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Lipid intake in infants from birth to 3 years old: review of current guidelines and knowledge gaps

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Abstract

Lipids are essential for child development. Nutritional recommendations are numerous, evolving over time and are often based on expert opinions more than evidence-based medicine. The objective of this review is to critically analyse the evolution of current nutritional recommendations, identify existing knowledge gaps, and propose avenues for improvement to optimize infant nutrition and development. A narrative literature review on Pubmed, EMBASE and Cochrane (2001-2022) has been conducted with keywords: “alpha-linolenic acid, arachidonic acid, children, cholesterol, docosahexaenoic acid, eicosapentaenoic acid, guidelines, infant, LC-PUFA, linoleic acid, lipids and dietary intakes, newborn, palmitic acid, toddler”. Among 861 articles identified, 133 were selected. The main current recommendations are issued by AFSSA, ANSES and FAO-WHO. In infants from 0 to 3 years of age the main challenge is to increase lipid intake while maintaining an optimal omega 6 / omega 3 ratio. Current recommendations are focused on polyunsaturated fatty acids, emphasising the intake of linoleic, eicosapentaenoic and docosahexaenoic acids without any specific recommendation for arachidonic acid before the age of 6 months. Points of interest, but without any recommendation, are the incorporation of milk fat, cholesterol, monounsaturated fatty acids, and saturated fatty acids for infants under 6 months. In conclusion, this article identifies knowledge gaps regarding the structural aspect of lipids and the integration of new categories of lipids in future recommendations to promote the quality of infant formulas.

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Abbreviations

AFSSA: French Agency for Food Safety

ALA: α-linolenic acid

ANSES: French Agency for Food, Environmental and Occupational Health and Safety

ARA: Arachidonic acid

CVD: Cardiovascular disease

DHA: Docosahexaenoic acid

DPA: Docosapentaenoic acid

EFA: Essential fatty acids

EFSA: European Food Safety Authority

EI: Energy Intake

EPA: Eicosapentaenoic acid

ESPGHAN: European Society of Pediatric Gastroenterology, Hepatology and Nutrition

FADS: fatty acids desaturases

FAO: Food and Agriculture Organization

FFA: Free fatty acids

LA: Linoleic acid

LC PUFA: Long-chain polyunsaturated fatty acids

MFGM: Milk fat globule membrane

MUFA: Monounsaturated fatty acids

n-3: omega 3

n-6: omega 6

RDA: Recommended Dietary Allowance

SFA: Saturated fatty acids

SFP: French Pediatric Society

TEI: Total Energy Intake

TFA: Total fatty acids

WAZ: weight-for-age Z score

WHO: World Health Organization

WLZ: weight-for-length Z score

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1- Introduction

Lipids constitute about 50% of energy intake (EI) in exclusively breast-fed infants. Exclusive breastfeeding for the first 6 months of life is a strong and consensual recommendation (1) (2) and human milk is used as a model to define fat and fatty acid (FA) intakes in early life for healthy infants.

Despite breastfeeding promotion campaigns, the rate of breastfeeding initiation remains low in France which has one of the lowest rate in Europe (around 66%), and has even tended to decline in recent years (3). In addition, to enhance breastfeeding support, it is therefore also important to define as accurately as possible the nutritional framework for infant formulas offered in the absence of breastfeeding.

Recent clinical studies have underlined the essential contribution of fats consumed by children to metabolic programming, and their involvement in the development of neuronal and immune functions in children under 3 years old (4). Thus, infant formulas currently available have a FA profile, which more or less faithfully reproduces the natural composition of human milk (5). However, regulations for infant formulas only define a limited number of parameters for lipids (6) (7) in terms of quantity, while leaving other criteria (such as the addition of arachidonic acid (ARA), and the source of fat, etc.) to the discretion of the manufacturer.

Finally, the public health messages may appear contradictory to the parents. Indeed, while prevention messages aimed at the lay public advise to reduce fat intake, young children need significantly higher proportion of EI from fat than adults (3 to 5 times higher for children younger than 3 years vs adults) (8) (9). It is therefore essential to establish clear recommendations to guide parents during the first 1000 days of life. Providing such recommendations is challenging because clinical trials are often not ethically feasible in nutrition, particularly in children, and in the absence of a strong meta-analysis, child nutrition remains a subject of debate among experts.

This literature review aims to provide a comprehensive analysis of current lipid intake recommendations for infants from birth to 3 years of age. By highlighting inconsistencies, contradictions, and gaps in existing guidelines, the study seeks to propose evidence-based pathways for enhancing nutritional strategies, particularly in the formulation of infant

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formulas, to better align with the physiological needs of young children during this critical developmental period.

2 Methods

This article is a narrative literature review on the topic of lipid recommendations for young children aged from birth to 3 years old. Review based on literature identified through searching on PubMed, Embase and Cochrane (2001-2022) conducted using the keywords: "alpha-linolenic acid (ALA), Arachidonic Acid (ARA), children, cholesterol, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), guidelines, infant, LC-PUFA, linoleic acid (LA), lipids and dietary intakes, newborn, palmitic acid, toddler".

The selection of relevant literature included articles in English and French and identified 861 articles in the following search engines: Pubmed (n= 620), Embase (n=60) and Cochrane (n= 181). Articles were excluded if they did not provide the information sought, if they had an insufficient number of cited references (< 2), if they presented redundant content or were deemed irrelevant, or published in a journal of insufficient importance (classified as "predator journal", without peer reviewed, low classification rank in the speciality (< D)).

After deduplication, there were 422 articles left and 104 were withdrawn after reviewing citations eligibility. After removing redundant citations, non-accessible and/or missing the information sought, 133 different articles were included (Figure 1).

3) Total lipids

3-1) Definition

Lipids are water-insoluble substances found in plant and animal tissues, essential for structural and energy needs (10). They exist in various forms, including triglycerides, which are the primary nutritional form; fatty acids are an important constituent of many of these lipids including triglycerides.

3-2) Energetic function

The body's physiological needs change with age and require specific nutrient intakes. Indeed, from birth to 3 years, the energy needs derived from total lipids are particularly important, as energy expenditure is high due to rapid growth during this stage of life. In the first months, lipids represent about 35% of weight gain, or 80-90% of the energy value of new tissues (11).

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3-3) Current recommendations

Current recommendations on the proportion of EI derived from lipids are not consensual and have varied over the years and between different scientific organisations, with an upward trend in recent years (Table 1).

Currently, the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) recommends 50 to 55% of EI from lipids in infants under 6 months similar to the lipid content of human breast milk and then 45 to 50% for children from 6 months to 3 years of age (12). In fact, epidemiological studies suggest adequate growth as long as lipids are above 30% of the EI (13) and below this, there is a risk of inadequate intake of energy and fat-soluble vitamins. However, the ANSES recommendation derives from the fact that lipid consumption lower than 50% of total EI (TEI) does not ensure the minimum requirements for certain essential FAs, such as omega 3, and fat-soluble vitamins for infants under 6 months. The 2014 recommendation from the (European Food Safety Authority) EFSA at around 40% for infants aged 6-12 months (14) is very similar to that of ANSES (45%).

4- Long-chain polyunsaturated fatty acids (PUFA)

4-1) Generalities

4-1-1) Definition

Polyunsaturated fatty acids (PUFA) are fatty acids with at least two double bonds, classified as long-chain when containing more than 12 carbon atoms. Essential PUFA, such as linoleic acid (LA) C18:2 (n-6) and alpha-linolenic acid (ALA) C18:3 (n-3), cannot be synthesized by the body and must be obtained through diet (15) (16). Omega-6 (LA, ARA) and omega-3 (ALA, DHA, EPA) families (Table 2) play critical roles in structural functions, inflammation modulation, and neurodevelopment.

4-1-2) Metabolism

Endogenous synthesis of DHA and ARA is influenced by the genetic polymorphism of the fatty acids desaturases (FADS) FADS1 and FADS2 genes, which encode for the desaturase 1 and 2 respectively and limit their synthesis; and by elongases 2/5 Furthermore, the activities of these enzymes is depending on the organ (eg liver, brain, testicle, kidney) in relation to their protein concentration levels and substrate availability (17). The synthesis of PUFA is dependent on various factors, such as diet, nutrients, age, nutritional status, and certain pathologies, particularly those associated with insulin resistance, as insulin induces the enzymatic activity involved in PUFA synthesis (18). Nutritional intake of DHA and ARA

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during infancy is important to ensure their availability for growth and development. There is a competition phenomenon between these PUFA since the essential fatty acids (EFA) conversion pathways use the same set of enzymes (desaturases and elongases) for the synthesis from their precursors ALA and LA (Figure 2) (19). A high intake of LA induces excessive synthesis of ARA, which in turn limits DHA and EPA synthesis from ALA, resulting in reduced local availability of LC n-3 PUFA (notably DHA) into membranes. An excessively high LA/ALA ratio in early in life is likely to have negative short- and long-term health effects by reducing cerebral DHA availability and uptake through competition with ALA in the conversion stages (20). In addition, high levels of circulating ARA compete with DHA for incorporation into neuronal membranes. Conversely, high levels of ALA improve the infant's DHA status (20) (21). Thus, dietary intakes of LA and ALA, and the balance between them, have the potential to affect LC PUFA status, also to affect numerous physiological functions such as neuro-cognitive development (22). Moreover, circulating DHA levels depend not only on the ratio of LA to ALA, but also on the amount of dietary preformed PUFA supplied (23); and in the opposite way, DHA plays a fundamental role in PUFA synthesis because it downregulates its own liver synthesis by inhibiting EPA elongation (24) (25).

4-1-3) Main functions

EFA, but especially their LC-PUFA derivatives, are esterified mainly in the phospholipids of cell membranes, where they have a structural and functional role from foetal life onwards. While PUFA can be used as an energy source, they have above all numerous physiological roles such as inflammation modulation, immunity and regulation of lipid metabolism, and they play an essential role in the functioning of the brain and vision. EFA deficiency impairs lipid and energetic metabolism, cell membrane structures, and intracellular signalling pathways. A deep and prolonged deficiency can be detrimental, hence there is a dependence to a diet containing both LA and ALA (22).

Structural and modulation of gene expression

In the form of phospholipids, these FAs are universal constituents of biological membranes; modulating their fluidity and the activity of the proteins they contain (enzymes, receptors, transporters, etc.). They are important for lipid synthesis in physiological barriers such as epidermis. They are also involved in the regulation of inflammation through the activation of

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transcription factors (26) (27): it is well documented that n-6 PUFA demonstrate a higher pro-inflammatory effect than the n-3 PUFA.

Immunity

FAs are precursors of oxygenated mediators that specifically modulate a wide range of cellular functions and can produce multiple effects: haemostasis, platelet aggregation, immune system activity, etc. (26).

A number of clinical studies have shown that LC PUFA can modulate a child's immune status, thereby potentially preventing allergy development. These studies show a positive association between n-6 PUFA levels in breast milk and the risk of developing asthma, while high levels of total n-3 FA are associated with a reduced risk of atopy (28).

The impact of high ARA intake in the evolution or triggering of common childhood inflammatory diseases such as asthma, eczema, atopic dermatitis and food allergies is specifically a topic of interest with ARA intake often inversely related to these allergic diseases (29) (30).

Neurological and ophthalmic

Furthermore some LC PUFA are involved from the foetal stage onwards in body growth, central nervous system development and, consequently, cognitive development and retinal function in children (20) (31).

Especially, DHA is central to foetal and infant growth, as well as retinal and visual development. It is a major lipid constituent of photoreceptor membranes, where it plays a crucial role in maintaining their structural and functional integrity (32). It has been shown, for example, that the intake of DHA from algae in infant formulas improves visual acuity in children as young as 12 months (33). This beneficial effect could be explained by the fact that DHA increases mitochondrial activity and has antioxidant, anti-inflammatory, anti-apoptotic and anti-angiogenic effects at retinal level. Since the continuous renewal of retinal membranes requires a constant supply of n-3 PUFA, DHA-rich diets may even improve retinal function, particularly where damage has already occurred. In particular, DHA is a precursor of oxygenated derivatives, giving it specific properties in the brain: anti-inflammatory effects and involvement in the apoptosis process (34).

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4-2) importance of PUFAs during pregnancy and breastfeeding

Polyunsaturated fatty acids (PUFAs), particularly DHA and ARA, are essential during pregnancy and breastfeeding due to their critical roles in fetal and infant development (35). DHA supports neurodevelopment, visual function, and cognitive growth, while ARA contributes to immune function and cellular signalling. Maternal diet significantly influences the PUFA composition of breast milk, as dietary intake of n-3 and n-6 fatty acids directly affects their levels in milk (36). For example, diets rich in DHA, such as those including fatty fish or DHA supplements, enhance DHA levels in breast milk, promoting optimal infant brain and retinal development (36). Conversely, high intake of LA can increase ARA levels but may reduce DHA synthesis due to competition for shared enzymatic pathways (ref 16). Gestational obesity further alters the lipid profile, often increasing n-6 PUFA levels while reducing n-3 PUFA concentrations, which may impact infant health (37). Therefore, balanced maternal dietary intake of n-3 and n-6 PUFAs during pregnancy and lactation is crucial for ensuring adequate PUFA transfer to the infant, supporting growth, immune function, and long-term health outcomes (38).

4-3) Long-term effect of PUFA intakes in children

Preclinical evidence underlines the deleterious short- and long-term role of excess LA, and it has been shown that an increase in dietary intake of LA in Western societies over the last few decades coincides with higher incidences of obesity (39) and immune diseases (40) at population level.

Projections for lipid intake from birth to 3 years emphasize the importance of maintaining a balanced lipid profile to support optimal growth and development while mitigating obesity risks. Lipid availability, particularly essential fatty acids like DHA and ARA, is critical during infancy, as these contribute to neurodevelopment, immune function, and metabolic programming (26). Maternal diet during pregnancy and lactation directly influences the lipid composition of breast milk, with high n-6 PUFA intake potentially reducing DHA levels due to enzymatic competition (36). This imbalance may predispose infants to inflammatory profiles and metabolic dysregulation. Maternal obesity further exacerbates these effects, altering breast milk lipid profiles by increasing n-6 PUFA and saturated fatty acids while reducing n-3 PUFA levels (41). In childhood, excessive lipid intake, particularly from diets high in SFA and trans fats, can contribute to adiposity and long-term obesity risks (42).

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Therefore, ensuring adequate intake of balanced lipids, particularly n-3 PUFAs, during early life is essential for preventing obesity and promoting lifelong health.

4-4) Current recommendations

LC-PUFA requirements vary from one child to another even within a population of healthy term infants, so the LC-PUFA composition of infant formulas is described as a range rather than as a single precise value.

4-4-1) Essential fatty acids

Table 3 summarises the main official recommendations for EFA intake and their evolution over the past three decades.

The current recommendations' evolution reflects the difficulty of setting a maximum limit for LA intake besides the experimental data available, showing possible adverse effects of high LA intakes as described before. Unlike the Recommended Dietary Allowance (RDA) proposed by AFSSA in 2001 (8), the ANSES 2011 report does not give a maximum value for LA and ALA (9). The 2010 the Food and Agriculture Organization and World Health Organization (FAO-WHO) report gives a range for ALA intakes between 0.2 and 0.3% EI (43), but no recommendation is given for LA.

Scientific societies and organisations worldwide have mainly specified the minimum physiological requirement for LA in order to limit the imbalance between the two PUFA families when n-3 PUFA consumption is low. In the 1970s, supplementation studies proposed a recommended minimum intake of LA representing 2.7% EI, based on the levels observed at that time in human milk. As for ALA, a minimum intake of 0.45% EI is recommended to obtain an optimal DHA status for nerve and visual functions (7). These values are currently recommended by ANSES (12), whereas FAO-WHO recommend slightly lower ALA intakes of 0.3% EI (43). It is of importance to note that only EFSA recommends both lower and upper limits for LA and ALA. Then, the 2016 European regulation based on EFSA's recommendations sets LA levels at between 500 and 1200 mg/100kcal and ALA levels at between 50 and 100 mg/100kcal (44).

EFSA's most recent evolution of EFA RDAs raises the lower limit of LA from 300 to 500 mg/100kcal and lowers the upper limit of ALA to 100 mg/100kcal due to the mandatory addition of DHA to infant formula, thus lowering the required level of its precursor ALA in

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the presence of the preformed dietary DHA provided to adequately cover the physiological needs of infants (14).

Regarding the LA/ALA ratio, the 2006 European directive on infant formulas and follow-on formulas states that it should be between 5 and 15 (44). As seen before, this ratio is important for the composition of cell membranes, brain and neurosensory development, and the child's overall health considering the competition phenomenon in EFA conversion pathways. Thus, any imbalance between these two PUFA families could have harmful consequences. However, the rate of conversion of ALA to DHA depends on the absolute amounts of intake of LA and ALA, and not only on their ratio (13). Therefore this ratio seems to be of less interest today and the ANSES and FAO-WHO reports in 2010, unlike their predecessors, no longer mention limits for this LA/ALA ratio (45). Nevertheless, this ratio can remain a practical benchmark in the context of an overall diet, and remains important in the event of excessive intakes of LA or inadequate intakes of DHA and EPA.

4-4-2) Long-chain polyunsaturated fatty acids

FAO-WHO and ANSES currently recommend providing preformed ARA and DHA for all children aged 0 to 6 months, i.e. 0.5% and 0.32% of total FAs for ARA and DHA respectively (Table 4). These values are based on average values from global surveys of human breast milk (46). For DHA, EFSA's recommendations focus in particular on the effect of DHA on children's visual functions: a level of DHA equal to 0.3% of total FAs in infant formulas is recommended to ensure good visual development in children (47).

For EFSA, ARA is optional even before 6-month-old. As for DHA derived from ALA (21), ARA indispensability, linked to its low formation by conversion of LA, has led to the definition of a minimum physiological requirement of 70 mg/d, ensuring sufficient accumulation of this PUFA in cerebral membranes (9). For infant formulas, this DHA intake should be between 20 and 50 mg/100 kcal, with no specific recommendation for ARA (44).

For EPA, only an EPA/DHA ratio < 1 was previously recommended for newborns and infants up to 6 months of age (9), but the current data available is insufficient to define a physiological requirement and a RDA for EPA. Table 4 shows the main changes in LC PUFA recommendations over time for children aged 0 to 3, according to the various scientific societies and organisations.

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5- Monounsaturated fatty acids

Monounsaturated fatty acids (MUFAs) are FAs that have a single unsaturated double bond in their carbon chain. They typically have between 16 and 18 carbon atoms in their carbon chain, although variations can exist. In quantitative terms, oleic acid is the major component of MUFAs, actively synthesised by cells and very abundant in all plant and animal foods. It therefore accounts for almost all the MUFAs in human nutrition.

Oleic acid C18:1 (n-9) is used as a source of energy and is a constituent of all types of lipids, particularly reserve triglycerides (adipose tissue) (1). Increasing the percentage of intakes of MUFAs, mainly oleic acid, at the expense of saturated fatty acids (SFAs), leads to a reduction in total cholesterol and LDL-C, without reducing HDL-C in adults (48).

According to the latest ANSES recommendations, the MUFAs RDAs are the same for children, adolescents and adults (9). Oleic acid intakes recommended by AFSSA (9) are between 15 and 20% TEI. This intake was set at 20% TEI in the agency's official report in 2011 (9).

MUFAs are constituent of human milk lipids (1.7g/100g). To date, there are no specific recommendations on MUFAs for infants (0-3 years). The only exception is that European directives recommend a maximum level of erucic acid C22:1 (n-9), equal to 1% of total fats for the preparation of infant formulas because of potential adverse effects of this specific minor MUFA (49) (50). As MUFAs, mainly oleic acid, are very well represented in both the plant and animal world, a varied and balanced diet provides adequate quantities.

6- Saturated fatty acids

6-1) Generalities

SFAs are fully hydrogen-saturated carbon chains, classified by chain length. This different SFA families have very different origins, metabolism and functions, and that it is therefore essential to distinguish between them (Table 2). Short-chain SFAs, like butyric acid, are synthesized by the body and support energy regulation. Medium-chain SFAs, found in coconut oil, are rapidly absorbed independently of chylomicrons and the lymphatic system, and used for energy. Long-chain SFAs, such as palmitic acid, are abundant in the diet and essential for cell membranes and protein acylation. (Table 2)

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Human milk contains about 2g of SFA per 100 g milk, and they account for almost half of total FAs. Palmitic acid is the main SFA in human milk comprising around 25% (51). SFA have several functions in the body, beyond being a source of energy; they are important constituents of membranes (52) and needed for the FA acylation of proteins. FA acylation regulates intracellular trafficking, protein-protein and protein lipid interactions and each FA confers different biochemical properties. SFAs can also regulate gene transcription such as recruitment of transcription factors (52) (53).

6-2) Short- and long-term effects of a low SFA diet in children

Questions have been raised about the appropriateness of recommending a reduction in SFA intake for children, as excessive restriction could lead to inadequate nutritional intake and subsequently have a negative impact on the child's normal growth and development. However, there was no evidence of adverse effects of reduced SFA intake on anthropometric measures of growth, cognitive development, or micronutrient intake in children (54) (55). In addition, clinical studies show that diets low in SFA are associated with statistically significant reductions in total and LDL cholesterol and diastolic blood pressure in children and adolescents aged between 2 and 19 years (56).

The Finnish STRIP study assessed the long-term effects of a low-SFA diet started early in infancy. Over a thousand healthy infants were included and randomised at the age of seven months. At the end of the follow-up, at the age of ten, it was shown that dietary current recommendations targeting SFA restriction could be initiated in young children without deleterious consequences for growth, with beneficial effects on atherosclerosis risk factors and arterial function in boys (57).

To our knowledge, there is no specifically paediatric study about the deleterious effect of long-chain SFA on cholesterolemia.

6-3) Current recommendations

The ANSES and WHO/FAO reports do not include any recommendations on SFAs for infants under 6 months of age, even though human milk provides 20 to 25% of energy in the form of SFAs (54). However, for infants and young children aged between 6 months and 3 years, ANSES recommends a total SFA intake of less than 12% TEI and 8% for lauric, myristic and palmitic acids (9). There are no recommended minimum intakes for short- and medium-chain SFAs, which are present in breast milk. Furthermore, the FAO-WHO report recommends a

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reduction in SFAs, without a reduction in lipids, in children aged over 2 years from families with hypercholesterolaemia. Regarding the composition of infant formulas, European regulations impose a maximum level of lauric and myristic acid of 20% of total fats, due to a possible atherogenic effect, while imposing no restrictions on other SFAs, such as palmitic acid (44).

7 Trans fatty acids

7-1) Generalities

Trans fatty acids (TFAs) have a trans configuration of hydrogen atoms around their double bonds. They can be naturally produced by ruminants or industrially synthesized through hydrogenation. Industrial TFAs, found in processed foods, are linked to cardiovascular risks, while natural TFAs in dairy and meat are less harmful (Table 2) (58) (59).

7-2) Long-term effects of trans fatty acids intakes in children

The harmful effects of industrial TFAs include an increase in LDL cholesterol and a drop in HDL cholesterol (60). Clinical studies and meta-analyses in adults have shown that an excessive intake of TFAs is associated with an increased risk of cardiovascular disease (CVD) in a dose-response manner (61). One study on Spanish children aged 4-5 years old found that the highest quartile of industrial, but not natural TFA intake was associated to overweight. Another study carried out by Greek researchers on a hundred or so mothers and their 3-month-old infants showed that mothers who consumed at least 4.5g of TFAs a day were almost 6 times more likely to have a body fat percentage 30% higher. In this case, the risk of the infant having a fat mass greater than 24% is more than doubled. This study showed an association between high consumption of TFAs and an increase in body fat in both mother and baby, raising the hypothesis that TFAs are an early determinant of obesity (62).

7-3) Current recommendations

In 2005, the ANSES set a maximum intake threshold for total TFAs at 2% TEI (63) and at 1.5% TEI for TFAs of ~~technological~~ industrial origin, whereas the WHO currently recommends limiting their consumption to less than 1% TEI (64) , an indication of the increase in the negative effects linked to CVD of this class of lipids in the diet of the general population. For infant formulas and follow-on formulas, the European legislation authorises a maximum level of TFAs of 3% of the total fat content, to allow milk fat to be used in infant formulas (49).

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8 Cholesterol

8-1) Generalities

Cholesterol is crucial for neurological development, cell membrane formation, and hormone synthesis. It is abundant in human milk ranging between 90 and 150 mg/L (10 times higher than that of vegetable oil-based formulas and 6 times higher than that of cow's milk-based formulas) (65), regulating endogenous cholesterol synthesis in infants. Breastfed infants have higher cholesterol levels than formula-fed infants, which may positively influence long-term cholesterol metabolism and cardiovascular health (Table 2) (66).

8-2) Long-term effects of a high cholesterol diet in children

8-2-1) Lipid profile in adulthood

The hypothesis of the long-term impact of a diet rich in cholesterol during childhood emerged in the 1980s with the epigenetic notion that a diet rich in cholesterol early in life could favourably regulate the metabolism of cholesterol and lipoproteins in adulthood (67) (68).

Animal studies in baboons suggest that the amount of cholesterol in the diet of the first few months of life (formula or breastfeeding) can affect adult cholesterol metabolism, but in a non-linear way (69). The potential impact of early life nutrition in CVD incidence has been calculated by the following model: if 30% of infants were exclusively breastfed, the reduction in endogenous cholesterol synthesis would result in a 0.15 mmol/l drop in adult cholesterol levels, and therefore a reduction in the prevalence of CVD of up to 5% in the population (70).

8-2-2) Cardiovascular risk

The role of dietary cholesterol in cardiovascular risk is still a matter of debate, and epidemiological or long-term follow-up studies do not allow us to conclude with certainty about the role of early exposure to cholesterol in childhood in relation to cardiovascular risk in adulthood, apart from pathologies such as familial hypercholesterolaemia (71) (72) (73). In fact, there is no evidence to support its role or lack of effect on cardiovascular risk, as it is not possible to separate its role from that of other nutrients such as TFAs, with which it is co-ingested.

Recent epidemiological studies comparing breastfeeding with milk formula show a higher risk of CVD in adulthood in infants fed with infant formulas containing no or low amounts of cholesterol. In a population of 109 young adults who died prematurely and were autopsied, atherosclerosis occurred in 60% of cases in individuals initially fed on artificial milk,

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compared with 25% of subjects fed on breast milk (74). In another study, it was shown that mortality rates from ischaemic heart disease were higher in a formula-fed population than in a breast-fed population, and that these mortality rates were associated with higher adult total and LDL cholesterol values in the formula-fed population (70). Of note, a major bias in human studies is the comparison of breast-fed newborns versus those fed artificial formula, without considering the cholesterol content of the formula and the proportion of breastfeeding, if any, and its duration.

8-3) Current recommendations

Besides the studies published on early exposure of cholesterol impact on long-term cardiovascular risk, to date, there is no recommendation for the addition of cholesterol to infant formula.

9 Molecular species carrying FA: glycerolipids, glycerophospholipids, sphingolipids, glycosphingolipids.

9-1) Generalities

Even if TG are the main lipids providing dietary FA, breast milk and dairy products contain also many other bioactive lipids such as polar lipids. Their properties depend on the quality of the FAs (75).

Polar lipids include mainly glycerophospholipids and sphingolipids. These molecules are amphiphilic, which means they have surface-active properties and can be used as emulsifiers of lipids (TAG) in a water medium (micelles), and can auto assemble to form liposomes or be part of mixed lipid micelles. They have two different parts: a hydrophilic "head" (phosphate group) and a hydrophobic "tail" constituted by two FAs in glycerophospholipids; the junction between these two parts is a glycerol molecule. They constitute the main part of the cell membranes (cell, mitochondria, endoplasmic reticulum, nucleus…) forming lipid bilayers and they influence the membrane's biophysical properties depending on the composition of their different components (FA unsaturation level, organic molecules attached to the phosphate group, etc). This large family of lipids has also many other roles: cellular signalling, inflammation pathway, neurological transmission, and intestinal mucosal integrity among others (76).

Saccharolipids are complex molecules containing FAs or a sphingosine branched on a sugar molecule. They are amphipathic and then incorporated in the cell membranes such as the

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phospholipids. They are involved in a large panel of physiological pathways such as immunological response, cell interaction (apoptosis, tissue repair), brain functions, or cholesterol regulation (77).

9-2) Current recommendations

To our knowledge, it is of interest to note that there is no formal recommendation about their level of supplementation in glycerophospholipids and sphingolipids in infant formula.

10 Discussion: gaps, controversies and paths of improvement for the recommendations on the lipid profile of infant formulas

The evolution of the current recommendations we have just detailed well demonstrates the progress in our understanding of the lipid requirements of infants and young children. Maintaining significant calorie intake while achieving an optimal omega 6 / omega 3 ratio is at the core of all recommendations put forth by various scientific organisations. The composition of breast milk stands as the gold standard for determining the infant's nutritional intake. Our literature analysis identifies several potential avenues for improvement based on the disparities between the composition of breast milk and the current recommendations regarding the composition of infant and follow-on formulas. These differences can be attributed either to technical difficulties in modifying infant formula or to the lack of studies providing answers to the raised questions.

10-1) Quantitative characterization of infant formulas' lipid profile

10-1-1) Quantitative differences in lipid profile between breast milk and infant formulas

Unlike infant formulas, breast milk mainly provides MUFAs (45-50%) such as oleic acid (n-9) and palmitoleic acid (n-7) in higher quantities than PUFA (15%), and also a large proportion of SFA (35-40%) like palmitic acid and myristic acid (table 5) (78). However, the precise quantity of MUFA and SFA reported in the literature may vary depending on the ~~studies~~ publications. Indeed, the composition of these FA in milk depends mainly on the nature of the mother's lipid reserves and her dietary intake during pregnancy and lactation. These FA come from both endogenous synthesis and the diet (9).

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10-1-2) SFA supplementation

Palm oil

The composition of infant formulas aims to be as close as possible to that of breast milk, in which palmitic acid represents about 25% of total FAs (51) . Palm oil constitutes a widely available source of palmitic acid, and consumption of formulas with palm oil is associated with an increase in weight-for-length (WLZ) in infants under 6 months, but a decrease in weight-for-age (WAZ) and WLZ in infants aged 6-12 months (79). Because of eco-responsibility, the use of palm oil is a concern for many parents, but currently there is no evidence suggesting that palmitic acid at the levels observed in infant formulas, or the presence of palm oil have a deleterious effect on child health. Still, current research suggests that other SFA sources, namely dairy lipids, can be more optimal than palm oil regarding global FA profile and TAG structure (see below). There are now infant milks made from other vegetable oils, such as coconut (80) but their intensive production may also have an ecological impact and their FA profile is also quite different from the human milk, notably a high proportion of C12 in coconut fat.

Dairy lipids

Dairy fats are rich in SFAs (60-65% of FAs including 30% of palmitic acid) and low in EFA (52). The varied profile of cow's milk (>400 different FA species) is a richness that vegetable oils lack, including palm oil. That means that infant formula with milk fat provides a greater variety of SFAs, and this complex profile is closer to breast milk that what can be achieved with vegetable oils alone (table 5).

Dairy lipids are often considered to be potentially deleterious for CV health in case of excessive intake, as they are rich in SFAs. However, many studies suggest that, when present in a balanced diet, in particular because of the short and medium chain SFAs and the presence of myristic acid, dairy milk fat optimizes cellular and tissue availability of the EFA and LC PUFA. In other words, dairy milk fat's SFAs could help the body to synthesize and/or maintain very long-chain, highly unsaturated FAs, particularly those of the omega-3 family such as Eicosapentaenoic acid (EPA) and DHA, provided of course that there is a sufficient intake of the precursor ALA. For example in primates, compared with a diet low in myristic acid (0.6%), a richer diet containing twice as much myristic acid (1.2%) is associated with an increase in EPA and DHA levels in phospholipids and DHA levels in cholesterol esters (81). This raise the hypothesis that in humans a diet with moderate myristic acid intakes (1.2% of

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EI), compared to a lower diet (0.6%), increases DHA and EPA levels in some plasma lipid classes, despite equivalent intakes of ALA.

These results suggest that higher dietary SFA of dairy origin contributes at least in part to the maintenance of long-chain n-3 PUFA (82).

At present, regulations do not specify the fat source to be used in infant formulas. It is up to the manufacturer's choice to either use only vegetable fats, such as palm oil or coconut oil, or to incorporate dairy lipids in form of milk cream or milk fat.

10-1-3) LC PUFA supplementation

Long-chain polyunsaturated fatty acids

Intake of LC PUFA in children have been correlated to neurological and immune benefits.

Numerous studies have examined the effect of LC PUFA supplementation on psychomotor and neurosensory development in childhood, particularly in premature infants due to the increased needs associated with their rapid growth. Better cognitive performance has been demonstrated when infant formulas enriched with LC-PUFA and milk fat globule membrane (MFGM) are consumed for more than 6 months (83). Paediatric nutritionists agree that it is important for children to receive sufficient and balanced quantities of LC PUFA from the foetal stage and for at least the first 6 months of their post-natal life; that any serious deficiency in EFA and LC-PUFA could have deleterious and irreversible consequences for the brain, hence the importance of supplementing infant milks and ensuring that the diet of pregnant or breast-feeding women is adequately covered in these FAs (84).

Moreover, the antenatal and neonatal periods should be favoured to influence the maturation of the immune system. Supplementing hydrolysates with n-3 PUFA could prevent allergies in at-risk populations (85). Fish oil supplementation during pregnancy leads to an increase in n-3 LC PUFA in breast milk and a decrease in n-6, more marked than in control mothers. Thus, n-3 PUFA levels are associated with IgA, IL10, IL6 and CD14 levels in breast milk on day 3, which could have a preventive effect on allergy risk (86). The number of studies is still limited and the evidence inconclusive so n-3 PUFAs supplementation is not the subject of official recommendations for allergy prevention. Further studies are needed to determine whether n-3 PUFA have an anti-allergy protective effect, and to determine the optimal dose and type of supplementation to ensure this putative anti-allergy effect.

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LC PUFA also appear to have an epigenetic programming effect during the period of early ante- and neonatal development in animals and humans (87). Thus, recent studies show that LC PUFA (DHA such as ARA) could have a long-term effect on children's body growth as they regulate the expression of genes responsible for the development of adipocytes (22).

ARA and DHA

To date, the European Commission has made it compulsory to add DHA to infant formula manufactured from February 2020 onwards, but the addition of ARA remains optional (88).

This decision comes from several arguments, mainly that no additional benefit for infants has been demonstrated after the addition of ARA and DHA to formulas. In terms of growth, compared to supplemented formulas, the absence of added ARA and DHA does not alter the growth of infants (weight, height, etc.) (89). In neurological terms, since a large proportion of DHA is found in the cerebral cortex, optimal cerebral development seems to be possible with DHA alone (90) (91). It should be remembered that DHA levels increase with age and depend mainly on diet, unlike ARA whose levels depend on age and very little on diet (92). The beneficial effect on visual acuity is associated only with DHA. In fact, supplementation during the first 4 months of life with DHA alone, without ARA, resulted in visual maturation at the age of 4 years that was identical to that of breast-fed children and superior to that of infants receiving a formula not enriched with DHA. From this study including 16 and 17 children in DHA alone and DHA + ARA supplemented groups respectively, the use of milk enriched with ARA and DHA seems not provide any benefit compared with formula enriched only with DHA (93). It should be noted that according to the Diamond study, DHA intakes higher than the DHA levels measured in breast milk are not associated with additional visual improvement (33).

However, the latest official recommendations from the European Commission and most learned organisations making the addition of ARA to infant formulas optional are the subject of real debate in the field of paediatric nutrition. Several groups of experts suggest that these 2 LC PUFA should be added simultaneously to infant formulas (88). They support this position because human milk, considered the gold standard in infant nutrition, contains more ARA than DHA (94). In addition, in the absence of adequate dietary intake, endogenous synthesis of ARA is insufficient to ensure the non-neurological biological functions in which it is involved (95). Specifically genetic variants of desaturases present in 30% of children reduce the endogenous synthesis of ARA (96), so a higher dietary intake of ARA is necessary in

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carriers of these variants. In fact, the 30% reduction in ARA and EPA is observed in the case of minor alleles of FADS, whereas DHA levels are less affected by this genetic variant than by dietary intake. FADS is a gene that appears to modulate the effect of nutrition on cognition and immune development (83). Miklavcic et al. suggest that increasing the supplementation of infant formulas to 34 mg/100kcal of ARA and 17 mg/100kcal of DHA prevents the reduction in ARA due to minor alleles (97). Without the addition of ARA, anti-inflammatory and immunosuppressive effects can be obtained and are undesirable in the post-natal period when there is a significant risk of infection.

For all these reasons, the addition of ARA to infant formulas, in addition to the mandatory addition of DHA, seems desirable. According to the Diamond study, the ARA/DHA ratio in infant formula could influence neurological development, and the respective proportions of ARA and DHA should also be taken into consideration, highlighting an important and relevant effect of the ARA/DHA ratio (98). Similarly, it has been shown that when infants receive both ARA and DHA supplementation, they perform better in terms of cognitive performance than when they receive DHA alone (99). The controversy mainly comes from the heterogeneous results of neurodevelopmental studies on DHA and ARA supplementation. It can be explained by several confounding factors: heterogeneity between studies, a wide variety of judgement criteria and methodological approaches, the impact of genetic variability modulating the rate of endogenous LC PUFA synthesis, the interaction of breastfeeding, which provides preformed LC PUFA, lifestyle, smoking and socio-economic status (1).

Therefore, the need for high-quality clinical trials is of the utmost importance to answer to these questions. The size of the samples chosen is a central parameter for assessing complex intellectual performance, identifying sex differences and the effect of different polymorphisms known to influence FA metabolism. The results of these trials will be important in forming the basis of evidence-based guidelines for LC PUFA formula supplementation for infants and young children.

10-1-4) Cholesterol supplementation

Human milk contains higher cholesterol content compared with commercial infant formulas containing only vegetable fats (table 5). While conclusive evidence from randomized clinical trials still lacking, the arguments supporting the addition of cholesterol to infant formula are based on its physiological functions; cholesterol is crucial for neurological development, cell membrane formation, and hormone synthesis. Because cholesterol is a key component of the

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developing brain, its addition to infant formulas may support the growth and functioning of the central nervous system.

A potential impact on lipid metabolism has been suggested by epidemiological studies. Breast-fed infants have higher plasma concentrations of total and LDL cholesterol (LDL-Ch) than formula-fed infants; however in the long term, studies have shown lower LDL-cholesterol in individuals who were breastfed. This difference is attributed to cholesterol in breast milk (15mg/100ml) which is absent in infant formula. Oral ingestion of cholesterol early in life may play a part in the hepatic development of lipid degradation enzymes or hepatic receptors for LDL-cholesterol. However, other studies have reported conflicting data regarding the assumed protective effect on the cardiovascular level, with similar cholesterol levels after the age of 1 year. (100) (101) (102).

Of note, the addition of cholesterol to infant formulas presents technological and economic challenges that currently limit its widespread implementation. However, the incorporation of milk fat globule membrane (naturally containing cholesterol) in infant formula is a possibility to achieve higher cholesterol content (cf below). Although the presence of significant amounts of cholesterol in human breast milk and epidemiological data suggesting its nutritional value, the current lack of recent and rigorous studies makes it challenging to formulate a recommendation on adding cholesterol to infant preparations.

10-2) Qualitative characterization of infant formulas' lipid profile

10-2-1) Triglycerides structure

Triglycerides (TG) are esters composed by one glycerol and three FAs. The main sources of TG are dairy products, vegetable oil and animal fats. Their primary role is energy-related: serving as reserves in adipose tissue and contributing to ATP production.

The position of some FAs in the triglyceride structure (sn-1 and sn-3 for the outer positions and sn-2 for the central position) can influence their digestion and absorption in the intestine. In this respect, TG structure is different in human, bovine or vegetable fat. Human and bovine milk fat contain a wide variety of FAs, whereas vegetable fat variety is poorer and depends on the vegetable specie used (blends are used to improve the variety). In human milk, the main TG structures are palmitic acid (C16) at the sn-2 position (see next paragraph) and oleic acid (18:1) at the sn-1 or sn-3 position. In bovine milk fat, palmitic acid (C16) at the sn-2 position is also the main TG structure (40-45% of the total amount of palmitic acid is branched at the

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sn-2) (103), with oleic acid (18:1) at the sn-1 or sn-3 position (104). Of note, butyrate is at the sn-3 and stearic (18:0) acid at the sn-1 position. In vegetable fat used for infant formula, palmitic acid at the sn-2 position is less frequent (10-20% only) (103), whereas higher level of SFA are present at the sn-1 and sn-3 position (105) compared to human and bovine milk (106).

sn-2 palmitate level optimisation

Palmitic acid (C16) is the most abundant SFA in breast milk and between 60-70% is esterified in the sn-2 position. During digestion, the action of lipases produces 2 free fatty acids (FFAs) (positions sn-1 and sn-3) and one monoacylglycerol. If palmitic acid is released as FFA because it was on sn-1/3 position, it can bind calcium and form insoluble calcium soaps which are not absorbed and can be associated to increased constipation and infant colic(107). Studies have shown a positive correlation between the sn-2 central position of palmitic acid on triglycerides and improved digestive comfort in children. This beneficial effect is linked to an increase in the number of Lactobacillus and Bifidobacteria in the intestine (105) (108), and secondly with the lower amount of calcium soaps in faeces, which favours the formation of softer stools (109) (103).

Recent studies also show that increasing the level of sn-2 palmitate in infant formula,using milk fat instead of palm oil, is associated with better development of motor skills in children at the age of 16 months and that the beneficial effects on neuronal development in children are associated with an increase in the level of bifidobacteria in the intestinal microbiota (110).

The optimisation of sn-2 palmitate level in infant milk formulas can be achieved either by industrial restructuring of vegetable fats (palm oil) or addition of milk fat instead of regular palm oil. This is because in dairy lipids, palmitic acid (C16:0) accounts for approximately 25% of total FAs and is mostly found in the sn-2 position (Figure 3). However, despite the importance of the positioning of FAs on the TG molecule for FAs bioavailability and the associated benefits on digestion and neuronal development, no recommendation has been formulated so far. Therefore, specific consideration on this point appears necessary for future recommendations.

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10-2-2) Fat emulsion ultrastructure

Differences in fat emulsion ultrastructure between breast milk and infant formulas

In terms of quality, the fat emulsion in human milk and infant formula differs significantly in both structural and biochemical terms.

The fat globules in human breast milk are distinguished from those in infant formula by their larger size and the presence of a phospholipid membrane that modifies intestinal absorption and may confer beneficial properties in terms of body composition and subsequent cardio-metabolic prevention (111). Phospholipids are also essential components of the neurological system and supplementation in animal diet improve brain myelinisation (112). In human clinical studies, supplementation of milk with phospholipids, including sphingomyelin, is associated with improvement of neurological development, mainly the cognitive efficiency (113).

In more details, in its native form, women's milk fat is organized into dispersed globules enveloped by a triple phospholipid membrane known as the MFGM, which originates from the fat-secreting epithelial cells of the mammary gland (114). These MFGMs comprise proteins inserted in the phospholipid's membranes mainly at the inner layer, an intermediate layer composed of the phospholipid triple membrane, and an outer layer consisting mainly of high-molecular-weight glycoproteins and sphingomyelin/cholesterol complexes (figure 4). Milk fat globules have an average diameter of around 3 to 5 µm, but show a wide size distribution (from 0.1 to 15 µm) in both women's and cow's milk (115). In infant formulas, on the other hand, the fat is dispersed as a result of the homogenization of vegetable oils in the presence of milk proteins. This process produces a stable micro-emulsion of plant lipids, mainly stabilized by caseins and potentially added stabilizers like lecithins, in the form of small lipid droplets with an average diameter of less than 0.5 µm and no membrane coating (figure 4).

Size of milk fat globules optimisation

Recent experimental data suggest that the size of milk fat globules is key parameter in the long-term beneficial effects of breastfeeding, particularly in protecting against metabolic syndrome and obesity (116). During the developmental period in mice, from weaning to young adulthood, consumption of a milk diet composed of large (10 µm) fat globules surrounded by a phospholipid membrane reduced total adipose tissue mass and circulating leptin levels by 25% in adulthood, compared to a diet with a droplet structure characteristic of

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infant milks (117). This beneficial effect on body composition is also accompanied by an improvement in the animal's metabolic status and, more specifically, insulin sensitivity, with a reduction in the HOMA index, fasting glycemia and circulating resistin levels. The authors hypothesize that changes in lipid absorption and digestion kinetics may in turn alter their metabolic utilization - the balance between catabolism by beta oxidation and lipogenesis. In rats, the absorption of small fat globules (0.4 µm) formed with adsorbed casein causes a marked reduction in postprandial beta oxidation of FAs, compared with large native globules. This difference is thought to result from a delay in the kinetics of triglyceride appearance in plasma, linked to slower gastric emptying and lipolysis when small fat globules are ingested (115) (118).

Recent studies show that the interfacial coating of breast milk fat globules with MFGM facilitates lipolysis by digestive lipases and bile salts naturally present in breast milk (114). Lipolysis being an interfacial process, gastric and pancreatic lipases hydrolyse fats at the oil-water interface. Thus, the composition and structure of the oil-water interface are likely to affect lipolysis in the gastrointestinal tract. In infants, levels of pancreatic lipase and bile salts are low compared to adults, so the products of gastric lipolysis play an important role in the digestion of milk lipids, compensating for the low levels of pancreatic lipase and emulsifying lipids, respectively. Today's infant formulas contain much smaller thick protein-coated fat droplets than the MFGM-coated fat globules of breast milk. Thus, infant formulas containing bigger fat droplets resulting from MFGM enable a digestion process closer to that of human milk (111).

Milk fat globule membrane supplementation

In humans, clinical studies have reported the beneficial effects of MFGM supplementation of infant formulas on neurocognitive development and protection against infectious agents, with no deleterious impact on growth (119) (120).

The COGNIS study is a prospective, randomized double-blind, nutritional intervention study. This study compared during their first 18 months of life 70 children fed with either a standard infant formula (SF, n = 29) or a bioactive compounds enriched-infant formula (EF, n = 41), and 33 breastfed (BF) children (reference group). The results suggest that enriched infant formula fed infants seem to show fewer behavioural problems up to 2.5 years compared to a standard infant formula-fed infants (121).

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In Indonesian infants aged under 8 weeks to 6 months and supplemented with MFGM complex lipids, a higher general intelligence quotient (IQ) and better hand-eye coordination and Griffiths scale performance IQ were found at 24 weeks of intervention compared to those fed without MFGM (122). Another trial in Swedish infants aged 2-6 months supplemented with MFGMs (Lacprodan MFGM-10) showed a higher Bayley-III cognitive score at 12 months compared with the unsupplemented group (123) (124).

In a Swedish double-blind randomized controlled trial including 160 formula-fed healthy term infants and 80 breastfed reference children, formula supplemented with a protein-rich MFGM concentrate given between 2 and 6 month, decreased infectious morbidity until 6 month of age (significantly lower incidence of acute otitis , lower antipyretic use, and lower serum concentrations of IgG against *pneumococci* after vaccination) (119) (125).

A Franco-Italian study in infants aged 14 days to 4 months, comparing supplementation with either MFGM-L (lipid-rich MFGM fraction) or MFGM-P (Lacprodan MFGM-10: the first MFGM ingredient to enter the global infant formula market, rich in phospholipids and gangliosides), showed no difference in weight gain for the 2 groups (126).

The use of MFGM in children nutrition can be provided from specific added products such as buttermilk-based ingredients or directly from milk cream.

These results call into question the historical choice of not including milk fat as part of infant formula, and may serve as a basis for new strategies to evolve the nutritional formulations of infant milks. Recently, some formulas have begun to add dairy lipids, whereas the majority of current infant formulas contain lipids of exclusively vegetable origin. This addition of dairy lipids positively impacts both triglycerides structure with increased sn-2 palmitate level and fat emulsion composition / ultrastructure with MFGM supplementation. By playing on the complementarity of plant and dairy lipids, rather than eliminating the latter, it seems possible to optimize the composition of infant formulas to make them more similar to breast milk. Preserving dairy lipids would thus have beneficial effects on child development, while retaining interesting taste properties.

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11 Conclusion

This narrative review highlights the consensus and changes in current recommendations for the lipid intake of young children under 3 years of age. The contribution of lipids to EI appears to be the most consensual recommendation at the international level. At present, the benefits of a diet rich in omega 3 and 6 are widely recognized in lipid recommendations for young children aged 0-3.

On the other hand, this work raises persistent questions about current recommendations such as the absence of regulations on the addition of ARA in infant formulas despite clinical evidence showing that concomitant supplementation of ARA and DHA can mimic the effects of breastfeeding and ensure good brain and retinal development in children. It also points out that the evolution of official recommendations mainly concerns the quantitative aspect of LC-PUFA while, other lipids present in breast milk such as SFAs MUFAs, cholesterol, EPA and the structure of lipids for infants under 6 months, remain without recommendations.

The introduction of milk fat, including sn-2 palmitate and MFGM, seems to be a relevant way to improve the quality of infant formula. However, further randomized controlled trials evaluating the nature and function of lipid matrices are needed to increase scientific knowledge, specifically studies assessing the impact of the structure of lipids ingested during the neonatal period in metabolism programming in adulthood. Recent animal studies have also reported promising results on the supplementation of cholesterol in infant formulas, but the underlying mechanisms still need to be better understood and could help in designing improved nutritional strategies. We are confident that these aspects will lead to future improvements in infant formula, and possibly to better preventive nutrition for future adults who cannot be initially breastfed.

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Table 1: Evolution of the recommendations on proportion of Energy Intake derived from lipids in children aged 0 to 3 years.

Year	**2006**		**2010**		**2011**	**2014**		**2016**
Organisation	FAO/WHO	ESPGHAN	FAO	EFSA	ANSES	SFP	EFSA	ANSES
(ref)	(1)	(127)	(43)	(45)	(9)	(13)	(14)	(12)
0-6 m	40-60%	39,6%-54%	40-60%	-	45-50%	-	50-55%	50-55%
6-12 m	-		35%	40%	45-50%	35-40%	40%	45-50%
12 – 24 m	-		35%	35-40%	45-50%	35-40%		45-50%
24 – 36 m	-		25-35%	35-40%	45-50%	35-40%		45-50%

EI: EI, ANSES: French Agency for Food, Environmental and Occupational Health and Safety, EFSA: European Food Safety Authority, ESPGHAN: European Society of Pediatric Gastroenterology, Hepatology and Nutrition, FAO: Food and Agriculture Organization, mo: month, m: month, SFP: French Paediatric Society, WHO: World Health Organization.

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Table 2: Main roles of lipids in child development

Fatty Acid Family	Fatty Acid	Food Sources	Specific Actions
Omega-3 (n-3)	**Alpha-linolenic acid (ALA)**	Flaxseed, rapeseed, walnut oils, Chia seeds, Walnuts, Hemp seeds.	Precursor for EPA and DHA; anti-inflammatory; supports brain and retinal development
	Eicosapentaenoic acid (EPA)	Fatty fish (e.g., salmon, mackerel, sardines, herring), fish oil, krill oil, shellfish (e.g., mussels, oysters), marine algae.	Anti-inflammatory; modulates immune response; supports cardiovascular health
	Docosahexaenoic acid (DHA)	Oily fish, algae	Essential for brain and retinal development; structural role in neuronal membranes
Omega-6 (n-6)	**Linoleic acid (LA)**	Sunflower, Corn, Grapeseed, Safflower, and walnut oi	Precursor for ARA; supports cell membrane structure; pro-inflammatory effects
	Arachidonic acid (ARA)	Red meat, organ meats, eggs, dairy products, fish, poultry, corn oil	Structural role in cell membranes; regulates inflammation, immunity, and bone development
Saturated Fatty Acids (SFA)	**Butyric acid (C4:0)**	Dairy products	Energy source; protects intestinal barrier; modulates cell proliferation
	Caproic acid (C6:0)	Dairy products, coconut oil	Rapidly absorbed; energy source for mitochondria
	Lauric acid (C12:0)	Coconut oil, palm oil	Antimicrobial properties; energy source
	Myristic acid (C14:0)	Dairy products, meat, palm oil	Supports protein acylation; enhances DHA and EPA levels in plasma lipid classes
	Palmitic acid (C16:0)	Dairy products, palm oil	Structural role in membranes; energy source; supports protein acylation
Monounsaturated Fatty Acids (MUFA)	**Oleic acid (C18:1 n-9)**	Olive oil, avocados, nuts	Reduces LDL cholesterol; supports cardiovascular health; energy source
Trans Fatty Acids	**Industrial trans fats**	Processed foods (hydrogenated oils)	Increases LDL cholesterol; reduces HDL cholesterol; associated with cardiovascular risk
	Natural trans fats	Dairy products, meat	Less harmful than industrial trans fats; moderate intake may not impair insulin sensitivity
Cholesterol	**Cholesterol**	Human milk, eggs, meat, dairy products	Essential for neurological development; regulates cell membrane fluidity; precursor for hormones

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Table 3: ALA and LA recommendations for children aged 0-3

Year	**2001**		**2006**	**2010**		**2011**	**2016**
Organisation	**EU**	**AFSSA**	**EU**	**FAO-WHO**		**ANSES**	**EU**
ref	(128)	(8)	(129)	(43)		(9)	(44)
LA							
0-2 d	> 300 mg/100kcal	2 - 4.5% EI	300 - 1200 mg/100 kcal	no recommendation	> 2.7 % EI		500 - 1200 mg/100 kcal
1-6 m							
6 m-3 y		2 - 5% EI					
ALA							
0-28 d	> 50 mg/100kcal	0.45 - 1.5% EI	>50 mg/100 kcal	0.2 - 0.3 % EI	> 0.45 % EI		50 - 100 mg/100 kcal
0-6 m							
6 m-3 y		0.4 - 1% EI					
LA/ALA							
0-28 d	5 - 15	4 - 10	5-15	Optional			
0-6 m							
6 m-3 y							

ALA: alpha-linolenic acid, d: day, EI: EI, AFSSA: French Agency for Food Safety, LA: linoleic acid, ANSES: French Agency for Food, Environmental and Occupational Health and Safety, FAO: Food and Agriculture Organization, m: month, WHO: World Health Organization, y: year.

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Table 4: ARA and DHA recommendations for children aged 0-3

Year	**2001**		**2006**	**2010**	**2011**	**2016**
Society	**EU**	**AFSSA**	**EU**	**FAO-OMS**	**ANSES**	**EU**
Reference	(128)	(8)	(49)	(1)	(9)	(44)
ARA						
0 - 28 d		0.1 - 0.25% EI	<1% of fat	0.4 - 0.6 % TFA	0.5% TFA	Optional
0 - 6 m						
6 m - 3 y		no recommendation			Optional	
DHA						
0 - 28 d		0.1 - 0.4% EI		0.2 - 0.36 % TFA	0.32% TFA	20-50 mg/100k cal
0 - 6 m						
6 m - 3 y		no recommendation			70 mg/j	
EPA						
0 – 28 d		0.05 - 0.15% EI				
0 - 6 m						
6 m - 3 y		no recommendation				
ARA/DHA						
0 – 28 d					1.6	
0 - 6 m						
6 m - 3 y						
EPA/DHA						
0 – 28 d			<1		<1	
0 - 6 m						
6 m - 3 y						
DHA/LCPUFA						
0 – 28 d			<1			
0 - 6 m						
6 m - 3 y						

AFSSA: French Agency for Food Safety, LC PUFA: long-chain polyunsaturated acids, TFA: total fatty acids, ANSES: French Agency for Food, Environmental and Occupational Health and Safety, ARA: arachidonic acid, d: day, DHA: docosahexaenoic acid, EFSA: European Food Safety Authority, EI: Energy Intake, EPA: eicosapentaenoic acid, FAO: Food and Agriculture Organization, m: month, WHO: World Health Organization, y: year.

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Table 5: Comparison of the nutritional lipid composition of breast milk, cow's milk and infant formulas based on vegetable oils (46) (130) (131) (108).

/100 ml	**Breast milk**	**Cow's milk**	**Infant formula (with vegetable oils as lipid sources; in this case palm oil and coconut oil)**	**Infant formula (with dairy product as lipid source)**
Fat (g)	3.2-3.6	3.6	2.6-4	2.6-4
Triglycerides %	98.1-98.8	97	N/A	98
Phospholipids %	0.26-0.8	1.5	≤ 7 ~~ou égal~~	
Cholesterol (mg/100ml)	9-15	1.0-33	Absent	
Fatty acids as % of total fatty acids				
SFA				
Butyric acid C4 :0	0.1	1.4	Nq	2.4
Caproic acid C6 :0	0.2	2.1	0.1	1.3
Caprylic acid C8 :0	0.3	1.7	1.0-1.5	1.7
Capric acid C10 :0	2	3.5	0.9-1.3	2.2
Lauric acid C12 :0	6.8	3.9	7.8-11.5	6.3
Myristic acid C14 :0	10.4	12.6	4.0-5.5	7.2
Palmitic acid C16 :0	25	29.5	18.2-25.4	18.9
MUFA				
Palmitoleic acid C16 :1	3.5	1.7	0.1-0.2	1.1
Stearic acid C18 :0	6.9	13.3	3.5-4.0	6.7
Oleic acid C18 :1	33.6	26.3	28.4-40.8	28.1
PUFA				
n-6 PUFA				
Linoleic acid C18:2	17	2.9	13.3-18.5	16.7
Arachidonic acid C20:4	0.5		Added 0.2-0.6 or not added: nq	-
n-3 PUFA				
Alpha-linolenic acid C18 :3	1.7	1.1	1.6-2.4	1.5
Docosahexaenoic acid C22:6	0.32		Added 0.2-0.3 or not added: nq	-

MUFA monounsaturated fatty acids, PUFA polyunsaturated fatty acids, SFA saturated fatty acids

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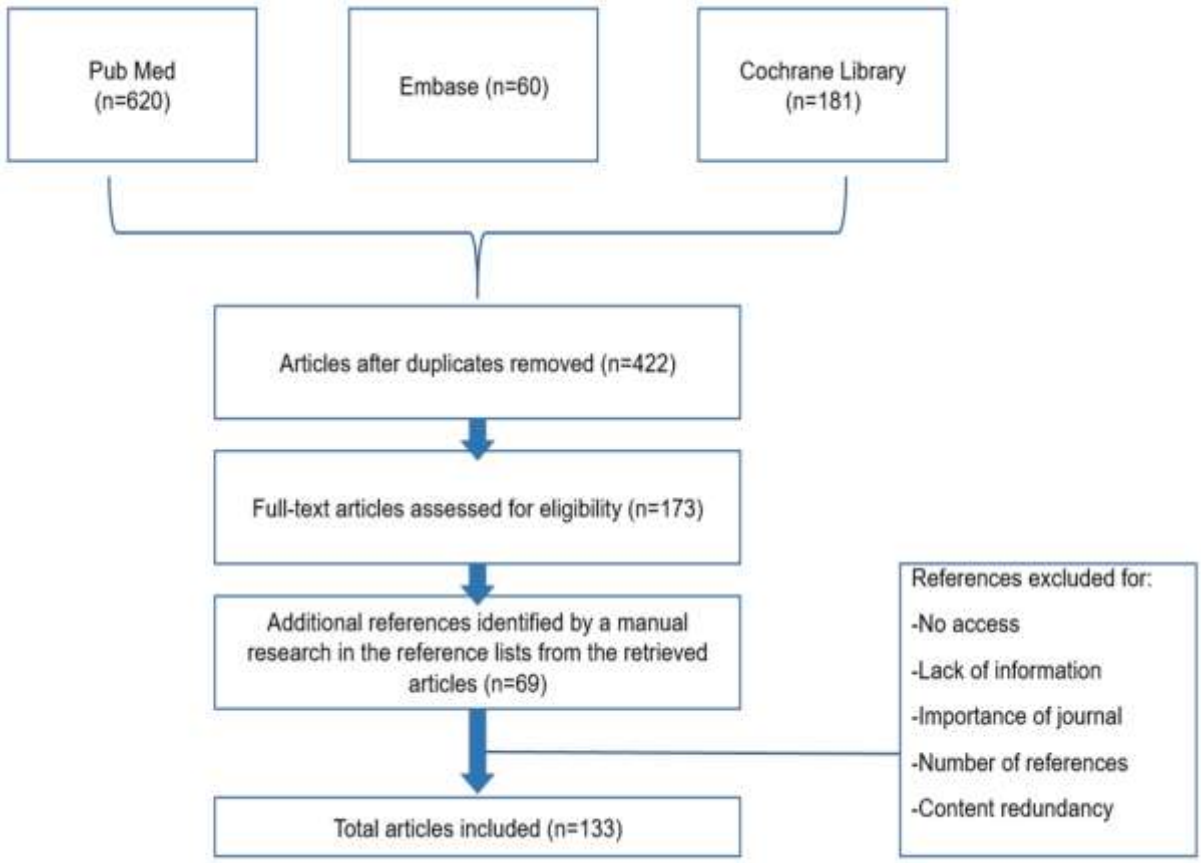

Figure 1: Flow chart showing the methodology used to carry out the narrative literature review

The search period was between 2001 and 2022. The selection of relevant literature included articles in English and French and identified 861 articles in the following search engines: PubMed (n=620), Embase (n=60), and Cochrane (n=181). Articles were excluded if they did not provide the information sought, had an insufficient number of cited references (<2), presented redundant content, or were deemed irrelevant. After deduplication, there were 422 articles left, and 104 were withdrawn after reviewing citations' eligibility. After removing redundant citations, non-accessible articles, and/or those missing the information sought, 133 different articles were included

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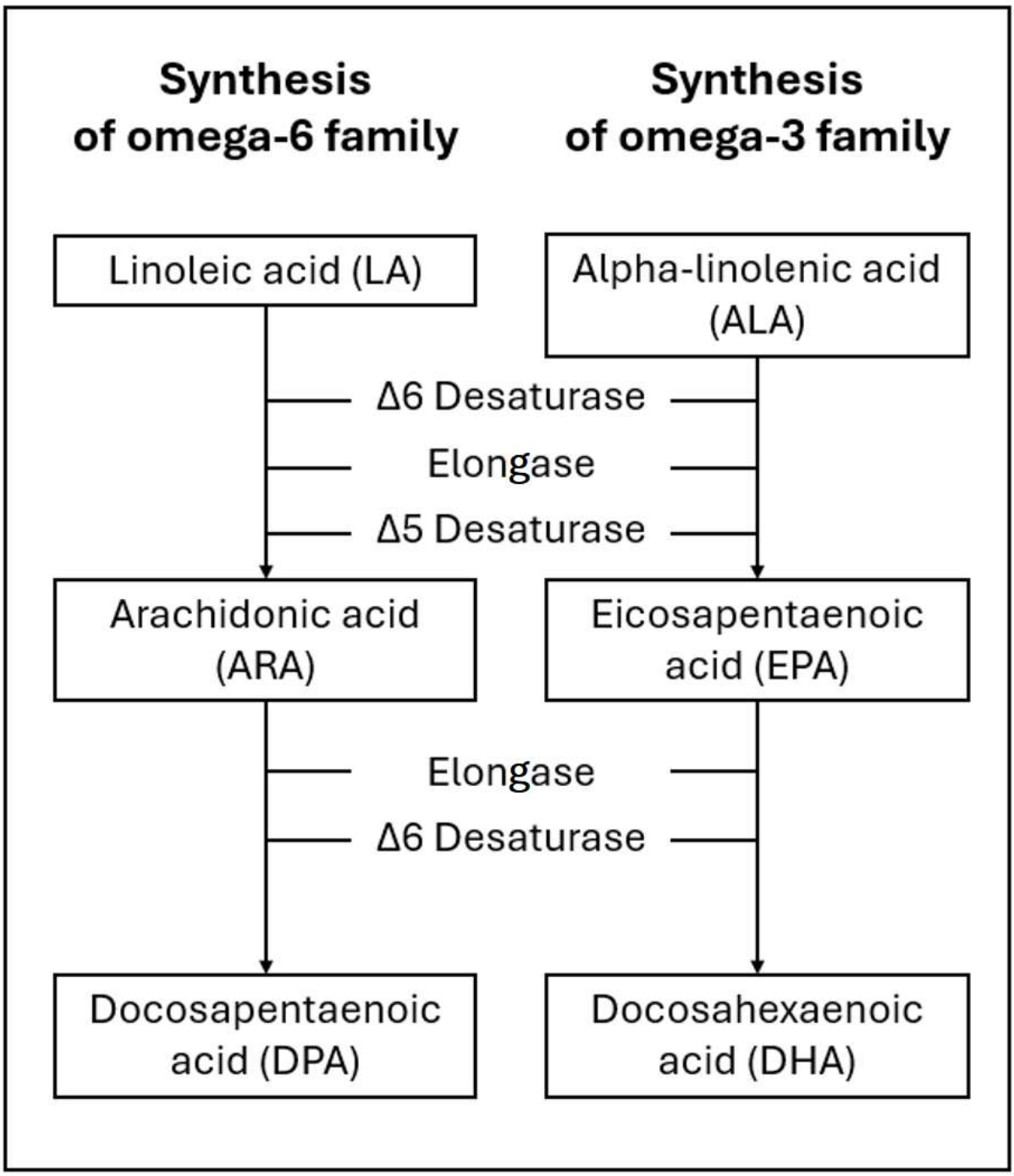

Figure 2: Conversion pathways for linoleic and alpha-linolenic acids

The synthesis of omega-6 and omega-3 FAs from their respective precursors, the EFA linoleic acid (LA) and alpha-linolenic acid (ALA), is illustrated here. The successive action of desaturases and elongases, which are common to both metabolic pathways, explains the competitive phenomenon that can occur with an excessive intake of one of the EFA

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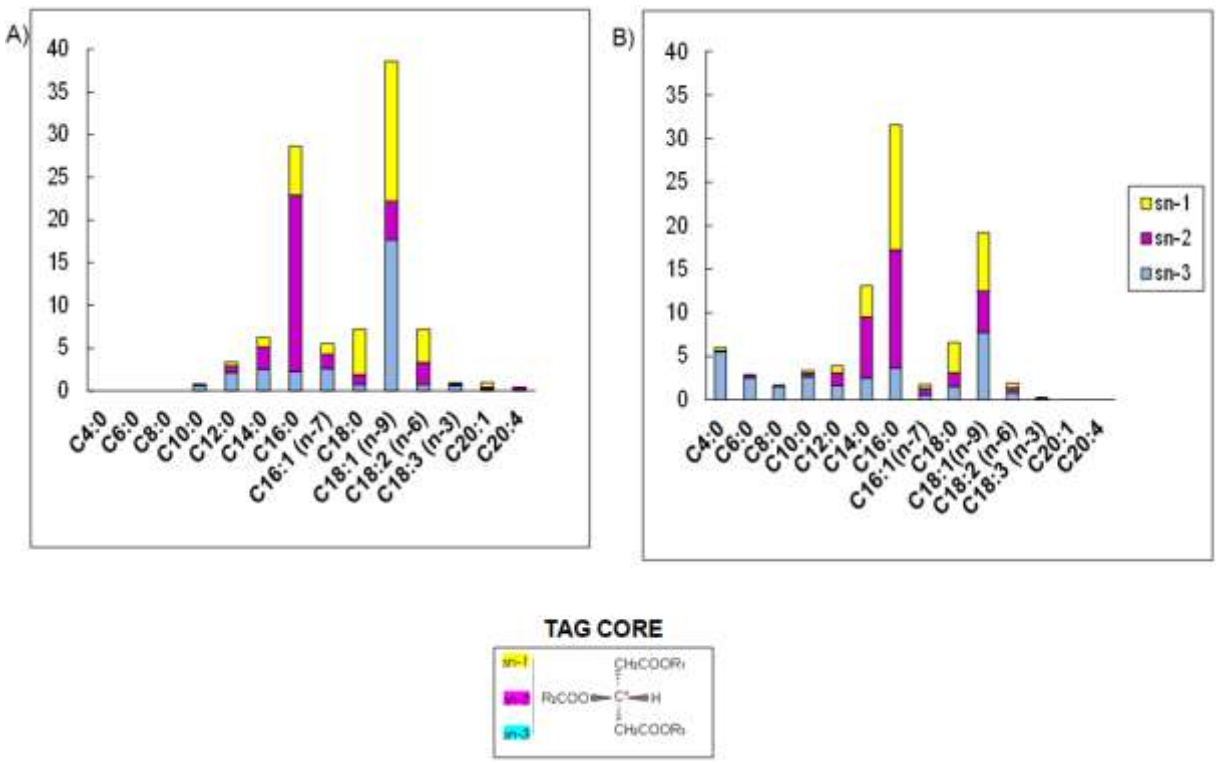

Figure 3: Comparative FAs composition and regiodistribution in Human milk fat A) and Bovine milk fat B) (% mol of main FAs > 0.5 % total)

This figure compares human versus bovine milk fat in terms of FA composition (expressed as % mol of main FAs > 0.5% of total) and also the positional distribution of FAs within the triglyceride molecule (Regio-distribution in the triacylglycerol (TAG) core between the external positions sn-1 and sn-3, or the middle position sn-2).

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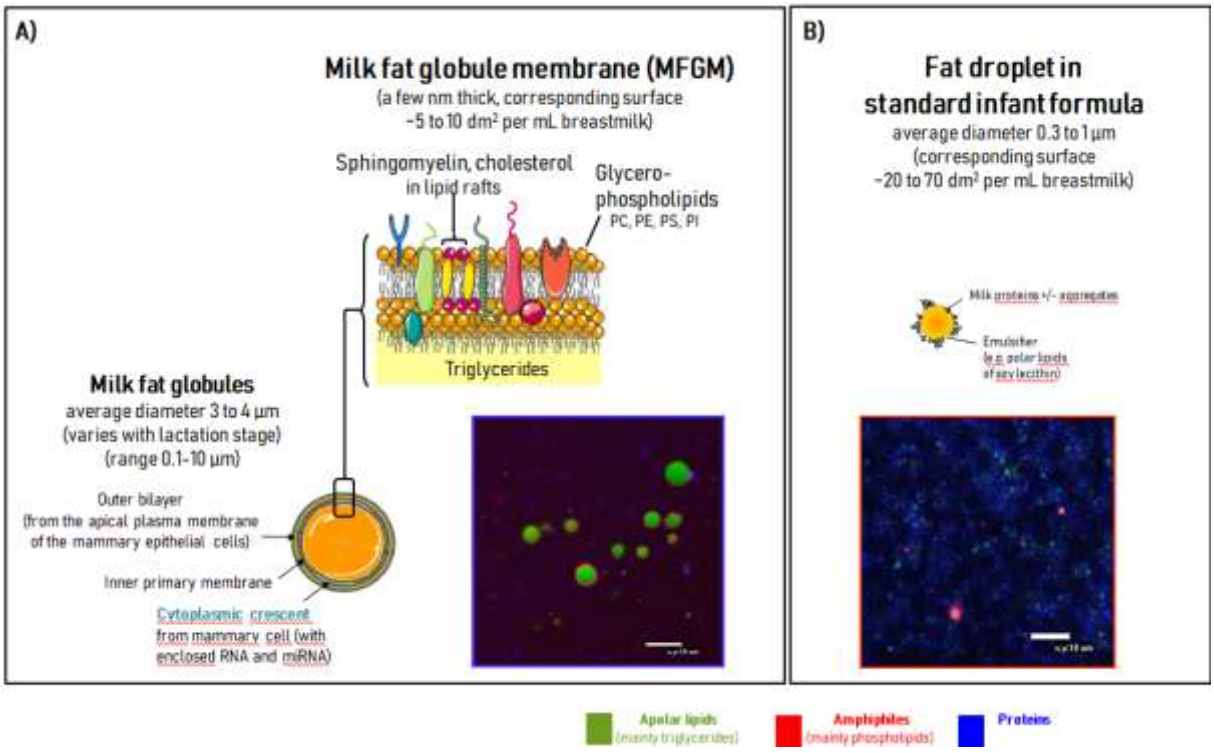

Figure 4: Structural differences in lipid droplets between breast milk containing the native milk fat globules (A) and the microemulsion of plant lipids in infant formula (B)

The structural differences between fat in mammalian milk and standard infant formula are presented. Panel A illustrates the structure of the milk fat globule with detailed milk fat globule membrane structure. Panel B, depicting the fat droplet in standard infant formula, highlights differences in terms of size (smaller diameter: 0.3-1 µm versus a few nm) and structure (aggregates of protein and emulsifier versus trilayers).

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