Bureau Nieuwe Voedingsmiddelen
Novel Foods Unit

Geconjugeerd linolzuurrijke olie

Conjugated linoleic acid rich oil

Tweede beoordeling van de veiligheid voor de consument, volgens de Europese verordening 258/97 betreffende nieuwe voedingsmiddelen en nieuwe voedselingrediënten

Second opinion regarding consumer safety, in accordance with European Regulation 258/97 concerning novel foods and novel food ingredients

aan/to:

de Minister van Volksgezondheid, Welzijn en Sport
the Minister of Health, Welfare and Sport

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Aan de orde is een tweede beoordeling volgens de Europese Verordening 258/97, over het gebruik van een olie rijk aan geconjugeerd linolzuur (CLA) als nieuw voedselingrediënt. De aanvrager is het Nederlandse bedrijf Lipid Nutrition BV. Het nieuwe product met merknaam Clarinol™ is afkomstig van saffloerolie. De CLA-rijke olie is niet direct beschikbaar voor de consument maar zal worden verwerkt in verschillende levensmiddelen.

Voedingssupplementen met CLA waren al op de markt in de EU voordat op 15 mei 1997 de verordening in werking trad. Voor een meer uitgebreide toepassing in gewone levensmiddelen is echter een veiligheidsbeoordeling als nieuw voedingsmiddel vereist. In het kader van de desbetreffende Europese toelatingsprocedure is deze tweede beoordeling uitgevoerd door het Bureau Nieuwe Voedingsmiddelen van het College ter Beoordeling van Geneesmiddelen. Het bureau heeft hiervoor de Commissie Veiligheidsbeoordeling Nieuwe Voedingsmiddelen geraadpleegd, hierna genoemd ‘de commissie VNV’.

Eerste beoordeling

De eerste beoordeling van de aanvraag voor markttoelating is verricht in Ierland door de *Food Safety Autority* (FSAI). De FSAI concludeert dat CLA-rijke olie veilig kan worden gebruikt mits het voldoet aan de productspecificatie en het assortiment beperkt blijft tot de voorgestelde producten. Tevens oordeelt de FSAI dat aanbevelingen en waarschuwingen voor gebruik van CLA-verrijkte producten duidelijk moeten worden geëtiketteerd om er voor te zorgen dat het gebruik beperkt blijft tot de doelgroep, te weten gezonde volwassenen die de nieuwe producten gaan gebruiken bij gewichtsbeheersing. Volgens de FSAI moet gebruik door kinderen jonger dan 5 jaar, zwangere vrouwen en vrouwen die borstvoeding geven worden ontraden.

Begripsbepaling

CLA is een verzamelnaam voor een groep meervoudig onverzadigde vetzuren met 18 koolstofatomen. De plaats in de keten van de twee dubbele koolstofbindingen kan variëren, maar ze komen altijd in geconjugeerde vorm voor, dat wil zeggen gescheiden door maar één enkele binding. De dubbele bindingen zijn van het cis- óf trans-type. Deze vetzuren zijn isomeren van het essentiële vetzuur linolzuur (C18:2) en zijn van nature ook in onze voeding aanwezig, zij het in geringe hoeveelheden, afkomstig van melk en vlees van herkauwers.

De CLA-rijke olie Clarinol™ bevat vetzuren voornamelijk in de vorm van triglyceriden en deze vetzuren bestaan voor bijna 80 % uit CLA. Ongeveer 74 % van de vetzuren bestaan uit vergelijkbare hoeveelheden van de CLA-isomeren cis-9,trans-11 en trans-10,cis-12 (zie pagina’s 3-5 van Bijlage A). De meest voorkomende andere vetzuren zijn oliezuur, palmitinezuur en stearinezuur.

Bevindingen van de commissie VNV

De commissie VNV heeft geen bezwaar tegen de toelating van CLA-rijke olie in de toepassing die de firma voorstelt, te weten een CLA-inname van 3 gram per dag, omdat er geen aanwijzingen zijn dat CLA de volksgezondheid ongunstig beïnvloedt. De commissie VNV baseert haar oordeel op de informatie in het dossier (waarvan de samenvatting is opgenomen als bijlage A), aanvullende informatie (Can08), en de eerste beoordeling door de FSAI (bijlage B). Ook heeft de commissie wetenschappelijke literatuur geraadpleegd. In aanvulling op de veiligheidsbeoordeling door de FSAI licht zij hieronder enkele kwesties nader toe en plaatst zij een aantal kanttekeningen.

CLA-rijke olie wordt verkregen door olie uit zaden van saffloer te behandelen met een combinatie van chemische middelen en enzymen. Saffloerolie (distelolie) is van nature rijk aan linolzuur. In het dossier wordt het uitgangsmateriaal aangeduid met 'ruwe' saffloerolie, saffloerolie rijk aan linolzuur van levensmiddelenkwaliteit, geraffineerde saffloerolie maar ook met geraffineerde, oliezuurrijke saffloerolie. Het is hierdoor niet duidelijk welke variant voor de productie van CLA-rijke olie wordt gebruikt. De isomerisatie van de vetzuren is een zuiver chemisch proces, maar in de andere fasen van het productieproces worden twee enzymen afkomstig van micro-organismen[1] gebruikt. Over de zuiverheid van deze enzympreparaten en over de veiligheid van gebruik in levensmiddelen bevat het dossier geen informatie. De aanvrager werkt volgens internationaal erkende procedures voor kwaliteitsbeheersing en commissie VNV gaat ervan uit dat mogelijke risico's voldoende worden bewaakt om de kwaliteit te waarborgen.

De commissie VNV is het grotendeels eens met de Ierse evaluatie van het toxicologisch proefdieronderzoek. Voor wetenschappelijk onderzoek aan vetten blijken varkens beter geschikt als proefdiermodel dan knaagdieren. In het dossier is echter alleen een summiere samenvatting opgenomen van subchronisch onderzoek bij varkens. Deze informatie is onvoldoende om de test te kunnen beoordelen. Daarnaast concludeert de commissie dat in het onderzoek met zwangere varkens geen toxicologische eindpunten zijn geëvalueerd. De aanvrager presenteert dit ten onrechte als toxicologisch reproductieonderzoek. De commissie erkent dat resultaten van veiligheidsonderzoeken bij mensen, mits van goede kwaliteit, relevanter zijn dan die met proefdieren. Toch vindt de commissie het een tekortkoming van het dossier dat degelijk toxicologisch onderzoek bij varkens met voldoende hoge CLA-dosering ontbreekt.

Chemisch gezien is CLA een transvetzuur. Dat bepaalde transvetzuren schadelijk zijn voor de gezondheid is alom bekend. De wetenschappelijke informatie hierover is gebaseerd

[1] Deze zogeheten lipasen zijn afkomstig van de gist *Candida rugosa* en van de schimmel *Rhizomucor miehei* en kennen een brede toepassing in de vet- en olie-industrie. *Candida rugosa's* lipase is door de Food and Drug Administration in de Verenigde Staten erkend als veilig voor menselijke gebruik (*generally recognized as safe, GRAS*). Over de lipase producerende schimmel *Rhizomucor miehei* wijst de commissie op een recent voorstel van EFSA dat dit organisme niet in aanmerking zou komen voor de QPS status bij gebrek aan gegevens over de afwezigheid van biologisch actieve secondaire metabolieten, waaronder mogelijke allergene verbindingen (EFSA07).

op transvetzuren van het type enkelvoudig onverzadigd[2], die het risico op coronaire hartziekten verhogen via een ongunstig effect op de lipoproteïnenconcentraties in het bloed. Deze transvetzuren moeten daarom zoveel mogelijk worden geweerd uit onze dagelijkse voeding (GR06, VWS08, Wil08). Het is echter niet bekend of meervoudige trans-onverzadigde vetzuren, zoals CLA, vergelijkbare kwalijke effecten zouden kunnen hebben. Omdat door de introductie van CLA in een breed assortiment levensmiddelen de inname van meervoudige trans-onverzadigde vetzuren fors zal toenemen, was de commissie VNV bezorgd over nadelige gezondheidseffecten als mogelijk gevolg van de verhoogde blootstelling. Zij heeft daarom de gegevens van mensgebonden onderzoek met CLA, over in het bijzonder bloedlipiden, zorgvuldig geëvalueerd.

De commissie VNV concludeert dat er voldoende interventieonderzoeken zijn gedaan (gerandomiseerd, dubbelblind, placebo-gecontroleerd) die aangeven dat er geen ongewenste effecten optreden. Bijna alle onderzoeken zijn uitgevoerd bij gezonde proefpersonen, al dan niet met overgewicht, die gedurende één tot drie maanden aan CLA-rijke olie werden blootgesteld. De gebruikelijke dosering was 3 à 4 gram CLA per dag. In één onderzoek met een blootstellingsperiode van één jaar is een dagelijkse dosering van 6 gram CLA bestudeerd. Uit de resultaten blijkt dat LDL-serumcholesterol, dat een belangrijke voorspeller is van coronaire hartziekten, niet in ongunstige zin verandert onder invloed van CLA. De commissie VNV is het eens met de eerste beoordelaar dat op basis van alle beschikbare informatie er geen aanwijzingen zijn dat CLA een ongunstig effect heeft op de lipoproteïnenconcentraties in het bloed.

Het menselijk lichaam verwerkt CLA-rijke olie op dezelfde manier als andere plantaardige spijsoliën. In verhouding met de totale hoeveelheid vet die men dagelijks binnenkrijgt is de 3 gram CLA, die de aanvrager voorstelt, laag (overeenkomend met net iets meer dan één energieprocent). Het lijkt de commissie VNV niet erg waarschijnlijk dat een dergelijke hoeveelheid CLA een grote impact op het vetmetabolisme zal hebben. Volgens de voedselconsumptiepeiling, uitgevoerd bij Nederlandse jongvolwassenen (19-30 jaar) in 2003, bedraagt de dagelijkse vetinname gemiddeld 77 gram bij vrouwen en 107 gram bij mannen (Hul05, VWS08). In dit perspectief zijn grote aantallen proefpersonen nodig om eventuele fysiologische veranderingen aan te kunnen tonen bij lage CLA doseringen. Uit gegevens van de verstrekte onderzoeken blijkt dat een dagelijks gebruik van 3 gram CLA geen aanleiding geeft tot bezorgdheid voor de volksgezondheid. De commissie VNV realiseert zich evenwel dat de beoordeelde onderzoeken in veel gevallen niet met omvangrijke groepen personen zijn uitgevoerd. Met betrekking tot de transvetdiscussie is er vooralsnog geen antwoord op de wetenschappelijke vraag of CLA het vermogen heeft het bloedlipidenpatroon te beïnvloeden en hoe dit effect zich verhoudt tot dat van enkelvoudig trans-onverzadigde

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[2] Deze enkelvoudige trans-onverzadigde vetzuren zijn aanwezig in industrieel (gedeeltelijk) geharde plantaardige oliën. De vetzuren die het meest zijn onderzocht zijn transisomeren van C18:1 (GR06). Daarnaast bevat onze voeding van nature transvetzuren in melk en vlees afkomstig van herkauwers. Dit zijn voor het overgrote deel ook enkelvoudig trans-onverzadigde vetzuren en de belangrijkste hiervan is vacceenzuur C18:1(n-7)*t* (Oom00, Hul05). Recente interventieonderzoeken hebben aangetoond dat deze dierlijke transvetzuren eveneens een ongunstig effect kunnen hebben op het bloedlipidenpatroon bij mensen. Echter de dagelijks geconsumeerde hoeveelheden zijn relatief gering waardoor deze vetzuren niet in belangrijke mate bijdragen aan het risico op coronaire hartziekten (Wil08).

vetzuren[1] of een 'neutraal' (controle) vetzuur zoals oliezuur. De commissie VNV wijst op een interventie-onderzoek dat hier meer inzicht in zou moeten verschaffen (Bro08). Dit is recent uitgevoerd bij Wageningen Universiteit met gezonde vrijwilligers die dagelijkse 19 gram innamen van één van de hierboven genoemde vetzuren. De evaluatie van de resultaten moet echter nog worden voltooid. Wel werd bij een vooronderzoek duidelijk dat consumptie van 19 gram CLA geen nadelige effecten had op belangrijke orgaanfuncties (dr. I. Brouwer, persoonlijke communicatie).

Er zijn geen gegevens over hoeveel CLA de Nederlandse bevolking dagelijks binnenkrijgt met de gewone voeding, maar de commissie VNV heeft een ruwe schatting gemaakt gebaseerd op transvetzuurinname met melk en vlees (en afgeleide producten, zie ook voetnoot 2). Volgens metingen in 2003 bij jongvolwassenen is dit gemiddeld 0,9 gram transvetzuren per dag (Hul05). De dagelijkse CLA-inname door consumptie van dergelijke producten is zeker een factor tien lager, en is dus minder dan 90 milligram. Deze hoeveelheid is redelijk vergelijkbaar met recente gegevens over inwoners van Portugal die gemiddeld 70 milligram CLA per dag consumeren grotendeels afkomstig van melk en kaas (Mar07). Dit is gebaseerd op gedetailleerde analysen van individuele CLA isomeren[3] in zuivelproducten en vlees. De onderzoekers stellen vast dat CLA het meest voorkomt in de cis-9,trans-11 vorm, en dat de trans-10,cis-12 isomeer van nature nauwelijks voorkomt. De commissie VNV concludeert dat wat men aan CLA binnenkrijgt met de dagelijkse voeding niet alleen beduidend minder is in vergelijking met 3 gram CLA met het nieuwe ingrediënt, ook de isomerenverhouding is totaal verschillend.

De aanvrager stelt voor CLA toe te passen in volgende productcategorieën: vruchten- en groentesappen, graanproducten, producten op basis van melk, poeders voor instant-dranken en voedingssupplementen. Per portie zullen de levensmiddelen 1,5 gram CLA bevatten (zie pagina 11-12 in bijlage A). De aanvrager heeft de CLA-inname berekend op basis van consumptiegegevens van de Engelse bevolking. Hierbij is ervan uitgegaan dat men uitsluitend de voorgestelde levensmiddelen waaraan CLA is toegevoegd zal nuttigen in het huidige eetpatroon. De FSAI baseert haar oordeel op resultaten in een rapport van april 2008 die de gegevens in het oorspronkelijke dossier vervangen. Voor de commissie VNV is het onduidelijk waarom de innameberekeningen zijn herzien. Uit de nieuwe gegevens blijkt dat gebruikers van de voorgestelde producten gemiddeld 0,7 gram of 0,9 gram CLA per dag consumeren, respectievelijk voor kinderen en volwassenen. Voor grootverbruikers onder hen komt de inschatting neer op dagelijks 2,0 à 3 gram CLA. Wat opvalt, is dat de bevolkingsgroep met het hoogste percentage gebruikers kinderen zijn (4-10 jaar oud). De commissie VNV is het eens met de aanvrager dat voor een betrouwbare inschatting een traditionele benadering, zoals die is toegepast, eigenlijk niet voldoet omdat geen rekening wordt gehouden met een bewuste keuze voor deze speciale producten. Gegevens uit consumentenonderzoek om dit in kaart te brengen ontbreken. De commissie is er echter niet van overtuigd dat de consument bij een breed aanbod van CLA-verrijkte levensmiddelen nog zo voedingsbewust zal zijn als voorgesteld door de aanvrager. De resultaten zijn

[3] De cis-9,trans-11 isomeer van CLA draagt voor 60-80 % bij aan het totale CLA gehalte. De isomeer die daarnaast het meeste voorkomt is de trans-7,cis-9 vorm, die voor 8-20 % bijdraagt aan totaal CLA. De trans-10,cis-12 isomeer van CLA vormt maar ten hoogste 0,5 % van alle CLA isomeren.

geruststellend in de zin dat mensen met hun huidig voedingspatroon niet meer zullen binnenkrijgen dan de voorgestelde 3 gram. Alleen door onderzoek van de consumptie onder vrije condities van gebruik kan worden geverifieerd of de werkelijke consumptie van CLA overeenkomt met de gewenste inname.

Voedingssupplementen met CLA-rijke olie zijn commercieel verkrijgbaar in de EU sinds 1995, ook in Nederland bij de meeste gewone drogisterijen. Volgens de aanvrager zijn er geen meldingen over ongewenste gezondheidseffecten. De commissie VNV veronderstelt dat het gebruik van dit voedingssupplement niet leidt tot klachten maar het is haar niet bekend of de aanvrager eventuele klachten van gebruikers registreert.

De commissie VNV is het eens met de FSAI dat op het etiket duidelijk moet worden vermeld voor welke bevolkingsgroep de nieuwe producten zijn bedoeld. De commissie deelt in algemene zin de aandacht van de FSAI voor onbedoeld gebruik door kwetsbare groepen, maar acht het niet waarschijnlijk dat incidentele consumptie van CLA-verrijkte producten door kinderen, zwangere vrouwen, en vrouwen die borstvoeding geven, aanleiding geeft tot gezondheidsproblemen. Gegevens van grootschalig veiligheidsonderzoek bij mensen met hogere doseringen dan 3-4 gram ontbreken. Er zijn daarom beheersmaatregelen nodig om te voorkomen dat de dagelijkse CLA consumptie de voorgestelde hoeveelheid van 3 gram overschrijdt. Dit betekent dat niet alleen het productassortiment beperkt en goed omschreven moet zijn, ook zullen portiegroottes duidelijk moeten worden gedefinieerd.

Conclusie

Samenvattend is de commissie VNV het eens met de positieve beoordeling door de FSAI. De commissie VNV wijst erop dat evaluatie van de veronderstelde gezondheidsbevorderende werking geen onderdeel is van haar beoordeling. Vanuit veiligheidsoverwegingen is de commissie VNV niet tegen het verwerken van CLA in levensmiddelen omdat zij geen aanwijzingen heeft dat het dagelijks gebruik van ten hoogste 3 gram zal leiden tot nadelige gezondheidseffecten.

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Assessment - English courtesy translation (August 21, 2008)

Introduction

The subject in question is a so-called second assessment, in accordance with European Regulation 258/97, regarding the use of an oil that is rich in conjugated linoleic acid (CLA) as a novel food ingredient. The applicant is the Dutch company Lipid Nutrition BV. The novel product, which bears the brand name of Clarinol^{TM}, is derived from safflower oil. The CLA-rich oil is not directly available to consumers, instead it will be incorporated into various foods.

Food supplements containing CLA were already being marketed in the EU prior to 15 May 1997, when the regulation came into effect. However, a novel food safety assessment is required for its more extensive use in ordinary foods. In the framework of the relevant European approval procedure, this second assessment was prepared by the Novel Foods Unit of the Medicines Evaluation Board. To this end, the Unit consulted the Committee on the Safety Assessment of Novel Foods (hereafter referred to as 'the VNV Committee').

Initial assessment

The initial assessment of the application for market authorisation was carried out in Ireland, by the Food Safety Authority of Ireland (FSAI). The FSAI concluded that CLA-rich oil can safely be used, provided that it meets the product specification and that the range remains limited to the proposed products. The FSAI also states that the recommendations and warnings pertaining to the use of products fortified with CLA should be clearly indicated on the product labelling. The aim of this is to ensure that use of the product remains restricted to the target group, which consists of healthy adults who intend to use the novel products in connection with weight management. The FSAI advises against the use of this product by children below the age of five, pregnant women and women who are breastfeeding infants

Specification

CLA is a collective term for a group of polyunsaturated fatty acids containing 18 carbon atoms. The exact locations on the chain of the two double carbon bonds can vary, but they are always conjugated, i.e. separated only by a single bond. The double bonds are either of the cis or trans type. These fatty acids are isomers of the essential fatty acid linoleic acid (C18:2). They occur naturally in our diet, albeit in small amounts, in the milk and meat of ruminants.

The CLA-rich oil Clarinol^{TM} contains fatty acids, mainly in the form of triglycerides. CLA makes up almost 80% of these fatty acids. Approximately 74 % of the fatty acids consists of similar quantities of the CLA isomers cis-9,trans-11 and trans-10,cis-12 (see pages 3 to 5 of Annex A). The other most commonly occurring fatty acids are oleic acid, palmitic acid, and stearic acid.

Findings of the VNV Committee

The VNV Committee has no objection to the authorisation of CLA-rich oil in the use proposed by the company, namely a CLA intake of 3 grams per day. This is because there is no evidence to suggest that CLA adversely affects public health. The VNV Committee bases its views on the information contained in the dossier (the summary of which is contained in Annex A), on additional information (Can08), and on the first assessment by the FSAI (Annex B). The Committee has also consulted the scientific literature. Supplementary to the safety assessment by the FSAI, the Committee has provided a further explanation of some issues and added a few comments.

CLA-rich oil is obtained by treating safflower seed oil with a combination of chemical agents and enzymes. Safflower seed oil (thistle oil) is naturally rich in linoleic acid. The starting material is referred to in the dossier as 'crude' safflower oil, food-grade safflower oil rich in linoleic acid, refined safflower oil, and as refined high oleic safflower oil. As a result, it is not clear which variant is used for the production of CLA-rich oil. While the isomerisation of the fatty acids is a purely chemical process, in the other phases of the production process two enzymes derived from microorganisms[1] are used. The dossier contains no information about the purity of these enzyme preparations nor any details concerning the safety aspect of their use in foods. The applicant follows internationally recognised quality control procedures. Accordingly, the VNV Committee assumes that any possible risks will be carefully monitored, in order to safeguard quality.

The VNV Committee is largely in agreement with the Irish assessment of the toxicological study in experimental animals. With regard to scientific research into fats, pigs have been shown to be more suitable experimental animal models than rodents. However, the dossier contains only a brief summary of a subchronic toxicity study in pigs. This is insufficient information on which to base an assessment of the study in question. In addition, the Committee concludes that no toxicological endpoints were assessed in the test on pregnant pigs. The applicant wrongly presents this as a reproduction toxicity study. The Committee acknowledges that the results of safety studies in humans (provided that these are of adequate quality) are more relevant than those obtained using experimental animals. Nevertheless, the Committee sees the omission of reliable toxicological studies in pigs, using sufficiently high doses of CLA, as a shortcoming of the dossier.

In chemical terms, CLA is a trans fatty acid. It is a widely known fact that certain trans fatty acids are harmful to health. The supporting scientific data is based on trans fatty acids

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[1] These lipases are derived from the yeast *Candida rugosa* and from the mould *Rhizomucor miehei*. They are widely used in the fat and oil industry. The United States Food and Drug Administration has recognised that *Candida rugosa's* lipase is safe for human use, characterising it as GRAS (*generally recognized as safe*). With regard to the lipase-producing mould *Rhizomucor miehei*, the Committee would like to draw attention to a recent proposal by the European Food Safety Authority (EFSA) that this organism does not qualify for Qualified Presumption of Safety (QPS) status. This is due to a lack of data concerning the absence of biologically active secondary metabolites, including potentially allergenic compounds (EFSA07).

of the monounsaturated[2] type, which adversely affect lipoprotein levels in the blood thereby increasing the risk of coronary heart diseases. Accordingly, these trans fatty acids must be excluded from our daily diet wherever possible (GR06, VWS08, Wil08). However, it is not known whether polyunsaturated trans fatty acids, such as CLA, could have similar detrimental effects. The introduction of CLA into a wide range of foods would lead to a substantial increase in the intake of polyunsaturated trans fatty acids. The Committee was therefore concerned that this increased exposure might result in adverse effects on health. Accordingly, it has carefully evaluated data from human studies involving CLA, particularly in relation to blood lipids.

The VNV Committee concludes that sufficient intervention studies have been carried out (randomised, double-blind, placebo-controlled) to enable the possibility of any adverse effects to be excluded. Virtually all of the tests were carried out in healthy human subjects (including some overweight individuals) who were exposed to CLA-rich oil for a period of one to three months. The usual dose was 3 to 4 g CLA per day. In one study, which involved a period of exposure of one year, the effects of a daily dose of 6 g CLA were investigated. The results showed that CLA caused no adverse changes in LDL serum cholesterol (a strong predictor for coronary heart diseases). The VNV Committee concurs with the first assessor that, on the basis of all the available information, there is no evidence that CLA exerts an adverse effect on lipoprotein levels in the blood.

The human body processes CLA-rich oil in the same way as it does other edible vegetable oils. In relation to the total amount of fat that people ingest each day, the 3 g CLA proposed by the applicant is very little indeed (corresponding to just over one percent of total energy intake). In the VNV Committee's view, this quantity of CLA is very unlikely to have a major impact on fat metabolism. According to a 2003 food consumption survey among young Dutch adults (aged 19 to 30), the average daily fat intake is 77 grams for women and 107 grams for men (Hul05, VWS08). From this perspective, large numbers of human subjects would be required to reveal any physiological changes that might be associated with low doses of CLA. Data from the submitted studies shows that the daily consumption of 3 g CLA gives no cause for concern with regard to public health. The VNV Committee is well aware that many of the studies assessed did not involve large groups of subjects. With regard to the trans fat debate, various scientific question remain as yet unanswered. For instance, can CLA influence the blood lipid pattern? If so, how does this relate to the effect produced by monounsaturated trans fatty acids[1] or by a 'neutral' (control) fatty acid, such as oleic acid? The VNV Committee makes reference to an intervention study that could provide a more detailed understanding of this issue (Bro08). This was a recent Wageningen University study in which healthy volunteers who ingested a daily dose of 19 g of one of the above-mentioned fatty acids. However, the evaluation of the results has not yet been completed. Nevertheless,

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2 These monounsaturated trans fatty acids are present in industrially (partially) hardened vegetable oils. The trans fatty acids investigated refer to trans isomers of C18:1 (GR06). Furthermore, trans fatty acids occur naturally in our diet, in the milk and meat of ruminants. Most of these are, in fact, monounsaturated trans fatty acids, the most important of which is vaccenic acid C18:1(n-7)*t* (Oom00, Hul05). Recent intervention studies have demonstrated that these animal trans fatty acids can also have an adverse effect on human blood lipid patterns. However, the amounts consumed on a daily basis are relatively small. As a result, these fatty acids do not contribute significantly to the risk of coronary heart diseases (Wil08).

a preliminary study has clearly demonstrated that the consumption of 19 g CLA has no adverse effects on major organ functions (Dr I. Brouwer, personal communication).

There is no data on the amount of CLA that the Dutch population ingest each day as part of their normal diet. However, the VNV Committee has made a rough estimation based on trans fatty acid intake with milk and meat (and products derived from these foods, see footnote 2). According to measurements in young adults in 2003, the average intake is 0.9 g trans fatty acids per day (Hul05). The daily CLA intake associated with the consumption of such products is at least a factor of ten lower, i.e. less than 90 mg. This amount is broadly comparable with recent data on the population of Portugal, who consume an average of 70 mg CLA per day, largely in milk and cheese (Mar07). This is based on detailed analyses of individual CLA isomers[3] in meat and dairy products. The researchers determined that CLA consists mostly of the cis-9,trans-11 form, and that the trans-10,cis-12 isomer seldom occurs naturally. The VNV Committee concludes that not only is the amount of CLA that people ingest as part of their daily diet substantially lower than the 3 g CLA in the novel ingredient, but the isomer ratio is also totally different.

The applicant proposes that CLA be used in the following product categories: fruit and vegetable juices, cereal products, milk-based products, dry weight beverages and food supplements. The foods will contain 1.5 g CLA per portion (see pages 11-12 in Annex A). The applicant has calculated CLA intake on the basis of consumption data for the population of England. This is based on the assumption that only the proposed foods containing CLA will be consumed in the current eating pattern. The FSAI bases its views on the results of a 2008 report which replaces the data in the original dossier. The VNV Committee is unclear about the need to review the intake calculations. The new data show that children using the proposed products consume an average of 0.7 g CLA per day. The corresponding figure for adults is 0.9 g. For the 'heavy users' in these groups, the estimate would be 2 g to 3 g CLA per day. Strikingly, the population group with the highest percentage of users are children (aged 4 to 10). The VNV Committee concurs with the applicant that a traditional approach of the type used here does not actually give a sufficiently reliable intake estimate. This is because it fails to take account of those who intentionally select these special products. The lack of relevant consumer research data prevents an accurate assessment of this phenomenon. However, the Committee is not convinced that consumers confronted with a wide range of foods fortified with CLA will be as food-conscious as the applicant suggests. The results are reassuring in that, given current dietary patterns, consumers will not ingest more than the proposed 3 g. The only way to verify that the actual consumption of CLA corresponds to the recommended intake is to investigate consumption levels under conditions of free use.

Food supplements containing CLA-rich oil have been commercially available in the EU since 1995. In the Netherlands too, they can be obtained from most high-street chemists. According to the applicant, there have been no reports of adverse effects on health. While the VNV Committee assumes that the use of this food supplement does not lead to any

[3] The cis-9,trans-11 isomer of CLA makes up 60-80 % of the total amount of CLA. The next most commonly occurring isomer is the trans-7,cis-9 form, which makes up 8-20 % of the total amount of CLA. The trans-10,cis-12 isomer of CLA accounts for no more than 0.5 % of all CLA isomers.

complaints, it does not know whether the applicant actually keeps a record of any user complaints.

The VNV Committee concurs with the FSAI that the label should clearly identify the population group for which the novel products are intended. In a general sense, the Committee shares the FSAI's concern for unintended use by vulnerable groups. It nevertheless considers that the occasional consumption of products fortified with CLA by children, pregnant women, and women who are breastfeeding infants will be unlikely to result in health problems. There is no data from large-scale safety studies in humans involving doses in excess of 3 g to 4 g. For this reason, control measures are required to ensure that daily CLA consumption does not exceed the proposed 3 g limit. This has a number of implications. The product range must be limited and well described, and portion sizes must be clearly defined.

Conclusion

In summary, the VNV Committee concurs with the favourable assessment by the FSAI. The VNV Committee points out that an evaluation of the claims regarding health-promoting effects does not fall within the scope of its assessment. On safety grounds, the VNV Committee is not against the incorporation of CLA in foods. This is because it has found no evidence to suggest that the daily consumption of no more than 3 g will result in adverse health effects.

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Samenvatting van het dossier / Summary of the dossier

APPLICATION FOR THE APPROVAL OF CLARINOL™ CLA-RICH OIL UNDER REGULATION (EC) NO 258/97 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF 27 JANUARY 1997 CONCERNING NOVEL FOODS AND NOVEL FOOD INGREDIENTS

On behalf of:

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12 October 2007

Final

NON-CONFIDENTIAL

SUMMARY

APPLICATION FOR THE APPROVAL OF CLARINOL™ CLA-RICH OIL UNDER REGULATION (EC) NO 258/97 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF 27 JANUARY 1997 CONCERNING NOVEL FOODS AND NOVEL FOOD INGREDIENTS

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INTRODUCTION

Lipid Nutrition B.V., propose to market Clarinol™, an oil that is rich in conjugated linoleic acid (CLA-rich oil), derived from safflower oil. CLA-rich oil has been previously consumed legally in the European as a food supplement in weight management products since 1996, however, after extensive consultations with the European Commission and the Member State Competent Authorities, it's use in food products themselves, such as yoghurts *etc*., is considered "novel", within the definition of *Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients* (European Parliament and the Council of the European Union, 1997)[1]. Article 1, point 2., of this regulation classifies a novel food ingredient as: …"foods and food ingredients which have not hitherto been used for human consumption to a significant degree within the Community" (before May 1997). It goes on to suggest a number of sub-categories on novel food ingredients, to which CLA-rich oil would fall under:

[1] Official Journal L 043 , 14/02/1997 P. 0001 – 0006 European Parliament and the Council of the European Union, 1997)

Category (e) – "foods and food ingredients consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating or breeding practices and having a history of safe food use"

However, since during the process the predominant fatty acid linoleic acid is converted to conjugated linoleic acid, involving a change in the orientation of the double bonds, CLA-rich oil could also be considered under:

Category (c) - "foods and food ingredients with a new or intentionally modified primary molecular structure"

Nevertheless, whichever of these categories is preferred, for the purposes of risk assessment and evaluation, this dossier follows the Section 4 of the Commission Recommendation of 1997 outlines recommendations made by the Scientific Committee on Food (SCF) pertaining to the "Scientific Classification of Novel Foods for the Assessment of Wholesomeness", which facilitates the safety and nutritional evaluation of a given novel food/food ingredient. Under this recommendation, CLA-rich oil would be considered as:

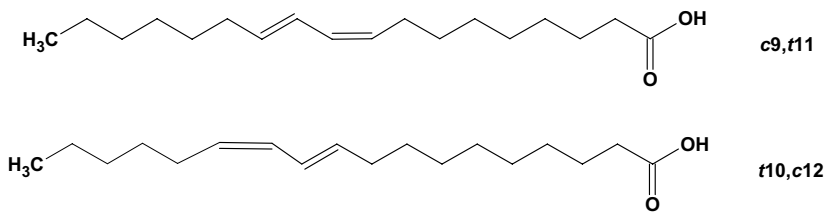
Class 2.1 as a "Complex Novel Food from non-GM source - the source of the novel food has a history of food use in the Community".

I. SPECIFICATION OF CLA-RICH OIL

I.1 Specification

CLA-rich oil is made from the processing of safflower oil. Its primary constituent in conjugated linoleic acid (CLA). CLA-rich oil consists of approximately 78% total CLA isomers and 74% of the 50:50 mixture of the *c*9,*t*11 and the *t*10,*c*12 isomers. The chemical structures of these isomers are shown in Figure I.1-1, below.

Figure I.1-1 Chemical Structure of the Two Primary CLA Isomers of CLA-rich Oil



The isomeric composition of CLA is important with regard to safety; as reviewed by Gaullier *et al.* (2002), CLA preparations consisting of approximately equal proportions of the *c*9,*t*11 isomer and the *t*10,*c*12 isomer are most favourable, but high levels of *trans,trans* fatty acids and other CLA isomers should be avoided. Appropriate production processes are also

important to assure the safety of CLA, such as those used in the production of CLA-rich oil as described in Section II.

The chemical specification for CLA-rich oil is presented in Table I.1-1.

Table I.1-1 Chemical Specification for CLA-rich Oil

Specification Parameter	Specification	Method
CLA total	≥ 78%	High resolution capillary gas chromatography
CLA (*c*9,*t*11 + *t*10,*c*12 isomers)	≥ 74%	High resolution capillary gas chromatography
CLA *c*9,*t*11 isomers	≥ 36%	High resolution capillary gas chromatography
CLA *t*10,*c*12 isomers	≥ 36%	High resolution capillary gas chromatography
Trans fatty acids[1]	≤ 2%	High resolution capillary gas chromatography
Free Fatty Acid	≤ 1%	Titration method / ISO 660
Diglycerides	≤ 25%	High performance size exclusion chromatography
Monoglycerides	≤ 1%	High performance size exclusion chromatography
Water	≤ 0.1%	H-III 3a (92) / ISO 4317 / Karl-Fisher titration method
Peroxide Value	≤ 1 meq O_2/kg	AOCS Cd 8b-90 (97)

[1] Defined as C16+C18+C20+C20+C22 total trans not conjugated

I.2 Potentially Toxic Inherent Constituents, External Contaminants and Nutrients

Independent analysis has been obtained for three non-consecutive production batches of CLA-rich oil and a representative sample of the raw material, safflower oil, from which the product is derived (see Section III.2).

I.2.1 Heavy Metals

The levels of any trace metals in the starting safflower oil are shown to be significantly reduced on processing to form CLA-rich oil. For vegetable oils, EU contaminants legislation only specifies a limit of 0.1 mg/kg for lead and all batches fall below this level (Commission Regulation 1881/2006; Commission of the European Communities, 2006b).

I.2.2 Dioxins and Dioxin-Like PCBs

The results of dioxins and dioxin-like PCBs testing for crude safflower oil and three production batches of CLA-rich oil show that all levels are below the maximum levels permitted by the EU (Commission Regulation 199/2006; Commission of the European Communities, 2006c).

I.2.3 Polyaromatic Hydrocarbons (PAHs)

Polyaromatic hydrocarbons (PAHs) have been analysed in accordance with the substance list recommended by the EU in Commission Regulation 1881/2006 regarding contaminants

in foodstuffs (Commission of the European Communities, 2006b) which is based on the current SCF guidelines (SCF, 2002 and JECFA, 2006). Under EU Regulation a maximum benzo(a)pyrene level of 2.0 µg/kg (wet weight) has been set for vegetable oils as a marker for PAHs contamination in general and the results for this contaminant for crude safflower oil and three batches of CLA-rich oil show that the levels of all PAHs tested were considered to be within the acceptable range by the analytical laboratory.

I.2.4 Pesticides

Agrochemical-approved pesticides may be used during the production of crude safflower oil. A pesticides screen was conducted for crude safflower oil and three production batches of CLA-rich oil in accordance with EU Regulations 396/2005 (European Parliament and the Council of the European Union, 2005). All pesticide residues were within the acceptable range for crude safflower oil and below detection limits for the batches of CLA-rich oil.

I.2.5 Aflatoxins

No traces of aflatoxins were observed above the limits of detection for crude safflower oil and for the three production batches of CLA-rich oil.

I.3 Nutrients

As stated above, CLA-rich oil is produced from safflower oil, which is naturally rich in linoleic acid (typically 67 to 83%; AOCS, 2006). The linoleic acid (LA) in safflower oil is essentially converted to conjugated linoleic acid (CLA) *via* an isomerisation process as described in Section II. The production process does not result in the increase or formation of any components at levels that would represent a safety concern.

I.3.1 Fatty Acids

The fatty acid profiles of crude safflower oil (starting material) and three batches of CLA-rich oil are presented in Table I.3.1-1.

Table I.3.1-1 Fatty Acid Profiles of Crude Safflower Oil and Three Lots of CLA-rich Oil

Fatty Acid	Batch Results % composition of total fatty acids (GC analysis)			
	Safflower Oil	CLA-rich Oil 6503	CLA-rich Oil 7131	CLA-rich Oil 5263
C14:0, myristic	0.1	0.1	0.1	<0.1
C16:0, palmitic	6.3	4.4	4.5	4.0
C16:1, palmitoleic	0.1	0.1	0.1	0.1
C17:0, margaric	0	<0.1	0.1	<0.1
C18:0, stearic	2.3	2.3	2.2	2.2
C18:1, trans (sum of isomers)	0	<0.1	<0.1	0.1

Table I.3.1-1 Fatty Acid Profiles of Crude Safflower Oil and Three Lots of CLA-rich Oil

Fatty Acid	Batch Results % composition of total fatty acids (GC analysis)			
	Safflower Oil	**CLA-rich Oil 6503**	**CLA-rich Oil 7131**	**CLA-rich Oil 5263**
C18:1, oleic	12	12.1	12.3	11.4
C18:2, trans	0.1	0.4	0.3	0.5
C18:2, linoleic (LA)	77.9	1.8	1.2	1.1
C18:2, CLA *c*9,*t*11	0	36.5	36.8	36.7
C18:2, CLA *t*10,*c*12	0	37.9	37.7	37.9
C18:2, CLA *c*9,*c*11	0	0.9	0.9	0.8
C18:2, CLA *c*10,*c*12	0	0.8	0.9	1.1
C18:2, CLA 11,13 (stereochemistry unspecified)	0	0.6	0.8	1.0
C18:2 CLA *t, t*	0	1.3	1.4	2.0
C18:2, oxidised CLA (unspecified)	0	0.2	0.4	0.3
C18:3 (n-3), α-linolenic acid (ALA)	0.1	-	-	-
C20:0, arachidic	0.4	0.3	0.3	0.3
C20:1, eicosenoic	0.2	0.2	0.1	0.2
C22:0, behenic	0.2	0.2	0.1	0.1
C24:0, lignoceric	0.1	0	0	0
Total Fatty Acids	99.8	100	100	99.9
C18:2, CLA total *c*9,*t*11 + *t*10, *c*12	0	74.3	74.5	74.6
C18:2 CLA total	0	78.2	78.9	79.8
Total saturated fatty acids (SAFA)	9.6	7.3	7.2	6.8
Total monounsaturated fatty acids (MUFA)	12.3	12.4	12.4	11.8
Total polyunsaturated fatty acids (PUFA)	78.1	80.2	80.0	81.1

I.3.1.1 Trans Fatty Acids

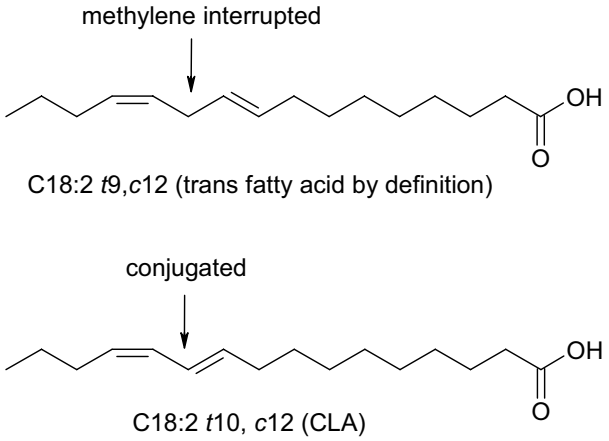
The Codex Alimentarius Commission (CAC, 2005) has proposed the following definition for trans fatty acids:

"..all the geometrical isomers of monounsaturated and polyunsaturated fatty acids having non-conjugated [interrupted by at least one methylene group (-CH2-CH2-)] carbon-carbon double bonds in the trans configuration"

In chemical terms, the definition only includes trans polyunsaturated fatty acids where the double bonds are separated by a methylene group (*i.e.*, CH_2), such as would be formed from linoleic acid (C18:2, *c*9, *c*12) if a double bond was isomerised from the *cis* to the *trans* geometry without a concomitant change in position (C18:2 *c*9, *t*12 or C18:2 *t*9, *c*12, see Figure I.3.1.1-1). Isomerisation of linoleic acid (C18:2 *c*9, *c*12) to form conjugated linoleic acid involves both a change in the geometry and the position of a double bond (*e.g.*, C18:2

*c*9, *t*11 or C18:2 *t*10, *c*12) to yield a structure in which the double bonds are no longer methylene interrupted but conjugated (see Figure I.3.1.1-1 and Section II). The definition of a trans fatty acid, therefore, does not include any of the possible isomers of CLA, because in all cases, the double bonds are conjugated and not methylene interrupted. This distinction is also supported by the Danish Authorities, under Executive Order No 160 (Danish Veterinary and Food Administration, 2003) on the content of trans fatty acids in oils and fats which defines trans fatty acids as the sum of all C14, C16, C18, C20, C22 fatty acid isomers with one or more trans double bonds and specifies that polyunsaturated systems contain methylene interrupted double bonds. Using this definition, the total trans fatty acids in crude safflower oil and three batches of CLA-rich oil are are less that the 2% limit set in the product specification.

Figure I.3.1.1-1 Schematic of Trans Fatty Acids (by Definition) and CLA Isomers



I.3.2 Unsaponifiable Matter

The unsaponifiable matter was isolated from crude safflower oil and three batches of CLA-rich oil and its sterol content determined by GC analysis.

The sterol profile for both crude safflower oil and CLA-rich oil are similar to that of other commonly available oils of plant origin, including sesame seed, borage, evening primrose and olive oils.

I.4 Commercial Scale Batch Manufacturing Results

The analytical information for three commercial scale batches of CLA-rich oil show that all batches comply with the product specification.

I.5 Stability

The stability of CLA-rich oil has been monitored over time for a variety of different storage conditions (temperature, light exposure *etc.*) by measuring the typical indicators of stability

(colour, fatty acid profile, peroxide value *etc*.). CLA-rich oil is stable in air for approximately a month if stored in the dark, however for long term storage (*i.e*., greater than one month) the product should be kept in the dark under a nitrogen atmosphere. Stored dry, in the unopened original packaging, at temperatures between 10 to 20°C, and away from strong odours and direct sunlight, CLA-rich oil is stable for at least 36 months.

The stability of CLA-rich oil can be improved by addition of safe and suitable antioxidants. Antioxidants are added in accordance with the requirements of Directive 95/2/EC (as amended) on food additives other than colours and sweeteners (European Parliament and the Council of the European Union, 1995).

II EFFECT OF THE PRODUCTION PROCESS APPLIED TO CLA-RICH OIL

II.1 Overview of Production Process

An overview of the production process is provided in Figure II.1-1. The specific details of the commercial production of CLA-rich oil by Lipid Nutrition are proprietary but involve processes commonly employed by the fats and oils industry. The raw material used is food grade safflower oil rich in linoleic acid (C18:2, *c*9, *c*12, ≥76%) and containing very few other polyunsaturated fatty acids.

Figure II.1-1 Schematic Overview of the Manufacturing Process for CLA-rich Oil

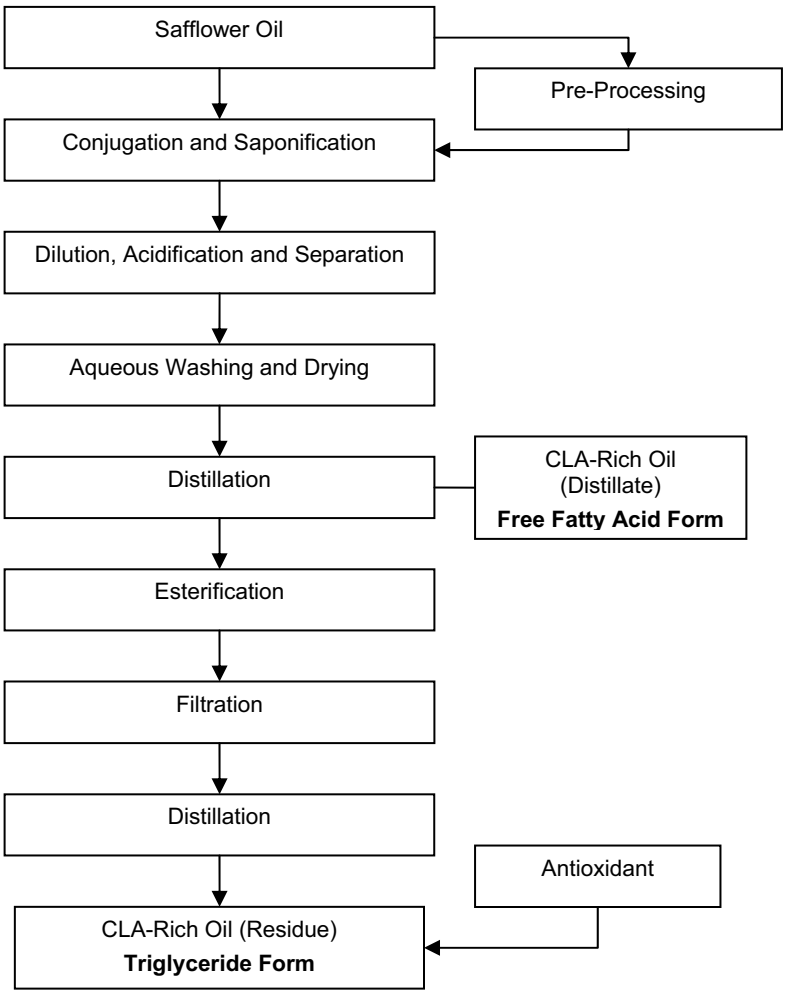
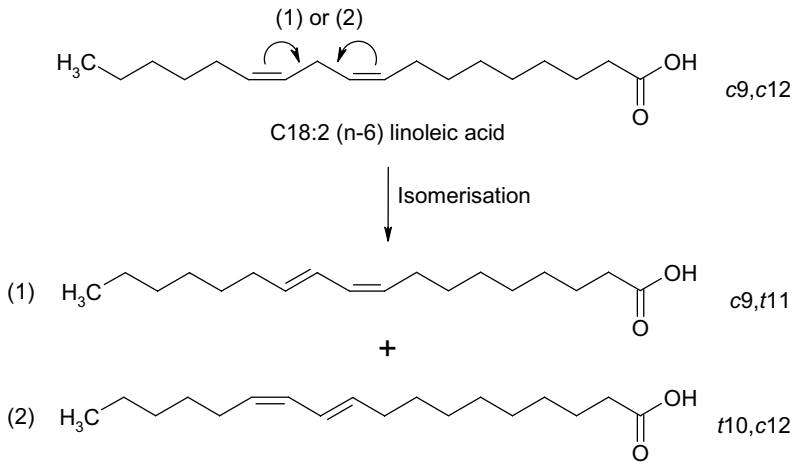


Figure II.1-2 Schematic of the Formation of Conjugated Linoleic Acid from Linoleic Acid



II.1.1 Protein Content

The manufacture of CLA-rich oil involves a number of purification and refinement steps that will ensure only minor traces (<30 mg/kg) of lipases (enzymes involved in one or two stages or preparation) or other proteins (from safflower) are present in the final product. The protein content has been measured for crude safflower oil and three production batches of CLA-rich oil. The results show that all contain less than 30 mg/kg protein. No allergen inducing proteins are reported to be associated with safflower oil and as a result, at these low levels the protein content is not a concern to safety.

II.2 History of the Production Process

Conjugated fatty acids have been prepared from linoleic-rich oil for incorporation in drying agents and varnishes for many years but only more recently have the processes been modified in order to yield products with suitable isomer content and variability for the food industry (Gunstone, 2003). The processes involved in the commercial production of CLA-rich oil are common to the fats and oils industry. For example, hydrolysis, isomerisation and esterification are all reactions traditionally employed for the modification of fatty acid material. In addition, techniques such as distillation, bleaching and deodorisation are all commonly employed within the industry to modify or improve the quality of food-grade oil.

II.3 Potential Hazards

II.3.1 Toxicological Hazards

See Section I.2.

II.3.2 Nutritional Hazards

See Section I.3.

II.3.3 Microbiological Hazards

See Section XII.

II.4 Control of the Production Process and Product Quality

CLA-rich oil production is conducted in accordance with the principles of Good Manufacturing Practice (GMP) and in compliance with EU Hygiene Legislation (EU Regulation 852/2004; European Parliament and the Council of the European Union, 2004). Lipid Nutrition's manufacturing site has a valid and independently certified Hazard Analysis and Critical Control Point (HACCP) system in place to assure the safety and quality of CLA-rich oil.

II.5 Potential Effect of Hazardous Substances on Public Heath

Section I provides information the potentially toxic inherent constituents, external contaminants and nutrients. In addition, toxicological information on the novel food is presented in Section XI. The production process is operated under a certified HACCP system and it is not anticipated that any hazardous substances are present in the final product. Intermediates in the production process undergo washing and distillation stages in order to remove unwanted impurities, excess reagents or by-products. In addition, the final bleaching and deodorisation stage of CLA-rich oil production involves the use of a range of purification aids that will further reduce the potential for any hazardous substances in the final product.

III HISTORY OF THE SOURCE ORGANISM

III.1 History of Safflower Oil

The raw material used for the manufacture of CLA-rich oil is refined safflower oil. This is sourced only from approved suppliers and to the general specifications laid down in the Codex Standard for Named Vegetable Oils Codex-*Stan 210* (Amended 2003, 2005) – this is provided in Appendix 6 (CAC, 2005). Only antioxidants that are approved under Directive 95/2/EC on food additives other than colours and sweeteners and Directive 94/35/EC on sweeteners for use in foodstuffs are used.

As well as being used as a dye for thousands of years, the safflower has been cultivated as a source of food oil throughout the world. The seeds (achenes) typically contain 25 to 30% oil with a linoleic acid content of about 75%, which is the highest known content of this fatty acid, hence it's selection as the source of CLA-rich oil.

Safflower oil species were produced more than 20 years ago by conventional breeding techniques and are widely available on the commercial marketplace. They are widely used as a replacement for or in combination with sunflower oil and are used in food products such as spraying oils for snacks and crackers *etc*., frying oils, for margarines, mayonnaise and salad dressings.

III.2 Taxonomy and Characteristics of Safflower

Safflower, *Carthamus tinctorius* L., is a member of the Compositae or Asteraceae family. It is an herbaceous, highly branched, thistle-like annual/winter annual, commonly with many elongated sharp spines on the leaves. Plants are typically up to 150 cm in height with drop-like flower heads (capitula) and, usually, brilliant yellow, orange or red flowers. Its four-sided achenes are smooth and usually have no pappus. The plant has a robust taproot which lets it thrive in arid climates. In India the crop is traditionally cultivated in the 'rabi' or winter dry season in mixtures with other 'rabi' crops, such as sorghum and wheat. After emergence, the crop remains in rosette form for some weeks before rapid elongation to its mature height. The florets are self-pollinating but can be aided by bees or other insects.

IX INTAKE/EXTENT OF USE OF CLA-RICH OIL

IX.1 Anticipated Food Uses and Maximum Use Level

Conjugated Linoleic Acids (CLA) is proposed for use in the EU in foods such as beverages (fruit juice and vegetable juice), cereal and cereal products (cereal bars, energy bars and slimming biscuits), food supplements (liquid nutritionally complete supplement drinks; powder nutritionally complete supplement drinks), milk and milk products (flavoured milk drinks; skimmed and low fat milk; soya milk; yogurt products), and miscellaneous [dry weight beverages (including drinking chocolate, cocoa, ovaltine and horlicks)].

CLA-rich oil will be added to foods for specific functional uses. Foods to which this ingredient is added will be labelled to disclose to consumers the presence of the ingredient and to provide directions and/or other relevant information about the functional uses. The functional uses will be a primary reason why consumers will purchase and consume the foods. In addition, such foods will be priced at a premium as compared to commodity foods that do not contain CLA because of the high cost of CLA-rich oil. Thus, foods to which CLA-rich oil is added will be specially labelled, marketed, and priced to reflect a functional use, and such foods will not be labelled, marketed, or priced like commodity foods. In this regard, CLA-rich oil is similar to plant sterols in the sense that the ingredient is added to food for a functional use that defines the intended use of the food to which it is added.

At this time, there is not a daily recommended intake level for CLA, but a level of 1.5 g CLA per serving is proposed so that, if consumers choose to do so, they can conveniently obtain 3.0 g CLA by consuming 2 servings of the target foods. The addition of CLA-rich oil to fortified food products will involve health and/or nutrition claims being made, and as such would be subject to the risk management principles laid down in *Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods* (European Parliament and the Council of the European Union, 2006). As part of this regulation, nutrient profiles will be introduced to control the types of food to which functional ingredients such as CLA-rich oil may be added.

Because the addition of CLA-rich oil will cause a food to be materially different from other commodity foods of its type, consumption of CLA-rich oil cannot be accurately estimated using solely a traditional consumption analysis that is based on historical consumption of the commodity foods. Instead, the estimate provided by the traditional analysis must be further evaluated by considering how CLA-rich oil-containing foods will be consumed for functional uses. Post-market surveillance data is also available to provide further reassurance. We present in the following sections a full discussion of these aspects.

IX.2 Estimated Exposure

Theoretical Calculations

Estimates for the intake of CLA in the EU were based on the proposed use-levels and food consumption data collected as part of the United Kingdom (U.K.) Food Standards Agency's, Dietary Survey Programme (DSP). Calculations for the mean and high-levels (90th, 95th, and 97.5th percentile) all-person and all-user intakes, and percent consuming were performed for each of the individual proposed food-uses for CLA. Similar calculations were used to determine the estimated total intake of CLA from all proposed food-uses combined. In both cases, the per person and per kilogram body weight intakes were reported for the following population groups:

children, ages 1 ½ to 4 ½ ;
young people, ages 4 to 10;
female teenagers, ages 11 to 18;
male teenagers, ages 11 to 18;
female adults, ages 16 to 64;
male adults, ages 16 to 64.

Of the individual population groups, male adults were determined to have the greatest mean and 97.5th percentile all-person (0.74 and 4.30 g/person/day, respectively) and all-user intakes (1.21 and 5.75 g/person/day, respectively) of CLA on an absolute basis; while children had the lowest all-person mean and 97.5th percentile of 0.44 and 2.23 g/person/day, respectively. Children and young people had the lowest all-user mean and 97.5%, respectively, with values of 0.71 and 2.47 g/person/day, respectively.

On a body weight basis, children were identified as having the highest mean and 97.5th percentile all-person (30.92 and 154.45 mg/kg body weight/day, respectively) and all-user (50.61 and 179.48 mg/kg body weight/day, respectively) intakes of CLA of any population group. Male adults had the lowest mean and 97.5th percentile all-person intakes of 8.75 and 49.05 mg/kg body weight/day, respectively. Adult males and male teenagers had the lowest all-user mean and 97.5th percentile intakes, respectively, of 15.13 and 59.72 mg/kg body weight/day, respectively.

Practical Considerations

Consumption data and information pertaining to the individual proposed food-uses for CLA were used to estimate the all-person and all-user CLA intakes of specific demographic groups in the U.K. population. Consumption, even at the 97.5th percentile, would not exceed 6 g of CLA-rich oil per day for any population group. This type of intake methodology is generally considered to be 'worst case' as a result of several conservative assumptions made in the consumption estimates. For example, it is often assumed that all food products within a food category contain the ingredient at the maximum specified level of use. In addition, it is well established that the length of a dietary survey affects the estimated consumption of individual users. Short-term surveys, such as the 4-day children's survey, may overestimate consumption of food products that are consumed relatively infrequently, particularly when weighted to 7 days (Gregory *et al*., 1995).

As stated above, it is intended that the target daily dose for adults is 3 g of CLA per day containing up to 1.5 g per serving. It is possible that consumers who intentionally seek CLA-containing foods would eat more than 2 servings per day for a short time – for example, 3 servings per day would provide 4.5 g CLA. However, long-term consumption at this level is unlikely for the reasons discussed above for the following reasons:

- The theoretical calculations above indicate that consumption of sufficient target foods to obtain 3.0 g CLA represents a much higher than average level of intake of these foods (a level at or above the 90th percentile level of intake). Thus, although consumers may seek to supplement their diet with CLA and may experience a short period of time of increased intake, it is unlikely that they will significantly change their habitual intake levels of the target foods over a long period of time.

- We have only requested approval for a narrow range of foods, *i.e.*, a limited number of beverages, yoghurt, and meal replacement bars. Because there is not a wide variety of target foods that could contain CLA-rich oil, and because very few of the target foods would in fact be formulated with CLA-rich oil, it would be difficult for many consumers to eat more than two servings a day of such foods.

Post-market Surveillance

Data from a published post-market surveillance study conducted in 2006 in Spain following the launch of a range of food products supplemented with CLA-rich oil (an equivalent

commercial product available since 2004 in the Spanish market in milk, yoghurt, and juice) provide some information that is relevant to the consumption analysis discussed above. This study interviewed 1,235 consumers of CLA-rich oil supplemented products. Eighty-three percent of consumers were women and the average age of respondents was 41 years. For the yoghurt product containing 1.5 g CLA-rich oil per serving, 93% of consumers consumed up to 2 servings per day. For juice and milk products where the level of CLA-rich oil was the same, the percentage of consumers eating up to 2 servings per day were 88 and 87% respectively. For both product categories combined, about 6% consumed 3 servings per day; about 3% consumed 4 servings per day, and less than 1% consumed more than 4 daily servings.

In addition, the post-market surveillance study included data on adverse effects: 98% of consumers reported no adverse effects; the most commonly reported effect was diarrhoea, followed by nausea and dyspepsia. Because this was not a controlled study, it is not known whether any of the reported adverse effects were actually attributable to CLA-rich oil (Anadón *et al.*, 2006).

IX.3 At Risk Groups

Potentially, at risk groups have been discussed extensively in Section 13, particularly with reference to cardiovascular disease, insulin resistance and maternal milk-fat deposition. Since in most cases CLA will be added to food products intended for normal adults to assist in their weight management regimes, this by nature should exclude, or at least minimise the probability that these products would be consumed by this population group, as in general pregnant and breast-feeding women are specifically advised by the medical profession not to diet.

IX.4 Geographical Restrictions

There are no anticipated geographical restrictions for the marketing of CLA-rich oils beyond local enforcement of relevant standards of identity for specified products and correct labelling translations *etc*.

IX.5 Replacement of Other Foods in the Diet

It is anticipated that where CLA-rich oil is added to foods, it will normally replace or partially replace, where possible, existing fat in the products. Where this is not the case CLA will contribute no more than approximately 5 g of fat to the diet of an adult or 45 kcals per day.

X INFORMATION FROM PREVIOUS HUMAN EXPOSURE TO CLA-RICH OIL

X.1 Previous Human Exposure

Background Consumption in the Diet

Background intakes of CLA-rich oil from CLA-isomers occurring naturally in foods like milk and meat, have previously been estimated for a number of populations. Notably in Finland and Germany estimations have ranged from 132 to 430 mg of CLA per day.

The highest level reported (*i.e.*, 1,000 mg/day) is that found in a Hare Krishna community in Australia. High levels of ghee and butter consumption appeared to be the reason for this high intake. Also, measurements of the CLA content in the breast milk of women in this population resulted in relatively high values, and were related to the high intake of CLA-containing products (McGuire and McGuire, 2002).

The most abundant isomer in dietary CLA is the *c*9,*t*11 isomer, which accounts for more than 90% of CLA intake in the diet (Bhattacharya *et al.,* 2006). This is different from CLA-rich oil, which consists of approximately equal proportions of the *c*9,*t*11 isomer and the *t*10,*c*12 isomer. Because background intake levels are low, they do not significantly affect the intakes from the intended food uses of CLA-rich oil, which are discussed in Section IX above.

Food Supplement Use

Commercial CLA-rich oil has been available on the EU market since 1995, mainly in food supplements. Food supplement products have therefore been consumed to a significant degree in the European Union prior to May 1997. Over this decade there has not been a single consumer complaint reported or documented for any adverse effect.

Typically these deliver a dose of up to 3 g of CLA per daily serving. The labelling requirements of *Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements*, for which CLA-rich oil would be considered an “other substance”, provide clear labelling instructions to control intakes, within Article 6 (European Parliament and the Council of the European Union, 2002).

XI NUTRITIONAL INFORMATION ON CLA-RICH OIL

XI.1 Nutritional Information on CLA-rich Oil

Nutrition Labelling

For the purposes of nutrition labelling CLA-rich oil is considered to be 100% fat. Of this approximately 7% is saturates; 12% is monounsaturates and 80% is polyunsaturates.

The energy value of CLA-rich oil is 9 kcal/g.

Nutritional Properties

The absorption, distribution, metabolism, and excretion (ADME) of CLA-rich oil is discussed in detail in Section XIII.2 and can be considered to be comparable to that of linoleic acid.

CLA-rich oil has been identified as being helpful for weight management products:

- Reducing the amount of body fat
- Increasing lean muscle mass.

Extensive published data are available to support claims in relation to these properties. Notable a meta-analysis conducted by Whigham *et al*. (2007) which provides the most concise comparative overview of these studies and thus is a pivotal source of evidence for health claims submissions.

Consequently CLA-rich oil will be added to foods intended for normal people as part of their weight management and weight loss regimes. Such CLA-fortified foods will not be marketed as being solely responsible for weight loss and will be labelled, in accordance with due diligence and general labelling requirements to state that such products should only be consumed as part of a healthy and balanced diet. Furthermore, as discussed in Section IX, the addition of CLA-rich oil to fortified food products will involve health and/or nutrition claims being made, and as such would be subject to the risk management principles laid down in *Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods* (European Parliament and the Council of the European Union, 2006). As part of this regulation, nutrient profiles will be introduced to control the types of food to which functional ingredients such as CLA-rich oil may be added. More specifically under Article 10, “Specific conditions”, it is stated:

2. Health claims shall only be permitted if the following information is included in the labelling, or if no such labelling exists, in the presentation and advertising:

(a) a statement indicating the importance of a varied and balanced diet and a healthy lifestyle;

(b) the quantity of the food and pattern of consumption required to obtain the claimed beneficial effect;

(c) where appropriate, a statement addressed to persons who should avoid using the food; and

(d) an appropriate warning for products that are likely to present a health risk if consumed to excess.

XII MICROBIOLOGICAL INFORMATION ON CLA-RICH OIL

XII.1 Microbiological Information

No microbiological contamination was observed for any of the production batches. CLA-rich oil is a water-free material, with a product specification for water content of less than 0.1%, and will therefore, not support microbial growth.

XIII TOXICOLOGICAL INFORMATION ON CLA-RICH OIL

Conjugated linoleic acid is the term given to a group of positional and geometric isomers of octadecadienoic acid. The conjugated double bonds (*i.e.*, the 2 double bonds are separated by 1 single bond) can be present in either the *cis* or *trans* configuration and are present predominantly in positions 8 and 10, 9 and 11, 10 and 12, or 11 and 13. CLA-rich oil is a food-grade preparation derived from processed safflower oil containing 78% total CLA isomers and 74% of a 50:50 mixture of *cis*-9,*trans*-11 and *trans*-10,*cis*-12 CLA isomers.

When reviewing the safety of fats such as CLA-Rich Oil, it is important to highlight some fundamental principles.

- First, the selection of test species is important when studying levels of fat in the diet. Laboratory animals, rodents in particular, do not have the same level of adipose tissue, and therefore the ability to store fat, as humans – a phenomenon that is of particular relevance to CLA studies conducted in mice. Consequently, effects that are often observed in animal models, such as the accumulation of fat in a variety of organs, are not necessarily relevant to predicting toxicity in humans. Humans are the most suitable model upon which to base accurate conclusions on the safety of CLA.

- Second, the safety evaluation should focus on the relevant isomeric form of CLA, *i.e.*, the 50:50 mixture. Other isomeric forms do not always produce comparable effects and data derived from such studies should be treated with caution.

- Third, both animal and human studies must be well designed, conducted and reported. There should be multiple doses, adequate duration of exposure, and a

sufficient number of subjects to provide statistical power to evaluate comparative safety based on valid endpoints and markers.

- Fourth, there should be a clear understanding the absorption and metabolic fate of CLA-Rich Oil.

Based on these principles, the order of priority in weighing the evidence of safety of CLA is as follows:

1. Well-designed and properly executed human studies using a 50:50 mixture, of appropriate duration and dose;

2. Well-designed and properly executed preclinical studies using a 50:50 mixture in appropriate animal models and in-vitro, that considered metabolism, dose dependency and mechanism of observed effects, and

3. Additional clinical and preclinical data on other isomers, to demonstrate that the totality of the evidence has been reviewed.

To summarize the relevant data:

- The metabolism of CLA has been widely studied and reported, and follows the standard pathway of dietary triglycerides. Numerous clinical trials have evaluated the effects of the 50:50 mixture and a number of other isomers on similar parameters. A comprehensive review of the clinical data has demonstrated that consumption of 50:50 CLA isomers (CLA-Rich Oil) at doses of up to 6 g/day for up to 1 year (Whigham *et al.*, 2004; Larsen *et al.*, 2006) and 3.4 g/day for up to 2 years (Gaullier *et al.,* 2004, 2005, 2007) is safe and has no significant effects on cardiovascular parameters (lipid metabolism, markers of inflammation, and markers of oxidative stress), insulin sensitivity and glucose, or maternal milk fat. For these “pivotal” studies, the levels of consumption represent the maximum dose consumed, rather than absolute safety endpoints. A single oral dose of up to approximately 15 g of CLA-Rich Oil (containing up to approximately 9 g of CLA isomers) in bioavailability studies has revealed no adverse events.

- Preclinical data have demonstrated an absence of significant toxicological, mutagenic, or reproductive and developmental effects. The no-observed-adverse-effect level (NOAEL) for the 50:50 mixture in the rat, based on a 13-week feeding study, was reported to be 5% in the diet, the highest level fed, which is equivalent to 2,433 and 2,728 mg/kg body weight/day for males and females, respectively. The same authors also reported the absence of the mutagenic potential of CLA, in two *in vitro* assays (reverse mutation and chromosomal aberration in human lymphocytes) (O’Hagan and Menzel, 2003). Such observations on the absence of mutagenicity/genotoxicity are further supported by chronic studies conducted by Park *et al.* (2005) who examined the effects of long-term feeding of male Fischer 344 rats

with a diet containing 1% CLA (41.9% c9,t11 and 43.5% t10,c12) (1,000 mg/kg body weight/day) for a period of 18 months. On a molecular structure and metabolic level, it is clear that CLA would not represent a carcinogenic risk above that of normal dietary triglycerides.

- Reproductive and developmental toxicity studies in rats and pigs also have demonstrated a lack of adverse effects on maternal food consumption and body weight, litter size, and offspring growth and development following exposure to CLA (0.25 to 2% in the diet) throughout gestation, lactation, and/or during a post-weaning period (Chin *et al.*, 1994; Bee, 2000; Poulos *et al.*, 2001).

The weight of the evidence strongly supports that CLA-Rich Oil is safe at the levels used in the pivotal studies.

Additionally, the processing conditions for CLA-rich oil are prohibitive to the retention of any residual proteins from the refined high oleic safflower oil raw material. Safflower/safflower oil itself is not associated with allergenicity and the results from over 30 clinical trials with CLA-rich oil have not reported any allergenic reactions in subjects.

Commercial CLA-rich oil has been available on the EU market since 1995, mainly in food supplements. Over this decade there has been no single consumer complaint reported or documented for any adverse effect.

In conclusion, the available scientific evidence summarized above indicates that Clarinol^{TM} CLA-rich oil would not produce adverse effects on human health when consumed at the intended levels in food described herein. The data and information summarized in this report demonstrate that Clarinol^{TM} CLA-rich oil, meeting appropriated food grade specifications and manufactured and used in accordance with current good manufacturing practice, would be safe under the conditions of intended use in foods.

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Eerste beoordeling / First assessment

May 9, 2008

Food Safety Authority of Ireland (FSAI),
Competent Authority for novel food in Ireland.

Initial Assessment of the Application for the Authorisation of Clarinol™ CLA-Rich Oil under *Article 4* of the Novel Food Regulation (EC) No. 258/97

Name of Applicant: Lipid Nutrition B.V.

Contact person(s): Mr Jaap Kluifhooft, Lipid Nutrition, & Mr Nigel Baldwin, Cantox.

Novel Food Classification: 2.1.

Introduction

A novel food application was submitted to the Food Safety Authority of Ireland (FSAI) in October, 2007, for the authorisation of Clarinol™, an oil that is rich in conjugated linoleic acid (CLA) and derived from safflower seed. The dossier, submitted under *Article 4* of the novel food Regulation (EC) No. 258/97, was formally accepted by the FSAI on November 23rd, 2007, by letter to Mr. Jaap Kluifhooft of Lipid Nutrition B.V. and copied to Mr. Andreas Klepsch of the European Commission.

The application for authorisation of Clarinol™ as a novel food ingredient was prepared pursuant to Commission Recommendation 97/618/EC concerning the scientific aspects and the presentation of information in support of an application to market novel foods and novel food ingredients in the EU. The applicant makes a case that Clarinol™ could be considered in two of the sub-categories listed in *Article 1.2.* of the novel food Regulation: (c) "foods and food ingredients with a new or intentionally modified primary molecular structure"; and (e) "foods and food ingredients consisting of, or isolated from plants, and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating or breeding practices and having a history of safe food use". In order to assess its wholesomeness, Clarinol™ is considered in Class 2.1. by the applicant; "Complex novel food from non-GM source which has a history of food use in the community" (Commission Recommendation 97/618/EC).

CLA represents a family of positional and geometric isomers of linoleic acid that is naturally present at low levels in the EU diet in foods such as meat and dairy products. CLA preparations consisting of approximately equal proportions of the two isomers *c*9, *t*11 and *t*10, *c*12 are favoured from a potential health benefit perspective, while high levels of trans-fatty acids and certain other CLA isomers can have negative health implications. Naturally occurring CLA predominantly consists of the *c*9, *t*11 isomer (90%) whereas the beneficial 50:50 mixture of *c*9,*t*11 and *t*10,*c*12 isomers make up three quarters of Clarinol™ that is processed from safflower seed oil.

The applicant intends to add Clarinol™ to a range of foodstuffs including beverages, cereal products, food supplements and milk products. Target foods will contain 1.5g of CLA per serving and will be marketed at a price reflecting the significant production cost of CLA-rich oil. A novel food authorisation is required as CLA has a history of consumption in supplement form but not in general foods in the EU prior to 1997 (Standing Committee, February 14, 2005).

Using the schemes set out in Commission Recommendation 97/618/EC, the information addressing the safety of CLA is set out as follows.

I. Specification of the novel food

Clarinol^{TM} is an oil derived from safflower seed that is predominantly made up of isomers of CLA (≥78%). The isomeric composition of CLA is important in that certain combinations have potential health benefits while other isomers, along with trans-fatty acids can have deleterious health effects. The CLA content in Clarinol^{TM} is primarily (≥74%) made up of equal proportions of two isomers (*c*9,*t*11 and *t*10,*c*12) and is reported to confer certain beneficial health effects. Though the chemical specification stipulates that CLA-rich oil consists of ≤2% of trans-fatty acids, batch test results indicate the actual levels are less than 1%.
Analysis of contaminants including heavy metals, dioxins, pesticides and aflatoxins were carried out by a reputable and accredited laboratory with the levels recorded within legal limits. The stability of CLA-rich oil can vary depending on various environmental conditions including temperature and light exposure but was greatest when stored at 25°C under nitrogen, where it was stable for greater than 42 months.

II. Effect of the production process applied to the novel food

The manufacturing process for CLA-rich oil is diagrammatically represented in Figure II.1-1 of the application dossier and includes processes commonly used in the fats and oils industry. The process begins with refined safflower seed oil that is rich in linoleic acid. CLA-rich oil is produced by a series of enzymatic reactions that include hydrolysis, isomerisation and esterification. The quality of the final CLA-rich oil is enhanced through mechanical and chemical processes including distillation, bleaching and deodorisation. An independently certified HACCP system is in place backed up by quality assurance and quality control programmes. Samples are tested at all stages of production for adherence to specifications, with product being discarded in the event of unsatisfactory deviation from those specifications.

III. History of the organism used as the source of the novel food

Carthamus tinctorius (Safflower) has been well characterised and has a considerable history of safe use in food around the world. Though an experimental GM safflower has been developed to produce human insulin in its seeds, the variety of safflower used for this product is non-GM. Safflower seed oil is used as cooking oil, in salad dressings and also in the colouring and flavouring of a variety of foods. Only the oil has a history of consumption as food in the EU.

IV. – VIII. Not applicable. No GMO involvement

IX. Anticipated intake/extent of use of the novel food

The EFSA Scientific Panel on Dietetic Products, Nutrition and Allergies (Opinion on the presence of trans-fatty acids in foods and the effect on human health of the consumption of trans-fatty acids, July 8, 2004) estimated the average natural dietary intake of CLA in the EU to be approximately 0.3 g/day. This estimate mirrors

findings in Germany and Finland and leads the applicant to suggest that CLA intake estimates predicted for food fortified with CLA should not be significantly affected by CLA naturally occurring in food. The applicant intends using Clarinol^{TM} in a range of products including beverages, cereal products, food supplements and milk products at a level of 1.5g CLA per serving. Recommended daily intake levels have yet to be established for CLA, however, the applicant's preferred intake of 3g per day is based on the levels required to achieve the purported health benefits (separate information provided by the applicant). Foods containing Clarinol^{TM} are to be specifically targeted at healthy, overweight adults as part of a weight management programme. The premium cost associated with CLA-containing foods will reflect the production cost of Clarinol^{TM} and may also help to reduce any excessive or indiscriminate consumption of such foods.

The applicant used food consumption data from the UK's Food Standards Agency to predict the intake of Clarinol^{TM} through the consumption of the target foodstuffs. Of the individual population groups surveyed, male teenagers were estimated to have the greatest mean and 97.5th percentile all-user intakes (0.92 and 3.12 g/person/day, respectively) of CLA. The estimated intakes represent a "worst case scenario" based on theoretical calculations that would be applicable to UK citizens, but could also apply to citizens of many other EU Member States. The applicant envisages a typical consumption of 3g per day, but intakes as high as 4.5g per day would be possible in some instances. Post market monitoring in 2006 following the 2004 launch of a limited range of products containing CLA-rich oil in Spain indicated that an average of 3 - 6g per day of CLA was consumed by adults, with only a few gastrointestinal health effects reported. The Spanish data indicates that consumption was within the predicted intake levels deduced by this applicant.

The applicant identifies certain at-risk groups in relation to potential health hazards from CLA consumption. The evidence of possible health effects in relation to cardiovascular disease, insulin resistance and maternal milk-fat deposition are dealt with separately in this report.

The applicant argues that pregnant and breast-feeding women are specifically advised by the medical profession not to diet. This, along with the fact CLA will be added to food products intended for healthy, overweight adults to assist in their weight management regimes, should minimise consumption of these products by this population group.

In general, estimates of CLA intake by children from fruit juices and milk products, (particularly yogurt and soya milk) and also from the category "dry weight beverages for slimming purposes" were somewhat high. However, the statistical reliability of some of these estimates is low because of limited sample numbers. This together with the fact that children are not a target for these food products means that intakes in this population group are not of major concern.

During discussions with the applicant it was agreed that foodstuffs containing added Clarinol^{TM} would be labelled to advise pregnant or lactating women and children less than five years of age not to consume these products.

X. Information from previous human exposure to the novel food or its source

As mentioned in section III, safflower has a significant history of use as a food ingredient worldwide, though only seed oil in supplement form has been available in the EU. The applicant provides data from Germany, Finland, USA and Australia on CLA intake levels from natural dietary sources. The data from Germany and Finland confirms that normal dietary CLA consumption in those Member States is within range of the EFSA estimate of 0.3g per day. The relatively high levels (1,000mg/day) identified in Australia are possibly explained by certain sub-groups (e.g. Hare Krishna) consuming high levels of particular dairy products. Naturally occurring CLA is predominantly made up of the *c*9,*t*11 isomer while the Clarinol^{TM} CLA-rich oil consists primarily of equal proportions of *c*9,*t*11 and *t*10,*c*12 isomers.

XI. Nutritional information on the novel food

CLA-rich oil is 100% fat of which 7% is saturated, 12% is monounsaturated and 80% is polyunsaturated. CLA-rich oil has an energy value of 9 kcal/g and will be added to foods as part of a weight management programme for overweight individuals. The applicant intends that added CLA will replace, or partially replace existing fat and in any case would add approximately 5g of fat or 45 kcals/day to the diet of an average adult.

XII. Microbiological information on the novel food

CLA-rich oil is a water-free material (water <0.1%) and does not support significant microbial growth. The batch analyses carried out did not detect the presence of any microbial contaminants.

XIII. Toxicological information on the novel food

Laboratory animals (particularly rodents) are not suitable for studies on dietary lipids as they do not have the same level of adipose tissue, and therefore the same fat storage capacity as humans. For this reason the applicant makes the reasonable argument that the safety assessment of CLA in food should be based primarily on human studies rather than traditional pre-clinical experimental studies in animals.

Absorption, Distribution, Metabolism and Excretion (ADME)
The absorption, distribution, metabolism and excretion of CLA are all similar to those of other fatty acids, including linoleic acid. Animal studies, confirmed by human studies, demonstrate that CLA is absorbed across the intestinal mucosa and distributed in tissues around the body, with some preference shown to plasma lipids, as well as milk and adipose tissue. CLA is metabolised via oxidation and desaturation, with metabolites excreted from the body primarily through exhaled air (as CO_2), and to some extent in urine and faeces.

Toxicity
A limited amount of animal data relating to toxicity is provided in the application. The oral LD_{50} in rats is reported to be >3g/kg.

Subacute/Subchronic toxicity – A robust 13 week study in rats fed CLA (79% 50:50 mixture of *c*9,*t*11 and *t*10,*c*12) concluded that 5% of CLA in the diet represented the "no-observed-adverse-effect-level (NOAEL), equivalent to 2,433 and 2,728 mg/kg/day for males and females respectively. The applicant noted profound changes in lipid metabolism in the mouse, with toxicity and fatty acid change in the liver. However, as already noted the mouse cannot cope with large changes in fat metabolism and is thus a poor model for studying the effects of CLA.

Mutagenicity – CLA (Clarinol^{TM} G-80) was not found to have any mutagenic potential when tested in a bacterial mutagenicity assay, nor did it produce chromosomal aberrations in human lymphocytes. The results of these studies indicate that CLA does not have genotoxic potential.

Chronic toxicity/Carcinogenicity – Classical carcinogenicity studies on CLA were not available, and the one long term study presented (an 18-month study in rats) examined the effects of a diet supplemented with 1% CLA (42% *c*9,*t*11 and 44% *t*10,*c*12). The long term study found no significant differences in tumour incidence between CLA fed rats and control animals which, the applicant argues, along with mutagenicity studies and knowledge of the structure and fate of CLA, suggests that CLA-rich oil does not pose a carcinogenicity risk. Effects on blood glucose were reported in this study, although the NOAEL was reported to be 1% CLA in the diet, the only dose tested.

Reproductive and Development Toxicity – A number of studies in rats and pigs did not identify any adverse effects on mothers or offspring that were on diets consisting of 0.25% to 2% CLA. Though significant uptake into the maternal mammary gland of CLA was reported for rats, there were no associated adverse effects.

Other toxicological studies – a number of toxicological studies have shown that CLA has effects on lipid metabolism, resulting in alterations in body composition and possible anti-atherogenic, anti-carcinogenic and immune modulatory effects

Initially there was some concern by FSAI that the absence of a robust chronic toxicity study may affect the quality of the safety assessment of the novel ingredient. However, during discussion with the applicant it was discovered that the majority of EU-authorised novel foods currently on the market, including a range of oils, had not been subjected to chronic pre-clinical studies. In addition, the preference for human over animal studies in assessing the safety of CLA was noted with respect to the significance of traditional pre-clinical studies.

Allergenicity

The risk of allergic reactions from the inclusion of Clarinol^{TM} in foodstuffs is considered to be low as Safflower is not known to contain any endogenous allergenic proteins. Therefore it is not a surprise that there have been no reports of allergenic reactions associated with the use of Clarinol^{TM} during the course of more than 30 clinical trials. In addition, the production process for Clarinol^{TM} is relatively protein-unfriendly, resulting in CLA-rich oil with almost no residual protein from the original safflower or the enzymatic production process.

Clinical studies

Numerous clinical studies on various preparations of CLA were provided by the applicant and examined by a medical expert engaged by the FSAI. The original manuscripts referred to in the section on "Summary of Clinical Studies Conducted with 50:50 Mixtures" as well as other relevant publications were reviewed along with the supplementary expert reports.

No safety concerns were raised by any of the studies which were based on CLA intakes up to a maximum of 6g per day. Overall the level of adverse events in test subjects were similar to those reported in placebo groups, while reported side effects were largely due to gastrointestinal changes. A prolonged study (2yr) of healthy males and females for the effect of CLA supplementation on body fat did not identify any significant changes to a range of clinical chemistry variables and no safety issues arose.

Many of the studies focused on parameters that have a potential bearing on cardiovascular health, as reflected by changes in risk factors such as serum lipids. However, there was no convincing data that showed CLA has a consistently negative influence on lipids.

The urinary excretion of isoprostanes is elevated in conditions associated with oxidation and inflammation, though the potential use of such a surrogate marker of oxidative stress requires careful consideration of factors such as natural variation in isoprostane excretion and the accuracy of various isoprostane measurement techniques. However, it is still a matter of some debate whether increased isoprostane excretion is directly associated with oxidative stress, or due to other factors such as enhanced availability of substrate or altered catabolism. A number of studies provided by the applicant linked increased levels of isoprostane excretion to the consumption of CLA.The FSAI medical expert considers that current scientific knowledge does not support the extrapolation of these data to imply a direct association between CLA consumption and oxidative stress. This stance is supported by a recent study provided by the applicant and relating to increased excretion of isoprostanes due to CLA consumption. The study, which is currently in press, concludes that CLA intake in humans may impair the breakdown of isoprostanes rather than increase their production, thereby resulting in higher levels being excreted.

Many studies have addressed the effects of CLA on insulin resistance and sensitivity which can be associated with increased risk of vascular events. However, while the individual isomers of CLA may result in an increase in insulin resistance, the 50:50 mixture of isomers (*c*9,*t*11 and *t*10,*c*12) present in Clarinol^{TM} seems to have a neutral, if not beneficial effect.

There were no significant effects on immune or vascular functions as a result of the supplementation of the diets of healthy individuals with a 50:50 mixture of CLA isomers. CLA was also observed to have no effect on the parameters of blood coagulation or platelet function and thus would not be expected to pose a bleeding risk.

A number of studies have shown that CLA has the potential to alter body fat and lean body mass. CLA consumption was not found to be associated with adverse effects on components of bone or muscle turnover and though results varied, the overall impact on body fat and its distribution around the body was considered to be neutral or even beneficial.

The information available on the effects of CLA on milk fat in lactating women and the consequences for breast fed children are conflicting and thus of limited use. Therefore, in the absence of further studies it is prudent that lactating women avoid dietary CLA supplementation. The medical expert concludes that the conflicting results evident in some of the studies presented may reflect differences in study duration, cohort composition, study settings, and, most importantly, supplement composition and the choice of an appropriate control fat. The expert concluded that with the exception of milk fat and possible concerns for lactating women, the clinical studies presented do not provide evidence of consistent adverse effects resulting from the consumption of the 50:50 mix of CLA isomers present in Clarinol^{TM}.

During discussions with the applicant it was agreed that foodstuffs containing added CLA would be labelled to advise pregnant or lactating women and children less than five years of age not to consume these products. In addition, the label would advise that that people on any form of medication should consult their physician prior to consuming CLA-containing products.

Conclusions

CLA-rich oil has been commercially available on the EU market in supplement form since 1995, with no adverse health effects reported. However, dietary supplements are consumed only by a certain proportion of the population, primarily adults who wish to improve their nutritional balance. Adding CLA-rich oil to a range of foodstuffs, as intended by the applicant, has the potential to expose many more people to this ingredient and thus a safety assessment is required under the novel food Regulation.

A number of conclusions can be drawn from this assessment:

1. Animals, particularly rodents are poor models for studying the effects of CLA on body fat, which led the applicant to assign more significance to clinical studies in humans rather than data from animal studies.

2. From the studies provided by the applicant, a medical expert engaged by the FSAI did not identify consistent clinical evidence of adverse health effects related to CLA consumption. While some of the studies provide conflicting evidence, on balance there is no new evidence that would raise any concerns for the safety of healthy people consuming CLA-containing foodstuffs as part of a weight-management programme. The medical expert advised that lactating women should avoid the consumption of foodstuffs with added CLA based on the limited evidence available.

3. The data presented on chronic toxicity, carcinogenicity and genotoxicity are in line with similar data for other novel food applications and considered adequate in light of the greater reliance on clinical studies.

CLA-fortified foodstuffs are to be targeted at healthy adults as part of a weight-management programme and will be marketed accordingly, at a premium price reflecting the production costs of CLA-rich oil. The relatively high theoretical intakes achieved by children through products such as yogurt and other dairy products, soya milk, and fruit juices will be addressed by the applicant through a system of advisory labelling. Potential concerns regarding CLA intake by pregnant and lactating women will be similarly addressed through a system of advisory labelling.

Recommendation

The FSAI is satisfied that the use of CLA (Clarinol^{TM}) in foodstuffs meets the criteria for novel food set out in *Article 3.1.* of the novel food Regulation. The FSAI does not have concerns about the safety of this ingredient provided the product specifications are adhered to, the limitation of the range of foodstuffs is maintained and that advisory/warning labels discussed with the applicant are applied consistently for the benefit of consumers.