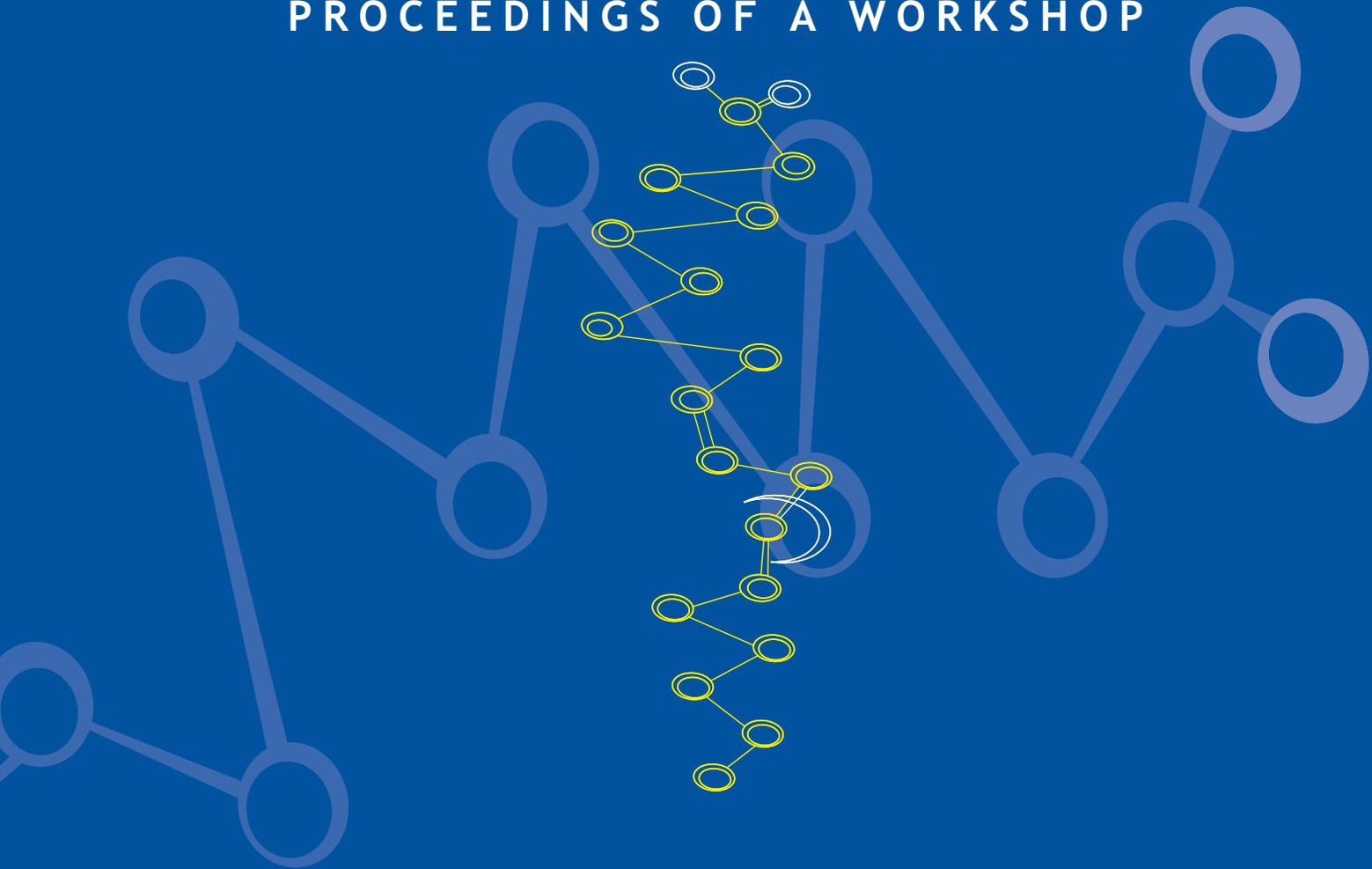


# PROCEEDINGS OF A WORKSHOP



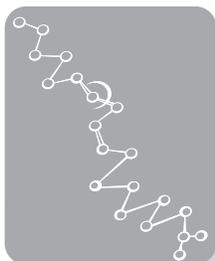
ON THE ROLE OF

# Conjugated Linoleic Acid in Human Health

March 13-15, 2003

Winnipeg, Canada • Fort Garry Hotel





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This Summary Report of the Workshop on the Role of Conjugated Linoleic Acid in Human Health is based on data provided by workshop participants in presentations, abstracts, posters and discussions.

March 13-15, 2003 Winnipeg, Manitoba, Canada

## Forward

On behalf of the Organizing Committee, it is a pleasure to present a summary of the proceedings together with abstracts arising from the 1st Canadian Workshop on Conjugated Linoleic Acid (CLA) and Human Health held in Winnipeg, March 13-15, 2003. The Workshop was organized to discuss the extraordinary potential of CLA as a functional food/nutraceutical in human health. Unlike conferences, workshops are deliberately structured to host a small but critical number of knowledgeable individuals to examine a very specific issue and to acquire a greater understanding of a problem or opportunity in a short period of time. Ideally there should be an outcome including an action plan. This Workshop was designed with that in mind. It brought together a group of Canadian and international leaders in CLA research to examine the state of current knowledge of CLA biology and physiology as it applies to human health. Cross fertilization of ideas was assured because participants included nutritionists, researchers, industry partners, government agencies, academe, and senior students and represented many disciplines.

While CLA and its active isomers have convincingly demonstrated important biological effects in small animals or in tissue culture systems, its widespread consumption as a nutraceutical is not based on extensive clinical research. It is important that recommendations regarding the use of CLA for health purposes to an individual or at the population level should be based on convincing evidence ideally achieved through clinical trials with sufficient power to establish effectiveness. Little is known about the usefulness of CLA in human disease processes such as the metabolic syndrome and obesity as well as diabetes or cancer. This information would be of enormous value to the average citizen, to the food industry, particularly dairy, beef and pork producers, and to commercial outfits that market CLA as a nutraceutical.

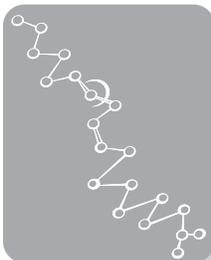
A workshop is successful when there is an opportunity for exchange of information and vigorous debate leading to the development of consensus around questions posed. This workshop helped identify areas of agreement as well as gaps where future research could be directed. The multidisciplinary mix of workshop participants facilitated networking and future collaborations of CLA researchers leading to health benefits and economic opportunities. Given the quality of the speakers and participants, we were confident that this would transpire.

The Workshop and these proceedings were made possible by the generous and unrestricted support of sponsors listed on the back cover of this document. We are grateful to these organizations and institutions for their encouragement and for providing the resources to assure a successful event.



**A. Angel, MD, FRCPC**

Professor of Medicine & Physiology, University of Manitoba  
President, Diabetes Research & Treatment Centre  
Chair, CLA Workshop Organizing Committee



## INTRODUCTION

A workshop was held in Winnipeg, Manitoba, in March 2003 to examine the role of conjugated linoleic acid (CLA) in the prevention and treatment of human disease. The workshop had three goals: 1) Review the quality of the evidence obtained from cell culture, animal and clinical research that supports a role for CLA in human health; 2) Provide a forum for exchanging information and stimulating debate about CLA's potential health effects; and 3) Promote networking among scientists and policymakers from academia, industry and government. Drawing on information from workshop presentations, posters and discussions, this report summarizes the current state of knowledge about CLA chemistry, metabolism and health effects; the technological challenges of developing CLA-enriched food products; current regulatory and marketing issues; and key challenges for researchers. A plan is proposed for future clinical research into the health effects of CLA.

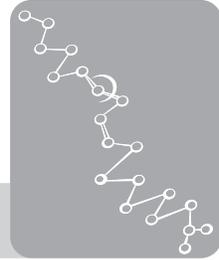
### Research Presentations

#### Chemistry and Metabolism of CLA

Conjugated linoleic acid (CLA) is a generic term used to describe a mixture of positional and geometric isomers or forms of linoleic acid. Linoleic acid is an 18-carbon polyunsaturated fatty acid with two double bonds, one occurring at position 9 and the other at position 12 in the carbon chain, both in the “cis” (meaning on the same side) configuration. Thus, the chemical structure of linoleic acid is *cis*-9, *cis*-12-octadecadienoic acid (1).

By comparison, the two double bonds in CLA can occur in several positions along the carbon chain—at positions 7 and 9, 8 and 10, 9 and 11, 10 and 12, 11 and 13, or 12 and 14. Each double bond can be found in either the “cis” or “trans” (meaning on opposite sides) configuration. Dr. John Kramer of Agriculture and Agri-Food Canada reported that 24 CLA isomers have so far been identified in dairy fats. The most prominent CLA isomer in rumen fats is *cis*-9, *trans*-11-CLA (abbreviated *c9,t11*-CLA), with minor amounts of *trans*-7, *cis*-9-CLA, (*t7,c9*-CLA), *trans*-11, *cis*-13-CLA (*t11,c13*-CLA), and *trans*-10, *cis*-9-CLA (*t10,c9*-CLA). The most commonly-occurring CLA isomers in synthetic mixtures are *c9,t11*-CLA and *t10,c9*-CLA, with minor amounts of *t8,c10*-CLA and *c11,t13*-CLA that are indicative of more severe heating conditions during synthesis of CLA from linoleic acid. Several of the CLA isomers have been shown to have different biological effects (Appendix, Abstract 1).

CLA occurs naturally in food products from ruminants such as cattle and sheep. In the rumen, CLA is synthesized by isomerization of linoleic acid by the action of the bacterium *Butyrivibrio fibrisolvens* (2). However, it has now been demonstrated that several unsaturated fatty acids form the common *trans*-11-octadecenoic acid (*t11*-18:1) by a combination of isomerization and biohydrogenation in the rumen; and the *t11*-18:1 transferred to the different tissues, including the mammary tissue, is re-synthesized to *c9,t11*-CLA by the action of delta-9-desaturase (3,4). The latter authors have demonstrated that about 70 to 80% of *c9,t11*-CLA in milk fat is produced by the action of delta-9-desaturase (5). This rumen bacterium may not be the only origin for CLA biosynthesis, because pork, chicken, seafood and vegetable oils also contain a small amount of CLA (1,6). Intestinal bacteria do not synthesize CLA in monogastric animals and humans (7);



therefore, these species must obtain CLA or its precursor t11-18:1 in the diet. The latter t11-18:1 is readily converted to the most common CLA isomer c9,t11-CLA by delta-9-desaturase in mammalian tissues.

The c9,t11-CLA isomer is the predominant CLA isomer in beef and milk fat from cows and sheep at 80-87% of total CLA, with t7,c9-CLA as the second most abundant CLA isomer (3 to 15%) and smaller amounts of t10,c12-CLA (8). Human milk and adipose fat also contain these CLA isomers at similar concentrations. Commercial supplements of CLA produced in 1996 typically contained mixtures of four positional CLA isomers (mainly t8,c10-CLA; c9,t11-CLA; t10,c12-CLA; and c11,t13-CLA). Today's CLA supplements consist primarily of the two CLA isomers c9,t11-CLA and t10,c12-CLA that have distinctly different biological and physiological activities. The ratio and purity of these isomers in commercial supplements is not assured and should be checked before use (9, Appendix, Abstract 1). The CLA mixtures are available as free fatty acids, as methyl or ethyl esters or lately as triacylglycerols. Although all the different forms of CLA have been shown to be absorbed in mammalian models, the triacylglycerol form is preferred for human studies.

#### **Current State of Knowledge about CLA's Health Effects**

Interest in the biologic effects of CLA began in 1979, when Dr. Michael Pariza, now at the University of Wisconsin, reported that raw and fried ground beef contained a factor that inhibited mutagenesis and carcinogenesis (10). His work stimulated research into the anticancer effects of CLA. According to Dr. Pariza, researchers have identified many of the biologic effects of CLA in animals over the past 20 years. What remains are questions about the effectiveness and safety of CLA in humans (Appendix, Abstract 2).

#### **Diabetes and Insulin Resistance**

CLA may have therapeutic potential in managing type 2 diabetes, according to Dr. Hope Anderson of the University of California (Appendix, Abstract 3). Type 2 diabetes mellitus is characterized by a variety of metabolic derangements, particularly hyperglycemia, insulin resistance and relative (rather than absolute) insulin deficiency (11).

CLA has been shown to improve oral glucose tolerance and delay the development of diabetes in rat models. Dr. Carla Taylor at the University of Manitoba presented data showing that dietary CLA improved oral glucose tolerance and lowered serum insulin levels in the fa/fa Zucker rat, a model of obesity and insulin resistance. In her study, weanling male lean and fa/fa Zucker rats were fed a 1.5% w/w CLA mixture or a control diet without CLA for eight weeks. The CLA-fed rats had lower serum glucose and insulin concentrations during an oral glucose tolerance test, smaller adipocytes, smaller pancreatic  $\beta$ -cells, decreased liver weight and decreased fatty liver than control rats (12, Appendix, Abstract 4).

Dr. Martha Belury of Ohio State University reported that CLA delayed the onset of hyperglycemia and diabetes in the diabetic fatty Zucker rat (Appendix, Abstract 5). In a human study, CLA decreased fasting blood glucose concentrations

in patients with type 2 diabetes, according to Dr. Belury. The 21 subjects in this pilot study were not taking medications for blood glucose control and were randomized to consume 6.0 g CLA or safflower oil daily for eight weeks (Appendix, Abstract 5). By the end of the 8-week intervention, 9 of 11 (81%) subjects on CLA supplementation experienced decreases in fasting plasma glucose compared with two out of 10 (20%) subjects not taking CLA (13). Despite these positive preliminary findings, Dr. Bengt Vessby of the University of Uppsala, Sweden, has reported that there is little evidence of any improvement in the metabolic status of humans after CLA supplementation (14).

### Metabolic Syndrome

Metabolic syndrome is a generic term for a cluster of risk factors that includes, obesity, hyperinsulinemia, hypertriglyceridemia, and hypertension. The condition has also been called syndrome X and insulin resistance syndrome (15). Definitions of the syndrome have been published by the World Health Organization (WHO), the European Group for the Study of Insulin Resistance (16) and the National Cholesterol Education Program (17). The definitions differ slightly in terms of measures and cutoff points.

Individuals with metabolic syndrome are predisposed to coronary heart disease (CHD) and type 2 diabetes (14). Obese individuals who accumulate fat mainly in the abdominal area are more likely to exhibit symptoms of the metabolic syndrome than those who do not, according to Dr. Benoît Lamarche of the Nutraceuticals and Functional Foods Institute, Laval University (Appendix, Abstract 6). Dr. Lamarche is studying the impact of the metabolic syndrome on cardiovascular disease (CVD) in men using prospective data from the Québec Cardiovascular Study. The study began in 1973 among 7,081 men aged 35-64 years. In a recent follow-up of participants, Dr. Lamarche reported that the presence of small, dense LDL particles, one of the key features of the metabolic syndrome, was associated with increased abdominal fat (18) and decreased survival in the study cohort (19). Dr. Lamarche also showed that men with marginally elevated plasma triglyceride levels as part of the metabolic syndrome ( $> 1.6$  mmol/L) had a 2- to 3-fold increased risk of CVD compared with men who had low plasma triglyceride concentrations. Finally, men who accumulated several features of the metabolic syndrome, namely high insulin and apo B concentrations and small, dense LDL particles had a 20-fold increase in CVD risk, thus clearly supporting the hypothesis that the metabolic syndrome is a key component of the pathophysiology leading to CVD (20).

### Cardiovascular Disease

CLA may be antiatherogenic. In rabbits, for example, a dietary level of 0.1% w/w CLA increased serum cholesterol and triglyceride concentrations but surprisingly inhibited atherosclerosis by 34%, while a dietary level of 1% w/w CLA caused significant regression of atheromata (21). According to Dr. Hope Anderson of the University of California, feeding CLA to rats decreased triglyceride concentrations significantly, with no change or a modest decrease in HDL cholesterol (Appendix, Abstract 3). Nonetheless, Dr. Roger McLeod of Dalhousie University provided data suggesting that both the  $t9,t11$ -CLA and  $t10,c12$ -CLA isomers stimulate triglyceride synthesis and storage in rat hepatoma cells, although the  $t10,c12$ -CLA isomer may also inhibit triglyceride secretion.

To test the role of CLA in lipoprotein metabolism *in vivo*, Dr. McLeod supplemented the high-fat, high-cholesterol diets of Syrian hamsters with 1% w/w  $t9,t11$ -CLA,  $t10,c12$ -CLA or linoleic acid. There were no differences in food consumption, weight gain or HDL levels between the control diet (linoleic acid) and CLA-supplemented diets, but plasma triglyceride levels were increased in the group fed  $t10,c12$ -CLA vs.  $t9,t11$ -CLA or linoleic acid (Appendix, Abstract 7). Dr. Lamarche also presented some preliminary work on CLA from the Nutraceuticals and Functional Foods Institute at

Laval University. Briefly, 16 healthy men were randomized to eat meals containing regular butter, which provided 0.2 g CLA/day, or meals containing a modified butter, which provided 2.2 g CLA/day (mostly t9,c11-CLA) over a period of four weeks. All foods were provided to study participants. Consuming CLA as part of a regular diet had no impact on blood lipids or on features of the metabolic syndrome (Desroches et al., unpublished observations).

### Adiposity and Body Composition

CLA has been shown to increase lean body mass and decrease body fat in pigs (22, 23), mice (24-28), rats (29) and chicks (24, 30). Dr. Peter Jones of McGill University reported that feeding CLA to animals decreased brown and white adipose tissue and body weight. Dr. Jones indicated that in mice the t10,c12-CLA isomer appeared more effective in lowering adipose tissue mass than the c9,t11-CLA isomer (31, Appendix, Abstract 8).

The effects of CLA on adiposity of humans have not been consistent. In one study of 47 overweight or obese adults, those randomized to consume 3.4 or 6.8 g CLA/day experienced a significant reduction in body fat mass after 12 weeks of treatment, even though there was no reduction in weight or body mass index in any of the groups. The CLA preparation used in this study was a mixture of the c9,t11-CLA and t10,c12-CLA isomers (32). However, Dr. Bengt Vessby of the University of Uppsala in Sweden reported at the workshop that consumption of 4.2 g CLA/day for three months by healthy volunteers decreased body fat slightly but had no effect on body weight or body mass index. According to Dr. Vessby, there was no clear relationship between CLA dosage or duration of intake and the reduction in body fat mass. Because CLA consumption increased plasma C-reactive protein (CRP) concentration and the enzymatic (prostaglandins) and non-enzymatic (isoprostanes) peroxidation of lipids in these volunteers, Dr. Vessby called for more long-term clinical studies using individual isomers in different populations (Appendix, Abstract 9).

### Regulation of Lipid Metabolism

Obesity is characterized by an increase in the number of adipocytes and in the amount of lipid stored in adipocytes. Adipocytes arise from a pool of existing preadipocytes, which differentiate into mature cells when the appropriate signal is given. Adipocyte differentiation is regulated by hormones, growth factors, cytokines and transcription factors. Several presenters addressed the effects of CLA on various aspects of adipocyte differentiation, including leptin secretion, PPAR-responsive genes and the differentiation and lipid filling of preadipocytes.

Leptin is a hormone-like protein synthesized by adipocytes. It regulates fat and energy storage and is an independent risk factor for cardiovascular disease (32). Dr. Carla Taylor of the University of Manitoba reported that in her study of weanling lean and fa/fa male Zucker rats, fa/fa rats fed CLA for eight weeks had lower serum leptin concentrations, and adipose tissues with reduced leptin mRNA levels and smaller adipocyte size compared with fa/fa rats fed a control diet (Appendix, Abstract 4). According to Ms. Patti Plett of the University of Manitoba, CLA isomers differ in their effects on leptin secretion. Ms. Plett conducted a dose response experiment showing that the c9,t10-CLA isomer stimulated, whereas the t10,c12-CLA isomer decreased, leptin secretion and adipocyte lipid. The results suggest that leptin production is greatest during initial lipid accumulation, then decreases somewhat as lipid stores expand (Appendix, Abstract 10).

CLA may also regulate genes responsive to peroxisomal proliferator-activated receptors (PPARs). PPARs belong to the steroid hormone receptor superfamily. Of the three types, PPAR $\alpha$  and PPAR $\beta$  are expressed in body tissues (e.g., heart, liver, muscle and brown adipose tissue) that catabolize fatty acids, whereas PPAR $\gamma$  is expressed in adipose tissue and

skeletal muscle and appears to be involved in adipocyte differentiation (33). Dr. N. Yukova of the Institute of Cardiovascular Sciences, St. Boniface Hospital Research Centre, investigated PPAR-responsive gene expression in insulin-resistant obese rats. In this study, weanling and *fa/fa* male Zucker rats were fed a 1.5% w/w CLA mixture or a control diet without CLA for eight weeks. The mRNA levels of PPAR-responsive fatty acid binding protein and acyl-CoA oxidase genes were elevated in liver of *fa/fa* rats fed CLA (Appendix, Abstract 11). Dr. Peter Jones of McGill University reported that  $\alpha$ , $\omega$ -CLA modulated gene expression in cultured 3T3-L1 preadipocytes (Appendix, Abstract 8).

Dr. Victor Gavino of the Université de Montréal reported no differences between two isomers— $\alpha$ , $\omega$ -CLA and  $\alpha$ , $\omega$ -CLA—on the extent of differentiation of stromal-vascular cells from human and hamster adipose tissues. The cells had been exposed to 50  $\mu$ M concentrations of various pure CLA isomers using linoleic acid as a control. The  $\alpha$ , $\omega$ -CLA isomer reduced lipid filling by 85% and 45% in human and hamster preadipocytes, respectively. By comparison, the  $\alpha$ , $\omega$ -CLA isomer decreased lipid filling in human cells by 30%, but had no effect on hamster cells compared with a control (Appendix, Abstract 12). Dr. Belury of Ohio State University also reported that CLA inhibited proliferation but stimulated lipid filling of 3T3-L1 cells (Appendix, Abstract 5).

### Bone Growth and Metabolism

Bone metabolism is orchestrated by three types of cells—chondrocytes, osteoblasts and osteoclasts—and their activities are affected by several local growth factors such as insulin-like growth factor (IGF-1), prostaglandin E2 (PGE2), and the cytokines interleukin-1 and tumor necrosis factor. Dr. Bruce Watkins at the Center for Enhancing Foods to Protect Health, Purdue University, described the effects of CLA on some biomarkers of bone metabolism in rats. For example, when supplied at a level of 1% w/w of the diet, CLA isomers depressed *ex vivo* synthesis of PGE2, serum IGF-1 and the rate of bone formation in male rats (34). At a dietary level of 0.5% w/w, CLA isomers maintained bone formation rates in growing male rats given a diet rich in omega-6 fatty acids. CLA isomers increased collagen synthesis in primary cultures of growth plate chondrocytes following a dose-dependent manner. Dr. Watkins also indicated that the effects of CLA on bone metabolism in rats is influenced by the type and amount of CLA isomers as well as the ratio of omega-6 to omega-3 fatty acids in the diet (Appendix, Abstract 13).

Dr. Hope Weiler of the University of Manitoba reported that CLA did not affect bone formation and resorption in a rat model of metabolic bone disease. Metabolic bone disease is characterized by elevated parathyroid hormone levels and increased rates of bone turnover. In her study, 52 weanling male Han:SPRD-cy rats were randomized to identical diets supplemented with and without CLA (1% of dietary fat) for eight weeks. CLA did not affect bone mass, but it decreased the release of PGE2 in kidney and attenuated parathyroid hormone levels by 60% (35, Appendix, Abstract 14).

### Immune Function

CLA may enhance humoral and cellular immune responses in animals and humans, according to Dr. Marianne O'Shea of Loders Croklaan. In a pig model of immunosuppressive viral disease, pigs fed CLA-supplemented diets for 42 days had significantly greater cellular immune responses as reflected in the increase of CD8+ cells than littermates fed a control diet (1% soybean oil) (Appendix, Abstract 15). A human study investigated the effects of CLA supplementation (1.7 g active isomers/day for 12 weeks) on humoral and cell-mediated immune responses. Hepatitis B vaccination was used as an antigen challenge model to investigate the humoral immune response. The seroprotection rate (i.e., the number of subjects with anti-HBv concentrations >10 IU/L compared with the number of subjects with titers <10 IU/L) was significantly higher ( $P=0.05$ ) for the CLA group compared to the control group (36).

### Renal Disease

In a rat model of renal interstitial inflammation and fibrosis associated with chronic renal disease, Dr. Howard Aukema of the University of Manitoba presented data supporting a role for CLA in ameliorating renal disease. In his study, male Han:SPRD-cy rats were fed a diet containing 1% CLA or a control diet for eight weeks. CLA-fed rats had higher urine creatinine levels and increased cyclooxygenase-2 (COX-2) protein expression in normal and diseased kidneys compared with control rats (Appendix, Abstract 16).

### Cancer

CLA is an effective anticarcinogen, inhibiting tumour development in the skin, mammary gland and forestomach of humans and rodents (7, 37). Dr. Catherine Field of the University of Alberta reported that CLA has been shown to inhibit tumour development at each stage of carcinogenesis: initiation, promotion and progression (Appendix, Abstract 17). In mammary, liver, colon and intestinal cells, CLA reduced angiogenesis and metastasis and increased cell death (apoptosis), thus suppressing tumour promotion and progression (38). Exposing young animals to CLA appears to provide protection against chemically-induced tumour development by making the immature mammary gland less susceptible to tumour formation later in life (38, 39). In humans, CLA inhibited the proliferation of malignant melanoma, breast, lung and colorectal cancer cell lines (40).

CLA and omega-3 fatty acids may inhibit tumour growth by slowing or stopping cell proliferation or by increasing apoptosis, according to Dr. Field. Omega-3 fatty acids have been shown to alter the fatty acid composition of phospholipids in cell membranes and reduce the availability of arachidonic acid. Arachidonic acid is an omega-6 fatty acid and the precursor of powerful eicosanoids, many of which promote inflammation and influence cancer processes. Dr. Field indicated that it is not known whether the cancer-protective effects of CLA are similar to those of the omega-3 fatty acids.

## Industry and Commercial Opportunities

### Developing CLA-Enriched Food Products

CLA shows promise as a fatty acid with positive health benefits. Mr. Brad McNish, president of Sepallo in Kelowna, BC, remarked that when it comes to considering the role of CLA in human health and disease prevention, it is important to understand the difference between CLA delivered in supplement form and CLA delivered in a food matrix (Appendix, Abstract 18). This section reviews research related to developing food products enriched with CLA.

### Dairy Products

Increasing the CLA content of milk and other dairy products involves feeding cows a high-fat diet rich in linoleic acid during the entire lactation period. Dr. Yvan Chouinard of Laval University indicated that the predominant CLA isomer in milk fat is c9,t11-CLA, which represents 80-90% of total CLA in dairy products. This isomer is an intermediate in ruminal biohydrogenation of linoleic acid, and a portion escapes the rumen and is incorporated in milk fat. Many dietary factors affect the CLA content of milk fat, including the addition of plant oils such as sunflower, soybean, canola and linseed oils to the diet, which increases substantially the c9,t11-CLA isomer in milk fat. Plant oils high in linoleic acid give the greatest response. The dietary addition of fish oil, fishmeal or marine algae also increases the CLA content of milk fat. The long-term effects of high-fat diets on cow health and performance are not known (Appendix, Abstract 19).

### Beef Products

Beef cattle produce CLA and deposit these isomers in the meat (41). The relative content of CLA in beef is affected by the type and maturity of pasture, the feedlot diet, addition of silage to the diet and the composition of the dietary oil or oilseed, according to Dr. Priya Mir of Agriculture and Agri-Food Canada. For example, beef from pastured animals has a higher CLA content than animals fed silage. In feedlot animals fed grain diets, including oil in the diet provided 77 mg CLA in a 3-oz serving of beef. The CLA isomers appear to be concentrated in intra-muscular and subcutaneous fat of beef cattle, and the concentration of c9,t11-CLA is greater than the concentration of t10,c12-CLA in all tissues, but the proportion of the latter CLA isomer is greater in subcutaneous fat (Appendix, Abstract 20).

### Pork Products

Pigs have an advantage over ruminants because of their ability to enrich tissues with CLA. Dr. Michael Dugan of Agriculture and Agri-Food Canada indicated that adding CLA to pig diets has been shown to increase muscle marbling fat and fat hardness—results that can potentially increase carcass value. Currently, BASF has the international marketing license to include CLA in animal feeds, but this practice has not been approved in Canada or the United States. Because swine accumulate relatively high levels of CLA in their tissues, pork and pork products may become an important vehicle for delivering CLA to consumers (Appendix, Abstract 21).

### Regulatory Issues Related to CLA

The Canadian Food and Drugs Act and Regulations was passed into law in 1953. Through its definitions of “food” and “drug”, this legislation currently restricts health-related claims for foods, food ingredients and natural health products, according to Ms. Kelley Fitzpatrick of the Richardson Centre for Functional Foods and Nutraceuticals at the University of Manitoba (Appendix, Abstract 22).

Beginning in 1999, Health Canada undertook three initiatives related to health claims for foods: 1) to adopt certain of the initial ten diet-based disease risk reduction claims approved in the United States under the National Labeling and Education Act; 2) to develop scientific standards of evidence and a guidance document on data requirements for supporting the validity of new health claims for foods; and 3) to develop an appropriate regulatory framework to allow product-specific health claims for foods (42). For nutrition labeling purposes, CLA is not considered a *trans* fat, according to Ms. Kelley. Therefore, a label statement regarding the *trans* fat content of a food will not include CLA.

### Product Development and Marketing

Bringing CLA-enriched food products to market not only involves educating consumers about the health benefits of CLA, but also the need to understand consumer behaviour. Ms. Cindy Thorvaldson of Alberta Milk indicated that most consumers (95%) are focused on maintaining health, and about three-quarters (72%) are concerned about maintaining or losing weight. Only 8% are concerned about preventing disease. The leading trends are health, convenience, pleasure and value. Because personal health is a key motivator, consumers continue to focus on foods that provide health benefits. Functional foods are a growing market segment, and consumers who use supplements and shop at health food stores lead the way in their awareness about functional foods. According to Ms. Thorvaldson, producers must get the right message to the right consumer at the right time. She also described an Alberta-based CLA Network, which involves an extensive group of researchers, the dairy, beef and crop industries and government committed to creating a unified approach to understanding CLA and its role in human health, developing natural production systems and products, and educating health professionals and consumers about health benefits and sources of CLA. The CLA Network is carrying

out a study to identify the profile of Canadians who use functional foods. The survey addresses such issues as consumer awareness of and knowledge about fats, including CLA; consumers' willingness to change their eating habits to include CLA-containing foods and/or supplements; and their preferences for dietary forms of CLA (e.g., natural vs. supplemental; dairy vs. meat) (Appendix, Abstract 23). Ms. Thorvaldson's messages were reinforced by Mr. Brad McNish of Sepallo, who indicated that consumers want innovative products, particularly from the dairy industry (Appendix, Abstract 18).

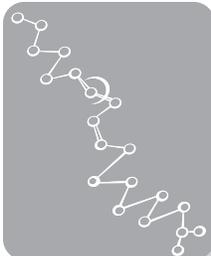
## Challenges for Researchers

Several research issues emerged in discussions among workshop presenters and invited discussants. A group led by Dr. Grant Pierce of the University of Manitoba and including Dr. Stephanie Atkinson of McMaster University, Dr. Susan Barr of the University of British Columbia, Dr. Bruce Holub of the University of Guelph and Dr. Tom Wolever of the University of Toronto identified the following areas deserving of future research:

- Purity of commercial CLA preparations used in research
- Analytic methods to ensure separation and identification of various CLA isomers
- Biologic effects of different CLA isomers
- Tissue differences in biologic effects
- Mechanisms of action
- Role of background diet, including the ratio of omega-6 to omega-3 fatty acids
- Dose response
- Size of CLA's effects relative to other diet interventions
- Short-term vs. long-term interventions
- Diet-gene interactions
- Effects of life stage (e.g., bone remodeling in children vs. bone maintenance in the elderly; sensitivity of children compared with adults)
- Adverse effects and safety
- Adequacy of CLA food databases
- Optimum delivery vehicle (foods vs. supplements)
- Methods of increasing the CLA content of foods
- Dietary requirement of CLA

## Action Plan for CLA Research

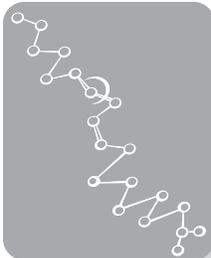
Members of the national organizing committee met at the close of the workshop to discuss an action plan for CLA research. The organizers recognized the success of the workshop in promoting collaborative research and networking opportunities among participants, and they outlined three strategies for moving CLA research forward: 1) Set research priorities, particularly in the areas of CLA mechanisms of action and efficacy and safety in human populations; 2) Identify funding sources for clinical trials such as the U.S. National Institutes of Health, Agriculture and Agri-Food Canada, INSERC, CIHR and industry (e.g., dairy, beef, nutraceutical); and 3) Expand the Alberta CLA Network across Canada to enhance the sharing of information about CLA research and build a community of CLA researchers.



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## APPENDIX

### ABSTRACTS

#### Abstract 1

##### THE CHEMISTRY AND PREVALENCE OF CLA ISOMERS IN ANIMAL SYSTEMS

J. K. G. Kramer\*, J. Zhou, C. Cruz-Hernandez and M. E. R. Dugan. Agriculture and Agri-Food Canada, Guelph, ON.

The chemistry of conjugated fatty acids, specifically octadecadienoic acids (18:2) (commonly referred to as conjugated linoleic acid or CLA), has provided many challenges to lipid analysts because of their unique physical properties, and the many possible positional and geometric isomers. After overcoming their acid labile properties during analytical procedures, it became evident that natural products, specifically dairy fats, contain one dominant (9c,11t-CLA), 3 intermediate (7t9c-, 9t11c- and 11t13c-CLA) and up to 20 more minor CLA isomers. The best analytical techniques to date include a combination of GC using 100 m highly polar capillary columns, silver-ion HPLC, and a combination of silver-ion TLC and GC to analyze also the 18:1 *trans* isomers that serve as precursors of CLA in biological systems. These analytical techniques have assisted commercial suppliers to prepare pure CLA isomers, and have made possible the evaluation of individual CLA for their nutritional and biological activity in animal and human models. It is increasingly evident that different CLA isomers have distinctly different physiological and/or biochemical properties. These techniques have also been essential to evaluate dairy fats for their CLA content, to design experimental diets to increase the level of CLA in dairy fats, and to determine the CLA profile in these CLA enriched dairy fats. These improved techniques were used to evaluate the CLA profile in pork products from pigs fed different commercial CLA mixtures.

#### Abstract 2

##### CLA IN HUMAN AND ANIMAL HEALTH: MECHANISMS AND PROSPECTS

M.W. Pariza. Food Research Institute, Department of Food Microbiology and Toxicology, University of Wisconsin-Madison, Madison, WI.

It is becoming increasingly apparent that the many reported physiological effects of conjugated linoleic acid (CLA) are due to specific actions of, as well as interactions between, the two known biologically-active isomers: *cis*-9,*trans*-11 CLA and *trans*-10,*cis*-12 CLA. Examples include biological effects induced by the independent action of one of the isomers, synergistic interactions involving both isomers, and even apparent opposition between the isomers. The signaling pathways through which the CLA isomers induce these effects are still largely unknown, but the modulation of lipoxygenase signaling pathways appears to be involved. It also appears that at least some effects may be induced by the parent compound(s) themselves rather than CLA metabolite(s). These observations and conclusions will be considered in the context of optimizing the utilization of CLA to maintain and/or improve human and animal health.

#### Abstract 3

##### INSULIN RESISTANCE-ASSOCIATED CARDIOVASCULAR DISEASE: POTENTIAL BENEFITS OF CLA

H. D. Anderson. University of California, San Francisco, CA.

Type 2 diabetes and associated cardiovascular disease have reached global epidemic proportions. Recent data from the World Health Organization (WHO) Multinational Study of Vascular Disease in Diabetes indicate that cardiovascular disease is the leading cause of mortality in patients with type 2 diabetes, accounting for 52% of deaths. Though insulin resistance plays a critical role in the pathogenesis of type 2 diabetes-related cardiovascular disease, other related risk factors often cluster in the same patient as what is termed the Metabolic Syndrome. According to the WHO definition, this constellation of risk factors includes hypertension, elevated plasma triglycerides, reduced HDL cholesterol, central obesity, and microalbuminuria. The Multiple Risk Factor Intervention Trial (MRFIT) demonstrated that whereas diabetes/insulin resistance is an independent risk factor for cardiovascular mortality, these other components of the Metabolic Syndrome confer additive risk. Thus, to effectively address cardiovascular disease in diabetics, intervention would ideally target all of these factors. Conjugated linoleic acid may represent such a candidate agent. The therapeutic potential of conjugated linoleic acid on insulin resistance-associated cardiovascular disease will be discussed, based on its reported effects on individual components of the Metabolic Syndrome.

#### Abstract 4

##### CLA EFFECTS IN OBESE HYPERINSULINEMIC FA/FA ZUCKER RATS

C. Taylor(1\*), N. Yurkova(2,3), A. Noto(1), T. Ryz(1), J. Zahradka(1), M. Zirk(1) and P. Zahradka(2,3). (1)Department of Human Nutritional Sciences, University of Manitoba, Winnipeg, MB. (2)Department of Physiology, University of Manitoba, Winnipeg, MB. (3)Institute of Cardiovascular Sciences, St. Boniface Research Centre, Winnipeg, MB.

The effects of dietary CLA on glucose tolerance and obesity were examined in the fa/fa Zucker rat, a model of obesity and insulin resistance. Weanling lean and fa/fa male Zucker rats were fed a 1.5% CLA mixture (InCLA and faCLA groups) or control diet (InCTL and faCTL groups) for 8 weeks. Despite similar body weight and fat pad weights, faCLA rats had lower serum leptin concentrations, reduced leptin mRNA levels in fat tissue and smaller adipocyte diameters than faCTL rats. Oral glucose tolerance was improved in faCLA rats based on lower serum glucose concentrations (12.8±1.2 vs 16.6±0.7 mM at 30 min, P<0.05) and insulin concentrations (P<0.05 at 0, 15, 30 and 60 min), and smaller area under the curve for glucose and insulin. Furthermore, the faCLA rats had smaller pancreatic β-cell diameters, and reduced fasting serum

concentrations of insulin and C-peptide (34% and 46% of faCTL rats, respectively). In summary, the dietary CLA mixture significantly improved oral glucose tolerance, attenuated hyperinsulinemia, and altered leptin metabolism in fa/fa Zucker rats without affecting body weight or fat pad weight. (Funding from Dairy Farmers of Canada and NSERC CRDPJ.)

**Abstract 5**  
CELLULAR AND MOLECULAR MECHANISMS OF CLA ACTION

M.A. Belury\* and C.S. Kennedy. The Ohio State University, Columbus, OH.

The incidence of type 2 diabetes mellitus is increasing in epidemic proportions in developed countries worldwide. Type 2 diabetes arises from a variety of etiological factors including environmental factors that affect obesity and dyslipidemia and non-modifiable factors including genetics, ethnicity and age. The delay of onset or therapy to reduce the severity of the disease through diet and other lifestyle approaches offers the possibility of reducing the severity of co-morbid disorders that contribute to morbidity and mortality. Co-morbid disorders that often exist with type 2 diabetes include cardiovascular disease, retinopathy and neuropathy. Numerous studies have shown that the dietary fatty acids, conjugated linoleic acids (CLA), reduce adiposity in experimental animals and recent studies suggest similar findings in humans. We have identified that dietary CLA delays the onset and improves lipid profiles in a rat model for type 2 diabetes. Subsequent studies have demonstrated that CLA may improve glucose metabolism by enhancing glucose uptake into muscle. Numerous investigators have shown CLA alters deposition of body fat in a depot-specific pattern. In non-diabetic animals that has also resulted in increased insulin resistance. We and others have found that CLA modulates numerous pathways involving lipid signaling and fatty acid oxidation. Pathways that may explain CLA's anti-adipogenic effects include modulation of  $\Delta 6$ -,  $\Delta 9$  desaturase metabolism as well as pathways modified by the transcription factor, peroxisome proliferator-activated receptors (PPARs). The potential ability of different isomers of CLA at various doses and durations (short- vs. long-term) to alter metabolic pathways through altering gene expression to ultimately affect type 2 diabetes mellitus will be discussed.

**Abstract 6**  
THE METABOLIC SYNDROME AND THE EFFECTS OF CLA IN OBESITY, DIABETES AND LIPOPROTEIN DISORDERS: THE QUÉBEC EXPERIENCE

B. Lamarche. Institute on Nutraceuticals and Functional Foods, Laval University, Québec.

The health hazards of obesity are well established. However, the fact that all obese individuals are not at equal risk of developing a disease is being increasingly recognized. The regional distribution of body fat has been identified as a very important component of the obesity-related health hazards. Among obese individuals, those who accumulate fat preponderantly in the abdominal area are more likely to present several metabolic perturbations of the metabolic syndrome such as increased plasma triglyceride and apolipoprotein B levels, an elevated total cholesterol/HDL cholesterol ratio, reduced plasma HDL cholesterol concentrations and small, dense LDL particles. This talk will focus on the risk associated with specific features of the metabolic syndrome using data from the Quebec Cardiovascular Study, an on-going prospective study of traditional and non traditional risk factors of ischemic heart disease (IHD) in men. Recent data from a nutritional intervention aimed at investigating the impact of CLA on several risk factors for IHD will also be reviewed.

**Abstract 7**  
EFFECTS OF CLA ON HEPATIC VERY LOW DENSITY LIPOPROTEIN METABOLISM

R. S. McLeod\*, A. LeBlanc, M. Langille and D. Currie. Dalhousie University, Halifax, NS.

We have studied the effect of conjugated linoleic acid (CLA) isomers on very low density lipoprotein (VLDL) metabolism in the rat hepatoma cell line, McA-RH7777. Incubation of the hepatoma cells with 0.4 mM fatty acid, both c-9, t-11 CLA and t-10, c-12 CLA stimulated an increase in rat hepatoma cell triglyceride (TG) levels suggesting that both isoforms of CLA stimulate TG synthesis and storage in the hepatocyte. Both isomers, like oleic acid, stimulated the secretion of B48-VLDL. When provided as a minor component of the total medium fatty acid (40 mM) to cultures containing myristic acid (at 0.36 mM), each CLA caused a shift of the VLDL density, suggesting they stimulate the assembly of more TG-rich VLDL. To test the potential roles of CLA in lipoprotein metabolism in vivo, we supplemented the high fat/cholesterol diets of Syrian Golden hamsters (an established model of diet-induced hyperlipoproteinemia) with 1% (w/w) c-9, t-11 or t-10, c-12 CLA or with LA. Compared to the LA control diet, there was no significant difference in food consumption or weight gain with either CLA during the 10 week experiment. Plasma cholesterol was also unaffected but plasma triglycerides were increased in the group fed t-10, c-12 CLA ( $p < 0.02$  vs LA or c-9, t-11 CLA). These results suggest that isomeric forms of CLA may have different effects on hepatic lipid and lipoprotein metabolism. (This work is supported by research funding from the Dairy Farmers of Canada.)

**Abstract 8**  
BODY COMPOSITION/ ADIPOSE MASS AND CONJUGATED LINOLEIC ACID EFFECTS

P.J. H. Jones. School of Dietetics and Human Nutrition, McGill University, Montreal, QC.

Accumulating data demonstrate that consumption of conjugated linoleic acid (CLA) modulates body composition, especially by suppressing the accumulation of adipose tissue in mice, rats, pigs, and humans. For instance, mice fed CLA-supplemented diets exhibited over 50% lower body fat and approximately 10% increased lean body mass relative to those fed control diets. Further work demonstrated that dietary CLA-induced reduction of adiposity could be sustained in mice even after CLA was removed from the diet. Site specificity to CLA-mediated effects has also been shown across various depots of fat mass, specifically retroperitoneal and epididymal white adipose tissue masses and brown adipose tissue. Isomer-specific effects of CLA on adiposity have been observed, where t-10, c-12 CLA appears more effective in lowering adipose tissue mass than c-9, t-11 CLA isomer in mice. In addition, t-10, c-12 CLA is most able to modulate gene expression in cultured 3T3-L1 pre-adipocytes. In adult humans, the ability of CLA to reduce adipose tissue mass has been shown repeatedly. For instance, supplementation with CLA (3.4-6.8

g/day) for 12 wk resulted in reduction in fat depot mass, body weight and BMI. Mechanisms explaining how CLA reduces adiposity likely involve pathways that regulate energy expenditure including increased metabolic rates and decreased nocturnal respiratory quotients, mediated possibly through enhanced sympathetic nervous activity. Assuming safety of use, existing data point to a role for dietary CLA in maintenance of healthy body weight.

#### Abstract 9

##### THE METABOLIC EFFECTS OF CLA IN HUMANS: THE SWEDISH EXPERIENCE

B. Vessby<sup>1</sup>, U. Risérus, A. Smedman and S. Basu. Unit for Clinical Nutrition Research, University of Uppsala, Uppsala, Sweden.

Conjugated linoleic acid (CLA) comprises a group of unsaturated fatty acid isomers with a variety of biological effects. CLA reduces body fat accumulation in animal models and has been ascribed significant effects on lipid and glucose metabolism. It has been suggested that the *trans* 10-*cis* 12 isomer is the active isomer as regards antiobesity and insulin sensitizing properties. The metabolic effects in humans are not well characterized. We have investigated the effects of CLA (given as the commercially available mixture of isomers and as the purified *trans* 10-*cis* 12 CLA isomer) on anthropometry, lipid and glucose metabolism and on markers of lipid peroxidation. Preliminary results indicate that CLA may slightly decrease body fat also in humans, particularly abdominal fat, but there is no effect on body weight or body mass index. There is no simultaneous improvement of lipid or glucose metabolism. Rather, the *trans* 10-*cis* 12 CLA isomer unexpectedly caused significant impairment of the peripheral insulin sensitivity as well as of blood glucose and serum lipid levels. In addition, CLA markedly elevated lipid peroxidation. Thus, the metabolic effects of CLA in humans seem complex and further studies, especially of isomer specific effects and during longer time periods, are needed.

#### Abstract 10

##### EFFECTS OF LINOLEIC ACID (LA) AND CONJUGATED LINOLEIC ACID (CLA) ON LEPTIN

P. Plett, H. Weiler and A. Angel<sup>1</sup>. Department of Medicine and Nutritional Sciences, University of Manitoba, Winnipeg, MB.

Leptin is an important regulator of feeding behavior and metabolic rate and its production is related to adipose mass. To determine the effects of dietary lipid composition on adipose mass and leptin levels, C57 BL/6C mice (n = 7 or 8 per group) were fed semi-synthetic diets containing 20% Safflower oil (SO, linoleic rich), 20% Flax oil (FX, linolenic rich), or standard Chow for 70 days. On DEXA analysis of adipose mass, SO had significantly more fat than FX and Chow mice (25.1 \* 2.3 g vs. 20.2 \* 0.6 and 14.6 \* 4.2 g, mean \* SEM respectively). Serum leptin was greater in SO (90.7 \* 3.7 ng/mL) vs. FX (74.9 \* 5.6 ng/mL) and Chow (33.1 \* 2.2 ng/mL). In contrast to LA, dietary CLA is thought to reduce adipose mass, an effect that appears to be isomer specific. Accordingly, the effects of C9-T11 and T10-C12 isomers of CLA on triglyceride and leptin production in differentiated 3T3-L1 cells were examined. Dose response experiments (0-100 µM) showed that the C9-T10 isomer stimulated and T10-C12 CLA reduced adipocyte lipid and leptin secretion. In time course experiments (0-11 days), a phasic profile was evident with a late fall in leptin secretion. These studies demonstrate that CLA isomers either stimulate or inhibit adipose lipid accumulation and leptin production, depending on isoform type and concentration. The results also suggest that leptin production is greatest early during lipid accumulation and decreases as lipid stores expand. (Supported by a grant from the Dairy Farmers of Canada.)

#### Abstract 11

##### DIETARY CONJUGATED LINOLEIC ACID (CLA) REGULATES PPAR-RESPONSIVE GENES AND IMPROVES CHARACTERISTICS OF THE METABOLIC SYNDROME IN INSULIN-RESISTANT OBESE RATS

N. Yurkova(2,3), A. Noto(1), T. Ryz(1), J. Zahradka(1), M. Zirk(1), P. Zahradka(2,3) and C. Taylor(1\*). (1)Department of Human Nutritional Sciences, University of Manitoba, Winnipeg, MB. (2)Department of Physiology, University of Manitoba, Winnipeg, MB. (3)Institute of Cardiovascular Sciences, St. Boniface Research Centre, Winnipeg, MB.

A potential mechanism for CLA action is activation of peroxisomal proliferator-activated receptors (PPARs), ligand-activated transcription factors involved in lipid and glucose metabolism. Our objective was to investigate whether dietary CLA alters body fat, glucose tolerance, adipokine synthesis and PPAR-responsive gene expression in insulin-resistant obese rats. Weanling lean and fa/fa male Zucker rats were fed a 1.5% CLA mixture (InCLA and faCLA groups) or control diet (InCTL and faCTL groups) for 8 wks. Final body and fat pad weights were not different between CLA and CTL groups. Oral glucose tolerance was significantly improved in the faCLA rats, concomitant with reduced pancreatic β-cell hypertrophy and less fatty liver. Measurement of adipokine expression showed that leptin and TNF-α mRNA was reduced (~1.5 fold and 2-3 fold, respectively), while resistin was up-regulated (2-fold) in adipose tissue from faCLA rats. The mRNA levels of the PPAR-responsive fatty acid binding protein (L-FABP) and acyl-CoA oxidase genes were elevated in liver of faCLA rats. Our results indicate that a dietary CLA mixture improves oral glucose tolerance, reduces fatty liver and attenuates β-cell hypertrophy in fa/fa Zucker rats, and that activation of PPAR-responsive genes may be involved in altering metabolism. (Funding from Dairy Farmers of Canada and NSERC CRDPJ.)

#### Abstract 12

##### TRANS-9,TRANS-11 CONJUGATED LINOLEIC ACID DECREASES TRIGLYCERIDE ACCUMULATION IN PRIMARY CULTURES OF PRE-ADIPOCYTES FROM HUMAN AND HAMSTER ADIPOSE TISSUES

V.C. Gavino<sup>1</sup>, G.G. Gavino and R.-M. Pelletier. Département de Nutrition, Université de Montréal, Montréal, QC.

CLA preparations exhibit several biological effects in various experimental models. This pleiotropic behaviour may be partly due to proportions of specific CLA isomers found in commercial preparations, given that each particular isomer may have unique biological properties relative to the other forms. Since it has been shown that CLA preparations favorably modulate lipid metabolism in mammals, we tested specific CLA isomers for their ability to influence lipid-filling in primary cultures of stromal-vascular cells from human and hamster adipose tissues. One such isomer is the *trans*-9,*trans*-11 form, present in milk fat and in commercial CLA preparations at approximately 10% and 6.5% of total CLA, respectively. We exposed cells to 50 µM concentrations of various pure CLA isomers using linoleic acid as control. Extent of differentiation,

measured by induction of cellular glycerol-3-phosphate dehydrogenase, was the same for all groups. The *trans-9,trans-11* isomer compared to linoleic acid, lowered lipid-filling by 85% and 45% in human and hamster pre-adipocytes, respectively. In contrast, the *trans-10,cis-12* isomer decreased lipid-filling in human cells by 30%, and had no effect on hamster cells compared to control. We conclude that the *trans-9,trans-11* isomer may contribute to the overall effect of CLA preparations on body fat. (Funded by the Dairy Farmers of Canada and by NSERC.)

#### **Abstract 13**

##### **ACTIONS OF CONJUGATED LINOLEIC ACID ON BONE METABOLISM**

B. Watkins(1,2\*), Y. Li(1), H. Lippman(1), S. Feng(1) and M. Seifert(2). (1)Department of Food Science, Center for Enhancing Foods to Protect Health, Purdue University, West Lafayette, IN. (2)Department of Anatomy and Cell Biology, School of Medicine, Indiana University, Indianapolis, IN.

Investigations on conjugated linoleic acid (CLA) in growing male rats, estrogen-deficient OVX rats, and osteoblast cell cultures indicate that the amount and type of CLA isomers influence bone metabolism. The actions of CLA isomers include their effects on moderating bone modeling, serum biomarkers of bone formation, transcription factors associated with osteoblast differentiation, and nodule formation in calvarial cell cultures. Supplementing diets with CLA isomers resulted in their enrichment in all bone tissue compartments of rats. When supplied at 1% of the diet to male rats CLA isomers depressed *ex vivo* PGE2 production in bone organ culture, serum IGF-I, and bone formation rate. In a subsequent study, a lower dietary level (0.5%) of CLA rescued bone formation rate in male growing rats that were given a diet containing a high level of n-6 fatty acids. Decreases in serum osteocalcin level and bone specific alkaline phosphatase activity were observed in rats fed CLA. Studies also demonstrated that CLA reduced transcription factor proteins involved in osteoblast differentiation. DEXA analysis of bone mineral content in OVX rats did not improve with CLA supplementation. Research on CLA revealed that the actions of these isomers in rat bone are dependent on the type of CLA isomer and the dietary ratio of n-6/n-3 fatty acids.

#### **Abstract 14**

##### **DIETARY CONJUGATED LINOLEIC ACID (CLA) AS A POTENTIAL TREATMENT FOR METABOLIC BONE DISEASE**

H. Weiler(1,2\*), S. Austin(1), S. Fitzpatrick-Wong(1), E. Nitschmann(2), N. Bankovic-Calic(2), R. Mollard(1), H. Aukema(1,2) and M. Ogborn(1,2). (1)Department of Human Nutritional Sciences, University of Manitoba, Winnipeg, MB. (2)Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, MB.

Metabolic bone disease is characterized by elevations in parathyroid hormone (PTH) along with elevated rates of bone turnover. This is a feature of chronic renal disease. Since release of PTH is dependent on prostaglandin E2 (PGE2) synthesis and CLA is known to reduce synthesis of PGE2, this study was conducted to examine if feeding conjugated linoleic acid (CLA) would suppress hyperparathyroidism and high turnover bone disease secondary to polycystic kidney disease (PKD). Fifty-two weanling male Han:SPRD-cy rats were randomized to identical diets supplemented with and without CLA (1% of dietary fat) for 8 weeks. Main outcome measurements were: kidney weight, urea nitrogen and creatinine clearance; parathyroid hormone (PTH), bone formation and resorption; and femur bone mass using dual energy x-ray absorptiometry. Serum PTH and bone turnover were elevated in PKD affected rats. CLA feeding resulted in attenuation of PTH levels in both affected and non-affected rats (by 60%), but did not alter bone formation and resorption. Bone mass was not affected by CLA. Reduction in PTH may open possibilities for CLA as an adjunctive therapy in secondary hyperparathyroidism. (This research was supported by grants from Dairy Farmers of Canada, The Children's Hospital Foundation of Manitoba Inc. and NSERC.)

#### **Abstract 15**

##### **MODULATION OF THE IMMUNE RESPONSE BY CONJUGATED LINOLEIC ACID: CLINICAL DEVELOPMENT FROM AN INDUSTRY PERSPECTIVE**

M. O'Shea(1\*), J. Bassaganya-Riera(2), R. Hontecillas(2) and I. Mohede(3). (1)Loders Croklaan, Lipid Nutrition, Channahon, IL. (2)Nutritional Immunology & Molecular Nutrition Laboratory, Department of Human Nutrition, Foods & Exercise, Virginia Polytechnic Institute and State University, Blacksburg, VA. (3)Loders Croklaan, Lipid Nutrition, Wormerveer, The Netherlands.

Results from *in vitro* experiments in lymphocytes and animal studies indicate that conjugated linoleic acid (CLA) enhances immune function. We have examined the effects of two CLA preparations (i.e., 50:50 and 80:20 of c9,t11:t10,c12) on antigen-specific responses in humans and using a pig model of immunosuppressive viral disease. The human immunization study reports the effects of CLA supplementation (1.7 g active isomers/day for 12 weeks) on humoral and cell-mediated immune responses. Specifically, Hepatitis B virus (HBV) vaccination was used to investigate the modulation of antigen-specific humoral immune responses by CLA. The seroprotection rate (SPR, i.e. the number of subjects with anti-HBV antibody concentrations >10 IU/L compared to the number of subjects with titers <10 IU/L) was significantly higher (P=0.05) for the 50:50 group compared to control or the 80:20 group. Our pig model of immunosuppressive viral disease consisted of an experimental vaccination and challenge with type-2 porcine circovirus (PCV2). Using this pig model we examined the regulation of antigen-specific proliferation of lymphocytes, lymphoid depletion (due to the infection) and immune suppression by CLA when compared with soybean oil (1% diet). Following 42 days of dietary supplementation, pigs (n=32) were immunized and monitored until day 63. Proliferation of lymphocytes in response to *ex vivo* stimulation with a recombinant capsid protein open reading frame 2 (ORF2) of PCV2 was assessed by PKH67 and blastogenesis assays. Serum samples were assayed for the presence of PCV2-specific antibodies using an indirect enzyme-linked immunosorbent assay and IFA. On days 49, 56, and 63, pigs fed CLA-supplemented diets had significantly greater cellular immune responses as reflected in the increase of CD8+ than the littermates fed isocaloric control diets (P < 0.05, 0.04, and 0.02, respectively). The findings from human and animal studies are suggestive that the CLA-induced enhancement of humoral and cellular responses could be maximized in immunocompromised individuals.

### Abstract 16

#### DIETARY CONJUGATED LINOLEIC ACID (CLA) EFFECTS ON THE KIDNEY

H. M. Aukema(1,2), N. Bankovic-Calic(2), L.I. Evans(1), E. Nitschmann(2), S. Fitzpatrick-Wong(1), H.A. Weiler(1,2) and M.R. Ogborn(1,2\*). (1)Department of Human Nutritional Sciences, University of Manitoba, Winnipeg, MB. (2)Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, MB.

Experimental health benefits of CLA include amelioration of malignancy and inflammatory disease. We therefore investigated the effects of dietary CLA on the kidney in the Han:SPRD-cy rat to study renal interstitial inflammation and fibrosis in chronic renal disease. Male rats were fed control diets or diets containing 1% CLA. After 8 weeks of feeding, CLA reduced renal interstitial inflammation ( $p < 0.001$ ), fibrosis ( $p = 0.03$ ), PGE2 release ( $p = 0.02$ ) and increased renal and hepatic CLA isomer content. Urine creatinine also was higher in diseased animals fed CLA ( $p = 0.012$ ). As CLA potentially alters eicosanoid synthesis, the protein expression of several related renal enzymes known to be altered in this disease, cytosolic phospholipase A2 (cPLA2), cyclooxygenase-1 (COX-1) and COX-2, were determined. Dietary CLA ameliorated the altered levels of cPLA2 and COX-2. Notably, the effect of CLA on COX-2 appears to be direct and not a result of disease, as CLA increased COX-2 protein expression in both normal and diseased kidneys. As inflammation and fibrosis are important components of the progression of chronic renal injury, CLA may be a useful agent in dietary amelioration of renal disease. (Supported by the Dairy Farmers of Canada, NSERC and the Children's Hospital Foundation of Manitoba.)

### Abstract 17

#### EVIDENCE FOR POTENTIAL MECHANISMS FOR THE EFFECT OF CLA ON TUMOUR METABOLISM AND IMMUNE FUNCTION: LESSONS FROM N-3 FATTY ACIDS

C. Field. University of Alberta, Edmonton, AB.

Both CLA and the long chain polyunsaturated n-3 fatty acids have been shown to reduce tumour growth in vitro and in vivo. The mechanisms by which fatty acids may affect the growth of tumour cells may be via: 1) slowing or stopping proliferation (via altering regulation of the cell cycle), or 2) increasing cell death (via necrosis and/or apoptosis). Both these hypotheses have been explored to explain the effects of n-3 fatty acids and CLA on tumours. Modulation of the host's immune system could also mediate the anticancer effects of fatty acids in vivo. While it is widely recognized that n-3 fatty acids can alter immune and inflammatory responses, considerably less is known about CLA. For n-3 fatty acids, several candidate mechanisms have been proposed for their immune effects, including changes in: 1) membrane structure and composition, 2) membrane-mediated functions and signals, 3) gene expression and 4) immune development. This presentation will compare and contrast the evidence for the potential mechanisms for the anticancer effects of n-3 fatty acids and CLA. In doing so it is hoped lessons learned from the study of n-3 fatty acids can be used to identify future research directions for CLA mechanistic studies in cancer. (Funding from NSERC, Alberta Agriculture Research Institute, Dairy Farmers of Canada and the Beef Information Centre.)

### Abstract 18

#### DEVELOPING CLA-ENRICHED DAIRY PRODUCTS

B. McNish. Sepallo, Kelowna, BC.

CLA is showing promise as a fatty acid with many positive health benefits. As scientists continue to develop an understanding of the many complex interactions of this nutrient, one thing is clear. Dairy products and the cows they come from are very well suited to deliver this potentially valuable fat to consumers. Can the dairy industry learn from its past as it saw milk consumption fall, to reposition itself by converting misconceptions into understanding? What work must science complete before the CLA message is ready for the consumer? Sepallo, a private company, examines the challenges of crafting a message and developing products to meet success in the marketplace.

### Abstract 19

#### CLA-ENRICHED DAIRY PRODUCTION

P.Y. Chouinard. Département des Sciences Animales, Université Laval, Québec, QC.

The predominant CLA isomer found in milk fat is *cis-9, trans-11*, and it represents 80 to 90% of the total CLA found in dairy products. This isomer is an intermediate in ruminal biohydrogenation of linoleic acid, and a portion escapes the rumen and is incorporated in milk fat. In addition, *cis-9, trans-11* CLA is synthesized from *trans-11* C18:1, another intermediate in ruminal biohydrogenation. This reaction involves the enzyme  $\Delta$ -9-desaturase, and accounts for over two-thirds of the CLA in milk fat. Many dietary factors are known to affect the CLA content of milk fat. Among these factors, the dietary addition of plant oils (sunflower, soybean, canola, and linseed) results in substantial increases in milk fat concentration of *cis-9, trans-11* CLA. In general, plant oils high in linoleic acid give the greatest response. An increase in milk fat concentration of CLA is also observed with dietary addition of fish oils, fish meal or marine algae. The technology is therefore available to produce high-CLA milk under commercial conditions. This production would require the dietary addition of vegetable over the entire lactation. The influence of long-term feeding of high fat diet on cow health and performance remains to be determined.

### Abstract 20

#### CONJUGATED LINOLEIC ACID (CLA) ENRICHED BEEF PRODUCTION

P.S. Mir(1\*), T.A. McAllister(1), S. Scott(2), J. Aalhus(3), V. Baron(3), D. McCartney(3), E. Charmley(4), L. Goonewardene(5), J. Basarab(6), E. Okine(7), R. J. Weselake(8) and Z. Mir(1).

(1)Agriculture and Agri-Food Canada (AAFC), Lethbridge, AB. (2)AAFC, Brandon, MB. (3)AAFC, Lacombe, AB. (4)AAFC, Nappan, NS. (5)Alberta Agriculture Food and Rural Development (AAFRD), Edmonton, AB. (6)AAFRD, Lacombe, AB. (7)University of Alberta, Edmonton, AB. (8)University of Lethbridge, Lethbridge, AB.

Canadian beef consumption is 31 kg per annum, or half of all meats (excluding poultry) consumed. Beef cattle produce CLA and deposit these compounds in the meat; thus beef consumers can receive bio-formed CLA. Beef can have both of the bio-active CLA isomers. The relative content of these CLA in beef depends upon the feeds consumed by the animals during production. Feeding beef cattle linoleic acid rich-osis

for extended periods of time increases the CLA content of beef. Beef from pastured, rather than from silage fed, cattle has a higher CLA content, but it appears to be related to the type and relative maturity of the pasture. In feedlot animals fed grain diets, inclusion of dietary oil along with hay during both the growth and finishing phases led to an increase in CLA content from 2.8 to 14 mg g<sup>-1</sup> of beef fat, which would provide 77 mg CLA in a 3oz serving of beef. The CLA appear to be concentrated in intra-muscular and subcutaneous fat of beef cattle, with the *trans* 10, *cis* 12 CLA being greater in the subcutaneous fat. (Research was supported by BIDE, Pioneer Canada, Round-Up 80 Ranch, ALIDF, ACC and AAFC-Matching Investments Initiative.)

**Abstract 21**  
**CLA PORK RESEARCH**

M. E. R. Dugan\*, J. L. Aalhus and J. K.G. Kramer. Agriculture and Agri-Food Canada, Lacombe, AB.

The driving force behind most CLA research in swine has been related to potential improvements in animal production. Early work using rodent models indicated feeding CLA could potentially reduce body fat, increase lean, increase growth rate and/or improve feed conversion efficiency. Producer backed funding organizations were, therefore, very receptive to proposals to extend this research to pigs and a number of studies have now been completed world-wide. In general, improvements in body composition have been found, but evidence indicating CLA improves growth rate or feed conversion has been limited. Inclusion of CLA into pig diets has, however, been shown to increase muscle marbling fat and fat hardness and both of these have potential to increase carcass value. Currently, BASF has the international marketing licence to include CLA in animal feeds, but to date, this practice has not been approved in Canada or the USA. If and when approval is granted, the next step in reaching CLA's economic potential would be to seek approval for claiming a CLA enrichment in pork and pork products. Given the ability of swine to accumulate relatively high levels of CLA in their tissues, pork and pork products might then become an important vehicle for delivery of physiologically significant levels of CLA to consumers. (Dr. Dugan's research has been supported by the Alberta Pork Producers Development Corporation, the Canada Alberta Hog Industry Development Fund, Conlinco Inc. and the AAFC Matching Investment Initiative.)

**Abstract 22**  
**REGULATORY ISSUES IN THE USE OF CLA IN FUNCTIONAL FOODS & NATURAL HEALTH PRODUCTS IN CANADA**

K.C. Fitzpatrick. Richardson Centre for Functional Foods & Nutraceuticals, University of Manitoba, Winnipeg, MB.

The Canadian Food and Drugs Act and Regulations, through its definitions of "food" and "drug", currently restricts health-related claims for foods, food ingredients and natural health products (NHP). Over the last few decades, scientific research has led to a large body of information demonstrating the benefits for health of many food and NHP ingredients. Health Canada has recognized the constraints of the current regulatory environment and has begun to develop regulations related to the allowance of health claims for functional foods and NHP. Health Canada has three initiatives underway in the area of health claims for foods: 1) to adopt US generic health claims within a Canadian context; 2) to develop scientific standards of evidence and a guidance document for supporting the validity of product-specific claims; and 3) to develop an overall regulatory framework for functional foods. In 2000, Health Canada announced approval for the use of five generic diet related health claims: sodium and hypertension; calcium and osteoporosis; saturated and *trans* fat and cholesterol and coronary heart disease; fruits and vegetables and cancer; and sugar alcohols and dental caries. Under a separate initiative, the Natural Health Products Directorate was established in March 1999 to regulate NHPs including requirements for product labeling, product quality and health claims. The potential significance to the industry of these legislative initiatives will be described.

**Abstract 23**  
**LINKING HUMAN HEALTH RESEARCH TO PRODUCT DEVELOPMENT AND MARKETING**

C. L. Thorvaldson. Alberta Milk, Edmonton, AB.

Human health research demonstrating positive health outcomes should be linked to the development of a marketable food product. This may seem like a monumental task; however, by embracing a new model of research collaboration, it is possible. When developing a new food product careful consideration must be given to understanding the consumer and the marketplace. Consumers' interest and knowledge in nutrition, and functional foods, as well as current trends are key. The impact of the media on consumers' knowledge, attitudes and beliefs about nutrition and food is of critical importance. From a researcher perspective, being able to effectively communicate results to consumers via the media is significant and guidelines for success do exist. We must learn how to connect with consumers to remain credible. The CLA Network is an example of this new method of collaboration in which a number of research teams work towards a common goal. A network is a new concept that was sought as a solution to the lack of technology transfer and product development coming from research. Networks are truly a paradigm shift from the traditional research. Funding agencies are looking at networks as a future model for research.

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