FOOD STANDARDS Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

SUPPORTING DOCUMENT 2

APPLICATION A1005
EXCLUSIVE USE OF TONALIN® CLA AS A NOVEL FOOD

Effects of Conjugated Linoleic Acid on Body Weight and Body Composition

December 2010

Contents

Glossary

AD	Air displacement plethysmography
BIA	Bioelectrical impedance assessment
BMI	Body mass index
BF	Body fat
BFM	Body fat mass
BW	Body weight
CLA	Conjugated linoleic acid
CI	Confidence interval
CT	Computed tomography
DXA	Dual-energy x-ray absorptiometry
EE	Energy expenditure
FFA	Free fatty acid
FFM	Fat free mass
FFQ	Food frequency questionnaire
FSANZ	Food Standards Australia New Zealand
Hydro	Hydro densitometry
IR	Infrared
ITT	Intention to treat
LBM	Lean body mass
LCD	Low calorie diet
ND	No data
NS	Not statistically significant
OGTT	Oral glucose tolerance test
PP	Per protocol
RER	Respiratory exchange ratio
RMR	Resting metabolic rate
RQ	Respiratory quotient
SAD	Sagittal abdominal diameter
VLCD	Very low calorie diet
WHR	Waist to hip ratio

BMI categories used throughout this report

Normal weight	<25
Overweight	25 to <30
Obese	BMI >= 30
Mildly obese	BMI 30-32
Moderately obese	BMI 30 to < 35
Severely obese	BMI 35-40

Summary

FSANZ undertook a systematic review to assess whether the CLA isomers *cis*-9, *trans*-11 (*c*9, *t*11) and *trans*-10, *cis*-12 (*t*10, *c*12) in an approximate 1:1 ratio reduce body weight or positively influence body composition, such as reducing body fat mass or increasing lean body mass. Twenty-six studies met the inclusion criteria for this assessment. To minimise the potential confounding effects of age, weight, and exercise, and to take into account duration of treatment, the studies were grouped according to the effect of CLA on body weight and body composition:

1. following initial weight reduction
2. in combination with prescribed exercise
3. in studies of 6-12 months duration in overweight and mildly obese adults
4. in studies of less than six months duration in normal weight, overweight and obese adults
5. in studies in overweight children and adolescents.

FSANZ also undertook a comparable meta-analysis of changes in body fat mass following CLA administration in adults to that undertaken in the meta-analysis by Whigham *et al*. (2007).

FSANZ concludes from these two approaches that the evidence is supportive of a small reduction in body fat mass of 1-2 kg among overweight or mildly obese adults as a result of consuming CLA in supplement form in the amount recommended by the Applicant. However, the clinical significance of this amount of fat loss at the individual level is likely to be minimal and, at a population level, any potentially beneficial effect of change in body fat mass on overall health would depend on simultaneous changes in factors such as blood lipids.

In addition, a range of uncertainties remain in relation to the effect of CLA on fat mass:

- there is no evidence of a dose effect
- as most of the research supporting the evidence for an effect on fat mass has been done in women and using supplements, the effect may not apply to other populations or when similar doses of CLA are added to food
- there is insufficient evidence of an effect on fat mass in children
- the means by which CLA might reduce body fat remain unclear although one study is suggestive of an increase in energy expenditure
- the methods used to measure changes in fat mass are at the limit of their validity when small changes of 1-2 kg are observed.

In terms of the effect of CLA on body weight, the trend is for a fall in body weight although it is not statistically significant, and there is limited evidence that CLA positively influences lean body mass or assists in maintaining weight or preventing weight regain following initial weight loss.

1. Introduction

The Applicant, Cognis GmbH, is seeking to amend Standard 1.5.1 – Novel Foods of the *Australia New Zealand Food Standards Code* (the Code) to approve the use of a chemically defined mixture of approximately equal amounts of the *cis*-9, *trans*-11 (*c*9, *t*11) and *trans*-10, *cis*-12 (*t*10, *c*12) CLA isomers in the form of triglyceride esters. They recommend 1.5 g Tonalin® CLA be added to individual serves of food with a recommended daily consumption of 4.5 g Tonalin® CLA. The reason for adding Tonalin® CLA to food is as a useful adjunct in weight control programmes and diets.

Interest in CLA is partly due to animal research indicating it affects body weight and body composition, potentially by altering energy expenditure (Plourde *et al.*, 2008). However, the effects can be species-specific and may not be able to be extrapolated to humans (Wahle *et al.* 2004).

2. Methods

FSANZ has undertaken a systematic review of the literature that included an analysis of the effect of CLA on measures of body composition (see Inclusion and Exclusion criteria below).

The meta-analysis by Whigham *et al.* (2007) describing the effect of CLA on change in fat mass is also considered. It includes studies published in 2006 or before and one study that was in press.

2.1 Literature Search Strategy

The Applicant provided numerous published peer reviewed papers. The reference lists of the papers provided were searched for further relevant work. In addition, FSANZ conducted a search in PubMed using the terms: conjugated linoleic acid OR CLA. The following limits were applied to the search: humans, controlled clinical trial. The search was last run on 31 March 2010. A CLA specific website was also searched http://fri.wisc.edu/clarefs.htm (last accessed on 23 November 2010).

2.2 Inclusion and Exclusion Criteria

The following inclusion criteria were used by FSANZ to select studies for detailed evaluation:

- a statement that the trial was randomised, double-blinded, and placebo-controlled
- either a parallel or crossover design
- the intervention had to be CLA in an approximate 1:1 ratio of the *c*9, *t*11 and *t*10, *c*12 CLA isomers
- one of the following had to be reported: body weight, body fat mass (kg), lean body mass (kg) or energy metabolism
- no co-interventions with potentially active substances, except diet and physical activity
- minimum duration of three weeks
- published as a full report to allow critical evaluation.

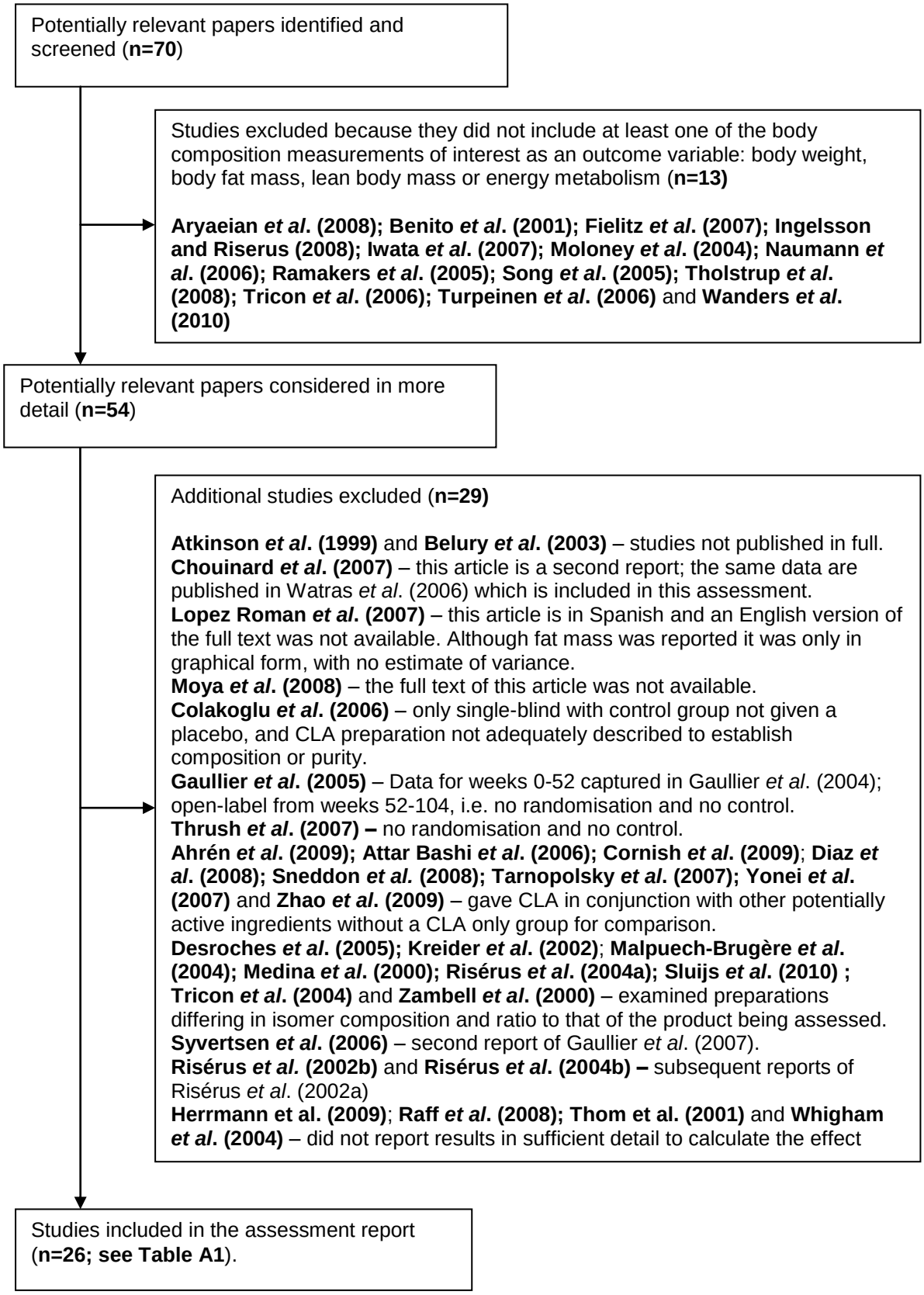

Figure 1: Flow of study consideration and reasons for exclusions in the systematic review

2.3 Studies identified

Figure 1 summarises the reason for exclusion of 44 of the 70 studies identified. Twenty-six studies have been included. The majority used a parallel study design[1]. Three studies utilised a crossover design[2] (Petridou *et al*., 2003 (which contains two studies); Pinkoski *et al*., 2006; Norris *et al*., 2009).

Unlike **SD1** and **SD3**, the focus of this report is on studies that included CLA in an approximate 1:1 ratio of the *c*9, *t*11 and *t*10, *c*12 CLA isomers. The reason for this difference is that **SD1** and **SD3** focus on safety whereas this report focuses on efficacy. As such, the assessment has only considered the potential efficacy of forms of CLA that are similar to Tonalin® CLA.

2.4 Administration and Form of Conjugated Linoleic Acid

Most studies administered CLA and placebo in the form of soft gel capsules which were identical in appearance. The purity of the CLA comprised between 70% to above 80% with the balance of capsule weight comprising other lipids. In this report, the dose of CLA, unless otherwise stated, refers to the total daily amount of *c9,t11* and *t10,c12* isomers. For example, if study participants were given 4 g of a CLA supplement per day but the total amount of the two CLA isomers of interest was 75% then the dose of CLA is reported as 3 g CLA per day.

A small number of studies administered CLA in food such as milk or yoghurt (Bonet-Serra *et al*., 2008; Laso *et al*., 2007; Nazare *et al*., 2007; Racine *et al*., 2010) but only Nazare *et al*. (2007) and Racine *et al*. (2010) added a control fat to the dairy product to replace the CLA.

2.5 Study Limitations and Confounding Factors

The Applicant wishes to incorporate CLA into foods. Because most studies provided CLA in capsule form, it is not clear whether it is appropriate to extrapolate findings from these studies to CLA incorporated into foods. The majority of studies reported that participants were asked to consume capsules at meal times. If this was done, then it might approximate CLA being digested as part of a complex food matrix; much as it would when incorporated into food directly.

The majority of studies had small sample sizes and none were large enough to meet the size determined by Whigham *et al*. (2007). Whigham and colleagues (2007) considered that for a parallel study, 44 participants were needed in each group to detect a significant change in fat mass (at $p<0.05$) of 1.1 kg or greater (with a standard deviation of 2.6 kg) after 12 weeks. Small sample sizes in a study, a small effect, or a larger than anticipated standard deviation, contribute to failing to identify an effect as statistically significant even when it occurs. Eight studies determined the required sample size at the start of the study to detect an effect on body composition (Gaullier *et al*., 2004; Gaullier *et al*., 2007; Lambert *et al*., 2007; Larsen *et al*. 2006; Nazare *et al*. 2007; Racine *et al*., 2010; Watras *et al*., 2006; Steck *et al*., 2007); although the numbers in these studies varied considerably and due to dropouts several would not have been sufficiently powered at the end of the study. Several studies noted that they were underpowered.

[1] Two or more groups are run in parallel where one group is given a placebo the other(s) the treatment for the duration of the study period. In this design the placebo group acts as a comparison for the treatment group.

[2] Study participants are given a treatment or placebo and then cross over to the opposite treatment/placebo; sometimes this involves a period where no treatment/control is administered called a 'washout' period. In this design each participant acts as their own control.

Although the inclusion criterion was studies that were randomised, double-blinded and placebo-controlled, none of the studies controlled for diet, although some studies provided dietary advice. Instead, participants were generally asked not to change their dietary or exercise practices throughout the study. If participants were aware that the purpose of the study related to diet and/or weight control then despite being requested not to change their diet and exercise practices, some may have done so. This should occur equally in both arms of a double-blinded trial and would potentially reduce the power of the study by reducing the difference in outcomes between the groups. Ideally then, the sample size should be increased to account for the reduced power.

In lieu of controlling for diet, the majority of studies asked participants to collect diet records, sometimes over extended periods of time. This represents a high degree of respondent burden and inaccuracies in these records would be expected. Changes in dietary intake may also occur as a result of the burden of keeping a record. Conversely some studies did not report collecting any data on diet or physical activity. Differences in respondent burden across the studies leading to different behaviours may account for some of the variation in study results. Given the relatively small sample sizes in the available studies, randomisation would not rule out such differences.

The majority of studies report a modified intention-to-treat analysis in which the results of those participants completing each relevant part of the study are included in the statistical analysis. Some studies reported that there were no dropouts or failure to comply with the protocol. Five studies did not report compliance with the protocol. Of those that did, compliance was generally good with the majority reporting greater than 80%. A small number of studies excluded participants with lower compliance.

The extent of the dropouts (i.e. study participants who did not complete the full study protocol) varied across studies, with two studies failing to report dropout rates at all. In combination with the small numbers in many trials, a high dropout rate can bias the results if the characteristics of the participants who complete the study differ substantially between the treatment and placebo groups.

A variety of methods of assessing body composition were used. The most common methods were bioelectrical impedance analysis, validated skinfold[3] assessment, dual-energy x-ray absorptiometry (DXA)[4] and computed tomography[5]. The literature commonly reports that all methods are not equal, and results should not be used interchangeably or compared (Fukagawa *et al*. 1990). Some methods also have a systematic tendency for relative over- or under-estimation (Folgelholm and van Marken Lichtenbelt, 1997).

Finally, studies captured in this assessment were predominantly undertaken using subjects in free-living situations. Although this means that the studies may underestimate the effect of CLA that would be seen in highly controlled clinical testing settings, it does mean that the results reflect the effect of CLA in a situation closer to that which would occur if CLA were available via food in the general food supply.

[3] Skinfold assessment involves measurement of skinfold thickness at specific locations on the body and applying validated formulae to calculate body fat.
[4] DXA uses two x-rays of different energy levels to determine the density of different body tissues. It is primarily used to determine bone density but it is also used to measure body composition.
[5] Computed tomography uses x-rays to build up a series of two dimensional pictures of the inside of the body. The series of images is then converted into a three dimensional representation.

2.6 Approach to the assessment

The focus of the assessment is on the change in means in the CLA groups relative to the change in the same measures in the placebo groups at the end of the study. Table A1 provides key information about studies including sample size, study duration, CLA dose and dietary/physical activity assessment. Tables A2a-A2f provide key findings. Not all studies reported enough results to allow the difference in effect between the two groups to be determined. All results are based on those who completed the study protocol, except where stated otherwise.

The assessment has been undertaken in two parts. Firstly, FSANZ divided the studies into sub-groups based on study design (see Section 3). The studies fall into five groups based on age of participant, whether or not weight loss was deliberately induced in the participants prior to CLA treatment, whether or not physical activity was also prescribed, and duration of studies. The results are therefore considered in the following five groupings because these study design differences may have an important influence on the results.

See Section	Studies in adults			
3.2		effect following initial weight reduction		
		effect without initial weight reduction		
3.3			in combination with physical activity	
			without concurrent physical activity	
3.4				studies lasting 6-12 months
3.5				studies lasting <6 months
3.6	Studies in children			

The studies have not been grouped according to whether CLA was administered in capsule form or in a food. As the Applicant is seeking to add CLA to food, studies where CLA has been administered via a food will be given special mention throughout the discussion.

For each study, effect sizes for body weight, lean body mass and body fat mass have been calculated by FSANZ[6], except where stated otherwise, and are shown in the tables. Also shown in the tables are the p values for the evidence of a change in the outcome variable of interest between placebo and the treatment group. The p values are those reported in the study, except where stated otherwise.

Secondly, FSANZ has undertaken a comparable meta-analysis to the meta-analysis published by Whigham *et al.* (2007) which investigated the effect of CLA dose and study duration on reduction in fat mass (see Section 4).

In addition, FSANZ has considered the effect of CLA on waist circumference. This assessment was drawn from the 67 studies originally identified (see Figure 1) where waist circumference was reported as an outcome measure (see Appendix 1).

[6] Effect size = Change in mean of the CLA group between baseline and the end of the study LESS change in mean of the control group between baseline and the end of the study.

3. Results of the sub-group analysis

3.1 Effect of CLA on body weight and body composition following initial weight reduction

Two studies (Table 1) examined the effect of CLA on weight regain following a period of energy restriction designed to achieve weight reduction. The diets in these studies were only tightly controlled during the initial weight reduction phase. Thereafter, guidance on food intake was provided, with one treatment group (those receiving the higher dose in Kamphuis *et al*., 2003) requiring participants to replace their habitual lunch with a protein-rich, low-energy supplement. These studies included overweight to moderately obese participants (BMI 25-35).

Table 1: Summary of findings: studies following initial weight reduction ordered according to dose

First author, year	CLA dose (g) (duration)	Number in the CLA group who completed the study (% who completed[§])	Effect sizes[†] (kg)		
			Δ BW	**Δ LBM**	**Δ BFM**
Kamphuis, 2003	1.4 (13 weeks)	14 (90%*)	1.4[‡**] NS	0.9[‡] p<0.05	-0.4[‡] NS
Kamphuis, 2003	2.7 (13 weeks)	13 (90%*)			
Larsen, 2006	2.7 (52 weeks)	38 (75%)	0.0 p=0.51	0.43 p=0.33	-0.6 p=0.56

More detail of results is provided in Table A2a at the rear of this report.

[§] Number in the CLA group who completed the study compared with the number of participants randomised to receive CLA treatment.

* Estimate only as number randomised to each treatment group was not explicitly stated.

[†] A positive effect size indicates that the CLA group increased their BW, LBM or BFM relative to the placebo group. A negative effect size indicates the reverse, but it does not necessarily mean that either group had a decline in absolute values.

[‡] Regression coefficient for pooled data across both study arms corrected for dosage.

** In Kamphuis *et al.* 2003, this figure is reported as 13.9. FSANZ has assumed that this is an error, given the other results in the table, and has reported the mean gain in body weight in the CLA group compared with placebo group as 1.4 kg.

NS Not significant i.e. p≥0.05.

In the Kamphuis *et al.* (2003) study all participants were placed on a 3-week very low energy diet before randomising them to receive 1.4 g or 2.7 g of CLA or corresponding amounts of oleic acid as the placebo respectively for 13 weeks. When the data from both treatment groups were pooled, there was a significant gain in lean body mass (0.9 kg; 95%CI: 0.1-1.6 kg) among the combined CLA group compared with the placebo group. There was a non-significant increase in body weight and a non-significant decrease in body fat mass in the CLA groups compared with the placebo group. There were no significant differences in physical activity between the groups.

Larsen *et al.* (2006) placed participants on an 8-week low energy diet. Only participants who lost ≥8% of their initial weight were randomised to receive either CLA (2.7 g/day) or olive oil. All participants were instructed in how to consume diets providing an estimated 1.25 MJ/day less than daily energy requirements calculated based on age, gender and body weight for 52 weeks. Both groups gained an average of 4.0 kg in body weight over the twelve month period and the authors note that adherence to the reduced energy diet decreased over the trial period. The CLA group experienced a non-significant gain of 0.4 kg of lean body mass and a non-significant decrease of 0.6 kg of fat mass relative to the placebo group.

Conclusion

The limited available evidence does not support a conclusion that CLA up to a dose of 2.7 g/day, over a period of one year, maintains weight or prevents weight regain, or maintains or improves body composition in overweight or obese people following initial weight loss.

3.2 Effect of CLA in combination with prescribed exercise on body weight and body composition

Four studies examined the effect of CLA on body weight and body composition with prescribed exercise[7] (Table 2). The diets in these studies were not controlled. These studies included normal, overweight and moderately obese participants (BMI 23-35).

Table 2: Summary of findings: studies including prescribed exercise ordered according to dose

First author, year	CLA dose (g) (duration)	Number in the CLA group who completed the study (% who completed[§])	Effect sizes[†] (kg)		
			Δ BW	**Δ LBM**	**Δ BFM**
Park, 2008	1.8 (8 weeks)	15 (100%)	0.63*	-0.2*	-0.5*
Nazare, 2007	2.6 (14 weeks)	21 (100%)	1.1*	-0.2*	0.5*
Adams, 2006	3.2 (4 weeks)	15 (100%)	-0.3 NS	No data	No data
Pinkoski, 2006 (Phase 1)	5 (7 weeks)	37 (97%)	No data	1.1 p=0.033	-1.2 p=0.028
Pinkoski, 2006 (Phase 2)	5 (7 weeks)	17 (63%)	-1.0 p=0.025	0.6 NS	-1.6 p=0.038

More detail of results is provided in Table A2b at the rear of this report.

[§] Number in the CLA group who completed the study compared with the number of participants randomised to receive CLA treatment.

[†] A positive effect size indicates that the CLA group increased their BW, LBM or BFM relative to the placebo group. A negative effect size indicates the reverse, but it does not necessarily mean that either group had a decline in absolute values.

* p values for these effect sizes were not reported in the studies.

NS Not significant i.e. p≥0.05.

[7] Several additional studies measured exercise as part of the study protocol (see Table A1) but these did not specifically prescribe a set amount or type of exercise.

Park *et al*. (2008) considered the effect of 1.8 g/day of CLA-rich oil or 2.4 g olive oil/day while participants engaged in a standard training program three times per week. The CLA group showed decreases in lean body mass and body fat mass and an increase in body weight relative to the placebo. The statistical significance of these effect sizes was not reported. Differences in diet or energy intake were not reported.

Nazare *et al*. (2007) considered the effect of CLA-enriched skim milk yoghurt in combination with regular physical activity (45 minutes, three times per week). The CLA group showed small increases in body weight and body fat mass and a small decrease in lean body mass relative to the placebo group. These effects were similar in males and females. The statistical significance of these effect sizes was not reported. None of the participants reported any change in their daily food intake.

The focus of the Adams *et al*. (2006) study was changes in visceral abdominal fat following treatment with CLA among overweight and moderately obese males; however, they did report body weight and BMI as well. All participants were undertaking a personalised resistance training program. The short duration of the treatment period of this study (four weeks) reduced the likelihood of changes in body weight being observed, although there were no changes between the treated or placebo groups in visceral abdominal fat either.

Pinkoski *et al*. (2006) examined the effect of CLA in combination with a resistance training program. Participants were stratified by gender and randomised to receive CLA (5.0 g/day) or sunflower oil for seven weeks. In the first study, the CLA group had a statistically significant increase in lean body mass (1.1 kg) and reduction in body fat mass (1.2 kg) relative to the placebo group; changes in body weight were not described. After the initial study, 17 participants agreed to cross over to opposite treatment groups for an additional seven weeks; blinding was maintained. The cross over in the non-random subset produced statistically significant differences in body weight (1 kg) and body fat mass (1.6 kg) but not lean body mass relative to the placebo group. There were no differences in dietary intake between groups during either phases of the study.

Conclusion

The limited available evidence does not support a conclusion that up to 5.0 g CLA/day over a period of 4 to14 weeks in combination with prescribed exercise reduces body weight or changes body composition in normal, overweight or moderately obese people.

3.3 Effect of CLA on body weight and body composition in studies of 6-12 months duration in adults

Three studies including overweight to mildly obese participants (BMI 25-32) were conducted for 6-12 months (Table 3).

Table 3: Summary of findings: studies 6-12 months duration in adults ordered according to dose

First author, year	CLA dose (g) (duration)	Number in the CLA group who completed the study (% who completed[§])	Effect sizes[†] (kg)		
			Δ BW	**Δ LBM**	**Δ BFM**
Watras, 2006	3.2 (6 months)	22 (83%**)	-1.7 p=0.04	0.0 p=0.8	-1.7 p=0.02
Gaullier, 2007*	3.4 (6 months)	42 (71%)	-0.9 p=0.15	0.4 p=0.22	-1.2 p=0.043
Gaullier, 2004, TAG arm*	3.4 (12 months)	55 (92%)	-2.0 p<0.05	0.6 NS	-2.6 p<0.05
Gaullier, 2004, FFA arm*	3.6 (12 months)	52 (85%)	-1.3 NS	0.7 p<0.05	-1.9 p<0.05

More detail of results is provided in Table A2c at the rear of this report.

[§] Number in the CLA group who completed the study compared with the number of participants randomised to receive CLA treatment.

** Estimate only as number randomised to each treatment group was not explicitly stated.

[†] A positive effect size indicates that the CLA group increased their BW, LBM or BFM relative to the placebo group. A negative effect size indicates the reverse, but it does not necessarily mean that either group had a decline in absolute values.

* The results for these studies are based on Intention to Treat analysis.

NS Not significant i.e. p≥0.05.

Watras *et al*. (2006) randomised participants to receive either 3.2 g CLA/day or a placebo of 4 g safflower oil/day. Compared to the placebo group, body weight and body fat mass both decreased significantly (1.7 kg) in the CLA group; although this was not reflected in a statistically significant difference in abdominal fat mass in the CLA group (data not shown). Over the duration of the study, there was a statistically significant decline in energy intake within the placebo group but not the CLA group and a statistically significant decline in exercise in the CLA group but not the placebo group; combined these two effects potentially negate the confounding effects of diet and exercise between the placebo and intervention groups. There were no between-group differences for either energy intake or exercise during the study.

Gaullier *et al*. (2007) was a six month study with the CLA group receiving 3.4 g CLA/day and the placebo group 4.5 g olive oil/day. Compared to placebo group, body fat mass decreased significantly (by 1.2 kg); this result was also reflected in other statistically significant body composition changes, including a significant loss of body weight, but only among obese participants of 1.9 kg (data not shown). There was a statistically significant decline in energy intake within the placebo group but not the CLA group and exercise did not differ within or between groups over the duration of the study.

Gaullier *et al*. (2004) was a one year study involving two CLA treatment groups; one group received CLA-triacylglycerol (TAG) (3.4 g/day) and the other CLA-free fatty acid (FFA) (3.6 g/day). The placebo was olive oil (4.5 g/day). The findings showed that compared to the placebo group, body fat mass decreased significantly in both the TAG arm (2.6 kg) and in the FFA arm (1.9 kg). There were statistically significant falls in energy intake within but not between each of the three groups and exercise did not differ within or between groups.

Conclusion

The limited evidence available, although not conclusive, supports a conclusion that between 3.2-3.6 g CLA/day taken over a period of 6-12 months by overweight or mildly obese people reduces body fat mass by an average of 1.2-2.6 kg. A similar conclusion however cannot be drawn for body weight, although the trend is for a fall in body weight. Effects on lean body mass are less consistent, with differences between zero and +0.7 kg reported.

3.4 Effect of CLA on body weight and body composition in studies less than six months duration in adults

The majority of studies conducted in adults were less than six months duration. They ranged from four to 16 weeks and involved 22 treatment groups (Table 4). These studies included overweight and obese participants (BMI 25-39), as well as normal weight participants (BMI <25).

Table 4: Summary of findings: studies less than 6 months duration in adults ordered according to dose

First author, year	CLA dose (g) (duration)	Number in the CLA group who completed the study (% who completed[§])	Effect sizes[†] (kg)		
			Δ BW	**Δ LBM**	**Δ BFM**
Mougios, 2001	0.7 (4 weeks) 1.4 (4 weeks)	10 (83%)	-0.6*	No data	-0.4*
Blankson, 2000	1.7 (12 weeks)	11 (92%)	-1.8 NS	0.9 NS	-2.6** p≤0.05
Noone, 2002	1.9 (8 weeks)	16 (100%)	1.8 NS	No data	No data
Petridou, 2003 (Phase 1)	2.1 (45 days)	9 (100%)	-0.3 NS	No data	-0.4 NS
Petridou, 2003 (Phase 2)	2.1 (45 days)	7 (88%)	-0.4 NS	No data	-0.4 NS
Laso, 2007 (BMI >30)	2.4 (12 weeks)	No data[#]	No data	-0.5 NS	0.9 NS
Laso, 2007 (BMI ≤ 30)	2.4 (12 weeks)	No data[#]	No data	-0.1 NS	-0.9 p=0.01
Risérus, 2002a	2.4 (12 weeks)	19 (100%)	-0.6 NS	0.6 NS	No data

First author, year	CLA dose (g) (duration)	Number in the CLA group who completed the study (% who completed[§])	Effect sizes[†] (kg)		
			Δ BW	**Δ LBM**	**Δ BFM**
Lambert, 2007 (men)	2.6 (12 weeks)	62 men and women completed the study	0.5*	0.3*	No data
Lambert, 2007 (women)	2.6 (12 weeks)		1.5*	0.3*	No data
Steck, 2007	2.6 (12 weeks)	16 (80%)	-0.03*	0.32*	-0.2*
Eyjolfson, 2004	2.9 (8 weeks)	7 (100%)	-1.4*	No data	No data
Risérus, 2001	3.1 (4 weeks)	14 (100%)	0.13 p=0.13	No data	No data
Taylor, 2006	3.2 (12 weeks)	21 (Not stated)	-1.1 p=0.06	No data	No data
Smedman, 2001	3.2 (12 weeks)	26 (100%)	0.19 p=0.664	No data	No data
Berven, 2000	3.4 (12 weeks)	25 (83%)	-1.2 p=0.12	1.3 p=0.18	-1.2 p=0.13
Blankson, 2000	3.4 (12 weeks)	7 (88%)	-1.8 NS	1.3 NS	-1.8** p≤0.05
Blankson, 2000	5.1 (12 weeks)	11 (100%)	-1.5 NS	0.6 NS	-0.4 NS
Steck, 2007	5.1 (12 weeks)	16 (89%)	-0.04*	0.31*	-0.3*
Norris, 2009 Phase 1	6.4 (16 weeks)	16 (73%)	-1.14 p=0.032	1.5 NS	-1.2 NS
Norris, 2009 Phase 2	6.4 (16 weeks)	22 (81%)	-1.76 p=0.032	0.65 NS	-1.7 NS
Blankson, 2000	6.8 (12 weeks)	10 (91%)	-2.2 NS	0.9 NS	-1.3** p≤0.05

More detail of results is provided in Table A2d at the rear of this report.

[§] Number in the CLA group who completed the study compared with the number of participants randomised to receive CLA treatment.

[†] A positive effect size indicates that the CLA group increased their BW, LBM or BFM relative to the placebo group. A negative effect size indicates the reverse, but it does not necessarily mean that either group had a decline in absolute values.

[#] Protocol compliant final n=43, however Laso *et al.*, give no detail of sample numbers in groups stratified according to BMI.

* p values for these effect sizes were not reported in the studies.

** Unlike most studies, Blankson *et al*. (2000) reported statistical significance as p≤0.05 rather than p<0.05.

NS Not significant i.e. p≥0.05.

Despite the number of studies of shorter duration and the range of outcome measures related to body weight and body composition, there were few statistically significant findings when treatment groups were compared with placebo groups. Several studies however, did not report the statistical significance of the effect sizes. It should be noted that the p-values for Blankson *et al*. (2000) are as reported in the paper and there has been no correction for the comparison of multiple intervention groups to the same control group. In addition, there was a wide range of results across studies using similar dose for similar duration.

Statistically significant falls in body fat mass were recorded in the CLA group relative to placebo groups (0.9 kg to 2.6 kg) in doses ranging from 1.7 g/day to 6.8 g per day. However, this applied to only four of the 22 treatment groups (Blankson *et al*., 2000; Laso *et al*., 2007), and three of these were in the same study (Blankson *et al*., 2000). Compared with other studies, this study was of a similar design, used similar methodologies to measure body weight and body composition and involved a similar number of participants. It did, however, offer a 'voluntary' exercise program and this may have confounded some of the results. For example, those consuming the highest dose of CLA (6.8 g/day) recorded a statistically significant increase in intensive training over the study period and a significant decrease in body fat mass relative to placebo, whereas those consuming 5.1 g CLA/day recorded a significant decrease in light training and did not show a significant fall in body fat mass relative to placebo. In this instance, the difference in training regimes may be contributing more to changes in body fat mass than CLA.

In the crossover study conducted by Norris *et al*. (2009), compared with the placebo group a significant fall in body weight was observed in the CLA group (up to a mean of 1.7 kg after 16 weeks) and this was reflected in a significant fall in BMI as well as in abdominal fat mass (data not shown). There were no significant differences in lean body mass in any of the studies of less than six months duration, but the variation in changes across studies (-0.9 to +1.5kg) was wider than those reported for studies of longer duration (Table 3). The short duration of these studies could hinder the ability to detect an effect in lean body mass, although only one of the three studies of longer duration (Gaullier *et al*., 2004; see Table 3) reported a significant increase in lean body mass.

Conclusion

Due to conflicting results and limitations in the study design, the available evidence is not sufficient to support a conclusion that up to 6.8 g CLA/day over a period of up to four months reduces body weight or positively changes body composition in either normal weight, or overweight and obese people.

3.5 Effect of CLA on body composition in children

Two published randomised, double-blinded, placebo-controlled trials of CLA in children were identified (Bonet Serra *et al*., 2008; Racine *et al*., 2010) (see Table A2e).

Bonet Serra *et al*. (2008) included 39 obese children and adolescents aged 8-19 years. They were given milk containing 3 g of CLA per daily serving, or milk with no added CLA. Both treatment and placebo groups were also involved in group therapy for the treatment of their obesity. After 16 weeks, weight, per cent body fat, BMI, and BMI Z score did not change in the CLA group relative to the placebo group. The authors suggest that the group therapy for the treatment of obesity offered to both the treatment and placebo groups could have masked the effects of CLA on weight loss.

Racine *et al*. (2010) included children aged 6-10 years with a BMI at or above the 85th percentile for their age. This study had a sufficient sample size (power of 80%) to detect a 2.3% or greater loss in body fat as statistically significant, if it occurred. Both the CLA (2.4 g) and the sunflower oil placebo (3 g) were added to 250 mL of chocolate flavoured skim milk. After six months of follow-up, there were several significant differences in body composition. While the body fat mass of both groups increased, the increase was significantly less in the CLA group (0.8 kg) compared with the placebo group (1.8 kg) (p=0.01). There was also a significant fall in abdominal fat in the CLA group compared with the placebo group (p=0.02).

In studies of changes in body weight and body composition in children and adolescents, changes in height and weight due to growth need to be accounted for. This was done by Racine and colleagues by assessing changes in height and body weight from baseline to follow up between the treatment and placebo groups. No significant differences were observed.

Conclusion

There is insufficient evidence to support an assessment of whether CLA reduces body fat accumulation in overweight and obese children. Further studies are needed before any conclusion can be drawn regarding the effect of CLA on body weight and body composition in this population group.

3.6 Effect of CLA on energy metabolism

Animal studies have often reported a change in energy expenditure associated with the consumption of CLA (Wang and Jones, 2004). Five studies directly assessing energy expenditure in humans following CLA consumption and which compared and reported the differences between the treatment and the placebo group were identified (Close *et al*., 2007; Kamphuis *et* al., 2003; Nazare *et al*. 2007; Pinkoski *et al*., 2006 and Watras *et al.*, 2006).

Two studies reported similar changes in respiratory exchange ratio between CLA and respective placebo groups (Pinkoski *et al.*, 2006; Watras *et al.*, 2006). Kamphius *et al*. (2003) reported a similar respiratory exchange ratio for CLA and placebo groups, but a higher resting metabolic rate at the end of ten weeks in the CLA group. Adjustment for lean body mass removed this difference suggesting CLA had no independent effect on resting metabolism.

Nazare *et al*. (2007) reported energy expenditure in terms of both total body weight and fat free mass. There were no between group comparisons but there was a significant increase in basal energy expenditure (per kg fat free mass; p=0.03) in the CLA group after 14 weeks but not in the placebo group. The size of the reported effect was equivalent to 263 kJ per day in a 70 kg person or a fat loss of about 2.4 kg per year. The potential mechanism/s was investigated but not identified.

Close *et al.* (2007) assessed waking and sleeping substrate utilisation in 19 subjects taken from a larger study (Watras *et al.*, 2006). After six months, protein and carbohydrate utilisation and respiratory quotient decreased, while fat oxidation increased in the CLA group relative to the safflower placebo during sleep. The authors themselves noted a number of study limitations including an uneven distribution in the number and gender of subjects in the CLA group (n=12; three males and nine females) versus the placebo group (n=7 females and no males), and differences in menstrual cycle that could not be controlled for. Further, the main study of which this group of subjects was a subset, reported a change in body composition in the CLA group relative to the placebo group. The authors do not report adjusting for the effect of this on substrate utilisation. Thus, the results need to be viewed with care in the context of those reported from other studies.

<u>Conclusion</u>

The studies available to date have predominantly reported no direct effect of CLA consumption on measures of substrate utilisation and energy expenditure. The study by Nazare *et al*. (2007), one of the few studies where CLA is added to food, is suggestive of an effect on energy expenditure but more studies of longer duration would be needed to confirm this effect. None of the studies reviewed suggest any adverse changes in energy metabolism due to CLA consumption.

4. Comparison of the Whigham et al. (2007) meta-analysis with a comparable meta-analysis undertaken by FSANZ

The purpose of the Whigham *et al.* (2007) meta-analysis was to investigate the effect of CLA dose and study duration on the efficacy of CLA as a treatment for improving body composition, specifically reduction in fat mass. The authors identified 18 eligible studies published in 2006 or earlier and a study in press from a search of Pubmed. The search was restricted to studies in which CLA was provided to humans in randomised, double-blinded, placebo-controlled trials and in which body composition was assessed by using a validated technique. They included studies of the 1:1 ratio CLA isomer preparation as well as two studies that included the single *t10, c12* isomer, but excluded studies investigating treatment groups that only received the *c9, t11* isomer. Whigham *et al*. (2007) also excluded studies where body composition was assessed by near infra-red interactance because this method 'has not proven to be a consistently accurate and precise method of measuring body composition'. Studies prescribing exercise were not separated from studies that did not prescribe exercise.

FSANZ has also assumed that Whigham *et al*. (2007) derived change in fat mass (kg) from the change in weight and change in percent fat mass for studies that did not report change in fat mass in kilograms (Eyjolfson *et al*., 2004; Lambert *et al.,* 2007; Risérus *et al*., 2002a; Smedman and Vessby, 2001; Taylor *et al*., 2006). This approach, if used by Whigham *et al*., (2007), may or may not give an accurate value. For these studies, no confidence intervals were reported by Whigham *et al*., (2007).

Based on the included studies, Whigham *et al*. (2007) investigated the effect of CLA dose using the data from each treatment group as a single data point (without weighting) in a linear regression analysis. From their analysis, Whigham *et al*. (2007) concluded that in the CLA group compared with placebo:

- the average fat loss was 0.09±0.08 kg/week ($p<0.001$)
- there was a dose effect on fat loss of 0.024 kg fat/g CLA/week ($p=0.03$)
- based on an adjusted mean CLA dose of 3.2 g/day, the average fat loss was a non-significant 0.09±0.07 kg/week.

4.1 Approach to FSANZ's meta-analysis

In order to compare the Whigham *et al.* (2007) results with those studies considered here, FSANZ has collated the effect sizes for change in body fat mass for those studies included in Whigham *et al*. (2007) as well as additional studies not included in their analysis.

In summary, ten studies included in Whigham *et al*. (2007) have not been included in FSANZ's analysis. These include: Atkinson *et al*. (1999) because the study was not published in full; Gaullier *et al*. (2005) because data for weeks 0-52 were captured in Gaullier *et al*. (2004) and data for weeks 52-104 did not include a placebo group; and Kreider *et al*. (2002), Malpuech-Brugere *et al*. (2004) and Risérus *et al*. (2004b) because they examined different CLA preparations to that of the product being assessed. In addition, the five studies that did not report change in fat mass in kilograms have also been excluded: Eyjolfson *et al*., 2004; Lambert *et al.,* 2007; Risérus *et al*., 2002a; Smedman and Vessby, 2001; Taylor *et al*., 2006.

Whigham *et al*. (2007) considered the weight regain studies of Kamphuis *et al*. (2003) and Larsen *et al*. (2006) separately from the meta-analysis of the weight loss studies. These have been excluded from FSANZ's meta-analysis.

Five additional studies in adults published since Whigham *et al.* (2007) have been considered in FSANZ's meta-analysis: Laso *et al*. (2007); Nazare *et al*. (2007); Park *et al*. (2008); Steck *et al*. (2007) and Norris *et al*. (2009).

In total, FSANZ's meta-analysis includes 13 studies (comprising 17 treatment arms) that reported data on changes in body fat mass among adults. Average results were calculated for three studies with multiple treatment arms (Blankson *et al*., 2000; Gaullier *et al*., 2004; Steck *et al*., 2007). One study reported standard errors, but these appear to be incorrect and FSANZ has assumed they are standard deviations (Laso *et al*., 2007). The majority of studies included overweight or moderately obese participants (BMI 25 to <35).

StatsDirect was used for the analysis (StatsDirect Ltd., 2008). The results from the random effects model and I^2 (Higgins *et al*., 2003) are reported. In most instances 95% CIs were not published but have been calculated by FSANZ from the published standard deviation or standard error of the mean, and the sample size.

4.2 Results of FSANZ's meta-analysis

Figure 2 shows the results of the studies by increasing duration. There is no heterogeneity among the studies (I^2 = 0%, 95% CI = 0% to 44.5%) despite a variation in duration ranging from 1.5 months to 12 months and doses of CLA ranging from 1.4 to 6.4 g/day.

Sub-group analysis was undertaken to investigate the effects of duration and dose of CLA on body fat mass. For duration, four sub-groups were used: 0-8 weeks; 12 weeks; 14-26 weeks and 52 weeks (Figure 3). Twelve weeks was used as one single time point because several of the studies were of 12 weeks duration. The single treatment arm of 52 weeks duration has been reported separately to reflect the approach taken by Whigham *et al.* (2007) who report a trend up to two years. For dose, three sub-groups were used: 2.6 g/day or less; 3.2 g/day to 4.3 g/day; and 5.0 g/day or more (Figure 4). The middle group most closely reflects the Applicant's recommended amount of CLA per day.

Figure 3 indicates a significant fall in body fat mass of just over one kg between weeks 12 and up to weeks 26. Although the graph shows a further significant fall up to 52 weeks of greater than 2 kg, this data point is based on only one treatment arm whereas the data for week 12 and weeks 14-26 are based on five treatment arms each.

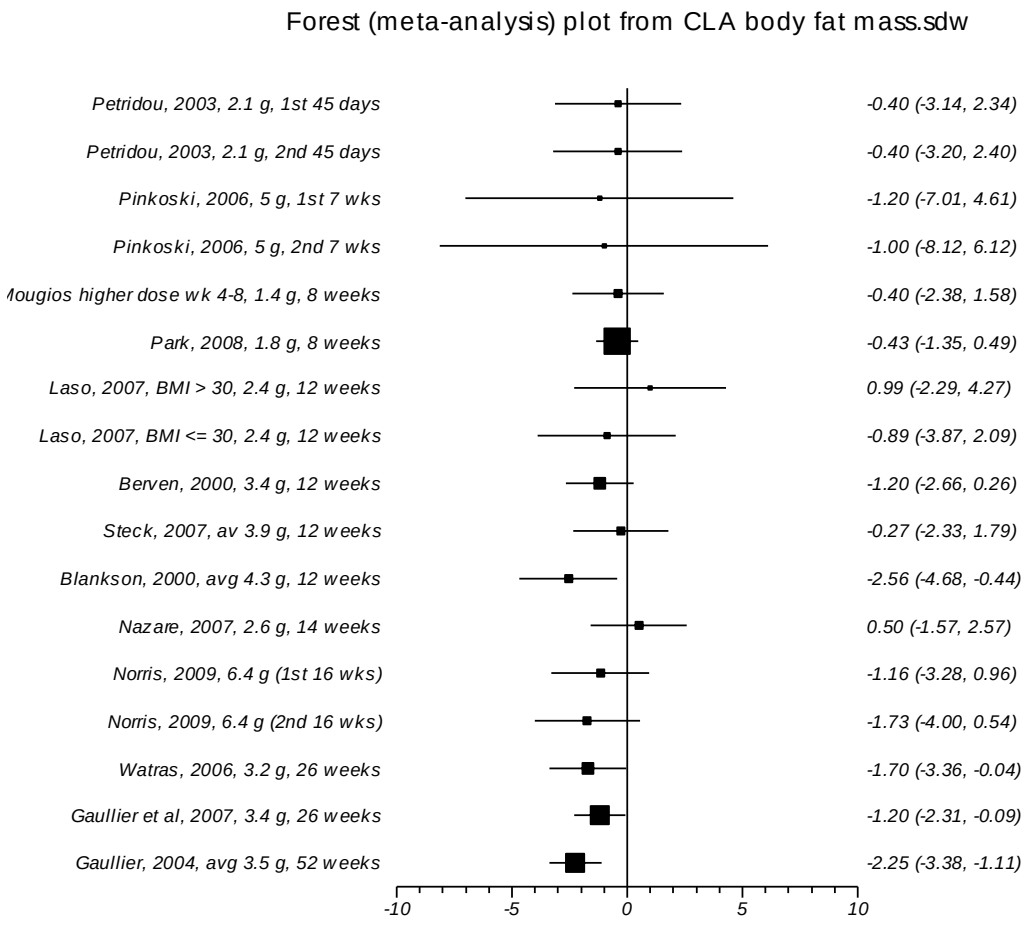

Figure 2: Effect of CLA versus placebo on body fat mass (ordered according to duration of study)

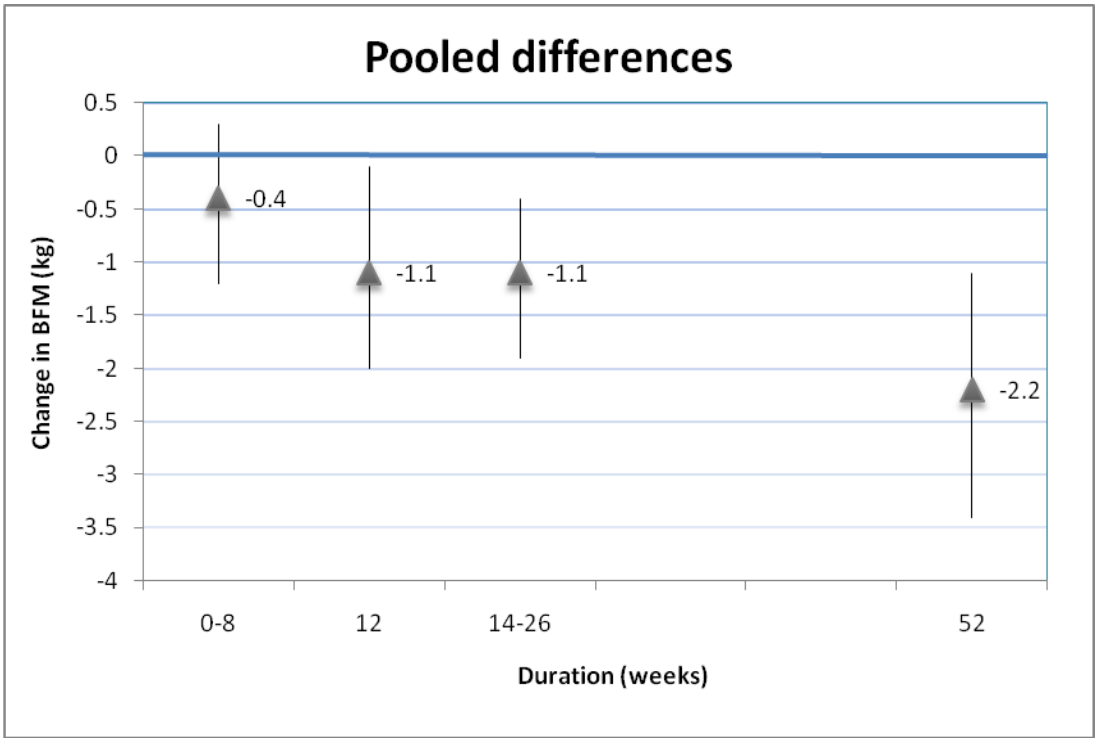

Figure 3: Change in body fat mass (BFM) depending on duration of study

Figure 4 shows that doses between 3.2 and 4.3 g are associated with a significant decrease in body fat mass (mean decrease of 1.6 kg; 95% CI = -2.2 to -1.0 kg; $p < 0.0001$). These data are based on six treatment arms and range in duration from 12 weeks to 12 months. Lower and higher doses were not associated with a statistically significant result; thus a dose effect is not apparent from these data.

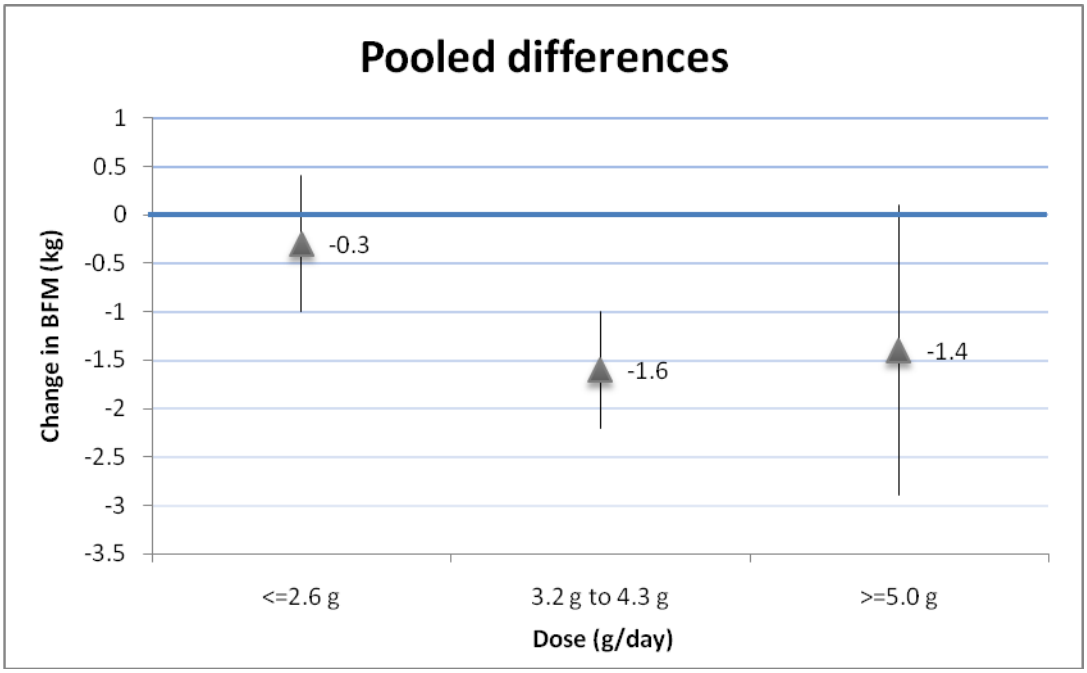

Figure 4: Change in body fat mass (BFM) depending on dose

4.3 Comparison of results from FSANZ's meta-analysis with results from the Whigham et al. (2007) meta-analysis

The results from FSANZ's analysis are similar to those reported by Whigham *et al*. (2007). Whigham *et al*. (2007) reported an average fat loss in the CLA group compared with placebo of 0.09±0.08 kg/week ($p<0.001$). This amount equates to a loss of fat of about 1.3 kg after 14 weeks and 2.3 kg after 26 weeks. FSANZ's analysis of studies between 14 and 26 weeks duration indicate a fall in fat mass of 1.1 kg (95% CI = -1.9 to -0.4 kg; $p = 0.003$), although a similar fall was evident at 12 weeks (1.1.kg; 95% CI = -2.0 to -0.1 kg; $p = 0.03$).

Despite the similarity in results, there were differences in approach between the two meta-analyses. Whigham *et al*. (2007) included multiple treatment arms for several studies (Blankson *et al*., 2000; Gaullier *et al*., 2004; Steck *et al*., 2007) whereas FSANZ included a single data point for each of these. In addition, Whigham *et al.* (2007) did not weight their treatment arms as occurred in FSANZ's analysis; thus study results based on small sample sizes contribute equally in weight to the few study results based on larger sample sizes.

One study included in Whigham *et al*. (2007) is a six month trial by Atkinson *et al*. (1999) in obese patients. This study was not included in FSANZ's analysis because it has only been reported as an abstract. Loss of fat mass in the CLA group was 1.3 kg compared to 1.0 kg in the placebo group; hence had these results been included in FSANZ's analysis, they may have reduced the estimated loss of body fat between 14 and 26 weeks.

Whigham *et al*. (2007) observed a dose effect based on their regression analysis; however FSANZ's analysis of dose was inconsistent. Whigham *et al*. (2007) also included studies with differing isomer concentrations to the CLA preparation proposed to be used by the Applicant; these have not been included in FSANZ's analysis because they did not meet the inclusion criteria. Individual isomers could have differing effects on fat loss and this may contribute to a disparity in results.

5. Discussion

Results from FSANZ's sub-group analysis involving 26 studies and 34 treatment arms indicate considerable inconsistency in the effect of CLA on changes in body weight, lean body mass and body fat mass.

Sample size is likely to be one factor contributing to the variable results. Many of the studies were relatively small and this is likely to have contributed to the failure to observe statistically significant results. For example, the majority of studies that report a significant decrease in body fat mass in the CLA group compared with the placebo group have sample sizes of greater than 30 participants per treatment arm. This suggests that many of the studies were underpowered although only a few studies reported their sample size calculations.

The considerable variation in the methods used to measure body composition could also be contributing to the inconsistent findings. Dual-energy x-ray absorptiometry (DXA) was the most commonly used method among studies that reported a significant reduction in body fat mass but it was used in less than 50% of the studies included in the assessment. The bioimpedence method (used in five studies) and skinfold measurements (used in three studies) are the least accurate (Kerr and Ackland, 2006) and were not associated with any significant body weight or body composition results. Of the methods used, DXA would be regarded as the most precise and accurate in determining body composition. However, the validity of this method is questionable when changes in fat mass of <2 kg in an individual are observed (Ellis, 2001).

There were no consistent patterns in relation to age. The majority of studies included participants aged 40-50 years, although in studies involving prescribed exercise, participants tended to be younger. There were also no consistent patterns in relation to BMI with the majority of studies involving overweight and obese participants. Few studies reported their results on the basis of gender; hence the effect of gender cannot be determined. However, most studies that included males and females had more female participants. This was not because more males dropped out than females but because many more females were recruited to the studies initially.

Despite these inconsistencies, an effect of CLA on body fat mass (mean loss of between 1.2 to 1.7 kg at six months and between 1.9 to 2.6 kg at 12 months) is apparent among studies with supplement doses of CLA ranging from 3 to 3.5 g/day. Although this finding is based on just three studies, they are among the better quality studies considered because they included larger sample sizes. In addition, two of the studies analysed their results based on the inclusion of all recruited participants; thus minimising the potential bias that might result from studies that excluded dropouts in their analysis. However, the finding relates primarily to women as there were about 4-5 times as many females as males in these longer duration studies.

FSANZ's meta-analysis and the published meta-analysis by Whigham *et al*. (2007) provide further support for a small effect of CLA on loss of body fat mass (about 1.1 kg) in studies between 12 and 26 weeks duration. Another published meta-analysis by Schoeller *et al*. (2009), using the same 18 studies included in Whigham *et al*. (2007), reported a small, but significant increase in fat free mass in response to CLA (0.3 kg). However, FSANZ notes that this result was not adjusted for changes in the placebo group. FSANZ has not conducted a comparable meta-analysis, but results from the systematic review found no consistent effect on lean body mass when the CLA group was compared with the placebo group.

Although none of the studies controlled for diet, the majority (17 of 26) measured dietary intake and slightly fewer studies measured physical activity (15 of 26). There were no significant differences between the CLA and placebo groups for either potential confounder where it was measured.

The Applicant is seeking to add CLA to food. However, few studies assessed the efficacy of CLA in food. Laso *et al*. (2007) and Nazare *et al*. (2007) were the only studies in adults where CLA was added to skim milk and yoghurt respectively. Bonet Serra *et al*. (2008) and Racine *et al*. (2010) considered its efficacy among overweight children when added to milk; however, the results from these studies were mixed.

6. Conclusion

FSANZ concludes that the evidence is supportive of a small reduction in body fat mass of 1-2 kg among overweight or mildly obese adults as a result of consuming CLA in supplement form in the amount recommended by the Applicant. However, the clinical significance of this amount of fat loss at the individual level is likely to be minimal and, at a population level, any potentially beneficial effect of change in body fat mass on overall health would depend on simultaneous changes in factors such as blood lipids.

In addition, a range of uncertainties remain in relation to the effect of CLA on fat mass:

- there is no evidence of a dose effect
- as most of the research supporting the evidence for an effect on fat mass has been done in women and using supplements, the effect may not apply to other populations or when similar doses of CLA are added to food
- there is insufficient evidence of an effect on fat mass in children
- the means by which CLA might reduce body fat remain unclear although one study is suggestive of an increase in energy expenditure
- the methods used to measure changes in fat mass are at the limit of their validity when small changes of 1-2 kg are observed.

In terms of the effect of CLA on body weight, the trend is for a fall in body weight although it is not statistically significant, and there is limited evidence that CLA positively influences lean body mass or assists in maintaining weight or preventing weight regain following initial weight loss.

Table A1: Summary of Study Participant Details and Protocols in the Studies that met the Inclusion Criteria

First Author, Year	Final n (m/f)	Dropouts	Initial BMI (kg/m^2)	Physical State	Age (years)	Duration (days)	CLA only (g/d)	Placebo, Dose (g/d)	Dietary/physical activity assessment
Adams *et al*., 2006	28 (28/0)	2 dropouts from placebo group	>25	Overweight or moderately obese	35-55	28	3.2	4.0 g safflower oil	3 day dietary record + 4 x FFQs; personalised resistance training
Berven *et al*., 2000	47 (30/17)	5 dropouts, 8 exclusions, 2 adverse events (possibly CLA-related)	27.5-39	Overweight or obese	≥18	84	3.4	4.5 g olive oil	Diet & physical activity were not reported
Blankson *et al*., 2000	47 (17/30)	8 dropouts, 5 dropouts, 1 adverse event	25-35	Sedentary, light or intense exercise	≥18	84	1.7, 3.4, 5.1, or 6.8	9 g olive oil	Diet was not assessed. Participants could join a light or intense exercise program. There were no significant differences in exercise between groups.
Bonet Serra *et al*., 2008	39 (13/26)	Not stated	$>95^{th}$ centile for age	Obese children & adolescents	8-19	112	3.0	Milk drink (2 x 100 g/d) without added CLA	Participants were given a diet & physical activity journal. Energy intake and physical activity fell in both groups during the study.
Close *et al*., 2007	19 (3/16)	4 dropouts all from placebo group	≥25 <30	Overweight	33±7	182	3.2	4.0 g safflower oil	7-day physical activity & 3 day diet records kept at baseline & study end. A sub-study of Watras *et al.* (2006) retained in this assessment for energy metabolism results only
Eyjolfson *et al*., 2004	16 (4/12)	None	~27	Sedentary	21.5±0.4	56	2.9	4.0 g safflower oil	Three 48 hour dietary records and a post study questionnaire on diet & activity were collected. Results are not reported; although dietary composition 48 hours before the OGTT was consistent in both groups.
Gaullier *et al*., 2004	157 (31/149) (at start of study)	23 dropouts – 10 due to adverse events, 1 due to pregnancy, 12 unspecified	25-30	Overweight	18-65	365	3.6 (FFA) / 3.4 (TAG)	4.5 g olive oil	Diet & activity were assessed by questionnaires at 0, 6 & 12 months. There were no significant differences in exercise between groups, but caloric intake decreased significantly

First Author, Year	Final n (m/f)	Dropouts	Initial BMI (kg/m^2)	Physical State	Age (years)	Duration (days)	CLA only (g/d)	Placebo, Dose (g/d)	Dietary/physical activity assessment
									in all groups between 0 and 12 months.
Gaullier *et al*., 2007	83 (21/84[+)]	35 dropouts (17 interv, 18 placebo)	28-32	Overweight	18-65	182	3.4	4.5 g olive oil	Diet & activity were assessed by questionnaires at 0 & 6 months. Caloric intake decreased significantly in the placebo group compared with baseline but not in the CLA group; however there were no differences between groups. There were no differences in exercise.
Kamphuis *et al*., 2003	54 (26/28)	6 dropouts; 1 for illness, 1 because of use of medication and 4 because of motivation reasons	25-30	Overweight	20-50	91	1.4 / 2.7	1.8 / 3.6 g oleic acid	Subjects placed on VLCD for 3 weeks prior to intervention resulting in a mean weight loss of 6.9%. Physical activity was monitored by accelerometer but only in the 2.7 g CLA and 3.6 g control groups. There were no significant differences in physical activity between these two groups.
Lambert *et al*. 2007	62 (26/38[a])	2 dropouts	<25	Regularly exercising (3 or more time per week)	21-45	84	2.6	3.9 g high oleic acid sunflower oil	Physical activity records throughout study quantified as metabolic equivalents. 3 x 4 day diet record. There were no significant differences in nutrient or energy intake or in training frequency.
Larsen *et al*., 2006	77 (Not stated)	18 dropouts by 26 weeks and a further 6 by 52 weeks (includes 6 withdrawn due to adverse events)	28-35	Normal weight, overweight or obese	18-65	365	3.6	4.5 g olive oil	Subjects placed on LCD for 8 weeks prior to intervention, ≥ 8% weight loss required for participation in treatment. Modest hypocaloric diet (-1250 kJ/day) was prescribed thereafter. Energy intakes fell in both groups, although there were no significant differences between the groups.
Laso *et al*., 2007	43 (33/10)	2 lost to follow up and 15 lost to protocol violation	25-35	Metabolic syndrome, overweight	35-65	84	3.0 in skim milk	Non- fortified skim milk	Six 3-day diet records & three FFQs. Subjects' results were excluded if daily energy intake varied by more than 10%. Physical activity monitored

First Author, Year	Final n (m/f)	Dropouts	Initial BMI (kg/m^2)	Physical State	Age (years)	Duration (days)	CLA only (g/d)	Placebo, Dose (g/d)	Dietary/physical activity assessment
				or obese					'throughout study' via questionnaire. Energy intake and exercise were similar between groups.
Mougios *et al*., 2001	22 (13/9)	2 dropouts, no adverse events	<30	Healthy	19-24	2 x 28	0.7 x 4 weeks then 1.4 x 4 weeks	1 g / 2 g soybean oil	All participants provided with a weekly dietary plan & diet records collected. There were no significant differences in energy or nutrient intake between the groups.
Nazare *et al.* 2007	44 (22/22)	None	23-27.5	Healthy	28.9 (SEM 1.14)	98	2.6 in yoghurt	Cream added to yoghurt	Maintain usual dietary habits + regular exercise 3 times per week. None of the participants reported any change in their daily food intake.
Noone *et al.* 2002	51 (23/28)	None	<25	Healthy	31.6 (SD 10.03)	56	1.9	3 g linoleic acid	Not stated.
Norris *et al*., 2009‡	35 (0/35)	20 dropouts, 3 due to time commitment; 3 due to GI complaints; 6 for unrelated health concerns; 2 glycaemia worsened; 3 due to inability to obtain venous access; and 3 were lost to follow up.	>30	Post-menopausal, type 2 diabetes, obese	≤70	112x2 and 28d washout	6.4	8.0g safflower oil	No significant differences were observed in reported dietary energy intake between the two groups. Physical activity was unchanged throughout the study.
Park *et al*., 2008	30 (3/27)	None	23-28	Healthy overweight (by Korean definition)	34-45	56	1.8	2.4 g olive oil	Ad libitum diet. Concurrent physical activity intervention of std training program 3 days/wk. Differences in diet or energy intake were not reported. No significant differences in exercise habits.
Petridou *et al*., 2003‡ (crossover study)	16 (0/16)	1 dropout due to illness	<30	Sedentary	19-24	45x2	2.1	3.0 g soybean oil	Subjects kept diet records throughout study & were asked not to change physical activity patterns. No significant differences in energy intake.
Pinkoski *et al*., 2006	75	9 dropouts (6 m, 3 f)	ND	Healthy, resistance	18-45	49	5.0	7.0 g	Physical activity was controlled as part of the intervention. Baseline & final 3

First Author, Year	Final n (m/f)	Dropouts	Initial BMI (kg/m^2)	Physical State	Age (years)	Duration (days)	CLA only (g/d)	Placebo, Dose (g/d)	Dietary/physical activity assessment
(parallel study)	(36/40)			trained				sunflower oil	day diet records were kept. There were no differences in dietary intake between groups.
Pinkoski *et al*., 2006‡ (crossover study)	17 (8/9)	10 dropouts (4 m, 6 f)	ND	Resistance trained	26-36	49	5.0	7.0 g sunflower oil	Physical activity was controlled as part of the intervention. There were no differences in dietary intake between groups.
Racine *et al*., 2010	53 (31/22)	10 chose not to participate, 7 dropped out and 2 did not qualify for data analysis	≥ 85^{th} percentile	Overweight & obese children	6-10	183	2.4	3.0 g sunflower oil	Ad libitum diet. Dietary advice provided at start of study. Differences in diet and physical activity were not reported. Treatments added to chocolate milk.
Risérus *et al*., 2001	24 (24/0)	1 dropout	29-35	Obese	39-64	28	3.1	4.2 g olive oil	Ad libitum diet. Diet interviews (ffq) at baseline and wk 4 to estimate dietary CLA intake. Differences in diet and physical activity were not reported.
Risérus *et al*., 2002a	57 (57/0)	3 dropouts	27-39	Metabolic syndrome, overweight or obese	43-63	84	2.4g (1;1 isomers) or 2.6g (t10,c12)	3.4 g olive oil	All men were encouraged to maintain their usual diet and exercise habits during the study. 3-day weighed food record kept at weeks 0 & 8. No significant differences in dietary intake occurred during the study.
Smedman and Vessby, 2001	50 (25/25)	3 exclusions due to poor compliance	19-35	Healthy	23-63	84	3.2	4.2 g olive oil	3 day weighted diet record kept at baseline, middle & end of study. There were no significant differences in dietary intake during the study.
Steck *et al*. 2007	48 (13/35)	3 ineligible for randomisation and 4 dropouts	30-35	Obese	18-50	84	3.2 or 6.4	8.0 g safflower oil	5x24-hour recalls collected over study's duration. Brief physical activity questionnaire at baseline, 6 & 12 weeks. Energy intake did not differ between groups whereas physical activity fell significantly for the placebo and the 6.4 g CLA groups but was not significantly different between groups.

First Author, Year	Final n (m/f)	Dropouts	Initial BMI (kg/m^2)	Physical State	Age (years)	Duration (days)	CLA only (g/d)	Placebo, Dose (g/d)	Dietary/physical activity assessment
Taylor *et al*., 2006	40 (40/0)	Not stated.	33 ± 3	Healthy, obese	35-60	84	3.2	4.5 g olive oil	No measures of diet or physical activity reported.
Watras *et al*., 2006	40 (8/32)	8 dropouts	25-30	Overweight	18-44	182	3.2	4.0 g safflower oil	7-day physical activity & 3 day diet records kept at baseline & study end. Reported energy intake was lower in the placebo group (p=0.06) but no significant differences in physical activity occurred between the groups.

Table A1 provides information on study participants and dosage regimes as well as identifying substances used as controls. The given amount for CLA in the *CLA only* column was calculated from the total amount of CLA or other CLA preparation and the reported purity; thus it is the amount of CLA isomers of interest (*c9,t11* and *t10,c12*) only. The total amount of CLA containing preparation was matched with the amount of control oil. Unless otherwise stated, no differences in baseline values for measured variables were identified between participants receiving CLA and control. However, sample sizes were too small to rule out such differences even though they may be reported as not statistically significant.
* The dose of the CLA preparation (all CLA isomers + other minor lipid components) was 4 g/day given in the form of four 1 g capsules; the soy oil control differed because only 0.5 g capsules were available and authors decided it would be better to administer the same number of capsules than the same amount of lipid.
‡ crossover study design; [†]The distribution at final analysis was not reported on a per protocol basis (n=83) but on the group included in the intention to treat analysis (n=105); [a] The final gender composition was not reported.

Acronyms: BFM– body fat mass; BMI – body mass index; BW – body weight; CLA – conjugated linoleic acid; f – females; LBM – lean body mass; LCD – low calorie diet; m – males; n – number of participants; ND no data provided.

Table A2a: Summary of Study Results: studies which used initial weight reduction

First Author, Year	Body Comp. Method	Group	In group Δ BW (kg)	*P*- value groups compared	In group Δ LBM (kg)	*P*- value groups compared	In group Δ BFM (kg)	*P*- value groups compared	Other body composition finding(s) (Between group comparisons only)
Kamphuis *et al*., 2003	Hydro. & DD	CLA (1.4 g)	3.4	↑ NS	3.3	↑ <0.05 pooled data corrected for dosage	0.2	↑ NS	↓ BF% ($p<0.05$) for pooled data corrected for dosage, gender and % body weight regain
		Con	1.4		1.4		0.0		
		CLA (2.7 g)	1.9		2.7		-0.7		
		Con	1.3		1.8		-0.3		
Larsen *et al*., 2006	DXA	CLA (3.6 g)	4.0	–NS	0.94	↑NS (0.33)	2.13	↓ NS	NS differences in waist and hip girth.
		Con	4.0		0.51		2.73		

Table A2b: Summary of Study Results: in combination with prescribed exercise

First Author, Year	Body Comp. Method	Group	In group Δ BW (kg)	*P*- value groups compared	In group Δ LBM (kg)	*P*- value groups compared	In group Δ BFM (kg)	*P*- value groups compared	Other body composition finding(s) (Between group comparisons only)
Adams et al., 2006	Calibrated electronic scale	CLA	-0.2	↓ NS	No data	No data	No data	No data	No differences in visceral abdominal fat
		Con	0.1						
Nazare et al., 2007	DXA	CLA	1.6	No data	0.0	No data	0.6	No data	No data
		Con	0.5		-0.5		0.8		
Park et al., 2008	BIA	CLA	-0.75	No data	-0.18	No data	-0.59	No data	No data
		Con	-0.12		0.04		-0.16		
Pinkoski *et al*., 2006 (parallel study)	AD	CLA (5.0 g)	No data		1.30**	↑ 0.033	-0.80*	↓ 0.028	No data
		Con			0.20		0.40		
Pinkoski *et al*., 2006 (crossover study)	AD	CLA (5.0 g)	0.3	↓ 0.025	0,4	↑ NS	-0.2	↓ 0.038	↓ in BF% (p=0.043)
		Con	1.3*		-0.2		1.4*		

Table A2c: Summary of Study Results: other studies in adults: 6-12 months duration

First Author, Year	Body Comp. Method	Group	In group Δ BW (kg)	*P*- value groups compared	In group Δ LBM (kg)	*P*- value groups compared	In group Δ BFM (kg)	*P*- value groups compared	Other body composition finding(s) (Between group comparisons only)
Gaullier *et al*., 2004 TAG arm	DXA	CLA (3.4 g)	-1.8*	↓ <0.05	0.6	↑ NS	-2.4*	↓ <0.05	↓ in BMI (p<0.05)
		Con	0.2		0.0		0.2		
Gaullier *et al*., 2004 FFA arm	DXA	CLA (3.6 g)	-1.1*	↓ NS	0.7*	↑ <0.05	-1.7*	↓ <0.05	NS differences in BMI
		Con	0.2		0.0		0.2		
Gaullier *et al*., 2007	DXA	CLA (3.4 g)	-1.2	↓ NS	0.6	↑ NS	-1.5	↓ <0.05	↓ in Leg fat (p=0.003) This occurred mainly in women and obese adults.
		Con	0.3		0.2		0.5		
Watras *et al*., 2006	Hydro., ^{18}O dilution & DXA	CLA (3.2 g)	-0.6	↓ ≤0.05	0.40	– NS	-1.00*	↓ ≤0.05	↓ in BF% (p≤0.05) NS differences in abdominal fat mass.
		Con	1.1		0.40		0.70		

Table A2d: Summary of Study Results: other studies in adults: <6 months duration

First Author, Year	Body Comp. Method	Group	In group Δ BW (kg)	*P*- value groups compared	In group Δ LBM (kg)	*P*- value groups compared	In group Δ BFM (kg)	*P*- value groups compared	Other body composition finding(s) (Between group comparisons only)
Berven *et al*., 2000	BIA	CLA (3.4 g)	-1.1	↓ NS	-0.2	↓ NS	-0.9	↓ NS	NS differences in BMI
		Con	-0.4		-1.5		0.3		
Blankson *et al*., 2000	DXA	CLA (1.7 g)	-0.4	↓ NS	0.87	↑ NS	-1.15	↓ ≤ 0.05	NS differences in BMI
		CLA (3.4 g)	-0.4		1.26		-1.73	↓ ≤ 0.05	
		CLA (5.1 g)	-0.1		0.54		-0.43	↓ NS	
		CLA (6.8 g)	-0.8		0.88		-1.30	↓ ≤ 0.05	
		Con	1.4		-0.05		1.47		
Eyjolfson *et al*., 2004	BIA	CLA (2.9 g)	0.6	No data	No data		No data		No data
		Con	2.0						
Lambert *et al*., 2007	DXA	CLA (2.6 g) (Men)	0.6	No data	0.2	No data	No data		No data
		Con (Men)	0.1		-0.1				
		CLA	1.4	No data	-0.2	No data			No data

First Author, Year	Body Comp. Method	Group	In group Δ BW (kg)	*P*- value groups compared	In group Δ LBM (kg)	*P*- value groups compared	In group Δ BFM (kg)	*P*- value groups compared	Other body composition finding(s) (Between group comparisons only)
		(2.6 g) (Women)							
		Con (Women)	-0.1		-0.5				
Laso *et al*., 2007	DXA	CLA (3.0 g) (BMI>30)	No data		0.06	↓ NS	0.32	↑ NS	NS differences in trunk fat, trunk lean tissue, BMI or waist circumference
		Con (BMI>30)			0.55		-0.67		
		CLA (3.0 g) (BMI≤30)			0.32	↓ NS	-0.61	↓ 0.01	↓ in trunk fat (p=0.05) NS differences in trunk lean tissue, BMI or waist circumference
		Con (BMI≤30)			0.42		0.28		
Mougios *et al*., 2001	Skin-fold	CLA (0.7, then 1.4 g)	-1.0	↓ NS	No data		-0.50	↓ NS	NS differences in BF% or sum of 10 skinfolds
		Con	-0.4				-0.10		
Noone *et al*., 2002	Not stated	CLA (1.9 TAG)	1.7	No data	No data		No data		No data
		Con	0.1						
Norris *et al*., 2009‡	DXA	CLA (6.4 g) (Diet 1)	-1.25	↓ 0.032	-0.41	↓ NS	-1.08	↓ NS	↓ in BMI (p=0.00) but an ↑ in trunk adipose tissue

First Author, Year	Body Comp. Method	Group	In group Δ BW (kg)	*P*- value groups compared	In group Δ LBM (kg)	*P*- value groups compared	In group Δ BFM (kg)	*P*- value groups compared	Other body composition finding(s) (Between group comparisons only)
		Con	-0.11		1.40		0.08		(p = 0.04) NS differences in waist circumference, WHR, SAD, triceps or subscapular skinfold thicknesses.
		CLA (6.4 g) (Diet 2)	-0/86		0.60		-1.59		
		Con	0/9		0.65		0.14		
Petridou *et al*., 2003‡	Skin-fold	CLA (2.1 g) (CLA-Con)	-0.1	↓ NS	No data		0.7	↑ NS	NS differences in BMI, BF% or sum of skinfolds
		Con (CLA-Con)	0.9				-0.6		
		CLA (2.1 g) (Con-CLA)	0.5	↑ NS			-1.0	↓ NS	
		Con (Con-CLA)	0.2				1.1		
Risérus *et al*., 2001	-	CLA (3.1 g)	-0.3	↓ NS	No data		No data		↓ in SAD (p=0.041) NS differences in waist circumference or WHR
		Con	-0.4						
Risérus *et al*., 2002a	-	CLA (2.4 g)	-0.46	↓	0.57	↑NS	No data		NS differences in BMI, waist circumference, SAD or %BF

First Author, Year	Body Comp. Method	Group	In group Δ BW (kg)	*P*- value groups compared	In group Δ LBM (kg)	*P*- value groups compared	In group Δ BFM (kg)	*P*- value groups compared	Other body composition finding(s) (Between group comparisons only)
		Con	0.14	NS	-0.02				
Smedman and Vessby, 2001	BIA & Anth.	CLA (3.2 g)	0.4	↑ NS	No data		No data		**↓ in BF% (=0.05)** NS differences in BMI, WHR or SAD
		Con	0.21						
Steck *et al*. 2007	DXA	CLA (3.2 g)	0.40	No data	0.65	No data	-0.17	No data	No data
		CLA (6.4 g)	0.39		0.64		-0.09		
		Con	0.43		0.33		0.14		
Taylor *et al*., 2006	BIA, CT & skin-fold	CLA (3.2 g)	-0.2	↓NS	No data		No data		↓ in arm and leg skin-folds ($p<0.05$) NS differences in BF%, BMI, waist and hip circumferences, WHR or torso skinfolds
		Con	0.9						

Tables A2a-A2d provide summarised mean change in reported results from baseline, with statistical comparisons (*P*-values) between CLA and control groups. The arrows in the *P*-value column indicate the direction of any change in the mean of the CLA group relative to the control such that ↓ indicates the CLA group experienced a relative decrease, ↑indicates the CLA group experienced a relative increase, and – indicates both the CLA group and the control group experienced the same magnitude of change in the same direction.
† Results as medians not means.
‡ Crossover study design

Statistical significance within group: * $p<0.05$; ** $p<0.01$.

Acronyms: AD – air displacement plethysmography ; BF% - body fat percentage; BFM – body fat mass; BIA – bioimpedance assessment; BMI – body mass index; BW – body weight; CLA – conjugated linoleic acid; Comp. – composition; Con – control group; CT – computed tomography; DXA – dual-energy x-ray absorptiometry; EE – energy expenditure; f – female; FFA – free fatty acid; Hydro. - hydrodensitometry; IR – infrared; ITT – intention to treat analysis; LBM – lean body mass; m – male; n – number of participants; ND – no data provided; NS – not statistically significant; SAD – saggital abdominal diameter; WHR – waist-to-hip ratio.

Table A2e: Summary of Study Results: children and adolescents

First Author, Year	Body Comp. Method	Group	In group Δ BW (kg)	*P*- value groups compared	In group Δ LBM (kg)	*P*- value groups compared	In group Δ BFM (kg)	*P*- value groups compared	Other body composition finding(s) (Between group comparisons only)
Bonet Serra *et al*., 2008	DXA and Bone Densitometer	CLA (3.0 g)	-4.5*	No data, but stated in text as NS	No data		No data		No differences in BMI, BMI Z score or BF%.
		Con	-0.3*						
Racine *et al*., 2010	DXA and Bone Densitometer	CLA (3.6 g)	3.2	↓ NS	2.4	↑ NS	0.8	↓ 0.01	↓ in BMI (p=0.04), BF% (p=0.001), peripheral fat (p<0.001), abdominal fat (p=0.02)
		Con	3.7		1.9		1.8		

* Results are expressed as medians.

Acronyms: BF – body fat; BFM – body fat mass; BMI – body mass index; CLA – conjugated linoleic acid; Con – control group; DXA – dual-energy x-ray absorptiometry; LBM – lean body mass; of participants; NS – not statistically significant.

Table A2f: Summary of Study Results: energy expenditure

First Author, Year	Group	Energy expenditure finding(s)
Close *et al*., 2007	CLA (3.2 g)	After six months, fat oxidation increased in the CLA group relative to the control during sleep ($p<0.05$).
	Con	
Kamphuis *et al*., 2003	CLA (1.4 g)	Increase in RMR independent of % body weight regain ($p<0.05$) but NS change in RMR after adjusting for LBM. NS change in RQ.
	Con	
	CLA (2.7g)	
	Con	
Nazare *et al*., 2007	CLA (2.6 g)	No between group comparisons but there was a significant increase in basal energy expenditure (per kg fat free mass) in the CLA group after 14 weeks but not in the placebo group.
	Con	
Pinkoski *et al*., 2006 (parallel study)	CLA (5.0 g)	NS change in RMR between CLA and control groups over time when expressed relative to LBM
	Con	
Pinkoski *et al*., 2006 (crossover study)	CLA (5.0 g)	NS change in RMR or RER between CLA and control groups.
	Con	
Watras *et al*., 2006	CLA (3.2 g)	NS changes in RMR & RER between CLA and control groups.
	Con	

Acronyms: CLA – conjugated linoleic acid; Con – control group; LBM – lean body mass; of participants; NS – not statistically significant; RER – respiratory exchange ratio; RMR – resting metabolic rate; RQ – respiratory quotient.

Appendix 1: Effect of CLA on waist circumference

Of the original 67 studies identified (see Figure 1 in this report), there were 12 studies that reported waist circumference measures in 18 arms, including five arms that did not use the 1:1 isomeric ratio CLA preparations. As shown in Table A4, these studies ranged from 4-26 weeks in duration and the mixed ratio studies are included for completeness. Figure A1 shows a graph of the various studies comparing comparative waist circumference, study time and CLA isomer mix type. Standard formulas were used to calculate the difference in effect between intervention and placebo groups where these were not reported by the authors.

There was variation in the direction of effect of CLA compared to placebo on waist circumference in the results. In some studies waist circumference decreased more in the CLA group, in others more in the placebo group.The results were not always in the same direction in studies that had multiple intervention groups. The strongest effect occurred in the study of Zhao *et al.* (2009) in hypertensive subjects in which both CLA and placebo groups were also given Rampiril. As noted in **SD1**, this study also contributed substantially to the heterogeneity in the results for HDL-cholesterol levels. The duration of the trial explained little of the variation among studies in the difference between the groups in waist circumference, either for all 1:1 isomer ratio studies (adjusted r^2=-0.03) or if Zhao *et al.* (2009) were excluded (adjusted r^2=-0.01). The results of Zhao *et al.* (2009) are influential on the results when the studies are combined. When the results of all studies were expressed on a 12-week basis, there was an average decline in waist circumference of -0.55cm for studies using the 1:1 CLA isomer preparation but only -0.16cm if Zhao *et al*. (2009) is excluded. As there was no association with duration of use, it is unclear whether the correction to a 12 week basis, or any longer time frame, is justified.

Table A4: Difference in waist circumference (cm) between CLA and placebo groups, ordered by duration of the trial

First Author, year	Isomers given	N int	N cont	Daily CLA dose (g/day) of c9,t11 and t10,c12	Duration (weeks)	Waist circumference in intervention group at baseline	Difference in waist circumference, as reported (cm)			Mean difference corrected to 12 weeks (cm)
							Mean	95% CI		
Risérus, 2001	1:1	14	10	3.1	4	120.1	-0.7	-2.0	0.5	-2.2
Herrmann, 2009	1:1	34	x	3.4	4	102.1	0.0	-2.2	2.2	0.0
Herrmann, 2009	c9,c11	34	x	3.4	4	102.3	0.2	-1.9	2.3	0.6
Herrmann, 2009	t10,c12	34	x	3.4	4	101.2	-0.9	-3.0	1.2	-2.7
Park, 2008	1:1	15	15	1.8	8	83.5	0.6	-1.8	3.0	0.9
Zhao, 2009	1:1	40	40	3.4	8	102.7	-3.5	-4.4	-2.6	-5.3
Taylor, 2006	1:1	21	19	3.2	12	112.0	0.8	-0.8	2.4	0.8
Risérus, 2002	t10,c12	19	19	2.4	12	116.0	-0.9	-2.0	0.1	-0.9
Risérus, 2002	1:1	19	19	2.4	12	112.5	-0.3	-1.5	1.0	-0.3
Risérus, 2004a	c9, t11	13	12	2.5	12	112.2	-0.6	-2.3	1.2	-0.6
Lambert, 2007 (women)	1:1	18	19	2.6	12	75.0	-1.2	-3.8	1.4	-1.2
Lambert, 2007 (men)	1:1	12	13	2.6	12	87.9	1.0	-2.7	4.7	1.0
Laso, 2007(BMI ≤ 30)*	1:1	10	11	2.4	12	101.4	0.3	-4.4	5.0	0.3
Laso, 2007 (BMI > 30)*	1:1	10	13	2.4	12	111.9	-0.5	-5.5	4.5	-0.5
Norris , 2009 (SAF to CLA)	1:1	{35	x	6.4	16	110.1	1.6	0.6	2.6	1.2
Norris, 2009 (CLA to SAF)	1:1	}	x	6.4	16	112.0	-1.7	-3.0	-0.4	-1.3
Sluijs, 2010	4:1	173	173	3.1	26	99.0	0.1	-0.7	0.9	0.0
Gaullier, 2007	1:1	42	41	3.4	26	99.3	-1.3	-3.4	0.8	-0.6

X cross-over design
Mean difference=CLA-placebo difference, so minus sign indicates greater decrease in the CLA group
* The SEM reported in this study were assumed to be SD because of their magnitude

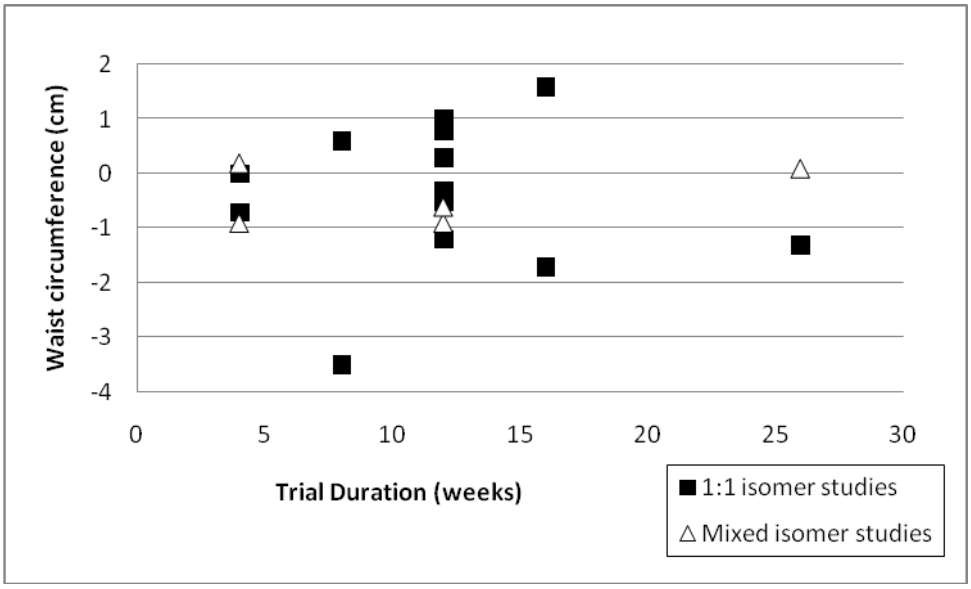

Figure A1: Difference in waist circumference by study duration and ratio of CLA isomers given

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