NUTRITION AND BIOCHEMISTRY OF TRANS AND POSITIONAL FATTY ACID ISOMERS IN HYDROGENATED OILS

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INTRODUCTION

Knowledge of the nutritional importance of dietary fats has greatly expanded since the time when fats were considered only a source of calories. We now know that dietary fats supply the essential fatty acids (linoleic and linolenic acid) that are precursors for prostaglandins and that they are important components of membrane structures. Fats also influence cell function, serve as carriers for fat-soluble vitamins, affect immunological function, and are associated or involved with a number of diseases and disorders.

We also know that hydrogenated fats contain many fatty acid isomers not present in unhydrogenated oils and that in 1975, 5.6 billion lb of hydrogenated vegetable oil were produced in the United States, which is an average of 28 lb/year/person (113).

These facts explain why food technologists, nutritionists, biochemists, and the medical community are interested in the nutritional value of hydrogenated vegetable oils. The presence of isomers in hydrogenated fats has caused considerable controversy and has prompted a number of reviews, books, symposia, and special committee reports (10, 23, 38, 53–55, 57, 70, 90, 93, 107, 111, 116, 172, 211, 213).

The purpose of this chapter is to summarize a variety of nutritional, biochemical, and related physiological data from animal and human studies that involve both hydrogenated vegetable oil and specific fatty acid isomers.

DIETARY SOURCES OF ISOMERIC FATTY ACIDS

The process of catalytic hydrogenation of vegetable oils was discovered in 1897 and is now extensively used to convert liquid oils to semisolid fats, which facilitates their formulation into margarines and shortenings. Partial hydrogenation also reduces the polyunsaturated fatty acid content of vegetable oils, which improves flavor stability and increases the length of time that cooking oils can be used in deep-fat-frying operations.
An important side reaction of catalytic hydrogenation is isomerization, which forms more than 20 trans (t) and cis (c) positional fatty acid isomers (28, 161, 183). The percentage of isomers in hydrogenated vegetable oil varies widely with hydrogenation conditions (15, 27, 28, 79, 93, 148, 161, 180, 183, 220), but typical hydrogenated soybean oil products contain about 12% t-18:1, 4% c-18:1, and 9% 18:2 and 18:3 positional and geometrical isomers. In the United States, hydrogenated soybean oil (HSBO) is the primary dietary source of fatty acid isomers, because about 90% of the hydrogenated vegetable oil produced is HSBO (114). HSBO is used in a variety of commercial food products other than margarines, shortenings, salad oil, and cooking oil. These include breads, cakes, pies, rolls, candies, cookies, crackers, mayonnaise, potato chips, roasted nuts, and many other snack and convenience foods. In fact, use of HSBO in processed foods is so widespread that it is nearly impossible to avoid consuming it.

In addition to hydrogenated vegetable oil, milk and ruminant fats also contribute to dietary isomeric fatty acids. Of the animal fats, only ruminant fats normally contain fatty acid isomers, which are formed primarily by biohydrogenation of linoleic and linolenic acid in the ruminant forestomach. Over 400 different fatty acid isomers have been identified in milk fat, but most are present only in trace amounts (160). Milk fat has from 2 to 5% total trans fatty acid isomers, depending on the ruminant diet and how long it remains in the forestomach. For example, summer butter has a higher percentage of trans isomers than winter butter (162) because of the higher percentage of roughage in the summer diet.

Hydrogenated marine oils (HMO) are a third source of dietary isomeric fats, in particular of isomers of the fatty acids with chains 20–22 carbons long. The use of fish and marine oils as edible oils is prohibited in the United States, although it is important in other countries. Nutritional studies related to HMO are not reviewed in this chapter.

**DIETARY INTAKE OF HYDROGENATED FATS AND FATTY ACID ISOMERS**

US Department of Agriculture (USDA) agricultural statistical data for 1980 estimated total production of animal and vegetable fats and oils for edible use at 12.7 billion lb and total edible fat disappearance at 169 g/day/person (1). Approximately 44% of this was partially hydrogenated vegetable oil. The nationwide food consumption survey of 1977–1978 (210) and the ten-state and HANES surveys (185) have shown that eating patterns vary considerably with age, sex, income, and life style. Fats and oils supplied about 40% of average total calories, and hydrogenated vegetable oil is estimated to contribute about
13.8% of this. Thus, hydrogenated vegetable oil is one of the more important sources of calories in the US diet. In comparison, protein supplies 16% of calories and all carbohydrates, 43%.

Based on analyses of numerous hydrogenated oil samples and total fat consumption, a weighted average has been used to calculate a daily average intake of individual cis and trans positional monounsaturated isomers, as summarized in Table 1 (52, 176). Other estimates of the total dietary trans fatty acid intake for the United States, Sweden, and other populations have been based on production/disappearance statistics, dietary recall data, and the duplicate portion technique. In general, intake of dietary trans fatty acid isomers is estimated at 5–9 g/day per person, or about 3–6% of dietary fat and 2–3% of total energy intake (2, 60, 61, 63, 65, 80, 115).

Analysis of human adipose tissue provides an alternative method of estimating dietary fatty acid isomer intake, because these isomers are not synthesized by humans. Adipose tissue fatty acids have a relatively long half-life of 400–600 days (39, 87), so adipose tissue reflects the long-term average of dietary isomeric fatty acid content (17). Studies of United Kingdom, German, and US populations show a range of 3.8–9.2% total trans content in adipose tissue (80, 153, 205a), which is consistent with many of the estimates based on consumption data. The distribution pattern for positional fatty acid isomers in the adipose tissue of several US subjects clearly resembles the pattern normally present in partially hydrogenated soybean oil (151, 154). A correlation coefficient of 0.97 for the distribution pattern of trans positional monoene isomers in adipose tissue was calculated by assuming that 90–95% of the isomeric fats in the adipose tissue are contributed by HSBO, and the rest by butter fat.

**PHYSIOLOGICAL AND METABOLIC STUDIES**

**Absorption**

The “digestibility” or absorption of hydrogenated fats was first investigated in the late 1920s, and in the early 1930s was extended to elaidic acid or “isooleic acid” (13, 195). These early rat studies and later investigations (156) indicated

| Table 1 Estimated daily consumption of specific positional octadecenoic acid isomers
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<td>Positional octadecenoic acid isomer (g)</td>
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<td>6</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>c-18:1</td>
</tr>
<tr>
<td>t-18:1</td>
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<tr>
<td>Total isomer content minus 9c-18:1 = 9.0 g</td>
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*Based on an estimated consumption of 34 g hydrogenated soybean oil containing 25% c-18:1 and 20% t-18:1.*
that absorption of hydrogenated fat is equivalent to absorption of nonhydrogenated fats and oils. Chemically synthesized individual fatty acid isomers and their triglycerides have melting points that vary from -13-54°C (14, 34, 66, 72, 73, 168, 169); recent animal studies with hydrogenated fats suggest that all isomers, including those with melting points higher than body temperature, are absorbed as well as oleic acid (57, 120, 121, 225). These animal studies have been confirmed by human studies with pure triglycerides containing deuterated cis and trans positional octadecenoic acid isomers (56, 58, 59); melting point, double bond position, and configuration have no measurable effect on the absorption of any isomer.

These in vivo results agree with the data for in vitro pancreatic lipase hydrolysis of a series of triglycerides containing a single cis positional octadecenoic acid isomer, a saturated fatty acid, and linoleic acid (9c, 12c-18:2) (101). Triglycerides containing 18:1 isomers with the double bonds in the 2 to 7 positions were found to inhibit lipase hydrolysis of triglycerides, which is necessary for fat absorption. The Δ8 to Δ16 cis positional 18:1 isomers, which are the ones present in hydrogenated fats, did not inhibit pancreatic lipase hydrolysis; this data suggests that hydrogenated fats should be well absorbed.

**Growth, Organ Size, and Longevity**

Long term and multiple-generation studies with rats (4, 5) and mice (214) fed partially hydrogenated vegetable fats have been reported. Pathological examination of organs showed no abnormalities. Growth, longevity, reproduction, and lactation also were unaffected by diets containing 9.5% hydrogenated oils. The trans content of the dietary fats fed was 35%, which was estimated to be ten times the level in human diets. Growth curves of controls and of rats fed 20% (by weight) HSBO containing 48% trans also showed no difference. No change in weight gain was reported when rats were fed 50 and 100 mg/day of a 1:1 mix of 9t-18:1; c,t-18:2; or t,t-18:2 plus c,c-18:2 for 4 weeks (138). The protein efficiency ratio for casein was not influenced in rats fed diets containing 7.8 or 20.1% (by weight) HSBO, and even diets containing 7.8% trielaidin had no nutritionally significant effect on protein utilization (98). In comparison to 9c-18:1, which had no effect (200, 221), addition of 6c-18:1 to rat novikoff hepatoma cell cultures reduced cell growth.

The only studies with hydrogenated fats that report lower growth rates and pathological abnormalities are those in which hydrogenated fats were fed to essential fatty acid-deficient (EFAD) rats (3, 89). In general, all fats except 9c-18:1 and c,c-18:2 appear to accentuate EFAD, and 18:0; 9t-18:1; t,t-18:2; and c,t-18:2 produced the most significant results. The structures of t,t- and c,t-18:2 apparently are similar enough to that of c,c-18:2 that they compete in reacylation of membrane phospholipids. This competition would enhance the removal or loss of the last remnants of c,c-18:2 and 20:4 from tissue. Other
nonessential fats probably also promote this effect by a mass action or dilution mechanism.

In contrast to animal studies, growth of bacteria (Escherichia coli) and yeast (Saccharomyces cerevisiae) cells was influenced by various positional 18:1 isomers. The cell lines used were mutants not capable of fatty acid synthesis, and they were forced to utilize those fats added to the medium. Growth of E. coli and S. cerevisiae was inhibited by addition of Δ8 to Δ13 t-18:1 positional isomers even in the presence of added 9c-18:1 (212). Growth inhibition was the greatest for the 4t-, 6t-, 7t-, 11t-, and 12t-18:1 isomers, which also promoted triglyceride accumulation in the cells. Addition of 9t-18:1 was reported to depress phospholipid synthesis and was considered to be the reason cells failed to divide (71). A more recent study reported normal cell growth with 9t- and 11t-18:1 when higher levels of adenosine monophosphate (AMP) were added. This suggests that trans acids provide sufficient membrane fluidity for cell growth and that they are involved in regulation of cell function (207).

In a related study with S. cerevisiae, the effects of a variety of other unsaturated 20- and 22-carbon fatty acids on growth were compared to those of the Δ2 to Δ15 t-18:1 series. The 2t- to 4t- and 13t- to 15t-18:1 isomers did not support growth, but 20:4 and 20:5 were twice as effective as 9c-18:1; 9c,12c-18:2; or 9c,12c,15c-18:3 (216). In contrast to the t-18:1 isomers, the 7c- to 10c-18:1 positional isomers were all about equally effective in supporting growth of E. coli and S. cerevisiae cells (152). The 14c- to 17c-18:1 acids did not support E. coli growth, and the 12c- to 17c-18:1 acids did not support yeast cell growth. The 5c-18:1 acid was effective for bacterial cell growth but not for yeast, and the 6c-18:1 was effective for yeast cell growth but not for bacterial growth. No obvious relationships between physical properties of the fatty acids and cell growth were noted.

Cell Function

The effects of various isomers on AMP requirements and growth of single cell organisms described above support the general concept that membrane lipids affect the microenvironment of the cell and influence cell functions. Red blood cell fragility data (41), swelling of cells in tissue culture (132), and mitochondria permeability studies (35) indicate that membrane permeability and fluidity are altered by fatty acid isomers.

Other evidence that isomeric fats influence cell function involve the inhibition of immunoglobulin interaction with lymphocytes by 9c-18:1; c,c-18:2; and 20:4, but not by saturated fatty acids and 9t-18:1 (78, 110). The difference in inhibition was associated with a change in membrane-bound calcium and depletion of adenosine triphosphate (ATP) levels in lymphocytes, which were attributed to uncoupled oxidative phosphorylation.

Rats fed hydrogenated fish oil for 15 weeks developed severe testicular
degeneration (100), and a diet containing a 50:50 mixture t,t- and c,c-18:2 reduced rat lung weights by 20% (231). Rats fed t,t-18:2 also had lower fibrinogen concentrations, longer bleeding, and shorter prothrombin times than rats fed corn oil (167). Addition of 9t- and t,t-18:2 to rat heart cell culture immediately arrested pulsation or beating (arrhythmia) of the cells, whereas 9c- and c,c-18:2 had only mild effects (222).

These effects should not be viewed with particular alarm in terms of effects on humans, because the experimental designs employed produce environments much different than those encountered by cells in normal in vivo conditions. No study of higher organisms using dietary fats similar to edible hydrogenated vegetable oil has shown any discernible effect on cell or organ function.

**EFFECT OF ISOMERIC FATS ON LIPID-METABOLIZING ENZYMES**

A number of in vivo investigations have provided evidence that hydrogenated fats and specific fatty acid isomers can influence the activity of the desaturases, elongases, acyltransferases, oxygenases, and prostaglandin synthetases.

**Desaturases and Elongases**

This section summarizes a number of in vivo studies that provide evidence that hydrogenated fats, specific isomers, and nonisomeric fatty acid (18:3w3, 20:3w6, and 20:4w6) inhibit desaturation and elongation of nonisomeric polyunsaturated fatty acids (209).

Rats fed 10 and 20% HSBO diets containing 49.5% t- and 1% c,c-18:2 displayed an increased amount of 20:2w9 in liver phospholipids, which was produced by the low 18:2 levels in the diet rather than by *trans* fatty isomers. The level of 20:4 was also lowered, which implies reduction of desaturase-elongase activity because of isomeric fatty acids (46, 47) or because of the low 18:2 levels in the diet. Others have reported that conversion of 9c-18:1 and 9c-16:1 to 20:3w9 and 20:4w7 was inhibited by addition of 9t- and t,t-18:2 to fat-free diets (166, 204), which also suggests reduction of desaturase-elongase activity. Rats fed an enriched *cis* and *trans* 18:1 fraction from HSBO exhibited reduced synthesis of 20:4 and accelerated synthesis of 20:5w3 and 20:3w9 (126, 165). This effect was correlated with the 12c-18:1 isomer. A similar reduction in 20:4 levels has also been observed for plasma lipids from human subjects fed mixtures of 9c-, 12t-, and 12c-18:1 (58).

Diets containing t,t-18:2 decreased the levels of 20:4 in rat liver and kidney lipids, which suggests that desaturation-elongation of 18:2 was inhibited (9, 109). In similar studies, synthesis of 20:3 in rat lung was also inhibited (231).

Data from suckling rat brain injected with 14C-labeled 18:0, 9c-18:1, 9t-18:1, and t,t-18:2 indicated that t,t-18:2 and 9c-18:1 inhibited desaturation-
elongation of c,c-18:2, while 9t-18:1 and 18:0 stimulated desaturase-elongase activity (37). Studies of rats fed EFAD diets showed elevated Δ6 desaturase-elongase activity, but results from rats fed EFAD diets containing 20% (by weight) of 9t- and t,t-18:2 indicated that t,t-18:2 suppressed the Δ6 desaturation-elongation sequence (118). The effect of 9t-18:1 was considered minor. In vivo rat data showed that 6c-18:1 inhibited conversion of 9c-18:1 to 20:3ω9 and conversion of 18:2ω6 to 20:4ω6, but diets containing 9c-18:1 had little effect (143). Feeding rats a mixture of 9t-18:1 and t,t,-; t,c-; and c,t-18:2 isomers inhibited Δ6 desaturase but not Δ9 desaturase (42). Studies in which fat-free diets containing added c,c- and t,t-18:2 or c,c,c-18:3 and t,t-18:2 were fed to rats demonstrated suppressed conversion of c,c-18:2 and c,c,c-18:3 to longer-chain-length polyunsaturated fatty acids (188).

Rats fed a mixture of t,t- and c,c-18:2 at 5 and 11% of calories had decreased levels of 20:3 and 20:4ω6 fatty acids in heart, kidney, lung, platelets, and adipose tissue, which also suggested inhibition of the desaturase-elongase system (108). In contrast, conversion of 20:3ω6 to 20:4ω6 increased when rats were fed HSBO (43% t-18:1, 2.4% t,c-18:2, and 16% c,c-18:2) for 28 and 43 weeks, which suggests an increase in Δ5 desaturase activity (84). Essential fatty acid–deficient rats fed ethyl elaidate for 12 weeks exhibited an increased rate for desaturation of 16:0 to 16:1 (74). Monoene isomers in hydrogenated marine oil produced lower 20:4 levels in rats due to competitive inhibition of Δ6 desaturase activity (91).

**Lecithin:Cholesterol Acyl Transferase**

Rats fed isomerized safflower oil containing 20.8% t-18:1 and 47.5% t,t-18:2 for 43 weeks showed an initial increase in lecithin:cholesterol acyl transferase (LCAT) activity, which decreased after 40 weeks (204). The depression of LCAT activity was probably due to 9t,12t-18:2 rather than 9t-18:1, based on other studies that indicated that LCAT and lipoprotein lipase activity did not change when EFAD rats were fed 5% 9t-18:1; however, when 5% 9t,12t-18:2 was added to the diet, LCAT and lipoprotein lipase activity decreased (165). Similarly, LCAT activity in liver from rats fed HSBO diets containing 12–50% total trans decreased as the percentage of trans increased (144).

**Oxygenases**

Respiratory activity of rat heart mitochondria was reduced when HSBO containing 48% t-18:1 and 3% 18:2 was fed for 6 weeks. These results suggested that t-18:1 isomers decreased the activity of the β-oxidation enzyme system (95). In a study related to oxidation of drugs, the activity of nicotinamide adenine dinucleotide phosphate (NADP) cytochrome c reductase and cytochrome p-450 decreased in rats injected intraperitoneally with 9c,12c-18:2; however, no effect was noted with 9t-18:1. Both fatty acids decreased aryl hydrocarbon hydrolase and nitroanisole demethylase activity (83).
Prostaglandin Synthetase

In vitro experiments with a limited number of polyunsaturated isomeric fatty acid structures suggest that conversion of 20:4 to prostaglandin (PG) is inhibited as a result of reduced cyclooxygenase activity. These and other studies involving trans fatty acids and PG are summarized in a number of reviews (54, 107, 137, 159).

When rats were fed a 1:1 mixture of 9t,12t- and 9c,12c-18:2, PGF$_{2a}$ levels in serum were 50% lower than in controls, but 20:4 levels were reduced by only 12%. This result and an observed increase in susceptibility of platelet aggregation to indomethacin for the 9t,12t-18:2 diet compared to a 9c,12c-18:2 diet imply that PG synthetase is inhibited by the t,t-18:2 isomer (96).

In vitro data with bovine seminal vesicals was used to demonstrate inhibition of PG synthetase by a number of 18- to 20-carbon-chain-length polyunsaturated isomers (150). For the isomers studied, levels of inhibition were generally low, except when the isomer contained a Δ12t double bond conjugated with a Δ14c double bond. Inhibition was 74% for 8c,12t,14c-20:3 and 54% for 5c,8c,12t,14c-20:4 (62). It is surprising that inhibition was not greater for the other isomers investigated, because 18:2 and 18:3 also inhibit PG synthetase (158).

In addition to the PG synthetase inhibition studies, a number of odd-chain-length cis polyunsaturated fatty acid (PUFA) isomers have been shown to be converted in vitro to biologically active PG isomers (16); however, these are not likely to be of nutritional importance.

EFFECT OF ISOMERIC FATS ON LIPOPROTEINS, TISSUE LIPIDS, AND FATTY ACID COMPOSITION

The influence of HSBO and specific fatty acid isomers on tissue, serum, and lipoprotein triglyceride (TG), phospholipids (PL), free fatty acids (FFA), cholesterol ester (CE), and cholesterol levels are related to cell function and enzyme activity. They are also related to the individual fatty acid composition of the various lipid classes.

Serum Lipid and Lipoprotein Concentrations

Several studies have investigated the effects of diets containing isomeric fats on serum lipid classes and lipoprotein levels in swine, rats, and rabbits. Results have been inconsistent, which may reflect variation in experimental design. For example, plasma CE, TG, PL, and cholesterol levels in swine fed HSBO (50% trans) were increased compared to levels in those fed corn oil diets, but the increase in lipid classes was the result of low levels of 18:2 in the HSBO diet rather than of its isomer content (117, 230). Subsequent studies with swine reported that HSBO diets containing additional 18:2 did not significantly
increase serum cholesterol, TG, and PL levels (49, 131). Lowering of high-density lipoprotein levels did occur when swine received diets containing trans fatty acid isomers, but no changes in the physical properties of lipoprotein fractions were observed (99).

Studies of rats fed margarine containing hydrogenated rapeseed oil showed no effect on serum cholesterol and PL levels (232). In fact, rats fed various HSBO diets containing 12–50% trans isomers were found to have lower serum cholesterol levels than rats fed corn oil (144). In contrast, rats fed an isomerized safflower oil fraction containing 20.8% t-18:1 and 47.5% t,t-18:2 for 43 weeks showed increases in serum cholesterol ester and PL levels but lower TG levels. Little change in liver, kidney, and heart lipid class composition occurred (204).

Rats fed safflower oil and then switched to hydrogenated coconut oil or a high-trans diet containing 50% t,t-18:2 and 24% t-18:1 showed an immediate decrease in high-density lipoprotein levels (181). An increase in low-density lipoprotein levels occurred with threonine-imbalanced rats fed elaidinized olive oil (187).

The most detailed study on the effect of hydrogenated vegetable fat on rat plasma lipid classes is that by Wood (225). Plasma TG, phosphatidylcholine (PC), FFA, and cholesterol concentrations increase after one week on the partially hydrogenated safflower oil (PHSFO) diet and then gradually decrease except for FFA. Other serum lipid levels (lysophosphatidylcholine, sphingomyelin, and CE) did not change.

Rabbits fed diets containing hydrogenated olive oil and t,t- and c,t-18:2 isomers from elaidinized safflower oil showed no significant changes in serum cholesterol and TG levels (127, 189). In rabbits fed 9t-18:1, however, serum cholesterol levels doubled (139, 140, 219).

The general impression is that isomeric fatty acids or hydrogenated vegetable oils have little effect on serum lipid class concentrations.

**Tissue Lipid Class Concentrations**

The effects of four different diets (HSBO, tallow, corn oil, and fat-free) on CE, PL, and TG levels were reported for rat adrenal, liver, heart, and lipoprotein classes (46). Comparison of a 20% (by weight) HSBO diet containing 48% trans and 1% 18:2 to a corn oil diet fed for 15 and 20 weeks indicated that HSBO significantly increased heart and very-low-density lipoprotein (VLDL) TG levels, reduced heart and high-density lipoprotein (HDL) PL levels, and increased adrenal CE level at 15 weeks. Effects of the diets on other tissue lipid levels were not significant. Considerable variation in 15- and 20-week data suggests that the low 18:2 level in the HSBO diet was probably a more important factor at 20 weeks than were tissue types or trans isomer levels.

Livers from threonine-deficient rats fed olive and corn oils contained 30% more lipid and lower low-density lipoprotein (LDL) levels than those rats fed
elaidinized olive oil and corn oil (187). In threonine-imbalanced rats, feeding 9t-18:1 compared to 9c-18:1 apparently prevented accumulation of liver lipids by increasing the transport or mobilization of lipids from the liver to other sites (186). A hydrogenated fish oil diet that contained long-chain isomers was reported to reduce TG levels by 50% in rat testicular lipids (100). Platelets from rats fed t,t-18:2 contained more CE and TG and less PL than rats fed corn oil (167).

Detailed data are available on the concentration of lipid classes in livers from rats fed partially hydrogenated safflower oil (225). The concentration of the major PL classes was not influenced, but there were moderate increases in liver TG concentrations compared to those for chow-fed rats. Thus, existing data indicate that except under extreme experimental conditions, hydrogenated fats have little influence on tissue lipid class composition.

**Fatty Acid Composition**

Much of the in vivo evidence that suggests that isomeric fatty acid alters desaturase-elongase activity is based on changes that occur in fatty acid composition. Changes in tissue fatty acid composition can also result from simple mass or dilution effects and from biochemical control of the fatty acid composition of lipid classes. For example, in phosphatidylcholine there is the well-known tendency for 16:0 to be paired with 20:4 in the same molecule. Triglycerides are also known to be esterified preferentially with unsaturated fats at the 2-acyl position. Selective placement of fatty acids in these lipids is apparently due to the effect of lipid structure on membrane permeability and cell function.

The modification of fatty acid composition by dietary cis and trans positional isomers in hydrogenated fats is complex. Modification of fatty acid composition probably is the result of a combination of several factors, including enzyme activity, enzyme selectivity, and dietary fat compositions. The effects of these factors vary with the tissue, specific lipid classes, and experimental conditions. The only generalization that can be made is that partially hydrogenated vegetable oil normally reduces 20:4ω6 and increases 18:1 levels.

Short-term human studies indicate that the positional octadecenoic acid isomers (9t-, 12t-, 12c-, 13t-, and 13c-) have different effects on plasma fatty acid composition (55, 56, 58, 59). In these studies, a single meal containing triglycerides of one or two deuterium-labeled fatty acid isomers plus deuterated oleic acid was fed, and fatty acid composition of plasma TG, CE, PC, and phosphatidylethanolamine (PE) were determined at maximum incorporation of the deuterated fats and compared to zero-hour data. Low levels (0.4–0.8%) of the fatty acid isomers incorporated into CE fractions had no effect on CE fatty acid composition. The relative percentage of the nonmonoenoic fatty acids in the TG fraction was reduced because of the increase in 18:1 from the meal fed.
For plasma PC and PE, a decrease from 0.7 to 0.4 in the polyunsaturated/saturated (P/S) fatty acids ratio occurred when the 12c- and 12t-18:1 isomers were fed. The change in the P/S ratio was the result of a large decrease in the 20:4 percentage and a moderate increase in the 16:0 percentage. Analysis of the 1- and 2-acyl PC fatty acids indicates that 12c-18:1 is incorporated selectively into the 2-acyl position, which is the reason for a decrease in polyunsaturated fatty acids. In contrast, the 9t-18:1 isomer did not decrease the P/S ratio of any lipid classes; however, the 13t- and 13c-18:1 positional isomers increased the P/S ratio from 0.6 to 0.9 in the PE fraction. These data suggest that each isomer has a different effect on human serum lipid fatty acid composition, and this conclusion is supported by rat data (20, 40, 95, 108, 109). A comprehensive compilation of fatty acid composition data is available for TG, PC, PE, SM, and phosphatidylyserine (PS) from heart, kidney, liver, hepatoma, lung, muscle, spleen, and adipose tissue of PHSFO- and chow-fed rats (225).

One point that seems clear is that adipose tissue fatty acid composition reflects the composition of dietary fat reasonably well and does not selectively incorporate or exclude any specific isomeric fatty acid.

HEALTH-RELATED NUTRITION STUDIES

A variety of diseases and metabolic disorders involve fat metabolism (22, 50, 51, 64). The more serious and common are coronary heart disease, cancer, multiple sclerosis, cystic fibrosis, and the variety of problems associated with or aggravated by obesity. Involvement of unhydrogenated dietary fats in the etiology of diseases is not well understood, and little is known about the effects of hydrogenated fats and oils.

Atherosclerosis

Dietary fat is implicated as a factor in the etiology of atherosclerosis, but although large population studies have generated a wealth of information, these studies were not designed to differentiate between effects of hydrogenated and nonhydrogenated fats. For example, the National Diet-Heart Study completed in 1968 (6) used hydrogenated and unhydrogenated fats to vary saturate:monounsaturate:polyunsaturate ratios in the various diets. However, data was not obtained on the trans fatty acid content of the dietary fats or on blood lipid samples.

At least 14 studies with smaller numbers of subjects have reported data that can be used to evaluate the effect of hydrogenated fats on blood lipids. The results of all but one of these studies (119) were reviewed in detail by Emken (57) and Applewhite (10). The subjects were students, prisoners, mental patients, monks, and nuns. Several different hydrogenated vegetable oils with iodine values of 55–109 and trans values of 10–70% were fed as dietary fats.
Serum cholesterol levels were monitored, and in some experiments TG and PL levels were also determined. Small increases (20–30 mg %) in serum cholesterol levels as a result of isomeric fatty acids in hydrogenated fats were observed in about half of the studies, and the others reported slight decreases. For those studies reporting serum TG and PL levels, the data were similar to the cholesterol data. The combined results indicate that replacement of hydrogenated fat with unhydrogenated fat in the diet is of little value in reducing serum lipid levels. Other factors such as total cholesterol intake, P/S ratio, general lifestyle, and genetic variability appear to have a greater influence on serum lipids than do dietary isomeric fatty acids.

Correlation of the trans fatty acid content of adipose tissue from United Kingdom subjects who died of heart disease and unrelated causes has been investigated. Initially, no significant correlation of heart disease and trans fatty acid was reported (205a), but recently adipose tissue from heart disease victims was found to contain higher levels of t-18:1 and t-16:1 (205b).

Animal studies can use invasive techniques and dietary extremes not permitted in human studies. Animal studies that have investigated the effect of diets containing hydrogenated fat on atherosclerosis have been reviewed previously (10, 111, 213) and are briefly summarized here. The development of arterial lesions in swine fed HSBO (50% trans) containing little 18:2 correlated with percent trans fatty acids (117), and as Applewhite pointed out (10), with low 18:2 levels. Other studies with swine fed HSBO containing higher levels of 18:2 vs unhydrogenated fats did not produce a higher incidence of fatty streaks, fibrous plaques, or lesions in the aorta and coronary artery than in swine fed unhydrogenated oil (49, 99, 131, 178).

Rabbit studies indicated trans fatty acids are hypercholesterolemic (139, 140, 179, 219), but no effect on aortic atherosclerosis and no differences in liver enzyme activities were found. A recent study with Vervet monkeys demonstrated no differences in serum or liver lipids or in the severity of atherosclerosis (111). Rats fed a 10% hydrogenated corn oil (42% trans) diet showed lower serum cholesterol levels, increased excretion of neutral and acidic steroids, and changes in steroid composition (201). Analysis of isolated cardiac sarcolemma tissue from rats fed 5% 9t-18:1 by weight showed membrane cholesterol content about 25% higher than that from rats fed 9c-18:1. Phospholipid levels were unaffected, with the 9t-18:1 mostly incorporated into PE and PC (12).

**Cancer**

The scientific literature is replete with studies involving the effects of dietary fat on tumor growth and development, but relatively few reports have specifically focused on the effects of hydrogenated vegetable oils and specific isomeric fats. Reviews of numerous epidemiological studies report a positive
correlation between increased dietary fat intake and breast cancer (77, 86, 102, 142, 224, 229). Epidemiological data also suggest that PUFA are associated with a higher incidence of tumors than are saturated fats (92), and a positive correlation between hydrogenated vegetable oil and cancer has been reported (60, 61). Several studies have reported that high dietary fat levels enhance development of tumors induced by various carcinogens (177, 217), and PUFA were found to promote tumors more effectively than saturated fats (29–31).

Others have critically reviewed the epidemiological data and the interpretation of the results from animals fed high-fat diets and have concluded that there is little evidence of a positive relationship between dietary fat and incidence of cancer in humans (82). A dietary intervention study with Finnish men replaced saturated fats in the diet with vegetable oil; they reported reduced mortality from coronary heart disease but no increase in mortality due to malignancy (208).

A few experiments suggest that fatty acids have weak carcinogenic properties. Data on the subcutaneous injection of mice with stearic, lauric, and oleic acids indicate that these fatty acids may be weak carcinogens (203). Mice fed 20% (by weight) olive oil diets containing 50% trielaidin or trilinoelaidin were reported to have a higher incidence of liver tumors than did controls (106). These findings are questioned because a number of similar studies with mice and rats have not reported an increased incidence of tumors. Limited biochemical data is available on tumor cell metabolism of fatty isomers. Ehrlich ascites tumor cells from mice fed elaidic acid incorporate about one half the percentage of 9t-18:1 as normal liver cells and show reduced total lipid content (11). A large increase in the percentage of 18:0 also occurred in the tumor cells of mice fed either 9c- or 9t-18:1. These data suggest that the tumor cells had lost much of their ability to regulate fatty acid composition of the cell lipids selectively, and the data are consistent with results published previously (227, 228). In contrast, leukemia cells from mice do not lose their mechanisms for selective acylation of the 1- and 2-acyl positions of phosphatidylcholine and ethanola­mine with saturated and polyunsaturated fatty acids (26).

**Prostaglandins and Related Studies**

The potent biological activity of prostaglandin (PG) and leukotrienes on a variety of cell and tissue functions has stimulated a tremendous amount of research. One reason is the interrelationship of PG and disorders such as atherosclerosis, hypertension, stroke, and platelet functions. For many years, researchers in prostaglandin biosynthesis and regulation have explored the importance of 20:4ω6 and 20:3ω6 fatty acids, the precursors for a large number of leukotriene and PG structures, and of linoleic acid, the precursor to 20:4 and 20:3 fatty acids. More recently, the ω3 fatty acids have been identified as having an important role in the regulation of PG biosynthesis and physiological effects of PG and PG-related structures (44). Dietary supplementation with ω3
fats has been reported to have significant physiological effects, especially on blood clotting, in spite of the relatively low levels of these fats in human tissue; there is little question that the amount of specific fatty acids in the diet can influence PG biosynthesis. As examples, the absolute amount of 18:2, rather than the percentage of 18:2 in the diet, appears to be responsible for increased PG levels. Addition of 20:4 to human diets increased the metabolite of PGE\(_2\) in urine by 47% and increased the reactivity of platelets (190). Consumption by humans of 1–2 g of 20:3\(\omega 6\) increased 20:3\(\omega 6\) and PGE levels in plasma. In rabbits, PGE\(_1\) levels increased 20- to 30-fold and PGE\(_2\) levels decreased by 25–50% when 20:3\(\omega 6\) was added to the diet (44).

What effect do specific isomeric fats present in hydrogenated oils have on the ratio and amounts of PG in tissue? Relatively few specific isomers and fats have been studied in experiments designed to provide answers to this question. Much of the present knowledge on this subject has been covered in several reviews (54, 88, 107, 137).

The studies from Kinsella’s laboratory have centered around the relation of the t,t-18:2 isomer to PG functions and synthesis (24, 96). In these studies, rats fed diets containing equal amounts of t,t- and c,c-18:2 developed reduced response to platelet aggregating agents, which implied inhibition of PG synthesis by t,t-18:2. The t,t-18:2 diets also decreased levels of the \(\omega 6\) fatty acids (18:2, 20:3, and 20:4) in heart, kidney, lung, platelet, and adipose tissues and reduced the levels of PGE\(_1\), PGE\(_2\), and PGF\(_2\) in serum. In rats fed various levels of t,t-18:2, hematological properties of red blood cells were affected at high levels of t,t-18:2, thromboxane B\(_2\) levels were decreased, and 6-ketoprostaglandin F\(_{1\alpha}\) levels were unchanged. Little or no effect was found at t,t-18:2 levels that correspond to those estimated present in human diets (24). The decrease in PG production by platelets was greater than the decrease in the fatty acid precursors, which suggests inhibition of PG synthetase by the t,t-18:2 isomer. Increased c,c-18:2 levels in serum PL suggested that conversion of c,c-18:2 to 20:4 was inhibited by t,t-18:2, which confirmed earlier results by Privett. However, Privett also reported that addition of c,c-18:2 to the diet nullified the effects of t,t-18:2 (165).

Other studies of rats fed hydrogenated fat reported higher PG levels than for fasted rats, which suggests that the additional dietary c,c-18:2 from hydrogenated fats more than compensates for PG synthetase inhibition by isomeric fats (159, 165).

INCORPORATION, DISTRIBUTION, AND TURNOVER OF FATTY ACID ISOMERS

Numerous studies have mapped the incorporation and distribution of isomeric fats into tissue and lipid classes. The results of many of these have already been discussed in terms of the implied effect of isomeric fats on enzyme activities.
and fatty acid composition, and they will be discussed later in terms of enzyme specificity. The purpose of this section is to discuss the levels of isomeric fats in the diet that are necessary to influence the isomeric fatty acid content of various tissues and lipid classes.

**Monoene Isomers**

In the section on absorption of fatty acid isomers, it was concluded that absorption of monoene isomers and un-isomerized fatty acids was similar. Many experiments have provided data that shows that after absorption, selective incorporation and exclusion of isomeric fats into individual lipid classes occur. The accepted concept is that metabolism and incorporation of each individual isomer depends on its double-bond configuration and position.

Of the various tissues, adipose tissue most nearly reflects diet composition (40, 171). The trans content of various tissue lipids from rats fed 10% (by weight) hydrogenated sunflower oil (32% trans) for 40 days was as follows: adipose, 9.4%; heart, 7.9%; liver, 7.3%; kidney, 3.0%; brain, 2.3% (20). This data illustrates the variation in distribution of trans fatty acids in tissues. Researchers have reported a specificity for incorporation of trans fatty acids into lipoprotein lipid classes (45, 184, 193). For example, the data in Table 2 suggest discrimination against incorporation of trans isomers into lipoprotein CE and PL fractions relative to TG. In related studies, 9t-18:1 was preferentially incorporated into the phospholipids of rat liver and adrenal tissues, and the LDL and HDL lipoprotein PL fractions contained higher percentages of 9t-18:1 with no preference for VLDL compared to 9c-18:1 (75, 186), but the lipoprotein TG and CE fractions contained less 9t- than 9c-18:1. Thus the trans content of the lipoprotein lipid classes depends upon which lipoprotein fraction is

<table>
<thead>
<tr>
<th>Animal model</th>
<th>Lipoprotein fraction</th>
<th>Trans (%) in lipid class</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Rat(^a)</td>
<td>VLDL</td>
<td>18.6 7.8 9.1 10.2</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>LDL</td>
<td>14.0 7.6 6.0 14.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HDL</td>
<td>15.3 8.8 19.0 2.2</td>
<td></td>
</tr>
<tr>
<td>Rat(^b)</td>
<td>VLDL</td>
<td>16.9 16.4 8.5 —</td>
<td>193</td>
</tr>
<tr>
<td></td>
<td>LDL</td>
<td>16.2 9.8 6.2 —</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HDL</td>
<td>10.1 2.0 11.1 —</td>
<td></td>
</tr>
<tr>
<td>Rabbit(^c)</td>
<td>VLDL</td>
<td>15.6 6.3 13.7 —</td>
<td>184</td>
</tr>
<tr>
<td></td>
<td>LDL</td>
<td>14.1 8.4 10.9 —</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HDL</td>
<td>9.8 7.5 12.7 —</td>
<td></td>
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</table>

\(^a\)20% by weight HSBO (48% trans) fed for 105 days.
\(^b\)25% by weight HSBO (44.5% trans) fed for 60 days.
\(^c\)20% by weight hydrogenated olive oil (37.6% trans) fed for 21 days.
analyzed, but results are not consistent enough to permit general conclusions. Lipoprotein lipid fatty acids are sensitive to sampling and experimental conditions, and \textit{trans} content might be expected to vary significantly for samples from fed and fasted rats (193).

For rat brain PC, 67\% of the total 9\textit{t}-18:1-1\textsubscript{4}C incorporated was in 1-acyl PC and 33\% was in 2-acyl PC (104). Rat placenta did not discriminate for 9\textit{t}-compared to 9\textit{c}-18:1-1\textsubscript{4}C, but fetal lipid contained four times more 9\textit{t}- than 9\textit{c}-18:1 (145). Enrichment of 9\textit{t}-18:1 in fetal lipid was not the result of selective incorporation into the PC-1 position, because equal amounts of 9\textit{t}-18:1 were incorporated into PC-1 and PC-2. In contrast, research from the same laboratory reported that fetal livers from progeny of rats fed hydrogenated corn oil (52\% \textit{trans}) contained 2.5\% \textit{trans} compared to 5\% \textit{trans} in the maternal plasma, and no \textit{trans} fatty acids were detected in fetal heart or brain lipids (141). Related data for distribution of 8\textit{t}- and 12\textit{t}-18:1 in egg yolk lipids showed selective incorporation into the PC-1 position (57, 120, 121).

These and other data (48, 95, 170, 227, 232) indicate that the \textit{trans} fatty acid content of tissues depends on tissue, lipid class, total fat in diet, \textit{trans} content of diet, and probably on duration of feeding, species, and fatty acid composition of diet. The position and configuration of the double bond also have important effects on the incorporation and distribution of \textit{cis} and \textit{trans} positional isomers present in hydrogenated fats and oils. In fact, the \textit{trans} fatty acid content of tissues is an underestimation of the total isomeric fatty acid content, and based on in vitro and in vivo evidence, the \textit{cis} fatty acid isomers are as important as the \textit{trans} isomers.

As an example, the relative levels of \textit{cis} and \textit{trans} positional 18:1 isomers incorporated into heart, adrenal, adipose, and liver lipids were determined for rats fed HSBO containing 12.3\% \textit{trans} (171). Adrenal and adipose were nonselective for individual \textit{trans} isomers, but heart and liver were selective for \textit{trans} isomers. For heart and liver, the 14\textit{t}-18:1 percentage was three times higher, 11\textit{c}-18:1 was two times higher, and 12\textit{t}-18:1 was three times higher than in the diet. The ratio of 12\textit{c}-, 13\textit{c}-, and 13\textit{t}-18:1 percentages in these tissues were approximately the same as in the diet, and the ratio for the 8\textit{t}-, 9\textit{t}-, and 10\textit{c}-18:1 percentages was lower. Only one fourth as much 10\textit{c}-18:1 was found in liver lipids, and the 10\textit{t}- and 11\textit{t}-18:1 were almost totally excluded.

In the most exhaustive rat study to date, Wood et al (227) fed partially hydrogenated safflower oil (51\% \textit{trans}) and determined the distribution of \textit{cis} and \textit{trans} positional 18:1 isomers in TG, PC, PE, PS, and phosphatidylinositol (PI) from kidney, muscle, heart, liver, lung, spleen, and adipose tissue. In addition, liver PL were analyzed for \textit{cis} and \textit{trans} positional 18:1 isomer distribution in the 1-acyl and 2-acyl positions of PC and PE. Varying levels of selective incorporation and exclusion of each specific isomer were reported. The more notable results were the very strong exclusion of 10\textit{c}-18:1 from liver...
CE, TG, and PL and of 10t-18:1 from PL. The 12t-18:1 isomer was concentrated in PC and PE. This study also showed selective incorporation of the 8t- and 9t-18:1 into tissue TG, exclusion of 10c-18:1, and selective incorporation of 8t-, 9t-, 12t-, 13t-, 14t-, 11c-, 12c-, 13c-, and 14c-18:1 into many of the various tissue organ PE, PC, and SM fractions. For rat liver phosphatidylcholine, preferential acylation of the one position occurred with 11t-, 12t-, 13t-, and 14t-18:1 and 8c-, 11c-, 10c-, and 14c-18:1 isomers. Preferential acylation of the 2-acyl PC position occurred with 9t-, 10t-, and 9c-18:1. For rat liver phosphatidylethanolamine, acylation of the one position was preferred with 12t-, 11c-, 12c-, and 13c-18:1, and acylation of the two position was preferred for the 10t- and 9c-18:1 isomers. Differences in PC and PE acyl specificity for the other positional isomers were small. For the 10c-18:1 isomer, only very small amounts were incorporated, which indicated strong exclusion for both acyl positions. In vivo rat studies with diets containing 6c-18:1 and 8c-18:1 showed that isomers were incorporated primarily into the 1-acyl position of liver PC and PE at the expense of saturated fats and into adipose TG at the expense of 9c-18:1 (94).

Analysis of positional 16:1 isomers in rat tissue TG identified the 7t- to 14t-16:1 isomers. The percentages for the 8t-, 9t-, 10t-, and 11t-16:1 isomers were approximately 45, 19, 12, and 11% respectively, depending on tissue source and indicated preferential chain shortening or partial degradation of the corresponding t-18:1 positional isomers. In contrast, chain shortening of the c-18:1 positional isomers appears to be of minor importance based on the low levels of c-16:1 positional isomers.

The incorporation of stable isotope-labeled monoenoic isomers into human plasma lipids has been reported for the 9t-, 12t-, 12c-, 13t-, and 13c-18:1 isomers relative to 9c-18:1 (52, 55, 56, 58, 59). Discrimination against esterification of cholesterol with the 12t- and 13t-18:1 isomers was nearly absolute, with moderate discrimination observed for the other isomers. Selective acylation of the one position of PC was observed for all the isomers. Negative selection or discrimination against acylation of the 2-acyl position of PC was found for all the isomers except 12c-18:1, which is preferentially incorporated into the 2-acyl PC position. Incorporation of both the 13c- and 13t-18:1 isomers into the various other phospholipids was negative in contrast to the positive selective incorporation of the 9t-18:1 isomer. These data clearly indicate that enzyme selectivities are different for each isomer and depend on both the position and the configuration of the double bond. Comparison of data on humans and on rats indicates a considerable difference between species in metabolism of these isomers.

Turnover of the fatty acid isomers in human plasma lipids was not significantly different from that of 9c-18:1, and it is consistent with data for the isomeric fatty acid content of human tissues and with data from rats fed
ISOMERIC FATTY ACIDS

hydrogenated fats and then switched to diets containing nonhydrogenated oils. Similar data have been reported for disappearance of trans fatty acids from human milk lipids (105). Turnover of trans fatty acids in nerve PL of rats was slower than for heart and liver PL. Also, the rate of depletion of trans fatty acids in nerve PL was 50% faster when consumption of trans fatty acid isomers occurred after weaning rather than before (123).

Diene Isomers

Data on incorporation and distribution of diene isomers into tissue lipids are mainly limited to the geometrical isomers of c,c-18:2. The t,t-18:2 content in tissues from rats fed diets containing 5% (by weight) of a 1:1 mixture of c,c- and t,t-18:2 for 12 weeks was heart, 2.8%; kidney, 7.1%; lung, 1.0%; adipose, 1.6% (108, 231). These levels of t,t-18:2 are comparable to those in rats fed a diet containing 5% (by weight) of a mixture of 20.8% 9t-18:1, 47.5% t,t-18:2, 21.3% 16:0, and 9.5% 18:0. Even in the absence of dietary c,c-18:2, the t,t-18:2 content of liver, heart, kidney, and serum lipids ranged from only 2.1 to 7.3% (204). Similarly, serum lipids from rabbits fed 6 g of t,t-18:2 per day for 84 days contained only 2.1–2.5% t,t-18:2 in the various PL fractions, but the t,t-18:2 contents were 11% for TG and 13% for CE (218). These levels of t,t-18:2 incorporation are low in view of the amounts in the diet. The data suggest a strong exclusion for incorporation of t,t-18:2, especially into PL.

In contrast to the rat data, studies of the laying hen using t,t-18:2-3H and c,c-18:2-14C showed a slightly lower incorporation of t,t-18:2 into egg CE and no difference between the incorporation of radioisotope-labeled t,t- and c,c-18:2 into egg neutral lipid and PL (122).

The use of 14C-labeled t,t-18:2 to monitor its incorporation into rat brain, liver, and fetal lipids has resulted in some interesting observations. Studies on positional distribution of t,t-18:2 into rat brain phosphatidylcholine are contradictory. Using t,t-18:2-14C, 90% of the 14C label was found in the 2-acyl position of PC (104), but analysis of brain PC and PE from rats fed unlabeled t,t-18:2 indicates a preferential distribution into the 1-acyl PC position, while c,t-18:2 was preferentially incorporated into the 2-acyl PC position (36, 164).

These latter results are consistent with liver data from EFAD rats fed mixtures of t,t- plus c,c-18:2 and t,t-18:2 plus c,c,c-18:3. In this study, the t,t-18:2 content of liver 1-acyl PC was four times higher than that of 2-acyl PC (188).

However, the opposite results were reported for rat fetal PC that used t,t-18:2-14C (146). In this study, 80% of the t,t-18:2-14C was incorporated into the 2-acyl position, which was similar to the distribution observed for c,c-18:2-14C. In a related study, the levels of t,t-18:2-14C incorporated into rat fetal and placenta lipids were, respectively, three and six times higher than the levels of c,c-18:2 (145). The main reason for this difference probably was the higher
utilization of c,c-18:2-14C by the maternal tissue, which lowered the amount available for transport across the placenta.

The observation that t-18:1 positional isomers are desaturated to c,t- and c,c-18:2 positional isomers by rat liver microsomes provided an opportunity to obtain data on the distribution of these in situ biosynthesized diene isomers into the various microsomal lipid classes (175). The pattern for incorporation of positional dienoic acid isomers was complex, and specific isomers did not follow any particular pattern. In general, the c,c-18:2 isomers were enriched in the PL fraction, and c,t-18:2 isomers were selectively esterified into the cholesterol ester fraction.

IN VITRO SPECIFICITIES OF ENZYME SYSTEMS FOR ISOMERIC FATS

Several of the enzymes involved in lipid metabolism have been investigated by in vitro techniques to determine specific enzyme activity for individual fatty acid isomers. The data reviewed in this section complement in vivo data by providing nutrition-related metabolic and biochemical information that is otherwise difficult to obtain.

As discussed in the previous section, in vivo distribution and incorporation of dietary fat into tissue lipids depend on many factors and involve interrelated enzyme reactions, including enzyme selectivity for specific substrates. In contrast, the distribution of isomeric fats in vivo is determined by selective recognition of the unsaturated isomeric fatty acid structure by specific enzymes or enzymatic systems, but other factors also can be involved.

Lipases

As noted above, in vitro hydrolysis of triglycerides containing c-18:1 positional isomers by pancreatic lipase is nonspecific for isomers with the double bond between the 8 to 15 carbons (101). Animal and human absorption data also suggest that there is little if any difference in the hydrolysis of triglycerides containing isomeric fats in hydrogenated oils. In contrast, phospholipase is known to hydrolyze fatty acids selectively at the 2-acyl position of phospholipids, but there is no evidence for selective deacylation based on geometric or positional configuration of the double bond.

Acyl CoA Synthetase

Many lipid enzyme reactions require that long-chain fatty acids first be activated by formation of the acyl CoA esters. Reaction rates for formation of the acyl CoA derivative by mitochondria and microsomal preparations have been reported for the Δ4 through Δ17 positional isomers of c-18:1 (129), t-18:1 (130), and 16:0/t-18:2/c,c-18:2 (128). The reaction rates for the trans fatty
Acid isomers were higher than for the cis isomers, and the rates for the even-numbered trans positional isomers were greater than for the adjacent odd-numbered trans isomers. For both cis and trans positional 18:1 isomers, rates were lowest when the double bond was near the center of the acyl chain, and the lowest rate was for the 10c-18:1 isomer. Rates for acyl CoA ester formation for t,t- and c,c-18:1 were not significantly different (120). Acyl CoA ester formation rates were sensitive to temperature, fatty acid/protein ratios, detergents, and pH, which suggests that in vitro rates may be quite different from in vivo rates. The kinetics for acyl CoA synthetase activation of c,c-18:2 ω5, ω7, ω8, and ω9 isomers indicate the largest enzyme specificity was for the 9c,12c structure, with the Δ9c bond identified as the main determinant of acyl CoA synthetase specificity (202).

**Oxidation**

Oxidation of fatty acyl CoA ester isomers involves several β-oxidation cycles until a double bond is encountered (see Figure 1). If the fatty acid double bond is originally in an odd-numbered position, it is then conjugated with the carbonyl group by a Δ^3_Δ^2 enoyl-CoA isomerase. For even-numbered positional isomers the enoyl-CoA isomerase is not needed; but, for cis position-

![Figure 1](image-url)
al isomers, a 3-hydroxy acyl-CoA epimerase is required to convert the D-3-hydroxy isomer to the L-3-hydroxy isomer. The remainder of the β-oxidation steps are the same for all isomers.

In vitro oxidation of the Δ4 to Δ16 positional cis and trans 18:1 isomers by rat heart and liver mitochondria has been followed by measurement of oxygen uptake (125). Based on oxygen uptake, even-numbered cis-18:1 isomers were oxidized more slowly than the adjacent odd-numbered cis isomers, and most even-numbered trans-18:1 isomers were oxidized more rapidly than adjacent odd-numbered trans isomers. The t-18:1 isomers also were oxidized more slowly than their respective cis isomers. Explanations suggested for the slower oxidation rates include slower rates for CoA ester formation, slower transfer through cell membranes, and differences in reaction rates for the steps involving enoyl isomerase and hydroxy acyl-CoA epimerase. However, various in vitro investigations have not provided conclusive evidence that any of these specific steps is the rate-controlling reaction.

Several investigators have employed radioisotope-labeled fatty acid substrates to compare in vivo oxidation of various isomers to fatty acids present in nonhydrogenated fats and oils. The in vitro oxidation rate (formation of CO₂ plus soluble products) by rat liver mitochondria for uniformly ¹⁴C-labeled 9c- and 9t-18:1 was 20% lower for the 9t-18:1 isomer (7). In contrast, it was noted that oxidation rates based on ¹⁴CO₂ formation of ¹⁴C-carboxy-labeled 9c- and 9t-18:1 were nearly identical. In other studies, rat heart perfused with fatty acids complexed with albumin removed 9c, 12c-18:2 from the perfusate more rapidly than 9t-18:1 and less rapidly than 9c-18:1 (223). Respiratory activity of heart mitochondria was lower when rats were fed HSBO containing 48% t-18:1 for six weeks (95). Oxidation rates for ¹⁴C-labeled t,t-; c,t-; t,c-; and c,c-18:2 isomers injected into developed rat brain were similar (36). All of the in vitro data based on ¹⁴CO₂ release and O₂ uptake are at least qualitatively in agreement with in vivo rat data, which also showed slower oxidation rates for 9t-18:1. For example, in vivo oxidation of 9c-18:1 was 8–10% greater than of 9t-18:1 (8). However, male rat heart homogenates recently were reported to oxidize 9c- and 9t-18:1 with equal efficiency, in contrast to female rat heart homogenates, which oxidize 9t-18:1 faster than 9c-18:1. In addition, heart oxidation rates for rats pre-fed diets containing trans isomers were substantially higher for both 9c- and 9t-18:1 (141).

Recently, peroxisomal oxidation has been estimated to be responsible for 10–50% of the fatty acid oxidized by the liver (157). Peroxisome oxidation rates for t-16:1 and t-18:1 were reported to be higher than for the c-16:1 and t-18:1 isomers, in comparison to β-oxidation rates by rat liver mitochondria, where the rates for the trans isomers were about one half those of the cis fatty acids.
Other studies have reported increased peroxisomal oxidation levels for rats fed HSBO, trans fatty acids, hydrogenated marine oils, and high-fat diets (33, 97, 149, 206). In contrast, a 26-week in vivo rat study using hydrogenated marine oil, rapeseed oil, and peanut oil diets showed no increase in peroxisomal oxidation rates (91).

Retroconversion

In vitro data have provided evidence that chain shortening or retroconversion occurs for a number of isomeric fatty acids and to a greater extent than for 9c-18:1 or 9c,12c-18:2. Examples of retroconversion reactions observed in rat heart perfused with various positional 18:1 isomers are: 8t- and 8c-18:1→14:1; 9t-18:1→5t-14:1; 10c-18:1→12:1; 11t-18:1→5t-12:1. Conversion of 11c-18:1 and 10t-18:1 to shorter-chain-length fatty acid products was not detected (223). Utilization of 9t-18:1-1014C by mouse sciatic nerve cells grown in tissue culture also resulted in five times more radioactivity in the 16:1 fraction than with 9c-18:1-1014C (21). More 14:1 was also produced from 9t-18:1-1014C.

These in vitro data are consistent with in vivo rat fetal phospholipid data that reported 30% more 14C in 16:1 from 9t-18:1 when dams were fed labeled 9t-18:1 and 9c-18:1 (145). Wood (225) identified positional 16:1 isomers in tissues from rats fed hydrogenated safflower oil acids. In addition, increased levels of 16:1 in many tissue lipids have been observed in in vivo studies where 18:1 isomers or HSBO were fed, and this suggests that chain shortening of 18:1 isomers to 16:1 isomers is of possible nutritional importance. The retroconversion data for isomeric fats indicate that the β-oxidation cycle is interrupted or slowed after 1- to 3-acyl CoA residues are removed and that the chain-shortened fatty acid is ejected from the cycle.

Phospholipid Acyl transferase

The preferential incorporation of trans fatty acid isomers into the 1-acyl position of phospholipids has been observed in many in vivo studies and is generally considered evidence of phospholipid acyl transferase specificity. A recent example is taken from a study of rats fed a diet containing 18.5% (by weight) HSBO composed of 12.3% t-18:1 and 25% 18:2. The percentage of t-18:1 isomers incorporated was 8–20 times higher in 1-acyl PC than in 2-acyl PC, depending on the tissue type analyzed (170). Data from rats fed HSFO containing known amounts of individual positional cis and trans 18:1 isomers show a general preferential incorporation of these isomers into the 1-acyl position of phospholipid classes from a number of organs (140).

The in vivo data are in general agreement with in vitro acyl CoA:phospholipid acyl transferase rates reported for a series of Δ2 to Δ17 cis and trans 18:1
isomers (155, 173). For the series of t-18:1 positional isomers, the acyl transferase rates for esterification of the 1-acyl PC position were much more sensitive to double-bond position than the 2-acyl PC rates, and 1-acyl PC rates were significantly higher. Acyl transferase rates for the 10t- and 14t-18:1 isomers were very low compared to their adjacent odd-numbered positional isomers. For 1-acyl PC, the highest rates were obtained for the 8-, 9-, 11-, and 13t-18:1 isomers. Within the series of cis positional 18:1 isomers, the acyl transferase rates were higher for the 5-, 8-, 10-, 12-, and 15c-18:1 isomers than for isomers with double bonds adjacent to these positions. The highest reaction rate was found for 12c-18:1, which was 20% higher than for 8c-18:1, the second highest rate. Surprisingly, the rate for 12c-18:1 was about nine times that of the rate for 9c-18:1. With purified rat liver microsomes, the rate for acylation of the 2-position of PC with 9c-18:1 was 2.4 times higher than the second highest rate, which was for 12c-18:1. In comparison, rates with crude microsome preparations for 12c-18:1 were 3.3 times higher than for 9c-18:1, the second highest rate. These data suggest that the 12c double bond has special biological significance and is one factor responsible for the observed selective incorporation of 9c, 12c-18:2 into the 2-acyl position of phosphatidylcholine.

Others also have reported selective acyl transferase activity for specific positional isomers. Rat brain acyl transferase selectively esterified the 11c-18:1 isomer at the 1-position of PC compared to 9c-18:1, which was selectively incorporated into the 2-acyl PC position (147). Similarly, perfused chicken liver selectively incorporated 18:0, 9t-, and 11t-18:1 into the 1-acyl position of PE and PC relative to 9c and 11c-18:1, which were selectively placed in the 2-acyl positions (18).

The relative activities of rat liver microsome acyl transferase for cis and trans isomers of various chain lengths were 100 for 9c-18:1; 76 for 9c-16:1; 45 for 9t-16:1; 32 for 9t-18:1; 12.5 for 11c-20:1; 5.3 for 11t-20:1; and 0 for 13c- and 13t-22:1 with 1-palmitylglycerol 3-phosphate as a cosubstrate (136). Thus, both chain length and double-bond configuration influence selectivity.

The relative incorporation of tritium-labeled Δ5 to Δ15 cis 18:1 isomers into rat liver mitochondria lipids has been compared to that of 9c-18:1-14C (194). All the tritium-labeled isomers were selectively incorporated into total phospholipids compared to 9c-18:1-14C. In general, the odd-numbered isomers were incorporated at lower levels than the adjacent even-numbered isomers, and amounts incorporated increased when the location of the double bond was closer to the carboxyl and methyl ends of the fatty acid chain. No selective incorporation into the 2-acyl position of PC was found for the isomers, and strong discrimination was found for 14c- and 15c-18:1 (194). Many of these in vitro and in vivo results are not consistent, and there is much to be learned about the factors that determine the activity and selectivity of acyl transferase for monounsaturated isomers.
Compared to rates for the 18:1 isomers, the acyl transferase rates for incorporation of the diunsaturated \textit{trans} isomers into rat, cow, and human red blood cell phosphatidylcholine were quite different (215). Acylation of the 1-acyl position of PC by human red blood cell stromata was barely detectable. For the 2-acyl PC position, the acyl transfer rates (mol/min/mg protein) catalyzed by human stromata were 0.7 for 18:0; 5.3 for 9c-18:1; 3.7 for 9t-18:1; 2.4 for t,t-18:2; 3.9 for c,t-18:2; 11.4 for t,c-18:2; 14.0 for c,c-18:2; and 8.1 for 20:4. The difference in rates between the 9c,12t- and 9t-,12c-18:2 isomers reflects the importance of the 12c double bond in acyl transferase reactions. Rates for rat stromata were similar, except that values for the 9t- and 9c-18:1 were reversed in comparison to the human data.

The acyl transferase rates for esterification of 1- and 2-acyl PE and PC also have been reported for the entire series (2,5- to 14,17-) of methylene-interrupted \textit{c,c}-18:2 positional isomers (174). All of the acyl transfer reaction rates for the 2-acyl PC position were greater than or equal to the rates for the 1-acyl PC position, which is consistent with the preference for placement of polyunsaturated fats at the 2-acyl PC position. Highest activities were obtained for the 5,8-; 11,4-; 9,12-; and 13,16-18:2 isomers relative to the isomers with adjacent double bond systems. With 2-acyl PC as the substrate, highest activities were for the 8,11-; 12,15-; 13,16-; and 14,17-18:2 isomers. Reaction rates were low for all isomers when 1-acyl phosphatidylethanolamine was the substrate; with 2-acyl phosphatidylethanolamine as the substrate, high activities were for the 8,11-; 10,13-; 11,14-; 12,15-; 13,16-, and 14,17-18:2 isomers. In vivo positional specificity for incorporation of 9c,15c-, and 12c,15c-18:2 isomers into rat liver PC has also been reported (198). The 9c,15c-18:2 isomers were almost exclusively esterified at the 2-acyl position of PC, while 12c,15c-18:2 was equally distributed between the 1- and 2-acyl positions; this agrees very closely with in vitro data. Both reaction rates and in vivo data indicate that both double-bond positions in 18:2 are involved in controlling the reaction rates, and that the entire methylene-interrupted diene system is an important structural feature. The fact that the highest rates were not obtained for 9,12-18:2 is unexpected, given the recognized biological importance of linoleic acid.

**Cholesterol Esterase and Hydrolase**

Biosynthesis of cholesteryl ester is catalyzed by acyl CoA:cholesterol acyl transferase (ACAT) and lecithin:cholesterol acyl transferase (LCAT). Oleoyl CoA is the best substrate for ACAT, and LCAT favors the formation of polyunsaturated cholesteryl esters (67, 68, 199). In rats, the predominant pathway for cholesteryl esters synthesis involves ACAT; in humans, LCAT is the primary enzyme responsible for plasma cholesterol ester formation.
Relative reaction rates have been reported for a pancreatic cholesterol esterase (source unknown) using a number of fatty acid substrates (112). Both fatty acid chain length and double-bond configuration are reported to have significant effects on the reaction rates. Relative to 9c-18:1, the reaction rates for 9t-18:1, 11t-18:1, and 11c-18:1 were 0.5, and for 9t,12-18:2 it was 0.7. For comparison, the rate for stearic acid was 0.2 and for lauric acid, 0.8.

With ACAT from rat liver microsomes, the esterification rates indicated strong preference for acyl CoA esters of 9c-18:1 (192). The rates for 11t-18:1, 9t-18:1, 9c,12c-, and 9t,12t-18:2 were approximately 33% of the 9c-18:1 rate and 80% for 11c-18:1. These data plus in vivo data for ACAT and in vivo human CE data for LCAT suggest that both enzymes are very sensitive to double-bond position and configuration.

In contrast, rat liver cholesterol hydrolase activity for cholesterol esters containing the cis-18:1 positional (Δ2 to Δ17) isomers was relatively nonspecific (69). Maximum activity was reported for the 9c double bond, and activity gradually decreased as the double-bond position was moved towards either end of the fatty acid acyl chain. Hydrolysis rates for both 9t-18:1 and 9t,12t-18:2 were intermediate between those of 9c-18:1 or 9c,12c-18:2 and 18:0 or 16:0 (191).

Desaturases and Elongases

Dietary fatty acids, including isomeric fatty acids, are interconverted by desaturation and elongation to yield a number of fatty acid products. The enzymes and reaction pathways for interconversions of many of the non-isomeric fatty acids have been reviewed (25, 196, 197). Generally, mammalian systems cannot introduce a new double bond between a double bond in the 9 position and the methyl end of the fatty acid chain, although a few species have this capability to a limited extent (76). The lack of significant Δ12 desaturase activity accounts for the requirement that diets contain 9c,12c-18:2 and for its designation as an essential fatty acid.

In addition to undergoing desaturation and elongation, isomeric fatty acids also function as competitive inhibitors for desaturase and elongase activity. In vivo evidence for inhibition of desaturation and elongation of 18:2 by t,t-18:2 has been reported that shows that t,t-18:2 suppresses 20:4 levels in rat tissues (9, 36, 37, 108, 165). Depression of Δ6 and Δ9 desaturase activity by t,t-18:2 and HSBO has also been reported for rat brain (37, 85), and desaturase-elongase rates for t,t-18:2 and c,t(t,c)-18:2 were about six times slower than for c,c-18:2 (36). Conversion of c,t-18:2 to 20:4 occurs readily, but 9t,12c-18:2 conversion to 20:4 is very slow (9, 19, 81, 166). The t,t-18:2 isomer also inhibits desaturation-elongation of 18:1 and 16:1 to 20:3ω9 and 20:4ω7 (166).
In vivo results suggested that HSBO diets depressed Δ6 and Δ9 desaturase activity in rat liver, but not Δ5 desaturase activity (85). Rat liver microsome data indicated the degree of inhibition for each of the Δ3 to Δ16t-18:1 isomers on desaturation of 16:0, 18:2, and 20:3 depended on double-bond position (134). Competitive inhibitors for the Δ5, Δ6, and Δ9 desaturases were strongest for the following isomers: 3-, 9-, 13-, and 15t-18:1 (Δ5 desaturase); 5-, 4-, 7- and 15t-18:1 (Δ6 desaturase); and 3-, 5-, 7-, 10-, 12-, and 13t-18:1 (Δ9 desaturase). Desaturation of 18:0 by rat liver microsomes was also inhibited by the Δ2-to Δ17c-18:1 isomers, the Δ2- to Δ12-18:1 acetylenic acids, and the 6t-; 9t-; and 11t-18:1 isomers (32). However, Downing et al reported that 18:1 acetylenic acids did not inhibit desaturase activity (43).

The desaturation products of various positional cis and trans 18:1 and 18:2 isomers summarized in Tables 3 and 4 are largely from rat liver microsome studies (133, 135, 163). In comparison to c-18:1 positional isomers, t-18:1 positional isomers were desaturated to both c,t- and c,c-18:2 isomers by rat liver microsome preparations. Only Δ9 desaturase activity for t-18:1 positional isomers was observed by Mahfouz et al (135), but Pollard et al (163) observed desaturation of 8t-18:1 at the Δ5-position. In addition, the octadecadienoic acid isomers formed from Δ11t-, Δ13-, Δ14-, and Δ15t-18:1 were subsequently desaturated at the Δ6-position. Desaturation studies of the Δ4- to Δ11c-18:1 isomers by rat liver microsomes reported that the 8c and 11c were desaturated by Δ5 desaturase, 9c-18:1 was desaturated by Δ6 desaturase, and 10c and 11c were very slowly desaturated (133, 163). The Δ4- to Δ7c-18:1 isomers were not desaturated. In addition, a few cis and trans 16:1 and 17:1 isomers were reported to be desaturated to 16:2 and 17:2 isomers (163). Recently, conversion of the t-18:1 isomers to t,c- and c,c-18:2 isomers was confirmed by in vivo studies with rats (124). The conversion of trans monounsaturated isomers to cis, cis polyunsaturated isomers by rat liver apparently involves an isomerase as well as a desaturase. The observation that cis and trans 18:1 positional isomers are converted to octadecadienoic acid isomers is a factor that has not been considered in the interpretation of most physiological and metabolic studies with isomeric fatty acids.

Elongation of the Δ4- to Δ15t-18:1 isomers by rat liver reported the Δ4-, Δ5-, Δ6-, Δ13-, Δ14-, and Δ15t-18:1 isomers were not elongated and that very low rates for elongation of Δ8-, Δ10-, Δ11-, and Δ12t-18:1 occurred. The Δ7t- and Δ9t-18:1 were elongated to 20:1 (103).

Previous data indicate that rats have enzyme systems capable of the biosynthesis of a large variety of fatty acids. Nineteen 18:1 isomers, fifteen 18:2 isomers, and nine 18:3 isomers identified in tissue lipids from rats on a fat-free diet have been reported (182), and other similar data have been published (225, 226). Presumably these isomers are formed by desaturation of endogenously synthesized 18:0. This ability to synthesize a wide range of
<table>
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<tr>
<th>Substrate (18:1 isomer)</th>
<th>18:2 Product(s) structure</th>
<th>Reference</th>
</tr>
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### Table 4  Desaturation of octadecadienoic acid isomers

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<td>92, 166, 146</td>
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<tr>
<td>12c,15c</td>
<td>none</td>
<td>198</td>
</tr>
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</table>

Isomers has not been demonstrated in humans, but it suggests that rats might be expected to have a greater capability to metabolize isomeric fats from dietary sources than do humans. If this is the case, then rat data are not an accurate reflection of isomeric fatty acid metabolism in humans.

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