malignant transforma- tion of normal cells or to induce cell differen- tiation. Carotenoids can stimulate gap-junc- tional communication between cells *in vitro*, an effect postulated to reduce the aberrant proliferation of carcinogen-initiated cells. In five studies, β -carotene at concentrations that were not cytotoxic was reported to decrease proliferation. In one study, lycopene was reported to be more effective than α - or β - carotene. In two reports, effects were seen in normal and dysplastic cells but not in cancer cells. The prevention of both malignant trans- formation and proliferation may be due to the formation of biologically active molecules from carotenoids. In rats, some carotenoids can modulate the activities of carcinogen- metabolizing enzymes.

Carotenoids have immunomodulating effects that could enhance cellular defence sys- tems, possibly involving tumour-specific anti-

gens. In three studies, β -carotene was reported to increase various parameters of immune responsiveness. In two studies, no increases were observed, although responses were reported in response to astaxanthin. Canthaxanthin was reported to increase immune responsiveness in one study but not in another in which different effector cells and end-points were used.

Both β -carotene and canthaxanthin increased expression of a receptor gene driven by the *RAR- β* promoter, but this finding was not confirmed in another study in which expression of the endogenous gene was studied. In human keratinocytes grown in organotypic culture, β -carotene and can- thaxanthin decreased expression of mature *keratin 10* and increased expression of *connex- in 43*.

Thus, carotenoids, because they may act in several different biological processes, should be considered nutritional modulators and not solely antioxidant or pro-oxidant molecules. Various mechanisms account for the observed protective effects, including delay in cell-cycle progression, decreased expression of proto- oncogenes, enhancement of intercellular communication, inhibition of metabolic activa- tion of promutagens, enhancement of detoxifi- cation of reactive metabolites and inhibition of mutagenicity related to oxidative damage. The similar effects of carotenoids with and without provitamin A activity indicate a direct protective role *in vitro*.

8.4 Other beneficial effects

Antioxidants, including β -carotene and carotenoids, have been suggested to be of value in the prevention of a number of chronic diseases. The only current therapeutic use of carotenoids is in the treatment of erythropoietic protoporphyria, a photosensi- tivity disease. Although the results of a number of observational studies suggest that carotenoids may be of value in the prevention of cardiovascular disease, the results of the intervention trials with β -carotene do not support this hypothesis. Lutein and zeaxan- thin have been suggested to play specific roles in the prevention of age-related macular

some situations can protect against cancer. As both provitamin A and non-provitamin A carotenoids have these properties, the mechanism(s) may not necessarily involve the formation of vitamin A and its biologically active metabolites. The mechanism(s) by which carotenoids inhibit carcinogenesis in experimental animals is not known.

Carotenoids can suppress cancer growth and development when they are applied to epithelial surfaces, when they are given orally and when injected into tissues. It is important to determine the uptake, transport and metabolism of the carotenoids in each case.

The natural site for carotenoids is membranes, where they affect the properties and those of associated processes and therefore potentially affect mechanisms of carcinogenesis. Research is required on carotenoid-cell membrane interactions in these situations and whether they are relevant to the prevention of cancer in humans.

Retinoids are clearly important in controlling cell differentiation and tissue growth. The morphogen, retinoic acid, can be formed directly from β -carotene in some circumstances. Central cleavage of carotenoids has been reported in many tissues, and there is evidence that the turnover of the provitamin A carotenoids β -carotene, α -carotene and β -cryptoxanthin is more rapid than that of the other major carotenoids in serum, suggesting conversion to retinol. Research should be conducted on the effects of carotenoids and carotenoid metabolites on events mediated by retinol receptors. This potential conversion could be studied by analysing endogenous responsive genes or by use of reporter constructs, which would allow the detection of activity ligands at levels as low as 10^{-10} mol/L.

Carotenoids are powerful quenchers of singlet oxygen and triplet sensitizers, a property that is relevant to the treatment of erythropoietic protoporphyria. Furthermore, carotenoids can act as either antioxidants or pro-oxidants in chemical systems. The popular hypothesis that any biological activity of carotenoids can be attributed to an antioxidant or pro-oxidant role has not been proved. Research is required to evaluate critically the

postulated antioxidant action of carotenoids *in vivo*, i.e. protection against oxidation mediated by free radicals. Interactions between carotenoids and vitamins E and C and other intracellular antioxidant defence mechanisms should also be studied.

There is accumulating evidence that metabolites of some of the common dietary carotenoids are produced oxidatively in biological fluids. Little is known about the basic mechanisms of oxidation of carotenoids or about reactions with free radicals. Research is required to understand the basic oxidative mechanisms that affect carotenoids *in vivo* in order to appreciate if and when carotenoids are influenced by such stresses.

Oxidative stress is a powerful signal (stimulator) of immune mechanisms. The operation of such mechanisms may be evident many years before clinical symptoms of disease appear; for example, a small depression in negative acute-phase proteins can be detected retrospectively 5–10 years before the appearance of clinical disease. Carotenoids are very sensitive to oxidation, and the presence of detectable oxidation products could be a useful marker of oxidative stress and of disease for use in epidemiological studies. Oxidation products of carotenoids may themselves have biological activity, and conversion within target tissues could explain much of their action. Research is needed to identify products of oxidation and metabolism and to examine their potential activity.

Major problems in assessing the cancer-preventive properties of carotenoids and in evaluating their adverse effects include the issues of antioxidant activity and their pro-oxidant role and the effects on lung cancer as related to cigarette smoking. The following research areas may be recommended:

- Development and application of suitable animal models for evaluating the oxidant and antioxidant properties of carotenoids *in vivo* and modulation of cigarette smoke-related biomarkers in the respiratory tract and cardiovascular system
- Implementation of phase-II trials to evaluate the oxidative and antioxidant effects of carotenoids and modulation of cigarette

smoke-related biomarkers in cells of the respiratory tract, e.g. pulmonary alveolar macrophages.

Intervention studies with high doses of β -carotene provide evidence that people who are current smokers are at increased risk for lung cancer and cardiovascular disease when given supplements of β -carotene. Research is needed on the metabolic effects that smoking has on tissue metabolism and human physiology and on the effect of tobacco smoke on carotenoids *in vivo*.

Smoking is clearly associated with lower serum levels of some carotenoids. Research is required to determine whether this occurs through effects on the diet or on metabolism. Studies to determine the effects of tobacco smoke on carotenoids and of the interaction of carotenoids with smoke-exposed tissues should be conducted to better understand why β -carotene had the effect it did and whether this effect is unique or is common to all carotenoids.

Most of the observational studies were unable to distinguish the effects of individual carotenoids from those of substances in fruits and vegetables. Refinement of dietary databases, repetition of studies with adequate methods for evaluating diets and new biomarkers of intake should be pursued. Another approach is to capitalize on the fact that human populations differ in their intake of carotenoids. Research in regions where subpopulations have high intakes of specific carotenes deserves high priority.

10. Evaluation

10.1 Cancer-preventive activity

10.1.1 Humans

There is *evidence suggesting lack of cancer-preventive activity* for β -carotene when used as a supplement at high doses. There is *inadequate evidence* with regard to the cancer-preventive activity of β -carotene at the usual dietary levels. There is *inadequate evidence* with respect to the possible cancer-preventive activity of other individual carotenoids.

10.1.2 Experimental animals

There is *sufficient evidence for cancer-preventive activity* of β -carotene in experimental animals.

This evaluation is based on models of skin carcinogenesis in mice and buccal pouch carcinogenesis in hamsters. Findings in models of liver carcinogenesis in rats, colon carcinogenesis in rats and pancreatic carcinogenesis in rats and hamsters provide further support to this conclusion.

There is *sufficient evidence for cancer-preventive activity* of canthaxanthin in experimental animals. This evaluation is based on models of skin carcinogenesis in mice and buccal pouch carcinogenesis in hamsters. Findings in models of tongue cancer in rats and stomach carcinogenesis in mice provide additional support to this conclusion.

There is *limited evidence* that α -carotene has cancer-preventive activity from single studies of models of liver, lung, skin and colon carcinogenesis. There is *limited evidence* that lycopene has cancer-preventive activity from models of colon, liver, mammary gland and lung carcinogenesis. There is *limited evidence* that lutein has cancer-preventive activity from experimental models of colon and skin carcinogenesis. There is *limited evidence* that fucoxanthin has cancer-preventive activity from models of skin and duodenal carcinogenesis.

10.2 Overall evaluation

The results of studies in experimental animals and clinical studies in humans with regard to the cancer-preventive activity of β -carotene are conflicting. There is sufficient evidence that β -carotene has cancer-preventive activity against cancers of the skin and buccal pouch in experimental animals, supported by the results of studies in models of cancer of the liver, colon and pancreas. Moreover, there is considerable *in-vitro* and *in-vivo* evidence in animals that β -carotene inhibits the induction or expression of cancer-related events.

In observational epidemiological studies, β -carotene in blood or in the diet has been associated with reduced risks for cancers at many but not all sites. It is unclear, however, to what extent β -carotene itself is responsible for the decreased risks observed. Three large clinical trials indicate that supplementation with substantial doses of β -carotene does not prevent lung cancer and may actually increase the risk

among individuals who are cigarette smokers. In a large, prospectively conducted study, supplementation with β -carotene is not effective. In other terms, the increased risk of lung cancer is not reduced by supplementation with β -carotene. There is clear evidence from other studies that

The discrepancy between the results of the *in-vitro* and human observational studies and the intervention studies with β -carotene. One important investigation is to carry out a study into the process of carcinogenesis. Further knowledge about the mechanism of action of carotenoids should be obtained. Interventions should be aimed at reducing cancer risk and it should be determined whether diets rich in carotenoids are responsible for the reduced risk of cancer in these populations.

Other carotenoids, such as α -carotene, lutein, lycopene, and fucoxanthin, are

on models of skin carcinoma, buccal pouch carcinomas, and in models of liver and colon carcinogenesis in rats and mice. There is support to this con-

cept for cancer-preventive activity in experimental animals. This is based on models in mice and buccal pouch carcinomas in hamsters. Findings in rats and stomach cancer provide additional sup-

port that α -carotene has been shown in single studies of rat and colon carcinogenesis. That lycopene has cancer-preventive activity in models of colon, lung and stomach carcinogenesis. That lutein has cancer-preventive activity in experimental models of colon and stomach carcinogenesis. There is limited evidence that lycopene has cancer-preventive activity in models of skin and duodenal

cancer in experimental animals. Findings in humans with regard to the cancer-preventive activity of β -carotene are limited. Sufficient evidence that β -carotene has cancer-preventive activity against lung and buccal pouch cancer in experimental animals is provided by the results of intervention trials in the liver, colon and stomach. There is considerable support in animals that β -carotene has cancer-preventive activity against induction or expression

of cancer. In epidemiological studies, β -carotene in the diet has been associated with a decrease in risk for cancers at many sites. It is unclear, however, to what extent β -carotene is responsible for the protective effect. Three large clinical trials of β -carotene supplementation with suboptimal doses of β -carotene does not prevent cancer and usually increase the risk

among individuals already at high risk (i.e. who are cigarette smokers or who have been occupationally exposed to asbestos). Although β -carotene is not known to be toxic in the short term, the intervention trials also suggest increased risks for cardiovascular death after supplementation. These trials do not provide clear evidence concerning cancers at specific sites other than the lung.

The discrepancies between the experimental and human observations and the findings from the intervention trials greatly complicate interpretation of the data on the effects of β -carotene. Understanding these discrepancies is an important aim of future research. Such investigation is also likely to provide insight into the process of carcinogenesis and increase knowledge about cancer prevention. Until such clarification is obtained, β -carotene supplements should not be recommended for use in cancer prevention in the general population and it should not be assumed that β -carotene is responsible for the cancer-protective effects of diets rich in carotenoid-containing fruits and vegetables.

Other carotenoids, canthaxanthin, α -carotene, lutein, lycopene and β -cryptoxan-

thin, have been investigated *in vitro* and in animal models, although not as extensively as β -carotene. There is sufficient evidence that canthaxanthin has cancer-preventive activity in animal models of cancers of the skin and buccal pouch, supported by the results of studies in models of cancers of the tongue and stomach. There is limited evidence that α -carotene, lycopene, lutein and fucoxanthin have cancer-preventive activity in a variety of animal models. Canthaxanthin inhibits the expression of cancer-related events *in vitro*.

The results of observational epidemiological studies for α -carotene, lycopene and lutein are much less extensive than those for β -carotene; no published results are available for canthaxanthin. These carotenoids have not been studied in human trials for cancer prevention. Pending further research into their cancer-preventive activity, supplemental canthaxanthin, α -carotene, lutein and lycopene should not be recommended for use in cancer prevention in the general population, and it should not be assumed that the protective effects of diets rich in carotenoid-containing fruits and vegetables are due to any individual carotenoid.