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Comparison of bovine milk fat and vegetable fat for infant formula: implications for infant health

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Abstract

Fat is an important component of human milk and infant formula (IF), delivering half of the energy a baby needs. Nowadays, mostly vegetable fats are used in IFs, however, the use of bovine milk fat in formulas is currently increasing. Bovine milk fat contains a different composition of fatty acids and lipid components than vegetable fats. We have compared the lipid profile of human and bovine milk to infant formulas with different fat sources. Furthermore, current knowledge of how infant digestion, absorption, metabolic responses, gut immunity, microbiota and/or cognition is affected by dietary fat is reviewed. The possible opportunities and drawbacks of the application of bovine milk fat in infant nutrition are described. Future perspectives for the development of IF containing bovine milk fat and future research directions are highlighted.

1 Introduction

Milk is essential for babies. For a newborn child breast milk is the preferred nutrition (EU Directive 2006/141). However, when breastfeeding is not an option, infant formula (IF) is the best alternative. About four percent of human milk consists of fat, which delivers approximately 50% of the total energy to infants (Manson & Weaver, 1997). Therefore, this is a major component to focus on in the development of optimal IF.

Currently, different fat sources are used for IF, of which most contain a mixture of vegetable fats. The most commonly used vegetable fats are coconut oil, corn oil, soybean oil, palm oil (palm olein, palm kernel oil), (high oleic) sunflower oil, high oleic safflower oil and low erucic acid rapeseed oil (Berger, Fleith, & Crozier, 2000; Mendonça, Araújo, Borgo, & Alencar, 2017). Besides vegetable fats, the addition of bovine milk fat to IF is quite common. Sun et al analyzed 180 infant formulas reflecting 75% of the market share in China, from which 66 products (37%) contained bovine milk fat. Bovine milk fat is added to IF in two different ways; either as anhydrous milk fat (containing triglycerides and other components like cholesterol and fat-soluble vitamins), or as full fat milk or cream (containing besides triglycerides and cholesterol all components of the fat globule membrane).

Until the 1970s, bovine milk fat was part of IF (Delplanque, Gibson, Koletzko, Lapillonne, & Strandvik, 2015; Innis, 2011), mainly through the use of whole milk in the recipes. However, as the formulas were further developed, animal fat was replaced by vegetable fats (Institute of Medicine, 2004). This was done for several reasons; to provide (higher levels of) mono- and poly-unsaturated fatty acids (Innis, 2011), and due to the fear of contaminants, like dioxins. Also, it was believed that formulas similar to home-made evaporated milk formulas increased the level of constipation (Fomon, 2001a), and the odor of regurgitated butterfat was found to be unpleasant (Fomon, 2001b). In addition, the cost of using bovine milk fat was high, compared to the alternatives found in vegetable fats. Today, research focus is on adding complex lipids and milk fat globular membrane components to support infants' development (Koletzko, 2016). Furthermore, EFSA states that "the obvious and previously used staple sources of fat for use in the production of IF and follow-on formula are cow's milk, to a certain extent goat's milk and different types of vegetable oils" (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2014). In this review, we compare the composition of human milk fat, bovine milk fat and vegetable fats and focus on their implications for infant health.

2 Lipid composition in bovine milk, human milk and infant formula

Human as well as bovine milk contains approximately 4% fat in the form of globules (Jensen, Ferris, Lammi-Keefe, & Henderson, 1990b; Månsson, 2008). During different stages of lactation the total fat content and fatty acid composition changes to a minor extent (Giuffrida et al., 2016; Kay et al., 2005; Moltó-Puigmartí, Castellote, Carbonell-Estrany, & López-Sabater, 2011; Qi et al., 2018; Stoop, Bovenhuis, Heck, & van Arendonk, 2009). However, since this is not the focus of this review, and since the recommendations for the composition of IF is the same for newborns and up to 6 months, we chose to only include mature human milk as comparison for IF in this review. Fat globules are filled with triglycerides, which represent 98% of the total fat (Jensen, Ferris, Lammi-Keefe, & Henderson, 1990a). The so-called milk fat globular membrane (MFGM), which is composed of proteins and lipids, cover the milk fat globules (MFG). Proteins within the MFGM include glycoproteins and enzymes (Dewettinck et al., 2008; Zou et al., 2015). The structure of the MFGM was recently reviewed by Martini et al. (Martini, Salari, & Altomonte, 2016) and nicely illustrated by Hernell et al (Hernell, Timby, Domellöf, & Lönnerdal, 2016). The lipids within the MFGM include mainly polar lipids, but also some neutral lipids like triglycerides, diglycerides, monoglycerides, sterols (mainly cholesterol) and gangliosides. Furthermore, bovine milk fat contains trace amounts of ether lipids, hydrocarbons, fat-soluble vitamins, flavor compounds and other minor compounds (Månsson, 2008). The triglyceride composition and structure, polar lipids and cholesterol are described in more detail below.

2.1 Triglycerides

The fatty acids in human and bovine milk fat, as well as in vegetable fat, are mostly present in the form of triglycerides (~98%). A triglyceride consists of a glycerol backbone with three fatty acids attached to it. Both the fatty acids and the triglyceride structure of different fat sources are described in the sections below.

2.1.1 Fatty acids

Nearly 200 different fatty acids, ranging from C4:0-C26:0, are present in human milk fat (Jensen, Ferris, Lammi-Keefe, & Henderson, 1990c; Månsson, 2008). For bovine milk fat this number is even higher, almost 400 fatty acids are present in bovine milk fat (Jensen et al., 1990a). Only about 15% of those are present at 1% or higher, the others are only present in trace amounts. Since most vegetable fats (except coconut oil) do not contain fatty acids ranging from C4:0-C12:0, and no odd-chain fatty acids (Dorni, Sharma, Saikia, & Longvah, 2018) the variety of fatty acids in vegetable fats is lower compared to bovine and human milk fat Table 1 shows the fatty acid composition of human milk, bovine milk and IF products with different fat blends. For clarity, very low abundant fatty acids were left out.

2.1.1.1 Fatty acids in human milk

Table 1 contains an average fatty acid composition of mature human milk (studies from 2000 until 2018 were included). Of all fatty acids in human milk, almost 98% are long-chain fatty acids (LCFA (>C10)), of which about 40% are saturated fatty acids (SFA). The remaining 2% of the fatty acids in human milk fat consist of medium-chain fatty acids (MCFA (C6:0-C10:0)). Most studies are not able to detect the short-chain fatty acid (SCFA) butyrate (C4:0) in human milk; however, some studies do report the presence of butyric acid in low concentrations. For example, Wan et al. showed that human milk of Chinese mothers contained 0.6 g butyric acid per 100 g fatty acids (Wan, Wang, Xu, Geng, & Zhang, 2010). The values represented in Table 1 are an estimation of the true levels in human milk. Analytical factors influence the fatty acid compositions, including differences in extraction protocols and detection methods. Furthermore, there is a natural variation both between individual mothers and between geographical regions (Kumar et al., 2016), since the fatty acid composition of human milk is influenced by diet as well as genetics. To give an insight in these regional differences, data from human milk obtained in Asia and Europa is presented. Some regional differences are observed, as the level of PUFA is somewhat higher in Asia compared to Europe, and the level of SFA and MUFA is somewhat lower. Overall, the fatty acid composition between regions is quite similar.

2.1.1.2 Fatty acids in bovine milk

About 70% of bovine milk fat consists of SFA. Of all fatty acids, almost 90% are LCFA, 6-7% are MCFA, and butyrate is present in about 3-4%. The most characteristic fatty acids for bovine milk fat are odd chain fatty acids, conjugated linoleic acid and butyrate. This latter fatty acid is not present in vegetable fats and only present in trace amounts in human milk.

Bovine milk fat contains higher levels of saturated fatty acids compared to human milk fat, about 67% vs 43% respectively, and lower levels of MUFA's (24% vs 36%) and PUFAs (2% vs 18%). Even though low in human milk, docosahexaenoic acid (DHA) and arachidonic acid (ARA) are present in even lower amounts in bovine milk fat. Similar to human milk fat, the main fatty acids present in bovine milk fat are oleic acid and palmitic acid (C16:0). In human breast milk, palmitic acid alone accounts for approximately 10% of the infant's energy intake, making palmitic acid a key nutrient for infants (Innis, 2015). In bovine milk fat, palmitic acid is present in higher levels compared to human milk fat (30% vs 22%), for oleic acid this is reverse (22% vs 34%). A major difference between human milk fat and bovine milk fat is the level of linoleic acid. Human milk fat contains around 15% linoleic acid, while in bovine milk fat this is only about 1.5%.

2.1.1.3 Fatty acids in vegetable fat

Different vegetable fats present in IF are blended in such a way that the fatty acid composition closely resembles that of human milk (Table 1). However, since different vegetable fats are used, there is also some variation between products. This is indicated by the ranges in Table 1, which shows examples of fat mixtures used in IF. Compared to an infant formula containing bovine milk fat, an infant formula that contains only vegetable fat contains lower levels of butyrate and MCFA and higher levels of MUFA. When a mixture of only vegetable fats is used, a source of palm oil needs to be added to reach a similar level of palmitic acid as found in human milk. A vegetable source of palmitic acid is palm (kernel) oil. IFs without palm oil contain only 8% of palmitic acid, and higher levels of oleic acid, linoleic acid and lauric acid compared to human milk fat.

2.1.2 TAG structure

A triglyceride consists of a glycerol backbone with three positions for fatty acids to attach, the outer positions are called sn-1 and sn-3, and the center position is called sn-2. Specific fatty acids have their own favorable position at the glycerol backbone, which differ among species. With the current analytical methods available, only the percentage of fatty acids at the sn-2 position of the total fatty acids can be determined. The fatty acids present at sn-1 and sn-3 cannot be determined separately.

2.1.2.1 TAG structure in human milk fat

In human milk, the main fatty acid, palmitic acid, is mostly placed at the sn-2 position, representing about 70-88% of the total palmitic acid, see Table 2 (Bracco, 1994; López-López, López-Sabater, Campoy-Folgoso, Rivero-Urgell, & Castellote-Bargalló, 2002; Sun, Wei, Su, Zou, & Wang, 2018). Of the other long-chain saturated fatty acids (LCSFA), 34-66% are also placed at the sn-2 position in human milk (López-López et al., 2002; Sun et al., 2018). The only exception is stearic acid (C18:0), of which only 10% is placed at the sn-2 position (López-López et al., 2002; Sun et al., 2018). The major TAG structures present in human milk are structures with palmitic acid at the sn-2 position, and oleic acid (18:1) attached to sn-1 or sn-3, like C18:1-C16:0-C18:2, C18:1-C16:0-C18:1, and C16:0-C16:0-C18:1 (Linderborg et al., 2014; Morera Pons, Castellote Bargalló, & López Sabater, 1998; Tu, Ma, Bai, & Du, 2017).

2.1.2.2 TAG structure in bovine milk fat

In bovine milk fat, butyrate is mostly located at sn-3. MCFAs, as well as C12:0-C16:0, are preferably located at the sn-1 and sn-2 positions. Stearic acid (18:0) is selectively located at position sn-1, while oleic acid is mostly present at sn-1 or sn-3 (Månsson, 2008). For bovine milk fat, the amount of palmitic acid at the sn-2 position is about 40-45% of the total amount of palmitic acid (Bracco, 1994). Sun et al. showed data for IFs containing bovine milk fat; however, the percentages of bovine milk fat used were not specified. Here, the percentage of LCSFA (excluding stearic acid) positioned at the sn-2, instead of sn-1 or sn-3, was between 30-49% (Sun et al., 2018). Like human milk fat, bovine milk fat contains a wide variety of fatty acids, resulting in many different triglyceride structures. Just like human milk, the major TAG structures in bovine milk fat contain palmitic acid in the sn-2 position, and oleic acid attached to the sn-1 or sn-3 position (Jensen, 2002; Michalski, 2009).

2.1.2.3 TAG structure in vegetable fat

The TAG structure of vegetable fats used in IF differ from human milk fat. For vegetable fat blends used in IF the amount of palmitic acid at the sn-2 position reaches levels of 10-20% (Bracco, 1994; Sun et al., 2018). Sun et al. reported that 19-59% of the LCSFA are positioned at the sn-2 position in IFs with vegetable fats, of which some contain interesterified palm oil (Sun et al., 2018). Clearly, in vegetable fat-based IF's, high levels of triglyceride structures with saturated fatty acids at the sn-1 and/or sn-3 position are present, such as C18:1-C18:1-C16:0, C16:0-C18:1-C16:0, C18:2-C18:1-C16:0, and C16:0-C18:2-C16:0 (Tu et al., 2017). Since less different fatty acids are present in vegetable fat, also the pool of triglycerides is less diverse compared to human and bovine milk fat.

2.1.2.4 Structured TAGs

The distribution of fatty acids along the glycerol backbone at the sn-2 vs sn-1/sn-3 positions can be changed with inter-esterification (Berger et al., 2000). Recently, TAGs generated through an enzymatic process from vegetable fats or combinations of vegetable and other fats e.g. from fish have become available (Álvarez & Akoh, 2016; Ghosh, Sengupta, Bhattacharyya, & Ghosh, 2016). The most common product is beta-palmitate, which is used in IF products currently on the market. Beta-palmitate is the resulting product of the enzymatic inter-esterification of palm oil and high oleic sunflower oil, where C16:0-C18:1n-9-C16:0 is transformed to C18:1n-9-C16:0-C18:1n-9 (L. Zou, Pande, & Akoh, 2016). These "structured TAGs" make it possible to produce IFs with TAG structures higher in sn-2 palmitate, often above 40% (ranging from 39-47%) of the total palmitic acid content (17-25%) (Bar-Yoseph, Lifshitz, & Cohen, 2013; Sun et al., 2018) .

2.2 Minor components

2.2.1 Polar lipids

Polar lipids encompasses amongst others phospholipids and sphingolipids. Those lipids contain a hydrophobic tail and a hydrophilic head (Dewettinck et al., 2008). Polar lipids have a fundamental role in milk; the emulsification of fat in water (Contarini & Povolo, 2013). The concentration of total polar lipids is comparable between human milk fat and bovine milk fat. Human milk fat contains about 20.4± 2.8 mg of polar lipids per 100 ml compared to 19.2 ± 0.8 mg of polar lipids per 100 ml for bovine milk fat (calculated from Zou et al., 2013). The composition of the different polar lipids is slightly different between the two different fat sources. Furthermore, the exact phospholipid content of the bovine globule membrane is dependent on the cow breed, season, feed of the cow and size of the globule (Z. Liu, Logan, Cocks, & Rochfort, 2017; Michalski, 2009). The main polar lipids present, in both the human and bovine fat globule membrane, are phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidylserine (PS), and sphingomyelin (SM) (Dewettinck et al., 2008; X. Zou et al., 2015). Human milk contains higher levels of sphingomyelin (40.2% ±1.1 vs 27.4 ±1.1) and phosphatidylserine (14.4 ± 2.0 vs 7.3 ± 1.0), while in bovine milk fat more phosphatidylethanolamine is present (12.5 ± 2.9 vs 30.2 ± 2.7) (Zou et al., 2013), see Figure 1. In IF, based on vegetable fat, the phospholipids are provided by lecithin, derived from either sunflower seeds or soybeans (Delplanque et al., 2015) and from residual bovine milk fat from skimmed milk powder (Berger et al., 2000). The phospholipids from skimmed milk powder also account for the presence of sphingomyelin, which cannot be sourced via plant-based fat blends. The level of phospholipids varies among IFs, but IFs consist mostly of PC, SM, and PE with lower levels of PI and PS (Braun, Flück, Cotting, Monard, & Giuffrida, 2010; Fong, Ma, & Norris, 2013).

2.2.2. Cholesterol

One of the minor components of human and bovine milk lipids are sterols, which make up 0.3% of total fat. Cholesterol constitutes about 95% of the total sterols. Human milk is a rich source of cholesterol, it contains about 90-150 mg/L of cholesterol (Berger et al., 2000; Koletzko, 2016). Bovine milk fat contains higher levels, around 300 mg/L of cholesterol (Jensen et al., 1990a), whereas IFs contain 0-4 mg/L of cholesterol (Koletzko, 2016). A recent study investigating sterol contents of IFs showed that IFs based on vegetable fats contained on average 0.185 mg/L of cholesterol (Claumarchirant, Matencio, Sanchez-Siles, Alegría, & Lagarda, 2015). In line with the findings on phospholipids, the cholesterol present in IF based on vegetable fats also mostly originates from small amount of milk fat present in skimmed milk (Berger et al., 2000). Newer types of IF, containing a blend of vegetable fats and bovine milk fat, contain higher levels of sterols, on average 0.927 mg/L (Claumarchirant et al., 2015), which is still surprisingly low. However, the amount of milk fat in these IF products was not specified, so the fraction of bovine milk fat might have been low. Calculations based on literature values (NEVO online) indicate that per addition of 10% bovine milk fat to a fat blend for infants formula 5.5 mg/L of cholesterol could be added.

3 Effects of milk fat related components on infant physiology and health

In recent years, the importance of dietary fats in infant nutrition has gained increasing scientific interest. Rather than merely a source of energy, it has become clear that the composition and structure of dietary fats in the infant diet could have profound influence on infant development, physiology and health. In this section, we will review how; 1) digestion/absorption, 2) metabolic responses, 3) gut immunity, 4) microbiota and 5) cognition could be affected by the composition and structure of milk fat related components. The main effects are illustrated in Figure 2. Since only very few studies have been performed to study the effects of these components in infants, other studies have been included to indicate possible interesting leads for infant health. These effects are indicated with a dotted line in Figure 2.

3.1 Digestion/absorption

3.1.1 Triglyceride digestion

The fat composition in the diet of infants affects the digestion and absorption of nutrients in infants. A well-studied example is the digestion and absorption of TAGs. During digestion, gastric and pancreatic lipases release the fatty acids positioned at the sn-1 and sn-3 positions of the TAG. As mentioned in paragraph 2.1.2, in human breast milk, these positions are predominantly occupied by MCFA, long-chain unsaturated fatty acids as well as low levels of butyrate. Butyrate and MCFA are, unlike LCFA, rapidly absorbed in the intestine as free fatty acids (FFA) (Innis, 2011). The sn-2 fatty acid remains on glycerol as sn2-monoglyceride (MAG). In human milk, the most abundant fatty acid in the sn-2 position is palmitic acid. Due to the more polar nature of the sn2-MAG, this fatty acid is more efficiently absorbed in the intestine in the form of sn2-MAG rather than as a FFA (Innis, 2015). In contrast, IF based on vegetable fats mainly has palmitic acid in sn1 and sn3 position, that are released by the digestive lipases, resulting in large amounts of unesterified palmitic acid, as well as other low absorbable FA, freely present in the lumen (Innis, 2011). These long-chain saturated FFA form complexes with calcium ions, generating non-absorbable soaps (Quinlan, Lockton, Irwin, & Lucas, 1995; Yao et al., 2014a). These calcium soaps are described to be associated with negative effects for infants, such as constipation, stool hardness (Bongers et al., 2007) (Nowacki et al., 2014a) and reduced bone mineralization (Litmanovitz et al., 2013). As described in section 2.1.2 bovine milk and human milk contain respectively 40-45% (Bracco, 1994) and 70-88% (Bracco, 1994; López-López et al., 2002; Sun et al., 2018) of the palmitic acid at the sn-2 position and therefore less soap formation will most likely occur with IF containing bovine milk fat.

3.1.2 Cholesterol absorption

Cholesterol is a key component in cell membranes, it is important in brain maturation through myelination, and cholesterol is a precursor for bile acids and steroid hormones (Haque, Mozaffar, & Mozaffor, 1992). Furthermore, cholesterol is an important structural part of chylomicrons and lipoproteins, which are key factors for the absorption and transportation of LCFA in the body.

As mentioned in section 2.2.2, IFs contain much less cholesterol than human breast milk (Claumarchirant et al., 2015; Huisman et al., 1996). The low amounts of total cholesterol in IF, is most likely the reason for the lower serum levels of total cholesterol and LDL cholesterol found in formula fed infants compared to breast fed infants (Shamir et al., 2003). Furthermore, it could explain the three times higher cholesterol synthesis rate seen in formula fed infants (Cruz et al., 1994), as these infants would have to compensate for the lack of total cholesterol otherwise present in human breast-milk. Studies suggest that supplementing IF with cholesterol, does not entirely correct the lower plasma cholesterol levels found in formula fed neonates or piglets, respectively (Bayley et al., 2002; Rioux & Innis, 1993). In contrast, Timby et al, showed that MFGM-enriched formula increased cholesterol levels, so at the age of 6 months, cholesterol levels were similar to breast-fed infants (Timby, Lönnerdal, Hernell, & Domellöf, 2014). Although these studies are not directly comparable, these observations may indicate that cholesterol associated with the MFGM is more easily absorbed by the infant intestine than free cholesterol. Another factor which may influence cholesterol absorption in infants is the presence of plant sterols in IF, such as brassicasterol, campesterol, stigmasterol, β-sitisterol and sitostanol, which are absent in human breast milk (Claumarchirant et al., 2015; Huisman et al., 1996). Total plant sterol levels exceeded the levels of total animal sterols in most formulas, except those with added anhydrous milk fat and/or MFGM, where total animal sterol levels were slightly higher than plant sterol levels (Claumarchirant et al., 2015). Plant sterols have been described to reduce cholesterol intestinal absorption in adults (Alphonse, Ramprasath, & Jones, 2017; Smet, Mensink, & Plat, 2012). However, the role of plant sterols in healthy term formula fed infants is unknown and needs to be investigated.

3.1.3 Effect of milk fat globular membrane on digestion and absorption

Bovine milk lipids in IF could also influence digestibility of proteins. *In vivo* and *in vitro* studies have shown that adding products including, but not exclusively containing MFGM and bovine milk fat to IF, leads to higher resistance of casein and β-lactoglobulin to digestion, as compared to formula based on vegetable fats. However, the exact composition and amount of the MFGM ingredients used in these studies are unknown and they may contain a variety of bioactive components. In a "minimally processed" model IF based on dairy fats with native MFG, casein and β-lactoglobulin were hydrolyzed slower, than the same formula after homogenization and pasteurization in an *in vitro* digestion system (Bourlieu et al., 2015). A similar reduction in protein digestion was reported in neonatal piglets receiving modified IF containing a mixture of milk and vegetable lipids and MFGM (Le Huërou-Luron et al., 2016). The resulting higher numbers of β-casein peptides in the gut, may exhibit bioactive functions that accelerates gut maturation (Le Huërou-Luron et al., 2016).

Lipolysis is also altered by lipid structure and components that are part of the MFGM, such as polar lipids. For example, the size and interfacial composition of MFG have shown to impact digestibility of lipids in simulated gastro-duodenal digestion (Garcia, Antona, Robert, Lopez, & Armand, 2014). Replacing polar lipids from soybean with milk polar lipids, changed the blood levels of lipids in mice after meals, with milk polar lipids resulting in a quicker elevation and clearance of plasma TAG (Lecomte et al., 2015). Finally, Mathiassen et al. showed that exchanging soy lecithin with dairy phospholipids increased gastric lipase activity by 2.5-fold (Mathiassen et al., 2015). Human breast milk contains bile-salt stimulated lipase (BSSL), which accounts for 20-40% of lipase activity in infants (Koletzko, Agostoni, Bergmann, Ritzenthaler, & Shamir, 2011). Since this lipase is not present in IF, formula-fed infants lack this extra lipase activity. Thus, the increased gastric lipase activity, when replacing soy lecithin with bovine milk polar lipids, might possibly be beneficial for formula-fed infants. A review about the structure of the milk fat and the relation with digestibility has been published by Bourlieu and Michalski (Bourlieu & Michalski, 2015).

3.2 Metabolic responses

Generally, the body compositions and growth curves differ between breastfed and formula-fed infants, as breastfed infants tend to have slower weight gain (Dewey, 1998) and breastfeeding shows less association with childhood obesity (Gunnell, Neher, & Safranek, 2016; Harder, Bergmann, Kallischnigg, & Plagemann, 2005). These differences on infant growth performance have been linked to protein concentration (and thereby energy density) (Koletzko et al., 2009; Weber et al., 2014) and general feeding practices (Appleton et al., 2018). Nevertheless, there has recently been increasing focus in literature on how the lipid composition of the infant diet influence metabolism and metabolic programing in infants as well.

3.2.1 Milk fat globule membrane, cholesterol, polar lipids and metabolic responses

The dietary lipid structure is a focus area within neonatal lipid metabolism research. Both the lipid droplet size, as well as the components of the MFGM, may possibly contribute to the preventive effects of breastfeeding on childhood obesity. Studies in mice have shown, that consumption of pellets with phospholipid-coated large lipid droplets, reduced fat accumulation and improved the metabolic profiles in adult mice (Oosting et al., 2012), and protected against obesity in adult life during a Western-style diet (highly processed, high saturated fat and high carbohydrate content) challenge (Baars et al., 2016). In a clinical study, where infants received a low-energy, low-protein, MFGM-enriched formula, cholesterol levels were normalized to the levels of breast-fed infants, most likely due to the cholesterol in MFGM (Timby, Lönnerdal, et al., 2014). However, there was no difference in growth performance between infants receiving standard or low-energy, low-protein, MFGM-enriched formula (Timby, Domellof, Hernell, Lonnerdal, & Domellof, 2014).

Interestingly, mice fed a high-fat diet rich in polar lipids (phospholipids and sphingolipids) from soybeans, showed white adipose tissue hypertrophy and inflammation. White adipose tissue hypertrophy is indicative of an imbalance in fat metabolism that is associated with obesity mechanisms. This was not observed when the mice were fed a similar high-fat diet based on milk polar lipids (Lecomte et al., 2016). In two other studies, feeding mice bovine milk sphingomyelin, compared to egg sphingomyelin, attenuated the consequences of high-fat-induced obesity in mice (Norris, Jiang, Ryan, Porter, & Blesso, 2016; Norris, Porter, Jiang, Millar, & Blesso, 2017). More long-term studies on infants are required to elucidate the relationship between MFGM, metabolism and metabolic programming. For a recent review on health-benefits of phospholipids in milk, see Verardo et al (Verardo, Gómez-caravaca, Arráez-román, & Hettinga, 2017).

3.2.2 Medium-chain fatty acids and metabolic responses

Since MCFA are not dependent on incorporation into the chylomicrons for absorption, MCFA are easily absorbed. Moreover, in contrast to LCFA, MCFA uptake in mitochondria occurs independent of the carnitine shuttling, contributing to a faster oxidation of MCFA (Marten, Pfeuffer, & Schrezenmeir, 2006). Since the uptake of MCFA is easier, compared to LCFA, IFs for premature born children are enriched with MCFA, in the form of medium-chain triglyceride fats. Consumption of MCFA has been shown to increase diet-induced heat generation and fat oxidation in adults (Kasai et al., 2002; Ogawa et al., 2007; Scalfi, Coltorti, & Contaldo, 1991), and in preterm infants the consumption of MCT was found to increase energy metabolism and improve thermoregulation (Telliez, Bach, Dewasmes, Leke, & Libert, 1998; Telliez, Bach, Leke, Chardon, & Libert, 2002) .

A few studies on rodents have investigated the impact of infant consumption of MCFA. In rats, high dietary intake of MCFA during pregnancy, prevented obesity in their offspring later in life (Dong et al., 2011). In a study of both rats and mice, increased early-in-life intake of MCFA protected against the negative effects of a high-energy diet in adulthood, such as fat accumulation and insulin sensitivity (Van de Heijning, Oosting, Kegler, & Van der Beek, 2017). In term infants, the role of MCFA on short- and long-term metabolism remains unclear.

3.2.3 Linoleic acid and metabolic responses

The essential fatty acid linoleic acid (LA) is needed by the body to synthesize arachidonic acid (ARA). Therefore, LA is added to IF in similar levels as found in human milk. The LA levels in commercially available IF are approximately around 16% of total FA (Table 1), which is similar to the LA levels in today's human milk. During the last 50-60 years the lipid composition in human breast milk has changed, so that today higher concentrations of LA are observed, from about 5% to 16% LA (Ailhaud et al., 2006), whereas levels of alpha-linolenic acid (ALA) have remained stable the past 40 years. This has brought up a lot of debate in the scientific field about the optimal level of LA and the optimal ratio with ALA (Gibson, Makrides, Koletzko, Brenna, & Craig-Schmidt, 2008; Simopoulos et al., 1994). In bovine milk, LA concentrations are approximately 10 times less than in the current human breast milk, 1.44% (Table 1). Bovine ALA levels are about half of the levels in human milk; 0.49% and 1.04%, respectively.

In recent studies on mice and rats, reducing LA (3.16 energy percentage (en%) vs 1.36 en%) in early life programmed towards relative metabolic resistance to a Western style diet (2.54 en%) in adult life. In mice, low LA diet (1.36 en% LA) decreased fat accumulation, reduced fasting TAG levels and lowered fasting leptin levels, whereas in rats a beneficial adipocyte composition was reported (Oosting, Kegler, van de Heijning, Verkade, & van der Beek, 2015). Furthermore, mice fed a Western-like diet high in LA and low in ALA (LA/ALA ratio 28), showed enhanced fat mass accumulation through four generations (Massiera et al., 2010). To elucidate the role of the ratio and levels of LA and ALA in infant nutrition more future research is required.

3.3. Gut immunity

The neonatal period is unique, in the sense that this is the time for maturation of the gut immune system and for the establishment of the gut microbiota. At birth, the gastrointestinal tract in humans is immature and adequate stimulation through diet and microbiota is essential for the gut to mature (Davis, Wang, & Donovan, 2017; M. Wang, Monaco, & Donovan, 2016). These processes are also influenced by the fat composition of the neonatal diet.

Dietary fats have been linked to host immune responses and have been associated with functions such as gut immune maturation, gut integrity and the establishment of gut immune homeostasis. Several studies have focused on the group of sphingolipids (including sphingomyelin, glycosphingolipids and gangliosides) and their potential protective functions against pathogenic bacteria and toxins, and their impact on gut immune maturation. The topic was recently reviewed by Nilsson (Nilsson, 2016). In particular, sphingosine-1-phosphate (S1P), a metabolite from the degradation of sphingomyelin has gained much interest due to its intestinal immune modelling functions (Kunisawa & Kiyono, 2012). These include a role in intestinal epithelial cell barrier function, proliferation of IgA producing cells and lymphocyte trafficking, as demonstrated in cell lines (Greenspon et al., 2011). Furthermore, imbalance of S1P may be involved in the development of diseases, which evolve due to inadequate regulation of the intestinal immune response, such as food allergies and intestinal inflammation, as reviewed recently by Kunisawa & Kiyonon (Kunisawa & Kiyono, 2016).

Besides the effect of sphingolipids, immunomodulatory effects of IF supplemented with bovine MFGM have been reported, in several animal and *in vitro* models, as well. The maturation of the mucosal immune system was accelerated in piglets receiving MFGM, based on the higher secretion of the immune system mediating cytokine interferon gamma from cells in the lymph nodes lining the small intestinal tissue (mesenteric lymph nodes). The authors indicate that these results might be related to the presence of sphingolipids in the MFGM fraction (Le Huërou-Luron et al., 2016). In some studies, gangliosides reduced proinflammatory signaling in the intestine in an *in vitro* gut model (Schnabl et al., 2009), whereas others have not observed this effect in preterm piglets (Møller et al., 2011).

Butyrate has been shown to have an important function in maintaining intestinal barrier function (Leonel & Alvarez-Leite, 2012). However, studies on Caco-2 cells have shown that in contrast to 2 mM butyrate, 8 mM butyrate has an adverse effect on a model for intestinal barrier function (Peng, He, Chen, Holzman, & Lin, 2007). Furthermore, intestinal mucosal injury has been associated with administration of SCFA to young neonatal rats (Nafday et al., 2005). An effect, which ceases with intestinal maturation. These studies have led to the hypothesis that too much SCFA, as a result of microbial overproduction, may be a cause of necrotizing enterocolitis (a major condition of illness in newborn children) in premature infants (Lin, 2004). However, when butyrate is digested (rather than produced by colonic microbes), butyrate is most likely rapidly absorbed in the upper gastrointestinal tract. The digestion and absorption of butyrate in premature and term infants is not well described in the literature, as this fatty acid is only present in human breast milk in very low levels (see Table 1). Therefore, further investigations are needed to elucidate the health effect of butyrate in bovine milk fat containing IF, since butyrate is digested and expected to be readily absorbed.

Clinical studies have shown that supplementing IF with bovine lipid components may potentially prevent some types of infection in infants as well. A fat blend containing bovine MFGM was shown to decrease episodes of bloody diarrhea in Peruvian infants/young children (Zavaleta et al., 2011) and reduce the risk of acute otitis media (middle ear infection) (Timby et al., 2015). On the contrary, a study on rotavirus diarrhea did not show any effect of supplementing IF with a spray-dried ganglioside concentrate (Poppitt et al., 2014) and the study by Timby et al. did not show a reduction in other types of infections. However, both studies were hampered by a low level of background infections. For reviews, see (Hernell et al., 2016; Rueda, 2007).

3.4 Microbiota

Distinct differences are observed in the microbiota between breast-fed and formula-fed infants (Davis et al., 2017; Kashtanova et al., 2016; Le Huërou-Luron, Blat, & Boudry, 2010) and it is wellknown that the gut microbiome plays a crucial role in the maturation of the gastrointestinal immune defense (Kaplan, Shi, & Walker, 2011; Stokes, 2017; M. Wang et al., 2016). Key factors modulating the microbiota are the presence of human milk oligosaccharides (Castanys-Muñoz, Martin, & Vazquez, 2016; Donovan & Comstock, 2016) and maternal factors (Mueller, Bakacs, Combellick, Grigoryan, & Dominguez-Bello, 2015). In addition, the lipid composition of the infant's diet could possibly alter the microbiota composition, as discussed below.

SCFA and MCFA are described to exhibit antimicrobial effects against E. *coli*, Listeria *monocytogenes* and Staphylococcus *aureus in vitro* and *in vivo* (Kelsey, Bayles, Shafii, & McGuire, 2006; Sprong 1999;). In particular, caprylic acid (C8:0) has shown inhibitory functions against pathogens, it both reduces bacterial growth in reconstituted IF (Choi, Kim, Lee, & Rhee, 2013) and weaning mortality in rabbits, fed a diet supplemented with caprylic acid-containing TAGs (Skrivanova, Skrivanova, Volek, & Marounek, 2009). For a review on dietary fatty acids and food-borne bacterial infections, see Harrison et al. (Harrison, Balan, & Babu, 2013). This review mainly focuses on effects observed in chickens or cell cultures.

Not much is known on the effect of milk fat on microbiota composition. In piglets, supplementing IF with bovine milk fat and MFGM increased Proteobacteria and Bacteroidetes while decreasing Firmicutes phyla, compared to piglets receiving formula exclusively based on vegetable lipids (Le Huërou-Luron et al., 2016).

IF with structured vegetable TAGs increased Bifidobacteria and Lactobacillus strains compared to IF containing standard vegetable fats in two clinical intervention studies with a duration of respectively 6 and 8 weeks (Yao et al., 2014a; Yaron et al., 2013).

Furthermore, adding gangliosides to IF reduced the levels of fecal E. *coli* and increased fecal Bifidobacteria in pre-term newborn infants (Rueda, Sabatel, Maldonado, Molina-Font, & Gil, 1998). Although the lipid composition in the diet of neonates indeed does alter gut microbiota, the mechanisms, as well as the effects of milk fat based IF on the microbiota composition in the child needs to be further elucidated.

3.5 Cognition

Population studies have established that even after elimination of socioeconomic factors, breast-fed infants have an advantage over formula-fed infants when measuring cognitive functions (Anderson, Johnstone, & Remley, 1999; Kramer et al., 2008). Although IFs continuously are being improved, these data suggest that the nutritional components, composition and structure of IF still needs to be optimized, in order to achieve optimal infant neurodevelopment.

3.5.1 Cognition and dairy fat components

Several individual lipid components present in human breast milk have been shown to be beneficial for brain development, including gangliosides, sphingomyelin and cholesterol. These lipids are all part of the MFGM and are present in lower concentration in IF, than in human breast milk, especially in formulas based entirely on vegetable fats (Claumarchirant et al., 2015; Pan & Izumi, 2000; B. Wang, Brand-Miller, McVeagh, & Petocz, 2001; Zeisel, Char, & Sheard, 1986).

Clinical studies have demonstrated that supplementing IF with bovine lipid components, including MFGM fraction (Timby, Domellof, et al., 2014), sphingomyelin (Tanaka et al., 2013) and gangliosides (Gurnida, Rowan, Idjradinata, Muchtadi, & Sekarwana, 2012), improves the cognitive score of infants. Besides clinical trials on infants evaluated by cognitive tests, animal studies have given more insight in the influence of certain lipid components on brain development and cognitive function. In mice, the diet was supplemented with bovine phospholipids to obtain large phospholipids-coated lipid droplets, which improved cognitive performance (Schipper, van Dijk, et al., 2016). Dietary cholesterol (Haque et al., 1992) and sphingomyelin (Oshida et al., 2003) improved brain myelination in mice and rats, respectively, whereas sialic acid supplementation increased the levels of these gangliosides in rat brain (Scholtz, Gottipati, Gajewski, & Carlson, 2013). Piglets received a diet supplemented with either MFGM, lactoferrin and prebiotics (Mudd et al., 2016) or a combination of bovine phospholipids and gangliosides (Liu et al., 2014), which in both cases induced physiological changes in the brain. Furthermore, mice fed diets supplemented with dairy lipids, were protected against cognitive impairment due to LPS challenge in adulthood (Dinel et al., 2016).

3.5.2. Interplay between arachidonic acid, docosahexaenoic acid, linoleic acid and dairy lipids

Today, supplementing IF with ARA (from fungus Mortierella alpina) and DHA from either single cell oil (algae) or from fish (tuna) has become common, to ensure adequate levels for normal infant brain development. DHA is essential for normal growth and development of the infant brain, where DHA accumulates during the first years of life (Bernard et al., 2017). Like DHA, ARA is important for infant neurological development and together, DHA and ARA, account for approximately 25% of fatty acids in the brain (Hadley, Ryan, Forsyth, Gautier, & Salem, 2016). When using human milk as a golden standard for IF, the ARA addition level should be higher than DHA levels (Koletzko, 2016; Lien, Richard, & Hoffman, 2017). Irrespective of the fat blend used, DHA and ARA are added as separate ingredients to IF. Recently some studies have investigated whether differences in the dietary fat blends may affect the efficiency of DHA accumulation in the blood cells and ultimately in brain tissues. It has been proposed that a dairy fat matrix enriched in ALA might improve DHA accretion in rodents (Du et al., 2012). It has been suggested that lowering the LA/ARA ratio increase brain DHA, as both compounds compete in the same pathway to be converted from LA to ARA, and ALA through EDA to DHA, respectively. This has been reviewed by Astrup et al. (Astrup et al., 2016). As mentioned before in paragraph 3.2.3, the levels of LA and the ratio with ALA in IF are under debate. In mice, reducing the LA in the maternal diet increased brain n-3 LC-PUFA (ALA, EPA, DPA (C22:5 n-3) and DHA) in the offspring (Schipper, Oosting, Scheurink, van Dijk, & van der Beek, 2016), whereas increasing ARA in sow diet increased DHA in piglet brains (Bazinet, McMillan, & Cunnane, 2003). However, this topic is a matter of much debate. In one clinical trial, formulas with lower LA:ALA ratios increased DHA and ARA levels in plasma and erythrocyte phospholipids, but was insufficient to ensure DHA and ARA levels that match the levels of circulation of a breast-fed infant (Makrides, Neumann, Jeffrey, Lien, & Gibson, 2000). This study did not, however, include dairy fat.

It has been speculated that the high levels of butyric acid and MCFA in dairy fat may possibly spare ALA from oxidation, as energy is generated from the rapid absorption and oxidation of butyric acid and MCFA (Gianni et al., 2018; Jones, 1994). Therefore, bioconversion from ALA to DHA might be favored.

Further studies involving infant clinical trials are needed to elucidate the potential cogitative benefits of adding dairy fats to IF.

4 Advantages and drawbacks of different fat source for IF

In this review, we have discussed the different components of bovine milk fat, and compared those to human milk fat and vegetable fat. Furthermore, we have reviewed the existing evidence from both clinical trials and animal studies, on how bovine milk fat impacts (infant) physiology and health. Based on this, we would like to highlight some of the advantages and drawbacks of different fat sources for IF.

Bovine milk fat contains valuable lipids, such as cholesterol, phospholipids and sphingolipids. These lipids are present in human milk, but cannot be obtained from vegetable sources (see paragraph 2.2). Although more research is needed, these components seem to have several beneficial effects on infant physiology and health, as discussed in this review. Furthermore, bovine milk fat contains a high variety of TAGs, with a high percentage of palmitic acid positioned at the sn-2 position, which is also the case in human milk (Bracco, 1994; López-López et al., 2002; Sun et al., 2018). It has been shown that a high percentage of palmitic acid at sn-2 could positively affect TAG digestion and absorption in infants, as well as the comfort of infants (Bongers et al., 2007; Nowacki et al., 2014b; Quinlan et al., 1995; Yao et al., 2014b). So in contrast to that what was thought in the 1960s (Fomon, 2001b), addition of bovine milk fat to IF might decrease constipation instead of causing it.

However, bovine milk fat cannot be used as a single source of lipids, as it contains higher levels of saturated fatty acids compared to human milk fat and lower levels of LCFA (LA and ALA) and DHA and ARA (Table 1). Because of the low levels of LA in bovine milk fat, adding vegetable fat is necessary to reach the required level of LA. A maximum of 67% of bovine milk fat can currently be used in IF, when using todays preferred LA levels. These LA levels are based on current breast milk levels. However, LA levels can be lowered from an average of 16g/100g fatty acids to about 6 g/100g fatty acids without challenging current Codex Alimentarius legislation (FAO) (Commission, 2011). The minimum level LA required, reflects the levels of LA in human milk at the start of industrialization, and preclinical studies indicate that lowering the LA levels may possibly have a positive impact of infant health (Massiera et al., 2010; Oosting et al., 2015).

In addition, bovine milk fat contains butyrate, which only is present in trace amounts in human milk, as well as elevated levels of MCFA (Table 1). Most likely, these components are rapidly absorbed and metabolized in infants. However, the nutritional needs of infants are complex matters, and although no adverse effects in infants have been reported on neither butyrate nor MCFA, the effect of elevated levels in IF on infant health and development remains unknown.

Vegetable fats can be blended in such a way, that they represent the fatty acid profile of human milk. This human milk profile includes some of the valuable LCFA (LA and ALA), which only can be obtained in low amounts from bovine milk fat. However, the structure of vegetable TAGs differ from that of human milk, which results in suboptimal digestion of specific triglycerides. To address this problem, vegetable fats can be re-structured by industrial processing. Thereby, a TAG structure with more palmitic acid in the sn-2 position can be obtained. Still, the overall TAG composition is less diverse compared to human and bovine milk fat TAGs.

A commonly used vegetable fat is palm oil, although some commercial parties avoid the inclusion of palm oil in IF (Leite et al., 2013; Lloyd et al., 1999; Oliveira De Souza et al., 2017). The latter is due to concerns related to digestion (discussed above), unsustainable production methods, and the presence of elevated levels of processing-induced contaminants in palm oil (i.e. glycidol esters and 3-monochloro-1,2-propanediol (3-MCPD-esters)) which are known to have adverse health effects (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2013). However, when palm oil is avoided, the level of palmitic acid, one of the most abundant FA in human milk, is very low (Table 1). Another possible concern is the presence of plant sterols in vegetable fats, which are not present in human milk. Although this issue has gained little attention, it deserves further investigation

The use of fat blends containing both bovine milk fat and vegetable fats seems to be a good solution for making the best possible IF. This will provide infants with both the valuable bovine milk lipids, which cannot be obtained from vegetable fats, as well as the necessary LCFA profile by adding vegetable fats. Furthermore, combined bovine milk and vegetable fat blends allow the production of palm oil-free fat blends with the same palmitic acid level as observed in human milk (Table 1). Independent on the major fat source used for IF, DHA and ARA are always added separately to the chosen fat blend to accomplish their preferred fatty acid composition.

Although the levels of palmitic acid at the sn-2 position is higher in IF's containing either bovine milk fat or structured vegetable TAGs, the levels of palmitic acid at sn-2 of human milk is still not reached in the current IFs (see Table 2). Addition of structured vegetable TAGs to a blend with bovine milk fat and vegetable fat opens new possibilities to increase the sn-2 percentages, and to get closer to the TAG composition of human milk. Another possibility to improve IF is the generation of phospholipid coated droplets. A disadvantage of all current fat blends is that, due to processing, all fat droplets have the same globule size. This is unlike human milk fat, which contains larger globules in varying sizes. A new concept has emerged, in which larger phospholipid coated droplets are produced (Gallier et al., 2015). These artificial lipid droplets are closer to human MFG than regular produced infant formula, since they have a more comparable particle size with human milk fat, compared to normal IF lipid droplets, and they contain bovine MFGM components at their membrane (Gallier et al., 2015). However, these globules contain TAGs from vegetable fat, which are structurally different from human milk fat. Probably, it would be more optimal if both the membrane components, globule size and TAG composition and structure would more closely resemble the composition of human milk fat.

5 Future perspectives

In this review we have pointed out several health effects of bovine milk lipids. Still, the health impact of some bovine lipids have not been studied in infants yet. Although butyrate is well-known to be produced by the microbiota in the lower gastrointestinal tract, the health effects of butyrate in IF needs to be studied. Furthermore, MCFA, as MCT fats, are known to affect metabolism. But more dedicated research is needed to elucidate how elevated MCFA levels in TAGs influence infant health. Clinical trials on MFGM do not always specify the dose and composition of the MFGM components used. Therefore, more research is needed to understand which specific MFGM components trigger the health effects that were found.

An alternative way to use bovine milk fat in IF in the future would be to use MFG with the milk fat globular membrane intact. Today, this is not possible due to the processing techniques used to produce IF powder, such as homogenization and spray drying. Recent work indicates that pasteurization after microfiltration may be a more gentle approach (Hansen et al., 2018). Mild processing seems to be a promising option to maintain bioactivity and structure of the milk components, but extensive research is required to identify technological options maintaining the nativity of the milk ingredients in a safe manner concerning microbiology. Technical possibilities include low heating, low or no homogenization, UV-C irradiation instead of pasteurization and alternative ways of (spray) drying. Current legislation does not allow the use of non-pasteurized milk for IF production, which makes collaboration between regulatory bodies and science a crucial part of any progress to take place in the future. However, recent investigations suggests that inactivation of bioactive components through donor human milk pasteurization is a key factor influencing growth performance in preterm infants (Li et al., 2017, 2018). Interestingly, UV-C treatment seem a promising alternative (Li et al., 2017).

In conclusion, inclusion of bovine milk fat in IF may bring additional health benefits to infant nutrition, as it delivers a variety of different components, which are present in human milk, but are lacking in vegetable fats. Hence, blending bovine milk fat with vegetable fat in combination with the development of more gentle processing techniques might be a future direction to improve IF.

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Abbreviation list

ALA	alpha-linolenic acid
ARA	arachidonic acid
DHA	docosahexaenoic acid
IF	Infant formula
LA	linoleic acid
LCFA	long-chain fatty acids (>C11:0)
LCSFA	long-chain saturated fatty acids
MAG	mono-acylglycerol
MCFA	medium-chain fatty acids (C6:0-C10)
MFGM	Milk fat globular membrane
MFG	Milk fat globules
MUFA	mono-unsaturated fatty acids
PUFA	poly-unsaturated fatty acids
SCFA	short-chain fatty acids (<C6:0)
sn	stereospecific nomenclature
TAG	triacylglycerol

Table 1: Fatty acid composition (g/100 g fatty acids) of human milk, bovine milk and infant formulas (IF) containing different fat sources (mean+range).

			Milk			IF		
Fatty acid			Human milk – Europe [1, a]	Human milk – Asia [2, a]	Bovine milk [3]	IFs containing vegetable fat blends [4, b]	IFs containing milk fat [5, c]	IFs containing palm oil free vegetable fat blend [6, d]
SCFA	C4:0	Butyric acid	ND	ND	3.50 (3.07-3.78)	ND	2.4	ND
MCFA	C6:0	Caproic acid	0.39 [8]	0.07 [7]	2.29 (2.07 – 2.46)	ND	1.3	0.2
	C8:0	Caprylic acid	0.19 (0.09-0.24)	0.17 (0.11-0.28)	1.38 (1.26-1.51)	1.2 (0.4-2.1)	1.7	2.5
	C10:0	Capric acid	1.29 (0.83-1.63)	1.31 (0.52-2.48)	2.94 (2.60-3.23)	1.1 (0.1-1.7)	2.2	1.8
LCFA	C12:0	Lauric acid	5.98 (4.15 – 8.33)	5.56 (2.97– 13.82)	3.87 (3.50-4.28)	5.4 (0.2-13.6)	6.3	13.4
	C14:0	Myristic acid	6.44 (4.98 – 9.38)	5.70 (3.50 – 12.12)	11.29 (10.67 – 11.94)	4.6 (0.9-7.0)	7.2	5.2
	C14:1	Myristoleic acid	0.18 [8]	0.26 (0.03-1.11) [9]	1.08 (1.01 – 1.19)	ND	0.8	ND
	C15:0	Pentadecanoic acid	0.25 (0.16-0.32)	0.20 (0.08-0.50)	1.03 (0.97-1.10)	ND	0.6	ND
	C16:0	Palmitic acid	21.93 (15.43-25.62)	21.78 (17.55-29.00)	30.20 (28.31 – 31.85)	26.3 (15.9-31.7)	18.9	7.7
	C16:1 n-7	Palmitoleic acid	1.98 (1.65-2.31)	2.44 (1.29-4.59)	1.57 (1.45-1.68)	0.6 (0.2-1.1)	1.1	0.1
	C17:0	Heptadecanoic acid	0.29 (0.22-0.33)	0.28 (0.19-0.41)	0.59 (0.53-0.72)	ND	0.3	ND
	C18:0	Stearic acid	7.37 (5.58-9.52)	5.58 (3.90-6.79)	9.85 (8.75-11.39)	5.3 (3.2-7.7)	6.7	3.2
	C18:1 n-9	Oleic acid	36.30 (28.93-41.69)	30.80 (21.85-36.96)	21.62 (19.37 – 24.25)	37.6 (31.6-42.3)	28.1	43.3
	C18:2 n-6	Linoleic acid (LA)	13.99 (10.16-16.59)	16.90 (7.53-24.29)	1.44 (1.36 – 1.76)	14.0 (10.0-18.9)	16.7	20.5
	C18:3 n-3	Alpha-linolenic acid (ALA)	0.76 (0.49-1.05)	1.47 (0.35-4.06)	0.49 (0.45-0.57)	1.6 (1.2-2.0)	1.5	1.8

	C20:0	Arachidic acid	0.21 (0.14-0.31)	0.32 (0.03-2.97)	0.14 (0.12 – 0.17)	ND	0.3	0.3
	C20:3 n-6	Dihomo-gamma-linolenic acid (DGLA)	0.38 (0.29-0.52)	0.42 (0.23-0.83)	0.07 (0.06-0.08)	ND	ND	ND
	C20:5 n-3	Eicosapentaenoic acid (EPA)	0.09 (0.05-0.13)	0.31 (0.07-1.59)	0.07 (0.06-0.09)	ND	-	0.0
	C22:0	Behenic acid	0.09 (0.05-0.13)	0.08 (0.05-0.14)	0.06 (0.05-0.07)	ND	0.1	0.4
	C20:4 n-6	Arachidonic acid (ARA)	0.47 (0.37-0.64)	0.64 (0.30-2.57)	0.04 (0.03 - 0.05)	0.3 (0.1-0.4)	-	0.3
	C24:0	Tetracosanoic acid	0.07 (0.03-0.16)	0.07 (0.01-0.14)	0.05 (0.04 – 0.07)	ND	ND	0.1
	C22:6 n-3	Docosahexaenoic acid (DHA)	0.28 (0.18-0.42)	0.55 (0.19-1.13)	0.01 (0.00-0.04)	0.2	-	0.2
Total SC/MCFA			*1.86*	*2.14*	*10.11*	*2.3*	*7.6*	*4.5*
Total LCSFA			*42.62*	*39.59*	*57.08*	*41.6*	*40.4*	*30.3*
Total SFA			*44.48*	*41.73*	*67.19*	*43.9*	*48*	*34.8*
Total MUFA			*38.45*	*33.50*	*24.27*	*38.2*	*30.0*	*43.4*
Total PUFA			*15.97*	*20.27*	*2.12*	*16.1*	*18.2*	*22.8*
Total UFA			*54.42*	*53.77*	*26.39*	*54.3*	*48.2*	*66.2*

[1:] (Barreiro, Regal, López-Racamonde, Cepeda, & Fente, 2017; López-López et al., 2002; Marangoni et al., 2000, 2002; Moltó-Puigmartí et al., 2011; Rist et al., 2007; Sala-Vila, Castellote, Rodriguez-Palmero, Campoy, & López-Sabater, 2005; Scholtens et al., 2009; Wijga et al., 2003), [2:] (Cruz-Hernandez, Goeuriot, Giuffrida, Thakkar, & Destaillats, 2013; Daud, Mohd-Esa, Azlan, & Chan, 2013; Glew et al., 2001; Jiang et al., 2016; Nayak et al., 2017; Shi et al., 2011; Sun et al., 2016; Wan et al., 2010; Y.-H. Wang et al., 2010; Wu, Lau, Chen, Wu, & Tang, 2010; Yuhas, Pramuk, & Lien, 2006), [3:] *(RIVM, 2016; van Valenberg, Hettinga, Dijkstra, Bovenhuis, & Feskens, 2013),* [4:] *(Straarup et al., 2006),* [5:] *(Berger et al., 2000; Prosser, Svetashev, Vyssotski, & Lowry, 2010),* [6:] *(Leite et al., 2013; Lloyd et al., 1999; Oliveira De Souza et al., 2017),* [7:] *(Wan et al., 2010),* [8:] *(Barreiro et al., 2017),* [9:] *(Jiang et al., 2016; Sun et al., 2016),* [a] *studies from 2000-2018 are included, data about breast milk for infants <12 months of age,* [b] *IF contained palm oils, rapeseed oil, soybean oil and coconut oil as major fats,* [c] *IF contained bovine milk fat, corn oil, and other non specified vegetable fats,* [d] *IF contained high oleic sunflower oil, coconut oil, soy oil as major fats, ND: not determined, SCFA: short-chain fatty acid, MCFA: medium-chain fatty acid, LCFA: long-chain fatty acid, LCSFA: long-chain saturated fatty acid, MUFA: mono-unsaturated fatty acid, PUFA: poly-unsaturated fatty acid, SFA: saturated fatty acids, UFA: unsaturated fatty acids, note: The analytical methods for fatty acid analyses used in the various cited papers are subject to inaccuracies in quantitative measurements over the whole range of fatty acid lengths.*

Table 2: Stereospecific distribution of C16:0 in human milk, bovine milk and vegetable fats

	% C16:0 at sn-2 position of total C16:0
Human milk	70-88% [1]
Bovine milk	40-45% [2]
Vegetable fats commonly used in IF	10-20% [3*]
Structured triglycerides	39-47% [3**]

[1:] (Bracco, 1994; López-López et al., 2002; Sun et al., 2018), [2:] (Bracco, 1994), [3:](Bracco, 1994; Sun et al., 2018) * *based on data of IFs containing vegetable fat without interesterified palm oil from figure 1 of Sun et al, 2018., ** based on data of IFs containing vegetable fat with interesterified palm oil from figure 1 of Sun et al, 2018*

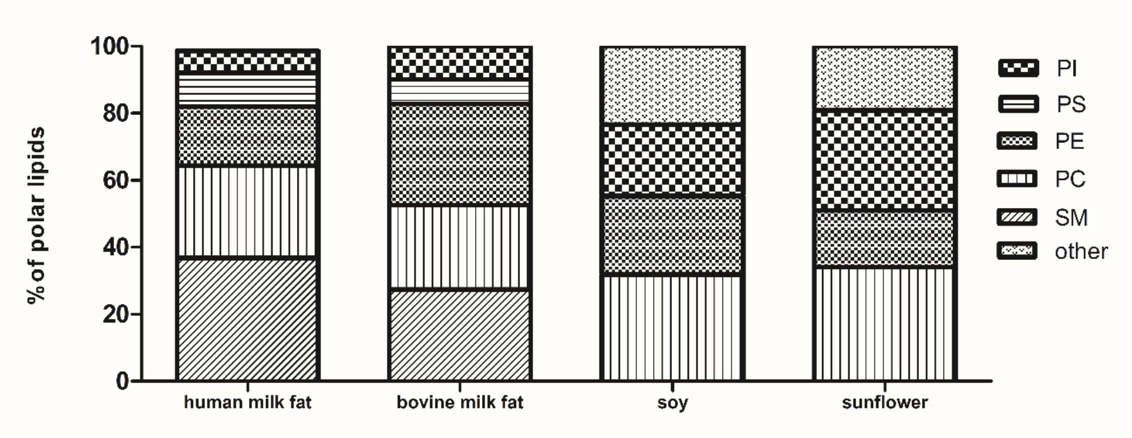

Figure 1: Relative proportion of polar lipids (% of polar lipids) from mature human milk and bovine milk (Cilla, Diego Quintaes, Barberá, & Alegría, 2016; X. Zou et al., 2013)*, and from soybeans and sunflower kernels* (van Nieuwenhuyzen & Tomás, 2008)*, (PE=phosphatidylethanolamine, PI=phosphatidylinositol, PS=phosphatidylserine, PC=phosphatidylcholine, SM=sphingomyelin).*

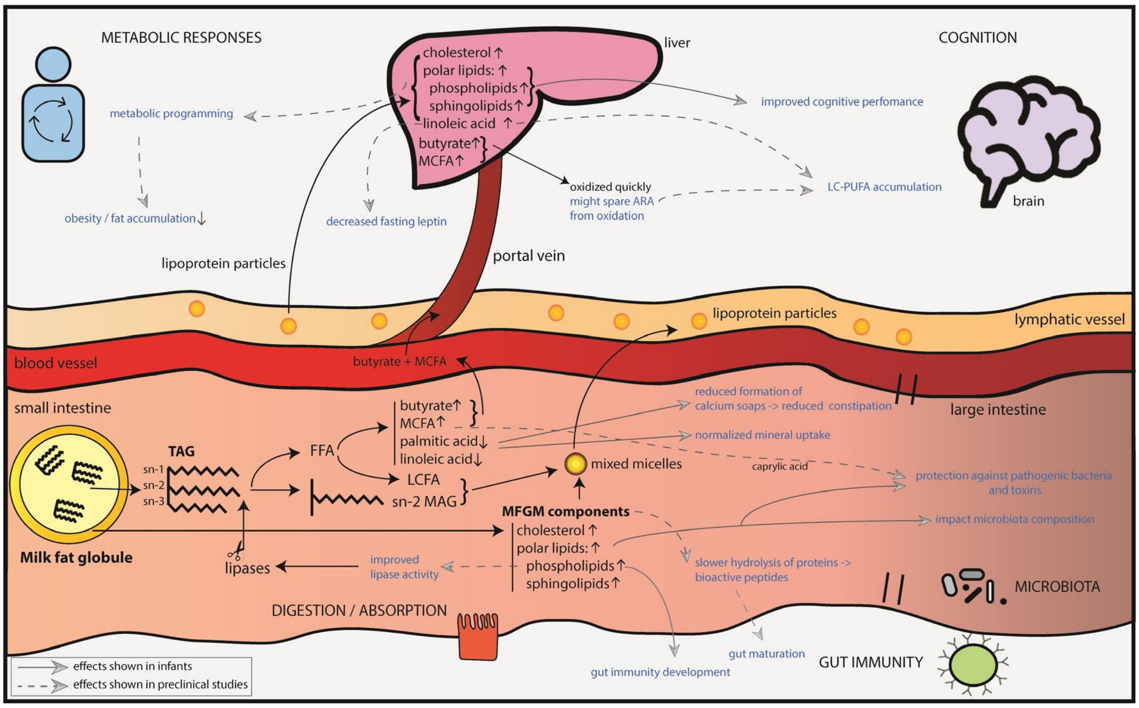

Figure 2: Schematic overview of the health effects of bovine milk fat (components) as described in this review, effects shown in infants are displayed with a solid arrow and effects shown in preclinical infants are displayed with a dotted arrow.