

NATURAL HEALTH PRODUCT

CONJUGATED LINOLEIC ACID

This monograph is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLA) and labels for natural health product market authorization. It is not intended to be a comprehensive review of the medicinal ingredient.

Notes

- ▶ Text in parentheses is additional optional information which can be included on the PLA and product label at the applicant's discretion.
- ▶ The solidus (/) indicates that the terms and/or statements are synonymous. Either term or statement may be selected by the applicant.

Date

July 31, 2018

Background

- ▶ There is insufficient evidence to support the use of Conjugated linoleic acid (CLA) as a weight loss aid. Consumers wishing to achieve weight loss should consult a health care practitioner/health care provider/health care professional/doctor/physician prior to taking CLA.
- ▶ The use of the term “may” in the use or purpose statements reflects the uncertainty of the evidence. For example, some reviews have concluded that CLA does not significantly affect body fat mass.
- ▶ The claim “May help to support a modest improvement to body composition” refers to evidence showing that CLA may modestly reduce body fat. Weak evidence also demonstrates that CLA may help to modestly increase lean muscle mass.
- ▶ The recommendations for decreased caloric intake and increased physical activity are included as components of the use or purpose statements in order to provide a health context.
- ▶ Though CLA has been administered to subjects for up to two years, there is insufficient evidence to support any benefits beyond 6 months. As such, a duration of use of 6 months has been included on the monograph.
- ▶ CLA does not exert positive effects on any health risk biomarkers (e.g. LDL-cholesterol, HDL-cholesterol, plasma glucose, plasma insulin, etc.) and there is some evidence to suggest that its use may be unsafe in particular subpopulations. As such, mandatory risk information is required on the PLA and label to identify subpopulations at risk.



Proper name(s), Common name(s), Source material(s)

Table 1. Proper name(s), Common name(s), Source material(s)

Proper name(s)	Common name(s)	Source material(s)	
		Common(s) name(s)	Preparation(s)
Conjugated linoleic acid	<ul style="list-style-type: none"> ▶ Conjugated linoleic acid ▶ CLA 	Conjugated linoleic acid	Synthetic

References: Proper name: Pariza 2004, Pariza et al. 2001; Common names: Pariza 2004, Pariza et al. 2001; Source material: FDA 2007, Pariza et al. 2001.

Route of administration

Oral

Dosage form(s)

This monograph excludes foods or food-like dosage forms as indicated in the Compendium of Monographs Guidance Document.

Acceptable dosage forms for the age category listed in this monograph and specified route of administration are indicated in the Compendium of Monographs Guidance Document.

Use(s) or Purpose(s)

- ▶ May help to support a modest improvement to body composition when used with a program of reduced intake of dietary calories and increased physical activity (Raff et al. 2009; Gaullier et al. 2007; Pinkoski et al. 2006; Gaullier et al. 2004; Kamphuis et al. 2003).
- ▶ May help to support a modest reduction in fat mass when used with a program of reduced intake of dietary calories and increased physical activity (Raff et al. 2009; Gaullier et al. 2007; Watras et al. 2007; Pinkoski et al. 2006; Gaullier et al. 2004).

The following combined use(s) or purpose(s) is/are also acceptable:

- ▶ May help to support a modest reduction in fat mass and a modest improvement to body composition when used with a calorie-reduced diet and increased physical activity (Raff et al. 2009; Gaullier et al. 2007; Watras et al. 2007; Pinkoski et al. 2006; Gaullier et al. 2004; Kamphuis et al. 2003).



Dose(s)

Subpopulation(s)

Adults 18 years and older

Quantity(ies)

3-5 grams of CLA, per day (Raff et al. 2009; Gaullier et al. 2007; Watras et al. 2007; Pinkoski et al. 2006; Gaullier et al. 2004; Kamphuis et al. 2003).

Notes

Additional information not to be submitted with the compendial PLA (although the quantity of CLA-rich oil may be requested at the NNHPD's discretion): Approximately 4-6.5 g CLA-rich oil provides 3-5 g CLA.

Direction(s) for use

Optional: Take with food (Watras et al. 2007; Kamphuis et al. 2003).

Duration(s) of use

Consult a health care practitioner/health care provider/health care professional/doctor/physician for use beyond 6 months (Gaullier et al. 2007; Watras et al. 2007; Gaullier et al. 2005; Gaullier et al. 2004).

Risk information

Caution(s) and warning(s)

- ▶ Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are obese or have cardiovascular disease (CVD) risk factors (e.g. high blood pressure, high cholesterol and/or triglycerides) (Tholstrup et al. 2008; Gaullier et al. 2007; Steck et al. 2007; Larsen et al. 2006; Taylor et al. 2006; Gaullier et al. 2005; Smedman et al. 2005; Gaullier et al. 2004; Basu et al. 2000a; Basu et al. 2000b).
- ▶ Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if your goal is to achieve weight loss.
- ▶ Consult a health care practitioner/health care provider/health care professional/doctor/physician prior to use if you are pregnant or breastfeeding.

Contraindication(s)

Do not use this product if you have cardiovascular disease (CVD), diabetes, metabolic syndrome or insulin resistance (Tholstrup et al. 2008; Gaullier et al. 2007; Steck et al. 2007; Larsen et al.

2006; Taylor et al. 2006; Gaullier et al. 2005; Smedman et al. 2005; Gaullier et al. 2004; Moloney et al. 2004; Basu et al. 2000a; Basu et al. 2000b).

Known adverse reaction(s)

Some people may experience gastrointestinal upset (Gaullier et al. 2007; Pinkoski et al. 2006; Berven et al. 2000; Blankson et al. 2000).

Non-medicinal ingredients

Must be chosen from the current Natural Health Products Ingredients Database (NHPID) and must meet the limitations outlined in the database.

Storage conditions

No statement required.

Specifications

- ▶ The finished product specifications must be established in accordance with the requirements described in the Natural and Non-prescription Health Products Directorate (NNHPD) Quality of Natural Health Products Guide.
- ▶ The medicinal ingredient must comply with the requirements outlined in the NHPID.
- ▶ The CLA-rich oil must comply with the chemical specifications: CLA total $\geq 78\%$; CLA (c9,t11 + t10,c12 isomers) $\geq 74\%$; CLA c9,t11 isomers $\geq 36\%$; CLA t10,c12 isomers $\geq 36\%$; CLA trans, trans $\leq 3\%$ (FDA 2007).
- ▶ The maximum peroxide value derived from CLA-rich oil must be ≤ 1 meq O₂/kg and be in accordance with the methods set out by the American Oil Chemists' Society (AOCS) and/or Pharmacopoeial analytical methods. This specification is necessary to ensure the oxidative stability of the CLA.

References cited

Basu S, Risérus U, Turpeinen A, Vessby B. 2000a. Conjugated linoleic acid induces lipid peroxidation in men with abdominal obesity. *Clinical Science* 99(6):511-516.

Basu S, Smedman A, Vessby B. 2000b. Conjugated linoleic acid induces lipid peroxidation in humans. *FEBS Letters* 468(1):33-36.

Berven G, Bye A, Hals O, Blankson H, Fagertun H, Thom E, Wadstein J, Gudmundsen O. 2000. Safety of conjugated linoleic acid (CLA) in overweight and obese human volunteers. *European Journal of Lipid Science and Technology* 102(7):455-462.



Blankson H, Stakkestad JA, Fagertun H, Thom E, Wadstein J, Gudmundsen O. 2000. Conjugated linoleic acid reduces body fat mass in overweight and obese humans. *The Journal of Nutrition* 130(12):2943-2948.

FDA 2007: United States Food and Drug Administration. Guidance for Industry Developing Products for Weight Management Draft Guidance [online]. Washington (DC): United States Department of Health and Human Services, U.S. Food and Drug Administration. [Accessed 2018 June 1]. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071612.pdf>

Gaullier JM, Halse J, Høivik HO, Høye K, Syvertsen C, Nurminiemi M, Hassfeld C, Einerhand A, O'Shea M, Gudmundsen O. 2007. Six months supplementation with conjugated linoleic acid induces regional-specific fat mass decreases in overweight and obese. *British Journal of Nutrition* 97(3):550-560.

Gaullier JM, Halse J, Høye K, Kristiansen K, Fagertun H, Vik H, Gudmundsen O. 2004. Conjugated linoleic acid supplementation for 1 y reduces body fat mass in healthy overweight humans. *The American Journal of Clinical Nutrition* 79:1118-1125.

Gaullier JM, Halse J, Høye K, Kristiansen K, Fagertun H, Vik H, Gudmundsen O. 2005. Supplementation with conjugated linoleic acid for 24 months is well tolerated by and reduces body fat mass in healthy, overweight humans. *The Journal of Nutrition* 135(4):778-784.

Kamphuis MM, Lejeune MP, Saris WH, Westerterp-Plantenga MS. 2003. The effect of conjugated linoleic acid supplementation after weight loss on body weight regain, body composition, and resting metabolic rate in overweight subjects. *International Journal of Obesity and Related Metabolic Disorders* 27(7):840-847.

Larsen TM, Toubro S, Gudmundsen O, Astrup A. 2006. Conjugated linoleic acid supplementation for 1 y does not prevent weight or body fat gain. *The American Journal of Clinical Nutrition* 83(3):606-612.

Moloney F, Yeow TP, Mullen A, Nolan JJ, Roche HM. 2004. Conjugated linoleic acid supplementation, insulin sensitivity, and lipoprotein metabolism in patients with type 2 diabetes mellitus. *The American Journal of Clinical Nutrition* 80(4):887-895.

Pariza MW. 2004. Perspective on the safety and effectiveness of conjugated linoleic acid. *The American Journal of Clinical Nutrition* 79(Supplement 6):1132S-1136S.

Pariza MW, Park Y, Cook ME. 2001. The biologically active isomers of conjugated linoleic acid. *Progress in Lipid Research* 40(4):283-298.

Pinkoski C, Chilibeck PD, Candow DG, Esliger D, Ewaschuk JB, Facci M, Farthing JP, Zello GA. 2006. The effects of conjugated linoleic acid supplementation during resistance training. *Medicine and Science in Sports and Exercise* 38(2):339-348.



Raff M, Tholstrup T, Toubro S, Bruun JM, Lund P, Straarup EM, Christensen R, Sandberg MB, Mandrup S. 2009. Conjugated linoleic acids reduce body fat in healthy postmenopausal women. *The Journal of Nutrition* 39(7):1347-1352.

Smedman A, Basu S, Jovinge S, Fredrikson GN, Vessby B. 2005. Conjugated linoleic acid increased C-reactive protein in human subjects. *British Journal of Nutrition* 94(5):791-795.

Steck SE, Chalecki AM, Miller P, Conway J, Austin GL, Hardin JW, Albright CD, Thuillier P. 2007. Conjugated linoleic acid supplementation for twelve weeks increases lean body mass in obese humans. *The Journal of Nutrition* 137(5):1188-1193.

Taylor JS, Williams SR, Rhys R, James P, Frenneaux MP. 2006. Conjugated linoleic acid impairs endothelial function. *Arteriosclerosis, Thrombosis, and Vascular Biology* 26(2):307-312.

Tholstrup T, Raff M, Straarup EM, Lund P, Basu S, Bruun JM. 2008. An oil mixture with trans-10, cis-12 conjugated linoleic acid increases markers of inflammation and in vivo lipid peroxidation compared with cis-9, trans-11 conjugated linoleic acid in postmenopausal women. *The Journal of Nutrition* 138(8):1445-1451.

Watras AC, Buchholz AC, Close RN, Zhang Z, Schoeller DA. 2007. The role of conjugated linoleic acid in reducing body fat and preventing holiday weight gain. *International Journal of Obesity* 31(3):481-487.

References reviewed

Aasen G, Fagertun H, Tonstad S, Halse J. 2009. Leg fat mass as measured by dual X-ray absorptiometry (DXA) impacts insulin resistance differently in obese women versus men. *Scandinavian Journal of Clinical and Laboratory Investigation* 69(2):181-189.

Adams RE, Hsueh A, Alford B, King C, Mo H, Wildman R. 2006. Conjugated linoleic acid supplementation does not reduce visceral adipose tissue in middle-aged men engaged in a resistance-training program. *Journal of the International Society of Sports Nutrition* 3(2):28-36.

Aminot-Gilchrist DV, Anderson HDI. 2004. Insulin resistance-associated cardiovascular disease: potential benefits of conjugated linoleic acid. *The American Journal of Clinical Nutrition* 79(6):1159S-1163S.

Atkinson RL. 1999. Conjugated Linoleic Acid for Altering Body Composition and Treating Obesity. In: Yurawecz MP, Mossoba MM, Kramer JKG, Pariza MW, Nelson GJ, editors. *Advances in Conjugated Linoleic Acid Research, Volume 1*, pp. 348-353. Champagne (IL): AOCS Press.

Aydin R. 2005. Conjugated linoleic acid: Chemical structure, sources and biological properties. *Turkish Journal of Veterinary and Animal Sciences* 29(2):189-195.



- Belury MA. 2002. Dietary conjugated linoleic acid in health: physiological effects and mechanisms of action. *Annual Review of Nutrition* 22:505-531.
- Belury MA, Mahon A, Banni S. 2003. The conjugated linoleic acid (CLA) isomer, t10c12-CLA, is inversely associated with changes in body weight and serum leptin in subjects with Type 2 diabetes mellitus. *The Journal of Nutrition* 133(1):257S-260S.
- Benito P, Nelson GJ, Kelley DS, Bartolini G, Schmidt PC, Simon V. 2001. The effect of conjugated linoleic acid on plasma lipoproteins and tissue fatty acid composition in humans. *Lipids* 36(3):229-236.
- Bhattacharya A, Banu J, Rahman M, Causey J, Fernandes G. 2006. Biological effects of conjugated linoleic acids in health and disease. *Journal of Nutritional Biochemistry* 17(12):789-810.
- Bos G, Snijder MB, Nijpels G, Dekker JM, Stehouwer CD, Bouter LM, Heine RJ, Jansen H. 2005. Opposite contributions of trunk and leg fat mass with plasma lipase activities: the Hoorn study. *Obesity Research* 13(10):1817-1823.
- Brown DW, Giles WH, Croft JB. 2001. White blood cell count: an independent predictor of coronary heart disease mortality among a national cohort. *Journal of Clinical Epidemiology* 54(3):316-322.
- Campbell B, Kreider RB. 2008. Conjugated linoleic acids. *Current Sports Medicine Reports* 7(4):237-241.
- Christ ER, Carroll PV, Albany E, Umpleby AM, Lumb PJ, Wierzbicki AS, Simpson HL, Sönksen PH, Russell-Ones DL. 2001. Normal VLDL metabolism despite altered lipoprotein composition in type 1 diabetes mellitus. *Clinical Endocrinology* 55(6):777-787.
- Colakoglu S, Colakoglu M, Taneli F, Cetinoz F, Turkmen M. 2006. Cumulative effects of conjugated linoleic acid and exercise on endurance development, body composition, serum leptin and insulin levels. *Journal of Sports Medicine and Physical Fitness* 46(4):570-577.
- Constans J, Conri C. 2006. Circulating markers of endothelial function in cardiovascular disease. *Clinica Chimica Acta* 368(1-2):33-47.
- DeFronzo RA, Tobin JD, Andres R. 1979. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *American Journal of Physiology* 237(3):E214-E223.
- Diaz ML, Watkins BA, Li Y, Anderson RA, Campbell WW. 2007. Chromium picolinate and conjugated linoleic acid do not synergistically influence diet- and exercise-induced changes in body composition and health indexes in overweight women. *Journal of Nutritional Biochemistry* 19(1):61-68.

EMEA 2007: European Medicines Agency. Guideline on Clinical Evaluation of Medicinal Products Used in Weight Control. London (GB): Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency.

Ens JG, Ma DW, Cole KS, Field CJ, Clandinin MT. 2001. An assessment of c9,t11 linoleic acid intake in a small group of young Canadians. *Nutrition Research* 21(7):955-960.

Erselcan T, Candan F, Saruhan S, Ayca T. 2000. Comparison of body composition analysis methods in clinical routine. *Annals of Nutrition and Metabolism* 44(5-6):243-248.

Eyjolfson V, Spriet LL, Dyck DJ. 2004. Conjugated linoleic acid improves insulin sensitivity in young, sedentary humans. *Medicine and Science in Sports and Exercise* 36(5):814-20.

FCWCLA 2003: First Canadian Workshop on CLA. Summary Report of the Workshop on the Role of Conjugated Linoleic Acid in Human Health. Proceedings on the Role of CLA in Human Health. March 13-15, 2003. Winnipeg (MB): National Organizing Committee of the First Canadian Workshop on Conjugated Linoleic Acid (CLA) and Human Health.

Fritsche J, Steinhart H. 1998. Amounts of conjugated linoleic acid (CLA) in German foods and evaluation of daily intake. *Zeitschrift für Lebensmittel-Untersuchung und-Forschung* 206(2):77-82.

Garton GA. 2007. Essential fatty acids. *Nutrition Bulletin* 10(3):153-164.

Gokce N, Keaney JF Jr, Hunter LM, Watkins MT, Menzoian JO, Vita JA. 2002. Risk stratification for postoperative cardiovascular events via non-invasive assessment of endothelial function: a prospective study. *Circulation* 105(13):1567-1572.

Herbel BK, McGuire MK, McGuire MA, Shultz TD. 1998. Safflower oil consumption does not increase plasma conjugated linoleic acid concentrations in humans. *The American Journal of Clinical Nutrition* 67(2):332-7.

Iwata T, Kamegai T, Yamauchi-Sato Y, Ogawa A, Kasai M, Aoyama T, Kondo K. 2007. Safety of dietary conjugated linoleic acid (CLA) in a 12-weeks trial in healthy overweight Japanese male volunteers. *Journal of Oleo Science* 56(10):517-25.

Jucker BM, Cline GW, Barucci N, Shulman GI. 1999. Differential effects of safflower oil versus fish oil feeding on insulin-stimulated glycogen synthesis, glycolysis, and pyruvate dehydrogenase flux in skeletal muscle. *Diabetes* 48(1):134-140.

Kreider RB, Ferreira MP, Greenwood M, Wilson M, Almada AL. 2002. Effects of conjugated linoleic acid supplementation during resistance training on body composition, bone density, strength, and selected hematological markers. *Journal of Strength and Conditioning Research* 16(3):325-334.



Lambert EV, Goedecke JH, Bluett K, Heggie K, Claassen A, Rae DE, West S, Dugas J, Dugas L, Meltzer S, Charlton K, Mohede I. 2007. Conjugated linoleic acid versus high-oleic acid sunflower oil: effects on energy metabolism, glucose tolerance, blood lipids, appetite and body composition in regularly exercising individuals. *British Journal of Nutrition* 97(5):1001-1011.

Larsen TM, Toubro S, Astrup A. 2003. Efficacy and safety of dietary supplements containing CLA for the treatment of obesity: evidence from animal and human studies. *Journal of Lipid Research* 44(12):2234-2241.

Laso N, Brugué E, Vidal J, Ros E, Arnaiz JA, Carné X, Vidal S, Mas S, Deulofeu R, Lafuente A. 2007. Effects of milk supplementation with conjugated linoleic acid (isomers cis-9, trans-11 and trans-10, cis-12) on body composition and metabolic syndrome components. *British Journal of Nutrition* 98(4):860-867.

Lind L. 2003. Circulating markers of inflammation and atherosclerosis. *Atherosclerosis* 169(2):203-214.

Lopez-Garcia E, Schulze MB, Meigs JB, Manson JE, Rifai N, Stampfer MJ, Willett WC, Hu FB. 2005. Consumption of trans fatty acids is related to plasma biomarkers of inflammation and endothelial dysfunction. *The Journal of Nutrition* 135(3):562-566.

Malpuech-Brugère C, Verboeket-van de Venne WP, Mensink RP, Arnal MA, Morio B, Brandolini M, Saebo A, Lassel TS, Chardigny JM, Sebedio JL, Beaufre B. 2004. Effects of two conjugated linoleic acid isomers on body fat mass in overweight humans. *Obesity Research* 12(4):591-598.

Masters N, McGuire MA, Beerman KA, Dasgupta N, McGuire MK. 2002. Maternal supplementation with CLA decreases milk fat in humans. *Lipids* 37(2):133-138.

McGuire MK, McGuire MA, Ritzenthaler KL, Schultz TD. 1999. Dietary Sources and Intakes of Conjugated Linoleic Acid Intake in Humans. In: MP Yurawecz, MM Mossoba, JKG Kramer, MW Pariza and GJ Nelson, editors. *Advances in Conjugated Linoleic Acid Research*, pp. 369-377. Champaign (IL): AOCS Press.

Mensink RP. 2005. Metabolic and health effects of isomeric fatty acids. *Current Opinions in Lipidology* 16(1):27-30.

Moloney F, Yeow TP, Mullen A, Nolan JJ, Roche HM. 2004. Conjugated linoleic acid supplementation, insulin sensitivity, and lipoprotein metabolism in patients with type 2 diabetes mellitus. *The American Journal of Clinical Nutrition* 80(4):887-895.

Mougios V, Matsakas A, Petridou A, Ring S, Sagredos A, Melissopoulou A, Tsigilis N, Nikolaidis M. 2001. Effect of supplementation with conjugated linoleic acid on human serum lipids and body fat. *The Journal of Nutritional Biochemistry* 12(10):585-594.



- Muniyappa R, Lee S, Chen H, Quon MJ. 2008. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. *American Journal of Physiology* 294(1):E15-E26. already emailed about similar issue with AJP
- Nagao K, Yanagita T. 2005. Conjugated fatty acids in food and their health benefits. *Journal of Bioscience and Bioengineering* 100(2):152-157.
- Nakamura YK, Flintoff-Dye N, Omaye ST. 2008. Conjugated linoleic acid modulation of risk factors associated with atherosclerosis. *Nutrition and Metabolism* 5:22.
- Noone EJ, Roche HM, Nugent AP, Gibney MJ. 2002. The effect of dietary supplementation using isomeric blends of conjugated linoleic acid on lipid metabolism in healthy human subjects. *British Journal of Nutrition* 88(3):243-251.
- Norris LE, Collene AL, Asp ML, Hsu JC, Liu LF, Richardson JR, Li D, Bell D, Osei K, Jackson RD, Belury MA. 2009. Comparison of dietary conjugated linoleic acid with safflower oil on body composition in obese postmenopausal women with type 2 diabetes mellitus. *The American Journal of Clinical Nutrition* 90(3):468-476.
- Park Y, Albright KJ, Storkson JM, Liu W, Pariza MW. 2007. Conjugated linoleic acid (CLA) prevents body fat accumulation and weight gain in an animal model. *Journal of Food Science* 72(8):S612-S617.
- Park Y, Albright KJ, Liu W, Storkson JM, Cook ME, Pariza MW. 1997. Effect of conjugated linoleic acid on body composition in mice. *Lipids* 32(8):853-858.
- Park Y, McGuire MK, Behr R, McGuire MA, Evans MA, Shultz TD. 1999. High-fat dairy product consumption increases $\delta 9c,11t-18:2$ (rumenic acid) and total lipid concentrations of human milk. *Lipids* 34(6):543-549.
- Park Y and Pariza MW. 2007. Mechanisms of body fat modulation by conjugated linoleic acid (CLA). *Food Research International* 40(3):311-323.
- Petridou A, Mougios V, Sagredos A. 2003. Supplementation with CLA: isomer incorporation into serum lipids and effect on body fat of women. *Lipids* 38(8):805-811.
- Pickup JC, Mattock MB, Chusney GD, Burt D. 1997. NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. *Diabetologia* 40(11):1286-1292.
- Pi-Sunyer FX. 1991. Health implications of obesity. *The American Journal of Clinical Nutrition* 53(Supplement 6):1595S-1603S.
- Plourde M, Jew S, Cunnane SC, Jones PJ. 2008. Conjugated linoleic acids: why the discrepancy between animal and human studies? *Nutrition Reviews* 66(7):415-421.

- Quyyumi AA. 2003. Prognostic value of endothelial function. *The American Journal of Cardiology* 91(12A):19H-24H.
- Ramos R, Mascarenhas J, Duarte P, Vicente C, Casteleiro C. 2009. Conjugated linoleic acid-induced toxic hepatitis: first case report. *Digestive Diseases and Sciences* 54(5):1141-1143.
- Reaven G. 2005. All obese individuals are not created equal: insulin resistance is the major determinant of cardiovascular disease in overweight/obese individuals. *Diabetes and Vascular Disease Research* 2(3):105-112.
- Ridker PM. 2003. High-sensitivity C-reactive protein and cardiovascular risk: rationale for screening and primary prevention. *The American Journal of Cardiology* 92(4B):17K-22K.
- Risérus U. 2006. Trans-fatty acids and insulin resistance. *Atherosclerosis Supplements* 7(2):37-39.
- Risérus U, Smedman A, Basu S, Vessby B. 2004. Metabolic effects of conjugated linoleic acid in humans: the Swedish experience. *The American Journal of Clinical Nutrition* 79(Supplement 6):1146S-1148S.
- Risérus U, Vessby B, Arner P, Zethelius B. 2004. Supplementation with trans10cis12-conjugated linoleic acid induces hyperproinsulinaemia in obese men: close association with impaired insulin sensitivity. *Diabetologia* 47(6):1016-1019.
- Risérus U, Vessby B, Arnlov J, Basu S. 2004. Effects of cis-9,trans-11 conjugated linoleic acid supplementation on insulin sensitivity, lipid peroxidation, and proinflammatory markers in obese men. *The American Journal of Clinical Nutrition* 80(2):279-283.
- Risérus U, Arner P, Brismar K, Vessby B. 2002. Treatment with dietary trans10cis12 conjugated linoleic acid causes isomer-specific insulin resistance in obese men with the metabolic syndrome. *Diabetes Care* 25(9):1516-1521.
- Risérus U, Basu S, Jovinge S, Fredrikson GN, Arnlov J, Vessby B. 2002. Supplementation with conjugated linoleic acid causes isomer-dependent oxidative stress and elevated C-reactive protein: a potential link to fatty acid-induced insulin resistance. *Circulation* 106(15):1925-1929.
- Risérus U, Berglund L, Vessby B. 2001. Conjugated linoleic acid (CLA) reduced abdominal adipose tissue in obese middle-aged men with signs of the metabolic syndrome: a randomized controlled trial. *International Journal of Obesity and Related Metabolic Disorders* 25(8):1129-1135.
- Ritzenthaler KL, McGuire MK, Falen R, Shultz TD, Dasgupta N, McGuire MA. 2001. Estimation of conjugated linoleic acid intake by written dietary assessment methodologies underestimates actual intake evaluated by food duplicate methodology. *The Journal of Nutrition* 131(5):1548-1554.



- Ryder JW, Portocarrero CP, Song XM, Cui L, Yu M, Combatsiaris T, Galuska D, Bauman DE, Barbano DM, Charron MJ, Zierath JR, Houseknecht KL. 2001. Isomer-specific antidiabetic properties of conjugated linoleic acid. Improved glucose tolerance, skeletal muscle insulin action, and UCP-2 gene expression. *Diabetes* 50(5):1149-1157.
- Salas-Salvado J, Marquez-Sandoval F, Bullo M. 2006. Conjugated linoleic acid intake in humans: a systematic review focusing on its effect on body composition, glucose, and lipid metabolism. *Critical Reviews in Food Science and Nutrition* 46(6):479-488.
- Samaras K, McElduff A, Twigg SM, Proietto J, Prins JB, Welborn TA, Zimmet P, Chisholm DJ, Campbell LV. 2006. Insulin levels in insulin resistance: phantom of the metabolic opera? *Medical Journal of Australia* 185(3):159-161.
- Schneider JG, Tompkins C, Blumenthal RS, Mora S. 2006. The metabolic syndrome in women. *Cardiology in Review* 14(6):286-291.
- Schoenhals K. 2004. Friendly fat: CLA may help you lose weight - conjugated linoleic acid. *Better Nutrition* 68(3):43-44.
- Sethi JK and Hotamisligil GS. 1999. The role of TNF alpha in adipocyte metabolism. *Seminars in Cell and Developmental Biology* 10(1):19-29.
- Silveira MB, Carraro R, Monereo S, Tébar J. 2007. Conjugated linoleic acid (CLA) and obesity. *Public Health Nutrition* 10(10A):1181-1186.
- Smedman A, Vessby B, Basu S. 2004. Isomer-specific effects of conjugated linoleic acid on lipid peroxidation in humans: regulation by alpha-tocopherol and cyclo-oxygenase-2 inhibitor. *Clinical Science* 106(1):67-73.
- Smedman A, Vessby B. 2001. Conjugated linoleic acid supplementation in humans--metabolic effects. *Lipids* 36(8):773-81.
- Smolders B, Lemmens R, Thijs V. 2007. Lipoprotein (a) and stroke: a meta-analysis of observational studies. *Stroke* 38(6):1959-1966.
- Song HJ, Grant I, Rotondo D, Mohede I, Sattar N, Heys SD, Wahle KW. 2005. Effect of CLA supplementation on immune function in young healthy volunteers. *European Journal of Clinical Nutrition* 59(4):508-517.
- Syvertsen C, Halse J, Hoivik HO, Gaullier J-M, Nurminiemi M, Kristiansen K, Einerhand A, O'Shea M, Gudmundsen O. 2006. The effect of 6 months supplementation with conjugated linoleic acid on insulin resistance in overweight and obese. *International Journal of Obesity* 31(7):1148-1154.
- Terpstra AH. 2001. Differences between humans and mice in efficacy of the body fat lowering effect of conjugated linoleic acid: role of metabolic rate. *The Journal of Nutrition* 131(7):2067-2068.



Terpstra AHM. 2004. Effect of conjugated linoleic acid on body composition and plasma lipids in humans: an overview of the literature. *The American Journal of Clinical Nutrition* 79(3):352-361.

Thom E, Wadstein J, Gudmundsen O. 2001. Conjugated linoleic acid reduces body fat in healthy exercising humans. *The Journal of International Medical Research* 29(5):392-396.

Thrush AB, Chabowski A, Heigenhauser GJ, McBride BW, Or-Rashid M, Dyck DJ. 2007. Conjugated linoleic acid increases skeletal muscle ceramide content and decreases insulin sensitivity in overweight, non-diabetic humans. *Applied Physiology, Nutrition, and Metabolism* 32(3):372-382.

Toomey S, McMonagle J, Roche HM. 2006. Conjugated linoleic acid: a functional nutrient in the different pathophysiological components on the metabolic syndrome? *Current Opinion in Clinical Nutrition and Metabolic Care* 9(6):740-747.

Tricon S, Burdge GC, Kew S, Banerjee T, Russell JJ, Grimble RF, Williams CM, Calder PC, Yaqoob P. 2004. Effects of cis-9,trans-11 and trans-10,cis-12 conjugated linoleic acid on immune cell function in healthy humans. *The American Journal of Clinical Nutrition* 80(6):1626-1633.

Tricon S, Burdge GC, Kew S, Banerjee T, Russell JJ, Jones EL, Grimble RF, Williams CM, Yaqoob P, Calder PC. 2004. Opposing effects of cis-9, trans-10,cis-12 conjugated linoleic acid on blood lipids in healthy humans. *The American Journal of Clinical Nutrition* 80(3):614-620.

Tricon S, Burdge GC, Williams CM, Calder PC, Yaqoob P. 2005. The effects of conjugated linoleic acid on human health-related outcomes. *Proceedings of the Nutrition Society* 64(2):171-182.

Tricon S, Yaqoob P. 2006. Conjugated linoleic acid and human health: a critical evaluation of the evidence. *Current Opinion in Clinical Nutrition and Metabolic Care* 9(2):105-110.

Van Lente F. 2000. Markers of inflammation as predictors in cardiovascular disease. *Clinica Chimica Acta* 293(1-2):31-52.

Wang Y, Jones PJ. 2004. Conjugated linoleic acid and obesity control: efficacy and mechanisms. *International Journal of Obesity and Related Metabolic Disorders* 28(8):941-955.

Wang Y, Jones PJ. 2004. Dietary conjugated linoleic acid and body composition. *The American Journal of Clinical Nutrition* 79(Supplement 6):1153S-1158S.

Whigham LD, Watras AC, Schoeller DA. 2007. Efficacy of conjugated linoleic acid for reducing fat mass: a meta-analysis in humans. *The American Journal of Clinical Nutrition* 85(5):1203-1211.



Whigham LD, O'Shea M, Mohede ICM, Walaski HP, Atkinson RL. 2004. Safety profile of conjugated linoleic acid in a 12-month trial in obese humans. *Food and Chemical Toxicology* 42(10):1701-1709.

WHO 2000: World Health Organization. Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation, 1999. Geneva (CH): WHO technical report series: 894. [Accessed 2009 October 28]. Available from: <http://www.atividadefisica.pro.br/artigos/WHO%20obesity.pdf>

Yudkin JS, Stehouwer CD, Emeis JJ, Coppack SW. 1999. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? *Arteriosclerosis, Thrombosis, and Vascular Biology* 19(4):972-978.

Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, Lang CC, Rumboldt Z, Onen CL, Lisheng L, Tanomsup S, Wangai P Jr, Razak F, Sharma AM, Anand SS; INTERHEART Study Investigators. 2005. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet* 366(9497):1640-1649.

Zambell KL, Keim NL, Van Loan MD, Gale B, Benito P, Kelley DS, Nelson GJ. 2000. Conjugated linoleic acid supplementation in humans: effects on body composition and energy expenditure. *Lipids* 35(7):777-782.