DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
21 CFR Part 101
[Docket No. 91N-0101]
RIN 0905-AB67

Food Labeling: Health Claims and Label Statements: Antioxidant Vitamins and Cancer

AGENCY: Food and Drug Administration, HHS

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is announcing its decision not to authorize the use on the label or labeling of foods of health claims relating to an association between antioxidant vitamins and cancer. However, FDA is authorizing a health claim relating substances in diets low in fat and high in fruits and vegetables (foods that are low in fat and may contain dietary fiber, vitamin A, and vitamin C) to a reduced risk of cancer. This action is in response to provisions of the Nutrition Labeling and Education Act of 1990 (the 1990 amendments) that bear on health claims, and was developed in accordance with the final rule on general requirements for health claims, published elsewhere in this issue of the **Federal Register**.

Based on the totality of the publicly available scientific evidence, including recently available evidence, the agency has concluded that there is not significant scientific agreement among qualified experts that a claim relating antioxidant vitamins to reduced risk of cancer is supported. The publicly available evidence does indicate, however, that diets rich in fruits and vegetables, which are generally low in fat and high in vitamin A (as beta-carotene), vitamin C, and dietary fiber, are associated with decreased risk of several types of cancer and there is significant scientific agreement that the evidence supports this association. The evidence is not sufficient to attribute the reduction in risk specifically to vitamin A (as beta-carotene), Vitamin C, or vitamin E, alone or in combination, or to other components of these diets. In order to evaluate further the relationship between antioxidant vitamins and cancer, FDA is planning to convene an advisory committee to review the available data and recommend whether a health claim for specific antioxidant vitamins and cancer should be authorized.

EFFECTIVE DATE: May 8, 1993

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SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of November 27, 1991 (56 FR 60624), FDA proposed to deny the use on food labeling of health claims relating antioxidant vitamins (specifically, vitamin C, vitamin E, and beta-carotene) to the risk of cancer. The proposed rule was issued in response to provisions of the 1990 amendments that bear on health claims and in accordance with the proposed general requirements for health claims for food (56 FR 60537). As amended by the 1990 amendments (Pub. L.101-535), the Federal, Food, Drug, and Cosmetic Act (the act) provides that a food is misbranded if it bears a claim that characterizes the relationship of a nutrient to a disease or health-related condition unless the claim is made in accordance with section 403(r)(3) or (r)(5)(D) of the act (21 U.S.C. 343(r)(3) or 343(r)(5)(D)).

Congress enacted the health claims provisions of the 1990 amendments to help U.S. consumers maintain good health through appropriate dietary patterns and to protect consumers from unfounded health claims. Section 3(b)(1)(A) of the 1990 amendments specifically requires the agency to determine whether claims respecting 10 nutrient-disease relationships meet the requirements of section 403(r)(3) or 403(r)(5)(D) of the act. The relationship between antioxidant vitamins and cancer is one of the claims required to be evaluated. In carrying out this inquiry, FDA chose for consideration three antioxidant vitamins: vitamin C, vitamin E, beta-carotene. Vitamins C and E were chosen because they are vitamins function as antioxidants. FDA chose beta carotene because it is an antioxidant, and because it is a provitamin and an important source of dietary vitamin A activity, FDA did not choose preformed vitamin A (retinol or retinoic acid) because its biological functions are not through an antioxidant role, and because vitamin A cannot function in an antioxidant fashion similar to that of beta-carotene (carotenoids) and vitamins C and E. FDA extended consideration of this topic area to all sources of antioxidant vitamins, i.e., both conventional foods and dietary supplements (56 FR 60624 at 60625).

FDA published a notice, in the **Federal Register** of March 28, 1991 (56 FR 12932), requesting scientific data and information on the 10 specific health claim topic areas identified in the 1990 amendments, including antioxidant vitamins and cancer. Relevant scientific studies and data received in response to this request were considered as part of the agency's review of the scientific literature on antioxidant vitamins and cancer in the proposed rule. Comments received in response to the notice and not specifically addressed in the proposed rule are summarized and addressed below.

In the proposed rule (56 FR 60624), FDA requested written comments on its tentative determination not to authorize a health claim for antioxidant vitamins and cancer. The agency specifically requested submission of data which directly bear on: (1) whether beta-carotene, vitamin C, and vitamin E per se, rather than some other component of food, decrease the risk of cancer in humans, and (2) the range of beta-carotene, vitamin C, and vitamin E intake that produce this effect. In addition, on January 30 and 31,1992, FDA held public hearings on all aspects of the proposed rules published in response to the 1990 amendments (57 FR 239, January 3, 1992).

In the **Federal Register** of July 23, 1992, FDA published a notice reopening the comment period for three specific health claim topics, including antioxidant vitamins and cancer (57 FR 32751). In that document, FDA noted that the agency had received or identified several new studies on the relationship between antioxidant vitamins and cancer, which appeared to present significant new information that was not identified in the studies that FDA reviewed in its proposal. FDA listed the new studies and requested comments on them. Using the some criteria as described in the proposed rule (56 FR 60624 at 60629), these new studies are reviewed below. Comments received on the new studies are incorporated into the discussion of comments that follows.

Altogether, the agency received approximately 100 comments from consumers, consumer advocacy groups, State health departments, organizations of health professionals, the food industry, and Government agencies. A number of comments were received that were more appropriately answered in other companion food labeling documents, and these were forwarded to the appropriate docket for response.

The Dietary Supplement Act of 1992 (H.R. 6181) established a moratorium on the implementation of the 1990 amendments with respect to dietary supplements. The Dietary Supplement

Act says that FDA can grant health claims for foods, including dietary supplements, under section 403(r)(3)(B)(i) of the act. However, it may not act on such claims under section 403(r)(5)(D) of the act until it establishes a standard to implement that section of the act, which the Dietary Supplement Act says may not occur until December 1993. Section 3(b)(1)(A)(x) of the 1990 amendments directs the agency to evaluate the antioxidant vitamins and cancer claim based on the standard that FDA is establishing for determining the reliability of health claims under section 403(r)(5)(D) of the act. In the November 27, 1991, proposal on general requirements for health claims, FDA proposed to adopt the standard that the 1990 amendments provide for conventional foods, which is set forth in section 403(r)(3)(B)(i) of the act, as the standard for dietary supplements. Given this fact, and the fact that antioxidant vitamins are found in numerous conventional foods as well as in dietary supplements, FDA broadened its inquiry to a determination as to whether it should grant a health claim on antioxidant vitamins and cancer for any foods.

Because the Dietary Supplement Act provides that FDA may grant claims using the significant scientific agreement standard specified in section 403(r)(3)(B)(i) of the act, and given the breadth of FDA's November 1991 proposal on antioxidant vitamins, FDA has decided to move forward to determine whether it can authorize a claim under section 403(r)(3)(B)(i) of the act for antioxidant vitamins and cancer. However, this rule does not apply to dietary supplements. While a manufacturer of a dietary supplement can make a claim on antioxidant vitamins and cancer without rendering Its product misbranded under section 403(r)(1)(B) of the act, the manufacturer should assure itself that the making of the claim will not misbrand the product under section 4 03 (a).

II. Review of New Scientific Evidence: Beta-carotene, Vitamin C, and Vitamin E (Review of the Scientific Literature Available From 1991 Through February 1992, and Publications Submitted as Part of Comments)

A. New Studies

As noted in the **Federal Register** of July 23, 1992, results of several human studies have been reported in the scientific literature on the association between antioxidant vitamin intake and risk of cancer since the drafting of the proposed rule. Additionally, comments received in response to the proposed, rule (56 FR 60624) noted some studies that FDA had overlooked in its proposal. FDA also identified some new studies through literature searches. Most of the new studies evaluated the effects of antioxidant vitamins in the larger context of diet and cancer, with some focusing primarily on the relationship of the antioxidant vitamins to fat and energy intakes. The recently available studies collectively addressed the relationship between antioxidant vitamins and a variety of types of cancer, including cancer of the breast, prostate, pancreas, uterine cervix, urinary bladder, colo-rectum, lung, and stomach.

Those studies submitted as comments which contributed to the totality of the scientific evidence on antioxidant vitamins and cancer are included in the following review. Those studies submitted as comments which were not germane to the topic or did not provide useful scientific information are addressed in the response to comments later in this final rule.

1. Overall cancer mortality rate

The relationship between vitamin C intake and total and cancer-related mortality rates in the United States was investigated through evaluation of the data from the National Health and Nutrition Examination Survey (NHANES I) (Ref. 1) (Table 1). The results indicated that higher vitamin C intakes are not significantly related to lower cancer mortality rates. The standardized mortality rate from all types of cancer collectively was a nonsignificant 0.78 for those taking supplemental vitamin C, compared with those who did not supplement with vitamin C.

2. Bladder cancer

A study of bladder cancer (Ref. 2) found that higher calculated vitamin E intake from foods was associated with slightly reduced risk of bladder cancer, after adjusting for smoking and total calories (Table 1). No association with cancer risk for the level of retinol or carotenoid intake was evident in this study. The participation rate was approximately 70 percent for the cases, the hospital-based controls, and the population-based controls. This study may have introduced bias by including prevalent cases (approximately 40 percent). Case-control studies usually select incident (newly diagnosed) cases. Prevalent cases are patients who have survived the disease for a period of time. Prevalent cases are generally not included in case control studies because the characteristics that contributed to

their survival may modify potential risk factors of disease.

3. Breast cancer

In a recent study on breast cancer and foods that contain antioxidant vitamins (Ref. 3), dietary carotene and vitamin C intakes from foods were found to be associated with protection, but use of these constituents as dietary supplements had no effect on risk of breast cancer (Table 1). Patients with breast cancer tended to eat fewer than 10 fruits and vegetables per week. There was a low participation rate (56 percent of eligible cases and 46 percent of eligible controls), which may have introduced bias into the study. It is unclear why a large percentage of those identified as eligible did not participate, and this makes extrapolation of the results to the general population more difficult.

Another case-control study of breast cancer (Ref. 4) reported a marginal protective association between fruits rich in beta carotene and risk of breast cancer when premenopausal and postmenopausal women were evaluated together (Table 1). There was also a marginal protective association found for calculated preformed vitamin A (i.e., retinol) intake in postmenopausal women. When both premenopausal and postmenopausal women were analyzed together, the study found no significant association between antioxidant vitamin intake and the risk of breast cancer. There was also no evidence in this study that vegetable consumption was associated with reduced risk of breast cancer.

A case-control study in France (Ref. 5) found significantly higher intake and higher serum levels of vitamin E and higher serum vitamin E/total cholesterol ratio in breast cancer cases than in controls [Table 1]. This effect remained after eliminating vitamin supplement users. Leukocyte vitamin E was elevated in cases; leukocyte vitamin C was also elevated in cases, but the elevation was not statistically significant. The report hypothesized that this effect may be the result of vitamin E-related metabolic alterations from breast cancer, rather than a cause of the disease.

Another case-control study on breast cancer (Ref. 6) found that diet was a more important risk factor for breast cancer in postmenopausal women than in premenopausal women (Table 3). After adjusting for energy intake, eduqation, and age at menarche, the studies found that the intakes of dietary vitamin C, beta-carotene, total retinol equivalents and cellulose were positively associated with reduced risk of breast cancer in postmenopausal

women. The findings demonstrated that there was a marginally higher risk of breast cancer associated with high intake of nutrients from animal products and, after adjusting for the confounders described above, a lower risk associated with high intake of fruits and vegetables.

4. Cervical cancer

A recent case-control study of invasive cervical cancer (Ref. 7) reported that a slightly lower risk was associated with higher consumption of fruits and fruit juices (Table 1). No significant difference in risk of invasive cervical cancer was evident based on level of consumption of vegetables or legumes. There was decreased risk associated with higher intakes of vitamin C, beta-carotene, and other carotenoids. When vitamin C and beta-carotene were included in the same statistical model, the association for beta-carotene was attenuated, but the protective effect of vitamin C remained significant. This suggested that while beta-carotene and vitamin C are often present simultaneously in foods, the observed effect was more closely associated with vitamin C than beta-carotene. These results are difficult to interpret because there is generally more measurement error for beta-carotene intake than for vitamin C intake, and the strength of correlations may be affected by the size of the error variance.

A companion study in the same population (Ref. 8) focusing on serologic indicators of antioxidant vitamin intake found that intake of vitamin A (i.e., retinol), cryptoxanthin, lycopene, alpha-carotene, lutein, and vitamin E (alpha-tocopherol) did not significantly differ between cases of invasive cervical cancer and controls (Table 1). In addition, beta-carotene levels remained steady as cervical cancer progressed, arguing against an effect of disease progression on serum level. After adjusting for age, study site, reproductive history, socioeconomic status, and papilloma virus infection, higher serum beta-carotene and gamma-tocopherol levels were associated with decreasing risk of the disease. Considered together, the two studies found an association between beta-carotene intake, serum levels of beta-carotene, and decreasing risk of cervical cancer. In general, the protective effects were stronger for foods than for specific nutrients.

A clinical survey of patients with abnormal cervical cell types (cervicitis or dysplasia) in a recent study (Ref. 9) involved only 75 women and was confounded by smoking habits (Table 1). It did not have sufficient statistical

power to find a significant difference in risk in relation to serum levels of antioxidant vitamins.

A case-control study of cervical intra-epithelial neoplasia in relation to dietary and serum carotenoids found ambiguous results for beta-carotene (Table 1) (Ref. 118). Protective associations were observed, however, for serum concentrations of the carotenoid lycopene and for dietary vitamin C.

5. Colorectal cancer

A study from the Balleric islands (Ref. 10) found no significant association between the risk of either colon or rectal cancer and the level of intake for vitamin A, retinol, carotene, vitamin C, or vitamin E (Table 1). There was a significant protective association for consumption of fiber from legumes and folic acid from cruciferous vegetables and reduced risk of cancer. The report stated that the findings support the recommendation for a diet high in vegetables as part of a lifestyle to reduce the risk of colorectal cancer.

6. Lung cancer

One of the new papers is a report of the results of a prospective cohort study (Ref. 11) regarding dietary intake of antioxidant vitamins and the risk of lung cancer in Finnish men (Table 1). The study found a protective effect associated with intake of foods rich in vitamins A, E, and C on the risk of lung cancer in nonsmokers. There was a strong protective association observed in this Finnish study between margarine intake and the risk of lung cancer in both smokers and nonsmokers. The report hypothesized that this finding was due to an effect of the vitamin E in margarine, although the researchers could not rule out an anticarcinogenic effect of some other constituent of margarine. Similarly, there was a Iower incidence of lung cancer associated with consumption of foods that contributed 80 percent of the vitamin C in the Finnish diet (fruits, potatoes, and vegetables). The study could not separate the role of these nutrients from that of the foods which contain them in this association of reduced risk of lung cancer with diet, and could not rule out anticarcinogenic effects of other, nonnutritive constituents of fruits and vegetables, such as terpenes, flavones, and phenols. Also, behaviors possibly associated with intake of antioxidant-rich foods, such as exercise, not smoking, and decreased fat intake, may reduce cancer risk. The report concluded that studies focused on dietary patterns, intake levels, and protection against lung cancer by other

constituents of antioxidant-rich foods are needed. Because the dietary estimate was based only on intake in the year preceding entry into the 20-year study, the estimate of antioxidant vitamin intake may not accurately represent the actual intake during the study duration since changes in diet and supplement use were likely over the 20 years of the study.

Another new case-control study evaluated diet during the year preceding diagnosis and serum vitamin concentrations at diagnosis with lung cancer (Ref. 12) (Table 1). The calculated mean dietary intakes of beta-carotene were 24 percent lower for lung cancer cases than for controls, and 10 percent for other epithelial cancer cases than for controls. Serum concentrations of beta-carotene, retinol, and vitamin E were lower in the cancer patients than in the controls by 58, 30, and 31 percent, respectively, for lung cancer, and 33, 11, and 14 percent respectively, for other epithelial cancer cases. The odds ratios for intakes of fruits and vegetables were rather irregular, and the associated trends were weaker than the trends for beta-carotene. The time period addressed in the dietary recall was the year prior to diagnosis. By comparison, cases in a 2-year period following sampling or interview are often excluded from prospective studies to help reduce the chance that the effects are a result of the cancer. Thus, the design of the study could have introduced bias related to deaths from preexisting cancer.

7. Oral and pharyngeal cancer

A population-based case-control study evaluated diet and dietary supplement use in relation to oral and pharyngeal cancer (Ref. 13) (Table 1). The results show decreased risk in association with higher consumption of fruits and vegetables and dietary supplements. In this four-State study, use of supplements was associated with being female, white, more highly educated, having a lower body mass, being a resident of California, and consuming more fruits and vegetables. Users of supplements of individual vitamin types were at lower risk after controlling for effects of tobacco, alcohol, and other risk factors. After adjustment for use of other supplements, vitamin E supplementation was the only one that remained associated with reduced risk.

8. Pancreatic cancer

A study on pancreatic cancer (Ref. 14) found a protective association between intake of dietary vitamin C and risk of pancreatic cancer after adjusting for

smoking and total calories (Table 1). Weak protective effects were also associated with vitamin A (i.e., retinol) and fiber intake and risk of Cancer. Pancreatic cancer is characterized by a very rapid clinical course and deterioration of the pancreas, so dietary interviews and histopathologic confirmation are often not feasible. The Zatonski study may have introduced bias by using surrogates for assessing dietary history in 71 percent of cases. Reliance on a surrogate adds to the difficulty of recall. The spouse was sought as the surrogate in this study, because spouses generally provide reasonable dietary histories. Radiographic diagnosis of pancreatic cancer was used in 57 percent of the cancer cases. In lieu of a histologic diagnosis, the possibility of inaccurate diagnosis cannot be dismissed. This is a flaw in the study because noncases may have been included in the case group, and the signs of pancreatic cancer could have been confused with those of cancers of the upper gastrointestinal tract.

Another study on pancreatic cancer (Ref. 15) reported a statistically significant protective effect of vegetable consumption on the risk of pancreatic cancer after adjusting for smoking and total calories (Table 1). Protective effects were also demonstrated for consumption of both fresh vegetables and cooked cruciferous vegetables. This study did not separate the role of the food versus nutrients in the noted protective effects. A large percentage of dietary interviews relied on a proxy or substitute, which may have introduced errors in the estimates of food consumption. Proxies may not be aware of the complete dietary habits of the case that they represent.

9. Prostatic cancer

A study in Madrid, Spain, found no association between dietary vitamin A or C intake and the risk of prostate cancer (Ref. 16) (Table 1). However, the report noted that the customary Mediterranean diet is rich in fruits and vegetables. Any protective effect may have been pervasive at all levels of intake observed.

A case-control study of men in Utah (Ref. 17) found only a slight protective association between vitamin A intake in older men and the risk of prostate cancer (Table 1). Beta carotene had a nonsignificant protective association for prostate cancer in men aged 45 to 67 years. Dietary fat in men aged 68 to 74 years was the strongest association between a dietary risk factor and prostate cancer.

10. Skin cancer

A nested case-control study of serum micronutrients and low incidence cancer in Finland found a large decrease in risk of melanoma in association with higher serum beta-carotene concentrations (Ref. 18) (Table 1). There was a significant association, also, between higher serum alpha-tocopherol concentrations and reduced risk of melanoma. However, the small size of the study and wide confidence intervals prevent drawing strong conclusions from this study.

11. Stomach cancer

A case-control study of stomach cancer in high- and low-risk areas of Germany found a significant strong protective association between vitamin C from fruits and vegetables (RR = 2.32 for the lowest against the highest quintile of calculated intake) and risk of stomach cancer (Ref. 19) (Table 1). The results also implicated local water supply and smoked meat as possible sources of carcinogens or their precursors.

It has been suggested that vitamin C may reduce the risk for some cancers, particularly stomach cancer, through an antioxidant role in which the vitamin blocks formation in the stomach of carcinogens such as nitrosamines (Refs. 20 and 21). Most nitrosamines are mutagenic and carcinogenic in test systems, and, thus, many studies of the possible role of vitamin C in reducing the risk of cancer have focused on nitrate, nitrite, nitrosamines, and mutagenicity.. Hence, several recent studies were directed toward relationships between vitamin C and formation of N-nitroso compounds, or between N-nitroso compounds and stomach cancer or precancerous pathology of the stomach. Data from such studies could prove useful in determining the specificity of vitamin C in relation to reduced risk of stomach cancer.

A case control study in Shanghai, China, found that urinary ascorbic acid was lower and urinary nitrate higher in patients with gastric cancer than in normal controls (Ref. 22) (Table 1). The urine was not mutagenic (Ames test) in controls but the urine of subjects with dysplasia was somewhat mutagenic and that from gastric cancer patients was highly mutagenic. Normal controls had low levels of N-nitroso compounds in gastric juice, compared with the higher levels in patients with chronic atrophic gastritis, dysplasia or gastric cancer. The mutagenicity of the urine may have been related to synthesis of N-nitroso compounds in the stomach, and

differences in this process may have been due to differences of ascorbic acid and nitrate. From studies of gastric cancer patients, without any other type of data, it is not clear whether the N-nitroso compounds are causal, predictive, or the result of gastric cancer.

The role of mutagenic/carcinogenic N nitrosamides in stomach cancer was evaluated in a study with a complex, integrated design in China (Ref. 23) (Table 1). The study included: (1) Measures of mutagenicity of extract of local fish sauce before and after nitrosation, (2) determination of the carcinogenicity of these nitrosated products in the growing rat, (3) assaying the N-nitrosamides in these products, and (4) correlation of N-nitrosamides in gastric juice with the severity of precarcinogenic pathological changes in the stomachs of human subjects. In the absence of nitrosation, none of the fish sauce extracts was mutagenic. After nitrosation, all samples were mutagenic in common mutagenicity tests (Ames and sister chromatid exchange tests). The local fish sauce extracts from only two villages were mutagenic in the micronucleus test. Four weeks after treating newborn rats with fish sauce, only those treated with the sauce that was mutagenic in all three tests showed marked precancerous dysplasia. After 16 weeks, the same treatment groups had cancerous ulceration in the glandular stomach, with dysplastic glands and cells that had penetrated the mucosa and infiltrated into submucosa and muscular layers of the gastric wall. The mean concentrations of N-nitrosamides in the nitrosated fish products were more than 15 times higher in the samples from a high-risk area than in the samples from a low risk area. The N-nitrosamide concentrations in gastric juice of human subjects had a strong positive correlation with the severity of pathological changes in the stomach.

A preliminary study in China (Ref. 24) found that N-nitroso compounds in the urine were higher in subjects with gastric dysplasia than in normal controls or subjects with chronic atrophic gastritis and/or intestinal-type metaplasia of the stomach (Table 1). The levels of N-nitroso compounds were lower in gastric juice than in the urine. With the small size and variability of this study, the N-nitroso compound levels in gastric juice could not be evaluated in relation to severity of stomach pathology.

The urinary concentrations of N-nitroso compounds and nitrate in urine of children from areas of low- and high-risk of stomach cancer in Costa Rica

have been studied (Ref. 25) (Table 1). The children were dosed with either 500 milligrams (mg) proline plus 200 mg ascorbic acid or 500 mg proline alone. (The proline was administered to assure that the quantities of N-nitrosoproline excreted were large enough to be chemically assayed in the 24-hour urine collected.) The amounts of N-nitrosoproline excreted were lower in the children from the low-risk area than from the high-risk area. In children from both areas, ascorbic acid treatment decreased the amount of N-nitroso-proline excreted. The N-nitrosoproline excretion had a highly significant positive correlation with the amount of nitrate excreted.

In a clinical trial involving English patients at high risk of stomach cancer (in this study, patients with atrophic gastritis, pernicious anemia, partial gastrectomy, or vagotomy), high doses of ascorbic acid (4 grams per day (g/day)) substantially decreased urinary N-nitroso compound excretion by all patients, except those with pernicious anemia (Ref. 26) (Table 1). All patients received their normal diets, but avoided vegetable and fruit juices during the 4 weeks of the ascorbic acid treatment and 4 weeks of post-treatment observation. Serum ascorbic acid levels indicated excellent compliance with the ascorbic acid treatment.

A clinical trial of nitrosation of added L-proline by a high level of endogenous nitrate in test meals that were either low or high in endogenous ascorbic acid found that dietary levels of ascorbic acid significantly inhibit nitrosation of proline by dietary nitrate (Ref. 27) (Table 1). The results indicate that not all subjects synthesized nitrosoproline in vivo, and those who did not were the subjects who failed to show inhibition by ascorbic acid. Those who had in vivo nitrosation (13 of 19 subjects) showed strong inhibition of this process by ascorbic acid.

These results are supported by the results of a study that found lower excretion of nitrosoproline in subjects eating a lacto-vegetarian diet than in subjects eating a free-choice diet (Ref. 28). Supplementation with as little as 6.0 mg/day ascorbic acid decreased nitrosoproline excretion by the lacto-vegetarians, but not by those eating free choice diets. Supplementation with ascorbic acid at 300 or 3,000 mg/day decreased nitrosoproline excretion by both groups. Similarly, an earlier study found that dietary ascorbic acid (330 mg/day, principally from lemon juice) strongly decreased urinary excretion of two nitrosated products of the anthelmintic drug piperazine that are potent carcinogens in animals (Ref. 29).

The inhibition of nitrosation by supplemental ascorbic acid decreases the mutagenicity of gastric juice (Ref. 30) and fecal mutagenicity (Refs. 31 and 32). Also, low concentrations of ascorbic acid in gastric juice are associated with chronic atrophic gastritis (Ref. 33) (Table 1), a condition widely considered to be premalignant (Ref. 34).

B. Conclusions From New Studies

1. Beta-carotene

Consistent with earlier studies reviewed in the proposed rule, these recent studies support findings that there is an inverse relationship between dietary intakes of green and yellow fruits and vegetables and the risk of cancer. This relationship is strongest for lung cancer. Intakes of the green and yellow fruits and vegetables have also been shown to be inversely associated with cervical cancer, but the evidence is not as consistent as with lung cancer. These studies were based on calculated Intakes of nutrients from these foods. However, it is not possible to determine from these studies what substance or substances in these foods were responsible for the results. Beta-carotene may be responsible for the effect, or its presence in these foods may simply serve as a marker for some other unmeasured substances that are responsible for the protective effect of fruits and vegetables. Mechanistic studies provide a theoretical basis (singlet oxygen quenching) on which to postulate a protective antioxidant effect by beta-carotene, but the evidence from experimental animal carcinogenesis studies is less supportive. The evidence continues to be consistent with the conclusions of the major authoritative documents (e.g., "The Surgeon General's Report on Nutrition and Health" (Ref. 35) (the Surgeon General's report); the National Research Council's (NRC's) Report on Diet and Health: Implications for Reducing Chronic Disease Risk (Ref. 36) (the Diet and Health report); and the recent Life Sciences Research Office (LSRO) review (Ref. 37)) that the consumption of fruits and vegetables is inversely associated with risk of some cancers.

2. Vitamin C

Current data are compatible with the tentative conclusion in the proposed rule that consumption of fruits and vegetables rich in vitamin C may protect against some types of cancer. These data also provide additional indications of a mechanism to explain the relationship between vitamin C and reduced risk of stomach cancer. The relatively small number of studies reported since

publication of the proposed rule are in agreement with earlier findings that consumption of fruits and vegetables is protective against cancer at several sites, particularly stomach cancer. The new studies, taken together with previous studies, indicate that consumption of fruits and vegetables is most consistently protective against cancers of the stomach, lung, and cervix, and less consistently protective at other sites. These data, however, are not sufficient to identify vitamin C versus other substances in these foods as being responsible for the observed protective effect.

The evidence from studies related to N-nitroso compounds is useful in identifying a mechanism, in human populations, whereby vitamin C could be responsible for decreasing the risk of some cancers, such as stomach cancer. The production of N-nitroso compounds with known carcinogenicity potential has been suggested as a cause of at least some stomach cancers in high-risk populations in China, Costa Rica, and Great Britain. The relevant data come from clinical trials showing the inhibition of nitrosation reactions in the stomachs of study populations, and epidemiological studies showing an association of N-nitroso compounds with precancerous and cancerous pathology of the stomach.

The results of the clinical trials on N-nitroso compound excretion, including new studies, indicate that levels of ascorbic acid from foods inhibit nitrosation reactions in humans by nitrite produced from dietary levels of nitrate, and that supplemental ascorbic acid within the range commonly obtained from foods (60 to 300 mg) can significantly decrease excretion of nitrosated products. Other new evidence shows that gastric juice and urinary nitrosamine concentrations are higher in normal persons in high-risk geographical areas than in normal persons living in low-risk areas, higher in persons with the more severe preneoplastic pathological changes in the stomach than in persons with less severe pathological changes, and higher in stomach cancer patients than in normal individuals. Ascorbic acid is only one determinant of endogenous nitrosation; dietary nitrate and its subsequent reduction to the nitrosating product nitrite by oral and gastric bacteria is also a strong determinant of endogenous nitrosation. Other determinants include nondietary influences such as smoking.

The carcinogenicity of N-nitroso compounds formed by endogenous nitrosation is determined by the amount of products formed and by their

chemical identities. The amounts formed are controlled by nitrate intake, nitrate reduction to nitrite, amounts of precursor amines available, and inhibition by ascorbic acid and other inhibitors of nitrosation. The identities of nitrosation products are determined by the identities of the precursor amines, available endogenously, in foods, or from other sources such as pharmaceutical products.

Although most of the several hundred nitrosamines and nitrosamides that have been tested are animal carcinogens, those used in evaluation of the potential for nitrosation in human subjects were selected because they are noncarcinogenic. Nevertheless, they provide a useful indicator of the effectiveness of vitamin C in decreasing the synthesis of carcinogenic members of the N-nitroso family of compounds. Studies of N-nitrosoproline, for example, must therefore be interpreted as indicators of nitrosation potential and associated risk of cancer, and not direct indicators of carcinogenic risk from that substance. It seems probable that the identities of precursor amines, and therefore of the N-nitroso compounds produced by endogenous nitrosation, will be different from one human population to another, depending on diet and other factors. Current scientific information is not sufficient to determine which specific mutagenic and carcinogenic N-nitroso compounds maybe responsible for stomach cancer in various human populations, and it is reasonable to expect that these may vary from one population to another. Nonetheless, vitamin C is an inhibitor of the nitrosation reaction through its interaction with nitrite, regardless of the identify of the amine or amide being nitrosated and the corresponding identity of the resulting nitrosamine or nitrosamide.

The possible relationship of urinary and gastric juice N-nitroso compounds with stomach cancer is shown by the association of these compounds with precancerous pathological changes in the stomach and by the association of these pathologies with elevated risk of stomach cancer. The concentrations of N-nitroso compounds in gastric juice and urine are, directly correlated with the degree of severity of the precancerous lesions in the stomach. The mutagenicity and carcinogenicity in test systems and expiremental animals of N-nitroso compounds from food sources provide suggest a cause-and-effect relationship of N-nitroso compounds and stomach cancer in humans.

These effects cannot be interpreted as indicating that all stomach cancers are attributable to N-nitroso compounds or any other chemical carcinogens, or that vitamin C or other antioxidants can eliminate the risk of stomach cancer. Current data do not allow the exclusion of other mechanisms, such as general antioxidant effects, from the possible protective effects of vitamin C. Furthermore, the data from clinical trials shelving inhibition of nitrosation reactions in the stomach, and epidemiological studies showing an association of N-nitroso compounds with precancerous and cancerous pathology of the stomach do not directly link vitamin C intakes with cancer risk or establish the validity of nitrosation reactions as a risk factor for stomach cancer in the U.S. population. These data provide a mechanistic basis for understanding a possible protective effect of vitamin C for stomach cancer risk. At this time however, nitrosation has not been accepted by the general scientific community as a validated risk factor for stomach cancer. One of the unresolved questions is whether studies of this mechanism from the Chinese and other populations, which differ from the U.S. population in genetic, dietary, and environmental risk factors, adequately explain the etiology of stomach cancer in the United States.

3. Summary of vitamin C and cancer risk

Results from the newer data are similar to results of studies reviewed in the proposed rule, which showed that diets high in fruits and vegetables were associated with a reduced risk of some cancers. Additionally, the new data on the relationship of vitamin C in inhibiting nitrosation reactions in the stomach, resulting in reduced production of N-nitroso compounds with known carcinogenicity, provide a basis for a mechanism by which vitamins C may reduce the risk of some cancers such as stomach cancer in some people. However, these studies were done in populations outside the United States, so their relevance to the pathology and etiology of the types of stomach cancer in the United Stales is controversial. Furthermore, nitrosation has not received acceptance by many experts as a valid and quantifiable risk factor or surrogate marker for stomach cancer risk. Its validity and utility as an endpoint for evaluating the effect of nutrients on stomach cancer risk, therefore, warrants further discussion.

4. Vitamin E

The latest available information since the publication of the proposed rule is not sufficient to reach a definite conclusion about an association between vitamin E intake and the risk of cancer. Some studies provide suggestive evidence of an association of lower plasma/serum concentrations and lower dietary intake of vitamin E with increased risk of cancer. Mechanistic and animal studies provide a theoretical basis on which to expect a protective effect, but human studies are inconsistent and do not provide a convincing pattern of support for that conclusion. Even if an effect of vitamin E were assumed, it would not be clear from current data which specific chemical of the tocopherol family was responsible for the observed effect.

III. Summary and Comments and The Agency's Responses

Several comments supported the proposed rule to disallow a claim for antioxidant vitamins and cancer, without giving a rationale. Others supported the proposed rule, indicating that a cause-and-effect relationship of lowered risk has been established for fruits and vegetables, but that it is not clear that this relationship is due to the antioxidant vitamins in those foods.

The three final LSRO reports (Refs. 37 through 39) submitted as comments, which provided independent up-to-date reviews of the scientific evidence, also reached similar conclusions; except for vitamin C and stomach cancer. The LSRO report on vitamin C and cancer (Ref. 39) noted the consistency of epidemiological findings associating high intakes of vitamin C or vitamin C-rich foods with reduced risk of stomach cancer, but noted that vitamin C was either not related to other cancer sites or that study results were much less clear about such relationships. The LSRO report on Vitamin A and cancer (Ref. 37) concluded that, for foods containing beta-carotene, the associations with decreased cancer risk could not be attributed specifically to beta-carotene or to any other carotene compound. The LSRO report on vitamin E and cancer (Ref. 38) concluded that there was not a clear association of decreased cancer risk with consumption of foods high in vitamin E, and the tentative associations observed could not be attributed to vitamin E rather than to some other component. The report further stated that studies on vitamin E with animals and in vitro test systems provide a theoretical basis on which reduced, risk of cancer can be hypothesized.

Many comments opposed the proposal not to allow a health claim for antioxidant vitamins and cancer. Issues raised in these comments are discussed below.

A. Scientific Standard and its Application

In the proposed rule (55 FR 60624), FDA reviewed the evidence and conclusions reached in recent authoritative documents from the Federal Government and other sources. The agency updated the evidence reached in these documents by reviewing all human studies in the literature subsequent to these documents, and by contracting with the LSRO of the Federation of American Societies for Experimental Biology (FASEB) for an independent review. The agency considered the results of animal studies to the extent that they clarified human studies or suggested possible mechanisms of action. The agency evaluated the strengths and weaknesses of individual studies and then assessed the strength of the overall combined evidence, taking into account the strength of the association, the consistency of findings, specificity of the association, evidence for a biological mechanism, and presence or absence of a dose-response relationship.

1. A number of comments discussed the types and weighing of data used by FDA in reaching its tentative position. Several comments noted that the proposed rule repeatedly suggested that epidemiological data are not enough, and that complete clarity must await the completion of clinical trials. One comment stated that clinical trials should be undertaken only when feasible and likely to yield a definitive answer, and that this is not the case for antioxidant vitamins and cancer. Other comments stated a belief that FDA favored prospective over case-control studies because they are less subject to misclassification and recall bias. One of these comments argued that there are advantages to case-control studies in cancer research and that concurrent followup (prospective cohort) studies are too expensive and time-consuming to be done often. The comment further noted that followup studies usually cannot address interactions and confounding factors because the necessary information does not exist or because too few subjects develop the cancer of interest, and that the case-control study is uniquely well-suited to the study of cancer and other diseases of long duration. A comment stated that most epidemiological studies handle the issue of nutrient intake from dietary supplements in a manner that obscures their impact, that many studies have insufficient power for specific outcomes, and that many involve inadequate or inappropriate questionnaires. Another comment stated

that the 1990 amendments do not set out a drug efficacy standard, but only require that there be significant scientific agreement that a claim is supported by the scientific evidence.

FDA disagrees that the proposed rule indicated that clinical trials are specifically required to support a health claim. FDA's proposed validity standards for health claims and conformance with these standards were discussed in the proposed rule on general requirements for health claims (56 FR 60537 at 60547 through 60549). In that document, FDA noted that, while intervention (i.e., clinical) studies are generally more reliable than observational studies for determining cause-and-effect relationships, the agency recognized that there are frequently reasons why the conduct of such studies is not feasible or ethical. FDA also noted that, in evaluating proposed claims, it would take into account the overall strengths and weaknesses of the available data, and that a combination of various types of studies can frequently compensate for deficiencies in individual studies and thus provide a stronger case to prove or disprove a hypothesis. Furthermore, regardless of the type study used (e.g., case-control versus prospective), study designs are most useful when they can determine whether or not an observed effect is due to the specific food component of interest.

In the proposed rule on health claims for antioxidant vitamins and cancer (56 FR 60624 at 60629 through 60630, 60633, 60636). FDA listed additional criteria used in evaluating the scientific evidence for each of the three antioxidant vitamins and risk of cancer. FDA again indicated that it assessed the weaknesses and strengths of individual studies; and then the agency assessed the strength of the overall evidence, taking into account the strength of the associations, the consistency of the findings, the specificity of the associations, the evidence for a biological mechanism, and the presence or absence of a dose-response relationship. FDA noted that the agency's tentative conclusions reflected the strength, consistency, and preponderance of the data as reported. FDA did not speculate about what the results of specific studies might have been if they had involved different designs, greater statistical power, or more specific questionnaires.

After reviewing the conclusions of the federal government and other authoritative reports and the updated literature review, FDA concluded that the evidence is strong that consumption of fruits and vegetables that are good

sources of beta-carotene and vitamin C are associated with lowered risk of cancer at a number of sites (56 FR 60624 at 60631, 60635, and 60638). However, the agency tentatively concluded that the data were not sufficient to establish that these two vitamins themselves were responsible for this association. The agency also noted that it was aware of ongoing clinical trials that, when completed, would provide valuable data about the specific effect of the antioxidant vitamins on the risk of cancer. However, the agency did not intend that this statement should be interpreted to mean that the results of these or other studies were a necessary condition for authorizing a health, claim for the antioxidant vitamins and risk of cancer. Rather, the agency simply stated this information to indicate its awareness of these studies and the rapidly evolving nature of the scientific evidence relative to the topic area. While FDA discussed the relative advantages and disadvantages and generally agreed upon weighting of various type of human studies in a generic sense, the agency did not intend to convey the impression that one type of study would be rejected or that clinical studies were required. Rather, it was the overall sufficiency of the available evidence that was important.

FDA has not required a drug efficacy standard for health claims on foods under the 1990 amendments. The requirements for demonstration of drug efficacy differ substantially from the scientific standard for authorization of health claims on foods. For example, clinical trials are necessary to gain approval of a new drug; as discussed above, they are not required for authorization of a health claim on food, if other types of available data are sufficient.

2. A comment expressed concern that the agency had used a more liberal standard in evaluating health claims for calcium and osteoporosis and lipids and cancer than for antioxidant vitamins and cancer. The comment cited the proposed rule on dietary lipids and cancer (56 FR 60764 at 60765 through 60766, November 27, 1991) in which FDA quoted from the diet and health report that data from epidemiological and experimental animal studies were sufficient to support a claim that dietary fat may influence the risk of some types of cancer, although the precise determination of the quantitative relationship and nature of the association between dietary fat and the overall risk of cancer has not been determined. The comment compared the proposed rule on antioxidant vitamins and cancer (56 FR 60624 at

60631 through 60632), arguing that FDA concluded that similar data are inadequate to support a claim for antioxidant vitamins and cancer. The comment claimed that distinctions between the arguments FDA used to accept a claim on lipids and cancer and reject a claim on antioxidant vitamins and cancer are illusory at best.

FDA disagrees with the assertion that the agency applied a variable standard for authorizing various health claims. For some topics such as calcium and osteoporosis, sodium and hypertension, lipids and heart disease, and lipids and cancer, there was a long history of review by expert panels from the Federal Government, the National Academy of Sciences, and other authoritative groups. These groups concluded that the science supports these nutrient/disease relationships, and this fact provides evidence for significant scientific agreement among qualified experts about the state of the evidence. In contrast, the authoritative reviews have concluded that the publicly available data do not support a conclusion that the antioxidant vitamins reduce cancer risk. In reviewing the recent human studies which became available subsequent to publication of these authoritative reports. FDA did not find compelling evidence that these nutrients were specifically responsible for reduced risk of cancer in persons consuming diets high in fruits and vegetables. Without such data, FDA could find no basis to conclude, counter to these previous conclusions of expert panels that, based on the totality of evidence, there is significant scientific agreement that an antioxidant vitamins/dancer claim is supported.

3. Some comments stated that FDA has relied on the Surgeon General's report (Ref. 35) and the Diet and Health report (Ref. 36) without considering all recent publications. These comments noted that the earlier authoritative reviews failed to consider all of the available data, and thus some of their conclusions may have rested on incomplete data. The comment also noted that the explosion of new research on the relationship between antioxidant nutrients and cancer has produced a large number of recently published studies which escaped the LSRO reviews. The comment also identified a number of studies included in the LSRO reviews that were not included in the tables published in the proposed rulemaking. The comment suggested that, while this may or may not have influenced the decisionmaking in this case, it might provide an incomplete picture to others who read the FDA proposal.

FDA disagrees with these statements. FDA considered not only the Surgeon General's report (Ref. 35) and the Diet and Health report (Ref. 36), but also all available recent publications that were relevant to the issue, including the recent review by the LSRO (Refs. 37 through 39). FDA recognizes that the authoritative review documents may not have considered and certainly did not cite every available publication related to the subject matter under consideration. FDA believes, however, that they authoritatively considered the original research publications and critical reviews necessary to reach accurate conclusions about the state of the scientific evidence on antioxidant vitamins and cancer.

The topics in the authoritative reports were evaluated by nationally recognized experts who would be expected to be familiar with all significant findings available at the time of the reports. Furthermore, except for the LSRO reports, these reports were subject to no requirements to list, as references, all available scientific literature. Most likely, they followed the common procedure of the scientific community and listed only those studies considered most relevant to the issues under review. FDA advises that any papers which were not cited in these reports but which commenters felt were important could have been submitted as comments to the public docket. Those that were submitted were included in FDA's review of new studies, or if not appropriate for inclusion in that section, are discussed in specific comments.

FDA also acknowledges that not every paper cited in the LSRO reviews was incorporated into the proposed rule. Conclusions from the LSRO preliminary reports were considered in developing FDA's proposed rule. Those relevant studies not included by FDA in the proposed rule, but cited by LSRO, have been included as new scientific evidence in this final rule (see section II. of this document).

The additional studies cited by one comment either are not sufficiently relevant to warrant their inclusion in the review of new scientific evidence, did not meet the inclusion criteria in the proposed rule, or are old enough to have been considered for inclusion in the Surgeon General's report (Ref. 35) and the Diet and Health report (Ref. 36) or the recent reviews by the LSRO (Refs. 37 through 39). There is broadly based scientific agreement of an association between dietary patterns high in fruits and vegetables and reduced risk of cancer, as acknowledged in the proposed rule, and in the Surgeon General's report (Ref. 35) and the Diet

and Health report (Ref. 36). However, studies that identify or confirm the established relationship of protective effects of fruits and vegetables on cancer risk without providing data on the unresolved question of the specificity of one or more of the antioxidant vitamins in relation to reduced risk of cancer are not helpful in supporting a health claim on antioxidant vitamins and cancer. Those studies that are newer and more nearly relevant to the issue of antioxidant vitamins and cancer, in contrast to fruits and vegetables, are summarized and cited in Table 2 (Refs. 41 through 59). One study described and listed in Table 2 (Ref. 46) is a further description of a study already reported elsewhere and considered in the proposed rule. Those listed by the comment but not included in the review of new scientific evidence in an earlier section of this document, and not cited in Table 2, were reviewed and found either to be not sufficiently relevant, to not have found significant results, or to be old enough to have been included in earlier reviews If that had been considered appropriate (Refs. 60 through 109).

4. Some comments argued that the biochemical data on the effects of antioxidant vitamins on the probable mechanisms of chemical carcinogenesis are strong evidence, and could stand alone in support of an association between antioxidant vitamins and cancer. One comment suggested that numerous studies have shown antitumorigenic effects of antioxidant vitamins in animal models, and, although not showing protective effects from every nutrient in every animal model and in every dosage regimen, quite consistently show a strong and significant protective effect. However, no data were submitted to support this assertion.

FDA disagrees with these comments. Although biochemical data can indicate the possibility of a protective effect of the antioxidant vitamins against cancer, they cannot demonstrate that the effect is one of practical importance in humans, in the context of the total daily diet, alone, support a health claim. FDA recognized in the proposed rule that animal and mechanistic data provide a strong theoretical basis on which to postulate that the antioxidant vitamins decrease the risk of cancer in humans. FDA does not agree, however, that such evidence alone are sufficient to support the conclusion that the effect is necessarily of practical importance in humans, in the context of the total daily diet.

5. Some comments stated that FDA's fragmented approach to considering the

evidence has made it difficult to see the extraordinary consistency of the data. These comments state that, although the 1990 amendments directed FDA to consider a health claim regarding "antioxidant vitamins and cancer," the agency chose to consider three antioxidants (beta-carotene, vitamin C, and vitamin E) separately. The comments stated that this approach is counter to the requirements of the 1990 amendments and is inherently incapable of revealing the consistency of the data on the antioxidant vitamins. A few comments stated that FDA should have reviewed selenium.

FDA disagrees with these comments. The term "antioxidant" defines a functional characteristic of a substance rather than its specific identity. Antioxidant nutrients include the vitamins under consideration and the mineral selenium. FDA has not considered selenium, because the 1990 amendments specified "antioxidant vitamins and cancer," and, although it is an antioxidant, selenium is not a vitamin.

FDA reasonably interpreted the language of the 1990 amendments to refer either to an independent effect of one or more of the vitamins with antioxidant characteristics (i.e., vitamins C and E, and the provitamin A, beta-carotene) or to an effect of a combination of two or more of the antioxidant vitamins. Certainly, FDA did not interpret the language of the act to mean that the only effect to be considered was that of the three antioxidant vitamins in combination. FDA recognizes that much of the data from surveys of dietary patterns and intakes of specific foods involve consumption of combinations of the antioxidant vitamins. The agency notes, however, that the composition of fruits and vegetables includes many substances other than the antioxidant vitamins, such as dietary fiber, and believes that the results of studies of fruit and vegetable intake cannot be interpreted as demonstrating that a combination of the antioxidant vitamins is responsible for the observed protective effects. FDA advises, however, that a petition in support of a health claim for a combined effect of the three antioxidant vitamins may be submitted for evaluation.

6. Some comments stated that, in the proposed, rule on antioxidant vitamins and cancer, FDA made a "Type II error" by failing to identify an effect when it exists. (In contrast, a Type I error is that of mistakenly identifying an effect when it does not exist.) The comments indicated that this type of error causes important health benefits that are

justified by the available evidence to be denied. These comments also stated that a benefit/risk analysis could properly be used to allow health claims because the agency had stated in the proposed rule that "FDA will use its discretion to give greater weight to those studies that are more persuasive regardless of the nature or age of the, studies."

FDA agrees that both types of error are possible. In general, decreasing the probability of a Type II error will increase the probability of a Type I error, and vice versa. In the proposed rule on general requirements for health claims (56 FR 60537 at 60547), FDA noted that the standard for conventional foods in the 1990 amendments required that the agency have a "high level of comfort that the claim is valid." FDA proposed that the same standard be used for both conventional foods and dietary supplements (56 FR 60357 at 60547). FDA believes that it has properly balanced the probabilities of making the two types of error by requiring that the totality of the data support the disease/nutrient relationship. Giving more weight to studies that are most persuasive, within the broader context of the strengths and weaknesses of individual studies and the types of evidence available, is appropriate in. assessing the totality of the evidence. This approach does not, however, permit selective use of studies supporting a relationship at the expense of evaluating those studies which fail to support the relationship. Moreover, FDA's cited statement in the proposal does not support use of risk/benefit analysis to evaluate a health claim. Such an analysis would be inappropriate. FDA is responsible for ensuring a safe food supply, and thus foods bearing health claims must be demonstrated to be safe and lawful. (See § 101.14(b)(3)(ii)).

7. A comment stated that, in proposing not to authorize health claims for antioxidant vitamins and cancer, FDA was inconsistent with its Cosponsorship, with the American Health Foundation, of a recent international conference on antioxidants and cancer. The comment stated that the overall content of the conference was to substantiate the protective effect of antioxidant vitamins against cancer.

FDA agrees that research discussed in the conference provided further evidence of the existence of plausible and substantiated mechanisms, including inhibition of nitrosation reactions, inhibition of free radical oxidations, and support of immune responses, through which antioxidant vitamins may decrease the risk of cancer. FDA also agrees that the

conference provided evidences of the association of consumption of foods that are good sources of beta-carotene and vitamin C with protection against certain cancers. The research presented at the conference was generally consistent with a protective relationship between antioxidant vitamins and cancer, but the conference organizers and participants did not directly address whether the evidence met the standards and criteria specified in the 1990 amendments.

B. Relationships Between Antioxidant Vitamins and Cancer

8. Some: comments asserted that a major problem with the proposal is that all cancers are referred to together. They further stated that the 1990 amendments do not specify or define antioxidant vitamins, and this makes it impossible for a regulation to be issued.

FDA disagrees. In the proposed rule (56 FR 60624 at 60633 through 60636), FDA broke out its review of vitamin C by type of cancer. There were insufficient data on beta-carotene and vitamin E for such an organizational structure. FDA does not believe that the organization of its review biased the conclusions. However, in the scientific review for this final rule, FDA organized its review of the effect of antioxidant vitamins by type of cancer. FDA's approach was again driven by the availability of data. As explained in the proposed rule, FDA selected beta-carotene, vitamin C, and vitamin E for review because they are vitamins (or, in the case of beta-carotene, a provitamin), they have antioxidant properties, and their known biological functions are through antioxidant activities.

9. Some comments disagreed with the statement by FDA that the amount of antioxidant vitamins needed to produce an effect must be identified. A comment also objected to the agency's statement that it would need to determine whether the food supply already provides that amount of the antioxidant vitamin, arguing that this is not a valid requirement because it does not consider variations in dietary intake. This comment stated that: (1) If FDA needs to know simply that effective levels may be obtained in a normal diet, the epidemiology can tell us that, and (2) if FDA is attempting to identify a specific amount, then this quest is misguided for several reasons. The reasons given included: (1) The required level is determined in part by the level of oxidant stress, (2) most of the epidemiologic data suggest that there is not a threshold, but rather a continuous trend of decreasing risk with increasing intake, and (3) the effective level may

well differ for different cancer sites. The comment stated that: (1) Protective levels are in the range attainable in the context of the total daily diet, and (2) in contrast to FDA statements or implications in the proposed rule, the antioxidant nutrient status of the U.S. population is not ample. No definition was given, however, for "ample."

FDA agrees that, if a cause-and-effect relationship has been shown for a particular type of cancer and a specific antioxidant vitamin, epidemiological data can be relied upon to indicate effective levels. FDA disagrees that any attempt to identify precise amounts of the antioxidant vitamins needed to decrease risk of cancer is misguided. The agency acknowledges the important considerations raised by the comment, but considers the rationale incomplete. Amounts of specific vitamins must be identified to provide a regulatory basis for the qualifying criteria for a health claim. In the final rule on general requirements for health claims published elsewhere in this issue of the **Federal Register**, FDA has concluded that foods that bear a health claim must contain meaningful amounts of the targeted nutrient relative to the claimed effect (in this instance, potential for reduction in cancer risk) (§ 101.14 (21 CFR 101.14)). Any alternative approach would be misleading to the consumer.

FDA agrees, however, that, if the cause-and-effect relationship has been shown, protective levels might include the range most commonly obtained from the diet. Because protective levels of the antioxidant vitamins are not known, it seems futile to speculate as to whether protective levels, if and when identified, will be attainable within the context of the total daily diet. As is explained fully in the preamble of the final rule on the general requirements for health claims published elsewhere in this issue of the **Federal Register**, it would not be permissible for a health claim to imply that levels clearly beyond the range attainable in the context of the total daily diet would be effective in reducing the risk of a disease or health-related condition.

FDA acknowledges that its statements about the need for information on the current dietary status for the antioxidant vitamins in the proposed rule were not clear. The agency also agrees that high average intake and high intake in major population groups-do not indicate that all individuals or population subgroups would have similarly high intakes. However, because of space limitations on food labels, it is not possible to provide information on the recommended nutrient intakes for major age and sex groupings or for all

situations which might affect need. Rather, labels will show a reference value, and educational programs will help consumers understand the relevance of the reference value to their individual needs.

10. A comment stated that results from epidemiological studies are sufficient to show that the antioxidant vitamins per se decrease the risk of certain cancers. Some comments claimed that FDA's statement that the effects of fruits and vegetables cannot be specifically attributed to the antioxidant vitamins is not valid and is biased against dietary supplements in that the data on antioxidant vitamins and cancer are no more confounded than those on dietary fat and cancer. A comment stated that, although FDA documents note repeatedly that the evidence for fruits and vegetables is strong, FDA nevertheless rejected a health claim on the antioxidant vitamins and cancer on two grounds: (1) The association could be due to other factors associated with fruit/vegetable intake, and (2) even if the protective factor is an antioxidant, it is not clear which nutrient is effective. Several comments stated that FDA should allow a qualified claim such as "a diet high in fruits and vegetables containing antioxidant vitamins may help reduce the risk of certain cancers."

FDA agrees that the scientific evidence is strongly supportive that diets high in fruits and vegetables are associated with a reduced risk of several types of cancer. Theoretical considerations and some research findings have suggested that several common components of fruits and vegetables, or substances at low concentrations in diets containing large quantities of these plant foods, may be responsible for reduced risk of cancer, including vitamin C, beta-carotene, other carotenoids. vitamin E (alpha-tocopherol) or other tocopherols, dietary fiber, folic acid, and other substances such as the indoles in cruciferous vegetables. Fruits and vegetables may also provide a protective effect because they are generally low in fat and calories, and because they may displace higher fat foods in the total diet. In the final rule on general requirements for health claims (§ 101.14), FDA notes that labeling statements relating ingestion of general food groups (e.g., fruits and vegetables), in which a specific substance is not implied, to a disease or health-related condition will not be regulated as health claims under §101.14, but will be subject to the requirement in section 403(a) of the act that they be truthful and not misleading.

FDA concludes that epidemiological studies of associations between food

consumption and cancer, in which the antioxidant vitamins are provided almost entirely by fruits and vegetables, are not likely by themselves to establish a cause-and-effect relationship between antioxidant vitamins and cancer sufficiently to generate significant scientific agreement. It is not possible from these studies alone to identify the particular substances or combination of substances responsible for the effect. FDA recognizes that many studies have used multiple regression procedures to control for potential confounders and to attribute specificity to statistically significant relationships. However, unless all effective components are measured, it is not possible to differentiate between a measured variable which may be serving as a marker for other unmeasured components in the food and a real effect of the measured nutrient itself.

As to the concern expressed that FDA intentionally discriminated against dietary supplements. FDA disagrees FDA, as stated in the proposed rule on general requirements for health claims (56 PR 60357), focused on the role of specific nutrients or foods as they relate to reduction in risk of a disease. regardless of source. The source of vitamin C, for example, could thus be naturally occurring vitamin C in foods, vitamin C added as a fortificant, or vitamin C obtained from dietary supplements. Consumers obtain their nutrients from a variety of sources. FDA's conclusions were driven by the nature of available evidence: for antioxidant vitamins and cancer, most of the available evidence is from studies on consumption of fruits and vegetables.

In regard to a health claim on conventional foods in which specific nutrients are named, such as "diets high in fruits and vegetables containing antioxidant vitamins may reduce the risk of cancer," FDA is persuaded by the comments that a similar claim may be useful, and that a similar claim is supported by the evidence. FDA, therefore, has decided to authorize a health claim relating low fat diets high in fruits and vegetables (which are low in fat and may contain vitamins A and C and dietary fiber) to a reduced risk of some types of cancer. Statements relating foods to cancer risk with acknowledgment of significant nutrient contributions of those foods to total diets are frequently the types of statements used in Federal Government and other dietary guidelines. The 1990 amendments clearly indicated that Congress intended that health claims on foods be a useful source of information to help Americans implement the U.S. Dietary Guidelines for Americans (Ref.

40). The authorized claim will provide such useful information.

11. One comment argued, that time-release formulations of antioxidant vitamins are superior to standard formulations in their ability to decrease the risk of cancer, and that cancer clinics are using them successfully.

This comment did not provide scientific support for a conclusion that time-release formulations of the antioxidant vitamins have been shown to provide any special benefit or advantage over standard formulations. The literature submitted in support of the assertion consisted of general, nonscientific review and position statements, and was not useful in assessing the totality of the scientific evidence on the relationship between antioxidant vitamins and cancer. Moreover, FDA does not consider the issue of time-release formulation to be relevant to this rulemaking.

12. One comment submitted a copy of the entire April 1, 1992, issue of Cancer Research (Vol. 52, pp. 2091s through 2126s). Some comments submitted a review (Ref. 110) of carotenes, vitamin C, and vitamin B as protective antioxidants in human cancers.

One paper in the submitted issue of Cancer Research addressed antioxidant vitamins and cancer (Ref. 111) concluded that increased intakes of fruits, vegetables, and carotenoids, and elevated blood levels of beta-carotene are consistently associated with reduced risk of lung cancer. Nevertheless this review concluded that, with current data, the effects of beta-carotene cannot be identified separately from those of other carotenoids, other constituents of fruits and vegetables, and associated dietary patterns.

The other review covered both animal experiments and epidemiologic research. Its overall conclusion was that antioxidant nutrients appear to play many important roles in protecting the body against cancer, but many important questions remain before dietary supplementation and/or food fortification can be recommended. In contrast, it concluded that there is a strong scientific basis for current dietary recommendations that emphasize frequent consumption of fruits and vegetables.

13. Another comment stated that the study on beneficial effects of dietary supplementation on longevity (Ref. 1) used inappropriate methods and therefore should not be used for identification of benefits from use of supplements. This comment stated that a major problem lies in the fact that cancers develop at different rates, thus

requiring more-time for conclusive studies.

FDA has indicated elsewhere in this document that this study did not find a significant effect of any antioxidant vitamin on cancer mortality. Thus, while the issue of the relevancy of the methods used may merit scientific review, it has no practical effect on the conclusions reached relative to-health claims.

C. Safety-Issues

14. Several comments disagreed with the statement by FDA in the proposed rule that high intakes of one vitamin without commensurate increases in the others may not support optimum status and functions for these nutrients. The comments stated that dietary supplements provide greater opportunity for deliberately balanced intakes of the antioxidant vitamins than do foods, and other comments asserted that FDA is wrong in stating that foods provide a better balance of antioxidant vitamins than do dietary supplements. The comments also suggested that interactions can be protective, as illustrated by data from animal experiments.

FDA agrees that dietary supplements allow the opportunity to provide a more controlled amount of nutrients than do foods. However, in the case of antioxidant vitamins and cancer, the scientific evidence from data that are customarily used in setting dietary goals and nutrition policy is not sufficient at present to identify an independent effect of these substances. Therefore, any attempt to define dosages or optimum balances among the three antioxidant vitamins is premature. The statement that foods may provide a better balance is consistent, therefore, with the limitation of current scientific evidence.

Additionally, FDA agrees with the statement that interactions can be either helpful or harmful. However, FDA's decision to propose not to authorize a health claim on antioxidant vitamins and cancer was not based on concern about toxicities or adverse interactions among nutrients, but, instead, on the insufficiency of the data available.

15. Some comments expressed concern that, if a health claim were permitted for vitamin C, the public might take supplemental doses far in excess of the Recommended Dietary Allowances, and that this could result in gastrointestinal disturbances, iron overload in some people, precipitation of calcium, oxalate kidney stones, disruption of copper metabolism, and induction of postnatal bleeding in women. They also stated that dietary

supplements should be required to list a warning statement regarding use of the supplement along with any health claim permitted.

FDA points out that most reports of possible adverse effects from ascorbic. acid ingestion have involved dosages of 3 to 30 g per day (Ref. 112). The Surgeon General's report (Ref. 35) states that amounts of vitamin C in excess of the Recommended Dietary Allowance may cause rare adverse effects, but does not identify how far above the Recommended Dietary Allowance values adverse effects are observed. The adverse effects noted include gastrointestinal disturbances, iron overload in susceptible individuals, altered metabolism of certain drugs, precipitation of calcium oxalate kidney stones, altered absorption (both positive and negative) of several minerals, and interference with several laboratory tests. The review article cited as the source of this information (Ref. 112) concluded that, although the effects listed should be considered possible, consumption of supplemental vitamin C leads to no significant adverse health effects in humans in general, but nevertheless individuals who have a history of kidney stone formation and those who experience iron overload should exercise caution before using supplemental vitamin C.

The Diet and Health report (Ref. 36) recommends avoiding taking dietary supplements in excess of the Recommended Dietary Allowance in any one day. It states that several vitamins and minerals, if consumed in excess, can be toxic and cause numerous adverse health effects, but that there is no evidence that the public is harming itself by the use of low levels of supplements. This report did not discuss the possible adverse effects of vitamin C in detail, but instead reprinted a table from a review article in which the adult oral minimum toxic dose was estimated to be between 1 and 5 g. The NRC's "Recommended Dietary Allowances" 10th ed. (Ref. 113) stated that many persons habitually ingest 1 g. or more of ascorbic acid without developing apparent toxic manifestations, although a number of adverse effects have been reported.

Additionally, the LSRO report (Ref. 39) indicates that intakes of ascorbic acid of up to 1 g/day are well tolerated (Ref. 114). Occasionally, intakes above this may be associated with nausea and diarrhea. Ascorbic acid intakes of 4 g/day were used in a long-term intervention trial on rectal polyps without adverse effects in a population of adult men and women (Ref. 115).

FDA is not currently authorizing a health claim relating antioxidant vitamins and cancer. If such an authorization occurs in the future, these conclusions about vitamin C may be used in evaluation of its safety.

16. Some comments addressed the issue of possible iron overload as a result of high vitamin C intake. The comments stated that vitamin C added to foods can increase the amount of iron absorbed. These comments refer to a longstanding concern that persons carrying the genetic trait for idiopathic hemochromatosis; and perhaps also persons with the heterozygous trait, are at risk of earlier onset of the disease or more severe effects if the intake or bioavailability of dietary iron is increased. One comment, however, concluded that the effect, although likely to be insignificant in normal individuals, may be slightly greater in those who are heterozygous for the gene for hereditary hemochromatosis. This comment noted that an effect as great as doubling of iron stores might result, under very specific conditions of iron to ascorbic acid ratio in the food, from switching to a vitamin C-fortified food from a nonfortified food and continuing this practice for several years. Such a situation is presumably unlikely to occur frequently, making the potential impact on iron status much smaller.

FDA recognizes that the role of vitamin C in enhancing iron bioavailability under short-term test conditions is well established (Ref. 11B). Studies in normal persons without the idiopathic hemochromatosis genetic trait show no increase in iron stores with chronic intakes of large amounts of supplemental ascorbic acid (Refs. 115 and 116). FDA, however was not able to find similar studies in patients with hemochromatosis, and no such data were submitted as comments. Thus, the issue of safety of ascorbic acid intakes in enhancing iron uptake by hemochromatosis patients, and the dose-response relationship of ascorbic acid in this effect, cannot be resolved from current data.

17. A comment stated that FDA makes much of the need to determine precise intake levels of beta-carotene, vitamin C and vitamin E regarding potential benefits, but resorts to the broadest generalizations when it comes to possible detrimental actions of excessive intakes of vitamins. The comment pointed out that the amounts of vitamin C in diets recommended by the U.S. Department of Agriculture (USDA) and the National Cancer Institute exceed 200 mg, and that the situation is analogous for vitamin E.

FDA agrees that the proposed rule described the need to identify levels of antioxidant vitamins that are effective in reducing the risk of cancer and that possibilities were discussed for adverse effects. The agency also is aware that current dietary patterns in the United States consistently result in average intake levels above current Recommended Dietary Allowances. The agency's discussions on effective intakes were presented because this issue can affect evaluations of safety. This information is also essential for determining qualifying criteria for foods bearing an authorized claim, and for deciding on the types of information needed to be included in a label statement. Estimates of current dietary intakes or intakes likely to occur if persons follow dietary guidelines are largely irrelevant to evaluating whether a nutrient/disease relationship exists.

IV. Decision Not to Authorize Health Claims Relating Antioxidant Vitamins and Cancer and to Authorize Health Claims Relating Substances in Fruits and Vegetables and Cancer

A. Scientific Evidence Regarding the Relationship between Antioxidant Vitamins and Cancer and Between Fruits and Vegetables and Cancer

FDA has reviewed numerous authoritative documents, including Federal Government reports, as well as recent research on diet and cancer risk. In addition, the agency considered all comments received in response to its proposed rule. The agency has concluded that the scientific evidence does not provide the basis for significant agreement among qualified experts that there is a relationship between antioxidant vitamins (specifically, beta-carotene, vitamin C and vitamin E) and a reduced risk of cancer. However, the publicly available scientific evidence does support an association between diets high in fruits and vegetables, which are good sources of two of the antioxidant vitamins (vitamin A as beta-carotene and vitamin C) and reduced risk of cancer.

Based on the scientific evidence in the proposed rule, the comments received, and new studies, FDA has reached the following decisions:

1.Vitamin E

Based on a review of the totality of the Scientific evidence and comments Received relative to the available Evidence, FDA concludes that the data Do no support a relationship of vitamin E to reduce risk of cancer and that There is not significant scientific Agreement that vitamin E reduces the

risk of cancer. Most studies on the possible protective effect of vitamin E have related plasma or serum levels of vitamin E (rather than fruit and vegetable consumption) to cancer risk. FDA recognizes that some evidence shows an association of low plasma/ serum levels of vitamin E and reduced cancer risk, but finds that the inadequacies in the available data, as noted in the proposed rule (56 FR 60624), have not been adequately addressed by newer data; comments received in response to the proposed rule were not sufficiently convincing to reverse the proposed conclusion.

FDA recognizes that the animal and biochemical data provide a basis on which to hypothesize a protective effect by vitamin E (alpha-tocopherol) in humans, but the data from epidemiological studies, although providing some suggestion of an effect, are not sufficient to conclude that such effects are of importance in humans. Therefore, although vitamin E has been shown to have antioxidant effects in humans, the data are not sufficient to associate such effects with protection against cancer.

2. Beta-carotene

Based on a review of the totality of the scientific evidence and comments received relative to the available evidence, FDA concludes that data do not support the relationship of beta-carotene (provitamin A) to reduced cancer risk. FDA also concludes that there is not significant scientific agreement that beta-carotene reduces the risk of cancer. However, the available data show an association of consumption of fruits and vegetables and calculated beta-carotene intakes from these foods with reduced risk for some types of cancer. The scientific evidence is not sufficient to conclude that beta-carotene in these foods is responsible for the protective effect. Beta-carotene has been shown to protect against chemical carcinogenesis in some animal models, and the biochemical and mechanistic data provide a plausible scientific basis on which to hypothesize a protective effect in humans.

3. Vitamin C

In the proposed rule, FDA recognized that mechanistic and animal studies suggest that vitamin C may reduce the risk of cancer through the mechanism of inhibition of nitrosamine synthesis. Cancer of the stomach is the likely site of highest N-nitroso compound exposure, and is the site for which the data were the most complete. However, FDA found that the data available at the time of the proposed rule were not

sufficient to establish the relationship between inhibition of N-nitroso compound synthesis and stomach cancer in humans. FDA also recognized, in the proposed rule, that higher intakes of fruits and vegetables, higher calculated intakes of vitamin C and increased blood levels of vitamin C are associated with lower risk of cancer of the stomach, and, more weakly, with cancers at other sites. New studies that are relevant to these issues are reviewed in previous sections of this document.

Epidemiological studies published since the review for the proposed rule further support the association of fruits and vegetables and calculated vitamin C intakes with protection against certain types of cancer, especially cancer of the stomach.

The studies showing the relationship of N-nitroso compounds (a class of compounds with known carcinogenicity to stomach cancer provide evidence for a mechanism by which a specific vitamin C effect might occur for this and other cancers (e.g., esophageal and uterine cervical). Formation of N-nitroso carcinogens in the stomach would be expected to have the greatest effect at the site of production and greatest exposure, the stomach, and lesser effects at distal sites that require absorption and translocation of the putative carcinogen before an effect could occur. In animal test systems, preformed N-nitroso compounds are multitarget organ carcinogens. These conclusions are consistent with the conclusions of the recent LSRO review (Ref. 39).

When considered together, the different types of data are suggestive, but not conclusive, that vitamin C may be responsible for at least part of the reduction in risk of stomach cancer associated with consumption of diets high in fruits and vegetables. The evidence for specificity of vitamin C includes epidemiological associations of decreased risk with higher intakes of vitamin-C containing fruits and vegetables, clinical trials that show decreased, concentrations of N-nitroso compounds after vitamin C supplements, and epidemiological associations of higher concentrations of N-nitroso compounds with higher risk of stomach cancer and precancerous pathology of the stomach. However, the N-nitroso compound data have not generally been validated as a basis for establishing a relationship between vitamin C and risk of stomach cancer in the U.S. population. At present there is not significant scientific agreement that this mechanism is an etiologic factor in stomach cancer risk in the United States, or that qualitative or quantitative changes in production and excretion of nitroso-compounds are a risk factor for stomach cancer.

In order to allow the issue of intermediate or surrogate markers (such as formation of N-nitroso compounds) for cancer risk to be more fully evaluated, FDA will be convening an advisory committee in the near future to make recommendations which can then be applied to evaluations of data for determining the scientific basis for health claims relating antioxidant vitamin intakes to cancer risk.

4. Fruits and vegetables

Dietary patterns that are low in fat and high in plant foods, including fruits and vegetables, are generally high in vitamin C and provitamin A (beta-carotene), and other nutrients such as dietary fiber, and are associated with a decreased risk of some types of cancer. The mechanisms responsible for this relationship are not known. Several factors could be important contributors to this protective effect. For example, fruits and vegetables are low in fat FDA has reviewed the evidence supporting the relationship between low fat diets and reduced risk of cancer and has concluded that there is sufficient scientific evidence and significant scientific agreement among qualified experts to support this relationship. (See the final rule on health claims for lipids and cancer published elsewhere in this issue of the **Federal Register**). FDA is, therefore, authorizing a health claim for fat and cancer. Thus, one possible mechanism whereby fruits and vegetables may contribute to reduced cancer risk is through displacement of higher fat foods in a diet, with a net effect of reducing total fat intakes.

The subject of this final rule relates to the possible protective mechanism of vitamins with antioxidant functions in reducing cancer risk. Three antioxidant vitamins were considered: Beta-carotene, vitamin C and vitamin E. Fruits and vegetables are the major food source of beta-carotene (pro-vitamin A) and vitamin C in the U.S. diet. Vitamin E is more ubiquitously distributed, but some vegetable oils and whole grain products are significant sources. Fruits and vegetables are also good sources of dietary fiber. The possible protective role of dietary fiber in reducing cancer risk has been discussed in the final rule on health claims for dietary fiber and cancer published elsewhere in this issue of the **Federal Register**.

Finally, fruits and vegetables contain a number of nonnutritional substances (e.g., indoles, phenols, flavones, and terpenes) which have been hypothesized to be possibly protective against cancer risk through antioxidant or other functions. Fruits and vegetables also contain many carotenoid compounds in addition to beta-carotene, the carotenoid which has the greatest pro-vitamin activity. While the other cerotenoids do not contribute significantly, if at all, to vitamin activity, they are antioxidants and, thus, may also provide a protective effect against cancer risk. The specific roles of these numerous, potentially protective substances in plant foods are not yet understood, and knowledge of their content in fruits and vegetables is lacking. Consequently, dietary intakes of these substances have not been estimated in human studies which show associations between fruit and vegetable intakes and cancer risk.

B. Conclusion Based on Scientific Evidence

In conclusion, while populations with diets rich in fruits and vegetables experience many health advantages, including lower rates of some types of cancers, it is not possible to specifically determine that the two antioxidant vitamins (i.e., beta-carotene and vitamin C) which are contained in fruits and vegetables are responsible for this effect, or to rule out the possibility of significant protective effects from nonmeasured components in these fruits and vegetables. Since many of these food substances (both nutritive and nonnutritive) coexist in fruits and vegetables, an observed correlation between a measured nutrient may be reflective of a "true" correlation between a coexistent, nonmeasured food substance. Currently, there is not significant scientific agreement as to whether the observed protective effects of fruit, and vegetable consumption against cancer risk are due to a single or combined effect of the antioxidant vitamins and other nutrients with antioxidant functions (i.e., selenium), to other nutritive components of such foods (such as dietary fiber), to unmeasured components of such diets (for example, nonnutritive components such as carotenoids, indoles or flavonoids), or to displacement of other known risk components (such as fats and calories) within the total diet.

Thus, the conclusion that diets low in fat and high in fruits and vegetables (foods which are low in fat and are generally good sources of vitamins A and C and dietary fiber) are associated with a reduced risk of cancer, is consistent with the available scientific evidence.

Because dietary patterns which have high consumption of fruits and vegetables are not only low in fat but

can also be characterized by high intakes of dietary fiber and vitamins A and C, these nutrients can serve as useful markers for identifying the types of foods which contribute to a dietary pattern that is associated with a reduced cancer risk. Calculated intakes of vitamin C and vitamin A (often but not always identifying the fraction from beta-carotene) from diets high in fruits and vegetables have been correlated with reduced cancer risk. Although it is not known if it is the antioxidant vitamin components or some other components of these diets that provide the protective effects against cancer, these nutrients are characteristic of protective foods. Therefore, FDA is authorizing the use on labels and labeling of health claims regarding the association between diets low in fat and high in fruits and vegetables and a reduced risk of cancer with specific mention that these diets and foods are generally rich sources of vitamin A (as beta-carotene), vitamin C, and dietary fiber.

V. Rationale For Final Rule

A. Relationship and Significance sections

New § 101.78(a) is consistent with the conclusions reached in the science review that it is fruits and vegetables which relate to the reduced risk of cancer, not the antioxidant vitamins per se. Yet because of the usefulness of vitamins A (as beta-carotene) and C and dietary fiber in identifying fruits and vegetables most likely to correlate with reduced cancer risk, these nutrients are specifically identified as being characteristic of the protective dietary pattern. Any one or a combination of these three nutrients can serve as the identifying marker. Since fruits and vegetables are also characterized by their absence of fat, and because of the identified relationship of low fat diets to reduced risk of cancer, this also is required to be a characterizing nutrient for the type of dietary patters associated with decreased cancer risk. Other components of the relationship statement, for example, risk factors, have been indicated, similar to other authorized health claims.

In new § 101.78(b), on the significance of the relationship between consumption of diets low in fat and high in fruits and vegetables and reduced risk of cancer, the summary includes the information that U.S. diets tend to be high in fat and low in fruits and vegetables. Discussion of current dietary guidelines on recommended servings of fruits and vegetables, and dietary fiber intakes are also given.

Because of the coexistence of all of these nutrients in fruits and vegetables, and because all have been associated with reduced risk of cancer, all four nutrients are indicated. Because the mechanism of the protective effect is not known and because it is not known which of these nutrients is effective, or if some combination of these nutrients is effective, the health claim is focused on fruits and vegetables as a product class and their relationship to cancer risk.

B. Nature of the Claim

In § 101.78(c)(2)(i), FDA is authorizing health claims relating substances in diets low in fat and high in fruits and vegetables to reduced risk of cancer. In new § 101.78{c)(2)(1)(A), the agency is requiring, similar to other authorized claims, that the relationship be qualified with the terms "may" or "might." These terms are used to indicate that not all persons will necessarily benefit from these dietary changes. In new § 101.78(c)(2)(i)(B), the agency, consistent with other authorized claims, is requiring that the claim not indicate that all cancers may be affected, but rather that the risk of "some types of. Cancer" or "some cancers" may be reduced. The relationship of dietary factors to various types of cancers appears to be variable; in many cases, the available data are inadequate to specifically identify which cancers will be affected.

In new § 101.78(c)(2)(i)(C), the agency is requiring that the claim characterize fruits and vegetables as foods that are low in fat and contribute vitamin A, vitamin C, and dietary fiber to the diet. All four nutrients must be identified as characteristic of this dietary pattern. As noted in the conclusions reached from the available scientific evidence, it is not known what substances in fruits and vegetables are responsible for their protective effect. The best documented relationship is for fat and cancer. Roles for dietary fiber and vitamins A and C have been speculated and intake of these nutrients from fruits and vegetables are correlated with cancer risk. By requiring that all characterizing nutrients by identified as characteristic of dietary patterns rich in fruits and vegetables without specifically attributing reduced cancer risk to a single nutrient, the claim is consistent with the current scientific knowledge. The claim should also minimize consumer confusion, since its wording is similar to current, dietary guidelines from the U.S. Government, including the National Cancer Institute. New § 101.78(c)(2)(i)(D) requires the claim to specify that the food bearing the claim contains at least one of the following:

Dietary fiber, vitamin A, or vitamin C. This statement is required in order to identify the contribution of the labeled food to the diet in an accurate and nonmisleading manner. Only those nutrients for which the labeled food qualifies as a good source under. § 101.54 may be identified in the health claim. Although the regulation does not restrict the manner in which these nutrient levels may be described, terms used must be consistent with other labeling regulations.

In new § 101.78(c)(2)(i)(E), FDA, consistent with other authorized health claims, is prohibiting the attribution of a specific reduction in risk to diets low in fat and high in fruits and vegetables. In new § 101.78(c)(2)(i)(F), (c)(2)(1)(G), (c)(2)(i)(H), and (c)(2)(i)(I), FDA is prohibiting, similar to other authorized health claims, more specific use of dietary terms than is warranted by the current state of the scientific evidence. These requirements also standardize use of these terms, thus minimizing consumer confusion as they compare food labels across products, or as they compare a health claim to the nutrition information panel. Section 101.78(c)(2)(i)(J) requires that health claims indicate that development of cancer is dependent on many factors. This requirement is intended to prevent consumers from being mislead that fruit and vegetable intake is the only factor connected with cancer risks.

C. Nature of the Food

New §101.78(c)(2)(ii)(A) requires that the food bearing the authorized health claim be or contain a fruit or vegetable. Because- the claim relates to diets high in those foods, it would not make sense for it to appear on the labeling of another type of food. A health claim that appears on a food that meets all the requirements in § 101.78(c)(2)(ii) but contains only a trivial amount of fruit or vegetables could be considered misleading and might misbrand the food under section 403(a) of the act.

FDA, consistent with the requirements for the health claim on fat and cancer (published elsewhere in this issue of the **Federal Register**), is requiring in new § 101.78(c)(2)(ii)(B) that foods bearing the authorized health claim be "low fat" foods or, alternatively, belong to a class of products that is "low in fat." Low fat diets are associated with reduced cancer risks. Low or negligible fat is also one of the characterizing nutrients for diets rich in fruits and vegetables. Since the effect of fat is not readily separated from the effect of other nutritive components of fruits and vegetables, it is required to be included as a qualifying nutrient.

In new § 101.78(c)(2)(ii)(C), FDA is requiring that fruits and vegetables bearing the health claim meet requirements for a "good source" (greater than or equal to 10 percent of the Reference Daily Intake (RDI)) for vitamin A and vitamin C, and greater than or equal to 10 percent of the Daily Reference Value (DRV) for dietary fiber. The requirement that these nutrients be present at 10 percent of the RDI or DRV is being established as a specific alternative to the 20 percent (i.e., "high") requirement for qualifying nutrients in the final rule on general requirements for health claims published elsewhere in this issue of the **Federal Register**. (See § 101.14(d)(2)(vii)). This alternate level was deemed useful to assure that most fruits and vegetables would be eligible for this health claim, because fruits and vegetables in general are the product class for which correlations with reduced cancer risk have been observed as opposed to specific fruits and vegetables. Moreover, as a product class, fruits and vegetables are significant sources of vitamins A and C and fiber in the U.S. dietary pattern. Without this alternative level very few fruits and vegetables would qualify for the health claim. This seems contrary to the available evidence and to the purpose of health claims.

This section also requires that the qualifying nutrients be based on "natural" levels in foods. This means that foods which require modification, for example, fortification with vitamins A or C or dietary fiber, in order to meet the qualifying criteria for the health claim, cannot bear the claim. This requirement is consistent with the scientific basis for the claim; that is, that fruits and vegetables in their native form correlate with reduced cancer risk. Since there are not sufficient data to specifically identify vitamins A and C and dietary fiber as causal, and because these nutrients are being used as markers for the substance(s) in fruits and vegetables that provide the observed effect, it is the native nutritional composition of the foods that identifies their usefulness. At the same time, this requirement does not prohibit fortification of qualifying foods with the characterizing nutrients, once the qualifying criteria have been met.

D. Optional Information

Under new § 101.78(d), similarly to other authorized health claims, health claims may identify additional risk factors for cancer. The regulation specifies the factors that may be listed; all are risk factors about which there is general scientific agreement. This additional information can provide a context that is useful for an understanding of the relationship of the diet to the disease, but, manufacturers are cautioned that it should not be presented in a way that is misleading to the consumer. A health claim may also indicate that reductions in fat intake and consumption of fruits and vegetables are part of a total dietary pattern that is consistent with the latest "Nutrition and Your Health: Dietary Guidelines for Americans" (Ref. 40) published jointly by the USDA and the Department of Health and Human Services (DHHS). Consistent with other health claim regulations, the claim may also include information on the prevalence of cancer in the United States. In order to ensure that this information is valid, the agency is requiring that it come from one of three specified authoritative sources.

Additionally, for the health claim relating substances in diets high in fruits and vegetables to reduced risk of cancer, the agency is allowing the use of the term "beta-carotene" in addition to the term vitamin A in listing nutrients that are characteristic of the protective dietary pattern. Beta-carotene is the form of the vitamin which has antioxidant functions. Therefore, the use of this term is consistent with a possible mechanism of action. On the other hand, if, after a food meets the qualifying criteria for a health claim, the food is fortified with vitamin A (as retinyl palmitate or another form of preformed vitamin A rather than with beta-carotene), then it would be misleading to indicate that its vitamin A content is primarily beta-carotene. Thus, FDA is permitting the term beta-carotene to be used in the claim only when the vitamin A in the food bearing the claim is beta-carotene.

E. Model Health Claims

In new § 101.78(e)(1) and (e)(2), FDA is providing several model health messages to help manufacturers understand the requirements of new § 101.78 and to help them understand the type of health claim that FDA considers to be appropriate. FDA is not prescribing specific language for claims, but certain elements are required, and these models include the required elements.

VI. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(11) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Economic Impact

In its food labeling proposals of November 27, 1991 (56 FR 60366 et seq.), FDA stated that the food labeling reform initiative, taken as a whole, would have associated costs in excess of the $100 million threshold that defines a major rule. Thus, in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96-354), FDA developed one comprehensive regulatory impact analysis (RIA) that presented the costs and benefits of all of the food labeling provisions taken together. That RIA was published in the **Federal Register** of November 27, 1991 (56 FR 60856), and along with the food labeling proposals, the agency requested comments on the RIA.

FDA has evaluated more than 300 comments that it received in response to the November 1991 RIA. FDA's discussion of these comments is contained in the agency's final RIA published elsewhere in this issue of the **Federal Register**. In addition, FDA will prepare a final regulatory flexibility analysis (RFA) subsequent to the publication of the food labeling final rules. The final RFA will be placed on file-with the dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23,12420 Parklawn Dr., Rockville, MD 20857, and a notice will be published in the **Federal Register** announcing its availability.

In the final RIA, FDA has concluded, based on its review of available data and comments, that the overall food labeling reform initiative constitutes a major rule as defined by Executive Order 12291. Further, the agency has concluded that although the costs of complying with the new food labeling requirements are substantial, such costs are outweighed by the public health benefits that will be realized through the use of improved nutrition information provided by food labeling.

VIII. References

The following references have been placed on file in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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List of Subjects in 21 CFR Part 101

Food labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food. Drug, and Cosmetic Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 101 is amended as follows:

PART 101—FOOD LABELING

1. The authority citation for 21 CFR part 101 continues to read as follows:

Authority: Secs. 4. 5, 6, of the Fair Packaging and Labeling Act (15 U.S.C. 1453, 1454, 1455); secs. 201, 301, 402, 403, 409, 701 of the Federal Food. Drug, and Cosmetic Act (21 U.S.C. 321, 331, 342, 343, 348, 371).

2. Section 101.71 is amended by adding new paragraph (d) to read as follows:

§ 101.71 Health claims: claims not authorized.

* * * * *

(d) Antioxidant vitamins and cancer.

3. New § 101.78 is added to subpart E to read as follows:

§ 101.78 Health claims: fruits and vegetables and cancer.

(a) *Relationship between substances in diets low in fat and high in fruits and vegetables and cancer risk.* (1) Cancer is a constellation of more than 100 different diseases, each characterized by the uncontrolled growth and spread of abnormal cells. Cancer has many causes and stages in its development. Both genetic and environmental risk factors may affect the risk of cancer. Risk factors include a family history of a specific type of cancer, cigarette smoking, alcohol consumption, overweight and obesity, ultraviolet or ionizing radiation, exposure to cancer-causing chemicals, and dietary factors.

(2) Although the specific roles of the numerous potentially protective substances in plant foods are not yet understood, many studies have shown that diets high in plant foods are associated with reduced risk of some types of cancers. These studies correlate diets rich in fruits and vegetables and nutrients from these diets, such as vitamin C, vitamin A, and dietary fiber, with reduced cancer risk. Persons consuming these diets frequently have high Intakes of these nutrients. Currently, there is not scientific agreement as to whether the observed protective effects of fruits and vegetables against cancer are due to a combination of the nutrient components of diets rich in fruits and vegetables, including but not necessarily limited to dietary fiber, vitamin A (as beta-carotene) and vitamin C, to displacement of fat from such diets, or to intakes of other substances in these foods which are not nutrients but may be protective against cancer risk.

(b) *Significance of the relationship between consumption of diets low in fat and high in fruits and vegetables and risk of cancer.* (1) Cancer is ranked as a leading cause of death in the United States. The overall economic costs of cancer, including direct health care costs and losses due to morbidity and mortality, are very high.

(2) U.S. diets tend to be high in fat and low in fruits and vegetables. Studies in various parts of the world indicate that populations who habitually consume a diet high in plant foods have lower risks of some cancers. These diets generally are low in fat and rich in many nutrients, including, but not limited to, dietary fiber, vitamin A (as beta-carotene), and vitamin C. Current dietary guidelines from Federal Government agencies and nationally recognized health professional organizations recommend decreased consumption of fats (less than 30 percent of calories), maintenance of desirable body weight, and increased consumption of fruits and vegetables (5 or more servings daily), particularly those fruits and vegetables which contain dietary fiber, vitamin A. and vitamin C.

(c) *Requirements.* (1) All requirements set forth in § 101.14 shall be met.

(2) Specific requirements. (i) *Nature of the claim*. A health claim associating substances in diets low in fat and high in fruits and vegetables with reduced risk of cancer may be made on the label or labeling of a food described in paragraph (c)(2)(ii) of this section, provided that:

(A) The claim states that diets low in fat and high in fruits and vegetables "may" or "might" reduce the risk of some cancers;

(B) In specifying the disease, the claim uses the following terms: "some types of cancer", or "some cancers")

(C) The claim characterizes fruits and vegetables as foods that are low in fat and may contain vitamin A, vitamin C, and dietary fiber.

(D) The claim characterizes the food bearing the claim as containing one or more of the following, for which the food is a good source under § 101.54: dietary fiber, vitamin A, or vitamin C;

(E) The claim does not attribute any degree of cancer risk reduction to diets low in fat and high in fruits and vegetables;

(F) In specifying the fat component of the labeled food, the claim uses the term "total fat" or "fat";

(G) The claim does not specify types of fats or fatty acids that may be related to risk of cancer;

(H) In specifying the dietary fiber component of the labeled food, the claim uses the term "fiber", "dietary fiber", or "total dietary fiber";

(I) The claim does not specify types of dietary fiber that may be related to risk of cancer; and

(J) The claim indicates that development of cancer depends on many factors.

(ii) Nature of the food. (A) The food shall be or shall contain a fruit or vegetable.

(B) The food shall meet the nutrient content requirements of § 101.62 for a "low fat" food.

(C) The food shall meet, without fortification, the nutrient content requirements of § 101.54. for a "good source" of at least one of the following: vitamin A, vitamin C, or dietary fiber.

(d) *Optional information.* (1)'The claim may include information from paragraphs (a) and (b) of this section, which summarize the relationship between diets low in fat and high in fruits and vegetables, and some types of cancer and the significance of the relationship.

(2) The claim may identify one or more of the following risk factors for development of cancer: Family history of a specific type of cancer, cigarette smoking, alcohol consumption, overweight and obesity, ultraviolet or ionizing radiation, exposure to cancer causing chemicals, and dietary factors.

(3) The claim may use the word "beta-carotene" in parentheses after the term vitamin A, provided that the vitamin A in the food bearing the claim is beta-carotene.

(4) The claim may indicate that it is consistent with "Nutrition and Your Health: Dietary Guidelines for Americans," US. Department of Agriculture (USDA) and the Department of Health and Human Services. (DHHS), Government Printing Office.

(5) The claim may include information on the number of people in the United States who have cancer. The sources of this information must be identified, and it must be current

information from the National Center for Health Statistics, the National Institutes of Health, or "Nutrition and Your Health, Dietary Guidelines for Americans," USDA and DHHS, Government Printing Office.

(e) *Model health claims.* The following model health claims may be used in food labeling to characterize the relationship between substances in diets low in fat and high in fruits and vegetables and cancer:

(1) Low fat diets rich in fruits and vegetables (foods that are low in fat and may contain dietary fiber, vitamin A, and vitamin C) may reduce the risk of some types of cancer, a disease associated with many factors. Broccoli is high in vitamins A and C, and it is a good source of dietary fiber.

(2) Development of cancer depends on many factors. Eating a diet low in fat and high in fruits and vegetables, foods that are low in fat and may contain vitamin A, vitamin C, and dietary fiber, may reduce your risk of some cancers. Oranges, a food low in fat, are a good source of fiber and vitamin C.

Dated: November 3, 1992.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

Note: The following tables will not appear in the annual Code of Federal. Regulations.

BILLING CODE 4160-01-F

TABLE 1
Human Studies. Antioxidant Vitamins and Cancer Through March 1, 1992

Study	Study Design	Subjects	Methods	Results	Comments
Basu et al., 1991. (Ref. 9)	Clinical survey of 75 subjects attending a referral clinic in the Bronx, New York for evaluation of abnormal screening Pap smear.	30 women with no cervicitis on pap smear, 45 women with histopathologically diagnosed dysplasia.	Pap smears, papilloma virus screening, age, parity, last menstrual period, contraceptive practice and duration, number of cigarettes per day and duration in years obtained from each patient. Venous sample obtained for micronutrient analysis: ascorbic acid, beta-carotene and retinol. Ascorbic acid levels were significantly lower in smokers, regardless of cervical status or detection of human papilloma virus infection.	Analysis directed at serum antioxidant levels in smokers versus nonsmokers. After dividing smokers and nonsmokers into groups, there was no significant difference in ascorbic levels in the women with cervical dysplasia and those without. Although not noted in the paper the serum retinol level was lower in smokers with cervical dysplasia than those without and serum beta-carotene levels were lower in smokers with cervical dysplasia than those without.	The study group was small, and both cigarette smoking and antioxidant level are continuous variables. The results do not show a significant association between cervical dysplasia and serum antioxidants.
Benito et al., 1991. (Ref. 10)	Case- - control study; colorectal cancer in Majorca, Spain.	Cases – 186 histologically confirmed colorectal cancer cases, diagnosed between July 1984 and Feb. 1988 Controls- - 295 population controls and 203 hospital controls. Both cases and controls had to be residents of Majorca for previous 10 years.	A food frequency questionnaire with data on 99 food items was used. Average frequency of consumption in previous year assessed. Local food consumption tables used to estimate intake. Age, sex, weight 10 years prior to interview, meals per day, education in years, occupation, and physical activity in workplace (surrogate for energy expenditure) were used in regression model.	There was no significant association between the risk of either colon or rectal cancer and level of vitamin A, retinol, carotene, vitamin C, or vitamin E intake.	Based on the significant inverse association between fiber from legumes and folic acid in cruciferous vegetable, the findings support a recommendation for diets high in vegetables, along with a healthy lifestyle including moderate intake of calories and adequate physical activity.

TABLE 1-CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Boeing and Frentzel-Beyme, 1991. (Ref. 19)	Environmental epidemiology study of stomach cancer; multicenter, hospital-based, case-control study in high- and low-risk areas for stomach cancer in Federal Republic of Germany.	An area with high stomach cancer mortality rate was compared with another area with a low rate. During the 2-year study period, 143 stomach cancer cases and 579 controls completed the interview.	Dietary information by recall was assessed for the last 5 years before onset of the disease. All interviews were coded by one person. Data were obtained on vitamin C intake source of water supply, years of refrigerator use, and use at home. Risk estimates were obtained by unconditional logistic regression methods.	A low intake of vitamin C relative risk (RR) = 2.32, 95% confidence interval (CI) 1.22 to 4..43 for lowest against highest quintile), noncentralized water supply (RR= 2.17, CI 1.14 to 4.13 against central water supply), refrigerator use for less than 25 years (RR = 1.33, CI 0.82 to 2.15 against more than 30 years, and use of spruce for smoking (RR= 3.33, CI 1.56 to 71.2) against not smoking at home), were identified as factors possibly causally related to stomach cancer occurrence.	The results are consistent with the hypothesis that increased intake of vitamin C reduces the risk of stomach cancer by inhibiting nitrosation reactions in the stomach, or by decreasing the carcinogenicity of putative carcinogens in smoke (especially polyaromatic hydrocarbons and nitrosamines). Also, the data implicate possible sources of carcinogens or carcinogen precursors (smoked meat and local water supply) in the occurrence of stomach cancer.
Bravo et al., 1991. (16)	Case-control study, Madrid, Spain prostatic cancer	Cases-90 men with histologically diagnosed prostatic carcinoma between January 1983 and December 1987. Controls- 180 male hospital patients with illnesses other than urologic disease or a primary tumor. Stratified by age and date of admission.	Standardized questionnaire covering occupation, medical, socioeconomic history, dietary factors including types and amounts of food eaten. Diet classified into five types; normal, rich in animal fat, rich in vegetable fat, deficient in vitamin A, and deficient in vitamin C. Food composition based on Madrid data. Odds ratio (OR) for diet, obesity and prostatic cancer calculated.	This study found no association between a diet deficient in vitamins A or C and the risk of prostatic cancer. The relationship between intake of vegetable fats and prostatic cancer was also not significant.	The diet of central Spain is rich in fruits and vegetables. It is possible that even the lowest quintile of intake for fruits and vegetables in Mediterranean areas are relatively high in relation to other cuisines. The results of this study may not be generalizable.
De Mesquita, et al., 1991. (Ref. 15)	Case-control; Netherlands; Pancreatic (exocrine) cancer; study conducted 1984 to 1988	164 cases (surrogates interviewed for 50% males and 46% females); 480 controls (surrogates interviewed for 34% males and 26% females)	Interview using dietary questionnaire containing 116 food items; dietary assessment covered year before interview; 68% of cases were histologically confirmed; others diagnosed clinically.	Adjusted for smoking and total calories: Daily consumption of vegetables statistically significant. Inverse association between intake of fresh vegetables, cooked cruciferous vegetables and pancreatic cancer.	Daily consumption of vegetables show a protective effect; large percentage of proxy interview of cases introduce bias

TABLE 1—CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Enstrom et al., 1992. (Ref. 1)	Populations data base analysis, National Health and Nutrition Examination Survey (NHANES I) data and a median of 10 years of prospective followup mortality.	11,348 men and women, aged 25 to 74 years at time of NHANES I survey, with a total of 1,809 deaths during the followup period.	Comprehensive nutritional status survey that included clinical, biochemical and dietary methods. The population was allocated into three groups: intake 50 <mg/day without supplements, intake •50 mg/day without supplements, and •50 mg/day with supplements. Followup mortality rates determined in total and for several specific causes, including cancer and heart disease.	Higher dietary intakes of ascorbic acid were associated with significant reduction total mortality rate and in the mortality from heart disease. These effects were enhances by supplements. The standardized mortality rate from cancer (total for all sites) was a nonsignificant 0.78 with supplemental ascorbic acid. In contrast with the results for total mortality and heart disease mortality, the results with cancer mortality were not significant because the standardized mortality rate was not a low and because the cohort size was decreased (heart disease produced approximately 40 percent of the total mortality, whereas cancer produced less than 25 percent).	These results do not provide support for a reduction in risk of any type of cancer by ascorbic acid. They cannot be interpreted, however, as contradicting that possibility. The mortality rate from cancer was not reduced as much with elevated vitamin C intake as were the total and heart disease rates, and the cohort size was substantially smaller. Any protective effect of vitamin C at one cancer site may have been masked by no effect at other sites, with the overall rate being apparently changed by a substantial but nonsignificant amount (22 percent) in a protective direction.
Gerber et al., 1991. (Ref. 5)	Montiplier, France observation of blood and cellular antioxidant levels in breast cancer cases and hospital controls	Cases: 48 women inpatients for breast cancer. Controls: 50 women first admission impatient neurology without cancer or circulatory disease.	Blood levels of zinc, copper, selenium, vitamins E and C measured. Cellular levels of selenium, vitamins E and C evaluated in most subjects. Subject identity codes used.	Significantly higher mean levels of vitamin E, total cholesterol and E/total cholesterol ratio found in breast cancer cases than in controls. Effect lost when vitamin pill users excluded, except vitamin E. Leukocyte vitamin E level also significantly higher. Serum Zinc level sign higher. Elevated leukocyte vitamin C in cases borderline sign. Mean leukocyte vitamin E level sign after vitamin pill users excluded.	Sample size small. Elevated plasma vitamin , leukocyte vitamin E, serum Zinc in breast cancer cases hypothesized to relate to facilitation of certain tumor growth by these antioxidants suggesting effect ultimately related to metabolic alteration. Future studies need to correlate tumor antioxidant level to resistance (chemo or natural) and tumor antioxidant level to blood level.

TABLE 1-CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Graham et al., 1991. (Ref. 3)	Case-control; New York; Postmenopausal breast cancer	439 incident cases; 494 age-matched community controls	Interview using dietary questionnaire on 172 foods; diet assessed 2 years before interview; all cases were histologically confirmed; results adjusted for age, education, age at first pregnancy, number of pregnancies, age at menarche, relative with breast cancer, and benign breast disease.	Cases and controls consumed same number of calories. Dietary carotene, vitamin C protective but no effect shown for supplement use; dietary fiber borderline protective RR= 0.7 (0.5 to 1.1); adjustment for total calories did not change results. Cases ate less of 10 fruits and vegetables in questionnaire.	Low participation rates may introduce bias: 56% of eligible cases and 46% of eligible controls participated in study, thus may not be able to generalize the results.
Gridley et al., 1992. (Ref. 13)	A population-based case-control study of oral and pharyngeal cancer, conducted during 1984 to 1985 in four areas of the United States.	The subjects included 1,262 controls nad 1,114 oral and pharyngeal cancer cases.	Interview were administered to obtain information on demographic variables, tobacco and alcohol use, diet, occupation, and medical history. Vitamin supplement use questions addressed years of use, age started, types of multivitamin products used (including brand) and uses of single nutrient supplements, vitamin shots obtained, and mineral products used.	Use of supplements was significantly associated with reduced risk of oral cancer. Use of supplements was associated with being female, white, more highly educated, being a California resident, having a lower body mass, and consuming more fruits and vegetables. Protracted use did not increase the apparent effects of supplements on cancer risk. Users of supplements of individual vitamins, including A, B-complex, C and E were at lower risk after controlling for effects of tobacco, alcohol and other risk factors. After adjustments, vitamin E supplementation was the only one that remained associated with reduced risk.	It is not clear that the lower risk among consumers of vitamin E supplements was due to the vitamin itself, because the finding are also associated with higher intakes of fruits and vegetables among supplement users. The findings are consistent with evidence from experimental animals, and should prompt further research on vitamin E in reducing the risk of cancer.

TABLE 1—CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Harris et al., 1991 (Ref. 12)	Case-controls study during the year before diagnosis with cancer in Oxford, U.K.	The subjects included 96 men with lung cancer, 75 men with other epithelial cancers, and 97 hospital controls.	Interviews were conducted within 1 year of diagnosis by one experienced interviewer who was the same for all subjects. The interviewer was not blinded about diagnosis. The questionnaire covered smoking history and usual dietary intake during the year preceding diagnosis. The known carotene values for the foods are for beta-carotene.	Calculated mean dietary intakes of beta-carotene were 24% lower for lung cancer cases than for controls, 10% lower for other epithelial cancer cases than for controls. Serum concentrations of beta-carotene, retinol, and vitamin E were lower in the cancer patients than in the controls by 58, 30, and 31 percent, respectively, for lung cancer, and 33, 11, and 14 percent, respectively for other epithelial cancer cases. The OR's were less than 1.0 in the two upper thirds of dietary carotene, with the trends having borderline significance. The OR's for vegetables were rather irregular, and the associated trends were weaker than the trends for beta-carotene.	The period of concern in the recall was the year prior to diagnosis, a time. By comparison, cases in the 2-year period following sampling or interview are often excluded from prospective studies because differences may be caused by the cancer. The results suggest that beta-carotene is protective against epithelial cancers, including lung cancer.
Herrero et al., 1991 (Ref. 8)	Case-control study multiple sites in Mexico, Central America, and Colombia.	748 cases invasive cervical cancer, 1,411 inpatient controls from neurology wards at these sites.	Assessment of consumption of 58 foods, including major sources of vitamin A, C, carotenoids, and folacin as well as medical and behavioral characteristics related to cervical cancer. Adjusted for age, study site, sexual and reproductive history, socioeconomic status, screening practice, and detection of human papillion virus.	Slightly lower risk for highest quartiles of consumption if fruit and fruit juice. Risk of cervical cancer not reduced in groups with highest consumption vegetables, foods of animal origin, complex carbohydrates, legumes, or folacin-rich foods. Evaluation of nutrient indices identified decreased risk associated with vitamin C, beta carotene, other carotenoids. Including vitamin C and beta carotene in the same model attenuated the association for beta carotene, but not for vitamin C.	Results consistent with other studies that support a protective effect of nutrients in fruits and vegetables against the development of invasive cervical cancer, however specific category of nutrient responsible not readily apparent. Associations were driven by relationships between diet and cervical cancer at two study sites. Higher socioeconomic status of subjects at these sites leaves open possibility of selection bias or an unidentified dietary pattern.

TABLE 1-CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Knight et al., 1991. (Ref. 27)	Clinical trial of nitrosation of L-proline load by diet-derived nitrate, and inhibition by dietary ascorbic acid.	The first study had 16 subjects of both sexes, aged 23 to 56 years, all nonsmokers. The second study had 19 females aged 20 to 28 years, including 5 smokers. All subjects avoided known sources of the nitrosation product and vitamin supplements for 72 hours before test meal consumption.	Test meal 1 was designed to supply a high level of dietary nitrate (172 mg/meal) accompanied by relative low levels of ascorbic acid (24 mg/meal). Test Meal 2 consisted of the same items as Test Meal 1, with the addition of foods rich in ascorbic acid (340 mg/meal). The nitrate level of Test Meal 2 was 197 mg. Both test meals contained 2.4 g dietary proline. In the first study, nitrosation was determined after consumption of low ascorbic acid meal (Test Meal 1) and, a week later, after consumption of the same meal with 500 mg of added L-proline. In the second stud, all subjects had nitrosation determined with added proline, first with the low ascorbic acid meal and then a week later with the high ascorbic acid meal. Urine was collected for 24 hours after each test meal, and assayed for nitrosoproline (NPRO) and nitrate.	In the first study, the background excretion of NPRO was increased by addition of free L-proline. In the second study, a lower excretion of NPRO occurred with the high ascorbic acid meal. This occurred despite a slightly 13 higher nitrate intake from Test Meal 2, compared with that form Test Meal 1. Some subjects (Subgroup A) had a low NPRO excretion after Test Meal 1, and this was strongly decreased after Test Meal 2, Containing high ascorbic acid foods.	Six subjects showed no change in NPRO after consumption of a test meal containing rich sources of ascorbic acid. These had low NPRO excretions with the low ascorbic acid meal. 13 subjects had much higher levels of NPRO excretion after the low ascorbic acid meal, but this was strongly inhibited by the inclusion of rich ascorbic acid sources in the meal, even though the ascorbic acid sources contributed some additional nitrate. The data suggest that not all individuals synthesized NPRO in vivo from the ingested precursors, and those who did not were the subjects who failed to show ascorbic acid inhibition of NPRO excretion. It was concluded that a normal western diet with plentiful content of fresh vegetables can provide sufficient nitrate to result in endogenous nitrosation, and that this process is substantially inhibited by inclusion of ascorbic acid rich foods.

TABLE 1–CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Knekt et al., 1991. (Ref 11)	Prospective cohort, 20-year followup for lung cancer in cancer free Finnish men.	4,538 cancer free men ages 20 to 69, baseline examination 1966 through 1972.	Dietary history estimated based on total habitual intake for previous year. Intake of antioxidant vitamins based on previously published analyses of Finnish foods.	Inverse relationship between intake of vitamins A, E, and C and incidence of lung cancer in nonsmokers. Relative risk between lowest and highest tertile of intake 2.5, 3.1 and 3.1 respectively. Inverse gradient between yellow, green and red vegetables (source of carotenoids) and lung cancer. No inverse gradient between preformed vitamin A and lung cancer. Strong inverse association for margarine intake (source of tocopherol) and incidence of lung cancer; significant inverse gradient for fruit intake (vitamin C source) despite low intake in this cohort.	Misclassification of intake and changes in intake were possible over followup, especially supplement use. Other substances in foodstuffs rich in antioxidant vitamin (e.g., terpenes, flavones, and phenols) may be anticarcinogenic. Studies needed on dietary patterns, intake levels, and protective effects of other constituents of diets.
Knekt et al., 1991. (Ref. 18)	A nested case-control study of serum micronutrients and cancer of low incidence in Finland.	The subjects were a total of 115 cases of cancer in 8 anatomical location categories (9 to 20 cases in each category) and 211 controls.	The site of primary cancer and date of diagnosis obtained form the cancer registry were linked to data obtained in the health examination date. Serum concentrations were determined from alpha-tocopherol, beta-carotene, retinol, retinol-binding protein, and selenium.	The crude mean level of serum alpha-tocopherol was 30% lower in persons with melanoma than in controls. The laryngeal and esophageal cases had alpha-tocopherol levels that were nonsignificantly lower. Accordingly for alpha-tocopherol, the relative risks of melanoma and was 0.2 (significant) and for cancers of the larynx and esophagus, 0.48 and 0.39 (nonsignificant). For beta-carotene, the relative risk of melanoma was 0.03 (highly significant).	Only melanoma patients had significantly lower serum alpha-tocoperol and beta-carotene levels than controls. Because the number of cases were small, no strong conclusions can be drawn from the results until they are confirmed in studies based on larger cohorts or on pooled data from several small samples.

TABLE 1-CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Potischman et al., 1991. (Ref. 7)	Case-control study 4 Latin American nations.	387 cases of invasive cervical cancer, 670 hospital controls.	Serum levels of eight micronutrients measured in cases and controls. Stage 1 and 2 cancer patients only included to minimize effects of disease on serologic markers.	Intake of retinol, cryptoxanthin, lycopene, alpha carotene, lutein and alpha tocopherol did not significantly differ between cases and controls. After adjustment for age, study site, sex and reproductive history, socioeconomic status, and papilloma virus higher serum beta carotene and gamma tocopherol levels associated with decreasing risk of disease.	Serum beta-carotene level constant as disease progression on nutrient value, while gamma tocopherol level was higher in cases and progressed with disease. In this study dietary and serum effects of beta carotene concordant, both parameters indicate a possible association between intake of beta carotene and reduced risk of invasive cervical cancer.
Reed et al., 1991. (Ref. 26)	Clinical observation and ascorbic acid trial in patients at high-risk for stomach cancer.	Sixty-two English men and women with either atrophic gastritis, pernicious anemia (PA), partial gastrectomy, or vagotomy; ages ranged form 28 to 77 years.	Serum ascorbic acid and gastric juice nitrite and total extractable N-nitroso compounds were determined before treatment, weekly during 4 weeks of ascorbic acid treatment (4 g /day) and for 4 weeks after discontinuation of treatment. All patients consumed their normal diets, but avoided vegetable and fruit juices during the experiment.	Many patients had low baseline serum levels of ascorbic acid, and compliance with treatment was confirmed by a marked rise during treatment. The levels were still high 4 weeks after the patients had been instructed to stop taking ascorbic acid, implying that many of them had not discontinued treatment. Baseline levels of N-nitroso compounds were high in all groups compared with the levels previously found in normal controls, but a highly significant decrease was observed during treatment with ascorbic acid in all groups except those with PA. Treatment produced juice nitrite levels in all groups except those with PA.	These data support the conclusion that high-dose ascorbic acid treatment reduces the intragastric formation of nitrite and N-nitroso compounds.

TABLE 1-CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Riboli et al., 1991. (Ref. 2)	Case-control; Spain; Bladder cancer	432 cases (all males); 792 controls; two sets of controls: population-based and hospital-based	Interview using dietary questionnaire containing 60 food groups; dietary assessment covered year before interview. Cases histologically confirmed.	Adjusted for smoking and total calories, a higher vitamin B intake was associated with a marginally significant reduction in risk of bladder cancer. No association found for retinol or carotene intake.	Slightly low participation rates (cases: 72% and controls: 71% hospital and 66% population); results possibly based by inclusion of 208 prevalent cases who may represent survivors of bladder cancer.
Richardson et al., 1991. (4)	Case-control; France; Pre-and Postmenopausal breast cancer	409 incident cases; 515 hospital controls (348 premenopausal and 575 postmenopausal for total study population)	Interview using dietary questionnaire on 55 foods; current diet assessed, but if changed over past 12 months, former diet was used; all cases were histologically confirmed; results adjusted for afe, menopausal status, family history of breast cancer, history of benign breast disease, alcohol consumption, and age at menarche.	Antioxidant vitamin intake had no significant effects on risk of breast cancer in premenopausal women and postmenopausal women; however, fruits rich in beta-carotene had a marginal protective effect (RR=1.4, CI=1.0 – 2.0) on breast cancer in this same group. In post-menopausal women retinol had a marginal protective effect (OR 1.8, CI=1.2 – 2.8), Beta-carotene and vitamin E intake had no significant effects on risk of breast cancer.	Study adds support to the hypothesis that fruit consumption may have a slight protective effect against breast cancer in all women (both premenopausal and postmenopausal women).

TABLE 1-CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Shi et al., 1991. (Ref. 22)	Case-control study in Shanghai, China comparing urinary ascorbic acid and nitrate in patients with gastric cancer and normal controls; urine mutagenicity in normal controls, dysplasia and gastric cancer; and gastric juice N-nitroso compounds in controls, chronic atrophic gastritis, and dysplasia/gastric cancer in patients.	Thirty cases of gastric cancer were selected and paired with dysplastic patients and normal controls of the same sex and age group.	All cases were diagnosed by endoscopy. Urinary ascorbic acid and nitrate were determined chemically. Urine mutagenicity was determined in the Ames test using _Salmonella typhimurim_ TA98 and TA100 strains, each with and without an activating S9 fraction. Four individual and the total N-nitroso compounds were chemically assayed in gastric juice.	The reduced ascorbic acid content of urine was lower in the gastric cancer group than in normal controls, while the content of nitrate was significantly higher in the cancer patients than in the controls. No mutagenicity was seen in the urines of the controls, whereas a low fraction of the urines from the dysplasia patients and a high fraction of the urines from the gastric cancer patients were mutagenic.	The lower excretion of ascorbic acid in the urine of gastric cancer patients could be either a cause or a result of the disease, but it is consistent with the hypothesis that this vitamin reduces the risk of this disease. The higher excretion of nitrate probably reflects a higher intake. Mutagenicity of the urine was directly associated with severity of pathology of the stomach. Normal controls had low levels of N-nitroso compounds in gastric juice, compared with chronic atrophic gastritis, dysplasia, or gastric cancer. The mutagenicity of the urine may have been related to synthesis of N-nitroso compounds in the stomach and differences in this process may have been due to differences in intakes of ascorbic acid and nitrate. These results support the hypothesis that N-nitroso compounds may be the cause of gastric cancer.

TABLE 1-CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Sierra et al., 1991. (Ref. 25)	Comparison of urinary concentration of nitrate and N-nitrosoamino acida in children from high- and low-risk areas for stomach cancer in Costa Rica.	One high-risk and one low-risk area for stomach cancer were chosen on criteria of rural location, large enough population of school age children and similar ethnic characteristics. From each area, 25 subjects aged 8 to 14 years were chosen at random for the oral treatments and urine collections.	Two samples of 12-hour overnight urine were collected from the children after they had ingested 500 mg proline with 200 mg ascorbic acid or 500 mg proline alone 1 hour after the evening meal. Urine samples were assayed for N-nitrosoproline and two other N-nitroso compounds, and nitrate.	All comparisons of levels of N-nitroso-proline were statistically significant. Thus, in both areas, the level was reduced by ingestion of ascorbic acid with proline, compared with that seen with proline alone. The level as higher in the high-risk area than in the low-risk area, for each type of dietary treatment. The N-nitrosoproline level correlated well with nitrate level.	The results indicate that children living in a high-risk area have a higher potential for endogenous nitrosation than those living in the low-risk area. Nitrate exposure may explain at least part of this difference. The data confirm that proline nitrosation can be substantially inhibited by ascorbic acid supplementation.
Sobala et al., 1991. (Ref. 33)	Case control study 56 patients scheduled for stomach endoscopy in Lyon, France.	Fifty-six adult patients referred for endoscopic exam for possible gastritis with no previous stomach surgery.	Patients fasted overnight. Gastric juice aspirated for ascorbic acid, total vitamin C, total bile acid, nitrite, nitrate and total Nitroso compouds (NOC's), and an aliquot of plasma was collected for vitamin C levels. 2 stomach biopsies; 1 cultured for Helicobacter and 1 submitted for bistopathology.	Of 56 patients, 12 completely normal on histopathology, 18 chronic superficial gastritis, 17 chronic gastritis with atrophy, and 9 had gastric reflux. 89% of chronic gastritis had Helicobacter infection. Intestinal metaplasia in this group significantly associated with gastric ascorbic acid, gastric vitamin C.	Age and gastric pH also significantly higher in chronic gastritis patients with intestinal metaplasia versus those without.

TABLE 1-CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
VanEenwyk et al., 1991. (Ref. 118)	A case-control study of cervical intra-epithelial neoplasia and dietary and serum carotenoids.	The subjects were 102 nonpregnant, nonpostpartus cases and matched controls from women who had no cervical cytologic abnormalities greater or equal to those of benign atypia.	Cases were identified with biopsy-confirmed cervical intraepithelial neoplasia (CIN) of grades I, II, or III. Participants completed a food frequency questionnaire provided by the National Cancer Institute. The conversion of foods to nutrients was performend with and without an adjustment for energy intake.	For serum lycopene, the odds ratios for CIN were significantly increased in the three lower quartiles. The finding for lycopene- rich foods were consistent with this result. CIN was not associated with lutein. Finding for alpha-carotene, beta-carotene and cryptoxanthin were ambiguous. The lower quartiles of dietary vitamin C were associated with significantly increased odds ratios for CIN.	The relatively low response rates (approximately 60 percent for cases and 50 percent for controls) could have introduced bias. An inherent limitation of case-control studies is the determination of exposure after the onset of disease, especially for serum studies- -dietary behavior may have changed after diagnosis and before bloods sampling. The finding of a protective association for lycopene but not other carotenoids indicates that caution must be used in attributing the effects of carotenoid-containing fruits and vegetables to beta-carotene, at least for this type of cancer.
West et al., 1991. (17)	Case-control study, Utah. Prostatic cancer.	Cases-358 men with prostatic cancer diagnosed between 1984 and 1985. Controls-679 population based controls matched for age and county of residence.	Histologically confirmed cases and controls interviewed using quantitative food-frequency questionnaire. Data was analyzed separately for middle (45 to 67) and older (68 to 74) age categories and by tumor aggressiveness.	Beta carotene had a nonsignificant protective effect for prostatic cancer in younger males. In older males, total vitamin A had a slight positive association with all prostate cancer OR=1.6, CI=0.9 to 2.4). There was little association vitamin C and beta-carotene and prostate cancer in older men.	The most significant association were seen for older males with aggressive tumors. Dietary fat was the strongest risk factor for these males.

It was not possible to blind interviewers to the case or control status of respondents. |
| You et al., 1991. (Ref. 24) | Comparison of N-nitroso compounds concentrations in urine and gastric juice from subjects with different degrees of premalignant pathology of the stomach | Twenty subjects with normal gastric mucosa, 20 subjects with chronic atrophic gastritis and/or intestinal metaplasia of the stomach, and 20 subjects with dysplasia of the gastric mucosa. | Twenty-four hour urine samples and gastric juice after an overnight fast were collected and assayed for N-nitroso-proline and two other N-nitroso compounds. | Levels of N-nitroso compounds in the urine were higher in subjects with gastric dysplasia than in normal controls or subjects with chronic atrophic gastritis/intestinal metaplasia. Levels of N-nitroso compounds were lower in gastric juice than in urine, and levels in gastric juice could not be evaluated by gastric pathology | Persons with gastric dysplasia had elevated urinary levels of N-nitroso compounds, and these subjects are exceptionally prone to stomach cancer. |

TABLE 1—CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Zaridze et al., 1991. (Ref. 6)	Case-control study, breast cancer, Moscow.	The subjects were 139 case-control pairs matched for age and neighborhood. Newly diagnosed cases of breast cancer between September 1987 to January 1989, and controls attending same clinics as cases for minor complaints.	Dietary assessment made with food frequency questionnaire for year prior to diagnosis of cases or attending clinic by controls. Assessment based on nutrient indices for 145 common food items. Data were analyzed separately for pre-and postmenopausal women.	Diet was a more important risk factor in breast cancer for postmenopausal women than for premenopausal women. After adjusting for age at menarche, energy intake, and education intake of vitamin C (OR 0.09) retinol equivalent and cellulose were protective in postmenopausal women. Nonsignificant association for mono-and disaccharides. Increased risk of breast cancer with high intake of total fat. In general results indicate a high risk of breast cancer associated with nutrients from animal products, low risk associated with high intake of nutrients from vegetables and fruits.	Associations between dietary fat and breast cancer in postmenopausal women were nonsignificant. Socio-economic status and education were positively associated with higher risk. These confounding factors may relate to the access to health care, overestimation of intake based on serving sizes, and other influences which were not evaluated.
Zatonski et al., 1991. (Ref. 14)	Case-control; Poland; Pancreatic (Exocrine) Cancer; study conducted 1985 to 1988	110 cases (surrogates interviewed for 71%); 195 controls (all directly interviewed)	Interview using dietary questionnaire containing 80 food items assessed diet 1 to 2 years before diagnosis. 43% of cases were histologically confirmed, remainder diagnosed radiologically	Adjusted for smoking and total calories: Inverse association between intake of vitamin C and pancreatic cancer; nonsignificant protective effect association with retinol, fiber.	The statistically significant nutrients (and fiber) are associated with fruits and vegetables. Substantial use of proxy interview of cases introduce bias.

TABLE 1—CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Zhang et al., 1991. (Ref. 23)	The role of mutagenic/ carcinogenic N-nitrosamides in stomach cancer was studies by (1) measuring mutagenicity of extracts of a local fish sauce before and after nitrosation, (2) determining the carcinogenicity of these extracts in rats, (3) determining the N-nitrosamides in these extracts, and (4) correlation of N-nitrosamides in gastric juice with severity of pathological changes in the stomach of human subjects.	Fish similar fish sauces were collected from areas with high- and low-risk for stomach cancer, nitrosated, assayed for N-nitrosamides and mutagenicity, and fed to rats for 4 or 16 weeks. Gastric juice was collected from 12 normal control, 14 chronic atrophic gastritis, 13 gastric dysplasia patients, and assayed for N-nitrosamides.	Fish sauce samples were extracteed with ethyl acetate and the extract was nitrosated with sodium nitrite under simulated gastric conditions. Mutagenicity was determined with the Ames test using Salmonella typhimurim strain TA100, a sister chromatic exchange assay, and a micronucleus test. The animal carcinogenicity assay was performed by gavaging for 3 days either nitrosated or nonnitrosated fish sauce extract to newborn rats and determining the effects in rats autopsied after 4 or 16 weeks. A total of 39 gastric juice samples were collected from patients after an overnight fast by fibroendoscopy.	In the absence of nitrosation, none of the fish sauce extracts was mutagenicity. After nitrosation, all samples had direct mutagenicity in the Ames test and induced sister chromatid exchange with a dose-response relationship. In the micronucleus test, fish sauce extracts from only two villages were active. Four weeks after treatment with fish sauce, only those rats treated with the sauce that was mutagenic in all three assays showed marked precancerous dysplasia. After 16 weeks, the same treatment group had cancerous ulceration in the glandular stomach, with dysplastic glands and cells that had penetrated the mucosa and infiltrated into submucosa and muscular layers of the gastric well. The mean concentrations of N-nitrosamides in the nitrosated fish products were more than 15 times higher in the samples from a high-rrish area than in the samples from a low-risk area. The N-nitrosamide concentrations in gastric juice were strongly positively correlated with the severity of pathological changes in the stomach.	These data strongly support the hypothesis that the etiology of human gastric cancer is closely related to intragastric formation of mutagenic/carcinogenic N-nitroso compounds, that the degree of pathological change is directly related to the exposure of these compounds, and that exposre to these carcinogens is higher in areas of high-risk for stomach cancer.

TABLE 2
Human Studies not included in the Review of New Scientific Evidence.

Study	Study Design	Subjects	Methods	Results	Comments
Orenteich et al., 1991. (Ref. 41)	Case-control study in Northern California measuring sera beta-carotene levels 15 years prior to diagnosis of lung cancer versus sera levels collected from controls taken at same time.	The subjects were 263,000 individuals participating in routine Health Maintenance Organization check-ups; 151 lung cancer cases, 302 matched controls with similar sera storage time.	Comparisons were made with 123 case control triplets. Catalogued sera were stored at −40 C for 15 to 22 years and assayed using High Performance liquid chromatography. Relative risk of lung cancer was estimated by logistic regression, statistical significance of difference in mean calculated using single t test.	RR was 3.0 for lung cancer in lowest versus highest quintile of beta-carotene intake. Trend less evident for retinol and alpha-tocopherol.	Carotenoids are highly reactive, and decay may have varied in sera based on other substances present. It is also possible that the difference in sera carotenoid level in future lung cancer cases was not correlated with nutritional intake, but was associated with other factors such as smoking or alcohol use.
Tuyns et al., 1992. (Ref. 42)	A case-control study of gastric cancer in two provinces of Belgium.	Subjects were 449 cases 3,524 controls.	Diet data were obtained by interview using a validated dietary history questionnaire. Food were classified into groupings based source, such as vegetables, fruits, breads, meats, fish, and dairy products, and on raw versus cooked. RR and probability values were calculated.	Consumption of both raw and cooked vegetables, including leafy and root types, were associated with reduced risk. Consumption of raw fruit, but not stewed or canned fruit, was associated with reduced risk. Consumption of dairy products increased risk, and some types of meat and fish increased risk, whereas consumption of lean meats decreased risk. Consumption of high P/S ratio fats increased risk.	The results show that consumption on fruits and vegetables reduces risk. The destruction of protective effects by cooking of fruits, and the risk associated with polyunsaturated fat consumption suggest, but alone are not sufficient to demonstrate, that the antioxidant vitamins reduce the risk of stomach cancer.
Toma et al., 1992. (Ref 43)	A clinical trial of beta-carotene (90 mg/day for three cycles of 3 months each) against oral, and evaluation after 24 months.	A total of 23 patients (aged 17 to 85) were included in the study and 18 (8 male and 10 female) were evaluated.	The leukoplakia lesions were examined macroscopically and microscopically at entry, and in the evaluated patients at the end of the study.	Among the 18 evaluated patients, 6 showed complete response, 2 partial response, 3 minimum response, and 6 stable disease.	The design examined the use of high-dose beta-carotene in treatment of prenoplastic conditions, and thus appear not to meet the 1990 amendments standards for dietary context of reduction of risk.
Swanson et al., 1992. (Ref. 44)	A case-control study of diet and lung cancer risk in Yunnan Province, China.	The subjects were 428 cases, aged 35 to 74 years, and 1,011 age-matched controls.	Interviews were conducted to obtain information about eating habits during adult life and to report usual intake frequency for 31 food items or groups.	The relative risk of lung cancer across increasing quartiles of food intake increased for consumption of meat. Cases tended to consume slightly more rice than controls. Risk decreased markedly across increasing quartiles dark green, leafy vegetables.	The specific constituent(s) responsible for the protective effects of vegetable consumption could both be identified, but carotenes other than beta-carotene, or compounds in cruciferous or Allium vegetables were stated to be possibilities.

TABLE 2—CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Longnecker et al., 1992 (Ref. 45)	Pooled data from five previously published studies with serum alpha-tocopherol values were analyzed for reduced risk of several types of cancer.	The five studies, in Finland, Hawaii, Maryland, Switzerland, and the United Kingdom, included approximately 93,000 subjects, both male and female, but serum alpha-tocopherol assays were performed only on approximately 300 cases and 1,300 controls.	Blood specimens had been stored for 0 to 14 years at temperatures of –20 to –75● C when serum was analyzed for alpha-tocopherol.	In comparison of cases versus controls, alpha-tocopherol values were consistently nearly equal, and, when numerical difference occur, the cases tended to be slightly lower than the controls. The crude OR's for colon and rectum cancer were consistently lower for the highest quartile of serum alpha-tocopherol values than for the lowest quartlile. The CI's of the collective data were quite wide, preventing significance of any real effects.	The results suggest that serum alpha-tocopherol concentration may be inversely related to risk of colorectal cancer. This is unclear, however, because the association between serum alpha-tocopherol level and decreased risk was modest, the confidence were wide, and the overall tests for trend in effect were not significant. Larger observational studies with dietary data are needed to determine whether vitamin E has a small but important effect on risk of colorectal cancer.
Fraser et al., 1991. (Ref. 46)	A prospective study with a 6-year followup from 1977 to 1982 on diet and lung cancer. California.	Subjects were 34,198 Seventh-Day Adventists, 61 of whom developed lung cancer in cohort.	A questionnaire was mailed to all subjects. Response exceeded 75% for non-Hispanic whites. Food frequency was determined for 51 different foods. Annual mailings in regard to hospitalization, and hospital record information were used to detect new cancer cases.	Fruit consumption had a strong protective effect for lung cancer; RR=0.26 for highest tertile of consumption, CI+0.10-0.70, p= 0.006.	This population is unique in that less than 4 percent admitted to smoking and approximately 50 percent are lacto-ovo vegetarians.
Stahelin et al., 1991. (Ref. 47)	A prospective study of men in Basel, Switzerland with a 12-year followup; plasma levels of antioxidant vitamins were correlated with mortality due to cancer at all sites.	The subjects were over 2,974 men from a cohort of 6,000 healthy volunteers employed in three pharmaceutical companies.	Serologic samples were collected from 2,974 men in 1971 to 1973 examination cycle. Information about deaths was obtained from employers and death certificates obtained. No vital statistics were obtained for eight individuals.	Overall cancer mortality was associated with low mean plasma carotene level adjusted for cholesterol, and vitamin C. Bronchus and stomach cancers were associated with low mean plasma carotene. Stomach cancer was associated with low mean vitamin C and lipid-adjusted vitamin A. Low levels of vitamin C increased the risk of stomach cancer (RR=2.17, p=0.05; and gastrointestinal cancer, RR=2.46 in older subjects, significance lost in this group of subjects with exclusion of first 2 years of followup.	Authors conclude that low serum antioxidant vitamin levels are associated with higher risk of subsequent cancer. Effects appear to be site specific. The role of nutrient intake, rather than serum levels, and other variables is unclear. Serum lipid, smoking, exercise, unidentified nutrients are associated with antioxidant vitamins may effect serum levels.

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TABLE 2—CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Baghurst et al., 1991. (Ref. 48)	A case-control study of diet and pacreatic cacner, in Adelaide, Australia.	The subjects were 104 cases of pancreatic cancer and 253 community controls.	A quantitative food- frequency questionnaire was used to assess intakes of 179 food items. Amount and contribution to diet were compared for 48 nutrients.	Cases consumed more eggs, sweet and fatty foods and less vegetables and fruits (p ●0.01 for dried grapes, lettuce, and broccoli consumption in females; p ●0.01 for dried grapes in males; 0.01 ●p●0.05 for tomatoes, green beans, and coleslaw in males; and 0.01● p●0.05 for brussels sprouts, cucumber, potato, and tomato in females). Cases consumed less beta-carotene, vitamin C, and vitamin E than controls.	Study supports view that fruit and vegetables have an important role in minimizing cancer of the pancreas, but provides information about relative, not quantative, amounts of the antioxidant vitamins.
La Vecchia et al., 1991. (Ref. 49)	A case-control study of dietary indicators for pharyngeal and oral cancer in Northern Italy during 1987 to 1989.	The subjects were 105 cases of oral and pharyngeal cancer and 1,169 hospital controls with acute nonneoplastic conditions.	Data were collected on usual frequency of consumption of 10 indicator foods before onset of digestive illness. Subjective scores were given (low, medium, and high) for seven items including wholemeal bread, pasta, fats, condiments.	There was significant protective association for consumption of six food items: milk, meat, cheese, carrots, green vegetables, and most strongly, for fruit (RR=0.8 and 0.2, respectively, for two highest tertiles).	The associations may reflect poorer nutritional status in cases. The observation that fruit appeared to be particularly protective may be of significance in terms of etiology and protection.
Hu et al., 1991. (Ref. 50)	A case-control study of dietary indicators for colon and rectal cancer in Harbin City, Heilogjiang province, China during 1985 to 1988.	The subjects were 3,336 histologically confirmed cases of colorectal cancer (111 colon, 225 rectal) and an equal number of hospital controls with nonneoplastic diseases. Matched for sex, age, and residence.	Data on frequency and quantity of consumption of food items were collected. OR's and confidence limits were computed for intake and risk of disease.	Higher intakes of vegetables, especially green vegetables, chives, celery, were associated with a protective effect against colorectal cancer. Reduced intakes of meat, eggs, bean products, and grain were associated with increasing risk of rectal cancer.	The data are supportive of a protective effect of vegetable intake, especially green vegetables, against colorectal cancer. Protective effect of meat, eggs, bean products, and grain against rectal cancer may reflect lower level of nutrition in this region of China.

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TABLE 2—CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
De Vet et al., 1991. (Ref. 51)	A case-control study of dietary indicators for cervial dysplasia; a multicenter study in the Netherlands during 1984 to 1987.	The subjects were 257 cases of cervical dysplasia and 705 controls from the general population.	A questionnaire was mailed regarding frequency of consumption of various food items containing beta-carotene, retinol, vitamin C, and dietary fiber.	Increased risk of cervical dysplasia was associated with increased intake of beta-carotene; Relative Risk = 2.31, CI = 1.27 to 4.19. No relationship was found for retinol intake, but both vitamin C and dietary fiber intake showed a nonsignificant inverse relationship with cervical dysplasia.	The findings do not support hypothesis that beta-carotene protects against cervical dysplasia, but suggest a greater risk with higher intakes.
Graha et al., 1990. (Ref. 52)	A case-control study for gastric cancer in three couties in Western New York during 1975 to 1985.	The subjects were 293 histologically confirmed case and neighborhood-, age-, and sex-matched controls.	The cases came from hospital records in all but five hospitals in a three- county area. A 2.5-hour interview scheduled with each case and control was used to assess total nutrient intake. There were no surrogate interviews.	Carotene: there was substantial decrease in risk of male gastric cancer in the highest quartile of intake, but no dose-response relationship. There was no association in females. An increase in risk of gastric cancer occurred with higher retinol intake. No relationship to cancer was noted for vitamins C and E. Intake of specific vegetables had a significantly associated decreased risk of gastric cancer; male: cucumbers, tomatoes, green peppers, carrots, onions, celery; female: onions, winter squash.	The study is supportive of a protective effect of specific vegetables against the risk of gastric cancer. Data does not provide specific support for a role of antioxidant vitamins in reducing the risk of gastric cancer.
Oreggia et al., 1991. (Ref. 53)	A case-controls study cancer of the tongue in Uruguay, 1987 to 1989.	The subjects were 57 cases of lingual cancer and 353 hospital based controls. The study was restricted to males.	The subjects were interviewed with a standard questionnaire about the use of tobacco, alcohol, and dietary intake.	Infrequent consumption of vegetables was associated with tongue cancer; RR= 5.3, CI=1.5-19.4. Tobacco and alcohol were the strongest risk factors.	The study does not provide direct support for a role of the antioxidant vitamins in cancer because of the limited data on nutrient intake presented.

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TABLE 2—CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Gridley et al., 1990. (Ref. 54)	A multicenter case-control study for oral and pharyngeal cancer in blacks in New Jersey, Atlanta, Los Angeles, and the San Francisco/ Oakland area during 1984 to 1985.	The subjects were 248 cases of oral cancer in blacks contacted and 190 participated in the study; all were identified from cancer registries. Of the 262 controls contacted, 201 participated. These were matched to cases on age, race, and sex. Those under 65 years of age were chosen from random digit dialing and over 65 from Health Care Financing Administration rosters.	Interviews were conducted on diet, occupation, tobacco, alcohol, demographics, and medical history. Questions were asked about 61 food frequencies, food preparation, and recent dietary changes. Indices and serving size data were obtained from NHANES II.	All fruits and vegetables, except legumes were associated with decreased risk of cancer in men. A significant protection was associated with intake of noncitrus fruits, green leafy vegetables, and vegetables eaten raw. All fruits and vegetables, except dark yellow vegetables, especially cruciferous vegetables, were associated with decreased risk of cancer in women. A protection was most evident for pharyngeal cancer. Intakes of carotene and vitamin C were associated with significantly reduced risk in men, while vitamin C was significant for reduced risk in women.	Lower consumption of fruits and vegetables in blacks may contribute to elevated rates of oral and pharyngeal cancer versus general population. The study is consistent with a prospective role of the antioxidant vitamins and also for the inducer compounds in cruciferous vegetables.
Rossing et al., 1989. (Ref. 55)	A case-control study for antioxidant vitamins and pharyngeal cancer in Washington State, 1980-1983.	The subjects were 166 cases (of 292 identified cases) between 20 and 74 years old. Surrogate next-of-kin were interviewed for 86 cases; the controls were 547 of 552 individuals from a population who were sex- and age-matched to the cases.	The subjects were asked to estimate food frequency in a questionnaire interview for 48 food items and vitamin supplements during the 1970's. USDA nutrient indices were used to estimate intakes.	A significant increase to risk of pharyngeal cancer was associated with low intake of vitamin C; RR=2.5, CI=1.5 to 4.2. The role of vitamin C supplementation was difficult to assess because of discrepancies between next of kin reporting and the remaining case group.	The study suggests a potential protective effect of vitamin C against pharyngeal cancer. The authors conclude that the data are compatible with other research reporting a protective effect of fruits and vegetables against pharyngeal cancer.

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TABLE 2—CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Ghardian et al., 1991. (Ref. 56)	A case-control study for nutritional factors and pancreatic cancer in Montreal, Canada, 1984 to 1988.	The subjects were 179 clinically diagnosed cases from 19 French-speaking hospitals and 239 controls matched for age, sex and residence.	A core questionnaire about lifestyle, occupation, drinking, smoking, medical history, etc. was administered. A food frequency questionnaire was given concerning 200 different items for times 1 year and 10 years before diagnosis. The controls were matched individually for same period.	The associations for antioxidant vitamin intakes (beta-carotene, vitamin C and E) and retinol to the risk of cancer were nonsignificant.	The authors suggest need for larger studies of the relationship between nutrient intake and pharyngeal cancer.
Heilbrun et al., 1989. (Ref. 57)	A nested case-control study of diet and colorectal cancer in Oahu, Hawaii, 1965-1985.	The cohort was 8,006 American Japanese men aged 65 to 85 years in 1985; there were 102 cases of colon cancer and 60 cases of rectal cancer, and 361 cancer-free males from cohort randomly selected as controls.	Nutrient intake estimates were based on representative 24-hour recall of fiber, vitamins, minerals, macronutrients.	For colon cancer, the lowest quintile intake of vitamin C had RR= 1.87, CI= 1.03 to 3.37. There was a nonsignificant association between carotene, vitamin A intake and colon cancer. There was no association between rectal cancer and intake of any of the antioxidant vitamins.	With exception of vitamin C intake and colon cancer, the study does not support a protective effect of the antioxidant vitamins against colorectal cancer.
Kato et al., 1990. (Ref. 58)	A case-control study of colorectal cancer, and adenoma in Nagoya, Japan, 1986 to 1990.	The subjects were 221 cases of histologically diagnosed colorectal cancer, 525 cases of colorectal adenoma, and 578 neighborhood controls.	The cases attended Aichi Hospital; the neighborhood controls were matched for sex, age, and residence and were selected by random dialing.	Daily vegetable intake was associated with lower risk of dietal colon adenoma; RR= 0.59, CI= 0.39 to 0.89, and rectal cancer; RR= 0.46, CI= 0.25 to 0.84.	The study supports a protective effect of vegetables against colorectal adenoma and carcinoma.
Graham et al., 1990. (Ref. 59)	A case-controls study esophageal cancer and nutrition in three counties in Western New York, 1975 to 1986.	The subjects were 178 cases of histologically diagneosed esophageal cancer, matched with neighborhood controls for age and sex.	The cases came from hospital records in all but five hospitals in the three-county area. A 2.5-hour interview was scheduled with each case and control to assess total nutrient intake. No surrogate interview.	Risk of cancer increased with increased consumption of foods containing retinol, not carotene.	The authors concluded that further studies are needed to distinguish risks of cancer of esophagus and elsewhere associated with retinol and carotene.