

October 9, 2003

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

RE: [Docket No. 03N-0076]

Dear Sir/Madam:

The North American branch of the International Life Sciences Institute (ILSI N.A.), respectfully submits the following comments directed to the Federal Register notice on July 11, 2003 (68 FR 41507) regarding the advance notice of proposed rulemaking (ANPR) on Food Labeling: *Trans* Fatty Acids in Nutrition Labeling; Consumer Research to Consider Nutrient Content Claims and Health Claims and Possible Footnote or Disclosure Statements.

ILSI N.A., a public, non-profit scientific foundation, advances the understanding and application of scientific issues related to the nutritional quality and safety of the food supply, as well as health issues related to consumer self-care products. The organization carries out its mission by sponsoring relevant research programs, professional education programs and workshops, seminars, and publications, as well as providing a neutral forum for government, academic, and industry scientists to discuss and resolve scientific issues of common concern for the well-being of the general public. ILSI N.A.'s programs are supported primarily by its industry membership.

The comments submitted address the request for information from scientific bodies concerning *trans* fatty acids (TFA) in nutrition labeling. In response to this request, members of the ILSI N.A. Technical Committee on Dietary Lipids (ILSI Lipids Committee) reviewed various intervention studies cited by the Food and Drug Administration (FDA) in the final rule on Food Labeling: *Trans* Fatty Acids in Nutrition labeling, Nutrient Content Claims, and Health Claims (68 FR 41434) and the proposed rule on Food Labeling: *Trans* Fatty Acids in Nutrition labeling, Nutrient Content Claims, and Health Claims (64 FR 62746).

Data from 16 intervention trials were reviewed, in which 17 control/comparison (control) and 27 treatment TFA intake levels were identified (1-16). One study (9) not cited by FDA in the ANPR has been included due to its inclusion in the Ascherio et al (17) analysis. All fatty acid intakes, when not reported as %En, were converted to %En, thereby permitting study comparisons on a similar basis. Also, LDL-C and HDL-C values expressed as mg/dL were converted to mM. The fatty acid intake and serum lipid data are summarized in **table 1**.

As a result of this review, ILSI N.A. respectfully submits that:

- 1) There is sufficient variation in the intake levels of TFA and SFA, across the numerous intervention trials, to allow modeling of fatty acid intake and its impact on serum cholesterol levels;

2003N-0076

C 32

- 2) It does not seem possible to make a meaningful distinction between the intake of *trans* fatty acids and saturated fatty acids (SFA) with respect to any differential impact on LDL cholesterol (LDL-C);
- 3) It does not seem possible to make a meaningful distinction between the intake of TFA and SFA with respect to any differential impact on HDL cholesterol (HDL-C), when TFA intake is less than 5% of total energy intake (5% En);
- 4) Published data suggest that the 90th percentile of TFA intake falls below 5%En in the North American diet ;
- 5) The most effective manner to predict changes in serum cholesterol levels, explaining the majority of the variance, is to consider the sum of TFA and SFA intake.

These conclusions are based on observations of the dietary levels of TFA and other fatty acids such as linoleic acid (LA) that were tested in the intervention trials, their associations with serum LDL-C and HDL-C, and how TFA intakes compare to those estimated from representative samples of the U.S. population.

It must be acknowledged that differences exist among the studies in design, objectives, test products, and populations, and that these studies have not been subjected to a rigorous meta-analysis. ILSI N.A. has undertaken to examine these studies through a thorough meta-analysis, with completion expected in early December, 2004.

Nonetheless, these datasets represent controlled studies of the relation between TFA intake, SFA intake, and serum lipids. As such conclusions drawn from these observations may assist the FDA in deliberations regarding TFA and food labeling.

- **Sufficient variation in TFA, SFA, and LA intakes across intervention trials exists to model intake effects on serum lipids**

TFA intakes ranged from 0 to 10.9%En. Control TFA intakes in the intervention studies ranged from 0 to 2.4%En, with 14 of 17 control TFA intakes being less than 1%En. TFA added to the diet for treatment ranged from 0 to 10.9%En, with 19 of 27 being greater than 3%En. The SFA and linoleic acid (LA) intakes across and within studies also varied. In the 44 control plus treatment diets, SFA ranged from 3.1 to 22.9%En, with 23 diets containing 10%En or more and 16 diets containing between 7 and 10%En. LA ranged from 0.8 to 15.6%En, with 31 diets containing at least 4%En and 9 diets having at least 10%En.

Changes in intake (treatment minus control) ranged from -1.2 to +10.9%En for TFA, -10.3 to +4.3%En for SFA, and -12.2 to +13.0%En for LA. The changes in TFA intakes were associated with little change in SFA intake (**figure 1**) but significant decreases in LA intakes (**figure 2**).

- **Intake of TFA do not differentially impact serum LDL-C compared to similar intakes of SFA**

Figures 3 and 4, respectively, plot changes in TFA intake (%En) against changes in LDL-C in relative (%) and absolute terms. Figures 5 and 6, respectively, plot changes in SFA intake (%En) against changes in LDL-C in relative (%) and absolute terms. There are two key points to note.

First, in all cases the slopes of the lines are similar. This strongly suggests that the impact on serum LDL-C of TFA intake and SFA intake are essentially indistinguishable. Second, higher order predictive equations provide very little additional explanation of the variance, suggesting that a linear regression is a reasonable model for these data (r^2 coefficients are provided for first, second and fourth order equations as examples, though the biological relevance of a fourth order equation may be difficult to interpret).

In summary, the data do not permit a meaningful distinction between the intake of *trans* fatty acids and saturated fatty acids (SFA) with respect to any differential impact on LDL cholesterol (LDL-C).

- **Intake of TFA do not differentially impact serum HDL-C compared to similar intakes of SFA, when TFA intakes are less than 5%En**

Figures 7 and 8, respectively, plot changes in TFA intake (%En) against changes in HDL-C in relative (%) and absolute terms. However in contrast to plots of LDL-C, higher order equations provide significantly greater predictive value, explaining a greater proportion of the variance. Most intriguing is the finding that there appears to be little impact on serum HDL-C when TFA intake is less than 5% En, when a second or fourth order equation is employed. Above this threshold, there is a clear inverse relationship, with increasing TFA intakes resulting in decreased serum HDL-C. Not surprisingly, a simple linear regression has negative slope, but this is a poor model of the data.

SFA intake (%En) appears to show no such threshold effect on serum HDL-C, in fact showing very little effect at all (figures 9 and 10).

In summary, the data do not permit a meaningful distinction between the intake of TFA and SFA with respect to any differential impact on HDL cholesterol (HDL-C), when TFA intake is less than 5% of total energy intake (5% En).

- **Mean population TFA intakes are below levels that significantly affect HDL-C**

The difficulties and limitations associated with estimating the TFA intake of free-living individuals, as well as FDA's caution to avoid over-interpreting dietary intake estimates and relationships to TFA intake levels used in intervention trials, must be acknowledged. (68 FR 41434 at 41446) Nonetheless, we believe the following observations may be useful to FDA in order to place these conclusions within the context of the North American diet.

TFA intakes have been estimated from food disappearance and availability data, diet records and food frequency questionnaires from various populations, chemical analysis of formulated or duplicate diets, and chemical analysis of adipose tissue. We believe that TFA intakes estimated from the CSFII are useful for drawing observations because they are derived from a representative sample of the U.S. population and are based on 24-hour recalled food intake, with or without 2-day recorded food intake. Energy intakes from the CSFII are likely to be underestimated by approximately 20 to 40% (18). However, the TFA data expressed as %En represent a reasonable, if not conservative, estimate of intake.

Allison et al estimated the mean TFA intake from the 1989-1990 CSFII for the total U.S. population aged 3 years and older to be 2.6%En, and from 2.6 to 2.8%En across various age and gender groups (18). FDA estimated the mean TFA intake for adults to be 2.91%En from the 1994-1996 CSFII. (8 FR 41434 at 41468) These population mean intakes are below the 5% En levels in the intervention trials associated with significant decreases in HDL-C. In addition, further inspection of Allison et al's results suggest that even the 90th percentile intake of TFA would fall below 5% En, in this population.

In summary, published data show that TFA intake, even at the 90th percentile, fall below the 5% En threshold when TFA significantly, and negatively, impact serum HDL-C.

- **The sum of TFA and SFA intakes provides the most robust predictor of changes in serum LDL-C**

When TFA and SFA intakes are combined, the most robust predictor of serum LDL-C is obtained, with an r^2 coefficient approximately 0.83. This is true when considering either relative (%) or absolute (mM) changes in serum LDL-C (figures 11 and 12 respectively). It is once again very interesting to note that higher order equations do not provide any significant improvement in explaining the variance, indicating that a linear regression presents a viable model of the data.

Since there is very little, if any, relation between SFA intake and HDL-C in these intervention trials, and the same is true for TFA intake below 5% En, summing the intake of these two fatty acids did not prove to be an effective predictor of serum HDL-C.

In summary, TFA and SFA intakes, when considered together, prove to be the most robust predictor of serum LDL-C.

- **TFA and SFA intakes must be considered together when examining their impact on serum cholesterol levels, and one is not distinguishable from the other within the context of the North American diet**

In conclusion, ILSI N.A. respectfully suggests that the data reviewed support the following:

- 1) Sufficient data exists to model the impact of TFA and SFA intake on serum cholesterol levels;
- 2) No meaningful distinction can be made between the intake of TFA and SFA with respect to impact on LDL-C;
- 3) No meaningful distinction can be made between the intake of TFA and SFA with respect to impact on HDL-C, when TFA intake is less than 5% En;
- 4) Published data indicate that the 90th percentile of TFA intake falls below 5% En
- 5) The sum of TFA and SFA intake is the most effective predictor of changes in serum lipid profile, explaining the majority of the variance.

ILSI N.A. encourages FDA to consider the observations presented regarding TFA and SFA intakes tested in intervention trials and how these intakes relate to changes in the intakes of other fatty acids, to changes in LDL-C and HDL-C, within the context of TFA intakes estimated from representative samples of the U.S. population.

Sincerely,

Richard M. Black, Ph.D.
Executive Director, ILSI North America

References

1. Aro A, Jauhiainen M, Partanen R, et al. Stearic acid, trans fatty acids, and dairy fat: effects on serum and lipoprotein lipids, apolipoproteins, lipoprotein(a), and lipid transfer proteins in healthy subjects. *Am J Clin Nutr* 1997;65:1419-1426.
2. de Roos NM, Bots ML, Katan MB. Replacement of dietary saturated fatty acids by trans fatty acids lowers serum HDL cholesterol and impairs endothelial function in healthy men and women. *Arterioscler ThrombVasc Biol* 2001;21:1233-1237.
3. Judd JT, Clevidence BA, Muesing RA, et al. Dietary trans fatty acids: effects on plasma lipids and lipoproteins of healthy men and women. *Am J Clin Nutr* 1994;59:861-868.
4. Judd JT, Baer DL, Clevidence BA, et al. Dietary cis and trans monounsaturated and saturated fatty acids and plasma lipids and lipoproteins in men. *Lipids* 2002;37:123-131.
5. Lichtenstein AH, Ausman LM, Carrasco W, et al. Hydrogenation impairs the hypolipidemic effect of corn oil in humans. Hydrogenation, trans fatty acids, and plasma lipids. *Arterioscler Thromb* 1993;13:154-161.
6. Lichtenstein AH, Ausman LM, Jalbert SM, Schaefer EJ. Effects of different forms of dietary hydrogenated fats on serum lipoprotein cholesterol levels. *N Eng J Med* 1999;340:1933-1940.
7. Mensink RP, Katan MB. Effect of dietary trans fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects. *N Eng J Med* 1990;323:439-445.
8. Nestel PJ, Noakes M, Belling GB, et al. Plasma lipoprotein lipid and Lp(a) changes with substitution of elaidic acid for oleic acid in the diet. *J Lipid Res* 1992;33:1029-1036.
9. Sundram K, Ismail A, Hayes KC, et. Al. Trans (Elaidic) fatty acids adversely affect the lipoprotein profile relative to specific saturated fatty acids in humans. *J Nutr* 1997;127:514S-520S.
10. Wood R, Kubena K, Tseng S, et al. Effect of palm oil, margarine, butter, and sunflower oil on the serum lipids and lipoproteins of normocholesterolemic middle-aged men. *J Nutr Biochem* 1993;4:286-297.
11. Zock PL, Katan MB. Hydrogenation alternatives: effects of trans fatty acids and stearic acid versus linoleic acid on serum lipids and lipoproteins in humans. *J Lipid Res* 1992;33:399-410.
12. Almendingen K, Jordal O, Kierulf P, et al. Effects of partially hydrogenated fish oil, partially hydrogenated soybean oil, and butter on serum lipoproteins and Lp(a) in men. *J Lipid Res* 1995;36:1370-1384.

13. Denke MA, Adams-Huet B, Nguyen BS. Individual cholesterol variation in response to a margarine- or butter-based diet--a study in families. *JAMA* 2000;284: 2740-2747.
14. Judd JT, Baer DJ, Clevidence BA, et al. Effects of margarine compared with those of butter on blood lipid profiles related to cardiovascular disease risk factors in normolipemic adults fed controlled diets. *Am J Clin Nutr* 1998;68:768-777.
15. Noakes M, Clifton PM. Oil blends containing partially hydrogenated or interesterified fats: differential effects on plasma lipids. *Am J Clin Nutr* 1998;68:242-247.
16. Wood R, Kubena K, O'Brien B, et al. Effect of butter, mono- and polyunsaturated fatty acid-enriched butter, trans fatty acid margarine, and zero trans fatty acid margarine on serum lipids and lipoproteins in healthy men. *J Lipid Res* 1993;34:1-11.
17. Ascherio A, Katan MB, Zock PL, et al. Trans fatty acids and coronary heart disease. *N Eng J Med* 1999;340:1994-1998.
18. Allison DB, Egan SK, Barraj LM, et al. Estimated intakes of trans-fatty acid and other fatty acids by the U.S. population. *J Am Diet Assoc* 1999;99:166-174.

Table 1. Fatty Acid Intakes and Serum LDL Cholesterol and HDL Cholesterol

Reference	Treatment	TFA (%En)	SFA (%En)	LA (%En)	LDL-C (mM)	HDL-C (mM)	Δ TFA (%En)	Δ SFA (%En)	Δ LA (%En)	Δ LDL-C (mM)	Δ HDL-C (mM)	Δ LDL-C (%)	Δ HDL-C (%)
Aro 1997 (1)	TFA	8.7	7.1	2.7	3.13	1.22	8.3	-7.9	-0.4	0.24*	-0.20*	8.3*	-14.1*
	STE†	0.4	15.0	3.1	2.89	1.42							
De Roos 2001	TFA	9.2	12.9	4.1	3.04	1.48	8.9	-10.0	-1.8	-0.01	-0.39*	-0.3	-20.9*
	SFA†	0.3	22.9	5.9	3.05	1.87							
Judd 1994 (3)	TFA (moderate)	3.8	13.0	6.0	3.54	1.40	3.1	-0.4	-0.1	0.20*	-0.02	6.0*	-1.4
	TFA (high)	6.6	12.7	6.2	3.60	1.38	5.9	-0.7	0.1	0.26*	-0.04*	7.8*	-2.8*
	OL†	0.7	13.4	6.1	3.34	1.42							
Judd 2002 (4)	TFA (moderate)	4.2	16.9	4.3	3.32	1.17	4.1	4.3	0.5	0.37*	-0.07*	12.5*	-5.6*
	TFA (high)	8.3	12.9	4.0	3.36	1.16	8.2	0.3	0.2	0.41*	-0.08*	13.9*	-6.5*
	OL†	0.1	12.6	3.8	2.95	1.24							
Lichtenstein 1993 (5)	Margarine	4.2	7.7	7.9	3.49	1.11	3.8	1.3	-0.6	0.26#	-0.03	8.0#	-2.6
	CO†	0.4	6.4	8.5	3.23	1.14							
Lichtenstein 1999 (6)	Semiliquid margarine	0.9	8.6	12.1	4.01	1.11	0.3	1.3	1.4	0.03	0.00	0.8	0.0
	Butter	1.3	16.7	2.1	4.58	1.16	0.7	9.4	-8.6	0.60*	0.05	15.1*	4.5
	Soft margarine	3.3	8.4	10.0	4.11	1.11	2.7	1.1	-0.7	0.13	0.00	3.3	0.0
	Shortening	4.2	8.6	7.2	4.24	1.11	3.6	1.3	-3.5	0.26*	0.00	6.5*	0.0
	Stick margarine	6.7	8.5	5.6	4.34	1.09	6.1	1.2	-5.1	0.36*	-0.02	9.0*	-1.8
	SBO†§	0.6	7.3	10.7	3.98	1.11							
Mensink 1990 (7)	TFA	10.9	10.0	4.2	3.04	1.25	10.9	0.5	0.2	0.37*	-0.17*	13.9*	-12.0*
	OL†	0.0	9.5	4.0	2.67	1.42							
Nestel 1992 (8)	TFA	6.7	10.0	6.6	4.27	0.98	4.3	1.0	1.3	0.37*	0.00	9.5*	0.0
	OL†	2.4	9.0	5.3	3.90	0.98							
Sundram 1997 (9)	TFA	6.9	7.4	5.3	3.81	1.05	6.9	-2.1	1.4	0.64*	-0.20*	20.2*	-16.0*
	OL†	0.0	9.5	3.9	3.17	1.25							
Wood 1993 (10)	Hard margarine	6.3	5.0	3.4	3.36	1.00	6.3	1.9	-12.2	0.13	0.00	4.0	0.0
	SO†	0.0 ^a	3.1	15.6	3.23	1.00							
Zock 1992 (11)	TFA	7.7	10.3	3.8	3.07	1.37	7.6	-0.7	-8.2	0.24*	-0.10*	8.5*	-6.8*
	LA†	0.1	11.0	12.0	2.83	1.47							
Almendingen 1995 (12)	PHSBO	8.5	11.0	5.4	3.58	1.05	7.6	-5.4	0.0	-0.23*	0.00	-6.0*	0.0
	PHFO	8.0	11.3	5.3	3.94	0.98	7.1	-5.1	-0.1	0.13	-0.07	3.4	-6.7*
	Butter†	0.9	16.4	5.4	3.81	1.05							
Denke 2000 (13)	Margarine	1.5 ^b	9.0	10.0 ^c	3.00	1.19	1.0	-7.0	7.0	-0.39*	0.00	-11.5*	0.0
	Butter†	0.5	16.0	3.0	3.39	1.19							
Judd 1998 (14)	TFA margarine	3.9 ^d	7.9 ^d	2.7 ^d	3.27	1.24	1.2	-3.3	1.6	-0.17*	-0.03	-4.9*	-2.4

Table 1. Fatty Acid Intakes and Serum LDL Cholesterol and HDL Cholesterol

Reference	Treatment	TFA (%En)	SFA (%En)	LA (%En)	LDL-C (mM)	HDL-C (mM)	Δ TFA (%En)	Δ SFA (%En)	Δ LA (%En)	Δ LDL-C (mM)	Δ HDL-C (mM)	Δ LDL-C (%)	Δ HDL-C (%)
	PUFA margarine	2.4 ^d	8.3 ^d	4.9 ^d	3.21	1.24	-0.3	-2.9	3.8	-0.23*	-0.03	-6.7*	-2.4
	Butter†	2.7 ^d	11.2 ^d	1.1 ^d	3.44	1.27							
Noakes 1998 (15)	Canola+TFA	2.1 ^d	8.9 ^d	5.8 ^{cd}	3.64	1.19	1.4	-6.6	3.0	-0.50*	-0.01	-12.1*	-0.8
	Canola-TFA	0.0 ^d	8.7 ^d	6.0 ^{cd}	3.61	1.28	-0.7	-6.8	3.2	-0.53*	0.08	-12.8*	6.7
	Butter†	0.7 ^d	15.5 ^d	2.8 ^{cd}	4.14	1.20							
Noakes 1998 (15)	PUFA+TFA	2.1 ^d	10.2 ^d	10.4 ^{cd}	4.23	1.17	1.4	-7.5	7.3	-0.47*	-0.10	-10.0*	-7.9
	PUFA-TFA	0.0 ^d	10.3 ^d	10.5 ^{cd}	3.98	1.23	-0.7	-7.4	7.4	-0.72*	-0.04	-15.3*	-3.1
	Butter†	0.7 ^d	17.7 ^d	3.1 ^{cd}	4.70	1.27							
Wood 1993 (16)	Hard margarine	6.7 ^d	5.0 ^d	0.8 ^d	3.47	1.16	5.5	-10.3	0.0	-0.31*	-0.06	-8.2*	-4.9
	Soft margarine	0.0 ^d	5.0 ^d	13.8 ^d	3.26	1.16	-1.2	-10.3	13.0	-0.52*	-0.06	-13.8*	-4.9
	Butter†φ	1.2 ^d	15.3 ^d	0.9 ^d	3.78	1.22							

Abbreviations: TFA, trans fatty acids; SFA, saturated fatty acids; LA, linoleic acid; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; %En, percent of energy; STE, stearic acid; OL, oleic acid; SBO, soybean oil; SO, sunflower oil; PHSBO, partially hydrogenated soybean oil; PHFO, partially hydrogenated fish oil; PUFA, polyunsaturated fatty acid

* $p \leq 0.05$

† Comparison diet

$p < 0.058$

§ Authors used butter as the control diet. For this analysis, treatments were compared to SBO

φ Authors compared test fats with each other. For this analysis, test fats were compared to butter

^a Not reported for nontest fat foods common to all diets

^b Fatty acid intakes based on 3-day food records

^c Total PUFA

^d Fatty acid values apply to test fat, not total fatty acids in diet

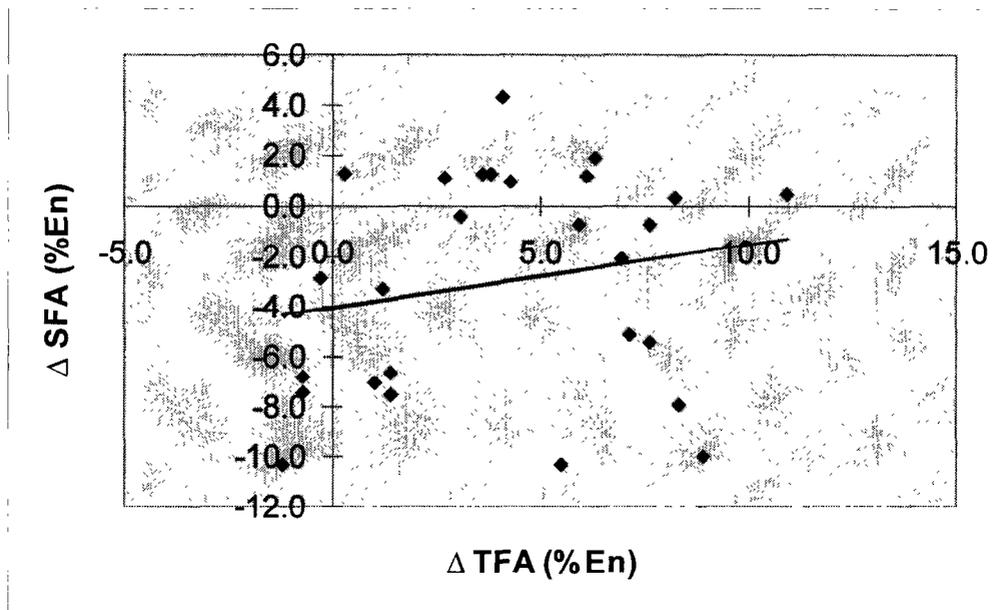


Figure 1. Change in saturated fatty acid intake vs. change in trans fatty acid intake from treatments listed in table 1.

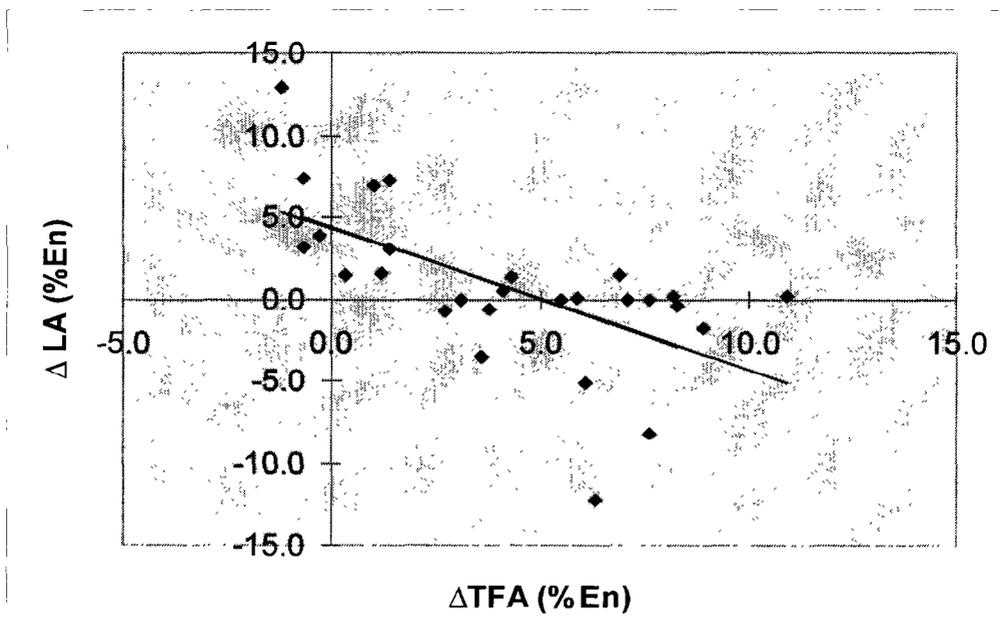


Figure 2. Change in linoleic acid intake vs. change in trans fatty acid intake from treatments listed in table 1.

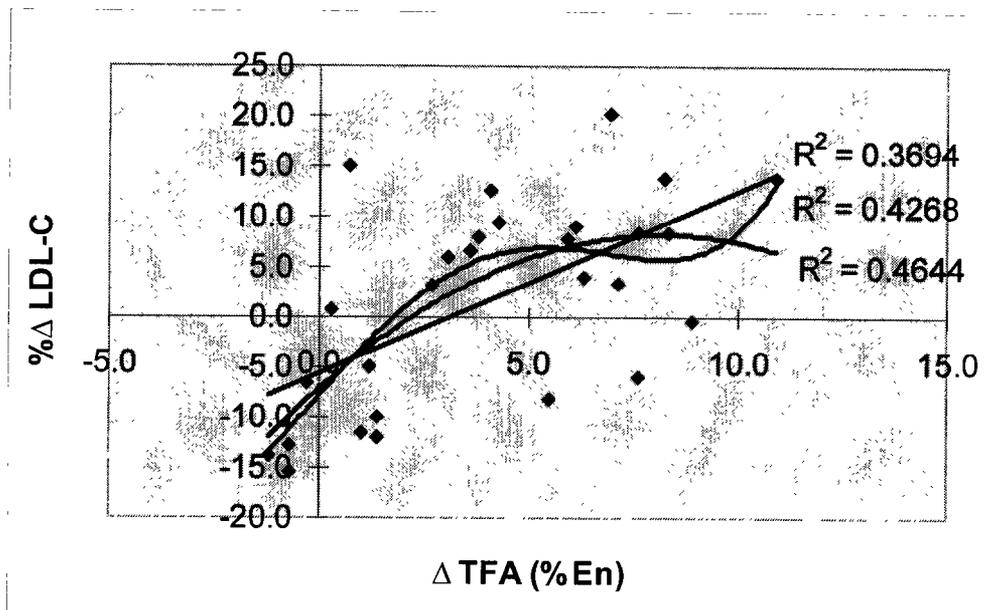


Figure 3. Percent change in LDL cholesterol vs. change in trans fatty acid intake from treatments listed in table 1. Lines plotted represent first, second and fourth order equations, with r^2 coefficients presented in that order.

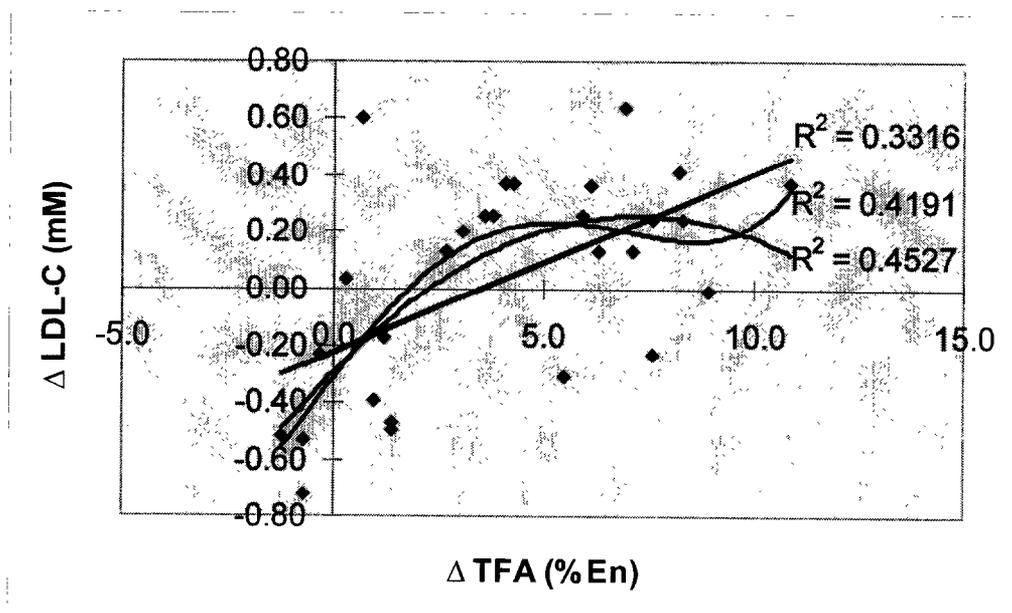


Figure 4. Absolute change in LDL cholesterol vs. change in trans fatty acid intake from treatments listed in table 1. Lines plotted represent first, second and fourth order equations, with r^2 coefficients presented in that order.

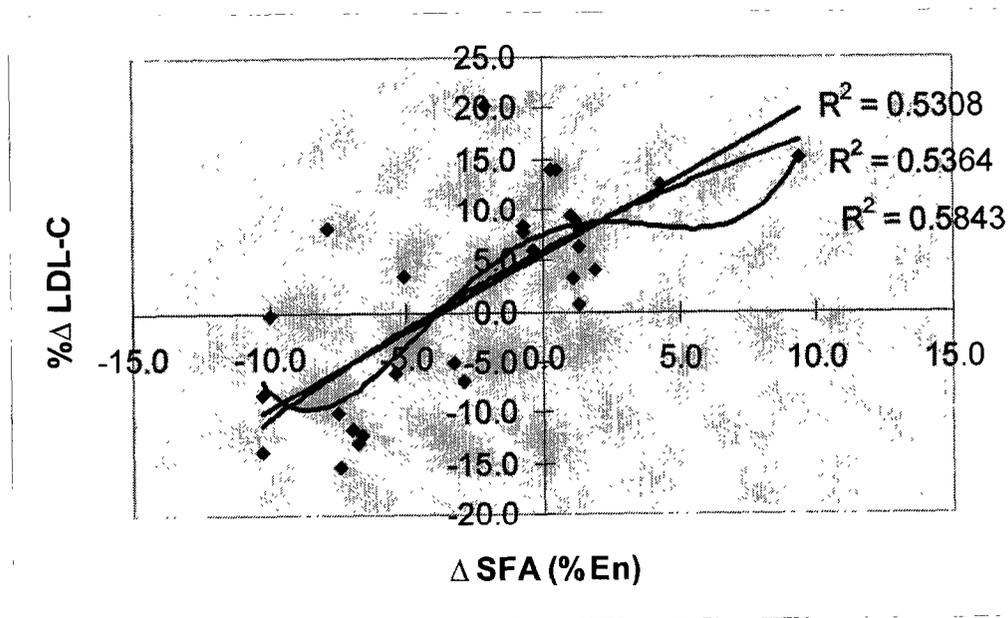


Figure 5. Percent change in LDL cholesterol vs. change in saturated fatty acid intake from treatments listed in table 1. Lines plotted represent first, second and fourth order equations, with r^2 coefficients presented in that order.

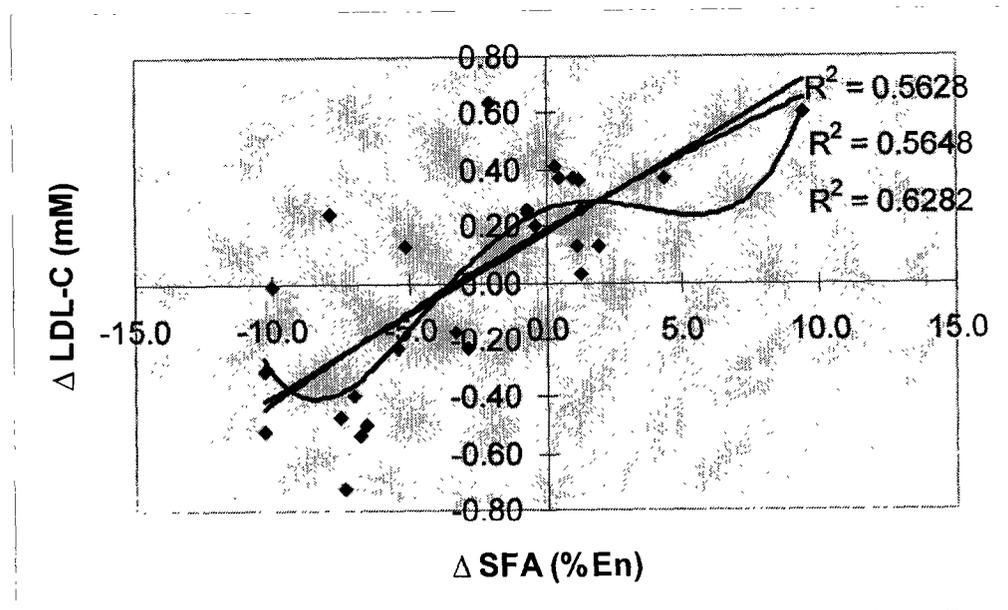


Figure 6. Absolute change in LDL cholesterol vs. change in saturated fatty acid intake from treatments listed in table 1. Lines plotted represent first, second and fourth order equations, with r^2 coefficients presented in that order.

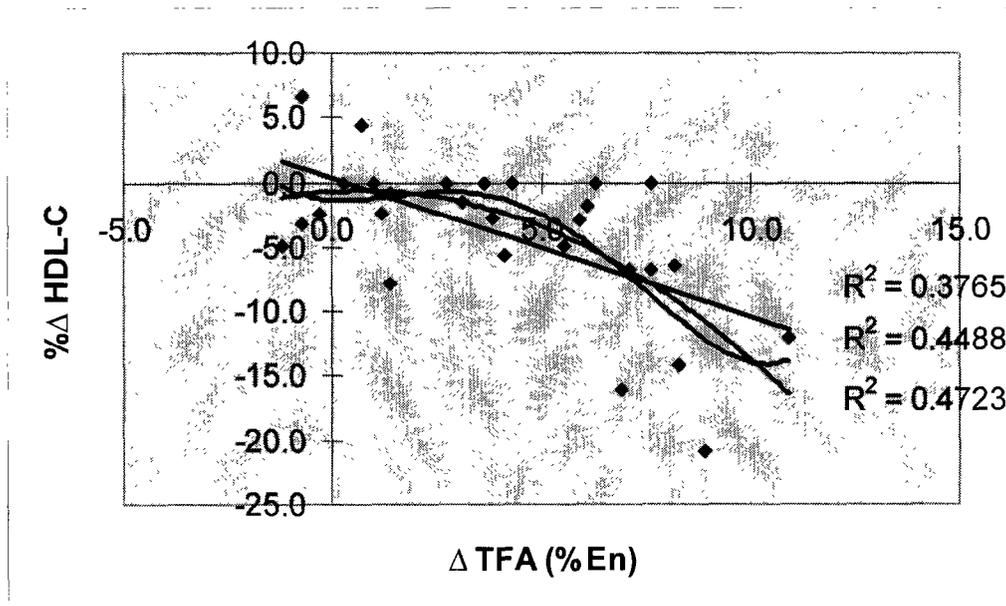


Figure 7. Percent change in HDL cholesterol vs. change in trans fatty acid intake from treatments listed in table 1. Lines plotted represent first, second and fourth order equations, with r^2 coefficients presented in that order.

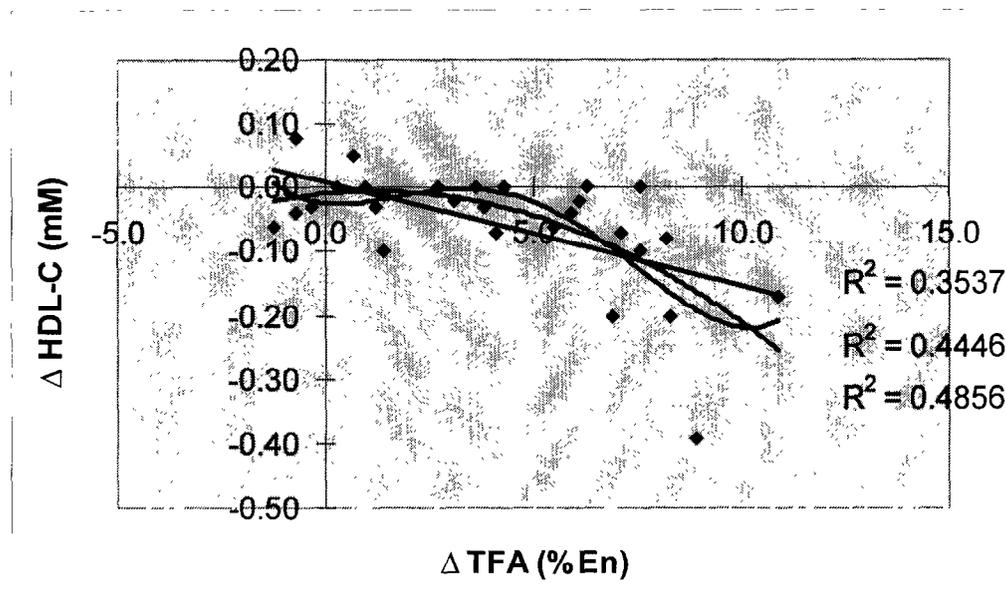


Figure 8. Absolute change in HDL cholesterol vs. change in trans fatty acid intake from treatments listed in table 1. Lines plotted represent first, second and fourth order equations, with r^2 coefficients presented in that order.

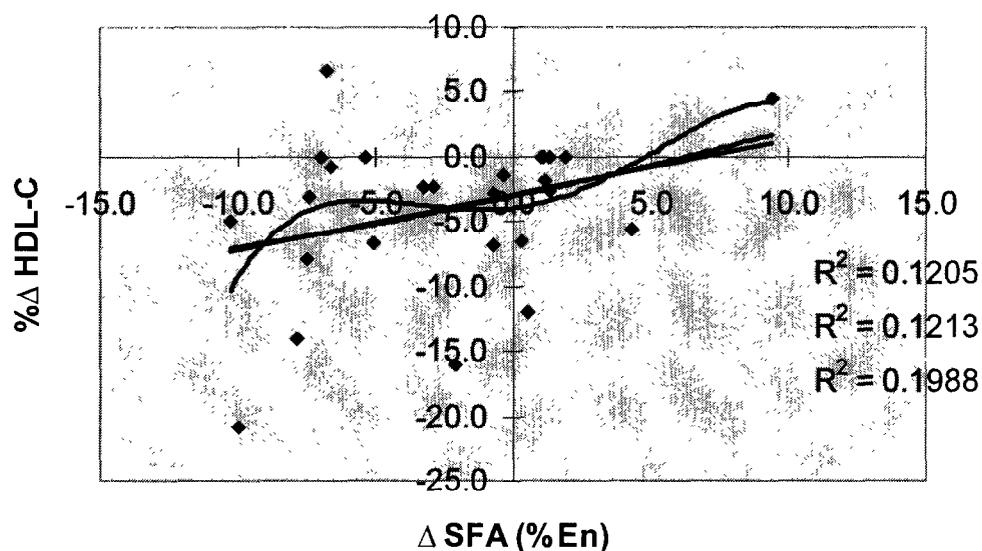


Figure 9. Percent change in HDL cholesterol vs. change in saturated fatty acid intake from treatments listed in table 1. Lines plotted represent first, second and fourth order equations, with r^2 coefficients presented in that order.

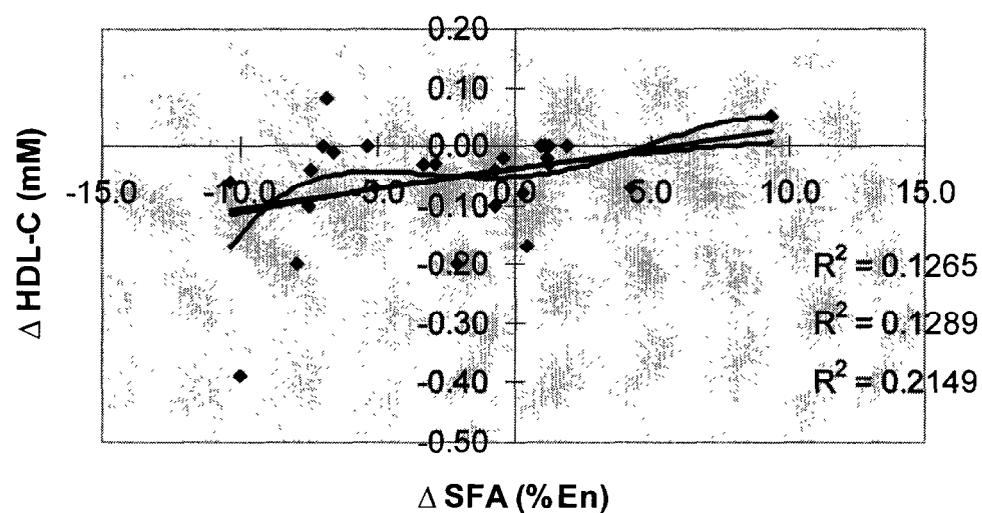


Figure 10. Absolute change in HDL cholesterol vs. change in saturated fatty acid intake from treatments listed in table 1. Lines plotted represent first, second and fourth order equations, with r^2 coefficients presented in that order.

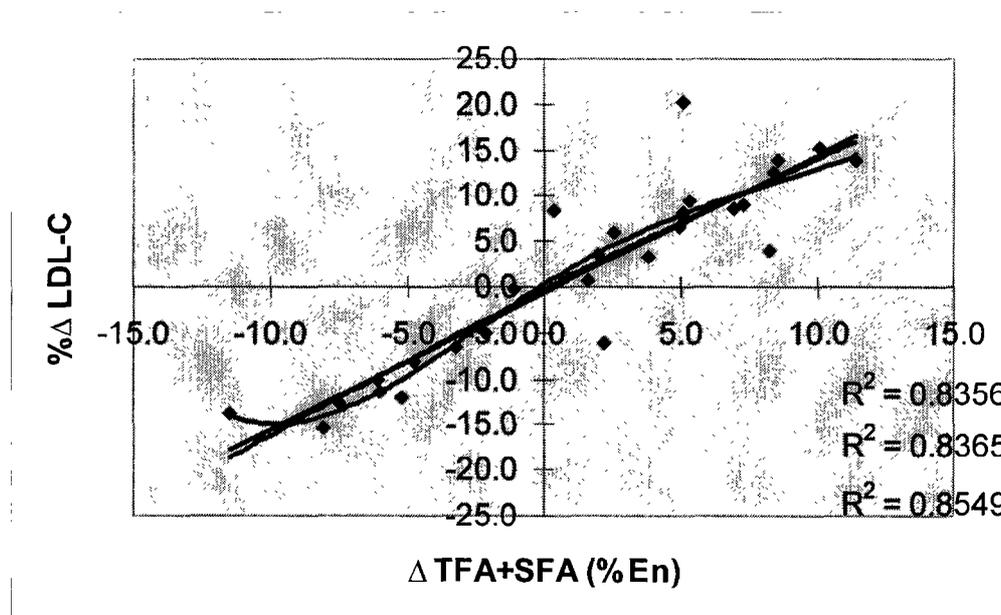


Figure 11. Percent change in HDL cholesterol vs. change in sum of trans and saturated fatty acid intake from treatments listed in table 1. Lines plotted represent first, second and fourth order equations, with r^2 coefficients presented in that order.

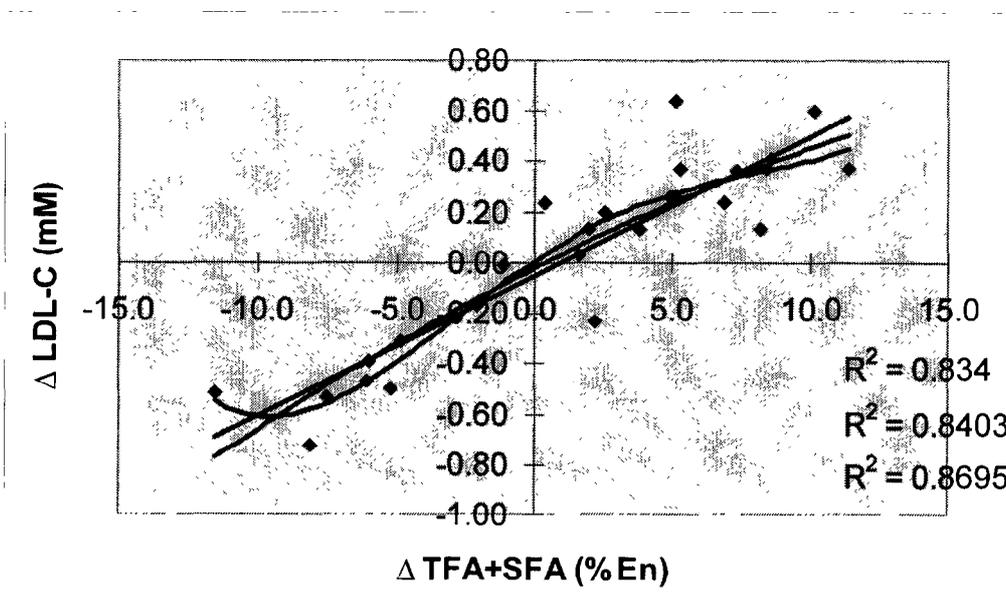


Figure 12. Absolute change in HDL cholesterol vs. change in sum of trans and saturated fatty acid intake from treatments listed in table 1. Lines plotted represent first, second and fourth order equations, with r^2 coefficients presented in that order.