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

SUPPORTING DOCUMENT 7

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

Summary of issues raised by the Applicant in December 2009 and FSANZ's response

Issue raised by Applicant	FSANZ's response
Blood lipids	
The Applicant concludes from a number of studies in the literature that consumption of Tonalin® CLA by healthy, overweight, obese or type-2 diabetic subjects was without adverse effects on fasting blood lipid levels. The Applicant asserts that the information and analysis provided "'demonstrates that Tonalin® CLA under the intended conditions of use (consumption of 4.5 g per day) does not unfavourably affect the human blood lipid profile".	FSANZ's consideration of the effect of CLA on blood lipids is provided in **SD1** and is summarised in Section 5.2 of the Assessment Report. The Applicant has not provided suitable studies to demonstrate the safety of consumption of added CLA to the diet to refute the risks identified relating to CLA's effect on key blood lipids and the risk of cardiovascular disease.
The Applicant however believes that the impact of changes in HDL-cholesterol levels on cardiovascular risk is very contentious. The Applicant provides a number of examples to highlight why this is the case, as well as some recent references to support their view. The Applicant concludes from relevant research over the last five years "that it is not the absolute level of HDL cholesterol that is important but the behaviour of the HDL". The Applicant further states that "any evaluation of a dietary intervention needs an HDL functional measure not just cholesterol".	In terms of public health and safety, FSANZ takes into consideration the well-characterised and internationally recognised data and clinical experience associated with plasma cholesterol levels as the key indicator of cholesterol-linked cardiovascular disease. Plasma/serum levels of lipoprotein-cholesterol, including HDL-cholesterol level, are well characterised and internationally recognised as key indicators of cholesterol-linked cardiovascular disease. Further discussion of this issue is noted in Section 5.3 of the Assessment Report. Importantly, there is no empirical evidence to indicate that CLA has any cardio-protective effects. The argument relating to functional HDL derives from the hypothesis that the increase in HDL-cholesterol level seen with saturated fats may not reflect an increase in beneficial (i.e. functional) HDL-cholesterol. As CLA decreases HDL-cholesterol levels, a 'functional' argument would need to propose that only non-functional HDL-cholesterol is affected by CLA and the functional HDL-cholesterol is unaffected. No data has been presented showing this and so FSANZ is only able to examine change in total HDL-cholesterol levels.

Issue raised by Applicant	FSANZ's response
The Applicant comments that at the dosages specified, Tonalin® CLA has no significant effect on LDL-cholesterol levels and that FSANZ should not describe the result of the meta-analysis as a 'possible' effect.	FSANZ notes that it has used the term 'probable' not 'possible' to apply to its overall conclusion about the effect on LDL-cholesterol. The wording has been amended from that previously seen by the Applicant to clarify that FSANZ regards its conclusion of an effect of the 1:1 isomer mix on LDL-cholesterol, is 'probable' based on several sets of studies including a dose-response analysis of studies that used the two isomers alone or in any ratio. As well, an appropriately powered study using a higher dose of the 4:1 (*cis*-9, *trans*-11: *trans*-10, *cis*-12) CLA isomers also increased LDL-cholesterol to a higher level of statistical significance. When the findings of all studies of different CLA isomer ratios were combined there was also a statistical significant increase in LDL-cholesterol further supporting the findings of the meta-analysis. This is further explained in **SD1** and Sections 5.2.2 and 5.2.3 of the Assessment Report.
The Applicant notes that *trans* fatty acid (TFA) (in particular non-conjugated trans fatty acids, such as partially hydrogenated vegetable oils) at higher levels of intake do have an adverse effect on blood lipids by elevating LDL-cholesterol and lowering HDL-cholesterol levels in a dose-dependent manner. However, they note that there is no dose-response relationship noted in the small lowering effect of CLA on HDL-cholesterol level. They further note that under the intended conditions of use (FSANZ believes the Applicant means this to refer to the amount suggested for daily consumption to achieve the stated purpose; i.e. 4.5 g/day of Tonalin® CLA) CLA has no significant effect on LDL-cholesterol. The Applicant noted that the meta-analysis they commissioned did not find a dose-response relationship for HDL-cholesterol and that FSANZ has not examined this.	FSANZ has addressed this issue in detail in **SD1**, including the dose-response assessment of CLA isomers, following the EpiSAG meeting. FSANZ notes that the meta-analysis commissioned by the Applicant included studies and abstracts published up till 1 March 2009. Despite including the high dose trial of Wanders *et al*. (2008), which used approximately 23 g CLA/day in a 4:1 isomer ratio, the results were adjusted back to a dose of 5 g. Consequently, the Applicant's meta-regression did not examine the full range of doses that have been tested in the studies that they included. Further, the meta-analysis commissioned by the Applicant does not describe how the lack of dose response was assessed, e.g. there is no presentation of any statistics or a beta-coefficient for the slope/lack of slope. More recently, Brouwer *et al*. (2010) have also examined the dose-response relationship of the 1:1 and other ratios of the CLA isomers across the full range of doses tested. Unlike the other meta-analyses, they restricted their studies to those in which subjects had stable body weight and also recalculated the results of all studies to account for the different fatty acid profiles of the control fats used.

Issue raised by Applicant	FSANZ's response
	They report a significant increase in LDL-cholesterol level and a non-significant decrease in HDL-cholesterol level and a significant increase in the LDL/HDL ratio across the range tested (up to 7% energy or approximately 23g CLA in a diet of 9270kJ) when compared to *cis*-mono-unsaturated fatty acids.
Tonalin® CLA as a TFA	
The Applicant notes that the definition of *trans* fatty acid in the Code for labelling purposes (within Standard 1.2.8 – Nutrition Information Requirements) is different and inconsistent with that used in a variety of international and overseas definitions. They indicate that "under Codex Alimentarius, FDA [the US Food and Drug Administration], European and other representative definitions, conjugated linoleic acid isomers are excluded from the definition of trans fat". "Thus FSANZ's statement that Tonalin® CLA is accurately described as a trans fat is true locally but not at an international level".	FSANZ addresses the chemistry and structure of CLA in Section 2.2 of the Assessment Report. FSANZ has not made any distinction relating to CLA and *trans* fatty acid definitions, neither within the Code nor from other international regulatory definitions. FSANZ has indicated that chemically CLA is a TFA since it contains a *trans* double bond within its chemical structure. This is the case for all the various CLA isomers. However, FSANZ has not used its labelling classification of CLA as a TFA, based on structure, to make the determination that CLA has an adverse effect on lipid levels. FSANZ examined the trials in humans to determine the effect on lipids. FSANZ concluded, based on studies published up to April 2010 (detailed in **SD1**), that there is an adverse effect. FSANZ concludes that, based on the currently available evidence, the 1:1 isomer mix of CLA affects HDL- and probably LDL-cholesterol levels adversely and in a direction that is similar, but not necessarily identical, to that of TFAs. This is quite different from the effect of *cis*-polyunsaturates, monounsaturates and saturated fats.
Cardiovascular disease risk	
The Applicant has asserted that cholesterol levels *per se* are not as important to the assessment of cardiovascular risk because increasing the amount of HDL-cholesterol does not reduce the risk of cardiovascular events (Ornish *et al*., 1998; Briel *et al*., 2009)	High levels of plasma/serum LDL-cholesterol and lower concentrations of HDL-cholesterol are strongly associated with cardiovascular disease, due to the development of atherosclerosis (Frishman, 1998). Population studies have consistently demonstrated an inverse association between HDL-cholesterol levels with the risk of coronary heart disease (Sharma *et al*., 2009; Natarajan *et al*., 2010).

Issue raised by Applicant	FSANZ's response
	The applicability of the Applicant's arguments to provide direct support for the safety of CLA in the entire population is uncertain. This argument is discordant with the generally well accepted and supported prognostic and treatment paradigms from around the world that are based on the clear association between plasma/serum cholesterol levels and cardiovascular risk, including HDL-cholesterol. Further details are provided in Section 5.3 of the Assessment Report.
Inflammatory biomarkers	
HDL-cholesterol can act as either a pro-inflammatory, atherogenic species or a protective molecule depending on dietary intervention (Roberts *et al*., 2006; deGoma *et al*., 2008).	While a number of inflammatory markers, both anti- and pro-inflammatory in nature, have been associated with cardiovascular disease, this area of inflammation research is still insufficiently developed to support evidence based medicine (Lowe, 2005; Libby *et al*., 2009) (see Section 5.4.1 of the Assessment Report). It should be noted that a number of inflammatory mediators have been found to be associated with changes to the risk profile for cardiovascular disease in humans, including the pro- and anti-inflammatory behaviour of HDL-cholesterol. This is an ongoing, complex area of scientific and clinical research. The potential merits for using these inflammatory markers to drive diagnostic and/or therapeutic interventions have been discussed in a number of literature reviews (Wilson, 2004; Savoia and Schiffrin, 2006; Ridker, 2007; Ramos *et al.*, 2009). Further details are provided in Section 5.3 of the Assessment Report.
Body composition	
FSANZ's conclusions about the effect of Tonalin® CLA on body composition are incorrect and inconsistent with the current scientific literature. In particular, FSANZ's conclusions are at odds with the meta-analysis performed by Whigham *et al*. (2007) that concluded that CLA does have a beneficial effect on body composition.	FSANZ's consideration of the effect of CLA on body composition is provided in Sections 6.1.1 and 6.1.2 of the Assessment Report and in SD2.

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