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Conjugated linoleic acid (CLA): A ruminant fatty acid with beneficial effects on human health

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Abstract

Conjugated linoleic acids (CLA) may influence the onset and severity of several chronic diseases, including various cancers, atherosclerosis, obesity, bone density loss, and diabetes. These findings are of special interest to the agriculture community, because dietary sources of CLA are almost exclusively beef and dairy products. Thus, a better understanding of the specific isomers and mechanisms responsible for these positive effects of CLA on human health would be both prudent and economically beneficial. To date, research related to the advantages of CLA consumption on human health has been conducted using experimental laboratory animals and cell culture systems. These data consistently show that relatively low levels of CLA can influence risk of cancer. Further, very recent investigations suggest that the predominate CLA isoform (*cis*-9, *trans*-11 CLA or rumenic acid) found in beef and milk fat possesses anticarcinogenic effects but does not alter body composition; the *trans*-10, *cis*-12 CLA has been shown to inhibit lipogenesis. Clearly, further work, especially using human subjects, will be required to characterize the potential benefits of CLA consumption on human health. Moreover, we suggest that foods naturally containing high amounts of CLA (e.g., beef and dairy products) be considered as meeting the definition of functional foods.

Key Words: Conjugated Linoleic Acid, Humans, Diet, Cancer, Health, Fats

Introduction

Diet is considered a contributing factor to the onset or progression of some cancers, such that epidemiological studies indicate diet composition may be related to 35% of human cancer deaths (Doll, 1992). A few substances in the human diet have been identified as anticarcinogens, but most are of plant origin and are only present in trace concentrations. However, conjugated linoleic acid (**CLA**), a component of ruminant fat, introduces an exciting twist to what we know about diet and cancer. Conjugated linoleic acid refers to a mixture of positional and geometric isomers of linoleic acid (18 carbons) with two double bonds separated by one single bond. Further, each double bond can be in the *cis* or *trans* configuration. Therefore, many forms of CLA are possible (Sehat et al., 1999; Yurawecz et al., 1999a, b), but the main form present in foods from ruminant animals is the *cis*-9, *trans*-11 CLA, which was recently given the trivial name rumenic acid (**RA**; Kramer et al., 1998a). The presence of this fatty acid in ruminant products arises from its formation in the rumen. Conjugated linoleic acid is unique among the naturally occurring anticarcinogens in that it is potent at extremely low levels and present in foods from ruminant animals. This review will address the potential health effects of CLA in humans. For more details on the regulation of CLA in milk and beef, see the review by Bauman et al. (2000).

CLA: Multiple Isomers and Multiple Biological Actions

There are many isomers of CLA, and the distribution of naturally occurring isomers is quite different from that commercially produced (Sehat et al., 1999; Yurawecz et al., 1999a,b). This is important because it is the commercially produced mixes of CLA that have been generally used as the testing material for the cancer, atherosclerosis, growth, and diabetes experiments. Is it possible or probable that one isomer could cause such diverse metabolic events as reduction in tumor development or growth, protection of arterial walls from plaque formation, alterations in circulating lipoproteins and cholesterol, promotion of lean growth while diminishing fat deposition, and regulation of milk fat synthesis? It is unlikely that one isomer is responsible for all biological activities and, thus, future research and discussion concerning CLA isomers and their biological importance should focus on effects of each specific isomer. In fact, much current research concerning the effects of CLA is related to understanding the roles of individual isomers of CLA. This should be kept in mind throughout the remainder of this review.

Potential Health Effects of Conjugated Linoleic Acid

CLA and Cancer. The National Academy of Sciences (NRC, 1996) publication *Carcinogens and Anticarcinogens in the Human Diet* concluded that ". . . conjugated linoleic acid (CLA) is the only fatty acid shown unequivocally to inhibit carcinogenesis in experimental animals." The discovery that CLA can inhibit carcinogenesis was directed principally by Michael Pariza of the University of Wisconsin. He initially found a mutagenesis modulator as well as bacterial mutagens in methylene chloride extracts of fried ground beef (Pariza et al., 1979, 1983). The inhibitory activity was also present in raw ground beef, suggesting that it was not necessarily produced as a result of cooking (Pariza et al., 1979). Pariza and Hargraves (1985) then demonstrated that crude and partially purified modulator fractions from fried ground

beef inhibited the initiation of mouse epidermal tumors by 7,12-dimethylbenz[*a*]anthracene (**DMBA**) when applied to the skin 5 min before DMBA. Further purification of the modulator fractions led to discovery of the presence of derivatives of linoleic acid with conjugated double bonds (Ha et al., 1987). Topical application of CLA before DMBA and promotion by 12-*O*-tetradecanoylphorbol-13-acetate (**TPA**) reduced both the number of papillomas and the tumor incidence (Ha et al., 1987). Ha et al. (1990) then determined that mice gavaged with CLA and treated with benzo(*a*)pyrene had about 50% of the forestomach neoplasias and reduced tumor incidence.

The next series of important advances in the effects of CLA on cancer focused on prevention of mammary cancer. Ip et al. (1991) for the first time fed CLA as a part of a rat's diet and demonstrated an effect of dietary CLA on DMBA-induced mammary tumors. Ip et al. (1991) also reported a dose-dependent reduction in incidence and number of mammary tumors in rats fed CLA (Table 1). Further work (Ip et al., 1994) determined that even smaller concentrations of CLA were effective in reducing mammary tumor incidence and number; as little as 0.1% of the diet as CLA reduced the total number of mammary tumors present at autopsy (Figure 1). They also demonstrated that results were similar with either DMBA, a carcinogen that requires metabolic activation, or with methylnitrosourea (**MNU**), a direct alkylating agent. In this study, Ip et al. (1994) moved to shorter-term feeding studies in which CLA was fed only from weaning for about 5 wk during a period of rapid mammary development. Administration of carcinogen occurred at the end of the diet intervention, at which time all rats received the same diet devoid of CLA. Further evaluations of the effects of timing and duration of CLA consumption on mammary cancer have demonstrated that feeding of CLA during a period of rapid mammary development clearly protects against mammary cancer; however, continuous intake of CLA is required for inhibition of tumorigenesis when CLA feeding is started after MNU administration (Ip et al., 1995, 1997a). Ip et al. (1996) demonstrated that the protective effect of CLA on mammary cancer is independent of level and type (corn oil vs lard) of fat in the diet. Further, the suppression of mammary tumor formation by CLA was not influenced by intake of linoleic acid at dietary levels that promote mammary tumor formation (Ip et al., 1997b).

Recent evidence has also demonstrated that CLA is effective in reducing the growth of human breast (Visonneau et al., 1997) and prostate cancer cells (Cesano et al., 1998) implanted into immune-deficient animals. Evidence that dairy products can elicit prevention of cancer has been provided by recent investigations by Ip et al. (1999). Using the standard MNU mammary tumor model, Ip et al. (1999) fed rats from weaning until 50 d of age a diet without additional CLA or with CLA from various sources. Reduction in tumor incidence and number occurred regardless of whether the CLA was provided by commercial sources or through butter (Table 2). The *cis*-9, *trans*-11 CLA (i.e., RA) provided as the relatively pure isomer or in butter possessed the ability to inhibit cancer. This is the CLA isomer found naturally in dairy products and beef. Evidence of the anticarcinogenic properties for other isomers of CLA awaits appropriate experimentation.

Mechanism of Action in the Prevention of Cancer. Although the effects of CLA on carcinogenesis are dramatic, little information is available on the mechanisms by which CLA prevents or inhibits cancer. Scimeca et al. (1994) reviewed the effects of CLA on events associated with carcinogenesis. Their review pointed out that CLA has the potential to act at many points of cancer development, including tumorigenesis, promotion, mitogenesis, mutagenesis, carcinogen activation and detoxification, and signal transduction. Conjugated linoleic acid is also thought to have antioxidant capacity. More recent evidence suggests that CLA competes with linoleic acid in the biosynthesis of arachidonic acid, the precursor of eicosanoids, which is associated with tumor promotion. Banni et al. (1995) and Sebedio et al. (1997) have reported that CLA is metabolized to conjugated linolenic (18:3) and eicosatrienoic (20:3) acids as well as two isomers of arachidonic acid (20:4). The presence of these unusual isomers indicates that CLA can take part in desaturation and chain-elongation pathways. These intermediates may inhibit the synthesis of more commonly occurring eicosanoids. Further, Liu and Belury (1998) determined that CLA decreased prostaglandin E synthesis and altered arachidonate metabolism in cultured keratinocytes. It is logical that, as dramatic as the effect of CLA is on cancer, the range of mechanisms responsible for inhibition of tumor formation and development is broad and extensive.

CLA and Atherosclerosis. Lee et al. (1994) demonstrated that rabbits fed an atherogenic diet providing 0.5 g CLA/d exhibited lower circulating LDL cholesterol and somewhat lower triglyceride concentrations. They also concluded from examination of the aortas that plaque development was reduced. Nicolosi et al. (1997) fed hamsters atherogenic diets containing varying levels of CLA and found reduced total circulating cholesterol concentrations. However, fatty streak formation was unaffected. A recent study (Munday et al., 1999) using the C57BL/6 mouse atherosclerosis model contradicts the work of Lee et al. (1994) and Nicolosi et al. (1997). Munday et al. (1999) reported that mice fed CLA had an increased serum HDL-cholesterol:total cholesterol ratio and lower serum triglycerides but increased development of aortic fatty streaks. Interestingly, recent epidemiological evidence shows no increase in risk of coronary heart disease with greater butter consumption, but intake of margarine, which lacks CLA, actually was associated with an increased risk of heart disease (Gillman et al., 1997). Thus, more studies are needed to determine whether CLA is beneficial or harmful in the development of atherosclerosis in humans.

CLA and Nutrient Partitioning. Another biological phenomenon investigated more recently concerns alterations in growth and body composition. During periods of catabolic stress caused by endotoxin injections, chickens (Cook et al., 1993) and mice (Miller et al., 1994) lose less body weight when fed a diet containing CLA. These observations suggest that CLA could alter tissue loss. Chin et al. (1994) demonstrated that CLA may also affect tissue gain; rat pups nursing dams fed diets containing CLA were larger than pups nursing dams fed diets without CLA. Even though no consistent response in milk protein content was observed, the CLA content of rat milk was enriched in the dams fed CLA; fat content of the milk was not reported. Further, they (Chin et al., 1994) demonstrated that postnatal weight gains were increased 7% in rats fed CLA. Conversely, Belury and Kempa-Steczko (1997) noted slower growth rates in young adult mice fed CLA. Although body composition was not measured, lipid content of liver increased with greater CLA intake. More recent evidence now suggests that CLA may, in fact, alter body composition. Mice fed diets containing 0.5% CLA exhibited nearly 60% less fat with an almost 10% increase in protein (Park et al., 1997). Similar studies have demonstrated improved lean growth in growing pigs fed CLA-enriched diets (Ostrowska et al., 1999). Pork tissues normally contain only trace (< 0.1%) concentrations of CLA; however, concentrations were enriched to between 1 to 6% in all tissues examined when pigs were fed a commercial CLA at 2% of the diet from 60 to 106 kg live weight (Kramer et al., 1998b). In the very near future, pork could become a source of CLA in the human diet if pork producers adopt the use of CLA as a tool to reduce backfat thickness. West et al. (1998) have also demonstrated a dramatic reduction in adipose depot weight in mice fed CLA. They attributed the decrease in adipose partly to reduced energy intake and increased metabolic rate. However, in a double-blind, placebo-controlled study in obese subjects, preliminary evidence of an alteration in body composition in humans due to CLA was not detected (Pariza, 1998). Further work is necessary to determine whether humans can alter their amount of lean or adipose tissue through dietary supplementation of CLA and, if so, which isomer is responsible for this effect.

Recent evidence demonstrates distinct differences between the *cis*-9, *trans*-11 and *trans*-10, *cis*-12 CLA isomers on lipid metabolism. Studies in mice (Park et al., 1999b) demonstrated that changes in body composition were attributable to the *trans*-10, *cis*-12 CLA but not to the *cis*-9, *trans*-11 isomer. Further, the *trans*-9, *trans*-11 isomer of CLA was without effect on body composition. In vitro, the *trans*-10, *cis*-12 CLA reduced lipoprotein lipase activity, intracellular triacylglycerol and glycerol, and enhanced glycerol release into the medium (Park et al., 1999b), but the *cis*-9, *trans*-11 and *trans*-9, *trans*-11 failed to affect these components. Commercial mixtures of CLA infused into the abomasum of lactating cows dramatically reduced milk fat percentage and hence lipogenesis (Chouinard et al., 1999; Bauman et al., 2000). Recently, Baumgard et al. (2000) reported that the active isomer of CLA causing milk fat depression (decreased mammary lipogenesis) was the *trans*-10, *cis*-12 CLA; no effects were detected with infusion of *cis*-9, *trans*-11 CLA. Finally, the expression (Lee et al., 1998) or activity (Bretillon et al., 1999) of hepatic stearoyl-CoA desaturase was not altered by the *cis*-9, *trans*-11 CLA but the activity (Bretillon et al., 1999) of the enzyme was reduced by the *trans*-10, *cis*-12 isomer of CLA. Clearly, all isomers of CLA are not equal with respect to lipid metabolism. Further data are needed before making similar statements with regard to other biological effects of CLA.

CLA and Diabetes. Feeding of CLA to rats prone to developing diabetes normalized glucose tolerance and improved hyperinsulinemia as effectively as currently used medications (Houseknecht et al., 1998). The CLA was a mixture containing approximately 90% isomers of CLA with 42% *cis*-9, *trans*-11 and *trans*-9, *cis*-11 CLA, 43.5% *trans*-10, *cis*-12 CLA, 1% *cis*-9, *cis*-11 CLA, 1% *cis*-10, *cis*-12 CLA, 1.5% *trans*-9, *trans*-11 and *trans*-10, *trans*-12 CLA, 0.5% linoleic acid, 5.5% oleic acid, and 5% unidentified compounds. These fatty acids were fed at 1.5% (by weight) of the diet for 2 wk. The study was short-term and needs to be replicated and extended before the results can be applied to human health. Nonetheless, if CLA can improve glucose homeostasis and inhibit body fat accretion as demonstrated in mice, rats, and pigs, then CLA may be beneficial to humans prone to diabetes. This remains an exciting area of research.

CLA and the Immune System. Previous work (Cook et al., 1993; Miller et al., 1994) suggesting that CLA affected growth and body composition also demonstrated that this effect may have been mediated through the immune system. In their work with rats, Cook et al. (1993) determined that CLA enhanced a T-cell-dependent response to intradermal foot pad injections of phytohemagglutinin. Splenocytes from mice fed CLA had increased blastogenesis to phytohemagglutinin (Miller et al., 1994). These findings have been confirmed by others (Chew et al., 1997; Wong et al., 1997), and further research (Cook and Pariza, 1998) is evaluating the impact of CLA on autoimmune disorders and type I hypersensitivity (allergic reactions).

CLA and Bone. Finally, research indicates that CLA may play a role in bone health. Li and Watkins (1998) have demonstrated that through altered fatty acid composition and PGE$_2$ production in bone organ cultures, CLA isomers have the potential to influence bone formation and resorption.

Dietary Sources of CLA

Even though other CLA isomers can be found in foods for humans, traditionally the predominate form has been RA. Rumenic acid represents greater than 80% of the CLA present in milk fat and over 75% of the CLA present in beef fat

(Chin et al., 1992; McGuire et al., 1999; Sehat et al., 1999; Yurawecz et al., 1999a). Numerous publications have focused on the concentration of CLA in foods (see McGuire et al., 1999). However, it is recognized that the CLA and RA contents of most foods are somewhat variable due to differences mainly in environmental conditions and diet of the originating ruminant species (Bauman et al., 2000). Using various methodologies, estimates of RA intake have ranged from 50 to 1,000 mg/d (see McGuire et al., 1999). However, most estimates of dietary intake of RA are 50 to 250 mg/d in the United States and 350 to 430 mg/d in Germany (McGuire et al., 1999). Reported differences in RA intake probably relate to higher fat consumption in some populations (e.g., Germany) as well as higher concentrations of RA in foods found in some regions (McGuire et al., 1999). Sources of RA in the American diet are primarily dairy and beef products (Figure 2). However, CLA as well as RA intake can now be increased by the ingestion of industrially produced CLA supplements available from "health food" stores. Unfortunately, these supplements also provide other CLA isomers, as well as additional identified and unidentified fatty acids. These products have been available for over 4 yr, and although the supplements are marketed for their potential role as promoters of lean body mass accretion in body builders, there are few data to support that claim.

Should We Fortify or Enrich Foods with CLA or Rumenic Acid?

We have examined the presence of CLA in human milk and infant formula (McGuire et al., 1997). Human milk contained more CLA than did all brands of infant formula tested; over 80% of the CLA present was RA. Because of the potential for altered growth and body composition, it may be important to fortify infant formula with CLA. For people of other ages, beef and dairy products are the predominate sources of RA in the diet (McGuire et al., 1999). Greater consumption of foods rich in RA increases circulating concentrations of RA (Britton et al., 1992; Huang et al., 1994). Further, in lactating women consuming large quantities of dairy products and beef, the concentration of RA in their milk was increased compared to when the women consumed little dairy or beef products (Park et al., 1999a), again confirming the importance of intake in determining human RA status.

The species of bacteria that make CLA from linoleic acid can be found in the human colon (Brown and Moore, 1960). To determine whether the circulating status of CLA can be altered by consumption of linoleic acid, Herbel et al. (1998) fed subjects an oil and vinegar dressing for 6 wk that increased linoleic acid consumption 2.5-fold. However, at the end of the dietary intervention, no change in circulating concentration of CLA was detected. This suggests that CLA may need to be present in the diet of humans to affect CLA status.

However, new evidence suggests that *cis*-9, *trans*-11 CLA is produced within mammalian tissues through the conversion of *trans*-11 18:1 (vaccenic acid) by the action of Δ-9 desaturase (Santora et al., 2000). It is possible the humans may utilize that pathway to produce their own CLA. Again though, the principal substrate for the reaction, *trans* vaccenic acid, is a fatty acid of ruminant origin (Wolff et al., 1998), so benefits to humans would come from consuming beef and dairy products.

Does the Presence of CLA Make Dairy Products and Beef Functional Foods?

One question of interest is whether we should strive to increase the natural CLA content of beef and dairy products or just focus on greater consumption of those products currently available. Data published by Knekt et al. (1996) show clearly that only minor increases in consumption of milk (e.g., two servings/day or an equivalent of 55 mg/d additional RA) are associated with a decrease in the risk of breast cancer. Therefore, it may not be necessary to alter RA content of beef and dairy products to benefit human health. However, basal intake of RA was approximately 300 mg/d (Knekt et al., 1996). This has significant implications to Americans, because RA intake has been estimated to be only 50 mg/d in some groups of American adults (McGuire et al., 1999). Thus, it may be more reasonable that we focus simply on increasing the basal intakes of dairy products and beef in the United States without altering total caloric intake. For example, if butter were substituted for margarine in the current American diet, RA intake would increase approximately 50 mg/d. In summary, the recent data of Ip et al. (1999) demonstrating the anticarcinogenic property of RA coupled with the epidemiological data of Knekt et al. (1996) and the initial work of Pariza and Hargraves (1985) using extracts of grilled ground beef suggest strongly that dairy products and beef have the ability to reduce breast or skin cancer. Thus, foods containing significant amounts of RA should be considered functional foods.

Implications

Conjugated linoleic acids (CLA) are potent anticarcinogens. Until recently, however, it has not been known which of the CLA isomers possessed the ability to inhibit cancer. Recent data have demonstrated that the *cis*-9, *trans*-11 18:2 (rumenic acid) isomer, the predominate form of CLA found in foods from ruminant animals, contains anticarcinogenic properties. Because of the presence of this potent anticarcinogen, foods such as dairy and beef products should be considered functional foods.

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Notes

Table 1. Effect of conjugated linoleic acid (CLA) consumption on the presence of mammary tumors in rats[a]

Dietary CLA, %	DMBA[b]	Tumor incidence, %	Number of tumors	Total tumor weight, g
0	Yes	80.0	81	148.5
0.5	Yes	66.7	55	114.3
1.0	Yes	46.7	36	77.5
1.5	Yes	40.0	32	68.9
1.5	No	0	0	0

[a]Data from Ip et al. (1991). Rats (n = 30 per group) were fed diets containing CLA for 2 wk before administration of carcinogen to promote mammary tumor development. Rats were maintained on the dietary treatments until euthanized 24 wk after carcinogen administration. The CLA preparation contained 42.5% *cis*-9, *trans*-11 and *trans*-9, *cis*-11 CLA, 43.0% *trans*-10, *cis*-12 CLA, 1.3% *cis*-9, *cis*-11 CLA, 1.2% *cis*-10, *cis*-12 CLA, 2.3% *trans*-9, *trans*-11 and *trans*-10, *trans*-12 CLA, 6.5% linoleic acid, and 3.3% unidentified compounds.

[b]Dimethylbenz[*a*]anthracene.

Table 2. Incidence and number of mammary tumors in rats fed different sources of conjugated linoleic acid (CLA)[a]

Group	Dietary CLA, %	Tumor incidence, %	Number of tumors
Control	0.1	93	92
Butter CLA[b]	0.8	50	43
Product A CLA[c]	0.8	53	46
Product B CLA[d]	0.8	57	48

[a]Adapted from Ip et al. (1999). Feeding of CLA was started from weaning and continued until adminstration of methyl-nitrosourea (MNU) at 55 dof age. After MNU administration, all animals (*n* = 30 per group) were fed a diet without CLA and sacrificed 24 wk later.

[b]Identified isomers of CLA included 92% *cis*-9, *trans*-11 and 4.8% *cis*-7, *trans*-9.

[c]Identified isomers of CLA included 81% *cis*-9, *trans*-11 and 17% *cis*-9, *cis*-11.

[d]Identified isomers of CLA included 25.3% *cis*-9, *trans*-11, 36.5% *trans*-10, *cis*-12, 17.6% *cis*-11, *trans*-13, and 15.3% *trans*-8, *cis*-10.
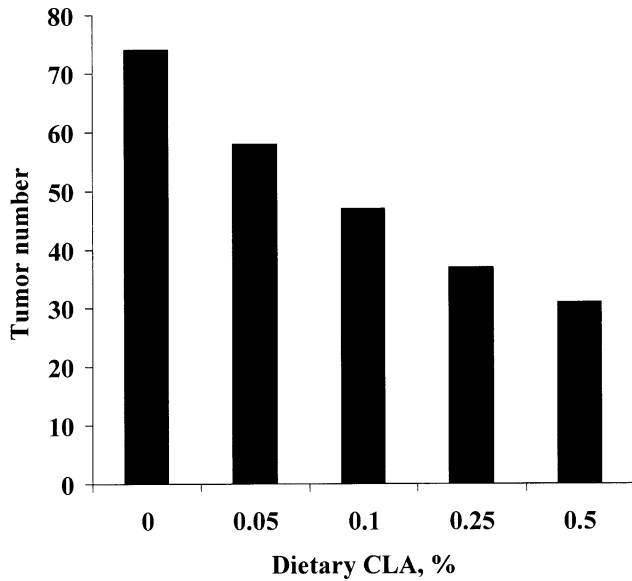
Figure 1. Effect of dietary conjugated linoleic acid (CLA) on incidence of mammary tumors in rats (Ip et al., 1994). Rats (n = 50 per group) were fed diets containing CLA for 2 wk before administration of dimethylbenz[*a*]anthracene (DMBA) to promote mammary tumor development. Rats were maintained on the dietary treatments until they were killed 36 wk after DMBA administration. The CLA preparation contained 43.3% *cis*-9, *trans*-11 and *trans*-9, *cis*-11 CLA, 45.3% *trans*-10, *cis*-12 CLA, 1.9% *cis*-9, *cis*-11 CLA, 1.4% *cis*-10, *cis*-12 CLA, 2.6% *trans*-9, *trans*-11 and *trans*-10, *trans*-12 CLA, 4.4% linoleic acid, and 1.4% unidentified compounds.
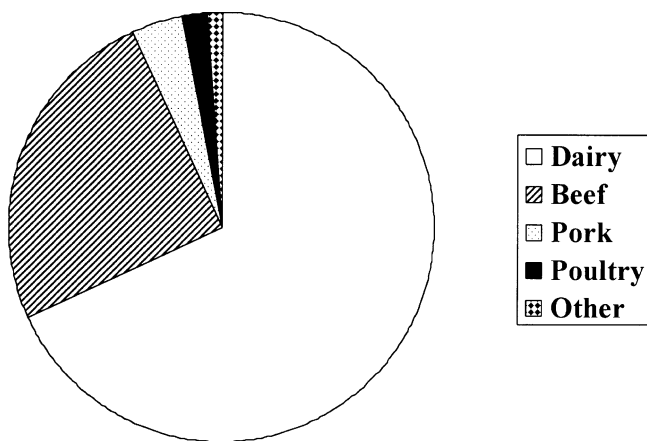

Figure 2. Sources and distribution of rumenic acid (*cis*-9, *trans*-11 conjugated linoleic acid) in the human diet determined by 3-d records of food consumed by subjects in the Pacific Northwest (McGuire et al., 1999). The database contained concentrations of conjugated linoleic acid for over 800 foods.

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