Trans-Fatty Acids

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Naturally occurring (fatty acids) FAs usually have the cis-configuration. Nevertheless, under certain conditions (e.g. partial catalytic hydrogenation or enzymatic hydrogenation), a double bond in FAs may change from a cis (Z) to a trans (E) configuration (geometric isomerization) and/or move to other positions in the carbon chain (positional isomerization). TFAs mediate increase of LDL levels and decrease of HDL levels in blood, which may lead to health consequences (e.g. cardiovascular diseases), even if this association is unclear considering the small proportion (about 10%) of cholesterol participating in atherosclerosis, re-questioning the interest of statins in this context. However, awareness is strongly suggested about industrial hydrogenation and subsequently possible excessive consumption of deleterious TFAs.

Keywords: cis-trans fatty acids ; Health ; Cardiovascular diseases ; Statins ; trans-fatty acids ; Catalytic hydrogenation

1. Introduction

Unlike other dietary fats, trans-fatty acids (commonly shortened to trans fats or TFAs) are neither essential nor salubrious and, in fact, their consumption can lead to higher risk of some pathologies, such as cardiovascular diseases [1].

TFAs arise through partial hydrogenation or isomerization (i.e. reduction in unsaturation) of cis unsaturated fatty acids (UFAs) [1]. TFAs can be produced by two major sources: (1) the bio-hydrogenation, which is naturally occurring in ruminants (e.g. cows, sheep) and involves bacterial enzymes (e.g. desaturases) as catalysts and (2) the partial catalytic hydrogenation of vegetables or fish oils, which is an industrial process that requires hydrogen gas and a metal catalyst in order to modify the physical– chemical properties of UFAs (e.g. decrease in their oxidation sensitivity, solidification of vegetable fat products) [1].

In terms of quantitative distribution, the total content of TFAs and isomers, in either natural (i.e. pasture) or industrial (i.e. conventional) food products, can largely vary between products, while the qualitative nature of TFAs is usually quite similar [2]. As a result, the fat in milk, butter, cheese and beef approximately contains 2-9 % TFAs, whereas industrial products such as margarines and "shortenings" (e.g. containing partially hardened vegetable oils such as baking or frying fats) can reach over 50 % of total FAs [2][3][4].

Furthermore, TFAs qualitatively differ according to the feeding source. Indeed, feeding of pasture (i.e. natural fat foods) results in high amounts of vaccenic acid (i.e. oleic acid isomer trans-11 aka 18:1 D11 trans), which can be converted in mammals into small amounts of the conjugated linoleic acid (CLA) 18:2 cis-9, trans-11 [2][5], whereas conventional feeding (i.e. industrial/hydrogenated fat foods) mainly results in high amounts of elaidic acid (i.e. oleic acid isomer trans-9 aka 18:1, D9 trans) [2][6]. In some cases, such as during partial hydrogenation of fish oils, trans-isomers of the omega-3 eicosapentaenoic acid (EPA aka 20:5) and docosahexaenoic acid (DHA aka 22:6) are predominant [7]. Besides, gamma-linoleic trans-isomers (18:2) and of alpha-linolenic acid (18:3) may arise from deep fat frying [8].

Nowadays, ruminant fats are considered as the major source of TFAs in most European countries because of the step reduction in the production and intake of industrial TFAs [9]. It was predicted that it will likely become so in the USA [10]. Nevertheless, the specific effects of ruminant TFAs on health are unclear as they can hardly be discriminated from the industrial ones. Indeed, the current epidemiological and experimental studies remain limited and controversial to correctly associate TFAs intake, whatever their origins, with the risk of causing deleterious human health effects (e.g. "non-communicable diseases" such as cardiovascular diseases, obesity, diabetes or cancers) [11][12][13][14][15][16][17][18][19][20][21][22]. For instance, a debatable positive association between industrial TFAs consumption and the risk of developing coronary heart disease has been shown and further explained by a TFAs-mediated increase in the plasmatic LDL level (low-density lipoprotein or "bad cholesterol") and decrease in the plasmatic HDL level (high-density lipoprotein or "good cholesterol") [1][11][12][14][15][18][19][20][21][22]. In this context, one can notably argue about the presence of TFAs in a number of products such as marketed capsules promoted for weight loss for which no strong evidence of their safety in humans has been demonstrated [23][24].

Eventually, the 2004 World Health Organization (WHO) Global Strategy on Diet, Physical Activity and Health endorsed the recommendation that TFAs intake should not exceed 1 % of the total energy intake (TEI) [25]. In 2007, the PAHO/WHO Task Force on "Trans Fat Free Americas" recommended that industrial TFAs should be eliminated from the food supply across the American continent [26]. Ultimately, in addition to other proposals (e.g. food labeling, health claims regulation disclosing fat content of foods supplied in restaurants and food programs), this same organization suggested that TFAs content should not reach more than 2 % of total fat in vegetable oils and margarines, and no more than 5 % in other foods [26]. Despite these international recommendations, only few governments have implemented a TFA policy. For instance, in France, strategies to reduce TFAs consumption are still required and shall range from public health approaches such as the use of dietary guidelines and health promotion programs, mandatory labeling of TFAs content in food and voluntary agreements with the food industry to reduce TFAs content and produce alternative healthier fat sources.

2. Definition, nomenclature and properties of fatty acids: an overview

2.1. Definition and nomenclature of cis-fatty acids

The term fatty acid (FA) designates any one of the aliphatic monocarboxylic acids that can be liberated by hydrolysis from naturally occurring fats and oils [27][28]. FAs play multiple and essential cellular roles (e.g. energy production, membrane structures, immune cell regulation, cell signaling, gene expression and regulation) [29][30][31][32][33].

Depending on the absence or presence of a double bond, the FA is called "saturated" (SFA) (e.g. palmitic acid 16:0, arachidic acid 20:0) or unsaturated (UFA), respectively [7][33]. When the chain presents one or several double bonds, the FA is called monounsaturated (MUFA) or polyunsaturated (PUFA), respectively [7][33]. Thereby, MUFAs occur naturally in various animal and vegetable fats and can be obtained by biotransformation of SFAs [34]. MUFA group is represented by the oleic acid (18:1), which belongs to the family omega 9 (x9 or serial n-9). It is formed by a chain of 18 carbons and one double bond in configuration cis at the position 9 (aka D9, which represents the number of carbon atoms from the a-carbon/carboxylic group (–COOH) to the nearest double bond). The PUFA group is divided into two major families: (1) under the appellation omega-3 (x3 or serial n-3) such as linolenic acid 18:3, EPA 20:5 or DHA 22:6 and (2) under the appellation omega-6 (x6 or serial n-6) such as linoleic acid 18:2 or arachidonic acid 20:4 [7][33]. Their classification (i.e. omega-3 or omega-6) is obtained by subtracting the highest double bond—which is, respectively, located three or six carbons away from the "omega" carbon/opposite end of the carboxyl group (e.g. 15 in the case of alinolenic acid)—from the number of carbons in the FA (e.g. 18 in the case of a-linolenic acid). The PUFAs linolenic and linoleic acids are essential in humans—they cannot be synthesized by the organism and cannot be obtained from biotransformation of SFAs or MUFAs—and so, they must be provided by food (e.g. vegetables), preferentially at the 5/1 ratio [34]. Eventually, by successive elongations and desaturations, PUFAs can be converted into longer unsaturated carbonated FAs chain (e.g. linolenic acid 18:3 can be converted into EPA 20:5 which, in turns, can be converted into DHA 22:6) [34].

Eventually, several ways exist to write an unsaturated FA, depending on the terminology adopted by biochemists, chemists and physiologists [35][36]. In the chemist's terminology, the carbon atoms are counted fromthe carboxyl group (–COOH)which put theemphasis on the double bond closet to this group (D-notations) [35]. However, in the biochemist's and physiologist's terminology, a new numbering system for the unsaturation ofFAs called the "omega nomenclature" was proposed by Holman RT in 1964 and consists of counting the carbon atoms from the methyl (–CH3) determining the metabolic family, noted by xx (e.g. x3) or better n-x (n for the total number of carbon, x being the position of the distal double bond) [36]. For instance, linoleic acid (aka cis-9, cis-12-octadecadienoic acid) can also be written 18:2 9c, 12c; 18:2 D9, 12 or 18:2 (n-6) or 18:2 x6 [7][33].

2.2. Definition and properties of trans-fatty acids

Naturally occurring FAs usually have the cis-configuration. Nevertheless, under certain conditions (e.g. partial catalytic hydrogenation or enzymatic hydrogenation), a double bond in FAs may change from a cis (Z) to a trans (E) configuration (geometric isomerization) and/or move to other positions in the carbon chain (positional isomerization) [7][37]. In configuration cis, the two hydrogen atoms are on the same side of the carbon chain with respect to the double bond, a situation that produces a bend in the FAs, whereas in the configuration trans, the two atoms of hydrogen are diagonally opposed to each other, straightening the carbon chain (Fig. 1). For instance, oleic acid (18:1) can be found either as a geometric trans-isomer called elaidic acid (18:1 9t) or as a positional trans-isomer called vaccenic acid (18:1 11t) (Fig. 1). The case of PUFAs is more complex since their double bonds can be found in configuration trans or cis/trans. Indeed, linoleic acid (18:2 9c, 12c) can be found in three possible geometric isomers: 18:2 9c, 12t; 18:2 9t, 12c and/or 18:2 9t, 12t as well as in two positional isomers 18:2 9c, 13t and/or 18:2 9c, 11t (Fig. 2). In natural conjugated linoleic acid (CLA), the collective name for a range of conjugated octadecadienoic geometrical and positional isomers, 18:2 9c, 11t, is always the major isomer formed during microbial biohydrogenation of LA. In industrial preparations, the 9c, 11t and 10t, 12c isomers

are the major components. CLA can occur naturally at low levels in a range of products, but is highest (about 0.5 % of total fat) in ruminants, both in meat and in dairy products. It is also produced on an industrial scale by alkaline isomerization of LA (e.g. from sunflower or safflower oil) and is often referred to as commercial CLA [38]. Interestingly, CLA is a fatty acid that is currently receiving considerable attention because of a range of properties that may make a positive contribution to health at moderate doses [38]. Eventually, the physical–chemical properties of FAs have further implications in health and industrial applications (e.g. preparation of shortenings). Thereby, in addition to be characterized by a higher rigid carbon (acyl-) chain, TFAs differ from cis-FAs by their polarity and by a much higher melting point than FAs [39]. For instance, oleic acid 18:1 9c melts at 4 C, whereas its trans-isomers, the elaidic acid 18:1 9t and vaccenic acid 18:1 11t, melt between 42 and 44 C and 44 and 45 C, respectively [39].

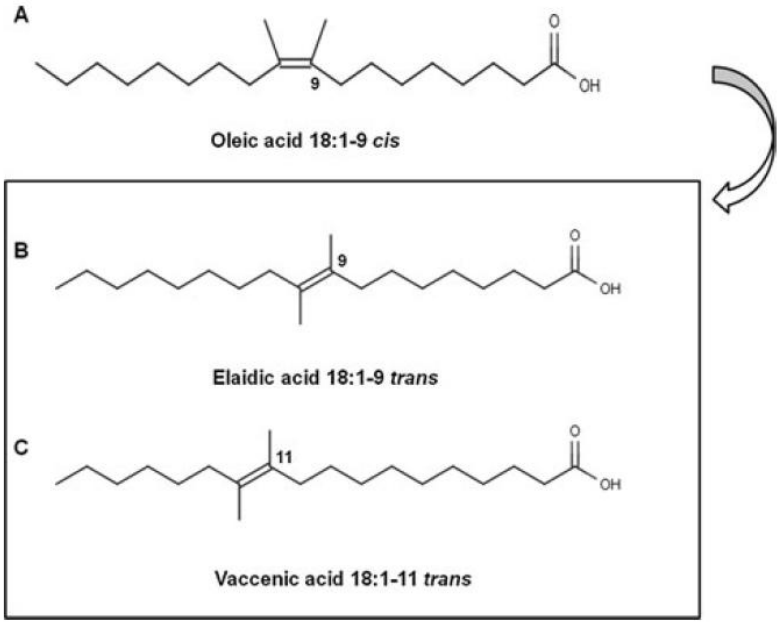

Figure 1. Isomers of the oleic acid (aka cis-D9-Octadecenoic acid, C18H34O2 or 18:1-9c). a Represents this MUFA in its configuration cis (Z). In this configuration, hydrogen atoms are on the same side of the carbon chain with respect to the double bond, a situation that produces a bend in the FAs. Cis-oleic acid can be transformed into configuration trans (E). In this case, the two atoms of hydrogen are diagonally opposed to each other, straightening the carbon chain. Thereby, trans-isomers of (a) can be either b geometric, represented by the elaidic acid (18:1 9t), which is mostly encountered in partially hydrogenated products (i.e. industrial fat foods such as margarines) or c positional represented by the vaccenic acid (18:1 11t), frequently observed in biohydrogenated dairy products (i.e. natural fat foods such as milk). The structures were assessed using online available lipid maps tools [40][41].

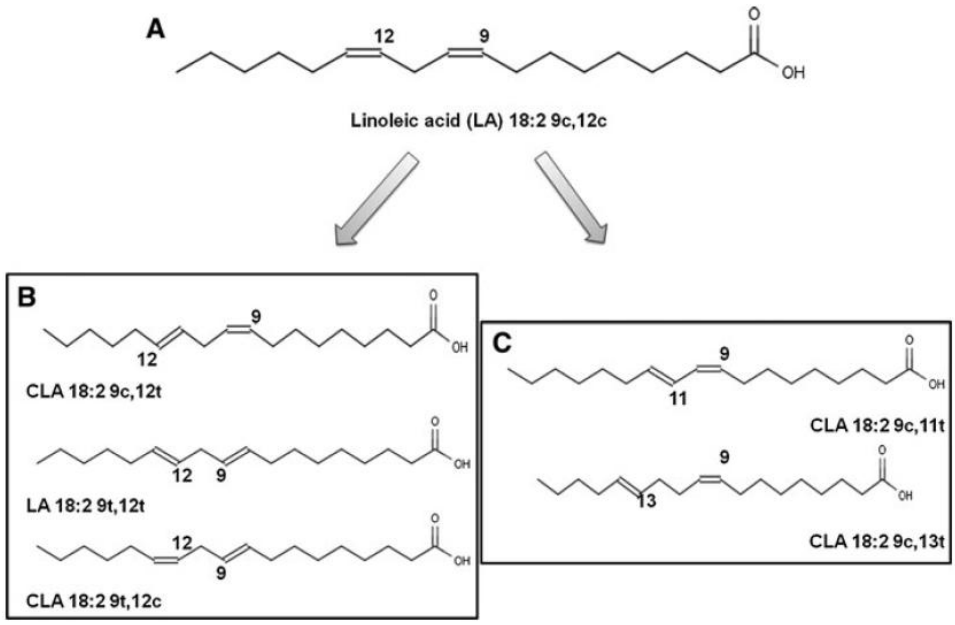

Figure 2. Isomers of the linoleic acid (aka cis-D9, cis-D12-Octadecenoic acid, C18H32O2 or 18:2-9c, 12c). **a** Represents this PUFA in its configuration cis, which can be transformed into: **b** three possible geometric isomers: 18:2 9c, 12t; 18:2 9t, 12t and 18:2 9t, 12c of linoleic acid (LA) or: c two possible positional isomers: 18:2 9c, 11t and 18:2 9c, 13t of LA. The

structures were assessed using online available lipid maps tools [40][41].

3. Potential effects of TFAs on health

Most TFAs—with the exception of some CLAs which, at moderate doses, would present some therapeutic benefits [38]—can negatively affect the human health and so be involved in several chronic pathologies and biological processes.

3.1. TFAs and cardiovascular diseases

Cardiovascular diseases (CVDs) are known to be the first cause of human death worldwide [42]. Importantly, arterial hypertension is considered as one of the major risk factors for both CVD (about 50 %) and death [42]. Several epidemiologic and experimental studies underlines the preponderant role of high levels of cholesterol low-density lipoproteins (C-LDL or "bad cholesterol") and low levels of cholesterol high-density lipoproteins (C-HDL or "good cholesterol") on atherogenesis and its consequences [43][44][45][46].

However, there is increasing consensus that dietary fats can also affect the CVDs risk via factors other than C-LDL and C-HDL [47][48]. Thereby, in vivo modulating factors such as TFAs [49], triglycerides [50], homocysteine [51], lipoprotein(a) [52] and plasminogen activator inhibitor-1 (PAI-1) [53] and clotting factors such as FVII [54] when relatively increased, as well as a natural anticoagulants when significantly decreased, appear to be important to better explain the etiology of CVDs and their complications.

Interestingly, most retrospective case–control and prospective cohort studies reported positive associations, even after adjustments of confusion factors (e.g. smoking, age, obesity and high blood pressure), between a relatively high consumption of TFAs (3 g/day) and the risk to develop CVDs [11][13][55][56][57][58][59][60][61][62][63][64][65]. In fact, TFAs consumption corresponding to 2 % TEI can increase the cardiovascular risk of 25 % [15], suggesting that the threshold of 2 % TEI should not be considered as an acceptable reference by competent authorities. That is certainly one of the reasons why the 2004 WHO Global Strategy on Diet, Physical Activity and Health has subsequently recommended an intake of TFAs lower than 1 % TEI [25]. The respect of 1 % TEI is applied in many countries, ruminant fats being a more important source than industrially partially hydrogenated fats.

Mechanistically, TFAs could represent a strong risk factor in the development of CVDs by molecular mechanisms involving (1) increase in plasmatic cholesteryl ester transfer protein (CETP) activity [66][67]; (2) increase in C-LDL level [68][69][70][71]; (3) decrease in C-HDL levels [68][69][70][71]; (4) stimulation of pro-inflammatory molecules [e.g. tumor necrosis factor-a (TNF-a), interleukin-6 (IL-6), C-reactive protein (C-RP)] [72][73]; and (5) endothelial dysfunction [72][73].

Interestingly, TFAs [e.g. vaccenic acid (18:1 11t)] would be, consequently, more atherogenic than SFAs (e.g. palmitic acid, 16:0) which increased both C-LDL and C-HDL [69].

Eventually, although the importance of C-LDL and C-LDL/C-HDL ratio is relatively debated to explain the etiology of CVDs, the implication of TFAs in the development of CVDs appears prominent and thus TFAs should be considered as preventive and therapeutic targets (Fig. 3).

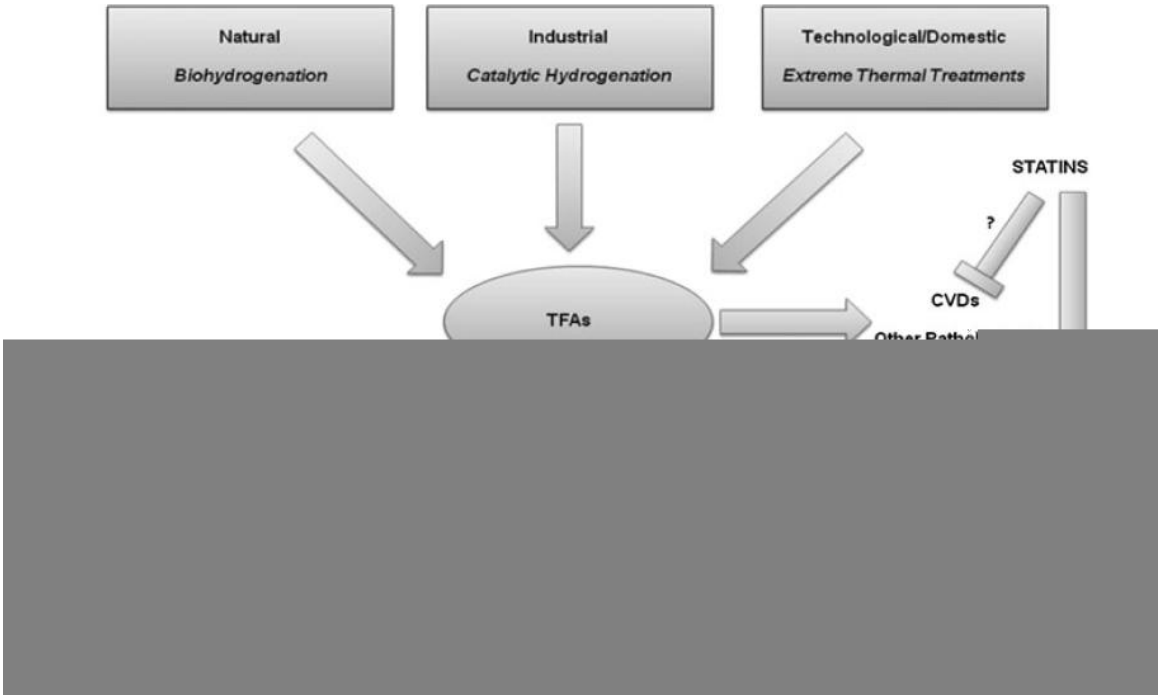

Figure 3. Schematic representation of the interrelations between TFAs and health status. Briefly, TFAs can originate from three known sources (natural, industrial and technological/domestic). Once overproduced or overconsumed (arrow symbols as marking activation), most TFAs may cause deleterious effects on health such as potentially increasing the risk of cardiovascular diseases (CVDs) by concomitantly reducing the HDL levels and stimulating the LDL production in the blood, which can be targeted by cholesterol-lowering drugs such as statins, albeit the role of cholesterol in the cardiovascular physiopathology remains controversial. Eventually, efficient prevention (e.g. information on TFAs, personalized nutritional chart, quick blood test, longitudinal follow-up of patients, etc.) and novel therapy strategies (hammer symbols marking inhibition or blockade) against TFAs might be then required.

3.2. TFAs and other possible health effects

3.2.1. TFAs and metabolic disorders

Most TFAs can be considered as modifiable dietary risk factors for metabolic syndrome, diabetes mellitus (aka type 2 diabetes or T2D) and obesity.

Indeed, relatively high TFAs intake can cause metabolic dysfunction in humans: It can adversely affect circulating lipid levels, trigger systemic inflammation, induce endothelial dysfunction and increase visceral adiposity, body weight as well as insulin resistance (i.e. low insulin sensitivity) [74][75][76][77]. The mechanisms behind such effects are unclear, but could involve several possible components such as altered physiochemical membrane properties, fuel partitioning (via altered fat oxidation and carbohydrate oxidation) or altered gene expression [78].

However, rodent studies suggested that supplementation of a CLA mixture (18:2 9c, 11t and 18:2 10t, 12c) could be beneficial for the management of insulin resistance, reduce the corporal fat mass and improve the lipid metabolism, whereas 18:2 10t, 12c alone was associated with greater insulin resistance [79]. In humans, the CLA isomers, 18:2 9c, 11t and 18:2 10t, 12c, have opposite effects with regard to the total cholesterol/c-HDL ratio. Thereby, 18:2 9c, 11t would have a beneficial effect, while 18:2 10t, 12c would have a deleterious effect translated by an increase in insulin resistance in obese individuals presenting a metabolic syndrome [80].

Nevertheless, relatively high consumption of CLAs does not prevent obesity. Indeed, it has been shown that daily consumption of a drinkable dairy product containing up to 3 g of CLA isomers for 18 weeks had no statistically significant effect on body composition in overweight, middleaged men and women [81].

Eventually, the lack of longitudinal and dose-effects studies does not allow us to clearly conclude about the importance of TFAs and CLAs.

3.2.2. TFAs and cancers

High content ofTFAs was associated with an increased risk of cancers, mainly human breast and colorectal cancers [82][83][84]. However, other studies reported no increase in the rate of those cancers when greater intake of dietary fat and fat subtypes, including TFAs, was consumed, at least among older and postmenopaused women [85][86]. Interestingly,

experimental studies suggest promising effects of some CLAs (e.g. 18:2 9c, 11t) on cancer risk in animal models and in breast cancer cells [87][88][89]. However, these effects have, until now, not been confirmed in humans.

Taken together, TFAs may be associated with the risk of some cancers. Nevertheless, further studies are still definitively required to solidify this hypothesis. Indeed, method limitations as well as lack of some experimental considerations could explain bias and contradictory results. In the benefice of doubts, the precautionary principle to limit TFAs consumption should be applied.

3.2.3. TFAs and teratogeny: from mother to early infant development and lactation

TFAs ingestion by pregnant women could affect the fetal development due to the presence of TFAs in the maternal milk and their transplacental passage [90][91].

Indeed, while some 18:2 CLA trans-isomers (e.g. 18:2 9t,12c) are overrepresented in umbilical plasma, 18:1 transisomers (e.g. 18:1 9t) were predominantly found in maternal plasma [92]. Since the TFAs composition in human milk fat was mainly represented by oleic acid 18:1 isomers (range: D9–12t) and an inverse relation between the weight at birth and the elaidic acid (18:1 9t) level was observed in premature babies, the occurrence of a transplacental passage of elaidic acid was strongly suggested [93]. Furthermore, it has been shown that newborns with low venous umbilical DHA levels and high levels of umbilical TFAs had poor neurologic conditions at 18 months [94]. Overall, it is now admitted that poor maternal DHA status can affect infant's brain and retinal development [95].

Mechanistically, TFAs transported across the placenta and secreted in human milk in amounts that depend on the maternal dietary intake may have adverse effects on infant growth and development through interfering with essential FA metabolism, direct effects on membrane structures or metabolism or secondary to reduce the intakes of the cis essential FAs in either mother or child [96].

Overall, those limited data point out the risk for pregnant and breast-feeding mothers to consume industrial TFA-containing products, while consumption of essential FAs such as the omega-3 DHA would be largely beneficial.

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