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

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[9-11]

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

Executive Summary

Introduction

On 22 February 2008, FSANZ received an Application from Cognis GmbH via Axiome Pty Ltd to amend Standard 1.5.1 – Novel Foods of the *Australia New Zealand Food Standards Code* (the Code) to approve the exclusive use of a specific brand (Tonalin® CLA) of a conjugated linoleic acid (CLA) triglyceride preparation as a novel food. The stated reason for its addition to food is as a useful adjunct in weight control programs and diets.

Tonalin® CLA is a mixture of approximately equal quantities of the *cis*-9, *trans*-11 and *trans*-10, *cis*-12 CLA isomers in the form of triglyceride esters (approximately 80%) and other fatty acids (approximately 20%). In this report, we refer to this as a 1:1 isomer mix, for convenience, despite the presence of other fatty acids. CLA is a collective term for a mixture of isomers of linoleic acid in which the two double bonds are conjugated (separated by one single bond). The *cis*-9, *trans*-11 CLA isomer (rumenic acid) is found mainly in ruminant animal products and is at least 70% or more of the natural CLA in food (estimated to be approximately 0.3 g/day). The *trans*-10, *cis*-12 CLA isomer is less commonly found in nature, with its natural occurrence in the diet being only between 0-2% of the total CLA.

Novel foods (and ingredients) are not permitted to be added to food for sale in Australia and New Zealand unless they are listed in Standard 1.5.1. The Applicant is seeking to add Tonalin® CLA as an ingredient to a number of food products. An assessment of this Application is therefore required to determine whether permission can be granted for inclusion of Tonalin® CLA as a novel food in Standard 1.5.1. Reference to the assessment of Tonalin® CLA in the Report also includes comparable CLA preparations that contain a similar mix of the 1:1 CLA isomers.

Risk Assessment

FSANZ has undertaken a comprehensive risk assessment of the potential addition of CLA to food, at the Applicant's recommended level of consumption of 4.5 g/day of Tonalin® CLA (which is equivalent to 3.5 g of unesterified CLA). CLA in this context includes comparable CLA preparations to Tonalin® CLA. The risk assessment is documented in a series of Supporting Documents (SD1-SD4) provided with this Report.

The risk assessment was informed by peer reviews of earlier drafts of SD1 and SD2. In addition, FSANZ convened an Epidemiology Scientific Advisory Group (EpiSAG) to consider a range of scientific and clinical issues related to the risk assessment. The EpiSAG comprised six members with expertise in epidemiology, nutrition, cardiovascular disease, diabetes and biostatistics.

FSANZ concludes that there is evidence of adverse effects on blood lipids (decreasing HDL-cholesterol and probably increasing LDL-cholesterol levels) as a result of consuming the 1:1 CLA isomer mix in the Applicant's recommended amount. The potential for increased CVD risk on a population basis is not insignificant, and is estimated to be up to 5% at the level of intake of CLA proposed by the Applicant, but could be higher if individuals exceed the recommended level of intake. In addition, the potential adverse effect on glucose homeostasis among people with type 2 diabetes, although arising from limited available evidence, is of concern and warrants further investigation, particularly given the prevalence of both diagnosed and undiagnosed diabetes and pre-diabetes in Australia and New Zealand.

In terms of the effect of CLA on weight control, FSANZ's assessment concluded there was a statistically significant but small loss in body fat of between 1-2 kg after 3-6 months consumption of the recommended daily amounts of the 1:1 CLA isomer mix. However, the potential benefit of this small loss in body fat remains unknown due to insufficient evidence of the mechanism of action of CLA and of the pattern of fat loss.

FSANZ therefore concludes that, on balance, the evidence of potential harm is stronger than the evidence for potential benefit and that the benefit and harm may not necessarily accrue to the same individuals. EpiSAG members agreed with FSANZ's conclusion.

FSANZ also considers that there is insufficient information about the effect of CLA on a number of vulnerable population groups (individuals with pre- and existing type 2 diabetes; women with gestational diabetes; individuals at high risk of cardiovascular disease; obese children and adolescents; and older persons) who would be at potentially greater risk from undesirable changes in blood lipids or glucose homeostasis.

A dietary intake assessment was not undertaken as part of the risk assessment because the estimates of risk and benefit were based on the recommended intake of 3.5 g/day of unesterified CLA; thus precluding the need to estimate dietary intakes in any greater detail.

Risk Management

FSANZ investigated a range of possible risk management strategies that could be used to manage the public health and safety risks identified from the risk assessment. The strategies investigated were to:

- restrict the foods to which CLA was permitted to be added
- limit the amount of CLA that could be added to foods
- mandate certain advisory or warning statements that needed to be applied to labels of food containing added CLA
- produce information material to inform the community about consuming food with added CLA.

An evaluation of these risk management strategies concluded that they would not be adequate to mitigate the risks identified in the risk assessment. The reasons for this are:

1. restricting the foods to which CLA can be added would not provide an adequate control mechanism to reduce CLA intake for individuals (especially people at high risk of adverse effects)

2. limiting the amount of CLA that can be added to foods would be self-defeating because it would reduce the ability of individuals to consume the amount of CLA recommended by the Applicant to fulfil the claimed stated purpose

3. mandating certain advisory or warning statements on foods that contain added CLA was considered not to be sufficient to protect sub-populations at higher risk, especially those individuals not aware they may be at higher risk

4. using education material to convey complex messages that are potentially conflicting, especially when the potential benefit has not been adequately demonstrated, was not deemed appropriate to address the public health and safety risks identified.

Greater detail about FSANZ's consideration of the risk management options is provided in Section 11 of the report.

Decision

To reject the Application.

Reasons for Decision

FSANZ's decision to reject this Application is made having regard to matters listed in section 18 of the FSANZ Act. In relation to the objective to address public health and safety, FSANZ concludes:

- The overall evidence base was not sufficient to demonstrate the safety of Tonalin® CLA at the recommended intake of 4.5 g/day.

- The available evidence suggests that consumption of Tonalin® CLA at the levels proposed by the Applicant may have adverse effects on cardiovascular disease and may adversely affect glucose tolerance in consumers with type 2 diabetes. Potential adverse and potential beneficial effects may not occur in the same individual and individuals would be unlikely to be able to self-diagnose relevant risk factors and self-exclude from consumption of Tonalin® CLA where appropriate.

- Investigation of possible risk management strategies to manage the potential risks identified, such as restricting the foods to which CLA can be added, limiting the amount of CLA added to food, mandating advisory labelling statements, or producing education materials, concluded that there were concerns that they would not be adequate to mitigate the risks identified.

In relation to the other matters listed in section 29 of the FSANZ Act, FSANZ concludes:

- The available evidence does not demonstrate that a net benefit would arise from approving the addition of Tonalin® CLA to food.

- There are no appropriate non-regulatory measures that are relevant in the assessment of this Application.

- There are no directly relevant New Zealand standards. FSANZ is aware that Tonalin® CLA is available in New Zealand in capsule form as a dietary supplement; regulated under the Dietary Supplements Regulations.

The decision to reject this Application does not preclude any Applicant submitting a new Application for this substance if, in the future, additional, robust scientific studies that address the safety concerns underpinning the current decision become available.

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SUPPORTING DOCUMENTS

The following materials, which were used in the preparation of this Assessment Report, are available on the FSANZ website at
http://www.foodstandards.gov.au/foodstandards/applications/applicationa1005conj3859.cfm

SD1: Consideration of the effect of a 1:1 isomer mix of CLA on HDL- and LDL-cholesterol levels
SD2: Effects of CLA on body weight and body composition
SD3: Effect of CLA on glucose homeostasis
SD4: Chemical safety of a 1:1 isomer mix of CLA
SD5: Submission of the Applicant to FSANZ's preliminary Assessment Report – December 2009
SD6: Submission of the Applicant to FSANZ's draft Assessment Report – April 2011
SD7: Summary of issues raised by the Applicant in December 2009 and FSANZ's response
SD8: Summary of issues raised by the Applicant in April 2011 and FSANZ's response

Outcome notes from a meeting of the Epidemiology Scientific Advisory Group (EpiSAG) convened to address the scientific and clinical issues relating to the risk assessment of adding CLA to the food supply.

INTRODUCTION

On 22 February 2008, FSANZ received an Application from Cognis GmbH via Axiome Pty Ltd to amend Standard 1.5.1 – Novel Foods of the *Australia New Zealand Food Standards Code* (the Code) to approve the exclusive use of a specific brand (Tonalin® CLA) of a conjugated linoleic acid (CLA) triglyceride preparation as a novel food. The Application is seeking exclusive permission for Tonalin® CLA in accordance with clause 3 of Standard 1.5.1.

FSANZ accepted this Application under section 26(1) of the FSANZ Act. In making the decision to accept the Application, FSANZ decided that the Application contained all of the information required by the Application Handbook at that time. In addition, FSANZ concluded on the basis set out in Section 1 of this Report (The Regulatory Problem) that the Application related to a matter which may be developed as a food regulatory measure. The Application was not so similar to a previous application or proposal that it ought to be rejected.

Tonalin® CLA is a mixture of approximately equal quantities of the *cis*-9, *trans*-11 and *trans*-10, *cis*-12 CLA isomers in the form of triglyceride esters (approximately 80%) and other fatty acids (approximately 20%). In this report we refer to this as a 1:1 isomer mix, for convenience, despite the presence of other fatty acids. Tonalin® CLA is produced by chemical isomerisation of safflower oil containing high levels of linoleic acid under alkaline conditions. Reference to the assessment of Tonalin® CLA in the Report also includes CLA preparations that contain a similar mix of the 1:1 CLA isomers. Unless otherwise specified, when referring to the effects of CLA in the Report, and not a specific CLA preparation (i.e. Tonalin® CLA), this refers to the 1:1 isomer blend of unesterified CLA and is approximately 80% of the commercial CLA preparation.

The Applicant has advised that Tonalin® CLA is intended to be used as an ingredient of food to assist in weight control programs and diets. FSANZ has taken this to be the stated purpose. Specifically, the Applicant has articulated the purpose of adding Tonalin® CLA to foods in their Application as:

> *The purpose of the novel food is as an ingredient in functional foods designed as useful adjuncts in weight control programmes and diets. Numerous studies have consistently demonstrated the benefit of the novel food in producing a significant decrease in body fat whilst maintaining lean body mass.*

Tonalin® CLA is proposed to be added as an ingredient to foods such as milk products, soy beverages, fruit-based beverages, yoghurt and yoghurt products, nutrition bars, table spreads, formulated meal replacements/supplementary foods and formulated supplementary sports foods. Other possible applications for Tonalin® CLA that have been identified by the Applicant include cheese/cheese products, ice cream and frozen desserts, dairy desserts, sauces and toppings (including mayonnaise and salad dressings) and formulated beverages. The Applicant indicates that a daily consumption of 4.5 g of Tonalin® CLA (which is equivalent to 3.5 g of unesterified CLA) is recommended to achieve the stated purpose. The Applicant recommends 1.5 g of CLA is added to individual serves of food.

How FSANZ has assessed this Application

FSANZ provided a preliminary Assessment Report and the accompanying Supporting Documents (**SD1**, **SD2** and **SD3**) to the Applicant in September 2009, allowing them to submit comments before the Assessment Report was finalised.

The Applicant provided a submission of comments to these documents (provided with this Report as **SD5**) in December 2009.

FSANZ subsequently addressed issues raised in the submission and amended the documents as determined from the assessment of the issues to complete the Assessment Report and adjusted the Supporting Documents as required. A summary of FSANZ's response to the issues is provided in **SD7** . FSANZ activated the Epidemiology Scientific Advisory Group (EpiSAG) and supplemented its membership with experts in relevant fields to assist in the consideration of this Application.

FSANZ also provided a revised version of the draft Assessment Report, revised Supporting Documents (**SD1**, **SD2**, **SD3)** and a new Supporting Document **(SD4**) and the EpiSAG Outcome Notes to the Applicant in December 2010, allowing them to submit comments before the Assessment Report was finalised. The Applicant provided a submission of comments to these documents (provided with this Report as **SD6**) in April 2011. A summary of FSANZ's response to the issues is provided in **SD8** .

1. The Regulatory Problem

Novel foods (and ingredients) are not permitted to be added to food for sale in Australia and New Zealand unless they are listed in Standard 1.5.1. An assessment of this Application is therefore required to determine whether permission can be granted for inclusion of Tonalin® CLA as a novel food in Standard 1.5.1.

FSANZ had not previously assessed or characterised the risk to the Australian and New Zealand population from consumption of Tonalin® CLA. Thus, FSANZ assessed the safety and potential public health impact of this product taking into particular consideration the Applicant's request to permit the addition of Tonalin® CLA to a wide variety of commonly eaten foods. In addition, as Tonalin® CLA is a fatty acid, its effect on blood lipids was an important component of the assessment. The Applicant's claim that Tonalin® CLA assists in weight control programs and diets also needed to be assessed to ensure that consumers are not misled as to the efficacy of this product and to comply with the Ministerial Council Policy Guidelines relevant to the Application.

2. Background

2.1 The current Standard

Standard 1.5.1 lists novel foods which are permitted to be used in Australia and New Zealand. It also sets out conditions of use of approved novel foods, including risk management measures such as labelling. Under clause 3 of Standard 1.5.1, a novel food or novel food ingredient may be sold for a 15-month exclusive use period in a specified brand and class of food, subject to any specified conditions of use. Permission for exclusive use of a novel food is listed in the Table to clause 3 of Standard 1.5.1. The exclusive use permission reverts to a general permission under clause 2 of Standard 1.5.1 after the 15-month exclusive use period expires.

2.2 Chemical description of Tonalin® CLA

CLA is a collective term for a mixture of isomers of linoleic acid in which the two double bonds are conjugated (separated by one single bond). The isomers differ with respect to the position of the two double bonds along the C-18 chain. Many CLA isomers are found in nature, with the predominant form being *cis*-9, *trans*-11 CLA (rumenic acid) which occurs mainly in ruminant animal food products.

Chemically, CLA is a polyunsaturated fatty acid since it has two double bonds: one *cis* bond and one *trans* bond. However, CLA can also be accurately described as a *trans* fatty acid by virtue of a single *trans* bond in each of the two isomers in Tonalin® CLA. Unlike linoleic acid which has two double bonds in the *cis* configuration, CLA has one double bond in the *trans* configuration and one double bond in the *cis* configuration (see structures below for the two main CLA isomers in the Tonalin® CLA preparation).

cis-9, *trans*-11 conjugated linoleic acid

trans-10, *cis*-12 conjugated linoleic acid

An additional difference is that CLA has only one single bond between the double bonds (i.e. conjugated) whereas linoleic acid has two single bonds between the double bonds (i.e. methylene-interrupted). Tonalin® CLA also contains monounsaturated fatty acids (oleic acid 10-20%), polyunsaturated fatty acid (linoleic acid ≤ 3%) and saturated fatty acids (< 8%).

2.3 International permissions for CLA

Currently, there is little consistency with the regulation of CLA (specifically Tonalin® CLA) as a novel food ingredient in international food standards around the world.

The Applicant notes that currently CLA is approved for use and is sold in *food supplements* in the European Union. However, this use predates the introduction of the novel food Standard since significant consumption of CLA occurred prior to 15 May 1997 when this Standard came into effect. In Spain, the use of CLA has been approved in liquid yoghurt, milk, processed cheese and orange juice since 2004-2005.

Tonalin® CLA has been self-assessed as a Generally Recognized As Safe (GRAS) substance under the US FDA regulations (GRAS notice No. GRN 000232) in 2008 (FDA, 2008). This GRAS notification was submitted as a joint submission by Cognis GmbH (the Applicant for this Application) and Lipid Nutrition B.V.

The Applicant is currently seeking approval for Tonalin® CLA as a novel food in Europe. The European Food Safety Authority (EFSA) published two opinions on CLA preparations (Tonalin® CLA and a comparable CLA preparation) in mid May 2010. EFSA concluded ‘‘that the safety of Tonalin® CLA [referred to as the commercial name Tonalin® TG 80] has been established for the proposed uses at doses of 4.5 g per day (corresponding to 3.5 g CLA), up to six months. The safety of CLA consumption for periods longer than six months has not been established under the proposed conditions of use’ (EFSA, 2010a). EFSA is a risk assessment organisation which provides risk assessments to the European Commission for their management of identified risks. The European approval process had not been completed as of 1 May 2011.

FSANZ notes that EFSA has written a Scientific Opinion on Dietary Reference Values of Fats, which includes reference to CLA (EFSA, 2010b). The document focuses on the natural occurrence of CLA in the diet from ruminants rather than as CLA supplements or CLA added to the diet as a novel food ingredient.

In addition to the above, EFSA also released its scientific opinion on health claims related to CLA in October 2010 (EFSA, 2010c). In this opinion, EFSA rejected the following health claims submitted to it: maintenance or achievement of a normal body weight; increase in lean body mass; increase in insulin sensitivity; protection of DNA, proteins and lipids from oxidative damage; and contribution to immune defences by stimulation of production of protective antibodies in response to vaccination. The EFSA opinions are produced from an assessment of the portfolio of studies and evidence provided to EFSA by industry to support their requested health claim. EFSA is not required to independently assess further studies and evidence not provided to them. FSANZ has not assessed any health claims as part of the assessment of this Application. However, it has assessed the applicability of the 'stated purpose' of the Application, and it has independently assessed other studies, not just those provided by the Applicant.

3. Objectives

In developing or varying a food standard, FSANZ is required by its legislation to meet three primary objectives which are set out in section 18 of the FSANZ Act. These are:

- the protection of public health and safety; and
- the provision of adequate information relating to food to enable consumers to make informed choices; and
- the prevention of misleading or deceptive conduct.

In developing and varying standards, FSANZ must also have regard to:

- the need for standards to be based on risk analysis using the best available scientific evidence;
- the promotion of consistency between domestic and international food standards;
- the desirability of an efficient and internationally competitive food industry;
- the promotion of fair trading in food; and
- any written policy guidelines formulated by the Ministerial Council.

The Ministerial Council Policy Guideline: *Addition to Food of Substances other than Vitamins and Minerals* includes policy principles in regard to substances added to food other than to achieve a solely technological function such as novel foods. According to these guidelines, permissions should be granted where:

- the purpose for adding the substance can be articulated clearly by the manufacturer (i.e. the 'stated purpose'); and
- the addition of the substance to food is safe for human consumption; and
- the substance is added in a quantity and a form which is consistent with delivering the stated purpose; and
- the addition of the substance is not likely to create a significant negative public health impact to the general population or sub population; and

- the presence of the substance does not mislead the consumer as to the nutritional quality of the food.

4. Key risk assessment questions to be answered

FSANZ developed the following risk assessment questions based on the quantities of Tonalin® CLA (4.5 g per day which is equivalent to 3.5 g CLA per day) proposed to be added to the food supply by the Applicant.

1. What is the chemical and toxicological safety of adding CLA?

2. What effect does CLA have on blood lipids?

3. If CLA has an effect on blood lipids, what effect might this have on the risk of cardiovascular disease?

4. Are there other potential risks to the population as a whole or sub-populations associated with the consumption of CLA?

5. What is the evidence that CLA delivers the stated purpose?

6. Is CLA already present in the diet? If so, how much extra CLA will the population consume if CLA is added to food in the amounts requested by the Applicant?

7. If there are both risks and benefits associated with the consumption of CLA, do the benefits outweigh the risks?

RISK ASSESSMENT

FSANZ has undertaken a comprehensive risk assessment which is documented in a series of Supporting Documents. The risk assessment was informed by peer reviews of earlier drafts of two of these Supporting Documents – SD1 and SD2. In addition, FSANZ convened an Epidemiology Scientific Advisory Group (EpiSAG) to consider a range of scientific and clinical issues related to the potential addition of CLA to the food supply in the amounts proposed by the Applicant. The EpiSAG comprised six members with expertise in epidemiology, nutrition, cardiovascular disease, diabetes and biostatistics.

Below is a summary of the responses to the key risk assessment questions.

5. Potential risks

5.1 What is the chemical and toxicological safety of CLA?

FSANZ has undertaken a full assessment (**SD4**) of all safety-related data submitted as part of the Application. The chemical safety dossier consisted of a range of studies in animals and humans. FSANZ has evaluated these studies, with a focus on those studies using a CLA mix containing approximately 1:1 of the two major isomers, *cis*-9, *trans*-11 and *trans*-10, *cis*-12 CLA.

Overall, no toxicological endpoint relevant to humans was identified by FSANZ based on the information submitted in the chemical safety dossier. Based on the absence of any identifiable toxicological hazard, it was not considered necessary to establish a reference health standard (such as an acceptable daily intake) for CLA specifically.

5.1.1 Postulated mode of action of Tonalin® CLA

As stated in the Introduction, the stated purpose of Tonalin® CLA is to assist in weight control programs and diets (also see **SD2**). FSANZ sought to understand the proposed mode of action of Tonalin® CLA in achieving the stated purpose to determine whether this may indicate a safety concern.

The Applicant provided reports from the literature in support of the stated purpose. From these, the Applicant claimed that the mode of action of Tonalin® CLA could be attributed to:

1. inhibition of lipid uptake in the adipose tissue by modulating lipoprotein lipase and a reduction in the expression or activity of stearoyl-CoA desaturase

2. increase in energy expenditure in adipose tissue and skeletal muscle by uncoupling protein 2 expression

3. increase in fatty acid oxidation in muscle, liver and adipose tissue by increasing the activity of carnitine palmitoyltransferase.

However, the Applicant has not provided any empirical evidence supporting these actions and thus they remain highly speculative and are, therefore, an area of uncertainty.

FSANZ also investigated the effect of CLA on energy metabolism in SD2. Five studies were identified but no direct effect of CLA consumption on measures of substrate utilisation and energy expenditure were reported. The study by Nazare *et al*. (2007) 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 suggested any adverse changes in energy metabolism due to CLA consumption.

5.2 What effect does CLA have on blood lipids?

FSANZ investigated the effect of consumption of CLA on blood lipids in humans (see **SD1**, with the summary provided below). FSANZ focused its consideration of the effect of CLA intake on HDL- and LDL-cholesterol levels because they were commonly reported in the scientific literature and are both independent risk factors for cardiovascular disease.

As stated in Section 2.2, CLA is a polyunsaturated fatty acid with one *cis* bond and one *trans* bond. It can also be described as a *trans* fatty acid because of the single *trans* bond in each of the two isomers in Tonalin® CLA. The effects of classes of dietary fatty acids (saturated, *cis*-monounsaturated, *cis*-polyunsaturated and *trans* fatty acids) on blood lipids are well characterised (Mozaffarian and Clarke, 2009): some fatty acids affect blood lipids in a favourable way while others produce adverse effects. At the time the Application was received, no systematic review had quantitatively characterised the effect of consuming a polyunsaturated fatty acid with a conjugated *trans* bond on HDL- or LDL-cholesterol levels.

FSANZ undertook a comprehensive review by first examining the scientific literature and evidence supplied by the Applicant. FSANZ found variable results in published studies of the effects of CLA on blood lipids, with favourable effects of CLA being reported by some authors and unfavourable effects being reported by others. FSANZ's assessment was hindered by the inconsistency of published results and a lack of statistical power for key health related parameters.

To address the lack of statistical power, FSANZ undertook a series of meta-analyses[1]. The models of Mozaffarian and Clarke (2009) (describing the relative effects of saturated, *cis*-monounsaturated, *cis*-polyunsaturated and *trans* fatty acid on HDL- and LDL-cholesterol levels) were used to interpret the results of the meta-analysis. Full details of the meta-analysis are described in **SD1**.

5.2.1 Effect of a 1:1 isomer ratio on HDL-cholesterol level

Saturated, *cis*-monounsaturated and *cis*-polyunsaturated fatty acids all raise the level of HDL-cholesterol to a similar extent. For the analysis of effect of CLA on HDL-cholesterol levels, FSANZ therefore grouped together trials of the 1:1 CLA isomer mix that used any of these fats as the control.

The average effect of CLA at these doses was **to lower HDL-cholesterol** by 0.036 mmol/L (95% Confidence Interval (CI): -0.069 to -0.002 mmol/L, p=0.04); a statistically significant result.

The measured effect of CLA lowering HDL-cholesterol by 0.036 mmol/L is slightly larger than the predicted effect when 2-3% of energy from saturated or *cis*-unsaturated fat is replaced with *trans* fatty acids (Mozaffarian and Clarke, 2009).

5.2.2 Effect of a 1:1 isomer ratio on LDL-cholesterol level

Cis-unsaturated fatty acids affect the LDL-cholesterol level differently from saturated and *trans* fatty acids. Saturated and *trans* fatty acids raise the LDL-cholesterol level whereas the LDL- cholesterol level is lowered by unsaturated fatty acids. Polyunsaturates lower the LDL-cholesterol level more than monounsaturates do. The trials that used predominantly unsaturated controls in one group (often olive oil or high oleic sunflower oil) were grouped separately from the trials using predominantly saturated or *trans* fatty acid controls owing to the difference in direction of effect predicted in the control group. The results from 1.4-5.6 g 1:1 isomer mixes of CLA were averaged across trials.

In trials with unsaturated fatty acid controls, the average effect of CLA was **to raise LDL-cholesterol** levels by 0.049 mmol/L (95% CI = -0.008 to 0.106 mmol/L; p=0.09); a statistically non-significant result. Because there were only three studies that used a variety of saturated fat controls, an overall average was not calculated for these studies. No study that used the 1:1 isomer ratio used a trans fat control group.

All these results are consistent with Mozaffarian and Clarke (2009) who predict that if 2-3% of energy from *cis*-monounsaturated fats is replaced with *trans* fatty acid, then LDL-cholesterol levels would be elevated by 0.1-0.15 mmol/L.

5.2.3 Overall effect of the two isomers individually or in any ratio on HDL- and LDL-cholesterol levels

The studies identified also contained arms that tested the isomers individually or in a 4:1 (*cis*-9, *trans*-11:*trans*-10, *cis*-12) isomer ratio. During the consideration of the Application, a high dose CLA study (approximately 23 g for those consuming 9270kJ) with more power than other studies, was reported (Wanders *et al*., 2010). EpiSAG members concurred with FSANZ that it would be reasonable to combine these studies with studies of the 1:1 ratio because the effects on lipids were not obviously different.

[1] A quantitative method of combining the results of independent studies (usually drawn from the published literature) and synthesising summaries and conclusions which may be used to evaluate therapeutic effectiveness, plan new studies, etc., with application chiefly in the areas of research and medicine.

Taking a weighted average of all studies with doses less than 6 g CLA, there was a **decrease in HDL-cholesterol** of 0.031 mmol/L (95% CI = -0.06 to -0.001; p=0.04) and an **elevation of LDL-cholesterol** of 0.057 mmol/L (95% CI = -0.0002 to 0.113; p = 0.051). If the high dose study was also included in the average, there was a **decrease in HDL-cholesterol** of 0.032 mmol/L (95% CI = -0.06 to -0.004; p = 0.02) and an **elevation of LDL-cholesterol** of 0.120 mmol/L (95% CI = 0.074 to 0.165; p < 0.0001).

Due to the availability of more recent studies not available for earlier analyses, and the increased dose range of some studies when the single isomer and other ratios are added to the results of the 1:1 ratio trials, a dose-response relationship was examined. There was a statistically significant relationship for both lipid outcomes. Compared to any fatty acid, there was a change in HDL-cholesterol of -0.005 mmol/L per gram of CLA (p=0.04) for all studies and of -0.009 mmol/L per gram of CLA (p=0.03) when the high dose study of Wanders *et al.* (2010) was excluded. Compared to *cis*-unsaturates, there was a change in LDL-cholesterol of 0.012 mmol/L per gram of CLA (p<0.001) for all studies and of 0.021 mmol/L per gram of CLA (p=0.003) when Wanders *et al.* (2010) was excluded.

Based on these results (as well as the results from section 5.2.2), FSANZ concludes that the 1:1 isomer mix probably has an effect on LDL-cholesterol.

Only one study compared CLA (a 4:1 *cis*-9, *trans*-11:*trans*-10, *cis*-12 ratio of the isomers) to industrial trans fat as the control; this study also used a second control group of high oleic sunflower oil (rich in *cis*-mono-unsaturated fatty acid). All were given at 7% energy in the diet (Wanders *et al*., 2010). CLA had the same effect in lowering HDL-cholesterol as industrial trans fat and elevated LDL-cholesterol compared to high oleic sunflower oil. The effects of CLA were comparable but not identical to industrial trans fat in this study.

5.2.4 Conclusion

FSANZ concludes that the 1:1 isomer mix of CLA reduces HDL-cholesterol levels compared to any fatty acid controls and probably elevates LDL-cholesterol levels when compared to *cis*-unsaturated fats. This effect on blood lipids is not consistent with the effect of a *cis*-polyunsaturated fatty acid and is more consistent with that of a *trans* fatty acid.

5.3 If CLA has an effect on blood lipids, what effect might this have on the risk of cardiovascular disease?

Extensive epidemiological data and clinical studies have identified numerous risk factors associated with adverse cardiovascular outcomes (Frishman, 1998; Wang *et al.*, 2006; Martin *et al*., 2008). Key/classic risk factors associated with cardiovascular disease include: elevated LDL-cholesterol plasma/serum concentrations; cigarette smoking; hypertension; reduced HDL-cholesterol plasma/serum concentrations; family history of premature coronary heart disease; older age; diabetes and male gender (NCEP, 2002; Wang *et al.*, 2006). From these well-characterised risk factors, the measurement of plasma/serum HDL- and LDL-cholesterol has widespread use and utility in the diagnosis, prevention and treatment of cardiovascular diseases. For example, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) (2002) guidelines (from the USA), indicate that a low HDL-cholesterol level is a significant and independent risk factor, and is inversely related to coronary heart disease (a major form of cardiovascular disease).

Meta-analyses of several major, published studies from the Framingham Heart Study (FHS), Multiple Risk Factor Intervention Trial (MRFIT), Lipid Research Clinics Prevalence Mortality Follow-up Study (LRCF) and the Coronary Primary Prevention Trial (CPPT) indicated that each increase in HDL-cholesterol of 0.026 mmol/L would decrease the risk of future cardiovascular disease by 2% for men and 3% for women (Gordon *et al.*, 1989).

The NCEP guidelines are well recognised and endorsed by the National Heart, Lung, and Blood Institute; the American College of Cardiology Foundation; and the American Heart Foundation (Grundy *et al.,* 2004). Similar guidelines have been adopted by Australian (National Heart Foundation of Australia, 2001 & 2005) and New Zealand (New Zealand Guideline Group, 2003 & 2009) health bodies.

EFSA's recent opinion on CLA as a novel food ingredient (EFSA, 2010a) is consistent with FSANZ's assessment of the effect of CLA on HDL- and LDL-cholesterol levels. However, based on the findings from Briel *et al*. (2009), EFSA concluded that these effects were unlikely to have an impact on coronary heart disease risk. FSANZ sought additional advice on this issue from EpiSAG members. They considered that a decrease in HDL-cholesterol and a rise in LDL-cholesterol levels of the magnitude estimated from FSANZ's analysis was 'non-trivial' and could increase the overall risk of cardiovascular disease in the population by up to 5%[2] at the level of intake recommended by the Applicant, with a higher risk associated with increased intakes.

In making this conclusion, EpiSAG members noted that an estimate of the effect of CLA on the ratio of total:HDL-cholesterol was a better indicator of risk of cardiovascular disease, but agreed that HDL- and LDL-cholesterol levels are independent risk factors for cardiovascular disease. FSANZ did not report findings in terms of the ratio of total:HDL-cholesterol because the CLA studies generally did not report this ratio in their results. A recent review by Brouwer *et al*. (2010) reported a dose-response relationship for the LDL:HDL relationship when CLA isomers individually, or in any ratio, replace mono-unsaturated fat.

5.4 Are there other potential risks to the population as a whole or sub-populations associated with the consumption of CLA?

In assessing other potential risks, FSANZ has considered the effect of increased consumption of CLA on inflammatory biomarkers, glucose homeostasis and breast milk composition. Consideration of these risks is based primarily on evidence from studies in humans. Further potential risks are also summarised based on the discussion among EpiSAG members. In addition, potential risks identified in the EFSA opinion on the safety of CLA (EFSA, 2010a) have also been summarised.

5.4.1 Effect of CLA on inflammatory biomarkers

The Applicant provided studies relating to the effect of consumption of CLA on inflammatory biomarkers in humans.

There are more than a dozen key circulating markers of inflammation with a possible association with cardiovascular disease risk (Lowe, 2005; Sarwar *et al.*, 2009). Some studies of CLA in humans have reported the effect on a small number of these inflammatory biomarkers (see **SD4** and **SD7** under the heading 'Inflammatory biomarkers') . However, while there is a growing body of experimental literature demonstrating the possible utility of using inflammatory biomarkers to indicate cardiovascular risk; it is not sufficiently developed to be incorporated into evidence-based medicine (Lowe, 2005; Libby *et al.*, 2009).

[2] EpiSAG members based their estimate of up to 5% increased risk of CVD on the following: the 0.036 mmol/L decrease in HDL can be roughly estimated as a 1-2% decrease in HDL. If the increase in LDL from CLA is considered at the same time (which corresponds to about a 1% increase in CVD risk), it is estimated that the overall increase in CVD is up to 5%. EpiSAG members did note however, that limitations of the available evidence make it challenging to estimate the exact magnitude of the effect of CLA on risk of CVD.

In addition, the mode of action of CLA in humans is not well characterised (see Section 5.1.1). The extrapolation of some anti-inflammatory actions by the Applicant, but none of the pro-inflammatory actions of various isomeric mixes of CLA, from *in vitro* studies and animal models to the clinical setting remains speculative. While this information may be reasonable as a study-generating hypothesis, it gives neither support for the postulated benefits nor evidence of safety. For further comment, see **SD7.** Thus, for weight to be given to the claims of beneficial effect from the postulated anti-inflammatory effects of specific CLA isomers, specific testing in humans would need to be conducted and provided.

EFSA (2010a) concluded that the 'observed increase in plasma and urinary concentrations of isoprostanes, which may indicate an increase in lipid peroxidation[3], and the increase in some markers of subclinical inflammation (i.e. 15-*keto*-dihydroprostaglandin F2α, and possibly C-reactive protein) associated with CLA consumption, together with the limited data available on the effects of CLA on vascular function, may indicate a potential for vascular damage (i.e. atherosclerosis) in the longer term'.

EFSA (2010a) did not form a conclusion about the effect of CLA on inflammatory biomarkers but noted that 'none of the studies had been designed to address the effects of CLA on sub-clinical inflammation'. They also noted that the results were inconsistent.

5.4.2 Effect of CLA on glucose homeostasis

The Applicant provided studies relating to the effect of consumption of CLA on plasma insulin and glucose homeostasis in humans.

Studies of CLA in humans have shown mixed results in relation to effects on glucose intolerance and insulin sensitivity (Park, 2009). FSANZ therefore investigated the effect of consumption of CLA on glucose homeostasis (see **SD3**, with the summary provided below). This assessment includes 20 human studies of CLA with *cis-9, trans-11* and *trans-10, cis-12* isomers in a 1:1 ratio. Eight studies reported testing the effect of CLA on glucose homeostasis as part of the study objective. The remaining 12 studies had other primary objectives, such as testing the effect of CLA on body weight, but reported measures of fasting glucose or insulin concentrations as secondary outcomes.

Two studies assessed the effect of CLA on insulin sensitivity using the euglycaemic clamp technique that is recognised as the 'gold standard' method for directly determining insulin sensitivity in humans. Two studies used oral glucose tolerance tests to measure glucose tolerance directly. The majority of human studies assessed fasting blood insulin and glucose concentrations, and sometimes estimated insulin sensitivity from these using surrogate indices. The surrogate indices have been validated against the clamp technique.

The majority of studies in the assessment reported non-significant results, including the two studies that employed the 'gold standard' clamp technique. Among these were two well conducted studies in type 2 diabetics that reported significant adverse effects of CLA on measures of glucose homeostasis (Moloney *et al*., 2004; Norris *et al*., 2009). Both studies of diabetics used surrogate indices, but only one used oral glucose tolerance tests.

Indicators of glucose homeostasis may respond differently to interventions, depending on the health status of the subjects. However, the description of participants in the studies was not adequate for clearly dividing the studies into groups with diabetes, impaired glucose metabolism, metabolic syndrome or normal metabolism. In addition, the variable design of the small number of studies in this assessment limits comparison of results across studies.

[3] An increase in lipid peroxidation is indicative of oxidative stress leading to cell damage.

The inconsistent, but small, results across the studies may relate to subject characteristics and/or study design. The two studies of CLA in children and adolescents also do not allow any conclusions to be drawn for this group.

EpiSAG members noted that favourable effects on fasting blood glucose and fasting insulin, and lipid metabolism, as would be expected in response to reduced body fat (see Section 6.1, in particular Section 6.1.3), have not been demonstrated in the available studies of CLA.

EFSA (2010a) recently concluded that 'CLA consumption does not appear to have adverse effects on insulin sensitivity or blood glucose' for up to six months. However, they also concluded that the safety of 3-6 g of CLA per day by people with type-2 diabetes 'has not been established under the proposed conditions of use'.

In summary, the available data raise questions but do not permit a conclusion about the effect of CLA on glucose homeostasis in the general population. However, the two studies in people with diabetes (Moloney *et al*., 2004; Norris *et al*., 2009) indicate that CLA could pose a risk for people with type 2 diabetes.

5.4.3 Effect of CLA on breast milk composition

The Applicant provided studies relating to the effect of consumption of CLA on human breast milk composition.

Five studies, with small sample sizes, investigated the effect of CLA consumption by mothers on the total fat content and fatty acid composition of human milk. A randomised controlled crossover study done by Masters *et al*. (2002) in nine breast feeding women given 1.2 g of CLA or olive oil a day for five days with a washout period of seven days showed a significant ($p<0.05$) reduction in total milk fat while the women were consuming CLA. However, subsequent randomised controlled crossover studies by the same research group and others could not replicate these results.

Hasin *et al*. (2007) reported that neither a daily intake of 0.6 g of predominantly *cis*-9, *trans*-11 CLA nor 0.6 g of predominantly *trans*-10, *cis*-12 CLA for five days changed the total fat content of milk from 12 mothers when compared with olive oil. Mosley *et al*. (2007) also reported that neither 1.2 g nor 2.5 g CLA (1:1 isomer blend) for five days changed the total fat content of milk from 12 mothers when compared with safflower oil. There were some differences between these three studies (Masters *et al.* (2002), Hasin *et al.* (2007) and Mosley *et al.* (2007)) conducted by the same research group including the dose and isomeric composition of CLA, choice of control lipid, duration of the washout period, maternal body composition, and the stage of lactation but the authors were unable to do more than speculate on what might account for the difference between the original and subsequent studies.

A study by Ritzenthaler *et al*. (2005) also reported no difference in total milk fat content between mothers given daily doses of 0.2 g (n=11) or 0.4 g (n=12) of *cis*-9, *trans*-11 CLA in cheese for eight weeks and those given cheese with no added CLA. Bertschi *et al*. (2005) also reported similar total milk fat content when mothers (n=16) consumed high *cis*-9, *trans*-11 CLA (0.5 g/day for 10 days) butter as when they consumed margarine.

All five studies reported changes in the specific composition of the fat content of milk including increases in the amount of the CLA form(s) that were supplemented (Bertschi *et al*., 2005; Hasin *et al*., 2007; Mosley *et al*., 2007; Masters *et al*., 2002; Ritzenthaler *et al*., 2005). This is consistent with other studies reporting that the fat composition of milk is at least partially determined by the fat composition of the maternal diet (Anderson *et al*. 2005).

EFSA (2010a) did not form a conclusion about the effect of CLA on human milk secretion and content. FSANZ concurs with this view based on the available evidence. The effect of CLA on breast milk composition was not considered by EpiSAG members.

5.4.4 Other potential risks

EFSA (2101a) considered a range of other potential risks based on human studies , in addition to those already described above. They relate to the increased risk of atherosclerosis and insufficient evidence of safety in the long term based on liver function. In terms of liver function, they concluded that consumption of CLA by 'normal weight, overweight, and obese non-diabetic subjects does not appear to have adverse effects on liver function at the proposed conditions of use up to six months; however the effect on liver steatosis[4] has not been addressed when CLA is consumed for periods of longer than six months'.

FSANZ posed the question of other potential risks to EpiSAG members. Their response focused on the type of study that would need to be done to improve the level of evidence regarding the effect of CLA in human populations. In their opinion the study design would :

- be of longer duration (e.g. most reversal studies on metabolic syndrome are 1-2 years)
- be sufficiently powered design to show a beneficial effect on fasting glucose and fasting insulin, if it exists
- assess the effect of CLA on inflammatory markers, Apoliprotein$_a$ (Lp(a)) and liver function
- focus on assessment of CLA's effect on pre-diabetic subjects with central obesity
- investigate the pattern/location of fat loss (see Section 6.1).

6. Potential benefits

6.1 What is the evidence that CLA delivers the stated purpose?

FSANZ has interpreted the Applicant's stated purpose as an assessment of the effect of Tonalin® CLA (or comparable products) at the amounts proposed to be added to food on body weight, lean body mass and body fat mass (see **SD2**).

6.1.1 FSANZ's analysis of the effect of CLA on body weight, lean body mass and body fat mass based on a systematic review of the literature

FSANZ investigated the effect of CLA on body weight and body composition among adults and children separately. The range of methods used to measure body weight and body composition in the studies included in FSANZ's analysis are described in Tables A2a-A2e in **SD2**.

The evidence is suggestive, but not conclusive, 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. A similar conclusion cannot be drawn for body weight, although the trend is for a fall in body weight.

[4] Liver steatosis refers to fatty degeneration of the liver.

However, there is no evidence of a dose effect and there is insufficient evidence to draw a conclusion about the effect on fat mass when CLA is added to food. The clinical significance of 1-2 kg of fat loss at the individual level is likely to be minimal. 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. 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 also limited evidence that CLA positively influences lean body mass or assists in maintaining weight or preventing weight regain following initial weight loss.

Only two published randomised controlled trials on the effect of CLA in obese children and adolescents were identified (Bonet Serra *et al*., 2008; Racine *et al*., 2010). Bonet-Serra *et al.* (2008) used CLA in conjunction with group therapy. No differences in body weight or body composition between the treatment and placebo groups were reported. By contrast, Racine and colleagues (2010) reported several significant differences in body composition after six months of treatment with CLA. Thus, based on these limited data, further studies are needed before any conclusions can be drawn regarding the effect of CLA on body weight or body composition in children and adolescents.

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

In addition to the analysis of body weight and body composition in adults described in section 6.1.1, FSANZ undertook a similar meta-analysis to that undertaken by Whigham *et al.* (2007) and compared the two. The comparison included only results for the CLA-treated groups compared with placebo: it did not include results for the CLA-treated groups only.

The purpose of the Whigham *et al.* (2007) meta-analysis was to investigate the influence of CLA dose and study duration on the efficacy of CLA as a treatment for improving body composition, specifically reduction in fat mass. The meta-analysis included studies of the 1:1 ratio CLA isomer preparation as well as two studies that included the single *trans-10, cis-12* isomer, but it excluded studies investigating treatment groups that only received the *cis-9, trans-11* isomer.

FSANZ's meta-analysis included 13 studies (comprising 17 treatment arms of the 1:1 isomer CLA preparations) that reported data on changes in body fat mass among adults. There were some studies that were common to both meta-analyses and FSANZ included five additional studies in adults published since Whigham *et al.* (2007) was published (see **SD2** for further details).

The results from FSANZ's analysis were 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 sub-group analysis of studies between 14 and 26 weeks' duration indicated a significant fall in fat mass of 1.1 kg (95% CI = -1.9 to -0.4 kg; $p=0.003$), and studies of 12 weeks duration also indicated a similar fall in fat mass (1.1 kg; 95% CI = -2.0 to -0.1 kg; $p = 0.03$).

6.1.3 Loss of body fat without a concurrent decrease in body weight and increase in lean body mass

In considering the effect of CLA on body composition, EpiSAG members noted that the results in studies of 6-12 months duration in overweight and mildly obese adults indicated a significant, but small, loss of body fat without a concurrent significant decrease in body weight (see Table 3 in **SD2**). This raised the question that body fat may be redistributed rather than lost.

In response, FSANZ reviewed the evidence for distribution of body fat pre- and post-treatment with CLA in the studies that used dual-energy x-ray absorptiometry (DXA)[5] as the method of determining body composition. Ten of the adult studies and the two studies involving children and adolescents used DXA. However, there were few additional results reported in relation to body fat distribution. Among the adult studies, Gaullier *et al*. (2007) reported a significant decrease in leg fat (mainly in women and in obese adults) (-0.8 kg; p=0.003) but not arm fat or abdominal fat, despite a significant decrease in total fat mass of -1.2 kg (p=0.043). In overweight, but not obese, study participants, Laso *et al*. (2007) reported both a significant decrease in body fat mass (-0.9 kg; p=0.01) as well as abdominal fat (-0.5 kg; p=0.05). By contrast, Norris *et al*. (2009) reported a significant increase in abdominal fat mass in the CLA-treated group (>2.0 kg in both weeks 0-16 and weeks 20-36; p=0.04) but a non-significant decrease in total fat mass. In the study by Racine *et al*. (2010) which included children aged
6-10 years, there was a significant difference in body fat mass (1.0 kg; p=0.01). This was comprised of a smaller increase in fat mass in the CLA-treated group (+0.8 kg) compared with the placebo group (+1.8 kg), and was accompanied by a similar decrease in per cent abdominal fat (-0.5%; p=0.02) in the CLA-treated group compared with the placebo group.

In summary, the few studies that reported additional data on body fat distribution show mixed results. Thus, no conclusion can be drawn as to the distribution of fat loss but uncertainty remains when the evidence indicates a reduction (albeit small) in body fat without a concurrent decrease in body weight and increase in lean body mass.

6.1.4 Waist circumference

The potential beneficial effect of CLA on waist circumference was raised by another applicant requesting permission for use of CLA (A1012, subsequently withdrawn).

FSANZ found a total of 12 studies which had reported waist circumference measures in 18 arms, including five study arms that did not use the 1:1 CLA isomer preparations (see Appendix 1 in **SD2**). These studies ranged from 4-26 weeks in duration but there was no apparent association with degree of waist circumference reduction and duration. FSANZ calculated that, if the results for the 1:1 isomer mix studies are corrected to 12 weeks, then the unweighted average change in waist circumference in the CLA group is 0.55 cm less than the control group if Zhao *et al*. (2009) is included. However it is only 0.16 cm less than the control group if Zhao *et al*. (2009) is excluded (because all subjects in that trial were prescribed an anti-hypertensive drug). These very small mean reductions would have no appreciable effect on health.

[5] EpiSAG members considered that DXA is able to measure fat mass and lean body mass as well as the distribution of body fat. Accordingly, DXA is capable of determining redistribution of body fat mass.

6.1.5 Conclusion

Although a statistically significant, but small, loss in body fat was observed in the two meta-analyses (1-2 kg after 3-6 months) (Whigham *et al*. 2007 and FSANZ's meta-analysis investigating body fat changes), FSANZ considers that there are substantial uncertainties that detract from the strength of this evidence. These uncertainties are discussed in Section 8 and summarised in Section 9. They are sufficient to conclude that consumption of CLA at the level recommended by the Applicant does not deliver the stated purpose.

7. Estimated intake of CLA

7.1 Is CLA already present in the diet? If so, how much extra CLA will the population consume if CLA is added to food in the amounts requested by the Applicant?

The *cis*-9, *trans*-11 isomer is the most common CLA isomer that occurs naturally in food. This isomer is present in ruminant meat and dairy products and accounts for >70% of the natural CLA in food (McLeod *et al*., 2004). The *trans*-10, *cis*-12 CLA isomer on the other hand, is comparatively rare in food (0-2% of the total CLA content from ruminant products (Fritsche *et al*., 1999)). Together, these naturally-occurring CLA isomers contribute about 0.5 to 2.0% of the fatty acids in the human diet. Various other CLA isomers may also be present in these foods.

Based on the levels of CLA naturally-occurring in food, FSANZ estimated that consumption of CLA (in products and at levels proposed by the Applicant) would result in an increase of 2-fold and >50-fold over the current levels of intake of the *cis*-9, *trans*-11 and *trans*-10, *cis*-12 isomers, respectively, in consumers of the products.

8. Consideration of the risks versus the benefits of consuming CLA

8.1 If there are both risks and benefits associated with the consumption of CLA, do the benefits outweigh the risks?

FSANZ posed this question to EpiSAG members. They concluded that it is extremely likely that the effect of CLA on blood lipids is adverse and the available evidence is sufficient to have confidence in this conclusion. The adverse effects of CLA on blood lipids are especially important for population groups such as type 2 diabetics, undiagnosed and pre-diabetics and those with metabolic syndrome.

EpiSAG members considered that the potential benefit from taking CLA has not been demonstrated primarily because the evidence does not adequately show which compartment of body fat is changing or by what mechanism the changes in body fat are occurring. This comment stemmed from the lack of evidence supporting a concurrent loss in body weight or an increase in lean body mass. Thus, some of the fat 'lost' may be redistributed to other parts of the body (such as the liver). These changes would be difficult to detect in the studies conducted, because DXA is not capable of detecting small changes in body fat of 1-2 kg at the individual level (Ellis, 2001). EpiSAG members also noted that the observed unfavourable changes in parameters such as insulin sensitivity would not be expected if body fat was lost rather than redistributed.

Taking into consideration the advice from EpiSAG members, FSANZ concluded that the evidence for adverse effects on blood lipids is much stronger than the evidence for a favourable effect of CLA on body composition.

9. Uncertainties in the evidence

There is currently insufficient data on the effects of CLA on the following population groups:

- individuals with pre- and existing type 2 diabetes, including evidence relating to effects of CLA on micro-vascular complications and longer term study of the effects of CLA on glycosylated haemoglobin
- women with gestational diabetes
- individuals at high risk of CVD, including those who have experienced a cardiac infarction
- obese children and adolescents
- older persons.

In addition, information is needed on the effects of CLA on inflammatory markers and the full range of markers of cardiovascular disease risk in these populations, particularly given the large proportion of the Australian population that, according to the AusDiab[6] study, are unaware that they have type 2 diabetes, are pre-diabetic and/or have dyslipidaemia (International Diabetes Institute, 2001).

The major uncertainty about safety of CLA is with regard to redistribution of body fat. CLA appears to produce a small reduction in body fat stores, but there is insufficient evidence of the mechanism and pattern of this effect and insufficient evidence to confirm that the effect leads to beneficial physiological outcomes. Lost body fat may be metabolised or redistributed in a way that results in harm, not benefit.

In summary, FSANZ considers that the level of uncertainty about the safety of CLA in various population sub-groups, as well as the uncertainty about CLA's mechanism of action in reducing body fat given an inconsistent pattern in weight loss (see Section 6.1.1), is considerable.

10. Risk assessment summary

Despite the limitations of the evidence base, FSANZ has undertaken a comprehensive risk assessment of the potential addition of CLA to food at the recommend level of consumption of 4.5 g/day of Tonalin® CLA (which is equivalent to 3.5 g of unesterified CLA). CLA in this context includes comparable CLA preparations to Tonalin® CLA.

The risk assessment was informed by several sources: the evidence provided by the Applicant during the assessment period; FSANZ's independent investigation of the evidence; advice from an Epidemiological Scientific Advisory Group who were asked to consider a range of scientific and clinical issues related to the potential addition of CLA to the food supply; and EFSA's scientific opinion on CLA released in May 2010 (EFSA, 2010a).

FSANZ concludes that there is evidence of adverse effects on blood lipids (decreasing HDL-cholesterol and probably increasing LDL-cholesterol levels) as a result of consuming CLA in the Applicant's recommended amount.

[6] AusDiab – The Australian Diabetes, Obesity and Lifestyle Study is a longitudinal cohort study which began in 1999.

The potential for increased CVD risk on a population basis is not insignificant, and is estimated to be up to 5% at the level of intake of CLA proposed by the Applicant, but could be higher if individuals exceed the recommended level of intake. In addition, the potential adverse effect on glucose homeostasis among people with type 2 diabetes, while less conclusive due to insufficient evidence, warrants further investigation, particularly given the prevalence of both diagnosed and undiagnosed diabetes and pre-diabetes in Australia and New Zealand.

In terms of potential benefits, FSANZ considers that although a statistically significant, but small, loss in body fat was observed (1-2 kg after 3-6 months) there is insufficient evidence of the mechanism and pattern of fat loss and insufficient evidence to confirm that the fat loss leads to beneficial physiological outcomes.

FSANZ therefore concludes that, on balance, the evidence of potential harm is stronger than the evidence for potential benefit and that the benefit and harm may not necessarily accrue to the same individuals. EpiSAG members agreed with FSANZ's conclusion.

FSANZ also considers that there is insufficient information about the effect of CLA on a number of vulnerable population groups (individuals with pre- and existing type 2 diabetes; women with gestational diabetes; individuals at high risk of cardiovascular disease; obese children and adolescents; and older persons) who would be at potentially greater risk from undesirable changes in blood lipids or glucose homeostasis.

A dietary intake assessment was not undertaken as part of the risk assessment because the estimates of risk and benefit were based on the recommended intake of 3.5 g/day of CLA; thus precluding the need to estimate dietary intakes in any greater detail.

RISK MANAGEMENT

11. Risk Management Strategies

The Applicant requested an amendment to Standard 1.5.1 – Novel Foods to approve the exclusive use of Tonalin® CLA as a novel food. The stated purpose for Tonalin® CLA is as a useful adjunct in weight control programs and diets. The Applicant indicates that a daily consumption of 4.5 g of Tonalin® CLA (which is equivalent to 3.5 g of unesterified CLA) is recommended to achieve the stated purpose.

Based on the risk assessment summary in Section 10 of this Report, FSANZ investigated possible risk management strategies that could be employed to minimise the potential public health and safety risks associated with consumption of CLA.

The risk management strategies are specifically aimed at:

- Sub-population groups, at greater risk of CVD
- General population, at risk of CVD
- Overconsumption of CLA and therefore at increased risk of CVD

The possible risk management strategies are outlined below.

- Restrict the food(s) which can contain added Tonalin® CLA. This would reduce the population intake of Tonalin® CLA.

- Limit the amount of Tonalin® CLA that is permitted to be added to foods. This would also reduce the population intake of Tonalin® CLA.

- Mandate certain advisory or warning statements for foods that contain added Tonalin® CLA. Such labelling statements would provide advice to consumers about appropriate consumption of foods containing Tonalin® CLA.

- Produce a FSANZ Fact Sheet or implement other education mechanisms to inform the community about appropriate consumption of foods containing Tonalin® CLA.

FSANZ's consideration of the effectiveness of these risk management options is provided below.

11.1 Restrict the range of foods to which Tonalin® CLA can be added

The Applicant requested approval for Tonalin® CLA to be permitted in a broad range of commonly eaten foods including milk products, soy beverages, fruit-based beverages, yoghurt, nutrition bars, table spreads, formulated meal replacements and supplementary foods and formulated supplementary sports foods.

FSANZ considered restricting the range of foods to which Tonalin® CLA is added, but concluded that this measure would not sufficiently protect public health and safety, as required by section 18 of the FSANZ Act. Although a restriction on food vehicles would reduce population exposure to CLA, it would not provide an adequate control mechanism to reduce the CLA intake of individuals. As there is evidence that CLA as a novel food ingredient has an adverse effect on blood lipids, this effect is particularly important for individuals with type 2 diabetes, pre-diabetes and individuals at high risk of cardiovascular disease.

There is insufficient data on the dietary consumption patterns and habits of consumers who would purchase foods containing CLA to determine how intakes would vary with the approval of Tonalin® CLA as a novel food ingredient. However, it is possible that some consumers would actively seek out foods containing Tonalin® CLA for their weight loss potential (noting that consumers are unlikely to distinguish between fat loss and weight loss). It is also possible that individuals most likely to seek out these products are those most vulnerable to its adverse effects.

FSANZ concludes that this measure is unlikely to be effective in limiting consumption by both sub-populations at increased risk of CVD, as well as the general population.

11.2 Limit the amount of Tonalin® CLA that can be added to food

The Applicant has sought permission to add 1.5 g CLA per individual serve of food. FSANZ considered placing restrictions on the amount of Tonalin® CLA that could be added to a serve of food to address the health risks outlined in Section 10. However, imposing such a limit would be self-defeating because it would reduce the ability of individuals to consume the required amount of CLA to fulfil the claimed stated purpose. It may also encourage individuals to consume more foods with added Tonalin® CLA to try to achieve the stated purpose. This might further reduce the capacity of consumers to achieve weight loss.

11.3 Mandate advisory or warning statements on labels of food containing added Tonalin® CLA

The Applicant informed FSANZ that it provides a number of advisory statements on commercial food products that contain Tonalin® CLA in the Spanish market[7]. These statements are to the effect that the product is not recommended for people with special dietary needs (pregnant and lactating women, children younger than 5 years and people with diabetes). The Applicant did not request any specific labelling statements to be mandated in their Application to FSANZ.

FSANZ considered the potential to use advisory or warning statements to inform consumers about the risks of consuming foods containing added CLA. In general, advisory or warning statements are used to advise consumers about a potential risk to public health or safety associated with consuming a food. They provide an important risk management strategy particularly when targeting population sub-groups.

There is sufficient evidence available to conclude that consuming CLA at the recommended intake presents an increased risk to consumers. As noted earlier in this Report, there may be increased risk for those individuals with type 2 diabetes, pre-diabetes, and those at high risk of cardiovascular disease. Therefore, FSANZ considers that an advisory or warning statement would not be sufficient to protect the population from the increased risk of consuming foods with added Tonalin® CLA. Furthermore, the prevalence of diagnosed and undiagnosed diabetes, impaired glucose tolerance and impaired fasting glucose in Australian adults aged 25 and older is estimated to be over 20% (Dunstan *et al*., 2002) and approximately half of those with these conditions are unaware of it. In New Zealand the proportion of undiagnosed diabetes to diagnosed diabetics may be less (Sundborn *et al*., 2007). Diabetes rates are higher in Indigenous than non-Indigenous persons in both countries (Penm, 2008; Sundborn *et al*., 2007). There are also many population subgroups for which there is insufficient data to determine the effects of CLA (women with gestational diabetes, overweight and obese children and adolescents, and older persons).

11.4 Produce FSANZ education materials to inform the community about foods containing added Tonalin® CLA

FSANZ considered the use of education materials to inform the community about foods containing added Tonalin® CLA either alone, or in combination with other risk management strategies. Consumer education materials can be used to increase community knowledge of the benefits and risks associated with certain foods or food ingredients. However, where the messages to be conveyed are complex and potentially conflicting, the effectiveness of such an approach may be limited. In the case of CLA, the potential benefit of consuming CLA has not been adequately demonstrated. There is also the difficulty of reaching the target population by these means. In view of the risk assessment conclusions, FSANZ considers that education material would not adequately address the public health and safety risks associated with Tonalin® CLA.

12. Other Risk Management Issues

12.1 Risk management matters relating to fatty acids

FSANZ also needs to be aware and have regard to other matters as part of its risk management of the Application.

[7] As indicated in Section 2.3, the use of CLA has been approved in Spain in liquid yoghurt, milk, processed cheese and orange juice since 2004-2005.

One of these matters is the international and national nutritional guidelines related to fatty acids. Dietary recommendations by both national governments (NHMRC & NZ MoH, 2006) and by the heart associations in both countries (NHFA, 2009; Sneddon 1999) recommend increasing the consumption of *cis*-unsaturated fatty acids and decreasing the consumption of saturated fatty acids and *trans* fatty acids. This is because *cis*-unsaturates favourably affect HDL-and LDL-cholesterol levels (compared to carbohydrate) whereas saturated and *trans* fatty acids both increase LDL-cholesterol levels (compared to carbohydrate and the *cis*-unsaturated fatty acids). *Trans* fatty acids decrease HDL-cholesterol levels compared to *cis*-unsaturates (Mensink *et al*., 2003; Mozaffarian and Clarke, 2009). It is recommended that the combined intake of saturated and *trans* fatty acids should not exceed 10% energy in adults (NHMRC & NZ MoH, 2006). There are also Australian and New Zealand Government initiatives to reduce the presence of *trans* fatty acids in the food supply and these also note the need not to inadvertently increase saturated fatty acid intake as explained in more detail in the references (Reuss *et al*., 2009, FSANZ, 2009).

FSANZ's analysis shows that the 1:1 CLA isomer mix decreases HDL-cholesterol and probably increases LDL-cholesterol levels compared to *cis*-unsaturates. Therefore, FSANZ concludes that the 1:1 CLA isomer mix should be grouped in the 'eat less of' class with saturated and *trans* fatty acids.

Regulatory permission for addition of a novel food ingredient into the food supply that is highly likely to have unfavourable effects on HDL-and LDL-cholesterol levels could be seen to be inconsistent with government guidelines to reduce the population consumption of *trans* fatty acids without increasing saturated fatty acid intake.

OTHER RELEVANT CONSIDERATIONS

A consideration of the other requirements set out in section 18 of the FSANZ Act to those already discussed above and those of section 29 of the FSANZ Act are provided below.

13. Other Section 18 Objectives

The objectives and the other matters FSANZ must have regard to in the consideration of this Application are set out in section 18 of the FSANZ Act (see Section 3 of this Report). The protection of public health and safety has been dealt with in the risk assessment section and summarised in Section 10. The other objectives and relevant considerations are dealt with below.

13.1 The provision of adequate information relating to food to enable consumers to make informed choices

The objective of the provision of adequate information relating to food to enable consumers to make informed choices is not relevant to the current assessment of this Application.

13.2 The prevention of misleading or deceptive conduct

The prevention of misleading or deceptive conduct is also not directly relevant to the current assessment of this Application.

13.3 The need for standards to be based on risk analysis using the best available scientific evidence

FSANZ's risk analysis as part of the assessment of this Application has been based on the best and most recent scientific evidence in terms of scientific studies (**SD1**, **SD2**, **SD3** and **SD4**).

FSANZ has also had earlier drafts of SD1, the assessment of CLA on HDL- and LDL-cholesterol levels and SD2, the assessment of CLA on body composition, independently peer reviewed. As well, FSANZ convened a group of independent external experts (the EpiSAG) to consider a range of scientific and clinical issues related to the risk assessment.

13.4 The promotion of consistency between domestic and international food standards

Currently, there is little consistency with the regulation of CLA (specifically Tonalin® CLA) as a novel food ingredient in international food standards around the world (see section 2.3).

FSANZ takes account of all relevant matters which includes safety assessments and opinions from other international food regulatory agencies as part of its assessment of an application to permit a novel food ingredient. FSANZ is required to perform an independent assessment of the safety of any novel food that is not currently permitted in the Code before it can be permitted to be added to food sold in Australia and New Zealand. The primary objective of section 18 of the FSANZ Act is the 'protection of public health and safety' as noted in section 3 of this Report.

FSANZ's conclusions differ from that of some other regulatory agencies around the safety of adding CLA to a broad range of food products, since FSANZ's risk assessment concludes that there is a public health and safety risk.

13.5 The desirability of an efficient and internationally competitive food industry

Approving the use of Tonalin® CLA would allow the Applicant to supply their novel food ingredient to a number of food manufacturers for use in the production of a wide range of foods. Approving the use of Tonalin® CLA would also allow industry to produce these foods to compete in overseas markets where Tonalin® CLA may already be permitted, or may be permitted in the future. These benefits are outweighed by the potential public health risks associated with permitting Tonalin® CLA use in food (see Section 10, risk assessment conclusions).

13.6 The promotion of fair trading in food

FSANZ has evaluated all of the available information but does not consider that there are any matters relevant to this consideration.

13.7 Any written policy guideline formulated by the Ministerial Council

Section 15 of this Report addresses how FSANZ has had regard to the Ministerial Council policy guideline relevant to this Application.

14. Other Section 29 matters

In assessing the Application, FSANZ has had regard to the following matters as prescribed in section 29 of the FSANZ Act:

- Whether costs that would arise from a food regulatory measure developed or varied as a result of the application outweigh the direct and indirect benefits to the community, Government or industry that would arise from the development or variation of the food regulatory measure.

- Whether other measures (available to the Authority or not) would be more cost-effective than a food regulatory measure developed or varied as a result of the application.

- Any relevant New Zealand standards.

- Any other relevant matters.

14.1 Costs and benefits

In Section 8.1, FSANZ assessed the risks and benefits to consumers of consuming added CLA. It was concluded that the evidence for adverse effects on blood lipids is much stronger than the evidence for a favourable effect of CLA on body composition. On this basis, the likely costs associated with the addition of CLA to food, due to the associated potential adverse health outcomes, are concluded to be greater than the likely benefits.

14.2 Any other measure that can be used to address the Application than a food regulatory one

Permission has been sought for Tonalin® CLA to be an approved novel food. Novel foods can be added to the food supply only if they are listed in Standard 1.5.1. Currently, there is no permission to add Tonalin® CLA to the food supply within the Code. There are no other measures appropriate for assessing the permission to add Tonalin® CLA to the food supply available to FSANZ.

14.3 Any relevant New Zealand Standards

There are no directly relevant New Zealand standards. FSANZ is aware that Tonalin® CLA is available in New Zealand in capsule form as a dietary supplement regulated under the Dietary Supplements Regulations.

Standard 1.5.1 is a joint Australia and New Zealand Standard.

14.4 Any other relevant matters

There are no other relevant matters applicable to this Application.

15. Ministerial Council Policy Guidelines

FSANZ needs to have regard to any policy guidelines formulated by the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council) in its assessment of this Application. There is one Policy Guideline relevant to this Application: the Policy Guideline – *Addition to Food of Substances other than Vitamins and Minerals* (abbreviated here to Policy Guideline).

15.1 Policy Guideline – Addition to Food of Substances other than Vitamins and Minerals

FSANZ has assessed the Application paying regard to the policy principles in this Policy Guideline as explained in the sections below.

15.1.1 The purpose for adding the substance can be articulated clearly by the manufacturer (i.e. the 'stated purpose')

The Applicant has clearly articulated the purpose of adding Tonalin® CLA to foods in their Application as:

> *The purpose of the novel food is as an ingredient in functional foods designed as useful adjuncts in weight control programmes and diets. Numerous studies have consistently demonstrated the benefit of the novel food in producing a significant decrease in body fat whilst maintaining lean body mass.*

15.1.2 The addition of the substance to food is safe for human consumption

The policy principle refers to the matter of the safety for human consumption of the addition of the substance to food. As discussed in Section 5.1 and in greater detail in **SD4**, FSANZ has not identified any chemical safety risks from the consumption of Tonalin® CLA. However, there is a risk to population health as well as to some individual consumers of Tonalin® CLA from an adverse effect on blood lipids as concluded in Section 5.

15.1.3 The substance is added in a quantity and a form which is consistent with delivering the stated purpose

FSANZ has assessed the findings of studies that administered CLA consistent with the Applicant's specified formulation to determine whether the stated purpose could be delivered. This assessment is contained in **SD2** with the summary and conclusions provided in Section 6.1. FSANZ concludes that the addition of Tonalin® CLA to the proposed food products would not be consistent with the stated purpose because there is a substantial level of uncertainty associated with the evidence supporting the small decrease in body fat of 1-2 kg.

15.1.4 The addition of the substance is not likely to create a significant negative public health impact to the general population or subpopulation

FSANZ considers that the addition of Tonalin® CLA as a novel food ingredient would create a negative public health impact because of its adverse effect on blood lipids and the estimated increased risk of cardiovascular disease that this would create among consumers of the product. Sub-groups in the population, such as those at increased risk of cardiovascular disease and people with pre- and existing type 2 diabetes, are likely to be at even greater risk.

15.1.5 The presence of the substance does not mislead the consumer as to the nutritional quality of the food

This policy principle is not relevant for the assessment of the Application since FSANZ concludes that there is a public health and safety risk from the consumption of CLA added to food that cannot be mitigated by any risk management strategies. Therefore, there is no need to consider the nutritional qualities of food containing added CLA.

16. Options

The options for the assessment of this Application are:

1. reject the Application

2. accept the Application and prepare a draft variation to Standard 1.5.1 (for public comment)

16.1 Consideration of option 1

FSANZ's primary objective, as stated in section 18 of the FSANZ Act, is the protection of public health and safety.

For this Application, FSANZ considers the health risks of adding Tonalin® CLA as a novel food ingredient to the food supply outweigh the health benefits (see Section 10).

16.2 Consideration of option 2

FSANZ addressed whether any risk management strategies could be employed that would satisfactorily mitigate the risks to public health and safety identified from the risk assessment.

These various risk management options are addressed in Section 11.

FSANZ concluded that there are no appropriate risk management options available that could adequately mitigate the risks identified.

16.3 Preferred option

The preferred option is option 1, which is to reject the Application. The preferred option is based on an assessment of the relevant scientific studies available at this time, both provided by the Applicant and independently sourced from the literature by FSANZ.

CONCLUSION

17. Decision

Decision

To reject the Application.

Reasons for Decision

FSANZ's decision to reject this Application is made having regard to matters listed in section 18 of the FSANZ Act. In relation to the objective to address public health and safety FSANZ concludes:

- The overall evidence base was not sufficient to demonstrate the safety of Tonalin® CLA at the recommended intake of 4.5 g/day.

- The available evidence suggests that consumption of Tonalin® CLA at the levels proposed by the Applicant may have adverse effects on cardiovascular disease and may adversely affect glucose tolerance in consumers with type 2 diabetes. Potential adverse and potential beneficial effects may not occur in the same individual and individuals would be unlikely to be able to self-diagnose relevant risk factors and self-exclude from consumption of Tonalin® CLA where appropriate.

- Investigation of possible risk management strategies to manage the potential risks identified, such as restricting the foods to which CLA can be added, limiting the amount of CLA added to food, mandating advisory labelling statements, or producing education materials, concluded that there were concerns that they would not be adequate to mitigate the risks identified.

In relation to the other matters listed in section 29 of the FSANZ Act, FSANZ concludes:

- The available evidence does not demonstrate that a net benefit would arise from approving the addition of Tonalin® CLA to food.

- There are no appropriate non-regulatory measures that are relevant in the assessment of this Application.

- There are no directly relevant New Zealand standards. FSANZ is aware that Tonalin® CLA is available in New Zealand in capsule form as a dietary supplement; regulated under the Dietary Supplements Regulations.

The decision to reject this Application does not preclude any Applicant submitting a new Application for this substance if, in the future, additional, robust scientific studies that address the safety concerns underpinning the current decision become available.

18. Review

The Applicant has a right of appeal to the Administrative Appeals Tribunal in accordance with section 143 of the FSANZ Act.

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