Trans fatty acids, lipoproteins, and coronary risk[1]

Peter L. Zock and Martijn B. Katan

Abstract: Most dietary fatty acids contain at least one double bond, which is usually in the *cis* configuration. However, biohydrogenation in the rumen of cows and sheep, or catalytic hydrogenation of vegetable oils in the food industries, will convert some of the *cis* double bonds to the *trans* configuration. *Trans* fatty acid intake in western Europe and North America probably ranges from 5 to 15 g/day. Major dietary sources are frying fats used in industrial food preparation, margarines, and other spreads. In the past, margarines contained up to 50% *trans* fatty acids; however, these are now being phased out. *Trans* fatty acids raise serum low density lipoprotein (LDL) cholesterol and lower high density lipoprotein (HDL) cholesterol in humans when substituted for *cis* unsaturated fatty acids in the diet. These effects may be mediated by the cholesteryl ester transfer protein. *Trans* fatty acids also increase lipoprotein (*a*) levels relative to other fatty acids. The effects of *trans* fatty acids on the risk profile for coronary heart disease are thus unfavorable, and labels of food products should state the *trans* fatty acid content.

Key words: *trans* fatty acids, diet, lipoproteins, cholesterol, coronary heart disease.

Résumé : La plupart des acides gras contiennent au moins une double liaison, généralement en position *cis*. Toutefois, la biohydrogénation dans le rumen des vaches ou des brebis, ou l'hydrogénation catalytique des huiles végétales dans les industries alimentaires, convertissent une partie des doubles liaisons *cis* en configuration *trans*. On estime que les apports d'acides gras *trans* se situent dans la plage de 5–15 g/jour en Europe occidentale et en Amérique du Nord. Les acides gras *trans* se retrouvent principalement dans les graisses à friture utilisées dans les préparations industrielles, les margarines et autres produits à tartiner. Toutefois, ils sont en voie d'être éliminés des margarines qui, dans le passé, en contenaient jusqu'à 50%. Les acides gras *trans* augmentent le taux de cholestérol LDL sérique et diminuent le taux de cholestérol HDL chez les humains lorsqu'ils remplacent l'acide gras insaturé *cis* dans le régime alimentaire. Ces effets pourraient être induits par la protéine de transport des esters de cholestéryl. Les acides gras *trans* augmentent aussi les taux de lipoprotéine (*a*) comparativement aux autres acides gras. Ainsi, les acides gras *trans* augmentent les facteurs de risque de maladie coronarienne; par conséquent, la teneur en *trans* devrait apparaître sur les étiquettes des produits alimentaires.

Mots clés : acides gras *trans*, régime alimentaire, lipoprotéines, cholestérol, maladie coronarienne.
[Traduit par la Rédaction]

Introduction

In the past few years, possible adverse health effects of *trans* fatty acids have stimulated considerable discussion. Two recent reports have summarized the nature and health effects of *trans* fatty acids; a report from The British Nutrition Foundation (1995) gives a clear and balanced overview. An industry-sponsored report by the International Life Sciences Institute (Expert Panel on Trans Fatty Acids and Coronary Heart Disease 1995) extensively reviews the link between *trans* fatty acids and coronary heart disease risk, but its conclusions have been subject to some criticism (Willett and Ascherio 1995; Katan 1995*a*). The present paper summarizes recent human studies that investigated the effects of *trans* fatty acids on serum lipoprotein levels. The nature of *trans* fatty acids and their occurrence in the diet is briefly addressed.

Received June 22, 1996.

P.L. Zock[2] and M.B. Katan. Department of Human Nutrition, Wageningen Agricultural University, Bomenweg 2, 6703 HD Wageningen, The Netherlands.

[1] This paper has undergone the Journal's usual peer review.
[2] Author for correspondence.

Structure and formation of *trans* fatty acids

In Western diets, about 20–25% of total daily energy intake is provided by fatty acids that contain at least one double bond. Such fatty acids are called unsaturated, because under certain conditions they can take up hydrogen atoms, which are added to the double bonds. After all the double bonds have been converted into single bonds, the fatty acid stops taking up hydrogen and it is then called saturated. The most common configuration of double bonds in dietary fatty acids is *cis* (Fig. 1). Biohydrogenation in the rumen of cows and sheep, or catalytic hydrogenation of vegetable oils by the food industry, converts unsaturated fatty acids into saturated fatty acids, but unsaturated fatty acids with one or sometimes two double bonds in an unusual geometric configuration (Fig. 1; *trans* instead of *cis*) or position (positional *cis* isomers) may also be created. Geometric (*cis–trans*) and positional isomers usually occur together; therefore, in theory, effects ascribed to *trans* could also partly be due to positional *cis* isomers. Figure 1 shows elaidic acid with the *trans* double bond in the $\Delta 9/n{-}9$ position. In fact, partially hydrogenated fats contain a broad range of positional *trans* isomers, with the position of the *trans* double bond ranging from position $\Delta 6/n{-}12$ to position $\Delta 16/n{-}2$

Fig. 1. Structure of *cis* and *trans* monounsaturated fatty acids with 18 carbon atoms. Both oleic (*cis*) and elaidic (*trans*) acids have their double bond in the Δ9/*n*–9 position. Partially hydrogenated fats also contain isomers of these two fatty acids, with the position of the double bond ranging from position Δ6/*n*–12 to position Δ16/*n*–2 (Expert Panel on Trans Fatty Acids and Coronary Heart Disease 1995).

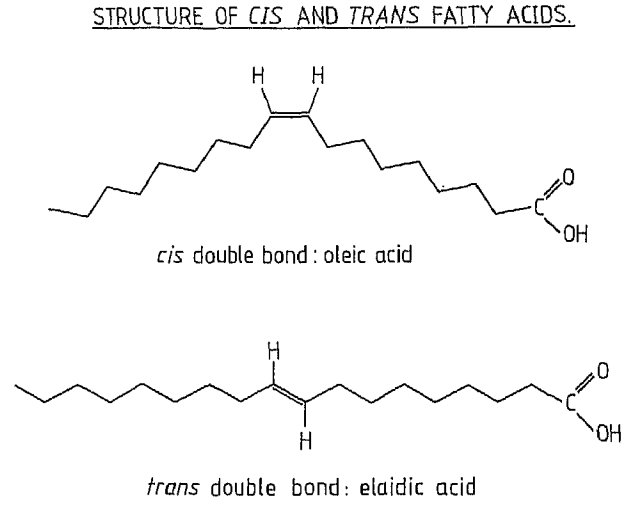
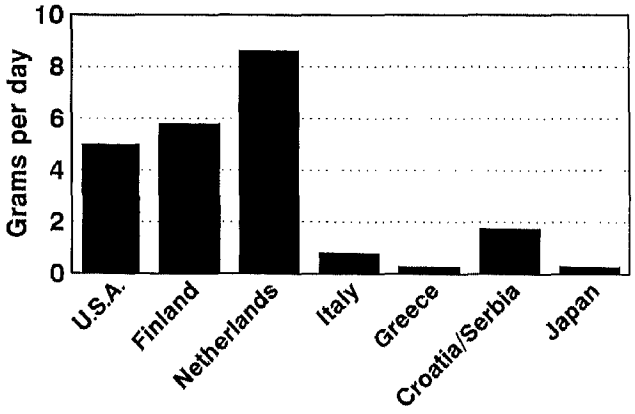


Fig. 2. Intake of *trans* fatty acids with chain lengths of 16 or 18 carbon atoms in seven countries: assessment by chemical analysis in 1987 of diets as reported in 1960 (De Vries et al. 1997). In addition to C16 and C18 *trans* fatty acids, diets in The Netherlands and Finland contained appreciable amounts of *trans* isomers with chain lengths of 20 and 22 carbon atoms, formed during partial hydrogenation of fish oils.



(Expert Panel on Trans Fatty Acids and Coronary Heart Disease 1995), and elaidic acid is not always the predominant *trans* fatty acid in such fats (Sampugna et al. 1982).

Intake of *trans* fatty acids

There are no recent reliable figures for the intake of *trans* fatty acids in various countries. Estimates from per capita disappearance data indicate that about 10–15 years ago average intake in western Europe and the United States probably ranged from about 5 to15 g/day, or 2–5% of total daily energy intake (Senti 1985; British Nutrition Foundation's Task Force 1987; Enig et al. 1990; Hunter and Applewhite 1991), but estimates

Table 1. *Trans* fatty acid content of commonly used spreads and shortenings sold in the United States.

Type of fat	Total fatty acids (g/100 g)	No. of grams/14-g serving
Full-fat margarines[a]	20.8 (11.7–32.1)	2.1 (1.0–3.1)
Reduced-fat spreads[b]	11.2 (3.2–15.2)	0.5 (0.2–1.0)
Shortenings[c]	19.5 (14.8–24.3)	2.6 (2.0–3.3)

Note: Products were purchased in April 1995 in Boston, Mass. Values are means of analyses using Fourier transform infrared spectroscopy and gas–liquid chromatography after preparation of *cis* and *trans* isomers with silver ion thin layer plates (Department of Human Nutrition, Wageningen Agricultural University, The Netherlands). Values in parentheses are ranges.

[a]Average of 6 brands: Promise spread, Fleischmann's soft spread, Fleischmann's, Kraft Parkay, Star, and Mazola margarines.

[b]Average of 3 brands: Land O'Lakes light (40% fat), Shedd's (50% fat), and Nucoa smart beat "trans-free" (14% fat) spreads.

[c]Average of 2 brands: Crisco and Star shortenings.

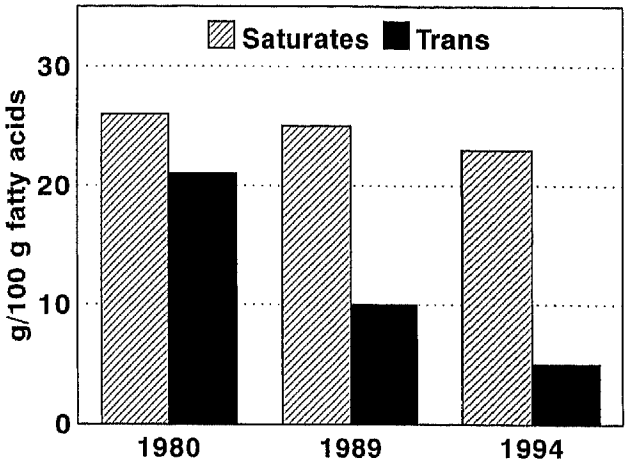
of intake levels of up to 27 g/day, depending on the type of diet, have been reported (British Nutrition Foundation's Task Force 1987). Chemical analysis of the diets of men reported in the Seven Countries Study (De Vries et al. 1997) showed considerable differences in the intake of *trans* fatty acids from ruminant fats and partially hydrogenated vegetable oils between countries, with levels in The Netherlands and Finland being high and those in southern Europe being low (Fig. 2). In addition, diets in The Netherlands and Finland contained appreciable amounts of *trans* isomers from partially hydrogenated fish oils (Brussaard 1986). In view of the rapid changes now occurring in fat processing (Katan 1995*b*), per capita intake in these countries will probably fall to levels of about 5 g/day or less.

Major sources of *trans* fatty acids are partially hydrogenated fats in the form of shortenings and frying fats used in industrial food preparation, in margarines and other spreads, and from dairy products and meat. About 3–8% of the fatty acids in butter, cheese, milk, beef, and mutton are *trans* (Pfalzgraf et al. 1994). Much larger amounts can be formed during the partial hydrogenation (hardening) of vegetable and fish oils. Table 1 gives the *trans* fatty acid content of popular margarines and shortenings sold in the United States in 1995; up to 32% of the fatty acids in these products are *trans*. In the past, margarines and shortenings could contain up to 50% *trans* fatty acids (Rice et al. 1962); however, these are now being phased out (Fig. 3), and in western Europe and Canada most margarines will soon contain little or no *trans* fatty acid (Katan 1995*b*). Shortenings high in *trans* fatty acids will continue to be produced and will find their way into baked goods, convenience foods, and fats for commercial deep-fat frying.

Effect of *trans* fatty acids on serum lipids and lipoproteins

Trans fatty acids cannot be considered foreign substances; they are present in the meat and milk of animals and they are formed transiently in human tissues during the breakdown of *cis* fatty acids. In addition, animal studies have yielded no evidence of toxic effects (Senti 1985). Several studies have examined the effects of *trans* fatty acids on serum total cholesterol levels. However, the results of older studies are often

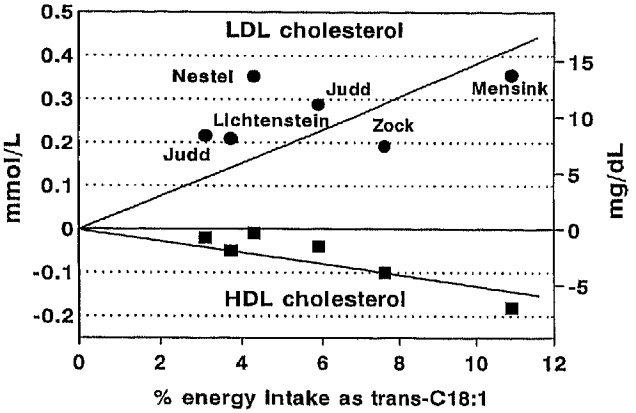
Fig. 3. Average saturated and *trans* fatty acid content in Dutch vegetable full fat margarines, 1980–1994. Analyses by the Department of Human Nutrition, Wageningen Agricultural University, The Netherlands.



difficult to interpret, because fatty acid intake between the different dietary regimens was not well balanced. Two of the older studies did directly compare the effects of *trans* and *cis* monounsaturated fatty acids (*trans*-C18:1 and *cis*-C18:1) on serum total cholesterol levels, but results were not consistent. Mattson et al. (1975) found no difference in effect between *trans*-C18:1 and *cis*-C18:1, while the studies of Vergroesen and Gottenbos (1975) showed that *trans*-C18:1 might be hypercholesterolemic. The discrepancy between these two well-controlled studies remains unexplained.

More recently it has been suggested that, compared with *cis*-C18:1, a high intake of *trans*-C18:1 increases levels of cholesterol in LDL (low density lipoprotein) but lowers those in HDL (high density lipoprotein) (Mensink and Katan 1990). However, volunteers consumed about 11% of energy from *trans*-C18:1, and it was questioned whether the results could be extrapolated to lower intake levels (Reeves 1991). Since then, several groups have studied the effects of *trans* fatty acids from partially hydrogenated vegetable oils (Zock and Katan 1992; Nestel et al. 1992; Lichtenstein et al. 1993; Judd et al. 1994). When the data are combined into a linear model (Fig. 4), each additional percent of dietary energy as *trans* fatty acids results in an increase in LDL cholesterol of 0.040 mmol/L or 1.5 mg/dL (95% confidence interval, 0.021–0.058 mmol/L) and a decrease in HDL cholesterol of 0.013 mmol/L or 0.4 mg/dL (95% confidence interval, −0.018 to −0.007 mmol/L) (Zock et al. 1995). Figure 4 suggests that our studies (Mensink and Katan 1990; Zock and Katan 1992), which used higher doses of *trans* fatty acids, somewhat underestimated the effect on LDL cholesterol. We employed a feeding period of 3 weeks, assuming that this period was long enough for lipoprotein levels to stabilize after a dietary change. It may be possible that 3 weeks is not long enough for LDL and HDL cholesterol levels to stabilize after a change in *trans* intake. An alternative explanation is that the dose–response relation between *trans* fatty acid consumption and lipoprotein cholesterol is not linear, with the effects levelling off at higher intake levels (Fig. 4). On the other hand, a preliminary report from a Malaysian study (Sundram et al. 1995) suggests that a

Fig. 4. Overview of the effects on lipoprotein cholesterol levels of substituting *trans* monounsaturated fatty acids for oleic acid. Data are derived from six isoenergetic dietary comparisons between *trans* monounsaturated and *cis* unsaturated fatty acids (Mensink and Katan 1990; Zock and Katan 1992; Nestel et al. 1992; Lichtenstein et al. 1993; Judd et al. 1994). Differences between diets in fatty acids other than *trans* monounsaturates and oleic acid were adjusted for by using prediction equations from a meta-analysis of 27 controlled trials (Mensink and Katan 1992). The regression lines were forced through the origin because a zero change in intake will produce no change in lipoprotein concentrations. Reproduced from Zock et al. (1995).



diet supplying 7% of energy as *trans*-C18:1, fed for 4 weeks, raises LDL cholesterol levels and lowers HDL cholesterol levels more than was observed by Zock and Katan (1992). Obviously more experiments are needed to define the precise shape of the dose–response curve. Nevertheless, the data clearly indicate that diets containing *trans*-C18:1 fatty acids raise LDL cholesterol and lower HDL cholesterol relative to diets containing the *cis* isomer oleic acid. In addition, there seems to be no evidence for a threshold below which *trans* fatty acids do not affect lipoprotein cholesterol levels.

Thus, dietary studies in humans show that *trans* fatty acids from partially hydrogenated vegetable oils raise the level of atherogenic LDL cholesterol and lower the level of the "good" or HDL cholesterol when compared with *cis* fatty acids. However, *trans* fatty acids formed by industrial hydrogenation are derived not only from vegetable oils but also, in some countries, from fish oils. In contrast with vegetable oils, hydrogenated fish oils also contain *trans* fatty acids with 20 and 22 carbon atoms and one or more double bonds. In a recent Norwegian study, Almendingen et al. (1995) compared the effects of partially hydrogenated fish oil, partially hydrogenated soybean oil, and butter on serum lipoprotein levels. Serum LDL cholesterol levels were similar for the butter and the partially hydrogenated fish oil diets. The partially hydrogenated soybean oil diet, however, lowered serum LDL cholesterol relative to the partially hydrogenated fish oil and butter diets. Serum HDL cholesterol levels were the same for the butter and partially hydrogenated soybean oil diets, but significantly lower for the partially hydrogenated fish oil diet. Thus, this study shows that the unfavourable effects of *trans* fatty acids are not limited to those with 18 carbon atoms, as *trans* fatty acids with 20 or 22 carbon atoms also have an adverse effect on the serum lipoprotein profile. Figure 5 shows the effects of

Table 2. Effect of *trans*-rich diets on blood Lp(a) levels in recent trials.

Reference	*Trans* fatty acids		Lp(a) levels on *trans*-rich diets relative to other diets
	%[a]	Source[b]	
Nestel et al. 1992	7	Rapeseed and palm oils	↑ vs. palmitic acid
			= vs. oleic acid
			↑ vs. baseline saturated fat
Mensink and Katan 1992	11	High oleic acid sunflower oil	↑ vs. saturated fat
			↑ vs. oleic acid
	8	High oleic acid sunflower oil	↑ vs. stearic acid
			↑ vs. linoleic acid
Lichtenstein et al. 1993	4	Corn oil	= vs. unmodified corn oil
			= vs. baseline saturated fat
Almendingen et al. 1995	9	Soybean oil	↑ vs. butter
	8	Fish oil	↑ vs. butter
Aro et al. 1996	9	Vegetable oil	↑ vs. stearic acid
			↑ vs. baseline milk fat

Note: ↑, Lp(a) levels higher with *trans*-rich diet; =, no significant difference.

[a]The percentage of total energy supplied by *trans* fatty acids in the *trans*-rich diet. The reference diets contained between 0.5 and 2.5% of energy as *trans* fatty acids.

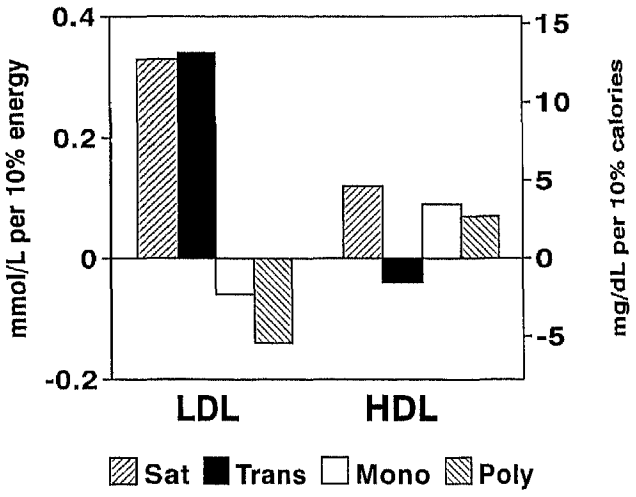
[b]The type of *cis* unsaturated oils from which *trans* fatty acids were formed by partial hydrogenation.

the different classes of dietary fatty acids side by side. *Trans* fatty acids apparently raise LDL cholesterol to about the same extent as saturated fatty acids and, unlike other fatty acids, they considerably lower HDL cholesterol. The effects of *trans* fatty acids on serum lipoproteins thus appear to be at least as unfavorable as those of saturated fatty acids. The mechanisms by which *trans* fatty acids influence lipoprotein cholesterol are as yet unclear, but there are indications that the cholesterol ester transfer protein (CETP) may be involved (Abbey and Nestel 1994; Van Tol et al. 1995).

Trans fatty acids and other risk factors for coronary heart disease

Another plasma lipoprotein thought to produce cardiovascular disease is lipoprotein (*a*) (Lp(a)). There is now appreciable evidence that *trans* fatty acids tend to raise Lp(a) levels (Table 2). Nestel et al. (1992) measured Lp(a) levels by radioimmunoassay and found that Lp(a) levels were higher with *trans* fatty acids than with palmitic or oleic acid, but that the difference with oleic acid failed to reach statistical significance. Mensink et al. (1992) measured Lp(a) levels by enzyme-linked immunosorbent assay (ELISA). They found that *trans* fatty acids resulted in higher Lp(a) levels than saturated fat, oleic acid, linoleic acid, and stearic acid. Lichtenstein et al. (1993) did not observe an increase in Lp(a) levels measured with ELISA. This suggests that *trans* fatty acids in lower doses do not affect Lp(a). However, the statistical power of this trial may have been limited, owing to the lower dose or relatively small number of subjects. Almendingen et al. (1995) found that *trans* fatty acid from partially hydrogenated soybean oil, as well as from partially hydrogenated fish oil, raised Lp(a) levels compared with a diet rich in butter. A preliminary report by Aro et al. (1995*b*) indicates that *trans* fatty acids increase Lp(a) relative to stearic acid or milk fat. Thus, *trans* fatty acids seem to be one of the rare dietary factors that affect Lp(a) levels, even though the effect is modest compared with genetically determined differences.

Fig. 5. Effects of saturated, *trans* monounsaturated, *cis* monounsaturated, and *cis* polyunsaturated fatty acids on LDL and HDL cholesterol. Values were obtained by meta-analysis of 32 controlled dietary trials in humans (Mensink and Katan 1992; Zock et al. 1995).



Blood pressure, yet another risk factor for cardiovascular disease, is not affected by *trans* fatty acids (Mensink et al. 1991; Zock et al. 1993).

Evidence from epidemiologic studies

The experiments described above indicate that *trans* fatty acids have adverse effects on blood lipoproteins. Cross-sectional observations showed that in free-living subjects, habitual consumption of *trans* fatty acids is also associated with higher LDL cholesterol and lower HDL cholesterol levels (Troisi et al. 1992; Siguel and Lerman 1993). The question then becomes whether high intake levels of *trans* fatty acids indeed promote coronary heart disease (CHD) in the population. In the absence of controlled clinical trials on *trans* fatty acids and

CHD, one must rely on epidemiologic observations. Several case-control studies have shown a higher intake of *trans* fatty acids or margarines in CHD patients than in control subjects (Thomas 1992; Tzonou et al. 1993; Siguel and Lerman 1993; Ascherio et al. 1994), although this could not be confirmed by others (Aro et al. 1995*a*; Roberts et al. 1995). In two large cohort studies, one of women (Willett et al. 1993) and one of men (Ascherio et al. 1996) in the United States, the intake of *trans* fatty acids was an independent predictor of CHD. In the Framingham study (Gillman et al. 1995), consumption of margarine at entry was associated with the incidence of CHD in men in the following 20 years.

Consumption of foods high in *trans* fatty acids may be part of a lifestyle that involves many other factors that affect CHD; such confounders are difficult to exclude. Thus, epidemiologic studies cannot prove that *trans* fatty acids cause CHD. Nevertheless, the effects of *trans* fatty acids on plasma lipoproteins are unmistakable, and together with the positive associations between *trans* fatty acid intake and CHD observed in epidemiologic studies, they give credence to a causal link.

Conclusions

Dietary *trans* fatty acids raise plasma LDL cholesterol levels and lower HDL cholesterol levels when exchanged for *cis* unsaturated fatty acids. The exact dose–response relationship between the amount of *trans* fatty acids and their effect on lipoproteins needs further study, but there is no evidence for a threshold below which *trans* fatty acids do not affect lipoprotein cholesterol. *Trans* fatty acids also raise Lp(a) levels relative to other fatty acids. These effects seem to be shared by *trans* fatty acids from various sources and with different isomer compositions. The effects of *trans* fatty acids on blood lipoproteins and the risk of cardiovascular disease are thus unfavourable, and labels of food products should state the *trans* fatty acid content. Claims for other adverse health effects of *trans* fatty acids remain to be substantiated.

Acknowledgements

The authors thank Dr. Karin Michels for her contribution to assessing the *trans* content of U.S.A. margarines. This work was supported by a grant from the Foundation for Nutrition and Health Research, The Netherlands.

References

Abbey, M., and Nestel, P.J. 1994. Plasma cholesteryl ester transfer protein activity is increased when *trans*-elaidic acid is substituted for *cis*-oleic acid in the diet. Atherosclerosis, **106**: 99–107.

Almendingen, K., Jordal, O., Kierulf, P., Sandstad, B., and Pedersen, J.I. 1995. Effects of partially hydrogenated fish oil, partially hydrogenated soybean oil and butter on serum lipoproteins and Lp[a] in men. J. Lipid Res. **36**: 1370–1384.

Aro, A., Kardinaal, A.F.M., Salminen, I., Kark, J.D., Riemersma, R.A., Delgado-Rodriguez, M., Gomez-Aracena, J., Huttunen, J.K., Kohlmeier, L., Martin, B.C., Martin-Moreno, J.M., Mazaev, V.P., Ringstad, J., Thamm, M., van't Veer, P., and Kok, F.J. 1995*a*. Adipose tissue isomeric *trans* fatty acids and risk of myocardial infarction in nine countries: the EURAMIC study. Lancet, **345**: 273–278.

Aro, A., Jauhiainen, M., and Mutanen, M. 1995*b*. Effects of stearic acid and trans fatty acids on serum lipids, apoproteins and lipoprotein(a). Atherosclerosis, **115**: S15. (Abstr.)

Aro, A., Jauhiainen, M., Partanen, R., Salminen, I., and Mutanen, M. 1996. Stearic acid, *trans* fatty acids, and dairy fat: effects on serum and lipoprotein lipids, apolipoproteins, lipoprotein(a), and lipid transfer proteins of healthy subjects. Am. J. Clin. Nutr. In press.

Ascherio, A., Hennekens, C.H., Buring, J.E., Master, C., Stampfer, M.J., and Willett, W.C. 1994. Trans-fatty acids intake and risk of myocardial infarction. Circulation, **89**: 94–101.

Ascherio, A., Rimm, E.B., Giovannucci, E.L., Spiegelman, D., Stampfer, M., and Willett, W.C. 1996. Dietary fat and risk of coronary heart disease in men: cohort follow-up study in the United States. Br. Med. J. **313**: 84–90.

British Nutrition Foundation's Task Force. 1987. *Trans* fatty acids. The British Nutrition Foundation, London, U.K. pp. 5–7.

British Nutrition Foundation Task Force. 1995. Trans fatty acids. The British Nutrition Foundation, London, U.K. pp. 1–65.

Brussaard, J.H. 1986. How much *trans* fatty acids does the Dutch diet contain? [In Dutch.] Voeding (The Hague), **47**: 108–111.

De Vries, J.H.M., Jansen, A., Kromhout, D., Van de Bovenkamp, P., Van Staveren, W.A., Mensink, R.P., and Katan, M.B. 1997. The fatty acid and sterol content of food composites of middle-aged men in seven countries. J. Food Compos. Anal. In press.

Enig, M.G., Atal, S., Keeny, M., and Sampugna, J. 1990. Isomeric trans fatty acids in the U.S. diet. J. Am. Coll. Nutr. **9**: 471–486.

Expert Panel on Trans Fatty Acids and Coronary Heart Disease. 1995. Trans fatty acids and coronary heart disease risk. *Edited by* P.M. Kris-Etherton. Am. J. Clin. Nutr. **62**: 655S–708S.

Gillman, M.W., Cupples, L.A., Gagnon, D., Posner, B.M., Ellison, C., and Castelli, W.P. 1995. Margarine intake and subsequent heart disease. Circulation, **91**: 925. (Abstr.)

Hunter, J.E. and Applewhite, T.H. 1991. Reassessment of *trans* fatty acid availability in the US diet. Am. J. Clin. Nutr. **54**: 363–369.

Judd, J.T., Clevidence, A., Muesing, R.A., Wittes, J., Sunkin, M.E., and Podczasy, J.J. 1994. Dietary *trans* fatty acids: effects on plasma lipids and lipoproteins of healthy men and women. Am. J. Clin. Nutr. **59**: 861–868.

Katan, M.B. 1995*a*. Commentary on the supplement *Trans fatty acids and coronary heart disease risk.* Am. J. Clin. Nutr. **62**: 518–519.

Katan, M.B. 1995*b*. Exit *trans* fatty acids. Commentary. Lancet, **346**: 1245–1246.

Lichtenstein, A.H., Ausman, L.M., Carrasco, W., Jenner, J.L., Ordovas, J.M., and Schaefer, E.J. 1993. Hydrogenation impairs the hypolipidemic effect of corn oil in humans. Hydrogenation, *trans* fatty acids, and plasma lipids. Arterioscler. Thromb. **13**: 154–161.

Mattson, F.H., Hollenbach, E.J., and Kligman, A.M. 1975. Effect of hydrogenated fat on the plasma cholesterol and triglyceride levels of man. Am. J. Clin. Nutr. **28**: 726–731.

Mensink, R.P., and Katan, M.B. 1990. Effect of dietary trans fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects. N. Engl. J. Med. **323**: 439–445.

Mensink, R.P., and Katan, M.B. 1992. Effect of dietary fatty acids on serum lipids and lipoproteins: a meta-analysis of 27 trials. Arterioscler. Thromb. **12**: 911–919.

Mensink, R.P., de Louw, M.H.J., and Katan, M.B. 1991. Effects of dietary trans fatty acids on blood pressure in normotensive subjects. Eur. J. Clin. Nutr. **45**: 375–382.

Mensink, R.P., Zock, P.L., Katan, M.B., and Hornstra, G. 1992. Effect of dietary cis and trans fatty acids on serum lipoprotein[a] levels in humans. J. Lipid Res. **33**: 1493–1501.

Nestel, P., Noakes, M., Belling, B., McArthur, R., Clifton, P., Janus, E., and Abbey, M. 1992. Plasma lipoprotein lipid and Lp(a) changes with substitution of elaidic acid for oleic acid in the diet. J. Lipid Res. **33**: 1029–1036.

Pfalzgraf, A., Timm, M., and Steinhart, H. 1994. Gehalte von trans-Fettsäuren in Lebensmitteln. Z. Ernährungswiss. **33**: 24–43.

Reeves, R.M. 1991. Effect of dietary *trans* fatty acids on high-density and low-density lipoprotein cholesterol in healthy subjects. N. Engl. J. Med. **324**: 339.

Rice, E.E., Weiss, T.J., and Mattil, K.F. 1962. Composition of modern margarines. J. Am. Diet. Assoc. **41**: 319–322.

Roberts, T.L., Wood, D.A., Riemersma, R.A., Gallagher, P.J., and Lampe, F.C. 1995. *Trans* isomers of oleic and linoleic acids in adipose tissue and sudden cardiac death. Lancet, **345**: 278–282.

Sampugna, J., Pallansch, L.A., Enig, M.G., and Keeny, M. 1982. Rapid analysis of *trans* fatty acids on SP-2340 glass capillary columns. J. Chromatogr. **249**: 245–255.

Senti, F.R. 1985. Health aspects of dietary *trans* fatty acids. Federation of American Societies for Experimental Biology, Bethesda, Md. pp. 1–111.

Siguel, E.N., and Lerman, R.H. 1993. Trans-fatty acid patterns in patients with angiographically documented coronary artery disease. Am. J. Cardiol. **71**: 916–920.

Sundram, K., Anisah, I., Hayes, K.C., Jevamalar, R., and Pathmanathan, R. 1995. *Trans*-18:1 raises cholesterol more than *cis*-mono or saturated fats in humans. FASEB J. **9**: A440. (Abstr.)

Thomas, L.H. 1992. Ischaemic heart disease and consumption of hydrogenated marine oils in England and Wales. J. Epidemiol. Community Health, **46**: 78–82.

Troisi, R., Willett, W.C., and Weiss, S.T. 1992. *Trans*-fatty acid intake in relation to serum lipid concentrations in adult men. Am. J. Clin. Nutr. **56**: 1019–1024.

Tzonou, A., Kalandidi, A., Trichopoulou, A., Hsieh, C.-C., Toupadaki, N., Willett, W., and Trichopoulos, D. 1993. Diet and coronary heart disease: a case-control study in Athens, Greece. Epidemiology, **4**: 511–516.

Van Tol, A., Zock, P.L., Van Gent, T., Scheek, L.M., and Katan, M.B. 1995. Dietary trans fatty acids increase serum cholesterylester transfer protein activity in man. Atherosclerosis, **115**: 129–134.

Vergroesen, A.J., and Gottenbos, J.J. 1975. The role of fats in human nutrition: an introduction. *In* The role of fats in human nutrition. *Edited by* A.J. Vergroesen. Academic Press, New York. pp. 1–41.

Willett, W.C., and Ascherio, A. 1995. Response to the International Life Sciences Institute report on *trans* fatty acids. Am. J. Clin. Nutr. **62**: 524–526.

Willett, W.C., Stampfer, M.J., Manson, J.E., Colditz, G.A., Speizer, F.E., Rosner, B.A., Sampson, L.A., and Hennekens, C.H. 1993. Intake of *trans* fatty acids and risk of coronary heart disease among women. Lancet, **341**: 581–585.

Zock, P.L., and Katan, M.B. 1992. Hydrogenation alternatives: effects of trans fatty acids and stearic acid versus linoleic acid on serum lipids and lipoproteins in humans. J. Lipid Res. **33**: 399–410.

Zock, P.L., Blijlevens, R.A.M.T., de Vries, J.H.M., and Katan, M.B. 1993. Effects of stearic acid and trans fatty acids verus linoleic acid on blood pressure in normotensive women and men. Eur. J. Clin. Nutr. **47**: 437–444.

Zock, P.L., Mensink, R.P., and Katan, M.B. 1995. Dietary trans fatty acids and lipoprotein cholesterol. Am. J. Clin. Nutr. **61**: 617. (Letter)