**trans** Fatty acids: infant and fetal development\(^1\) \(^2\) \(^3\)

**Susan E Carlson, M Thomas Clandinin, Harold W Cook, Edward A Emken, and Lloyd J Filer Jr**

**ABSTRACT**  This review evaluates scientific data associated with the possibility that trans fatty acids compromise fetal and infant early development. Concerns have been triggered by research that has heightened our awareness of the importance of n-3 and n-6 fatty acids; shown that trans fatty acids inhibit \(\Delta6\) desaturation of linoleic acid; identified trans fatty acid isomers in fetal, infant, and maternal tissues; and reported an inverse association between the trans fatty acid content of tissue lipids and measures of growth and development. Animal studies provide little evidence that trans fatty acids influence growth, reproduction, or gross aspects of fetal development. However, these models may not have been appropriate for addressing all the subtle effects that influence development of human infant retinal, neural, or brain function. Human studies are hampered by the complexity of the interrelations among nutritional, genetic, and environmental factors and by ethical considerations that constrain the research design. Existing data have not established a causal relation between trans fatty acid intake and early development. Conclusions cannot be drawn from the possible association found between trans fatty acid exposure and lower n-3 and n-6 long-chain polyunsaturated fatty acids and growth because of confounding factors. Few studies addressed the question of whether trans fatty acids adversely affect human fetal growth. One study reported a correlation between the trans fatty acid content of plasma and birth weight of preterm infants and one study reported a relation between preterm births and the trans fatty acid content of maternal plasma. Limited associative data have addressed whether trans fatty acids adversely affect fetal and infant neurodevelopment and growth. The interpretation of existing research and development of recommendations should be done cautiously. Suggestions for research to clarify these issues are made.  *Am J Clin Nutr* 1997;66:717S–36S.

**KEY WORDS**  trans Fatty acids, early development, infant, fetus, lipids, growth, metabolism

**INTRODUCTION**  The nutritional and biological effects of trans fatty acids from partially hydrogenated vegetable oils and other sources have been investigated extensively. Several review articles provide background information and summarize results from a wide variety of studies in animals and humans (1–5). A review by Berra (6) addresses some of the issues related to trans fatty acids and infant nutrition.

In North America and northern Europe, considerable concern exists about the effects of fat consumption on plasma cholesterol concentrations and atherosclerosis. Most research with trans fatty acids has focused on whether these isomers increase the risk of coronary artery disease. In recent years numerous studies have reported results that complicate our understanding of the basic relations between diet and heart disease. For example, all saturated fats are not equally cholesterolemic: trans fatty acids are metabolically different from cis and saturated fatty acids, and the n-6 and n-3 polyunsaturated fatty acids have disparate effects on coronary disease. Results from both older and more recent studies indicate that trans fatty acids are more cholesterolemic than cis fatty acids and less cholesterolemic than lauric (12:0) and myristic (14:0) acids. However, no studies have examined the effect of trans fatty acids in a diet with adequate essential fatty acids on the development of fatty streaks or atheromatous changes in blood vessels early in life. Most of the more rigorous human and animal studies indicate that dietary trans fatty acids are not a significant risk factor for acute myocardial infarction (1–5).

Less information is available on the effects of trans fatty acids on fetal and infant growth and development than on effects of trans fatty acids on heart disease. With few exceptions, adverse effects of trans fatty acids on growth, reproduction, and longevity were not detected by investigations using several animal species and multigeneration experiments (5, 7). The same is true for other fatty acids (branched chain, conjugated diene, short chain, long chain, brominated, and oxygenated) present in a normal diet. In contrast, negative health or physiologic effects of specific fatty acid structures can be shown in animal models when these fatty acids are fed in high amounts [e.g. acetylenic acids are potent inhibitors of eicosanoid synthesis, erucic acid causes fat deposits in myocardium, 12:0 increases serum cholesterol and low-density lipoprotein (LDL) concentrations, stearic acid disrupts reproduction, and odd-carbon medium-chain fatty acids suppress fatty acid oxidation].

The recent suggestion that trans fatty acids may affect human fetal growth and infant development (8–11) has prompted a review of this issue by government and health organizations (4, 12, 13). The concern about trans fatty acids centers on two observations: an inverse association between the percentage of trans fatty acids and n-6 long-chain polyunsaturated fatty acids.
acids in plasma lipids from premature infants (8-10) and a negative correlation between trans fatty acids and birth weight of premature infants (9, 11). One explanation suggested for the negative correlation is that trans fatty acids inhibit desaturation of essential fatty acids. All common dietary 18-carbon unsaturated fatty acids competitively inhibit Δ6 desaturation; the degree of inhibition is proportional to their relative rate of desaturation. Linoleic acid (18:2n-6) is a stronger inhibitor of Δ6 desaturation than is oleic acid (18:1) (14, 15). The long-chain n-3 fatty acids products formed from linolenic acid (18:3n-3) are also strong inhibitors of both Δ6 and Δ5 desaturation of n-6 fatty acids (16).

The trans-18:1 isomers are poor substrates for Δ6 desaturase and should have a minimal effect on Δ6 desaturation of 18:2n-6 and 18:3n-3. Inhibition of Δ6 desaturation is likely one of several mechanisms that prevent excess production and accumulation of long-chain n-6 and n-3 polyunsaturated fatty acids in cell membranes. However, there is still much that is not understood about the regulation of n-6 and n-3 fatty acids (17). For example, it is not known why the addition of arachidonic acid (20:4n-6) to some cultured cell lines stimulates the conversion of 18:2n-6 to 20:4n-6 (18, 19) or why supplementation of human diets with 20:4n-6 enhances the conversion of deuterium-labeled dihomo-γ-linolenic acid (20:3n-6) to 20:4n-6 (20). Fatty acid composition data for blood lipids suggest that a marginal essential fatty acid deficiency develops in mothers during pregnancy and lactation (13, 21), but it is difficult to determine from blood lipid data whether a mother’s stores of essential fatty acids are sufficient for the requirements of fetal development. The regulation of fatty acid composition of tissue lipids cannot be explained by what we know about desaturation and acylation of phospholipids and β-oxidation.

Determining whether trans fatty acids affect human fetal and infant growth and development is a complicated issue that is difficult to investigate. It is difficult to control for many factors (eg, nutritional status, lifestyle, genetic background, and general health of the mother) that may influence fetal growth, neurodevelopment, and maturation. Mechanisms appear to exist in a normal fetus and infant that can compensate for some nutritional and environmental diversity, which may obscure some of the effects of trans fatty acids.

The role of trans fatty acids and other fatty acids, such as 18:1, in infant growth and development is an important issue that has not been extensively examined. The purpose of this review is to summarize the fundamental biochemical and related nutritional information and to discuss the strengths, consistencies, and inconsistencies with respect to trans fatty acids and early development.

**NUTRITIONAL FACTORS INFLUENCING FETAL GROWTH AND DEVELOPMENT**

A variety of factors influence fetal growth and development [see review by Susser and Stein (22)]. The conclusions of Susser and Stein, based primarily on an analysis of pregnancy and nutritional data collected during the Dutch famine of 1944-1945, demonstrate the effect of famine (acute malnutrition) on fertility, maternal weight, prematurity, birth weight, and infant growth. Susser and Stein also reviewed studies of second-generation effects as reported by Lumey et al (23). When famine reduced total energy and protein intake to one-third the usual level, infant birth weight, length, and head circumference were reduced and postnatal deaths were increased. At 19 y of age, obesity and catch-up growth for height and weight were more evident in persons exposed to famine during the first 4 mo of gestation, but mental performance was unimpaired. At age 50 y, there was an association between famine exposure and schizophrenia, which was stronger for women than men (24).

Studies by Rush et al (25) found no relation between improved maternal nutrition and birth weight or the percentage of low-birth-weight infants in mothers enrolled in the US Department of Agriculture’s Women, Infants and Children (WIC) supplemental food programs. However, head circumference at birth was greater for infants of mothers in the WIC program than for control infants. Women living in developing countries deliver more low-birth-weight infants than are reported for developed countries. Factors that may be responsible for this difference are chronic marginal nutrient intake, increased exposure to infectious disease, higher use of tobacco and alcohol, hard physical labor, and poor sanitation.

The dominant factors that influence the percentage of low-birth-weight infants in the United States are maternal race, age, and lifestyle (use of tobacco or alcohol) (Table 1). Maternal racial origin, in particular, strongly influences the incidence of low-birth-weight infants (26). Multiple births is another factor related to birth weight. Trends in the percentage of low-birth-weight infants by race born in the United States from 1970 to 1993 are shown in Figure 1 (26). The overall rate for infants born with birth weights < 2500 g in 1993 was 7.2%, the highest rate reported since 1976. In 1980, low-birth-weight infants were 6.8% of total births. The rise from 6.8% in 1980 to 7.2% in 1993 can be attributed to an increase in multiple births, which are nine times more likely to be of low birth weight than are singletons. Thus, as the multiple birth ratio increased from 19.3 to 25.2 per thousand births during this time, an increase in the incidence of low-birth-weight infants occurred. This effect was more pronounced among white mothers, who account for 79% of total births and thereby drive overall trends. In vitro fertilization and other therapies for infertility are known to result in multiple births. During the past

**Table 1**

<table>
<thead>
<tr>
<th>Age</th>
<th>White</th>
<th>Black</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>6.0</td>
<td>13.3</td>
<td>7.2</td>
</tr>
<tr>
<td>&lt; 15 y</td>
<td>10.4</td>
<td>16.3</td>
<td>13.5</td>
</tr>
<tr>
<td>&gt; 25-29 y</td>
<td>5.3</td>
<td>13.1</td>
<td>6.4</td>
</tr>
<tr>
<td>40-44 y</td>
<td>7.5</td>
<td>17.0</td>
<td>8.7</td>
</tr>
<tr>
<td>Smoker</td>
<td>10.1</td>
<td>22.6</td>
<td>11.8</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>5.2</td>
<td>12.0</td>
<td>6.6</td>
</tr>
<tr>
<td>Drinker</td>
<td>NA</td>
<td>NA</td>
<td>14.2</td>
</tr>
<tr>
<td>Nondrinker</td>
<td>NA</td>
<td>NA</td>
<td>7.2</td>
</tr>
</tbody>
</table>

1 Adapted from reference 26. NA, not available.
decade, these practices were more frequently used by white women.

Normal functioning of the brain at any stage of development depends on the number and location of neurons, degree of differentiation (structure and metabolism), ability of neurons to generate action potentials, number of synapses between neurons and between neurons and their targets, differentiation of synapses, organization of the total network for sensory reception, information processing, and action responses (27). Nutritional factors may interfere with developmental processes during these critical periods (28). However, the effect on the developing brain would show regional variation (29). Model experiments show that dietary fatty acids induce modifications in the lipid composition of cell membranes and organelles in the brain (30–33). An alteration in the fatty acid composition of brain lipids may ultimately affect functioning of the brain via changes in cell growth (34), cell division (35, 36), or enzyme activities (34, 37, 38) or by distorting brain cell structures (39). Even under conditions of a nutritionally adequate diet, brain metabolism may be influenced by variations in the quantitative and qualitative aspects of fatty acids in the food consumed (31, 33, 40).

Functional connections in the nervous system are established through the growth of neurites (axons and dendrites) and formation of synapses. Molecules that mediate axon growth and extension occur through expanded motile structures at the axon tip (41). These distinctive structures, termed "growth cones," are a highly specialized feature of neuronal differentiation that specifically contributes to establishing cell-to-cell connections. Fine spikes (called filopodia) that extend beyond the axon tip generally perform receptive processes (42). The period of neuronal differentiation with formation of dendrites and synapses is a prenatal and a postnatal event in both humans and rats (43). The fatty acid composition of membranes during these processes is altered by changes in dietary fat intake (44, 45). Mechanisms involved in growth and guidance of axons appear to be both specific and nonspecific; axons can be directed toward a specific target (cell connection) (46, 47) or they can follow preformed pathways (48). Coordination of several simultaneous events may be operational in producing the precise axon-target pathway.

Stages of brain morphogenesis ensue in each brain region in a specifically timed series of events, with each period critical for the development of the next (49). The various time scales occurring in each brain region are further complicated by the migration of cells between regions. Because of the general inability of the brain to regenerate cells and its dependence on specialized interactions, any misdirected, mistimed, or absent developmental event can disrupt the systematic progression toward normal development. A disruption in the proper formation of a certain structure or specific neuronal pathway can potentially lead to structural aberrations (50). These structural changes may be irreversible and thus can result in functional deficits if future developmental events are unable to compensate for them. No specific information is available on compensatory mechanisms. Changes in brain membrane composition can be induced by dietary fat (31), but a specific mechanism for how these changes in the fatty acid composition of lipid may change brain development and function is not clear. Various studies imply that dietary fat may alter brain functions and behavior, but the linkage of specific developmental events with biochemical events in the brain has not been made.
FOOD SOURCES AND ESTIMATED CONSUMPTION

Sources

Trans Fatty acid isomers are a side product of catalytic hydrogenation of vegetable oils and of biohydrogenation in the rumen of animals. Sources of trans fatty acids in the US diet are foods that contain partially hydrogenated vegetable oil (eg, margarine and shortening) and ruminant fat (eg, meat and dairy products). In some European countries, hydrogenated marine oils are an additional source of dietary trans fatty acids. In recent years, the amount of trans fatty acids in European and North American diets has remained relatively constant. The trend toward decreased total fat intake and production of margarines with a lower trans fatty acid content may reduce trans fatty acid intake (51–54; SK Egan, C Caughman, LM Barra, JS Douglas, BE Sever, JT Heimbach, unpublished observations, 1996).

Partially hydrogenated vegetable oil is the primary source of trans fat in the US food supply, providing 80–90% of the trans fatty acids in the diet. Partial hydrogenation reduces the polyunsaturated fatty acid content of vegetable oils, increases their melting point, and improves their oxidative and thermal stability. These changes facilitate the use of liquid vegetable oils in a variety of food products. The trans fatty acid content of food products containing partially hydrogenated vegetable oil varies widely within a product category and among categories (55) (Table 2). The main reasons for this variability are that (1) the trans fatty acid content of partially hydrogenated vegetable oil depends on the type of hydrogenation catalyst and conditions (eg, temperature, hydrogen pressure, and time), (2) food products often contain a blend of different types of partially hydrogenated and unhydrogenated vegetable oils (eg, soybean, canola, corn, and sunflower), (3) the proportion of hydrogenated and unhydrogenated oil in these blends is varied to obtain the desired physical properties, and (4) the total fat content can vary considerably within a product category. In contrast with the variation in the total trans fatty acid content, the variability of the relative percentages of the individual trans fatty acid isomers is small. The relative percentages of the major trans-18:1 isomers in products containing partially hydrogenated vegetable oil are 9.7% 8t-18:1, 17.3% 9r-18:1, 21.7% 10r-18:1, 20.3% 11r-18:1, 14.0% 12r-18:1, 9.7% 13r-18:1, and 5.0% 14r-18:1. These trans-18:1 isomers represent ~90% of the total trans fatty acids. The 9r,12c-18:2 and 9c,12r-18:2 isomers are present in about equal amounts and represent ~9% of the total trans fatty acids (5).

The trans fatty acid content of dairy fat is more constant. For example, butter contains ~3.4% (range 2–7%) trans fatty acids. The variation in the trans fatty acid content of butter occurs because milk fat from grass-fed animals typically has a higher trans fatty acid content than does milk fat from grain-fed animals (7). Thus, the trans fatty acid content of winter

<table>
<thead>
<tr>
<th>Product category</th>
<th>Percentage of total fat</th>
<th>trans Content per serving</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t-18:1</td>
<td>t,c, or c,t-18:2</td>
</tr>
<tr>
<td>Margarine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stick, hard, soy (n = 52)</td>
<td>24.1 (19-41)</td>
<td>2.1 (0-7)</td>
</tr>
<tr>
<td>Tub, soft, soy (n = 44)</td>
<td>14.4 (9-21)</td>
<td>1.9 (0-9)</td>
</tr>
<tr>
<td>Shortening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commercial, soy (n = 2)</td>
<td>33.6 (30-38)</td>
<td>3.8 (3-4)</td>
</tr>
<tr>
<td>Household, soy (n = 28)</td>
<td>14.5 (9-27)</td>
<td>4.1 (1-7)</td>
</tr>
<tr>
<td>Oils</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooking, soy (n = 12)</td>
<td>8.0 (5-11)</td>
<td>2.8 (1-6)</td>
</tr>
<tr>
<td>Salad, soy (n = 3)</td>
<td>0.9 (0-3)</td>
<td>0.7 (0-2)</td>
</tr>
<tr>
<td>Bakery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cookies, sugar (n = 43)</td>
<td>15.0 (3-32)</td>
<td>1.8 (0-5)</td>
</tr>
<tr>
<td>Cake, coffee (n = 3)</td>
<td>9.6 (9-11)</td>
<td>1.0 (0.8-1.1)</td>
</tr>
<tr>
<td>Bread, commercial (n = 43)</td>
<td>6.8 (0-30)</td>
<td>1.2 (0-4)</td>
</tr>
<tr>
<td>Fast foods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk shake (n = 12)</td>
<td>2.0 (2-3)</td>
<td>0.3 (0-1)</td>
</tr>
<tr>
<td>Hamburger (n = 11)</td>
<td>3.6 (3-5)</td>
<td>0.3 (0-0.5)</td>
</tr>
<tr>
<td>Snacks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chips, potato (n = 24)</td>
<td>10.0 (0-34)</td>
<td>1.7 (0-7)</td>
</tr>
<tr>
<td>French fries (n = 11)</td>
<td>18.7 (3-32)</td>
<td>1.4 (0-3)</td>
</tr>
<tr>
<td>Dairy products</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Butter (n = 10)</td>
<td>2.9 (2-6)</td>
<td>0.3 (0-1)</td>
</tr>
<tr>
<td>Milk, whole (n = 4)</td>
<td>2.1 (2-3)</td>
<td>0.8 (0.7-1)</td>
</tr>
<tr>
<td>Meats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beef, lean, raw (n = 9)</td>
<td>3.2 (2-5)</td>
<td>0.2 (0-0.3)</td>
</tr>
<tr>
<td>Pork, lean, raw (n = 7)</td>
<td>0.2 (0-0)</td>
<td>0.00 (0-0)</td>
</tr>
<tr>
<td>Chicken, lean, raw (n = 3)</td>
<td>0.9 (1-1)</td>
<td>0.3 (0.2-0.4)</td>
</tr>
</tbody>
</table>

1. f (range in parentheses). Adapted from Nutrient Data Bank Bulletin Board (US Department of Agriculture) and reference 55.
2. n is number of individual means from different data sets used to calculate a mean of means.
butter is lower than that of summer butter. The distribution of the trans-18:1 isomers in butter differs from the distribution in partially hydrogenated vegetable oil in that the 11t-18:1 isomer represents \(\approx 60\%\) of the total trans-18:1 isomers (5).

**trans Fatty acid intake**

The methods used to calculate intake of the trans fatty acid isomers in the US diet produce different estimates (1, 56–65) (Table 3). Estimates of trans fatty acid intake based on availability or disappearance data are the highest (8.1–12.8 g/d per capita). Estimates based on food questionnaire data are the lowest (2.6–4.6 g/d). These differences are not unexpected because availability data tend to overestimate actual intake whereas questionnaire, diet-record, and recall data generally underestimate intake (67).

Estimates for trans fatty acid intake based on composition data are included in Table 3 to illustrate the correlation between the trans fatty acid content of human milk and adipose tissue and dietary trans fatty acid intake (66, 68). The relation between the elaidic acid (t-18:1) content of adipose tissue and estimates for dietary trans fatty acids (\(r^2 = 0.73\)) is expressed by the following linear regression equation (Figure 2) (57–59, 63, 69–78):

**trans Fatty acids in diet (g/d)**

\[
= 1.52 \pm 2.40 \text{ (} \% \text{ t-18:1 in adipose tissue)} \quad (1)
\]

[Adipose tissue data for studies with small numbers of subjects are not included (79–84).]

Another approach used to estimate trans fatty acid intake is to measure their concentration in adipose tissue. Animal data indicate that the percentage of trans fatty acids in adipose tissue is about half that found in dietary fat (5). For human milk, the following equation has been used to express the relation between percentage trans fatty acids in milk and percentage trans fatty acids in diet (66):

\[
t-18:1 \text{ in milk (})\%\text{ } = 1.49 + 0.42 \times \text{dietary } t-18:1 \text{ (})\%\text{ } \quad (2)
\]

This relation is based on limited data and has not been independently confirmed.

The total trans fatty acid content of the US diet, estimated from adipose tissue, is 8.0 g/d (10% of a diet containing 80 g fat), of which 6.4–6.7 g is from partially hydrogenated vegetable oil. Human milk from US subjects contains 3.7 \(\pm 2.3\%\) t-18:1 (65), which translates to \(\approx 5.3\%\) t-18:1 or 4.2 g/d, again assuming fat intake of 80 g/d. The highest reported t-18:1 content for milk samples is 5.9 \(\pm 2.5\%\) t-18:1 for a group of 198 Canadian mothers (85), which indicates that their diet contained 10.5% t-18:1 or 8.4 g/d, assuming a fat intake of 80 g/d. The authors estimated 10.6 g total dietary trans fatty acids/d for a 78-g fat intake by using the percentage of total trans fatty acids in milk rather than the percentage of t-18:1 as was used in the original regression equation.

Intakes of both total fat and trans fatty acids vary widely among individuals, as illustrated by the consumption data reported for British adults (4). Mean trans fatty acid intake was 5.6 g/d for men and 4.0 g/d for women (5.5% and 5.4% of mean total fat intake, respectively). However, intake at the 97.5 percentile was 11.3 g/d for men and 8.8 g/d for women. The general frequency distribution pattern for individual trans fatty acid intakes was skewed such that trans intakes were less than the means for \(\approx 61\%\) of the men and \(\approx 80\%\) of the women.

Data from phase I of the third National Health and Nutrition Examination Survey (1988–1991) show that mean dietary fat intake is 95 \(\pm 67\) (median: 90) to 116 \(\pm 87\) (median: 106) g/d for males aged 20–60 y and 63 \(\pm 45\) (median: 59) to 75 \(\pm 52\) (median: 70) g/d for females aged 20–60 y (86). These data for total fat intake also show that the total fat intake frequency-distribution curve is skewed.

In summary, for US diets, means for estimated dietary trans fatty acid intakes as a percentage of total fatty acid intake are \(\approx 5\%\) (food-questionnaire data), 10.3% (availability data),

<table>
<thead>
<tr>
<th>TABLE 3</th>
</tr>
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<tbody>
<tr>
<td>Estimated per capita consumption of dietary trans fatty acids in the United States*</td>
</tr>
<tr>
<td>Basis for estimate</td>
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<tr>
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<tr>
<td></td>
</tr>
<tr>
<td>Disappearance data</td>
</tr>
<tr>
<td>Disappearance data</td>
</tr>
<tr>
<td>Food-frequency data (n = 115 F)</td>
</tr>
<tr>
<td>Food-frequency data (n = 748 M)</td>
</tr>
<tr>
<td>Food-frequency data (n = 220 M, 62 F)</td>
</tr>
<tr>
<td>Analysis of duplicate diets (n = 8)</td>
</tr>
<tr>
<td>Adipose data (n = 115 F); 4.4% total trans*</td>
</tr>
<tr>
<td>Adipose data (n = 76 M); 3.6% total trans*</td>
</tr>
<tr>
<td>Adipose data (n = 118 M); 4.17% total trans*</td>
</tr>
<tr>
<td>Milk data (n = 52); 3.7% t-18:1*</td>
</tr>
<tr>
<td>Adipose data (n = 76 M); 2.7% t-18:1*</td>
</tr>
</tbody>
</table>

*NA, not available.

* For calculation of trans fatty acid intake (g/d), percentage total trans fatty acids in adipose tissue was multiplied by 2.0 and then multiplied by the estimate for total dietary fat intake.

* 0.5% cis-trans conjugated diene isomers of linoleic acid are not included in the total percentage trans fatty acid adipose value.

* trans Fatty acid intake (g/d) calculated from the regression equation for human milk (66) and data for milk lipid samples from reference 65.

* trans Fatty acid intake (g/d) calculated from the regression equation (see Figure 2) and adipose tissue data from reference 63.
8.1% (disappearance data), 8.4–10% (adipose data), and 5.3% (milk data), but the uncertainty associated with these means is large. The median values of ~8% and ~6.4 g/d appear to be reasonable best-guess estimates for the \( \text{trans} \) fatty acid content of the diets of US mothers.

**BIOCHEMICAL AND METABOLIC INTERACTIONS OF \( \text{trans} \) FATTY ACIDS**

Mammalian systems cannot permanently introduce a bond of the \( \text{trans} \) geometric configuration into fatty acyl chains (only temporarily in intermediates of de novo fatty acid synthesis and \( \beta \)-oxidation); only \( \text{cis} \) double bonds are produced by the oxygen-dependent desaturases of mammalian tissues. Thus, \( \text{trans} \) fatty acids found in the lipids of body tissues of humans and other mammals must be derived from dietary sources, whether they accumulate in complex lipids as the original \( \text{trans} \) fatty acid or as a product of desaturation, elongation, or oxidation still containing a \( \text{trans} \) double bond.

Extensive evidence indicates that incorporation of acyl chains containing \( \text{trans} \) double bonds occurs in body tissues and fluids of humans and experimental animals (5, 7). In general, there is limited selectivity for, but some apparent discrimination against, incorporation of \( \text{trans} \) fatty acids (5, 7). Thus, \( \text{trans} \) fatty acids are not excluded from any metabolically active body tissue and accumulation of \( \text{trans} \) fatty acids relative to other dietary fatty acids usually reflects dietary intake generally but not quantitatively. The extent of incorporation of individual \( \text{trans} \) fatty acid isomers into tissue lipids can be different for specific tissues and for phospholipid and neutral lipid classes within a tissue (2). Different relative metabolic turnover rates for fatty acids in different tissues are partly responsible for tissues accumulating different percentages of \( \text{trans} \) fatty acids (eg, metabolically active tissues, such as liver and adipose, accumulate more \( \text{trans} \) fatty acids than does brain tissue). Different acylation-deacylation rates for complex lipids also contribute to this effect.

Studies with rats during late stages of fetal development indicate little discrimination in placental transport among \( \text{cis} \)-18:1; \( \text{cis} \)-12:1; \( \text{cis} \)-18:2; or monoenes and dienes with \( \text{cis} \) bonds (87). The \( \text{trans} \) fatty acid content of the following tissue lipids decreases in the order listed: maternal plasma > placenta > fetus. In feeding studies with pigs, inclusion of partially hydrogenated fish oil or soybean oil containing 19–36% \( \text{trans} \) fatty acids in maternal diets did not alter fatty acid composition of brain in fetal (88) or suckling (89) piglets; moderate alterations were observed in other organs of suckling animals. Discrimination against incorporation of \( \text{trans} \) fatty acids into human fetal tissue has been suggested (2, 90), although most studies indicate that absorption and reesterification of acyl chains containing \( \text{trans} \) double bonds are not highly selective. Generally, \( \text{trans} \) fatty acids occur in cord blood lipids at concentrations lower than in maternal blood (91), although one study indicates similar percentages of \( \text{trans} \) fatty acids in maternal and infant plasma at the time of delivery (8). The extent to which placental transfer and fetal incorporation of \( \text{trans} \) fatty acids are influenced by the presence of essential fatty acids is not known.

Animal studies would usually be used to provide information about the possible significance of maternal-fetal transfer of fatty acids. However, although experimental animals have been fed partially hydrogenated vegetable oil containing \( \text{trans} \) fatty acids for several generations without effects on growth, reproduction, and longevity (92–96), these studies do not address the major concern that has been raised in studies of infants and children, namely that \( \text{trans} \) fatty acids may alter neural long-chain polyunsaturated fatty acid accumulation and thereby alter neural function. Two animal studies reported elevated brain 22:5n–6 concentrations after fairly high intakes of \( \text{trans} \) fatty acids (89, 97), evidence that brain long-chain polyunsaturated fatty acids may be influenced by \( \text{trans} \) fatty acid intake. No animal study has looked at neural function.

**Metabolic conversions of \( \text{trans} \) fatty acids**

A wide variety of \( \text{trans} \) monounsaturated and \( \text{cis} \),\( \text{trans} \) polyunsaturated fatty acids can be desaturated, elongated, and oxidized to produce unusual isomers compared with \( \text{cis} \) fatty acids normally involved in membrane structures, eicosanoid
production, and signal transduction (14). It is generally assumed that fatty acids containing trans double bonds can be substrates for the same enzymes involved in metabolism of unsaturated fatty acids with cis double bonds (see Figure 3). Monoenoic fatty acids (one trans double bond) are generally the most prominent class of dietary trans fatty acids. Several positional isomers of trans monoenoic can be converted by oxidative desaturation to products containing cis,trans-; trans-cis-; or cis,cis-configurations (98, 99), but such conversions have not been observed in vivo when there have been adequate concentrations of essential fatty acids (100, 101). Dietary fatty acids containing trans bonds in either the Δ7- or Δ11-position in the acyl chain are the best substrates for oxidative insertion of a Δ9 cis bond by the Δ9 desaturase that is usually most active with stearoyl-CoA and present in many mammalian tissues, including liver, mammary gland, and brain. In contrast, the potential for desaturation of a trans monoenoic acyl chain at the Δ6 or Δ5 positions is relatively low. Thus, conversion of trans fatty acids to more unsaturated products is possible but generally is restricted relative to desaturation of saturated or cis-monoenoic fatty acids. trans Acyl chains, particularly 18:1 isomers, can be elongated to 20- and 22-carbon fatty acids by chain-elongation complexes associated with the endoplasmic reticulum or, possibly, mitochondria (102). Like unaltered dietary trans fatty acids, the desaturation and elongation products are incorporated into phospholipids (103); however, amounts of conversion products are small and usually are not found in tissue lipids.

Polysaturated fatty acyl chains containing at least one trans bond and additional cis or trans bonds can be further converted by desaturation and chain elongation but usually at considerably lower rates than that for 9c,12c-18:2. No conversion of 9t,12t-18:2 to trans 20:4 was noted in developing brain (104) and in rats deficient in essential fatty acids (105), but other evidence supports formation of small amounts of 20:4 containing one or more trans bonds at rates that are 1–10% that of 9c,12c-18:2 formation in neonatal brain (106). Accumulation of intermediates with one or more trans bonds, including 18:3, 20:3, or the 20:2 product of direct elongation, can be nearly equal to or greater than that of intermediates derived

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**FIGURE 3.** Desaturation and chain elongation and β-oxidation of dietary essential fatty acids in animal tissues. Desaturase-catalyzed desaturation steps are indicated by the horizontal arrows and elongase-catalyzed 2-carbon chain-elongation steps by the downward-pointing vertical arrows. β-Oxidation steps are shown by the upward-pointing vertical arrows. Type size for individual fatty acids reflects qualitatively the relative accumulation in tissues. For example, large type size indicates fatty acids that are major components of tissue lipids and small type size indicates fatty acids that are minor components of tissue lipids.
from 18:2. These results suggest that Δ5 desaturation may be the most limiting step in the conversion of 9t,12t-18:2 to a trans 20:4 isomer.

The metabolism of 9c,12c- or 9t,12t-18:2 appears to be more complex than the metabolism of 9c,12c- or 9t,12t-18:2. In mouse liver, 9c,12c-18:2 was converted to 20:4 at a rate approximately equal to that of 9t,12t-18:2, whereas conversion of 9t,12t-18:2 was only about 20% as effective (107). Accumulation of intermediates (ie, 18:3 and 20:3) in the conversion of a mixture of 9t,12c- and 9c,12c-18:2 to 20:4 is not extensive in neonatal rat brain (106). Although there is less experimental evidence comparing conversion of fatty acids containing both a trans and a cis n-3 bond to more polyunsaturated fatty acids, a recent report indicates potential for converting this class of trans fatty acids in brain and retina (97). Accordingly, many polyunsaturated fatty acids with one or more trans bonds can be converted by desaturation and chain elongation to more unsaturated derivatives but, in general, rates of conversion are appreciably less than for more abundant fatty acids containing only cis double bonds. Some conversion of trans fatty acids by desaturation and chain elongation can occur, but metabolites of trans fatty acids cannot substitute for essential fatty acids or their products. Furthermore, polyunsaturated fatty acids formed from 18:2n-6 and 18:3n-3 isomers containing trans bonds do not accumulate in adult human tissue lipids and appear to be of limited nutritional and metabolic significance; however, their potential for influence in developing tissues remains unknown.

Although there is some controversy in the literature about the relative rates of oxidation and chain shortening of trans fatty acids relative to cis or saturated fatty acids, substantial evidence indicates that β-oxidation rates in rats for trans-18:1 isomers are lower than for 9c-18:1 (108–111). In humans, oxidation rates in whole-body studies with 13C-labeled fatty acid substrates (112) and with heart homogenates (113) were similar for 9t-18:1 and 9c-18:1. The oxidation system found in peroxisomes is used for β-oxidation of trans unsaturated fatty acids (114, 115), but relative contributions of the peroxisomal and mitochondrial systems are not clear.

Interactions of trans fatty acids with metabolism of other fatty acids

Competition of trans fatty acids with the normal metabolism of fatty acids without trans double bonds is apparent in most studies, and specific interactions are complex and varied. Generally, competitive interactions have been shown only in the presence of a deficiency of essential fatty acids or in isolated tissue preparations, suggesting a limited effect under normal conditions. In brain preparations from neonatal rats, desaturation of stearoyl-CoA by the Δ9 desaturase is unaltered by t-18:1, but 9t,12t-18:2 inhibits Δ9 desaturase by ≈35%; however, this is considerably less than the 50% inhibition by 9c,12c-18:2 (116). In studies with human skin fibroblasts, 9t-18:1 increased Δ9 desaturation of stearic acid (18:0) whereas 11t-18:1 and 9t,12t-18:2 had no effect (117).

Competitive interactions of trans fatty acids with metabolism of essential fatty acids seem even more complicated. It is well established that 18:2n-6 and 18:3n-3 are metabolized to the prominent end products 20:4n-6 and eicosapentaenoic acid (20:5n-3), respectively, by a pathway involving Δ6 desaturation, chain elongation, and Δ5 desaturation (Figure 3) (118, 119). Alternative pathways may be used in specific cells and certain nutritional situations (120). Further metabolism of 20:5n-3 to docosahexaenoic acid (22:6n-3), classically thought to involve a chain-elongation step and Δ4 desaturase (118), now appears possible by a pathway involving two chain-elongation steps, Δ6 desaturation, and a chain-shortening step (121, 122), the latter occurring in peroxisomes (123). A similar pathway may be involved in the conversion of 20:4n-6 to docosapentaenoic acid (22:5n-6) (124).

Nothing is known about the influence of trans fatty acids on this so-called Sprecher pathway, but that is appreciable information about the interaction of trans fatty acids with the initial alternating sequence of Δ6 desaturation, chain elongation, and Δ5 desaturation in the formation of 20:4n-6 and 20:5n-3 (Figure 3). In intact animals and rat-liver preparations, Δ6 and Δ5 desaturases are inhibited by some but not all 1t-18:1 positional isomers (125, 126). In studies with cells in culture, all trans monoenes inhibited Δ5 desaturation of 20:3n-6 with 18:2n-6 as the initial substrate, with little evidence for discrimination based on the position of the trans bond in the acyl chain. By contrast, 20:5n-3 formation from 18:3n-3 was inhibited only by trans fatty acids with a trans bond in the 11- or 12-position; none of the cis monoenoic isomers significantly altered the formation of 20:4n-6 or 20:5n-3 (127). Inhibition by trans fatty acids is greater for n-6 than for n-3 fatty acids (128). Numerous studies indicate that 9t,12t-18:2 decreases the formation of both 20:3n-6 and 20:4n-6 (98, 116, 126, 127, 129–134) and increases accumulation of 20:3n-9 (129); however, diets containing partially hydrogenated vegetable oils have little t-t-18:2.

In cultured cells, the presence of a trans bond in the 12-position in dienoic isomers inhibits formation of both 20:4n-6 and 20:5n-3, and the inhibition is especially marked when a Δ9 trans bond also is present. By contrast, trans bonds in the 9- or 15-position along with a cis bond in the 12-position have little effect (126). Overall, fatty acids containing trans bonds could influence the metabolism of 18:2n-6 and 18:3n-3, the extent depending on the position of the trans bond and the presence of another cis or trans bond in the acyl chain. Competition of trans and cis fatty acids for incorporation into tissue phospholipids may also influence the apparent effects of trans fatty acids on overall essential fatty acid metabolism (135, 136). Metabolites of trans fatty acids may inhibit essential fatty acid metabolism more than their direct precursors. trans Metabolites should have little metabolic effect because their amounts in human tissue are low. Selective interaction of trans fatty acids with essential fatty acid metabolism appears to be most relevant when essential fatty acid intake is low. Fortunately, consumption of essential fatty acids by the US population is more than adequate, and the percentage of fat energy contributed by essential fatty acids has doubled over the past 50 y (27, 137).

Placenta (138) and fetal and neonatal liver and brain (139, 140) can desaturate and elongate saturated and polyunsaturated fatty acids. Although their roles relative to direct maternal supply of required fatty acids for development are not clearly understood, these enzyme systems may have an important role when the dietary supply is restricted by providing acyl chains and derivatives at crucial developmental stages, particularly for the central nervous system when neurite proliferation and myelination are most active. Competition from maternal trans
fatty acid isomers could add a complicating dimension, particularly if the essential fatty acid supply is restricted.

Conversion of trans fatty acids to unusual products resembling prostanooids usually formed from 20:4n-6 were reported (141, 142), but these derivatives may not have significant biological activity. This synthesis of oxygenated derivatives containing trans bonds appears to occur only in the absence of the more natural prostanooid precursor fatty acids, mainly 20:4n-6, derived from essential fatty acids. Limited evidence indicates that trans fatty acids probably do not normally interfere with cyclooxygenase or lipoxygenase activities (143). Examinations from rat studies show that 2% of energy from 18:2n-6 is sufficient for preventing undesirable effects of trans fatty acids on essential fatty acid metabolism (96), and this appears to apply to eicosanoid formation (95). Experiments in which trans fatty acids do interfere with eicosanoid formation have been described as situations of essential fatty acid deficiency that would be influenced by any added fatty acid—trans, saturated, or 18:1—to cause undesirable perturbations of these key metabolic reactions (144).

Little is known about the effects of trans fatty acids on de novo synthesis of fatty acids. The effect of trans fatty acids on the synthesis of n-6 and n-3 long-chain fatty acids might be exacerbated in fetal and developing tissues at stages when de novo processes are used and might also alter the lipid composition of maternal milk at the level of mammary gland metabolism, but there is no direct evidence for these interactions.

Of particular interest is the potential for interaction of trans fatty acids with enzymatic activities in peroxisomes. In addition to being potential substrates for β-oxidation within the subcellular organelles, trans fatty acids might interact with the final peroxisomal chain-shortening step involved in the formation of 22:6n-3 (122).

Incorporation into and release from major cellular lipids

Dietary studies indicate that selective accumulation of dietary trans fatty acids does not occur and that the trans fatty acid content of body tissues is lower than that of dietary fats (5, 7). However, both bond configuration and position can influence acylation in vivo and in vitro. In general, there is preference for acylation of trans fatty acids relative to their cis analogs at the sn-1 position, and overall acylation rates for trans fatty acids are intermediate to those of cis and saturated fatty acids (105, 145–148). Because palmitic acid (16:0) and 18:0 are found almost exclusively in the sn-1 position of phosphatidylincholine, their much higher rate of esterification would result in discrimination against esterification of trans isomers relative to the amounts in the diet. trans Fatty acids in body tissues are found predominantly in phosphatidylincholine and phosphatidylethanolamine because these phospholipids are the major components of cell membranes. Most prominent discrimination against trans fatty acid acylation appears to be in the formation of cholesterol ester; relatively little trans fatty acid is found as cholesterol ester in serum or in cellular lipids.

Triacylglycerols contain most of the trans fatty acids of adipose tissue. The potential for formation of diacylglycerol-containing trans fatty acid, either from membrane phospholipids or to a lesser extent from triacylglycerol, might have implications in signal transduction processes within cells, considering the important second messenger role of diacylglycerol in the activation of protein kinase C (149); little is known about the potential of this class of diacylglycerol as kinase activators or inhibitors. Furthermore, the release of trans fatty acids from phospholipids may influence signal transduction processes, particularly where kinase isoforms known to be activated by released cis unsaturated fatty acids (149) are involved. There appears to be no direct information about a potential role of trans fatty acids in such intracellular signaling.

Of increasing interest is the role of unsaturated fatty acids in gene expression through processes mediated by receptor and response elements (150). Fatty acids interact with the retinoid and peroxisomal proliferator families of receptors in transmitting signals through response elements to mediate genome expression (151). The extent to which trans fatty acids might have specificity in substitution, activation, or inhibition of this level of signal transduction to the genome requires direct experimental evaluation. Will trans fatty acids exhibit properties in these systems that are intermediate to their cis and more saturated counterparts or might the interaction be more specific?

Regulation of enzyme activities at the membrane level

Because trans fatty acids have physical properties intermediate to their cis and more saturated analogs, their presence in membrane phospholipids may differentially alter the microenvironment of membrane-associated enzymes. Changes in the activities of several enzymes, such as ATPases, adenylate cyclase, and fatty acid desaturases by trans fatty acid modification of membrane fluidity have been indicated (152–155). Changes in β-adrenergic receptor characteristics were also observed (152, 156). Supplementation of cells with trans fatty acids alters mitochondrial membrane function and amino acid transport. However, most effects of trans fatty acids on membrane-associated functions are not observed when adequate amounts of essential fatty acids are also present. Furthermore, a study with human subjects indicated that erythrocyte fluidity and insulin binding are not influenced by different amounts of dietary trans fatty acids (157). Saturated fatty acids have been shown to decrease insulin sensitivity, suggesting the possibility that trans fatty acids, like saturated acids, may alter endocrine responses. Little is known about influences of trans fatty acids on membrane properties during early development.

FETAL AND INFANT GROWTH AND DEVELOPMENT

Fatty acid composition of tissue lipids

Human infants, unlike infants of other species, rapidly accumulate body fat synthesized from glucose-derived carbohydrate during the third trimester (Figure 4). Glucose, the primary energy source for fetal development, reaches the fetus from maternal circulation via placental transport and is used for synthesis of fat, glycogen, and nonessential amino acids (159). Because most body fat is provided by lipogenesis with carbohydrate as a carbon source, it has a high content of 16:0, palmitoleic acid (16:1), and 18:1 (158, 160, 161). The log-log plot of body weight versus total fatty acids, fatty acids synthesized from carbohydrate precursors (16:0, 18:0, 16:1, and 18:1), and essential fatty acids (18:2n-6 and 20:4n-6) displays the marked difference between fetal fatty acid content achieved via placental transfer and fetal fatty acids accumu-
FIGURE 4. Total fat (●), total fatty acids (▲), fatty acids synthesized from carbohydrate (16:0, 18:0, 16:1, and 18:1) (○), and essential fatty acids (18:2n-6 and 20:4n-6) (●) of human fetuses as a function of fetal weight. Data from reference 158 and LJ Filer Jr, DW Anderson, and SJ Foman, unpublished observations, 1968.

The dilution of the essential fatty acid pool by carbohydrate-derived fatty acids needs to be considered when interpreting fetal fatty acid data. As shown in Figure 4, the total weight of n-6 fatty acids remains fairly constant as body weight increases. If the weight data are converted to percentage data, however, the relative percentages for n-6 fatty acids decrease because of the large increase in fatty acids synthesized from carbohydrate. Data for trans fatty acids are not available, but the dilution effect would apply to all fatty acids that are not synthesized from carbohydrate. Larger infants with more body fat would be expected to have a lower percentage of trans fatty acids in plasma lipid classes (more dilution from synthesized fat), which is consistent with the inverse relation between the percentages of t-18:1 in plasma lipids and birth weight of premature infants reported by Koletzko (9).

Fatty acid composition data should be expressed in both absolute and relative terms when comparing fetal and maternal tissue lipid data because in a normal pregnancy the absolute amount of total fatty acids and essential fatty acids in maternal plasma increases throughout gestation in concert with an in-

FIGURE 5. Log-log plot of lipids versus fetal body weight: ●, total fatty acids; ▲, fatty acids synthesized from carbohydrate; and ●, 18:2n-6 plus 20:4n-6.
crease in the concentration of plasma phospholipids (20). Thus, absolute fatty acid concentrations differ severalfold between maternal and fetal plasma, but these differences are masked when the data are expressed as percentages (8). For example, total fatty acid and essential fatty acid concentrations in umbilical plasma are much lower than those in maternal plasma because the phospholipid concentration is lower. When these data are expressed as a percentage of total phospholipid fatty acids, the percentages of total n-3, 20:4n-6, and 22:6n-3 in cord-blood phospholipids are higher than the percentages in maternal plasma phospholipids. The percentage of 18:2n-6 in cord blood is lower because the n-3 and n-6 long-chain fatty acids compete with 18:2n-6 for the 2-acyl position of the phospholipids.

Data similar to those shown in Figures 4 and 5 for intrauterine accretion of trans fatty acids into human fetal tissue lipids are not available. The only report to consider the relation between t-18:1 in maternal plasma and human fetal tissue was limited to the first trimester and suggested that t-18:1 accumulation increased in fetuses with gestation time (163). An early study found prepuce tissue collected from 22 newborn infants and placental lipids from 6 mothers contained < 0.5% total trans fatty acids (164). Ohlrogge et al (90) reported low amounts of t-18:1 (0.1% and 0.9%) in adipose tissue obtained from two premature infants. More recently, Koletzko (9) reported total trans fatty acids to be 1.95 ± 0.17% in sterol esters, 1.6 ± 0.1% in triacylglycerols, and 1.08 ± 0.07% in phospholipids of plasma from 29 premature infants. The percentage of trans fatty acids in fetal plasma and tissue lipids was lower than the percentages found in maternal plasma lipids and supports the concept that transport of trans fatty acids across the placenta is inhibited. In contrast, polyunsaturated fatty acids appear to be selectively transported to developing fetuses. For example, in one study the transport rates from the maternal side of the placenta to the fetal side were 43% higher for 18:2n-6 and 75% higher for 18:3n-3 than for cis-18:1n-9 (165) and in another study the percentage of 20:4n-6 and 22:6n-3 in cord blood was higher than that in maternal plasma (20).

Sources and accumulation of trans fatty acids for fetuses and infants

The first evidence that trans fatty acids could be transferred from mother to fetus came from a series of studies in rats by Moore and Dhopleshwarkar (87, 146, 166), who found trans fatty acids administered to pregnant rats in placental phospholipids and in fetuses. About 60% of the trans fatty acids recovered were in phospholipids, with most of the remainder in triacylglycerols. In humans, Koletzko and Muller (8) reported similar percentages of trans fatty acids in the plasma of full-term infants and their mothers, whereas Ayyagari et al (167) found half as much t-18:1 in cord blood plasma triacylglycerols and phospholipids of full-term infants as in maternal plasma. Stender et al (91) found lower concentrations in cord blood than in maternal plasma lipids. Comparison of the trans fatty acid content of adipose tissue and placenta from six pregnant women undergoing cesarean sections found that maternal adipose tissue contained 1.5-6.8% total trans fatty acids and that placental lipids contained < 0.5% total trans fatty acids (164). The last three studies are consistent with results of animal studies showing discrimination against the transport of trans fatty acids into fetal tissue. Although trans fatty acids can be transferred to human fetuses, attempts have not been made to quantify the amount of trans or positional isomers of fatty acids transferred during intrauterine life or to determine the concentration of these isomers in specific tissues.

No data are available on fetal or newborn brain lipids, but adult brain total lipid contains < 0.5% trans fatty acids. Isomers of trans fatty acids have been found in rat brain lipids (168, 169) but not in brain lipids of newborn or suckling piglets from sows fed a ration containing partially hydrogenated soybean oil (24% trans fatty acids) plus 4% added safflower oil (88, 89). In studies of piglets, no effect of trans isomers on nerve conduction velocity was detected (170). The percentage of trans fatty acids in animal and human brain lipids is consistently much lower than the percentage of trans fatty acids in the diet. These results seem to reduce the possibility that exposure of human infants in utero to trans fatty acids would influence the physical properties of brain lipid membranes or affect function; however, there are no direct data addressing this issue.

The trans fatty acid content of human milk is variable and is related to dietary amounts (Table 4). Trans fatty acid concentrations in US infant formula are low because formula does not contain partially hydrogenated vegetable oil. Thus, a formula-fed infant's diet would contain almost no trans fatty acids; however, a 6-kg infant receiving breast milk containing 4% trans fatty acids would consume ~33 g total fat, or ~1.3 g trans fatty acids/d (~0.2 g · d⁻¹ · kg body wt⁻¹). For most populations studied, formula-fed infants have much lower intakes of trans fatty acids than do breast-fed infants (175–177). Spain is an exception among developed countries in that human milk was reported to contain only 0.95% of total fatty acids as trans fatty acid isomers (174), which was lower than the amount of trans fatty acid isomers found in infant formula in Spain. The recommendation has been made to omit trans fatty acid isomers from infant formulas or, at least, to ensure that they are consumed in lower amounts by formula-fed infants than by breast-fed infants (178). However, this recommendation is arbitrary because the trans fatty acid isomer content of human milk is variable, reflecting the trans fatty acid content of the mother's diet.

Beginning around 4 mo of age, most infants in the United States are fed foods other than human milk or formula (179). The trans fatty acid isomer content of most commercially available infant formula and infant foods is low (176), but some infants receive little commercially prepared infant food during the first year of life and instead consume the same foods as older children and adults in the household after 6 mo of age. The effect of this practice on trans fatty acid isomer intake in infancy has not been studied, but such practice would introduce more trans fatty acids into an infant's diet than if only infant foods were fed. The increase in the trans fatty acid content of plasma and erythrocyte phospholipids, which is low at birth, is diet related. One report showed that trans fatty acids increase in erythrocyte phospholipids from birth to age 6–9 y (180) and another determined that the trans fatty acid isomer content of plasma triacylglycerols and phospholipids increased until ~age 5 y but not thereafter (181).
TABLE 4
trans Fatty acid isomer content of human milk lipids

<table>
<thead>
<tr>
<th>Subjects and diet</th>
<th>Total trans(^2)</th>
<th>t-18:1</th>
<th>“trans” 18:2(^4)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>US (n = 11); 5.0% trans (estimated)</td>
<td>3.9 (2.7–4.4)(^4)</td>
<td>3.4 (2.6–4.5)</td>
<td>0.2 (0.0–1.1)</td>
<td>62</td>
</tr>
<tr>
<td>US (n = 3); habitual</td>
<td>ND</td>
<td>3.1</td>
<td>ND</td>
<td>175</td>
</tr>
<tr>
<td>US (n = 8); 11.8% trans</td>
<td>ND</td>
<td>6.5 (4.2–9.0)</td>
<td>ND</td>
<td>66</td>
</tr>
<tr>
<td>US (n = 52); vegetarian and omnivorous</td>
<td>4.3</td>
<td>3.7 ± 2.3(^5)</td>
<td>ND</td>
<td>65</td>
</tr>
<tr>
<td>US (n = 8); 1.0% trans(^6)</td>
<td>ND</td>
<td>1.8 (1.6–3.9)</td>
<td>ND</td>
<td>66</td>
</tr>
<tr>
<td>Canada (n = 14); habitual</td>
<td>2.6 ± 0.4</td>
<td>2.5 (0.5–4.5)</td>
<td>0.10 ± 0.4</td>
<td>171</td>
</tr>
<tr>
<td>Canada (n = 14); 35% trans(^6)</td>
<td>ND</td>
<td>5.8</td>
<td>ND</td>
<td>171</td>
</tr>
<tr>
<td>Canada (n = 14); 13% trans(^6)</td>
<td>ND</td>
<td>2.5</td>
<td>ND</td>
<td>171</td>
</tr>
<tr>
<td>Canada (n = 14); 0% trans(^6)</td>
<td>ND</td>
<td>2.0</td>
<td>ND</td>
<td>171</td>
</tr>
<tr>
<td>Canada (n = 198); habitual</td>
<td>7.2 ± 3.0</td>
<td>5.9 ± 2.5</td>
<td>0.94</td>
<td>84</td>
</tr>
<tr>
<td>Germany (n = 15); habitual</td>
<td>4.4 (2.2–6.0)</td>
<td>3.1 (1.5–4.4)</td>
<td>0.20 (0.1–0.5)</td>
<td>172</td>
</tr>
<tr>
<td>Nigeria (n = 10); habitual</td>
<td>1.2 (0.8–10.3)</td>
<td>0.9 (0.5–4.9)</td>
<td>0.12 (0.1–0.4)</td>
<td>173</td>
</tr>
<tr>
<td>Spain (n = 38); habitual</td>
<td>1.3</td>
<td>1.0 ± 0.5</td>
<td>0.22 ± 0.06</td>
<td>174</td>
</tr>
</tbody>
</table>

\(^1\) ND, no data provided in reference.
\(^2\) Percentage total trans fatty acids may be high for some data because the tentatively identified t-14:1, t-16:1, and t-t-18:2 fatty acids probably included some cis positional fatty acid isomers.
\(^3\) t-t-18:2 was not included in the sums for all the “trans” 18:2 data listed.
\(^4\) t, range in parentheses.
\(^5\) t ± SD.
\(^6\) trans Fatty acid content of margarine used to replace margarine and butter in habitual diet.

Effects of trans fatty acids on essential fatty acid status and growth

As discussed in the section on interactions of trans fatty acids with metabolism of other fatty acids, trans fatty acids may compete with the essential fatty acids, 18:2n–6 and 18:3n–3. However, these competitive interactions have been shown only in the presence of diets deficient in essential fatty acids. The essential fatty acid intake (18:2n–6 plus 18:3n–3) of US women of child-bearing age is 12 g/d (Table 5), two times higher than the requirement recommended for pregnant women by the FAO/WHO expert committee (13). For pregnant and lactating women, the recommended intake of essential fatty acids is 2.2 and 3–4 g/d higher, respectively, than for other adults (13). The estimated intake of 18:2n–6 plus 18:3n–3 of pregnant and lactating women in the lowest 10th percentile exceeds the recommended requirement for pregnancy by ~20% and meets the recommendation for lactation. Jonnalagadda et al (182) calculated that a hypothetical average US diet containing stick or soft margarine would provide twice the amount of 18:2n–6 recommended for pregnant women. Although intake data indicate adequate availability of 18:2n–6 in the mother’s diet, recent fatty acid composition data for umbilical plasma lipids suggest that fetuses born at term may be marginally deficient in n–6 and n–3 fatty acids (183, 184). The relatively high percentage of the markers for essential fatty acid (20:3n–9 and 22:5n–6) deficiency in umbilical plasma phospholipids in fetal tissues is consistent with this possibility (185). The positive association between plasma phospholipid 20:4n–6 and postnatal growth of premature infants fed diets high in 18:2n–6 and 18:3n–3 but without n–3 or n–6 long-chain polyunsaturated fatty acids suggests that the 20:4n–6 status of many premature infants may be inadequate (186). Plasma phosphatidylcholine 20:4n–6 concentration accounted for 38%, 35%, and 19% of the variance in body weight at 2, 4, and 6.5 mo, respectively. The 20:4n–6 status of premature infants during the first 6 mo may be marginal and

TABLE 5
Intake per day of total fat and polyunsaturated fatty acids for females aged 20–39 y\(^7\)

| Item | Means | Percentile |
|------|-------|------------|------------|------------------|------------------|
| g/d | % of energy\(^8\) | 10% | % of energy\(^8\) | 10% | 95% | 95% |
| Total fat | 61 | 36.8 | 31 | 32.4 | 108 | 40.4 |
| Total polyunsaturated fatty acids | 12 | 7.2 | 5 | 5 | 23 | 8.6 |
| 18:2n–6 | 10.6 | 6.4 | 4.5 | 4.7 | 20.7 | 7.8 |
| 18:3n–3 | 1.1 | 0.7 | 0.5 | 0.5 | 2.2 | 0.8 |
| 20:4n–6 | 0.07 | 0.04 | 0.02 | 0.02 | 0.16 | 0.06 |
| 20:5n–3 | 0.09 | 0.05 | 0.00 | 0.00 | 0.41 | 0.15 |

\(^7\) Data from the 1987–1988 US Department of Agriculture Nationwide Food Consumption Survey.
\(^8\) Total energy: 6243 kJ (1492 kcal).
\(^9\) Total energy: 3602 kJ (861 kcal).
\(^10\) Total energy: 10.06 MJ (2404 kcal).
could be due to separation of the infant from mother-to-fetus transfer of n-3 and n-6 long-chain polyunsaturated fatty acids; however, interindividual variability in 20:4n-6 is large (186).

Several recent studies raised the possibility that maternal trans fatty acid intake could adversely influence status of both the n-3 and n-6 families and is related to birth weight. Results from the studies that are the most relevant to the question of whether trans fatty acids affect fetal development are summarized in Table 6. A definitive answer to this central question is not possible because studies in this area are few, observed effects are small, results are inconsistent, and the possibility of confounding factors or bias from a variety of sources has not been explored. A brief summary of the two studies (9, 10) that reported a relation between trans fatty acids and premature birth is provided in the following two para-

### Table 6

<table>
<thead>
<tr>
<th>Reference and tissue source</th>
<th>Fatty acid</th>
<th>Total lipid</th>
<th>Lipid class</th>
<th>Correlation and significant differences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TG</td>
<td>PL</td>
<td>CE</td>
</tr>
<tr>
<td>9, 179</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma of preterm infants</td>
<td>t-18:1</td>
<td>ND</td>
<td>0.80 ± 0.06</td>
<td>0.61 ± 0.05</td>
</tr>
<tr>
<td>(n = 29)</td>
<td>Total trans</td>
<td>ND</td>
<td>1.62 ± 0.10</td>
<td>1.08 ± 0.07</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma from mothers of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>preterm infants</td>
<td>Total trans</td>
<td>ND</td>
<td>(17.54 ± 1.58)</td>
<td>(24.94 ± 3.55)</td>
</tr>
<tr>
<td>(n = 23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma from mothers of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>full-term infants</td>
<td>Total trans</td>
<td>ND</td>
<td>(11.24 ± 0.55)</td>
<td>(15.63 ± 2.94)</td>
</tr>
<tr>
<td>(n = 21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8, 11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal plasma</td>
<td>t-18:1</td>
<td>1.21 ± 0.10</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>(n = 30)</td>
<td>Total trans</td>
<td>1.99 ± 0.14</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Full-term infant cord</td>
<td>t-18:1</td>
<td>1.00 ± 0.11</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>blood (n = 30)</td>
<td>Total trans</td>
<td>1.66 ± 0.14</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>167, 187</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal plasma</td>
<td>t-18:1</td>
<td>2.57 ± 1.09</td>
<td>1.44 ± 0.50</td>
<td>ND</td>
</tr>
<tr>
<td>(n = 50)</td>
<td></td>
<td>[1.07-7.8]</td>
<td>[0.4-2.6]</td>
<td></td>
</tr>
<tr>
<td>Full-term infant cord</td>
<td>t-18:1</td>
<td>1.15 ± 0.50</td>
<td>0.52 ± 0.25</td>
<td>ND</td>
</tr>
<tr>
<td>blood (n = 50)</td>
<td></td>
<td>[0.1-2.7]</td>
<td>[0.1-1.2]</td>
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</tr>
<tr>
<td>181</td>
<td></td>
<td></td>
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<tr>
<td>Plasma from children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at birth (n = 10)</td>
<td>Total trans</td>
<td>1.91</td>
<td>0.69</td>
<td>2.02</td>
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<tr>
<td>1-12 mo (n = 17)</td>
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<td>1.84</td>
<td>1.02</td>
<td>1.91</td>
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<tr>
<td>1-5 y (n = 15)</td>
<td></td>
<td>2.81</td>
<td>1.64</td>
<td>1.45</td>
</tr>
<tr>
<td>1-15 y (n = 68)</td>
<td></td>
<td>2.72 ± 1.23</td>
<td>1.78 ± 0.72</td>
<td>1.66 ± 1.76</td>
</tr>
<tr>
<td>188</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma from children</td>
<td>t-18:1</td>
<td>1.23 ± 0.08</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>aged 1-15 y (n = 53)</td>
<td>Total trans</td>
<td>1.78 ± 0.01</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>180</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBCs from children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 104)</td>
<td>Total trans</td>
<td>0.62 ± 0.13</td>
<td>1.52 ± 0.42</td>
<td>ND</td>
</tr>
<tr>
<td>at birth</td>
<td></td>
<td>2.07 ± 0.61</td>
<td>2.11 ± 0.38</td>
<td>ND</td>
</tr>
<tr>
<td>1-3 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-9 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-15 y</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

1. TG, triacylglycerol; PL, phospholipid; CE, cholesterol ester; ND, no data reported; RBCs, red blood cells; LCPUFA, long-chain polyunsaturated fatty acid.
2. Two references are cited in some entries because all the data from a study were not always included in one reference.
3. Correlations and significant differences apply to all tissue sources in a study.
4. ± SE.
5. ± SD. Values in parentheses are mg/dL.
6. ± SD; range in brackets.
graphs. No relation was found between birth weight and trans fatty acid content of plasma total lipid in full-term infants (11).

Koletzko (9) reported an inverse relation between trans fatty acids and long-chain polyunsaturated fatty acids in the plasma lipid classes of 29 preterm infants 4 d after delivery (birth weight: 1700 ± 127 g, gestational age: 33.6 ± 1.4 wk; mean ± SD). The percentage of trans fatty acids in the plasma lipid classes and the strongest correlations with long-chain polyunsaturated fatty acids are listed in Table 6. The correlation between the percentage of trans fatty acids and the ratio of 20:4n-6 to 18:2n-6 (r = -0.47, P < 0.01) was interpreted as evidence that trans fatty acids reduce 20:4n-6 synthesis by inhibiting Δ6 desaturase activity. trans Fatty Acid composition data for plasma phospholipids were not significantly correlated with long-chain polyunsaturated fatty acids. The correlations between birth weight and percentage of total trans fatty acids in phospholipids (r = -0.40) and between birth weight and percentage of n-18:1 in cholesterol esters (r = -0.50) were significant (P < 0.01).

Jendryczko et al (10) measured trans fatty acid concentrations in plasma of 23 women delivering preterm (before 34 wk of pregnancy) and 21 women with full-term deliveries. Average birth weights were 1235 g for preterm infants and 2278 g for full-term infants. Concentrations of trans fatty acids in plasma triacylglycerols, phospholipids, and cholesterol esters from mothers of preterm and full-term infants are listed in Table 6. The trans fatty acid concentrations in plasma lipids from mothers who delivered preterm infants were significantly greater (P < 0.05 for triacylglycerols and phospholipids; P < 0.005 for cholesterol esters) than those for mothers who delivered full-term infants. Negative correlations were found between birth weight and trans fatty acid concentrations of plasma phospholipids and cholesterol esters and between gestational age and trans fatty acid concentrations of plasma phospholipids and cholesterol esters (Table 6). Correlations with triacylglycerol data were not significant. Data were not adjusted for possible confounding factors.

The question of whether maternal intake of trans fatty acids adversely influences n-3 and n-6 long-chain polyunsaturated fatty acid status is important because Koletzko and Braun (189) and Leaf et al (190) reported a strong relation between lower plasma 20:4n-6 concentrations and birth weight in preterm infants. Koletzko reported that both total trans fatty acid isomers and n-18:1 in plasma phospholipids were inversely associated with total n-6 metabolites and plasma phospholipid 20:4n-6 in healthy children (1-15 y old) (179, 188). Koletzko (179) and Ayagari et al (187) reported an inverse association between trans fatty acids and 22:6n-3 in plasma lipids of infants.

The correlations of trans fatty acids with maternal diets, preterm births, and long-chain polyunsaturated fatty acid data were interpreted by Koletzko and Jendryczko et al to suggest that trans fatty acids impair synthesis of long-chain polyunsaturated fatty acids and intrauterine growth. However, these correlation data do not rule out other explanations. An alternative explanation consistent with the experimental results is that the trans fatty acid content of infant plasma lipids is a marker for maternal intake of long-chain polyunsaturated fatty acids. Maternal diets that are high in trans fatty acids from partially hydrogenated vegetable oils would be expected to contain less fat from meat, eggs, and fish, which are sources of n-6 and n-3 long-chain polyunsaturated fatty acids.

Low concentrations of long-chain polyunsaturated fatty acids in low-birth-weight infants may be related to maternal diet, placental function, or fetal metabolism (190). The interruption of the transfer of 20:4n-6 and other long-chain polyunsaturated fatty acids from mother to infant is suggested as an explanation for why a low 20:4n-6 percentage in plasma of preterm infants is related to birth weight (186). In contrast, umbilical-vein blood lipid data for C18 fatty acids from low-birth-weight infants do not suggest that maternal-to-infant transfer of n-18:1 is reduced by premature birth (190). Therefore, premature birth itself may contribute to a lower percentage of 20:4n-6, but a proportional reduction in trans fatty acid concentrations may not occur. As discussed in the section “Fatty acid composition of tissue lipids,” other factors also influence plasma lipid fatty acid composition. Thus, it is difficult to determine the precise reasons for the negative correlation observed between 20:4n-6 and trans fatty acids.

The fatty acid composition pattern for erythrocyte membrane phospholipids of children changes with age and approximates an adult pattern within a few months of birth (180). One significant change is an increase in 18:2n-6 and a decrease in n-6 long-chain polyunsaturated fatty acids. The exceptions are percentages of trans fatty acids and 18:3n-3, which are low at birth and do not reach the adult pattern until 6-9 y of age. In young children the negative correlations reported between trans and long-chain polyunsaturated fatty acids could reflect age and diet effects rather than inhibition of Δ6 desaturase and impaired synthesis of long-chain polyunsaturated fatty acids.

Studies in swine (89) and rats (97) showed that the percentage of 22:5n-6 in brain phosphatidylethanolamine increased when diets were fed having trans fatty acid contents about threefold higher than those in human diets. Because an increase in 22:5n-6 can be a marker for poor n-3 fatty acid status (185, 191), this observation raises the possibility that exposure to trans fatty acid isomers could decrease neutral 22:6n-3 accumulation. Exactly how this could occur is not clear, because milk 22:6n-3 was also low in sows fed diets high in trans fatty acids (192). Although there is no direct evidence to indicate that trans fatty acid intake affects brain function, structure, or development, this area merits further investigation.

If trans fatty acids reduce concentrations of n-3 and n-6 fatty acids in fetal tissues, differences in intrauterine exposure to trans fatty acids could be one factor contributing to the variability in concentrations of n-3 and n-6 long-chain polyunsaturated fatty acids in premature and full-term infants. This idea is supported by a report that full-term infants with higher concentrations of circulating t- and ε-18:1 had lower concentrations of n-3 and n-6 long-chain polyunsaturated fatty acids (187). It would be interesting to study whether accumulation of trans fatty acids in liver cell membranes coupled with the low fetal hepatic essential fatty acid concentrations (183, 184) could reduce hepatic synthesis of 20:4n-6 and 22:6n-3 (193) and reduce accumulations of 20:4n-6 and 22:6n-3 in fetal tissues. Impaired Δ6 desaturase activity due to trans fatty acid isomers is not likely to be totally responsible for the reduced accumulation of 20:4n-6 or 22:6n-3 observed in full-term infants (187). Synthesis of 20:3n-9 from 9c-18:1 requires Δ6
desaturase. Thus the observed elevated concentration of 20:3n-9 in fetal tissues (185) and the capability of low-birth-weight premature infants to rapidly synthesize 20:4n-6 and 22:6n-3 from 14C-labeled 18:2n-6 and 18:3n-3 (194) are evidence of considerable Δ6 desaturase activity.

The theory that trans fatty acids could decrease fetal and neonatal n-6 and n-3 tissue concentrations bears further study because 20:4n-6 is necessary for normal growth (195) and 22:6n-3 is required for normal retinal electrophysiology (196, 197), visual acuity (198), and cognition (199). Several studies indicate that premature infants may require dietary n-3 and n-6 long-chain polyunsaturated fatty acids for optimal retinal physiology, visual grating acuity, cognition, and growth (186, 200–208). For full-term infants, evidence for a benefit of dietary long-chain polyunsaturated fatty acids is controversial and so far the potential benefit for full-term infants is limited to a possible effect on visual acuity (209, 210).

CONCLUSIONS

Present knowledge about the biological effects of trans and other fatty acids on human fetuses and infants is summarized in this monograph. There is little direct information from human observations on which to base conclusions. Because the issue is complex, it is prudent to exercise caution when drawing conclusions and developing recommendations from observational or tissue fatty acid composition data. It is also important to assess the strengths and weaknesses of each kind of study and then evaluate the total evidence against specific criteria, such as strength of association, dose-response relation, temporally correct association, consistency of association, specificity of association, and biologic plausibility. The overall strength of the evidence should be assessed on a continuum from highly likely to very inconclusive and should be based on the totality of clinical, laboratory, and epidemiologic evidence.

The evaluation of risk to the developing infant is a complex phenomenon requiring familiarity with the principles of early embryonic and fetal growth and development as well as the pathophysiologic mechanisms by which genetic and environmental factors perturb these processes. Although our understanding of the control of human embryonic development and of the factors and mechanisms that can adversely affect the fetus is still incomplete, a substantial body of scientific information has enabled the development of strategies for investigating suspected linkages between environmental (including nutritional) factors and particular adverse developmental outcomes.

In general, before a conclusion is made that a causal relation exists, there should be sound evidence that exposure to the putative causal agent is epidemiologically associated with a characteristic outcome, that this association cannot be explained by other factors, and that a biologically plausible mechanism exists. Ideally, clinical studies should confirm that the relevant agent can and does reach the site of action and that increasing doses of the agent above a threshold is associated with more frequent or more severe effects.

The evidence that trans fatty acids have important metabolic effects during early development of fetuses and newborns is not extensive. The potential for interference with normal processes could be greatest during periods of most active cell growth, membrane expansion, metabolism, and overall developmental processes. Emerging research has added to our understanding of the influence of trans fatty acid exposure on the syntheses of n-3 and n-6 fatty acids. Whether dietary amounts of trans fatty acids transferred from the mother during fetal development and suckling of the newborn or from formula and other dietary sources during early infant growth are likely to influence normal metabolism of other classes of fatty acids specifically during early stages of development remains to be definitively addressed.

The complexity of this issue restricts the conclusions that can be drawn from available information. The following are some initial conclusions:

1) trans Fatty acids inhibit Δ6 desaturase of 18:2n-6 and increase requirements for essential fatty acids of rats.
2) The diet of pregnant and lactating US women meets or exceeds recommended requirements for the essential fatty acids 18:2n-6 and 18:3n-3.
3) trans Fatty acids are transferred by the placenta to the fetus and incorporated into fetal tissues.
4) Animal studies indicate that trans fatty acids have no obvious teratogenic or growth effects on the fetus.
5) trans Fatty acids in plasma of human premature infants may be inversely associated with n-6 and n-3 long-chain polyunsaturated fatty acids in membrane lipids.
6) Existing data have not established a causal relation between trans fatty acid intake and changes in early development.

Additional research is needed to determine
1) how demographic factors influence dietary trans fatty acid intake and how to improve the reliability of estimates of dietary trans fatty acid intake;
2) whether the conversion in infants of 18:2n-6 and 18:3n-3 to 20:4n-6 and 22:6n-3, respectively, is influenced by concentrations of trans fatty acids in tissue lipids or diet;
3) which individual trans and cis fatty acid isomers are the most relevant to study;
4) the interrelation among trans fatty acid intake, n-3 and n-6 long-chain polyunsaturated fatty acid status, and measures of development;
5) the possibility that trans fatty acids have a unique effect on specific tissues;
6) the effect of trans fatty acid intake on birth weight, length of gestation, and reproductive data from populations with cultural and dietary diversity; and
7) whether metabolism of trans fatty acids by human fetuses and infants is substantially different from that of adults.

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