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From: [redacted]
Sent: Monday, 4 April 2011 11:34 AM
To: [redacted]
Cc: [redacted] Contact Bioresco
Subject: A1005 CLA: Response to FSANZ Panel Report

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Dear [redacted]

Thank you for your patience while we finalised this response.

I refer to your request for comment on the findings of a panel convened by FSANZ in relation to the safety of conjugated linoleic acid (CLA) as part of the FSANZ assessment of Application A1005.

I attach -

(1) A report from Professor Peter Clifton that sets out the scientific concerns we have with the panel's findings. Professor Clifton MMBS B Med SCi, MRCP, FRACP, PhD is a physician who treats patients with heart disease, obesity, type 2 diabetes and lipid disorders and works in research at Baker IDI Heart and Diabetes Institute. He has run a lipid clinic at Flinders Medical Centre for the last 25 years. His PhD was on HDL cholesterol and much of his research (over 200 papers) has been focused on lipid metabolism. He has consulted to FSANZ on plant sterols. His expertise and experience in this area cannot be dismissed.

(2) A commentary on FSANZ safety assessment by Dr Albert Barr of Bioresco (Bioresco is a regulatory affairs consultant to the Applicant Cognis).

In addition to these attachments, we make three further submissions-

(a) There appears to be something of a simplistic "demonisation" of CLA as being a trans-fat. The Applicant insists that the assessment of CLA must address its specific characteristics rather than resort to what is little more than unscientific name-calling. In particular, general statements about the function and/or effect of trans fats should not form part of FSANZ's assessment unless it can show that CLA itself has such function or effect.

(b) As you will not doubt be aware, there has been a delay in the European Union's consideration of CLA. While EFSA has provided what is in general a positive safety assessment of CLA (provided to you previously), the EU approval anticipated in March has been deferred to later this year. The Applicant remains of the view that the safety concerns in FSANZ's assessment report are most appropriately addressed through controls over labelling and end food use, rather than through denial of market access. While the Applicant understands that FSANZ is not obliged by its legislation to follow the EU lead, the Applicant is concerned for international

harmonisation to ensure that any such controls in different countries align to the greatest extent possible. Until the EU finalises its approach to CLA, the Applicant is not in a position to provide FSANZ with any submissions on such controls in the Australian context. The EU consideration of CLA is a matter beyond the control of the Applicant, and the Applicant's inability to provide information, within the timeframe required by FSANZ, on how such controls might address FSANZ's concerns should not be held against it. The Applicant still wishes to provide FSANZ with submissions on this point as soon as the EU consideration is finalised, and requests that any finalisation of FSANZ's assessment of A1005 be deferred accordingly.

(c) A further point is that A1005 is an application for novel food approval. It has been under consideration by FSANZ now for many years. In the intervening time, products containing added CLA have been sold in the New Zealand market as dietary supplements under the New Zealand Food Act. Given that the definition of "novel food" excludes foods that have a history of consumption in Australia or New Zealand, it is likely that at some point in time CLA will no longer be a "non-traditional food" requiring novel food permission and accordingly will be available for free use in foods without restriction. As stated at (2) above, the Applicant would prefer a sensible risk management approach to CLA that sees FSANZ's concerns addressed through labelling and/or end food use controls. However, foods containing CLA will remain on the market in New Zealand as dietary supplements, and it would be somewhat incongruous for FSANZ to totally deny market access for an ingredient that may in fact become freely available for sale in the not too distant future.

For completeness, this response is provided without prejudice as to the Applicant's rights under administrative law. In particular, the formation and briefing of the external panel without any input or involvement of the Applicant, and contrary to a written undertaking from FSANZ, remains of deep concern such that any use of the panel's findings is considered by the Applicant sufficient to taint any outcome. The fact that the panel's findings has been provided to us for comment, and our response attached, does not overcome this basic flaw in process and in providing the attached response, the Applicant should not be taken to have waived or diminished its concerns and rights in this regard.

Please contact either myself or [redacted] if you wish to further discuss anything raised in this response.

Yours faithfully

[redacted]

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Professor Peter Cliftion's Comments.

[1] HDL cholesterol.

"The evidence that CLA lowers HDL-cholesterol (HDL) is convincing and raises health concerns at the population level. 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 corollary of this kind of argument is that some people will experience a large rise in HDL cholesterol and potentially lower their risk. These changes are essentially measurement noise and need not be considered.

Certainly HDL falls in comparison with other kinds of fat but the addition of CLA per se to a person's diet does not produce HDL to fall and this has not been seen in my meta analysis where there was a non significant 1.4% fall in HDL cholesterol after the addition of CLA. This is similar to what would be seen with the addition of 5g of protein or carbohydrate ie a zero effect.

I don't think the fall in HDL in comparison with fat should be taken into account in calculating CVD risk. 1. there is no data that changing HDL up or down in an intervention changes CVD outcomes (as opposed to clear evidence with LDL). 2. Saturated fat is a potent HDL elevator but does not reduce CVD risk and may elevate it. 3. The observations between HDL and CVD outcomes are very clear in prospective within country studies ie having a low HDL cholesterol is bad. Lowering HDL cholesterol by eating more carbohydrate as in Asia does not increase CVD (in fact it is lower) in comparison with countries with higher fat intakes and higher HDL cholesterol.

[2] LDL Cholesterol

"CLA exerts effects on blood lipids that are similar but possibly not identical to the effects of TFA based on the limited data available"

Probably true-hence they should be treated the same. TFA are not restricted and are just counted as saturated fat. CLA could be treated in the same way. At the levels (2-2.5g/d) suggested for food there would be very little effect on LDL cholesterol as my meta analysis shows no significant change and the FSANZ meta analysis is of borderline significance.

[3] CVD risk.

More importantly CVD risk is actually decreased by high adipose tissue levels of 9c, 11t by 49% (see Smit et al 2010). This paper shows that that a high intake of dairy fat containing 9C,11t is beneficial not harmful despite this isomer not elevating HDL cholesterol. This is an important paper and does not support the FSANZ claim of an increase in CVD of 5% or more. I am surprised it has not been cited at all.

[4] Diabetics.

EpiSag made the point that it was not well tested in diabetics and when it had been tested there were adverse findings.

Norris (2009) found no effect of CLA in a crossover study on fasting glucose and insulin despite a significant 2kg loss of weight over 32 weeks ($p<0.01$ vs PUFA). CLA had no beneficial or harmful effect whereas PUFA did. A 2kg weight loss would be unlikely to change glucose or insulin regardless of the presence of CLA. There was no rise or fall in LFTS (n=35).

In the Moloney (2004) parallel study (n=32) fasting glucose increased by 6.3% but the OGTT was not different hence the effect on glucose metabolism not clear. HDL actually increased, fibrinogen was reduced; both of these effects are not consistent with an adverse effect on insulin sensitivity.

[5] Fat Distribution

"The unknown mechanism of effect of CLA on BFM 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."

This is only true with genetic lipodystrophies and HIV induced lipodystrophy. Otherwise a reduction in fat mass leads to a benefit, more so if it is visceral fat rather than peripheral fat

[6] DEXA scan and fat distribution.

FSANZ said the DEXA finding of reduced fat content could be due to fat redistribution. This is completely wrong- redistribution will not lower % fat. Only loss of fat will do this.

[7] Inhibition and activation of PPAR gamma.

It is known that PPAR gamma activators increase fat mass in humans, sometimes quite considerably in subcutaneous fat depots (including abdominal depots) without a change in visceral fat (reviewed by Yang and Smith 2007) but rosiglitazone and not piopglitazone is associated with an increased cardiovascular risk despite a very significant lowering of glucose. Usually there is a lowering of TG and HDL with an

elevation of TC and LDL cholesterol (Olansky 2003, Singh 2007, Lincoff 2007). This suggests activation of PPAR gamma is not necessarily beneficial, hence PPAR gamma inhibitors of which CLA is likely to be one are not necessarily harmful. Pioglitazone increases HDL cholesterol by 0.2, LDL cholesterol by 0.1 and lowers TG by 0.05 in poorly controlled diabetics on insulin (Tan 2010)

Relative mRNA expression levels for lipid synthesis and transport including diacylglycerol acyltransferase (DGAT1/2), fatty acid translocase (CD36/FAT), fatty acid transport protein (FATP) are increased by glitazones. Therefore PPAR gamma inhibitors should promote fat decrease, especially peripherally, with no effect on visceral fat. In adipocytes t10c12 inhibits PPAR gamma activation (Granlund 2003) although c9t11 is a stimulator of PPAR gamma (Sakuma 2010). In hamsters the mixture lowers fat mass without an effect on liver size or lipids (Joseph 2010). This suggests the fat lowering effect of the PPAR gamma inhibition by c10t12 is counterbalanced by the activation effect of c9t11 which prevents alterations in lipids or liver fat. Thus 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 (reviewed by Reynolds and Roche 2010).

In human fat CLA (4.25g/d for weeks of both isomers separately or the 50:50 mixture) modifies several genes involved in fat regulation. LDLR, FASN, SCD, FADS1 and UCP2 were induced, while ABCA1, CD36 and CA3 were repressed. Transcription factors PPARgamma, NFAT5, CREB5 and EBF1, the adipokine NAMPT, members of the insulin signaling cascade SORBS1 and IGF1 and IL6ST were repressed, while the adipokine THBS1 and GLUT4 involved in insulin signaling were induced. Compared to trans-10,cis-12 CLA and the CLA mixture the cis-9, trans-11 CLA isomer exerted weaker effects. Only CD36 (-1.2 fold) and THBS1 (1.5 fold) were regulated. The CLA effect on expression of PPARgamma and leptin genes depends on the PPARgamma2 genotype (Herrmann 2009).

[8] Atherosclerosis/inflammation

In animal models CLA induces regression of atherosclerosis via PPAR gamma activation of SorLA which is involved in monocyte attraction (McCarthy 2010). CLA-isomers inhibit monocyte migration and reduce the inflammatory output of the macrophage (McCelland et al 2010)

1% CLA (c9,t11:t10c12, 80:20) causes regression of early atherosclerosis in apoE k/O mice fed 1% cholesterol with an increase in PPAR alpha and gamma expression in the aorta with decreased macrophage accumulation (Toomey 2006).

In mice, CLA prevented inflammation-driven colorectal cancer by activating PPAR gamma and modulating regulatory T cells and macrophages (Bassaganya-riera 2010)

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(1) ESFA Submission

As far as I could see, no reference is made in FSANZ' updated report of our three submissions to EFSA in which we have addressed the topics which were - and still are of concern to FSANZ. The reason may be that these submissions were provided as "commercial in confidence". At that time this was justified because of Lipid Nutrition's simultaneous application for CLA in both the EU and AU/NZ. By now, LN has withdrawn its application in AU/NZ and EFSA has published its opinions on the safety of CLA (Tonalin for Cognis, Clarinol for LN). Therefore, the "commercial in confidence" status can be lifted for the following four Bioresco reports:

(a) supplementary information in reply to Member State's comments and questions dated June 23, 2009;

(b) supplementary information in reply to EFSA's comments and questions dated January 18, 2010;

(c) supplementary information for consideration by EFSA's NDA panel dated February 8, 2010; and

(d) supplementary information in reply to EFSA's comments and questions dated March 24, 2010.

The submissions (a) to (c) helped resolve EFSA's concerns about potential adverse effects of CLA on blood lipid levels. Submission (d) then addressed the last unresolved aspect, i.e. oxidative damage, which in fact became a focus of EFSA interest only after all other aspects had been largely resolved.

To recite from the abstract of EFSA's opinion: "The Panel considers that CLA consumption does not appear to have adverse effects on insulin sensitivity, blood glucose control or liver function for up to six months, and that observed effects on blood lipids are unlikely to have an impact on cardiovascular risk."

However, EFSA also states that the safety of CLA consumption for periods longer than six months has not been established and that the safety of CLA consumption by type-2 diabetics has not been established. These reservations may be resolved by risk management measures. In addition, we will also continue the dialogue with EFSA on these points in due course.

Since in the EU CLA may be used in food supplements as not-novel food, the EU Commission asked all Member States whether any cases of adverse events had been brought to their attention. No such events were reported. Also in the US, where

CLA is sold in food supplements in significant amounts, adverse effects have not been reported.

(2) Cholesterol

The question of whether or not there are effects of CLA (1:1 mix of the c9,t11 and t10,c12 isomers) on blood cholesterol levels (HDL-C, LDL-C, total C) has been examined in detail by the Applicant, EFSA and FSANZ and has been the subject of three meta-analyses (by Prof. Clifton, FSANZ, Herrmann et al. 2009a (as cited in Bioresco's report of 18/01/10). Depending upon the applied inclusion/exclusion criteria of studies, the results differed slightly. However, regardless of whether the observed subtle changes were significant or not, they were in absolute terms very small ("background noise") and similar to the changes that might be obtained by other dietary modifications. This is a relevant consideration because the assessment of the safety of a (novel) food (ingredient) is never absolute but is always relative to the safety of existing food, for which there is an *a priori* presumption of safety.

In this context, a statement from a publication by Mensink et al. (2003) may be cited: "effects of diet on biomarkers such as blood lipids can never replace studies that employ disease or death as outcomes" (in first para of Discussion of the article). If there is agreement with this statement, it is interesting to note the results of recent meta-analyses on the association of saturated fat intake and CHD, stroke or CVD. Contrary to prevailing belief (and certain dietary recommendations), 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). Similarly, insufficient evidence exists to judge the effect on CHD risk of replacing SFAs with MUFAs according to a recent expert panel review (Astrup et al., 2011). Yet, other reviewers concluded that there is strong evidence for MUFAs as protective factors (Mente et al., 2009). A third group of authors concluded that there is insufficient evidence to judge the effect on CHD risk of replacing SFAs with MUFAs (Astrup et al., 2011). Linoleic acid was tentatively identified as a risk factor for CHD death (3 studies only) (Skeaff & Miller, 2009). In a review on dairy food intakes and the metabolic syndrome it was found that the majority of studies suggested a beneficial effect (Crichton et al., 2011).

Despite these conflicting conclusions, there was agreement among the different reviewers on one single item, namely 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 (Astrup et al., 2011; Siri-Tarino et al., 2010; Mente et al., 2009; Skeaff & Miller, 2009; Crichton et al., 2011). In this regard it was also suggested that individual SFAs may have different cardiovascular effects (Astrup et al., 2011) and the same is probably true for MUFAs, PUFAs and carbohydrates.

This leaves us with the question against what should CLA be tested and - more importantly - when it has been tested, what would the result mean? In my opinion, it would tell us not more than what we know already: any small effect of CLA on CHD risk factors (up or down, if there is any) would be well within the range of changes that occur with regular food components. Moreover, there is an important point which we should not forget: we eat food, not food ingredients - and certain health effects (such as CHD, CVD) may be more related to food patterns than to individual foods. It is in fact likely that many traditional foods and food ingredients would, if examined using the same approach taken by FSANZ in relation to CLA, show equal if not worse safety concerns.

(3) TFAs

Safety concerns with regard to CLA are derived (by FSANZ) directly from corresponding concerns about trans fatty acids (TFAs). If this were not true, every approved novel food ingredient should have been tested in people suffering from a prediabetic condition or overt type-2 diabetes. Now with regard to TFA, a study has shown that dairy TFAs given at a dose of 5.58 g/d for four weeks did not change peripheral insulin sensitivity in overweight women (Tardy et al., 2009). The same was true when industrial TFA was given at a dose of 15 g/d to overweight postmenopausal women for 16 weeks (Bendsen et al., 2011a). In healthy young women, the absence of an adverse effect of industrial TFA (5.1% of energy for 4 weeks) on insulin sensitivity has been demonstrated already before (Louheranta et al., 1999). Only in an early 6-week study it has been shown that the intake of both TFAs and SFAs (20% of energy) induces an increase of postprandial insulinemia (but not glycemia) in obese type-2 diabetic patients (Christiansen et al., 1997). Accordingly, it has been concluded in a recent review that there is limited evidence for a weak association at high TFA intakes, but very little convincing evidence that habitual exposure to TFA as part of a standard western diet significantly contributes to the risk of diabetes or insulin resistance (Thompson et al., 2010).

The data on effects of CLA on insulin sensitivity have been reviewed in Bioresco's communications to EFSA (dated 18/01/2010 and 08/02/2010). It was concluded that CLA has no adverse effect on glucose homeostasis and insulin sensitivity neither in healthy nor overweight and/or diabetic subjects.

For postmenopausal obese type-2 diabetic women this has been demonstrated most recently by the group of Norris et al. (2009) and Asp et al. (2011). The absence of long-term effects of CLA has been demonstrated in the study by Gaullier et al., (2004) which has been re-evaluated by Schrezenmeir (2006) and Herrmann et al. (2009a as cited in Bioresco's communication of 18/01/10).

(4) Fat Deposition

(TFAs have been suspected to promote abdominal and hepatic fat deposition. While the intake of CLA has been demonstrated to lead to a small, yet significant decrease of body fat (Whigham et al., 2007; Raff et al., 2009;Norris et al., 2009), the question about hepatic lipidosis was upheld in view of such effects in certain animal studies. A recent human study in which the volunteers received 15.7 g/d (!) TFA for a period of 16 weeks, now demonstrates that TFA does not affect liver fat deposition (Bendsen et al., 2011b). A human study with intake of a CLA mix different from Tonalin (80% c9,t11 and 20% t10,c12) at a dose of 14 g/d for 3 weeks also showed that CLA has no adverse effects on liver function related plasma parameters (Wanders et al., 2010).

(5) Other Risk Assessment and Risk Management Comments

According to FSANZ' draft Executive Summary on Application A1005, a number of concerns remain which, it is said, cannot be properly addressed by common risk management procedures, i.e. restriction of the range of foods which may contain CLA, limiting the amount of CLA in different types of food, as well as label information.

Specifically, the Authority arrives at the following conclusions of its risk assessment:

(a) According to FSANZ, there is strong evidence of adverse effects of CLA on blood lipids (i.e., blood cholesterol) due to the ingestion of CLA at the Applicant's recommended amounts.

While the Applicant disagrees with this conclusion and maintains that effects (if there are any) are well within the range of fluctuation due to the overall composition of the diet (which is presumed to be safe) and the individual dietary pattern (which is not regulated), he proposes - as a precautionary risk management procedure - to limit the use of CLA to specified foods and in specified amounts.

For example, FSANZ might in addition consider authorising the use of CLA in foods which may lawfully be claimed to be cholesterol-free, because the consumption of such foods is

also expected to have a favorable effect on the overall daily cholesterol intake.

The Applicant also agrees that recommendations of use should be mandatory for CLA containing foods.

(b) According to FSANZ, there is some concern about potential adverse effects of CLA on glucose homeostasis in type-2 diabetics.

In the opinion of the Applicant there is no reason to expect such long-term effects because the tissue steady-state of CLA is reached within a few days/weeks and because any effect on glucose homeostasis (for which there is no evidence) would be seen within a short period of time, i.e. is not a type of effect that is accumulating over time. The absence of long-term effects has been shown directly in a study with CLA in humans (Gaullier et al., 2004). Animal studies confirm that there is no accumulation of any kind of toxicity over time.

However, if this remains a concern it can be addressed through risk management. For example, FSANZ might consider a labelling requirement directing people with impaired glucose tolerance (incl. diabetes) to consult their doctor when consuming a food containing added CLA.

The Applicant acknowledges that there may be people with undiagnosed diabetes who might consume CLA. However, there is no general warning label on foods with a high glycemic index, or a high cholesterol level, for such persons. Since many regular foods pose an equal or greater risk to undiagnosed diabetics, the concern for CLA containing products appears to be disproportionate. Again, if FSANZ maintains its concern, it should address it through appropriate risk management measures, such as permitting CLA only in foods with a medium or low glycemic index.

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