DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 101

[Docket No. 91N-0097]

RIN 0905-AD08

Food Labeling: Health Claims and Label Statements: Dietary Fat and Cancer

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is authorizing the use on the labels and labeling of certain foods of health claims relating to an association between dietary fat and cancer. This final rule is issued under provisions of the Nutrition Labeling and Education Act of 1990 (the 1990 amendments) and was developed in accordance with the final rule on general requirements for health claims, which is published elsewhere in this issue of the **Federal Register**. The agency has concluded that, based on the totality of the scientific evidence, there is significant scientific agreement among qualified experts that diets low in fat may reduce the risk of some cancers. Therefore, FDA has concluded that claims on certain foods relating fat reduction to reduced risk of cancer are justified.

EFFECTIVE DATE: May 8, 1993.

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SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of November 27, 1991 (56 FR 60764), FDA proposed to authorize the use on food labeling of health claims relating diets low in fat to reduced risk of some types of cancer, particularly breast, colon, and prostate, in the general population (hereafter referred to as the lipids/cancer proposal). The lipids/cancer proposal was issued under provisions of the 1990 amendments (Pub. L. 101-535) that bear on health claims and in accordance with the proposed general requirements for health claims for foods (November 27, 1991, 56 FR 60537). As amended in 1990, 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)).

Section 3(b)(1)(A) of the 1990 amendments specifically requires that the agency 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 lipids and cancer is one of the claims required to be evaluated. In the **Federal Register** of March 28, 1991 (56 FR 12932), FDA published a notice requesting scientific data and information on the 10 specific topic areas identified. 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 lipids and cancer and were included in the lipids/cancer proposal. Comments received in response to the notice and not specifically addressed in the lipids/cancer proposal are summarized and addressed below.

In addition to evaluating the scientific evidence, the lipids/cancer proposal identified qualifying and disqualifying nutrient levels for foods bearing health claims on fat and cancer. The lipids/cancer proposal also specified mandatory and optional information for health claim statements and provided sample messages. FDA requested written comments in response to its proposed rule. In addition, FDA held public hearings on January 30 and January 31,1992, on all aspects of the proposed rules published in response to the 1990 amendments, including health claims for lipids and cancer.

II. Summary of Comments and the Agency's Responses

In response to its proposed health claim regulation on lipids and cancer, the agency received approximately 80 letters, each containing one or more comments, from consumers, consumer groups, health care professionals, professional organizations, State and local governments, a foreign government, trade associations, and industry. A number of comments received on this proposed rule were more appropriately addressed in other documents, and these comments were forwarded to the appropriate docket for response.

A. Validity Issues

1. Many comments addressed the basic issue of whether FDA should permit any health claims about total fat and/or any particular type of fat and cancer on food labeling. Several comments objected to the lipids/cancer claim and suggested that results from epidemiologic studies are often inconclusive and do not provide the information necessary to identify the type of fat that is responsible for cancer. Some comments felt that claims about saturated fat and cancer, but not about total fat and cancer, may be justified, but did not provide any data to document this conclusion. Other comments noted that results from animal studies suggest that dietary lipids do not affect noncarcinogen-induced tumorigenesis. Some comments suggested that animal studies reported conflicting results on the relationship between dietary lipids and cancer. Other comments expressed concern that rodent studies were extrapolated to humans without considering species differences.

Conversely, there was widespread support from organizations of nutritionists, organizations of health professionals, scientific societies, consumers, and food manufacturers for the agency's proposed rule. Most of these comments took the position that there was adequate scientific evidence to support claims about total fat and cancer, and concurred that these claims should be permitted. Some of these comments stressed that the recommendations from Federal government agencies and other authoritative scientific organizations, which concluded that diets high in fat increase the risk of cancer, are widely accepted in the scientific community.

FDA agrees that the totality of scientific evidence provides considerable support for a claim about the relationship between high intakes of dietary fat and increased risk of some cancers and that the conclusions and recommendations reached in a number of Federal government and other authoritative documents about this relationship demonstrate the existence of significant scientific agreement among experts qualified by experience and training to evaluate such evidence. In developing its proposed regulation, FDA has reviewed Federal government reports and other review documents as well as recent research articles relevant to dietary lipids and cancer risk. Authoritative documents consistently and independently conclude that dietary fat contributes to the risk of some cancers. Among human studies, results of international correlational studies consistently and strongly show that dietary fat may play a role in cancer. Also, the independent review by the Life Sciences Research Office (LSRO) concurred with FDA's conclusion that high fat intake increases

the risk of developing cancers. Furthermore, as discussed in section III of this preamble, new studies that became available for review after the publication of the lipids/cancer proposal are consistent with the agency's conclusion that high fat intake is associated with increased risk of some cancers.

FDA considers it appropriate to permit health claims about fat and cancer without identification of the type of fat that is responsible for the cancer. As the agency explained in the preamble of the proposal (56 FR 60764 at 60773), the available scientific evidence is inconclusive in linking a specific type of fat to cancer risk. As presented in the proposal, some evidence has been found in both human studies and animal studies that all three types of fat (saturated, monounsaturated, and polyunsaturated) may be associated with the risk of some types of cancer. Because it was not possible to clearly identify a particular type of fat or fatty acid, and because several types of fatty acids have been implicated in cancer risk, the agency based its claim on the total fat content of the diet, rather than on any specific type of fat or fatty acid. Further, as explained in section III of this preamble, the evidence from new animal studies generally supports the conclusion drawn in the proposal that total dietary fat is associated with the risk of cancer. Of course, if more conclusive evidence becomes available about specific roles of different types of fat, any interested person may submit a petition under the provisions of new § 101.71 to revise the regulation on identification of the specific types of fat that affect cancer risk, or FDA may itself initiate action to revise the regulation.

The agency does not consider the absence of evidence from noncarcinogen-induced tumorigeneses in animal studies to be a major flaw in determining the adequacy of the scientific evidence to support a relationship between dietary fat and cancer. The data, which indicate that fats cannot initiate tumorigenesis (tumor growth), do not call into question the validity of FDA's evaluation of animal studies. The current understanding of the process of tumorigenesis involves a two stage model: initiation of the carcinogenic process, followed by promotion of tumor growth. During initiation, a normal cell is altered to become a latent cancer cell. This is presumably accomplished when a carcinogen interacts with and subsequently alters the genetic apparatus of the cell. During tumor promotion, the altered genes are expressed to make new cells, a process leading ultimately to autonomous cell growth that is no longer responsive to normal physiologic growth regulatory signals. As FDA explained in the preamble of the lipids/cancer proposal. current knowledge about tumor growth shows that dietary fat affects the promotional stage, not the initiation stage, of carcinogenesis (56 FR 60764 at 60768). Substances affecting the promotional stage of carcinogenesis are appropriate subjects of health claims because, in the promotion stage, the ultimate development of cancer that cannot be controlled by the body is still in question. Thus, risk of cancer may still be reduced in the promotion stage.

As described in the lipids/cancer proposal, FDA agrees that extrapolation of the data from animal studies to humans is limited by differences in metabolism and physiology between species. However, experiments in different animal species permit more intensive observation under controlled experimental conditions. The agency believes that a careful evaluation of animal studies provides useful information and can provide valuable insight into mechanisms involved and specificity of fat versus other nutrients. Thus, the agency critically evaluated animal studies using the evaluation criteria found in the lipids/cancer proposal (56 FR 60764 at 60767). Furthermore, the rodents, which are used in most of the studies reviewed,. have digestive and/or metabolic systems that are similar to humans and have been widely used in cancer studies. The agency did not include studies that utilized cell culture techniques because cells can be genetically transformed during the in vitro culture phase, thus generating data that are substantially different from findings in human physiology.

B. Cancer Sites

2. Although most comments took the position that claims about total fat and cancer should be permitted, a number of comments expressed differing opinions about whether claims should specifically address the types of cancer affected by a diet that is low in total fat. Several comments supported the agency's proposed § 101.73(b)(1)(iii) (56 FR 60764 at 60779) to restrict claims to cancer of the breast, colon, and prostate. One explained that, without some identification of affected cancers, the claims may be misinterpreted as meaning that all types of cancer are affected. The comment suggested that FDA require the phrase, "particularly colon, breast, and prostate cancer" in the health claim.

On the other hand, several comments suggested that FDA exclude the designation of specific cancer for the sake of simplicity or because of the inconclusiveness of the relevant scientific evidence. Some comments stated that the magnitude of the association between dietary fat and the risk of various cancers such as breast cancer, colon cancer, and prostate cancer varies so widely that it is misleading to presume that strong evidence supports each site. The comments asserted that claims should therefore not be site-specific.

FDA has reconsidered the issue of requiring claims to identify the specific sites of cancer that may be affected by total fat content in the daily diet. The agency no longer believes that the current state of the scientific evidence on this issue justifies such specific identification. As is fully discussed in the preamble of the lipids/cancer proposal (56 FR 60764 at 60772 and 60773), when FDA proposed such identification, the agency did so because an international correlation study found an association between fat intake and cancer of the breast, colon, and prostate, but not of cervical or lung (Ref. 38). The agency, therefore, concluded that the effect of fat on cancer may be site-specific. In view of the lack of evidence for other types of cancer, the agency believed health claims would not be justified unless the claims pertained only to cancer of the breast, colon, and prostate.

However, additional studies that were not available for review at the time of the lipids/cancer proposal contain further evidence that cancers of additional sites may also be affected by dietary fat intake. Further, the evidence for an association of an increased risk of breast cancer with dietary lipids appears not to be as strong as previously thought from the findings in many case-control and cohort studies (See section III of this document). Thus, FDA now concludes that the identification of specific sites of affected cancers is no longer as appropriate as FDA believed when it issued the proposal. In view of the weaker data on breast cancer and the possibility of a wider variety of affected sites, and taking into account comments received, FDA believes that health claims should not be permitted to refer to specific cancer sites. At the same time, the agency feels that it would be misleading to imply that risk of all cancers may benefit from low fat diets. Accordingly, FDA has included a provision in § 101.73(c)(2)(B) of the rule set forth below requiring that health claims use the terms "some types of cancer" or "some cancers" in specifying

the disease. All provisions in the rule addressing specific sites of cancer have also been revised accordingly.

FDA points out that the lack of consistency of more recent studies with earlier studies concerning the relationship between breast cancer and fat intakes does not bring into question the more general validity of conclusions pertaining to dietary fat intake and cancer that were discussed in the agency's response to the previous comment. The absence of clear evidence of a strong association between fat and breast cancer in many case-control studies may be due to the dietary homogeneity of the population studied. International correlation studies, which have the greatest variability in dietary fat intakes among the populations examined, have consistently found an association. But correlational studies cannot control for important confounding factors, such as family history of cancer and reproductive history, which may also explain the correlations found between fat intake and cancer mortality in these studies.

C. Advisability of Permitting Claims

3. Some comments asserted that, regardless of whether claims about total fat and cancer may be valid, such claims should not be permitted because of safety considerations. A number of comments maintained that health claims about total fat may increase the risk of heart disease from reduced intakes of certain nutrients (i.e., essential fatty acids and fat soluble vitamins). One of the comments stated that the polyunsaturated and monounsaturated fats in vegetable oils have well-documented advantages, particularly in beneficially affecting the ratio of blood total cholesterol to HDL-cholesterol (i.e., raising the level of HDL-cholesterol relative to total cholesterol levels). The comment also pointed out that vegetable fats are the primary source of vitamin E in U.S. diets, and asserted that half of the U.S. population is below the recommended level of consumption of this vitamin. The comment stated that there is emerging evidence for a protective role of vitamin E in cardiovascular and other important diseases.

The agency does not foresee that a health claim relating diets low in fat to reduced risk of cancer will increase the risk of coronary heart disease because of reductions in HDL cholesterol. Under the provision of 1990 amendments, FDA evaluated scientific evidence on the relationships between dietary fat intakes and the development of two chronic diseases, cancer, and cardiovascular disease, separately. FDA's evaluation of the lipids/cardiovascular disease relationship is found in a companion document elsewhere in this issue of **Federal Register**. In that document, FDA is requiring that foods bearing a saturated fat and cholesterol/heart disease claim be "low in fat" in addition to being low in saturated fat and cholesterol. All current dietary guidelines from the Federal government and other authoritative reports include recommendations for diets low in fat when dealing with diet and heart disease relationships. Diets containing 30 percent or less of calories from total fat are deemed helpful in reducing the risk of heart disease because they facilitate meeting dietary goals for saturated fat and cholesterol. Furthermore, these diets are useful in maintaining moderate calorie intakes and desirable body weights. None of the authoritative reports or guidelines have noted concerns or evidence for inadvertent safety problems if Americans were to follow general dietary guidelines for reducing fat intakes to 30 percent of calories or less. Admittedly, diets very low in fat may pose a risk. However, given current fat intakes in the U.S. population of approximately, on average 37 percent of calories from fat, and given the difficulty in lowering this level significantly within the context of dietary patterns in the United States, FDA has concluded that it is highly unlikely that the U.S. population will be able or motivated to lower total fat intakes to levels low enough to have adverse health effects. Indeed, reductions in total fat intakes, consistent with dietary guidelines, are likely to have a beneficial effect on blood HDL- to total-cholesterol ratios.

With respect to assertions that the lipids/cancer health claims will adversely affect the nutritional status of vitamin E or essential fatty acids or will have a negative impact on coronary heart disease because of decreased vitamin E consumption, FDA does not foresee that the lipids/cancer health claim will adversely affect the status of essential fatty acids and vitamin E. Deficiencies of essential fatty acids and vitamin E are very rare in the United States at this time. Furthermore, there is extensive epidemiologic evidence that low fat diets providing fat at 30 percent of calories or less are consumed by many population groups without apparent adverse effects (Ref. 141). Current dietary guidelines, which target no more than 30 percent of calories from fat to reduce coronary heart disease and cancer risks, are generally regarded as practical in controlling fat, saturated fat, cholesterol, and calorie intakes, and yet as more than adequate for providing adequate intakes of essential fatty acids, for facilitating absorption of fat-soluble vitamins, and for maintaining growth and development in children and adolescents 2 years of age and older (Ref. 141). Furthermore, the recommended approach to reducing intake of total fat is to increase consumption of vegetables, fruits, and whole grain products, choose lean meats, fish, and poultry, and low fat dairy products, and use fats and oils sparingly. These diets generally are not only low in fat, saturated fat, cholesterol, and calories, but also tend to be high in vitamins (including vitamin E and provitamin A). Additionally, essential fatty acid requirements can be adequately met with only about 1 percent to 5 percent of calories from fat, an intake level well below the recommended levels, and not practical to achieve in the United States. Thus, FDA sees little, if any possibility that consumption of diets consistent with current dietary guidelines for fat intake will result in significant reductions in intakes of essential fatty acids or fat-soluble vitamins. Consequently, an adverse effect on risk of coronary heart disease is unlikely. Furthermore, scientific evidence is not clear, as yet, regarding the postulated, protective role of vitamin E in preventing the autoxidation of polyunsaturated fatty acids, a possible risk factor for heart disease.

4. A comment stated that the lipids/cancer claim ignores the positive role of fats in a healthy diet.

FDA agrees with the comment that dietary fats have important functions in foods and as a source of essential fatty acids and other nutrients. In the proposed rule, FDA acknowledged the physiologic functions of dietary fats. As described above, the agency foresees beneficial effects of reducing fat intakes relative to cancer risk, but does not foresee that nutritional deficiencies or harmful effects to health will occur. The agency does not consider it necessary to include statements in the health message as to the beneficial role of fats. The purpose of health claims is to provide useful information to consumers on nutrient/disease relationships. However, as noted in the final rule on general principles for health claims published elsewhere in this **Federal Register,** certain statements, including general statements about the role of nutrients in maintenance of good health, are considered to be dietary guidance outside the scope of the 1990 amendments. These types of dietary

guidance would be permitted as long as the information contained in them is truthful and not misleading.

D. Other Issues

5. A few comments stated that the proposed rule focuses only on fat and does not require that claims discuss other dietary components (e.g., complex carbohydrates or dietary fiber). These comments asserted that such a narrow focus is misleading and would not serve to educate the public about the broad issue of diet and cancer. The comments emphasized that health claims should be presented in the context of a total diet

FDA agrees that health claims should be presented in a manner that enables the public to comprehend the relative significance of the claim in the context of the total daily diet. In fact, section 403(r)(3KB)(iii) of the act specifically requires that a regulation that authorizes a claim require that the claim be stated in such a manner.

However, a review of the relationships of other dietary factors and cancer risk (apart from antioxidant vitamins and dietary fiber, which are discussed in final rules published elsewhere in this issue of **Federal Register**), is beyond the scope of the Congressional mandate. Thus, FDA does not agree that the lipids/cancer claim must specifically address the significance of other nutrients such as complex carbohydrates, dietary fiber, saturated fat, or cholesterol in relation to cancer risk. However, any interested party may petition the agency, in accordance with criteria described in the final rule on general requirements for health claims published elsewhere in this **Federal Register**, for additional nutrient/cancer claims to be authorized. As proposed, the fat/cancer health claim must include a statement that the development of cancer depends on many factors. This information is essential for understanding the context of the nutrient/disease relationship.

6. A few comments urged FDA to require health claims to advise that reductions in fat intake to less than 30 percent of total calories may be needed to reduce the risk of cancer. The comment argued that such information is needed because consumers may otherwise believe they are making meaningful reductions in fat intake when that is not the case. This comment pointed to FDA's observation in the proposal (56 FR 60764 at 60773) that studies with small differences in fat intakes among test groups (from 32 to 37 percent of total calories) failed to find a significant reduction in cancer risk.

FDA does not agree that it would be appropriate to require this information in the lipids/cancer health claim. This information would unduly add to the length and complexity of the health claim. However, FDA concurs that this information could be very useful to consumers. Thus FDA has provided for optional use of this type of information as part of a health claim, because it is contained in the significance statement of the final rule (new § 101.73(b)), and information from this section of the rule is permitted to be used on the label (new § 101.73(d)(1)).

7. In its proposed rule, the agency requested comments on whether a food that qualifies for a "reduced fat" or other comparative claim should be permitted to bear a health claim relating dietary lipids and cancer. Several comments supported FDA's proposal that foods must be "low fat" or "fat free" in order to carry this health claim. However, some comments objected to FDA's definition of "low fat." In addition to comments specifically addressing the proposed "low fat" or "fat free" requirement, FDA received a large number of similar comments on the "low fat" requirement that appeared in the general requirements for health claims, proposal (56 FR 60537).

FDA advises that the final rule is retaining the "low fat" qualifying criterion for health claims concerning fat and cancer. ("Fat free" foods necessarily meet the definition of "low fat," therefore, to avoid redundancy, the agency is requiring only that a food meet the "low fat" definition.) Because the issue of "low" qualifying requirements is of a general nature (e.g., this criterion also pertains to the fat and heart disease health claim), most of the comments on this issue were filed in the docket of the proposal on general requirements for health claims. FDA has responded to all comments about this issue in the preamble of the final rule on general requirements for health claims, which appears elsewhere in this issue of the **Federal Register**. Discussions of FDA's definition of "low fat" are published elsewhere in this issue of the **Federal Register** in the final rule on requirements for nutrient content claims.

8. A few comments requested that FDA develop identical criteria for health claims on lipids and cancer and on lipids and cardiovascular disease, because the proposed criteria for these two topics are similar but not totally consistent, and any differences may be confusing to consumers. The comments further suggested that total fat be used as the "common denominator" because "consumers who reduce total fat intake are likely to be concurrently reducing saturated fat intake as well as cholesterol, even if not making a conscious attempt at either."

The agency will allow manufacturers to formulate their own claim combining the fat and cancer and the saturated fat/cholesterol and heart disease claim if the food meets the criteria for both claims. However, at this time, it is not appropriate to set identical requirements for health claims for dietary fat and cancer and for dietary saturated fat and cholesterol and risk of heart disease, because the two diseases differ in the nature of their relationship to dietary fat components. Current evidence demonstrates that it is total fat, rather than individual fat components, that is associated with an increased risk of cancer. However, there is a substantial body of evidence that demonstrates that high levels of saturated fat and cholesterol, rather than total fat, are associated with an increased risk of cardiovascular disease. For this reason, FDA has decided to maintain separate criteria for the fat/cancer and the saturated fat and cholesterol/heart disease health claims.

9. Several comments stated that the lipids/cancer health claim should identify energy intake as an independent factor for cancer rather than reduced fat intake, because energy excess, not fat, is the factor that increases risk of carcinogenesis. Another comment stated that, if fat has an independent effect on carcinogenesis, the need to reduce fat intake becomes more important, because by reduction of fat intake, reductions in intakes of energy and fat could be efficiently achieved.

FDA agrees that the scientific evidence on the association between dietary lipids and cancer includes studies that demonstrate that total energy intake may be an independent risk factor for cancer (Refs. 11, 17, and 23). However, the 1990 amendments instructed the agency to determine whether claims respecting dietary lipids and cancer, not energy intake and calories, meet the requirements of section 403(r)(3) of the act. The agency found that, currently, there is adequate evidence from animal studies and from human studies that total fat is a risk factor for some cancers, independent of the effect of total calories. Furthermore, decreasing the fat content of the diet appears to be a practical approach to reducing energy intakes and maintaining desirable body weights. However, if a health claim regarding energy intake and cancer is desired, such a claim can be handled by the petition process set forth in the general

requirements for health claims final rule published elsewhere in this issue of the **Federal Register**.

10. One comment suggested that FDA exclude omega-3 fatty acids from the calculation of total fat for deciding whether a food is "low fat" relative to cancer risk, because the effect of omega-3 fatty acids may be neutral or, even, tumor-suppressing.

The agency does not agree that the scientific evidence is adequate to establish that omega-3 fatty acids are neutral with respect to cancer risk. Most animal studies, although concluding that a diet high in fish oil suppresses tumorigenesis, have methodologic problems which make it difficult to extrapolate results to humans. Specifically, the diets used in most of these studies provided insufficient amounts of the essential fatty acid, linoleic acid, to support optimal tumor growth. Therefore, it is not possible to determine whether the observed tumor-suppression by the fish oil diets was caused by an insufficiency of essential fatty acids (linoleic acid) to support tumor growth, or by a direct inhibitory effect of the omega-3 fatty acids contained in the fish oils. FDA is, therefore, not persuaded to exclude omega-3 fatty acids from the calculation of total fat for deciding whether a food is "low fat" with regard to cancer risk.

However, interested persons who believe there is adequate scientific evidence to support a beneficial relationship between omega-3 fatty acids and cancer risk, may use the petition process described in the final rule on general requirements for health claims, published elsewhere in this **Federal Register**.

11. A number of comments on the general requirements proposal for health claims (56 FR 60537) suggested that FDA revise provisions of all health claims rules to be more understandable.

The agency agrees that all health claims rules should be made more understandable wherever practicable. FDA has, therefore, made a variety of nonsubstantive revisions of provisions of the regulations set forth below for clarity. For example, provisions have been grouped into general and specific requirements. The general requirements reference other regulations containing nutrition labeling requirements. The specific requirements are separated into requirements pertaining to the food and those pertaining to the claim. The model health claims have been simplified. The regulation has also been modified to permit fish and game meats that meet the requirements for "extra lean" in § 101.62 to bear the health claim. This change is in response to comments on the proposed fat and cardiovascular disease health claim, and will make both final rules consistent with each other. "Extra lean" fish and meats can play an important role in a low fat diet. Consistent with other health claims regulations, this regulation also permits the claim to indicate the prevalence of cancer in the United States.

12. A comment suggested that the final rule include a requirement that, in order to qualify for the lipids/cancer health claim, a food must contain a minimum amount of dietary fiber, because fiber intake is another dietary risk factor for cancer.

The agency disagrees that dietary fiber should be required to be included in a fat/cancer health claim, but does agree that diets rich in foods containing dietary fiber and many other nutrients are associated with reduced cancer risk. Dietary components that have been implicated in cancer development include fat, antioxidant vitamins, and fibers. Among these dietary components, fat intake has been reported as the most strongly associated component. Under the 1990 amendments, FDA evaluated scientific evidence on three separate health claim topics relevant to cancer: Fat and cancer, antioxidant vitamins and cancer, and fiber and cancer. Of these three topics, FDA has concluded that there is significant agreement about the relationship between fat and cancer. FDA's evaluation and decision about the other two health claims (published elsewhere in this issue of **Federal Register**) is that diets rich in fruits, vegetables and grain products, which are generally low in fat and high in dietary fiber and vitamins A and C, are associated with reduced cancer risk. However, the agency did not find the evidence sufficient to attribute this relationship to a specific nutrient contained in plant foods. Furthermore, the agency's review of scientific evidence found that almost all animal studies of fat and cancer employed defined experimental diets containing the same amounts of vitamins and fibers. Animal studies on the association of dietary fat with cancer development provide substantial support for the conclusion that the effect of fat intake on cancer development is independent of the effects of fiber and antioxidant vitamins. Therefore, the agency is not persuaded to add fiber content as a required qualifying criterion for the fat and cancer claim.

III. Review of New Scientific Evidence

In addition to its evaluation of the Comments, FDA has evaluated the scientific literature that has become publicly available since the issuance of the proposal. The following represents a summary of the agency's evaluation of this literature.

A. Human Studies

1. Studies Submitted as/with Comments

No new human studies that meet the criteria for selecting articles to review, which are described in the lipids/cancer proposal, were submitted with comments.

2. Update of the Scientific Literature

Studies that became available after publication of the lipids/cancer proposal are discussed below and described in Table 1.

A new correlational study on cancers of the colon, rectum, prostate, and breast was reviewed (Ref. 92). Incidence rates for these cancers and food consumption data were compared among Chinese in Shanghai, Chinese Americans in San Francisco, and Americans in Connecticut. The study demonstrated that the incidence rates for the four types of cancer were much higher among Americans and Chinese Americans than for Shanghai Chinese and that the Americans and Chinese Americans consumed much more meat and milk products than the Shanghai Chinese. The authors interpreted the results of the study to demonstrate that low fat diets were associated with the lower incidence rates of the four types of cancer found among the Shanghai Chinese. However, because the design of this study allowed correlations to be made only between a population's cancer incidence rates and its per capita food consumption, rather than studying individuals who actually have cancer, inferences cannot be made about the causal nature of diet on risk of cancer. The study was unable to control for important risk factors for these cancers, such as lifestyle factors, family history, reproductive and endocrine factors, total energy intake, and differences in body weight.

A new correlational study that compared dairy fat and lard intake data from 36 countries with cause-specific cancer mortality rates was also reviewed (Ref. 93). World Health Organization (WHO) mortality statistics for 1985-1987 were correlated with intake data obtained from 1979-1981 Food and Agricultural Organization (FAO) food balance sheets. FAO's food balance sheets are approximations of actual consumption and are not separated by age and sex. The authors were able to adjust for total caloric intake but were not able to adjust for potential confounding factors, such as smoking

and family history. The study demonstrated highly significant correlations between intakes of dairy fat or lard fat and mortality from all causes, total cancer, and colon and rectal cancer among both men and women and from lung cancer and prostate cancer for men and breast cancer for women.

a. *Pancreatic cancer*. The agency reviewed two new case-control studies on diet and pancreatic cancer, which were published in 1991 (see Table 1). One study conducted in Poland (Ref. 94) demonstrated no association between risk of pancreatic cancer and total dietary fat or saturated fat. The highest intake of dietary cholesterol measured in the study was associated with a statistically significant relative risk (the incidence of cancer of the exposed group/the incidence of cancer of the unexposed group) of 4.3 for pancreatic cancer. However, the highest intakes of monounsaturated fatty acids and of polyunsaturated fatty acids were associated with statistically significant decreased risks (see Table 1), the second case-control study, which was conducted in the Netherlands, did not analyze for total dietary fat or for saturated fat (Ref. 95). Consumption of eggs was associated with a statistically significant increased risk and daily consumption of vegetables showed a protective effect in this study.

b. *Bladder cancer*. One case-control study on bladder cancer conducted in Spain was reviewed (Ref. 96 and Table 1). An increased risk of bladder cancer was found with dietary saturated fat but not with total fat. The results of this study may be biased by the inclusion of 208 prevalent cases of bladder cancer, approximately half of the cancer cases. Case-control studies usually select incident cases of cancer for participation, which are new cases, i.e., those not previously diagnosed. Prevalent cases are patients who have survived the disease for at least some amount of time and are generally not included in case-control studies of cancer because the traits contributing to their survival may modify potential risk factors of the disease.

c. *Lung cancer*. A prospective cohort study on lung cancer published in 1991 was reviewed (Ref. 97 and Table 1). The cohort consisted of 1,878 men employed by the Western Electric Company in Chicago. The men were 40 to 55 years old in 1958 when enrolled in the study and were followed for 24 years. Dietary information was collected in 1958 and in 1959 when all the men were clinically free of cancer. After adjusting the results for smoking and percent of calories from fat, an increment of dietary cholesterol of 500 mg per day was associated with a relative risk of lung cancer of 1.9.

d. *Breast cancer*. Five new case-control studies on diet and breast cancer were reviewed (see Table 1). One study that examined only postmenopausal breast cancer found no association with dietary fat (Ref. 99). However, the study suffered from low participation rates among both the cases and controls, which prohibits generalization of the study results to the total population.

A case-control study of both premenopausal and postmenopausal breast cancer among Singapore Chinese showed no effect of diet on postmenopausal women (Ref. 100). No effect on breast cancer risk for premenopausal women was found for total fat, for saturated fat, for monounsaturated fatty acids or for cholesterol; polyunsaturated fatty acids demonstrated a protective effect. The median level of dietary total fat consumed on a daily basis was 33 grams (g) for cases and 34 g for controls; total fat intake ranged from 26 g to 41 g in this study. The authors did not adjust the results for total calories.

A French case-control study found limited evidence that fat is associated with breast cancer risk when the results were analyzed by menopausal status (Ref. 101). However, for all women analyzed together regardless of menopausal status, total fat was associated with a relative risk of 1.6, saturated fat was associated with a relative risk of 1.9 and monounsaturated fatty acids were associated with a relative risk of 1.7. Polyunsaturated fatty acids were not associated with risk of breast cancer. The results were not adjusted for total calories; thus, the increased risk associated with the fats may actually be due to a higher caloric intake by the cancer cases. Several food items were associated with an increased risk of breast cancer among all women, including high fat cheese, fruits rich in beta-carotene, and desserts and chocolate.

A case-control study conducted in Moscow found that dietary fat was not associated with risk of breast cancer in either premenopausal or postmenopausal women (Ref. 102). Gram levels of daily total fat intake were not provided. Several nutrients were associated with a protective effect, including polyunsaturated fatty acids, beta-carotene, vitamin C, calcium, and cellulose. Risks associated with food items were not examined in this study.

A large case-control study conducted in Italy examined the risk of breast cancer associated with fat intake from seasonings (Ref. 103). A moderate association was found for total fat seasonings and for butter and oil, but no association was found for margarine. The results were not adjusted for total calories and very limited dietary information was collected.

e. *Colorectal cancer*. Three new studies on colorectal cancer were reviewed (see Table 1). The most informative study of the three was conducted in Majorca (Ref. 104). An increased risk of colorectal cancer was found to be associated with total calories, and, after adjustment for total calories, an increased risk was also associated with cholesterol, protein, and carbohydrates (Ref. 104). A protective effect was demonstrated with fiber from legumes. Colorectal cancer risk was not found to be associated with high consumption of total dietary fats or saturated fats. However, this lack of association between colorectal cancer and dietary fat may be a result of the population's consumption of primarily monounsaturated fatty acids rather than animal fats.

f. *Prostate cancer*. Two additional case-control studies on the association between dietary factors and risk of prostate cancer were reviewed (Refs. 105 and 106 and Table 1). One study conducted in Spain from 1983 to 1987 found that risk of prostate cancer was increased by a diet rich in animal fats but not by a diet rich in vegetable fats (Ref. 105). Also, meat consumption was associated with increased risk, but different types of meat were not significantly linked to prostate cancer. The study did not adjust for total calories; however, the relative risks associated with animal fats and with meat consumption were large enough (see Table 1) that after adjustment for calories the relative risk estimate would most likely remain elevated.

A case-control study of prostate cancer conducted in Utah demonstrated that dietary factors were not associated with risk of prostate cancer among young men (aged 45 to 67 years) (Ref. 106). However, among men aged 68 to 74 years, risk was increased for total calories, and after adjustment for total calories, an increased risk was associated with total fat, protein, and also for monounsaturated fatty acids and polyunsaturated fatty acids. For both age groups, the baseline level of total fat intake was about or less than 66 g per day.

In addition to the studies in Table 1, several review articles on the relationship between dietary fat and cancer were published recently (Refs. 107, 108, 109, and 110). Two of these review articles stated that the evidence for a putative effect of dietary fat on breast cancer risk is based primarily on

international correlational studies, whereas case-control studies and cohort studies have found only weak associations or no association between dietary fat and breast cancer risk (Refs. 107 and 108). Kinlen (Ref. 107) suggests that the international correlations with fat may be a reflection of the effects of calorie restriction in poor countries or over-nutrition in affluent countries during the years of growth which directly influences known risk factors for breast cancer, such as age at menarche and body size.

A recent review on prostate cancer (Ref. 109) stated that, overall, the epidemiology studies on diet and prostate cancer implicate fat as the main dietary component associated with increased risk. Specifically, recent case-control studies are supportive of an association of fat to prostate cancer, whereas cohort studies have shown either an equivocal and no effect.

B. Animal studies

1. Studies Submitted as/with Comments

No new animal studies that meet the criteria for selecting articles to review, which is described in the lipids/cancer proposal, were submitted with comments.

2. Update of the Scientific Literature

FDA reviewed 22 new animal studies dealing with the relationship between dietary fat and cancer that were not available for review in the proposed rule (see Table 2). Dietary fat and mammary tumorigenesis was the subject of nine studies. The role of fat in colon tumorigenesis was evaluated in five studies, while the role of fat in tumorigenesis at pancreas, skin, or lymph were evaluated in two studies for each tumor site. Fat and leukemia or fat and liver tumor was the subject of one report for each tumor site.

a. *Role of total dietary fat*. Six mammary tumor studies examined the effects of total fat on tumorigenesis. Among these, three studies (Refs. 112, 113, and 114) reported a significant association of high dietary fat with the development of mammary tumors. For example, Kumaki and Noguchi (Ref. 112) measured the influence of high dietary fat on the malignant intensity and hormone receptors of 7, 12-dimethylbenzanthracene (DMBA)-induced mammary tumor in female rats fed either a low fat (0.5 percent corn oil) or a high fat (20 percent corn oil) diet after DMBA administration. Tumor incidences in the high fat fed group were significantly higher than in the low fat fed group (86 percent versus 46 percent, respectively) and tumors were significantly larger in the high fat fed group than in the low fat fed group (13.9 millimeters (mm) versus 7.9 mm, respectively). In this study, the 0.5 percent corn oil diet provided inadequate linoleic acid (about 0.3 percent by weight) for growth of the mammary tumors. The deficiency of linoleic acid, rather than decreased total fat, could have reduced tumorigenesis.

Cohen et al. (Ref. 113) examined the effects of dietary fat and fiber in the N-nitrosomethylurea (NMU)-induced rat mammary tumor model. The number of tumor-bearing rats and the mean number of tumors per rat were significantly higher in rats fed a high fat diet (23.5 percent corn oil) than in those fed a low fat diet (5 percent corn oil). The latent period was also significantly prolonged in the low fat fed group. The diets used by Cohen et al. were not isocaloric and body weights were significantly lower in the 5 percent corn oil group from weeks 11 to 15 of the study. Therefore, the results could have been caused by differences in energy intake rather than fat per se.

Gonzalez et al. (Ref. 114) studied the effects of different amounts and types of fat on the growth of human breast carcinoma in athymic nude mice. They reported that a diet with 20 percent corn oil by weight significantly elevated the volume of transplanted mammary tumors (estrogen-dependent MDA-MB231 and nonestrogen-dependent MCF-7) in mice, compared to effects of a diet containing 5 percent corn oil. Diets used in this study were not isocaloric and the differential intakes among groups confound an attribution of the dietary fat to the results per se. The MDA-MB23 cell line was estrogen-dependent and estrogen provided in the drinking water and implanted pellets may have affected tumor growth in these groups.

Studies by Zhu et al. (Ref. 115), Aksoy et al. (Ref. 116), and Khoo et al. (Ref. 117) reported no association between dietary total fat and tumorigenesis in rodents. Zhu et al. (Ref. 115) measured the effect of total dietary fat and dietary energy restriction on growth of methylnitrosourea (MNU)-induced mammary tumorigenesis in female rats. When the diets were isocaloric (50 kilocalories (kcal) per day or 35 kcal per day), tumor yield (number or weight) was not different between the two diet groups (45 percent fat diet by energy and 25 percent fat diet by energy). In this study, diets differed in the provision of linoleic acid: The 25 percent fat diet provided about 1.7 percent linoleic acid by weight. This amount was most likely inadequate for tumor growth.

Aksoy et al. (Ref. 116) attempted to identify effects of different levels of dietary fat on MNU-induced rat mammary tumorigenesis. These authors reported no difference in the incidence, yield, or mortality among groups fed diets containing 12 percent, 25 percent. and 45 percent fat by energy. The 12 percent or the 25 percent fat diets (which provided about 0.7 percent or 1.9 percent linoleic acid by weight) may not have provided adequate linoleic acid for tumor growth. In this study, rats consumed the same amount of calories, and body weights were not different among groups even though the experimental diets were not isocaloric.

Khoo et al. (Ref. 117) tested the anticancer effect of dietary stearic acid. In this study, mammary tumors were induced by NMU and cultured in vitro. The cultured, tumor cells were implanted in the flank of rats. Rats were fed either a powdered control diet or a diet containing 20 percent stearic acid by weight. Feeding was continued for 6 weeks before and 25 days after tumor implantation. The stearic acid-supplemented diet did not affect the growth (size or weight) of the transplanted tumors. The adequacy of dietary linoleic acid for tumor growth in this study cannot be determined because the fatty acid composition in the diet was not reported.

Six new studies examined the effects of dietary fat on development of chemically-induced colon tumors in rodents. Two studies measured the effect of total fat (Refs. 118 and 119). Nicholson et al. (Ref. 118) measured the influence of dietary fat (beef suet, rich in saturated fats and corn oil, rich in linoleic acid) on colorectal tumorigenesis. Wistar rats were fed diets containing 5 percent or 20 percent fat (beef suet or corn oil) by weight The 5 percent beef suet diet significantly reduced azoxymethane-induced colon adenocarcinoma compared to the 20 percent beef suet diet (12 carcinomas versus 28 carcinomas, respectively, in the 5 percent and 20 percent beef suet groups). The difference in tumor yield between the 5 percent corn oil and 20 percent corn oil diets was not statistically significant (1 carcinoma versus 2 carcinomas, respectively, between the 5 percent and 20 percent corn oil groups). The beef suet diets provided limited linoleic acid (0.6 percent to 1 percent).

Behling et al. (Ref. 119) measured the effects of varying levels of dietary calcium and butter fat on lipid utilization and development of colon tumors in dimethylhydrazine dihydrochloride (DMH)-initiated rats. These authors found no difference in

intestinal tumors in rats fed either a diet with 5 percent butter fat plus 1 percent corn oil or a diet with 20 percent butter fat plus 1 percent corn oil. The experimental diets provided limited linoleic acid (about 0.6 percent by weight), and this may have decreased the possibility of identifying effects of total dietary fat.

Hietanen et al. (Ref. 120) measured modulation by quantity and degree of saturation of dietary fat of oxidative stress and chemically-induced liver tumors in rats. These authors found a significantly increased incidence of liver tumors in rats fed a diet containing high levels of polyunsaturated fatty acids (PUFA; 25 percent sunflower seed oil by weight) compared to rats fed a diet containing low concentrations of polyunsaturated fatty acids (2 percent sunflower seed oil by weight). Tumor incidences were 80 percent versus 42 percent for groups fed 25 percent or 2 percent sunflower seed oil, respectively. The 2 percent PUFA diet in this study provided about 1.6 percent linoleic acid, which may not have been adequate for tumor growth. Body weight changes were not significantly different among groups, although diets were not isocaloric.

Smith et al. (Ref. 121) measured the effects of a high fat diet and a CCK-receptor antagonist on growth of a human pancreatic tumor cell line in nude mice. In this study, a high fat diet (20.3 percent fat by weight: 4.3 percent chow fat plus 16 percent corn oil) significantly increased tumor volume and protein content compared to values for tumors from mice fed a chow diet. Fatty acid composition of the chow diet was not reported. However, the chow diet may not have provided adequate linoleic acid for tumor growth, and a limitation of linoleic acid, rather than low total fat, could have reduced tumor growth.

Longnecker et al. (Ref. 122) studied the development of pancreatic neoplasms in elastase-1-simian virus transgenic mice. The authors reported no difference in incidence of tumor between groups of mice fed a 5 percent corn oil diet or a 20 percent corn oil diet. The applicability of the results of this study in genetically transformed mice to human cancer studies is not clear.

Thus, among the 11 studies that examined the effect of dietary fat on tumorigenesis, 6 studies (3 mammary tumor studies, 1 colon tumor study, 1 pancreatic tumor study, and 1 liver tumor study) reported significant reductions in the risk of tumorigenesis, measured by incidence, multiplicity, or latency, by reducing fat intakes from about 20 percent to about 5 percent. However, the evaluation of the studies was difficult because many studies suffered a critical and a common limitation in the methodology: diets were limited in linoleic acid, which is necessary for optimal tumor growth.

b. *Effects of types of fat*. Four studies examined the effects of different types of fat on mammary tumorigenesis (Refs. 117, 123, 124, and 125). All four studies reported inconsistent or insignificant effects of different types of fat.

Buckman et al. (Ref. 123) studied whether oleate influences the linoleate-enhanced metastasis of murine mammary tumors. Diets contained 13.5 percent to 61 percent linoleic acid and 12 percent to 47 percent oleic acid. Total fat was 20 percent by weight. Diets did not significantly affect latent period, incidence, or yield of tumors. These diets provided adequate linoleic acid for optimal tumor growth at the mammary gland. The authors reported that a low linoleic acid to low oleic acid diet reduced lung metastasis compared to the other three diets (low linoleic acid to high oleic acid, high linoleic acid to moderate oleic acid, and high linoleic acid to low oleic acid). Values were 10 nodules, 62 nodules, 78 nodules, and 90 nodules, respectively, for mice fed these four diets. The low linoleic acid to low oleic acid suppressed tumorigenesis, in terms of metastasis, in lung but not in liver.

Lasekan et al. (Ref. 124) fed rats diets with 20 percent fat by weight and examined DMBA-induced mammary tumorigenesis. The concentrations of linoleic acid and oleic acid, respectively, in the dietary fat were 72.9 percent and 12.4 percent linoleic acid-rich safflower oil diet (SL diet), 17.2 percent and 71.1 percent safflower oil diet (SO diet), 5.6 percent and 6.7 percent olive oil diet (OO diet), and 16.9 percent and 67.9 percent linoleic acid-rich olive oil diet (OL diet). The concentrations of linoleic acid in the diets were 14.6 percent (SL diet), 3.4 percent (SO diet), 1.1 percent (OO diet), and 3.4 percent (OL diet) by weight. Dietary concentrations of linoleic acid, oleic acid, or linoleic acid to oleic acid ratio did not consistently affect latent period, incidence, or yield of mammary tumors. The OO diet showed a significant tumor-lowering effect, which disappeared when linoleic acid was added. Tumors per rat were 3.0, 5.1, 3.5, and 5.0 in rats fed the OO, OL, SL, and SO diet, respectively. Because the OO diet was limited in linoleic acid, the findings support the "about 4 percent linoleic acid requirement" for mammary tumorigenesis in rodents (Refs. 20 and 71).

Khoo et al. (Ref. 117) also showed that 20 percent supplementation of stearic acid to a control diet did not affect mammary tumor growth in rats. Fatty acid composition of the control diet was not reported for this study, and the adequacy of linoleic acid content cannot be determined. Hirose et al. (Ref. 125) also reported no difference in mammary tumor yields between the 10 percent soybean oil group and the 10 percent safflower oil group. Both of these diets contained sufficient linoleic acid for optimal tumor growth.

Three studies (Refs. 118, 125. and 126) examined the effects of different types of fat on colon tumorigenesis. One study (Ref. 118) reported that a diet containing 20 percent beef suet produced significantly more tumor than a diet containing 20 percent corn oil (28 carcinoma versus 2 carcinoma. respectively). The 5 percent beef suet diet also elevated tumor yield compared to the 5 percent corn oil diet (12 carcinoma versus 1 carcinoma, respectively). The beef suet diets, although providing limited linoleic acid, nevertheless increased colon tumor development. The findings suggest that the effects of saturated fatty acids (SFA) may be promoting and those of polyunsaturated fatty acids (PUFA) may be protective for colorectal tumorigenesis.

Conversely, Nutter et al. (Ref. 126) measured the effects of dietary fat and protein on DMH-induced tumor development and immune responses in male mice. These authors reported that 4.7 percent beef tallow (BT) diets were protective for colon tumorigenesis in mice compared to 4.7 percent corn oil (CO) diets (3.2 tumor per tumor-bearing mouse versus 12.3 tumor per tumor-bearing mouse, BT versus CO, respectively). This study suffers limitations in methodology: the total fat level, 4.7 percent, was too low, and the beef tallow diet was limited in content of linoleic acid (about 0.3 percent by weight).

The other study by Hirose et al. (Ref. 125) reported that incidence or yield of experimental tumorigenesis at the colon was not different between the 10 percent soybean oil group and the 10 percent safflower oil group in rats. The diets provided adequate linoleic acid for optimal tumor growth.

Two studies on skin tumors (Refs. 127 and 128) were also reported. Locniskar et al. (Ref. 127) compared the effects of fish, coconut, and corn oils on skin tumors induced by DMBA and benzoylperoxide in mice. Leyton et al. (Ref. 128) measured the effects of different types of dietary fat on DMBA- and phorbolester (12-O-

tetradecanoylphorbol-13-acetate. TPA)-elicited tumorigenesis at mouse skin. Both studies found a significant protective effect of PUFA (corn oil) and a significant promoting effect of SPA (coconut oil) on skin tumorigenesis. In both of these studies, diet groups with the highest dietary corn oil (15 percent by weight in one study and 10 percent by weight in the other study as the sole fat source) showed the lowest yield of papilloma (3.4 tumors versus 11.7 tumors, 1 percent CO versus 15 percent CO in SENCAR mice) or carcinoma. The results differ from the "about 4 percent llnoleic acid requirement" for optimal tumorigenesis for mammary tumorigenesis in rodents (Refs. 129 and 130) and suggest that the linoleic acid requirement may be different for tumors at different sites.

The results of the recently reported studies show that, when the requirement of linoleic acid for optimal tumor growth is met, types of dietary fat do not have specific effects on tumorigenesis of the mammary gland. The study results on colon tumor are equivocal: dietary PUFA was promoting in one study and was protective in the other. The two studies in skin tumor consistently reported a protective role of dietary PUFA, which suggests a different level of linoleic acid requirement for tumorigenesis at different sites.

c. *Fat intake versus energy intake*. Because energy intake and fat intake are highly correlated, it is possible that the association between dietary fat and cancer is confounded by energy intake. It also has been demonstrated in animal and human studies that energy intake in excess of an essential requirement is of primary importance in determining the incidence of induced and spontaneous tumors. During the preparation of the proposal on the lipids and cancer health claim, FDA carefully reviewed studies with isocaloric diets or similar energy provisions. The agency reached the tentative conclusion that the totality of the evidence from both animal and human studies showed that the effect of dietary fat on tumorigenesis is independent of the effect of energy (Refs. 11,17, and 23).

Two new animal studies examined the relationship between fat and cancer with isocaloric diets or similar energy provisions (Refs. 115 and 116). One study (Ref. 115) reported that calorie restriction, rather than fat content, significantly reduced tumor growth in this study. Another study by Aksoy et al. (Ref. 116) reported no difference in the growth of mammary tumors among 12 percent, 25 percent, and 45 percent fat-fed groups. However, both of these negative studies suffered from the same methodological problem: diets were limited in linoleic acid (about 1.7 percent linoleic acid in one study and about 0.7 percent to 1.9 percent linoleic acid in the other). Because of this common limitation that linoleic acid in the diet was not sufficient for optimal tumor growth, the studies cannot be adequately evaluated for the effect of fat on cancer. In conclusion, although the newly reported studies were not adequate to evaluate the energy-independent effect of fat on cancer development, from several studies previously reviewed, the agency found adequate evidence to conclude that the effect of fat is independent of the effect of energy.

d. *Omega-3 fatty acids and fish oil*. In one study (Ref. 125), mammary tumor was induced by dimethylbenzanthracene and dimethylhydrazine, and the effects of perilla oil (an omega-3 fatty acid rich plant seed oil), soybean oil, and safflower oil were tested at 10 percent by weight. Incidence rates were not different among groups but the tumor yield was significantly lowered by perilla oil feeding, compared to soybean oil or safflower oil feeding (4.4 tumors, 6.5 tumors, and 5.7 tumors per rat: perilla oil, soybean oil, and safflower oil, respectively). Perilla oil is rich in linoleic acid (13.7 percent) compared to soybean and safflower oils, which contain 1.7 percent and 0.1 percent linoleic acid, respectively. Perilla oil is also relatively low in linoleic acid (15.9 percent) compared to soybean and safflower oils, which contain 52.6 percent and 74 percent linoleic acid, respectively. This study suffers the common methodological limitation in that perilla oil diet containing about 1.6 percent linoleic acid may have provided inadequate linoleic acid for tumor growth.

One recent study on colon tumorigenesis (Ref. 129) also reported a protective effect of omega-3 fatty acid. In this study, mice were fed a 19.2 percent fat diet with various sources: beef tallow, soybean oil, and a commercial fish oil product (MaxEPA). The MaxEPA diet significantly lowered and the beef tallow diet significantly elevated the yield of adenocarcinoma of the colon, compared to other groups (mean tumor per animal was 1.23 mean tumor. 0.47 mean tumor, and 0.23 mean tumor for the beef tallow, soybean oil, and fish oil group, respectively). Diets provided adequate linoleic acid for optimal tumor growth. This result suggests that the high fish oil diet (MaxEPA) may have a protective role in dimethylhydrazine-induced colon tumorieenesis in Swiss-Webster mice.

Another study (Ref. 125) found an inconsistent effect of different types of fat on tumorigenesis at the colon., A 10 percent perilla oil diet significantly lowered incidence of colon tumors compared to a 10 percent soybean oil diet or a 10 percent safflower oil diet in rats. Tumor incidences were 4 percent. 9 percent, or 9 percent for the perilla oil, soybean oil, or safflower oil diets, respectively. Tumor yield was not different among groups. In this study, the perilla oil diet provided about 1.6 percent linoleic acid by weight, which might have been limiting for optimal tumor growth.

There were two lymphoma studies (Refs. 130 and 131), which showed an adverse effect of omega-3 rich fatty acid on tumorigenesis. Both studies used AKR mice and examined the growth of xenograft lymphoma. The composition of dietary fat tested were fish oil versus beef tallow in one study and fish oil versus hydrogenated beef tallow in the other. Diets in both of these studies were severely limited in linoleic acid (0.01 percent to 0.48 percent by weight in one study and 0.004 percent to 0.18 percent by weight in the other study). Due to this methodological problem, the results are not useful for evaluating the effect of fat.

Hence, results of the recently reported studies are contradictory for the effect of omega-3 fatty acid on tumor development. One (Ref. 129) of the four studies studied the development of colon tumor with an adequate linoleic acid provision in the diet. In this study, the fish oil (MaxEPA) at 19.2 percent by weight significantly reduced tumor yield. The study, however, suffers from the limitation that the amount of dietary fish oil used was impractically high. Overall, the recent studies failed to adequately refute or support the effects of fish oil on tumorigenesis. Further studies are required to elucidate the effects and mechanism of omega-3 fatty acids on tumorigenesis.

e. *Mechanisms of carcinogenesis.* Although several mechanisms have been proposed, the biochemical mechanism by which fat affects tumorigenesis has not been definitely established. As discussed in the lipids/cancer proposal, hypotheses include fat-induced alteration in membrane peroxidation, immune function, gene expression, metabolism of chemical carcinogens, metabolism of hormones, metabolism of eicosanoids, and turnover rate of intestinal mucosal cells (56 FR 60764). Recent studies have not further elucidated the mechanisms for the effect of fat on tumorigenesis.

After reviewing the animal studies, Schatzkin et al (Ref. 132) concluded that increasing the amount of dietary fat increases mammary tumorigenesis, whether measured in terms of incidence, multiplicity, or latency; the production of tumors is enhanced when a high level of fat is fed after, not before initiation, suggesting a promotional effect of dietary fat; the tumor-enhancing effects of high levels of saturated or polyunsaturated fat are similar when the diets contain a minimal amount of polyunsaturated fat to provide essential fatty acids; and that dietary fat and total calorie intake seem to have separate tumor enhancing effects.

On the other hand, Kritchevsky (Ref. 133) noted that all of the studies relating to fat and experimental carcinogenesis show that increasing levels of dietary fat increases tumor incidence; the effect seems to be exerted principally in the promotion phase and plateaus at between 5 and 10 percent of fat in the diet; and energy from the fat-rich diets, rather than fat per se, may be the factor enhancing tumorigenesis. He concluded that:

> The possibility that the problem may be energy rather than fat permits us to make broader dietary choices without excluding specific nutrients. * * * The call for reductions in fat intake to 15 percent or 20 percent of energy may be considered drastic, but a modest reduction (perhaps to 30 percent of energy) might not be out of order.

Another comprehensive review of studies (Ref. 134) reached conclusions similar to those of Kritchevsky. The authors concluded that:

> High dietary fat (20 percent by weight or 40 percent by energy) significantly elevates incidence and multiplicity of mammary gland tumors induced chemically in rodents. High dietary total fat also clearly promotes tumorigenesis at the colon and pancreas. On the other hand, moderate to severe dietary restriction in animals yields fewer neoplasms, particularly in the mammary gland. Intake of a high-fat diet even at moderate restriction would not lead to promotion because the dietary restriction would have the opposite effect. This finding could obviously be transformed to humans. However, most human populations do not voluntarily undergo lifelong dietary restriction but rather eat ad libitum.

Therefore,

> A diet which is high in complex carbohydrate (65 percent to 70 percent by energy) and moderate in fat (20 percent to 25 percent) and protein (10 percent to 15 percent) would be recommended.

C. Conclusions About New Evidence

The agency has reviewed several new research articles, and several review papers, which were published since the proposal. Among the human studies, one correlational study was supportive of the hypothesis that high fat diets increase the risk of cancers of the colon, rectum, prostate and breast (Ref. 92). and another correlational study supported the relationship between increased cancer risk and dairy fat and lard fat (Ref. 93). A new case-control study on pancreatic cancer was consistent with the earlier reports that this cancer is not associated with dietary fat (Refs. 94). A study on bladder cancer suggested that an increased risk was associated with saturated fat but not with total fat (Ref. 96).

The results of several new human case-control studies on breast cancer demonstrated no effect of total dietary fat on postmenopausal breast cancer risk (Refs. 99, 100, and 102). Moreover, the evidence for an effect of dietary fat on premenopausal risk was extremely limited in the new studies reviewed, and the study that found an increased risk associated with fat for all women (not separated by menopausal status) did not adjust for total calories (Ref. 101). The case-control studies on breast cancer which examined associations with food found increased risks from total food (Ref. 101) and from fats used as seasonings (Ref. 103), but not from meat (Ref. 101).

However, for a number of reasons, case-control studies are at a disadvantage compared to correlational studies in their ability to detect an association between dietary fat and cancer risk. The range of dietary fat intake is usually narrow in case-control studies because the populations studied are homogenous in terms of dietary parameters. It is extremely difficult for an epidemiology study to detect an increase in cancer risk associated with dietary fat when the difference in fat intake between cases and controls is minimal. Also, the average fat content of the diet in Western countries is seldom less than 30 percent to 35 percent of total calories. Although it is not known for certain how low the fat content of a diet needs to be before a reduction in cancer risk is achieved, it is at least less than 30 percent of total calories. Thus, it is not surprising that the results of case-control studies investigating the relation between dietary fat and cancer are often equivocal.

A new study on colorectal cancer did not demonstrate an increased risk associated with total dietary fat or saturated fat but did show an increased risk with total calories and with cholesterol (Ref. 104). Two new case-control studies on prostate cancer both found an increased risk associated with dietary fat (Refs. 105 and 106).

The evidence from the new animal studies generally supports the conclusion drawn in the lipids/cancer proposal that dietary total fat is associated with the risk of cancer. Among eleven animal studies, six studies (three in mammary tumor, one in colon tumor, one in pancreatic tumor, and one in liver tumor) reported significant reductions in the risk of tumorigenesis, measured by incidence, multiplicity, or latency, by reducing fat intakes from about 20 percent to about 5 percent.

Regarding types of fat, the new studies provide the same conclusion as the one that the agency drew in the proposal: currently, there is not enough evidence to delineate specific roles of different types of fat on tumorigenesis. The new studies show that when the requirement of linoleic acid for optimal tumor growth is met, various types of dietary fat do not affect tumorigenesis at the mammary gland differently. The study results on colon tumor are equivocal; dietary PUFA was promoting in one study and was protective in the other. The two studies on skin tumor consistently reported a protective role of dietary PUFA, which suggests a different level of linoleic acid requirement for tumorigenesis at different sites.

It is difficult to disassociate the effect of fat from the effect of total energy. The two new animal studies did not provide further evidence that dietary fat has an energy-independent effect on carcinogenesis. There are two new studies that utilized isocalorie or similar calorie provisions (Refs. 115 and 116). One of these studies reported that energy intake rather than fat intake affects cancer development. However, both studies suffered the common methodologic limitation that linoleic acid in the diet was insufficient and were not adequate to evaluate the effect of fat. However, several studies previously reviewed by the agency (Refs. 11, 17, and 23) provided adequate evidence to conclude that the effect of fat is independent of the effect of energy.

As was the case with studies reviewed in the proposal, new studies on omega-3 fatty acid and tumor development do not provide conclusive evidence. Among the four new studies of omega-3 fatty acid and cancer, only one study (Ref. 129) in colon tumor provided adequate linoleic acid in the diet. The fish oil (MaxEPA) at 19.2 percent by weight significantly reduced tumor yield, suggesting that the fish oil may reduce DMH-induced colon tumor risk. The study, however, suffered from the limitation that the amount of dietary

fish oil used was unpractically high. Additional studies are required to elucidate the effects arid mechanisms of omega-3 fatty acids on tumorigenesis.

The new studies reviewed did not further elucidate the mechanisms for the effect of fat on tumorigenesis. The existing hypotheses include alterations in membrane peroxidation, membrane fluidity and microenvironment, immune function, gene expression, metabolism of chemical carcinogens, metabolism of hormones, metabolism of eicosanoids, and turnover rate of intestinal mucosal cells (as discussed in the lipids/cancer proposal).

Thus, new animal studies provide Some, although inconclusive, evidence that dietary total fat is associated with risk of some cancers. Mammary tumor, colon tumor, pancreatic tumor, and liver tumor may be affected. Evidence is inconclusive regarding specific roles of different types of fat including fish oils. The evaluation of the new studies was greatly hampered by the common limitation in the experimental design of limited linoleic acid in the diet.

As discussed previously in this preamble, several comments suggested that FDA drop the specification of types of cancer affected from the health claim. In view of the new evidence, FDA believes that the scientific evidence on lipids and risk of specific cancers is not as yet definitive. Further evidence has to be accumulated to draw clear conclusions regarding effects of different types of fat, effects at different tumor sites, effects of omega-3 fatty acids, the quantitative relationship between fat and energy, and mechanisms by which fat affects cancer development. Methodological limitations in the human and animal studies on dietary lipids and cancer are discussed in the lipids/cancer proposal and elsewhere in this document.

In conclusion, the evidence found in the new studies in humans and animals supports the agency's tentative conclusion in the proposal that the totality of publicly available scientific evidence supports an association between dietary fat and cancer risk. Evidence is also accumulating that total energy intake is an additional risk factor for cancer. However, the evidence for which types of cancer are affected is equivocal. Therefore, the agency is not authorizing the phrase "particularly cancers of the colon, breast, and prostate" or any other site to be included in the health claim.

IV. Environmental Impact

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

V. 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.

VI. References

The following references have been placed on display 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.

1. DHHS, Public Health Service, "Healthy People 2000: National Health Promotion and Disease Prevention Objectives," DHHS Pub. No. (PHS) 91-50213, a, pp. 412-416 and 119-120, U. S. Government Printing Office, Washington, DC, 1991.

2. Park, Y. K., and E. A. Yetloy, "Trend Changes in Use and Current Intakes of Tropical Oils in the United States," *American Journal of Clinical Nutrition*, 51:738-48.

3. National Research Council, Commission on Life Sciences, National Research Council, "Diet and Health. Implications for Reducing Chronic Disease Risk," Committee on Diet and Health, Food and Nutrition Board, National Academy Press, Washington, DC, 1989.

4. DHHS, "The Surgeon General's Report on Nutrition and Health," DHHS (PHS) Pub. No. 88-50210 (GPO Stock No. 017-001-00465), pp. 177-203, U.S. Government Printing Office, Washington, DC, 1988.

5. National Research Council, "Recommended Dietary Allowances." 10th ed., Food and Nutrition Board, Commission on Life Sciences, National Academy Press, Washington, DC, 1989.

6. USDA, DHHS, "Nutrition and Your Health: Dietary Guidelines for Americans," Home and Garden Bulletin, No.232, U.S. Government Printing Office, Washington, DC, 1990.

7. World Health Organization, "Diet, Nutrition, and the Prevention of Chronic Diseases," WHO Technical Report Series 797, pp. 62-94, World Health Organization, Geneva, 1990.

8. Federation of American Societies for Experimental Biology, LSRO, "The Role of Dietary Lipids in Cancer," in press, 1991.

9. Health and Welfare, Canada, "Nutrition Recommendations, the Report of the Scientific Review Committee-1990," Canadian Government Publishing Centre, Ottawa, Canada, 1990.

10. Shao, R., M. L. Dao, N. K. Day, and R. A. Good, "Dietary Manipulation of Mammary Tumor Development in Adult C3H/Bi Mice (43041)," *Proceeding of Society of Experimental Biology and Medicine*, 193(4):313-317, 1990.

11. Welsch, C. W., J. L. House, B. L. Herr, S. J. Eliasberg, and M. A. Welsch, "Enhancement of Mammary Carcinogenesis by High Levels of Dietary Fat: A Phenomenon Dependent on Ad Libitum Feeding," *Journal of the National Cancer Institute*, 82:1615-1620, 1990.

12. Adams, L. M., J. R. Trout, and R. A. Karmali, "Effect of N-3 Fatty Acids on Spontaneous and Experimental Metastasis of Rat Mammary Tumour 13762," *British Journal of Cancer*, 61(2):290-291, 1990.

13. Sinkeldam, E. J., C. P. Kuper, M. C. Bosland, V. M. H. Hollanders, and D. M. Vedder, "Interactive Effects of Dietary Wheat Bran and Lard on N-methyl-N'-nitro-N-nitroguanidine-induced Colon Carcinogenesis in Rats," *Cancer Research*, 50(4):1092-6, 1990.

14. Newberne, P. M., D. Bueche, S. Riengropitak, and T. F. Schrager, "The Influence of Dietary Levels of Vitamin A and Fat on Colon Cancer," *Nutritional Cancer*, 13:235-242, 1990.

15. Deschner, E. E., J. S. Lytle, G. Wong, J. F. Ruperto, and H. L. Newmark, "The Effect of Dietary Omega-3 Fatty Acids (Fish Oil) on Azoxymethanol-induced Focal Areas of

Dysplasia and Colon Tumor Incidence," *Cancer*, 66:2350-2356, 1990.

16. Reddy. B. S., C. Burill, and J. Rigotty, "Effect of Diets High in Omega-3 and Omega-6 Fatty Acids on Initiation and Postinitiation Stages of Colon Carcinogenesis," *Cancer Research*, 51:487-491, 1991.

17. Birt, D. F., A. D. Julius, L. T. White, and P. M. Pour, "Enhancement of Pancreatic Carcinogenesis in Hamsters Fed a High-fat Diet Ad Libitum and at a Controlled Caloric Intake," *Cancer Research*, 49:5848-5851, 1989.

18. Appel, M. J., A. van Garderen-Hoetmer, and R. A. Woutersen, "Azaserine-induced Pancreatic Carcinogenesis in Rats: Promotion by a Diet Rich in Saturated Fat and Inhibition by a Standard Laboratory Chow," *Cancer Letters*, 55:239-248, 1990.

19. Birt, D. F., A. D. Julius, E. Dwork, T. Hanna, L. T. White, and P. M. Pour, "Comparison of the Effects of Dietary Beef Tallow and Corn Oil on Pancreatic Carcinogenesis in the Hamster Model," *Carcinogenesis*, 11(5):745-758, 1990.

20. Ip, C., "Fat and Essential Fatty Acid in Mammary Carcinogenesis," *American Journal of Clinical Nutrition*, 45:218-224, 1987.

21. Imaida, K., H Sato, H. Okamiya, M. Takahashi, and Y. Hayashi, "Enhancing Effect of High Fat Diet on 4-Nitroquinoline 1-oxide-induced Pulmonary Tumorigenesis in ICR Male Mice," *Japan Journal of Cancer Research*, 80:499-502, 1989.

22. Katz, E. B., and E. S. Boylan, "Effects of Reciprocal Changes of Diets Differing in Fat Content on Pulmonary Metastasis from the 13762 Rat Mammary Tumor," *Cancer Research*, 49:2477-2484, 1989.

23. Birt, D. F., L. T. White, B. Choi, and J. C. Pelting, "Dietary Fat Effects on the Initiation and Promotion of Two-stage Skin Tumorigenesis in the SENCAR Mouse," *Cancer Research*, 49:4170-4174, 1989.

24. Borgeson, C. E., L. Pardini, R.S. Pardini, and R. C. Reitz, "Effects of Dietary Fish Oil on Human Mammary Carcinoma and on Lipid-metabolizing Enzymes," *Lipids*, 24(4):290-295, 1989.

25. Fritsche, K., and P. V. Johnston, "Effect of Dietary Alpha-linolenic Acid on Growth, Metastasis, Fatty Acid Profile and Prostaglandin Production of Two Murine Mammary Adenocarcinomas," *Journal of Clinical Nutrition*, 120:1601-1609, 1990.

26. Sakaguchi, M., S. Rowley, N. Kane, C. Imray, A. Davies, C. Jones, M, Newbold, M. R. B. Keighley, P. Baker, and J.P. Neoptolemos, "Reduced Tumour Growth of the Human Colonic Cancer Cell Lines COLO-320 and HT-29 In Vivo by Dietary N~3 Lipids," *British Journal of Cancer*, 62:742-747, 1990.

27. O'Connor, T. P., B. D. Roebuck, F. J. Peterson, B. Lokesh, J. E. Kinsella, and T. C. Campbell, "Effect of Dietary Omega-3 and Omega-6 Fatty Acids on Development of Azaserine-induced Preneoplastic Lesions in Rat Pancreas," *Journal of the National Cancer Institute*, 81:858-863, 1989.

28. Orengo, I. F., H. S. Black, A. H. Kettler, and J. E. Wolf, "Influence of Dietary Menhaden Oil Upon Carcinogenesis and Various Cutaneous Responses to Ultraviolet Radiation," *Photochemical Photobiology*, 49(1):71-77, 1989.

29. Locniskar, M., M. A. Belury, A. G. Cumberland, K. E. Patrick, and S. M. Fischer, "Lack of a Protective Effect of Menhaden Oil on Skin Tumor Promotion by 12-o tetradecanoylphorbol-13-acetate," *Carcinogenesis*, 11(9):1641-1645, 1990.

30. Yam, D., A. Fink, L Nir, and P. Budowski, "Insulin-tumour Interrelationships in EL4-lymphoma or Thymoma-bearing Mice, II. Effects of Dietary Omega-3 and Omega-6 Polyunsaturated Fatty Acids," *British Journal of Cancer*, 62:897-902, 1990.

31. Ling, P. R., N. W. Istfan, S. M. Lopes, V. K. Babayan, G. L. Blackburn, B. R. Bistrian, "Structured Lipid Made from Fish Oil and Medium-chain Triglycerides Alters Tumor and Host Metabolism in Yoshida-sarcoma-bearing Rats," *American Journal of Clinical Nutrition*, 53:1177-1184, 1991.

32. Dupont, J., P. J. White, M. P. Carpenter, E. J. Schaefer, S. N. Meydani, E. E. Elson, M. Woods, and S. L. Gorbach, "Food Uses and Health Effects of Corn Oil," *Journal of the American College of Nutrition*, 9:438-470, 1990.

33. Pariza, M. W., "Dietary Fat and Cancer Risk: Evidence and Research Needs," *Annual Review of Nutrition*, 8:167-183, 1988.

34. Barone, J., and J. R. Hebert, "Dietary Fat and Natural Killer Cell Activity," *Medical Hypotheses*, 25:223-226, 1988.

35. Erickson, K. L. and N. E. Hubbard, "Dietary Pat and Tumor Metastasis," Nutrition Reviews, 48:6-14, 1990.

36. Lane, H. W., and J. T. Carpenter, "Breast Cancer: Incidence, Nutritional Concerns, and Treatment Approaches," *Journal of American Diet Association*, 87:765-769, 1987.

37. Prentice, R. L., F. Kakar, S. Hursting, L. Sheppard, R. Klein, and L. H. Kushi, "Aspects of the Rationale for the Women's Health Trial," *Journal of the National Cancer Institute*, 80:802-814, 1988.

38. Hursting, S. D., M. Thomquist, and M. M. Henderson, "Types of Dietary Fat and the Incidence of Cancer at Five Sites," *Preventive Medicine*, 19:242-253, 1990.

39. Knekt, P., D. Albanes, R. Seppanen, A. Aromaa, R. Jarvinen, L. Hyvonen, L. Teppo, and E. Pukkala, "Dietary Fat and Risk of Breast Cancer," *American Journal of Clinical Nutrition*, 52:903-908, 1990.

40. Howe, G. R., C. M. Friendenreich, M. Jain, and A. B. Miller, "A Cohort Study of Fat Intake and Risk of Breast Cancer," *Journal of the National Cancer Institute*, 83:336-340, 1991.

41. Mills, P. K., J. F. Annegers, and R. L. Phillipis, "Animal Product Consumption and Subsequent Fatal Breast Cancer Risk Among Seventh-day Adventists," *American Journal of Epidemiology*, 127:440-453, 1988.

42. Rohan, T. E., A. J. McMichael, and P. A. Baghurst, "A Population-based Case-control Study of Diet and Breast Cancer in Australia," *American Journal of Epidemiology*, 128:478-489, 1988.

43. Gerber, M., S. Richardson, P. Crastes de Paulet, H. Pujol, and A. Crastes de Paulet, "Relationship Between Vitamin E and Polyunsaturated Fatty Acids in Breast Cancer," *Cancer*, 64:2347-2553, 1989.

44. Iscovich, J. M., R. B. Iscovich, G. Howe, S. Shiboski, and J. M. Kaldor, "A Case-control Study of Diet and Breast Cancer in Argentina," *Internal Journal of Cancer*, 44:770-776, 1989.

45. Pryor, M., M. L. Slattery, L. M. Robison, and M. Egger, "Adolescent Diet and Breast Cancer in Utah," *Cancer Research*, 49:2161-2167, 1989.

46. Toniolo, P., E. Riboli, P. Protta, M. Charrel, and A. P. M. Cappa, "Calorie-providing Nutrients and Risk of Breast Cancer," *Journal of the National Cancer Institute*, 81:278-286, 1989.

47. Ewertz, M., and C. Gill, "Dietary Factors and Breast-cancer Risk in Denmark," *Internal Journal of Cancer*, 46:779-784, 1990.

48. Mettlin, C. J., E. R. Schoenfeld, and N. Natarajan, "Patterns of Milk Consumption and Risk of Cancer," *Nutrition Cancer*, 13:89-99, 1990.

49. Simard, A., J. Vobecky, and J. S. Vobecky, "Nutrition and Lifestyle Factors in Fibrocystic Disease and Cancer of the Breast," *Cancer Detection Prevention*, 14:567-572, 1990.

50. Van't Veer, P., F. J. Kok, H. A. M. Brants, T. Ockhuizen, F. Sturmans, and R.J. Hermus, "Dietary Fat and the Risk of Breast Cancer," *International Journal of Epidemiology*, 19:12-18, 1990.

51. Van't Veer, P., E. M. van Leer, A. Rietdijk, F. J. Kok, E. G. Schouten, R. J. J. Hermus, and F. Sturmans, "Combination of Dietary Factors in Relation to Breast-cancer Occurrence," *International Journal of Cancer*, 47:649-653, 1991.

52. Eld, A. and E. M. Berry, "The Relationship Between Dietary Fat, Adipose Tissue Composition, and Neoplasms of the Breast," *Nutritional Journal of Cancer*, 11:173-177, 1988.

53. Holm, L., E. Callmer, M. Hjalmar, B. Lidbrink, B. Nilsson, and L. Skoog, "Dietary Habits and Prognostic Factors in Breast Cancer," *Journal of the National Cancer Institute*, 81:1218-1223, 1989.

54. Boyd, N. F., M. Cousins, M. Beaton, E. Fishell, B. Wright, E. Fish, V. Kriudov, G. Lockwood, D. Tritchler, W. Hanna, and D. L. Page, "Clinical Trial of Low-fat, High-carbohydrate Diet in Subjects with Mammographic Dysplasia: Report of Early Outcomes," *Journal of the National Cancer Institute*, 80:1244-1248, 1988.

55. Verreault, R., J. Brisson, L. Deschenes, F. Naud, F. Meyer, and L. Belanger, "Dietary Fat in Relation to Prognostic Indicators in Breast Cancer," *Journal of the National Cancer Institute*, 80:819-825, 1988.

56. Boyd, N. F., V. McGuire, E. Fishell, V. Kuriov, G. Lockwood, and D. Tritchler, "Plasma Lipids in Premenopausal Women with Mammographic Dysplasia," *British Journal of Cancer*, 59:766-771, 1989.

57. Brisson, J., R. Verreault, A. S. Morrison, S. Tennina, and F. Meyer, "Diet, Mammographic Features of Breast Tissue, and Breast Cancer Risk," *American Journal of Epidemiology*, 130:14-24, 1989.

58. Boyd, N. F., and V. McGuire, "Evidence of Lipid Peroxidation in Premenopausal Women With Mammographic Dysplasia," *Cancer Letters*, 50:31-37, 1990.

59. Neoptolemos, J. P., H. Clayton, A. M. Heagerty, M. J. Nicholson. B. Johnson, J. Mason, K. Manson, R. F. L. James, and P. R. F. Bell, "Dietary Fat in Relation to Fatty Acid

Composition of Red Cells and Adipose Tissue in Colorectal Cancer," *British Journal of Cancer*, 58:575-579, 1988.

60. Insull, W., M. Henderson, R. L. Prentice, and D. J. Thompson, "Results of a Randomized Feasibility Study of a Low-Fat Diet," *Archives of Internal Medicine*, 150:421-427, 1990.

61. West, D. W., M. L. Slavery, L. M. Robison, K. L. Schuman, M. H. Ford, A. W. Mahoney, J. L. Lyon, and A. W. Sorensen, "Dietary Intake and Colon cancer: Sex- and Anatomic Site-specific Associations," *American Journal of Epidemiology*, 130:883-894, 1989.

62. Willett, W. C., M. J. Stampfer, G. A. Colditz, B. A. Rosner, and F. E. Speizer, "Relation of Meat, Fat, and Fiber Intake to the Risk of Colon Cancer in a Prospective Study Among Women," *National England Journal of Medicine*, 323:1664-1672, 1990.

63. Ghadirian, P., A. Simard, J. Baillargeon, P. Maisonneuve, and P. Boyle, "Nutritional Factors and Pancreatic Cancer in the Francophone Community in Montreal, Canada," *Internal Journal of Cancer*, 47:1-6, 1991.

64. Goodman, M. T., L. N. Kolonel, C. N. Yoshizawa, and J. H. Hankin, "The Effect of Dietary Cholesterol and Fat on the Risk of Lung Cancer in Hawaii," *American Journal of Epidemiology*, 128:1241-1255, 1988.

65. Steineck, G., U. Hagman, M. Gerhardsson, and S. E. Norell, "Vitamin A Supplements, Fried Foods, Fat and Urothelial Cancer, A Case-referent Study in Stockholm in 1985-87," *International Journal of Cancer*, 45:1006-1011, 1990.

66. La Vecchia, C., E. Negri, A. Decarli, B. D'Avanzo, L. Gallotti, A. Gentile, and S. Franceschi, "A Case-control Study of Diet and Colorectal Cancer in Northern Italy," *International Journal of Cancer*, 41:492-498, 1988.

67. Benito, E., A. Obrador, A. Stiggelbout, F. X. Bosch, M. Mulet, N. Munoz, and J. Kaldor, "A Population-based Case-control Study of Colorectal Cancer in Majorca, I. Dietary factors," *International Journal of Cancer*, 45:69-76, 1990.

68. Franceschi, S., D. Serraino, A. Carbone, R. Talamini, and C. La Vecchia, "Dietary Factors and Non-Hodkin's Lymphoma: A Case-control Study in the Northeastern Part of Italy," *Journal of Nutritional Cancer*, 12:333-341, 1989.

69. Franceschi, S., E. Bidoli, A. E. Baron, S. Barra, R. Talamini, D. Serraino, and C. La Vecchia, "Nutrition and Cancer of the Oral Cavity and Pharynx in North-East Italy," *International Journal of Cancer*, 47:20-25, 1991.

70. Ries, L. A. G., B. F. Hankey, B. A. Miller, A. M. Hartman, B. K. Edwards, "Cancer Statistics Review, 1979-88," *National Cancer Institute*, NIH Pub. No. 91-2789, 1991.

71. Ip, C., C. A. Carter, and M. M. Ip, "Requirement of Essential Fatty Acid for Mammary Tumorigenesis in the Rat," *Cancer Research*, 45:1997-2001, 1985.

72. Byers, T. E., and A. H. Mokdad, (Abstract), "Dietary Fat and the Risk of Cancers of the Breast, Prostate, and Colon in a 17-year Prospective Study," FASEB Abstract 1116.

73. Brown, M., National Cancer Institute, memo of telephone conversation, unpublished document, 1991.

73a. Howe, G. R., T. Hirohata, T. G. Hislop, J. M. Iscovich, J. Min-Yuan, K. Katsouyanni, F. Lubin, E. Marubini, B. Modan, T. Rohan, P. Toniolo, and Y. Shunzhang, "Dietary Factors and Risk of Breast Cancer: Combined Analysis of 12 Case-control Studies," *Journal of the National Cancer Institute*, 82:561-569, 1990.

74. Buiatti, E., D. Palli, A. Decarli, D. Amadori, C. Avellini, S. Bianchi, C. Bonaguri, F. Cipriani, P. Cocco, A. Giacosa, E. Marubini, C. Minacci, R. Puntoni, A. Russo, C. Vindigni, E. F. Praumeni, Jr., and W. J. Blot, "A Case-control Study of Gastric Cancer and Diet in Italy: II. Association with Nutrients," *International Journal of Cancer*, 45:896-901, 1990.

75. Baghurst, P. A., A. J. McMichael, A. H. Slavotinek, K. I. Baghurst, P. Boyle, and A. M. Walker, "A Case-control Study of Diet and Cancer of the Pancreas," *American Journal of Epidemiology*, 134:167-179, 1991.

76. Demirer, T., F. Icli, O. Uzunaligmoglu, and O. Kucuk, "Diet and Stomach Cancer Incidence: A Case-control Study in Turkey," *Cancer*, 65:2344-2348, 1990.

77. DeVerdier, M. G., U. Hagman, G. Steineck, A. Rieger, and S. E. Norell, "Diet, Body Mass and Colorectal Cancer: A Case-Referent Study in Stockholm," *International Journal of Cancer*, 46:832-838, 1990.

78. Farrow, D. C. and S. Davis, "Diet and the Risk of Pancreatic Cancer in Men," *American Journal of Epidemiology*, 132:423-431, 1990.

79. Jain, M., J. D. Burch, G. R. Howe, H. A. Risch, and A. B. Miller, "Dietary Factors and Risk of Lung Cancer: Results From a Case-control Study, Toronto, 1981-1985," *International Journal of Cancer*, 45:287-293, 1990.

80. Kato, I, S. Tominaga, Y. Ito, S. Kobayashi, Y. Yoshii, A. Matsuura, A. Kameya, and T. Kano, "A Comparative Case-control Analysis of Stomach Cancer and Atropic Gastritis," *Cancer Research*, 50:6559-6564, 1990.

81. La Vecchia, C., E. Negri, B. D'Avanzo, S. Franceschi, A. Decarii, and P. Boyle, "Dietary Indicators of Laryngeal Cancer Risk," *Cancer Research*, 50:4497-4500, 1990.

82. Vecchia, C. L., E. Negri, B. D'Avanzo, M. Ferraroni, A. Gramenzi, R. Savodelli, P. Boyle, and S. Franceschi, "Medical History, Diet and Pancreatic Cancer," *Oncology*, 47:463-466, 1990.

83. Maclure, M. and W. Willett, "A Case-control Study of Diet and Risk of Renal Adenocarcinoma," *Epidemiology*, 1:430-440, 1990.

84. Mettlin, C. J. and M. S. Piver, "A Case-control Study of Milk-drinking and Ovarian Cancer Risk," *American Journal of Epidemiology*, 132:871-876, 1990.

85. Stemmermann, G. N., Nomura, A., and Chyou, P-H, "The Influence of Dairy and Nondairy Calcium on Subsite Large-bowel Cancer Risk," *Diseases of the Colon and Rectum*, 33:190-194, 1990.

86. Slattery, M. L., M. C. Schumacher, D. W. West, L. M. Robison, and T. K. French, "Food-consumption Trends Between Adolescent and Adult Years and Subsequent Risk of Prostate Cancer," *American Journal of Clinical Nutrition*, 52:752-757, 1990.

87. Shun-Zhang, Y., L. Rui-Fang, X. Da-Dao, and G. R. Howe, "A Case-control Study of Dietary and Nondietary Risk Factors for Breast Cancer in Shanghai," *Cancer Research*, 50:5017-5021, 1990.

88. Slattery, M. L., M. C. Schumacher, K. R. Smith, D. W. West, and N. Abd-Elghany, "Physical Activity, Diet, and Risk of Colon Cancer in Utah," *American Journal of Epidemiology*, 128:989-999, 1988.

89. Hislop, T.G., P. R. Band, M. Deschamps, V. Ng, A. J. Coldman, A. J. Worth, and T. Labo, "Diet and Histologic Types of Benign Breast Disease Defined by Subsequent Risk of Breast Cancer," *American Journal of Epidemiology*, 131:263-270, 1990.

90. Suarez-Varela, M. M., A. Llopis-Gonzalez, A. Casillo-Collado, and I. Vitoria-Minana, "Cancer of the Rectum in Relation to Components of the Spanish Diet," *Journal of Environmental Pathology and Toxicologocial Oncology*, 10:214-219, 1990.

91. Life Sciences Research Office, Federation of American Societies for Experimental Biology, "Evaluation of Publicly Available Scientific Evidence Regarding Certain Nutrient-Disease Relationships: 10. Lipids and Cancer," 1991.

92. Yu, H., R. E. Harris, Y. T. Gao, R. Gao, and E. L. Wynder, "Comparative Epidemiology of Cancers of the Colon, Rectum, Prostate, and Breast in Shanghai, China versus the United States," *International Journal of Epidemiology*, 20:76-81, 1991.

93. Kesteloot, H., E. Lesaffre, and J. V. Joossens, "Dairy Fat, Saturated Animal Fat, and Cancer Risk," *Preventive Medicine*, 20:226-236, 1991.

94. Zatonski, W., K. Przewozniak, G. R. Howe, P. Maisonneuve, A. M. Walker, and P. Boyle, "Nutritional Factors and Pancreatic Cancer: A Case-Control Study From South-West Poland," *International Journal of Cancer*, 48:390-394, 1991.

95. De Mesquita, H. B. B., P. Maisonneuve, S. Runia, and C. J. Moeman, "Intake of Foods and Nutrients and Cancer of the Exocrine Pancreas: A Population-Based Case-Control Study in the Netherlands," *International Journal of Cancer*, 48:540-549, 1991.

96. Riboli, E., C. A. Gonzales, G. Lopez-Abente, M. Errezola, I. Izarzugaza, A. Escolar, M. Nebot, B. Hemon, and A. Agudo, "Diet and Bladder Cancer in Spain: A Multi-Centre Case-Control Study," *International Journal of Cancer*, 49:214-219, 1991.

97. Shekelle, R. B., A. H. Rossof, and J. Stamier, "Dietary Cholesterol and Incidence of Lung Cancer: The Western Electric Study," *American Journal of Epidemiology*, 134(5):480-484, 1991.

98. Goodman, M. T., "Re: Dietary Cholesterol and Incidence of Lung Cancer: The Western Electric Study," Letter to the Editor, *American Journal of Epidemiology*, 134(5):543-544, 1991.

99. Graham, S., R. Hellmann, J. Marshall, J. Freudenheim, J. Venna, M. Swanson, M. Zielezny, T. Nemoto, N. Stubbe, and T. Raimondo, "Nutritional Epidemiology of Postmenopausal Breast Cancer in Western New York," *American Journal of Epidemiology*, 134(6):552-566, 1991.

100. Lee, H. P., L. Gourley, S. W. Duffy, J. Esteve, J. Lee., and N. E. Day, "Dietary Effects on Breast Cancer Risk in Singapore," *Lancet*, 337:1197-1200, 1991.

101. Richardson, S., M. Gerber, and S. Cenee, "The Role of Fat, Animal Protein and Some Vitamin Consumption in Breast Cancer: A Case-Control Study in Southern France," *International Journal of Cancer*, 48:1-9, 1991.

102. Zaridze, D., Y. Lifanova, D. Maximovitch, N. E. Day, and S. W. Duffy, "Diet, Alcohol Consumption and Reproductive Factors in a Case-Control Study of Breast Cancer in Moscow," *International Journal of Cancer*, 48:493-501, 1991.

103. D'Avanzo, B., E. Negri, A. Gramenzi, S. Franceschi, F. Parazzini, P. Boyle, and C, La Vecchia, "Fats in Seasoning and Breast Cancer Risk: An Italian Case-Control Study," *European Journal of Cancer*, 27(4):420-423, 1991.

104. Benito, E., A, Stiggelbout, F. X. Bosch, A. Obrador, J. Kaldor, M. Mulet, and N. Munoz, "Nutritional Factors in Colorectal Cancer Risk: A Case-Control Study in Majorca," *International Journal of Cancer*, 49:161-167, 1991.

105. Bravo, M. P., E. Castellanos, and J. del Ray Calero, "Dietary Factors and Prostatic Cancer," *Urology International*, 46:163-166, 1991.

106. West, D. W., M. L. Slattery, L. M. Robison, T. K. French, and A. W. Mahoney, "Adult Dietary Intake and Prostate Cancer Risk in Utah: A Case-Control Study With Special Emphasis on Aggressive Tumors," *Cancer Causes and Control*, 2:85-94, 1991.

107. Kinlen, L. J., "Diet and Breast Cancer," *British Medical Bulletin*, 47(2):462-469, 1991.

108. Evers, S., "Diet-Disease Relationships: Public Health Perspectives," *Progress in Food and Nutrition Science*, 15:61-83, 1991.

109. Nomura, A. M. Y., and L. N. Kolonel, "Prostate Cancer: A Current Perspective," *American Journal of Epidemiology*, 13:200-227, 1991.

110. Roberfroid, M. B., "Dietary Modulation of Experimental Neoplastic Development: Role of Fat and Fiber Content and Calorie Intake," *Mutation Research*, 259:351-362, 1991.

111. Browner, W. S., J. Westenhouse, and J. A. Tice, "What If Americans Ate Less Fat? A Quantitative Estimate of the Effect on Mortality," *Journal of the American Medical Association*, 265(24):3285-3291, 1991.

112. Kumaki, T. and M. Noguchi, "Effects of High Dietary Fat on the Total DNA and Receptor Contents in Rats With 7, 12-Dimethylbenz(a)anthracene-Induced Mammary Carcinoma," *Oncology*, 47:352-358, 1990.

113. Cohen, L. A., M. E. Kendall, E. Zang, C. Meschter, and D. P. Rose, "Modulation of N-Nitrosomethylure-Induced Mammary Tumor Promotion by Dietary Fiber and Fat," *Journal of the National Cancer Institute*, 496-501, 1991.

114. Gonzalez, M. J., R. A. Schemmel, J. I. Gray, L. Dugan Jr., L. G. Sheffield, and C. W. Welsch, "Effect of Dietary Fat on Growth of MCF-7 and MDA-MB231 Human Breast Carcinomas in Athymic Nude Mice: Relationship Between Carcinoma Growth and Lipid Peroxidation Product Levels," *Carcinogenesis*, 12:1231-1235, 1991.

115. Zhu, P., E. Frei, B. Bunk, M. R. Berger, and D. Schmahl, "Effect of Dietary Calorie and Fat Restriction on Mammary Tumor Growth and Hepatic As Well As Tumor Glutathione in Rats," *Cancer Letters*, 57:145-152, 1991.

116. Aksoy, M., M. Beth, M. R. Berger, and D. Schmahl, "Effects of Different Levels of Dietary Fat on Methyl-Nitrosourea-Induced Mammary Carcinogenesis in Correlation With Parameters of Fat Metabolism in Female Sprague-Dawley Rats," *Archiv Fur Geschwulstforschung*, 60:109-115, 1990.

117. Khoo, D. E., C. B. Wood, and N. A. Habib, "Failure of Dietary Stearic Acid to Influence the Growth of a Transplanted Mammary Tumour," *Surgical Research Communications*, 9:45-51, 1990.

118. Nicholson, M. L., J. P. Neoptolemos, H. A. Clayton, I. C. Talbot, and P. R. F. Bell, "Inhibition of Experimental Colorectal Carcinogenesis by Dietary N-6 Polyunsaturated Fats," *Carcinogenesis*, 11:2191-2197, 1990.

119. Behling, A. R., S. M. Kaup, L. L. Choquette, and J. L. Greger, "Lipid Absorption and Intestinal Tumor Incidence in Rats Fed on Varying Levels of Calcium and Butterfat," *English Journal of Nutrition*, 64:505-513, 1990.

120. Hietanen, E., H. Bartsch, J. C. Bereziat, M. Ahotupa, A. M. Camus, J. R. P. Cabral, and M. Laitinen, "Quantity and Saturation Degree of Dietary Fats as Modulators of Oxidative Stress and Chemically-Induced Liver Tumors in Rats," *International Journal of Cancer*, 46:640-647, 1990.

121. Smith, J. P., S. Kramer, and S. Bagheri, "Effects of a High-Fat Diet and L364, 718 on Growth of Human Pancreas Cancer," *Digestive Diseases and Sciences*, 35:726-732, 1990.

122. Longnecker, D. S., E. T. Kuhlmann, and D. H. Freeman, Jr., "Characterization of the Elaste 1-Simian Virus 40 T-Antigen Mouse of Pancreatic Carcinoma: Effects of Sex and Diet," *Cancer Research*, 50:7552-7554, 1990.

123. Buckman, D. K., R. S. Chapkin, and K. L. Erickson, "Modulation of Mouse Mammary Tumor Growth and Linoleate Enhanced Metastasis by Oleate," *Journal of Nutrition*, 120:148-157, 1990.

124. Lasekan, J. B., M. K. Clayton, A. Gendron-Fitzpatrick, and D. M. Ney, "Dietary Olive Oil and Safflower Oils in Promotion of DMBA-Induced Mammary Tumorigenesis in Rats," *Nutrition and Cancer*, 13:153-163, 1990.

125. Hirose, M., A. Masuda, N. Ito, K. Kamano, and H. Okuyama, "Effects of Dietary Perilla Oil, Soybean Oil and Safflower Oil on 7, 12-Dimethylbenz[a]anthracene(DMBA) and 1,2-Dimethylhydrazine (DMH)-Induced Mammary Gland and Colon Carcinogenesis in Female SD Rats," *Carcinogenesis*, 11:731-735, 1990.

126. Nutter, R. L., J. D. Kettering, R. M. Aprecio, D. A. Weeks, and D. S. Gridley, "Effects of Dietary Fat and Protein on DMH-Induced Tumor Development and Immune Responses," *Nutrition and Cancer*, 13:141-152, 1990.

127. Locniskar, M., M. A. Belury, A. G. Cumberland, K. E. Patrick, and S. M. Fischer, "The Effect of Dietary Lipid on Skin Tumor Promotion by Benzoyl Peroxide: Comparison of Fish. Coconut, and Corn Oil," *Carcinogenesis*, 12:1023-1028, 1991.

128. Leyton, J., M. L. Lee, M. Locniskar, M. A. Belury, T. J. Slaga, D. Bechtel, and S. M. Fischer, "Effects of Type Dietary Fat on Phorbol Ester-elicited Tumor Promotion and Other Events in Mouse Skin," *Cancer Research*, 51:907-915, 1991.

129. Lindner, M. A., "A Fish Oil Diet Inhibits Colon Cancer in Mice," *Nutrition and Cancer*, 15:1-11, 1991.

130. Ayachi, N. E., M. Begin, D. Mercier, G. Ells, and D. Oth, "Suspectibility of RDM4 Lymphoma Cells to LAK-Mediated Lysis Is Decreased in Tumor Bearers Fed Fish Oil High Fat Regimen," *Cancer Letters*, 49:217-224, 1990.

131. Oth, D., G. Mercier, P. Tremblay, H. M. Therien, M. E. Begin, G. Ells, and E. Potworcwski, "Modulation of CD4 Expression on Lymphoma Cells Transplanted to Mice Fed (N-3) Polyunsaturated Fatty Acids," *Biochemica et Biophysica Acta*, 1027:47-52, 1990.

132. Schatzin, A., P. Greenwald, D. P. Byar, C. K. Clifford, "The Dietary Fat-Breast Cancer Hypothesis Is Alive," *Journal of American Medical Association*, 261:3284-3287, 1989.

133. Kritchevsky, D., "Diet and Cancer," *CA-A Cancer Journal for Clinicians*, 41:329-333, 1991.

134. Weisburger, J. H. and E. L. Wynder, "Dietary Fat Intake and Cancer," *Hematology/Oncology Clinics of North America*, 5:7-23, 1991.

135. Bunce, 0. R. and S. H. Abou-Ei-Ela, "Eicosanoid Synthesis and Ornithine Decarboxylase Activity in Mammary Tumors of Rats Fed Varying Levels and Types of N-3 and/or N~6 Fatty Acids," *Prostaglandins Leukotrines and Essential Fatty Acids*, 41:105-113, 1990.

136. Wan, J. M. F., N. W. Istfan, C. C. Chu, G. L. Blackburn, and B. R. Bistrian, "Comparative Effects ofW-3 and W-6 Polyunsaturated Fatty Acids on Protein Metabolism in Rats Bearing the Mammary Adenocarcinoma," *Metabolism*, 40:577-584, 1991.

137. Takata, T., T. Minoura, H. Takada, M. Sakaguchi, M. Yamamura, K. Hioki, and M. Yamamoto, "Specific Inhibitory Effect of Dietary Eicosapentaenoic Acid on N-nitroso-N-methylurea-induced Mammary Carcinogenesis in Female Sprague-Dawley Rats," *Carcinogenesis*, 11:2015-2019, 1990.

138. Yeung, K. S., G. E. McKeown-Eyssen, G. F. Li, E. Glazer, K. Hay, P. Child, V. Gurgin, S. L. Zhu, J. Baptista, M. Aloe, D. Mee, V. Jazmaji, D. F. Austin, C. C. Li, and W. R. Bruce, "Comparisons of Diet and Biochemical Characteristics of Stool and Urine Between Chine Populations with Low and High Colorectal Cancer Rates," *Journal of the National Cancer Institute*, 83(1):46-50, 1991.

139 Geltner-Allinger. U., B. Brismar, F. P. Remholt, G. Anderson, and J. J. Rafter, "Soluble Fecal Acidic Lipids and Colorectal Epithelial Cell Proliferation in Normal Subjects and in Patients with Colon Cancer," *Scandinavian Journal of Gastroenterology*, 26:1069-1074, 1991.

140. Clausen, M. R., H. Bonnen, and P. B. Mortensen, "Colonic Fermentation of Dietary

Fibre to Short Chain Fatty Acids in Patients with Adenomatous Polyps and Colonic Cancer," *Gut*, 32:923-928, 1991.

141. National Cholesterol Education Program, "Population Strategies, for Blood Cholesterol Reduction," DHHS, PHS, NIH, NIH Pub. No. 90-3046, 1990.

142. O'Neill, I. K., M. T. Goldberg, E. E. I. Ghissassi, and M. Rojas-Moreno, "Dietary Fiber, Fat, and Beef Modulation of Colonic Nuclear Aberrations and Microcapsule-trapped Gastrointestinal Metabolite of Benzo(a)pyrene-treated C57/B6 Mice Consuming Human Diets," *Carcinogenesis*, 12:175-180, 1991.

143. Jenski, L. J., L. Sturdevant, W. D. Ehrmger, and W. Stillwell, "Omega-3 Fatty Acids Increase Spontaneous Release of Cytosolic Compounds from Tumor Cells," *Lipids*, 26:353-358, 1991.

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 (21U.S.C, 321, 331, 342, 343, 348, 371).

2. New § 101.73 is added to subpart E to read as follows:

§ 101.73 Health claims: dietary fat and cancer.

(a) *Relationship between fat and cancer*. (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) Among dietary factors, the strongest positive association has been found between total fat intake and risk of some types of cancer. Based on the totality of the publicly available scientific evidence, there is significant scientific agreement among experts, qualified by training and experience to evaluate such evidence, that diets high in total fat are associated with an increased cancer risk. Research to date, although not conclusive, demonstrates that the total amount of fats, rather than any specific type of fat, is positively associated with cancer risk. The mechanism by which total fat affects cancer has not yet been established.

(3) A question that has been the subject of considerable research is whether the effect of fat on cancer is site-specific. Neither human nor animal studies are consistent in the association of fat intake with specific cancer sites.

(4) Another question that has been raised is whether the association of total fat intake to cancer risk is independently associated with energy intakes, or whether the association of fat with cancer risk is the result of the higher energy (caloric) intake normally associated with high fat intake. FDA has concluded that evidence from both animal and human studies indicates that total fat intake alone, independent of energy intake, is associated with cancer risk.

(b) *Significance of the relationship between fat intake 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 high in calories. The average U.S. diet is estimated to contain 36 to 37 percent of calories from total fat. Current dietary guidelines from the Federal Government and other national health professional organizations recommend that dietary fat intake be reduced to a level of 30 percent or less of energy (calories) from total fat. In order to reduce intake of total fat, individuals should choose diets which are high in vegetables, fruits, and grain products (particularly whole grain products), choose lean cuts of meats, fish, and poultry, substitute low-fat dairy products for higher fat products, and use fats and oils sparingly.

(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 diets low in fat 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 "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) In specifying the nutrient, the claim uses the term "total fat" or "fat";

(D) The claim does not specify types of fat or fatty acid that may be related to the risk of cancer;

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

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

(ii) *Nature of the food*. The food shall meet all of the nutrient content requirements of § 101.62 for a "low fat" food; except that fish and game meats (i.e., deer, bison, rabbit, quail, wild turkey, geese, ostrich) may meet the requirements for "extra lean" in § 101.62.

(d) *Optional information*. (1) 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.

(2) The claim may include information from paragraphs (a) and (b) of this section which summarize the relationship between dietary fat and cancer and the significance of the relationship.

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

(4) 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 describe the relationship between dietary fat and cancer:

(1) Development of cancer depends on many factors. A diet low in total fat may reduce the risk of some cancers.

(2) Eating a healthful diet low in fat may help reduce the risk of some types of cancers. Development of cancer is associated with many factors, including a family history of the disease, cigarette smoking, and what you eat.

Dated: October 30, 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
Lipids and Cancer: Human Studies 1991 to Present

Study	Study Design	Subjects	Methods	Results	Comments
Zatonski et al., 1991 (Ref. 941)	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; diet assessed 1 to 2 years before interview; 43% of cases were histologically confirmed and remainder diagnosed radiologically	Adjusted for smoking and total calories; Total fat RR=0.3 (0.1-1.0) SFA: RR=0.3 (0.1-1.0) MUFA: RR=0.1 (0.3-0.6) PUFA: RR=0.2 (0.1-0.6) Cholesterol: RR=4.3 (1.6-11.6)	Only cholesterol showed a positive relation with pancreatic cancer; substantial use of proxy interview of cases introduces bias; median daily total fat intake was 113 g for cases and 105 g for controls
de Mesquita, et al., 1991 (Ref. 95)	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; diet assessed 1 year before interview; 68% of cases were histologically confirmed; others diagnosed clinically	Adjusted for smoking and total calories: Oil and Fats: RR=1.1 for highest quintile (NS) Total meat: RR=1.6 for highest quintile (NS) Cheese: RR=0.8 (NS) Milk: RR=0.8 (NS) Eggs: RR=2.3 and daily consumption of vegetables RR=0.3 for highest quintile (statistical significance and test for trend significance for both)	Total fat and saturated fat not analyzed in this study; consumption of eggs is associated with a statistically significant increased risk and daily consumption of vegetables show a protective effect; large percentage of proxy interview of cases may introduce bias
Riboli, et al., 1991 (Ref. 96)	Case-Control; Spain; Bladder Cancer; Study conducted 1985 to 1986	432 cases (all males); 792 controls; 2 sets of controls: population-based and hospital-based	Interview using dietary questionnaire containing 60 food groups; diet assessed 1 year before interview; all cases histologically confirmed	Adjusted for smoking and total calories: Total Fat: No association Saturated Fat: RR=2.2 (1.4-3.6) for highest quintile and trend highly significant (p=.0005) PUFA, MUFA: No associations Cholesterol: RR=1.4 (0.9-2.2) P/S Ratio: RR=0.7 (0.5-1.0)	Increased risk associated only with saturated fat; no association with total fat. Mean daily total fat intake was 99 g for cases and 95 g for controls Slightly low participation rates (cases: 72%; controls: 71% hospital and 66% population); results possibly biased by inclusion of 208 prevalent cases because they are survivors
Shekelle, et al., 1991 (Ref. 97)	Prospective Cohort; Western Electric Co. employees, Chicago; Lung Cancer	1,878 men aged 40 to 55 years in 1958 followed 24 years	Dietary information on foods and beverages consumed preceding 28 days collected at exam 1 and exam 2, 1 year later (all clinically free of cancer)	Adjusted for smoking and percent calories from fat: Dietary Cholesterol: 605-794 mg/day RR=1.3 795-1,909 mg/day RR=1.9 (results similar when adjusted for energy intake) Multivariable model implicated cholesterol from eggs but not from other sources	Increment of dietary cholesterol of 500 mg/day associated with RR=1.9 (1.1-3.4) Followup data not available so cannot assess changes in dietary cholesterol after baseline measurement

TABLE 1
Lipids and Cancer: Human Studies 1991 to Present

Study	Study Design	Subjects	Methods	Results	Comments
Graham, et al., 1991 (Ref. 99)	Case-Control; New York; Postmenopausal Breast Cancer; Study conducted 1986 to 1989	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, benign breast disease, and Quetelet index	Cases and controls consumed same calories. No association found between breast cancer risk and total fat or saturated fat: Fat RR=0.9 (0.6-1.4); SFA RR=1.0 (0.7-1.5). Dietary carotene, vitamin C protective but no effect shown for supplement use; dietary fiber borderline protective RR=0.7 (0.5-1.1); adjustment for total calories did not change results	No association found between breast cancer risk and dietary fat. Mean daily total fat consumption was 82 g for cases and 83 g for controls. Low participation rates may introduce bias: 56% of eligible cases and 46% of eligible controls participated in study, thus results may not be generalizable to total population
Lee, et al., 1991 (Ref. 100)	Case-Control; Signapore Chinese; Pre- and Postmenopausal Breast Cancer; Study conducted 1986 to 1988	200 incident cases (109 premenopausal and 91 postmenopausal); 420 age-matched hospital controls (207 premenopausal and 213 postmenopausal)	Interview using dietary questionnaire on 90 foods; diet assessed 1 year before interview; all cases were histologically confirmed; results adjusted for age and age at birth of first child for premenopausal women and for age, height, education, nulliparity, family history of breast cancer for postmenopausal women	Postmenopausal women: no significant effects for any dietary variable Premenopausal women: Total fat, SFA, MUFA, and cholesterol showed no significant effect; P/S Ratio: RR=0.4 (0.2-0.8): Decreased risks found for PUFA: RR=0.5 (0.3-0.8); increased risk found for red meat after controlling for all other dietary variables: RR=4.0 (1.9-8.5)	Results not adjusted for total calories. No effect of diet on postmenopausal women. No effect found for total fat, SFA, MUFA, cholesterol and protective effect found for PUFA on premenopausal women. Median daily fat consumption was 33 g Hospital controls may have misrepresented their usual diet if preclinical symptoms (1 year before interview) affected diet
Richardson, et al., 1991 (Ref. 101)	Case-Control; France; Pre- and Postmenopausal Breast Cancer; Study conducted 1983-1982	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 histologically confirmed; results adjusted for age, menopausal status, family history of breast cancer, history of benign breast disease, alcohol consumption, and age at menarche	Multivariate Model: All women: Fat 1.6 (1.1-2.2) SFA 1.9 (1.3-2.6) MUFA 1.7 (1.2-2.5) PUFA, cholesterol no significant effects Premenopausal women: MUFA 2.0 (1.1-3.7) SFA, MUFA, retinol, beta-carotene, fat, vitamin E no significant effects Postmenopausal women: SFA: 2.0 (1.2-3.1) Retinol: 2.8 (1.2-2.8) Total fat, MUFA, beta-carotene, vitamin E no significant effects Food Associations (all women): Total Food RR=1.7 (1.1-2.4); High fat cheese RR=1.4 (1.0-1.9); Desserts and chocolate RR=1.7 (1.2-2.5); Meat, Olive Oil, Nuts- nonsignificant	Results not adjusted for total calories or for body size. Limited evidence that fat is associated with breast cancer risk when analyzed by menopausal status. Total food was positively associated. Use of hospital controls could lead to selection of controls whose diseases are associated with high fat diets, although study excluded cardiovascular disease controls

TABLE 1—CONTINUED

Study	Study Design	Subjects	Methods	Results	Comments
Zaridze, et al., 1991 (Ref. 102)	Case-Control; Moscow; Pre and postmenopausal Breast Cancer; Study conducted 1987 to 1989	139 incident cases (58 premonopausal and 81 postmenopausal); 139 clinic controls (54 premenopausal and 85 postmenopausal) matched by age and neighborhood	Dietary questionnaire on 145 food items; diet assessed for average consumption during year prior to diagnosis for cases and for year prior to interview for controls. Data analyzed for pre- and postmenopausal women separately. Adjusted for total energy for all analyses; weight, height and Quetelet's index were assessed but none had a significant effect so results were not adjusted for these variables	Prememopausal women: Adjusted for total energy, age at menarch, age at first birth: Magnesium intake: RR= 02 (.0005-.08) only significant finding Postmenopausal women: adjusted for total energy, age at menarche, and education: Total fat, SFA, MUFA, cholesterol, protein: Nonsignificant PUFA: RR=0.1 (0.03-0.7) Mono- and disaccharides: RR=0.02 (0.002-0.3) Cellulose: RR=0.04 (0.01-0.3) Beta-carotene, vitamin C, potassium, calcium, magnesium, and retinol equivalents all showed significant protective effects	Dietary fat not associated with breast cancer risk in either pre- or postmenopausal women. Results showing protective effects of some nutrients are difficult to interpret due to multiple comparisons and multiple models used in analysis, especially in light of the small number of study participants
D'Avanzo et al., 1991 (Ref. 103)	Case-Control; Italy; Pre- and postmenopausal Breast Cancer; Study conducted 1983 to 1989	2,663 incident cases (1,122 premenopausal and 1,541 postmeno-pausal); 2,344 controls and 1,460 postmenopausal)	Dietary questionnaire on few selected indicator foods to obtain data on fat intake in seasonings (butter, margarine and oil); current diet assessed; all cases histologically confirmed; results adjusted for age, area of residence, education, history of benign breast disease, family history of breast cancer, nulliparity, age at first birth, age at menarche, menopausal status, age at menopause, body mass index, oral contraceptive and other female hormone use	Total Fat (from seasonings) RR=1.5 (1.2-1.7) Butter RR=1.6 (1.2-2.1) Oil RR=1.2 (1.0-1.6) No effect shown with margarine consumption	Results not adjusted for total calories. Moderate association between intake of added fat in seasonings and breast cancer risk. Use of hospital controls could lead to selection of controls whose diseases are associated with high fat diets, although gastrointestinal diseases were excluded. Assessment of current diet rather than diet before onset of illness could bias results. Very limited dietary information available.
Benito, E., et al., 1991 (Ref. 104)	Case-Control; Majorca; Colorectal Cancer; Study conducted 1984 to 1988	286 incident cases; 295 population controls and 203 hospital (ophthalmology and orthopedic); controls matched to cases by age and sex	Interview using dietary questionnaire on 99 food items; diet assessed in year preceding interview; all cases histologically confirmed; results adjusted for total calories and for age, sex, estimated weight 10 years prior to interview, number of meals per day, education, job category, and activity in the workplace	RR's for quartiles of consumption: Total Calories: RR=1.0, 1.6, 1.6, 2.6 After adjustment for total calories: Cholesterol: RR=1.0, 0.9, 1.7, 1 7 Fiber from legumes: RR=1.0, 0.8, 0.5, 0.4 Protein; RR=1 0, 1 1, 1 7, 2 5 Carbohydrate: RR=1 0, 1 5, 1 4, 2 2 No effects found for total fat or saturated fats	Increased risk of colorectal cancer found for total calories, cholesterol, protein, and carbohydrates and protective effect found for fiber from legumes. No effect on colorectal cancer risk was found for increased consumption of total fats or saturated fats. This lack of association may be due to the population's consumption mainly of MUFAs rather than animal fats. Mean percentage of calories from fat was 37% for colon cancer cases, for rectal cancer cases and for controls

TABLE 1—continued

Study	Study Design	Subjects	Methods	Results	Comments
Young, et al., 1991 (Ref. 138)	Correlational (Biochemical) Study: China and American; Colorectal Cancer	42 male and 50 female Chinese and 34 male and 33 female Chinese Americans; the two populations have fourfold difference in colorectal cancer risk	24-hour food, urine and stool samples analyzed; all subjects were randomly selected from volunteers	Chinese American diets were higher in fat and protein and lower in carbohydrates, stools contained more cholesterol and bile acids, and no difference in fatty acids, and urine contained more 3-methyl-histidine and malonaldehyde. Authors interpreted results to demonstrate that high fat, high protein, low carbohydrate diets are associated with increased colorectal cancer risk	Authors interpretation does not follow from study's findings due to methodological flaws: results are correlational only--no cases of colorectal cancer actually existed among participants; diet was assessed for 24 hours only; Chinese had higher participation rate than Americans; confounding by environmental and lifestyle factors were not controlled for in study
Geltner-Allinger, et al., 1991 (Ref. 139)	Case-Control; Sweden; Colon Cancer	35 cases (16 men, 19 women); 46 population controls (26 men, 20 women)	Limited dietary intake information, diet assessed for preceding year; stool samples analyzed for bile acids and lipid concentrations; rectal biopsies collected for colonic epithelial cell proliferation rate analysis	No differences found in the concentration of fecal bile acids or in colonic cell proliferation rates. No differences found in dietary intake of fat and fiber; female cases consumed slightly more calcium than controls (574 mg versus 370 mg)	Biological marker study; very small numbers of participants and very limited dietary assessment. No conclusions can be drawn from this study
Clausen, et al., 1991 (Ref. 140)	Clinical Study; Denmark; Colon Cancer	17 patients with colonic adenomas, 17 patients with colon cancer, and 16 healthy controls	Analyzed stool samples for short chain fatty acids; compared molar production velocities of short chain fatty acids from glucose, ispagula, wheat bran, and albumin in fecal incubations; no dietary assessment conducted	Fecal concentrations of total short chain fatty acids and concentrations and ratios of the individual fatty acids did not differ among the two sets of patients and controls. Molar production velocities did not differ except for the ratio of butyrate production to total short chain fatty acid production from fiber was reduced in colon cancer and adenoma patients compared to controls	Authors speculate that the low ratios of colonic butyrate formation combined with low fiber diets may increase the risk of colonic neoplasia. Study provides very limited evidence that high fiber diets may reduce the risk of colon caner, and no information is provided by study as to type of fiber responsible

TABLE 1 -- continued

Study	Study Design	Subjects	Methods	Results	Comments
Yu, et al., 1991 (Ref. 92)	Correlational Study; China and U.S.; Colon, Rectal, Prostate and Breast Cancer	Chinese in Shanghai, Chinese Americans and Americans compared	Incidence rates of cancers of the colon, rectum, female breast, and prostate compared using Connecticut SEER data for White Americans, San Francisco SEER data for Chinese Americans, and data from the cancer registry at the Shanghai Tumor Institute for Shanghai Chinese. Incidence rates were standardized to the 1970 age distribution of the world population Food consumption data compared using FAQ data for U.S. and from two Chinese publication sources for China	Incidence rates for colon cancer among Americans were 4 times the Chinese rates, for rectal cancer among Americans were 2 times the Chinese rates, for prostate cancer among Americans were 26 times Chinese rates, and for postmenopausal breast cancer among Americans were 10 times the Chinese rates. Americans consumed 6 times more meat and eggs, 55 times more milk, slightly more fats and oils, and 3 times more fruit than Chinese	Study was correlational in design; there is no way to determine by this study if the persons who actually have these cancers also eat the putative diet. Study did not control for the very important known risk factors of these cancers such as lifestyle factors, family history, reproductive factors, and endocrine factors
Kesteloot, et al., 1991 (Ref. 93)	Correlational Study; 36 countries; Total Cancer and several types of cancer	Men and Women in 36 countries	Cause-specific cancer mortality rates using 1985 to 1987 WHO data were compared with dairy and lard fat intake obtained from food balance sheets from 1979 to 1981 FAQ data	Highly significant correlations were found between dairy fat plus lard fat intake and mortality from all causes, total cancer, colon, and rectal cancer among both men and women and from lung cancer and prostate cancer for men only and breast cancer for women only. Correlations remained significant when adjusted for total caloric intake or for total caloric intake minus total fat intake	Study was correlational in design; this, the diet of the persons with the diseases studied are not being analyzed directly. Study did not control for the very important known risk factors of these cancers such as lifestyle factors (e.g., smoking), family history, reproductive factors, and endocrine factors. Food balance sheet data from FAQ are approximations of actual consumption and these data are not separated by age and sex
Bravo, et al., 1991 (Ref. 105)	Case-Control; Spain; Prostate Cancer; study conducted 1983 to 1987	90 cases; 180 controls from same hospital matched by age and date of hospital admission; controls were those with diseases other than urologic diseases or a primary tumor	Interview on types and amounts of food usually consumed; obesity measured by body mass index; all cases were histologically confirmed; results were not adjusted for total calories	Risk of prostate cancer was increased by a diet rick in animal fats: RR=2.6 (1.3-5.0) Diets rich in vegetable fats, and vitamins A and C deficiencies were not associated with increased risk of prostatic cancer. Meat consumption was associated with increased risk: RR=2.3 (1.2-4.4) but different types of meat were not significantly associated with increased risk. No risk associated with obesity	Study demonstrates an increased risk of prostate cancer with diets rich in animal fats and with meat consumption. Results were not adjusted for total calories which severely limits the validity of the results. Hospital controls used, some with gastrointestinal diseases, and usual diet was assessed so that disease may have affected diet

TABLE 1--continued

Study	Study Design	Subjects	Methods	Results	Comments
West, et al., 1991 (Ref. 106)	Case-Control; Utah; Prostate Cancer; Study conducted 1984 to 1985	358 incident cases (179 aged 45 to 67 and 179 aged 68 to 74); 679 population-based controls (387 aged 45 to 67 and 292 aged 68 to 74), matched by county of residence	Interview using dietary questionnaire containing 183 foods; cases' diet assessed for 3-year period prior to diagnosis or prior to symptoms; controls' diet assessed 3 year prior to interview; all cases histologically confirmed; interviewers not blinded to case or control status of respondent. Results were adjusted for total calories. Interaction and confounding between dietary variables and demographic and lifestyle factors were assessed but none found; therefore, authors reported only crude relative risks	No associations between dietary variables and prostate cancer found for men 45 to 67 years of age, either for all tumors combined or when subdivided by tumor aggressiveness. Males aged 68 to 74: For all tumors: Total Fat RR=1.7 (1.0-3.1) Protein RR=1.7 (1.0-2.9) For aggressive tumors: Total Calories RR=2.5 (1.0-6.5) Total Fat RR=2.9 (1.0-8.4) MUFA RR=3.6 (1.3-9.7) PUFA RR=2.7 (1.1-6.8) No dose-response seen; cholesterol not associated with prostate cancer risk for either age group	Study demonstrates that dietary fat is associated with prostate cancer risk among older men. Bias may have been introduced due to low participation rates: 77% of eligible cases and 77% of eligible controls participated. Interviewers were not blinded as to case or control status of respondent; this may have introduced bias if the interviewers were aware of the association between dietary factors and prostate cancer

TABLE 2
Lipids and Cancer: Animal Studies

Study	Objectives/ Tumor Types	Experimental Animals	Methods	Results	Comments
Cohen et al., 1991 (Ref. 113)	Tested effects of fats and fiber in the N-nitromethylurea-induced rat mammary tumor model	Virgin female F-344 rats 5-day old 30/groups	Diet: varied in fat and fiber I 23.5% CO II 23.5% CO plus 10% fiber III 5% CO IV 5% CO plus 10% fiber The fiber was soft white wheat bran. Base diet was AIN-76A Rats received intravenous N-nitrosomethyleurea (NMU) and fed diets for 15 weeks Tumor incidence and development measured. Blood levels of 17B-estradiol and progesterone also measured	5% CO diet sign reduced incidence (63 versus 90%) and multiplicity (1.1 versus 2.5 tumors per rat) and significance prolonged latency period compared to 23.5% CO diet Fiber significance reduced incidence and multiplicity of tumors in the 23.5% CO group but not in the 5% CO group No difference in hormone levels	Nonisocaloric diets used; food consumption not reported; significantly decreased body weight in the low fat, compared to other groups
Gonzalez et al., 1991 (Ref. 114)	To measure affects of different amounts and types of fat on growth of human breast carcinoma in athymic nude mice	Athymic nude mice Female 5 to 13 weeks old	Diet: I 5% CO, 3.87 kcal/g II 20% CO, 4.55 kcal/g III 20% butter, 4.55 kcal/g IV 19% BT + 1% CO, 4.55 kcal/g V 19% FO (MO) + 1%, 4.55 kcal/g linoleic acid level (wt %) I 2.8 II 11.2 III 0.36 IV 0.9 V 0.75 After tumor transplantation, mice were fed the diets for 6 to 8 weeks. Tumor growth (number and volume of carcinoma) measured as well as lipid peroxidation in carcinoma Human breast cancer cell lines, MCF-7 and MDA-MB231, were used	Higher tumor volume in the high CO group (V) than low CO group (I); significant in the MDA-MB23 cell line transplanted mice. (0.4-4 cm3 versus o.2-3, 4 cm3, II versus I) Among high fat groups (II-V), high CO significantly raised and FO significantly lowered tumor volume Tumor volume was intermediate in the BT and butter group MCF-7 carcinoma MDA-MB231 carcinoma mean carcinoma volume (cm3) (A) (B) I 3.4 0.5 0.2 II 4.0 1.5 0.4 III 2.4 1.2 0.1 IV 2.4 0.8 V 0.2 0.6 0.0 Significance: I II III IV versus II I versus II II versus V I versus III II versus V II vs V V vs V	Diets III, IV, and V did not provide adequate linoleic acid for tumor growth The carcinoma cell line MDA-MB23, but not the MCF-7, was estrogen-dependent, and mice in this group was provided with exogenous estrogen in the drinking water; biologic plausibility to extrapolate the result to human is questioned

TABLE 2-- continued

Study	Objectives/ Tumor Types	Experimental Animals	Methods	Results	Comments
Zhu et al., 1991 (Ref. 115)	To measure effects of dietary calorie restriction and fat reduction on growth of mammary carcinoma in rats	Female Sprague-Dawley rats 50-day old 19 to 23/groups	Diet: calorie restriction versus fat I 50kal/day, 45 energy % fat II 35 kcal/day, 45 energy % fat III 50 kcal/day, 25 energy % fat IV 35 kcal/day, 25 energy % Diet I & II III & IV (wt%) PO 16.28 7.8 lard 3.04 1.46 SSO 2.39 1.14 Rats were injected with methylnitrosourea (MNU) and fed Diet I until tumor size was approximately 1 cm3 then fed with the experimental diets for 10 ± 2 weeks. Tumor development and liver glutathione measured	No difference in tumor number and weight between diets I and III, and II and IV 30% caloric reduction significantly reduced tumor yield (I versus II, and III versus IV)	Linoleic acid in diets III and IV may not have been adequate for tumor growth: therefore, comparisons between I and III or II and IV are not valid to test the effect of total fat
Buckman et al., 1990 (Ref. 123)	To measure whether oleate influence the linoleate-enhanced metastasis of murine mammary tumor	Weanling Female SALB/cAnN mice 12/groups	Diet: 20 wt% total fat I II III IV (wt%) SO 15.5 15.5 2.6 2.6 Triolein 0 4.5 11.5 0 CCO 4.5 0 5.9 17.4 18:2n-6/oil 61 .5 15.5 13.5% 18:2n-6/diet 12.2 12.3 .1 2.7% 18:1n-9/oil 10.5 24.5 47 12 Spontaneous tumor cell line (4526 murine mammary tumor cell line) was injected into mammary fat pad of mice and metastasis to lung, kidney, and liver measured	No difference in latency period, incidence, or yield of tumors among groups Most metastasis found in lung, some in lover, none in kidney Lung metastasis was significantly higher in the low linoleic acid to low oleic acid group (iv) compared to the other three groups (10, 62, 78, & 90 nodules: low linoleic to low oleic, low linoleic to high linoleic, high linoleic to moderate oleic, & high linoleic to low oleic, respectively No difference in liver metastasis among groups	Tumor cells grown in vitro were used; ability to extrapolate to humans is limited The effect of total fat not tested The effect of oleic acid not consistent Diets provided adequate linoleic acid and were isocaloric
Khoo et al., 1990 (Ref. 117)	To test the anticancer effect of stearic acid in transplanted mammary tumorigenesis in rats	Female F344 rats 4 to 6-week old 30/groups	Diet: Control powdered diet (fat content not reported) and the control diet plus 20% stearic acid by weight Rats were fed the diets for 6 weeks before and 25 days after tumor implantation. Mammary tumor was induced in the rats by nitrosomethylurea and maintained in passage. The 8th passage cells were implanted in the flank of rats	Dietary stearic acid did not significantly affect the growth (size or weight) of transplanted tumor. Dietary stearic acid did not affect FA composition in tissues	Composition or level of dietary fat not provided: adequacy of linoleic acid cannot be judged. If the control diet was common chow or fat free diet both diets contained insufficient linoleic acid for tumor growth

TABLE 2-- continued

Study	Objectives/ Tumor Types	Experimental Animals	Methods	Results	Comments
Aksoy et al., 1990 (Ref. 116)	To identify effects of different levels of dietary fat on MNU-induced rat mammary carcinogenesis	Female Sprague-Dawley rats 5- day-old 90/3 groups	Diet g/100g I II III . PO 3 7.8 16.3 lard 0.56 1.46 3.04 SSO 0.44 1.14 2.39 Total fat 12 25 45 (energy %) Rats were fed experimental diets for 6 months and methylnitrosourea (MNU) -induced tumor development and plasma lipids measured	No difference in tumor incidence, or yield, or in mortality among groups	Diet I and II may not have provided adequate linoleic acid for mammary tumor growth Nonisocaloric diets used; however, rats consumed the same amount of calories and body weights were not different among groups
Lasekan et al., 1990 (Ref. 124)	To compare effects of safflower and olive oils on DMBA-induced mammary tumorigenesis	Female Weanling Sprague-Dawley rats 25/groups	Diet: 20 wt% fat High linoleic acid SO: SL diet High oleic acid SO: SO diet Olive oil: OO diet OO diet w/linoleic acid supplementation : OL diet Linoleic content (wt%) . SL 14.6 SO 3.4 OO 1.1 OL 3.4 Rats were fed the diets for 16 weeks, and 7, 12-DMBA-induced tumorigenesis measured	No difference in lag time or incidence OO diet significantly lowerd tumor yield compared to SO or OL diets Linoleic supplementation of the OO diet (makes the OL diet) significantly enhanced the yield; no difference in yield between OO and OL diets Tumors Diet /rat statistics SL 3.5 a,b SO 5.0 a OO 3.0 b OL 5.1 a (statistical: different letters in the statistics column show a significant difference)	Isocaloric diets; no difference in body weight or food intakes among groups OO diet which was limited in linoleic acid content resulted in a significantly lower tumor yield. This result was abolished by supplemental linoleic acid; the results support a linoleic acid requirement of about 4% by weight for induced mammary tumor genesis in rodents
Hirose et al., 1990 (Ref. 125)	The effects of diets supplemented with perilla oil (n-3 linoleic rich) and soybean and safflower oils (n-6, linoleic-rich) on DMBA-induced mammary and colon carcinogenesis	Female SD rate 5-week old 10/groups	Diet: 10% perilla oil 10% SBO 10% SO SO SBO perilla oil 18:2n-6 74 52.6 15.9% 20:4n-6 - 0.3 0.1% 18:3n-3 0.1 .7 13.7 Rats were fed the diets for 33 weeks after the injection of initiator (7, 12-DMBA) and promotor (1, 2-dimethylhydrazine, DMH). Incidence and development of tumor measured	Mammary Perilla oil significantly lowered tumor yield compared to SBO or SO (4.4, 6.5, 5.7, tumors per rat: perilla oil, SBO, or SO, respectively) No difference in yield between SBO and SO. No difference in incidence among groups Colon perilla oil significantly lowered tumor incidence compared to SOB or SO (4, 9, or 9% incidence); perilla oil, incidence between SO and SBO No difference in yield among groups	Parilla oil may not have provided adequate linoleic acid for tumor growth

TABLE 2-- continued

Study	Objectives/ Tumor Types	Experimental Animals	Methods	Results	Comments
Kumaki and Noguchi, 1990 (Ref. 112)	To measure the influence of high dietary fat on malignant intensity and hormone receptors of DMBA-induced mammary carcinoma	Female 50-day old Virgin Sprague-Dawley rats 36 to 38/groups	Diet I 0.5% CO II 20% CO Rats were fed diets for 20 weeks, and 7, 12-DMBA-induced incidence and growth of tumor tested. DNA index, S-phase fraction and hormonal receptors for estrogen, progesterone were also tested.	High fat diet significantly elevated incidence (86 versus 46%), size (13.9 versus 7.9 mm diameter) and shortened latency period (10.0 versus 13.9 weeks) compared to low fat diet No difference in hormonal receptors	Low fat diet did not provide adequate linoleic acid for growth of tumor or the animal Nonisocaloric diets used; however, body weight was not different between groups
Wan et al., 1991 (Ref. 136)	To compare effects of fish oil on protein synthesis and catabolism of mammary tumor grown in the peritoneal cavity	Female Pathogen-free F344 rats 60 ± 5 g	Diet I 19.5% MO + 0.5% SO II 20% SO Rats were fed the diets for 5 weeks, inoculated with mammary ascites tumor cells (13762 MAT) and fed the diets for 2 weeks Tumor size, protein turnover, and plasma lipids were measured	No difference in tumor weight between groups Signficant decrease in tumor volume by FO feeding Significantly increased w-6 FA and significantly reduced w-3 FA in plasma lipids No difference in protein turnover rate in tumor or in whole body between two diet groups Significantly prolonged liver protein turnover in FO group compared to SO group	Rats were pair-fed and diets were isocaloric FO diet did not provide adequate linoleic acid for tumor growth Additional antioxidants (vitamin E and tertiary butylhydroquinone) were used
Takata et al., 1990 (Ref. 137)	To measure the effects of two different types of unsaturated FA on NMU-induced mammary carcinogenesis	Female Sprague-Dawley rats 6-week old 10 (control) and 30 (test)/groups	Diet: 5 wt% I) 4.7 wt% EPA plus 0.3 wt % linoleate II) 5 wt% linoleate Rats fed the diets for 20 weeks, N-nitrose-N-methylurea (NMU) -induced tumor incidence and yield tested	Significantly lower tumor incidence and yield (weight or number) in the EPA group EPA diet reduced prostaglandins (PGE2, TXB2, and 6-keto PGF1) in tumor, compared to linoleic acid diet	EPA diet did not provide adequate linoleic acid for tumor growth or animal growth. Unrealistically low total fat

TABLE 2--continued

Study	Objectives/ Tumor Types	Experimental Animals	Methods	Results	Comments
Bunce and Abou-El-Ela, 1990 (Ref. 135)	To measure eicosanoid sythesis and ornithine decarboxylase activity in mammary tumors in rats fed varying levels of n-3 and n-6 fatty acids	Virgina female Sprague-Dawley rats 50-day old 25/groups	Diet CO PO BCO BO MO (wt% per diet) I 20 - - - - II - 20 - - - III - - 20 - - IV - - - 20 - V 15 - - - 5 VI 10 - - - 10 VII 5 - - - 15 VIII - - - 10 n-6FA U-3FA . (% per diet) I 12.1 0 II 16.8 0 III 11.3 .3 IV 12.6 0 V 9.3 1.4 VI 6.5 2.9 VII 3.6 1.2 VIII 6.7 2.9 Rats were administered i.g. 7, 12-DMBA and fed diets for 112 days Incidence and multiplicity of the tumor examined. Prostaglandin (PGE, LTB4, and LTC4) synthesis and ornithine decarboxylase (ODC) activity also tested	Incidence of adenocarcinoma: significantly lower in groups III, VI, and VII then groups II, IV, and VIII; n-3 FA level or n-6 FA/n-3FA ratio did not consistently affect the incidence Tumor yield (number/rat) was significantly lower in group II than groups IV and III; n-3 or n-6 FA did not consistently effect the yield No difference in latency period among groups	Diets provided adequate linoleic acid for growth of the animal as well as the tumor
O'Neill et al., 1991 (Ref. 142)	To measure modulation of colonic nuclear aberrations and micorcapsule-trapped gastro-intestinal metabolism in benzopyrene treated mice consuming human diets	Male c57/B6 mice 6-week old 36/6 groups	Diet: I & II III IV V Fat 15 45 15 energy% Protein 2.7 .1 2.7 2.7 wt% Fiber 2.1 2.1 2.1 5.6 wt% Fiber: nonstarch polysaccharide. Protein: beef protein Mice were fed the diets for 3 weeks and received benz(a)pyrene by gavage. Colonic nuclear aberration was examined histologically and by using HPLC	Benz(a)pyrene increased the nuclear aberrations by 8-fold The extent of benz(a)pyrene-induced nuclear aberrations was decreased to 2-to 3-fold by increased fiber or fat in the diet	FA composition in the diet not reported and the adequacy of dietary EFA is not known Nuclear aberration, not cancer development, was measured

TABLE 2--continued

Study	Objectives/ Tumor Types	Experimental Animals	Methods	Results	Comments
Nutter et al., 1990 (Ref. 126)	To measure effects of dietary fat and protein tumor development and immune responses	Weaning, BALB/c mice Male 280/10 groups	Diet: varied in fat and protein Total fat: 5 wt% Total protein: 11 wt% Diet CO BT Casein NFDM Lyophilized beef (wt%) I 4 7 31.5 II 2.9 - 13 4 III 4 7 31.5 IV 5 12.1 - V 5 20 Diet V was AIN-76A diet Mice were fed until 51 weeks of age. Incidents and development of the dimethylhydrazine (DMH) - induced tumor as well as immune response was measured. DMH was injected subcutaneously for 10 weeks	CO plus NFDM diet significantly elevated tumor yield compared to other groups Number of tumors per tumor-bearing mouse I 12.3 II 2.6 III 3.2 IV 5.3 V 4.4	Total fat levels in the diets do not match between the levels described in the Methods and the levels found in authors' Table 1 BT diets may not have provided adequate linoleic acid for growth of tumor The effect of CO on tumor yield was not consistent
Nicholson et al., 1990 (Ref. 118)	To measure the influence of dietary fats (beef suet rich in saturated fat and corn oil rich in linoleic acid) on colorectal carcinogenesis	Wistar rats Male 5-week old 57/groups	Diet 5% beef suet (BS) 20% beef suet 5% corn oil 20% corn oil FA composition in diet linoleic arachidonic (%) 5%bs 12.7 2.3 20%bs 5.4 0.5 5%CO 42.4 0.9 20%CO 48.6 0.5 Animals were fed the diets for 16 weeks before and 6 weeks after azoxymethane, which was injected once a week for 6 weeks. Yield (%) of adenoma and carcinoma measured. Mucosal and tumor FA composition also measured	No difference in adenoma yields The BS diets produced significantly more carcinoma than CO diets (1 versus 12 carcinoma, 5% CO versus 5% BS); 2 versus 28 carcinoma, 20% CO versus 20% BS) 20% BS produced significantly more carcinoma than 5% BS (28 versus 12 carcinoma; 20% BS versus 5% BS); difference for CO was nonsignificant (2 versus carcinoma; 20% CO versus 5% CO) Arachidonic acid was higher in tumors than in colonic mucosa regardless of fat source N-6 FA may suppress the development of colorectal carcinoma. The data also suggest an association of prostaglandins with colorectal tumor development	Nonisocaloric diets used; however, no difference in food consumptioni or in body weight BS diets, which may have provided insufficient linoleic acid for tumor growth, had elevated tumorigenesis. The results suggest linoleic acid requirements may be different for different tumor sites

TABLE 2--continued

Study	Objectives/ Tumor Types	Experimental Animals	Methods	Results	Comments
Behling et al., 1990 (Ref. 119)	To measure the effect of varying levels of dietary calcium and butterfat on cecal enzyme activity and development of DMH-initiated colon tumors in rats	Weaning male Sprague-Dawley rats 112/4 groups	Diet: I 1% CO + 5% butter fat + 2.5 g Ca/kg II 1% CO + 5% butter fat +10g Ca/kg III 1% CO + 20% butter fat +2.5 g Ca/kg IV % CO + 20% butter fat +10g Ca/kg Diets fed for 2 weeks before and 31 to 34 weeks after the injection of DMH Incidence and development of intestinal tumor examined. Enzymic activity in cecum and lipid extraction in feces also measured	No difference in tumor yield among groups High Ca increased fecal lipids	All diets may not have provided adequate linoleic acid for tumor growth The study focused on the effect of Ca, not lipids
Lindner, 1991 (Ref. 129)	The effect of n-3 PUFA on colon cancer in mice. Effects of high fat and high cholesterol free diets in mice	Swiss-Webster mice 6 to 7-week old 174/4 goups	Diet BT SO FO Low fat MaxEPA (wt%) Tot fat 19.2 19.2 19.2 3.5 n-6FA 3.5 14.3 .8 2.0 n-3FA 0 4.4 0 MUFA 7.5 2.8 5.2 1.0 Mice were fed the diets for 4 weeks, received 1.2-DMH for 11 weeks Tumor development in the intestinal tract (from esophagus to rectum) was examined. Plasma lipids also examined	Significantly higher body weight in BT groups than low fat or FO groups and in SO group than low fat group No difference in mortality Higher colon tumor incidence in the BT groups; significance between BT and FO groups. Tumor incidence in other sites (kidney, liver, skin, and scrotum) was lower in the BT group (significance between BT and low fat group) Colon tumor No difference in adenoma yield. Significantly higher adenocarcinoma in BT group than SO or FO group. FO was protective; adenocarcinoma yield was the lowest in the FO group; significance between FO and BT group. (Mean tumors per animal 1,23, 0.47 and 0.23; BT, SO and FO) Oleic acid and MUFA content (%) in the plasma or in colon mucosa were linearly correlated with tumor yield; dietary MUFA was reflected in plasma but not in colon mucosa n6 PUFA or linoleic acid was not associated w/tumor yield; dietary level of linoleic acid was reflected in plasma and colon mucosa n-3 PUFA and EPA level in plasma or colon mucosa was significantly, negatively correlated w/tumor production	The FO (MaxEPA) may have a protective role in DMG-induced colon tumorigenesis in Swiss-Webster mice The effect of carcinogen, DMH, was different among sites of tumorigenesis and the findings cannot be generalized to cancer sites beyond colon

TABLE 2--continued

Study	Objectives/ Tumor Types	Experimental Animals	Methods	Results	Comments
Smith et al., 1990 (Ref. 121)	The effects of high fat diet and CCK-receptor antagonist on growth of human pancreatic tumor cells in nude mice	Male 5 to 6-week old Athymic nude mice 15/groups	Diet 4.3% fat chow diet 20.3% fat diet: 4.3% fat in the chow + 16% CO Mice were injected w/SW-1990 human pancreatic adenocarcinoma cell line and fed the diets for 23 days. The effects of dietary fat and CCK-receptor antagonist L364718 on pancreatic tumor development examined	Among L364718 untreated animals, the high fat diet significantly increased tumor volume and protein content in tumor, compared to the chow diet L364718 significantly decreased tumor yield; endogenous CCK (cholecystokinin) may promote the growth of pancreatic tumor in mice	FA composition of chow diet not reported. The chow diet may have provided insufficient linoleic acid for tumor growth Tumor cells, assayed in vitro, were used
Longnecker et al., 1990 (Ref. 122)	To measure the development of pancreatic neoplasms in elastase-1-simian virus transgenic mice	Elastase 1 simian virus transgenic mice Strain Tg (Ela-1, SV4oE) Bri1 18 Female and male 11 to 23/groups	Diet chow: 5-6% fat AIN-76A: 5% CO Hi-fat: 20% CO Diets were fed for 22 to 23 weeks. At autopsy, incidence and multiplicity of the tumor examined	Incidence of exocrine carcinoma: significantly reduced by chow diet No difference between AIN-76A and high fat diets Incidence of islet cell tumor: no difference among groups	Genetically transformed, transgenic mice were used: extrapolation of results to human is questionable Extremely low total fat Linoleic acid content of the chow diet is not known
Oth et al., 1990 (Ref. 131)	The modulation of CD4 expression in lymphoma transplanted to mice fed n-3 PUFA	Adult AKR mice	Diet No fat, basal diet I 1% FO II 1% BT III 4% FO IV 4% BT V 6% FO VI 6% BT VII 8% FO VIII 8% BT IX 16% FO X 16% BT FO: 23 7% SFA, 30.3% n-3 FA, 1.3% linoleic acid Experimental diets were fed for 6 weeks before and 2 weeks after tumor xenograft by intraperitoneal transplantation. RDM-4 tumors in ascites were harvested and examined. Cell surface markers tested as well	Considerably (statistics not tested) faster tumor growth in the FO-fed donor than in the BT- or no-fat-fed donors Significantly reduced CD4 cell surface marker in the FO groups than BT groups; other markers such as CD8, H2K, Thy-1, and LFA-1 markers were not affected No effects of total fat	Both BT and FO Diets may not have provided adequate linoleic acid for tumor growth

TABLE 2--continued

Study	Objectives/ Tumor Types	Experimental Animals	Methods	Results	Comments
Ayachi et al., 1990 (Ref. 130)	To test the suspectability of lymphoma cells to lymphokine-activated killer (LAK) cells in mice fed high fat, fish oil diets	AKR mice	Diet 4% FO 4% HBT 8% FO 8% HBT 16% FO 16% HBT n-6 FA content HBT: 0.1 wt% FO: 2.2 wt% Mice were fed the diets for 6 weeks before and 12 to 15 weeks after the intraperitoneal graft of RDM4 lymphoma cells	Tumor yield was significantly greater in the FO group than in the HBT group FO increased resistance of lymphoma cells to lysis by lymphokine activated killer cells in vitro No effect of total fat	Experimental diets may not have provided adequate linoleic for growth of tumor and the mice Total fat in 4 to 8% fat diets was unrealistically low Due to the limitation in dietary linoleic acid, results are not useful for evaluating the effect of fat
Locniskar et al., 1991 (Ref. 127)	To compare the effects of fish, coconut, and corn oils on skin tumor promotion by benzoyl peroxide in mice	Weanling Female SENCAR mice 30/groups	Diet: 10% total fat CCO / CO / MO (wt%) A 8.5 / 1.5 / - B 7.5 / 1.5 / 1.0 C 4.5 / 1.5 / 4.0 D - / 1.5 / 8.5 E - / 10.0 / - Mice were fed 5% CO diet for 3 weeks treated with an initiator, 7,12-DMBA, fed 10% CO diet for 52 weeks, and treated with benzoylperoxide (promoter) biweekly. Latency, incidence, and Ornithine decarboxylase (ODC), vascular permeability, and hyperplasia of the dorsal skin were also examined	Papilloma Significantly higher cumulative tumor probability in Diet A than Diet B, D, and E, but not C. Papilloma yield was significantly greater in Diet A or Diet C than Diet B, D, and E (Tumor probability was mathematically calculated) Carcinoma Significantly higher tumor incidence and cumulative tumor probability in Diet A and Diet E: no difference in incidence among Diet B, C and D. Carcinoma yield not reported No difference in ODC activities or vascular permeability among groups. Significantly greater hyperplasia in Diets B and C than Diets A, D, and E	Low total fat in the diets Except Diet E, all the diets many have provided inadequate linoleic acid for tumor growth. Diet E with adequate linoleic acid resulted in the longest latency period, lowest tumor incidence, and least tumor yield The results suggest that growth of skin tumor may not require 4% dietary linoleic acid and that the effect of dietary fat on tumorigenesis is site-specific In the 10% fat diet, high PUFA in the diet showed a protective effect and high SFA in the diet showed a promoting effect while the effect of n3 FA-rich diet was intermediate

TABLE 2--continued

Study	Objectives/ Tumor Types	Experimental Animals	Methods	Results	Comments
Layton et al., 1991 (Ref. 128)	To measure effects of type of dietary fat on phorbol-ester-elicited tumor promotion in mouse skin	Female SENCAR and DBA/2 mice 4-week old 30 mice/groups	Diet Initiation period: 5 wt% total fat CO CCO C18:2n-6 all 1.7% 3.3% 1.0% promotion period: 15 wt% total fat CO CCO C18:2n-6 I 1.0 14 0.8 II 3.6 11.4 2.2 III 6.0 9.0 3.5 IV 7.9 7.1 4.5 V 9.9 5.1 5.6 VI 12.5 2.5 7.0 VII 15. 0. 8.4 7,12-DMBA initiated and 12-0-tetradecancyl-phorbol-13-Acetate(TPA)-promoted papilloma development determined	Papilloma incidence: No difference among groups Signficant inverse correlation between CO level and papilloma yield (r= 0.92), 5.4 tumors versus 11.7 tumors per mouse; 15% CO versus 10% CO in SENCAR mice). Similar results found in DBA/2 mice The results suggest that increasing dietary CO or decreasing SFA may suppress skin tumor in mice TPA elevated epidermal PGE2 in all diet groups: the extent was negatively correlated with dietary CO	The effect of total fat not tested Low PUFA/high SFA diet significantly enhanced DMBA- and TPA-induced skin tumor-yield than high PUFA/low SFA diet; this result is inconsistent with the 4 to 5 wt% linoleic acid requirement found in mammary and pancreatic tumorigenesis in rats. The results suggest that the effect of dietary fat may be specific for tumor sites
Jenski et al., 1991 (Ref. 143)	To measure the release of cytosolic components from leukemic cells inoculated into mice fed menhaden oil or coconut oil	BALB/c mice Female and male 4/groups	Diet I 10% MO + basal chow diet II 10% CCO + basal chow diet III 20% MO + ICN fat free diet IV 20% HCO + ICN fat free diet Mice were fed the diets for 5 weeks, inoculated intraperitoneally with murine leukemia cell line T27A, and fed the diets for 1 week Membrane permeability of tumor cells was examined in vitro by examining 51CR release from the cells	Increased membrane permeability in the MO groups The enhanced membrane permeability was correlated with n-3 FA (DHA and EPA) incorporated into the tumor cells	Diets may not have provided adequate linoleic acid for optimal tumor growth Tumor development not measured. Eradication of tumor was measured indirectly by measuring cell permeability intravenously

TABLE 2--continued

Study	Objectives/ Tumor Types	Experimental Animals	Methods	Results	Comments
Hietanen et al., 1990 (Ref. 120)	To test the modulation of dietary fat, varied in the quality and the quantity, of the oxidative stress and chemical-induced liver tumors in rats	Male wistar rats 4-week old	Diet SSO land (wt%) I 2 0 II 1 III 12.5 0 IV 1 11.5 V 25 0 VI 1 24 Rats were fed for 10 weeks prior and 33 weeks after the N-nitrosodimethylamine (NDMA) administration by gavage Tumor prevalence as well as plasma lipids and lipid peroxidation were measured	High-PUFA diet (25% SSO) significantly elevated tumor incidence compared to low PUFA diet (2% SSO), (80% versus 42%; 25% SSO versus 2% SSO) Fat type did not significantly affect tumor incidence High-PUFA diets (25% or 12.5% SSO) reduced plasma cholesterol and TG concentration compared to high SFA diets (25% or 12.5% lard diets)	Except 12.5% SSO and 25% SSO diets, all diets may have provided inadequate linoleic acid for tumor growth Nonisocaloric diets used: body weight changes were not significantly different among groups Due to limitations in study design, the effect of dietary fat on cancer development cannot be evaluated

Abbreviations
BCO: black currant seed oil
BO: borage oil
BS: beef suet
BT: beef tallow
Ca: calcium
CO: corn oil
CCO: coconut oil
DMBA: 7, 12-dimethylbenzanthracene
DMH: 1, 2-dimethylhydrazine
EPA: eicosapentaenoic acid
EFA: essential fatty acid
FO: fish oil
FA: fatty acid
HBT: hydrogenated beef tallow
HCO: hydrogenated corn oil
i.p.: intraperitoneal
MO: menhaden oil
MUFA: monounsaturated fatty acid
NFDM: nonfat dried milk
PO: palm oil
PUFA: polyunsaturated fatty acid
PrO: primrose oil
RR: relative risk
SSO: sunflower seed oil
SFA: saturated fatty acid
SBO: soybean oil
SO: safflower oil

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