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

SUPPORTING DOCUMENT 8

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

Summary of issues raised by the Applicant in April 2011 and FSANZ's response

Issue raised by Applicant	FSANZ'S response
Chris Preston's comments	
CLA as a TFA	
The Applicant argues that FSANZ has oversimplified the assessment by viewing CLA as a trans fatty acid (TFA). It claims the assessment should consider CLA's specific characteristics, and not consider the effect of trans fats unless it can show CLA has the same function or effect.	FSANZ has explicitly addressed and assessed the effect of Tonalin® CLA, and comparable 1:1 CLA isomer preparations, on a range of potential health effects. In doing so, FSANZ has not assumed CLA has the function of a TFA. FSANZ's assessment of the effect of CLA preparations, comparable to Tonalin® CLA, on blood lipids is provided in SD1 and summarised in Section 5.2 of the Assessment Report. FSANZ also notes, that in response to the EpiSAG's view that "CLA exerts effects on blood lipids that are similar but possibly not identical to the effects of TFA based on the limited data available", Professor Clifton in his submission on behalf of the Applicant, (see **SD6** and also noted below) appears to agree with this view as he writes "Probably true – hence they should be treated the same".
Consistent risk management options compared to European Union	
The European Commission (EC) has deferred their consideration of the European Food Safety Authority (EFSA) risk assessment opinion of the same CLA preparation as this Application. The Applicant had hoped to provide the EC consideration to FSANZ to seek international harmonisation of regulatory approaches to their CLA preparation. The Applicant believes the safety concerns noted in FSANZ's Assessment Report are more appropriately addressed through controls over labelling and end product use not by denying market access. Due to the EC delay the Applicant requests FSANZ defer the finalisation of the assessment until the EC decision can be provided.	As the Applicant notes in its submission, FSANZ is not obliged by its legislation to follow what other international regulatory agencies decide (noting there is no international Codex approach to novel foods regulation). There are times when FSANZ will arrive at a different decision to that of other agencies, for a variety of reasons, including the scientific evidence available at the time the decision is made. FSANZ has considered various risk management options to address the risks identified from the risk assessment. However, having regard to the current evidence the risk management options are not considered to be sufficiently effective to manage the identified risks (see Section 11 of the Assessment Report, as well as discussion later in this Table).
Products containing added CLA sold as dietary supplements in New Zealand	
An argument is mounted by the Applicant that since products containing added CLA have been sold in New Zealand as dietary supplements there is some history of consumption of CLA in Australia and New Zealand.	The Applicant submitted the Application requesting FSANZ assess Tonalin® CLA as a novel food in 2008. FSANZ is obliged under the FSANZ Act to assess the merits of the Application; that is permission to add Tonalin® CLA as a novel food to a wide variety of foods.

Issue raised by Applicant	FSANZ'S response
The definition of novel food excludes food that has a history of consumption in Australia and New Zealand. It is therefore likely that at some point in time CLA will no longer be considered a 'non-traditional food' requiring a novel food permission. At this stage CLA would be available to be added to food without restriction. It would be somewhat incongruous if FSANZ denied market access to the ingredient while products containing CLA are sold as dietary supplements in New Zealand, or could be freely available for sale in future (when no longer considered novel).	
Professor Peter Clifton's comments	
HDL cholesterol	
The Applicant refers to the key outcomes of the EpiSAG Outcome Notes which state that: "The 95% confidence interval of the mean decrease in HDL is not the appropriate basis for considering the potential risk to individuals. Individual risk should be based on the mean minus two standard deviations; this number would cover 97.5% of the population. Thus some individuals may experience a considerably larger fall in HDL which amounts to an added concern." The Applicant notes that this also includes the mean plus 2 standard deviations. This means that some people will experience a large rise in HDL-cholesterol and potentially lower their risk. The view expressed is that essentially these changes are measurement noise and need not be considered.	FSANZ notes the Applicant's comment relating to the estimation of individual risk using the mean and SD. This conclusion by the EpiSAG, whilst of interest, was not used in the Assessment Report as a basis for the recommended decision to reject. FSANZ's overall conclusion relates to population risk: that the addition of Tonalin® CLA to the proposed food products would on average lower HDL-cholesterol .
The Applicant's meta-analysis of the effect of consumption of added CLA on HDL-cholesterol levels did not produce a statistically significant effect; there was a non significant reduction of 1.4%. In his view this is similar to that seen after the addition of 5 g of protein or carbohydrate; that is a zero effect.	The Applicant's meta-analysis reports a statistically significant, standardised mean difference of -0.233 mmol/L related to consumption of (mostly) 1:1 CLA isomer mix on HDL-cholesterol ($p<0.001$, Figure 10 in the Applicant's meta-analysis provided to FSANZ). The Applicant further concludes, after an explanation, that this represents a difference of about 5-6% (page 9 of the Applicant's meta-analysis). These numbers are different to what is stated in the current submission.

Issue raised by Applicant	FSANZ'S response
	As FSANZ notes in Section 5.2 of the Assessment Report, the doses used in these studies are small. Studies with either larger numbers of subjects or higher doses are needed to study the effect more definitively. FSANZ's meta-analysis on the effect of consumption of added 1:1 isomer mix (the same CLA preparation as the Applicant's) on blood lipids is detailed in **SD1** and summarised in section 5.2.1 of the Assessment Report. This showed there is a significant effect in lowering HDL-cholesterol relative to other fatty acids (predominantly cis-unsaturated fatty acids)
The Applicant does not believe reductions in HDL-cholesterol should be taken into account when determining CVD risk for the following reasons: 1. There are no data showing that changes in HDL-cholesterol in an intervention changes CVD risk (as opposed to the clear evidence relating to changes in LDL-cholesterol). 2. Saturated fat raises HDL-cholesterol but it does not reduce CVD risk but may actually elevate it. 3. The observations between levels of HDL-cholesterol and CVD risk are very clear in prospective within-country studies i.e. having a low HDL-cholesterol level for people increases CVD risk. But consumers in Asia who have lower HDL-cholesterol by consuming more carbohydrates do not have an increase in their CVD risk (it is lower) compared to consumers in countries with higher HDL-cholesterol that have higher fat intakes.	In response to the three reasons: 1. Section 5.3 of the Assessment Report discusses the relationship of HDL-cholesterol and heart disease risk. In addition, the EpiSAG came to a different conclusion from the Applicant: "the evidence that CLA lowers HDL-cholesterol (HDL) is convincing and raises health concerns at the population level". FSANZ also notes in a recent paper by Knopp *et al*. (2008) that current clinical practice aims to raise HDL-cholesterol to reduce CVD risk. 2. Future studies may reveal whether the lower level of HDL-cholesterol in response to CLA compared to other fatty acids (predominantly cis-unsaturated fatty acids) in the trials reflects a difference in reduction in functional or non-functional HDL. At present the change in HDL-cholesterol compared to other fatty acids is a signal for caution. 3. FSANZ agrees that within-country cohort studies show an inverse relationship between HDL-cholesterol levels and heart disease risk. Between-country studies often have different results from within-country studies because there are a number of differences in addition to variation in HDL-cholesterol levels, such as smoking rates, alcohol consumption and other risk factors not related to diet, which affect cardiovascular disease risk and therefore confound such analysis.

Issue raised by Applicant	FSANZ'S response
LDL-cholesterol	
At the proposed levels of use of CLA (2-2.5 g/day) added to food, Professor Clifton's meta-analysis indicates there is no significant effect on LDL-cholesterol while FSANZ's meta-analysis is of borderline significance. He agrees with FSANZ that CLA appears to exert similar effects on blood lipids to that of TFA, so they should be treated the same. He states that since TFA are not restricted and are counted as saturated fat, CLA should be treated the same. FSANZ has interpreted this statement as meaning the addition of TFA to food is not restricted by the Code.	The significance of the meta-analysis is discussed fully in the Assessment report. FSANZ agrees that the 1:1CLA isomer mix has similar effects on LDL-cholesterol to that of TFA. It seems sensible that the 1:1 CLA isomer mix should be grouped together with TFA and saturated fat with respect to public health advice on intake. Although the Code does not restrict trans or saturated fatty acids, public health recommendations are that the combined trans and saturated fatty acids intakes should be less than 10% energy whereas intakes in Australia and New Zealand are higher than this. Adding Tonalin® CLA to the diet, and grouping it with TFA and saturated fat, as suggested by the Applicant, would increase the intake of this group. This is discussed further in Section 12.1 of the Assessment Report. FSANZ further notes that it has considered TFA levels in the diet and has recommended that non-regulatory approaches were appropriate considering the current levels in Australia and New Zealand and the WHO guideline relating to TFA. Industry action had been effective in reducing manufactured TFA. The absence of a regulatory measure should not be construed as an absence of concern over TFA levels in food.

Issue raised by Applicant	FSANZ'S response
CVD risk	
A recent paper (Smit *et al*., 2010) indicates that CVD risk is reduced by having high adipose tissue levels of the *cis*-9, *trans*-11 CLA isomer (the common form of CLA naturally found in dairy foods). This paper shows that high consumption of dairy products containing this CLA isomer has beneficial effects not harmful ones, despite this CLA isomer not elevating HDL-cholesterol.	FSANZ did not include this paper in the risk assessment because it describes biomarkers of dairy food intake whereas the Applicant is seeking permission to add Tonalin® CLA derived from safflower oil. (Trials using dairy fat as the source of CLA were excluded from the FSANZ meta-analysis for the same reason). In a non-supplemented diet, the *cis*-9, *trans*-11 CLA isomer is derived primarily from dairy foods and other ruminant fat (e.g. beef, lamb). Therefore, the adipose tissue CLA levels measured by Smit *et al*. (2010) in Costa Rica are a marker of dairy food consumption in general, as well as being markers of *cis*-9, *trans*-11 CLA intake in particular. In their case-control study, adipose fat was determined approximately one month after subjects had a heart attack. Finding a favourable association with adipose tissue CLA levels might indicate that the CLA is the responsible factor. Equally, they might indicate that some other component of dairy foods might be the responsible factor. For example, Mozaffarian *et al.* (2010) comment that trans-palmitoleic acid is found almost exclusively in ruminant foods. Their cohort study found lower incidence of diabetes in those consumers (US adults) with higher plasma trans-palmitoleic acid levels, after adjusting for dairy food intake. They propose that this fatty acid, rather than any other component, might be the important factor in dairy foods. As both trans-palmitoleic and CLA are found in dairy/ruminant foods, the results of Smit *et al*. (2010) would reflect an association with this fatty acid as well as the CLA they measured. Tonalin® CLA contains only one of the compounds found in dairy foods (the *cis*-9, *trans*-11 isomer). The other component (the *trans*-10, *cis*-12 isomer) is not found in food to any great extent. Therefore FSANZ believes that it is unclear whether the results of Smit *et al*. (2010) can be extrapolated to Tonalin® CLA.

Issue raised by Applicant	FSANZ'S response
Diabetics	
The Applicant states that EpiSAG "made the point" that CLA had not been "well tested in diabetics".	FSANZ agrees with this statement. In the list of uncertainties in Section 9 of the Assessment Report, FSANZ states that there is a lack of data on the effects of CLA in individuals with pre- and exing type 2 diabetes.
The Applicant disagrees with FSANZ's conclusions in relation to the effect of CLA on 'diabetics' based on the findings in Norris *et al*. (2009) and Moloney *et al*. (2004).	FSANZ's consideration of the effect of CLA on glucose homeostasis is described in detail in SD3. In relation to the two studies referred to by the Applicant (Norris *et al*., 2009; Moloney *et al*., 2004), FSANZ states on p. 16 of SD3 that subjects in these studies that were taking CLA "were more resistant to insulin at the end of the studies compared to controls". The difference between the treated and the control groups was significant (p=0.05) based on changes in HOMA-IR (Homeostasis Model Assessment of Insulin Resistance). These findings were the basis of FSANZ's conclusion that these "two well conducted studies raise safety concerns about the effects of CLA on people with type 2 diabetes". After having regard to the Applicant's response FSANZ concludes that its previous statement remains valid; noting that it is not a definitive conclusion about the safety of CLA in this population group but that the two studies are sufficient to raise concerns about its safety. The EpiSAG came to a similar view. Their analysis and conclusions on this topic are provided in agenda item 4a of the Outcome Notes from the meeting. The EpiSAG concluded "that there is good evidence that CLA is likely to be hazardous for people with type 2 diabetes, based upon the results of two well-conducted studies (Moloney *et al*., 2004; Norris *et al*., 2009) and the adverse effects of CLA on blood lipids".
Fat distribution	
The Applicant disagrees with FSANZ's statements in the Assessment Report dealing with fat loss. The Applicant notes the EpiSAG's conclusion that "The unknown mechanism of effect of CLA on BFM (body fat mass) is an important safety concern because it is a false assumption that any fat loss is good. Some mechanisms and patterns of fat loss may produce harmful effects". The Applicant rebuts this statement by stating that "this is only true for specific cases, being genetic lipodystrophies and HIV induced lipodystrophy. Otherwise a reduction is fat mass leads to a benefit, more so if it is visceral fat rather than peripheral fat".	The EpiSAG's conclusion in relation to the effect of CLA on mechanisms and patterns of fat arose from a discussion of what they considered was the need to distinguish between the effect of CLA on weight loss and its effect on different compartments of body fat. They considered that "if subcutaneous body fat stores are being reduced, but visceral body fat stores are increasing at the same time, the overall effect is bad" and they noted that the available evidence could not distinguish which is taking place (see p. 15 of the EpiSAG Outcome Notes). There was no discussion that this potentially 'bad' effect was restricted to specific cases, but the discussion occurred in the context of all overweight and obese people.

Issue raised by Applicant	FSANZ'S response
DEXA scan and fat distribution	
The Applicant disagrees with FSANZ's view that the DEXA finding of reduced fat content could be due to fat distribution. The Applicant states that "a redistribution will not lower the fat percentage, only loss of fat will do this".	FSANZ agrees that only fat loss will lower the percentage of fat in the body, but argues that the ability to measure fat loss accurately depends on the sensitivity of the method used. In relation to CLA and body fat loss, FSANZ concluded in the SD2 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, FSANZ and EpiSAG members considered that there was uncertainty surrounding this finding. This uncertainty stemmed from the fact that although DEXA is capable of determining redistribution of body mass at the individual level, "DEXA is not capable of detecting small changes in body fat of 1-2 kg". Thus, small changes in body fat without a concurrent loss in body weight as well as unfavourable changes in insulin sensitivity led EpiSAG members to the conclusion that "some of the fat 'lost' may be redistributed to other parts of the body (such as the liver)" (see p. 18 of the Assessment Report).
Inhibition and activation of PPAR gamma	
The Applicant has made note of various studies involving the inhibition or activation of the PPAR gamma receptor.	It is not clear why this information has been provided by the Applicant as no argument has been put forward in support of the Applicant's consideration of the safety of CLA or how it relates to the FSANZ assessment of the Application. Nonetheless, FSANZ has inferred that the Applicant wishes to highlight some purported benefits of CLA related to PPAR gamma inhibition and gene expression involved in 'fat regulation'. Peroxisome proliferator-activated receptors (PPAR) are part of a family of ligand-activated transcription factors involved in fatty acid oxidation and lipid metabolism. To date, three PPAR isoforms have been identified: PPAR alpha, PPAR gamma and PPAR delta. These isoforms have various physiological functions: PPAR alpha is expressed in the liver, heart, skeletal muscle and kidney; and is associated with lipid and lipoprotein metabolism.

Issue raised by Applicant	FSANZ'S response
	PPAR gamma is expressed in white and brown adipose tissue; and is associated with adipocyte differentiation, lipid storage and glucose metabolism. PPAR delta is expressed in many tissues and stimulates fatty acid oxidation. Genome-wide gene expression systems (microarray) such as that conducted by Herrmann *et al*. (2009b) (referenced by the Applicant), have limited utility in terms of ascertaining efficacy or safety, in the absence of proteomic and physiological studies in the key animal species, namely humans. The limited discourse on gene expression and the activation of PPAR gamma by selective CLA isomers does not provide sufficient evidence of a unified mechanism of action or allay the key safety concerns associated with CLA. FSANZ has previously noted in the Assessment Report and in response to issues raised by the Applicant in December 2009, that the mode of action of CLA has been poorly characterised (see Section 5.1.1 of the Assessment Report) and that there is currently limited utility in using inflammatory biomarkers in support of CLA purported benefits (see Section 5.4.1 of the Assessment Report). So while Reynolds and Roche (2010) (quoted by the Applicant) noted "Evidence suggests that c9,t11-CLA is responsible for the anti-inflammatory effect attributed to CLA while t10, t12-CLA appears to be responsible for anti-adipogenic effects" the same authors also conclude that "Whilst CLA may ameliorate certain aspects of the inflammatory response, particularly within cellular and animal models, the relevance of this has yet to be clarified within the context of human health".
Atherosclerosis/inflammation	
The Applicant has made note of four animal-based studies on the regression of atherosclerosis and the prevention of inflammation-driven colorectal cancer.	It is not clear why this information has been provided as no argument has been put forward in support of the Applicant's consideration of the safety of CLA or how it relates to the FSANZ assessment of the Application. Nonetheless, FSANZ has inferred that the Applicant wishes to highlight some purported benefits of CLA related to the regression of atherosclerosis and the prevention of a form of cancer. Unfortunately, the information is too limited in nature to fully characterise the purported benefits of CLA in these disease settings in animals. Importantly, the relevance to human health has not been established and does not ameliorate the concerns associated with CLA's effects on blood lipids.

Issue raised by Applicant	FSANZ'S response
Dr Albert Bär's comments	
European and US experience as food supplements	
The Applicant queries why FSANZ did not mention the Applicant's submissions to EFSA in its updated Assessment Report (and suggests that the reason may be that the Applicant provided them as commercial-in-confidence). These were three submissions the Applicant provided to EFSA to address specific areas of concern. These documents were provided to EFSA after the Applicant had provided their submission to FSANZ's request for more information to address FSANZ's concerns on 1 December 2009, so they were thought to be relevant for FSANZ to also consider. The Applicant also mentioned a fourth, earlier, document provided to EFSA dated 23 June 2009.	On 2 June 2010, the Applicant sent FSANZ the three submissions that it had provided to EFSA to address specific EFSA concerns that are noted in this submission. These three documents are referred to as (b), (c) and (d) in the Applicant's current submission, being dated 18 January 2010, 8 February 2010 and 24 March 2010. The three documents were provided to the FSANZ Board, along with a summary of the issues contained in them and FSANZ's response in June 2010. FSANZ notes that the issues raised in the submissions the Applicant provided to EFSA have been addressed during FSANZ's assessment. FSANZ has no record that it received a copy of the fourth document (report (a), dated 23 June 2009 in the current submission). However it did receive a detailed response to a request from FSANZ for more information from the Applicant on 15 June 2009, which was used in FSANZ's consideration of the Application. The conclusion was that the additional information in the three documents did not provide any new arguments that would alter FSANZ's conclusions. EFSA's opinion on the CLA applications is noted in the FSANZ Assessment Report.
The Applicant notes that in Europe "CLA may be used in food supplements as not-novel food". Member states were asked by the European Commission whether there had been any adverse events from this use and the Applicant states "No such events were reported". The Applicant indicates this is also the same situation in the US "where CLA is sold in food supplements in significant amounts, adverse effects have not been reported".	Diabetes and heart disease have a number of risk factors (and long latency periods) and it would require large scale long-term epidemiological studies to make causal links between supplement CLA intake and incidence, especially given programs to reduce or manage other risk factors such as trans and saturated fat intakes, smoking rates and cholesterol and blood pressure control. FSANZ therefore concludes that the lack of reports of adverse effects where Tonalin® CLA has been marketed to date is not sufficient to assure safety. As noted above, the Applicant has requested Tonalin® CLA be assessed in Europe under European novel food regulations.

Issue raised by Applicant	FSANZ'S response
Cholesterol	
The Applicant notes that there are three meta-analyses that evaluated the effect of consumption of added CLA on blood lipids. The results differ slightly but all are small in absolute terms. It is noted that studies with disease or death outcomes are preferable to studies of biomarkers. The Applicant notes recent analyses showing that "there is no or only weak evidence for concluding that the intake of saturated fat (SFAs) is associated with an increased risk of CHD or CVD (Siri-Tarino *et al*., 2010, Mente *et al*., 2009)". There is also debate about whether replacing SFAs with mono-unsaturated fatty acids (MUFA) is beneficial (Astrup *et al*., 2011, Mente *et al*., 2009) and that linoleic acid was tentatively identified as a risk factor in three studies (Skeaff and Miller, 2009). The Applicant further notes a review showing that dairy foods are beneficial for metabolic syndrome (Crichton *et al*., 2011). The Applicant indicates that the one thing these studies agree on "that more research is needed to clarify the role of different dietary fats in comparison to other fats and/or different types of carbohydrates on factors that could influence CHD risk". The Applicant's view is that the effect of CLA on CVD risk factors is small and would be within the range of changes that occur with regular food components.	FSANZ agrees that disease and death outcomes are always preferable when looking for causal associations, but as the 1:1 isomer mix is new, such studies are not available. Currently, studies of the accepted biomarkers for CHD, metabolic syndrome etc are the best available evidence. Like others previously, Siri-Tarino *et al*. (2010) comment that the effect of saturated fatty acids on disease depends on what macronutrient replaces it. This is outlined in SD1. Siri-Tarino *et al*. (2010) conclude "Evidence from clinical trials and prospective epidemiologic studies support the cardiovascular benefit of substituting polyunsaturated fat for saturated fat, but the benefit of reducing saturated fat below 9% has not been evaluated". They argue that dietary guidance which focuses on reducing total fat intake in the population and increasing carbohydrate intake needs to be questioned because few studies show benefit if saturated fat is replaced with carbohydrate. They note that consumption of refined carbohydrate has some undesirable effects on lipid levels. Mente *et al*. (2009) concluded that there was strong evidence for a protective effect on CHD of MUFA and an adverse effect of TFA from cohort studies and that the evidence was less strong for saturated fats. The evidence for the protective effect of poly-unsaturated fatty acids (PUFA) came from trials. FSANZ notes that it is not clear how well the issue of iso-energy replacement was dealt with in this analysis. Skeaff and Miller (2009) reviewed cohort studies and controlled trials with heart disease endpoints. They report variable results for the cohort studies and comment that errors in reporting would reduce the strength of any true associations. When trials which replaced SFA with PUFA were examined there was a significant 20-50% reduction in heart disease incidence, cardiac death and total mortality.

Issue raised by Applicant	FSANZ'S response
	These conclusions have also been supported by an independent expert panel FSANZ convened to assess these issues, as noted in the EpiSAG Outcome Notes. FSANZ believes that the effect of the 1:1 CLA isomer mix on HDL- and LDL-cholesterol is approximately the same as would be predicted if unsaturated fats were replaced with TFA on an equal energy basis (see **SD1** and Sections 5.2 and 5.3 of the Assessment Report). 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. As noted above in the response to Professor Clifton's comments, the finding that dairy foods do not seem to have the effects that would be predicted from their saturated fat content is not new. FSANZ notes that dairy foods contain many substances not found in Tonalin® CLA manufactured from safflower oil that is the novel food being assessed.
Insulin sensitivity	
The heading in the Applicant's submission is TFAs, but the issues raised are related to insulin sensitivity. The Applicant provided analysis from scientific studies that consumption of TFA (dairy, as well as industrial) provided very little convincing evidence that consumption of TFA as part of a standard western diet contributes to the risk of diabetes or insulin resistance. The Applicant also made the same argument relating to the effects of consumption of CLA on insulin sensitivity, as provided in its communications to EFSA which were forwarded to FSANZ in June 2010. The Applicant concludes that CLA consumption has no adverse effect on glucose homeostasis and insulin sensitivity, in either healthy or overweight and/or diabetic subjects. The Applicant refers to five studies in support of this conclusion (Norris *et al*., 2009, Asp *et al*., 2011 Gaullier *et al*., 2004, Schrezenmeir, 2006 and Herrmann *et al*. 2009a).	FSANZ's response is focused on the effect of the 1:1 isomers of CLA on insulin sensitivity; not TFAs (from dairy or industrial sources) and their potential effect on insulin sensitivity. FSANZ's review of the evidence of the effect of CLA on glucose homeostasis (described in detail in SD3) included 20 human studies of CLA with the *cis*-9, *trans*-11 and *trans*-10, *cis*-12 isomers in a 1:1 ratio. The studies of Norris *et a*l. (2009) and Gaullier *et al*. (2004) were included in SD3. FSANZ concluded that "the available data raises questions but do not permit a conclusion about the effect of CLA on glucose homeostasis in the general population" but that "two well conducted studies raise safety concerns about the effects of CLA on people with type 2 diabetes". One of the well conducted studies was Norris *et al*. (2009).

Issue raised by Applicant	FSANZ'S response
	Herrmann *et al*. (2009a) is an unpublished report that was made available to FSANZ in June 2010. This paper is a meta-analysis of seven studies that investigated the effect of CLA on insulin resistance. The results showed no effect on insulin resistance assessed as HOMA-IR when comparing CLA with placebo. However, this meta-analysis included study participants both with and without diabetes. As the presence of diabetes might well affect the results combining these studies could obscure results in an important group. As stated above, FSANZ's own systematic review of the literature found no significant results in studies involving healthy subjects but did raise concerns about the effect of CLA on people with type 2 diabetes. Asp *et al*. (2011) was published after FSANZ completed its risk assessment of CLA and Schrezenmeir (2006) is an unpublished report. Asp et al. (2011) is a second analysis from Norris *et al*. (2009) described in SD3; hence some data from this study are already included in FSANZ's review. Asp *et al*. (2011) report additional results for the effect of CLA on glucose homeostasis including QUICKI, HbA1c and OGTT (which are indirect measures of insulin sensitivity) that were not reported in Norris *et al*. (2009). As noted in SD3, "QUICKI is proportional to 1/log(HOMA)". Therefore, the non-significant decrease in QUICKI reported by Asp *et al*. (2011) is essentially the same adverse finding as the increase in HOMA-IR reported by Norris *et al*. (2009). Asp *et al*. (2011) also report a significant increase in HbA1c (p=0.03), and higher 2-hour post-prandial glucose level following OGTT (p=0.05) for CLA versus safflower oil. Thus, Asp *et al*. (2011) provides additional detail of adverse effects on glucose homeostasis and insulin sensitivity in obese diabetic women from the study by Norris *et al*. (2009). This is contrary to the opinion of the Applicant in interpreting the findings in this paper. Schrezenmeir (2006) calculated the HOMA-IR index using the original data from the 12-month-long study by Gaullier *et al*. (2004). The study investigated the effect of the 1:1 isomers of CLA (both triacylglycerol and free fatty acid forms). Schrezenmeir (2006) reported that neither CLA form had a significant effect on HOMA-IR compared to the control group. FSANZ notes this finding but reasserts its main concern which is the potentially adverse effect of CLA on people with type 2 diabetes. The Gaullier study, and therefore Schrezenmeir's analysis, were undertaken on healthy, overweight participants.

Issue raised by Applicant	FSANZ'S response
Fat deposition in the liver	
A recent human study indicates that high daily consumption of TFA does not affect liver fat deposition. A human study with high daily intakes of CLA (different isomer composition to the Applicant's preparation, being 4:1 *cis*-9, *trans*-11: *trans*-10, *cis*-12) also showed CLA had no adverse effects on liver function related plasma parameters.	FSANZ agrees with the analysis noted by the Applicant on these studies, but they do not address any of the risk assessment concerns raised by FSANZ, since liver fat deposition was not a particular concern FSANZ noted in the assessment. FSANZ notes on p. 14 of the Assessment Report that the effect of fatty degeneration of the liver has not been addressed when CLA is consumed for periods of longer than six months. This was a conclusion from EFSA's CLA assessment in 2010. As noted, FSANZ excluded studies that dealt with the consumption of TFA in general since the assessment was conducted on CLA.
Other risk assessment and risk management comments	
The Applicant, while disagreeing with the overall risk assessment conclusions of FSANZ, proposes different precautionary risk management options to address the concerns. These options would be to limit the use of the CLA preparation to specified foods and in specified amounts. One suggestion is for FSANZ to permit CLA to be added to foods which are cholesterol free, since the Applicant believes the overall consumption of such food would have an overall positive effect on cholesterol intake.	FSANZ investigated various risk management options to manage the risks identified from its risk assessment in Section 11 of the Assessment Report. FSANZ's consideration of the effect of restricting the range of foods to which CLA can be added is outlined in Section 11.1 of the Assessment Report. FSANZ's main concern with this risk management approach is that there are no appropriate ways food regulators have of restricting/limiting consumption of these products by consumers who are at an increased risk. Vulnerable consumers include people with type 2 diabetes, pre-diabetes or people already at risk of cardiovascular disease. FSANZ would have similar concerns in the case of permitting the addition of CLA to "cholesterol-free" (or other highly defined) foods only. The Applicant has not provided any evidence to indicate that these risk management options would be effective in limiting intake to only those consumers at low risk.

Issue raised by Applicant	FSANZ'S response
The Applicant proposes that recommendations of use should be mandatory for foods containing added CLA.	This is taken by FSANZ to mean the Applicant proposes statements be added to labels of foods containing added CLA, though it does not indicate what statements would be appropriate. Section 11.3 of the Assessment Report addresses whether the use of advisory labelling would be an effective risk management measure. The Applicant has not provided any evidence that labelling would be an effective measure in addressing the specific concerns discussed in that section.
The Applicant disagrees with FSANZ's risk assessment conclusion that there are safety concerns about the consumption of added CLA to food for people with type 2 diabetes. However, to risk manage these concerns, the Applicant suggests labelling as an appropriate response, such that people with type 2 diabetes should consult their doctor when consuming a food containing added CLA.	See above.
The Applicant acknowledges that there may be people with undiagnosed type 2 diabetes who might consume food with added CLA. They note however that there are many other foods available that have no general warning label, such as foods with a high glycemic index, or a high cholesterol level which pose a risk to people with undiagnosed diabetes. A risk management option FSANZ could use to address this concern is to only permit added CLA to foods with a low or medium glycemic index.	FSANZ's response to this suggested risk management option is essentially the same as that noted above dealing with the suggestion of permitting CLA to be added to "cholesterol free" food i.e. there is no evidence of the effectiveness of such an approach. Section 11.1 of the Assessment Report addressed the management option of restricting the range of foods to which CLA can be added.

References

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