EVALUATION OF THE HEALTH ASPECTS OF CAROTENE 
(β-CAROTENE) AS A FOOD INGREDIENT

1979

Prepared for

Bureau of Foods 
Food and Drug Administration 
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE 
WASHINGTON, D.C.

Contract No. FDA 223-75-2004
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Life Sciences Research Office
Federation of American Societies
for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014
NOTICE

This report is one of a series concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior sanctioned food substances as food ingredients, being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-75-2004 with the Food and Drug Administration (FDA), U.S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and that its resources are particularly suited to marshaling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office (LSRO), established by FASEB in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to review and evaluate the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their experience and judgment with due consideration for balance and breadth in the appropriate professional disciplines. The Select Committee's evaluations are being made independently of FDA or any other group, governmental or nongovernmental. The Select Committee accepts responsibility for the content of each report. Members of the Select Committee who have contributed to this report are named in Section VII.

Tentative reports are made available to the public for review in the Office of the Hearing Clerk, Food and Drug Administration, after announcement in the Federal Register, and opportunity is provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the substances covered by the report. The data, information, and views presented at the hearing are considered by the Select Committee in reaching its final conclusions. Reports are approved by the Select Committee and the Director of LSRO, and subsequently reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures the reports are approved and transmitted to FDA by the Executive Director of FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of all of the individual members of its constituent societies.

Kenneth D. Fisher, Ph.D., Director
Life Sciences Research Office
FASEB
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I. INTRODUCTION

This report concerns the health aspects of using carotene (β-carotene) as a food ingredient. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (1), which summarizes the world's scientific literature from 1920 through 1973.* To assure completeness and currency as of the date of this report this information has been supplemented by searches of over 30 scientific and statistical reference sources and compendia that are generally available; use of new, relevant books and reviews and the literature citations contained in them; consideration of current literature citations obtained through computer retrieval systems of the National Library of Medicine; searches for relevant data in the files of FDA; and by the combined knowledge and experience of members of the Select Committee and the LSRO staff. In addition, announcement was made in the Federal Register on August 3, 1979 (FR 44:45759-45760) that opportunity would be provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the health aspects of using carotene (β-carotene) as a food ingredient. No request was received.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the premarking clearance that is required for food additives. It is stated in the Act and in the Code of Federal Regulations (2) [21 CFR 170.3 and 170.30] that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. These sections of the Code also indicate that expert judgment is to be based on the evaluation of results of credible toxicological testing or, for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. FDA (2) recognizes further [21 CFR 170.30] that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The Select Committee on GRAS Substances of LSRO is making its evaluation of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety, the Committee, in accordance with FDA's guidelines, is relying primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health. While the

*The document (PB-241 950/5WJ) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
Committee realizes that a conclusion based on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited, it recognizes that there can be instances where, in the judgment of the Committee, there are insufficient data upon which to base a conclusion. The Committee is aware that its conclusions will need to be reviewed as new and better information becomes available.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on carotene (β-carotene) and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of this substance under the Federal Food, Drug, and Cosmetic Act.
II. BACKGROUND INFORMATION

Carotenoids are aliphatic or aliphatic-alicyclic hydrocarbons composed of eight isoprene groups in which a series of conjugated double bonds form a characteristic chromophoric system. They, together with their closely related oxygen derivatives (apo-carotenoids) constitute the carotenoids, a class of compounds widely distributed in nature and responsible for much of the yellow, orange, and red coloration of plants. All are related structurally to lycopene, the bright red pigment of tomatoes, which can be considered the parent compound of this group (Figure I).

The existence of either a cis- or a trans-configuration at each of the double bonds makes many isomeric forms possible. However, in nature, the carotenoids are found predominantly in the all-trans form. They are involved in the photosynthetic processes of plants and exert a protective effect on chlorophyll (3, 4). Some carotenoids also serve as precursors for vitamin A (retinol), an essential nutrient for man, and this property represents their principal importance to man and the higher animals. Moore (5) in 1930 was the first to show that "carotene" could be converted to vitamin A in vivo. This demonstration stimulated an intensive search for other natural or synthetic carotenoids with a similar potential. Over 400 carotenoids have now been identified (6), of which approximately a score possess some provitamin A activity (Table I) (7). Of this group β-carotene is the most important for man. The structural relationship of β-carotene and vitamin A is shown in Figure I. Virtually all compounds with provitamin A activity possess either the retinyl or the 3-dehydroretinyl moiety. The only apparent exceptions in Table I are canthaxanthin and astaxanthin, which can serve as provitamins A in fish but have little or no biological activity in mammalian species.

The Committees of the International Union of Nutrition Sciences and of the American Institute of Nutrition have recommended that the term "provitamin A carotenoid(s)" be used as the generic descriptor for all carotenoids exhibiting qualitatively the biological activity of β-carotene. This has become the nomenclature policy of the Journal of Nutrition (8). Until recently vitamin A activity in foods has been expressed as international units (IU), 1.0 IU being equivalent to 0.3 μg vitamin A (retinol), or 0.6 μg β-carotene (9). The National Research Council (NRC) (9) has recommended that food analyses should list separately retinol, carotene, and other provitamin A carotenoids so that "retinol equivalents" can be calculated. The retinol equivalent is regarded as a preferable measure of vitamin A activity because of the considerably poorer utilization of dietary carotenoids than of retinol. By definition, 1.0 retinol equivalent equals 1 μg retinol, 6 μg carotene, or 12 μg other provitamin A carotenoids. In terms of IU, 1.0 retinol equivalent equals 3.33 IU retinol or 10 IU β-carotene.
FIGURE I

Structural Relationship of β-Carotene and Vitamin A

Lycopene

β-Carotene

Vitamin A
<table>
<thead>
<tr>
<th>Compound</th>
<th>Moiety Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrocarbons</strong></td>
<td></td>
</tr>
<tr>
<td>α-carotene</td>
<td>Retinyl: α-retinyl&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>β-carotene</td>
<td>(Retinyl:)&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>γ-carotene</td>
<td>Retinyl: geranyl-geranyl-4,8-diene</td>
</tr>
<tr>
<td>3-dehydro-β-carotene</td>
<td>Retinyl: 3-dehydroretinyl</td>
</tr>
<tr>
<td>β-zeacarotene</td>
<td>Retinyl: geranyl-geranyl-4-ene</td>
</tr>
<tr>
<td>Homo-β-carotene</td>
<td>Retinyl: retinylvinyl</td>
</tr>
<tr>
<td>Bis-3,3'-dehydro-β-carotene</td>
<td>(3-dehydroretinyl:)&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td><strong>Oxygenated derivatives</strong></td>
<td></td>
</tr>
<tr>
<td>Cryptoxanthin</td>
<td>Retinyl: 3-hydroxyretinyl</td>
</tr>
<tr>
<td>Echinone</td>
<td>Retinyl: 4-ketoretinyl</td>
</tr>
<tr>
<td>5,6-epoxy-β-carotene</td>
<td>Retinyl: 5,6-epoxyretinyl</td>
</tr>
<tr>
<td>Torularhodin</td>
<td>Retinyl: geranyl-geranyl-4,8,12-tetraen-16-oic acid</td>
</tr>
<tr>
<td>Dehydrodolutein&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3-dehydroretinyl: 3-hydroxyretinyl</td>
</tr>
<tr>
<td>Canthaxanthin&lt;sup&gt;d&lt;/sup&gt;</td>
<td>(4-ketoretinyl:)&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Astaxanthin&lt;sup&gt;d&lt;/sup&gt;</td>
<td>(3-hydroxy-4-ketoretinyl:)&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td><strong>Apocarotenol derivatives</strong>&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>β-apo-14'-carotenol</td>
<td>Retinyl: ethanol</td>
</tr>
<tr>
<td>β-apo-12' -carotenol</td>
<td>Retinyl: α-methylbutenal</td>
</tr>
<tr>
<td>Methyl β-apo-12' carotenoate</td>
<td>Retinyl: methyl α-methylbutenoate</td>
</tr>
<tr>
<td>β-apo-10' -carotenol</td>
<td>Retinyl: γ-methylhexadienal</td>
</tr>
<tr>
<td>β-apo-8' -carotenol</td>
<td>Retinyl: α,ε-dimethyloctatrienal</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adapted from reference 7
<sup>b</sup> Colon (:) indicates a double bond joining two moieties, head to head
<sup>c</sup> Retinyl moiety is the hemimolecule of β-carotene, cleaved between C<sub>1,5</sub> and C<sub>1,5'</sub> (Figure 1)
<sup>d</sup> Appreciable activity only in fish
<sup>e</sup> Derivatives of β-carotene with one β-ionone ring and part of side chain removed
"Carotene" is classified as GRAS when used as a nutrient and/or dietary supplement in food [21 CFR 182.5245] (2) and in animal feed [21 CFR 582.5245] (10). The specific carotene isomer is not indicated. The Select Committee assumes that the term refers to β-carotene, as this is the only form available in quantity commercially; it is the only carotene authorized as a food colorant [21 CFR 73.95] (11); and it is the only isomer for which food grade specifications have been established in the Food Chemicals Codex (12). Furthermore, the Select Committee has found no evidence that any other carotene isomer is used by food manufacturers, with the possible exception of minute quantities from plant extracts, such as carrot oil [21 CFR 73.300] (11), used as coloring agents. For these reasons, β-carotene is the only carotenoid evaluated in this report.

β-Carotene is authorized as a food colorant exempt from certification (11). It has also been found acceptable for use in food by the Joint FAO/WHO Expert Committee on Food Additives (13) as well as by a number of individual countries (4).

Synthetic crystalline β-carotene of high purity and uniform color has been available commercially since 1954 and has virtually replaced the natural form as a provitamin A source and as a colorant (4). It is soluble in carbon disulfide, benzene, and chloroform; sparingly soluble in ether, vegetable oils, and hexane; and virtually insoluble in water, acids, alkalies, methanol, and ethanol (12). About 0.5 to 0.8 mg β-carotene dissolves in 1 ml of fat or oil, producing a deep orange-yellow solution (4). Food grade β-carotene must assay between 96 and 101 percent C40H56, melt with decomposition between 176° and 182°C, and dissolve completely in chloroform in a 1 in 100 solution. It must contain not more than 3 parts per million of arsenic or 10 parts per million of heavy metals expressed as lead. Its residue on ignition must be not more than 0.2 percent (12).

β-Carotene is not affected by changes of pH, reducing conditions, or metals and metal salts normally encountered in food processing. It is sensitive to photooxidation in the presence of air, but resistant when oxygen has been excluded (4). Hydrogenation, as employed in the hardening of vegetable fats, completely destroys carotene's biological activity (14). Heat-sterilized and frozen foods generally retain good carotenoid stability throughout normal temperature shelf life. However, there is a significant decrease of carotene activities in dehydrated and powdered fruits and vegetables, unless they are carefully processed and stored hermetically sealed, in inert atmospheres (4).

Two preparations of β-carotene have been developed to assure stability and solubility in most foods: an oil suspension of micropulverized crystals for fatty foods, and emulsions or beadlets containing carotene in supersaturated or colloidal solutions for water-based foods. These preparations can be added to a number of foods, which can then be processed normally and stored. The average loss of β-carotene after 12 months' storage of various foods at 23°C was about 5 percent (4).
III. CONSUMER EXPOSURE DATA

Significant amounts of carotene and other provitamin A carotenoids are present in fruits, and especially in vegetables. The richest natural source thus far reported is red palm oil, which contains 410 mg β-carotene per kg oil (15). The carotene content of typical fruits and vegetables is listed in Table II.

No reliable estimate is available of the per capita ingestion of carotene from normal food sources, since it will vary widely depending on the dietary habits of the individual. In 1966, Greaves and Tan (16) estimated that about 60 percent of the vitamin A activity in the diet was derived from carotene and 40 percent from preformed vitamin A. The total daily vitamin A intake reported in a recent nationwide survey of individuals 1 to 74 years of age (17) for the period 1972-1974 averaged 4800 IU. If the estimate of Greaves and Tan is still valid, this intake would represent a contribution of 2880 IU from carotene or about 1.7 mg daily expressed as β-carotene.

A subcommittee of the National Research Council (NRC) (18) surveyed manufacturers in 1970 to determine the level of addition of GRAS substances to foods, and estimated the possible average daily intake of these substances by persons in various age groups. Based on information supplied by manufacturers who reported adding the substances to at least one food product in the category, a weighted mean was calculated for the usual and the maximal percentage addition of the substances to foods in that category. Such weighted means for the usual levels of addition of carotene are presented in Table III. Because some foods in these categories probably contain no added carotene or much lower levels than listed in Table III, the estimated levels of addition are likely to be very high.

The NRC subcommittee has used these data, together with information on the mean frequency with which foods in each category are consumed, and the mean portion size of these various foods, to estimate the possible average daily intake of the added carotene in several age groups. These calculations yield the following estimates of possible daily consumption: 1 mg for infants up to 5 months; 14 mg for infants 6 to 11 months; 26 mg for children 12 to 23 months; and 37 mg for persons more than 2 years of age. These values are greatly in excess of the amounts actually added and the NRC subcommittee has recognized that in most cases, its calculations of possible intakes are overstated.* This is

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations" of the NRC Subcommittee's report (18). The Select Committee finds this explanation reasonable, and concurs in the first recommendation in Section XII of the same report, that "In order to conduct a more accurate survey of the intake of substances used in food processing, food consumption data collected specifically for this purpose is needed."
TABLE II

Carotene Content of Foods*

<table>
<thead>
<tr>
<th>Fruits</th>
<th>mg/kg</th>
<th>Vegetables</th>
<th>mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apricots (dried)</td>
<td>36</td>
<td>Mint</td>
<td>110</td>
</tr>
<tr>
<td>Melons, yellow</td>
<td>20</td>
<td>Parsley</td>
<td>80</td>
</tr>
<tr>
<td>Peaches (dried)</td>
<td>20</td>
<td>Carrots (canned)</td>
<td>70</td>
</tr>
<tr>
<td>Apricots</td>
<td>15</td>
<td>Spinach (boiled)</td>
<td>60</td>
</tr>
<tr>
<td>Apricots (stewed)</td>
<td>12</td>
<td>Turnip greens (boiled)</td>
<td>60</td>
</tr>
<tr>
<td>Prunes (dried)</td>
<td>10</td>
<td>Beet greens (boiled)</td>
<td>50</td>
</tr>
<tr>
<td>Prunes (stewed)</td>
<td>5</td>
<td>Kale (boiled)</td>
<td>50</td>
</tr>
<tr>
<td>Cherries, sour (canned)</td>
<td>5</td>
<td>Mustard greens (boiled)</td>
<td>50</td>
</tr>
<tr>
<td>Plums</td>
<td>2.2</td>
<td>Watercress</td>
<td>30</td>
</tr>
<tr>
<td>Bananas</td>
<td>2</td>
<td>Broccoli (boiled)</td>
<td>25</td>
</tr>
<tr>
<td>Currants, black</td>
<td>2</td>
<td>Celery</td>
<td>20</td>
</tr>
<tr>
<td>Gooseberries</td>
<td>1.8</td>
<td>Endive</td>
<td>20</td>
</tr>
<tr>
<td>Olives, green (canned)</td>
<td>1.5</td>
<td>Lettuce</td>
<td>10</td>
</tr>
<tr>
<td>Cherries</td>
<td>1.2</td>
<td>Tomato Juice</td>
<td>7</td>
</tr>
<tr>
<td>Tangerines</td>
<td>1</td>
<td>Tomatoes (canned)</td>
<td>5</td>
</tr>
<tr>
<td>Avocados</td>
<td>1</td>
<td>Brussels sprouts</td>
<td>4</td>
</tr>
<tr>
<td>Blackberries</td>
<td>1</td>
<td>Cabbage</td>
<td>3</td>
</tr>
<tr>
<td>Raspberries</td>
<td>0.8</td>
<td>Beans, runner (boiled)</td>
<td>3</td>
</tr>
<tr>
<td>Rhubarb</td>
<td>0.6</td>
<td>Peas (boiled)</td>
<td>3</td>
</tr>
<tr>
<td>Pineapple</td>
<td>0.6</td>
<td>Peas, dried (boiled)</td>
<td>0.8</td>
</tr>
<tr>
<td>Oranges (and juice)</td>
<td>0.5</td>
<td>Cauliflower</td>
<td>0.3</td>
</tr>
<tr>
<td>Strawberries</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apples</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*This table is adapted from reference 4; values are expressed as β-carotene and are for raw foods, unless otherwise noted.
TABLE III

Level of Addition of Carotene to Foods by Food Category (18)

<table>
<thead>
<tr>
<th>Food category</th>
<th>Carotene weighted mean mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baked goods, baking mixes</td>
<td>16</td>
</tr>
<tr>
<td>Grain products, such as pastas or rice dishes</td>
<td>107</td>
</tr>
<tr>
<td>Fats and oils</td>
<td>10</td>
</tr>
<tr>
<td>Frozen dairy desserts, mixes</td>
<td>22</td>
</tr>
<tr>
<td>Processed fruits, juices, and drinks</td>
<td>188</td>
</tr>
<tr>
<td>Meat products</td>
<td>50</td>
</tr>
<tr>
<td>Processed vegetables, juices</td>
<td>$^{a}$28</td>
</tr>
<tr>
<td>Sweet sauces, toppings, syrups</td>
<td>$^{a}124$</td>
</tr>
<tr>
<td>Gelatins, puddings, fillings</td>
<td>$^{a}18$</td>
</tr>
<tr>
<td>Soups, soup mixes</td>
<td>$^{a}24$</td>
</tr>
<tr>
<td>Gravies, sauces</td>
<td>$^{a}39$</td>
</tr>
<tr>
<td>Dairy products analogs</td>
<td>$^{a}1$</td>
</tr>
<tr>
<td>Baby food formulas</td>
<td>$^{a}1$</td>
</tr>
</tbody>
</table>

$^{a}$Based on data submitted by fewer than four respondents.
readily apparent from comparison of these values with data from available nutritional surveys. For example, the NRC calculations suggest a daily intake of 37 mg of added carotene, equivalent to 62,000 IU of vitamin A, for persons 2 years and older. As determined by a comprehensive nationwide nutritional survey (17), this is more than ten times the total intake from all sources of preformed vitamin A plus provitamin A (4800 IU) by this age group.

The per capita daily "intake" of added β-carotene can also be estimated from the quantities reportedly used by food manufacturers (19). Calculations based on these values suggest an average daily per capita intake in 1975 of approximately 0.2 to 0.3 mg of added β-carotene. Even this value probably overestimates the actual consumption of added β-carotene because of wastage and other losses. That it probably represents the upper limit of added β-carotene intake is suggested by data from still another source. The bulk of β-carotene added to foods is used to color margarine and to increase its vitamin A content (20). Regulations require that each pound of margarine contain the equivalent of at least 15,000 IU of vitamin A [21 CFR 166.110] (2). In regular margarine about one-third of this requirement is met by the addition of β-carotene (3.0 to 3.6 mg per lb), and in whipped margarine one-half to two-thirds comes from this source (4.8 to 6.0 mg per lb) (21). In 1978, approximately 2.5 billion lbs of margarine were produced in the United States (20). The β-carotene added to margarine would represent a per capita daily ingestion of about 0.1 mg. The Select Committee believes 0.2 to 0.3 mg per capita represents a reasonable estimate of the daily ingestion of β-carotene added to all foods.
IV. BIOLOGICAL STUDIES

Intestinal absorption

The absorption of β-carotene and of the other carotenoids from the gastrointestinal tract is influenced by a number of factors. These include the source of the carotenoid, the animal species, the nature and amount of other foodstuffs in the diet, the level of carotene intake, and the presence of emulsifying agents. The early literature is replete with studies on the availability of carotenes in food. A Joint FAO/WHO Expert Group in 1967 reviewed 19 reports in which the absorption of carotene from various sources was determined in human subjects (22). The most common sources investigated were carrots and spinach. In these studies, the difference in carotene content between that ingested and that found in the feces was assumed to represent the amount absorbed. No account was taken of possible carotenoid destruction or its conversion to vitamin A in the gut. The Expert Group concluded from its review that only one-third of the β-carotene in foods becomes available to man. Rao and Rao (23) estimated the carotene absorption from Indian diets to be about 50 percent. They also reported that crystalline β-carotene was almost completely absorbed by their subjects, indicating that carotene is more readily absorbed in its free state than when sequestered in plant cells.

Such studies, however, did not differentiate between carotene absorption and its conversion to vitamin A in the intestinal mucosa. It is now known that the intestine is the most important site for this conversion. The intestinal conversion of carotene to vitamin A has been demonstrated in rats (24), chicks (25), guinea pigs (26), goats (27), sheep (27), rabbits (27), and man (28). Much of the carotene disappearing from the intestinal tract and originally believed to be absorbed as such, is actually absorbed as vitamin A. Goodman et al. (28) fed labeled β-carotene to patients with cannulae in their thoracic ducts. Only 20 to 30 percent of the radioactivity absorbed into the lymph was from unchanged β-carotene, while the remainder was present as vitamin A esters. In the rat, even less unchanged β-carotene was absorbed; virtually all the absorbed radioactivity of the labeled β-carotene appeared in the vitamin A ester fraction (28). Similarly, the pig absorbed little unchanged carotene, but converted it to vitamin A in the intestine before absorption (29).

β-Carotene is poorly absorbed if the level of dietary fat or oil is low. Roels et al. (30) attributed the widespread vitamin A deficiency in Central Africa to this fact. When the diet was supplemented with fat, β-carotene absorption increased remarkably (from less than 5 to about 45 percent) with corresponding increases of carotene and vitamin A levels of the blood serum. Similarly, coconut oil added to the diet of vitamin A-deficient Indonesian children significantly increased carotene absorption (31). The nature of the fat also appears to influence carotene
absorption. Brown and Bloor (32) reported that rats receiving unsaturated fatty acids as the major source of fat in a diet containing carrots stored more vitamin A in their livers than rats receiving saturated fatty acids. The nature and level of protein in the diet have also been claimed to affect carotenoid utilization. James and ElGindi (33) reported that rats receiving casein stored two to five times as much vitamin A in their livers, on the same carotene intake as rats fed isocaloric amounts of lower quality proteins, such as zein or gluten. Low protein diets also reduced the utilization of carotene (14).

Surface active agents (34), or conjugated bile salts (35) improved the absorption of carotenoids, presumably by reducing the particle size. Thompson (14) found carotene to be effectively utilized even in dry powder preparations if the particles were less than 1 micron in size. The level of carotene intake also influenced its absorption and utilization. A sixteenfold increase in the dose of β-carotene fed to cows produced only a fourfold increase in milk carotene and vitamin A.

Conversion to vitamin A

Moore (5) in 1930 fed large amounts of carotene to rats and found that the vitamin A content of the liver increased strikingly. He concluded correctly that carotene was a precursor of the vitamin, but incorrectly that the conversion occurred in the liver. This conclusion was generally accepted until Sexton et al. (36) in 1946 discovered that vitamin A-deficient rats died despite the parenteral administration of large amounts of carotene. Large amounts of carotene, but no vitamin A, were found in the livers of these animals. When carotene was given orally, vitamin A appeared first in the intestinal walls and only later in the liver (24). Subsequent workers have shown that some conversion to vitamin A occurs when a water-soluble form of carotene is administered parenterally, but the conversion is usually less than that produced by the intestine after oral administration (37-40). The site(s) of the extraintestinal conversion has not been definitely established. Vitamin A has been detected in the serum of rats after intravenous injection of carotene, even after the removal of the liver, thyroid, stomach, intestines, pancreas, kidneys, gonads, or lung tissues (40,41). Worker (41) concluded that the ability to convert injected carotene into vitamin A is not exclusive to any single organ or tissue.

The exact mechanism by which β-carotene is transformed in the body to vitamin A is still uncertain. The simplest mechanism would be by oxidation at the central (15,15') double-bond to form two aldehyde molecules, which would then be reduced to vitamin A. Goodman and Huang (42) have isolated the requisite aldehyde, retinal, from cell-free homogenate fractions of rat intestinal mucosa incubated with β-carotene in the presence of oxygen. They attributed this oxidation to a dioxygenase reaction in which molecular
oxygen is added to the central double-bond of \( \beta \)-carotene without the loss of hydrogen (43). A partially purified enzyme capable of cleaving \( \beta \)-carotene has been prepared from intestinal homogenates of various species (7,42,44,45). The relative activity of the enzyme varied considerably with the species studied. Olson and Lakshmann (7) found that the enzyme from rabbit intestine cleaved \( \beta \)-carotene more than ten times as rapidly as that from hog. The retinal resulting from this cleavage was reduced to retinol (vitamin A) which was then esterified and transported in the lymph similarly to preformed vitamin A (43).

This reaction should yield two molecules of vitamin A from each molecule of \( \beta \)-carotene. However, most investigators have found only a 1:1 ratio (3). Glover and coworkers (46,47) advanced an alternative mechanism of \( \beta \)-carotene conversion to explain this discrepancy. They suggested that \( \beta \)-carotene is degraded by oxidations starting at a terminal double-bond to yield only a single molecule of vitamin A. This is the pathway \( \beta \)-carotene apparently follows when it is oxidized chemically (48). Ganguly and Murthy (49) after reviewing evidence for both suggested mechanisms concluded that although the conversion process was still "far from clear", the weight of evidence appeared to favor the central fission theory.

Man's ability to convert \( \beta \)-carotene to vitamin A appears to be limited, but the mechanism controlling this conversion has not been elucidated. Zaynoun et al. (50) administered 75 to 200 mg \( \beta \)-carotene daily for several months to patients without elevating their plasma vitamin A levels above the normal range. Pollitt (51) estimated that 10 percent or less of ingested carotene is converted to vitamin A.

**Distribution**

Unconverted carotene is absorbed into the lymph and transported to the blood stream. In common with vitamin A and most other lipids, \( \beta \)-carotene in the blood serum is associated as a lipoprotein (52). It is concentrated in the \( S_f \) 3-9 class of the low density lipoproteins in normal human subjects (53,54), whereas vitamin A esters are found primarily in the \( S_f \) 10-100 lipoproteins (54).

Carotene is distributed more evenly throughout the body fat than is vitamin A. It tends to accumulate in the fatty tissues, accounting in part, for the yellow coloration of adult depot fat in man and other animals. In animals with yellow fat, the adrenals and the corpora lutea may contain significant amounts of carotene (29).

Serum carotene levels have been reported for individuals of both sexes, various age groups, and with differing cultures and dietary habits. The values vary widely, reflecting the dietary
intake (55). Ross and Parker (56) have summarized some of the earlier studies, revealing more than a twofold range of serum carotene values, from 18 to over 400 μg per dl, with most values falling between 100 and 200 μg per dl. In their study of 227 normal men and women between 15 and 75 years of age, receiving mixed diets, they reported a range of 70 to 300, with a mean value of 153 μg per dl. Age or sex had no apparent influence on the serum levels. More recent studies suggest somewhat lower normal values. Bjornson et al. (57) reported a range of 15 to 79 μg per dl in normal subjects. Ross and Parker (56) concluded that the dietary intake for the preceding 2 weeks should be known in order to interpret serum carotene values. The responsiveness of serum carotene to dietary changes is also evident in the report of Wald et al. (58) in which the level decreased from 100 to 200 to approximately 50 μg per dl or lower, when subjects were restricted to a diet very low in carotene. In a similar study, the serum carotene values of six young adults (139 to 310 μg per dl) fell sharply during the first week of a diet low in carotene and then decreased slowly before leveling off at 30 to 44 μg per dl (59).

When large doses of β-carotene are given orally, blood serum levels of 500 to 1000 μg per dl can be attained, with elevated levels persisting for many weeks after administration has been discontinued. Corbett et al. (60) administered 100 mg β-carotene daily to nine patients for 4 months. The average blood serum levels rose from 91 to 576 μg per dl. Seven weeks after stopping β-carotene supplementation, the mean serum level was 268 μg per dl. The pretreatment level was not reached until 26 weeks after the last dose of β-carotene.

Metabolism

Little is known of the fate of β-carotene not converted to vitamin A. Fishwick and Glover (47) administered crystalline $^{14}$C-β-carotene orally to vitamin A-deficient rats and measured the radioactivity in expired air and in various tissues. About 50 to 70 percent of the dose was not absorbed, 2 percent was eliminated as $^{14}$CO$_2$, 3 percent was found in the liver as unchanged carotene and 14 percent as vitamin A. Approximately 3 percent of the radioactivity was detected in sterol and fatty acid fractions. Thus, some of the β-carotene had been degraded to yield intermediary metabolites as well as vitamin A. The metabolites were not identified, but the results indicate that the β-carotene was attacked at positions in addition to the central double-bond.

Krause and Sanders (61) detected only 1.5 percent of the absorbed radioactivity in liver vitamin A when $^{14}$C-β-carotene was fed to rats. An average of 15 percent of the absorbed radioactivity was found in the fatty acid fraction and 40 percent in nonsaponifiable material. About 5 percent was detected in the expired carbon dioxide, and the remaining 40 percent could not be accounted for.
Bieri and Pollard (38) also suggested the formation of non-vitamin A metabolites from \( \beta \)-carotene. Four hours after the intravenous injection into rats of \( \beta \)-carotene, only two-thirds of the injected dose could be accounted for as carotene or as vitamin A. No carotene was excreted in the urine or feces. The metabolites were not identified.

**Acute toxicity**

Banziger and Hane (62) tested four samples each of cis- and trans-\( \beta \)-carotene in CF-1 mice of both sexes weighing 17 to 25 g. The samples were suspended in 5 percent gum acacia solution and 10 g carotene per kg body weight were given orally. The mice were observed for 72 hours. There were no deaths among the 40 mice receiving trans-\( \beta \)-carotene and only one among the 40 dosed with cis-\( \beta \)-carotene.

Wells and Hedenburg (63) in 1916 injected guinea pigs intraperitoneally with 100 or 200 mg "natural carotin" (about 300 or 600 mg per kg body weight) dissolved in olive oil. A slight rise in body temperature was observed 2 to 6 hours after injection. Control animals receiving olive oil alone showed a similar rise. The urine of the animals receiving carotene was of a deep reddish-brown color. The guinea pigs were killed after 4 days. At necropsy, considerable amounts of fatty yellow material were observed in the peritoneum but there were no signs of inflammation or other local changes. Twenty mg carotene in olive oil (about 60 mg per kg) were also injected intradermally into two guinea pigs. Edema and inflammation, but no necrosis, were noted at the injection sites.

Zbinden and Studer (64) injected 10 female rats intramuscularly with 1 g \( \beta \)-carotene (about 6 g per kg) in oil. No apparent ill-effects were observed and necropsies 3 to 48 days later revealed only a spreading inflammation within the injection area, with a few foreign body giant cells at the site of \( \beta \)-carotene crystals. Bagdon et al. (65) determined the acute oral toxicity of \( \beta \)-carotene in two young beagle dogs by administering an initial dose of 250 mg per kg body weight. The dose was doubled on successive days until a single dose of 8 g per kg was given on the sixth day. No toxic manifestations were detected at any time.

**Short-term studies**

Zbinden and Studer (64) fed young rats of both sexes 1 g \( \beta \)-carotene per kg body weight daily for 100 days. The weight gain of the male rats lagged slightly behind that of the controls. No significant changes were detected in the blood or in any of the organs examined. Other rats received 4.5 mg \( \beta \)-carotene (about 25 mg per kg) intramuscularly twice daily, 5 days per week for 17
weeks. The animals grew normally and their general condition was good. Large cysts containing oil and β-carotene were present in all animals at the site of injection. Fatty infiltration of the Kupffer cells of the livers and partial epithelial desquamation of the convoluted tubules in the kidneys were noted. No pathological changes were apparent in the lungs, spleen, epidermis, bones, or marrow.

Rabbits were fed 500 mg β-carotene per kg body weight five times weekly for 11 weeks (64). No significant changes were noted in their general condition and the tissues appeared normal at necropsy. Two dogs were given 100 mg per kg body weight of β-carotene daily in gelatin capsules, one for 104 days and the other for 200 days. During this time, a total of 149 and 221 g, respectively, of β-carotene were consumed. The Kupffer cells showed fatty infiltration and the kidneys some epithelial desquamation. The other organs were normal.

Bagdon (66) explored the possible toxic effects of oxidation products of β-carotene by adding to rat diets, either crystalline β-carotene or a mixture containing 25 percent "degradation products" (not further identified). Forty Sprague-Dawley rats of both sexes were fed each of these preparations at 1 percent levels in the diet (about 1 g per kg body weight) for 13 weeks. No untoward effects were observed in either group on growth, general condition, food consumption, or hemopoietic tissues. Gross and microscopic findings were not unusual. The only significant observation was a decreased incidence of fatty infiltration in Kupffer cells of animals receiving the mixture of β-carotene and degradation products compared with the Kupffer cells of animals receiving crystalline β-carotene alone.

Schärer et al. (67) administered 1 g β-carotene by stomach tube to young male rats 5 days weekly for 4 weeks. The animals were killed at 1, 8, or 15 days after completion of the carotene administration. Weight gains and liver function tests were normal. Necropsies revealed slight yellowish discolorations of body fat, but all organs were otherwise normal. Yellow pigment deposits were noted in the liver, but not in the kidneys or other organs. Similar results were obtained (68) when smaller doses were administered for longer periods. Young male rats were given 100 or 500 mg β-carotene per kg body weight 5 days weekly for 34 weeks. The carotene was administered as a 20 percent solution in arachis oil. Growth, general condition, blood picture, kidney and liver function tests, and organ histology were normal. Davies and Moore (69) fed rats 8 mg carotene daily in the diet (about 80 mg per kg) for 34 days. It was estimated that only about 1 percent was absorbed. No harmful effects were noted.

Bagdon et al. (65) gave two dogs 2 g β-carotene per kg by mouth daily for 21 days. The dogs tolerated this dosage without ill-effect, except for a slight diarrhea. These investigators then administered 1, 10, or 100 mg per kg to dogs orally 5 days
weekly for 13 weeks. No signs of toxicity were observed at any of the dose levels. The hematological values remained normal. At necropsy, the livers of the carotene-fed animals showed deposition of "material" in the Kupffer cells. A few kidney sections were slightly hyperemic and many of the collecting tubules contained small amounts of amorphous deposits in the lumen. No changes were apparent in the heart, spleen, adrenals, gastrointestinal tract, gall bladder, pancreas, gonads, bone marrow, thyroid, pituitary, central nervous system, or bladder.

Lewis and Reti (70) gave about 800 mg per kg per day of "crystallized carotene" (presumably β-carotene) orally to young rats for 10 days. During the latter period of the experiment, about 40 percent of the administered carotene was found in the feces. Significant amounts were detected in the liver and adrenals. Growth of the rats was normal and no signs of toxicity were apparent. The number of the animals tested was not stated. The authors stated, but offered no documentation, that rats tolerated well, "high" doses of carotene which they injected intravenously and intraperitoneally.

Long-term studies

Young Wistar rats (15 male and 15 female) were fed a diet containing 0.1 percent β-carotene for 110 weeks (65). The rats consumed an estimated 50 to 100 mg β-carotene per kg per day (about 80,000 to 160,000 IU) during this period. The growth rate and the food consumption of the β-carotene-fed rats did not differ significantly from control animals. Hemoglobin, erythrocytes, and total and differential leucocyte counts during the 70th experimental week were normal. Four animals from each group were sacrificed after 1 year and all surviving animals after 110 weeks, at which time their tissues were examined for pathologic changes. The livers of both β-carotene-treated and control rats occasionally showed slight peripheral fatty infiltration, but no other changes. The Kupffer cells of the β-carotene group were filled with a fatty, fluorescing material which was thought to be vitamin A. There were no histopathologic changes in any of the other tissues examined and no signs of hypervitaminosis A. No tumors were reported.

Human studies

The most obvious sign of excessive carotene intake is the development of an orange pigmentation of the skin. This was first noted in 1907 in some diabetic patients by von Noorden (71) who considered it to be a manifestation of diabetes. This conclusion is understandable, for before the introduction of insulin, the diabetic diet was rich in carotenoid foods: fruit, vegetables, butter, and eggs. Similar pigmentation has now been observed in numerous non-diabetic patients and presumably normal individuals after
the consumption of large amounts of carrots or other rich sources of carotene. The term carotenemia was coined by Hess and Myers in 1919 (72). In mild carotenemia, the nasolabial folds, the palms of the hands, and the soles of the feet become pigmented. In severe cases, a generalized tanning of the skin may result. However, the sclera is not affected, a sign which helps distinguish this condition from jaundice (73).

Most reported cases of carotenemia resulted from the consumption for prolonged periods of large amounts of carrots (73-75). Cohen (74) stated that he had observed over 50 cases of severe carotenemia in persons consuming 4 to 8 pounds of raw carrots daily. Other cases resulted from drastic reducing diets featuring carrots as a major foodstuff. Almond and Logan (73) reported the occurrence of carotenemia in a breast-fed infant, whose mother had consumed large quantities of carrots during the last 6 or 7 months of pregnancy. The mother had continued this diet after the birth of the child. Within 2 months, the child had developed a yellowish coloration, which disappeared when a milk formula with no added carotene was substituted for the breast feeding.

Carotenemia has been reported also after consumption of large amounts of squash or oranges in Japan (76) and of palm oil or mangoes in Ghana (77). The average serum carotene levels of 82 persons studied was 712 μg per dl with individual values as high as 1950 μg per dl (77). This compares with normal concentrations of 100 μg per dl or less (74,78). When the carotene-containing food was omitted from the diet, the yellow pigmentation generally faded in 2 to 6 weeks (74). It is generally agreed that carotenemia is a harmless condition. However, Escamilla (79) observed carotenemia in patients with myxedema, and Cohen (74) reported that plasma carotene levels in hypothyroid patients were significantly higher than in normal individuals. Cohen speculated that the thyroid promotes the conversion of carotene to vitamin A and that the high levels of carotene in the blood of hypothyroid patients is a reflection of decreased converting capacity.

Carotene has been used as a prophylactic or therapeutic agent in cases of abnormal photosensitivity. In some individuals it has been used for considerable periods of time and thus provides additional evidence of its low toxicity. β-Carotene strongly absorbs 400nm light (80) and was first used topically to screen out ultraviolet radiation in persons sensitive to sunlight (81). Kesten (81) in 1951 reported that the application of β-carotene cream reduced the erythema and prevented itching and urticaria in a photosensitive patient. Later, Mathews (82) showed that β-carotene injected intraperitoneally protected mice against lethal photosensitization. These results led to experimental trials in man of orally administered carotene to protect against ultraviolet irradiation. Körner and Hammer (83) determined the threshold level of ultraviolet irradiation in groups of normal men and women. One
group of 20 volunteers then received 100 mg β-carotene per day orally for 20 days and a second group the same amount of β-carotene together with 200 mg tocopherol acetate and 400 mg ascorbic acid. The investigators claimed both preparations provided significant protection against ultraviolet irradiation and were well tolerated. Approximately half the subjects in each group developed a yellowish skin coloration.

β-Carotene has been used as a photoprotective agent in erythropoietic protoporphyria, an inborn error of porphyrin metabolism whose cardinal manifestation is an extreme photosensitivity. It was first tested in 1970 by Mathews-Roth et al. (84) with encouraging results on three patients with this condition. Since then, Mathews-Roth and her collaborators have reported treatment of 133 patients with erythropoietic protoporphyria (85,86). They reported that 84 percent of these patients were able to tolerate sunlight without development of signs or symptoms for at least three times longer than before treatment. Of 39 patients with other forms of photosensitivity, only 7 showed similar improvement with β-carotene treatment. Children below 8 years of age received 15 to 90 mg β-carotene, and adults 180 mg per day. The majority of these patients were observed for 2 years or more. The only reported untoward effect was loose stools in a single patient. Most patients received β-carotene only during spring and summer since the tests were conducted in the New England area. The maximal protection occurred after 1 to 3 months of therapy and persisted for 1 to 2 months after discontinuing the β-carotene. The investigators recommended that the blood carotene levels be maintained between 600 and 800 µg per dl plasma, which usually required a daily intake of 120 to 180 mg per day for adults.

Goerz and Ippen (87) gave 20 patients with erythropoietic protoporphyria and 19 with other photodermatoses daily oral doses of 50 to 150 mg β-carotene alone, or combined with canthaxanthin, for periods of 15 to 51 months. During therapy, the carotene blood level averaged about 700 µg per dl. No side effects were noted except for a yellow discoloration of the skin. Mosshall and Bjornsson (88) claimed oral administration of β-carotene is the only effective treatment of ultraviolet light sensitivity. They suggested that the photoprotection is due to free radical scavenging or singlet oxygen quenching, although they did not rule out the possible role of β-carotene in absorbing 400 nm light. Corbett et al. (60) administered 100 mg β-carotene daily or placebo for a 4-month period to patients with erythropoietic protoporphyria in a controlled cross-over trial. They could discern no significant benefit of the carotene, but their dosage was less than that recommended by Mathews-Roth (85). No harmful effects were reported.

Despite massive doses of β-carotene used in the above studies, the levels of vitamin A in the plasma or serum seemed little affected. In no case was there evidence of hypervitaminosis A. Zaynoun et al. (50) gave 16 patients 50 to 200 mg β-carotene daily for 2 to 18 months. The dosage was adjusted to maintain
plasma levels at 500 to 1000 µg per dl. After cessation of therapy, the plasma levels slowly returned to pretreatment values over many weeks. Plasma vitamin A level was not elevated above the normal range. Mathews-Roth et al. (88) reported the vitamin A concentration in blood to be within normal limits in a child receiving 30 mg and in an adult receiving 180 mg carotene per day, despite marked elevations in plasma carotene levels (250 µg and 864 µg per dl, respectively). Similarly, Goerz and Ippen (87) noted no increase in vitamin A levels in the blood of patients receiving long-term carotene therapy. Pollitt (51) observed that man is a very inefficient converter of carotene to vitamin A and concludes that there is no real risk of inducing hypervitaminosis A in patients receiving β-carotene.

It has been reported that patients with retinitis pigmentosa have reduced blood levels of vitamin A and carotenoids. Campbell et al. (89) gave 17 patients 100 mg β-carotene in gelatin impregnated beaded daily for a year. The vitamin A level in the blood increased slightly; six patients showed improved visual fields and five reported improved dark adaptation. No adverse effects were reported. Treatment with vitamin A, vitamin E, or both was more effective than with carotene. Greenberg et al. (78) administered β-carotene to 15 human adults at a daily dose equivalent to 100,000 IU of vitamin A (about 60 mg) for 3 months. Serum carotene levels rose from 128 to 308 µg per dl within 1 month and remained at this level for the remainder of the observation period. Carotene concentrates in daily dose equivalents of 5,000 to 40,000 IU of vitamin A (about 3 to 24 mg) were fed to 19 other subjects. No ill-effects were reported.

Special studies

Reproduction. To test the effect of β-carotene on fertility, Schärer and Studer (68) administered 100 or 500 mg per kg by stomach tube 5 days per week for 34 weeks to young male Wistar rats. Upon attaining weights of about 250 g in 10 weeks, the rats were mated with virgin females. All the carotene-treated males proved fertile and did not differ from controls in the number of females impregnated or in the number of offspring produced. No adverse effects were found in blood counts, kidney or liver function, organ weight, or in the histology of a variety of tissues and organs.

Sherwood et al. (90) tested the effect of carotene of undefined purity on the changes in the vaginal epithelium of rats (strain not reported) fed a commercial dog feed. Two groups of rats, 150 days old, were given by mouth carotene in cottonseed oil equivalent to 1500 IU and 3750 IU (about 4 and 9 mg carotene per kg body weight) respectively, of vitamin A daily for 15 days. The controls received the oil alone. A large number of young, nucleated epithelial cells were noted in both groups receiving carotene, indicating a rapid growth of the vaginal epithelium. Con-
trol rats maintained a normal vaginal picture. The authors attributed this growth to the production of excessive amounts of vitamin A. However, other investigators have found that carotene administered to rats and other animals is not converted into excessive amounts of vitamin A.

Both male and female Wistar rats were maintained on a diet containing 0.1 percent β-carotene (about 50 to 100 mg per kg per day) for four successive generations with no signs of hypervitaminosis A or other toxic manifestations (65). First and second generation rats were bred during the 16th experimental week, and the third generation animals during the 40th week. Number of litters, days to parturition, litter size, and weight at birth, were normal throughout three successive reproductive cycles.

Carcinogenicity. Barry et al. (91) in 1935 included carotene of unspecified structure and composition in screening a large series of hydrocarbons for carcinogenicity. A solution of 0.3 g carotene in 100 ml benzene was applied topically to the interscapular region of ten mice twice weekly. Seven mice survived at least 6 months and one mouse for 488 days. No epitheliomas or papillomas were observed.

Teratogenicity. Komatsu (92) studied the teratogenic effects of β-carotene given to pregnant Wistar rats. The basal diet was stated to be nutritionally complete although no fat source was indicated. Three groups of rats received respectively 180, 360, and 1800 mg β-carotene per kg body weight by mouth from the 9th to 12th day of pregnancy. The report does not make clear whether these quantities were administered as single or multiple doses during this period. The rats were compared with those receiving 300,000 IU vitamin A per kg, and with a control group receiving physiological saline. All fetuses were removed on the 21st day. Resorptions occurred in the vitamin A-treated group and among those receiving 180 and 3600 mg per kg β-carotene, but not in rats receiving the intermediate dosage (360 mg per kg). Deformities of the 14th rib and shortening of various bones were observed in the fetuses of the vitamin A-treated animals but not in the control or carotene-treated group. Incomplete sternebral ossification was reported in all three carotene groups. The significance of this observation is puzzling since 16.7 percent of the control group was also affected and the incidence was higher (80.0 percent) among fetuses whose mothers received 180 mg per kg carotene per kg body weight than among those (55.8 percent) whose mothers had received 20 times this amount. The Select Committee has found no other study bearing on these findings.

Mutagenicity. β-Carotene exhibited no mutagenic activity in microbial assays with Salmonella typhimurium, strains TA-1535, -1537, -1538, -98, and -100 and Saccharomyces cerevisiae strain D4 with and without activation by tissue homogenates and supernatants from mouse, rat, and monkey (93).
V. OPINION

Carotene is a general term describing certain polyene hydrocarbons containing 40 carbon atoms. Three of these, α-, β-, and γ-carotene, as well as some closely related oxygen-containing carotenoids, exhibit provitamin A activity. β-Carotene is the most active of the carotenes and the only one which is available commercially. It is added to food, chiefly margarine, both as a coloring agent, and for its vitamin A potential.

Early studies of the health aspects of "carotene" were performed with preparations of uncertain composition and purity. However, it is apparent from the sources of carotene utilized and the purification procedures adopted, that the active principle in these studies was largely β-carotene, so that the results are relevant to the present review. Since the development of synthetic β-carotene for commercial use in 1954, nearly all research on "carotene" has employed a crystalline and well-defined product.

The average daily intake of carotene from natural sources is estimated to be about 2 mg per day which is equivalent to approximately 3300 IU of vitamin A. Substantially larger amounts may be ingested in diets rich in colored vegetables. The Recommended Dietary Allowance of vitamin A from all sources is 5000 IU for adults. Consumption information from various sources suggests that the per capita daily intake of β-carotene added to foods is 0.2 to 0.3 mg.

Doses several orders of magnitude greater than would conceivably be used as additives in food have proved nontoxic to various animal species given β-carotene orally in acute, short- and long-term studies. A single study suggested some impairment in neonatal skeletal development when 180 mg per kg or more of carotene were administered, daily to rats, but this study has not been confirmed.

When given in moderate amounts, carotene is readily converted to vitamin A. However, this conversion is limited when large amounts of carotene are administered. The regulatory mechanism has not been elucidated. Doses of 180 mg (300,000 IU) daily for 2 or more years have been taken orally by patients suffering from certain types of photosensitivity with no evidence of hypervitaminosis A or other harmful effects.

In the light of these considerations, the Select Committee concludes that:

There is no evidence in the available information on carotene (β-carotene) that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when it is used at levels that are now current or that might reasonably be expected in the future.
VI. REFERENCES CITED


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VII. SCIENTISTS CONTRIBUTING TO THIS REPORT

1. Members of the Select Committee on GRAS Substances:

*Joseph F. Borzelleca, Ph.D., Professor of Pharmacology, Medical College of Virginia, Health Sciences Division, Virginia Commonwealth University, Richmond, Virginia.

Harry G. Day, Sc.D., Professor Emeritus of Chemistry, Indiana University, Bloomington, Indiana.

Samuel J. Fomon, M.D., Professor of Pediatrics, College of Medicine, University of Iowa, Iowa City, Iowa.

Bert N. La Du, Jr., M.D., Ph.D., Professor and Chairman, Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan.

John R. McCoy, V.M.D., Professor of Comparative Pathology, New Jersey College of Medicine and Dentistry, Rutgers Medical School, New Brunswick, New Jersey.

Gabriel L. Plaa, Ph.D., Professor and Chairman, Department of Pharmacology, University of Montreal Faculty of Medicine, Montreal, Canada.

Michael B. Shimkin, M.D., Professor of Community Medicine and Oncology, School of Medicine, University of California, San Diego, La Jolla, California.

Ralph G.H. Siu, Ph.D., Consultant, Washington, D.C.

Marian E. Swendseid, Ph.D., Professor of Nutrition, University of California School of Public Health, Los Angeles, California.

John L. Wood, Ph.D., Distinguished Service Professor, Department of Biochemistry, University of Tennessee Medical Units, Memphis, Tennessee.

George W. Irving, Jr., Ph.D., (Chairman), Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, Maryland.

*Did not participate in the final opinion reached in this report.
2. LSRO staff:

Kenneth D. Fisher, Ph.D., Director
Frederic R. Senti, Ph.D., Associate Director
Richard G. Allison, Ph.D., Staff Scientist
Sue Ann Anderson, Ph.D., Staff Scientist
Herman I. Chinn, Ph.D., Senior Staff Scientist
John M. Talbot, M.D., Senior Medical Consultant

Report submitted by:

October 25, 1979
Date

George W. Irving, Jr., Chairman
Select Committee on GRMS Substances