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Attention: Mr. D. Stockwell – General Manger, Food Standards (Wellington)
Food Standards Australia New Zealand
PO Box 7186
Canberra BC, ACT 2610

1 December, 2009

Dear Mr Stockwell,

re: Application A1005 – Exclusive Use of Tonalin® CLA as a Novel Food

I refer to your correspondence dated 10 November 2009 (and previous correspondence dated 19 September 2009 and 28 September 2009) concerning the above application. In collaboration with Bioresco Limited (the regulatory affairs consultant for Cognis GmbH, applicant for this application) we submit the following in response to the Preliminary Assessment Report.

Classification:

According to the Australia New Zealand Food Standards Code, *trans* fatty acids means the total number of unsaturated fatty acids where one or more of the carbon-carbon double bonds are in the *trans* configuration. In contrast, the Codex Alimentarius Commission, of which Australia is a member, agreed in November 2004 that *trans* fatty acids are defined as all the geometrical isomers of unsaturated fatty acids having non-conjugated carbon-carbon double bonds in the *trans* configuration. Correspondingly, the US FDA defines *trans* fatty acids as all unsaturated fatty acids that contain one or more isolated double bonds in a *trans* configuration. Thus under Codex Alimentarius, FDA, European and other representative definitions, conjugated linoleic acid isomers are excluded from the definition of *trans* fat. Thus FSANZ' statement that Tonalin® CLA is accurately described as *trans* fat is true locally but not at an international level.

Effect on Blood Lipids:

Non-conjugated *trans* fatty acids, particularly those present in partially hydrogenated vegetable oils, have, at higher levels of intake, an adverse effect on blood lipids by elevating LDL-cholesterol and lowering HDL-cholesterol in a dose-dependent manner. However, both Professor Clifton's meta-analysis and the meta-analysis conducted by FSANZ demonstrate that CLA, under its intended conditions of use, has no significant enhancing effect on LDL cholesterol. The small lowering effect on HDL cholesterol exhibits no dose-response relationship according to Prof. Clifton's analysis. FSANZ has not examined this dose-response relationship. Thus, FSANZ'

statement that the effect of Tonalin CLA on blood lipids is consistent with the behaviour of a trans fatty acid, lacks substantiation. Professor Clifton has reviewed FSANZ' Preliminary Assessment Report and S1 report and has provided a detailed response to these reports in respect to effects on blood lipids, copy of which is attached. I would refer you also to comments provided by Dr Bär in his previous response (4/6/09).

Current use of CLA in the EU:

In the EU, CLA may be used, and is used, in food supplements as a not novel food (significant consumption of CLA in this application has occurred prior to 15 May 1997). In Spain, the use of CLA in liquid yoghurt, milk, processed cheese and orange juice was granted in 2004/2005. Milk with added CLA is consumed in significant amounts since then without interruption. An application for authorization of CLA for use in a variety of foods is pending. The European Food Safety Authority (EFSA) is currently assessing the safety of CLA under its intended condition of use. On an earlier occasion, EFSA has stated already that there is no evidence of adverse effects of CLA supplements containing mixtures of the t10,c12 and c9,t11 CLA isomers (EFSA, 2004).

Expert Opinion:

In addition to the expert opinion provided by Professor Peter Clifton in respect to the safety of CLA for the intended purpose, the five independent scientific experts that formed the GRAS Expert Panel for evaluation of CLA-rich Oil also concluded that Tonalin® CLA (and Clarinol^{R} CLA) is safe under its intended conditions of use. A copy of the GRAS report was provided to FSANZ and I would refer you specifically to the Expert Panel's comment in respect to cardiovascular disease risk. Note that the US FDA have accepted this report with no further questions (GRAS Notice No. GRN 000232).

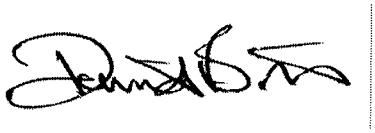
Efficacy:

FSANZ claims in its Preliminary Assessment Report (SD2) that the effect of CLA intake on bodyweight and body composition is equivocal and that the evidence available is not sufficient to conclude that Tonalin CLA at the intake proposed would achieve the stated purpose. However, it appears that the meta-analysis by Whigham (2007)[1] which concluded that CLA does have a beneficial effect on body composition, has not been considered by FSANZ. We refer you also to the respective comments by Professor Clifton in his report.

Standard 1.5.1 (Novel Foods) is a standard primarily concerned with safety. We have demonstrated the safety of Tonalin® CLA at the proposed use levels and for its intended purpose. Any decision to reject the application would be out of step with international regulation (creating an artificial trade barrier), incorrect in terms of the international scientific consensus as to safety, and inappropriate ahead of the EFSA report. Thus, we urge FSANZ to reconsider the recommended decision in the Preliminary Assessment Report and recommend approval as requested by this application.

Yours sincerely

D.L.Bill



c.c.
Dr.A.Bär – Bioresco Limited, Basel, Switzerland

1. Leah D Whigham, Abigail C Watras, and Dale C Schoeller (2007) Efficacy of conjugated linoleic acid for reducing body mass: a meta-analysis in humans. *Am J Clin Nutr* 2007;85:1203-11

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Response to FSAZ Assessment of CLA-application A1005.

Peter Clifton Bakeridi Heart and Diabetes Institute.

FSANZ proposes to not allow the use of CLA on the basis of adverse effects on lipids, namely a lowering of HDL cholesterol and a possible elevation of LDL cholesterol. I believe FSANZ is wrong on both counts.

LDL cholesterol.
The meta analysis conducted by FSANZ and by the applicant shows that Tonalin CLA at the dosages specified has no significant effect on LDL cholesterol. The effect was smaller than 2% and was not significant. It is therefore not scientifically correct to say there is a "possible" effect. On conventional statistical grounds there is no effect and this has been shown in a large meta analysis. A statement about a "possible" effect would be rejected by a high ranking journal.

HDL cholesterol.
Whether changes in HDL cholesterol induced by dietary change have any effect on cardiovascular risk is a very contentious issue and it is not at all clear as FSANZ imply. A very simple illustration shows the dilemma. Saturated fat is very powerful at elevating HDL cholesterol and no one advocates saturated fat for CVD prevention. Replacing saturated fat with carbohydrate lowers HDL cholesterol and there is evidence from the Dean Ornish low fat studies that this lowering of HDL cholesterol does not have a negative impact on the benefit seen in coronary regression and clinical events (Ornish et al 1998). In addition a meta analysis of 108 randomised trials with 299,310 showed association between treatment induced change in HDL cholesterol on cardiovascular events after adjustment for changes in LDL cholesterol(Briel et al 2009). Thus available data suggest that merely increasing the amount of HDL cholesterol with a drug (or diet) does not reduce the risk of cardiovascular events.

If Tonalin CLA replaced carbohydrate in a food product HDL cholesterol would not change if the original or modified product were consumed. This scenario would apply to fruit juices, fruit products and high sugar desserts and toppings

If Tonalin CLA replaced saturated fat in a food product then HDL cholesterol would fall if 100g of the modified product was consumed compared with the original product. Given the known effects of saturated fat it is very unlikely that the cardiovascular risk associated with consuming the Tonalin modified product would

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increase. This scenario would apply when Tonalin is added to full or reduced fat dairy products

If Tonalin CLA replaced monounsaturated fat then HDL cholesterol would fall as above but CVD risk would be very unlikely to change given the work of Briel et al. This would apply to monounsaturated fat rich margarines and spreads.

If Tonalin CLA replaced polyunsaturated fat then it is possible that CVD risk associated with the modified food might increase marginally as linoleic acid has been associated with cardioprotection and CLA does not behave like a cis polyunsaturated fat and probably does not have the cardioprotection of linoleic acid. Thus it is suggested that Tonalin CLA not replace polyunsaturated fat but replace some other component in a polyunsaturated fat-rich spread or margarine.

What has become clear over the last 5 years is that it is not the absolute level of HDL cholesterol that is important but the behaviour of the HDL. HDL can be converted to a pro inflammatory, atherogenic species by feeding saturated fat and conversely low fat diets and exercise can convert HDL to a protective molecule despite a fall in HDL cholesterol (Roberts 2006, DeGoma 2008) so any evaluation of a dietary intervention needs an HDL functional measure not just cholesterol. For instance a high carbohydrate diet lowers HDL cholesterol compared with poly, mono and saturated fat but the effect on FMD is similar to both unsaturated fats but FMD twice the value seen compared with a saturated fat die (Keogh et al 2005).

Role of Tonalin weight loss.

I agree with FSANZ that the effect is small but the Wigham 2007 meta analysis shows a clear effect with a reduction in fat mass for the CLA group alone (0.05 +/- 0.05 kg/wk; P<0.001) and for the CLA group compared with placebo (0.09 +/- 0.08 kg/wk; P<0.001) so the statement that CLA is not fit for purpose is incorrect.

30/11/09

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