

**Additional commentary on the systematic review of the evidence for a relationship between trans-fatty acids and blood cholesterol**

**Prepared by: Food Standards Australia New Zealand**

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**Executive Summary**

| **Does trans fatty acid intake affect blood cholesterol concentrations?** | |
| --- | --- |
| **Food health relationship** | Increased trans fatty acid consumption increases total and LDL cholesterol concentrations |
| **Degree of certainty**  (GRADE rating) | Total cholesterol: ⊕⊕⊕⊕ ‘High’  LDL-cholesterol: ⊕⊕⊕⊕ ‘High’ |
| **Component** | **Notes** |
| ***Body of evidence*** | An existing systematic review and meta-analysis of randomised controlled trials (RCTs) examining LDL-cholesterol (LDL-C) concentrations was updated to include 11 relevant studies up to March 2014. Because the existing systematic review covered a wider field than that needed for the current purpose, only the 29 relevant studies (35 data points) were brought forward into the update. The findings are consistent with the previous evidence. The effect on HDL-cholesterol (HDL-C) was included as it helps to interpret changes in total cholesterol (total-C) concentration. |
| ***Consistency*** | The existing review found dose-response relationships for LDL-C and HDL-C concentrations. When the additional studies identified in the update were added, there was a dose-response relationship showing significant increases in total-C and LDL-C and a significant decrease in HDL-C when cis mono unsaturated fat is replaced with trans fatty acid intake on an isoenergetic basis in the diet. The results apply to people with normal or elevated blood cholesterol concentrations. The majority of RCTs showed that increased trans fatty acid consumption increased LDL-C concentrations, although this was more evident at higher intakes. Sensitivity analyses did not change the direction of these effects. Effect on total-C concentration was smaller than on LDL-C concentration. This is consistent with the effect on HDL-C concentration. |
| ***Causality*** | RCTs provide a strong study design for causal evidence. The existing review found dose-response relationships for LDL-C and HDL-C concentrations. Some studies in the review used high intakes not realistically attainable within a normal diet. More recent studies, which were generally of high or adequate quality cluster around low intakes which limited the ability of this review to consider the dose response relationship for potential threshold levels or nonlinearity. |
| ***Plausibility*** | The mechanisms by which trans fatty acids contribute to changes in blood lipid profiles remain uncertain. Several potential mechanisms exist, including increased plasma activity of cholesteryl ester transfer protein enzyme which has been proposed to be the driver of increased LDL-C concentrations. |
| ***Generalisability*** | One study was conducted in Australia and most of the remainder were conducted in Europe or North America. Populations covered by the reviewed studies covered a wide range of ages and included people with both normal and elevated blood cholesterol concentrations. The results apply to healthy adults with normal cholesterol concentrations but cannot be generalised to children. |

FSANZ commissioned a report that included a systematic review of the relationship between trans fatty acid (TFA) consumption and blood total-C, LDL-C and HDL-C concentrations (Hafekost et al. 2014). This review updated an existing systematic review by Brouwer et al. (2010) following the requirements of Schedule 6 – Required elements of a systematic review in the *Australia New Zealand Food Standards Code*.

The updated review described that replacing cis mono unsaturated fatty acids with TFA increased LDL-C concentrations significantly. HDL-C was examined because this also affects the direction of any change in total-C concentration and so would affect the interpretation of changes in LDL-C concentrations. There was also a non-significant reduction (i.e. an undesirable direction of effect) in HDL-C concentrations (Hafekost et al. 2014). Consequently, changes in total-C might be smaller than changes in LDL-C, but still reflect an overall undesirable change.

The existing review (Brouwer et al. 2010) examined LDL-C and HDL-C but did not specifically examine total-C or provide much information about whether baseline cholesterol concentration had an important effect on the results. Hafekost et al. (2014) described the results of newly identified studies on total-C concentrations but did not combine this information with that from earlier studies. Therefore additional work, described below, assesses whether the trials included in the existing review also supported a relationship for total-C concentration, and whether relationships varied by baseline cholesterol status of study participants. FSANZ concludes that there is a ‘High’ degree of certainty that increasing intake of trans fatty acids increases total-C and LDL-C.

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Abbreviations

CLA conjugated linoleic acid

ECU Edith Cowan University

HDL-C high density lipoprotein cholesterol

LDL-C low density lipoprotein cholesterol

TFA trans fatty acid

total-C total cholesterol

RCT Randomised controlled trial

# Introduction

The data which currently underpin the pre-approved health claim relating to TFAs, saturated fatty acids and blood cholesterol listed in Schedule 4 – Nutrition, health and related claims in the *Australia New Zealand Food Standards Code* (the Code) were considered in this review.

The currency of pre-approved health claims is being considered during the transition period for Standard 1.2.7. The relationship between TFAs and blood total-C and LDL-C concentrations was considered during the development of the Standard and was included in the then Schedule 2 to Standard 1.2.7 (now Schedule 4) (see Table 1) following advice from the former Scientific Advisory Group (FSANZ 2005[[1]](#footnote-1)). Table 1 shows that the permitted food or property of food is *saturated and trans fatty acids.* This review considers only TFAs. The relationship with saturated fatty acids will be covered in a separate review.

**Table 1**: Pre-approved high level health claim for TFAs in Schedule 4

| **Column 1** | **Column 2** | **Column 3** | **Column 4** | **Column 5** |
| --- | --- | --- | --- | --- |
| **Food or property of food** | **Specific health effect** | **Relevant population** | **Context claim statements** | **Conditions** |
| Saturated and trans fatty acids | Reduces total blood cholesterol or blood LDL cholesterol |  | Diet low in saturated and trans fatty acids | The food must meet the conditions for making a nutrition content claim about low saturated and trans fatty acids |

As part of a separate, but parallel process, FSANZ commissioned a review of the effects of TFAs on various outcomes from the Edith Cowan University (ECU). To examine the effect of TFAs on blood lipids, the ECU review (Hafekost et al. 2014[[2]](#footnote-2)) updated an existing systematic review by Brouwer et al. (2010) following the requirements of Schedule 6 in the Code. The ECU report was received in July 2014 and placed on the FSANZ website in January 2015 after being submitted to the Australia and New Zealand Ministerial Forum on Food Regulation as part of a report on the monitoring of TFA levels in foods in the two countries.

The ECU report updates an existing review of the relationship between TFA and blood cholesterol concentrations (Hafekost et al. 2014). This current document provides additional commentary on three aspects of this relationship.

1. None of the existing reviews (Mensink et al, 2003; Mozaffarian and Clarke, 2009; Brouwer et al, 2010) examining the effect of TFAs on total-C, LDL-C or HDL-C concentrations have specifically considered whether the effect is present in both normo- and hypercholesterolaemic participants. This needs to be specifically considered for the context of examining the relationship for health claims purposes in Australia and New Zealand.

In this review, hypercholesterolaemia is defined as total-C concentrations ≥5.5 mmol/L (Therapeutic Goods Administration Office of Complementary Medicine, 2014).

1. Schedule 4 lists total-C and LDL-C as health effects of saturated and TFAs. The ECU review updated an existing systematic review that described the effect of TFA on each of LDL-C and HDL-C but did not contain a review of the effect of TFA on total-C. Therefore the GRADE assigned by the ECU authors to the relationship with total-C, of ‘Moderate’, was based on studies published between 2010 and 2014. The current paper considers whether the results of studies published prior to 2010 allow the GRADE for the relationship between TFAs and total-C to be increased to ‘High’.
2. The ECU review combined the overall meta-analysis result of Brouwer et al. (2010) with the additional studies identified in their update but did not specifically comment on the range of results across the studies included in Brouwer et al. (2010). This is presented below.

Using the ECU review and the supplementary information provided below, an overall conclusion is drawn regarding the relationship of TFAs with total-C, LDL-C and HDL-C concentrations in all the studies and in studies of people with normal cholesterol concentrations. Although HDL-C is not listed in the Schedule as a health effect (Table 1), FSANZ also assesses HDL-C when assessing total-C or LDL-C to check for possible adverse effects.

# Overview of existing reviews

Over time, the focus of clinical management of cholesterol concentrations has changed from using total-C as the screening parameter to a greater emphasis on sub-fractions (i.e. ‘bad cholesterol’ versus ‘good cholesterol’) and their ratios. This may explain why earlier reviews included total-C and more recent reviews of the effects of TFAs have focused on sub-fractions and their ratios and have not always included total-C in their analysis. Although there are a number of reviews of the effects of TFAs on blood lipid fractions, a number of these reviews also focus on lipid ratios. FSANZ identified three reviews that report total-C and/or LDL-C and/or HDL-C. The studies included in the three reviews discussed below, are given in Table 2. They are classified as having been done in normocholesterolaemic populations if mean baseline total-C concentration was <5.5 mmol/L.

## Mensink et al. 2003

This review described the effect of exchanging different classes of fatty acids, and individual fatty acids, for each other or for carbohydrate, on an isoenergetic basis. It was the first review to specifically quantify the effect of TFAs on cholesterol concentrations. The following inclusion/exclusion criteria and search information were described by the authors:

* adults (> 17 y) without disturbances of lipid metabolism or diabetes
* food intake thoroughly controlled and described, with dietary fatty acids as the sole variable; cholesterol intake had to be constant, by adding dietary cholesterol to some trial arm diets if necessary; excluded studies focused on very-long-chain (n−3) polyunsaturated fatty acids
* feeding periods > 13 days
* outcomes: total- C and sub-fractions (LDL-C, HDL-C)
* original research studies published in English between January 1970 and December 1998 were selected through a computer-assisted literature search, reference lists scanned and hand-searching of (unspecified) journals
* parallel, crossover, or Latin-square design included; before-and-after (sequential) designs that lacked a control group excluded.

The authors identified 60 trials which yielded 159 data points that met their criteria. Of these, eight trials gave 18 data points for TFAs. Only one of these studies was published prior to 1990.

## Mozaffarian and Clarke 2009

This review of the randomised controlled trials reporting a range of serum lipid-related outcomes was conducted as part of a WHO Scientific Update on Trans Fatty Acids (<http://www.who.int/nutrition/topics/trans_fatty_acids/en/>). The following inclusion/exclusion criteria were described by the authors:

* studies excluded if they were of subjects selected for some disorder (such as diabetes or dyslipidaemia), changes in body weight were not part of the exclusion criteria
* controlled conditions that ensured compliance (metabolic ward studies, data about dietary fatty acids or dietary cholesterol reported); interventions with liquid formula diets excluded from the main analysis
* each dietary period lasted at least 2 weeks
* outcomes: total-C and fractions, apolipoproteins measured at the end of each intervention
* Medline searches, scanning relevant reference lists, and hand searching nutrition journals through January 2008
* crossover or parallel design randomized trials.

## Brouwer et al. 2010

By the time this review was done, the body of research had expanded to include studies of the effect of TFAs found in ruminant foods and also synthetic preparations of various isomers of conjugated linoleic acid (CLA), a fatty acid with one cis bond and one trans bond. One CLA isomer – cis-9, trans-11 – is found in ruminant and dairy fat. The following inclusion/exclusion criteria were described by the authors:

* human studies; trials in which subjects lost or gained significant amounts of weight were excluded
* dietary trials using industrial TFAs, CLA or other ruminant TFAs, including CLA supplements
* outcomes: studies had to report both LDL-C and HDL-C
* treatment periods had to last at least 13 days
* parallel, crossover, or Latin-square design studies included, sequential designs excluded
* Medline searched for all relevant original-research papers published in English between January 1990 and January 2010; search terms: “(trans fat OR trans fatty acids, OR CLA) AND LDL”; reference lists scanned.

The focus of the analysis was on the ratio of LDL-C and HDL-C and whether this was different for the three classes of TFAs. A larger number of studies were included compared to the two earlier reviews because some inclusion criteria were less stringent. Hence, compared to the two earlier reviews, this review contains some studies that might be regarded as lower quality owing to a lack of full details about the dietary intake of participants during the trial.

## 2014 Update by ECU (Hafekost et al. 2014)

The 2014 update used the selection criteria of Brouwer et al. (2010) to identify studies, with one exception. Brouwer et al. (2010) included mixtures of synthetic isomers of conjugated linoleic acid (CLA) (which are made from safflower oil) are currently not permitted to be added to food in Australia and New Zealand. The cis-9, trans-11 CLA isomer is found in food from ruminants. Therefore studies of CLA which used only the cis-9, trans-11 CLA isomer were included in the update whereas studies that used other CLA isomers, with or without the cis-9, trans-11 isomer, were excluded.

Three data points were brought forward from Brouwer et al. (2010) into the 2014 update: i) the overall effect for industrial TFAs (23 studies); ii) the overall effect observed in studies which had enriched the ruminant TFA content of dairy fat by biofortification (feeding CLA acid to cows, 5 studies); and iii) data from one study which had used only synthetic cis-9, trans-11 CLA (which is identical with the primary CLA in ruminant fat). Studies included in the review by Hafekost et al. 2014 are shown in Table 2.

## Commentary

Among the three reviews the detail of the search strategy and other criteria vary and some factors are left for the reader to infer. For example, only Mensink et al. (2003) specifically mention excluding trials using omega-3 fats even though margarines in some countries may contain oils from marine sources. Mensink et al. (2003) state that they only included studies in adults whereas this is not specifically stated in the other two reviews. Other criteria varied among the reviews. Mensink et al. (2003) restricted their selection to adults without dyslipaemia or diabetes who were given highly controlled diets. Mozaffarian and Clarke (2009) were slightly less restrictive in that their definition of dyslipaemia appears to have excluded lower degrees of hyperlipidaemia. Brouwer et al. (2010) were less restrictive again in this regard. The first two reviews included only studies carried out in a controlled/metabolic ward type of situation whereas Brouwer et al. (2010) did not have this restriction but did state that they excluded studies where significant bodyweight changes were reported during the trial.

FSANZ considers that the conclusions of the reviews by Mensink et al. (2003) and Mozaffarian and Clarke (2009) are drawn from high quality studies owing to the restrictions on dietary control as part of their inclusion criteria. The looser dietary control criteria for the analysis of Brouwer et al. (2010) would allow some lower quality studies in addition to the high quality studies to be included. The ECU update review noted that some of the new studies they identified were of a lower quality than older studies (Hafekost et al. 2014).

## Summary of studies included in the reviews

Table 3 shows the overall effect from the four reviews. The results are calculated as an isoenergetic exchange of 1% of energy of the comparator macronutrient for TFAs. Mensink et al. (2003) chose carbohydrate as their comparator whereas the other reviews used cis mono unsaturated fatty acid (cis-MUFA). However, it is accepted that carbohydrate and cis-MUFA have essentially the same effect on cholesterol concentrations as each other and so the results shown in the table are essentially comparable.

# Additional considerations

## Cholesterol status of participants

The TFA studies available to Mensink et al. (2003) were all conducted in normocholesterolaemic subjects (Table 2), although this was not a specific inclusion criterion for the review. Among the eight trials in their analysis, they found that substituting 1% energy from carbohydrate with (industrial) TFAs increased LDL-C and total-C concentrations. The increase in total-C was smaller than the increase in LDL-C (Table 3).

Mozaffarian and Clarke (2008) used similarly strict criteria for trial description, but lifted the criterion regarding cholesterol status of participants. However only one of the 13 trials included in their review had hypercholesterolaemic participants (Table 2). They found a significant adverse effect on HDL-C, in addition to the previously reported effects on LDL-C and total-C (Table 3).

Unlike the two earlier reviews, Brouwer et al. (2010) did not require the included studies to have had tightly control of food provided to participants (e.g. by providing all food consumed) and consequently included a greater number of studies for the period up to 2008 (covered by the other two reviews). Their analysis of industrial TFAs included additional studies conducted in both normocholesterolaemic and hypercholesterolaemic subjects (Table 2). In relation to industrial TFAs Brouwer et al. (2010) reported identical or larger changes in LDL-C and HDL-C compared with the previous reviews (Table 3). The five studies of ruminant TFA were all conducted in participants with normal cholesterol concentrations and effects on LDL-C and HDL-C were very similar to the effect seen in the industrial TFA trials. None of the studies using industrial TFA showed a favourable change in LDL-C whereas 2 of the 5 ruminant studies had a favourable change.

More than half of the studies published after the review of Brouwer et al. (2010) and added to the 2014 update (Hafekost et al. 2014) were conducted in normocholesterolaemic participants (Table 2). When the studies involving normocholesterolaemic participants are combined with the data brought forward from Brouwer et al. (2010), the results for LDL-C and HDL-C do not change previous results importantly (Table 3). (When considered alone, the effect for the studies contained in the update was a smaller effect on LDL-C and total-C than the previous estimates. About half the new studies use ruminant TFAs, and studies using this substance tend to give smaller amounts in the test diet to study participants than studies testing industrial TFAs, hence a smaller effect would be expected.)

Therefore FSANZ concludes that the relationship applies to people with normal cholesterol concentrations.

**Table 2:** Studies included in the four systematic reviews (shaded studies were conducted in subjects with baseline mean total-C concentration >5.5mmol/L)

| Study | | | Study included inreview shown belowa | | | |
| --- | --- | --- | --- | --- | --- | --- |
| Author, year of publication | Total-C (mmol/L)b | type of TFAc | Mensink et al. 2003 | Mozaffarian & Clarke, 2009 | Brouwer et al. 2010, industrial or ruminant TFA sub-groups | Hafekost et al. 2014 |
| Laine et al. 1982 | <5.5**b** | i | y | y | - | - |
| Mensink and Katan, 1990 | 4.75 | i | y | y | y | y |
| Zock and Katanl. 1992 | 4.84 | i | y | y | y | y |
| Nestel et al. 1992 | 5.90 | i | - | - | y | y |
| Lichtenstein et al. 1993 | 6.16 | i | - | - | y | y |
| Judd et al. 1994 | 5.30 | i | y | y | y | y |
| Almendingen et al. 1995 | 5.35 | i | y | y | y | y |
| Aro et al. 1997 | 4.75 | i | y | y | y | y |
| Sundram et al. 1997 | 5.02 | i | - | - | y | y |
| Judd et al. 1998 | 5.12 | i | y | y | y | y |
| Muller et al. 1998 | 5.30 | i | y | y | y | y |
| Lichtenstein et al. 1999 | 6.30 | i | - | y | y | y |
| de Roos et al. 2001 | 5.00 | i | - | y | y | y |
| Judd et al. 2002 | 4.77 | i | - | y | y | y |
| French et al. 2002 | 5.37 | i | - | - | y | y |
| Han et al. 2002 | 6.55 | i | - | - | y | y |
| Lovejoy et al. 2002 | <4.0b,d | i | - | y | y | y |
| Dyerberg et al. 2004 | 5.06 | i | - | - | y | y |
| Desroches et al. 2005 | 4.90 | r | - | - | y | y |
| Lichtenstein et al. 2006 | 5.75 | i | - | - | y | y |
| Vega-Lopez et al. 2006 | 6.55 | i | - | - | y | y |
| Tricon et al. 2006 | 5.40 | r | - | - | y | y |
| Tholstrup et al. 2006 | 4.05 | r | - | - | y | y |
| Sundram et al. 2007 | 5.03 | i | - | y | y | y |
| Chardigny et al. 2008 | 4.74 | i,r | - | - | y | y |
| Motard-Belanger et al. 2008 | 4.32 | i,r | - | - | y | y |
| Wanders et al. 2010 | 4.54 | i | - | - | y | y |
| Teng et al. 2010 | 4.6 | i | - | - | - | y |
| Gagliardi et al. 2010 | 5.3d | r | - | - | - | y |
| Takeuch et al. 2011 | 3.96 | i | - | - | - | y |
| Bendsen et al. 2011 | 5.54 | i | - | - | - | y |
| Labonte et al. 2011 | 4.32 | i,r | - | - | - | y |
| Lacroix et al. 2012 | 5.11 | r | - | - | - | y |
| Pintus et al. 2013 | 6.26 | r | - | - | - | y |
| Takeuchi et al. 2013 | 4.66 | i | - | - | - | y |
| Venkatramanan et al. 2010 | 5.00 | r | - | - | - | y |
| Naumann et al. 2006 | 6.08 | o | - | - | y | y |
| Joseph et al. 2011 | 6.31 | o | - | - | - | y |

a (y) study included in the review; (-) study not included in the review

b baseline total-C concentrations given for separate groups

c (i) industrial TFA tested; (r) ruminant TFA tested via biofortification of dairy fat; (o) synthetic cis-9, trans-11 conjugated linoleic acid used

d total-C concentration during/at end of the study period

**Table 3:** Effect of increasing TFA intake by 1% energy in exchange for the stated comparator macronutrient

| Author, year | Description of Intervention | Literature search | Comparator | Mean (mmol/L) (95% CI) | | |
| --- | --- | --- | --- | --- | --- | --- |
| LDL–C | HDL-C | Total-C |
| Mensink et al. 2003 | Highly controlled food intake studies, no lipid or glucose metabolism disturbances | 1970-December 1998 | Carbohydrate | +0.04  (+0.02 to +0.06) | 0.00  (−0.01 to +0.01) | +0.03  (+0.02 to +0.04) |
| Mozaffarian & Clarke, 2009 | Controlled food intake studies | To January 2008 | cis-MUFA | +0.04  (+0.02 to +0.05) | -0.01  (-0.02 to -0.00) | +0.03  (+0.02 to +0.05) |
| Brouwer & al. 2010 | Subset of industrial TFA studies | To January 2010 | cis-MUFA | +0.05  (+0.04 to +0.06) | −0.01 (−0.01 to −0.01) | Not reported |
| Subset of ruminant TFA studies | +0.05 (−0.00 to +0.09 | −0.01 (−0.03 to +0.01) | Not reported |
| Hafekost et al. 2014 | Food intake (industrial or ruminant TFA) or supplement studies including ruminant CLA studies | 2010-March 2014 | cis-MUFA | +0.01  (-0.04 to +0.07)  New studies only**a** | -0.02  (-0.05 to +0.01)  New studies only **a** | +0.02  (-0.03 to +0.07)  New studies  only**a** |
| +0.04  (+0.03 to +0.06)  Including relevant**b** studies from Brouwer et al. | -0.01  (-0.03 to +0.01)  Including relevant **b**studies from Brouwer et al. | Not applicable |

**a** Wanders et al. was published early in 2010 and was included in Brouwer et al.(2010); hence it was excluded in the new studies grouping for LDL-C and HDL-C, but was included in the summary of total-C which had not been analysed by Brouwer et al. Hence the analysis for total C includes one study more than the analyses for LDL-C and HDL-C. Note also that the study using CLA by Naumann et al.(2006) was included in the Brouwer et al.(2010) review but is shown as a separate line of data in the ECU updated analysis because, as described by Hafekost et al.(2014) this was the only CLA study that met the inclusion criteria for the current review

**b** studies relevant to the current purpose, studies included in Brouwer et al.(2010) that used mixed CLA isomers were excluded

## Relationship with total-C

Table 3 shows that the two earlier reviews described the effect of isoenergic exchange of TFA on total-C concentrations, but Brouwer et al. (2010) did not because their focus was on the ratio of LDL-C and HDL-C. None of the reviews provide individual data points for the studies included in their analyses.

All reviews agree that the effect of TFAs on LDL-C when all studies are combined is approximately +0.04 mmol/L per 1% increase in energy from TFAs in exchange for carbohydrate/cis-MUFA. Reviews that have examined total-C show the change in total-C mirrors the change in LDL-C in direction but not necessarily in magnitude. The two earlier reviews show that the magnitude of effect on HDL-C is about one quarter of the magnitude of effect on LDL-C. Most of total-C is LDL-C and HDL-C and the reminder (e.g. very low density lipoprotein cholesterol) is small. Table 2 shows that the effect on mean total-C is very similar to that which might be calculated by subtracting the mean effect on HDL-C from the mean effect on LDL-C in the reviews that have done all three analyses.

FSANZ considers that the GRADE rating of the TFA-total-C relationship of ‘Moderate‘ suggested by the ECU review authors (which is based solely on studies published from 2010 onwards) can be increased to ‘High’ (Appendix 1) for the following reasons:

* the degree of certainty that increasing TFA intake (by isoenergetic exchange with carbohydrate or cis-MUFA) increases LDL-C and decreases HDL-C is rated HIGH
* the increase in LDL-C is approximately 4-fold larger than the decrease in HDL and so simple subtraction indicates that total-C would therefore increase with iso-energetic increase in TFA intake
* analyses of various subsets of data confirm that total-C increases with isoenergetic increase of TFA intake.

FSANZ considers that there is a ‘High’ degree of certainty that increasing TFA intake (by isoenergetic exchange with carbohydrate or cis-monounsaturated fats) increases LDL-C (Appendix 1).

FSANZ notes that the analysis of HDL-C by ECU is not statistically significant (p = 0.2) but that one study which has a high weight in Figure 4a is marked ‘non estimable’ (Figure 4b, Hafekost et al, 2014). When FSANZ recalculated the data in Figure 4b to include this study, the confidence intervals become narrower and exclude the null effect (p = 0.03).

## Consistency across studies

I2 was 31% for LDL-C and 61% for HDL-C for the overall meta-analysis (Hafekost et al, 2014). The presence of a dose-response effect would be one cause of a high heterogeneity among studies (i.e. inconsistent results). Figures 1 and 2 show the individual data points of the studies included in the existing review, Brouwer et al. (2010) and the new studies identified in the update by Hafekost et al. (2014).

Comparison of these graphs shows that the new studies are consistent with the pattern of the earlier studies. There is a dose-response relationship. It is also evident that the more recent studies have tested lower intakes than the body of earlier studies. Consequently there is a spread of results on both sides of no effect at low intakes. At higher intakes, the effect is more consistently either an increase for LDL-C or a decrease for HDL-C.

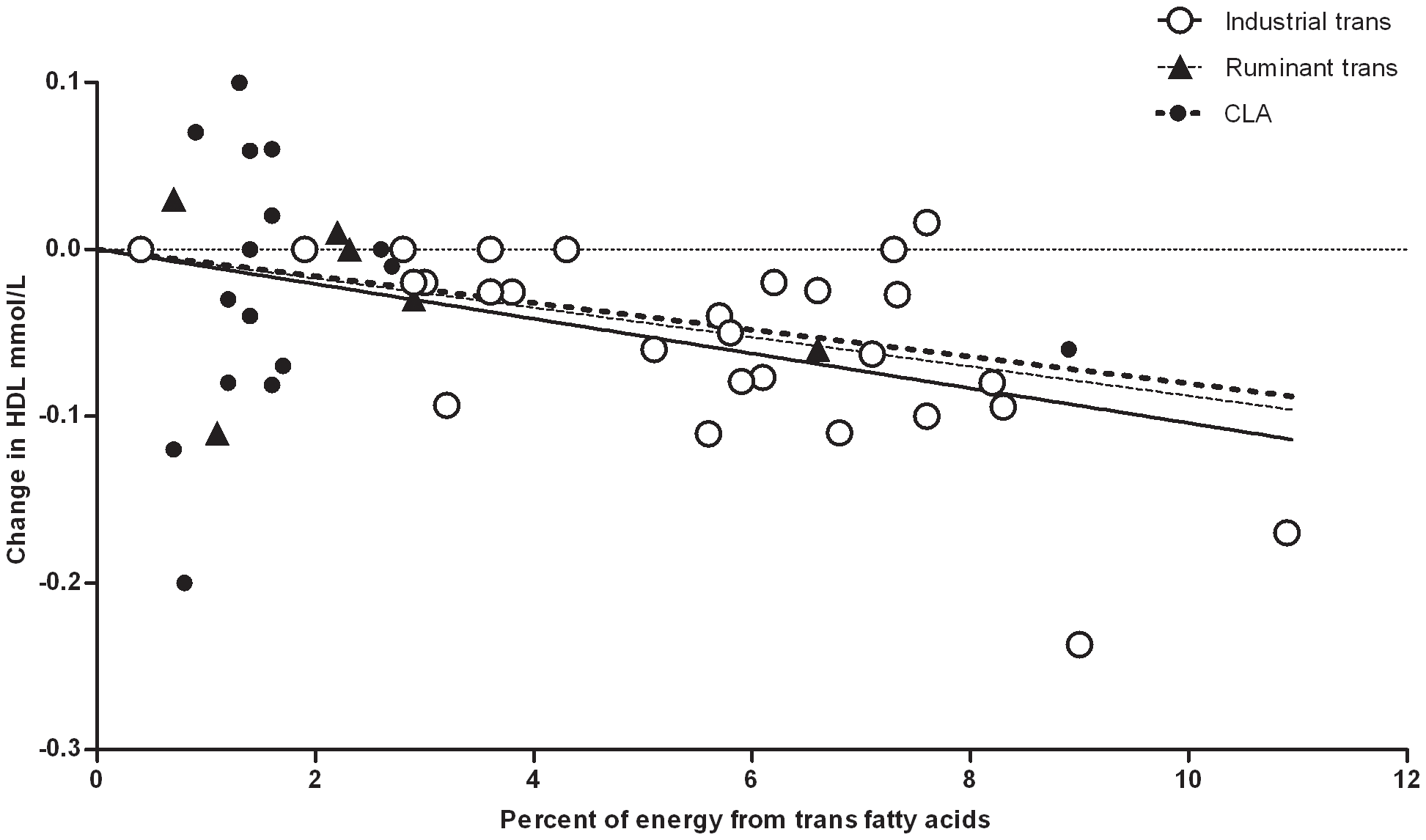
# Conclusion

FSANZ considers that the updated systematic review of the relationship between TFAs and three blood lipid concentrations does not alter previous conclusions and shows that, when exchanged on an isoenergetic basis for cis-monounsaturated fats, there is a ‘High’ degree of certainty that increasing TFA intake increases total-C and LDL-C and a ‘High’ degree of certainty that TFA lowers HDL-C. Most of the studies in the reviews were conducted in adults with normal cholesterol concentrations and some studies in adults with elevated cholesterol concentrations.

Graph with percent energy from fatty acids on the x axis and change in LDL-C on the y axis showing studies from the existing review by Brouwer.

Graph with percentage of energy intake from TFAs on the x axis and effect estimate (change in LDL-C) on the y axis for studies included in the updated review (Hakefost et al. 2014). 

**Figure 1:**  Studies of the effects of TFAs on LDL-C included in the existing review (upper graph, Brouwer et al. 2010 doi:10.1371/journal.pone.0009434.g004) and identified in the update (lower graph Hafekost et al. 2014). Note that only one of the studies using CLA (the black dots in the upper graph) was brought forward into the current review because the update considered only the cis-9,trans-11 isomer of CLA when used alone. Hence this study (Naumann et al. 2006) does not appear in the lower graph.



Graph with percentage of energy intake from TFAs on the x axis and effect estimate (change in HDL-C) on the y axis for studies included in the updated review (Hakefost et al. 2014).

**Figure 2:**  Studies of the effect of TFAs on HDL-C included in the existing review (upper graph, Brouwer et al. 2010 doi:10.1371/journal.pone.0009434.g005) and identified in the update (lower graph Hafekost et al. 2014). Note that only one of the studies using CLA (the black dots in the upper graph) was brought forward into the current review because the update considered only the cis-9,trans-11 isomer of CLA when used alone. Hence this study (Naumann et al. 2006) does not appear in the lower graph.

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# Appendix 1: GRADE summary of findings table

Question: Does increasing TFA intake affect blood cholesterol concentrations? *(Quantitative results expressed per 1% increase in energy intake from TFA in exchange for cis-monounsaturated fatty acids)*

| **Quality assessment of body of evidence** | | | | | | |  | **Mean effect estimate**  **(mmol/L)**  **(95% CI)** | **Quality1**  **(degree of certainty in relationship)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Number of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Considerations** | **Participants** |
| **Increase in LDL-cholesterol2** | | | | | | | | | |
| 9 studies added to 1 existing meta-analysis | RCTs | low | some# | none | none | Dose-response relationship | 2218 | +0.04  (+0.03, +0.06) | ⊕⊕⊕⊕  High |
| **Reduction in HDL-cholesterol3** | | | | | | | | | |
| 9 studies added to 1 existing meta-analysis | RCTs | low | some# | none | none | Dose-response relationship, but overall effect not significant | 2218 | -0.01  (-0.02, -0.001) | ⊕⊕⊕  High |
| **Increase in total cholesterol (studies published from 2010 onwards)2** | | | | | | | | | |
| 10 | RCTs | low | some | none | some**4** | Dose-response relationship plausible | 411 | +0.02  (-0.03, + 0.07) | ⊕⊕⊕  Moderate |
| **Increase in total cholesterol (based on results from all studies and results for LDL cholesterol and HDL cholesterol )** | | | | | | | | | |
| 9 studies considered together with the results of existing meta-analyses | RCTs | low | N/A | some | N/A | Conclusions drawn on direct analysis of total cholesterol and indirectly by considering the effects on LDL and HDL cholesterol | N/A | Not calculated directly, +0.03 by difference from previous reviews of LDL and HDL cholesterol, supports previous significant results of this magnitude | ⊕⊕⊕⊕  High |

**1** these relationships were not downrated despite having some inconsistency owing to the presence of a dose-response gradient

**2** data taken from Hafekost et al. (2014)

**3** data taken from Hafekost et al. (2014), revised analysis

**4** total cholesterol (analysis of studies published from 2010 onwards) were not statistically significant

N/A not applicable

1. Report is available at <http://www.foodstandards.gov.au/consumer/labelling/nutrition/pages/reviewsforhighlevelc3090.aspx> [↑](#footnote-ref-1)
2. Report is available at (<http://www.foodstandards.gov.au/science/monitoringnutrients/Pages/Monitoring-of-trans-fatty-acids.aspx> [↑](#footnote-ref-2)