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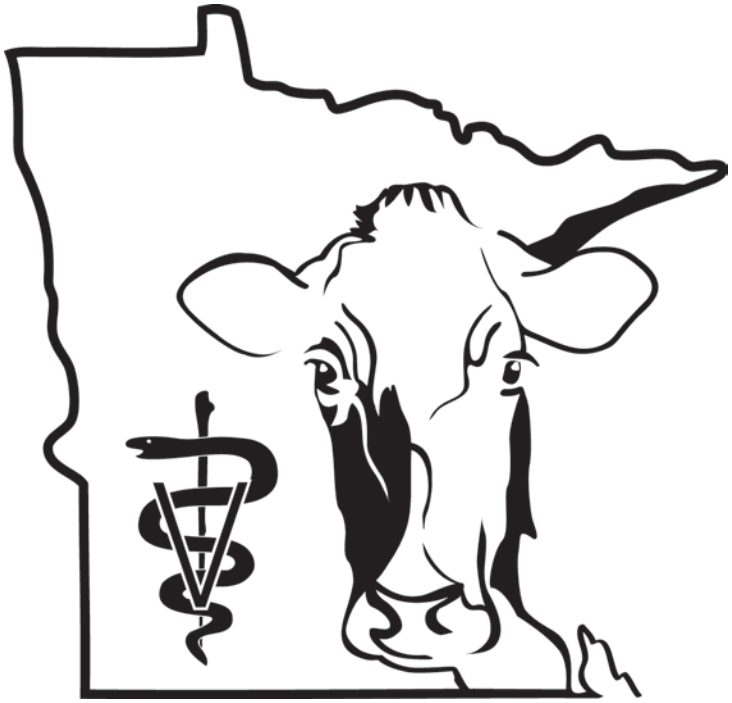

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Animal Products and Human Health: Perceptions, Opportunities and Challenges[1]

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INTRODUCTION

Traditionally, most research reports at the Cornell Nutrition Conference have been related to the productivity and well-being of food producing animals. Indeed, that was the primary goal of agricultural research in the US throughout the 20th Century. Gains in new knowledge from this research and the ability of advisors and producers to apply this knowledge have been remarkable with the productivity and milk yield per cow doubling over the last 50 years. During this time there has been little focus given to improving the nutrient profile of food products. However, consumers are increasingly interested in the connection between foods, nutrition and health. This interest often lacks a real science basis as evidenced by recent success in the development of niche markets based on perceived differences in food quality related to production practices (e.g. organic vs. conventional). This has led to an increased focus on research and agricultural practices that may improve the nutrient profile of food products, with scientists being increasingly asked to clarify the role of specific foods and food components in health maintenance and disease prevention. In this review we will focus on dairy products but many of the considerations apply equally to other animal-derived foods. In the following sections we will provide a brief overview of the role that milk and milk products play in a healthful diet and the potential functional food components present in dairy products with emphasis on milk fat. We will then consider two significant challenges that face the dairy industry regarding dairy fats and human health - saturated and *trans* fats.

FUNCTIONAL FOODS

Animal products make a significant contribution to our nutrient supply including energy, high quality protein and several key minerals and vitamins. While these foods provide essential nutrients, there is also growing consumer recognition of the link between diet and health. This awareness impacts food choices and the phrase "functional food" is a generic term often used to describe this concept. "Functional foods" is a collective term for any food or food component that may provide a health benefit beyond those associated with the traditional nutrient content of the food product (Milner, 1999). A recent National Academy of Sciences report identified research on these bioactive food components in foods as a key focus area for future research to enhance human health through nutrition (NRC, 2003). Research on functional foods addresses the activity of these food components in the prevention of chronic diseases such as cancer or cardiovascular disease (CVD). Thus, the role of functional food components is specifically in health maintenance and the prevention of chronic disease, rather than in the pharmaceutical treatment of disease. To be considered a

[1] Adapted from Bauman, D. E. and A. L. Lock. 2006. Animal products and human health: perceptions, opportunities and challenges. Proc. Cornell Nutr. Conf. pp. 45-57.
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functional food, the bioactive component must be consumed as a natural component of the diet rather than taken as a dietary supplement, further emphasizing the link between nutrition and health status.

Biomedical models are essential to investigate the role of functional food components in preventing chronic diseases, and these animal and cellular models have proven invaluable. Identification of bioactive components has been a major focus in research with fruits and vegetables and these functional food components have been featured for their health-promoting properties in popular press articles. Foods of animal origin have been less extensively investigated, but recent research has established that an impressive array of bioactive components are also present in animal-derived foods including milk and dairy products (Table 1).

Table 1. Partial list of bioactive components in milk that have human health implications.[1]

Milk protein components	**Milk fat components**	**Other**
	Cancer	
Whey proteins	Conjugated linoleic acid	Calcium
Casein	Vaccenic acid	Lactose
Lactoferrin	Sphingolipids	Vitamins A and D
α-Lactalbumin	Butyric acid	Oligosaccharides
Peptides	13-Methyltetradecanoic acid	Nucleosides
	Ether lipids	Probiotics
	Cardiovascular Health	
Whey proteins	Conjugated linoleic acid	Calcium
Casein	Oleic acid	Vitamin D
	Omega-3 fatty acids	
	Hypertension	
Whey proteins		Calcium
		Potassium
	Immune Response	
Whey proteins	Conjugated linoleic acid	Probiotics
MFGM[2] proteins		
	Bone Health	
Peptides	Conjugated linoleic acid	Calcium
		Phosphorus
		Vitamin K

[1] Adapted from Bauman et al. (2006).

[2] Milk-fat-globule membrane.

Several of the functional food components listed in Table 1 are found in milk fat and this offers exciting opportunities. Perhaps the most significant discovery relating to the functional food opportunities for milk fat involves conjugated linoleic acid (CLA) and we have highlighted aspects of the biology of CLA at previous Cornell Nutrition Conferences

(Lock and Bauman, 2003). Milk fat contains many CLA isomers, but rumenic acid (RA; *cis*-9, *trans*-11 CLA) predominates and it is this isomer that has functional food properties in relation to cancer and atherosclerosis. The uniqueness of RA in ruminant-derived foods is related to rumen biohydrogenation of unsaturated fatty acids. The RA in milk fat originates mainly from endogenous synthesis by mammary Δ^9-desaturase from vaccenic acid (VA; *trans*-11 18:1), a biohydrogenation intermediate produced in the rumen. Thus both VA and RA are present in dairy products, generally in a ratio of about 3:1. The anticancer effects of CLA have been consistently demonstrated with animal models and in vitro studies for a wide range of cancer types. Likewise, RA and CLA mixtures have been shown to improve the plasma lipoprotein-cholesterol profile and reduce atherogenic lesions in various animal models of coronary heart disease (Bauman et al., 2005). VA has similar effects by virtue of its being converted to RA by Δ^9-desaturase. Of special importance, the beneficial effects have been demonstrated in animal models when RA and VA were provided in the natural form (esterified *cis*-9, *trans*-11) in a naturally-enriched food (dairy products). However, extending results from biomedical models to implications as functional food components in humans is challenging and problematic (Bauman et al., 2005). Both cancer and CVD are chronic diseases with a lack of consensus biomarkers, especially for cancer. Furthermore, it is difficult to achieve an accurate estimate of the intake of CLA over the long latency period of these diseases due to the difficulty in CLA analysis and the fact that the CLA content of ruminant-derived foods is highly variable even when expressed on a fat basis.

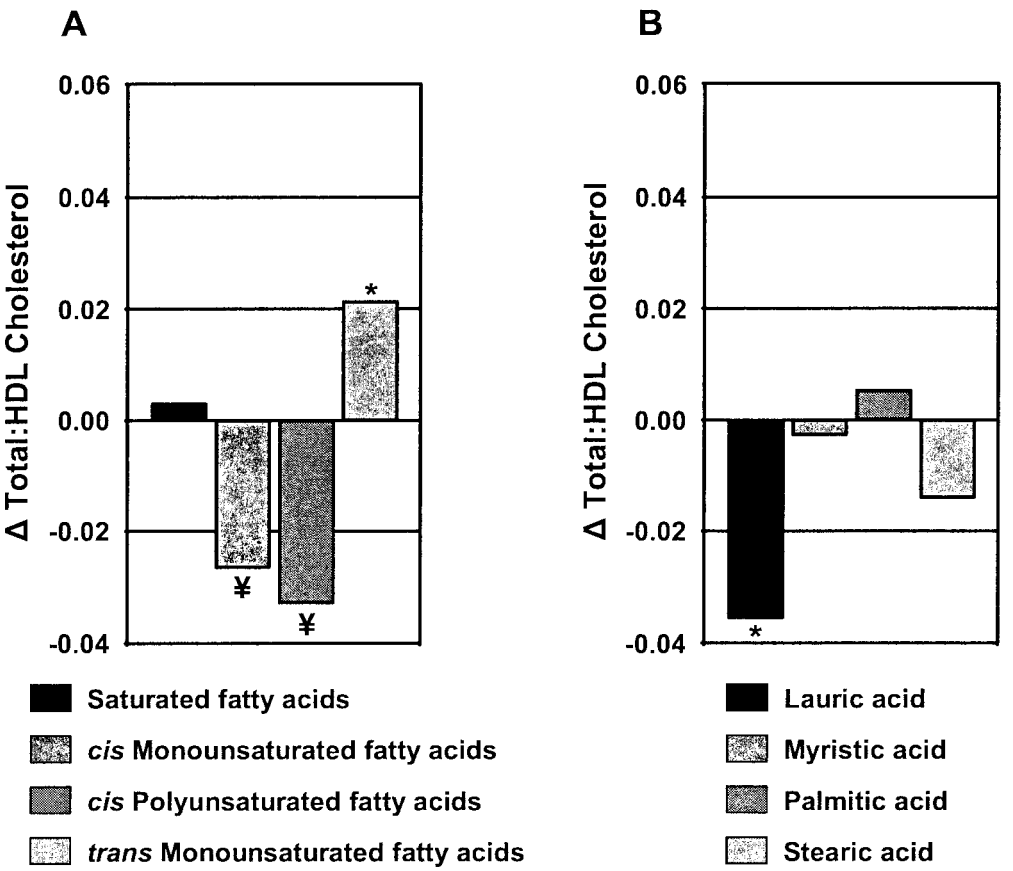
SATURATED FATTY ACIDS

For half a century, the concept of eating healthy has become synonymous with avoiding dietary fat, especially saturated fat, and on a population basis, a low saturated fat diet remains at the heart of nutritional advice for lowering plasma cholesterol and reducing CVD risk. Both the United States (U.S. Department of Health and Human Services and U.S. Department of Agriculture 2005) and United Kingdom (Department of Health 2005) have recently re-affirmed targets for reducing saturated fat intake to no more than 10% and 11% of energy intake, respectively). The recommendation to specifically reduce dietary intake of saturated fatty acids (SFA) principally arises from epidemiological evidence that raised plasma cholesterol represents a primary, independent risk factor for the development of premature atherosclerosis, e.g the Framingham Study (Dawber, 1980) and the Multiple Risk Factor Intervention Trial (MRFIT; Stamler et al., 1986) coupled with experimental evidence that raised plasma cholesterol is associated with high levels of saturated fat consumption (Keys et al., 1965; Hegsted et al., 1965). Initial research indicated that intake of SFA was the major determinant of circulating cholesterol with myristic acid (14:0) alone accounting for over two-thirds of the variation (Hegsted et al., 1965). However, subsequent investigations demonstrated this was much to simplistic and today over 270 factors affecting plasma cholesterol have been identified (Maijala, 2000). Nevertheless, a reduction in intake of saturated fat continues to be a major dietary recommendation. However, the clear findings of carefully controlled feeding studies (often undertaken in Metabolic Wards) have proven much harder to reproduce in free-living individuals (Salter, 2005).

Some recent reviews of epidemiologic and experimental studies examining the relationships among dietary cholesterol, fats, and high serum cholesterol with atherosclerosis and CVD have concluded that these links are inconclusive and results are often contradictory (German and Dillard, 2004; Hu et al., 1999; Parodi, 2004; Ravinskov, 1998; Ravinskov et al., 2002). As reviewed at last year's meetings in the presentation by Salter (2005), even though HMGCoA reducase inhibitors (cholesterol-lowering drugs, statins) clearly reduce cardiovascular morbidity and mortality and these effects may be related, at least in part, to the impact of these drugs on oxidative stress and inflammatory processes within the artery wall. In reviewing the history and politics behind the diet-heart hypothesis, Taubes (2001) concluded that after 50 years of research, there was little evidence that a diet low in saturated fat prolongs life. Clearly, the relationship of fats and cholesterol to CHD is more complex then initially thought and the risk of CVD is multifaceted (Mangiapane and Salter, 1999). In a recent systematic review which included over 30,000 person years of observation, Hooper et al. (2001) concluded that *"Despite decades of effort and many thousands of people randomized, there is still only limited and inclusive evidence that the effects of modification of total, saturated, monounsaturated, or polyunsaturated fats on CVD morbidity and mortality"*.

The Nutrition Committee of the American Heart Association has emphasized the diversity in the biological effects of individual fatty acids and the need to evaluate specific fatty acids with respect to a range of variables related to the risk of CVD (Kris-Etherton et al., 2001). About 60% of the fatty acids in milk fat are saturated and of these there is consensus that 4:0, 6:0, 8:0, 10:0 and 18:0 have no effect on circulating cholesterol. Of the SFA in milk fat, only lauric (12:0), myristic (14:0) and palmitic (16:0) acids have been shown to increase blood levels of cholesterol and LDL-cholesterol when added as dietary supplements (Kris-Etherton and Yu, 1997; Nicolosi, 1997), but these represent only about 25% of the fatty acids in milk fat. Furthermore, advances in this area have established that lauric, myristic, and palmitic acids also result in increases in circulating HDL-cholesterol, a change that is associated with a reduced risk of CHD. Thus, the pattern of changes of circulating cholesterol in different lipid fractions is an important consideration, and several investigations suggest that comparisons of the total cholesterol : HDL-cholesterol ratio is among the best indicators of atherogenic risk. Mensink et al. (2003) recently conducted a meta-analysis of the effects of different fatty acids using data from 60 studies with humans and expressed changes on this basis. As illustrated in Figure 1, ratios for 12:0, 14:0 and 16:0 provide little or no evidence for an atherogenic effect when compared to an isoenergenic substitution with carbohydrate; in fact the ratio for lauric acid was significantly decreased. When compared by fatty acid group, the meta analysis revealed no effect of saturated fat when compared to carbohydrate substitution on an isoengeric basis (Figure 1). However, the well established antiatherogenic effect of monounsaturated and polyunsaturated fats was demonstrated, whereas intake of *trans* fatty acids resulted in changes in the ratio indicative of an increased atherogenic risk.

Figure 1. Predicted changes in the ratio of serum total to HDL cholesterol when carbohydrates constituting 1% of energy are replaced isoenergetically with fatty acids; a meta-analysis of 60 Trials. Panel A: saturated, *cis* monounsaturated, *cis* polyunsaturated, or *trans* monounsaturated (* = $P < 0.05$; ¥ = $P < 0.001$). Panel B: lauric acid (12:0), myristic acid (14:0), palmitic acid (16:0), or stearic acid (18:0) (* = $P < 0.001$). Adapted from Mensink et al. (2003).



Individuals do not consume SFA as a dietary entity, but rather as fats in food and investigations of the relationship of dairy product consumption and cholesterol and CVD also challenge the appropriateness of previous recommendations. Milk fat intake has been shown to be negatively associated with serum cholesterol in children (Samuelson et al., 2001) and a range of cardiovascular risk factors in older adults (Smedman et al., 1999; Warensjo et al., 2004). Furthermore, a number of epidemiological studies have found no association or a slight beneficial association between intake of milk and dairy products with variables related to the risk of CVD (e.g. Elwood et al., 2004; Gartside et al., 1998; Hu et al., 1999). Elwood et al. (2004) reviewed the available data from 10 cohort studies (4 UK, 4 USA, 1 Netherlands, 1 Japan) which, in total, comprised almost 400,000 subjects and over 8500 heart attacks or strokes; they concluded that *"...cohort studies provide no convincing evidence that milk is harmful. ...the studies, taken together, suggest that milk drinking may be associated with a*

small but worthwhile reduction in heart disease and stroke risk." These results are further supported by an analysis using the 1999-2002 NHANES data set which allowed for the examination of the effect of dairy consumption on blood lipids in adults; across the data set there were no significant differences in plasma total, LDL- or HDL-cholesterol or triglycerides despite the number of servings of dairy increasing from <1 to >4.5 per day (Fulgoni, 2005). Overall, the available evidence does not provide support for the concept that consumption of dairy products adversely affects the risk of CVD.

Finally, it is noteworthy that in most countries, reducing saturated fat intakes within the general population has proven difficult (Salter, 2005). Despite this fact, CVD mortality has dropped dramatically in the last 30 years. The reasons for these declines are not fully understood, but appear to be due to a combination of improved treatment of individuals and changes in risk factor levels within the whole population. In England and Wales, it has been estimated that 42% of the decrease observed between 1981 and 2000 was due to improved treatment, while 58% was due to risk factor reductions within the population (Unal et al. 2004). Particularly striking is the fact that of the latter, by far the biggest impact was reduction in smoking, with lesser effects of reduced blood pressure and cholesterol (48, 9.5 and 9.6% of overall deaths prevented, respectively). Considering the emphasis that has been given to reducing plasma cholesterol concentrations over the past 20 to 30 years, it is perhaps surprising that this has not contributed more to the decline in CVD (Salter, 2005).

• *TRANS* FATTY ACIDS

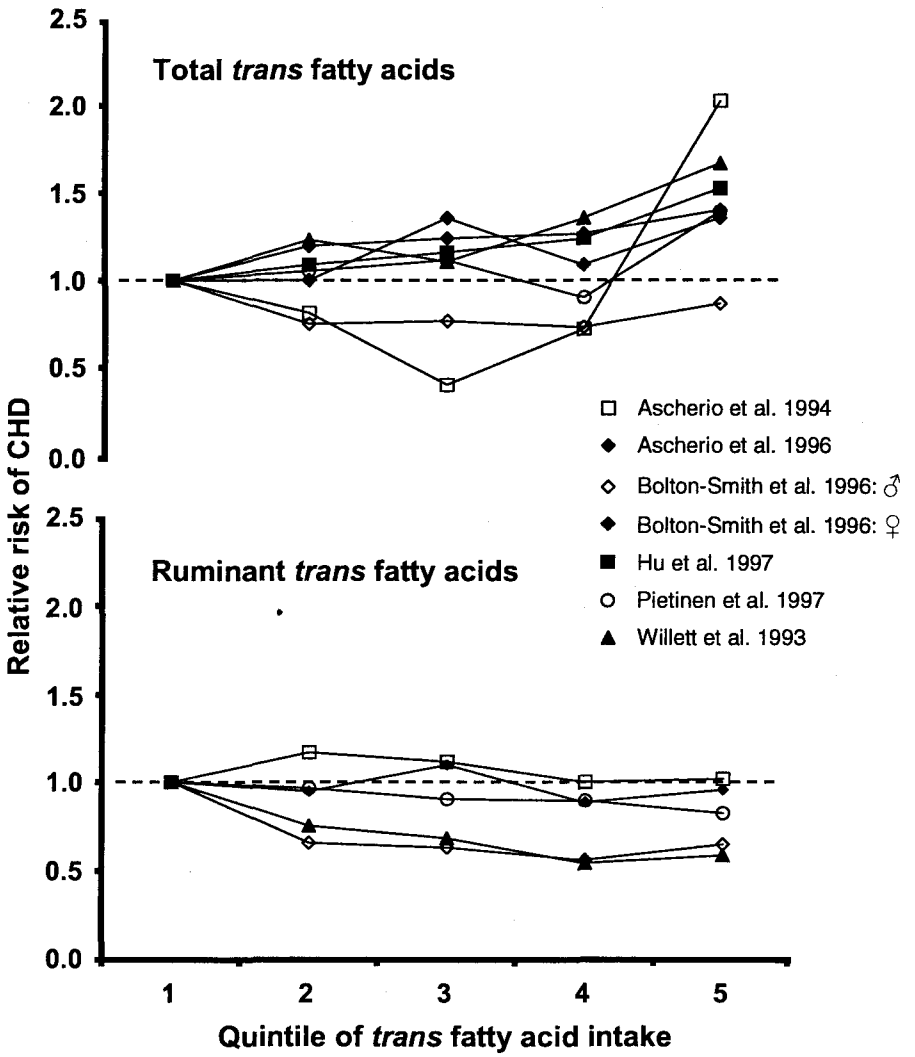
Trans fatty acids (TFA) have been associated with the risk of CVD (IOM, 2002) and beginning in 2006, the FDA mandated that the *trans* fat content of foods and dietary supplements be listed on nutrition labels (US FDA, 2003). The double bond in unsaturated fatty acids present in foods is typically of a *cis* configuration. However, TFA also occur and *trans* monounsaturated fatty acid isomers with 18 carbons (*trans*-18:1 acids) are the predominant TFA in the human diet. Generally, *trans* double bonds are introduced into fatty acids either by chemical processes during the formation of partially hydrogenated vegetable oils (PHVO; industrial sources) or in the formation of intermediates during rumen biohydrogenation (natural sources). In the production of PHVO, the goal is to obtain a fat with specific structural properties that has increased stability and shelf-life and improved product quality, with PHVO being used extensively in many prepared foods such as bakery products, cooking fats, and margarine. Unsaturated fatty acids are toxic to many rumen bacteria and to counter this they carry out an extensive biohydrogenation of dietary lipid. Thus, natural sources of TFA in human diets come from the consumption of dairy products and ruminant meats. The average daily intake of *trans* fat in the US population is estimated to be approximately 5.8 g/d or 2.6% of daily calories, with 80% originating from industrial sources and 20% from ruminant-derived foods (US FDA, 2003). However, with the adoption of mandatory nutrition labeling, the food industry is rapidly finding alternative practices that allow for a marked reduction in the use of PHVO in the production of processed food products. Thus, we anticipate the intake of TFA from ruminant sources will remain constant but increase as a proportion of total intake because of the reduction in the consumption of TFA from industrial sources.

During the past 50 years many studies have investigated the effect of TFA on plasma lipid levels, with current public health policy strongly recommending a reduction in the intake of TFA (IOM, 2002). Data from controlled human intervention studies have consistently demonstrated that diets containing TFA result in an increased serum total cholesterol and LDL-cholesterol and decreased HDL-cholesterol. This is clearly illustrated in the meta-analysis of sixty human trials by Mensink et al. (2003) as discussed earlier (see Figure 1, Panel A). These changes in blood lipids are associated with an increased risk of CVD and represent the primary basis for current public health recommendations and the mandatory listing of *trans* fat content on food nutrition labels (US FDA, 2003).

It is important to note that the dietary intervention studies cited above involved TFA from industrial sources. These results and others from similar studies have been broadly extrapolated to imply that high consumption of any and all TFA isomers is associated with an increased risk of CVD. However, it is increasingly clear that generalizations about fat and fatty acids are of limited value and often misleading, which in turn causes public confusion and erroneous perceptions. Rather, one must consider biological effects and nutritional value on the basis of individual fatty acids (Lock and Bauman, 2004). Industrial and natural sources differ in isomeric pattern and content of TFA (Craig-Schmidt, 1998; Lock et al., 2005). PHVO generally contain about 40-60% TFA and the isomer profile is a Gaussian distribution that centers on *trans*-9, *trans*-10, *trans*-11 and *trans*-12 18:1. In contrast, ruminant fat contains 1-8% TFA and VA is the major isomer. These differences are of importance because the position of the *trans*-double bond can influence both physiological properties and the rate of biochemical reactions (Parodi, 2004). As previously discussed, the TFA in ruminant fat includes CLA isomers, mainly RA, but these have been excluded from nutrition labeling in the US because of their reported beneficial effects on health maintenance as discussed earlier.

Prospective epidemiological studies consistently support the findings from intervention studies for an association between higher intakes of TFA and increased risk of CVD. A number of these have data that allow a comparison of food sources, and results indicate the positive association with risk of CHD can be explained entirely by the intake of TFA from PHVO (Figure 2) (Ascherio et al., 1994; 1996; Willett et al., 1993; Bolton Smith et al., 1996; Gillman et al., 1997; Pietinen et al., 1997). In contrast, for the relationship between the intake of naturally-derived TFA and risk of CVD these studies observed a significant negative association, an inverse non-significant association, or no association. However, the direct comparisons between TFA sources are confounded because actual intake of TFA across quintiles is much lower for natural sources as compared to industrial sources (Weggemans et al., 2004)

Figure 2. Relative risk of coronary heart disease with increasing relative intake (quintiles) of total and ruminant-derived *trans* fatty acids. Risks are relative to the risk in the lowest quintile of *trans* fatty acid intake; the fully adjusted model is presented for each study. Adapted from Lock et al. (2005).



Other investigations show an increase in incidence of CVD with increasing margarine intake, but not with butter intake (Gillman et al., 1997) and case-control studies from Greece (Tzonou et al., 1993) and Italy (Tavani et al., 1997) have reported increased risk of CVD as intake of margarine increased. During the period when these studies were conducted, margarines would have contained substantial quantities of TFA (Parodi, 2004). It has also been reported that the intake of *trans*-9 and *trans*-10 18:1 were positively correlated with CHD, whereas the intake of VA was not (Hodgson et al., 1996). Furthermore, a German case-control study reported that subjects with angiographically documented CVD had less RA in their adipose tissue (i.e. less intake of ruminant fats) than control subjects (Fritsche et

al., 1998). Finally, it has also been shown recently that inflammation markers associated with CVD risk were increased by dietary TFA from PHVO (Baer et al., 2004). Although some studies have reported no differences in the effects of *trans*-9 18:1 and VA on blood lipoprotein concentrations (Meijer et al., 2001), the weight of evidence does not support these findings.

Based on the above results, TFA from ruminant fats appear to differ in their relationship to the risk of CVD, although a definitive conclusion will require more investigations. The basis for this possible difference relates to differences in the specific fatty acid isomers in the fat sources. In addition to potential adverse effect of TFA isomers such as *trans*-9 and *trans*-10 that predominate in industrial sources, the most significant difference may be that the VA that predominates in ruminant fat can be converted to RA via Δ^9-desaturase. Several studies have established that humans are capable of this conversion (see review by Palmquist et al. (2005)), and Turpeinen et al. (2002)) estimated that approximately 20% of VA was converted to RA in humans, thereby doubling RA supply. Thus, this enzyme system may be key in differentiating VA from other *trans* 18:1 fatty acids. Overall, the results summarized here provide a clear indication that differences in the *trans*-18:1 isomer distribution between ruminant and industrial sources may be of special significance in relation to human health effects.

Finally, two recent papers have examined the impact of milk fat naturally enriched in TFA on biomarkers of CVD risk in humans (Desroches et al., 2005; Tricon et al., 2006). Despite the fact that the subjects significantly increased their intake of TFA from these products no negative effects on plasma cholesterol markers was observed. Also of significance was the fact that from the initiation of the Tricon et al. (2006) study through to completion subjects doubled their intake of dairy products but did not observe negative effects on CVD biomarkers.

CONCLUSIONS

There is growing recognition of the consumer desire for more healthy and nutritious foods. The contributions of animal-derived foods in supplying essential nutrients are well established, but consumers are increasingly aware that foods also contain components that may have positive effects on health maintenance and disease prevention. Dairy products contain a number of functional food components and one of these is CLA, specifically RA, because of its potential as an anticarcinogenic and antiatherogenic component of our diet. VA is also present in milk fat and its contribution to RA must be considered because it supplies precursor for the endogenous synthesis of RA in humans. On this basis, VA would also be considered as a functional food component in dairy products with potential benefits to human health. The public perception of both saturated and *trans* fatty acids in dairy products are significant challenges that face the dairy industry because of their perceived negative effects on human health. However, individuals do not consume these fatty acids as a dietary entity, but rather as fats in foods and overall, the available evidence does not provide support for the concept that consumption of dairy products adversely affects the risk of CVD. Clearly, the education of the public that not all fatty acids are equal is required. This is of special importance with the introduction of *trans* fatty acid labeling of foods as undesirable and the fact that both VA and RA are *trans* fatty acids.

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