Cyclic fatty acid monomers or the potential wild card in *trans* fats

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Sir:

We wish to bring to the research community a proposition for a modification or a diversification in the direction of the knowledge on *trans* fats. Our proposition is based on the following three elements.

First, there is a general consensus that industrial *trans* fats are recognized as really bad for the health since they have been associated with an increased risk of coronary heart diseases (Bendsen *et al*., 2011; Mozaffarian and Clarke, 2009) and, as a consequence, many countries have banned or limited the amount per serving of partially hydrogenated vegetable oils from food products, whereas the World Health Organization has established a framework for their elimination (WHO, 2019). But the data available seem arguable for both a dose-response analysis of the effects of industrially produced *trans* fatty acid on plasma lipoproteins and for varying levels of observed effects between studies (Brouwer et al., 2010). In addition, the abundant work carried out during the last 50 years on the health effects of industrial and ruminant *trans* fats has yet to provide conclusive answers as to why industrial *trans* fats are pro-atherogenic whereas ruminant *trans* fats appear to be neutral or, in some cases, beneficial (Destaillats *et al*., 2008; Brouwer *et al*., 2010, Wang *et al*., 2009; Tyburczy *et al*., 2009).

Second, cyclic fatty acid monomers are degradation products from vegetable oils that consist mainly of 5 and 6 membered-ring fatty acids (Dobson *et al*., 1995 and 1996) (Fig 1). Their formation is heat driven, faster for *trans* fatty acids (Desmarais *et al*., 2020) such as found in partially hydrogenated fats, and cannot be prevented when processing temperatures are 180˚C and higher since they form through a concerted cycloaddition mechanism involving double bonds (Destaillats and Angers, 2005). The content of CFAMs from thermal processes of vegetable oils will vary depending on the thermal processing conditions, and levels ranging from 0.01 to 0.66% have been reported in edible fats and oils from normal thermal processing operations such as partial hydrogenation (Rojo and Perkins, 1987) and frying (Frankel *et al*., 1987; Christie *et al*. 1993). CFAMs are known to cause fatty livers (Iwaoka and Perkins, 1976).

Third, a recent animal study (Mboma *et al*., 2018a and 2018b) has shown that CFAMs from *alpha*-linolenic acid at 0.05% in no *trans*-fat diets has affected pro-atherogenic markers in a similar manner to *trans* fatty acids fed at much higher levels. Indiviual CFAM isomers in the canola and soybean oils used by Mboma *et al*. ranged from 0.001 to 0.076 % of the oil (Table 1), and the content was ten times lower in the diets. Here, we wish to emphasize that with such low amonts of individual CFAM isomers, which are well within the range of their content in thermally processed oils, as mentionned above, Mboma *et al*. reported increases of 25% in the levels of plasma total cholesterol and 52% in VLDL-cholesterol + LDL-cholesterol, higher ratios (+66%) of total cholesterol to HDL-cholesterol, and lower levels (- 22%) of HDL-cholesterol compared with animals fed non-CFAM diets. These trace levels of CFAMs also caused an accumulation of triglycerides in the liver and induced hepatomegaly, two characteristics of the non-alcoholic fatty liver disease.

By interlocking the above mentionned information on CFAMs and *trans* fats, we come to the conclusion that the CFAMs present in industrial *trans* fats and oils could conceivably be a major contributor to the negative health effects which have been wholly attributed to (industrial) *trans* fatty acids. As such, we suggest the scientific community involved in this research field to now consider the CFAMs content in the studies.

We believe that this is important because studies on industrial *trans* fats have not reported the CFAM levels in the processed fats, although they are necessarily present at variable levels due to their chemical formation mechanism. This lack of CFAMs characterization in fats and oils used in nutrition and health studies may be due to a combination of factors such as a non awareness of the presence of CFAMs in heat treated oils (i.e. partially hydrogenated oils), and to their very low levels in those oils, which is exacerbated by the several structural isomers of CFAMs. Indeed, CFAMs at pro-atherogenic levels will likely go unnoticed in a routine FAME analysis by GC of a vegetable oil or fat, but methods for their identification and quantification, although somewhat complex, are available (Sébédio *et al.*, 1994). Despite their common presence in processed foods at low/trace levels, and, consequently, in the human diet, CFAMs remain a highly under-investigated class of fatty acids whose oxidized structures may resemble those of signal molecules such as cyclopentenone prostanoids (Medina *et al.,* 2018).

In brief, by proposing a change in the direction of the knowledge on *trans* fats in the research community, we believe that it will result in significant advancements such as a better understanding of the metabolic and dietary behavioral impacts that have been, until now, attributed to *trans* fatty acids from industrial *trans* fats. It has the potential to provide explanations as to why the data available in the scientific literature are arguable for a dose-response analysis of the effects of industrially produced *trans* fatty acid on plasma lipoprotein levels and for varying levels of observed effects between studies. We opine that such variations in the observed effects may well simply arise from the CFAMs present at different levels in the *trans* fats used for the studies.

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Figure 1. Basic structures of cyclic fatty acid monomers from *alpha*-linolenic acid. Each basic structure consists of four configuration (Z, E and *cis*, *trans*) isomers (adapted from Destaillats and Angers, 2005; Dobson *et al*., 1995).