Nutrition and Cancer
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/hnuc20

Isomeric fatty acids and tumorigenesis: A commentary on recent work

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Published online: 04 Aug 2009.

To cite this article: J. Edward Hunter , Clement Ip & Edward J. Hollenbach (1985) Isomeric fatty acids and tumorigenesis: A commentary on recent work, Nutrition and Cancer, 7:4, 199-209, DOI: 10.1080/01635588509513856

To link to this article: http://dx.doi.org/10.1080/01635588509513856

Isomeric Fatty Acids and Tumorigenesis: A Commentary on Recent Work

J. Edward Hunter, Clement Ip, and Edward J. Hollenbach

Abstract

This article critically reviews the existing, although limited, literature concerning trans *fatty acids and tumorigenesis. Neither epidemiological nor experimental studies published to date have demonstrated any valid association between* trans *fatty acid ingestion and tumorigenesis. A recent study showed that under controlled conditions, a fat with a high content of* trans *fatty acids did not promote the development of mammary tumors induced in rats by 7,12-dimethylbenz[a]anthracene to any greater extent than did a comparable fat with a high content of* cis *fatty acids. In addition, in this study a high* trans *fat was less tumor promoting than was a blend of fats that simulated the dietary fat composition of the United States and had a lower level of* trans *fatty acids. Another study using comparable* cis *and* trans *fats demonstrated that the high* trans *fat did not affect the growth and metastasis of implanted mammary tumors in mice relative to the high* cis *fat. Also, two recent studies reported no significant difference in the development of induced colon tumors in rats fed diets high in* cis *or* trans *fatty acids. The results of these and other studies are consistent with the conclusion that* trans *fatty acids are not uniquely related to tumor development.*

(Nutr Cancer 7, 199–209, 1985)

Introduction

The term "isomeric fatty acid" is commonly used in referring to unsaturated fatty acids in which some of the double bonds have been rearranged from the *cis* to the *trans* configuration or in which *cis* or *trans* double bonds have migrated to new positions in the fatty acid chain. Isomeric fatty acids are formed during partial hydrogenation of fats and oils. This process is used to impart desirable stability and physical properties to fats and oils so they can be used in such food products as salad and cooking oils, shortenings, margarines, and specialty fats. In addition, small amounts of isomeric fatty acids occur naturally in foods such as milk, butter, and tallow as a result of microbial biohydrogenation in ruminants (1,2).

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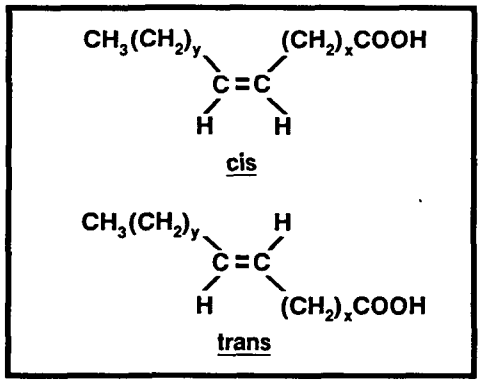

Figure 1. *Cis* and *trans* isomers of a monoenoic acid. [From Beare-Rogers (Ref. 3).]

The widespread usage of partially hydrogenated vegetable oil in the United States during the past 60 to 70 years has caused some individuals to raise concerns about possible adverse consequences of consuming the isomeric fatty acids present in these products. Previous studies on nutritional and biological effects of isomeric fatty acids have focused primarily on whether or not *trans* fatty acids[1] may play a role in the development of atherosclerosis. In contrast, relatively few investigators have studied isomeric fatty acids with respect to cancer development. This paper critically reviews the existing, although limited, literature concerning *trans* acids and tumorigenesis and points out a novel approach whereby the effects of *trans* acids on tumor development may be studied under controlled conditions. This procedure involves comparing the effects of a fat high in *trans* fatty acids to those of a fat high in *cis* fatty acids, which has been specially blended to have a fatty acid composition very similar to that of the *trans* fat.

Nature and the Occurrence of *Trans* Fatty Acids

Unsaturated fatty acids in foods can exist in either the *cis* or *trans* configuration (Figure 1). In the *cis* form, the hydrogen atoms are on the same side of the double bond, whereas in the *trans* form, they are on the opposite. *Trans* fatty acids have higher melting points than do the corresponding *cis* fatty acids; this accounts, in part, for the firmer consistency of a partially hydrogenated fat compared with an unhydrogenated fat. The orientation of a *trans* double bond is associated with the straightening of the hydrocarbon chain; thus, the structure more closely resembles a saturated straight-chain molecule (Figure 2).

Because most of the unsaturated fatty acids in vegetable oils consist of oleic and linoleic acid with some linolenic acid, the majority of *trans* acids generated during hydrogenation have a chain length of 18 carbon atoms. The predominant C_{18} *cis* and *trans* fatty acids are monoenes (isomers of octadecenoic acid), with their double bonds at carbons 6 to 14 from the carboxyl end. Among *cis* isomers, double bonds at positions 9 and 12 dominate. Among *trans* isomers, double bonds at positions 9 through 11 are the most common. Smaller amounts of geometric and/or positional isomers of dienoic acids also are formed, mainly *cis, trans* and *trans, cis,* and minor amounts of *trans, trans* octadecadienoic acid isomers. The levels and the types of *cis* and *trans* and the positional isomers present in partially hydrogenated fats depend on the hydrogenation conditions, such as the temperature and duration of the reaction and the type of catalyst used.

Over the past 60 to 70 years, consumption of partially hydrogenated fats has increased gradually to the level where they now constitute about 44% of the "visible fat" consumed in American diets (4). "Visible fat" refers to fats such as salad and cooking oils, margarine, shortening,

[1]In this paper, we use the term *trans* fatty acids (or simply *trans* acids) to refer to *trans* unsaturated fatty acids.

and butter. Rather broad ranges of total *trans* fatty acids have been reported in various foods. Dutton (5) listed four shortenings ranging from 16.6% to 29.2% *trans* fatty acids and two liquid oils ranging from 4.9% to 12.0% *trans* fatty acids. Carpenter and Slover (6) reported total *trans* levels of ten brands of margarine ranging from 14% to 36%. Beare-Rogers and coworkers (7) found that among 50 brands of margarine, *trans* levels ranged from less than 5% to 45%–50%. Kummerow (8) noted that a selection of stick margarines contained from 25% to 30%, tub margarines 15% to 25%, shortenings 20% to 30%, and salad oils 0% to 15% total *trans* fatty acids. Recently Enig and others (9) reported *trans* monoene levels in 35 food types. Ranges for partially hydrogenated salad and cooking oils were 7% to 9.4%, for shortenings 8.7% to 35%, for tub margarines 6.8% to 18%, and for stick margarines 16% to 31%.

There are currently no reliable data on the consumption of *trans* fat in the United States. However, it is possible to make reasonable estimates. Emken (10) estimated the daily consumption of *trans* 18:1 isomers (the most abundant *trans* isomers in human diets) to be about 7 g/day. This is based on an estimated daily per capita consumption of 34 g of partially hydrogenated soybean oil, having an average total *trans* value of 20%. Using data on market size, market share, and composition of various products made from partially hydrogenated fats and oils, Hunter (11) estimated a per capita availability of *trans* fatty acids of about 7.6 g/day. From another point of view, considering that the composition of unsaturated fatty acids of adipose tissue reflects that of the diet and that a range of 2.0% to 5.8% *trans* fatty acids has been reported in human adipose tissue (12), an adult male consuming his RDA of 2,700 calories/day (13) of a diet providing 38% calories as fat (14) would ingest around 2.3 to 6.6 g of *trans* fatty acids per day. This range is consistent with the estimates of Emken and Hunter. On the other hand, Enig and co-workers (15) estimated a total *trans* fatty acid intake of slightly more than 12 g/person/day. This estimate is not supported by reliable data and appears to be excessive.

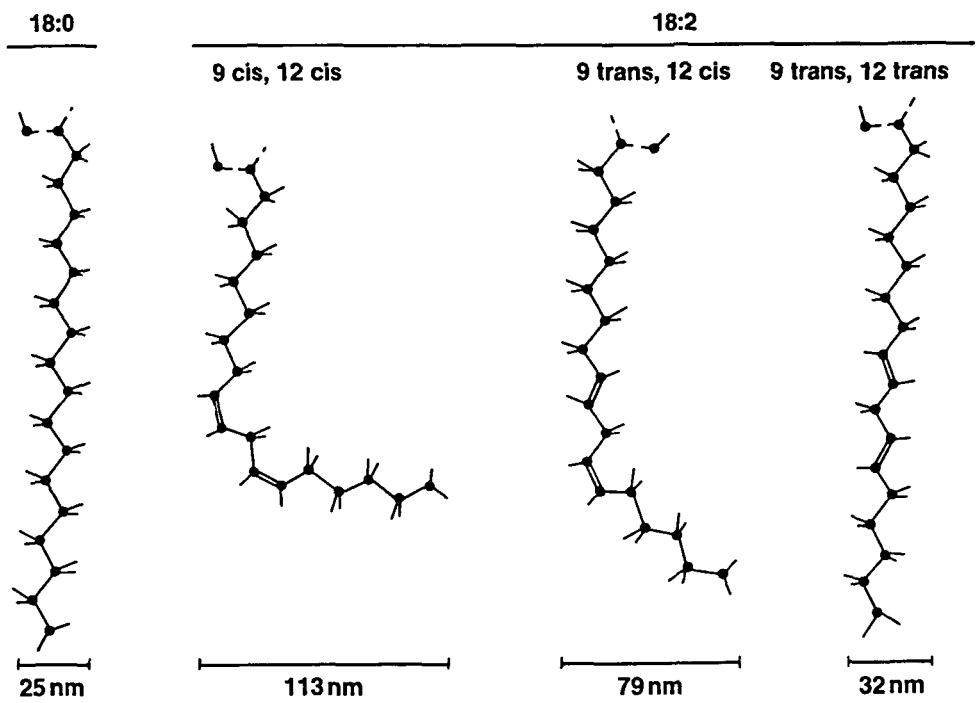

Figure 2. Relative sizes and shapes of stearic acid (18:0) and three isomers of octadecadienoic acid (18:2). [From Beare-Rogers (Ref. 3).]

Nutritional and Biological Effects of *Trans* Fatty Acids

There are numerous reviews and comprehensive studies on the nutritional and biological effects of *trans* fatty acids (3,16–27). Most focused on whether or not *trans* fatty acids play a role in the development of atherosclerosis. In general, these studies show that diets high in *trans* monoene (largely 18:1), but adequate in essential fatty acids, are not uniquely atherogenic. On the other hand, concerns have been raised about the safety of *trans*-9, *trans*-12-octadecadienoic acid which, at high dietary levels, can impair $\triangle 6$ desaturase activity and decrease prostaglandin synthesis in experimental animals (22). However, this *trans, trans* diene is present in only trace amounts in commercially hydrogenated fats (16,28) and in beef fat (29). Therefore, it is only a minor component in fats ingested by humans. Studies in which high levels of partially hydrogenated fats (containing predominantly *trans* monoenes) were fed to animals for long periods of time have demonstrated no overall adverse effects (18–21).

Recent work by Ohlrogge and colleagues (12,30) demonstrated that all *cis* and *trans* octadecenoate positional isomers which are present in partially hydrogenated vegetable oils are incorporated into human tissue lipids. These investigators reported that the turnover rates of the octadecenoate positional isomers evidently are fast enough to prevent any significant accumulation in human tissues of these isomers. Furthermore, neither the *trans*-9, *trans*-12 isomer nor the mixed *trans, cis* or *cis, trans* isomers have been found in heart tissues of patients dying of atherosclerotic or other disease states (31).

In contrast to the extensive literature on isomeric fatty acids in relation to atherosclerosis, relatively few investigators have studied isomeric fatty acids with respect to cancer. Recently, the National Academy of Sciences issued a report consisting of a series of recommendations for research related to dietary components and nutritional factors and cancer incidence (32). One of several recommendations was to determine the role, if any, of *trans* unsaturated fats in the development of tumors. The remainder of this article critically reviews the literature involving the possible relationship between *trans* acids and tumorigenesis and discusses how it may be studied under controlled conditions.

Trans Acids in Relation to Cancer: Epidemiological Study

It is generally agreed that during the past 10 to 20 years there has been increased use of vegetable fats, primarily salad and cooking oils, a significant portion of which are partially hydrogenated. Enig and others (15) reported associations between the increased per capita intake of fat and cancer mortality during a 60-year period, which they believe is explained by the consumption of *trans* fatty acids. These authors found positive correlations between mortality from cancer with total fat and vegetable fat consumption, but they did not with animal fat or with total or individual unsaturated fatty acids in vegetable fats. The positive correlation could be explained by the presence of *trans* acids in vegetable fats, and thus the consumption of *trans* acids was tentatively related to the apparent increased mortality from various cancers.

This work has been severely criticized (33–35). A major criticism was the erroneous conclusion of Enig and co-workers that the increased consumption of vegetable fat (including *trans* fatty acids) is positively correlated with increased total cancer mortality and with increased mortality from breast and colon cancers. On the contrary, American Cancer Society data (36) indicate that age-adjusted mortality rates from breast and colon cancers (and most other forms of cancer) have changed little or even decreased during the last 40 to 50 years. Total cancer mortality has increased because mortality from lung cancer has increased; however, this has been associated with increased cigarette smoking, not with the consumption of fat or other dietary components. Thus, it is not valid to relate *total* cancer mortality to dietary fat. The report of Enig and co-workers was also criticized as being largely a study of correlations and had little independent evidence on mechanisms that might argue for or against inferences of cause-and-effect relationships.

In their reply to this criticism, Enig and co-workers (37) acknowledged that reevaluation of their data indicated no discernible correlation between dietary fat and colon cancer mortality. However, they stated that mortality from "fat-related" cancers—breast, colon, and pancreas—has been increasing slightly. On the other hand, American Cancer Society data (36) indicate that this increase may be explained by an increase in mortality between 1935 and 1965 from pancreatic cancer alone. Pancreatic cancer is much less common and has not been as closely associated with fat intake as have breast or colon cancer. Enig and co-workers also agreed that they had not shown a cause-and-effect relationship between cancer mortality and fat consumption. However, they asserted their belief that processed vegetable fats should be more carefully investigated with respect to cancer incidence and mortality, although they presented no data in support of this suggestion.

Trans Acids in Relation to Cancer: Experimental Studies

A recent study by Awad (38) reported that ingestion of elaidic acid (*trans*-9-18:1) reduced the survival time of mice bearing the Ehrlich ascites tumor. This study involved feeding mice diets that contained either 5% elaidic acid or 5% olive oil for four weeks, injecting them with Ehrlich ascites tumor cells, and then maintaining the animals on these diets until they died. Awad reported that mice fed the elaidic acid diet not only had reduced survival rates compared with mice fed the olive oil diet but also incorporated more thymidine into the DNA of their tumor cells. This, according to Awad, suggested that "*trans* fatty acids may be considered as promoters of tumor DNA synthesis."

Various shortcomings of this work have been pointed out (39). Results from this study are difficult to interpret because Awad (38) compared the feeding of a triglyceride (olive oil) to the feeding of a free fatty acid (elaidic acid); thus it was an incorrectly controlled experiment. A properly controlled experiment would be to compare feeding of olive oil with feeding of elaidic acid in triglyceride form or feeding the controls free oleic acid. In addition, the experimental fats had substantial differences in fatty acid composition and therefore were not directly comparable. The olive oil diet, for example, contained higher levels of both palmitic acid and linoleic acid than did the elaidic acid diet. Thus, Awad could not conclude that the reduced survival times of mice fed the elaidic acid diet were due to elaidic acid exclusively. It would have been equally valid to conclude that the higher levels of palmitic acid or linoleic acid were protective of the animals fed the olive oil diet.

Furthermore, elaidic acid feeding did not significantly increase the weight of the solid tumors. If *trans* acids were really stimulating tumor promotion, as suggested by Awad (38), then the solid tumors in these animals should have been larger than those in the animals fed the olive oil diet. In addition, the feeding of free fatty acids with melting points of around 45°C (the melting point of elaidic acid) should be of concern because the higher melting fats are poorly digested. This problem could have been a possible cause for the growth depression of mice fed the *trans* fat diet, even though they ate 17% more than did the olive oil group.

In addition to the study by Awad (38), a preliminary report by Brown (40) compared the effects of different types of dietary fat, including *trans* fat, in relation to the degree of saturation on the induction of spontaneous and dimethylhydrazine (DMH)-induced tumors in mice. The *trans* fat (35.4% *trans* monoene) was a blend of partially hydrogenated soybean oil, palm stearin, and safflower oil. In general, Brown found that after 17 months there were no significant differences in the development of spontaneous or induced liver and mammary tumors among mice fed fats high in *cis*-monoene, *cis*-diene, or *trans*-monoene. Also, the quantity of dietary fat (5% or 17% by weight, fed isocalorically) did not influence appreciably the incidence of tumors. The unexpected absence of colon tumors in animals given DMH was thought to possibly have been related to the presence of cellulose fiber and the absence of cholesterol in the diets. Both of these factors have been reported to influence colon carcinogenesis. Brown has com-

pleted histopathologic examination of the suspected tumors (personal communication), and the results essentially confirm the incidence of gross liver and mammary lesions previously reported (40).

Although not related directly to tumorigenesis, recent studies by Watanabe, Sugano, and others (41–43) showed that feeding rats diets high in *trans* monoenes versus diets high in *cis* monoenes did not cause changes in bile flow or in concentrations of biliary cholesterol or bile acids. These results may be relevant to the development of colon cancer because increased levels of bile acids have been reported to be associated with development of colon tumors (44). The lack of stimulation by *trans* acids of bile acid production observed by these researchers suggests that *trans* acids are no more likely than are *cis* acids to promote the development of colon tumors.

A recent report by Hogan and Shamsuddin (45) compared the promotional effects of a high *trans* fatty acid diet (25% elaidic acid) with a high *cis* fatty acid diet (25% oleic acid) or with a chow diet (4.5% fat) on the development of colon tumors induced by the carcinogen azoxymethane. The diets were maintained for at least 20 weeks after the carcinogen treatment began. Although the investigators reported a higher incidence of large intestinal carcinomas in the *trans* fatty acid diet group (11 rats out of 30 had tumors) compared with either the *cis* fatty acid diet group (7 rats out of 30 had tumors) or a chow-fed group (5 rats out of 30 had tumors), the differences in tumor incidence between the *cis* and *trans* fatty acid groups and between the *trans* and chow-fed groups were not statistically significant. However, this study was somewhat unrealistic because the investigators fed diets high in free fatty acids rather than diets in which the fatty acids were in triglyceride form. In addition, the diets contained no supplemental linoleic acid, and therefore the rats were likely essential fatty acid deficient. Subsequently, a study by Watanabe and co-workers (46) demonstrated that a diet high in *trans* monoene (9% partially hydrogenated corn oil) did not promote the development of 1,2-dimethylhydrazine-induced colon tumors to any greater extent than did a diet high in *cis* monoene (10% olive oil). At present, there are no other published studies we are aware of that relate the intake of *trans* fatty acids to colon carcinogenesis.

Abraham and Hillyard (47) studied the effect of columbinic acid on the growth of a transplantable mammary adenocarcinoma in mice. Columbinic acid has two *cis* double bonds at carbons 9 and 12 (similar to linoleic acid) and a *trans* double bond at carbon 5. For comparisons, mice were placed on diets containing either oleic or linoleic acid. Each of the three fatty acids was added at a level of 1% by weight. The diets were maintained for seven weeks.

These investigators found that columbinic acid, when compared with oleic acid, produced no statistically significant effect on tumor mass, whereas linoleic acid resulted in a significant increase. Body weights of mice fed the oleic or columbinic acid diets were not different, but they were significantly less than were those fed the linoleic acid diet. This is most likely a result of the lack of essential fatty acids in the oleic or columbinic acid diets. Noting that columbinate is not converted to prostaglandins, Abraham and Hillyard (47) suggested that their results are consistent with the view that prostaglandin production is required for tumor enhancement by polyunsaturated fats.

Food products contain *trans* fatty acids as triglycerides. To properly evaluate the biological effects of *trans* fatty acids in a partially hydrogenated fat, a triglyceride of similar fatty acid composition and with fatty acids in the *cis* configuration should be used as the control. This approach was used by Mattson and colleagues (48) in studying the effects of a hydrogenated fat on plasma cholesterol and triglyceride levels in humans. The use of an unhydrogenated fat (from which the partially hydrogenated fat is derived) as a control would be misleading, because the two fats have different fatty acid profiles. Recently, we (49) investigated the effect of feeding a fat containing approximately 38% *trans* fatty acids (designated *trans* fat) on the induction of mammary tumors by 7,12-dimethylbenz[*a*]anthracene (DMBA) in rats. The corresponding control fat (designated *cis* fat) was specially blended to have a fatty acid composition

similar to that of the *trans* fat, but it consisted only of *cis* isomers. In addition, we designed a third blend, which we call "American" fat, to simulate the food fat composition in the United States (50,51). This blend consisted of approximately 6% *trans* fatty acids.

The fatty acid composition of these three fats, as determined by gas chromatography, is shown in Table 1. The *trans* fat was a partially hydrogenated mixture of 50% soybean oil and 50% cottonseed oil. It was high in monoenes and low in dienes and other polyenes. The *cis* fat consisted of 58% olive oil, 40% cocoa butter, and 2% coconut oil. The American fat was composed of 27% tallow, 15% butter fat, 13% lard, 22% partially hydrogenated soybean oil (as shortening), 17% partially hydrogenated soybean oil (as salad and cooking oil), 5% peanut oil, and 1% corn oil. Each fat was present in the diet at two levels: 5% and 20% by weight. Considering the virtual absence of linoleic acid in the *trans* fat (as indicated by the *cis, cis*-lipoxygenase value), 1% of corn oil was added to the *trans* fat diet to prevent essential fatty acid deficiency. The same amount of corn oil also was added to the *cis* fat diets to minimize differences in fatty acid composition between the *cis* fat and *trans* fat diets. Therefore, the low-fat diets contained 4% *trans* or *cis* fat plus 1% corn oil, and the high-fat diets contained 19% *trans* or *cis* fat plus 1% corn oil. All diets were fed for 24 weeks after DMBA treatment. (As a matter of convenience, the low-fat and high-fat *trans* or *cis* diets will be referred to as 5% and 20% *trans* or *cis* diets, respectively.) The concentrations of linoleic acid and *trans* acids in each diet are shown in Table 2.

Results of this study are summarized in Table 3. In general, tumor incidence and tumor yield were not significantly different in rats fed either the *trans* fat or the *cis* fat, at both the 5% and 20% levels. Because the *cis* fat was the control for the *trans* fat in this study, we concluded that *trans* versus *cis* isomerization of fatty acids has no detectable effect in modifying mammary tumorigenesis. A further inspection of the data showed that the 20% American fat diet was most effective in promoting the development of mammary neoplasia, although the American fat had a much lower total *trans* fatty acid level (6.4%) than did the *trans* fat (38.3%). This suggests that this tumor model is more responsive to the intake of linoleic acid and is independ-

Table 1. Fatty Acid Composition of Dietary Fats[a]

Fatty Acid	American Fat	*Cis* Fat	*Trans* Fat
10:0		0.1	
12:0	0.5	0.8	1.3
14:0	2.6	0.4	1.0
16:0	20.0	17.1	17.6
17:0	2.0		
18:0	13.0	15.7	15.9
18:1	39.8	54.7	57.5
18:2	17.8	8.5	6.1
18:3	2.0	0.6	0.2
20:0		0.8	0.3
22:0	0.3	0.3	
Trans, %	6.4[b]	ND[c]	38.3[b]
Cis,cis lipoxygenase, %	16.9	8.4	ND[c]

a: Expressed as percent of total fatty acids.
b: Capillary GC and IR spectroscopy gave comparable results for total *trans* levels. Capillary GC indicated that the *trans* fat consisted of about 92% *trans* monoene and the American fat, about 80% *trans* monoene.
c: ND, not detectable.

Table 2. Levels of Linoleic Acid[a] and *Trans* Acids in Various Diets

Dietary Fat	5% Dietary Fat, g/100 g of diet		20% Dietary Fat, g/100 g of diet	
	Linoleic acid	*Trans* acids	Linoleic acid	*Trans* acids
American fat	0.85	0.32	3.4	1.3
Cis fat[b]	0.96		2.2	
Trans fat[b]	0.62	1.5	0.62	7.3

a: Based on analysis of *cis,cis* lipoxygenase values.
b: Includes contribution of 1% corn oil added to these diets.

Table 3. Final Tumor Incidence and Tumor Yield of Rats Treated with DMBA and Fed Diets Containing Various Types and Levels of Fat

Type of Fat	Level of Fat	Tumor Incidence	Total No. of Tumors
Trans fat	5%	4/25 (16%)	9
	20%	8/25 (32%)	18
Cis fat	5%	6/25 (24%)	16
	20%	10/25 (40%)	27
American fat	5%	8/25 (32%)	21
	20%	17/25 (68%)	56

ent of *trans* fatty acid consumption. Our study also demonstrated that a fat with a high content of *trans* fatty acids does not promote mammary tumor formation to any greater extent than does a comparable fat with a high content of *cis* fatty acids.

We also determined that the rats in all diet groups, including those fed the *trans* fat, were adequate in essential fatty acids because the ratios of 20:3/20:4 fatty acids in heart total lipids ranged from 0.017 to 0.026. This range is considerably lower than 0.4, the ratio below which the minimum requirement for linoleic acid is reported to have been met (52). In addition, the incorporation of *trans* isomers into the mammary tissue and heart was found to be dependent on the quantity of *trans* fat in the diets (Table 4). About 9.7% of the fatty acids in the mammary fat pads were found to be in the *trans* configuration in rats fed 4% *trans* fat (plus 1% corn oil) and 26% of the fatty acids were *trans* isomers in rats fed 19% *trans* fat (plus 1% corn oil). In mammary fat pads of rats ingesting the 5% or 20% American fat diets, the levels of *trans* isomers were 2.3% and 4.8%, respectively. Also, as shown in Table 4, hearts of animals fed the *trans* fat diets had higher levels of *trans* fatty acids than did those of animals fed the American fat diets, again reflecting the greater intake of *trans* fatty acids by animals consuming the high *trans* fat diets. On the other hand, the extent of *trans* acid incorporation into the heart lipids was not as great as the incorporation into mammary fat pads, indicating that these two tissues do not accumulate *trans* isomers in a parallel manner. Mammary fat pads and heart lipids of animals ingesting the *cis* fat did not contain detectable levels of *trans* acids.

Cis and *trans* fats having similar fatty acid composition also were used in a recent study by Erickson and co-workers (53) to investigate the effects on the growth of implanted mammary tumors in mice. The mice were fed the experimental diets for two weeks before and up to three weeks after implantation of the tumor cells. These investigators found that there were no differences in tumor growth rate or final tumor size in mice fed diets containing low (5%) or high (20%) levels of high *trans* or high *cis* fats. Erickson and co-workers also reported that *trans*

Table 4. Effect of Dietary Fat Type and Level on Mammary Fat Pad and Heart *Trans* Fatty Acid Levels[a]

	Total *Trans* Fatty Acids			
	Mammary fat pad		Heart	
Dietary Fat	5% Dietary fat	20% Dietary fat	5% Dietary fat	20% Dietary fat
American fat	2.3 ± 0.3	4.8 ± 0.3	2.1 ± 0.2	2.9 ± 0.7
Trans fat	9.7 ± 0.9	26.0 ± 1.1	4.3 ± 0.2	7.9 ± 1.3

a: Expressed as percent of total fatty acids, mean ± SD for 7 or 8 rats.

fatty acids were less effective than were *cis* fatty acids in promoting metastasis of the implanted tumor cells. Overall, these results are consistent with those of Selenskas and others (49), indicating that *trans* fatty acids do not promote the development of mammary tumors to any greater extent than do *cis* fatty acids.

Conclusion

In conclusion, we wish to emphasize the importance of using properly designed fats when studying the biological effects of *trans* fatty acids. Under controlled conditions, a fat with a high content of *trans* fatty acids has been found not to promote the development of mammary tumors induced in rats by DMBA to any greater extent than does a comparable fat with a high content of *cis* fatty acids. Similarly, a high *trans* fat has been reported not to affect the growth and metastasis of implanted mammary tumors in mice relative to a comparable high *cis* fat. In addition, two recent studies have reported no significant difference in the development of induced colon tumors in rats fed diets high in *cis* or *trans* fatty acids. Overall, epidemiological and experimental studies published to date have demonstrated no valid association between *trans* fatty acid ingestion and tumorigenesis.

Submitted 13 July 1984; accepted in final form 23 August 1985.

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