CODEX ALIMENTARIUS COMMISSION E

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Agenda Item 10 **CX/NFSDU 12/34/13**

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CODEX COMMITTEE ON NUTRITION AND FOODS FOR SPECIAL DIETARY USES
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PROPOSAL TO REVIEW THE CODEX DEFINITION OF TRANS FATTY ACIDS FOR LABELLING PURPOSES WITH RESPECT TO CONJUGATED FATTY ACIDS

BACKGROUND PAPER

Prepared by Australia

1 INTRODUCTION

At its meeting in 2011, the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) discussed a possible revision of the definition of trans fatty acids for labelling purposes. During discussion, Australia advanced the view that the definition could be reviewed in relation to the current exclusion of conjugated fatty acids on the basis of recent scientific evidence. However, since that part of the definition fell outside the scope of discussion, the Committee noted that this was a new issue and invited Australia to prepare a proposal for consideration of new work in 2012 (REP 12/NFSDU,para 14).

This Background Paper presents the history of the development of the Codex definition and associated footnote, and the basis of the exclusion of conjugated fatty acids from the definition. It also presents the relevant conclusions from recent government assessments of the evidence for the health effects in humans of conjugated linoleic acid (CLA), a predominant type of conjugated fatty acids. These assessments focused on CLAisomers produced from safflower oil.

This information is prepared to assist the Committee's consideration of the attached Proposal for New Work to review the definition of trans fatty acids with respect to conjugated fatty acids.

2 BACKGROUND

2.1 ORIGINAL CODEX DEFINITION OF TRANS FATTY ACIDS FOR LABELLING

The Codex Committee on Food Labelling (CCFL) requestedCCNFSDU in 2003 to develop a definition of *trans*fatty acids (TFAs).

The 2004 session of CCNFSDU considered a Discussion Paper prepared by Malaysia and Denmark (CX/NFSDU 04/11) containing aproposed definition of trans fatty acidsdrafted on the basis of chemical structure and the AOCS method of determination:

> For the purpose of the Codex guidelines on Nutrition Labelling and other related Codex Standards and Guidelines, *trans* fatty acids are defined as all the geometrical isomers of monounsaturated and polyunsaturated fatty acids having non-conjugated [interrupted by at least one methylene group (-CH_2-CH_2-)] carbon-carbon double bonds in the trans configuration. This includes the *trans*monoenes (mainly stereoisomers of elaidic acid) and the *trans* isomers of polyunsaturated fatty acids (e.g. *trans*dienes, *trans*trienes, etc.) with non-conjugated carbon-carbon double bonds, produced through hydrogenation of oils and fats (both vegetable and animal/marine origin) in the presence of a suitable chemical catalyst.
>
> The definition however *excludes* those conjugated *trans* fatty acids present naturally in animal fats and their products which include conjugated linoleic acid (CLA).

The CCNFSDU considered the proposed definition (ALINORM 05/28/26, para 143-147) and referred the following draft definitionto CCFL based only on chemical structure:

> For the purpose of the Codex Guidelines on Nutrition Labelling and other related Codex Standards and Guidelines, trans fatty acids are defined as all the geometrical isomers of monounsaturated and polyunsaturated fatty acids having non-conjugated interrupted by at least one methylene group (-CH_2-CH_2-) carbon-carbon double bonds in the trans configuration.

The 2005 session of CCFL (ALINORM 05/28/22, para 91-96) inserted commas around *interrupted by at least one methylene group* and deleted *(-CH_2-CH_2-)* from the above text.

In 2006, CCFL (ALINORM 06/29/22, para 123-135; Appendix V) discussed the draft definition. Some delegations were concerned that it was not technically correct since monounsaturated trans fatty acids cannot be conjugated (para 127-128), however the draft was not changed.

CCFL proposed the definition at Step 5of the accelerated procedure for placement in the Codex Guidelines on Nutrition Labelling with the following footnote:

> Codex Members may, for the purposes of nutrition labelling, review the inclusion of specific trans fatty acids (TFAs) in the definition of TFAs if new generally accepted scientific data become available.

The purpose of Footnote 3 provided for Codex members to review the inclusion of specific trans fatty acids in the definition if new generally accepted scientific data demonstrated that their nutritional effects differed from those observed for TFAs in general (ALINORM 06/29/22, para 129).

The definition and footnote in Box 1 below were adopted by the Commission in 2006.

BOX 1

Codex Definition for Labelling Purposes (Codex Guidelines on Nutrition Labelling (CAC/GL 2 – 1985)

2.9 **Trans Fatty Acids**[3]: For the purpose of the Codex Guidelines on Nutrition Labelling and other related Codex Standards and Guidelines, trans fatty acids are defined as all the geometrical isomers of monounsaturated and polyunsaturated fatty acids having non-conjugated, interrupted by at least one methylene group, carbon-carbon double bonds in the trans configuration.

[3]Codex Members may, for the purposes of nutrition labelling, review the inclusion of specific trans fatty acids (TFAs) in the definition of TFAs if new scientific data become available.

2.2 EXCLUSION OF CONJUGATED FATTY ACIDS FROM CODEX DEFINITION

Background information appended to the 2004 Discussion Paper summarised information on the nature, occurrence and potential adverse health effects of trans fatty acids. The information provided was not meant to be a comprehensive review of the subject but served to promote understanding of the proposed definition of trans fatty acids. The introduction referred to the existence of several systematic reviews on trans fatty acids, but attention was drawn only to the systematic review by the US Institute of Medicine (IOM) (2002) that established dietary reference intakes for fat, fatty acids and other nutrients.

The Discussion Paper specifically mentioned conjugated linoleic acid (CLA) in relation to its chemical structure, natural occurrence in milk fat and potential health benefits according to evidence from cell culture studies and animal studies. No reference was made to potentially adverse health effects at that time.

The relevant paragraph stated:

> Recent studies suggest that not all species of TFA are "bad". A group of naturally-occurring *trans* geometric and positional isomers of *cis*-linoleic acid possess carbon double bonds that are "conjugated" and have been given the collective term "conjugated linoleic acid" (CLA). CLA, consisting mainly of the *cis*-9, *trans*-11 and *trans*-10, *cis*-12 isomers, are formed in mammalian cells by the action of the enzyme Δ^9desaturase and therefore occur naturally in milk fat and dairy products (Adlof et al., 2000; Pariza at [sic] al., 2001; Santora et al., 2000). CLA are suggested to have beneficial effects on human health such as the inhibition of carcinogenesis and atherogenesis primarily based on cell culture studies and animal studies (Ha et al., 1989; Kritchevsky et al., 2000; Parodi, 1999). However, further research work needs to be done to reinforce these findings.

The US Institute of Medicine (2002) identified the adverse effects of overconsumption of trans fatty acids (p. 494) but no similar assessment was given for conjugated fatty acids. In Chapter 11 – *Macronutrients and Healthful Diets*, the potential health benefits of consumption of CLA are discussed, although the section concludes (p. 838):

> To date, there are insufficient data in humans to recommend a level of CLA at which beneficial health effects may occur.

Footnote 3

Footnote 3 was appended to the definition of trans fatty acids during discussion at CCFL and it states:

> [3]Codex Members may, for the purposes of nutrition labelling, review the inclusion of specific trans fatty acids (TFAs) in the definition of TFAs if new scientific data become available.

The purpose of the footnote (ALINORM 06/29/22, para 129) was in response to suggestions from some delegations that some trans fatty acids may confer a benefit:

> 129 Codex Members may review the inclusion of specific trans fatty acids if new generally accepted scientific date demonstrates that their nutritional effects differ from those observed for trans fatty acids in general.

The footnote thus provides for national authorities to exclude additional trans fatty acids from the definition if new evidence demonstrates different (presumably beneficial) effects from trans fatty acids in general. However, it is matter of interpretation whether thefootnote provides scope for national authorities to include conjugated fatty acids in national definitions of trans fatty acids if new generally accepted data demonstrates that the nutritional effects of conjugated fatty acids are similar to those generally observed for trans fatty acids.

This project provides the opportunity also to review the footnote text and to consider if the scope of national discretion is appropriate.

3 WHO AND FAO DEFINITIONS OF TRANS FATTY ACIDS

The introduction to the WHO Scientific Update on Health Consequences of Trans Fatty Acids (Nishida C &Uauy R,2009) does not provide an independent definition of trans fatty acids, but instead, quotes the 2004 draft of CCNFSDU's definition. This quotation is given in the context of general reference to several CCNFSDU and CCFL meetings from 2001 to 2006.

The FAO Food and Nutrition Paper No. 91, (FAO, 2010) reports the outcomes of a 2008 joint FAO/WHO Expert Consultation on Fats and Fatty Acids in Human Nutrition. In describing the acronym 'TFA', it says:

> TFA refers to the major *trans*fatty acids in our diet which are typically isomers of 18:1 *trans* derived from partially hydrogenated vegetable oils.
>
> Some fatty acids (e.g. *trans*monoenes, conjugated linoleic acid [CLA], etc.) are members of more than one chemical classification but by convention are interpreted as in only one category (*trans* monoenes in MUFA, CLA in PUFA, etc.).

WHO advised CCNFSDU in 2011 that the WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health is planning to review and update the recommendations on fat and fatty acids in 2012-13 (REP12/NFSDU, para 22).

4 STRUCTURE OF CONJUGATED FATTY ACIDS

The characteristic structure of conjugated fatty acids is defined in the current Codex definition of trans fatty acids, i.e. [polyunsaturated] fatty acids having non-conjugated, interrupted by at least one methylene group, carbon-carbon double bonds in the trans configuration.

CLA is a fatty acid with one *cis*, and one *trans* double bond in a conjugated configuration. The IOM (2002) referred to nine different isomers of CLA in food but identified only *cis*-9,*trans*-11 and *trans*-10,*cis*-12 CLA as possessing biological activity, with *cis*-9, *trans*-11 CLA being the predominant dietary form in meat, milk and other dairy products(p. 428; p. 480). These two isomers have also been chemically produced from fatty acids in safflower oil for the purpose of addition to food or use in food supplements, including in different ratios from those found in food.

5 GOVERNMENT REVIEWS OF HEALTH EFFECTS OF CLA

Since 2006, several government regulatory or scientific agencies have assessed the health effects of CLA isomers in relation to the regulation of addition of CLA to certain foods to a maximum level. Attachment 1 provides excerpts from the conclusions of such assessments that are known to Australia. This may not be a comprehensive list.

It is not known whether any assessments of conjugated fatty acids apart from CLA have been done. Several of the scientific reviews below have primarily or exclusively examined the effects of concentrated CLA isomers added to food or as food supplements, rather than CLA from meat and dairy foods. Higher intakes of CLA than possible from naturally occurring CLA have therefore been studied.

The evidence base for the health effects of conjugated fatty acids (CLA) has grown considerably over the past 10 years, particularly in relation to human studies. The parameters assessed by five agencies in relation to CLA are listed in Table 1. All of these assessments considered evidence of potential adverse health effects. Brazil, Europe and Australia New Zealand also considered potentially favourable health effects related to changes in body weight and body composition.

Table 1: Parameters examined in assessments of CLA

Australia New Zealand (FSANZ)	**Brazil (ANVISA)**	**Europe (EFSA)**	**France (AFSSA)**	**United States (FDA)**
Glucose homeostasis	Insulin sensitivity and glucose metabolism;	Insulin sensitivity and glucose metabolism	Insulin resistance	Insulin sensitivity
HDL- and LDL-cholesterol levels	Blood lipids	Blood lipids and lipoproteins	Circulating lipoproteins	
	Markers of lipid peroxidation Markers of inflammation	Markers of lipid peroxidation and markers of systemic (subclinical) inflammation and adipokines	Markers of oxidative stress and inflammation	Cardiovascular disease parameters – biomarkers of inflammation – isoprostanes
		Vascular function and Vascular damage		Cardiovascular disease parameters – endothelial function
	Liver function and liver steatosis	Liver function and liver steatosis		
		Impact on milk secretion and content		Milk fat deposition
		Adverse events		
		Immune defence		
Body weight and body composition	Body fat loss	Normal body weight Lean body mass		

6 CHANGE IN EVIDENCE BASE OF HEALTH EFFECTS OF CONJUGATED FATTY ACIDS

The evidence for health effects of conjugated fatty acids considered by CCNFSDU in 2003-4 was based on only animal and *in vitro* evidence of potential health benefits. This is contrasted with the currently available and more relevant human evidence of the potential adverse and beneficial health effects of conjugated fatty acids. CCNFSDU is requested to consider whether the change in evidence base over the last decade is sufficient to warrant a review of the definition of trans fatty acids and associated footnote.

7 OPTIONS FOR THE COMMITTEE TO CONSIDER

The Proposal for New Work isat Attachment 2.

The options are:

1. Submit the Proposal for New Work to the Commission.
2. Not proceed with new work and maintain the current definition and footnote.

8 OTHER RELEVANT MATTERS

8.1 Methods of analysis

At its last session, CCFL agreed to request that CCNFSDU consider requesting CCMAS to review method AOCS Ce 1H-05 for trans fatty acids in foods as it is applicable only to certain types of fats and oils. CCFL also noted that the method AOAC 996.06 is already recognised as a Type II method for the measurement of

saturated fatty acids (REP12/FL para 36). If CCNFSDU agrees to seek advice from CCMAS about the AOCS method of analysis for trans fatty acids, CCNFSDU could also consider seeking advice on the capability of that method to measure all or classes of conjugated fatty acids.

8.2 Extension of application of the trans definition

Although the application of the definition is currently restricted to nutrition labelling, trans fatty acids are regulated in the Codex Standard for Infant Formula and Formulas for Special Medical Purposes Intended for Infants (CODEX STAN 72-1981, 2007 Revision) without a definition for trans fatty acids in that Standard. Following the completion of this work, the Committee may wish to consider a future Proposal for New Work to broaden the application of the trans fatty acid definition to other Codex texts.

9 REFERENCES

Nishida C, Uauy R (2009) WHO Scientific Update on *trans*fatty acids. EJCN, 63: S2 http://www.nature.com/ejcn/journal/v63/n2s/abs/ejcn200913a.html Accessed September 2012

FAO (2010).Fat and fatty acids in human nutrition.Report of an expert consultation.Food and Nutrition Paper 91. Food and Agriculture Organization, Rome www.fao.org/docrep/013/i1953e/i1953e00.pdf Accessed September 2012

Institute of Medicine (2002) Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. The National Academies Press, Washington D.C http://www.nap.edu/catalog.php?record_id=10490#toc Accessed September 2012

9.1 REFERENCES TABLE A1, ATTACHMENT 1

ANIVSA (2007) Esclarecimentossobre as avaliações de segurança e eficácia do ÁcidoLinoléicoConjugado – CLA
http://portal.anvisa.gov.br/wps/portal/anvisa/anvisa/home/alimentos/!ut/p/c5/rZDLcrJAEIWfxQfQ6QEcYAnITS4jl6jMhhpBjRAMJQro04f8--TfpHvRi65T3zkHMTTtlfeXM79fPq_8A-0RI7lha44k-wBAdANcexmSZUTBXgPaoT1IeVI9W_dVv-IKnhCuTAhfwRBM916fIZBLN7lZQVq367DGQZhqY1DpHi5UvLUiU9s0zPOz2cTKfmQBFb6deJHj2gCCSlNlBa6Uxo7qGdTCeHLCfvH6T__9hx9Gg__oMQqdz-aIMsTkfGsLiuPZeOpA1sE1U8eiYImRACj9w0Z-Zwl_ylojdjk0i6FoFrBQRUlQsCKLS4IlQiS0S7NhNBR3MM3DBOyLhvIu6pwQuFCVh0cTR_Nkb79v3vK5-havir4_6UeRDwMG7ESmXihSWBFrNM-GKNHAa3TONKNM4OPINYbNK99wIpYdvygnZUxOveVvn8SvT8O7VD3GzLh2NGZ-QsZ5xeBI200r75SUSoHT0fvmcTvkWzW-74SbWKK26X0SOwOeMgzabPYFs6bMAA!!/dl3/d3/L2dBISEvZ0FBIS9nQSEh/?pcid=a94176004138a678bd9cbdc5ae04202e Accessed September 2012.

ANSES (2011) Opinion of ANSES on a "safety assessment of the use of an oil enriched with Conjugated Linoleic Acid (CLA)"
http://www.anses.fr/Documents/NUT2011sa0185.pdf (in French)

http://www.anses.fr/Documents/NUT2011sa0185EN.pdf(in English) Accessed September 2012.

EFSA (2010a) Scientific Opinion of the safety of "conjugated linoleic acid (CLA)-rich oil" (Tonalin® TG80) as a Novel Food ingredient; Scientific Opinion of the safety of "conjugated linoleic acid (CLA)-rich oil" (Clarinol®) as a Novel Food ingredient
http://www.efsa.europa.eu/en/efsajournal/doc/1600.pdfhttp://www.efsa.europa.eu/en/efsajournal/doc/1601.pdf Accessed September 2012.

EFSA (2010b) Scientific Opinion on the substantiation of health claims related to conjugated linoleic acid (CLA) isomers and contribution to the maintenance or achievement of a normal body weight (ID 686, 726, 1516, 1518, 2892, 3165), increase in lean body mass (ID 498, 731), increase in insulin sensitivity (ID 1517), protection of DNA, proteins and lipids from oxidative damage (ID 564, 1937), and contribution to immune

defences by stimulation of production of protective antibodies in response to vaccination (ID 687, 1519) pursuant to Article 13(1) of Regulation (EC) No 1924/20061
http://www.efsa.europa.eu/en/efsajournal/doc/1794.pdf Accessed September 2012.

EFSA (2012) Statement of the safety of "conjugated linoleic acid (CLA)-rich oils" Clarinol® or Tonalin® TG 80 as Novel Food ingredients
http://www.efsa.europa.eu/en/efsajournal/doc/2700.pdf Accessed September 2012.

FDA (2008) Agency Response Letter GRAS Notice No.GRN 000232
http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/ucm153908.htmAccessed September 2012.

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http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/ucm185684.htmAccessed September 2012.

FSANZ (2011) Application A1005 – Exclusive use of Tonalin® CLA as a novel food
http://www.foodstandards.gov.au/_srcfiles/A1005%20Tonalin%20CLA%20SD1%20Lipids.pdf
http://www.foodstandards.gov.au/_srcfiles/A1005%20Tonalin%20CLA%20SD3%20Glucose.pdfhttp://www.foodstandards.gov.au/_srcfiles/A1005%20Tonalin%20CLA%20SD2%20Body%20comp.pdfAccessed September 2012.

10 ATTACHMENTS

1 Extracts relating to health effects from recent government assessments of CLA
2 Draft Proposal for New Work
.

ATTACHMENT 1

Table A1: Extracts from recent government assessments of CLA relating to health effects

ASSESSED HEALTH EFFECTS(mainly in humans)**	**RELEVANT DISCUSSION AND CONCLUSIONS**
1) **Australia New Zealand, 2011;** Food Standards Australia New Zealand (FSANZ) Application A1005 – Exclusive use of Tonalin® CLA as a novel food	
HDL- and LDL-cholesterol levels; Glucose homeostasis; Body weight and body composition	**CONCLUSIONS** **Blood lipids** The above results indicate that the 1:1 isomer mix of CLA in the range <6 g reduces HDL-cholesterol when compared to saturated and *cis*-unsaturated fats. There was a trend in the FSANZ meta-analysis, albeit not significant, towards an elevation of LDL-cholesterol when the 1:1 isomer mix (<6 g) was compared to oils rich in *cis*-unsaturates. There were a number of other studies that used the isomers singly or in a different ratio. One of these used a 4:1 *c-9,t-11:t-10,c-12* ratio of CLA found a significant reduction in HDL-cholesterol and a significant increase in LDL-cholesterol compared to a control of high oleic sunflower oil (Wanders *et al.*, 2010). The [Expert Scientific Advisory Group] advised that they thought it was reasonable to combine the studies that used either or both of the isomers only to examine the effect on lipids. There was a statistically significant dose response relationship showing a decrease in HDL and an increase in LDL as dose of CLA increased when only studies using <6g were included and also when the high dose study of Wanders *et al.*, (2010) was included. Although the primary focus of the current assessment is on the 1:1 isomer ratio, FSANZ regards the results of the analysis of any ratio of the two isomers as supporting the view that the 1:1 isomer ratio probably has an effect on LDL-cholesterol. These effects on both lipids are clearly different from the effects expected of a *cis*-polyunsaturated fatty acid (Mozaffarian and Clarke, 2009). FSANZ concludes that the 1:1 isomer CLA mixture has a different effect on these lipids from that of a *cis*-polyunsaturated fat. Based on currently available evidence, the effect of the 1:1 isomer mix of CLA on lipids is consistent with that of industrial trans fats. As noted above, the New Zealand and Australian heart disease risk charts use the total/HDL ratio as the predictor, with increasing values indicating increasing risk. The decrease in HDL-cholesterol has an unfavourable effect on the total/HDL ratio and this is exacerbated by the likely increase in LDL-cholesterol level. In summary, FSANZ concludes that the 1:1 isomer mix of CLA decreases HDL-cholesterol levels. The trend towards an increased LDL-cholesterol level in the 1:1 studies and the significant dose-response relationship seen when the 1:1 and other studies were combined leads to the conclusion that the 1:1 ratio probably has an adverse effect on LDL-cholesterol, which is an additional concern.

Glucose homeostasis

Few studies testing the 1:1 isomer ratio have assessed the effect of CLA on insulin sensitivity directly using the 'gold standard' clamp technique. The two studies using this technique have reported no significant effect of CLA (Risérus*et al*., 2002a and Syvertsen*et al*., 2006). Few studies have measured glucose tolerance using the OGTT, and the inconsistent results from these studies may be related to the variation in health and weight status of participants in the trials (Lambert *et al*., 2007 and Moloney *et al*., 2004). A larger number of studies have estimated insulin resistance via the HOMA index. The majority reported no statistically significant effect of CLA on HOMA. Significant adverse effects of CLA were reported via increased estimates of HOMA in two studies involving diabetics only (Moloney *et al*., 2004 and Norris *et al*., 2009).

Indicators of glucose homeostasis may respond differently 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. There were a number of instances where studies described their participants, for example, as healthy but also had exclusion criteria such as BMI<35kg/m^2. Additional mean baseline data then indicated elevated blood pressure or other characteristics that could define the presence of metabolic syndrome in at least some of the participant population. The variation in body weight or proportion with normal or abnormal glucose metabolism among the studies may account for some of the variation in results between studies. Consequently it is unclear which of the studies described above could be extrapolated to the population without metabolic syndrome. An additional source of methodological variation among the studies is the variety of glucose homeostasis markers reported and the small number of studies that have used the 'gold-standard' method of the clamp technique. The two studies of CLA in children and adolescents do not allow any conclusions to be drawn for this group.

The available data raises questions but does not permit a conclusion about the effect of CLA on glucose homeostasis in the general population. Two well conducted studies raise safety concerns about the effects of CLA on people with type 2 diabetes.

Body weight and composition

FSANZ concludes 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, the clinical significance of this amount of fat loss at the individual level is likely to be minimal and, 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.

In addition, a range of uncertainties remain in relation to the effect of CLA on fat mass:

- there is no evidence of a dose effect
- 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 insufficient evidence of an effect on fat mass in children
- the means by which CLA might reduce body fat remain unclear although one study is suggestive of an increase in energy expenditure
- the methods used to measure changes in fat mass are at the limit of their validity when small changes of 1-2 kg are observed.

	In terms of the effect of CLA on body weight, the trend is for a fall in body weight although it is not statistically significant, and there is limited evidence that CLA positively influences lean body mass or assists in maintaining weight or preventing weight regain following initial weight loss.
2) **Brazil, 2007;** AgênciaNacional de VigilânciaSanitária **(**ANVISA**)** Brazilian Health Surveillance Agency Esclarecimentossobre as avaliações de segurança e eficácia do ÁcidoLinoléicoConjugado – CLA Clarified security assessments and effectiveness of Conjugated Linoleic Acid - CLA	
Insulin sensitivity and glucose metabolism; Blood lipids; Markers of lipid peroxidation; Markers of inflammation; Liver function and liver steatosis Body fat loss	[…] Aalimentação dos sereshumanosfornecepequenasquantidades de CLA oriundos da gordura do leite e de carnes de animaisruminantes, sendoquemais de 70% do CLA nessesalimentos é representadoporapenas um isômero, o c9, t11-CLA (McLeod et al., 2004). Estimativas de ingestão de CLA porhumanosvariam de 140mg a 1g/dia, dependendo da metodologiautilizada e dos hábitosalimentares da população. O CLA produzidoquimicamente e disponívelcomercialmenteemalgunspaísessãopreparações de misturas de isômeros, contendogeralmente 40% de c9, t11-CLA, 40% de t10, c12-CLA e 20% de outros isômeros (McLeod et al., 2004). […] As principaisquestões e evidênciascientíficasquelevaramaoindeferimento de todas as solicitaçõesrealizadasaté o momentoestãosintetizadas a seguir: - A ingestão de CLA recomendadapelasempresassuperaemmais de vintevezes as quantidadesusualmenteconsumidaspelapopulação, o quelevantapreocupaçõesquanto à segurança de usodessesprodutos. - Existemevidênciascientíficasobtidasemanimais de experimentação e emhumanosdemonstrandoque a suplementação com CLA podecausarefeitosadversos. - Estudosexperimentaisconduzidosemanimais e estudos de revisãodemonstraramque a suplementação de CLA podelevaraoaumento do fígado, esteatosehepática, hiperinsulinemia e diminuição dos níveisséricos de leptina (West et al., 1998; DeLany et al., 1999; West et al., 2000; Tsuboyama-Kasaoka et al., 2000; Kelly, 2001; Clement et al., 2002; Takahashi et al., 2002; Roche et al., 2002; Yamasaki et al., 2003; Poirier et al, 2005). - Estudosrandomizadosduplo-cegos com homensobesosdemonstraramqueosgruposrecebendosuplementação com o isômero t10, c12-CLA tiveram um aumentosignificativo da resistência à insulina, da glicemia, do estresseoxidativo e dos marcadores de inflamação e umareduçãosignificativa dos níveis de HDL colesterolquandocomparados com osgrupos placebos (Riserus et al., 2002a; Riserus et al., 2002b). - Indivíduos com diabetes tipo 2 suplementados com umamistura de isômeros de CLA poroitosemanasdemonstraramumadiminuição dos níveisséricos de leptina (Belury et al., 2003). - Riserus et al. (2004) demonstrarampormeio de um estudorandomizadoduplo-cego com homensobesosque a suplementação com o isômero c9, t11-CLA aumentousignificativamente a resistência à insulina e a peroxidaçãolipídicaquandocomparado com o grupo placebo.

	- Osmecanismosbioquímicos de ação dos diferentesisômeros e suainteraçãoaindanãoforamadequadamenteelucidados e comprovados, sendoque a maioriadesses dados é oriunda de estudosexperimentaisemcamundongos e de estudos in vitro (Pariza, 2004; McLeod et al., 2004; Wang and Jones, 2004). - As evidênciasexistentessugerem, porexemplo, que o CLA podeinfluenciar a apoptose e a diferenciaçãocelular, alterar o balançoenergético, inibir a lipogênese e aumentar a oxidaçãolipídica, entre outros (Pariza, 2004; McLeod et al., 2004; Wang and Jones, 2004). - Os dados científicossobreaeficácia do CLA emhumanostambémsãocontroversos. Terpstra (2004) destacaqueosestudosrealizadosemhumanossobreosefeitos da suplementação de CLA naperda de gordura corporal tiveramefeitoconsideravelmentemenordoqueosobtidosemestudosexperimentais com ratos. **IV. ConsideraçõesFinais** Assim, as evidênciascientíficasavaliadasaté o momentonãocomprovam a segurança de uso e aeficácia do ácidolinoléicoconjugadoisoladooucomoingredientealimentar. Osefeitosadversosobservadosemmuitosestudosprecisamsermelhoresesclarecidos e entendidos. Tambémsãonecessáriosmaisestudosbemcontroladosqueelucidemadequadamenteosmecanismos de ação dos diferentesisômeros e suainteraçãoemsereshumanos e quecomprovemsuaeficácia.Portanto, com o intuito de proteger e promover a saúde da população, o ácidolinoléicoconjugadoisoladooucomoingredientealimentarparaseradicionadoemváriosalimentosnãodevemsercomercializados no Brasilcomoalimentoatéqueosrequisitoslegaisqueexigem a comprovação de suasegurança de uso, mecanismos de ação e eficáciasejamatendidos **TRANSLATION FROM PORTUGUESE USING GOOGLE** […] The feeding of humans provides from small amounts of CLA of milk fat and meat of ruminant animals and more than 70% of CLA in these foods is represented by only one isomer, c9, t11 CLA-(McLeod et al. , 2004). Estimates of intake of CLA by humans range from 140mg to 1g/day, depending on the methodology used and the population's eating habits. CLA chemically produced and commercially available in some countries are preparations of mixtures of isomers, usually containing 40% c9, t11 CLA-40% t10, c12 CLA-and 20% other isomers (McLeod et al. 2004) […] The main issues and scientific evidence that led to the rejection of all requests made to date are summarized below: - The recommended intake of CLA by the companies that is more than twenty times the amount usually consumed by the population, which raises concerns about the safety of these products. - There is scientific evidence obtained in experimental animals and humans showing that supplementation with CLA may cause adverse effects. - Experimental studies conducted in animals and review studies have shown that supplement of CLA can lead to the enlargement of the liver, fatty liver, hyperinsulinemia and reduced levels of leptin (West et al., 1998; DeLany et al., 1999; West et al., 2000; Tsuboyama-Kasaoka et al., 2000, Kelly, 2001, Clement et al., 2002, Takahashi et al., 2002, Roche et al., 2002; Yamasaki et al., 2003;

	Poirier et al , 2005). - Randomized double-blind studies have shown that obese men with the groups receiving supplementation with isomer t10, c12-CLA had a significant increase in insulin resistance, blood glucose, oxidative stress and markers of inflammation and a significant reduction in the levels of HDL cholesterol compared to the placebo group (Riserus et al. 2002a; Riserus et al., 2002b). - Individuals with type 2 diabetes supplemented with a mixture of CLA isomers for eight weeks showed a decrease in serum leptin (Belury et al., 2003). - Riserus et al. (2004) demonstrated through a randomized double-blind study of obese men that supplementation with isomer c9, t11-CLA significantly increased insulin resistance and lipid peroxidation when compared with the placebo group. - The biochemical mechanisms of action of different isomers and their interaction have not been adequately clarified and proven, and most of these data is derived from experimental studies in mice and in vitro studies (Pariza, 2004, McLeod et al., 2004; Wang and Jones, 2004). - The available evidence suggests, for example, the CLA can influence cell differentiation and apoptosis, changing the energy balance, to inhibit lipogenesis and increased lipid oxidation, among others (Pariza, 2004, McLeod et al., 2004, and Wang Jones, 2004). - Scientific data on the efficacy of CLA in humans are also controversial. Terpstra (2004) points out that studies in humans on the effects of CLA supplementation on body fat loss effect were considerably lower than those obtained in experimental studies with rats. **IV. Final Thoughts** Thus, the scientific evidence evaluated to date does not prove the safety of use and effectiveness of conjugated linoleic acid alone or as a food ingredient.The adverse effects observed in many studies to be better clarified and understood. Also needed are more well-controlled studies to elucidate properly the mechanisms of action of the different isomers and their interaction in humans and to prove their efficacy.Therefore, in order to protect and promote the health of the population, conjugated linoleic acid alone or as a food ingredient to be added to various foods should not be marketed in Brazil as a food until the legal requirements that require proof of their safety use, mechanisms of action and efficacy are met.
2A) **Europe, 2010;** European Food Safety Agency (EFSA) Panel on Dietetic Products, Nutrition and Allergies Scientific Opinion of the safety of "conjugated linoleic acid (CLA)-rich oil" (Tonalin® TG 80) as a Novel Food ingredient Scientific Opinion of the safety of "conjugated linoleic acid (CLA)-rich oil" (Clarinol®) as a Novel Food ingredient	
Insulin sensitivity and glucose metabolism; Blood lipids; Lipoproteins; Markers of lipid peroxidation; Markers of systemic (subclinical) inflammation and adipokines;	**DISCUSSION** The applicant[s] provided sufficient information regarding the production, the composition, the stability and the estimated intake of [Tonalin® TG 80] [Clarinol®]CLA-rich oil[s]. *In vitro* data suggest that the *t*10,*c*12 CLA isomer is involved in the regulation of fatty acid synthesis and mediating suppression of insulin sensitivity in mature human adipocytes. This isomer has also been reported to be responsible for undesirable effects on fat and glucose metabolism *in vivo*. Mice seem to be particularly sensitive to the effects of CLA on fat and glucose metabolism. However the extent of the effects of CLA on insulin sensitivity, but also on hepatic fat accumulation and markers of cardiovascular risk appears to be species-dependent. The focus of the safety assessment therefore relies mainly on human studies. The available data from non-

Vascular function; Vascular damage; Liver function and liver steatosis; Impact on milk secretion and content; Adverse events.	human studies do not indicate a risk for genotoxicity, reproductive toxicity, carcinogenicity or allergenicity. The administration of the 1:1 isomer mixture of CLA to normal weight, overweight and obese non-diabetic subjects does not appear to have adverse effects on insulin sensitivity, blood glucose control or liver function at the proposed conditions of use for up to six months. Effects of CLA consumption over periods longer than six months on insulin sensitivity and liver steatosis have not been adequately addressed in humans. With respect to type-2 diabetic subjects, the evidence provided does not establish the safety of CLA under the proposed conditions of use, since the CLA 1:1 isomer mixture appears to adversely affect both static (HOMA-IR) and dynamic (ISI, OGIS) surrogate markers of insulin sensitivity as well as fasting blood glucose and no studies on blood glucose control (e.g., HbA1c) are available for periods of consumption beyond eight weeks. Under the proposed conditions of use, CLA has no effect on LDL-cholesterol concentrations or the LDL:HDL-cholesterol ratio, and the magnitude of the changes observed in HDL- and triglyceride concentrations are unlikely to have an impact on CVD risk. However, the observed increase in plasma and urinary concentrations of isoprostanes, which may indicate an increase in lipid peroxidation, and the increase in some markers of subclinical inflammation (i.e., 15-*keto*-dihydroprostaglandin $F_{2\alpha}$ and possibly CRP) 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. No data on effects of CLA intake on the arterial wall have been provided in humans. 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. Long-term effects of CLA intake on insulin sensitivity and the arterial wall have not been adequately addressed in humans. The evidence provided does not establish the safety of CLA consumption by type-2 diabetic subjects under the proposed conditions of use. **CONCLUSIONS** The Panel concludes that the safety of [Tonalin® TG 80] [Clarinol®]CLA-rich oil, an oil with approximately 80% CLA 1:1 mixture of *t*9,*c*11 and *t*10,*c*12 isomers, has been established for the proposed uses at intakes [4.5 g per day (corresponding to 3.5 g CLA)] [3.75 g Clarinol®per day (corresponding to 3 g CLA)], for up to six months. The safety of CLA consumption or periods longer than six months has not been established under the proposed conditions of use. The safety of CLA consumption by type-2 diabetic subjects has not been established.
2B) **Europe, 2012;** European Food Safety Agency (EFSA) Panel on Dietetic Products, Nutrition and Allergies Statement of the safety of "conjugated linoleic acid (CLA)-rich oils" Clarinol®andTonalin® TG 80 as Novel Food ingredients	
Insulin sensitivity and glucose metabolism; Blood lipids; Lipoproteins; Markers of lipid peroxidation;	**DISCUSSION** In its previous opinions […], the Panel considered that CLA consumption did not appear to have adverse effects on insulin sensitivity, blood glucose control or liver function for periods up to six months, and that the observed effects on blood lipids were unlikely to have an impact on cardiovascular disease risk. However, the observed increase in plasma and urinary concentrations of isoprostanes, which may indicate an increase in lipid peroxidation, and the increase in some markers of subclinical inflammation (i.e., 15-*keto*-dihydroprostaglandin $F_{2\alpha}$ and possibly CRP) associated with CLA consumption, together with the limited data available on the effects

Markers of systemic (subclinical) inflammation; Vascular function and vascular damage; Liver function and liver steatosis.	of CLA on vascular function, may indicate a potential for vascular damage (i.e., atherosclerosis) in the long term. Long-term effects of CLA intake on insulin sensitivity, the arterial wall or liver steatosis had not been adequately addressed in humans. The evidence provided did not establish the safety of CLA consumption by type-2 diabetic subjects under the proposed conditions of use. The Panel considers that the additional information provided does not contain evidence that would modify the previous conclusions reached by the Panel regarding the effects of CLA on insulin sensitivity, blood glucose control, blood lipids, lipid peroxidation, or subclinical inflammation. The Panel also considers that the new studies provided do not address longer-term (> 6 months) effects of CLA intake on insulin sensitivity, the arterial wall or liver steatosis, or the safety of CLA in type-2 diabetic subjects, under the proposed conditions of use. **CONCLUSIONS** The Panel considers that the additional information provided does not contain evidence that would modify the previous conclusions reached by the Panel. The Panel concludes that the safety of Clarinol®andTonalin® TG 80,two oils with approximately 80 % of the CLA 50:50 mixture of *t-9,c-11* and *t-10,c-12*isomers, has been established for the proposed uses and daily doses(3.75 g Clarinol® and 4.5 g Tonalin® TG 80 corresponding to approximately 3 g and 3.5 g of CLA, respectively) for 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. The safety of CLA consumption by type-2 diabetic subjects has not been established.

2C) **Europe, 2010;** European Food Safety Agency (EFSA) Panel on Dietetic Products, Nutrition and Allergies

Scientific Opinion on the substantiation of health claims related to conjugated linoleic acid (CLA) isomers and contribution to the maintenance or achievement of a normal body weight (ID 686, 726, 1516, 1518, 2892, 3165), increase in lean body mass (ID 498, 731), increase in insulin sensitivity (ID 1517), protection of DNA, proteins and lipids from oxidative damage (ID 564, 1937), and contribution to immune defences by stimulation of production of protective antibodies in response to vaccination (ID 687, 1519) pursuant to Article 13(1) of Regulation (EC) No 1924/20061

Normal body weight Lean body mass Insulin sensitivity Oxidative damage Immune defence	**CONCLUSIONS** On the basis of the data presented, the Panel concludes that the food constituent, conjugated linoleic acid (CLA) isomers *c*9, t11 and *t*10, *c*12, which is the subject of the health claims, is sufficiently characterised. **Contribution to the maintenance or achievement of a normal body weight** The claimed effects are “weight management”, “body weight management” and “weight management, fat metabolism enhancement”. The target population is assumed to be the general population. Contribution to the maintenance or achievement of a normal body weight is a beneficial physiological effect. A cause and effect relationship has not been established between the consumption of an equimolar mixture of the CLA isomers *c*9, *t*11 and *t*10, *c*12 and contribution to the maintenance or achievement of a normal body

	weight. **Maintenance of lean body mass** The claimed effect is "the support of lean body mass". The target population is assumed to be the general population. An increase in lean body mass is a beneficial physiological effect. A cause and effect relationship has not been established between the consumption of an equimolar mixture of the CLA isomers *c*9, *t*11 and *t*10, *c*12 and an increase in lean body mass. **Increase in insulin sensitivity** The claimed effect is "insulin sensitivity". The target population is assumed to be the general population. An increase in insulin sensitivity is a beneficial physiological effect. A cause and effect relationship has not been established between the consumption of an equimolar mixture of the CLA isomers *c*9, *t*11 and *t*10, *c*12 and an increase in insulin sensitivity. **Protection of DNA, proteins and lipids from oxidative damage** The claimed effects are "antioxidativity" and "antioxidant capability". The target population is assumed to be the general population. Protection of DNA, proteins and lipids from oxidative damage may be a beneficial physiological effect. A cause and effect relationship has not been established between the consumption of an equimolar mixture of the CLA isomers *c*9, *t*11 and *t*10, *c*12 and the protection of DNA, proteins or lipids from oxidative damage. **Contribution to immune defences by stimulation of production of protective antibodies in response to vaccination** The claimed effect is "immune health". The target population is assumed to be the general population. The Panel considers that contribution to immune defences by stimulation of production of protective antibodies in response to vaccination is a beneficial physiological effect.A cause and effect relationship has not been established between the consumption of an equimolar mixture of the CLA isomers *c*9, *t*11 and *t*10, *c*12 and contribution to immune defences by stimulation of production of protective antibodies in response to vaccination.
3) **France**, **2011**;Expert Committee on Human Nutrition (CES Human Nutrition), Agency for Food, Environmental and Occupational Health and Safety (ANSES) Opinion of ANSES on a "safety assessment of the use of an oil enriched with Conjugated Linoleic Acid (CLA)"	
Change in circulating lipoproteins; Insulin resistance; Markers of oxidative stress and inflammation.	**CONCLUSION OF THE CES** On the basis of studies not included in the EFSA 2009 Opinion or published afterwards, the CES on Human Nutrition has assessed the risks related to CLA consumption: • risks related to a change in circulating lipoproteins (elevated LDL-C/HDL-C ratio); • risks related to increased insulin resistance, particularly in diabetics; • risks related to increased inflammatory markers. This assessment revealed that none of these studies reported beneficial effects of mixtures of isomers c9,t11 and t10,c12 on lipid risk

	factors for cardiovascular disease (LDL-C, HDL-C, triglycerides, LDL-C/HDL-C). However, adverse or harmful effects were sometimes reported, particularly an elevated LDL-C/HDL-C ratio. As far as insulin resistance is concerned, numerous *in vitro* and animal studies have shown a harmful effect of isomer t10,c12. However, no studies undertaken in humans are available to assess the relevance of these results for humans. Because the new studies undertaken with equimolar mixtures of isomers c9, t11 (rumenic acid) and t10,c12 are contradictory and report, in half of cases, a harmful effect on insulin sensitivity, they confirm the reservations previously expressed by AFSSA in its report on *trans* fatty acids (AFSSA, 2005) and its Opinions of 23 March 2007 and 11 July, 2008. Lastly, regarding inflammation and oxidative stress, the new data in the literature confirm that in humans, consumption of a CLA mixture containing 50% rumenic acid and 50% t10,c12 increases: • markersof oxidative stress (8-iso-prostaglandin F2α). The observed effect appears greater than that found through smoking (Tomey*et al.* 2007) or from the equivalent consumption of *trans* fatty acids (C18:1, *trans*). • certainmarkers of inflammation (increase in plasma levels of CRP in some studies, levels of 15-keto-prostaglandin F2α and the number of circulating leukocytes). However, these results should be qualified since: • Some authors suggest that in this context, the increase in 8-iso- prostaglandin F2α is not solely a reflection of increased oxidative stress. • The increase in circulating concentrations of CRP and leukocytes that has been observed in individuals supplemented with CLA has been small. Isomer t10,c12 has also been found to cause inflammation of the white adipose tissue *in vivo* in mice and *in vitro* in human adipocyte cultures. As with insulin resistance, it appears that isomer t10,c12 is responsible for the main identified effects such as the increase in markers of lipid peroxidation and inflammation. As expressed by AFFSA in 2005, studies not reporting risks related to "equal mixtures of 18:2 c9,t11 and t10,c12 cannot obscure the results obtained for 18:2 t10,c12. It appears difficult to accept the argument according to which the effects of one of the products cancel out those of the other". Thus, the new data do not report any beneficial effects on the analysed parameters, but sometimes report harmful effects with CLA mixtures. If these harmful effects are combined, the risk of cardiovascular disease and metabolic syndrome could increase. The CES on Human Nutrition therefore considers that, on the basis of the new available data, the risks related to the consumption of CLA mixtures remain ambiguous. […]
5A) **United States of America, 2008;** Food and Drug Administration (FDA) Agency Response Letter GRAS Notice No. GRN 000232, July 11, 2008	
Cardiovascular disease	[….]

parameters – biomarkers of inflammation – isoprostanes – endothelial function; Insulin sensitivity; Maternal milk fat deposition.	The subject of the notice is a glyceride mixture composed predominantly of a 1:1 mixture of *cis*-9, *trans*-11 and *trans*-10, *cis*-12 conjugated linoleic acids. For the purpose of this letter, FDA refers to the subject of the notice as "CLA-isomers." The notice informs FDA of the view of Lipid Nutrition and Cognis that CLA-isomers are GRAS, through scientific procedures, for use as an ingredient in certain specified foods within the general categories of soy milk, meal replacement beverages and bars, milk products and fruit juices at levels not to exceed 1.5 grams (g) per serving. As part of their notice, Lipid Nutrition and Cognis include the report of a panel of individuals (Lipid Nutrition and Cognis' GRAS panel) who evaluated the data and information that are the basis for Lipid Nutrition and Cognis' GRAS determination. Lipid Nutrition and Cognis consider the members of their GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food. Lipid Nutrition and Cognis' GRAS panel reviewed and discusses CLA-isomers' composition, method of manufacture, specifications, and intended estimated dietary intake. Lipid Nutrition and Cognis' GRAS panel also discusses published and unpublished studies conducted with CLA-isomers. Based on this review, Lipid Nutrition and Cognis' GRAS panel concluded that CLA-isomers are GRAS when used as an ingredient in soy milk, meal replacement beverages and bars, milk products, and fruit juices at a level of 1.5 g per serving. [….] Based on the 1994-1996, 1998 USDA Continuing Survey of Food Intakes by Individuals (CFSII) data on the foods to which CLA-isomers are intended for addition and the intended use levels, Lipid Nutrition and Cognis estimate the intake of their CLA-isomers would be 1.22 grams per person per day (g/p/day) at the mean and 2.33 g/p/d at the 90th percentile. […] Lipid Nutrition and Cognis note that the *cis*-9, *trans*-11 isomer accounts for 90% of CLA intake in the diet. For the general United States population, Lipid Nutrition and Cognis note that the estimated mean intake of CLA from natural dietary sources is 0.21 and 0.15 g/p/day for men and women, respectively. Lipid Nutrition and Cognis state that the metabolism of CLA has been extensively studied and reported in published literature and follows the standard pathway of dietary triglycerides. Lipid Nutrition and Cognis conclude that a review of the published clinical data demonstrates that consumption of CLA-isomers at levels of up to 6 g/p/day for up to 1 year and 3.4 g/p/day for up to 2 years is safe. In bioavailability studies, single oral intakes of up to approximately 15 g of CLA in oil (containing up to approximately 9 g of CLA-isomers) resulted in no reported adverse events. […] Lipid Nutrition and Cognis discuss three aspects of the safety of CLA-isomers with regard to cardiovascular disease. The first aspect is the effect of CLA-isomers on biomarkers of inflammation. Included in this discussion are human intervention studies that report no effect on lipid parameters and trials which show statistically significant changes in lipid parameters, but remain within population range. Literature reports state that consumption of the single *trans*-10, *cis*-12 CLA isomer resulted in increased C-reactive protein (CRP) levels, while consumption of the 1:1 CLA-isomer mixture did not. Another study in healthy men showed no adverse effects of consumption of either isomer on CRP levels. Lipid Nutrition and Cognis also discuss a study of men and women without cardiovascular disease that assessed traditional risk factors and CRP. The study reports that for those with elevated traditional risk factors, higher CRP levels indicate cardiovascular disease risk, whereas elevated CRP levels alone provided no further prognostic

	information beyond traditional office examination risk factor assessment to predict future cardiovascular disease events. Lipid Nutrition and Cognis conclude that human studies conducted with CLA-isomers demonstrate no effect on biomarkers of inflammation related to cardiovascular disease risk. The second aspect of cardiovascular disease discussed by Lipid Nutrition and Cognis addresses the results of human studies that demonstrate increased levels of isoprostanes with consumption of CLA-isomers. Lipid Nutrition and Cognis note that increased levels of isoprostanes are detected in diseases involving inflammation and oxidative stress above normal levels of isoprostanes found in animal and human biological fluids. Lipid Nutrition and Cognis state that a certain level of ongoing lipid peroxidation takes place and is incompletely suppressed by antioxidant defenses, even in the normal state. Lipid Nutrition and Cognis conclude that no association between isoprostanes and cardiovascular disease risk has been determined. The third aspect of cardiovascular disease discussed by Lipid Nutrition and Cognis addresses a study that reports impaired endothelial function in healthy overweight men who consumed CLA-isomers. The notifier concludes that this study was marked by variability in samples, thus preventing a reliable conclusion. In contrast, additional studies conducted with CLA-isomers report no significant effects on arterial elasticity and that soluble vascular cell adhesion molecule (a plasma biomarker of endothelial dysfunction) decreased in comparison with a placebo group. Lipid Nutrition and Cognis address the safety of CLA-isomers with respect to insulin sensitivity. They state that studies that rely on fasting serum glucose and insulin measures as markers of metabolic change were not considered to be pivotal to their GRAS determination since these methods are inherently variable. Instead, Lipid Nutrition and Cognis discuss studies which report oral glucose tolerance and clamp techniques to demonstrate that CLA-isomers present no adverse effects on glucose and insulin. Lipid Nutrition and Cognis address the effects of CLA-isomers on milk fat deposition. They state that naturally occurring dietary and biological phenomena can alter milk fat production in humans, and only one published study reported significant effects on milk fat deposition. The negative results from the majority of human milk studies contradict animal studies which demonstrate milk fat deposition after CLA administration. The notifier states the effects of CLA on milk fat production seen in cows and rodents cannot be relied on as evidence of the effects of CLA on lipogenesis in humans due to differences in the physiology and biochemistry between ruminants or rodents, and humans. The notifier reports that one human study shows a reduction of milk fat associated with CLA consumption, whereas a more recent study from the same authors using the same protocol showed no effect. Lipid Nutrition and Cognis conclude that the consumption of CLA-isomers by lactating women would not affect milk fat levels beyond the range of normal biological variation, and published reproductive and developmental toxicity studies with CLA-isomers in rats and pigs demonstrate a lack of adverse effects on maternal food consumption and body weight, litter size, and offspring growth and development. […] Based on the information provided by Lipid Nutrition and Cognis, as well as other information available to FDA, the agency has no questions at this time regarding Lipid Nutrition and Cognis' conclusion that CLA-isomers, meeting the specifications listed in GRN 000232, are GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of CLA-isomers. As always, it is the continuing responsibility of Lipid Nutrition and Cognis to ensure that food ingredients these firms market are safe, and are otherwise in compliance with all applicable legal and regulatory

	requirements. […]
5B) **United States of America, 2009;** Food and Drug Administration (FDA) Agency Additional Correspondence Letter GRAS Notice No. GRN 000232, September 8, 2009	
	[…] The subject of the notice is a glyceride mixture composed predominantly of a 1:1 mixture of *cis*-9, *trans*-11 and *trans*-10, *cis*-12 conjugated linoleic acids (hereinafter referred to as "CLA isomers"). The notice informed FDA of the view of Lipid Nutrition and Cognis that CLA isomers are GRAS, through scientific procedures, for use as an ingredient in certain specified foods within the general categories of soy milk, meal replacement beverages and bars, milk products and fruit juices at levels not to exceed 1.5 grams (g) per serving. This level is predicated on Lipid Nutrition and Cognis' expected use of approximately two servings per day. The supplement dated April 22, 2009, seeks confirmation that the FDA does not disagree with the determination of Lipid Nutrition and Cognis that CLA isomers are GRAS for use in certain specified foods within the general categories of soy milk, meal replacement beverages and bars, milk products and fruit juices at levels up to 3 g per person per day. Based on the information provided by Lipid Nutrition and Cognis in GRN 000232, the supplement dated April 22, 2009, and other information available to FDA, the agency has no questions at this time regarding Lipid Nutrition and Cognis' conclusion that CLA isomers are GRAS at levels up to 3 g per person per day. The agency has not, however, made its own determination regarding the GRAS status of the subject use of CLA isomers. As always, it is the continuing responsibility of Lipid Nutrition and Cognis to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements. […]

****** Some assessments rely only on submitted information
[…] indicates omitted text not relevant to the scientific assessment

ATTACHMENT 2

PROPOSAL TO REVIEW THE CODEX DEFINITION OF TRANS FATTY ACIDS FOR LABELLING PURPOSES WITH RESPECT TO CONJUGATED FATTY ACIDS

PROJECT DOCUMENT

1 Purpose and Scope of New Work

The purpose of the work is to review the definition of trans fatty acids in the Codex Guidelines on Nutrition Labelling (CAC/GL 2-1985) with respect to the present exclusion of conjugated fatty acids in the light of recent human evidence. The need for, and clarity of, the associated footnote will also be reviewed.

The scope of the work will compare the current evidence for adverse and favourable health effects of conjugated fatty acids with that oftrans fatty acids to determine whether conjugated fatty acids should remain excluded from the definition of trans fatty acids.

The work will not consider the differentiation into ruminant and industrial trans fatty acids since this matter was considered by CCNFSDU in 2011.

2 Relevance and Timeliness

The definition of trans fatty acids for food labelling purposes is given in the Codex Guidelines on Nutrition Labelling (CAC/GL 2-1985) and also applies to the Codex Guidelines for Use of Nutrition and Health Claims (CAC/GL 23-1997). National authorities have discretion to decide the labelling conditions under which trans fatty acid content of food is declared or taken into account. CCFL is developing conditions for a 'trans free' content claim (REP12/FL, para 34) so it is timely to review the underpinning definition before work starts on any quantified conditions for this claim.

In addition to the presence of ruminant and industrially produced conjugated fatty acids in foods, concentrates of certain isomers of conjugated linoleic acid (CLA) are permitted addition to foods and food supplementsin some jurisdictions.

The evidence for the health effects of conjugated fatty acids in humans has grown considerably since Codex last considered the definition of trans fatty acids.

The Codex Nutritional Risk Analysis Principles and Guidelines note that nutritional risk analysis considers the risk of adverse health effects from intakes of nutrients and related substances and the predicted reduction in risk from proposed management strategies. The definition of trans fatty acids supports the nutrition labelling of foods and conditions for certain fatty acid claims and to that extent, it could be considered to contribute to the management of nutritional risk.

3 Main Aspects to be Covered

The work will compare the current evidence in humans for the adverse and favourable health effects of conjugated fatty acids with that of trans fatty acids. The CCFNSDU will then determine whether conjugated fatty acids should remain excluded from the definition of trans fatty acids.

The need for an associated footnote and the clarity of the footnote will also be reviewed.

4 Assessment against the Criteria for the Establishment of Work Priorities

1 Diversification and potential impediments to international trade

The regulation for labelling of conjugated fatty acids in foods and food supplementshas recently been considered by several jurisdictions with diverse outcomes. Although the Codex footnote provides for jurisdictions to determine their own view of conjugated fatty acids, the scope of the footnote is not clear. A recently reviewed definition and footnote would provide up-to-date guidance to jurisdictions, particularly those without the resources to take advantage of the latitude provided by the footnote.

2 Scope of work and establishment of priorities between the various sections of the work

The scope of work comprises the definition of trans fatty acids and its associated footnote. The work will not consider the differentiation of the definition into ruminant/industrial trans fatty acids since this matter was considered by CCNFSDU in 2011.

3 Work already undertaken by other international organisations in the field and/or suggested by relevant international intergovernmental bodies

Reviews of the adverse and favourable health effects of conjugated fatty acids, particularly isomers of CLA, have been conducted in the past 5 years by government regulatory or scientific agencies in at least Europe; France; Australia New Zealand and the United States. WHO has advised that it is planning to review and update the international recommendations on fat and fatty acids in 2012-13.

4 Amenability of the subject of the proposal to standardization

This Proposal for New Work relates to an existing Codex definition and footnote.

5 Consideration of the global magnitude of the problem or issue.

There is global interest in trans fatty acids both from a food regulatory and public health nutrition perspective. Several jurisdictions have taken steps to reduce the level of industrial trans fatty acids in their food supplies. Having the definition of trans fatty acids in Codex texts reflect a recent review of the evidence could contribute to greater consistency of the labelling of trans fatty acids in traded foods and food supplements.

5 Relevance to Strategic Goals

The most relevant Strategic Goals are:

Goal 1 Promoting sound regulatory frameworks, in particularActivity 1.3 – Review and develop Codex standards and related texts for food labelling and nutrition

Review of the definition and footnote will assist the promotion of sound regulatory frameworks based on updated evidence.

Goal 2 Promoting widest and consistent application of scientific principles and risk analysis

The review will consider more recent evidence and decision making will adopt a risk-based approach.

6 Information on the relation between the Proposal and Other Existing Documents

A definition of trans fatty acids underpins the provisions in the Codex Guidelines on Nutrition Labelling (CAC/GL 2-1985) and the Codex Guidelines for Use of Nutrition and Health Claims (CAC/GL 23-1997) related to the declaration of trans fatty acid content and conditions of claims for saturated fatty acid and cholesterol content of foods.

In 2012, CCFL agreed to develop conditions for trans fatty acid free content claims and has requested advice from CCNFSDU in preparation for that work (REP12/FL, para 34). The definition of trans fatty acids will be critical in determining any quantitative conditions for trans fatty acid free claims.

7 Identification of any Requirement for and Availability of Expert Scientific Advice (such as from FAO/WHO)

CCNFSDU was advised that the WHO Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health plans to review and update the recommendations on fat and fatty acids in 2012-13 (REP12/NFSDU, para 22). If appropriate in terms of scope and timing, CCNFSDU could seek advice from WHO on a definition of trans fatty acids with respect to conjugated fatty acids as part of the review.

8 Identification of any need for Technical Input to the Revision from External Bodies so that this can be Planned

None foreseen.

9 Proposed Timeline for Completion of the New Work

December 2012	Endorsement of Proposal for New Work by CCNFSDU
July 2013	Approval of Proposal for New Work by Commission
November 2014	Consideration of evidence base and potential WHO/FAO input and possible draft revised definition at Step 2 and advancement to Step 3
November 2015	Consideration of draft revised definition at Step 5 of the accelerated procedure
July 2016	Adoption of revised definition by Commission

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