Food and Chemical Toxicology 98 (2016) 269–281

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Trans fatty acids and cholesterol levels: An evidence map of the available science

DeAnn J. Liska [a, *], Chad M. Cook [a], Ding Ding Wang [b], P. Courtney Gaine [c], David J. Baer [d]

[a] Biofortis Clinical Research, Addison, IL, USA
[b] D & V Systematic Evidence Review Consulting, Bronx, NY, 10461, USA
[c] ILSI North America (Formerly), The Sugar Association (Presently), Washington, DC, 20005, USA
[d] U.S. Department of Agriculture, Beltsville Human Nutrition Research Center, USA

ARTICLE INFO

Article history:
Received 18 January 2016
Received in revised form
1 July 2016
Accepted 4 July 2016
Available online 7 July 2016

Keywords:
Cholesterol
Cardiovascular disease
Margarine
Trans fats

ABSTRACT

High intakes of industrial trans fatty acids (iTFA) increase circulating low density lipoprotein cholesterol (LDL-C) levels, which has implicated iTFA in coronary heart disease (CHD) risk. Published data on iTFA and LDL-C, however, represent higher intake levels than the U.S. population currently consume. This study used state-of-the-art evidence mapping approaches to characterize the full body of literature on LDL-C and iTFA at low intake levels. A total of 32 independent clinical trials that included at least one intervention or control group with iTFA at ≤3%en were found. Findings indicated that a wide range of oils and interventions were used, limiting the ability to determine an isolated effect of iTFA intake. Few data points were found for iTFA at <3%en, with the majority of low-level exposures actually representing control group interventions containing non-partially hydrogenated (PHO) oils. Further, it appears that few dose-response data points are available to assess the relationship of low levels of iTFA, particularly from PHO exposure, and LDL-C. Therefore, limited evidence is available to determine the effect of iTFA at current consumption levels on CHD risk.

1. Introduction

Trans fatty acids (TFA) are unsaturated fatty acids that contain at least one non-conjugated double bond in the *trans* configuration, and can be found naturally in ruminant foods (rTFA) or industrially produced oils (iTFA). Partially hydrogenated oils (PHO) are a major source of iTFA and were responsible for high intakes in the 1970s–1980s, when margarines were advocated over butter to reduce saturated fat intakes (Lichtenstein, 2014). Subsequent studies demonstrated that substitution of butter with TFA-containing margarines decreased low-density lipoprotein cholesterol (LDL-C) levels (Judd et al., 1998; Lichtenstein et al., 1999; Denke et al., 2000). Since the early 1990s, however, numerous studies have suggested that high TFA intakes may be associated with negative health outcomes. Specifically, direct evidence from clinical trials has shown that dietary TFA intakes >3% of energy (% en) increase blood levels of LDL-C when compared to unsaturated fatty acids. These observations led to the U. S. Food and Drug Administration (FDA) final ruling in 2003 (21 CFR 101.9(c)(2)(ii)) requiring that the Nutrition Facts panels of all packaged food labels must include the quantity of TFA per serving effective January 1, 2006 (Eckel et al., 2007). In response, average intakes of TFA at the population level were reduced, indicating nutrition labeling was a successful approach; however, in June of 2015 the FDA revoked the Generally Recognized as Safe (GRAS) status of PHO based on concerns that these ingredients contribute iTFA to the diet (FDA, 2015).

The scientific basis for the FDA removing the GRAS status of PHO was derived from expert reports that assumed a linear relationship exists between iTFA at any intake above 0 g and increased LDL-C. However, there is a disparity between the current estimates of habitual iTFA intake in the U.S. and the generally higher levels of iTFA intakes used in the dietary intervention studies that were represented in these expert reviews used to support the FDA Notice (FDA, 2013). That is, after the 2003 nutrition labeling, iTFA intakes decreased substantially and current mean intakes of iTFA are estimated to be around 1 g/person/day, or ~0.5%en based on a 2000 kcal daily intake (Doell et al., 2012). This more recent data on iTFA intakes has led to questions about whether the data used in influential publications (reviews/meta-analyses) actually contain data representative of current intakes. In particular, the reviews

* Corresponding author. 221 E. Lake Street, Addison, IL, 60101, USA.
E-mail address: deann.liska@mxns.com (D.J. Liska).

http://dx.doi.org/10.1016/j.fct.2016.07.002

Abbreviations

%en	percent of total energy
CLA	conjugated linoleic acid
CHD	coronary heart disease
CVD	cardiovascular disease
DRI	Dietary Reference Intakes
FDA	Food and Drug Administration
g	grams
GRAS	Generally Recognized as Safe
HDL-C	high-density lipoprotein cholesterol
IOM	Institute of Medicine
LDL-C	low-density lipoprotein cholesterol
LMP	lauric, myristic, and palmitic acids (C12:C16 saturated fatty acids)
MUFA	monounsaturated fatty acids
PHO	partially hydrogenated oils
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PUFA	polyunsaturated fatty acids
SFA	saturated fatty acids
TFA	*trans* fatty acid
iTFA	industrial *trans* fatty acids
rTFA	ruminant *trans* fatty acids

used by FDA extrapolated from higher TFA intake data to low-dose exposures used the assumption of a linear relationship (Ascherio et al., 1999; Brouwer et al., 2010; Mensink et al., 2003; Mozaffarian and Clarke, 2009). It is important to consider that many compounds in food do not affect metabolism in a linear fashion at all intake levels, but rather can exhibit a threshold effect. Thus, a controversy has developed around whether a linear relationship exists between iTFA and LDL-C at levels of intakes closer to current consumption patterns, or whether a threshold intake level exists at which a particular iTFA exposure would not increase LDL-C. It is unclear what evidence is available to assess the effects of low-dose TFA exposure on circulating cholesterol levels.

As a result of the controversy, we designed an evidence map to characterize the available literature and address whether an evidence-based approach to this question could be implemented. Evidence mapping is an innovative method to describe the quantity, design, and characteristics of research in broad topic areas and is a useful method to inform policy makers on research gaps (Wang et al., 2016). Evidence maps have been used to provide clarity to other controversial areas, for example, sugar-sweetened beverage intake and health outcomes (Althuis and Weed, 2013). Although evidence mapping is used in many areas of policy, it is still not standard in nutrition. Because iTFA represents a heterogeneous family of fatty acid isomers found in a vast variety of oils, it was our hypothesis that studies relevant to this question may not have been included in pivotal nutrition policy reviews due to the broad nature of terminologies used. Therefore, the evidence map approach provided a novel opportunity to identify and evaluate the characteristics and scope of available literature in this field of study. Moreover, evidence maps are useful in describing gaps in knowledge as well as aspects of reporting that can limit the ability to translate evidence used for public health.

Our objective was to describe the totality of published human studies, with a specific focus on data relevant to dose-response relationships (e.g., intervention trials) examining iTFA intake as a substitute for other oils or fats on changes in LDL-C. Additionally, we used the evidence map to identify what studies were included in recent nutrition policy influencing publications, specifically those of Ascherio et al., 1999, Brouwer et al., 2010, Mensink et al., 2003, and Mozaffarian and Clarke, 2009, as well as a review by FDA scientists that was not included in previous policy discussions (Trumbo and Shimakawa, 2011). Gaps in knowledge and suggestions for reporting standards are also identified.

2. Methods

There are currently no methodological standards for evidence mapping as this is a novel approach to apply to nutrition, therefore, this evidence-based assessment followed the procedures outlined in Wang et al. (2016) and was consistent with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standards (Moher et al., 2009) and previous evidence map publications (Althuis and Weed, 2013; Bragge et al., 2011). Briefly, the search strategy was designed to be broad, identifying a wide range of publications to be further refined against a pre-designated inclusion/exclusion criteria. As shown in Fig. 1, a two-step approach was used. First, a search was conducted to identify all studies that may have included a TFA intervention. This broad-based search included both natural and industrial oil terminologies, names of processed ingredients and foods that generally contain TFA, and individual fatty acids. Second, a search was conducted to identify all studies that included a relevant outcome measurement of lipoprotein lipids, specifically LDL-C.

2.1. Search methodology

Literature searches were conducted in two databases, Medline® (PubMed) and Scopus®, employing the National Library of Medicine's Medical Subject Headings keyword nomenclature developed for Medline®. Searches spanned the time period from inception of the database to January 2014. Results from these two searches were combined and filtered for human studies published in the English language. The resulting titles, abstracts, and keywords of all articles identified were screened using a web-based citation screening tool, Abstrakr™ (http://abstrackr.cebm.brown.edu/) with a low threshold to exclude irrelevant abstracts.

To assure quality and consistency of abstract review, a pilot test was conducted on a randomly selected subset (10%; n = 250) of abstracts, which were reviewed independently by two investigators. Results indicated a high inter-rater reliability (243/250; 97.2%); therefore, the initial abstract screening continued with one reviewer.

2.2. Selection criteria

Criteria were established to identify all published clinical trials (randomized and non-randomized/not-reported), prospective cohort studies, and case-control studies that were designed to assess the relationship between consumption of iTFA at all intake levels and changes in fasting lipoprotein lipids, specifically LDL-C. In general, studies eligible for review had to be published in the English language with human subjects that included a comparison of iTFA intake to either *cis*-monounsaturated fatty acid (MUFA) and/or saturated fatty acid (SFA) intake and had an outcome measurement of LDL-C. Studies that contained only one iTFA intervention compared to a carbohydrate replacement or a predominantly polyunsaturated fatty acid (PUFA) oil, and those with only rTFA and no iTFA comparison were excluded. Studies that provided fats intravenously as well as studies using fat as a vehicle for evaluating the effects of other components such as phytosterols, medium-